Fluorowane nitryloiminy
jako unikatowe bloki budulcowe do zastosowań
w syntezie organicznej

Fluorinated nitrilimines as unique building blocks
for applications in organic synthesis

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Rozprawa doktorska wykonana pod kierunkiem

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[**D6**] A. Kowalczyk, M. Jasiński
4,5-dihydro-1,2,4-triazin-6(1H)-ones
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Streszczenie

Ze względu na szczególne właściwości fluorowanych związków organicznych, przekładające się na ich różnorodne zastosowania praktyczne, jeden z ważnych obszarów współczesnej syntezy organicznej koncentruje się na poszukiwaniu wydajnych metod otrzymywania tego typu połączeń. W tym kontekście, w ramach niniejszej pracy zwróciłam uwagę na *fluorowane nitryloiminy*, formalnie pochodne trifluoroacetonitrylu, jako atrakcyjne bloki budulcowe do syntezy trifluorometylowanych heterocykli azotowych. Aby zbadać reaktywność tytułowych 1,3-dipoli dostępnych *in situ* z odpowiednich prekursorów hydrazonoilowych, testowałam je wobec trzech wybranych grup odczynników tj. (*i*) arynów (benzynów) jako przykładowych wysoce reaktywnych dipolarofili bogatych w elektrony, (*ii*) chalkonów oraz pokrewnych α,β-nienasyconych związków karbonylowych jako modelowych dipolarofili zubożonych elektronowo, a także (*iii*) estrów naturalnych α-aminokwasów jako dwufunkcyjnych reagentów elektrofilowo-nukleofilowych.

Pierwszy projekt miał na celu sprawdzenie, czy możliwe jest zastosowanie generowanych *in situ* pochodnych benzynu jako odczynników wyłapujących CF_3-nitryloiminy (również generowane *in situ*), i w tym przypadku wykazałam, że zaprojektowaną reakcję (3+2)-cykloaddycji można skutecznie realizować w roztworach organicznych uzyskując pochodne indazolu sfunkcjonalizowane w pozycji C(3) grupą CF_3. Kluczowym rozwiązaniem było zastosowanie TBAF jako źródła anionu fluorkowego, który w reakcji pełnił dwojaką rolę tj. jako *odczynnika desililującego* względem prekursora benzynu oraz *zasady* w równoległej reakcji dehydro-halogenowania prekursora nitryloiminy. Ponadto, zademonstrowałam wydajny dostęp do *N*-niepodstawionego 3-CF_3-indazolu, ważnego półproduktu do otrzymywania bardziej złożonych pochodnych *N*-alkilowych i *N*-acylowych tego heterocykla, w tym analogu znanego leku przeciwnowotworowego (*Lonidamidu*).

Kolejny wątek badań dotyczył reakcji Huisgena pomiędzy tytułowymi nitryloiminami oraz enonami. Jak wykazałam, zaprojektowane

(3+2)-cykloaddycje przebiegają regio- i diastereoselektywnie i prowadzą do bardzo użytecznych syntetycznie 5-acylo-3-CF_3-pirazolin. Co istotne, wspomniane cykloaddukty można łatwo aromatyzować przy zastosowaniu aktywowanego MnO_2, a w zależności od użytego rozpuszczalnika, utlenianie przebiega wysoce chemoselektywnie, albo na sposób *dehydrogenatywny* (w rozpuszczalnikach polarnych) albo *deacylujący* (r. niepolarne). Ponadto, zbadałam mechanochemiczne warianty w/w transformacji, a opracowaną strategię zaadaptowałam do przygotowania ważnej grupy kwasów 3-CF_3-pirazolo-alkanokarboksylowych.

W ostatnim projekcie zbadałam reaktywność tytułowych nitryloimin wobec estrów α-aminokwasów uzyskując pochodne 3-CF_3-1,2,4-triazyny jako wyłączne produkty powstające na drodze dwuetapowej (3+3)-annulacji. Wykazałam szeroki zakres stosowalności opracowanej metody uzyskując trzy serie różnorodnie podstawionych produktów, a w przypadku chiralnych związków wyjściowych obserwowałam pełny transfer czystości optycznej. Dla wybranych produktów skutecznie przeprowadziłam transformacje grup funkcyjnych, w warunkach łagodnego utleniania i redukcji, potwierdzając użyteczność syntetyczną tej klasy heterocykli fluorowanych.

Abstract in English

Fluorinated organics exhibit unusual physio-chemical properties and for this reason, they have found numerous practical applications. Consequently, there is remarkable need for straightforward access to various fluoroorganics, and the development of new synthetic methods is one of major goals of modern organic synthesis. In this context, the presented PhD thesis focuses on the chemistry of little known fluorinated nitrile imines, formally derived from trifluoroacetonitrile, as building blocks for preparation of nitrogen heterocycles. In order to examine the reactivity of the title nitrilimines, they were tested towards three selected groups of reagents, namely (*i*) arynes (benzynes) as extremely reactive electron-rich dipolarophiles, (ii) chalcones as well as structurally related α,β-unsaturated compounds selected as model electron-deficient dipolarophiles, and (*iii*) amino acid esters indicated as attractive bifunctional electrophilic/nucleophilic agents.

The main goal of the first project was to check whether it would be possible to apply *in situ* generated arynes/benzynes as suitable agents for trapping CF_3-functionalized nitrile imines (also available *in situ*). As demonstrated, the designed (3+2)-cycloaddition reaction can be successfully carried out in dry organic solvents such as THF leading to indazoles bearing the CF_3 group at C(3) of the heterocycle. Application of TBAF as a convenient source of fluoride anion (which play a dual role of *desililating agent* in aryne generation and *a base* in dehydrohalogenation step) should be considered a key achievement. Furthermore, an easy route towards *N*-unsubstituted 3-CF_3-indazole as handful building block in preparation of *N*-alkylated and *N*-acylated analogues was also demonstrated.

Another project was focused on (3+2)-cycloadditions of title nitrile imines and chalcones (but also other enones). As demonstrated, the designed Huisgen reactions proceed highly regio- and diastereoselectively, and leads to 5-acyl-3-CF_3-pyrazolines recognized as highly useful precursors of the respective pyrazoles. Particularly, the mentioned intermediates could be smoothly aromatized with activated MnO_2, and depending on the solvent

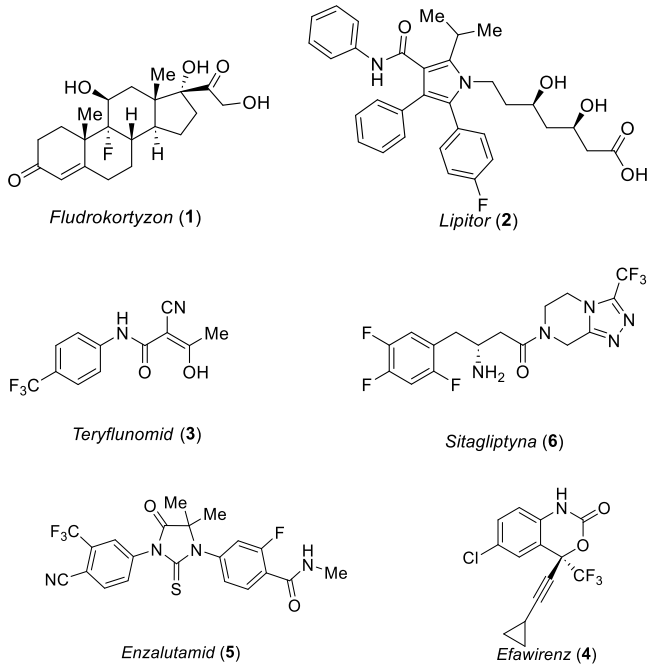
applied, the oxidation proceed either via dehydrogenative pathway (in polar solvents) or by deacylation (in non-polar media). Moreover, the mechanochemical approach of the mentioned reactions was checked, and the devised protocols were applied for preparation of biologically relevant 3-CF_3-pyrazole-alkanecarboxylic acids.

The final project of the Thesis was aimed at application of title nitrile imines in a formal stepwise (3+3)-cycloaddition reaction with natural α-amino esters to access hitherto unknown trifluoromethylated 1,2,4-triazine derivatives. The scope and limitations of the devised reaction was checked in detail, and three series of variously functionalized final products were obtained, including enantiomerically pure 3-CF_3-1,2,4-triazines derived from chiral starting materials. Model functional group transformations in selected products, carried out under mild oxidation/reduction conditions, demonstrated remarkable synthetic usefulness of this class of fluorinated heterocycles.

Komentarz do rozprawy doktorskiej

1.1. Znaczenie fluorowanych heterocykli azotowych

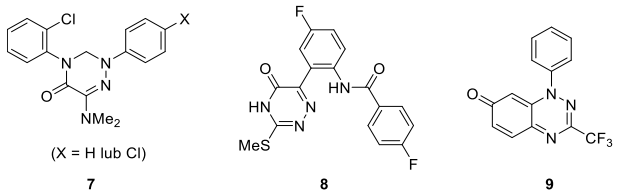
Od wielu lat obserwuje się stały wzrost zainteresowania związkami organicznymi zawierającymi w swojej strukturze atom/atomy fluoru bądź grupy fluoroalkilowe, zarówno jako atrakcyjne obiekty badawcze w obszarze syntezy organicznej, jak również pod kątem ich różnorodnych praktycznych zastosowań.[1] Jak wykazano, poprzez wprowadzenie silnie elektroujemnego podstawnika zawierającego atomy fluoru można w kontrolowany sposób zmieniać właściwości fizykochemiczne oraz aktywność biologiczną substancji.[2–4] Przykładowo, obserwuje się m.in. zwiększoną aktywność biologiczną oraz poprawę stabilności metabolicznej, co pozwala na dłuższy czas działania związku w organizmie, a także podwyższoną lipofilowość, która ułatwia penetrację cząsteczki w głąb komórek biologicznych. Taka modyfikacja wpływa również na właściwości kwasowo-zasadowe oraz efekty konformacyjne. Fluorowane związki organiczne znalazły liczne zastosowania w różnych gałęziach przemysłu, przede wszystkim w obszarze chemii materiałowej,[4–6] agrochemii[7] oraz medycynie.[8–10] Szczególnie dotyczy to ostatniej grupy, w której fluorowane heterocykle znajdują uznanie jako skuteczne leki o różnorodnej aktywności (*Rysunek 1).* Jednym z pierwszych tego typu połączeń jest opatentowany i wprowadzony do obiegu w drugiej połowie ubiegłego wieku *Fludrokortyzon* (**1**), będący monofluorowaną pochodną kortyzolu, należącego do grupy glikokortykosteroidów.[11] Inny, zaliczany do najlepiej sprzedających się leków w 2010 roku to *Lipitor* (**2**), stosowany w profilaktyce chorób naczyniowo-sercowych.[11] Dobrze udokumentowane są również właściwości przeciwzapalne *Teryflunomidu* (**3**), wysoka aktywność *Efawirenzu* (**4**) wobec wirusa HIV, skuteczność *Enzalutamidu* (**5**) w leczeniu nowotworu prostaty oraz zastosowania *Sitagliptyny* (**6**) w terapii cukrzycy typu II.



Rysunek 1. Struktury wybranych leków fluorowanych.

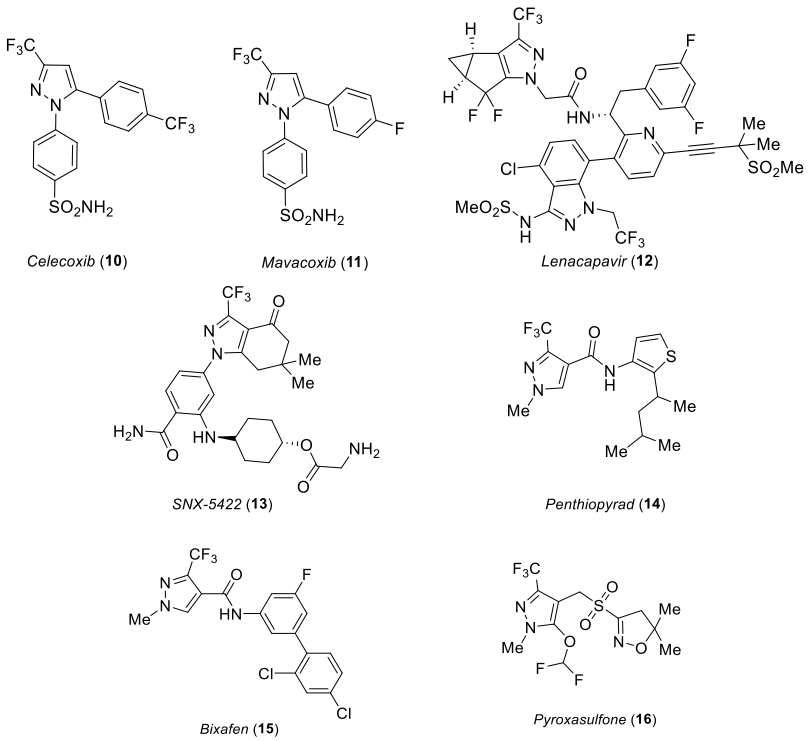
Ze względu na interesujące właściwości fizykochemiczne oraz biologiczne, jak również stosunkowo dużą dostępność, w ostatnich latach obserwuje się wzmożone zainteresowanie fluorowanymi pochodnymi (w tym przede wszystkim pochodnymi di- i tri-fluorometylowanymi) 5-cio oraz 6-cioczłonowych heterocykli azotowych.[12–14] W niniejszej pracy szczególną uwagę poświęcono dwóm klasom heterocykli tj. pochodnym 1,2,4-triazyny oraz pirazolu, w tym analogom skondensowanym (bicyklicznym). Niefluorowane związki tego typu są szeroko rozpowszechnione w naturze, podczas gdy liczne doniesienia potwierdzają duży potencjał ich fluorowanych analogów pod względem zastosowań praktycznych. Jak wykazano, wprowadzenie atomu halogenu do mono- oraz bicyklicznych pochodnych 1,2,4-triazyny wydatnie podwyższa aktywność przeciwnowotworową i przeciwbakteryjną (*Rysunek 2*).[15,16] Przykładowo,

Krauth i inni opisali pochodne typu **7** wykazujące skuteczne działanie antyproliferacyjne przeciwko linii komórkowej K562 (przewlekłej białaczce szpikowej) w połączeniu z niezwykle niską cytotoksycznością.[17] W 2014 roku grupa Khana wykazała, że podstawienie pierścieni arylowych atomami fluoru poprawia właściwości biologiczne w przypadku analogów związku **8**, rozpoznanego jako inhibitor replikacji wirusa HIV-1 oraz kinazy CDK2.[18] Ponadto zauważono, że podstawienie pozycji C(2) grupą trifluorometylową w bicyklicznej 1,2,4-triazynie **9** poprawiło znacznie właściwości inhibujące reduktazę tioredoksyny (Trx), w stosunku do jej niefluorowanego analogu.[19]



Rysunek 2. Struktury wybranych bioaktywnych halogenowanych pochodnych 1,2,4-triazyny.

Bardzo dużym zainteresowaniem cieszą się już od wczesnych lat 90' ubiegłego wieku pochodne 3-trifluorometylopirazolu (*Rysunek 3*).[20–22] Najbardziej znanym przykładem jest wprowadzony na rynek ponad 20 lat temu *Celecoxib* (**10**), wykazujący silne właściwości przeciwzapalne (selektywny inhibitor COX-2). Równie dobrze znany, wykorzystywany w leczeniu weterynaryjnym, jest jego strukturalny analog *Mavacoxib* (**11**). Ponadto, związki zawierające pierścień 3-triflurometylowanego pirazolu badane były pod kątem takich aktywności biologicznych jak (a) przeciwwirusowe, w przypadku *Lenacapaviru* (**12**), obecnie będącego w III fazie badań przeciwko wirusowi HIV, czy (b) przeciwnowotworowe, w przypadku *SNX-5422* (**13**) – związek w II fazie badań klinicznych. Ponadto liczne pochodne oparte na pierścieniu 3-trfluorometylopirazolu znalazły zastosowania w agrochemii m.in. jako fungicydy (np. *Penthiopyrad* (**14**) i *Bixafen* (**15**)) i herbicydy (np. *Pyroxasulfone* (**16**)).[22]



Rysunek 3. Wybrane biologicznie aktywne pochodne 3-trifluorometylopirazolu.

W świetle aktualnych doniesień na temat olbrzymiego potencjału aplikacyjnego wspomnianych klas fluorowanych *N*-heterocykli, równolegle do pogłębionych badań materiałowych wzrasta znaczące zapotrzebowanie na opracowanie nowych, wydajnych i ekonomicznie uzasadnionych metod ich syntezy, jak również procedur otwierających dostęp do bardziej złożonych pochodnych, niedostępnych w oparciu o klasyczne strategie wykorzystujące typowe komponenty fluorowane. I tak, w ostatnich latach w Uniwersytecie Łódzkim, opracowano dogodną drogę dojścia do trwałych prekursorów fluorowanych nitryloimin pochodnych trifluoroacetonitrylu, a także wykazano wysoką użyteczność tej klasy 1,3-dipoli w syntezie

CF_3-sfuncjonalizowanych heterocykli azotowych i azotowo-siarkowych. Mając na uwadze fakt, że tytułowe nitryloiminy należą do grupy 1,3-dipoli przebadanych, jak dotąd, w bardzo ograniczonym stopniu, w ramach niniejszej pracy doktorskiej podjęto próby opracowania nowych metod otrzymywania pochodnych pirazolu i 1,2,4-triazyny opartych na formalnych reakcjach, odpowiednio, (3+2)- oraz (3+3)-cykloaddycji.

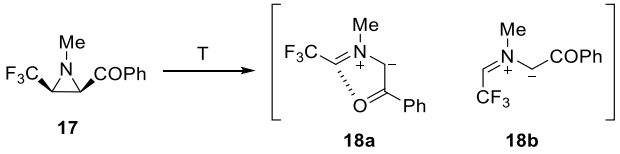
1.2. Trifluorometylowane 1,3-dipole w reakcjach (3+2)-cykloaddycji

Jedna z najważniejszych strategii syntezy heterocykli pięcioczłonowych opiera się na reakcjach (3+2)-cykloaddycji odczynników 1,3-dipolarnych z odpowiednimi dipolarofilami (tzw. reakcja Huisgena).[23] Choć w literaturze znane są przykłady skutecznego zastosowania fluorowanych dipolarofili w reakcji 1,3-dipolarnej cykloaddycji, głównie alkenów o wyższych masach cząsteczkowych,[24–26] to w odniesieniu do syntezy małych heterocykli sfunkcjonalizowanych bezpośrednio grupą CF_3 jest niewiele doniesień, co związane jest głównie z ograniczonym dostępem do odpowiednich substratów oraz ich lotnością i toksycznością. Z tego powodu, praktyczne znaczenie znajdują metody oparte na zastosowaniu trifluorometylowanych 1,3-dipoli, zwykle generowanych *in situ* z odpowiednich prekursorów, w obecności reaktywnego dipolarofila. W tej grupie reagentów do najchętniej wykorzystywanych odczynników należy zaliczyć ylidy azometinowe, tlenek trifluoroacetonitrylu, 2,2,2-trifluorodiazoetan, nitrony oraz nitryloiminy, a poniżej podsumowano wybrane przykłady ich zastosowań.

1.2.1. Ylidy azometinowe

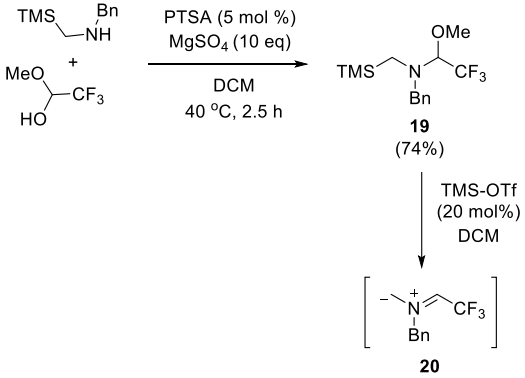
Jeden z pierwszych przykładów zastosowania fluorowanych syntonów 1,3-dipolarnych do syntezy trifluorometylowanych heterocykli dotyczy ylidów azometinowych. Ylidy należą do grupy 1,3-dipoli typu allilowego i w reakcji z odpowiednimi C=C dipolarofilami prowadzą do pochodnych pirolu (tj. pirolidyn).[27]

W 1994 roku zespół Tanaki zaprezentował metodę typu *one-pot*, w której trifluorometylowaną pochodną **17** wykorzystano do generowania ylidu poprzez termiczne otwarcie pierścienia azirydynowego (*Schemat 1)*.[27] Reaktywność wygenerowanych w tych warunkach ylidów azometinowych **18a**/**18b** testowano wobec wybranych alkenów, między innymi styrenu oraz eteru butylowo-winylowego, otrzymując oczekiwane (3+2)-cykloaddukty z wydajnościami odpowiednio 81% i 89%.



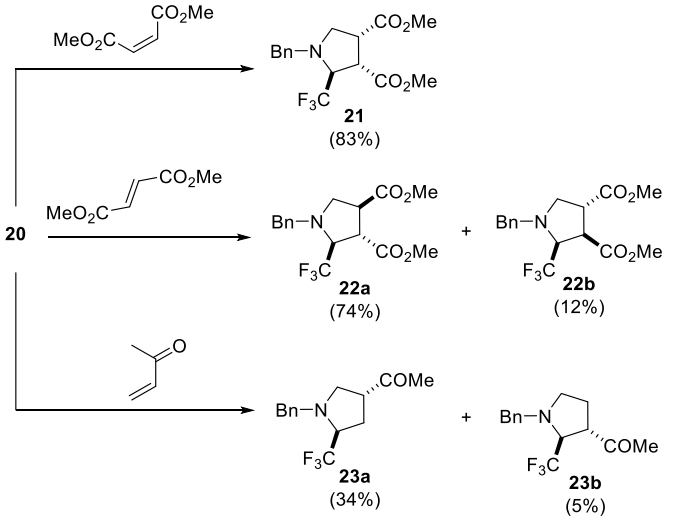
*Schemat 1. Termiczne otwarcie pierścienia azirydyny prowadzące do trifluorometylowanego ylidu azometinowego **18a/18b**.*

W innym przykładzie zaprezentowanym w 2012 roku jako prekursor ylidu zastosowano eter hemiaminalu **19** uzyskany w wyniku kondensacji odpowiedniej aminy z hemiacetalem (*Schemat 2).*[28] Następnie, otrzymany związek **19** pod działaniem kwasu Lewisa (ale także kwasów Brønsteda) generuje *in situ* ylid **20**.



*Schemat 2. Synteza prekursora oraz warunki generowania ylidu **20**.*

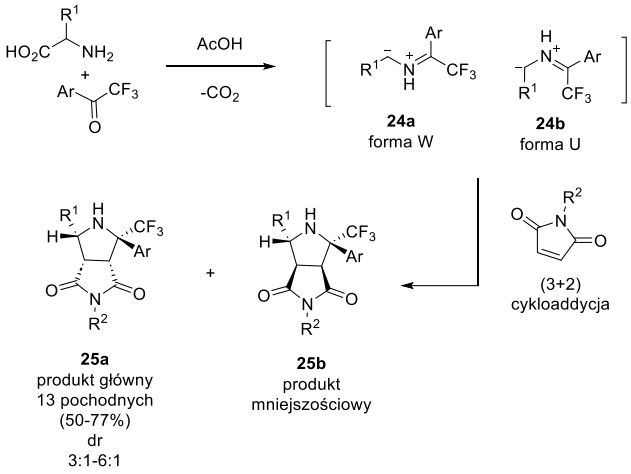
Autorzy przebadali reakcje ylidu **20** wobec wybranych zubożonych elektronowo dipolarofili C=C uzyskując spodziewane (3+2)-cykloaddukty pochodne pirolidyny, z dobrą lub umiarkowaną, odpowiednio, chemo-, regio- oraz diastereoselektywnością (*Schemat 3*). Przykładowo, w reakcji z maleinianem dimetylu uzyskano wyłącznie jeden produkt (związek **21**), podczas gdy zastosowanie fumaranu dimetylowego w roli dipolarofila prowadziło do mieszaniny diastereoizomerów **22a** i **22b**. Podobnie, reakcje z monopodstawionymi alkenami cechowały się umiarkowaną regio-selektywnością (produkty **23a** i **23b**) i niską wydajnością reakcji.



*Schemat 3. Reakcje wyłapywania ylidu **20** zubożonymi elektronowo C=C dipolarofilami.*

Podejście do reakcji (3+2)-cykloaddycji w wariancie typu *one-pot* sprawdziło się także dla *N*-monopodstawionych ylidów azometinowych typu **24**.[29] Oczekiwane produkty uzyskano na drodze katalizowanej kwasem octowym dekarboksylacyjnej/dehydratacyjnej reakcji generowania ylidu **24** z trifluorometylowanego ketonu i glicyny oraz następczej 1,3-dipolarnej cykloaddycji z maleimidami. W przedstawionej na *Schemacie 4.* sekwencji

reakcji Autorzy otrzymali serię pochodnych pirolidyny typu **25** z dobrymi wydajnościami, jednak zawsze w postaci mieszaniny dwóch diastereoizomerów, co tłumaczy się istnieniem równowagi pomiędzy dwoma izomerycznymi ylidami tj. formy W (**24a**) oraz U (**24b**).

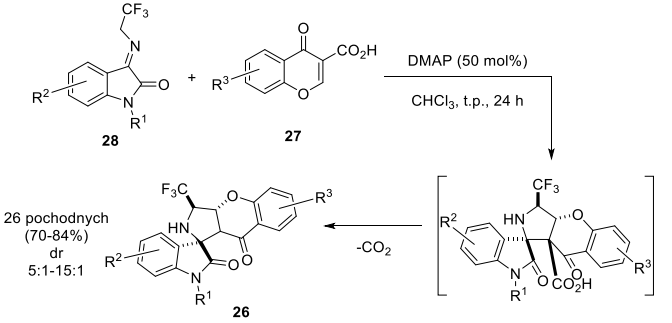


*Schemat 4. Generowanie ylidu **24** i jego reakcja z maleimidami.*

Inny wariant dekarboksylatywnej reakcji 1,3-dipolarnej cykloaddycji z wykorzystaniem trifluorometylowanych ylidów azometinowych zaprezentował Liu w podejściu do syntezy wielopierścieniowych układów spirocyklicznych pochodnych pirolidyny i oksoindolu typu **26** (*Schemat 5*).[30]

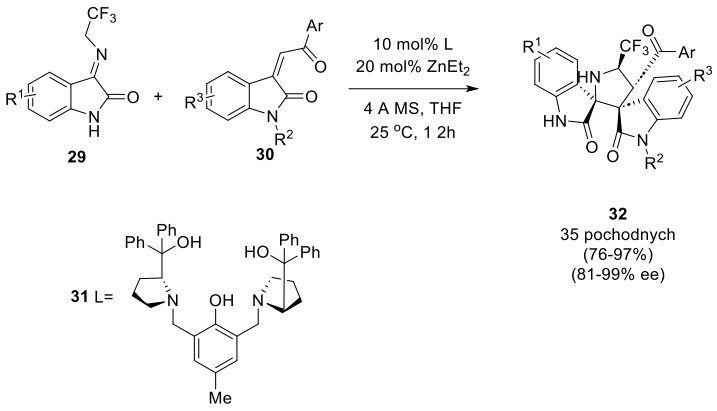
W toku prac optymalizacyjnych wykazano kluczową rolę 4-dimetyloaminopirydyny (DMAP) zastosowanej w roli katalizatora (50 mol%) oraz grupy karboksylowej ulokowanej w pozycji C(3) chromonu **27**, umożliwiających wydajną (3+2)-cykloaddycję typu Michaela-Mannicha do ketiminy **28** pochodnej trifluoroetyloizatyny oraz następczą spontaniczną dekarboksylację (*Schemat 5*). Warto zauważyć, że w pierwszym etapie reakcji generowane są cztery centra stereogeniczne z bardzo dobrym nadmiarem diastereomerycznym (10:1), a produkty na ogół izolowano z wysoką wydajnością (>70%). Zastosowanie ketimin **28** podstawionych na atomie

azotu grupami o różnorodnych właściwościach elektronowych nie miało większego wpływu na wydajności reakcji oraz jej diastereoselektywność. Podobnie, nie stwierdzono istotnego wpływu rodzaju podstawnika R^2 ulokowanego w pierścieniu oksoindolowym substratu **28** na wydajność oraz wynik stereochemiczny. Ponadto, wstępne eksperymenty zrealizowane w wariancie katalizy asymetrycznej ujawniły, że badana transformacja może być dobrym narzędziem do syntezy produktów enancjomerycznie wzbogaconych.



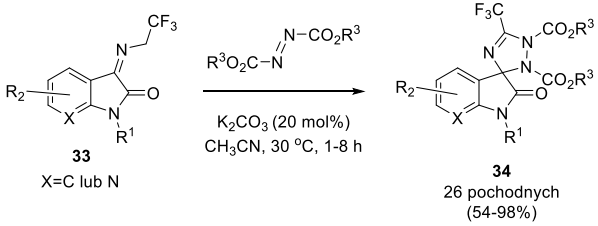
*Schemat 5. Dekarboksylatywna (3+2)-cykloaddycja fluorowanych ketimin **28** jako prekursorów ylidów.*

W 2020 roku zaprezentowano asymetryczną reakcję 1,3-dipolarnej cykloaddycji podobnych, *N*-niepodstawionych CF_3-ylidów azometinowych pochodnych **29** z indolinonami **30**, z wykorzystaniem katalizatora **31,** w warunkach dualnej katalizy w obecności jonów cynku (ligand zawiera w swojej strukturze zarówno zasadę Brønsteda, jak i centrum kwasowe Lewisa) (*Schemat 6*).[31] Autorzy przetestowali procedurę z użyciem różnorodnie podstawionych ligandów, jak i substratów. Związki zawierające cztery centra stereogeniczne typu **32** otrzymano z wysoką wydajnością, a także enancjoselektywnością i diastereoselektywnością.



*Schemat 6. Asymetryczna (3+2)-cykloaddycja trifluorometylowanych ylidów **29** w podejściu do spirocyklicznych pochodnych indolu **32**.*

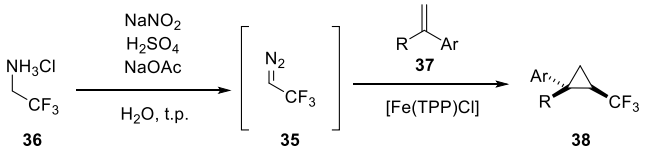
Wysoką reaktywność analogicznej grupy reagentów (ketiminy *N*-2,2,2-trifluoroetyloizatyny **33**) testowano wobec azodikarboksylanów i wykazano, że w stosunkowo łagodnych warunkach (K_2CO_3, 30 °C) zachodzi formalna (3+2)-cykloaddycja do wiązania N=N azodikarboksylanu prowadząc do 1,2,4-triazolowych pochodnych spiroindolowych **34**, które izolowano z wysokimi wydajnościami (*Schemat 7*).[32] Autorzy wykazali, że opracowana metoda cechuje się szerokim zakresem stosowalności, a także umożliwia syntezę produktów w skali gramowej.



*Schemat 7. Trifluorometylowane spiro-1,2,4-triazoliny **34** w reakcji 1,3-dipolarnej cykloaddycji ylidów pochodnych **33** i azodikarboksylanów.*

1.2.2. Trifluorodiazoetan

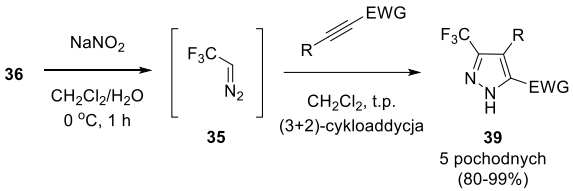
2,2,2-Trifluorodiazoetan (**35**) zsyntezowano po raz pierwszy w roku 1943 i opisano jako produkt cechujący się niską temperaturą wrzenia (ok. 13 °C) oraz wybuchowym charakterem.[33] Prawdopodobnie z tych powodów przez kilka kolejnych dekad nie budził szczególnego zainteresowania ze strony chemików syntetyków. Wraz z postępem w obszarze technik laboratoryjnych oraz wzrostem zapotrzebowania na nowe odczynniki do syntezy heterocykli azotowych sfunkcjonalizowanych ugrupowaniem CF_3, w 2010 roku Morandi i Carreira opisali metodę generowania 2,2,2-trifluorodiazoetanu *in situ* w reakcji odpowiedniej aminy **36** z $NaNO_2$, w wodnym roztworze kwasu siarkowego(VI) (*Schemat 8*).[34] Tak uzyskany 1,3-dipol w obecności katalizatora żelazowo-porfirynowego [Fe(TPP)Cl] przekształcał się w odpowiedni karben, który wyłapywano pochodnymi styrenu **37** uzyskując z dobrymi wydajnościami trifluorometylowane cyklopropany **38**. Od tego czasu, wiele zespołów badawczych podjęło badania w obszarze wykorzystania CF_3CHN_2 generowanego *in situ*, przede wszystkim w reakcjach formalnych (3+2)-cykloaddycji.



*Schemat 8. Generowanie trifluorodiazoetanu (**35**) jako źródło karbenu in situ.*

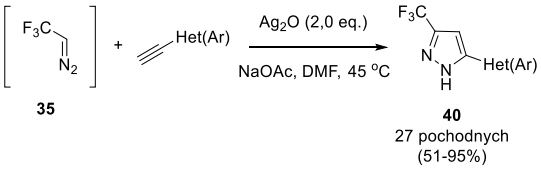
W 2014 roku Mykhailiuk i współpracownicy wykazali, że generowany *in situ* 2,2,2-trifluorodiazoetan (**35**) można skutecznie wyłapać zubożonymi elektronowo alkinami (*Schemat 9*).[35] Reakcja przebiegająca w łagodnych warunkach prowadziła do odpowiednich pirazoli typu **39**, które na ogół wydzielano z wysokimi wydajnościami. Jednakże, metoda ta cechuje się umiarkowanym zakresem stosowalności, jako że alifatyczne oraz

nieaktywowane alkiny aromatyczne nie wchodzą w reakcję z 1,3-dipolem **35** w opracowanych warunkach.



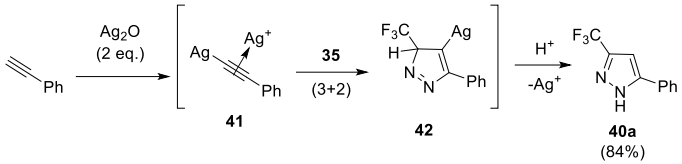
*Schemat 9. Reakcje (3+2)-cykloaddycji diazoetanu (**35**) ze zubożonymi elektronowo alkinami.*

Problem ograniczonej reaktywności (hetero)aromatycznych alkinów wobec generowanego *in situ* trifluorodiazoetanu rozwiązano w zespole J.-A. Ma poprzez zastosowanie dwukrotnego nadmiaru tlenku srebra(I) w roli katalizatora (*Schemat 10*).[36]



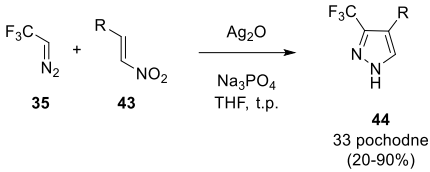
Schemat 10. (3+2)-Cykloaddycje trifluorodiazoetanu z (hetero)aromatycznymi alkinami.

W ten sposób Autorzy otworzyli dogodny dostęp do pochodnych pirazolu typu **40** podstawionych w pozycji C(5), a wzmożoną reaktywność acetylenów wytłumaczono tworzeniem się w pierwszym etapie reakcji odpowiedniego acetylenku srebra, który dodatkowo aktywowany jest kolejnym ekwiwalentem Ag(I) poprzez oddziaływanie tego kwasu Lewisa z orbitalem π acetylenku (kompleks **41**). Tak utworzony reaktywny związek pośredni natychmiast reaguje z CF_3CHN_2 dając pirazolan srebra **42**, który po obróbce wodnej prowadzi do oczekiwanego pirazolu **40a** jako produktu formalnej (3+2)-cykloaddycji (*Schemat 11*).



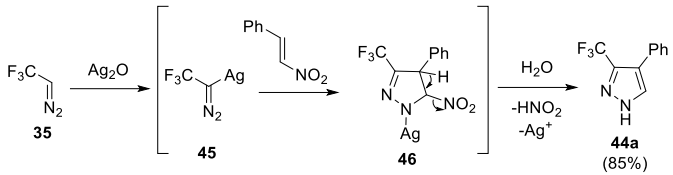
Schemat 11. Proponowany mechanizm (3+2)-cykloaddycji acetylenów aromatycznych z trifluorodiazoetanem w warunkach katalizy Ag_2O.

Trzy lata później ten sam zespół zastosował analogiczne rozwiązanie katalizy tlenkiem srebra(I) dla reakcji (3+2)-cykloaddycji trifluorodiazoetanu z nitroalkenami (hetero)aromatycznymi i alifatycznymi **43**, uzyskując dostęp do pirazoli podstawionych w pozycji C(4) **44** (*Schemat 12*).[37] Warto podkreślić, że w opisywanej strategii *one-pot* grupa nitrowa aktywująca alken pełniła dodatkowe dwie role tj. podstawnika kierującego oraz grupy opuszczającej w procesie aromatyzacji pierwotnie utworzonej pirazoliny.



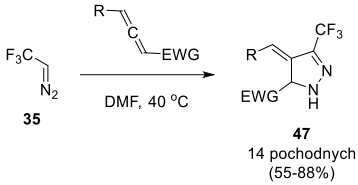
Schemat 12. Katalizowana tlenkiem srebra(I) (3+2)-cykloaddycja trifluorodiazoetanu do nitroalkenów

Jak zaprezentowano na *Schemacie 13.* Autorzy pracy postulują, że wygenerowany *in situ* 1,3-dipol **35** w pierwszej kolejności reaguje z Ag_2O prowadząc do związku pośredniego **45**, który wyłapany styrenem daje 5-nitropirolidynę **46**. Następcza eliminacja i protonowanie pozycji N(1) prowadzi do końcowego produktu **44a**.



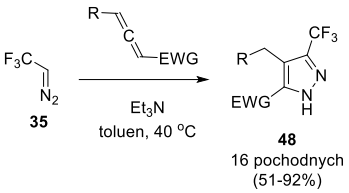
*Schemat 13. Proponowany mechanizm reakcji 1,3-dipola **35** z nitroalkenami w warunkach katalizy Ag_2O.*

Nieco wcześniej opisano reakcję (3+2)-cykloaddycji generowanego *in situ* CF_3CHN_2 ze zubożonymi elektronowo allenami.[38] Najlepsze rezultaty zanotowano prowadząc reakcję w DMF, w podwyższonej temperaturze, a jako główne produkty wydzielono względnie trwałe egzometylidenowe pochodne pirazoliny **47** (*Schemat 14*).



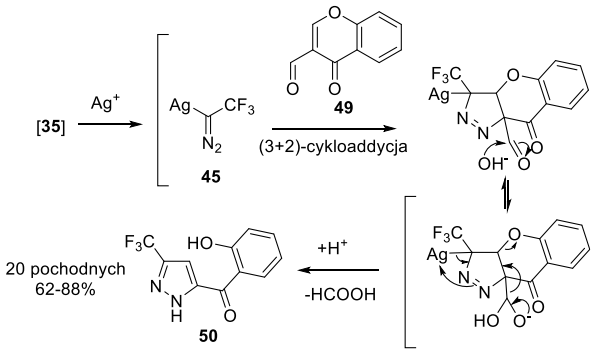
Schemat 14. (3+2)-Cykloaddycja generowanego in situ trifluorodiazoetanu ze zubożonymi elektronowo allenami.

Jak należało oczekiwać, dodatek katalitycznych ilości zasady organicznej (takiej jak np. Et_3N) do mieszaniny poreakcyjnej, skutkował następczą ilościową izomeryzacją do odpowiednich pochodnych pirazolu **48** (*Schemat 15*).



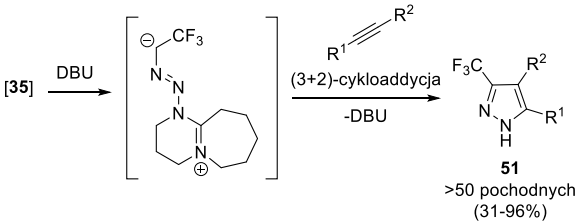
*Schemat 15. Regioselektywna (3+2)-cykloaddycja trifluorodiazoetanu **35** do aktywowanych allenów.*

W 2019 opisano interesującą metodę otrzymywania 3-trifluorometylowanych 5-(*orto*-hydroksybenzoilo)pirazoli **50**, grupy połączeń ważnej m.in. z punktu widzenia możliwych zastosowań farmakologicznych. W opisywanym podejściu zastosowano generowany *in situ* 2,2,2-trifluorodiazoetan (**35**) oraz formylochromon (**49**), a wymaganą reaktywność uzyskano już w obecności jednego równoważnika katalizatora srebrowego.[39] Przebieg reakcji wyjaśniono postulując powstawanie kluczowego związku pośredniego **45** (tego samego jak w pracy opisującej reakcje z nitroalkenami), który po addycji do wiązania C=C chromonu, następczej addycji anionu hydroksylowego do grupy formylowej i dekarboksylacji prowadzi – po standardowej wodnej obróbce w warunkach kwaśnych – do produktu głównego **50** (*Schemat 16*).



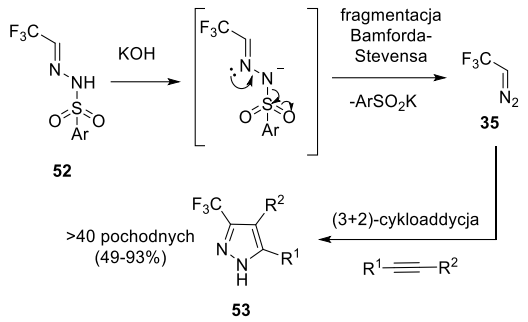
*Schemat 16. Zastosowanie trifluorodiazoetanu i formylochromonów w syntezie 5-acylopirazoli **50**.*

Odmienny sposób aktywacji trifluorodiazoetanu (**35**) w reakcjach ze zubożonymi elektronowo alkinami opisano w roku 2019, stosując DBU w roli katalizatora.[40] W pracy przebadano serie terminalnych i wewnętrznych acetylenów, wykazano szeroki zakres stosowalności metody i wysoką regioselektywność studiowanej (3+2)-cykloaddycji uzyskując, odpowiednio, C(5)-sfunkcjonalizowane lub w pełni podstawione pochodne 3-CF_3-pirazolu **51**, które na ogół izolowano z dobrymi wydajnościami.



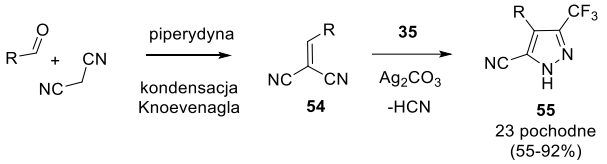
*Schemat 17. (3+2)-Cykloaddycja trifluorodiazoetanu **35** do alkinów w wariancie katalizy DBU.*

W dwóch innych pracach z lat 2019 i 2020 wskazano hydrazony pochodne 2,2,2-trifluoroetyloaminy typu **52** jako dogodne, alternatywne źródło generowanego *in situ* trifluorodiazoetanu (**35**), a skuteczność metody zaprezentowano w reakcjach z wybranymi alkinami.[41,42] W pracach zademonstrowano syntezę ponad 40 pochodnych 3-trifluoro-metylopirazolu **53**, które izolowano z dobrymi lub znakomitymi wydajnościami (*Schemat 18*). Kluczowy etap reakcji generowania 1,3-dipola **35** opiera się na indukowanej silną zasadą fragmentacji hydrazonu (reakcja Bamforda-Stevensa).



*Schemat 18. Tosylohydrazon **52** jako dogodne źródło trifluorodiazoetanu w syntezie pochodnych pirazolu **53**.*

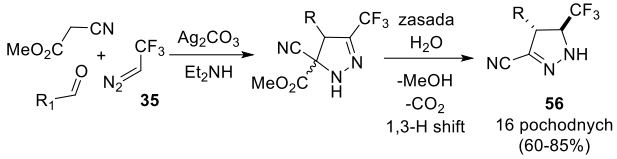
Dostęp do 3-trifluorometylowanych pochodnych pirazolu jest również możliwy poprzez zastosowanie trójskładnikowej reakcji domino z użyciem trifluorodiazoetanu oraz malononitrylu i aldehydu.[43] Autorzy w pierwszym etapie generowali w warunkach kondensacji Knoevenagla cyjanostyreny **54**, które następnie wyłapywano generowanym *in situ,* w obecności soli srebra CF_3CHN_2 (**35**) (*Schemat 19*). Końcowe produkty aromatyczne **55** powstają wskutek spontanicznej eliminacji cyjanowodoru, w obecności anionu węglanowego.



*Schemat 19. Synteza CF_3-pirazoli **55** z użyciem trifluorodiazoetanu oraz dicyjanoalkanów w roli dipolarofili.*

Opisana metoda znajduje zastosowanie również dla innych odczynników z grupy aktywnych metylenów, takich jak cyjanooctanu metylu, jednakże w tym wypadku obserwowano spontaniczną dekarboksylację, a jako główne produkty izolowano 3-trifluorometylo-5-cyjanopirazoliny **56** (*Schemat 20*). Obie wspomniane transformacje cechowały się stosunkowo

szerokim zakresem stosowalności, wysoką selektywnością i wydajnością, a w przypadku kilku produktów modelowych zademonstrowano wybrane wtórne transformacje potwierdzające użyteczność syntetyczną tej klasy pochodnych.



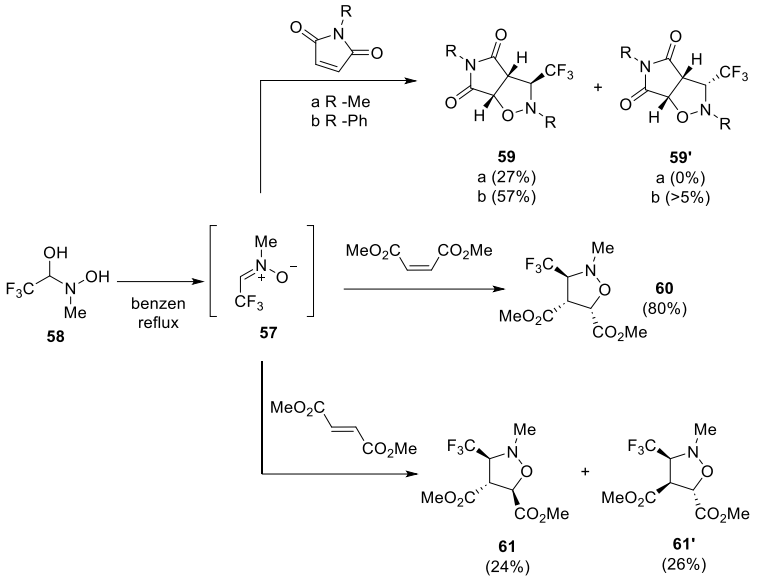
*Schemat 20. Wielokomponentowa reakcja typu domino z użyciem 1,3-dipola **35**.*

1.2.3. Trifluorometylowane nitrony

Nitrony należą do grupy względnie stabilnych 1,3-dipoli (można je wydzielać i przechowywać) i z tego powodu chemia tej klasy reagentów jest szeroko uprawiana i bardzo dobrze rozpoznana, przede wszystkim w odniesieniu do reakcji (3+2)-cykloaddycji oraz addycji nukleofilowej, a w ostatnich latach także w kontekście reakcji rodników ketylowych oraz C-H aktywacji w warunkach katalizy metalami grup przejściowych.[44] Nitrony stanowią dogodne bloki budulcowe do otrzymywania różnorodnych układów heterocyklicznych, w tym do syntezy totalnej naturalnych alkaloidów, jak również chiralnych aminoalkoholi i amin. W przeciwieństwie do klasycznych aldo- i ketonitronów alifatycznych oraz (hetero)-aromatycznych, ich perfluorowane analogi strukturalne, a w szczególności pochodne fluoralu, są znacznie mniej rozpoznane.

W latach 80' ubiegłego wieku zespół Tanaki zwrócił uwagę na *C*-trifluorometylo-*N*-metylonitron (**57**), dostępny *in situ* w reakcji dehydratacji odpowiedniego hemiaminalu **58**, jako modelowy związek w reakcjach ze zubożonymi elektronowo lub nieaktywowanymi olefinami (*Schemat 21*).[45] Jak wykazano, w reakcjach nitronu **57** z dipolarofilami o konfiguracji *Z* (np. maleimidy, maleiniany) zgodnie z oczekiwaniem otrzymywano wyłącznie

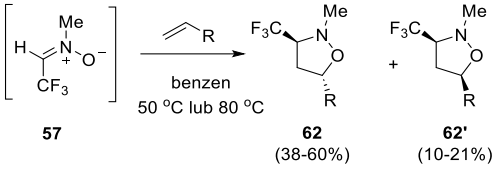
produkty *syn* w postaci 4,5-*cis*-dipodstawionych izoksazolidyn, odpowiednio, **59** oraz **60**. W reakcji nitronu z fumaranem dimetylu w mieszaninie poreakcyjnej znaleziono izomeryczne izoksazolidyny **61** i **61'** (ca. 1:1) co sugeruje uzgodniony charakter studiowanych reakcji (3+2)-cykloaddycji.



*Schemat 21. Generowanie trifluorometylowanego nitronu **57** oraz jego reakcje z wybranymi aktywowanymi olefinami.*

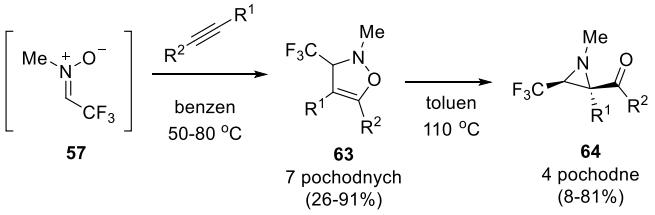
Z drugiej strony, w reakcjach CF_3-nitronu **57** z wykorzystaniem monopodstawionych alkenów w roli dipolarofili (takich jak styren, 1-okten, alkohol allilowy) obserwowano preferencyjne powstawanie produktów o konfiguracji *anti*, podczas gdy oczekiwane pochodne izoksazolidyny **62** i **62'** wydzielano z całkowitymi, umiarkowanymi wydajnościami 55-71% (*Schemat 22*). Jest to dość istotna obserwacja, jako że w przypadku analogicznych reakcji (3+2)-cykloaddycji z użyciem klasycznych niefluorowanych nitronów uzyskuje się przeważnie *cis*-izoksazolidyny jako produkty główne. Ten efekt odwrócenia selektywności Autorzy tłumaczą silnym wpływem grupy trifluorometylowej na energie orbitali 1,3-dipola,

tj. obniżeniem energii orbitalu HOMO wraz z nieznacznym podwyższeniem energii orbitalu LUMO.



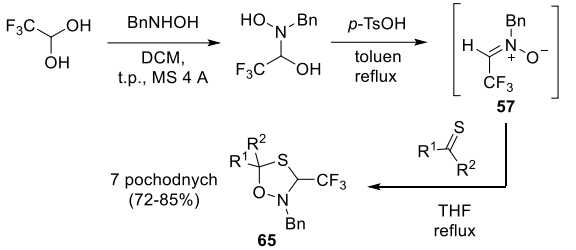
*Schemat 22. Stereochemia reakcji (3+2)-cykloaddycji trifluorometylowanego nitronu **57** z terminalnymi olefinami.*

Obecność silnie elektrono-wyciągającej grupy CF_3 może w istotny sposób podwyższać trwałość niektórych heterocykli, jak zademonstrowano na przykładzie pochodnych izoksazoliny uzyskiwanych w reakcjach (3+2)-cykloaddycji nitronu **57** z alkinami (*Schemat 23*).[46] Powstające z wysoką regio-selektywnością cykloaddukty **63** można było wydzielić i scharakteryzować, a przegrupowanie do odpowiednich acylowanych pochodnych aziridyny **64** obserwowano dopiero w temperaturze wrzącego toluenu, podczas gdy niefluorowane analogi przekształcają się spontanicznie w tego typu acylo-azirydyny już w temperaturze pokojowej. Wspomnianą podwyższoną stabilność produktów **63** Autorzy tłumaczą stabilizującym wpływem grupy CF_3 na sąsiednie wiązanie N–O (wskutek znacznego obniżenia gęstości elektronowej tego wiązania).



*Schemat 23. (3+2)-Cykloaddycja CF_3-nitronu **57** do alkinów oraz następcze termiczne przegrupowanie pierwotnie powstających pochodnych izoksazoliny **63** do acyloazirydyn **64**.*

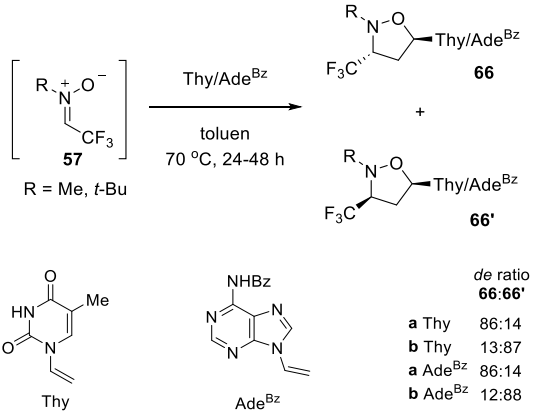
W innej pracy wykazano, że trifluorometylowany *N*-benzylonitron **57** (R = Bn), dostępny w reakcji kondensacji hydratu fluoralu z *N*-benzylo-hydroksyloaminą (po następczej dehydratacji pośredniego hemiaminalu, katalizowanej mocnym kwasem takim jak kwas *para*-toluenosulfonowy), chętnie wchodzi w reakcje cykloaddycji z odczynnikami tiokarbonylowymi, znanymi jako odczynniki superdipolarofilowe (*Schemat 24*). Przykładowo, w pełni regioselektywnej (3+2)-cykloaddycji z tioketonami otrzymano serię stosunkowo trwałych pochodnych 1,4,2-oksatiazolidyny **65**, które wydzielono z wysokimi wydajnościami.[47] Co nietypowe, stwierdzono wyraźnie większą reaktywność nitronu **57** (R = Bn) wobec tioketonów (cyklo)alifatycznych, aniżeli wobec tioketonów aromatycznych i/lub hetero-aromatycznych.



*Schemat 24. Synteza trifluorometylowanych pochodnych 1,4,2-oksatiazolidyny **65** w regioselektywnej (3+2)-cykloaddycji nitronu **57** z tioketonami.*

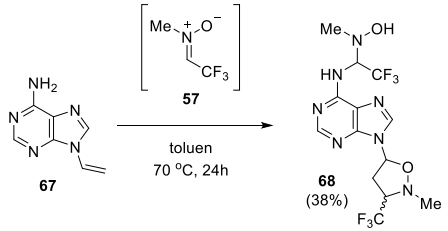
W literaturze fachowej można odnaleźć również doniesienia na temat reakcji (3+2)-cykloaddycji CF_3-nitronów z enaminami, np. winylowymi pochodnymi zasad azotowych takich jak tymina i adenina (*Schemat 25*).[48] Przeprowadzone cykloaddycje charakteryzowały się całkowitą regioselektywnością oraz dobrą diastereoselektywnością (*exo*- vs. *endo*-) zależną od rozmiaru podstawnika ulokowanego na atomie azotu grupy nitronowej. I tak, w przypadku pochodnej metylowej jako produkt faworyzowany wskazano addukt *endo*- **66**, natomiast wprowadzenie sterycznie wymagającego podstawnika *tert*-butylowego w centralną pozycję

1,3-dipola skutkowało odwróceniem selektywności i jako główny materiał wydzielono produkt addycji *exo*- **66'**.



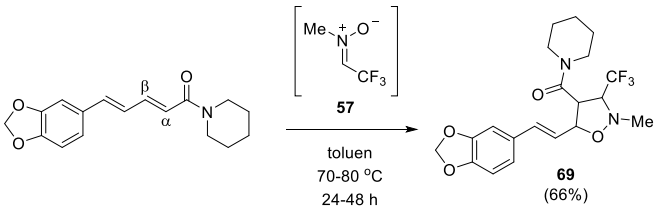
Schemat 25. Reakcje (3+2)-cykloaddycji nitronów z N-winylowymi pochodnymi tymidyny i adeniny

Warto wspomnieć, że zastosowanie *N*-niezabezpieczonej pochodnej adeniny **67** w analogicznej reakcji prowadzonej w gorącym toluenie ujawniło znaną, dwojaką reaktywność nitronu **57**, który prócz spodziewanej (3+2)-cykloaddycji do podstawnika winylowego ulegał również addycji do wolnej grupy aminowej NH_2 znajdującej się w pozycji C(6), prowadząc do produktu **68** (*Schemat 26*).



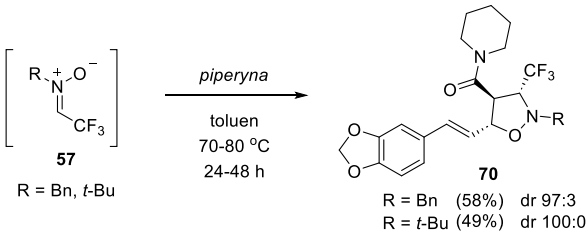
*Schemat 26. Dwojaka reaktywność (addycja nukleofilowa i 1,3-dipolarna cykloaddycja) nitronu **57** wobec pochodnej adeniny **67**.*

Interesującym przykładem całkowicie chemo- oraz regioselektywnej (3+2)-cykloaddycji nitronu **57** jest reakcja z wykorzystaniem piperyny w roli dipolarofila (*Schemat 27)*. Piperyna jest alkaloidem naturalnie występującym m.in. w czarnym pieprzu, odpowiadającym za ostro-gorzki smak przyprawy, a jej struktura charakteryzuje się obecnością dwóch wiązań podwójnych sprzężonych z grupą amidową i pierścieniem aromatycznym. Z tego powodu, w reakcjach z 1,3-dipolami można oczekiwać konkurencyjnej addycji do obu wiązań C=C w pozycjach α,β oraz γ,δ (jak to jest obserwowane np. w przypadku addycji ylidów azometinowych). Jednakże, w przypadku reakcji piperyny z nitronem **57**, zaobserwowano addycję wyłącznie do wiązania sąsiadującego z elektronowyciągającą grupą amidową, a pochodną izoksazoliny **69** znaleziono jako jedyny produkt międzycząsteczkowy, który wydzielono z wydajnością 66% (*trans*/*cis*: 87:13) (*Schemat 27*).[49]



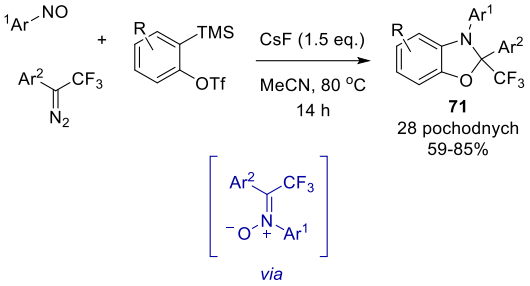
*Schemat 27. Chemoselektywność reakcji (3+2)-cykloaddycji piperyny z nitronem **57**.*

W odniesieniu do diastereoselektywności powyższej transformacji, Autorzy przebadali serię CF_3-nitronów typu **57** różnorodnie podstawionych na atomie azotu i wykazali, że zwiększenie zawady sterycznej w tej pozycji faworyzuje produkt *trans*. I tak, w przypadku *N*-benzylowego analogu w mieszaninie poreakcyjnej znaleziono ślady drugiego regioizomeru (dr 97:3), podczas gdy wprowadzenie podstawnika *tert*-butylowego skutkowało utworzeniem wyłącznie jednego diastereoizomeru *trans*-izoksazoliny typu **70** (*Schemat 28*).



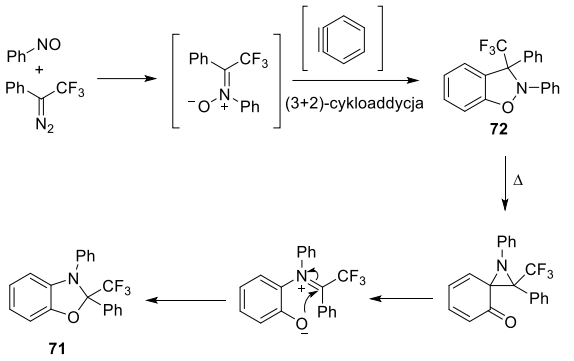
Schemat 28. Reakcja (3+2)-cykloaddycji N-podstawionego nitronu z piperyną.

W 2023 Mohanan i współpracownicy zaprezentowali nowatorskie podejście do generowania *in situ* CF_3-nitronów, formalnie pochodnych ketonów arylowo-trifluorometylowych, stosując jako prekursory substraty nitrozoarylowe oraz diazozwiązki.[50] W zaprezentowanej na *Schemacie 29*. reakcji kaskadowej, w roli dipolarofili użyte zostały pochodne arynu (benzynu), które również generowano *in situ* z odpowiednich triflanów sililowych, w obecności CsF jako źródła anionu fluorkowego. Nieoczekiwanie, jako główne produkty reakcji zidentyfikowano pochodne benzoksazoliny **71** (zamiast oczekiwanych izomerycznych benzoizoksazolin), a opracowana metoda charakteryzuje się szerokim spektrum stosowalności i dobrymi wydajnościami uzyskiwanych produktów.



*Schemat 29. Trójkomponentowa synteza trifluorometylowanych pochodnych benzoksazoliny **71**.*

W trakcie badań nad mechanizmem reakcji (*Schemat 30*) stwierdzono, że zgodnie z oczekiwaniem, w pierwszym etapie zachodzi reakcja (3+2)-cykloaddycji prowadząca do nietrwałych pochodnych benzoizoksazoliny **72**, które w warunkach reakcji ulegają spontanicznemu przegrupowaniu inicjowanemu termicznym rozpadem wiązania N-O dająca pochodne azirydyny. Rearomatyzacja układu przebiegająca poprzez otwarcie trójczłonowego pierścienia azridyny oraz 1,5-cyklizację zwitterionu (addycja fenolanu do kationu iminiowego) prowadzi do produktu końcowego **71**.



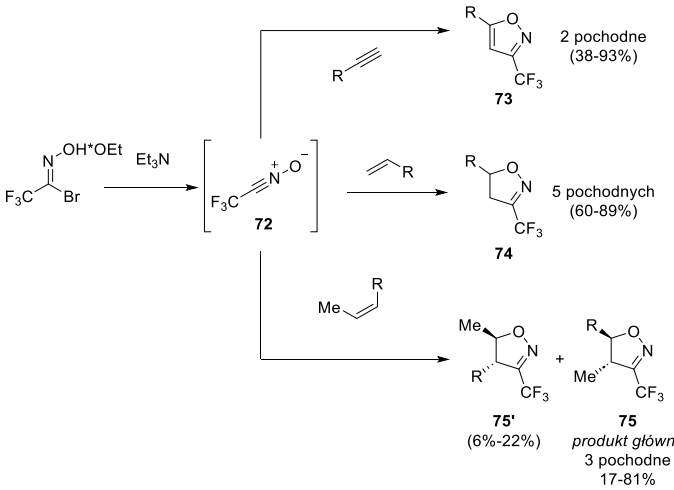
*Schemat 30. Proponowany mechanizm przegrupowania (3+2)-cykloadduktów **72** do izomerycznych benzoksazolin **71**.*

1.2.4. Tlenek trifluoroacetonitrylu

Tlenki nitryli należą do grupy wysoce reaktywnych 1,3-dipoli typu propargilowego (o strukturze liniowej), znanych od wczesnych lat 70' ubiegłego wieku i dostępnych wyłącznie *in situ*, najczęściej w reakcjach dehydrohalogenowania prekursorów tj. halogenków hydroksyiminoilowych (metoda Huisgena) lub dehydratacji pierwszorzędowych nitrozwiązków (metoda Muakayiamy).[51,52] W ostatnich dekadach tlenki nitryli intensywnie eksploatowano w syntezie różnorodnych pochodnych heterocyklicznych (tlenowych, azotowych i mieszanych 5- oraz 6-członowych), a także wykorzystywano w syntezie złożonych produktów naturalnych.

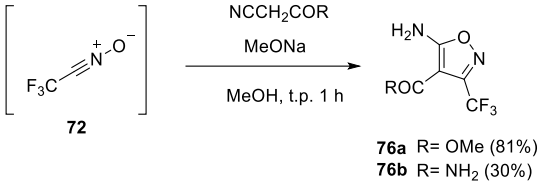
W przeciwieństwie do dobrze poznanych tlenków arylonitryli, jak dotąd opublikowano skromną liczbę prac poświęconych chemii tlenku trifluoroacetonitrylu (CF_3CNO, **72**), przede wszystkim z uwagi na bardzo wysoką reaktywność i tym samym podatność do ulegania nieodwracalnej dimeryzacji do odpowiedniego *N*-tlenku oksadiazolu.[53]

Wspomniany tlenek trifluoroacetonitrylu (**72**) najłatwiej generuje się w reakcji bromku trifluoroacetohydroksymoilu z zasadą organiczną (np. Et_3N), w rozcieńczonych roztworach organicznych, w obecności dostatecznie reaktywnego dipolarofila (*Schemat 31)*. Przykładowo, tlenek **72** skutecznie testowano wobec olefin i pochodnych acetylenu uzyskując spodziewane produkty (3+2)-cykloaddycji.[54] W przypadku niesymetrycznych dipolarofili C=C i C≡C (w szczególności monopodstawionych) stwierdzono wysoce regioselektywny przebieg reakcji uzyskując pochodne odpowiednio, izoksazolu **73** lub dihydroizoksazolu **74**, które izolowano z umiarkowanymi lub dobrymi wydajnościami.



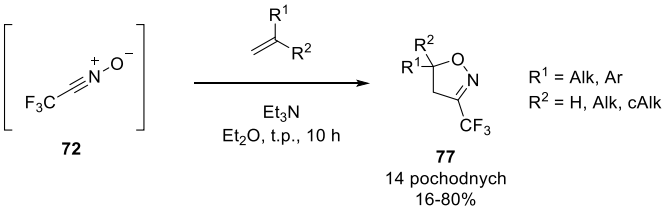
*Schemat 31. Generowanie tlenku trifluoroacetonitrylu (**72**) oraz jego reakcje z wybranymi olefinami i alkinami.*

Podobnie, w przykładzie na *Schemacie 32*, tlenek **72** w obecności takich aktywnych związków metylenowych jak cyjanooctan metylu lub cyjanoacetamid, oraz mocnej zasady (MeONa), ulega regioselektywnej (3+2)-cykloaddycji do odpowiednich enolanów prowadząc do pochodnych izooksazolu **76a** (81%) i **76b** (30%).[55]



*Schemat 32. Reakcje (3+2)-cykloaddycji tlenku **72** do cyjanooctanu metylu i cyjanoacetamidu prowadzące do pochodnych 5-aminoizoksazolu **76a** i **76b**.*

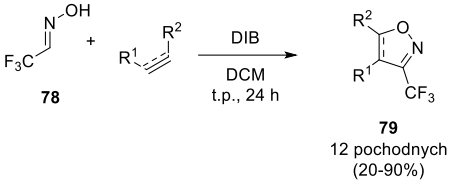
W innej pracy traktującej o reakcjach (3+2)-cykloaddycji tlenku trifluoroacetonitrylu (**72**) zbadano serię nieaktywowanych lub wzbogaconych elektronowo olefin, w łagodnych warunkach (temperatura pokojowa, Et_3N w roli zasady). W zdecydowanej większości reakcji prowadzonych z mono- oraz 1,1-dipodstawionymi alkenami, w tym również metylidenoalkanami, obserwowano w pełni regioselektywny przebieg cykloaddycji, z wyraźną tendencją do tworzenia produktów podstawionych w pozycji C(5) pierścienia 2-izoksazolinowego typu **77** (*Schemat 33)*.[56]



Schemat 33. (*3+2)-Cykloaddycje tlenku **72** do pochodnych etylenu.*

Warto wspomnieć, że tlenek **72** można również generować w reakcji utleniania odpowiedniego aldoksymu **78**, np. przy użyciu

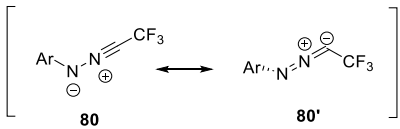
(bis-acetoksy)-jodobenzenu (DIB) (*Schemat 34*).[57] Tak wygenerowany 1,3-dipol został skutecznie wyłapany wybranymi dipolarofilami acetylenowymi i pochodnymi etylenu, a odpowiednie pochodne 1,2-oksazolu **79** wyizolowano z dobrymi wydajnościami i z wysoką regioselektywnością.



*Schemat 34. Generowanie tlenku trifluoroacetonitrylu (**72**) w warunkach utleniania aldoksymu **78** przy użyciu DIB, w obecności dipolarofili C=C lub C≡C.*

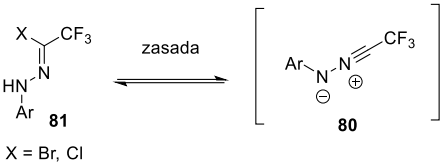
1.2.5. Nitryloiminy

Iminy trifluoroacetonitrylu **80** należą do propargilowo-allenowego typu 1,3-dipoli i podobnie jak wcześniej omawiane reagenty trifluorometylowane charakteryzują się zubożoną gęstością elektronową wskutek silnego efektu wyciągającego w kierunku grupy CF_3 (*Schemat 35*).[58,59,60] Pierwsze doniesienia na temat metod generowania oraz reaktywności CF_3-nitrylomin datuje się na wczesne lata 80' ubiegłego wieku (grupa Tanaki), jednak przez kolejne trzy dekady zainteresowanie tytułowymi 1,3-dipolami było marginalne, głównie ze względu na ograniczony dostęp do taniego, komercyjnego źródła fluoralu, przy jednocześnie bardzo wymagającej i nisko wydajnej metodzie jego syntezy.



*Schemat 35. Dwie wybrane (z sześciu głównych) struktury rezonansowe trifluorometylowanych nitryloimin **80**.*

Co ważne, w przeciwieństwie do tlenku trifluoroacetonitrylu (**72**), CF_3-nitryloiminy **80** ulegają dimeryzacji tylko w nieznacznym stopniu, a z uwagi na odwracalny charakter reakcji dehydrohalogenowania prekursorów hydrazonoilowych typu **81**, poprzez dobór zasady o odpowiedniej mocy można kontrolować stacjonarne stężenie 1,3-dipola **80** (*Schemat 36*).[61]



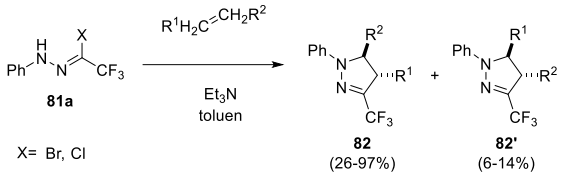
*Schemat 36. Generowanie CF_3-nitryloimin **80** z wykorzystaniem prekursorów hydrazonoilowych w obecności zasady.*

Obecnie obserwuje się wzmożoną aktywność kilku grup badawczych w obszarze chemii generowanych *in situ* imin trifluoroacetonitrylu **80**, m.in. zainspirowaną obiecującymi rezultatami prac zrealizowanych na Wydziale Chemii Uniwersytetu Łódzkiego.[62] I tak, w ostatnich kilku latach opublikowano kilkanaście prac, w których nitryloiminy **80** zademonstrowano jako niezwykle użyteczne bloki budulcowe do syntezy produktów trifluorometylowanych, ze szczególnym uwzględnieniem reakcji (3+2)-cykloaddycji do różnorodnych C=C, C≡C, C=S oraz C=N dipolarofili.[58,63–65]

1.2.5.1. (3+2)-Cykloaddycje do wiązań C=C i C≡C

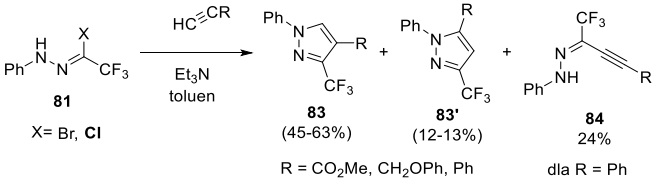
Pionierską pracą na temat chemii trifluorometylowanych nitryloimin **80** jest artykuł z 1982 roku opublikowany przez zespół Tanaki.[66] W publikacji zaprezentowano syntezę dwóch prekursorów modelowej nitryloiminy (chlorku i bromku **81**), sfunkcjonalizowanej grupą fenylową na *N*-końcu, której reaktywność testowano wobec kilku wybranych olefin i pochodnych acetylenu. O ile w przypadku monopodstawionych dipolarofili C=C, takich jak akrylan metylu lub styren, obserwowano bardzo dobrą konwersję i wysoką

regioselektywność (3+2)-cykloaddycji, w reakcjach z nieaktywowanymi 1,2-dipodstawionymi olefinami zanotowano niskie wydajności produktów powstających w postaci mieszanin regioizomerów **82** i **82'** (*Schemat 37*).



*Schemat 37. Reakcje (3+2)-cykloaddycji CF_3-nitryloimin **80** do nieaktywowanych olefin prowadzące do mieszaniny izomerycznych pochodnych 4,5-dihydro-1H-pirazolu **82** i **82'**.*

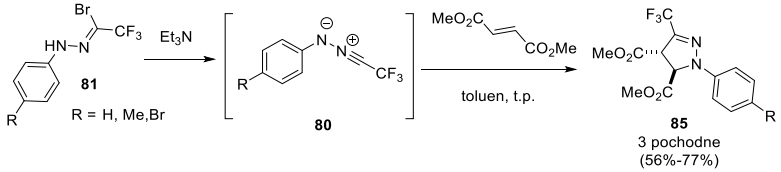
Co więcej, w tej samej pracy wykazano, że zastosowanie terminalnych acetylenów jako partnerów reakcyjnych dla nitryloimin **80** prowadzi nie tylko do mieszaniny izomerycznych pochodnych pirazolu **83** i **83'**, ale w obecności mocnych zasad, także do produktów addycji nukleofilowej odpowiedniego anionu acetylenowego do 1,3-dipola (produkt **84**), co stanowi zasadnicze ograniczenie w stosowaniu tego typu C≡C dipolarofili (*Schemat 38*).



Schemat 38. Reakcja (3+2)-cykloaddycji trifluorometylowanych nitryloimin do terminalnych alkinów.

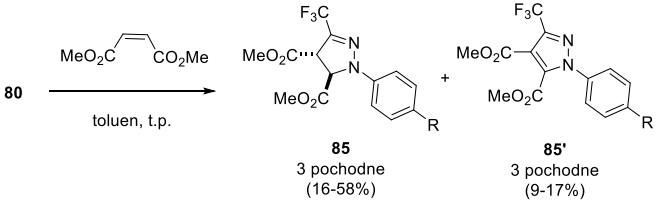
W innej pracy z wczesnych lat 80' ubiegłego wieku opisano reakcje serii trzech CF_3-nitryloimin typu **80** wyłapywanych przy pomocy fumaranu dimetylu oraz maleinianu dimetylu, wybranych jako modelowe olefiny o zdefiniowanej konfiguracji przy wiązaniu C=C (odpowiednio *E* i *Z*).[67] Jak wykazano, w reakcji (3+2)-cykloaddycji do fumaranu dimetylu otrzymywano

względnie trwałe pochodne *trans*-pirazoliny, które wydzielano z dobrymi wydajnościami (*Schemat 39*).



*Schemat 39. Reakcje (3+2)-cykloaddycji nitryloimin **80** z fumaranem dimetylu.*

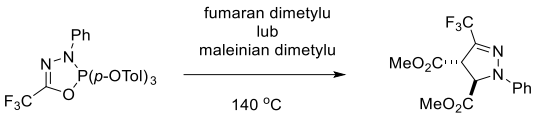
W przypadku reakcji z maleinianem dimetylu izolowano mieszaniny dwóch produktów tj. *trans*-pirazolin typu **85** (obserwowanych we wcześniejszych reakcjach z fumaranem) oraz odpowiednie pirazole **85'**. Natomiast nie znaleziono (3+2)-cykloaddyktów o konfiguracji *cis*, co może wskazywać na etapowy, nieuzgodniony mechanizm tego typu addycji (*Schemat 40*).



*Schemat 40. Reakcje (3+2)-cykloaddycji nitryloimin **80** z maleinianem dimetylu.*

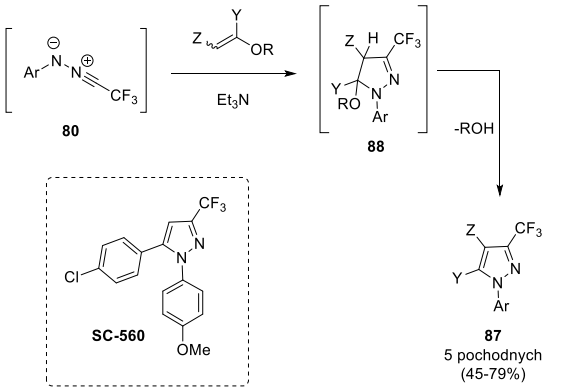
Inna praktyczna informacja z wczesnych prac grupy Tanaki dotyczy obserwacji, że wykorzystanie bromków hydrazonoilowych **81** jako prekursorów nitryloimin **80** pozwala na zastosowanie łagodniejszych warunków (niższa temperatura, łagodniejsza zasada) w porównaniu do odpowiednich chlorków, wymagających podwyższonej temperatury (np. wrzący toluen).[67] Ponadto, jako alternatywne, ale znacznie mniej użyteczne źródło CF_3-nitryloimin **80** wskazano pochodne oksadiazofosfolu typu **86**, które

nie wymagają obecności zasady ale uwalniają 1,3-dipol w dość agresywnych warunkach termicznych (140 °C) (*Schemat 41*).



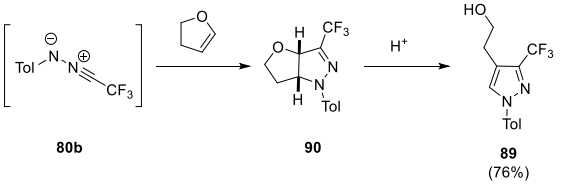
*Schemat 41. Pochodna oksadiazofosfolu **86** jako alternatywne źródło nitryloimin **80** generowanych w warunkach termolizy.*

Jeden ze skutecznych sposobów kontrolowania regiochemii reakcji (3+2)-cykloaddycji obejmuje zastosowanie niesymetrycznych dipolarofili, sfunkcjonalizowanych przynajmniej jednym podstawnikiem o wyraźnie odmiennym charakterze elektronowym. Takie podejście do syntezy 3-trifluorometylowanych pochodnych pirazolu **87** zaprezentowano w roku 2018, stosując etery winylowe jako substraty wobec *in situ* generowanych nitryloimin **80**.[62] Zgodnie z oczekiwaniem, reakcja cykloaddycji prowadzona w łagodnych warunkach (temperatura pokojowa, Et_3N jako zasada) przebiegała całkowicie regioselektywnie, a po spontanicznej eliminacji alkoholu z pierwotnie utworzonych pirazolin **88**, jako jedyne produkty izolowano odpowiednie pirazole **87** (*Schemat 42*). Warto podkreślić, że wybrana w toku prac optymalizacyjnych zasada pełni podwójną rolę (indukuje reakcję dehydrohalogenowania oraz katalizuje eliminację cząsteczki ROH z pośredniej pirazoliny), stąd zapewniony nadmiar zasady skutecznie przyśpiesza oraz zwiększa wydajność badanej transformacji. Jedocześnie, opracowana metoda charakteryzuje się szerokim zakresem stosowalności i umożliwia szybki dostęp do alkilowych i arylowych C(4)- i/lub C(5)-podstawionych pochodnych pirazolu **87**, w tym związków o udokumentowanej aktywności biologicznej (np. inhibitorów COX, takich jak *SC-560*).



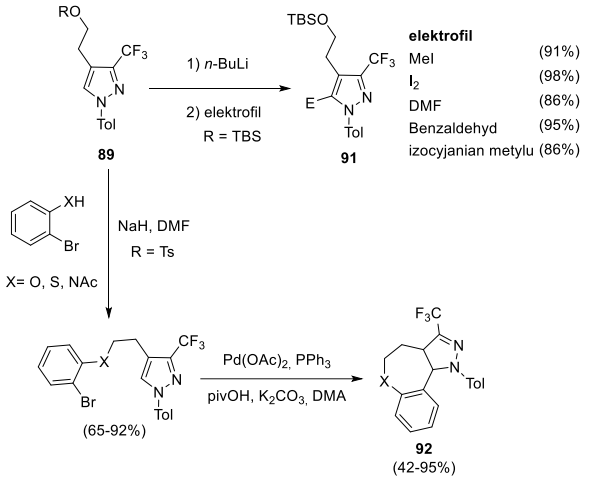
*Schemat 42. Synteza pochodnych 3-trifluorometylowanego pirazolu **87**.*

W tej samej pracy, poprzez zastosowanie cyklicznych eterów enoli w roli dipolarofili otworzono dostęp do mało poznanej grupy pochodnych 3-CF_3-pirazolu **89** sfunkcjonalizowanych w pozycji C(4) ugrupowaniem ω-hydroksyalkilowym dającym nowe możliwości w syntezie bardziej złożonych produktów opartych na pierścieniu 3-trifluorometylowanego pirazolu (*Schemat 43*). Co ciekawe, pośrednie bicykliczne pirazoliny **90** charakteryzowały się podwyższoną trwałością w porównaniu z ich monocyklicznymi analogami, a proces aromatyzacji pierścienia pirazolowego skutecznie katalizowano dodatkiem kwasu Brønsteda w trakcie obróbki wodnej mieszanin poreakcyjnych.



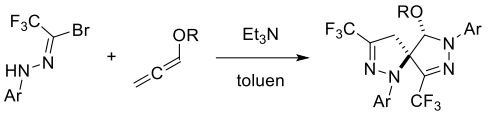
*Schemat 43. Cykliczne etery enoli w reakcji (3+2)-cykloaddycji z nitryloiminami **80**.*

Wysoką użyteczność syntetyczną pirazoli **89** zademonstrowano m.in. w reakcjach selektywnego deprotonowania pozycji C(5) przy użyciu odczynników organolitowych i wyłapania odpowiedniego anionu elektrofilami (produkty typu **91**) oraz w reakcjach funkcjonalizacji grupy hydroksylowej i następczej cyklizacji w warunkach katalizy Pd prowadzących do pochodnych tricyklicznych **92** (*Schemat 44*).



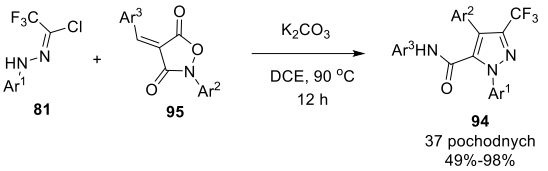
*Schemat 44. Wybrane transformacje 4-(ω-hydroksyalkilo)pirazoli **89**.*

W innej pracy pochodzącej z Uniwersytetu Łódzkiego nitryloiminy **80** generowano *in situ* w obecności alkoksyallenów, uzyskując serię stosunkowo trwałych pochodnych spiro-bipirazoliny **93**, powstających wskutek formalnej podwójnej, sekwencyjnej (3+2)-cykloaddycji do obu wiązań C=C kumulenu (*Schemat 45*).[68] W każdym z testowanych przypadków stwierdzono niemal pełną regioselektywność, a produkty końcowe o konfiguracji *anti* izolowano z umiarkowanymi wydajnościami do ok. 50%.



*Schemat 45. Podwójna (3+2)-cykloaddycja nitryloimin **80** do alkoksyallenów.*

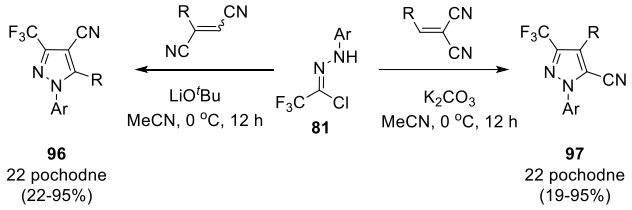
Podobny efekt zwiększonej kontroli regioselektywności reakcji (3+2)-cykloaddycji z użyciem nitryloimin **80** można osiągnąć stosując pochodne olefin sfunkcjonalizowane grupami elektronowyciągającymi. W 2021 roku J.-A. Ma i współpracownicy zaprezentowali metodę syntezy polipodstawionych pirazoli **94** opartą na dekarboksylatywnym wariancie reakcji (3+2)-cykloaddycji z użyciem izoksazolidynodionów **95** w roli dipolarofili (*Schemat 46*).[69] Serię docelowych produktów otrzymano w wyniku chemo- i regioselektywnej (3+2)-cykloaddycji **80** do wiązania egzo-arylidenowego wyjściowego izoksazolidynodionu, a pierwotnie utworzony cykloaddukt ulegał w warunkach podwyższonej temperatury (DCE, 90 °C) spontanicznej aromatyzatywnej dekarboksylacji. Warto zauważyć, że inicjującą reakcję dehydrohalogenowania chlorku hydrazonoilowego **81** można wydajnie przeprowadzić także z użyciem zasady nieorganicznej (K_2CO_3).



*Schemat 46. Dekarboksylatywny wariant (3+2)-cykloaddycj nitryloimin **80** do isoksazolidinedionów w syntezie pirazoli **94***

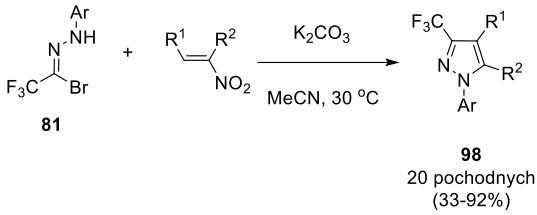
W kolejnych pracach Zespołu J.-A. Ma jako nie mniej użyteczne dipolarofile do wykorzystania w reakcjach z nitryloiminami **80** wskazano cyjanoalkeny (*Schemat 47*).[70] W zależności od ich podstawienia Autorzy

otrzymali w pełni regioselektywnie pochodne pirazolu. I tak, wykorzystując w roli dipolarofila 1,2-dicyjanopodstawione alkeny otrzymywali jako jedyny addukt pochodne 4-cyjanopirazolu **96**, natomiast 1,1-dicyjanopodstawione alkeny w reakcji z nitryloiminami **80** prowadziły wyłącznie do pochodnych 5-cyjanopirazolu **97**. Obserwowana selektywność może wynikać z sekwencyjnego przebiegu reakcji. Następna analiza aktywności wybranych produktów **96** i **97** wykazała, że wprowadzenie grup CN w pozycji C(4) wzmaga właściwości przeciwzapalne związku.



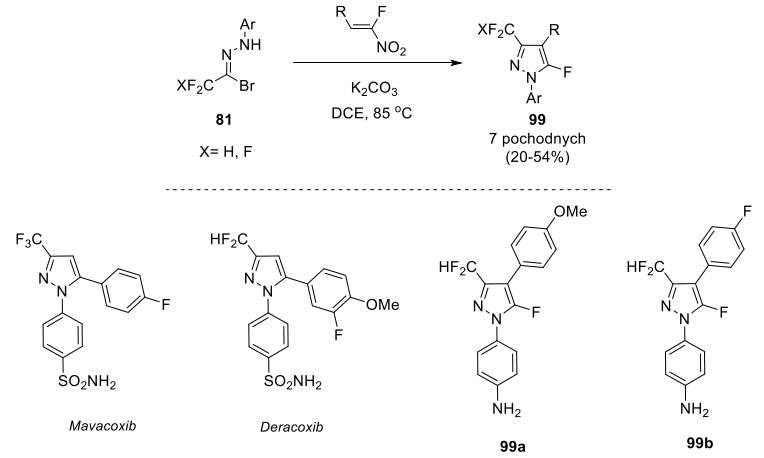
*Schemat 47. Synteza pochodnych 4-/5-cyjanopirazolu **96/97** z użyciem cyjanoalkenów jako dipolarofili w reakcjach z nitryloiminami **80**.*

Podobną efektywność zademonstrowano w przypadku reakcji nitryloimin **80** oraz nitroalkenów uzyskując oczekiwane produkty **98** (*Schemat 48*).[71] Analogicznie jak w przypadku cyjanoalkenów, grupa NO_2 w dipolarofilu pełniła rolę podstawnika kierującego oraz grupy opuszczającej na finalnym etapie aromatyzacji pierścienia pirazolowego.



*Schemat 48. Synteza pirazoli **98** z użyciem nitroalkenów jako dipolarofili w reakcjach z nitryloiminami **80**.*

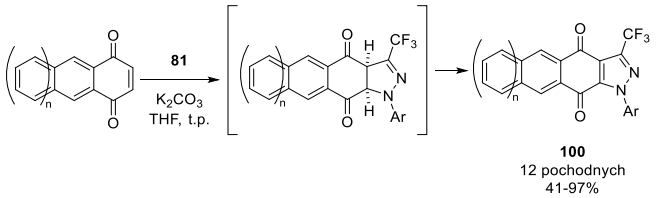
W analogicznym postępowaniu z wykorzystaniem fluorowanych nitroalkenów jako partnerów reakcyjnych dla generowanych *in situ* nitryloimin **80** uzyskano dostęp do dotychczas trudno dostępnych pochodnych 5-fluoro-3-trifluorometylopirazoli **99** oraz ich analogów CHF_2, potencjalnie ważnych z punktu widzenia możliwych praktycznych zastosowań (*Schemat 49*).[72] Autorzy inspirując się strukturami kilku znanych farmaceutyków z klasy pochodnych 3-CF_3-pirazolu (*Deracoxib*, *Mavacoxib*) zaprojektowali serię produktów typu **99a-b**, które zgodnie z oczekiwaniem wykazywały wzmożoną aktywność inhibicyjną wobec enzymów COX-1 / COX-2 (co odpowiada za właściwości przeciwzapalne) w porównaniu do związków referencyjnych.



Schemat 49. Synteza 3-CF_3/CHF_2-5-fluoropirazoli.

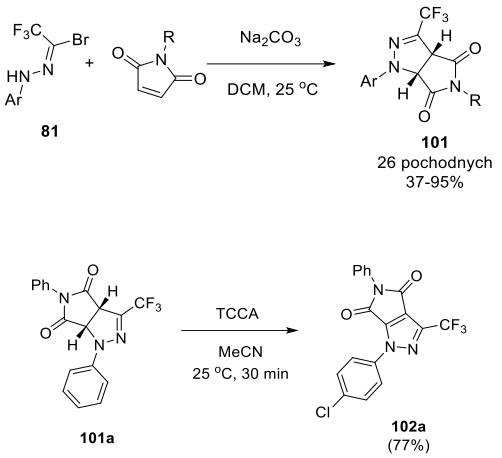
Generowane *in situ* trifluorometylowane nitryloiminy **80** mogą również znaleźć zastosowanie w syntezie materiałów organicznych o pożądanych cechach fotofizycznych, jak pokazano w pracy z roku 2021, w której w roli dipolarofili przetestowano serię 1,4-chinonów.[73] W wyniku chemoselektywnej (3+2)-cykloaddycji nitryloiminy **80** do wiązania C=C chinonu oraz spontanicznej oksydatywnej aromatyzacji pierścienia pierwotnie utworzonej *cis*-pirazoliny, jako główne produkty wydzielono

policykliczne pochodne **100** (*Schemat 50*). Uzyskane barwne produkty cechowały się pasmem absorpcji o umiarkowanej intensywności w obszarze 310-340 nm oraz znacznym efektem hipsochromowym wraz ze wzrostem charakteru elektronowyciągającego podstawników obecnych w pierścieniu aromatycznym na atomie N(1).



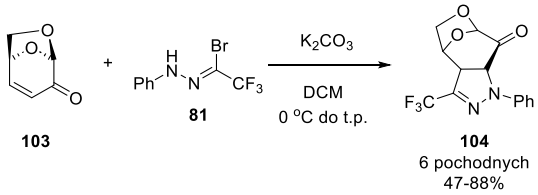
*Schemat 50. Synteza policyklicznych pirazoli **100** pochodnych 1,4-chinonów.*

W bardzo podobnej pracy autorstwa Y. Hu i współpracowników (2023) iminy trifluoroacetonitrylu **80** wyłapywano przy pomocy maleimidów uzyskując dostęp do trwałych *cis*-bicyklicznych pirazolin typu **101**.[74] Warto zaznaczyć, że utlenianie pochodnych pirazoliny **101** wydajnie zrealizowano w łagodnych warunkach (MeCN, temperatura pokojowa) przy użyciu kwasu trichloroizocyjanurowego (TCCA), jednakże, w przypadku pochodnych *N*-fenylowych jako główne produkty izolowano pirazole **102** powstające wskutek równoczesnego chlorowania pozycji *para* pierścienia benzenowego (*Schemat 51*).



*Schemat 51. Bicykliczne pirazoliny **101** pochodne maleimidów; synteza i utlenianie z użyciem TCCA.*

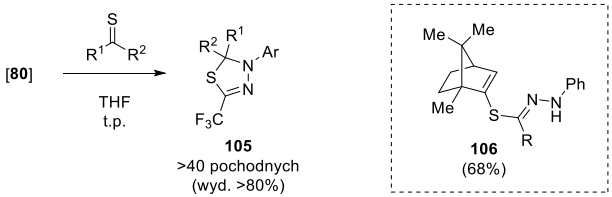
W jednej z najnowszych publikacji zaprezentowano przykład wysoce regioselektywnej (3+2)-cykloaddycji CF_3-nitryloimin **80** do *levoglukosenonu* (**103**), chiralnego enonu z grupy produktów naturalnych.[75] Zaobserwowana regiochemia reakcji (atom azotu 1,3-dipola przyłącza się w pozycję α względem grupy C=O) potwierdza ogólną tendencję tego typu (3+2)-cykloaddycji z użyciem fluorowanych nitryloimin **80** i enonów, co pisano w części badań własnych niniejszej rozprawy.



*Schemat 52. CF_3-Pirazoliny **104** pochodne levoglukosenonu.*

1.2.5.2. (3+2)-Cykloaddycje do wiązań C=S

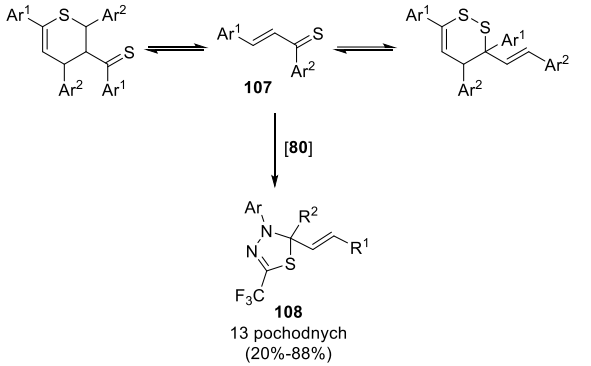
Pierwsze doniesienia na temat wykorzystania superdipolarofili tiokarbonylowych w reakcjach z nitryloiminami **80** zaprezentowano dopiero w roku 2016. W reakcjach przetestowano serię różnorodnych tioketonów aromatycznych i heteroaromatycznych, w tym pochodnych ferrocenu, uzyskując we wszystkich przypadkach 5-trifluorometylo-2,3-dihydro-1,3,4-tiadiazole **105** jako wyłączne produkty, które wydzielono z bardzo dobrymi wydajnościami (*Schemat 53*).[64] Podobnie, pełną regioselektywność zanotowano również w reakcjach **80** z tioketonami (cyklo)alifatycznymi, uzyskując oczekiwane (3+2)-cykloaddukty **105**, nawet w przypadku tak sterycznie wymagających substratów jak tioketon di-*tert*-butylowy.[63] Jedynie w przypadku reakcji z enolizującą (*R*)-tiokamforą, oprócz spodziewanego (3+2)-cykloadduktu do wiązania C=S (wydajność 21%) jako główny produkt addycji nukleofilowej do *C*-końca 1,3-dipola zidentyfikowano związek **106**.



*Schemat 53. Regioselektywna (3+2)-cykloaddycja nitryloimin **80** do tioketonów aromatycznych i alifatycznych.*

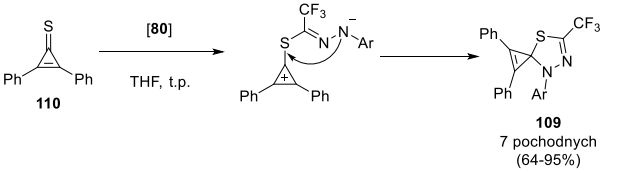
Ciekawym rozszerzeniem tematyki dotyczącej reakcji związków tiokarbonylowych z trifluorometylowanym nitryloiminami **80** było zastosowanie mało poznanych tiochalkonów.[58] Tiochalkony najłatwiej przygotowuje się w reakcji tionowania chalkonów odczynnikiem Lawessona, jednakże, ze względu na ich wysoką reaktywność, wydzielony materiał poreakcyjny stanowi skomplikowaną mieszaninę produktów dimeryzacji, z których w roztworach uwalniają się niewielkie ilości monomerycznych tiochalkonów. Zastosowanie bromków hydrazonoilowych **81** jako źródła CF_3-nitryloimin w łagodnych warunkach, umożliwiło selektywne wyłapanie

monomerycznych form tiochalkonów **107** i wydzielenie spodziewanych (3+2)-cykloadduktów do wiązania C=S dipolarofila (związek **108**), zwykle z dobrymi wydajnościami potwierdzającymi bardzo wysoką chemo- i regioselektywność studiowanej transformacji (*Schemat 54*).



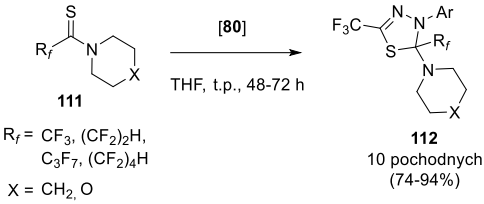
*Schemat 54. Chemo- i regioselektywna (3+2)-cykloaddycja nitryloimin **80** do wiązania C=S monomerycznych tiochalkonów.*

W podobnym postępowaniu otrzymano serię nietypowych spiro-pochodnych 1,3,4-tiadiazolu **109** stanowiących produkt chemoselektywnej formalnej (3+2)-cykloaddycji nitryloimin **80** do wiązania C=S difenylo-cyklopropentionu (**110**).[76] Mając na uwadze znaną bierność klasycznych nitryloimin wobec tioketonu **110**, Autorzy wskazują na prawdopodobny, etapowy mechanizm reakcji podkreślający jednocześnie wysoce tiofilowy charakter C-końca fluorowanego 1,3-dipola (*Schemat 55*).



*Schemat 55. Synteza spiro-1,3,4-tiadiazoli **109** pochodnych cyklopropentionu.*

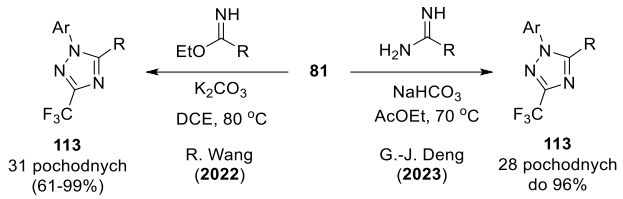
Wspomniana powyżej, unikatowa cecha nitryloimin **80** została potwierdzona w reakcjach z mało reaktywnymi, zubożonymi elektronowo (per)fluorowanymi tioamidami typu **111**.[77] W zoptymalizowanych warunkach reakcji (THF, temperatura pokojowa, do 72 h) otrzymano serię docelowych (3+2)-cykloadduktów **112** z bardzo dobrymi wydajnościami >70% (*Schemat 56*).



*Schemat 56. Fluorowane tioamidy jako C=S dipolarofile w reakcji (3+2)-cykloaddycji z nitryloiminami **80**.*

1.2.5.3. (3+2)-Cykloaddycje do wiązań C=N

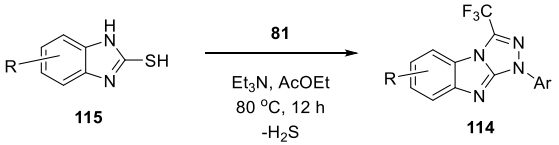
Pierwsze próby syntezy trifluorometylowanych pochodnych 1,2,4-triazolu poprzez reakcję (3+2)-cykloaddycji nitryloimin **80** do nienasyconych wiązań węgiel-azot podejmowane były przez zespół Tanaki, ale jedyny umiarkowanie skuteczny rezultat opisano dla reakcji z wykorzystaniem dicykloheksylokarbodiimidu (DCC).[78] Dopiero w ostatnim czasie (2022) zaprezentowano wydajną metodę syntezy, w której w roli dostatecznie reaktywnego dipolarofila zastosowano iminy eterów, i w stosunkowo łagodnych warunkach (DCE, 80 °C, K_2CO_3) przygotowano serię produktów typu **113**, wyizolowanych z bardzo dobrymi wydajnościami (*Schemat 57*).[79] Jak wykazano na kilkudziesięciu przykładach, zakres stosowalności metody obejmuje różnorodnie podstawione grupy arylowe ulokowane na *N*-końcu 1,3-dipola oraz podstawniki alkilowe, cykloalifatyczne, arylowe i hetero-arylowe po stronie dipolarofila.



Schemat 57. (3+2)-Cykloaddycje CF_3-nitryloimin do C=N dipolarofili.

Zbliżoną koncepcję dojścia do trifluorometylowanych 1,2,4-triazoli **113**, z zastosowaniem amidyn w roli dipolarofili, zaprezentowała w 2023 grupa G.-J. Denga, wskazując na podobny zakres stosowalności opracowanej metody (*Schemat 57*).[80]

Inną, ciekawą z punktu widzenia chemoselektywności, metodę syntezy skondensowanych pochodnych 1,2,4-triazolu **114** opisał zespół J. Cai (2023).[81] Zaprezentowana na *Schemacie 58.* strategia opiera się na reakcji CF_3-nitryloimin **80** z 1*H*-benzo[*d*]imidazolo-2-tiolami **115**, przy czym Autorzy postulują nukleofilowy atak *N*-końca 1,3-dipola na „tiokarbonylowy" atom węgla jako etap inicjujący formalną (3+2)-cykloaddycję, przebiegającą z eliminacją cząsteczki H_2S.



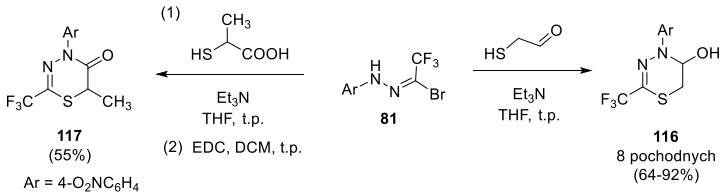
*Schemat 58. Synteza skondensowanych 1,2,4-triazoli **114** w reakcji formalnej (3+2)-cykloaddycji CF_3-nitryloimin do benzo[d]imidazolo-2-tioli **115**.*

Mając na uwadze stały wzrost zainteresowania fluorowanymi pochodnymi triazolu w kontekście zastosowań farmakologicznych,[82] można oczekiwać kolejnych doniesień potwierdzających wysoką użyteczność imin trifluoroacetonitrylu typu **80** jako bloków budulcowych do syntezy CF_3-triazoli.

1.2.5.4. Reakcje (3+3)-annulacji

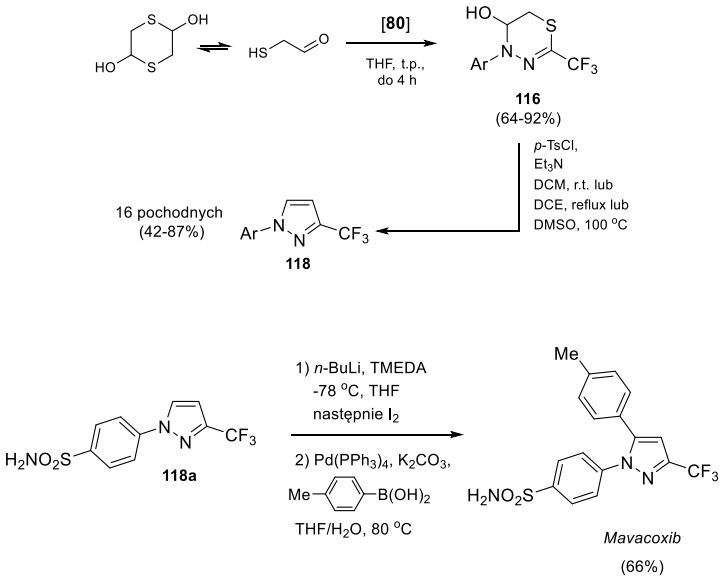
W poprzednich sekcjach niniejszej dysertacji trifluorometylowane nitryloiminy **80** zostały przedstawione jako 1,3-dipolarne komponenty reakcji Huisgena.[61] Z drugiej strony, zwitterionowy charakter nitryloimin, jak również wielu innych 1,3-dipoli, umożliwia ich zastosowanie w formalnych reakcjach cykloaddycji-(3+3), -(3+4) i wyższych, zwanych również reakcjami annulacji. Przykładem takiego typu reaktywności jest wspomniana wcześniej dimeryzacja *N*-tlenków nitryli. Analogicznie, dobór odpowiedniego reagenta zawierającego dwa centra o odmiennej elektronowości (elektrofilowe oraz nukleofilowe) np. w położeniu geminalnym, powinien otworzyć dostęp do produktów 6-cioczłonowych.

Przykładowe reakcje (3+3)-annulacji fluorowanych nitryloimin typu **80** z wybranymi odczynnikami α-merkaptokarbonylowymi zaprezentowano na *Schemacie 59.* I tak, w wyniku kondensacji **80** z merkaptoacetaldehydem (dostępnym *in situ* z handlowego dimeru) uzyskano serię pochodnych 5-hydroksy-1,3,4-tiadiazyny **116** z bardzo dobrymi wydajnościami (na ogół >90%).[65] Analogicznie, w reakcjach (3+3)-cyklizacji z α-merkaptokwasami otrzymano odpowiednie 5-okso-pochodne 1,3,4-tiadiazyn **117**, choć w tym przypadku, w drugim etapie reakcji realizowanej *one-pot*, konieczne było zastosowanie odpowiedniego odczynnika sprzęgającego w celu utworzenia wiązania hydrazydowego.



*Schemat 59. (3+3)-Annulacje nitryloimin **80** z odczynnikami α-merkaptokarbonylowymi.*

W kolejnej pracy pochodzącej z naszego Zespołu, powyższe obserwacje rozwinięto w kierunku syntezy 1-arylo-3-trifluorometylopirazoli typu **118**. Tego typu pochodne 3-CF_3-pirazolu stanowią atrakcyjny przedmiot badań pod kątem selektywnej funkcjonalizacji pozycji C(4) i C(5) pierścienia, jednakże, są stosunkowo trudno dostępne klasycznymi metodami opartymi np. na kondensacji pochodnych hydrazyny ze związkami β-dikarbonylowymi (lub ich ekwiwalentami).[22] W zaprezentowanej na *Schemacie 60.* procedurze *one-pot*, nitryloiminy **80** kondensuje się z merkaptoacetaldehydem, a następcza aktywacja grupy hydroksylowej w pośredniej 1,3,4-tiadiazynie **116** (przy użyciu *p*-TsCl, w obecności zasady), skutkuje spontaniczną dehydratacją oraz kontrakcją pierścienia wskutek termicznej ekstruzji siarki elementarnej (reakcja Eschenmosera).[83] Należy podkreślić, że opracowaną metodę skutecznie zaadaptowano do syntezy trzech znanych farmaceutyków (*SC-560*, *Celecoxib* i *Mavacoxib*).



*Schemat 60. (3+3)-Annulacja nitryloimin **80** z merkaptoacetaldehydem jako kluczowy etap syntezy 1-arylopirazoli **118**.*

Podsumowując, nitryloiminy **80**, generowane *in situ* z łatwo dostępnych prekursorów hydrazonoilowych **81**, stanowią atrakcyjną grupę odczynników fluorowanych do zastosowań w syntezie organicznej, w szczególności do przygotowania trifluorometylowanych heterocykli 5-cio oraz 6-cioczłonowych, uzyskiwanych w oparciu o reakcje, odpowiednio, (3+2)-cykloaddycji oraz (3+3)-annulacji. W ramach niniejszej pracy doktorskiej zbadano nowe wątki chemii imin trifluoroacetonitrylu, obejmujące oba wspomniane typy reakcji z wykorzystaniem chalkonów, generowanych *in situ* arynów, a także estrów α-aminokwasów, a najważniejsze osiągnięcia badań własnych podsumowano w postaci pięciu prac oryginalnych, opublikowanych w czasopismach o zasięgu międzynarodowym.

2. Omówienie rezultatów badań własnych

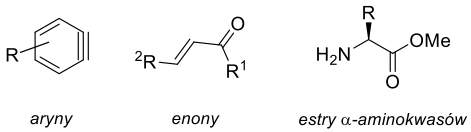
Przedmiotem niniejszej rozprawy były badania podstawowe z obszaru syntezy organicznej dotyczące chemii mało rozpoznanej grupy fluorowanych nitryloimin **80**, dostępnych *in situ* w środowisku reakcji z odpowiednich prekursorów (halogenków hydrazonoilowych **81**), jako atrakcyjnych bloków budulcowych do syntezy heterocykli azotowych sfunkcjonalizowanych ugrupowaniem CF_3. Z uwagi na wciąż ograniczoną liczbę doniesień na temat reaktywności i zakresu stosowalności tytułowych nitryloimin w syntezie heterocykli 5- i 6-cioczłonowych, celem mojej pracy było przebadanie ich zachowania wobec trzech wybranych klas reagentów tj. dwóch grup dipolarofili o odmiennych cechach elektronowych do zastosowania w reakcjach (3+2)-cykloaddycji (*Rysunek 4*):

arynów (głównie pochodnych benzynu) jako przykładowych, wysoce reaktywnych C≡C dipolarofili bogatych w elektrony i

enonów (przede wszystkim chalkonów) jako łatwo dostępnych C=C dipolarofili zubożonych elektronowo

oraz

estrów α-aminokwasów jako chiralnych reagentów dwufunkcyjnych (elektrofilowo-nukleofilowych) do zastosowania w reakcjach annulacji-(3+3).



*Rysunek 4. Ogólne struktury reagentów (arynów, enonów i estrów α-aminokwasów) wytypowanych do badań nad reaktywnością nitryloimin **80**.*

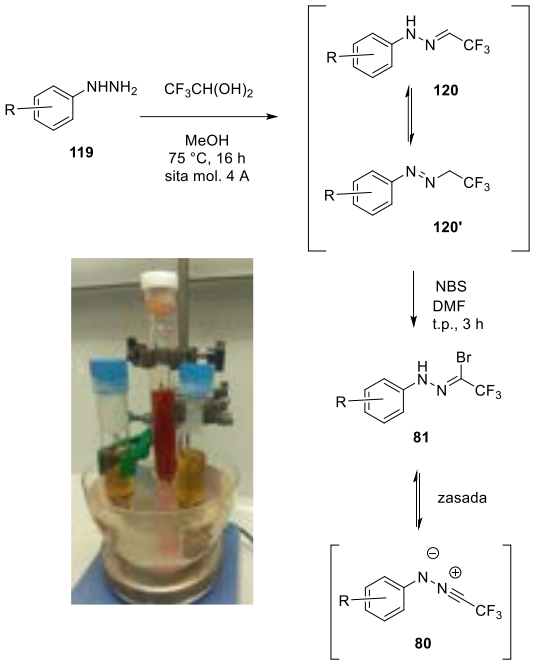
W ramach prac wykazałam, że w zoptymalizowanych warunkach reakcji prowadzonych w roztworach lub bez rozpuszczalnika, aktywowanych mechanochemicznie, wytypowane grupy odczynników są dogodnymi

partnerami reakcyjnymi dla fluorowanych nitryloimin **80** i otwierają, alternatywny dla metod opisanych w literaturze fachowej, dostęp do trifluorometylowanych pochodnych indazolu, pirazolu oraz 1,2,4-triazyny. Jako szczególnie ważne osiągnięcie w przedłożonej pracy warto wskazać opracowanie zależnej od polarności rozpuszczalnika *deacylującej vs. dehydrogenatywnej* aromatyzacji 5-acylopirazoli, realizowanej przy użyciu MnO_2. Wspomnianą metodę zaadaptowałam do syntezy ważnej z punktu widzenia możliwych praktycznych zastosowań klasy kwasów ω-(3-CF_3-pirazol-4-ylo)alkanokarboksylowych.

2.1. Synteza prekursorów nitryloimin

Podobnie jak znakomita większość innych nitryloimin,[61] tytułowe iminy trifluoroacetonitrylu są związkami nietrwałymi, aczkolwiek, dostępne są *in situ* tj. bezpośrednio w środowisku reakcji z odpowiednich halogenków hydrazonoilowych. Prosta i tania metoda syntezy prekursorów tego typu została opisana w literaturze i zoptymalizowana w ramach wcześniejszych prac zrealizowanych w Katedrze Chemii Organicznej i Stosowanej, Wydziału Chemii Uniwersytetu Łódzkiego. Wspomniana dwuetapowa procedura opiera się na termicznej (75 °C) kondensacji arylohydrazyny **119** z hydratem fluoralu, prowadzonej w szczelnie zamkniętej ampule, w obecności aktywowanych sit molekularnych (*Schemat 61*).[84] Uzyskane w ten sposób arylohydrazony fluoralu **120** (w roztworach występujące w równowadze tautomerycznej z odpowiednią formą azową **120'**) poddaje się selektywnemu bromowaniu w pozycji azometinowej z użyciem *N*-bromosukcynoimidu (NBS) w łagodnych warunkach.[47] Surowe bromki hydrazonoilowe **81** oczyszcza się za pomocą standardowej chromatografii kolumnowej i wykorzystuje do generowania nitryloimin **80** poprzez potraktowanie zasadą organiczną lub nieorganiczną, w roztworze jak i w ciele stałym (młyn kulowy).

Przedstawioną na *Schemacie 61.* syntezę bromków **81** realizowałam rutynowo, uzyskując porcje pożądanych prekursorów nitryloimin, (kilkanaście różnych pochodnych), w skali do kilku gramów.

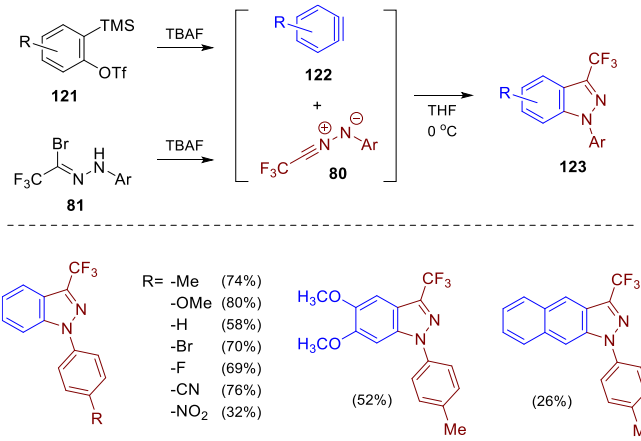


*Schemat 61. Dwuetapowa synteza bromków hydrazonoilowych **81** stosowanych jako prekursory trifluorometylowanych ntryloimin **80** oraz fotografia typowego zestawu reakcyjnego stosowanego w syntezie pośrednich hydrazonów **120**.*

2.2. Reakcje (3+2)-cykloaddycji nitryloimin z arynami (praca [D1])

Pierwsze próby reakcji modelowego bromku hydrazonoilowego z triflanem *o*-trimetylosilylofenylowym (**121**) miały na celu sprawdzenie, czy możliwe jest wyłapanie generowanego *in situ* arynu **122**, innym odczynnikiem generowanym *in situ* tj. 1,3-dipolem **80** (*Schemat 62*). Zachęcające wyniki wstępnych eksperymentów z użyciem wybranych zasad organicznych i nieorganicznych do indukcji nitryloiminy **80**, pozwoliły na wydzielenie produktu i jego identyfikację jako pożądanej pochodnej CF_3-indazolu **123**. W trakcie prac optymalizacyjnych, inspirując się publikacją

z grupy Mosesa,[85] wykazałam, że anion fluorkowy może z powodzeniem służyć nie tylko jako odczynnik desiliujący wobec prekursora arynu, ale w ściśle bezwodnych warunkach jest dostatecznie mocną zasadą dla inicjowania reakcji dehydrohalogenowania bromku **81**. Najlepsze wyniki zanotowałam z wykorzystaniem TBAF (4,0 equiv., 0 °C) jako źródła F^- uzyskując oczekiwany produkt **123** z wydajnością 74%, podczas gdy próby użycia soli nieorganicznych takich jak świeżo wyprażony CsF, nie dawały oczekiwanych efektów.

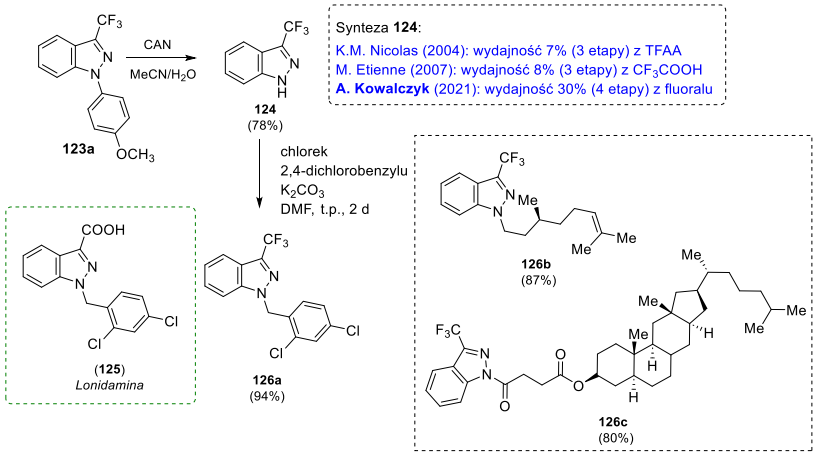


*Schemat 62. Reakcje (3+2)-cykloaddycji nitryloimin **80** z arynami **122**.*

W kolejnym etapie prac sprawdziłam zakres stosowalności metody (*Schemat 62*) testując benzyn wobec serii nitryloimin podstawionych w pozycji *para* pierścienia benzenowego ulokowanego na atomie azotu 1,3-dipola grupami o różnym charakterze elektronowym. We wszystkich przypadkach otrzymałam oczekiwane pochodne 3-CF_3-indazolu typu **123**, które wydzieliłam metodami chromatografii kolumnowej z dobrymi wydajnościami w zakresie 58-80%. Jedynie w przypadku silnie elektronowo zubożonej nitryloiminy **80** (podstawionej grupą NO_2) zaobserwowałam widoczny spadek wydajności (32%). Z drugiej strony, wprowadzenie do pierścienia dipolarofila (benzynu) dwóch grup silnie elektronodonorowych

(metoksylowych) nie miało istotnego wpływu na przebieg reakcji z modelową nitryloiminą, natomiast rozbudowanie sprzężonego układu wiązań (reakcja z naftynem) prowadziło do mieszaniny produktów, z której oczekiwany (3+2)-cykloaddukt wyizolowałam z wydajnością 26%.

Mając na uwadze fakt, że syntezy bardziej złożonych fluorowanych pochodnych indazolu otrzymywanych poprzez proste transformacje rdzenia heterocyklicznego (np. *N*-alkilowanie) cieszą się dużym zainteresowaniem, w kolejnym kroku podjęłam próby opracowania dostępu do *N*-niepodstawionej pochodnej **124** (*Schemat 63*). W pracy wykazałam wysoką skuteczność reakcji utleniającego dearylowania analogu *p*-metoksylowego **123a** w reakcji z CAN, uzyskując pożądany produkt **124** z wydajnością całkowitą 30% (po czterech etapach, wychodząc z fluoralu). Warto wspomnieć, że jest to jak dotąd najbardziej wydajna droga dojścia do tego ważnego prekursora; jego syntezę opisały np. zespoły Nicholasa[86] (7% po 3 etapach, z bezwodnika trifluorooctowego) oraz Etienne[87] (8% po 3 etapach, z trifluorooctanu etylu). Uzyskany związek poddałam wybranym reakcjom alkilowania i acylowania. Przykładowo, w reakcji z chlorkiem 2,4-dichlorobenzylu, w łagodnych warunkach (K_2CO_3, DMF, temperatura pokojowa), otrzymałam fluorowany analog strukturalny *Lonidaminy* (**125**), znanego leku przeciwnowotworowego.[88]

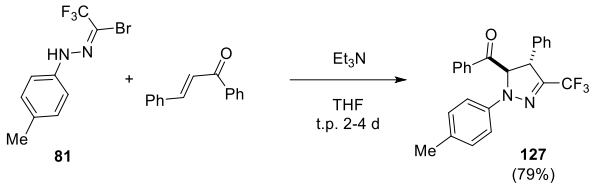


*Schemat 63. Synteza fluorowanego analogu Lonidaminy (**125**) i innych pochodnych CF_3-indazolu.*

2.2. Reakcje (3+2)-cykloaddycji nitryloimin z enonami (prace [D2, D3, D4])

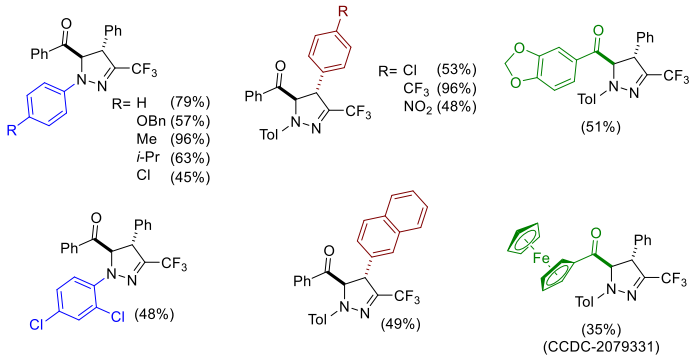
Jak wspomniano w pierwszej części rozprawy, w ostatnich dekadach wiele uwagi poświęcono opracowaniu wydajnych metod syntezy oraz transformacji pochodnych pirazolu sfunkcjonalizowanych atomami fluoru bądź grupami fluoroalkilowymi. W tym kontekście, na pierwszy plan wysuwają się pochodne 3-trifluorometylopirazolu,[22] rozpoznanego jako atrakcyjny motyw strukturalny do syntezy licznych związków bioaktywnych o potwierdzonych zastosowaniach agrochemicznych i medycznych. Mając na uwadze powyższe fakty oraz wciąż znikomą liczbę doniesień na temat zastosowań imin trifluoroacetonitrylu **80** do otrzymywania wspomnianego heterocykla, w ramach kolejnego wątku pracy doktorskiej podjęłam badania mające na celu sprawdzenie możliwości wykorzystania do tego celu chalkonów (a także innych enonów) jako grupy wyjątkowo łatwo dostępnych i tanich dipolarofili, a uzyskane rezultaty stanowiły podstawę trzech publikacji oryginalnych.[89–91]

Wstępne eksperymenty wykazały, że (3+2)-cykloaddycje chalkonów z nitryloiminami zachodzą w roztworach organicznych (suchy THF, Et_3N jako zasada) już w temperaturze pokojowej i w ciągu kilku dni prowadzą do spodziewanych pochodnych *trans*-5-benzoilo-4,5-dihydropirazolu **127** jako głównych lub jedynych produktów międzycząsteczkowych (*Schemat 64*).[89]



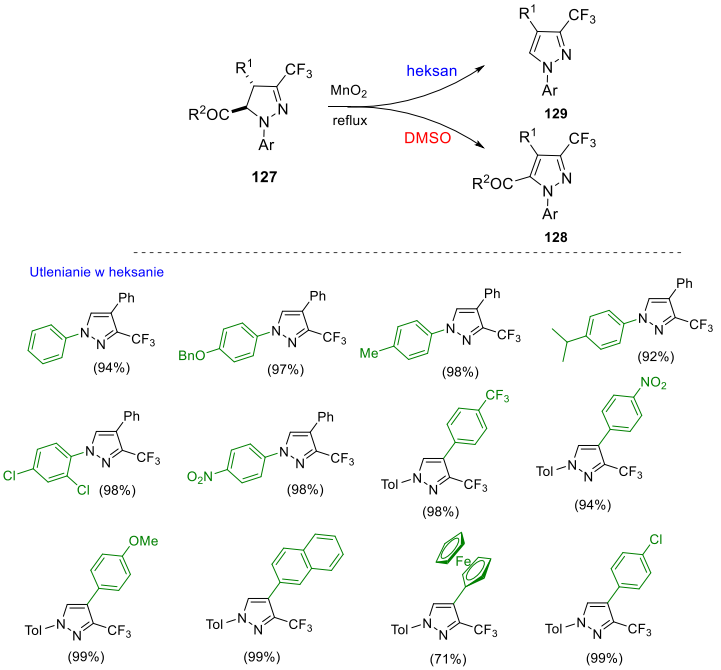
*Schemat 64. Reakcja modelowej nitryloiminy z chalkonem prowadząca do pochodnej 5-benzoilopirazoliny **127**.*

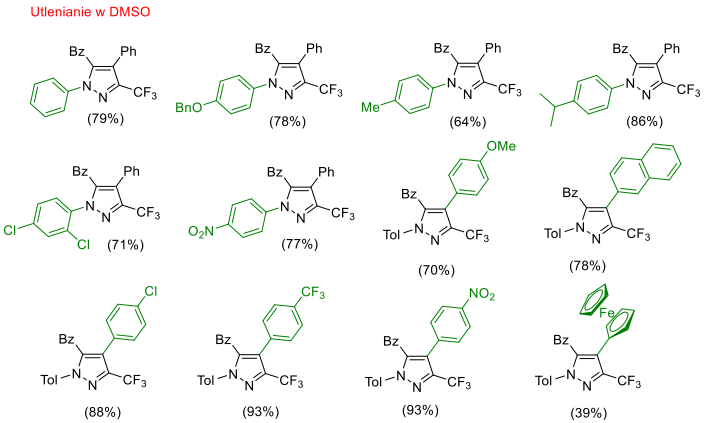
W nielicznych przypadkach obserwowałam obecność śladowych ilości drugiego regioizomeru tj. 4-acylopirazolin (zwykle w stosunku ok. 25:1). Pożądane produkty izolowałam metodami chromatograficznymi (kolumna lub sączenie przez cienką warstwę silikażelu), a następnie charakteryzowałam standardowymi metodami spektroskopowymi; w kilku przypadkach strukturę dodatkowo potwierdziły pomiary rentgenograficzne (*Rysunek 5*).



*Rysunek 5. Struktury wybranych pirazolin typu **127**.*

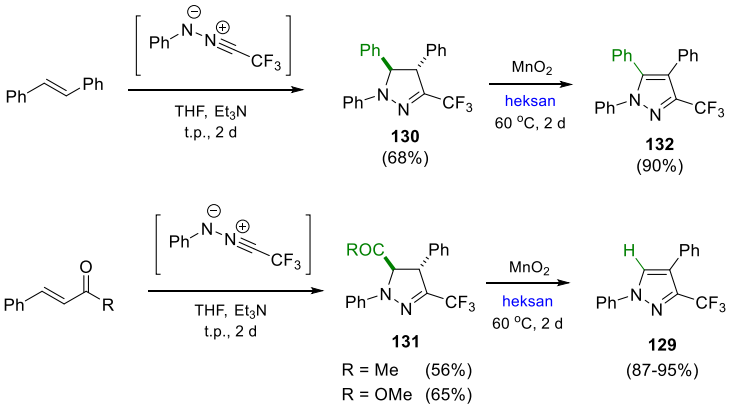
Kolejny etap pracy realizowany wspólnie z dr Gretą Utecht-Jarzyńską miał na celu znalezienie optymalnych warunków aromatyzacji powyższych pirazolin **127**. Spośród przetestowanych utleniaczy (np. $K_3[Fe(CN)_6]$, DDQ, IBX, $NaIO_4$) najlepsze rezultaty zanotowaliśmy w przypadku aktywowanego tlenku manganu(IV) (MnO_2), skutecznego m.in. w utlenianiu niektórych związków karbonylowych w łagodnych warunkach.[92] Co więcej, w trakcie badań optymalizacyjnych ujawnił się silny efekt rozpuszczalnikowy tego utleniacza wobec pirazolin **127**. I tak, w reakcjach prowadzonych w rozpuszczalnikach polarnych (DMSO lub DMF) uzyskiwałam spodziewane produkty utleniania dehydrogenatywnego (produkty typu **128**), podczas gdy w analogicznych reakcjach realizowanych w takich rozpuszczalnikach niepolarnych jak heksan lub toluen, jako wyłączne produkty wydzielałam pirazole **129**, powstające wskutek utleniania deacylującego (*Schemat 65*).





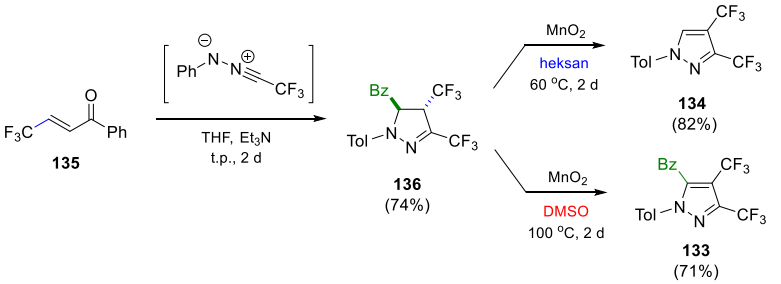
*Schemat 65. Efekt rozpuszczalnikowy w reakcji utleniania 5-acylo-3-CF_3-pirazolin **127** przy użyciu aktywowanego MnO_2 oraz struktury wybranych par produktów typu **128** i **129**.*

Aby sprawdzić zakres stosowalności metody deacylatywnego utleniania przy użyciu MnO_2, przygotowałam trzy kolejne pirazoliny (typu **130** i **131**; pochodną stilbenu, (*E*)-4-fenylo-3-buten-2-onu oraz cynamonianu metylu). W analogicznych warunkach reakcji prowadzonych w heksanie, w temperaturze 60 °C, jako wyłączne produkty utleniania otrzymałam odpowiednie pochodne pirazolu **132** oraz **129**, z atomem wodoru w pozycji C(5) (*Schemat 66*). Te wyniki wskazują, że pirazoliny sfunkcjonalizowane grupą acylową (Ac) lub metoksykarbonylową (COOMe) również ulegają preferencyjnej dekarboksylatywnej aromatyzacji indukowanej MnO_2.



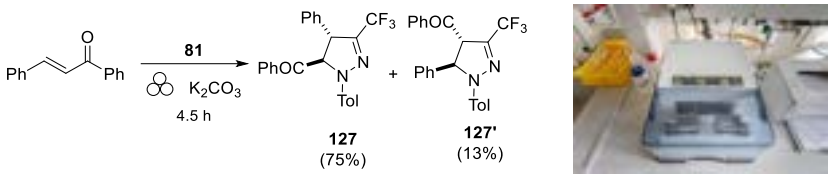
*Schemat 66. Utlenianie pochodnych pirazoliny **130** i **131** przy pomocy MnO_2, w heksanie.*

Co więcej, opracowaną metodę skutecznie zaadaptowałam do syntezy dwóch modelowych bis-trifluorometylowanych pochodnych pirazolu **133** (otrzymanego w wariancie dehydrogenatywnym) oraz **134** (uzyskanego w wariancie deacylującym), jako że pochodne tego typu wzbudzają duże zainteresowanie ze strony przemysłu agrochemicznego.[93,94] W tym celu jako dogodny dipolarofil wykorzystałam dostępny w Zespole (*E*)-4,4,4-trifluoro-1-fenylo-2-buten-1-on (**135**), który w reakcji z nitryloiminą **80** dostarczył kluczowy półprodukt – pirazolinę **136**, wyizolowaną z wydajnością 74% (*Schemat 67*).



*Schemat 67. Synteza oraz utlenianie bis-trifluorometylowanych pochodnych pirazoliny **136**.*

Opisane powyżej reakcje (3+2)-cykloaddycji nitryloimin z chalkonami prowadzone w klasyczny sposób tj. z użyciem rozpuszczalnika organicznego (THF) oraz Et_3N jako zasady przebiegają w wysoce regio- oraz całkowicie diastereoselektywny sposób, jednakże, typowy czas reakcji wynosił 2-4 dni, a wydajności produktów **127** były zmienne, w zakresie 44-96%. Z tego powodu, celem kolejnego wątku badań było sprawdzenie możliwości prowadzenia powyższych reakcji bez użycia rozpuszczalnika, w warunkach aktywacji mechanochemicznej.[90,95,96] Zaproponowane podejście okazało się dogodnym narzędziem do syntezy 1,3,4-tripodstawionych fluorowanych pochodnych pirazolu na drodze deacylującego utleniania pośrednich 5-acylopirazolin, choć warto zaznaczyć pewne różnice w odniesieniu do standardowych metod stosowanych wcześniej. Przede wszystkim, zastosowanie młyna kulowego oraz K_2CO_3 jako zasady pozwoliło zredukować czas reakcji do <20 godzin oraz zwiększyć wydajność syntezy, jednakże, kosztem regioselektywności (we wszystkich przypadkach uzyskano mieszaniny regioizomerów **127**/**127'**, zwykle w stosunku ca. 4:1) (*Schemat 68*).

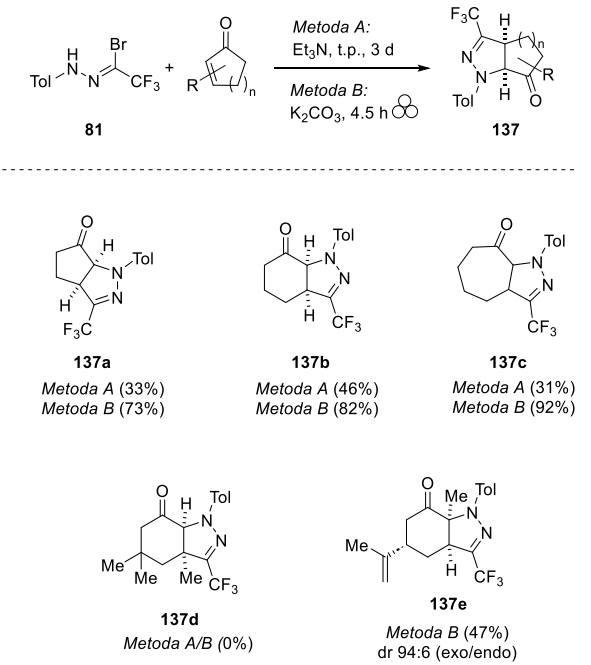


*Schemat 68. Produkty **127** i **127'** powstające podczas mechanochemicznie indukowanej (3+2)-cykloaddycji modelowej nitryloiminy typu **80** z chalkonem oraz fotografia stosowanego młyna kulowego.*

Następnie sprawdziłam przebieg indukowanej mechanochemicznie reakcji utleniania pirazolin **127** z użyciem MnO_2. Jak opisano wcześniej, w wariancie tradycyjnym (tj. w roztworze) w zależności od polarności użytego rozpuszczalnika utlenianie przebiegało deacylująco (heksan, 60 °C, 2 dni) lub na sposób dehydrogenatywny (DMSO, 100 °C, 2 dni). Zastosowanie młyna kulowego w reakcji utleniania **127** przy pomocy nadmiaru aktywowanego MnO_2 pozwoliło zredukować czas transformacji do

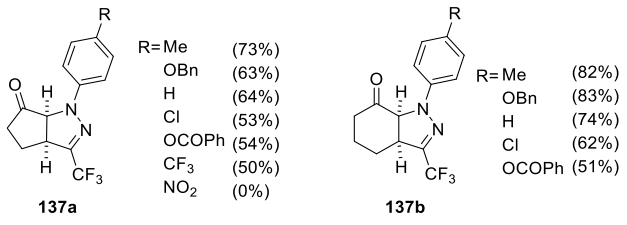
1.5 godziny, a jako jedyne produkty otrzymywane były 5-niepodstawione pochodne 3-CF_3-pirazolu typu **129**, powstające na drodze deacylatywnej aromatyzacji. W publikacji zaproponowano mechanizm studiowanej reakcji oraz wskazano zakres metody mechanochemicznej, obejmujący szeroki wachlarz fluorowanych, jak również niefluorowanych nitryloimin oraz różnorodnie sfunkcjonalizowane chalkony.

Logicznym rozwinięciem podjętych badań było włączenie enonów cyklicznych jako związków wyjściowych, które w wyniku (3+2)-cykloaddycji z nitryloiminami **80** powinny prowadzić do odpowiednich bicyklicznych pirazolin **137**. Następcze deacylujące utlenianie półproduktów **137** powinno otworzyć dostęp do ważnej grupy kwasów alkanokarboksylowych sfunkcjonalizowanych w pozycji ω pierścieniem 3-CF_3-pirazol-4-ylowym.[91] Istotnie, w reakcjach (3+2)-cykloaddycji wybranych cykloenonów z modelową nitryloiminą **80**, realizowanych analogicznie do opracowanych wcześniej procedur ogólnych tj. w roztworze (*Metoda A)* lub w warunkach indukcji mechanochemicznej (*Metoda B*), otrzymałam spodziewane produkty *cis*-bicykliczne typu **137** z bardzo dobrymi wydajnościami 73-92% w drugim przypadku (*Metoda B*) (*Schemat 69*). Jedynie w reakcji z zastosowaniem izoforonu w roli dipolarofila, pomimo całkowitej konsumpcji substratów, otrzymałam skomplikowaną mieszaninę poreakcyjną w której nie zidentyfikowałam oczekiwanego produktu (3+2)-cykloaddycji. Z drugiej strony, w reakcji enancjomerycznie czystego (*S*)-karwonu z nitryloiminą, w młynie kulowym, otrzymałam spodziewany cykloaddukt **137e** jako jedyny produkt reakcji, który wyizolowałam z wydajnością 47% (dr, exo/endo 94:6). Zaobserwowana doskonała chemo- oraz wysoka diastereo-selektywność tej reakcji dobrze koresponduje z wcześniej opisanymi wynikami eksperymentalnymi oraz teoretycznymi dotyczącymi selektywności (3+2)-cykloaddycji karwonu z klasycznymi nitryloiminami diarylowymi.[97,98]



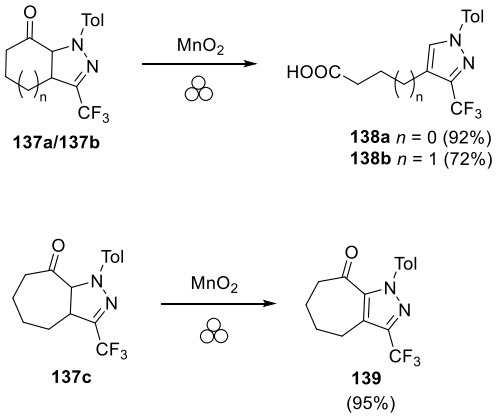
*Schemat 69. Synteza bicyklicznych pirazolin **137** w reakcji (3+2)-cykloaddycji enonów cyklicznych z nitryloiminami **80**.*

Następnie zbadałam zakres stosowalności metody w odniesieniu do charakteru elektronowego podstawników obecnych w pierścieniu aromatycznym nitryloiminy **80**, i w reakcjach wobec 2-cyklopentenonu oraz 2-cykloheksenonu uzyskałam *cis*-bicykliczne pirazoliny **137a** oraz **137b**. Jak pokazano na *Rysunku 6*, wraz ze wzrostem elektrono-akceptorowego charakteru podstawnika ulokowanego na *N*-końcu 1,3-dipola obserwowałam spadek wydajności reakcji, a w przypadku pochodnej sfunkcjonalizowanej grupą NO_2, nie uzyskałam pożądanego produktu.



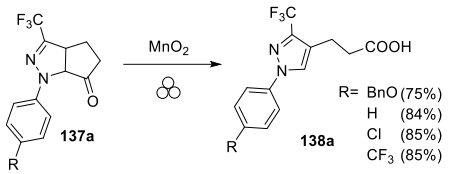
*Rysunek 6. Struktury bicyklicznych pirazolin **137a** i **137b** pochodnych 2-cyklopentenonu oraz 2-cykloheksenonu.*

Mając w ręku pirazoliny **137**, wybrane pochodne przetestowałam w reakcji utleniania (wariant mechanochemiczny) z użyciem nadmiaru aktywowanego MnO_2 *(Schemat 70)*, obserwując interesujący zmienny przebieg reakcji zależny od rozmiaru pierścienia pochodzącego od cykloenonu. I tak, w przypadku utleniania pochodnej 2-cyklopentenonu **137a** otrzymałam wyłącznie kwas **138a** (92%) jako produkt utleniania deacylującego. Utlenianie wyższego homologu **137b** w analogicznych warunkach również prowadziło do odpowiedniego kwasu **138b** (72%), ale w mieszaninie zidentyfikowałam niewielkie ilości bicyklicznego pirazolu **138b'** jako produktu utleniania dehydrogenatywnego. Natomiast utlenianie pochodnej 2-cykloheptenonu **137c** prowadziło wyłącznie do aromatycznego produktu bicyklicznego **139** (95%). Należy przypuszczać, że obserwowany trend związany jest ze znanym problemem naprężeń torsyjnych w układach bicyklicznych i w przypadku najbardziej naprężonej pochodnej 2-cyklopentenonu **137a** (a także homologu **137b** pochodnego 2-cykloheksenonu) faworyzowany jest deacylatywny wariant aromatyzacji.



*Schemat 70. Deacylatywny vs. dehydrogenatywny przebieg reakcji utleniania bicyklicznych pirazolin **137** przy użyciu MnO_2.*

Konsekwentnie, wychodząc z odpowiednich bicyklicznych pirazolin **137a** pochodnych 2-cyklopentenonu, w mechanochemicznej reakcji utleniania deacylatywnego indukowanego aktywowanym MnO_2, otrzymałam serię docelowych kwasów propionowych **138a** sfunkcjonalizowanych w pozycji C(3) grupą 3-CF_3-pirazol-4-ylową (*Schemat 71*). Produkty przekazano stałym współpracownikom Zespołu do dalszych badań pod kątem analizy ich aktywności przeciwzapalnej i przeciwnowotworowej. Ponadto, aby zademonstrować użyteczność kwasów typu **138a** w syntezie bardziej złożonych pochodnych, wybrany kwas karboksylowy przekształciłam w odpowiedni ester metylowy oraz *N*-benzyloamid, w standardowych warunkach syntezy estrów (metoda Fischera) i amidów (reakcja przez chlorek kwasowy).



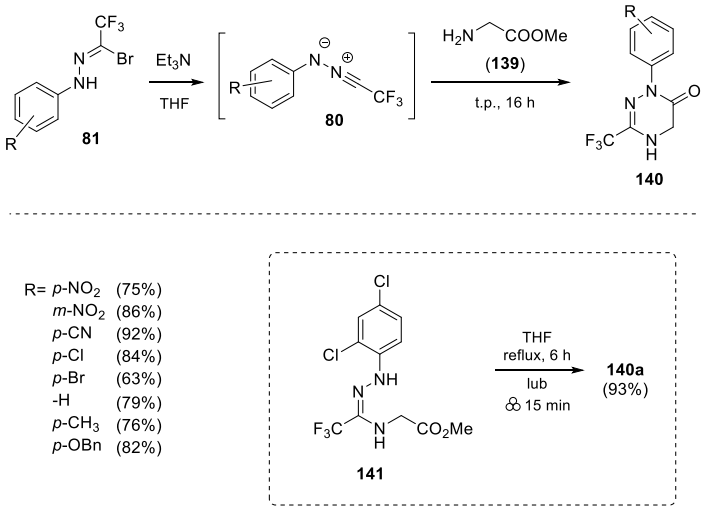
*Schemat 71. Synteza docelowych kwasów propionowych **138a** w reakcji deacylatywnego utleniania bicyklicznych pirazolin **137a**.*

2.3. Reakcje (3+3)-annulacji z α-aminoestrami (prace [D5, D6])

Jak zasygnalizowano w części literaturowej niniejszej rozprawy, w ostatnim czasie w naszym Zespole opracowano reakcje (3+3)-annulacji trifluorometylowanych nitryloimin ze związkami α-merkaptokarbonylowymi, prowadzące do 6-członowych produktów pochodnych 1,3,4-tiadiazyny.[76] Mając na uwadze fakt, że estry α-aminokwasów mają podobne do związków α-merkaptokarbonylowych położenie grup funkcyjnych (geminalne centrum nukleofilowe i elektrofilowe), podjęłam próbę wykorzystania tych pierwszych w syntezie dotychczas nieznanych 3-trifluorometylowanych pochodnych 1,2,4-triazyny.[99] W ramach przygotowań merytorycznych do tego zadania, zebrałam doniesienia literaturowe na temat metod syntezy pokrewnych, fluorowanych i niefluorowanych 1,2,4-triazyn, które zreferowałam w formie krótkiej pracy przeglądowej.[100]

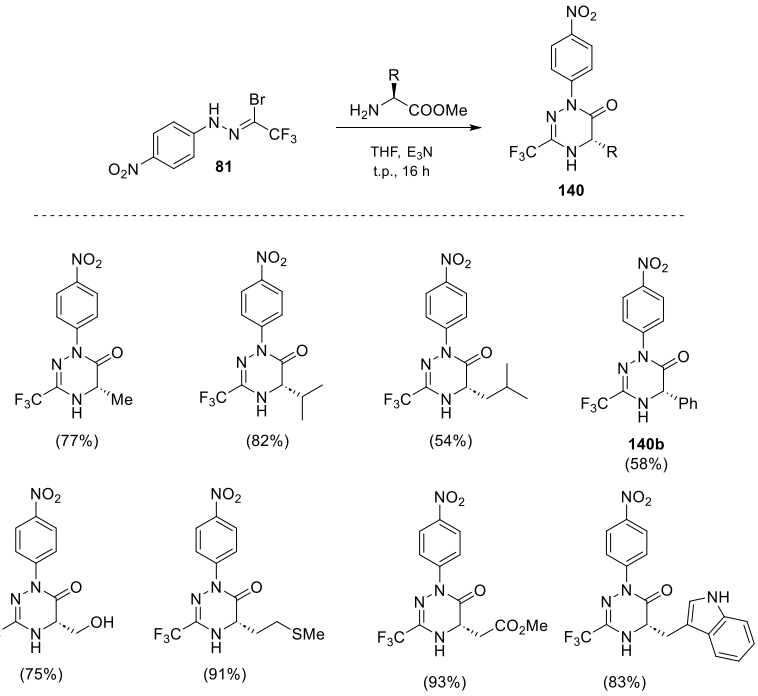
Wstępne eksperymenty prowadziłam w klasycznych warunkach (roztwory organiczne, Et_3N jako zasada, temperatura pokojowa) z użyciem nitryloiminy **80** oraz estru metylowego glicyny (**139**) i we wszystkich próbach uzyskałam spodziewany produkt (3+3)-annulacji **140** (*Schemat 72*), który izolowałam z wydajnością >70%. Strukturę **140** (R = NO_2) potwierdziłam w oparciu o standardowe pomiary spektroskopowe; przykładowo, w widmie ^{1}H NMR znalazłam przy δ = 4.30 poszerzony dublet (J ≈ 1.5 Hz), który przypisałam atomom wodoru grupy C(5)-H_2, a także charakterystyczne absorpcje od grup NH i $C_6H_4NO_2$, odpowiednio przy δ = 5.31 (poszerzony

singlet) oraz δ = 7.92 i δ = 8.27 (system AB). Z kolei w widmie ^{13}C NMR znalazłam diagnostyczne kwartety przy δ = 118.2 ($^{1}J_{C\text{-}F}$ = 275.2 Hz) oraz δ = 137.3 ($^{2}J_{C\text{-}F}$ = 37.8 Hz), które przypisałam, odpowiednio, grupie CF_3 oraz atomowi C(3) pierścienia 1,2,4-triazyn-6-onu **140**. Podobnie, zgodnie z oczekiwaniem w widmie ^{19}F NMR obecny był pojedynczy sygnał (singlet) od grupy CF_3, zlokalizowany przy δ = 70.6. Zakres stosowalności metody względem charakteru elektronowego podstawnika obecnego w pierścieniu aromatycznym nitryloiminy zbadałam stosując glicynian metylu (**139**) uzyskując spodziewane produkty annulacji typu **140**, które na ogół wydzielałam z bardzo dobrymi wydajnościami (63-93%). Jedynie w przypadku wysoce zubożonej elektronowo nitryloiminy **140a**, sfunkcjonalizowanej na *N*-końcu grupą 2,4-dichlorofenylową, jako produkt główny wydzieliłam pośredni produkt addycji nukleofilowej **141**, który ulegał cyklizacji dopiero w bardziej agresywnych warunkach (gorący THF lub młyn kulowy).



*Schemat 72. Synteza pochodnych 1,2,4-triazyny **140** w reakcji (3+3)-annulacji fluorowanych nitryloimin **80** z estrami aminokwasów.*

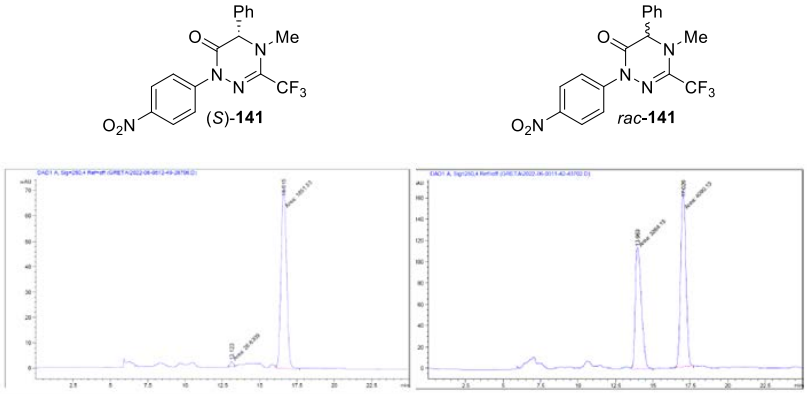
W kolejnych eksperymentach przetestowałam serię wybranych α-aminoestrów wobec nitryloiminy **80** (R = NO_2). Także w tych przypadkach, otrzymałam spodziewane pochodne 1,2,4-triazyn-6-onu **140**, które wydzieliłam z dobrymi wydajnościami, niezależnie od rodzaju podstawnika w pozycji α wyjściowego aminoestru (np. alkil, aryl, podstawniki zawierające takie grupy funkcyjne jak hydroksylowa, estrowa, tioeterowa oraz indolowa). Wybrane produkty tej serii przedstawiono na *Schemacie 73*.



*Schemat 73. Reakcja modelowej nitryloimny **80** (R = NO_2) z α-aminoestrami.*

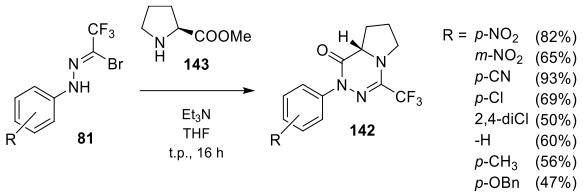
Zasadnicze pytanie w przypadku transformacji z wykorzystaniem chiralnych, enancjomerycznie czystych substratów dotyczy stopnia czystości optycznej produktów. Aby sprawdzić czy na etapie cyklizacji nie dochodzi do racemizacji, podjęłam próby ustalenia czystości w przypadku pochodnej (*S*)-fenyloglicyny **140b**, jako teoretycznie najbardziej podatnego na

racemizację związku w serii posiadającego centrum chiralności w pozycji benzylowej. Dla celów porównawczych przygotowałam próbkę racemicznego produktu *rac*-**140b** wychodząc z handlowo dostępnego racematu fenyloglicynianu metylu. Nieoczekiwanie, ani standardowe pomiary NMR z zastosowaniem chiralnych odczynników solwatujących (kwas (+)-(*S*)-migdałowy, kwas (+)-(*R*)-(*tert*-butylo)(fenylo)fosfonotionowy) ani analizy HPLC na chiralnym podłożu nie dały jednoznacznych rezultatów, być może ze względu na obecność wolnej grupy NH w pochodnej **140b** (możliwa tautomeria N(1)-N(3)). Z tego powodu, przekształciłam oba 1,2,4-triazyn-6-ony **140b** i *rac*-**140b** w odpowiednie pochodne *N*-metylowe **141** oraz *rac*-**141**, a analiza HPLC potwierdziła czystość optyczną pierwszej z nich (*Rysunek 7*).



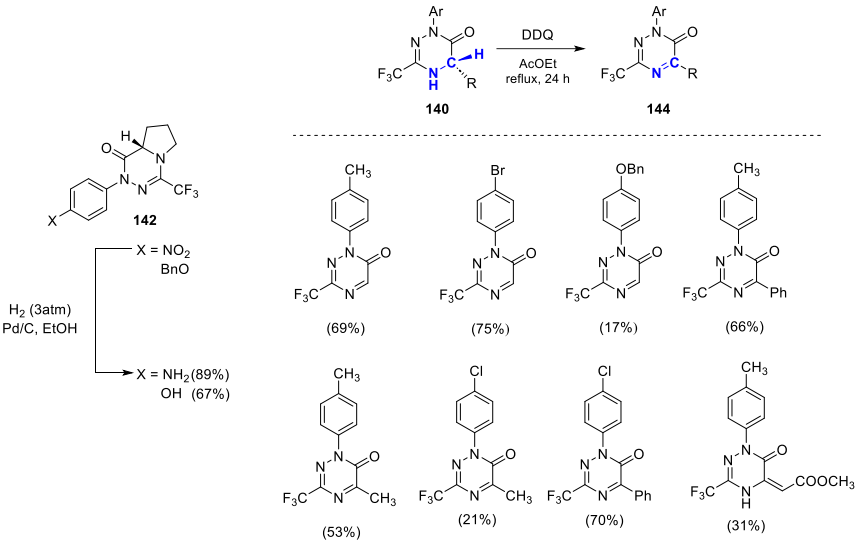
*Rysunek 7. Chromatogramy optycznie czystej pochodnej **141** oraz rac-**141**.*

Równolegle, magistrant z Zespołu Kamil Świątek, podjął pracę w kierunku syntezy produktów bicyklicznych typu **142**, pochodnych proliny (*Schemat 74*). W analogicznych warunkach reakcji (3+3)-annulacji L-prolinianu metylu **143** z fluorowanymi nitryloiminami uzyskał serię enancjomerycznie czystych produktów **142**, obserwując nieznaczny wpływ charakteru elektronowego podstawników obecnych w 1,3-dipolu na wydajność reakcji (spadek wydajności wraz ze wzrostem charakteru elektronodonorowego).



*Schemat 74. Synteza bicyklicznych 1,2,4-triazyn **142** w reakcji (3+3)-annulacji nitryloimin **80** z L-prolinianem metylu **143**.*

Aby sprawdzić trwałość układu bicyklicznego w związkach typu **142**, przeprowadzono wybrane transformacje grup funkcyjnych (*Schemat 75*). Przykładowo, w warunkach katalitycznego uwodornienia (H_2, Pd/C) można było skutecznie zredukować grupę nitrową oraz odbezpieczyć eter benzylowy, co otwiera nowe możliwości dla funkcjonalizacji związków typu **142** poprzez wykorzystanie grup NH_2 oraz OH. Z drugiej strony, zaobserwowałam dużą podatność pierścienia w monocyklicznych 1,2,4-triazyn-6-onach **140** na chemoselektywne utlenianie wiązania C–N. I tak, w reakcjach z DDQ, we wrzącym AcOEt, otrzymałam serię trifluorometylowanych 1,2,4-triazyn **144** (*Schemat 75*). Warto nadmienić, że wstępne badania biologiczne tej serii wykazały, że produkty **144** pochodne glicyny wykazują wzmożoną aktywność przeciwgrzybiczą i przeciwnowotworową.[101]



*Schemat 75. Wybrane transformacje pochodnych 1,2,4-triazyny **140** i **142**.*

Podsumowanie

Głównym celem niniejszej rozprawy było zbadanie reaktywności trzech wybranych grup odczynników organicznych wobec unikatowej klasy trifluorometylowanych nitryloimin, jako wciąż mało poznanych ale bardzo użytecznych 1,3-dipoli generowanych *in situ*. W ramach pracy eksperymentalnej przebadałam reakcje tytułowych nitryloimin wobec arynów, enonów oraz estrów aminokwasów, a uzyskane rezultaty podsumowane zostały w pięciu publikacjach oryginalnych, jak również były rozpowszechniane na kilkudziesięciu konferencjach krajowych i zagranicznych.

W ramach wątku dotyczącego wykorzystania arynów jako wzbogaconych elektronowo, wysoce reaktywnych dipolarofili C≡C wykazałam, że:

(a) nitryloiminy łatwo ulegają (3+2)-cykloaddycji do benzynów prowadząc do odpowiednich pochodnych 3-CF_3-indazolu,

(b) utleniające dearylowanie pochodnej *p*-MeO-C_6H_4 otwiera łatwy dostęp do *N*-niepodstawionego 3-CF_3-indazolu, rozpoznanego jako użyteczny półprodukt m.in. w syntezie fluorowanych analogów znanych farmaceutyków.

W ramach wątku dotyczącego wykorzystania enonów jako C=C dipolarofili wobec fluorowanych nitryloimin wykazałam, że:

(a) chalkony ulegają reakcji (3+2)-cykloaddycji z nitryloiminami prowadząc do odpowiednich 5-acylo-3-CF_3-pirazolin z dobrymi wydajnościami oraz wysoką regio- i diastereoselektywnością,
(b) wspomniane powyżej pirazoliny ulegają wydajnej aromatyzacji przy zastosowaniu MnO_2, przy czym w zależności od rodzaju medium utlenianie przebiega na sposób deacylatywny (heksan) lub dehydrogenatywny (DMSO),
(c) reakcje (3+2)-cykloaddycji enonów z nitryloiminami, a także utlenianie deacylatywne odpowiednich pirazolin można skutecznie realizować w wariancie mechanochemicznym,
(d) opracowaną metodę zaadaptowano do syntezy ważnej klasy kwasów 3-CF_3-pirazolo-alkanokarboksylowych.

W badaniach na reakcjami (3+3)-annulacji nitryloimin wykazałam, że:

(a) estry naturalnych aminokwasów stanowią dogodną klasę reagentów nukleofilowo-elektrofilowych do reakcji (3+3)-annulacji z trifluorometylowanymi nitryloiminami prowadząc do pochodnych 1,2,4-triazyn-6-onu z zachowaniem czystości optycznej związków wyjściowych,
(b) zastosowanie prolinianu metylu w analogicznych warunkach otwiera dostęp do odpowiednich pochodnych bicyklicznych,
(c) pierścień 3-CF_3-1,2,4-triazyn-6-onu jest trwały w warunkach łagodnego utleniania i redukcji, co pozwala na transformacje grup funkcyjnych i otwiera możliwość dalszej funkcjonalizacji.

3. Pozostała działalność naukowa

3.1. Udział w projektach naukowo-badawczych

G1 2023-2024, Kierownik grantu Inicjatywa Doskonałości Uczelnia Badawcza – Uniwersytet Łódzki, numer grantu: 9/DGB/2022 *„Fluorowane benzodipirazole o symetrii płaszczyznowej i osiowej”* (Opiekun grantu: dr hab. Marcin Jasiński, prof. UŁ)

G2 2021-2024, Wykonawca grantu Inicjatywa Doskonałości Uczelnia Badawcza – Uniwersytet Łódzki, numer grantu: 3/IDUB/DOS/2021 *„Synteza i analiza aktywności przeciwnowotworowej trifluorometylowanych 1,2,4-triazyn-6-onów”* (Kierownik grantu: dr hab. Marcin Jasiński, prof. UŁ)

G3 2017-2018, Kierownik grantu Studenckie Granty Badawcze Uniwersytetu Łódzkiego *„Synteza pochodnych N-fosfonometyloleucyny i badania ich właściwości ekotoksykologicznych”* (Opiekun grantu: prof. Jarosław Lewkowski)

3.2. Zgłoszenia patentowe

Z1 M. Jasiński, A. Kowalczyk, G. Utecht-Jarzyńska
Sposób wytwarzania kwasów 3-(3-trifluorometylopirazol-4-ylo)propanowych
Zgłoszenie nr P.445908 (25.08.2023)

3.3. Wykaz pozostałych publikacji niewchodzących w skład rozprawy doktorskiej

D7 D. Rogacz, J. Lewkowski, M. Siedlarek, R. Karpowicz, A. Kowalczyk
The Effect of New Thiophene-Derived Diphenyl Aminophosphonates on Growth of Terrestrial Plants
Materials **2019**, 12(*12*), 2018

3.4. Spis komunikatów konferencyjnych

3.4.1. Wystąpienia ustne

K1 A. Kowalczyk, K. Świątek, G. Utecht-Jarzyńska, M. Jasiński *„Wykorzystanie imin trifluoroacetonitrylu w syntezie fluorowanych pochodnych 1,2,4-triazyn-6-onu*" X Łódzkie Sympozjum Doktorantów Chemii (Łódź, 18-19.05.2023)

K2 A. Kowalczyk, G. Utecht-Jarzyńska, K. Świątek, M. Jasiński, "*The CF_3-nitrile imine: valuable building block for the synthesis of 3-trifluoromethylpyrazoles",* 20th European Symposium on Fluorine Chemistry, (Berlin, 14-19.08 2022)

K3 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, „*Polipodstawione 3-trifluorometylopirazole: synteza poprzez deacylujące utlenianie pirazolin",* XII Zjazd Magistrantów i Doktorantów Łódzkiego Środowiska Chemików (e-Zjazd, 17.06.2021)

K4 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, „*Wpływ rozpuszczalnika na utlenianie trifluorometylowanychpochodnych pirazoliny tlenkiem manganu(IV)*", e-Zjazd Wiosenny Sekcji Studenckiej Polskiego Towarzystwa Chemicznego (e- Zjazd, 27-29.05.2021)

K5 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, „*Synteza pochodnych 1H-indazolu w reakcji (3+2)-cykloaddycji arynow z iminami trifluoroacetonitrylu*", e-Zjazd Zimowy Sekcji Studenckiej Polskiego Towarzystwa Chemicznego (e-Zjazd, 19.12.2020)

3.4.2. Wystąpienia posterowe

K6 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński *„ Zastosowanie nitryloimin w syntezie trifluorometylowanych kwasów pirazolylo-alkanokarboksylowych"* Zjazd Zimowy Sekcji Młodych Polskiego Towarzystwa Naukowego (Łódź, 09.12.2023) Komunikat został **wyróżniony** nagrodą za najlepszy plakat od firmy RYVU Therapeutics S.A.

K7 A. Kowalczyk, K. Świątek, G. Utecht-Jarzyńska, M. Jasiński *„CF_3-nitrile imines: new applications in the synthesis of pyrazole derivatives”* XVth Mini-Symposium on Current Problems of Organic Chemistry (Łódź, 15.09.2023)

K8 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński *„CF_3-nitrile imines: new applications in the synthesis of pyrazole derivatives”* 22nd European Symposium on Organic Chemistry (Gandawa (Belgia), 09-13.07.2023)

K9 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński *„Trapping of in situ generated trifluoroacetonitrile imines with electron-rich dipolarophiles”* 7th Fluorine Days (Poznań, 18-22.06.2023)

K10 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, *„Addycje fluorowanych nitryloimin do dipolarofili C=C/C≡C”* Zjazd Wiosenny Sekcji Młodych Polskiego Towarzystwa Chemicznego (Chęciny, 3-7.05.2023)

K11 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, *„Synteza pochodnych pirazoli w reakcji mechanochemicznego deacylującego utleniania 5-acylopirazolin”* Zjazd Zimowy Sekcji Młodych Polskiego Towarzystwa Chemicznego (Opole, 10.12.2022)

K12 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, *„Polyfunctionalized pyrazoles through mechanochemical deacylative oxidation of 5-acylpyrazolines”*, XXIII International Symposium “Advances in the Chemistry of Heteroorganic Compounds” (Łódź, 28.10.2022)

K13 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, *„Polyfunctionalized pyrazoles through mechanochemical deacylative oxidation of 5-acylpyrazolines”*, XVth International Mini-Symposium on Current Problems in Organic Chemistry (Łódź, 27.10.2022)

K14 A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński, *„Synthesis of polysubstituted 3-trifluoromethylpyrazole derivatives via solvent-dependent oxidations of 5-acylpyrazolines”,* 10th International Meeting on Halogen Chemistry (Łódź, 05-08.09.2022)

K15 A. Kowalczyk, K. Świątek, G. Utecht-Jarzyńska, M. Jasiński, *„Fluorinated 1,2,4-triazin-6(1H)-ones through (3+3)-annulation of trifluoroacetonitrile imine*”, 20th European Symposium on Fluorine Chemistry (Berlin, 14-19.08.2022)

K16 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, „Access to *trifluoromethylated ω-(1H-pyrazol-4-yl)-alkanoic acids through deacylative oxidation of bicyclic pyrazolines"*, 22nd Tetrahedron Symposium Catalysis for a Sustainable World, (Lizbona, 28.06–01.07.2022)

K17 A. Kowalczyk, I. Sieja, G. Utecht-Jarzyńska, M. Jasiński, *„Synteza i wybrane transformacje bicyklicznych 3-trifluorometylopirazolin"*, IX Łódzkie Sympozjum Doktorantów Chemii (Łódź, 19-20.05.2022)

K18 A. Kowalczyk, M. Celeda, G. Utecht-Jarzyńska, M. Jasiński, *„Iminy trifluoroacetonitrylu w akcji, czyli dostęp do fluorowanych pochodnych 1,2,4-triazyn-6-onów w jednym akcie"*, Zjazd Zimowy Sekcji Młodych Polskiego Towarzystwa Chemicznego (Poznań, 29.01.2022)

K19 A. Kowalczyk, M. Celeda, G. Utecht-Jarzyńska, M. Jasiński, *„Trifluorometylowane 1,2,4-triazynony pochodne aminokwasów naturalnych*", 63 Zjazd Naukowy Polskiego Towarzystwa Chemicznego (e-Zjazd, 13-16.092021)

K20 A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, *„Synthesis of CF_3-functionalized heterocycles by trapping in situ-generated trifluoroacetonitrile imines with electron-rich dipolarophiles*", 21st Tetrahedron Symposium (e-Zjazd, 21-24.06.2021)

K21 G. Utecht-Jarzyńska, A. Kowalczyk, M. Jasiński, *„Access to trifluoromethylated indazoles by trapping of arnes with in situ generated trifluoroacetonitrile imines*" "Advances in the Chemistry of Heteroorganic Compounds" (Łódź, 22.11.2019)

K22 A. Kowalczyk, **"***Badania nad syntezą i właściwościami herbicydowymi C,C'-dipodstawionych pochodnych N-fosfonometyloglicyny***"**, X Sesji Magistrantów i Doktorantów Łódzkiego Środowiska Chemików (Łódź, 04.06.2019) Komunikat został **nagrodzony** Wyróżnieniem Dziekana Wydziału Chemii Uniwersytetu Łódzkiego

K23 A. Kowalczyk, "*Optymalizacja wybranych doświadczeń z chemii organicznej jako pomoc w pracy początkującego nauczyciela*.", X Sesji

Magistrantów i Doktorantów Łódzkiego Środowiska Chemików (Łódź, 4.06.2019)

K24 A. Kowalczyk, J. Lewkowski, R. Karpowicz, P. Rychter, D. Rogacz, „*Synthesis of C-substituted derivatives of N-phosphonomethylleucine* XXI International Symposium „Advances in the Chemistry of Heteroorganic Compounds" (Łódź, 23.11.2018)

K25 A. Kowalczyk, J. Lewkowski, D. Rogacz, P. Rychter, „*Synteza pochodnych N-fosfonometyloleucyny i badania ich właściwości ekotoksykologicznych*", 61 Zjazd Naukowy Polskiego Towarzystwa Chemicznego (Kraków, 17-21.09.2018)

3.5. Pozostała działalność

P1 Opieka nad eksperymentalną pracą licencjacką: Izabela Sieja *„Bicykliczne pirazoliny Pochodne fluorowanych nitryloimin"* Uniwersytet Łódzki (2022)

P2 2019-2023 udział w przygotowywaniu oraz przeprowadzaniu serii pokazów w ramach *Akademii Ciekawej Chemii* organizowanej na Wydziale Chemii Uniwersytetu Łódzkiego

P3 14-25.01.2018 praktyki w Zespole dr hab. Piotra Rychtera, prof. UJD w Katedrze Biochemii, Biotechnologii i Ekotoksykologii Wydziału Nauk Ścisłych, Przyrodniczych i Technicznych Uniwersytetu Jana Długosza w Częstochowie

P4 16.07-27.09.2018 staż w Centrum Transfer Technologii UŁ realizowanego w ramach projektu „Staż na Start" przez Biuro Karier UŁ

P5 2016-2024 członek oraz przewodnicząca (2018-2020) *Naukowego Koła Chemii Kosmetycznej* działającego na Wydziale Chemii Uniwersytetu Łódzkiego

P6 2016-1017 przygotowywanie oraz przeprowadzanie zajęć laboratoryjnych w ramach programu *Uniwersytet Łódzki dla dzieci*

Bibliografia

[1] P. Kirsch **2004**, *Modern Fluooroorganic Chemistry. Synthesis, Reactivity, Applications*, Wiley-VCH, ISBN 3-527-30691-9

[2] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur *Chem. Soc. Rev.* **2008**, *37*, 320-330 https://doi.org/10.1039/B610213C

[3] D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308-319, https://doi.org/10.1039/B711844A

[4] V. Nenajdenko (Red.) **2014**, *Fluorine in Heterocyclic Chemistry 5-Membered Heterocycles and Macrocycles* Springer https://doi.org/10.1007/978-3-319-04346-3

[5] Y. Liu, L. Jiang, H. Wang, H. Wang, W. Jiao, G. Chen, P. Zhang, D. Hui, X. Jian *Nanotechnology Reviews* **2019**, *8*(1), 573-586 https://doi.org/10.1515/ntrev-2019-0051

[6] X. Chen K. Fan, Y. Liu, Y. Li, X. Liu, W. Feng, X. Wang *Adv. Mater*. **2022** *34*, 2101665 https://doi.org/10.1002/adma.202101665

[7] Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata *iScience 23* **2020**, 101467 https://doi.org/10.1016/j.isci.2020.101467

[8] C. Zhang, K. Yan, C. Fu, H. Peng, C. J. Hawker, A. K. Whittaker *Chem. Rev.* **2022**, *122*(1), 167-208 https://doi.org/10.1021/acs.chemrev.1c00632

[9] D. B. Tiz, L. Bagnoli, O. Rosati, F. Marini, L. Sanciento, C. Santi *Molecules* **2022**, *27*(5), 1643 https://doi.org/10.3390/molecules27051643

[10] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, W. A. Soloshonok, H. Liu *Chem. Rev.* **2014**, *114*(4), 2432-2506 https://doi.org/10.1021/cr4002879

[11] J. Han, A. M. Remete, L. S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V. A. Soloshonok, D. O'Hagan *J. Fluorine Chem.* **2020**, *239*, 109639 https://doi.org/10.1016/j.jfluchem.2020.109639

[12] A. Gakh, Y. Shermolovich *Curr. Top. Med. Chem.* **2014**, *14*, 952-965 doi: 10.2174/1568026614666140202210424

[13] F. Liu, B. Sameem *Targets in Heterocyclic Systems* **2021**, *14*, 502-516 https://doi.org/10.17374/targets.2022.25.502

[14] F. Meyer *Chemical Communications* **2016***, 52*, 3077-3094 https://doi.org/10.1039/c5cc09414c

[15] S. Cascioferro, B. Parrino, V. Spanò, A. Carbone, A. Montalbano, P. Barraja, P. Diana, G. Cirrincione *Eur. J. Med. Chem.* **2017,** *142*(15), 328-375 https://doi.org/10.1016/j.ejmech.2017.08.009

[16] R. Kumar, T. S. Sirohi, H. Singh, R. Yadav, R. K. Roy, A. Chaudhary, S. N. Pandeya, *Mini-Rev. Med. Chem.* **2014**, *40*, 168-207,

[17] F. Krauth, H. M. Dahse, H. H. Rüttinger, P. Frohberg *Bioorg. Med. Chem.* **2010** 1816-1821 doi: 10.1016/j.bmc.2010.01.053

[18] M. S. I. Makki, R. M. Abdel-Rahman, K. A. Khan J. Chem. **2014**, 2014, 430573 http://dx.doi.org/10.1155/2014/430573

[19] M. Sweeney, R. Coyle, P. Kavanagh, A. A. Berezin, D. L. Re, G. A. Zissimou, P. A. Koutentis, M. P. Carty, F. Aldabbadh Bioorg. Med. Chem. **2016**, 24, 3565-3570 https://doi.org/10.1016/j.bmc.2016.05.066

[20] K. Kaur, V. Kumar, G. K. Gupta *J. Fluorine Chem.* **2015**, *178*, 306-326 https://doi.org/10.1016/j.jfluchem.2015.08.015

[21] F. Mohr **2009**, *Gold Chemistry: Applications and Future Directions in the Life Sciences,* Wiley-VCH

[22] P. K. Mykhailiuk *Chem. Rev.* **2021**, *121*, 1670-1715 https://doi.org/10.1021/acs.chemrev.0c01015

[23] M. Bregust, H. U. Reissig *Angew. Chem. Int. Ed.* **2020**, *59*, 12293-12307 https://doi.org/10.1002/anie.202003115

[24] J. Jakowiecki, R. Loska, M. Mąkosza *J. Org. Chem.* **2008**, *73*, 5436-5441 https://doi.org/10.1021/jo800721w

[25] S. Bigotti, L. Malpezzi, M. Molteni, A. Mele, W. Panzeri, M. Zanda *Tetrahedron Lett.* **2009**, *21*, 2540-2542 https://doi.org/10.1016/j.tetlet.2009.03.059

[26] H. Wójtowicz-Rajchel, H. Koroniak *J. Fluor. Chem.* **2012**, 225-230 https://doi.org/10.1016/j.jfluchem.2011.11.005

[27] K. Tanaka, S. Nagatani, M. Ohsuga, K. Mitsuhashi *Bull. Chem. Soc. Jpn.* **1994**, *67*(2), 589-591 https://doi.org/10.1246/bcsj.67.589

[28] G. Tran, R. Meier, L. Harris, D. L. Browne, S. V. Ley *J. Org. Chem.* **2012**, *77*, 11071-11078 https://doi.org/10.1021/jo302052m

[29] X. Zhang, M. Liu, W. Zhang, M. Legris,W. Zhang *J. Fluorine Chem.* **2017**, *204*, 18-22 https://doi.org/10.1016/j.jfluchem.2017.10.003

[30] X.-W. Liu, J. Yue, Z. Li, D. Wu, M.-y. Tian, Q.-L. Wang, Y. Zhou, *Tetrahedron* **2020**, *76*, 131678 https://doi.org/10.1016/j.tet.2020.131678

[31] Y. Yi, Y. Z. Hua, H. J. Lu, L. T. Lu, M. C. Wang *Org. Lett.* **2020**, *22*(7), 2527-2531 https://doi.org/10.1021/acs.orglett.0c00283

[32] J. Gu, X. Li, Y. Zhang, Z. Sun, L. Li, J. Meng, R. Xing, X. Shi, Y. Fu, L. Wang, R. Guo *J. Org. Chem.* **2024**, *89*(4), 2364-2374 https://doi.org/10.1021/acs.joc.3c02377

[33] H. Gilman, R. G. Jones *J. Am. Chem. Soc.* **1943**, *65*(8), 1458-1460 https://doi.org/10.1021/ja01248a005

[34] B. Morandi, E. M. Carreira *Angew. Chem. Int. Ed.* **2010**, *49*, 938-941 https://doi.org/10.1002/anie.200905573

[35] E. Y. Slobodyanyuk, O. S. Artamonov, O. V. Shishkin, P. K. Mykhailiuk *Eur. J. Org. Chem.* **2014**, *2014*(12), 2487-2495 https://doi.org/10.1002/ejoc.201301852

[36] F. Li, J. Nie, L. Sun, Y. Zheng, J. A. Ma *Angew. Chem. Int. Ed.* **2013**, *52*, 6255-6258 https://doi.org/10.1002/anie.201301870

[37] Z. Chen, Y. Zheng, J. A. Ma, *Angew. Chem.* **2017**, *129*(16), 4640-4645 https://doi.org/10.1002/ange.201700955

[38] F. G. Zhang, Y. Wei, Y. P. Yi, J. Nie, J. A. Ma *Org. Lett.* **2014**, 3122-3125 https://doi.org/10.1021/ol501249h

[39] X. Peng, X. Zhang, S. Li, Y. Lu, L. Lan, C. Yang *Org. Chem. Front.* **2019**, *6*, 1775 doi: 10.1039/c9qo00324j

[40] S. Lv, H. Zhou, X. You, Y. Xu, H. Zhu, M. Wang, H. Liu, Z. Dai, G. Sun, X. Gong, X. Sun, L. Wang *Commun. Chem.* **2019**, *2*(69) https://doi.org/10.1038/s42004-019-0168-6

[41] X. Zhang Z. Liu, X. Yang, Y. Dong, M. Virelli, G. Zanoni, e. A. Anderson, X. Bi *Nat. Commun.* **2019**, *284* https://doi.org/10.1038/s41467-018-08253-z

[42] H. Wang, Y. Ning, Y. Sun, P. Sivaguru, X. Bi *Org. Lett.* **2020**, *22*, 2012-2016 https://doi.org/10.1021/acs.orglett.0c00395

[43] A. Kumar, S. Mathew, M. F. Jamali, S. Ahmad, R. Kant, K. Mohanan *Adv. Synth. Catal.* 2023, *365*, 2218–2224 https://doi.org/10.1002/adsc.202300322

[44] S. I. Murahashi, Y. Imada *Chem. Rev.* **2013**, *119*, 4684-4716 https://doi.org/10.1021/acs.chemrev.8b00476

[45] K. Tanaka, Y. Sugimoto Y. Okaafuji, M. Tachikawa, K. Mitsuhashi *J. Heterocycl. Chem.* **1989**, *26*, 381-385 https://doi.org/10.1002/jhet.5570260221

[46] K. Tanaka, M. Ohsuga, Y. Sugimoto, Y. Okafuji, K. Mitsuhashi *J. Fluorine Chem.* **1988**, *39*(1), 39-45 https://doi.org/10.1016/S0022-1139(00)82735-9

[47] G. Mlostoń, E. Obijalska, M. Celeda, w. Mittermeier, A. Linden, H. Heimgartner *J. Fluorine Chem.* **2014**, *165*, 27-32 https://doi.org/10.1016/j.jfluchem.2014.05.015

[48] M. Kurpianowicz, M. Kaźmierczak, E. Muszyńska, K. Bzdęga, H. Wójtowicz-Rajchel *J. Fluorine Chem.* **2018**, *212*, 112-121 https://doi.org/10.1016/j.jfluchem.2018.05.009

[49] M. Singh, A. V. Amrutha Krishnan, R. Mandal, J. Samanta, V. Ravichandiran, R. Natarajan Y. P. Bharitkar, A. Hazra *Mol. Divers.* **2020**, *24* 627-639 https://doi.org/10.1007/s11030-019-09969-w

[50] M. F. Jamali, M. Ahmad, S. P. Chandrasekharan, K. Mohanan *Org. Lett.* **2023**, *25*(41), 7551-7556 https://doi.org/10.1021/acs.orglett.3c02895

[51] K. Livingstone, G. Little, C. Jamieson, *Synthesis* **2021**, *53*, 2399-2407 https://doi.org/10.1055/a-1389-1281

[52] K. A. Kumar, M. Govindaraju, P. Jayaroopa, G. Vasanth Kumar *Int. J. Pharm., Chem. Biol. Sci.* **2012**, *3*(1), 91-101

[53] D. P. Del'tsova, É. S. Ananyan, N. P. Gambaryan *Russ. Chem. Bull* **1971**, *20*, 296-299 https://doi.org/10.1007/BF00869028

[54] K. Tanaka, H. Masuda, K. Mitsuhashi *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2184-2187 https://doi.org/10.1246/bcsj.57.2184

[55] K. Tanaka, T. Suzuki, S. Maeno, K. Mitsuhashi, *J. Heterocycl. Chem.* **1986**, *23*(5), 1535-1538 https://doi.org/10.1002/jhet.5570230556

[56] T. D. Truskanova, N. V. Vasil'ev, A. F. Gontar', A. F. Kolomiets, G. A. Sokol'skii *Chem. Heterocycl. Compd.* **1989**, *25*, 815-817 https://doi.org/10.1007/BF00472756

[57] R. S. B. Gonçalves, M. Dos Santos, G. Bernadat, D. Bonnet-Delpon, B. Crousse *Beilstein J. Org. Chem.* **2013**, *9*, 2387-2394 https://doi.org/10.3762/bjoc.9.275

[58] P. Grzelak, G. Utecht, M. Jasiński, G. Mlostoń *Synthesis* **2017**, *49*(10), 2129-2137 doi:10.1055/s-0036-1588774

[59] J. D. Hepworth, J. A. Hudson, D. A. Ibbitson, G. Hallas *J. Chem. Soc., Perkin Trans. 2* **1972**, 13, 1905-1908 https://doi.org/10.1039/P29720001905

[60] J. E. True, T. D. Thomas, R. W. Winter, G. Gard *Inorg. Chem.* **2003**, *42*(14), 4437-4441 https://doi.org/10.1021/ic0343298

[61] C. Jamieson, K. Livingstone **2020**, *The Nitrile Imine 1,3-Dipole. Properties, Reactivity, Applications* Springer, https://doi.org/10.1007/978-3-030-43481-6

[62] G. Utecht, A. Fruziński, M. Jasiński *Org. Biomol. Chem.* **2018**, *16*(8), 1252-1257 DOI: 10.1039/c7ob03126b

[63] G. Utecht, J. Sioma, M. Jasiński, G. Mlostoń *J. Fluorine Chem.* **2017**, *201*, 68-75 https://doi.org/10.1016/j.jfluchem.2017.07.014

[64] G. Mlostoń, K. Urbaniak, G. Utecht, D. Lentz, M. Jasiński *J. Fluorine Chem.* **2016**, *192*, 147-154 https://doi.org/10.1016/j.jfluchem.2016.10.018

[65] G. Utecht-Jarzyńska, A. Michalak, J. Banaś, G. Mlostoń, M. Jasiński *J. Fluorine Chem.* **2019**, *222-223*, 8-14 https://doi.org/10.1016/j.jfluchem.2019.04.012

[66] K. Tanaka, S. Maeno, K. Mitsuhashi *Chem. Lett.* **1982**, *11*(4), 543-546 https://doi.org/10.1246/cl.1982.543

[67] K. Tanaka, S. Maeno, K. Mitsuhashi *J. Heterocycl. Chem.* **1985**, *22*(2), 565-568 https://doi.org/10.1002/jhet.5570220271

[68] G. Utecht, G. Mlostoń, M. Jasiński *Synlett* **2018**, *29*(13), 1753-1758 DOI: 10.1055/s-0037-1610454

[69] Y. C. Tian, J. K. Li, F. G. Zhang, J. A. Ma *Adv. Synth. Catal.* **2021**, *363*(8), 2093-2097 https://doi.org/10.1002/adsc.202100091

[70] Y. Zhou, C. F. Gao, H. Ma, J. Nie, J. A. Ma, F. G. Zhang *Chem. Asian J.* **2022**, *17*(15), e202200436 https://doi.org/10.1002/asia.202200436

[71] K. H. Wang, H. Liu, X. Liu, C. Bian, J. Wang, Y. Su, D. Huang, Y. Hu *Asian J. Org. Chem.* **2022**, *11*(6), e202200103 https://doi.org/10.1002/ajoc.202200103

[72] N. Zhang, H. a, C. W. Cheung, F. G. Zhang, M. Jasiński, J. A. Ma, J. Nie *Org. Biomol. Chem.* **2023**, *21*, 5040-5045 https://doi.org/10.1039/D3OB00644A

[73] G. Utecht-Jarzyńska, K. Nagła, G. Mlostoń, H. Heimgartner, M. Plausiak, M. Jasiński *Beilstein J. Org. Chem.* **2021**, *17*, 1509-1517 https://doi.org/10.3762/bjoc.17.108

[74] Y. Feng, B. Chang, Y. Ren, F. Zhao, K. H. Wang, J. Wang, D. Huang, X. Lv, Y. Hu *Tetrahedron* **2023**, *136*, 133353 https://doi.org/10.1016/j.tet.2023.133353

[75] G. Mlostoń, K. Urbaniak, M. Palusiak, Z. J. Witczak, E. U. Würthwein *Molecules* **2023**, *28*(21),7348 https://doi.org/10.3390/molecules28217348

[76] G. Utecht-Jarzyńska, M. Jasiński, K. Świątek, G. Mlostoń, H. Heimgartner *Heterocycles* **2021**, *101*(1), 251-262 DOI: 10.3987/COM-19-S(F)20

[77] G. Utecht-Jarzyńska, S. S. Mykhaylychenko, E. B. Rusanov, Y. G. Shermolovich, M. Jasiński, G. Mlostoń *J. Fluorine Chem.* **2021**, *242*, 109702 https://doi.org/10.1016/j.jfluchem.2020.109702

[78] K. Tanaka, O. Honda, K. Minoguchi, K. Mitsuhashi *J. Heterocycl. Chem.* **1987**, *24*(5), 1391-1396 https://doi.org/10.1002/jhet.5570240532

[79] Y. Zhang, J. L. Zeng, Z. Chen, R. Wang *J. Org. Chem.* **2022**, *87*(21), 14514-14522 https://doi.org/10.1021/acs.joc.2c01926

[80] D. Wang, X. Wan, Y. Zhou, J. Liu, J. Cai, G. J. Deng *Asian J. Org. Chem.* **2022**, *12*(1), e202200674 https://doi.org/10.1002/ajoc.202200674

[81] K. Cen, J. Wei, Y. Feng, Y. Liu, X. Wang, Y. Liu, Y. Yin, J. Yu, D. Wang, J. Cai *Org. Biomol. Chem.* **2023**, *21*, 7095-7099 https://doi.org/10.1039/D3OB01133J

[82] I. Ullah, M. Ilyas, M. Omer, M. Alamzeb, Adnan, M. Sohail *Front. Chem.* **2022**, *10*, https://doi.org/10.3389/fchem.2022.926723

[83] K. Świątek, G. Utecht-Jarzyńska, M. Palusiak, J. A. Ma, M. Jasiński *Org. Lett.* **2023**, *25*(24), 4462-4467 https://doi.org/10.1021/acs.orglett.3c01437

[84] A. Wojciechowska, M. Jasiński, P. Kaszyński *Tetrahedron* **2015**, *71*, 2349-2356 https://doi.org/10.1016/j.tet.2015.03.015

[85] C. Spiteri, S. Keeling, J. E. Moses *Org. Lett.* **2010**, *12*, 3368-3371 https://doi.org/10.1021/ol101150t

[86] M. Nicholas, K. K. O'Dell, *Heterocycles* **2004**, *63*(2), 373-382 10.3987/COM-03-9926

[87] J. Teichert, P. Oulié, K. Jacob, L. Vendier, M. Etienne, R. M. Claramunt, C. López, C. P. Medina, I. Alkorta, J. Elguero *New J. Chem.* **2007**, *31*(6), 936-946 https://doi.org/10.1039/B617988F

[88] S. Di Cosimos, G. Ferretti, P. Papaldo, P. Carlini, A. Fabi, F. Cognetti *Drugs of Today* **2003**, *39*(3), 157-74 doi: 10.1358/dot.2003.39.3.799451

[89] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *Org. Lett.* **2022**, *24*(13), 2499-2503 https://doi.org/10.1021/acs.orglett.2c00521

[90] G. Utecht-Jarzyńska, A. Kowalczyk, M. Jasiński *Molecules* **2022**, *27*(23), 8446 https://doi.org/10.3390/molecules27238446

[91] A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński, *J. Fluorine Chem.* **2022**, *272*, 110206 https://doi.org/10.1016/j.jfluchem.2023.110206

[92] F. M. Menger, C. Lee *Tetrahedron Lett.* **1981**, *22*(18), 1655 https://doi.org/10.1016/S0040-4039(01)90402-2

[93] M. Maue, I. Adelt, W. Giencke, M. Heil, P. eschke, B. W. Krueger, F. Muehlthau, A. Friedrich, A. Sudau, K. Raming, U. Ebbinghaus-Kintscher, M. Adamczewski, A. Voerste, U. Goergens, T. Kapferer, M. W. Drewes, A. Becker (2010) Novel halogen-substituted compounds, TW201029573

[94] F. Zhang, Y. Zhou, J. Ma (2021) 3-trifluoromethyl-5-cyano pyrazole compound and preparation method thereof, CN113135856

[95] T. Nikonovich, **2024**, *Mechanochemical C-N bond-forming reactions and their application in pharmaceutical synthesis* Tal Tech Press https://doi.org/10.23658/taltech.5/2024

[96] G.-W. Wang *Chem. Soc. Rev.* **2013**, *42*(18), 7668-7700 https://doi.org/10.1039/C3CS35526H

[97] M. Ríos-Gutiérrez, L. R. Domingo, M. Esseffar, A. Oubella, M. Y. Ait Itto *Molecules* 2020*, 25*(5), 1085 https://doi.org/10.3390/molecules25051085

[98] A. Oubella, M. Y. Ait Itto, A. Auhmani, A. Riahi, A. Robert, J.-C. Daran, H. Morjani, A. A. Parshi, M. Esseffar *J. Mol. Struct.* **2019**, *1198*, 126924 https://doi.org/10.1016/j.molstruc.2019.126924

[99] A. Kowalczyk, K. Świątek, M. Celeda, G. Utecht-Jarzyńska, A. Jaskulska, K. Gach-Janczak, M. Jasiński *Materials* **2023**, *16*(2), 856 https://doi.org/10.3390/ma16020856

[100] A. Kowalczyk, M. Jasiński *Chem. Heterocycl. Compd.* **2022**, *58*, 585-587 https://doi.org/10.1007/s10593-022-03138-y

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A straightforward access to 3-trifluoromethyl-1H-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile'

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A straightforward access to 3-trifluoromethyl-1*H*-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile

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ABSTRACT

In situ generated arynes react with nitrile imines derived from trifluoroacetonitrile at 0 °C in THF solutions yielding 3-trifluoromethyl-1*H*-indazole derivatives as the only intermolecular products. The reaction corresponds the expected (3 + 2)-cycloadditions which belong to the *Type III* (inverse-electron-demand) of Sustmann's classification. Subsequent CAN-mediated dearylation of the model *N*-(*p*-methoxy)phenyl indazole leads to *N*-unsubstituted analogue, which easily undergoes alkylation and acylation reactions. Presented protocol offers a superior method for preparation of the 3-CF_3 substituted indazole derivatives.

1. Introduction

In the current organic synthesis the (3 + 2)-cycloadditions (the *Huisgen reaction*) are considered as a powerful and universal tool for the preparation of five-membered heterocycles [1]. Thus, reactions of ethylenic or acetylenic dipolarophiles with 'nitrogen-centered' 1,3-dipoles such as nitrile imines, nitrile oxides, nitrile ylides, nitrones or azomethine ylides open access to variety of *N*-heterocyclic systems i.e. pyrazole, isoxazole, pyrrole, isoxazoline, and pyrroline derivatives, respectively [2a–f]. Moreover, the (3 + 2)-cycloadditions of organic azides with alkynes, performed in the presence of Cu(I) salts (the *click reactions*) are known as a group of the most widely applied transformations of organic compounds with great importance for interdisciplinary studies [[2]2g]. In a series of our recent publications, trifluoroacetonitrile imines of type **1** generated in situ from the corresponding hydrazonoyl bromides **2** were demonstrated as a useful 1,3-dipoles for the efficient introduction of the CF_3 group into the 5-membered nitrogen heterocycles with diverse number of heteroatoms. For example, trapping of *in situ* generated **1** with thiocarbonyl dipolarophiles such as thioketones, thiochalcones or thioamides led to 1,3,4-thiadiazole derivatives of type **3** in a fully chemo- and regioselective manner [3] (Scheme 1). On the other hand, trifluoroacetonitrile imines **1** were reported to react smoothly with electron-rich C=C dipolarophiles yielding the corresponding pyrazole derivatives **4** also in a completely selective fashion [4]. In contrast, the (3 + 2)-cycloadditions of **1** with acetylenic dipolarophiles are lesser explored presumably due to low regioselectivity [5]. In these reactions, formation of complex mixtures of products resulting from the competitive additions of acetylide ions derived from some terminal acetylenes is a serious limitation.

Notably, there is a growing number of publications dealing with both (3 + 2)- and (4 + 2)-cycloadditions of arynes **5** [6]. These highly congested and therefore very reactive intermediates can be used either as dipolarophiles or dienophiles and they are currently easily accessible under mild conditions via fluoride anion-induced elimination from *ortho*-substituted (trialkylsilyl)aryl triflates **6** as commercially available, common precursors (Scheme 2) [7]. In this context, preparation of 1-substituted 1*H*-indazoles via *the Huisgen reaction* from the in situ generated benzynes **5** and *C,N*-di(hetero)aryl-functionalized nitrile imines was described as a promising method to synthesize these type of the fused heterocycles [8]. Prompted by these results reported for the first time by Moses' group, we decided to examine a series of trifluoroacetonitrile imines **1** with selected arynes **5** in order to prepare hitherto little known 3-trifluoromethylated 1*H*-indazoles [9]. Furthermore, the target products seemed to be an interesting class of organic substrates for further functionalization, e.g. *via* dearylation of the N(1) atom followed by alkylation or acylation at this position.

Hence, the goal of the present study was the synthesis and selected transformations of 3-trifluormethyl-1*H*-indazoles via in situ trapping of

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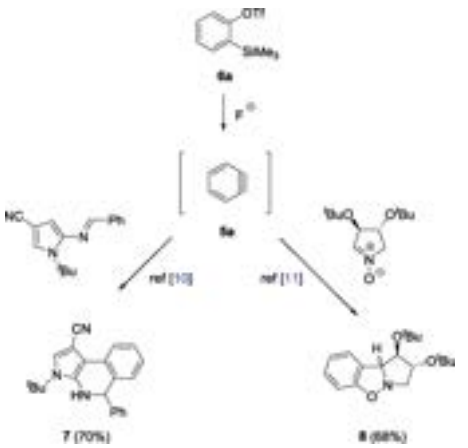
arynes with the title fluorinated nitrile imines derived from trifluoroacetonitrile.

2. Results and discussion

The starting nitrile imines **1** were generated based on a procedure routinely applied in our laboratory for a longer time, i.e. by dehydrobromination of hydrazonoyl bromides **2** with an organic or inorganic base, in anhydrous aprotic solvents [3,4]. In a test experiment, corresponding precursor of the nitrile imine **1a** (0.5 mmol) bearing the NMR-diagnostic *p*-tolyl group, and *o*-trimethylsilyl-phenyl triflate (**6a**, 0.75 mmol) were treated with tetrabutylammonium fluoride (TBAF, 1.3 mmol) in dry THF at room temperature. As expected, the application of the two-fold amount of TBAF assured dual role of the fluoride anion for both, smooth generation of benzyne (**5a**) as well as for dehydrohalogenation of hydrazonoyl bromide **2a**. According to the TLC tests, triflate **6a** was fully consumed after 20 min, and the ^{1}H NMR spectrum registered for crude reaction mixture revealed the presence of the expected (3 + 2)-cycloadduct **9a** along with unreacted nitrile imine precursor **2a**, which were isolated in 42 % and 38 % yield, respectively. Optimization of the reaction conditions revealed that the increased amounts of both triflate **6a** (2.0 equiv.) and TBAF (4.0 equiv.) are necessary for complete consumption of the bromide **2a** (Table 1). Neither the change of the solvent (MeCN) nor the decrease of the reaction temperature to –20 °C showed remarkable impact on the reaction outcome. Notably, the replacement of TBAF by CsF as a source of fluoride anion was unsuccessful and the reduced solubility of the latter in THF can be the explanation of that result. Thus, by running the reaction of **2a** with two-fold excess of benzyne precursor **6a** and four-fold excess of TBAF, in THF at 0 °C, the desired (3 + 2)-cycloadduct **9a** was isolated in satisfactory yield of 74 % (Table 1, entry 4; Scheme 3). The pure product was isolated by column chromatography, and its structure was confirmed by spectroscopic methods. For example, in the ^{19}F NMR spectrum the signal of the CF_3 group appeared as a singlet located at –60.8 ppm. Furthermore, in the ^{13}C NMR the characteristic quartets attributed to the CF_3 moiety and the C(3) atom were found at 122.0 ($^{1}J_{C,F}$ = 269.2 Hz) and 135.8 ($^{2}J_{C,F}$ = 38.4 H Hz) ppm, respectively. Finally, high resolution MS measurements for the sample confirmed the molecular formula of 1-(*p*-tolyl)-3-trifluoromethyl-1*H*-indazole (**9a**) as $C_{15}H_{11}F_3N_2$.

The optimized conditions were applied for a series of experiments performed with diverse *para*-substituted nitrile imines **1b**-**1 g** and the model benzyne (**5a**) (Scheme 3). In all the studied cases, the desired indazoles of type **9** were isolated as sole intermolecular products in satisfactory to high yields (58–80 %) with one exception of the representative **9g** (32 %) functionalized with electron-withdrawing NO_2 group.

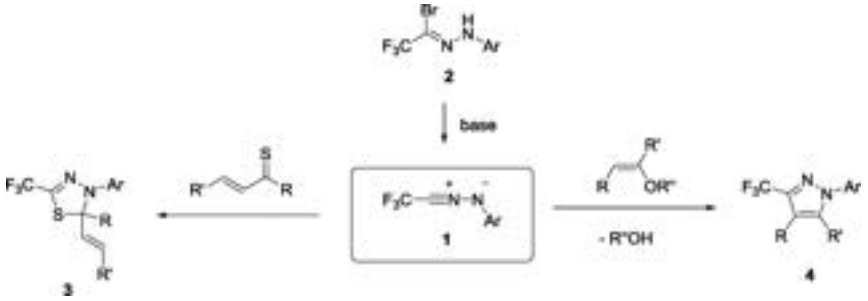


Scheme 2. Generation of benzyne (**5a**) and its cycloaddition reactions with selected heterodienes and 1,3-dipoles leading to the respective benzo-fused systems **7** and **8** as initial products of cycloaddition reactions (for details see, Refs. [10] and [11]).

In extension of the study, two further arynes, namely 4,5-dimethoxybenzyne (**5b**) and naphtyne (**5c**), were also examined in reactions with a model N-(*p*-tolyl)trifluoroacetohydrazonoyl bromide (**2a**). Remarkably, introduction of two electron-donating OMe groups in **5b** did not affect the course of the (3 + 2)-cycloaddition, and the product **9h** was isolated in satisfactory yield of 52 %, comparable with other studied reactions (see Table 1). However, the reaction performed with in situ generated naphtyne (**5c**) led to a complex mixture and the expected product was isolated as a colourless solid in 26 % yield only.

The mechanism of the studied reaction requires a brief comment. Very likely, formation of the fused indazole system **9** occurs via concerted but rather asynchronous (3 + 2)-cycloaddition. Taking into account that the presented reactions occur with participation of electron-deficient 1,3-dipoles **1** and electron-rich arynes **5**, they can be classified to *Type 3* (inverse-electron-demand) according to Sustmann's classification of the 1,3-dipolar cycloadditions [12].

In the second part of the study, selected indazole derivative **9b** bearing electron-rich *p*-methoxyphenyl group was used for further transformations aimed at the preparation of new analogues of some



Scheme 1. Reactions of trifluoroacetonitrile imines with exemplary C=S and C=C dipolarophiles leading to 2,3-dihydro-1,3,4-thiadiazoles **3** and pyrazoles **4**, respectively.

Table 1
Optimisation of the reaction conditions by using **2a** and **6a** as model substrates.

Entry

	6a (equiv.)[a]	F^- source (equiv.)[a]	Solvent	Temp.	Time	**9a** [%][b]
1	1.5	CsF, 2.5	THF	rt	24 h	NR
2	1.5	TBAF, 2.5	THF	rt	20 min	42 [c]
3	1.5	TBAF, 3.0	THF	rt	20 min	58 [d]
3	2.0	TBAF, 4.0	THF	rt	20 min	72
4	2.0	TBAF, 4.0	THF	0 °C	1 h	74
5	2.0	TBAF, 4.0	THF	−20 °C	1 h	70
6	2.0	TBAF, 4.0	THF	−78 °C	1 h	46
7	2.0	TBAF, 4.0	MeCN	0 °C	1 h	71

[a] with respect to hydrazonoyl bromide **2a**; all experiments were performed in a 0.5 mmol (**2a**) scale.
[b] isolated yield.
[c] unreacted **2a** was recovered in 38 % yield.
[d] traces (<5 %) of starting **2a** were found in the crude mixture.

indazole-derived biologically active compounds which are of current interest [13]. The initial conversion of a multi-step transformation of **9b** was dearylation using ceric ammonium nitrate (CAN) and this process is depicted in Scheme 4. The reaction was performed in a MeCN/H_2O mixture, at 5 °C. After standard aqueous workup followed by column chromatography, the expected indazole **10** lacking a substituent at *N*(1) was obtained in satisfactory 78 % yield. Its structure was confirmed spectroscopically, and the ^{13}C NMR spectrum showed again the diagnostic signal of the C(3) atom as a quartet located at 135.9 ($^2J_{C,F}$ =38.2 Hz) ppm, along with the signal of the CF_3 group found at 122.0 ($^1J_{C,F}$ =268.9 Hz), indicating the presence of a single tautomeric form under the measurement conditions (rt, $CDCl_3$) within the NMR accuracy of >0.1 %.

Next, the obtained NH-indazole derivative **10** was checked as a nucleophilic reagent in alkylation and acylation at the *N*(1) atom using selected electrophiles. For example, treatment of **10** with an excess of 2,4-dichlorobenzyl chloride under mild conditions (room temperature, K_2CO_3, in DMF) afforded after 2d the desired *N*-benzylated derivative **11** in excellent yield (94 %). This is worth of mentioning that this product constitutes a new structural analogue of lonidamine (**12**); the latter is a well-known medicine used for the cancer treatment [14].

Two more functionalization of indazole **10** were also performed via alkylation using (*S*)-citronellyl bromide and acylation with cholestanyl-functionalized succinyl monochloride. In both cases, the expected enantiopure products **13** and **14** were obtained in good yields of 87 % and 80 %, respectively (Fig. 1). These results demonstrate that indazole **10** can be explored as a useful building block for the preparation of new terpene- and steroid-containing conjugates. Compounds of this type are of interest e.g. in the context of their antiviral activity [15].

3. Conclusions

The presented method of the synthesis of 3-trifluoromethylated 1*H*-indazoles via the (3 + 2)-cycloaddition of the in situ generated both trifluoroacetonitrile imines and arynes offers a convenient access to these heterocycles which are of interest as versatile building blocks for preparation of potentially biologically active, fluoromethylated *N*-heterocycles. The importance of fluorinated indazoles is demonstrated by numerous original and review publications [16]. Due to synthetic limitations in preparation of trifluoroacetonitrile imines, only *N*-arylated indazoles can be directly accessed by the presented method. However, a straightforward CAN-mediated dearylation opens a highly efficient access to known N(1)H-indazole in high yield. It is worth of mentioning that in comparison to other reported methods the procedure described herein can be considered as a method of choice for preparation of this relevant, fluorinated building block [17]. As demonstrated in the present study, the latter indazole displays the expected nucleophilic behavior in alkylation and acylation reactions. On the other side, described results show once more high utility of the in situ generated arynes as highly reactive dipolarophiles for the synthesis of fused, functionalized nitrogen heterocycles.

4. Experimental part

4.1. General information

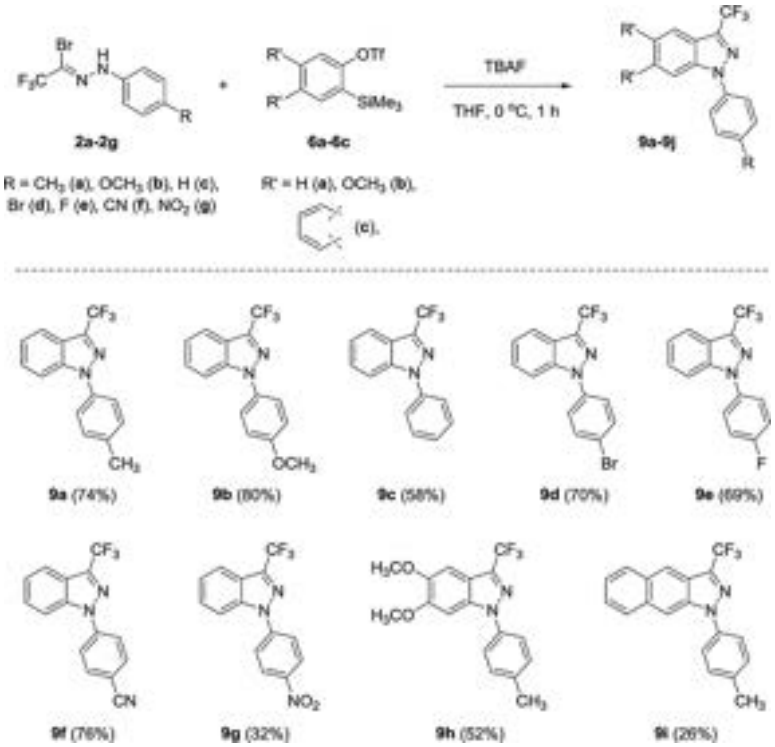
If not stated otherwise, reactions were carried out under inert atmosphere (argon) in a flame-dried flasks with addition of the reactants by using syringes; subsequent manipulations were conducted in air. Products were purified by standard column chromatography (CC) on silica gel (230–400 mesh), deactivated prior to use with 2 % Et_3N in petroleum ether, by using freshly distilled solvents (petroleum ether, CH_2Cl_2, EtOAc). THF was dried over sodium–benzophenone and freshly distilled before usage; anhydrous DMF is available commercialy and was used as received. NMR spectra were measured on a Bruker AVIII instrument (^1H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz). Chemical shifts are reported relative to solvent ($CDCl_3$) residual peaks (^1H NMR: $\delta = 7.26$ ppm, ^{13}C NMR: $\delta = 77.0$ ppm) or to $CFCl_3$ (^{19}F NMR: $\delta = 0.00$ ppm) used as external standard. Multiplicity of the signals in ^{13}C NMR spectra were assigned based on supplementary 2D measurements (COSY, HMQC, HMBC). MS (ESI) were performed with a Varian 500-MS LC Ion Trap; high resolution MS (ESI-TOF) measurements were measured with a Synapt G2-Si mass spectrometer (Waters). IR spectra were measured with an Agilent Cary 630 FTIR spectrometer, in neat. Elemental analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument. Melting points were determined in capillaries with a MEL-TEMP apparatus (Aldrich) or with a polarizing optical microscope (Opta-Tech), and are uncorrected. Hydrazonoyl bromides **2a**–**2g** were prepared by treatment of the respective trifluoroacetaldehyde arylhydrazones [18] with *N*-bromosuccinimide in dry DMF as described [[3]3a]. Cholestan-3-yloxycarbonylpropionyl chloride (**16**) was prepared following the literature procedure [19].

4.2. General procedure for the synthesis of 3-trifluoromethyl-1H-indazoles 9

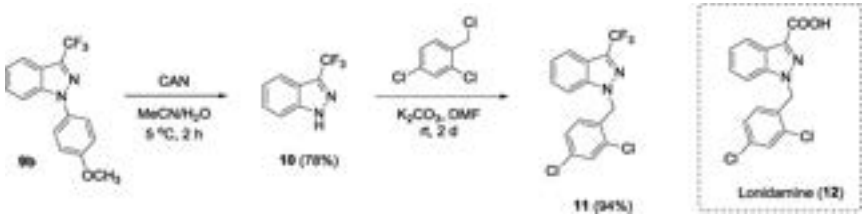
To a mixture of the respective hydrazonoyl bromide of type **2** (0.5 mmol) and benzyne precursor **5** (1.0 mmol) in dry THF (5 mL) at 0 °C was added dropwise TBAF (1 M in THF, 2.0 mL, 2.0 mmol) and the resulting was stirred for 1 h. After solvent was removed under reduced pressure, the resulting mixture was purified by standard column chromatography (CC) on SiO_2 (washed with 2 % Et_3N in petroleum ether) using petroleum ether – dichloromethane mixtures as an eluent to give product **9** as spectroscopically pure samples.

4.2.1. 1-(p-Tolyl)-3-trifluoromethyl-1H-indazole (9a)

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 102 mg (74 %), pale yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ 2.46 (s, 3 H, Me), 7.34–7.36 (m, 1 H), 7.36 (d_{br}, $J \approx 8.2$ Hz, 2 H, Tol), 7.47–7.51 (m, 1 H), 7.59 (d_{br}, $J \approx 8.2$ Hz, 2 H, Tol), 7.71 (d_{br}, $J \approx 8.6$ Hz, 1 H), 7.91–7.93 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.1 (Me), 111.0, 120.3 (2 CH), 121.2 (*i*-C), 122.0 (q, $^1J_{C,F}$ =269.2 Hz, CF_3), 123.2, 123.5, 127.9, 130.1 (CH, 2 CH, CH, 2 CH), 135.8 (q, $^2J_{C,F}$ =38.4 Hz, C-3), 136.7, 138.0, 140.0 (3 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.8 (s, CF_3) ppm; IR (neat): ν 2925, 1612, 1502, 1433, 1352, 1173, 1128, 1030, 821, 746 cm^{-1}; EI-HRMS: *m/z* $[M]^+$ calcd for $C_{15}H_{11}F_3N_2$: 276.0874; found: 276.0878.



Scheme 3. Synthesis of 3-trifluoromethyl-1*H*-indazole derivatives **9a**–**9i** by the (3 + 2)-cycloaddition of arynes **5a**–**5c** with nitrile imines **1a**–**1g.**



Scheme 4. Synthesis of *N*-unsubstituted indazole **10** by CAN-mediated dearylation of **9b** and subsequent alkylation leading to lonidamine analogue **11.**

*4.2.2. 1-(4-Methoxyphenyl)-3-trifluoromethyl-1H-indazole (**9b**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1), 117 mg (80 %), colourless solid, mp 65–66 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (s, 3 H, Me) 7.07 (d, J = 8.9 Hz, 2 H), 7.32–7.36, 7.46–7.50 (2 m, 1 H each), 7.36 (d, J = 8.9 Hz, 2 H), 7.64 (d_{br}, $J \approx$ 8.6 Hz, 1 H), 7.91 (d_{br}, J = 8.2 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 55.6 (OMe), 110.9, 114.8, 120.2 (CH, 2 CH, CH), 121.0 (*i*-C), 122.0 (q, $^1J_{C,F}$ =269.0 Hz, CF_3), 123.1, 125.3, 127.9, (CH, 2 CH, CH), 132.1 (*i*-C), 135.6 (q, $^2J_{C,F}$ =38.3 Hz, C-3), 140.2, 159.3 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.7 (s, CF_3) ppm; IR (neat): ν 2926, 1526, 1502, 1431, 1253, 1188, 1154, 1132, 1030, 828, 741 cm^{-1}; EI-HRMS: m/z [M]$^+$ calcd for $C_{15}H_{11}F_3N_2O$: 292.0823; found: 292.0828.

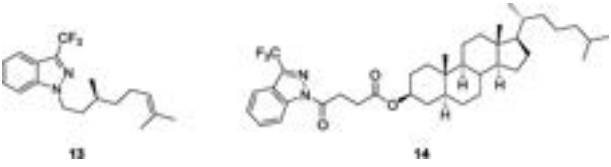


Fig. 1. Structures of chiral 3-trifluoromethylindazole-conjugates **13** and **14** obtained by alkylation or acylation of **10** with (*S*)-(+)-citronellyl bromide (**15**) or cholestan-3-yloxycarbonylpropionyl chloride (**16**).

*4.2.3. 1-Phenyl-3-trifluoromethyl-1H-indazole (**9c**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 76 mg (58 %), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.38, 7.44–7.46, 7.51–7.53 (3 m, 1 H each), 7.56–7.59 (m, 2 H), 7.72–7.74 (m, 2 H), 7.75 (d, J = 8.6 Hz, 1 H), 7.92–7.94 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 111.3, 120.4 (2 CH), 121.3 (*i*-C), 121.9 (q, $^1J_{C,F}$ =269.3 Hz, CF_3), 123.3, 123.6, 128.0, 128.1, 129.6 (CH, 2 CH, CH, CH, 2 CH), 136.2 (q, $^2J_{C,F}$ =38.4 Hz, C-3), 139.2, 140.0 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.9 (s, CF_3) ppm; IR (neat): ν 3064, 1660, 1599, 1497, 1433, 1352, 1298, 1259, 1128, 949, 748 cm^{-1}; EI-HRMS: *m/z* [M]$^+$ calcd for $C_{14}H_9F_3N_2$: 262.0718; found: 262.0725.

*4.2.4. 1-(4-Bromophenyl)-3-trifluoromethyl-1H-indazole (**9d**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 119 mg (70 %), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.39, 7.52–7.55 (2 m, 1 H each), 7.61–7.64 (m, 2 H), 7.68–7.73 (m, 3 H), 7.93 (dd, J = 0.8, 8.2 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.8, 120.6 (2 CH), 121.4, 121.5 (2 *i*-C), 121.8 (q, $^1J_{C,F}$ =269.4 Hz, CF_3), 123.6, 124.9, 128.4, 132.8 (CH, 2 CH, CH, 2 CH), 136.7 (q, $^2J_{C,F}$ =38.5 Hz, C-3), 138.2, 139.8 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.0 (s, CF_3) ppm; IR (neat): ν 2926, 1516, 1489, 1433, 1257, 1182, 1130, 1026, 949, 829, 746 cm^{-1}; EI-HRMS: *m/z* [M]$^+$ calcd for $C_{14}H_8BrF_3N_2$: 339.9823; found: 339.9829.

*4.2.5. 1-(4-Fluorophenyl)-3-trifluoromethyl-1H-indazole (**9e**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1), 97 mg (69 %), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24–7.30 (m, 2 H), 7.35–7.39, 7.49–7.54 (2 m, 1 H each), 7.65–7.70 (m, 3 H), 7.93 (d_{br}, $J \approx$ 8.2 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.7 (CH), 116.6 (d, $^2J_{C,F}$ =23.1 Hz, 2 CH), 120.4 (CH), 121.2 (*i*-C), 121.8 (q, $^1J_{C,F}$ =269.3 Hz, CF_3), 123.4 (CH), 125.4 (d, $^3J_{C,F}$ =8.6 Hz, 2 CH), 128.3 (CH), 135.2 (d, $^4J_{C,F}$ =3.1 Hz, *i*-C), 136.2 (q, $^2J_{C,F}$ =38.4 Hz, C-3), 140.0 (*i*-C), 161.9 (d, $^1J_{C,F}$ =248.4 Hz, *i*-CF) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.9 (s, CF_3), –113.0 (m_c, Ar-F) ppm; IR (neat): ν 2929, 1606, 1523, 1501, 1433, 1259, 1236, 1177, 1154, 1127, 1026, 840, 746 cm^{-1}; EI-HRMS: *m/z* [M]$^+$ calcd for $C_{14}H_8F_4N_2$: 280.0624; found: 280.0630.

*4.2.6. 4-(3-Trifluoromethyl-1H-indazol-1-yl)benzonitrile (**9f**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), 109 mg (76 %), yellow solid, mp 127–128 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42–7.44, 7.58–7.61 (2 m, 1 H each), 7.82 (d_{br}, $J \approx$ 8.6 Hz, 1 H), 7.86–7.89, 7.92–7.97 (2 m, 2 H, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.9 (CH), 111.1 (CN), 118.0 (*i*-C), 120.9 (CH), 121.5 (q, $^1J_{C,F}$ =269.7 Hz, CF_3), 121.9 (*i*-C), 123.0, 124.1, 129.0, 133.7 (2 CH, CH, CH, 2 CH), 137.9 (q, $^2J_{C,F}$ =38.7 Hz, C-3), 139.7, 142.7 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.3 (s, CF_3) ppm; IR (neat): ν 3310, 2225 (CN), 1605, 1506, 1287, 1159, 938, 748 cm^{-1}; EI-HRMS: *m/z* [M]$^+$ calcd for $C_{15}H_8F_3N_3$: 287.0670; found: 287.0674.

*4.2.7. 1-(4-Nitrophenyl)-3-trifluoromethyl-1H-indazole (**9g**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), 49 mg (32 %), yellow solid, mp 140–141 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42–7.46, 7.61–7.64 (2 m, 1 H each), 7.86 (d_{br}, $J \approx$ 8.6 Hz, 1 H), 7.97 (dd, J = 0.7, 8.2 Hz, 1 H), 8.00, 8.46 (2 d_{br}, $J \approx$ 9.1 Hz, 2 H each) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.9, 121.0 (2 CH), 121.5 (q, $^1J_{C,F}$ =269.7 Hz, CF_3), 122.0 (*i*-C), 122.7, 124.3, 125.4, 129.2 (2 CH, CH, 2 CH, CH), 138.2 (q, $^2J_{C,F}$ =38.8 Hz, C-3), 144.2, 146.3 (2 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.4 (s, CF_3) ppm; IR (neat): ν 3090, 1522, 1496, 1344, 1174, 1121, 948, 773 cm^{-1}; EI-HRMS: *m/z* [M]$^+$ calcd for $C_{14}H_8F_3N_3O_2$: 307.0569; found: 307.0572.

*4.2.8. 5,6-Dimethoxy-1-(p-tolyl)-3-trifluoromethyl-1H-indazole (**9h**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1), 87 mg (52 %), orange solid, mp 112–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.46 (s, 3 H, Me), 3.93, 3.98 (2 s, 3 H each, OMe), 7.00, 7.14 (2 s, 1 H each), 7.35, 7.54 (2 d_{br}, $J \approx$ 8.2 Hz, 2 H each, Tol) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.1 (Me), 56.1, 56.2 (OMe), 91.9, 98.8 (2 CH), 114.5 (*i*-C), 122.1 (q, $^1J_{C,F}$ =269.0 Hz, CF_3), 123.4, 130.2 (2 CH each), 135.0 (q, $^2J_{C,F}$ =38.0 Hz, C-3), 135.8, 136.7, 137.9, 147.9, 151.8 (5 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.7 (s, CF_3) ppm; IR (neat): ν 2927, 1614, 1510, 1475, 1432, 1290, 1214, 1150, 1007, 826, 734 cm^{-1}; EI-HRMS: *m/z* [M]$^+$ calcd for $C_{17}H_{15}F_3N_2O_2$: 336.1086; found: 336.1088.

*4.2.9. 1-(p-Tolyl)-3-trifluoromethyl-1H-benzo[f]indazole (**9i**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 9:1), 42 mg (26 %), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.48 (s, 3 H, Me), 7.42 (d_{br}, $J \approx$ 8.2 Hz, 2 H, Tol), 7.44–7.47, 7.49–7.53 (2 m, 1 H each), 7.71 (d_{br}, $J \approx$ 8.2 Hz, 2 H, Tol), 7.92 (d_{br}, $J \approx$ 8.3 Hz, 1 H), 8.04 (d_{br}, $J \approx$ 8.3 Hz, 1 H), 8.18, 8.48 (2 s, 1 H each) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.2 (Me), 106.7, 119.2 (2 CH), 121.4 (*i*-C), 122.0 (q, $^1J_{C,F}$ =269.2 Hz, CF_3), 123.2 (2 CH) 124.8, 126.9, 128.0, 129.1 (4 CH), 129.9 (*i*-C), 130.2 (2 CH), 133.1 (*i*-C), 135.8 (q, $^2J_{C,F}$ =38.5 Hz, C-3), 137.0, 137.6, 138.3 (3 *i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.9 (s, CF_3) ppm; IR (neat): ν 2922, 1608, 1524, 1510, 1489, 1358, 1105, 1010, 818, 744 cm^{-1}; HRMS (ESI-TOF): *m/z* [M+H]$^+$ calcd for $C_{19}H_{14}F_3N_2$: 327.1109; found: 327.1111.

*4.3. Synthesis of 3-trifluoromethyl-1H-indazole (**10**) [17]*

To a magnetically stirred solution of 1-(4-Methoxyphenyl)-3-trifluoromethyl-1*H*-indazole (**9b**, 146 mg, 0.5 mmol) in MeCN (20 mL) at 5 °C a solution of ceric ammonium nitrate (1.37 g, 2.4 mmol) in H_2O (12 mL) was added. The resulting mixture was stirred for 2 h at this temperature, then neutralized to pH = 7 with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The residue was purified by flash column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) to give *N*-unsubstituted indazole **10** (73 mg, 78 %) as colourless solid.

Mp 96–97 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.35, 7.50–7.54 (2 m, 1 H each), 7.62 (d_{br}, $J \approx$ 8.5 Hz, 1 H), 7.89 (dd_{br}, $J \approx$ 0.7, 8.3 Hz, 1 H), 11.57 (s_{br}, 1 H, NH) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 110.5 (CH), 119.5 (*i*-C), 119.9 (CH), 122.0 (q, $^1J_{C,F}$ =268.9 Hz, CF_3), 123.1, 128.1 (2 CH), 135.9 (q, $^2J_{C,F}$ =38.2 Hz, C-3), 141.0 (*i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.8 (s, CF_3) ppm; IR (neat): ν 3184, 3161, 2936, 1475, 1432, 1230, 1186, 1153, 1115, 1028, 911, 743 cm^{-1}; (–)-ESI-MS (*m/z*): 184.9 (100, [M−H]$^-$); elemental analysis calcd (%) for $C_8H_5F_3N_2$ (186.1): C 51.62, H 2.71, N 15.05; found: C 51.65, H 3.01, N 14.97.

4.4. Synthesis of 1-(2,4-dichlorobenzyl)-3-trifluoromethyl-1H-indazole (11)

To a solution of 3-trifluoromethyl-1*H*-indazole (**10**, 93 mg, 0.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (5 mL), 2,4-dichlorobenzyl chloride (117 mg, 0.6 mmol) in DMF (1 mL) was added at room temperature. The reaction mixture was stirred for 48 h, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) to afford **11** (162 mg, 94 %) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.73 (s, 2 H, CH_2), 6.76 (d_{br}, $J \approx 8.4$ Hz, 1 H), 7.13 (dd, $J = 2.0$, 8.4 Hz, 1 H), 7.29–7.33 (m, 1 H), 7.40–7.48 (m, 3 H), 7.87–789 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 50.1 (CH_2), 109.8, 120.3 (2 CH), 120.6 (*i*-C), 121.8 (q, $^1J_{C,F} = 269.0$ Hz, CF_3), 123.0, 127.7, 127.8, 129.5, 129.6 (5 CH), 132.0, 133.1, 134.6 (3 *i*-C), 134.9 (q, $^2J_{C,F} = 38.4$ Hz, C-3), 140.6 (*i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.7 (s, CF_3) ppm; IR (neat): ν 2926, 1502, 1431, 1382, 1237, 1115, 1088, 987, 749 cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}F_3N_2Cl_2$: 345.0173; found: 345.0174.

4.5. Synthesis of (S)-1-(3,7-dimethyloct-6-en-1-yl)-3-trifluoromethyl-1H-indazole (13)

To a solution of *N*-unsubstituted indazole **10** (93 mg, 0.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (5 mL), (*S*)-(+)-citronellyl bromide (131 mg, 0.6 mmol) in DMF (1 mL) was added at room temperature. The reaction mixture was stirred for 24 h, then diluted with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and solvents were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) to yield product **13** (141 mg, 87 %) as a colourless oil.

$[\alpha]_D^{20} = -1.73$ ($c = 0.11$, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.00 (d, $J = 6.6$ Hz, 3 H, Me), 1.19–1.28, 1.37–1.45, 1.45–1.53 (3 m, 1 H each), 1.58, 1.66 (2 s, 3 H each, 2 Me), 1.72–1.81 (m, 1 H), 1.90–2.05 (m, 3 H), 4.36–4.53 (m, 2 H, NCH_2), 5.02–5.07 (m, 1 H), 7.28 (ddd, $J = 2.5$, 5.2, 8.0 Hz, 1 H), 7.44–7.48 (m, 2 H), 7.84 (d_{br}, $J = 8.0$ Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 17.6, 19.4 (2 Me), 25.3 (CH_2), 25.6 (Me), 30.1 (CH), 36.5, 36.7, 47.8 (3 CH_2), 109.6, 120.2 (2 CH), 120.4 (*i*-C), 122.0 (q, $^1J_{C,F} = 268.6$ Hz, CF_3), 122.4 (CH), 124.2 (=CH), 127.0 (CH), 131.6 (*i*-C), 133.6 (q, $^2J_{C,F} = 38.1$ Hz, C-3), 140.1 (*i*-C) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –60.4 (s, CF_3) ppm; IR (neat): ν 2932, 1718, 1506, 1433, 1228, 1157, 1120, 1075, 978, 745 cm^{-1}; HRMS (ESI-TOF): *m/z* $[M-H]^-$ calcd for $C_{18}H_{22}F_3N_2$: 323.1735; found: 323.1740.

4.6. Cholestan-3-yl 4-(3-trifluoromethyl-1H-indazol-1-yl)-4-oxobutanoate (14)

To a solution of indazole **10** (186 mg, 1.0 mmol) and 4-dimethylaminopyridine (DMAP, 366 mg, 2.44 mmol) in dry DCM (10 mL), cholestan-3-yloxycarbonylpropionyl chloride (558 mg, 1.1 mmol) in dry DCM (10 mL) was added dropwise. The mixture was stirred under argon at room temperature until the starting indazole was fully consumed (TLC monitoring, 1 h). The mixture was quenched with water (20 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with 2 % HCl (10 mL), then with 5 % $NaHCO_3$ (10 mL) and water (3 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by standard column chromatography (SiO_2, petroleum ether/AcOEt 8:1) to give **14** (525 mg, 80 %) as a light yellow solid.

Mp 126–128 °C. $[\alpha]_D^{20} = +11.96$ ($c = 0.27$, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.58–0.63 (m, 1 H), 0.64, 0.78 (2 s, 3 H each, 2 Me), 0.80–0.85 (m, 1 H), 0.85, 0.86 (2 d, $J = 2.7$ Hz, 3 H each, 2 Me), 0.89 (d, $J = 6.5$ Hz, 3 H, Me), 0.92–1.04 (m, 4 H), 1.04–1.17, 1.17–1.28, 1.28–1.38 (3 m, 5 H each), 1.42–1.49, 1.49–1.56 (2 m, 2 H each), 1.56–1.61, 1.61–1.66 (2 m, 1 H each), 1.71 (dt, $J = 3.5$, 13.3 Hz, 1 H), 1.76–1.84 (m, 2 H), 1.95 (dt, $J = 3.1$, 12.5 Hz, 1 H), 2.82, 3.56 (2 t, $J = 6.6$ Hz, 2 H each, 2 CH_2), 4.70–4.76 (m, 1 H, OCH), 7.43–7.49, 7.60–7.66, 7.82–7.87, 8.46–8.48 (4 m, 1 H each) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 12.0, 12.2, 18.6 (3 Me), 21.2 (CH_2), 22.5, 22.8 (2 Me), 23.8, 24.2, 27.4 (3 CH_2), 28.0 (CH), 28.2, 28.5, 28.8, 30.1, 32.0, 33.9 (6 CH_2), 35.4 (*i*-C), 35.4, 35.8 (2 CH), 36.1, 36.7, 39.5, 39.9 (4 CH_2), 42.6 (*i*-C), 44.6, 54.2, 56.2, 56.4 (4 CH), 74.4 (OCH), 115.8, 120.1 (2 CH), 120.8 (q, $^1J_{C,F} = 270.6$ Hz, CF_3), 121.8 (*i*-C), 125.7, 130.5 (2 CH), 140.1 (q, $^2J_{C,F} = 38.7$ Hz, C-3), 140.1 (*i*-C), 171.6, 172.5 (2 C = O) ppm; ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.5 (s, CF_3) ppm; IR (neat): ν 2930, 2855, 1730 (C = O), 1520, 1374, 1206, 1150, 1109, 1006, 913, 772 cm^{-1}; ESI-MS (*m/z*): 679.8 (100, $[M + Na]^+$); elemental analysis calcd (%) for $C_{39}H_{55}F_3N_2O_3$ (656.9): C 71.31, H 8.44, N 4.26; found: C 71.22, H 8.44, N 4.27.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

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References

[1] (a) R. Huisgen, 1,3-dipolar cycloadditions. Past and future, Angew. Chem. Int. Ed Engl 2 (1963) 565–598, 1,3-Dipolare Cycloadditionen; Rückschau und Ausblick, Angew. Chem. 75 (1963) 604–637;
(b) M. Breugst, H.-U. Reissig, The Huisgen reaction: milestones of the 1,3-dipolar cycloaddition, Angew. Chem. Int. Ed 59 (2020) 12293–12307. Die Huisgen-Reaktion: Meilensteine der 1,3-dipolaren Cycloaddition, Angew. Chem. 132 (2020) 12389–12404.

[2] (a) J.F. Sharp, Nitrile ylides and nitrile imines in 'The chemistry of heterocyclic compounds, in: A. Padwa, W.H. Pearson (Eds.), Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products', Vol. 59, J. Wiley & Sons, New York, 2002, pp. 473–537. Chapter 7;
(b) C. Jamieson, K. Livingstone, The Nitrile Imine 1,3-dipole. Properties, Reactivity and Applications, Springer Nature Switzerland AG, 2020, pp. 50–52;
(c) F. Heaney, Nitrile oxide/alkyne cycloadditions – a credible platform for synthesis of bioinspired molecules by metal-free molecular clicking. Eur. J. Org. Chem., 2019, pp. 3049–3058;
(d) D.A. MacKenzie, A.R. Sherratt, M. Chigrinova, L.L.W. Cheung, J.P. Pezacki, Strain-promoted cycloadditions involving nitrones and alkynes–rapid tunable reactions for bioorthogonal labeling. Curr. Opin. Chem. Biol., 2014, pp. 81–88;
(e) B. Mandal, B. Basu, Synthesis of β-lactams through alkyne-nitrone cycloadditions. Top. Heterocycl. Chem., 2013, pp. 85–110, for applications of nitrone/alkyne cycloaddition in the synthesis of β-lactams, see;
(f) A.V. Gulevskaya, J.I. Nelina-Nemtseva, 1,3-Dipolar cycloaddition reactions of azomethine ylides and alkynes. Chem. Heterocycl. Compds., 2018, pp. 1084–1107;
(g) M. Meldal, F. Diness, Recent fascinating aspects of the CuAAC click reaction. Trends Analyt. Chem., 2020, pp. 569–584.

[3] (a) G. Mlostoń, K. Urbaniak, G. Utecht, D. Lentz, M. Jasiński, Trifluoromethylated 2,,3-dihydro-1,3,4-thiadiazoles via the regioselective (3+2)-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones, J. Fluorine Chem. 192 (2016) 147–154;
(b) G. Utecht, J. Sioma, M. Jasiński, G. Mlostoń, Expected and unexpected results in reactions of fluorinated nitrile imines with (cyclo)aliphatic thioketones, J. Fluorine Chem. 201 (2017) 68–75;
(c) G. Mlostoń, P. Grzelak, G. Utecht, M. Jasiński, First [3+2]-cycloadditions of thiochalcones as C=S dipolarophiles in reactions with fluorinated nitrile imines, Synthesis 49 (2017) 2129–2137;
(d) G. Utecht-Jarzyńska, M. Jasiński, K. Świątek, G. Mlostoń, H. Heimgartner, Novel trifluoromethylated spiro-1,3,4-thiadiazoles via [3+2]-cycloaddition of 2,3-diphenylcyclopropenethione with selected *in situ*-generated nitrile imines derived from trifluoroacetonitrile, Heterocycles 101 (2020) 251–262;

(e) G. Utecht-Jarzyńska, S.S. Mykhaylychenko, E.B. Rusanov, Y.G. Shermolovich, M. Jasiński, G. Mlostoń, Highly fluorinated 2,3-dihydro-1,3,4-thiadiazole derivatives via (3+2)-cycloadditions of tertiary thioamides with nitrile imines from trifluoroacetonitrile, J. Fluorine Chem. (2020) *submitted*.

[4] (a) G. Utecht, A. Fruziński, M. Jasiński, Polysubstituted 3-trifluoromethylpyrazoles: regioselective (3+2)-cycloaddition of trifluoroacetonitrile imines with enol ethers and functional group transformations, Org. Biomol. Chem. 16 (2018) 1252–1257;
(b) G. Utecht, G. Mlostoń, M. Jasiński, A straightforward access to trifluoromethylated spirobipyrazolines through a double (3+2)-cycloaddition of fluorinated nitrile imines with alkoxyallenes, Synlett 29 (2018) 1753–1758;
(c) G. Utecht-Jarzyńska, A. Michalak, J. Banaś, G. Mlostoń, M. Jasiński, Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: an access to fluorinated 1,3,4-thiadiazine derivatives via (3+3)-annulation, J. Fluorine Chem. 222–223 (2019) 8–14. For representative application of trifluoroacetonitrile imines 1 in the synthesis of 6-membered systems, see:.

[5] K. Tanaka, S. Maeno, K. Mitsuhashi, Preparation of trifluoroacetonitrile phenylimine and its reactions with some dipolarophiles, Chem. Lett. (1982) 543–546, for analogous reactions with common alkyl/aryl nitrile imines, see Ref. [2c].

[6] (a) R. Sanz, Recent applications of aryne chemistry to organic synthesis. A review, Org. Prep. Proced. Int. 40 (2008) 215–291;
(b) P.M. Tadross, B.M. Stoltz, A comprehensive history of arynes in natural product total synthesis, Chem. Rev. 112 (2012) 3550–3577;
(c) D. Pérez, D. Peña, E. Guitián, Aryne cycloaddition reactions in the synthesis of large polycyclic aromatic compounds, Eur. J. Org. Chem. (2013) 5981–6013;
(d) M.A. Alam, K. Shimada, A. Jahan, D. Nasrin, M. Kudrat-E-Zahan, M. Shahabuddin, Tha advances and applications of arynes and their precursors to synthesize the heterocyclic compounds: a review, Am. J. Heterocycl. Chem. 3 (2017) 47–54.

[7] (a) Y. Himeshima, T. Sonoda, H. Kobayashi, 1 Fluoride-induced, 2-elimination of *o*-trimethylsilyl-phenyl triflate to benzyne under mild conditions, Chem. Lett. 12 (1983) 1211–1214;
(b) D. Peña, A. Cobas, D. Pérez, E. Guitián, An efficient procedure for the synthesis of ortho-trialkylsilylaryl triflates: easy access to precursors of functionalized arynes, Synthesis 10 (2002) 1454–1458.

[8] C. Spiteri, S. Keeling, J.E. Moses, New synthesis of 1-substituted-1*H*-indazoles via 1,3-dipolar cycloaddition of in situ generated nitrile imines and benzyne, Org. Lett. 12 (2010) 3368–3371.

[9] S. Fustero, A. Simón-Fuentes, O. Delgado, R. Román, in: V.G. Nenajdenko (Ed.), Fluorinated Pyrazoles and Indazoles, in Fluorine in Heterocyclic Chemistry, Vol 1, Springer, 2014, pp. 279–322.

[10] J.-C. Castillo, A. Tigreros, Y. Coquerel, J. Rodríguez, M.A. Macías, J. Portilla, Synthesis of pyrrolo[2,3-c]isoquinolines via the cycloaddition of benzyne with arylideneaminopyrroles: photophysical and crystallographic study, ACS Omega 4 (2019) 17326–17339.

[11] F.M. Cordero, B.B. Khairnar, A. Ranzenigo, A. Brandi, Cycloaddition of benzyne with alkoxy-substituted pyrroline N-oxides: unexpected rearrangement to an N-phenylpyrrole, SynOpen 2 (2018) 25–29.

[12] R. Sustmann, Orbital energy control of cycloaddition reactivity, Pure Appl. Chem. 40 (1974) 569–593.

[13] S.-G. Zhang, C.-G. Liang, W.-H. Zhang, Recent advances in indazole-containing derivatives: synthesis and biological perspectives, Molecules 23 (2018) 2783.

[14] (a) S. Di Cosimo, G. Ferretti, P. Papaldo, P. Carlini, A. Fabi, F. Cognetti, Lonidamine: Efficiacy and safety in clinical trials for the treatment of solid tumors, Drugs Today 39 (2003) 157–174;
(b) L. Guo, A.A. Shestov, A.J. Worth, K. Nath, D.S. Nelson, D.B. Leeper, J. D. Glickson, I.A. Blair, Inhibition of mitochondrial complex II by the anticancer agent lonidamine, J. Biol. Chem. 291 (2016) 42–57.

[15] (a) S. Ke, N. Li, T. Ke, L. Shi, Z. Zhang, W. Fang, Y.-N. Zhang, K. Wang, R. Zhou, Z. Wan, Z. Yang, G. Zhang, Y. Wei, Synthesis and evaluation of steroidal thiazoline conjugates as potential antiviral agents, Future Med. Chem. 10 (2018) 2589–2605;
(b) M. Ibrahim-Ouali, F. Dumur, Recent syntheses of steroidal derivatives containing heterocycles, Arkivoc i (2019) 304–339.

[16] (a) R.M. Claramunt, C. López, C. Pérez-Medina, M. Pérez-Torralba, J. Elguero, G. Escames, D. Acuña-Castroviejo, Fluorinated indazoles as novel selective inhibitors of nitric oxide synthase (NOS): synthesis and biological evaluation, Bioorg. Med. Chem. 19 (2009) 6180–6187;
(b) G.N. Lipunova, E.V. Nosova, V.N. Charushin, O.N. Chupakhin, Fluorine-containing indazoles: synthesis and biological activity, J. Fluorine Chem. 192 (2016) 1–21;
(c) J.S. Tash, R. Chakrasali, S.R. Jakkaraj, J. Hughes, S.K. Smith, K. Hornbaker, L. L. Heckert, S.B. Ozturk, M.K. Hadden, T.G. Kinzy, B.S.J. Blagg, G.I. Georg, Gamendazole, an orally active indazole carboxylic acid male contraceptive agent, targents HSP90AB1 (HSP90BETA) and EEF1A1 (eEF1A), and stimulates transcription in rat sertoli cells, Biol. Reprod. 78 (2008) 1139–1152.

[17] (a) D.K. O'Dell, K.M. Nicholas, Synthesis of 1*H*-indazoles by reductive cyclisation of *o*-nitro-ketoximes, Heterocycles 63 (2004) 373–382;
(b) J. Teichert, P. Oulié, K. Jacob, L. Vendier, M. Etienne, R.M. Claramunt, C. López, C.P. Medina, I. Alkorta, J. Elguero, The structure of fluorinated indazoles: the effect of the replacement of a H by F atom on the supramolecular structure of NH-indazoles, New J. Chem. 31 (2007) 936–946;
(c) G.-D. Zhu, J. Gong, V.B. Gandhi, K. Woods, Y. Luo, X. Liu, R. Guan, V. Klinghofer, E.F. Johnson, V.S. Stoll, M. Mamo, Q. Li, S.H. Rosenberg, V. L. Giranda, Design and synthesis of pyridine-pyrazolopyridine-based inhibitors of protein kinase B/Akt, Bioorg. Med. Chem. 15 (2007) 2441–2452.

[18] A. Wojciechowska, M. Jasiński, P. Kaszyński, Tautomeric equilibrium in trifluoroacetaldehyde arylhydrazones, Tetrahedron 71 (2015) 2349–2356.

[19] P. Kaszyński, M. Jasiński, S. Ciastek, S. Kapuściński, K. Gębicki, Molecular engineering of liquid crystalline derivatives of 6-oxoverdazyl, Arkivoc ii (2017) 345–368.

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Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions'

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Letter

Trifluoromethylated Pyrazoles via Sequential (3 + 2)-Cycloaddition of Fluorinated Nitrile Imines with Chalcones and Solvent-Dependent Deacylative Oxidation Reactions

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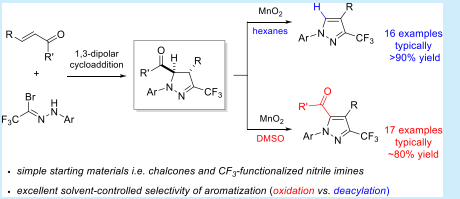
ABSTRACT: A general approach for preparation of two types of polyfunctionalized 3-trifluoromethylpyrazoles is reported. The protocol comprises (3 + 2)-cycloaddition of the *in situ* generated trifluoroacetonitrile imines with enones leading to *trans*-configured 5-acyl-pyrazolines in a fully regio- and diastereoselective manner. Initially formed cycloadducts were aromatized by treatment with manganese dioxide. Depending on the solvent used, the oxidation step either led to fully substituted pyrazoles (DMSO) or proceeded via a deacylative pathway to afford 1,3,4-trisubstituted derivatives (hexane) with excellent selectivity.



In the past two decades, great attention has been focused toward the chemistry of pyrazoles functionalized by introduction into the heterocyclic ring of either fluorine atom(-s) or fluoroalkylated groups.[1] In a series of recent publications they were reported as organic materials of remarkable practical importance, and specifically 3-trifluoromethylated pyrazole has been indicated as a privileged structural scaffold for a variety of agrochemicals, pharmaceuticals, and advanced materials.[1,2] For these reasons, development of new methods aimed at efficient and selective synthesis of multifunctionalized, fluorinated pyrazoles is a challenging problem in current organic synthesis.

In general, common access to 3-trifluoromethylpyrazoles relies on condensation of corresponding 1,3-dicarbonyl compounds (or their equivalents) with a functionalized hydrazines.[1−3] In addition, Lewis acid mediated cyclizations and related transformations of hydrazones are also applied.[4] Furthermore, some postcyclization, functional group interconversions leading to trifluoromethylated pyrazoles, and catalytic fluoroalkylations have been developed more recently.[5] Another powerful approach is based on 1,3-dipolar cycloadditions employing trifluoromethylated 1,3-dipoles and appropriate dipolarophiles. In the past decade, remarkable progress has been achieved in the chemistry of 2,2,2-trifluorodiazoethane; however, some drawbacks such as difficult handling, low selectivity, and the scope limited to pyrazoles lacking a substituent at N(1) have been pointed out.[6] In contrast, applications of alternative 1,3-dipolar intermediates, i.e. trifluoroacetonitrile imines **1**, offer access to *N*-functionalized heterocycles, and typically, their reactions proceed with excellent regio- and chemoselectivity.[7] Nevertheless, application of easily accessible nitrile imines **1** for preparation of the title 3-trifluoromethylated pyrazoles remain underexplored.

Some time ago, Oh (but also our group) demonstrated that by using electron-rich C=C dipolarophiles such as enamines or vinyl ethers,[8] the problem of low regioselectivity, reported by Tanaka in his pioneering work on 1,3-dipolar cycloadditions of **1** with nonactivated alkenes, could easily be overcome.[9] As shown in Scheme 1, the presence of $-NR_2$ or $-OR$ as a leaving group in an ethylenic dipolarophile assures complete regioselectivity in the (3 + 2)-cycloaddition step and the initially formed products undergo either spontaneous or Brönsted acid induced elimination of an amine or alcohol molecule, respectively, to give the final aromatized heterocycle. More recently, Ma and co-workers developed an interesting one-pot decarboxylative (3 + 2)-cycloaddition route leading to fully substituted CF_3-pyrazoles, starting with nitrile imines and isoxazolidinediones as dipolarophiles.[10] In that case, thermal extrusion of CO_2 from the corresponding intermediate was pointed out as a driving force leading to the final, aromatized product. Remarkably, neither of the methods developed thus far explores the orthogonal properties of the initially formed (3 + 2)-cycloadducts. Thus, in the search for new synthetic protocols toward polyfunctionalized 3-trifluoromethylpyrazoles, we envisioned possible access to three- and tetra-substituted analogues by using 5-acylpyrazolines as common

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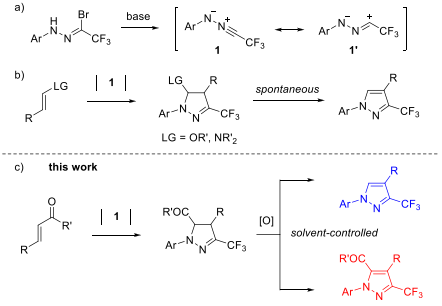
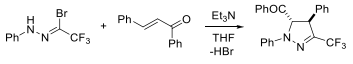
Scheme 1. General Schemes of (a) Generation of Nitrile Imines 1, (b) Their Reactions with Electron-Rich Alkenes, (c) and the Solvent-Controlled Synthesis of Polysubstituted 3-Trifluoromethylpyrazoles Reported Herein



precursors. The requisite starting materials can be obtained by employing azomethine imines as reported by Xie,[11] but they should also be accessible via anticipated regioselective (3 + 2)-cycloaddition of acyclic enones with *in situ* generated fluorinated nitrile imines **1** (Scheme 1). Here we report on the efficient synthesis of two distinct classes of polysubstituted 3-trifluoromethylpyrazoles via a two-step protocol comprising (*i*) diastereoselective (3 + 2)-cycloaddition of **1** with chalcones followed by (*ii*) solvent-controlled, competitive oxidation vs deacylative aromatization of the intermediate pyrazolines by using MnO_2 as a convenient oxidant.

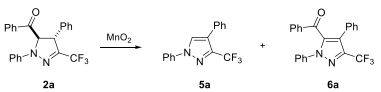
The model 5-benzoylpyrazoline **2a** was prepared by the reaction of chalcone **4a** with an excess of hydrazonoyl bromide **3a** in the presence of Et_3N as a base, at room temperature (Scheme 2).[7b] Gratifyingly, the expected *trans*-configured

Scheme 2. Synthesis of 3-Trifluoromethylpyrazoline 2a



pyrazoline **2a** was formed as the only product under the applied conditions. In the search for an efficient oxidizing reagent, we directed attention to MnO_2 as a common oxidant which has broadly been applied, e.g. in diverse dehydrohalogenation processes.[12,13] More importantly, despite its well-known mildness under neutral conditions, successful oxidation of some carbonyl compounds into respective carboxylic acids is also known.[14] The first experiment was aimed at oxidation of model pyrazoline **2a** with excess MnO_2 (ca. 85%, <10 μm), which was carried out in DCM solution, and the formation of a single product **5a** in ca. 37% yield was observed after 2 d at room temperature (Table 1, entry 1). Interestingly, in the ^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 1,4-diphenyl-3-trifluoromethylpyrazole (**5a**), along with the expected quartets found at δ = 122.7 ($^1J_{C-F}$ = 269.9 Hz) and δ = 140.5 ($^2J_{C-F}$ = 36.6 Hz) attributed to the CF_3 group and the C(3) atom, respectively, the presence of another quartet at δ = 128.8 ($J_{C-F} \approx$ 1.2 Hz) resulting from through-space coupling between F atoms and the *ortho*-C atoms of the neighboring Ph ring additionally confirmed the expected substitution pattern in **5a**.

Table 1. Oxidation of 3-Trifluoromethylpyrazoline 2a with MnO_2[a]



			ratio [%][b] (isolated yield)		
entry	solvent	temp	2a	5a	6a
1	DCM	rt	63	37	–
2	hexane	rt	46	54	–
3	toluene	rt	79	21	–
4	hexane	60 °C	–	96 (94)	4
5	hexane[c]	60 °C	–	98 (97)	2
6	THF	rt	89	11	–
7	MeCN	rt	90	10	–
8	DMSO	rt	100	–	–
9	MeCN	75 °C	–	53	47
10	DMF	100 °C	–	33	67
11	DMF	130 °C	–	35	65
12	DMSO	100 °C	–	7	93 (79)
13	DMSO[c]	100 °C	–	10	90 (81)
14	DMSO[d]	100 °C	–	8	92
15	DMSO[e]	100 °C	100	–	–

[a]Reaction conditions: a solution of **2a** (0.20 mmol) in corresponding solvent (3 mL) and solid MnO_2 (20 equiv) were stirred magnetically in a 10 mL flask for 2 d. [b]Estimated based on ^1H NMR spectra of crude mixtures. [c]1 mmol (**2a**) scale. [d]Reaction performed in the presence of atmospheric moisture (open flask). [e]Heating in absence of MnO_2.

Examination of the solvent effects revealed that decreased polarity of the organic medium favors deacylative oxidation leading to pyrazole **5a** (54% in hexane, entry 2), whereas only traces or no formation of this product was observed in THF, MeCN, and DMSO solutions.[15] Increasing the temperature of the hexane solution resulted in complete conversion of starting pyrazoline **2a** into **5a** (96%) which was accompanied only by trace amounts of 5-benzoyl-functionalized pyrazole **6a** formed as a side product. On the other hand, oxidation of **2a** at elevated temperature in polar media such as MeCN, DMF, and DMSO proceeded partially with preservation of the benzoyl group and led to mixtures of **5a** and **6a** (entries 9−12). In the latter experiment performed in DMSO, preferential formation of the tetrasubstituted product was observed. Gratifyingly, both oxidation reactions could successfully be scaled up (1.0 mmol) without any remarkable loss of selectivity (entries 5 and 13). Furthermore, the optimized deacylative protocol was found to be operationally very simple; both the benzoic acid formed as the only byproduct and the remaining solid MnO_2 could be filtered off to give, after removal of the solvent, spectroscopically pure product **5a**. Subsequent filtration of this material through a short silica gel pad provided analytically pure sample. The observed switch of chemoselectivity also deserves a brief comment. Possibly, the reaction carried out in the nonpolar hexane solution is initiated by oxidation at the benzyl-like position C(4) of the *trans*-configured pyrazoline **2** and proceeds preferentially via deacylative fashion due to close proximity of the benzoyl group and the "activated surface" of MnO_2. Apparently, replacement of the nonpolar solvent by polar DMSO reduces the oxidative potential of MnO_2,[12] and hence, observed *trans* elimination of two H-atoms takes place.

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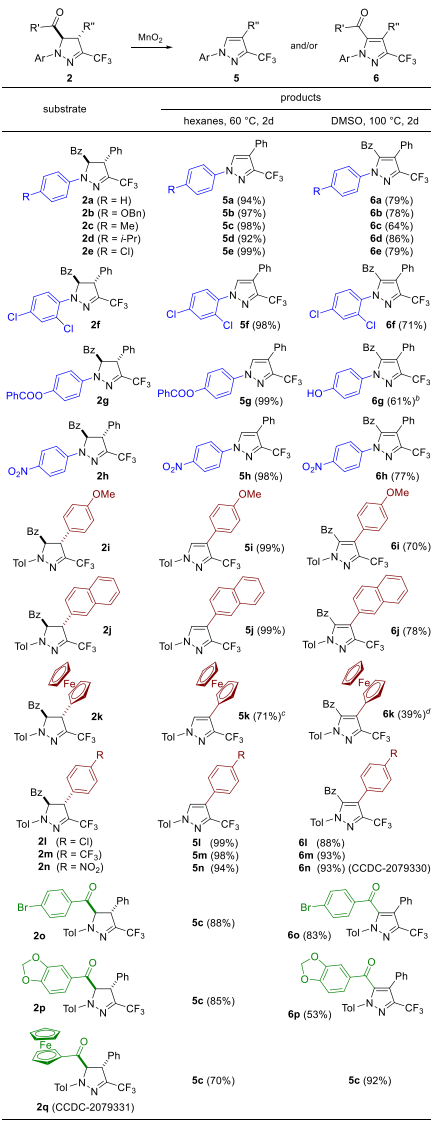
With the optimized conditions in hand, we investigated the scope and limitations of the developed solvent-controlled oxidation procedure. Hence, a series of 5-benzoylpyrazolines **2b**−**2q** were prepared in analogy to the model reaction depicted in Scheme 2 in acceptable yields of 44−96%, and next, the obtained products **2** were subjected to reaction with MnO_2 (Scheme 3; for detailed procedure, see Supporting Information). First, a series of pyrazolines **2b**−**2h**, derived from chalcone **4a** and differently substituted nitrile imines **1**, were examined in oxidation reactions.

In all the tested examples, the expected products **5** and **6** were formed in high yields and with excellent selectivity, regardless of the electronic (OBn, NO_2) and steric (2,4-di-Cl) features of the substituent present in the aryl ring located at N(1). Only in the case of 4-benzoyloxy derivative **2g** oxidation in hot DMSO proceeded with complete deprotection of the ester unit to afford phenol **6g** as the only product. Next, a second set of pyrazolines (**2i**−**2q**) obtained by condensation of differently substituted chalcones **4** with *p*-tolyl functionalized nitrile imine was examined. Again, excellent selectivity and high yields were noticed for this series except from the ferrocenyl-functionalized analogues **2k** and **2q**. In the first case, the presence of the redox-active Fc group located at C(4) interfered with complete selectivity of the oxidation to provide *ca.* 7:3 and *ca.* 6:4 mixtures of **5k** and **6k** in hexane and DMSO, respectively. On the other hand, introduction of ferrocenoyl unit at C(5) in pyrazoline **2q** favored debenzoylative aromatization to provide pyrazole **5c** as a major product in both experiments. The structures of two representative compounds in this series, **2q** and **6n**, were unambiguously confirmed by X-ray analysis.[16]

In order to demonstrate the essential role of the electron-withdrawing C═O group located at the C(5) in the formation of 1,4-disubstituted 3-trifluoromethylpyrazoles **5**, the stilbene-derived *trans*-pyrazoline **7** was synthesized and applied for the reaction with MnO_2 in hexane (Scheme 4). In that case, the expected 1,4,5-triphenyl-3-trifluoromethylpyrazole (**8**, 90%) was obtained as the sole product after 2 d of heating at 60 °C. Next, (*E*)-4-phenyl-3-buten-2-one and methyl *trans*-cinnamate were also reacted with nitrile imine **1a** to yield the expected pyrazolines **9a** and **9b**, respectively. Subsequent treatment with MnO_2 in hot hexane provided the known pyrazole **5a** lacking a substituent at C(5), hence indicating also methoxycarbonyl- and acetyl-functionalized pyrazolines as suitable substrates for the described deacylative aromatization reaction. Furthermore, two more bis-trifluoromethylated pyrazoles **5r** and **6r** were efficiently prepared via solvent-controlled oxidation starting with pyrazoline **2r** obtained via (3 + 2)-cycloaddition of nitrile imine **1c** with the known CF_3-functionalized enone, namely, with (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one (Scheme 4).[17] This result demonstrates again that electron-deficient nitrile imines **1** derived from trifluoroacetonitrile are very prone 1,3-dipoles which are able to react even with strongly electron-deficient dipolarophiles such as fluorinated thioamides,[7d] and fluorinated enones. It is also worth noting that the presented protocol nicely supplements previously reported methods for the synthesis of rarely reported bis-trifluoromethylated pyrazoles, which are of interest in the context of not only pharmaceutical applications but also coordination chemistry.[1b,6d,18]

In summary, a novel protocol for the synthesis of two types of 3-trifluoromethylated pyrazoles, by using 5-acylpyrazolines as common precursors for highly selective, solvent-dependent

Scheme 3. Oxidation of Pyrazolines 2 with MnO_2; Scope of Substrates[a]



[a]If not stated otherwise, the yields refer to isolated yields. [b]Obtained from pyrazoline **2g**. [c]The formation of **6k** (*ca.* 27% based on ^{1}H NMR of crude mixture) was observed. [d]The formation of **5k** (59%) was observed; yield estimated based on ^{1}H NMR spectrum of crude mixture.

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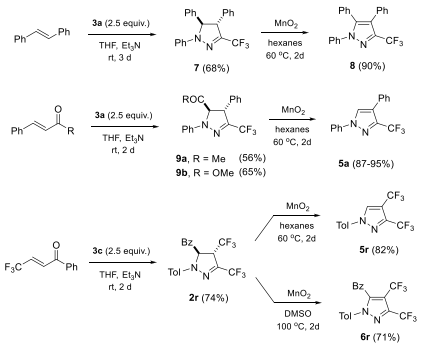
Scheme 4. Control Experiments Aimed at Aromatization of Pyrazole Ring



oxidative aromatization with MnO_2, was elaborated and examined in a series of experiments. Starting pyrazolines are readily available via fully regio- and diastereoselective (3 + 2)-cycloaddition reactions starting with corresponding chalcones and hydrazonoyl bromides applied as precursors of the *in situ* generated fluorinated nitrile imines, derived from trifluoroacetonitrile. The reported method is scalable and characterized by a wide tolerance of functional groups. For all these reasons it can be recommended for preparation of polysubstituted 3-trifluoromethylpyrazoles which can be of potential interest, e.g. for medicinal chemistry, crop protection industry, and materials chemistry. The presented work demonstrates once more the utility of 1,3-dipolar cycloaddition reactions (the Huisgen reaction[19]) in method development for synthesis of trifluoromethylated heterocycles.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00521.

FAIR data, including the primary NMR FID files, for compounds **2a**−**2r**, **5a**−**5r**, **6a**−**6r**, **7**, **8**, **9a**, and **9b** (ZIP)

Experimental procedures, characterization data and NMR spectra of all compounds (PDF)

Accession Codes

CCDC 2079230−2079231 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

‡A.K. and G.U.-J. contributed equally

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Fustero, S.; Simón-Fuentes, A.; Delgado, O.; Román, R. Fluorinated Pyrazoles and Indazoles. In *Fluorine in Heterocyclic Chemistry*, Vol. *1*; Nenajdenko, V., Eds.; Springer: Cham, 2014. (b) Mykhailiuk, P. K. Fluorinated pyrazoles: From synthesis to applications. *Chem. Rev.* **2021**, *121*, 1670.

(2) (a) Kirsch, P. *Modern Fluoroorganic Chemistry, Synthesis, Reactivity, Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2013. (b) Giornal, F.; Pazenok, S.; Rodefeld, L.; Lui, N.; Vors, J.-P.; Leroux, F. R. Synthesis of diversely fluorinated pyrazoles as novel active agrochemical ingredients. *J. Fluorine Chem.* **2013**, *152*, 2. (c) Kaur, K.; Kumar, V.; Gupta, G. K. Trifluoromethylpyrazoles as anti-inflamatory and antibacterial agents: A review. *J. Fluorine Chem.* **2015**, *178*, 306.

(3) Recent work: (a) Pianoski, K. E.; Poletto, J.; Vieira da Silva, M. J.; Ascencio Camargo, J. N.; Jacomini, A. P.; Gonçalves, D. S.; Back, D. F.; Moura, S.; Rosa, F. A. 1,2-Addition to trifluoromethylated *β*-enamino diketones: Regioselective synthesis of trifluoromethyl-containing azomethine pyrazoles and isoxazoles. *Org. Biomol. Chem.* **2020**, *18*, 2524. (b) Muzalevskiy, V. M.; Sizova, Z. A.; Panyushkin, V. V.; Chertkov, V. A.; Khrustalev, V. N.; Nenajdenko, V. G. *α,β*-Disubstituted CF_3-enones as a trifluoromethyl building block: Regioselective preparation of totally substituted 3-CF_3-pyrazoles. *J. Org. Chem.* **2021**, *86*, 2385. (c) Wan, C.; Pang, J.-Y.; Jiang, W.; Zhang, X.-W.; Hu, X.-G. Copper-catalyzed reductive ring cleavage of isoxazoles: Synthesis of fluoroalkylated enaminones and application for the preparation of celecoxib, deracoxib, and mavacoxib. *J. Org. Chem.* **2021**, *86*, 4557.

(4) Selected examples: (a) Wen, J.-J.; Tang, H.-T.; Xiong, K.; Ding, Z.-C.; Zhan, Z.-P. Synthesis of polysubstituted pyrazoles by a Platinum-catalyzed sigmatropic rearrangement/cyclization cascade. *Org. Lett.* **2014**, *16*, 5940. (b) Ji, G.; Wang, X.; Zhang, S.; Xu, Y.; Ye, Y.; Li, M.; Zhang, Y.; Wang, J. Synthesis of 3-trifluoromethylpyrazoles via trifluoromethylation/cyclization of *α,β*-alkynic hydrazines using a hypervalent iodine reagent. *Chem. Commun.* **2014**, *50*, 4361. (c) Yang, Y.; Hu, Z.-L.; Li, R.-H.; Chen, Y.-H.; Zhan, Z.-P. Pyrazole synthesis

via a cascade Sonogashira coupling/cyclization of *N*-propargyl sulfonylhydrazones. *Org. Biomol. Chem.* **2018**, *16*, 197. (d) Muzalevskiy, V. M.; Nenajdenko, V. G. Electrophilic halogenation of hydrazones of CF_3-ynones. Regioselective synthesis of 4-halosubstituted 3-CF_3-pyrazoles. *Org. Biomol. Chem.* **2018**, *16*, 7935. (e) Zhu, C.; Zeng, H.; Liu, C.; Cai, Y.; Fang, X.; Jiang, H. Regioselective synthesis of 3-trifluoromethylpyrazole by coupling of aldehydes, sulfonyl hydrazides, and 2-bromo-3,3,3-trifluoropropene. *Org. Lett.* **2020**, *22*, 809. (f) Wang, H.; Ning, Y.; Sun, Y.; Sivaguru, P.; Bi, X. Cycloaddition of trifluoroacetaldehyde *N*-triftosylhydrazone (TFHZ-Tfs) with alkynes for synthesizing 3-trifluoromethylpyrazoles. *Org. Lett.* **2020**, *22*, 2012.

(5) For exemplary functional group interconversions, see: (a) Zhang, Y.; Chen, Z.; Nie, J.; Zhang, F.-G.; Ma, J.-A. Development of cyanopyrazoles as building blocks to fungicide fluxapyroxad and analogues. *J. Org. Chem.* **2019**, *84*, 7148. (b) Trofymchuk, S.; Bugera, M. Y.; Klipkov, A. A.; Razhyk, B.; Semenov, S.; Tarasenko, K.; Starova, V. S.; Zaporozhets, O. A.; Tananaiko, O. Y.; Alekseenko, A. N.; Pustovit, Y.; Kiriakov, O.; Gerus, I. I.; Tolmachev, A. A.; Mykhailiuk, P. K. Deoxofluorination of (hetero)aromatic acids. *J. Org. Chem.* **2020**, *85*, 3110. For trifluoromethylations, see: (c) Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C. A radical approach to the copper oxidative addition problem: Trifluoromethylation of bromoarenes. *Science* **2018**, *360*, 1010. (d) Karmel, C.; Rubel, C. Z.; Kharitonova, E. V.; Hartwig, J. F. Iridium-catalyzed silylation of five-membered heteroarenes: High sterically derived selectivity from a pyridyl-imidazoline ligand. *Angew. Chem., Int. Ed.* **2020**, *59*, 6074. (e) Johansen, M. B.; Lindhardt, A. T. Copper-catalyzed and additive free decarboxylative trifluoromethylation of aromatic and heteroaromatic iodides. *Org. Biomol. Chem.* **2020**, *18*, 1417.

(6) (a) Li, F.; Nie, J.; Sun, L.; Zheng, Y.; Ma, J.-A. Silver-mediated cycloaddition of alkynes with CF_3CHN_2: Highly regioselective synthesis of 3-trifluoromethylpyrazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 6255. (b) Mykhailiuk, P. K. Three-component synthesis of fluorinated pyrazoles from fluoroalkylamines, $NaNO_2$ and electron-deficient alkynes. *Org. Biomol. Chem.* **2015**, *13*, 3438. (c) Britton, J.; Jamison, T. F. A unified continuous flow assembly-line synthesis of highly substituted pyrazoles and pyrazolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 8823. (d) Li, F.; Wang, J.; Pei, W.; Li, H.; Zhang, H.; Song, M.; Guo, L.; Zhang, A.; Liu, L. Direct [3 + 2]-cycloaddition of electron-deficient alkynes with CF_3CHN_2: Regioselective one-pot Synthesis of 3-trifluoromethylpyrazoles. *Tetrahedron Lett.* **2017**, *58*, 4344. (e) Zhang, X.; Liu, Z.; Yang, X.; Dong, Y.; Virelli, M.; Zanoni, G.; Anderson, E. A.; Bi, X. Use of trifluoroacetaldehyde N-Tfsylhydrazone as a trifluorodiazoethane surrogate and its synthetic applications. *Nat. Commun.* **2019**, *10*, 284. (f) Lv, S.; Zhou, H.; Yu, X.; Xu, Y.; Zhu, H.; Wang, M.; Liu, H.; Dai, Z.; Sun, G.; Gong, X.; Sun, X.; Wang, L. Lewis base-catalyzed intermolecular triazene alkyne cycloaddition for late-stage functionalization and scaffold diversification. *Commun. Chem.* **2019**, *2*, 69. Selected reviews: (g) Mertens, L.; Koenigs, R. M. Fluorinated diazoalkanes − a versatile class of reagents for the synthesis of fluorinated compounds. *Org. Biomol. Chem.* **2016**, *14*, 10547. (h) Mykhailiuk, P. K. 2,2,2-Trifluorodiazethane (CF_3CHN_2): A long journey since 1943. *Chem. Rev.* **2020**, *120*, 12718.

(7) (a) Mlostoń, G.; Urbaniak, K.; Utecht, G.; Lentz, D.; Jasiński, M. Trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles via the regioselective [3 + 2]-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones. *J. Fluorine Chem.* **2016**, *192*, 147. (b) Grzelak, P.; Utecht, G.; Jasiński, M.; Mlostoń, G. First (3 + 2)-cycloadditions of thiochalcones as C=S dipolarophiles: Efficient synthesis of 1,3,4-thiadiazoles via reactions with fluorinated nitrile imines. *Synthesis* **2017**, *49*, 2129. (c) Utecht-Jarzyńska, G.; Michalak, A.; Banaś, J.; Mlostoń, G.; Jasiński, M. Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: An access to fluorinated 1,3,4-thiadiazine derivatives via (3 + 3)-annulation. *J. Fluorine Chem.* **2019**, *222*−*223*, 8. (d) Utecht-Jarzyńska, G.; Mykhaylychenko, S. S.; Rusanov, E. B.; Shermolovich, Y. G.; Jasiński, M.; Mlostoń, G. Highly fluorinated 2,3-dihydro-1,3,4-thiadiazole derivatives via (3 + 2)-cycloadditions of tertiary thioamides with nitrile imines derived from trifluoroacetonitrile. *J. Fluorine Chem.* **2021**, *242*, 109702. For cycloadditions of closely related difluoromethylated nitrile imines see: (e) Han, T.; Wang, K.-H.; Yang, M.; Zhao, P.; Wang, F.; Wang, J.; Huang, D.; Hu, Y. Synthesis of difluoromethylated Pyrazoles by the [3 + 2] cycloaddition reaction of difluoroacetohydrazonoyl bromides. *J. Org. Chem.* **2022**, *87*, 498.

(8) (a) Oh, L. M. Synthesis of celecoxib via 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2006**, *47*, 7943. (b) Utecht, G.; Fruziński, A.; Jasiński, M. Polysubstituted 3-trifluoromethylpyrazoles: Regioselective (3 + 2)-cycloaddition of trifluoroacetonitrile imines with enol ethers and functional group transformations. *Org. Biomol. Chem.* **2018**, *16*, 1252.

(9) Tanaka, K.; Maeno, S.; Mitsuhashi, K. Preparation of trifluoroacetonitrile phenylimine and its reactions with some dipolarophiles. *Chem. Lett.* **1982**, *11*, 543.

(10) Tian, Y.-C.; Li, J.-K.; Zhang, F.-G.; Ma, J.-A. Regioselective decarboxylative cycloaddition route to fully substituted 3-CF_3-pyrazoles from nitrilimines and isoxazolidinediones. *Adv. Synth. Catal.* **2021**, *363*, 2093.

(11) Xie, H.; Zhu, J.; Chen, Z.; Li, S.; Wu, Y. Reaction of a trifluoromethylated N-monosubstituted hydrazone with α,β-ethenyl ketones: A novel synthesis of substituted pyrazolindines and pyrazolines. *Synthesis* **2011**, *2011*, 2767.

(12) (a) Fatiadi, A. J. Active manganese dioxide oxidation in organic chemistry − part I. *Synthesis* **1976**, *1976*.65 (b) Cahiez, G.; Alami, M.; Taylor, R. J. K.; Reid, M.; Foot, J. S.; Fader, L.; Sikervar, V.; Pabba, J. Manganese dioxide. *Encyclopedia of reagents for organic chemistry (e-EROS)*; John Wiley & Sons: Hoboken, NJ, 2017.

(13) Selected oxidants such as DDQ, IBX, $NaIO_4$, and $K_3[Fe(CN)_6]$ were also briefly checked, but they were ruled out as either no oxidation or no deacylative processes could be observed.

(14) Menger, F. M.; Lee, C. Synthetically useful oxidants at solid sodium permanganate surfaces. *Tetrahedron Lett.* **1981**, *22*, 1655.

(15) Ortega-Martínez, A.; Molina, C.; Moreno-Cabrerizo, C.; Sansano, J. M.; Nájera, C. Deacylative reactions: Synthetic applications. *Eur. J. Org. Chem.* **2018**, *2018*, 2394.

(16) CCDC 2077330 (**6n**) and CCDC 2077331 (**2q**).

(17) (a) Davies, A. T.; Taylor, J. E.; Douglas, J.; Collett, C. J.; Morrill, L. C.; Fallan, C.; Slawin, A. M. Z.; Churchill, G.; Smith, A. D. Stereospecific asymmetric *N*-heterocyclic carbene (NHC)-catalyzed redox synthesis of trifluoromethyl dihydropyranones and mechanistic insights. *J. Org. Chem.* **2013**, *78*, 9243. (b) Rulev, A. Yu.; Romanov, A. R. Unsaturated polyfluoroalkyl ketones in the synthesis of nitrogen-bearing heterocycles. *RSC Adv.* **2016**, *6*, 1984.

(18) (a) Parasar, D.; Ponduru, T. T.; Noonikara-Poyil, A.; Jayaratna, N. B.; Dias, H. V. R. Acetylene and terminal alkyne complexes of copper (I) supported by fluorinated pyrazolates: Syntheses, structures, and transformations. *Dalton Trans.* **2019**, *48*, 15782. (b) Lin, Y.; Zhu, D. P.; Du, Y. R.; Zhang, R.; Zhang, S. J.; Xu, B. H. Tris(pyrazolyl)-borate cobalt-catalyzed hydrogenation of C = O, C = C, and C = N bonds: An assistant role of a Lewis base. *Org. Lett.* **2019**, *21*, 2693. (c) Li, C.; Zhang, X.; He, J.; Xu, S.; Cao, S. Et_3N-Catalyzed cycloaddition reactions of α-(trifluoromethyl)styrenes with 2,2,2-trifluorodiazoethane to access bis(trifluoromethyl)-substituted pyrazolines. *Chin. J. Chem.* **2021**, *39*, 301.

(19) Breugst, M.; Reissig, H.-U. The Huisgen reaction: Milestones of the 1,3-dipolar cycloaddition. *Angew. Chem., Int. Ed.* **2020**, *59*, 12293.

(20) Gakh, A. A.; Shermolovich, Y. Trifluoromethylated heterocycles. *Curr. Top. Med. Chem.* **2014**, *14*, 952.

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Supporting Information

for

Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions

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1. General information

Experimental procedures: If not stated otherwise, reactions were carried out under inert atmosphere of argon, in flame-dried flasks; subsequent manipulations were conducted in air. THF was dried over sodium/benzophenone and freshly distilled before use; dichloromethane was dried over CaH_2 and freshly distilled before use; other anhydrous solvents (hexane, toluene, DMF, MeCN, DMSO) were purchased and used as received. Products were purified by filtration through short silica gel plug or by standard column chromatography (CC) on silica gel (230–400 mesh) by using freshly distilled solvents as eluents or by recrystallization from appropriate solvents. The NMR spectra were taken on a Bruker AVIII instrument (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz). Chemical shifts are reported relative to solvent residual peaks [for $CDCl_3$: ^{1}H NMR: δ = 7.26, ^{13}C NMR: δ = 77.16; for methanol-d_4 (CD_3OD): ^{1}H NMR: δ = 3.31, ^{13}C NMR: δ = 49.00][1] or to $CFCl_3$ (^{19}F NMR: δ = 0.00) used as external standard. Multiplicity of the signals in ^{13}C NMR spectra were deduced based on supplementary 2D measurements (HMQC, HMBC). The IR spectra were measured with an Agilent Cary 630 FTIR spectrometer, in neat. MS (ESI) were performed with a Varian 500-MS LC Ion Trap; high resolution MS (ESI-TOF) measurements were performed with a Synapt G2-Si mass spectrometer (Waters). Elemental analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument. Melting points were determined in capillaries with a MEL-TEMP apparatus (Aldrich) or with a polarizing optical microscope (Opta-Tech), and are uncorrected. Mechanochemical reactions were performed by using Retsch Mixer Mill MM400.

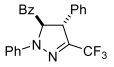
Starting materials: The nitrile imines precursors, *i.e.* hydrazonoyl bromides **3** were obtained by NBS-mediated electrophilic bromination of the corresponding trifluoroacetaldehyde arylhydrazones, in dry DMF at room temperature following general protocol.[2] The starting fluoral hydrazones were obtained according to a general literature procedure by condensation of aqueous fluoral hydrate (~75% in H_2O) with commercially available hydrazines in a closed ampoule at 75 °C, in methanol, in the presence of molecular sieves 4Å.[3] Chalcones **4** were purchased or prepared via Claisen–Schmidt condensation by using appropriate aldehydes and methyl ketones, in ethanol.[4] (*E*)-4,4,4-Trifluoro-1-phenyl-2-buten-1-one was prepared as described.[5] Activated MnO_2 (ca. 85%, <10 μm) was purchased (Sigma-Aldrich, product no. 217646-100G) and used as received (Figure S1). All the other commercially available solvents and starting materials were used as received.

Figure S1. Activated MnO_2 (ca. 85%, <10 μm; Sigma-Aldrich product no. 217646-100G) used in this study.

2. Synthetic procedures and characterization data

General procedure for synthesis of *trans*-pyrazolines 2a-2q, 7 and 9a,b: To a solution of the respective enone or stilbene (1.0 mmol) in a mixture of dry Et_3N (2.0 mL) and dry THF (5.0 mL) was added hydrazonoyl bromide **3** (2.5 equiv., in two equal portions; the second portion added after 24 h) and the stirring was continued at room temperature until the starting olefin was fully consumed (TLC monitoring, typically 2-4 days). The precipitates were filtered off and the solvents were removed under reduced pressure. The product was isolated by standard column chromatography (CC) using silica gel as the stationary phase and petroleum ether/dichloromethane or petroleum ether/EtOAc mixtures as an eluent.

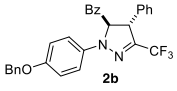
trans-5-Benzoyl-1,4-diphenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2a**)[6]:



2a

CC (SiO_2, petroleum ether/EtOAc 95:5): pale yellow solid, 311 mg (79%); mp 160–161 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.38 (dq, $^4J_{H\text{-}F} \approx 0.9$ Hz, $J_{H\text{-}H} = 5.6$ Hz, 1H, 4-H), 5.76 (d, $J_{H\text{-}H} = 5.6$ Hz, 1H, 5-H), 6.93-6.97, 7.02-7.05, 7.20-7.23, 7.25-7.29, 7.39-7.44, 7.48-7.52, 7.65-7.68, 7.87-7.89 (8m, 1H, 2H, 2H, 2H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.7, 74.3, 113.9, 120.9 (q, $^1J_{C\text{-}F} = 270.6$ Hz, CF_3), 121.6, 127.7, 129.0, 129.2, 129.3, 129.5, 129.7, 133.2, 134.7, 137.5, 138.1 (q, $^2J_{C\text{-}F} = 37.0$ Hz, C-3), 142.7, 192.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ –63.0 (s_{br}, CF_3). IR (neat) ν 1690, 1595, 1297, 1131 cm^{-1}. ESI-MS (*m*/*z*): 417.2 (100, $[M+Na]^+$), 395.1 (23, $[M+H]^+$). Anal. calcd for $C_{23}H_{17}F_3N_2O$ (394.1): C 70.04, H 4.34, N 7.10; found: C 70.21, H 4.34, N 7.32.

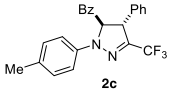
trans-5-Benzoyl-1-(4'-benzyloxyphenyl)-4-phenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2b**):



2b

CC (SiO_2, petroleum ether/EtOAc 95:5): light orange solid, 285 mg (57%); mp 62–63 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.39 (d_{br}, $J = 5.8$ Hz, 1H, 4-H), 5.01 (s, 2H, CH_2O), 5.73 (d, $J = 5.8$ Hz, 1H, 5-H), 6.89-6.92, 6.96-6.99, 7.20-7.22, 7.30-7.33, 7.35-7.43, 7.47-7.50, 7.64-7.67, 7.85-7.88 (8 m, 2H, 2H, 2H, 1H, 7H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.7, 70.6, 74.9, 115.2, 116.0, 121.0 (q, $^1J_{C\text{-}F} = 270.3$ Hz, CF_3), 127.6, 127.7, 128.1, 128.7, 129.0, 129.2, 129.3, 129.7, 133.2, 134.6, 137.0, 137.2 (q, $^2J_{C\text{-}F} = 36.8$ Hz, C-3), 137.3, 137.6, 154.1, 192.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ –62.3 (s_{br}, CF_3). IR (neat) ν 1694, 1510, 1230, 1120 cm^{-1}. ESI-MS (*m*/*z*): 501.5 (100, $[M+H]^+$). Anal. calcd for $C_{30}H_{23}F_3N_2O_2$ (500.2): C 71.99, H 4.63, N 5.60; found: C 71.96, H 4.66, N 5.81.

trans-5-Benzoyl-1-(4'-tolyl)-4-phenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2c**)[7]:

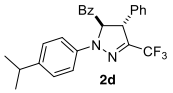


2c

CC (SiO_2, petroleum ether/EtOAc 95:5): light yellow solid, 392 mg (96%); mp 145–146 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.29 (s, 3H, Me), 4.38 (dq, $^4J_{H\text{-}F} \approx 1.0$ Hz, $J_{H\text{-}H} \approx 5.7$ Hz, 1H, 4-H),

5.78 (d_{br}, $J \approx 5.7$ Hz, 1H, 5-H), 6.96, 7.09 (2 d, $J = 8.6$ Hz, 2H each), 7.21-7.25, 7.40-7.45, 7.49-7.52, 7.66-7.69, 7.88-7.91 (5 m, 2H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.6, 74.5, 113.9, 121.0 (q, $^1J_{C\text{-}F} = 270.3$ Hz, CF_3), 127.6, 129.0, 129.1, 129.3, 129.7, 130.0, 131.0, 133.2, 134.6, 137.4 (q, $^2J_{C\text{-}F} = 36.8$ Hz, C-3), 137.6, 140.5, 192.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ −63.1 (s_{br}, CF_3). IR (neat) ν 1687, 1301, 1141, 1109, 1079 cm^{-1}. ESI-MS (m/z): 431.1 (100, $[M+Na]^+$), 409.2 (20, $[M+H]^+$), 389.2. Anal. calcd for $C_{24}H_{19}F_3N_2O$ (408.1): C 70.58, H 4.69, N 6.86; found: C 70.47, H 4.79, N 6.89.

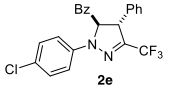
trans-5-Benzoyl-1-(4'-isopropylphenyl)-4-phenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2d**):



2d

CC (SiO_2, petroleum ether/EtOAc 95:5): light yellow solid, 275 mg (63%); mp 96–97 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (d, $J = 7.0$ Hz, 6H), 2.85 (hept, $J = 7.0$ Hz, 1H), 4.38 (dq, $^4J_{H\text{-}F} \approx 1.2$ Hz, $J_{H\text{-}H} = 5.6$ Hz, 1H, 4-H), 5.75 (d, $J_{H\text{-}H} = 5.6$ Hz, 1H, 5-H), 6.94-6.97, 7.11-7.14, 7.19-7.22, 7.39-7.43, 7.48-7.52, 7.65-7.68, 7.87-7.90 (7 m, 2H, 2H, 2H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.2, 33.5, 55.6, 74.4, 113.8, 121.0 (q, $^1J_{C\text{-}F} = 270.3$ Hz, CF_3), 127.4, 127.7, 129.0, 129.2, 129.3, 129.7, 133.2, 134.6, 137.4 (q, $^2J_{C\text{-}F} = 36.9$ Hz, C-3), 140.6, 142.1, 192.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s_{br}, CF_3). IR (neat) ν 1687, 1299, 1129 cm^{-1}. ESI-MS (m/z): 475.4 (100, $[M+K]^+$), 459.4 (59, $[M+Na]^+$), 437.4 (25, $[M+H]^+$). Anal. calcd for $C_{26}H_{23}F_3N_2O$ (436.2): C 71.55, H 5.31, N 6.42; found: C 71.70, H 5.36, N 6.62.

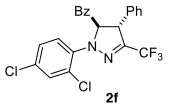
trans-5-Benzoyl-1-(4'-chlorophenyl)-4-phenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2e**):



2e

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1): light yellow solid, 193 mg (45%); mp 169–170 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.38 (dq, $^4J_{H\text{-}F} \approx 1.2$ Hz, $J_{H\text{-}H} = 5.3$ Hz, 1H, 4-H), 5.75 (d, $J_{H\text{-}H} = 5.3$ Hz, 1H, 5-H), 6.93-6.96, 7.18-7.23, 7.40-7.45, 7.49-7.52, 7.66-7.69, 7.85-7.88 (6 m, 2H, 4H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.7, 74.1, 115.0, 120.7 (q, $^1J_{C\text{-}F} = 270.6$ Hz, CF_3), 126.5, 127.6, 129.17, 129.20, 129.4, 129.5, 129.8, 132.9, 134.9, 137.1, 138.8 (q, $^2J_{C\text{-}F} = 37.0$ Hz, C-3), 141.3, 191.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.6 (s_{br}, CF_3). IR (neat) ν 1689, 1498, 1305, 1131 cm^{-1}. ESI-MS (m/z): 431.3 (43, $[M\{^{37}Cl\}+H]^+$), 429.3 (100, $[M\{^{35}Cl\}+H]^+$). Anal. calcd for $C_{23}H_{16}ClF_3N_2O$ (428.1): C 64.42, H 3.76, N 6.53; found: C 64.59, H 3.71, N 6.79.

trans-5-Benzoyl-1-(2',4'-dichlorophenyl)-4-phenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2f**):

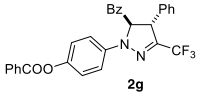


2f

CC (SiO_2, petroleum ether/EtOAc 95:5): light brown thick oil, 222 mg (48%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.42 (d_{br}, $J \approx 4.1$ Hz, 1H, 4-H), 6.51 (d, $J = 4.1$ Hz, 1H, 5-H), 7.25 (d, $J = 2.4$ Hz, 1H), 7.30 (dd, $J = 2.4$, 8.8 Hz, 1H), 7.34-7.36, 7.42-7.47, 7.61-7.64 (3 m, 2H, 5H, 1H), 7.78 (d, $J = 8.8$ Hz, 1H), 7.79-7.81 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 56.2, 75.2, 120.6 (q, $^1J_{C\text{-}F} = 271.1$ Hz, CF_3), 123.8, 126.3, 127.5, 128.0, 129.05, 129.09, 129.3, 129.80, 129.82, 130.2, 132.7, 134.6, 137.2, 140.2, 141.2 (q, $^2J_{C\text{-}F} = 37.0$

Hz, C-3), 192.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ −63.2 (s_{br}, CF_3). IR (neat) ν 1694, 1478, 1231, 1116, 1075 cm^{-1}. ESI-MS (*m*/*z*): 465.3 (55), 464.3 (23), 463.4 (100, $[M+H]^+$). Anal. calcd for $C_{23}H_{15}Cl_2F_3N_2O$ (462.1): C 59.63, H 3.26, N 6.05; found: C 59.57, H 3.49, N 6.32.

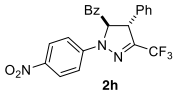
4-(*trans*-5′-Benzoyl-4′-phenyl-3′-trifluoromethyl-4′,5′-dihydro-1′*H*-pyrazol-1′-yl)phenyl benzoate (**2g**):



2g

reaction was carried out in hot THF (reflux; heated by immersing a reaction flask into an oil bath at 85 °C) for 4d. CC (SiO_2, petroleum ether/EtOAc 9:1): orange solid, 267 mg (52%); mp 79−80 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.41 (d_{br}, $J \approx 5.3$ Hz, 1H, 4′-H), 5.79 (d, J = 5.3 Hz, 1H, 5′-H), 7.07, 7.13 (2 d_{br}, $J \approx 9.0$ Hz, 2H each), 7.20-7.23, 7.41-7.53, 7.61-7.69, 7.88-7.91, 8.17-8.20 (5 m, 2H, 7H, 2H, 2H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.8, 74.4, 114.5, 120.8 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 122.6, 127.6, 128.7, 129.1, 129.2, 129.4, 129.7, 129.8, 130.3, 133.0, 133.7, 134.8, 137.2, 138.4 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C-3′), 140.5, 145.3, 165.5, 191.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.4 (s_{br}, CF_3). IR (neat) ν 1733, 1696, 1510, 1200, 1126, 1062 cm^{-1}. ESI-MS (*m*/*z*): 537.4 (98, $[M+Na]^+$), 515.4 (100, $[M+H]^+$). Anal. calcd for $C_{30}H_{21}F_3N_2O_3$ (514.2): C 70.03, H 4.11, N 5.44; found: C 70.17, H 4.31, N 5.26.

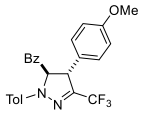
trans-5-Benzoyl-1-(4′-nitrophenyl)-4-phenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2h**):



2h

reaction was carried out in hot THF (reflux; heated by immersing a reaction flask into an oil bath at 85 °C) for 5d. CC (SiO_2, hexanes/EtOAc 9:1): red solid, 153 mg (35%); mp 82−83 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.43 (d_{br}, $J \approx 4.8$ Hz, 1H, 4-H), 5.88 (d_{br}, $J \approx 4.8$ Hz, 1H, 5-H), 7.02-7.05, 7.19-7.23, 7.44-7.56, 7.70-7.74, 7.85-7.89, 8.14-8.19 (6 m, 2H, 2H, 5H, 1H, 2H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.8, 73.5, 113.3, 120.3 (q, $^1J_{C\text{-}F}$ = 271.4 Hz, CF_3), 126.0, 127.5, 129.3, 129.5, 129.6, 130.1, 132.5, 135.3, 136.2, 141.5, 142.4 (q, $^2J_{C\text{-}F}$ = 37.5 Hz, C-3), 147.5, 190.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ −63.0 (s_{br}, CF_3). IR (neat) ν 1692, 1592, 1506, 1297, 1133, 1111 cm^{-1}. ESI-MS (*m*/*z*): 462.4 (100, $[M+Na]^+$), 440.3 (76, $[M+H]^+$). Anal. calcd for $C_{23}H_{16}F_3N_3O_3$ (439.1): C 62.87, H 3.67, N 9.56; found: C 62.84, H 3.80, N 9.47.

trans-5-Benzoyl-4-(4′-methoxyphenyl)-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2i**):

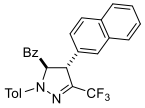


2i

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): light yellow solid, 342 mg (78%); mp 108−109 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 3.84 (s, 3H, OMe), 4.35 (dq, $^4J_{H\text{-}F} \approx 1.3$ Hz, $J_{H\text{-}H}$ = 5.6 Hz, 1H, 4-H), 5.72 (d, J = 5.6 Hz, 1H, 5-H), 6.92-6.95, 7.05-7.08, 7.11-7.15, 7.48-7.51, 7.45-7.48, 7.87-7.90 (6 m, 4H, 2H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.0, 55.5, 74.6, 113.8, 115.0, 121.0 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 128.8, 129.2, 129.3, 129.5, 130.0, 130.9, 133.2, 134.6, 137.7 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3), 140.5, 160.0,

192.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s_{br}, CF_3). IR (neat) ν 1696, 1599, 1513, 1297, 1126 cm^{-1}. ESI-MS (*m*/*z*): 439.4 (100, $[M+H]^+$). Anal. calcd for $C_{25}H_{21}F_3N_2O_2$ (438.2): C 68.49, H 4.83, N 6.39; found: C 68.33, H 4.86, N 6.49.

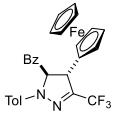
trans-5-Benzoyl-4-(2'-naphthyl)-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2j**):



2j

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1): yellow solid, 225 mg (49%); mp 74–75 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H, Me), 4.59 (dq, $^4J_{H\text{-}F} \approx 1.4$ Hz, $J_{H\text{-}H} = 5.6$ Hz, 1H, 4-H), 5.89 (d, $J = 5.6$ Hz, 1H, 5-H), 6.98-7.02, 7.10-7.13, 7.32-7.35, 7.46-7.50, 7.55-7.58, 7.66-7.70, 7.82-7.86, 7.89-7.95 (8 m, 2H, 2H, 1H, 2H, 2H, 2H, 1H, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.7, 74.3, 113.6, 121.0 (q, $^1J_{C\text{-}F} = 270.4$ Hz, CF_3), 124.7, 126.9, 127.00, 127.02, 128.0, 128.1, 129.2, 129.3, 130.03, 130.04, 131.0, 133.1, 133.4, 133.6, 134.6, 134.7, 137.3 (q, $^2J_{C\text{-}F} = 36.9$ Hz, C-3), 140.4, 192.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.2 (s_{br}, CF_3). IR (neat) ν 1692, 1517, 1118 cm^{-1}. ESI-MS (*m*/*z*): 481.2 (25, $[M+Na]^+$), 459.1 (100, $[M+H]^+$). Anal. calcd for $C_{28}H_{21}F_3N_2O$ (458.2): C 73.35, H 4.62, N 6.11; found: C 73.39, H 4.81, N 6.21.

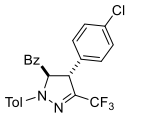
trans-5-Benzoyl-4-ferrocenyl-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2k**):



2k

CC (SiO_2, petroleum ether/CH_2Cl_2 2:1): thick orange oil, 196 mg (38%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me), 4.09, 4.20, 4.22, 4.25 (4 s_{br}, 1H, 1H, 5H, 2H, Fc), 4.41 (d_{br}, $J \approx 5.7$ Hz, 1H, 4-H), 5.69 (d, $J = 5.7$ Hz, 1H, 5-H), 7.03, 7.08 (2 d_{br}, $J \approx 8.5$ Hz, 2H each), 7.51-7.55, 7.63-7.67, 8.01-8.04 (3 m, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 50.7, 65.5, 68.28, 68.30, 68.8, 69.1, 75.8, 86.4, 114.0, 121.1 (q, $^1J_{C\text{-}F} = 270.3$ Hz, CF_3), 128.9, 129.3, 130.1, 131.3, 133.9, 134.4, 137.6 (q, $^2J_{C\text{-}F} = 36.8$ Hz, C-3), 140.8, 195.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ −61.3 (s_{br}, CF_3). IR (neat) ν 1692, 1517, 1122, 1059, 1003 cm^{-1}. ESI-MS (*m*/*z*): 539.6 (37, $[M+Na]^+$), 517.2 (100, $[M+H]^+$). Anal. calcd for $C_{28}H_{23}F_3FeN_2O$ (516.3): C 65.13, H 4.49, N 5.43; found: C 65.14, H 4.50, N 5.51.

trans-5-Benzoyl-4-(4'-chlorophenyl)-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2l**):

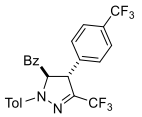


2l

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1): light yellow solid, 234 mg (53%); mp 155–156 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me), 4.35 (d_{br}, $J = 5.6$ Hz, 1H, 4-H), 5.70 (d, $J = 5.6$ Hz, 1H, 5-H), 6.90-6.93, 7.05-7.08, 7.13-7.16, 7.37-7.40, 7.49-7.53, 7.65-7.69, 7.85-7.88 (7 m, 2H, 2H, 2H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 54.9, 74.3, 113.9, 120.9 (q, $^1J_{C\text{-}F} = 270.3$ Hz, CF_3), 129.0, 129.1, 129.4,

130.0, 130.1, 131.2, 133.1, 134.8, 135.0, 136.1, 137.0 (q, $^{2}J_{C\text{-}F}$ = 37.0 Hz, C-3), 140.3, 191.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s_{br}, CF_3). IR (neat) ν 1692, 1517, 1297, 1121 cm^{-1}. ESI-MS (*m/z*): 465.4 (100, $[M+Na]^+$), 443.2 (19, $[M+H]^+$). Anal. calcd for $C_{24}H_{18}ClF_3N_2O$ (442.1): C 65.09, H 4.10, N 6.33; found: C 65.21, H 4.10, N 6.41.

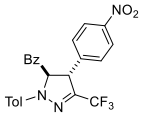
trans-5-Benzoyl-1-tolyl-3-trifluoromethyl-4-(4'-trifluoromethylphenyl)-4,5-dihydro-1*H*-pyrazole (**2m**):



2m

CC (SiO_2, petroleum ether/EtOAc 10:1, followed by recrystallization from hexanes): light yellow solid, 457 mg (96%); mp 151–152 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me), 4.43 (dq, $^{4}J_{H\text{-}F} \approx$ 1.3 Hz, $J_{H\text{-}H}$ = 5.4 Hz, 1H, 4-H), 5.74 (d, J = 5.4 Hz, 1H, 5-H), 6.91-6.95, 7.06-7.09, 7.32-7.35, 7.49-7.53, 7.66-7.70, 7.85-7.87 (6 m, 2H, 2H, 2H, 2H, 3H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.0, 74.1, 114.0, 120.9 (q, $^{1}J_{C\text{-}F}$ = 270.3 Hz, CF_3), 123.9 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz, CF_3), 126.8 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz, 2 *C*H), 128.1, 129.1, 129.5, 130.1, 131.3 (q, $^{2}J_{C\text{-}F}$ = 32.7 Hz, *i*-C), 131.4, 133.0, 134.9, 136.6 (q, $^{2}J_{C\text{-}F}$ = 37.3 Hz, C-3), 140.2, 141.4, 191.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.7, −62.3 (2 s, 2 CF_3). IR (neat) ν 1697, 1517, 1323, 1111 cm^{-1}. ESI-MS (*m/z*): 499.3 (100, $[M+Na]^+$), 477.3 (46, $[M+H]^+$). Anal. calcd for $C_{25}H_{18}F_6N_2O$ (476.1): C 63.03, H 3.81, N 5.88; found: C 62.89, H 3.95, N 6.10.\

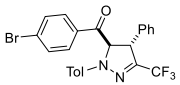
trans-5-Benzoyl-4-(4'-nitrophenyl)-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2n**):



2n

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1): yellow solid, 217 mg (48%); mp 222–223 °C (decomp.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 4.48 (dq, $^{4}J_{H\text{-}F} \approx$ 1.3 Hz, $J_{H\text{-}H}$ = 5.5 Hz, 1H, 4-H), 5.76 (d, J = 5.5 Hz, 1H, 5-H), 6.94, 7.08 (2 d_{br}, $J \approx$ 8.4 Hz, 2H each), 7.40 (d_{br}, $J \approx$ 8.7 Hz, 2H), 7.50-7.54, 7.68-7.72, 7.84-7.87 (3 m, 2H, 1H, 2H), 8.28 (d_{br}, $J \approx$ 8.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 54.8, 73.9, 114.0, 120.8 (q, $^{1}J_{C\text{-}F}$ = 270.2 Hz, CF_3), 125.0, 128.7, 129.0, 129.5, 130.1, 131.7, 132.9, 135.0, 136.0 (q, $^{2}J_{C\text{-}F}$ = 37.4 Hz, C-3), 140.0, 144.4, 148.3, 191.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.2 (s_{br}, CF_3). IR (neat) ν 1689, 1517, 1345, 1140, 1114 cm^{-1}. ESI-MS (*m/z*): 476.4 (100, $[M+Na]^+$), 454.4 (38, $[M+H]^+$). Anal. calcd for $C_{24}H_{18}F_3N_3O_3$ (453.1): C 63.57, H 4.00, N 9.27; found: C 63.71, H 4.22, N 9.44.

trans-5-(4'-Bromobezoyl)-4-phenyl-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2o**):

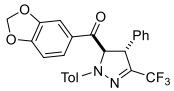


2o

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1): yellow solid, 326 mg (67%); mp 155–156 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 4.36 (dq, $^{4}J_{H\text{-}F} \approx$ 1.3 Hz, $J_{H\text{-}H}$ = 5.9 Hz, 1H, 4-H), 5.69 (d, J =

5.9 Hz, 1H, 5-H), 6.92, 7.08 (2 d_{br}, $J \approx 8.5$ Hz, 2H each), 7.19-7.22, 7.40-7.45, 7.63-7.66, 7.71-7.75 (4 m, 2H, 3H, 2H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.6, 74.6, 113.8, 120.9 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 127.6, 129.1, 129.8, 130.0, 130.2, 130.6, 131.2, 131.9, 132.7, 137.3, 137.4 (q, $^2J_{C\text{-}F}$ = 37.0 Hz, C-3), 140.3, 191.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s_{br}, CF_3). IR (neat) ν 1692, 1580, 1517, 1293, 1133, 1062 cm^{-1}. ESI-MS (*m*/*z*): 489.0 (100, [M{^{81}Br}+H]$^+$), 487.0 (98, [M{^{79}Br}+H]$^+$). Anal. calcd for $C_{24}H_{18}BrF_3N_2O$ (486.1): C 59.15, H 3.72, N 5.75; found: C 59.23, H 3.89, N 5.87.

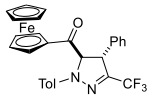
trans-5-[(3′,4′-Methylenedioxyphenyl)carbonyl]-4-phenyl-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2p**):



2p

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1): yellow solid, 231 mg (51%); mp 64–65 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me), 4.34 (dq, $^4J_{H\text{-}F} \approx 1.3$ Hz, $J_{H\text{-}H}$ = 5.8 Hz, 1H, 4-H), 5.64 (d, J = 5.8 Hz, 1H, 5-H), 6.08 (s, 2H, OCH_2O), 6.82 (d, J = 8.2 Hz, 1H), 6.89-6.92, 7.04-7.07, 7.18-7.21 (3 m, 2H each), 6.82 (dd, J = 1.8, 8.2 Hz, 1H), 7.38-7.42 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.9, 74.4, 102.4, 108.4, 108.8, 113.8, 121.0 (q, $^1J_{C\text{-}F}$ = 270.2 Hz, CF_3), 125.6, 127.7, 128.0, 128.9, 129.7, 130.0, 130.9, 137.4 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, C-3), 137.7, 149.0, 153.2, 190.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s_{br}, CF_3). IR (neat) ν 1685, 1603, 1517, 1443, 1252, 1118, 1036 cm^{-1}. ESI-MS (*m*/*z*): 475.1 (28, [M+Na]$^+$), 453.1 (100, [M+H]$^+$). Anal. calcd for $C_{25}H_{19}F_3N_2O_3$ (452.1): C 66.37, H 4.23, N 6.19; found: C 66.34, H 4.44, N 6.36.

trans-5-Ferrocenoyl-4-phenyl-1-tolyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**2q**):

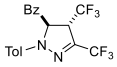


2q

CC (SiO_2, petroleum ether/CH_2Cl_2 2:1): red solid, 181 mg (35%); mp 160–161 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30 (s, 3H, Me), 4.19 (s, 5H, Fc), 4.49 (dq, $^4J_{H\text{-}F} \approx 1.3$ Hz, $J_{H\text{-}H}$ = 5.6 Hz, 1H, 4-H), 4.57, 4.60, 4.64, 4.87 (4 m_c, 4 × 1H, Fc), 5.21 (d, J = 5.6 Hz, 1H, 5-H), 7.09-7.16, 7.19-7.22, 7.36-7.42 (3 m, 4H, 2H, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 56.3, 69.7, 69.9, 70.2, 73.0, 73.3, 75.3, 76.7, 114.4, 121.0 (q, $^1J_{C\text{-}F}$ = 270.2 Hz, CF_3), 127.6, 128.8, 129.6, 130.0, 131.3, 137.9 (q, $^2J_{C\text{-}F}$ = 36.8 Hz, C-3), 138.0, 141.0, 198.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s_{br}, CF_3). IR (neat) ν 1681, 1521, 1118, 1059 cm^{-1}. ESI-MS (*m*/*z*): 539.3 (100, [M+Na]$^+$), 517.4 (55, [M+H]$^+$). Anal. calcd for $C_{28}H_{23}F_3FeN_2O$ (516.3): C 65.13, H 4.49, N 5.43; found: C 65.05, H 4.53, N 5.50.

Crystals of **2q** for an X-ray structure determination were obtained from hexane/dichloromethane solution by slow evaporation of the solvents.

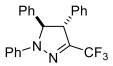
trans-5-Benzoyl-1-tolyl-3,4-bis(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**2r**):



2r

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1): yellow crystals, 296 mg (74%); mp 120–121 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me), 4.07 (dq$_{br}$, $J_{H\text{-}H} \approx 5.7$ Hz, $J_{H\text{-}F} \approx 7.9$ Hz, 1H, 4-H), 6.01 (d$_{br}$, $J \approx 5.7$ Hz, 1H, 5-H), 6.94, 7.07 (2 d$_{br}$, $J \approx 8.4$ Hz, 2H each), 7.57-7.61, 7.71-7.74, 8.04-8.07 (3 m, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 53.5 (q, $^2J_{C\text{-}F}$ = 31.8 Hz, C-4), 65.8, 114.4, 120.4 (q, $^1J_{C\text{-}F}$ = 269.3 Hz, 3-CF_3), 123.8 (q, $^1J_{C\text{-}F}$ = 280.6 Hz, 4-CF_3), 127.7 (q, $^2J_{C\text{-}F}$ = 40.1 Hz, C-3), 129.1, 129.6, 130.1, 132.4, 132.8, 135.2, 139.3, 191.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ –63.7 (q, $J_{F\text{-}F}$ = 5.0 Hz, 3-CF_3), –70.0 (dq, $J_{F\text{-}F}$ = 5.0 Hz, $J_{H\text{-}F}$ = 7.9 Hz, 4-CF_3). IR (neat) ν 1689, 1517, 1223, 1163, 1126 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{14}F_6N_2NaO$ 423.0908, found 423.0900. Anal. calcd for $C_{19}H_{14}F_6N_2O$ (400.1): C 57.01, H 3.52, N 7.00; found: C 57.14, H 3.56, N 7.09.

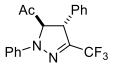
trans-1,4,5-Triphenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**7**)[8]:



7

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1): colourless solid, 249 mg (68%); mp 102–103 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.25 (dq, $J_{H\text{-}F} \approx 1.5$ Hz, $J_{H\text{-}H}$ = 6.5 Hz, 1H, 4-H), 5.23 (d, J = 6.5 Hz, 1H, 5-H), 6.88-6.91, 7.04-7.07, 7.15-7.23, 7.31-7.39 (4 m, 1H, 2H, 6H, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 61.2, 75.6, 114.4, 121.3 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, 3-CF_3), 121.3, 125.5, 127.6, 128.4, 128.5, 129.3, 129.5, 129.7, 138.5 (q, $^2J_{C\text{-}F}$ = 36.3 Hz, C-3),138.8, 140.2, 143.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ –62.6 (s$_{br}$, CF_3). IR (neat) ν 1504, 1143, 1118 cm^{-1}. ESI-MS (*m/z*): 367.2 (100, [M+H]$^+$). Anal. calcd for $C_{22}H_{17}F_3N_2$ (366.1): C 72.12, H 4.68, N 7.65; found: C 72.09, H 4.84, N 7.82.

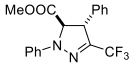
trans-5-Acetyl-1,4-diphenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**9a**):



9a

CC (SiO_2, petroleum ether/EtOAc 10:1): light yellow solid, 186 mg (56%); mp 134–135 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.19 (s, 3H, Me) 4.40 (d$_{br}$, $J \approx 6.0$ Hz, 1H, 4-H), 4.77 (d$_{br}$, $J \approx 6.0$ Hz, 1H, 5-H), 7.00-7.09, 7.16-7.20, 7.32-7.40 (3 m, 3H, 2H, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.6, 54.9, 78.4, 113.6, 120.7 (q, $^1J_{C\text{-}F}$ = 270.6 Hz, 3-CF_3), 122.0, 127.4, 128.9, 129.6, 129.8, 137.4 138.9 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C-3), 142.6, 204.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ –62.5 (s$_{br}$, CF_3). IR (neat) ν 1595, 1502, 1144, 1111 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{16}F_3N_2O$ 333.1215, found 333.1214.

Methyl (*trans*-1,4-diphenyl-3-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-4-yl)carboxylate (**9b**)[9]:



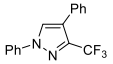
9b

CC (SiO_2, petroleum ether/EtOAc 15:1): light yellow solid, 226 mg (65%); mp 137–138 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.81 (s, 3H, OMe) 4.61 (d$_{br}$, $J \approx 5.2$ Hz, 1H, 4-H), 4.87 (d, J = 5.2

Hz, 1H, 5-H), 7.00-7.04, 7.12-7.15, 7.19-7.22, 7.32-7.41 (4 m, 1H, 2H, 2H, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 53.2, 55.6, 71.5 113.9, 120.8 (q, $^1J_{C\text{-}F}$ = 270.6 Hz, 3-CF_3), 121.8, 127.3, 128.8, 129.50, 129.53, 137.4, 139.2 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C-3), 142.7, 169.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ –62.5 (s_{br}, CF_3). IR (neat) ν 1730, 1595, 1282, 1230, 1118 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{16}F_3N_2O_2$ 349.1164, found 349.1164.

Synthesis of 3-trifluoromethylpyrazoles of type 5 and 8: A mixture of the respective pyrazoline **2** or **7** (0.2 mmol) in hexane (3 mL) and activated MnO_2 (ca. 85%, <10 μm, 8.0 mmol) was heated by immersing the reaction flask into a preheated oil bath at 60˚C for 2 d. The resulting mixture was cooled to room temperature, diluted with EtOAc (5 mL), filtered and the solvents were removed in vacuo. The crude material was purified by filtration through short silica gel pad by using petroleum ether/CH_2Cl_2 mixture or pure CH_2Cl_2 as eluents to afford spectroscopically pure product.

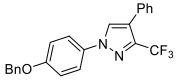
1,4-Diphenyl-3-trifluoromethyl-1*H*-pyrazole (**5a**)[10]:



5a

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1): colourless solid, 54 mg (94%); mp 40–41 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.40, 7.42-7.45, 7.47-7.53, 7.74-7.77 (4 m, 2H, 2H, 4H, 2H), 8.01 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 119.8, 121.7 (q, $^1J_{C\text{-}F}$ = 269.9 Hz, CF_3), 124.0 (q_{br}, $^3J_{C\text{-}F} \approx$ 1.0 Hz, C-4), 127.6, 127.9, 128.1, 128.7, 128.8 (q_{br}, $J \approx$ 1.2 Hz, 2 *ortho*-*C*H)*, 129.8, 130.4, 139.4, 140.5 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3); *through-space coupling. ^{19}F NMR (565 MHz, $CDCl_3$) δ –60.0 (s, CF_3). IR (neat) ν 1478, 1232, 1114 cm^{-1}. ESI-MS (*m/z*): 289.1 (100, $[M+H]^+$). Anal. calcd for $C_{16}H_{11}F_3N_2$ (288.1): C 66.66, H 3.85, N 9.72; found: C 66.55, H 3.88, N 9.88.

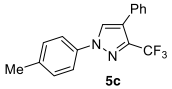
1-(4'-Benzyloxyphenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**5b**):



5b

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1): light orange solid, 76 mg (97%); mp 80–81 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.12 (s, 2H, OCH_2), 7.08 (d_{br}, $J \approx$ 9.0 Hz, 2H), 7.35-7.50 (m, 10H), 7.64 (d_{br}, $J \approx$ 9.0 Hz, 2H), 7.91 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 70.5, 115.8, 121.5, 121.8 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 123.6 (q_{br}, $^3J_{C\text{-}F} \approx$ 0.9 Hz, C-4), 127.6, 127.7, 128.0, 128.3, 128.7, 128.8 (q_{br}, $J \approx$ 1.2 Hz, 2 *ortho*-*C*H), 128.9, 130.5, 133.2, 136.6, 140.0 (q, $^2J_{C\text{-}F}$ = 36.8 Hz, C-3), 158.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.4 (s, CF_3). IR (neat) ν 1521, 1230, 1174, 1118 cm^{-1}. ESI-MS (*m/z*): 395.2 (100, $[M+H]^+$). Anal. calcd for $C_{23}H_{17}F_3N_2O$ (394.1): C 70.04, H 4.34, N 7.10; found: C 69.98, H 4.53, N 7.15.

4-Phenyl-1-(*p*-tolyl)-3-trifluoromethyl-1*H*-pyrazole (**5c**):

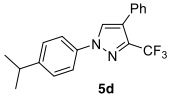


5c

CC (SiO_2, CH_2Cl_2): light yellow solid, 59 mg (98%); mp 59–60 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3H, Me), 7.30 (d_{br}, $J \approx$ 8.4 Hz, 2H), 7.37-7.40, 7.42-7.45, 7.48-7.50 (3 m, 1H, 2H, 2H), 7.62 (d_{br}, $J \approx$ 8.4 Hz, 2H), 7.97 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.1, 119.8, 121.7 (q, $^1J_{C\text{-}F}$ = 269.7 Hz,

CF_3), 123.7 (q_{br}, $^3J_{C\text{-}F} \approx 1.0$ Hz, C-4), 127.6, 128.0, 128.7, 128.8 (q_{br}, $J \approx 1.1$ Hz, 2 *ortho*-*C*H), 130.3, 130.5, 137.1, 137.9, 140.1 (q, $^2J_{C\text{-}F} = 36.6$ Hz, C-3). ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.4 (s, CF_3). IR (neat) *v* 1478, 1120, 1094 cm^{-1}. ESI-MS (*m*/*z*): 303.3 (100, $[M+H]^+$). Anal. calcd for $C_{17}H_{13}F_3N_2$ (302.1): C 67.54, H 4.33, N 9.27; found: C 67.50, H 4.59, N 9.09.

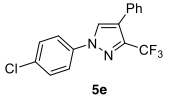
1-(4′-Isopropylphenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**5d**):



5d

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1): colourless oil, 61 mg (92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.9 Hz, 6H), 2.98 (hept, *J* = 6.9 Hz, 1H), 7.34-7.40, 7.42-7.45, 7.48-7.50, 7.64-7.66 (4 m, 3H, 2H, 2H, 2H), 7.97 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.1, 33.9, 119.1, 120.0, 121.7 (q, $^1J_{C\text{-}F} = 270.0$ Hz, CF_3), 123.7 (q_{br}, $^3J_{C\text{-}F} \approx 1.1$ Hz, C-4), 127.6, 127.7, 128.0, 128.7, 128.8 (q_{br}, $J \approx 1.3$ Hz, 2 *ortho*-*C*H), 130.4, 137.3, 140.2 (q, $^2J_{C\text{-}F} = 36.8$ Hz, C-3), 148.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.4 (s, CF_3). IR (neat) *v* 1480, 1170, 1114 cm^{-1}. ESI-MS (*m*/*z*): 331.2 (100, $[M+H]^+$). Anal. calcd for $C_{19}H_{17}F_3N_2$ (330.1): C 69.08, H 5.19, N 8.48; found: C 69.18, H 5.23, N 8.63.

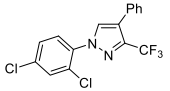
1-(4′-Chlorophenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**5e**):



5e

CC (SiO_2, CH_2Cl_2): thick colourless oil, 64 mg (99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.50, 7.68-7.71 (2 m, 7H, 2H), 7.98 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 120.9, 121.5 (q, $^1J_{C\text{-}F}$ = 270.0 Hz, CF_3), 124.3 (q_{br}, $^3J_{C\text{-}F} \approx 0.9$ Hz, C-4), 127.5, 128.2, 128.8(br)*, 129.9, 130.1, 133.6, 137.9, 140.8 (q, $^2J_{C\text{-}F} = 36.8$ Hz, C-3); *higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.6 (s, CF_3). IR (neat) *v* 1476, 1118, 1092 cm^{-1}. ESI-MS (*m*/*z*): 325.1 (49, $[M\{^{37}Cl\}+H]^+$), 323.1 (100, $[M\{^{35}Cl\}+H]^+$). Anal. calcd for $C_{16}H_{10}ClF_3N_2$ (322.1): C 59.55, H 3.12, N 8.68; found: C 59.61, H 3.38, N 8.64.

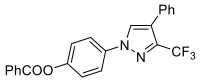
1-(2′,4′-Dichlorophenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**5f**):



5f

CC (SiO_2, CH_2Cl_2): thick colourless oil, 70 mg (98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.45, 7.47-7.50 (2 m, 4H, 2H), 7.58 (d, *J* = 2.3 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.97 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 121.5 (q, $^1J_{C\text{-}F}$ = 269.9 Hz, CF_3), 123.3 (q_{br}, $^3J_{C\text{-}F} \approx 0.9$ Hz, C-4), 128.2, 128.4, 128.78, 128.80*, 128.9 (q_{br}, $J \approx 1.1$ Hz, 2 *ortho*-*C*H), 129.2, 130.0, 130.7, 132.1, 135.6, 136.0, 140.8 (q, $^2J_{C\text{-}F} = 36.9$ Hz, C-3); *higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.6 (s, CF_3). IR (neat) *v* 1476, 1219, 1170, 1107 cm^{-1}. ESI-MS (*m*/*z*): 359.1 (63), 357.1 (100, $[M+H]^+$). Anal. calcd for $C_{16}H_9Cl_2F_3N_2$ (356.0): C 53.81, H 2.54, N 7.84; found: C 53.92, H 2.68, N 7.87.

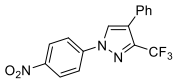
4-(4′-phenyl-3′-trifluoromethyl-1′*H*-pyrazol-1′-yl)phenyl benzoate (**5g**):



5g

CC (SiO_2, petroleum ether/CH_2Cl_2 1:2): colourless solid, 81 mg (99%); mp 114–115 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.56, 7.66-7.69, 7.80-7.83 (3 m, 9H, 1H, 2H), 8.01 (s_{br}, 1H, 5-H), 8.21-8.24 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 121.0, 121.6 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 123.2, 124.1 (q_{br}, $^3J_{C\text{-}F} \approx$ 1.0 Hz, C-4), 127.7, 128.2, 128.78, 128.84(br)*, 129.3, 130.2, 130.4, 134.1, 137.0, 140.7 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C-3), 150.3, 165.1; *higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.5 (s, CF_3). IR (neat) ν 1730, 1495, 1267, 1170, 1115 cm^{-1}. ESI-MS (*m/z*): 431.3 (100, $[M+Na]^+$), 409.3 (69, $[M+H]^+$). Anal. calcd for $C_{23}H_{15}F_3N_2O_2$ (408.1): C 67.65, H 3.70, N 6.86; found: C 67.54, H 3.85, N 6.85.

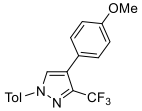
1-(4′-Nitrophenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**5h**):



5h

CC (SiO_2, petroleum ether/CH_2Cl_2 1:3): light orange solid, 65 mg (98%); mp 117–119 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.49 (m, 5H), 7.97 (d_{br}, $J \approx$ 9.2 Hz, 2H), 8.13 (s_{br}, 1H, 5-H), 8.40 (d_{br}, $J \approx$ 9.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 119.5, 121.3 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 125.4 (q_{br}, $^3J_{C\text{-}F} \approx$ 1.2 Hz, C-4), 125.7, 127.6, 128.6, 128.8 (q_{br}, $J \approx$ 1.1 Hz, 2 *ortho-C*H), 128.9, 129.5, 142.3 (q, $^2J_{C\text{-}F}$ = 37.2 Hz, C-3), 143.5, 146.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ –60.0 (s, CF_3). IR (neat) ν 1517, 1338, 1230, 1107 cm^{-1}. ESI-MS (*m/z*): 334.3 (100, $[M+H]^+$). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{11}F_3N_3O_2$ 334.0803, found 334.0804.

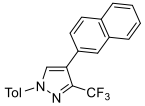
4-(4′-Methoxyphenyl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**5i**):



5i

CC (SiO_2, CH_2Cl_2): colourless solid, 66 mg (99%); mp 109–110 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3H, Me), 3.85 (s, 3H, OMe), 6.96 (d_{br}, $J \approx$ 8.8 Hz, 2H), 7.29 (d_{br}, $J \approx$ 8.3 Hz, 2H), 7.40 (d_{br}, $J \approx$ 8.8 Hz, 2H), 7.61 (d_{br}, $J \approx$ 8.3 Hz, 2H), 7.92 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.1, 55.4, 114.2, 119.1, 121.8 (q, $^1J_{C\text{-}F}$ = 269.9 Hz, CF_3), 122.8, 123.4 (q_{br}, $^3J_{C\text{-}F} \approx$ 1.0 Hz, C-4), 127.3, 130.0 (q_{br}, $J \approx$ 1.1 Hz, 2 *ortho-C*H), 130.2, 137.2, 137.8, 140.1 (q, $^2J_{C\text{-}F}$ = 36.4 Hz, C-3), 159.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.5 (s, CF_3). IR (neat) ν 1498, 1170, 1103 cm^{-1}. ESI-MS (*m/z*): 355.2 (26, $[M+Na]^+$), 333.3 (100, $[M+H]^+$). Anal. calcd for $C_{18}H_{15}F_3N_2O$ (332.1): C 65.06, H 4.55, N 8.43; found: C 64.89, H 4.70, N 8.52.

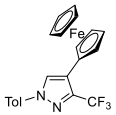
4-(Naphth-2′-yl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**5j**):



5j

CC (SiO_2, CH_2Cl_2): colourless solid, 70 mg (99%); mp 89–90 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H, Me), 7.30-7.33, 7.50-7.54 (2 m, 2H, 2H), 7.59 (dd, J = 1.8, 8.4 Hz, 1H), 7.64-7.67, 7.86-7.91 (2 m, 2H, 3H), 7.95 (m_c, 1H), 8.07 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 119.8, 121.8 (q, $^1J_{C-F}$ = 269.8 Hz, CF_3), 123.7 (q_{br}, $^3J_{C-F} \approx$ 1.0 Hz, C-4), 126.5, 126.6, 126.8 (q_{br}, $J \approx$ 1.0 Hz, *ortho*-*C*H), 127.7 (q_{br}, $J \approx$ 1.0 Hz, *ortho*-*C*H), 127.83, 127.84, 127.9, 128.2, 128.4, 130.3, 132.9, 133.4, 137.1, 138.0, 140.3 (q, $^2J_{C-F}$ = 36.8 Hz, C-3). ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.3 (s, CF_3). IR (neat) ν 1491, 1170, 1115 cm^{-1}. ESI-MS (*m*/*z*): 353.1 (100, $[M+H]^+$). Anal. calcd for $C_{21}H_{15}F_3N_2$ (352.1): C 71.58, H 4.29, N 7.95; found: C 71.61, H 4.34, N 8.06.

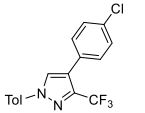
4-Ferrocenyl-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**5k**):



5k

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1): light orange solid, 58 mg (71%); mp 103–104 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3H, Me), 4.12 (s, 5H, Fc), 4.31, 4.57 (2 m_c, 2H each), 7.29, 7.61 (2 d_{br}, $J \approx$ 8.4 Hz, 2H each), 7.97 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 67.9 (q_{br}, $J \approx$ 2.1 Hz, 2 *ortho*-*C*H, Fc), 68.7, 69.7, 74.6, 119.7, 120.8 (q_{br}, $^3J_{C-F} \approx$ 1.3 Hz, C-4), 121.9 (q, $^1J_{C-F}$ = 269.4 Hz, CF_3), 126.6, 130.2, 137.1, 137.7, 139.4 (q, $^2J_{C-F}$ = 37.0 Hz, C-3). ^{19}F NMR (565 MHz, $CDCl_3$) δ –60.5 (s, CF_3). IR (neat) ν 1491, 1167, 1122, 1059 cm^{-1}. ESI-MS (*m*/*z*): 433.3 (44, $[M+Na]^+$), 411.3 (51, $[M+H]^+$), 410.3 (100, $[M]^+$). Anal. calcd for $C_{21}H_{17}F_3FeN_2$ (410.1): C 61.49, H 4.18, N 6.83; found: C 61.55, H 4.21, N 7.00.

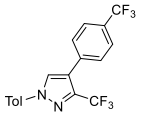
4-(4′-Chlorophenyl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**5l**):



5l

CC (SiO_2, CH_2Cl_2): colourless solid, 67 mg (99%); mp 71–72 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3H, Me), 7.30 (d_{br}, $J \approx$ 8.4 Hz, 2H), 7.40 (s_{br}, 4H), 7.61 (d_{br}, $J \approx$ 8.4 Hz, 2H), 7.96 (s_{br}, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 21.2, 119.8, 121.6 (q, $^1J_{C-F}$ = 270.1 Hz, CF_3), 122.5(br), 127.6, 128.95, 128.98, 130.1 (q_{br}, $J \approx$ 1.2 Hz, 2 *ortho*-*C*H), 130.3, 134.1, 137.0, 138.1, 140.1 (q, $^2J_{C-F}$ = 36.7 Hz, C-3). ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.5 (s, CF_3). IR (neat) ν 1498, 1223, 1126 cm^{-1}. ESI-MS (*m*/*z*): 359.3 (24, $[M+Na]^+$), 337.3 (100, $[M+H]^+$). Anal. calcd for $C_{17}H_{12}ClF_3N_2$ (336.1): C 60.64, H 3.59, N 8.32; found: C 60.73, H 3.78, N 8.27.

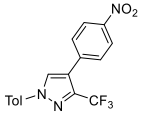
1-Tolyl-4-(4′-trifluoromethylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**5m**):



5m

CC (SiO_2, CH_2Cl_2): colourless solid, 72 mg (98%); mp 82–83 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H, Me), 7.31 (d_{br}, $J \approx 8.1$ Hz, 2H), 7.58-7.63 (m, 4H), 7.69 (d_{br}, $J \approx 8.1$ Hz, 2H), 8.02 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 119.9, 121.6 (q, $^1J_{C\text{-}F}$ = 269.7 Hz, CF_3), 122.3(br), 124.2 (q, $^1J_{C\text{-}F}$ = 272.2 Hz, CF_3), 125.8 (q, $^3J_{C\text{-}F}$ = 7.5 Hz, 2 *C*H), 127.9, 129.1(br), 130.1 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 130.4, 134.2(br), 136.9, 138.3, 140.2 (q, $^2J_{C\text{-}F}$ = 37.0 Hz, C-3). ^{19}F NMR (565 MHz, $CDCl_3$) δ –62.6, –59.4 (2 s, 2 CF_3). IR (neat) *v* 1484, 1323, 1163, 1103, 1066 cm^{-1}. ESI-MS (*m*/*z*): 371.3 (100, $[M+H]^+$). Anal. calcd for $C_{18}H_{12}F_6N_2$ (370.1): C 58.38, H 3.27, N 7.57; found: C 58.35, H 3.31, N 7.75.

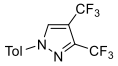
4-(4′-Nitrophenyl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**5n**):



5n

CC (SiO_2, CH_2Cl_2): colourless solid, 65 mg (94%); mp 155–156 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H, Me), 7.30-7.33, 7.61-7.66 (2 m, 2H, 4H), 8.08 (q_{br}, $^5J_{H\text{-}F} \approx 1.0$ Hz, 1H, 5-H), 8.27-8.29 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 119.9, 121.4 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 121.4 (q_{br}, $^3J_{C\text{-}F} \approx 0.9$ Hz, C-4), 124.1, 128.1, 129.4 (q_{br}, $J_{C\text{-}F} \approx 1.3$ Hz, 2 *ortho*-*C*H), 130.4, 136.7, 137.2, 138.5, 140.1 (q, $^2J_{C\text{-}F}$ = 37.2 Hz, C-3), 147.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.4 (s, CF_3). IR (neat) *v* 1517, 1342, 1111 cm^{-1}. ESI-MS (*m*/*z*): 348.3 (100, $[M+H]^+$). Anal. calcd for $C_{17}H_{12}F_3N_3O_2$ (347.1): C 58.79, H 3.48, N 12.10; found: C 58.84, H 3.61, N 12.11.

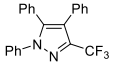
1-Tolyl-3,4-trifluoromethyl-1*H*-pyrazole (**5r**):



5r

CC (SiO_2, CH_2Cl_2): colourless oil, 48 mg (82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H, Me), 7.31, 7.56 (2 d_{br}, $J \approx 8.4$ Hz, 2H each), 8.20 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 113.3 (q_{br}, $^2J_{C\text{-}F} \approx 39.5$ Hz, C-4), 120.2 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 120.2, 121.2 (q, $^1J_{C\text{-}F}$ = 267.4 Hz, CF_3), 129.1 (q, $^3J_{C\text{-}F} \approx 4.1$ Hz, C-5), 130.5, 136.3, 139.2, 140.2 (qq, $J_{C\text{-}F}$ = 1.8, 39.8 Hz, C-3). ^{19}F NMR (565 MHz, $CDCl_3$) δ –61.6 (q, J = 5.2 Hz, CF_3), –56.9 (q, J = 5.2 Hz, CF_3). IR (neat) *v* 1506, 1238, 1141 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{12}H_9F_6N_2$ 295.0670, found 295.0663.

3-Trifluoromethyl-1,4,5-triphenyl-1*H*-pyrazole (**8**)[8,11,12]:



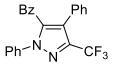
8

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1): colourless solid, 65 mg (90%); mp 162–164 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99-7.01, 7.18-7.26, 7.27-7.34 (3 m, 2H, 5H, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ

121.2(br), 121.7 (q, $^{1}J_{C\text{-}F}$ = 270.2 Hz, CF_3), 125.6, 127.7, 128.3, 128.4, 128.6, 128.7, 128.9, 130.46(br), 130.47, 130.6, 139.3, 140.9 (q, $^{2}J_{C\text{-}F}$ = 36.1 Hz, C-3), 142.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.5 (s, CF_3). IR (neat) ν 1152, 1122 cm^{-1}. ESI-MS (*m*/*z*): 387.2 (100, $[M+Na]^+$), 365.3 (85, $[M+H]^+$). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{16}F_3N_2$ 365.1266, found 365.1262.

Synthesis of fully substituted 3-trifluoromethylpyrazoles 6: A mixture of the respective 5-acylpyrazoline **2** (0.2 mmol) in DMSO (2.5 mL) and activated MnO_2 (ca. 85%, <10 μm, 8.0 mmol) was heated by immersing the reaction flask into a preheated oil bath at 100˚C for 2 d under vigorous stirring. The resulting mixture was cooled to room temperature, diluted with EtOAc (5 mL) and filtered. Water (10 mL) was added to the filtrate, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and the solvents were removed under reduced pressure. The resulting crude product was purified by short column chromatography (SiO_2) using petroleum ether/CH_2Cl_2 or petroleum ether/EtOAc mixtures.

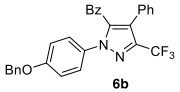
5-Benzoyl-1,4-diphenyl-3-trifluoromethyl-1*H*-pyrazole (**6a**):



6a

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1): colourless solid, 62 mg (79%); mp 112–114 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21-7.27, 7.29-7.32, 7.33-7.38, 7.40-7.43, 7.45-7.47, 7.64-7.66 (6 m, 5H, 2H, 3H, 1H, 2H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 121.4 (q, $^{1}J_{C\text{-}F}$ = 270.5 Hz, CF_3), 124.3 (q_{br}, $^{3}J_{C\text{-}F} \approx$ 1.0 Hz, C-4), 124.5, 128.35*, 128.37, 128.7, 128.9, 129.1, 129.4, 129.8, 130.0, 134.3, 136.1, 139.1, 139.8, 140.6 (q, $^{2}J_{C\text{-}F}$ = 36.6 Hz, C-3), 187.6; *higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.2 (s, CF_3). IR (neat) ν 1670, 1495, 1159, 1103 cm^{-1}. ESI-MS (*m*/*z*): 415.3 (83, $[M+Na]^+$), 393.3 (100, $[M+H]^+$). Anal. calcd for $C_{23}H_{15}F_3N_2O$ (392.1): C 70.40, H 3.85, N 7.14; found: C 70.26, H 3.95, N 7.33.

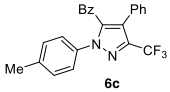
5-Benzoyl-1-(4'-benzyloxyphenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**6b**):



6b

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1): light yellow solid, 61 mg (78%); mp 131–134 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.90 (s, 2H, OCH_2), 6.80-6.82, 7.07-7.14, 7.16-7.22, 7.24-7.32, 7.51-7.53 (5 m, 2H, 5H, 3H, 7H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 70.3, 121.4 (q, $^{1}J_{C\text{-}F}$ = 270.5 Hz, CF_3), 123.9 (q_{br}, $^{3}J_{C\text{-}F} \approx$ 0.8 Hz, C-4), 126.0, 127.6, 128.27, 128.29(br), 128.33, 128.6, 128.7, 129.0, 129.8, 129.9, 132.3, 134.3, 136.0, 136.4, 139.7, 140.1 (q, $^{2}J_{C\text{-}F}$ = 36.6 Hz, C-3), 159.1, 187.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.1 (s, CF_3). IR (neat) ν 1672, 1230, 1163, 1126 cm^{-1}. ESI-MS (*m*/*z*): 521.4 (66, $[M+Na]^+$), 499.4 (100, $[M+H]^+$). Anal. calcd for $C_{30}H_{21}F_3N_2O_2$ (498.2): C 72.28, H 4.25, N 5.62; found: C 72.12, H 4.33, N 5.81.

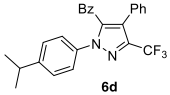
5-Benzoyl-4-phenyl-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6c**):



6c

CC (SiO_2, petroleum ether/CH_2Cl_2 3:1): colourless solid, 52 mg (64%); mp 134–135 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 7.19-7.22, 7.25-7.38, 7.45-7.49, 7.69-7.71 (4 m, 2H, 9H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 121.4 (q, $^1J_{C\text{-}F}$ = 270.5 Hz, CF_3), 124.1(br), 124.4, 128.32, 128.34, 129.7, 129.0, 129.88, 129.93(br), 130.0, 134.3, 136.0, 136.6, 139.2, 139.7, 140.3 (q, $^2J_{C\text{-}F}$ = 36.8 Hz, C-3), 187.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.1 (s, CF_3). IR (neat) ν 1670, 1103 cm^{-1}. ESI-MS (*m*/*z*): 429.3 (89, $[M+Na]^+$), 407.4 (100, $[M+H]^+$). Anal. calcd for $C_{24}H_{17}F_3N_2O$ (406.1): C 70.93, H 4.22, N 6.89; found: C 70.83, H 4.46, N 6.93.

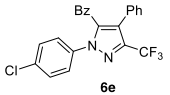
5-Benzoyl-1-(4'-isopropylphenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**6d**):



6d

CC (SiO_2, petroleum ether/EtOAc 95:5): colourless solid, 75 mg (86%); mp 126–127 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.9 Hz, 6H), 2.89 (hept, *J* = 6.9 Hz, 1H), 7.19-7.25, 7.27-7.30, 7.34-7.36, 7.39-7.43, 7.64-7.66 (5 m, 7H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.9, 33.9, 121.4 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 124.1(br), 124.5, 127.4, 128.31, 128.34, 128.6, 129.0, 129.88, 129.94(br), 134.3, 136.1, 136.8, 139.7, 140.2 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3), 150.0, 187.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.2 (s, CF_3). IR (neat) ν 1659, 1126 cm^{-1}. ESI-MS (*m*/*z*): 457.4 (100, $[M+Na]^+$), 435.4 (81, $[M+H]^+$). Anal. calcd for $C_{26}H_{21}F_3N_2O$ (434.2): C 71.88, H 4.87, N 6.45; found: C 71.60, H 4.81, N 6.47.

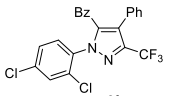
5-Benzoyl-1-(4'-chlorophenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**6e**):



6e

CC (SiO_2, petroleum ether/EtOAc 95:5): colourless solid, 67 mg (79%); mp 118–119 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20-7.24, 7.25-7.28, 7.34-7.36, 7.39-7.41, 7.42-7.46, 7.63-7.65 (6 m, 3H, 4H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 121.2 (q, $^1J_{C\text{-}F}$ = 270.5 Hz, CF_3), 124.6 (q_{br}, $^3J_{C\text{-}F} \approx$ 0.9 Hz, C-4), 125.8, 128.4, 128.5, 128.7, 128.8, 129.7, 129.89, 129.90(br), 134.6,135.0, 137.5, 139.7, 140.8 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C-3), 187.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.3 (s, CF_3). IR (neat) ν 1670, 1491, 1107 cm^{-1}. ESI-MS (*m*/*z*): 449.3 (100, $[M+Na]^+$), 427.3 (68, $[M+H]^+$). Anal. calcd for $C_{23}H_{14}ClF_3N_2O$ (426.1): C 64.72, H 3.31, N 6.56; found: C 64.49, H 3.47, N 6.40.

5-Benzoyl-1-(2',4'-dichlorophenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**6f**):

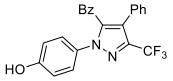


6f

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): colourless solid, 65 mg (71%); mp 86–87 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14-7.17, 7.20-7.23, 7.33-7.36 (3 m, 5H, 2H, 1H), 7.42 (dd, *J* = 2.2, 8.5 Hz,

1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.58-7.61 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 121.1 (q, $^1J_{C\text{-}F}$ = 270.6 Hz, CF_3), 124.4 (q$_{br}$, $^3J_{C\text{-}F} \approx$ 0.8 Hz, C-4), 128.2, 128.28, 128.30, 128.44, 128.8, 130.0, 130.2(br)*, 130.4, 131.9, 133.9, 135.2, 135.7, 136.5, 140.9 (q, $^2J_{C\text{-}F}$ = 37.0 Hz, C-3), 141.0, 186.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.3 (s, CF_3). IR (neat) *v* 1655, 1484, 1122 cm^{-1}. ESI-MS (*m/z*): 485.3 (66), 483.3 (100, [M+Na]$^+$), 463.3 (30), 461.3 (67, [M+H]$^+$). Anal. calcd for $C_{23}H_{13}Cl_2F_3N_2O$ (460.0): C 59.89, H 2.84, N 6.07; found: C 59.77, H 3.09, N 6.29.

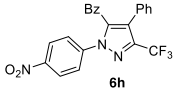
5-Benzoyl-1-(4'-hydroxyphenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**6g**):



6g

CC (SiO_2, petroleum ether/EtOAc 4:1): colourless solid, 50 mg (61%); mp 152−154 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 6.75-6.78, 7.23-7.32, 7.46-7.49, 7.62-7.64 (4 m, 2H, 9H, 1H, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 116.7, 122.8 (q, $^1J_{C\text{-}F}$ = 269.4 Hz, CF_3), 124.6(br), 127.3, 129.29, 129.34, 129.8, 130.4, 130.8, 131.0(br), 132.2, 135.5, 137.4, 140.8 (q, $^2J_{C\text{-}F}$ = 36.39 Hz, C-3), 141.5, 159.7, 189.1. ^{19}F NMR (565 MHz, CD_3OD) δ −60.5 (s, CF_3). IR (neat) *v* 3373, 1640, 1521, 1108 cm^{-1}. ESI-MS (*m/z*): 431.3 (100, [M+Na]$^+$), 409.4 (65, [M+H]$^+$). HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{16}F_3N_2O_2$ 409.1164, found 409.1160.

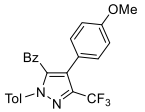
5-Benzoyl-1-(4'-nitrophenyl)-4-phenyl-3-trifluoromethyl-1*H*-pyrazole (**6h**):



6h

CC (SiO_2, petroleum ether/EtOAc 8:1): light yellow solid, 67 mg (77%); mp 110−111 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.34, 7.49-7.52, 7.68-7.72, 8.29-8.32 (4 m, 7H, 1H, 4H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 121.0 (q, $^1J_{C\text{-}F}$ = 270.8 Hz, CF_3), 124.8, 125.0, 125.5 (q$_{br}$, $^3J_{C\text{-}F} \approx$ 1.0 Hz, C-4), 128.2, 128.5, 128.8, 129.0, 129.9(br), 129.9, 134.9, 135.5, 139.9, 141.9 (q, $^2J_{C\text{-}F}$ = 37.0 Hz, C-3), 143.5, 147.4, 187.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.6 (s, CF_3). IR (neat) *v* 1666, 1595, 1521, 1342, 1126 cm^{-1}. ESI-MS (*m/z*): 460.3 (11, [M+Na]$^+$), 438.3 (100, [M+H]$^+$). Anal. calcd for $C_{23}H_{14}F_3N_3O_3$ (437.1): C 63.16, H 3.23, N 9.61; found: C 63.16, H 3.27, N 9.65.

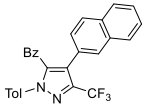
5-Benzoyl-4-(4'-methoxyphenyl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6i**):



6i

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): light yellow solid, 61 mg (70%); mp 113−114 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3H, Me), 3.73 (s, 3H, OMe), 6.76 (d$_{br}$, *J* ≈ 8.7 Hz, 2H), 7.15 (d$_{br}$, *J* ≈ 8.3 Hz, 2H), 7.21 (d$_{br}$, *J* ≈ 8.7 Hz, 2H), 7.25-7.28 (m, 2H), 7.31 (d$_{br}$, *J* ≈ 8.3 Hz, 2H), 7.42-7.45, 7.74-7.66 (2 m, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 55.3, 113.8, 121.1, 121.4 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 123.8 (q$_{br}$, $^3J_{C\text{-}F} \approx$ 0.8 Hz, C-4), 124.3, 128.7, 129.0, 130.0, 131.1(br), 134.3, 136.0, 136.7, 139.1, 139.6, 140.3 (q, $^2J_{C\text{-}F}$ = 36.5 Hz, C-3), 159.6, 187.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.2 (s, CF_3). IR (neat) *v* 1662, 1226, 1111 cm^{-1}. ESI-MS (*m/z*): 459.4 (29, [M+Na]$^+$), 437.4 (100, [M+H]$^+$). Anal. calcd for $C_{25}H_{19}F_3N_2O_2$ (436.1): C 68.80, H 4.39, N 6.42; found: C 68.56, H 4.43, N 6.62.

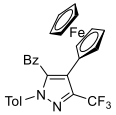
5-Benzoyl-4-(naphth-2′-yl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6j**):



6j

CC (SiO_2, petroleum ether/CH_2Cl_2 2:1): colourless solid, 71 mg (78%); mp 128–130 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H, Me), 7.15-7.20, 7.32-7.35 (2 m, 4H, 3H), 7.40 (dd, J = 1.7, 8.5 Hz, 1H), 7.42-7.46, 7.65-7.67 (2 m, 2H, 2H), 7.71 (d, J = 8.5 Hz, 1H), 7.72-7.76 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.3, 121.4 (q, $^1J_{C\text{-}F}$ = 270.5 Hz, CF_3), 123.9 (q$_{br}$, $^3J_{C\text{-}F} \approx$ 0.8 Hz, C-4), 124.4, 126.4, 126.5, 126.6, 127.4(br), 127.7, 128.1, 128.2, 128.7, 129.5(br), 129.8, 130.1, 132.8, 133.0, 134.3, 136.0, 136.6, 139.3, 139.9, 140.5 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3), 187.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.1 (s, CF_3). IR (neat) ν 1666, 1107 cm^{-1}. ESI-MS (*m/z*): 495.4 (100 $[M+K]^+$). Anal. calcd for $C_{28}H_{19}F_3N_2O$ (456.2): C 73.68, H 4.20, N 6.14; found: C 73.42, H 4.35, N 6.22.

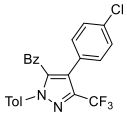
5-Benzoyl-4-ferrocenyl-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6k**):



6k

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): red solid, 40 mg (39%); mp 155–156 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 4.01 (s, 5H, Fc), 4.17, 4.42 (2 m$_c$, 2H each), 7.08-1.10, 7.25-7.27, 7.37-7.40, 7.51-7.54, 7.73-7.75 (5 m, 2H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 68.8, (q$_{br}$, $J \approx$ 2.6 Hz, 2 *ortho-C*H, Fc), 69.6, 73.5, 120.7(br), 121.7 (q, $^1J_{C\text{-}F}$ = 269.9 Hz, CF_3), 124.3, 129.1, 129.9, 130.0, 134.8, 136.5, 136.6, 138.7, 139.1, 139.4 (q, $^2J_{C\text{-}F}$ = 37.0 Hz, C-3), 189.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.6 (s, CF_3). IR (neat) ν 1659, 1234, 1159, 1111 cm^{-1}. ESI-MS (*m/z*): 537.3 (46, $[M+Na]^+$), 515.3 (63, $[M+H]^+$), 514.3 (100, $[M]^+$). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{22}F_3FeN_2O$ 515.1034, found 515.1034.

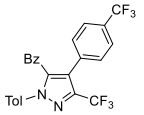
5-Benzoyl-4-(4'-chlorophenyl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6l**):



6l

CC (SiO_2, petroleum ether/EtOAc 10:1): colourless solid, 77 mg (88%); mp 92–93 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3H, Me), 7.14-7.16, 7.20-7.23, 7.27-7.31, 7.45-7.48, 7.62-7.64 (5 m, 2H, 4H, 4H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 121.3 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 122.7 (q$_{br}$, $^3J_{C\text{-}F} \approx$ 0.9 Hz, C-4), 124.3, 127.5, 128.7, 128.8, 129.8, 130.1, 131.2(br), 134.57, 134.58, 135.9, 136.5, 139.4, 139.8, 140.3 (q, $^2J_{C\text{-}F}$ = 36.8 Hz, C-3), 187.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.2 (s, CF_3). IR (neat) ν 1662, 1498, 1122 cm^{-1}. ESI-MS (*m/z*): 443.3 (56, $[M\{^{37}Cl\}+H]^+$), 437.4 (100, $[M\{^{35}Cl\}+H]^+$). Anal. calcd for $C_{23}H_{16}ClF_3N_2O$ (440.1): C 65.39, H 3.66, N 6.35; found: C 65.24, H 3.72, N 6.38.

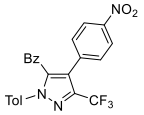
5-Benzoyl-1-tolyl-4-(4'-trifluoromethylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**6m**):



6m

CC (SiO_2, petroleum ether/EtOAc 10:1): light yellow solid, 88 mg (93%); mp 120–121 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H, Me), 7.15 (d_{br}, $J \approx 8.3$ Hz, 2H), 7.24-7.27 (m, 2H), 7.32 (d_{br}, $J \approx 8.3$ Hz, 2H), 7.41-7.45, 7.49-7.51, 7.61-7.63 (3 m, 3H, 2H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 121.2 (q, $^1J_{C-F}$ = 270.4 Hz, CF_3), 122.5(br), 124.0 (q, $^1J_{C-F}$ = 272.2 Hz, CF_3), 124.3, 125.3 (q, $^3J_{C-F}$ = 3.7 Hz, 2 *C*H), 128.8, 129.8, 130.1, 130.3, 130.4 (q, $^2J_{C-F}$ = 32.6 Hz, CF_3), 132.9(br), 134.6, 135.9, 136.4, 139.5, 140.0, 140.4 (q, $^2J_{C-F}$ = 37.0 Hz, C-3), 187.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ –62.8, –59.1 (2 s, 2 CF_3). IR (neat) ν 1662, 1159, 1111 cm^{-1}. ESI-MS (*m*/*z*): 475.4 (100, $[M+H]^+$). Anal. calcd for $C_{25}H_{16}F_6N_2O$ (474.1): C 63.29, H 3.40, N 5.91; found: C 63.22, H 3.40, N 6.18.

5-Benzoyl-4-(4'-nitrophenyl)-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6n**):

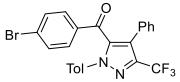


6n

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): light yellow solid, 84 mg (93%); mp 153–154 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H, Me), 7.15-7.17, 7.27-7.33, 7.44-7.50, 7.62-7.64, 8.10-8.13 (5 m, 2H, 4H, 3H, 2H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 121.1 (q, $^1J_{C-F}$ = 270.4 Hz, CF_3), 121.6(br), 123.6, 124.3, 129.0, 129.8, 130.1, 130.9(br), 134.9, 135.7, 136.0, 136.3, 139.7, 140.1, 140.3 (q, $^2J_{C-F}$ = 37.3 Hz, C-3), 147.7, 187.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.0 (s, CF_3). IR (neat) ν 1664, 1521, 1312, 1129 cm^{-1}. ESI-MS (*m*/*z*): 474.4 (53, $[M+Na]^+$), 452.4 (100, $[M+H]^+$). Anal. calcd for $C_{24}H_{16}F_3N_3O_3$ (451.1): C 63.86, H 3.57, N 9.31; found: C 63.94, H 3.58, N 9.25.

Suitable crystals of **6n** for an X-ray structure determination were obtained from hexane/dichloromethane solution by slow evaporation of the solvents.

5-(4'-Bromobenzoyl)-4-phenyl-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6o**):

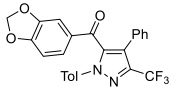


6o

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): colourless solid, 80 mg (83%); mp 147–148 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H, Me), 7.18-7.21, 7.25-7.30, 7.31-7.33 (3 m, 2H, 5H, 2H), 7.42, 7.53 (2 d_{br}, $J \approx 8.6$ Hz, 2H each). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.3, 121.3 (q, $^1J_{C-F}$ = 270.6 Hz, CF_3), 124.2 (q, $^3J_{C-F}$ = 0.8 Hz, C-4), 124.3, 128.48, 128.53, 128.8, 129.8, 129.9(br), 130.1, 131.2, 132.1, 134.8, 136.5, 139.2, 139.4, 140.4 (q, $^2J_{C-F}$ = 36.8 Hz, C-3), 186.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.2 (s, CF_3). IR (neat) ν 1685, 1252, 1118, 1036 cm^{-1}. ESI-MS (*m*/*z*): 509.2 (100, $[M\{^{81}Br\}+Na]^+$), 507.3 (80, $[M\{^{79}Br\}+Na]^+$), 487.3 (74,

[M{^{81}Br}+H]$^+$), 485.3 (67, [M{^{79}Br}+H]$^+$). Anal. calcd for $C_{24}H_{16}BrF_3N_2O$ (485.3): C 59.40, H 3.32, N 5.77; found: C 59.15, H 3.52, N 5.97.

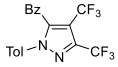
5-[(3',4'-Methylenedioxyphenyl)carbonyl]-4-phenyl-1-tolyl-3-trifluoromethyl-1*H*-pyrazole (**6p**):



6p

CC (SiO_2, petroleum ether/EtOAc 10:1): colourless solid, 48 mg (53%); mp 158–159 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3H, Me), 5.97 (s, 2H, OCH_2O), 6.62 (d, J = 8.1 Hz, 1H), 7.15-7.21, 7.24-7.33 (2 m, 4H, 7H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.3, 102.3, 108.1, 108.5, 121.4 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 123.4 (q$_{br}$, $^3J_{C\text{-}F} \approx$ 0.9 Hz, C-4), 124.2, 127.9, 128.3, 128.4, 129.2, 129.8(br), 130.0, 131.0, 136.6, 139.1, 139.8, 140.2 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, C-3), 148.5, 153.1, 185.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ –59.1 (s$_{br}$, CF_3). IR (neat) ν 1667, 1491, 1264, 1115 cm^{-1}. ESI-MS (*m/z*): 473.3 (100, [M+Na]$^+$), 451.3 (85, [M+H]$^+$). Anal. calcd for $C_{25}H_{17}F_3N_2O_3$ (450.1): C 66.67, H 3.80, N 6.22; found: C 66.61, H 3.82, N 6.40.

5-Benzoyl-1-tolyl-3,4-bis(trifluoromethyl)-1*H*-pyrazole (**6r**):



6r

CC (SiO_2, petroleum ether/EtOAc 95:5): colourless oil, 56 mg (71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H, Me), 7.14, 7.25 (2 d$_{br}$, $J \approx$ 8.2 Hz, 2H each), 7.46-7.49, 7.62-7.65, 7.74-7.76 (3 m, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.3, 111.9 (q, $^2J_{C\text{-}F}$ = 40.2 Hz, C-4), 120.0 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 120.8 (q, $^1J_{C\text{-}F}$ = 268.7 Hz, CF_3), 124.4, 129.3, 129.8, 130.3, 135.4, 135.5, 135.6(br), 140.0 (qq, $J_{C\text{-}F}$ = 2.2, 40.1 Hz, C-3), 140.3, 141.5 (q, $^3J_{C\text{-}F}$ = 2.7 Hz, C-5), 185.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ –61.4, –54.6, (2 q, $J_{F\text{-}F}$ = 5.9 Hz, 2 CF_3). IR (neat) ν 1677, 1506, 1208, 1148 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{19}H_{13}F_6N_2O$ 399.0932, found 399.0933.

3. Copies of ^{1}H and ^{13}C NMR spectra

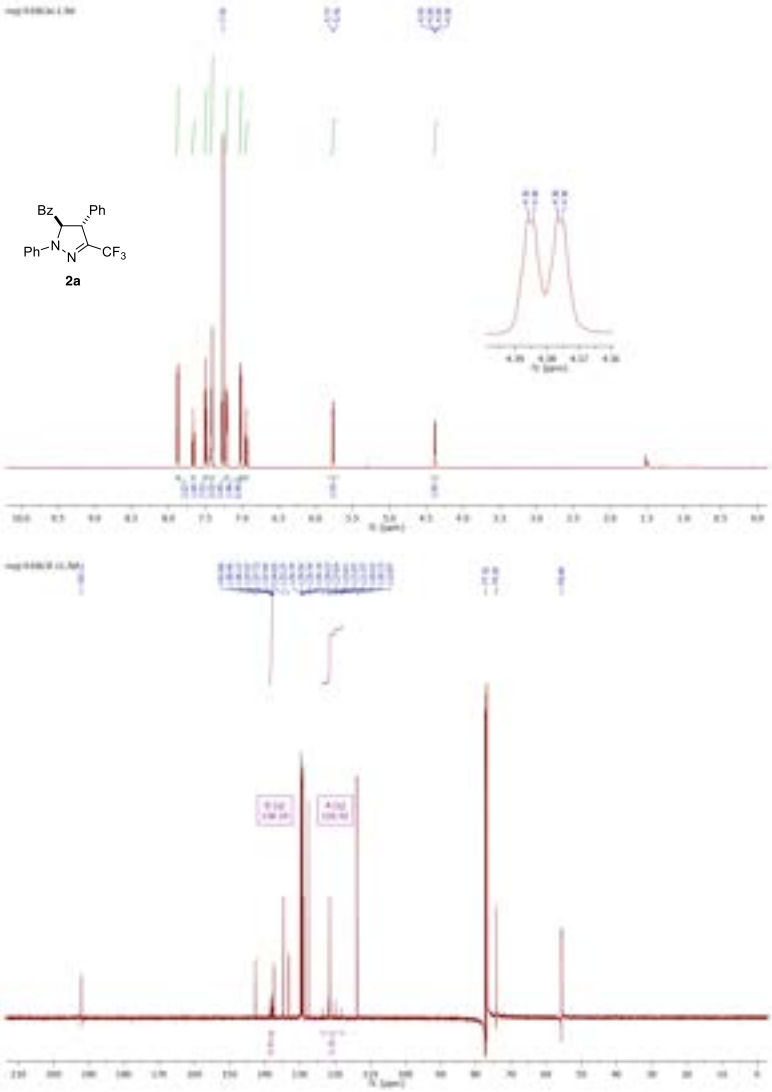


Fig S2. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2a**.

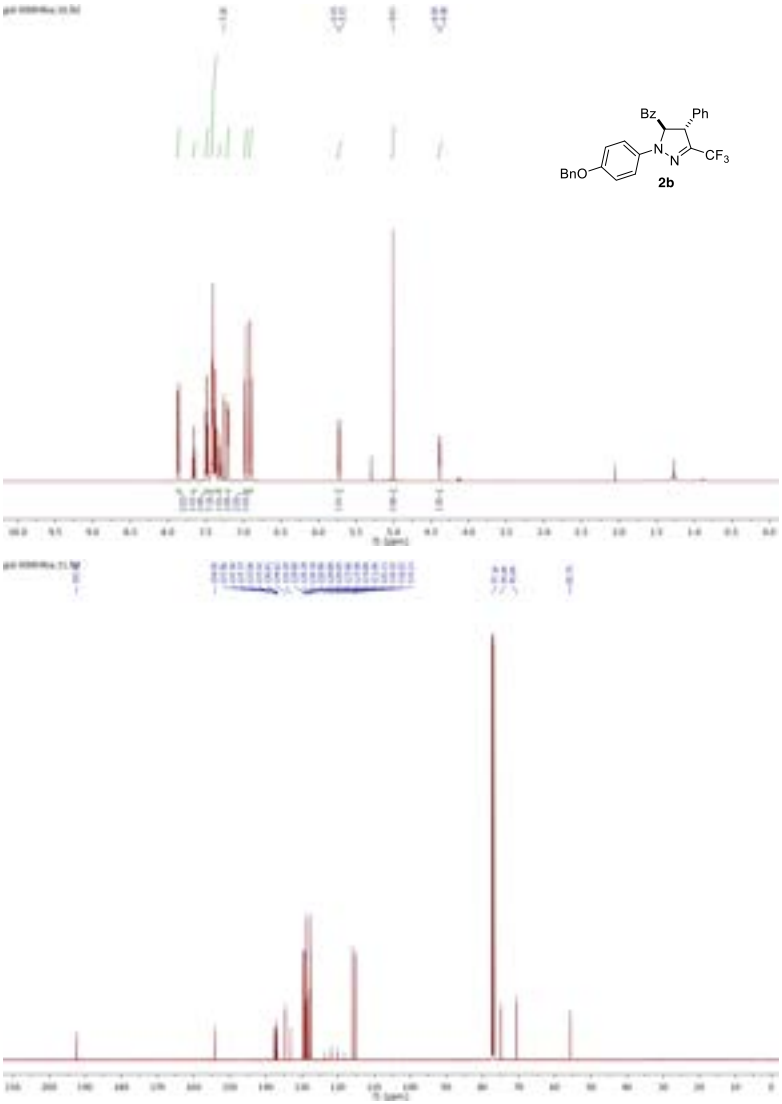


Fig S3. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2b**.

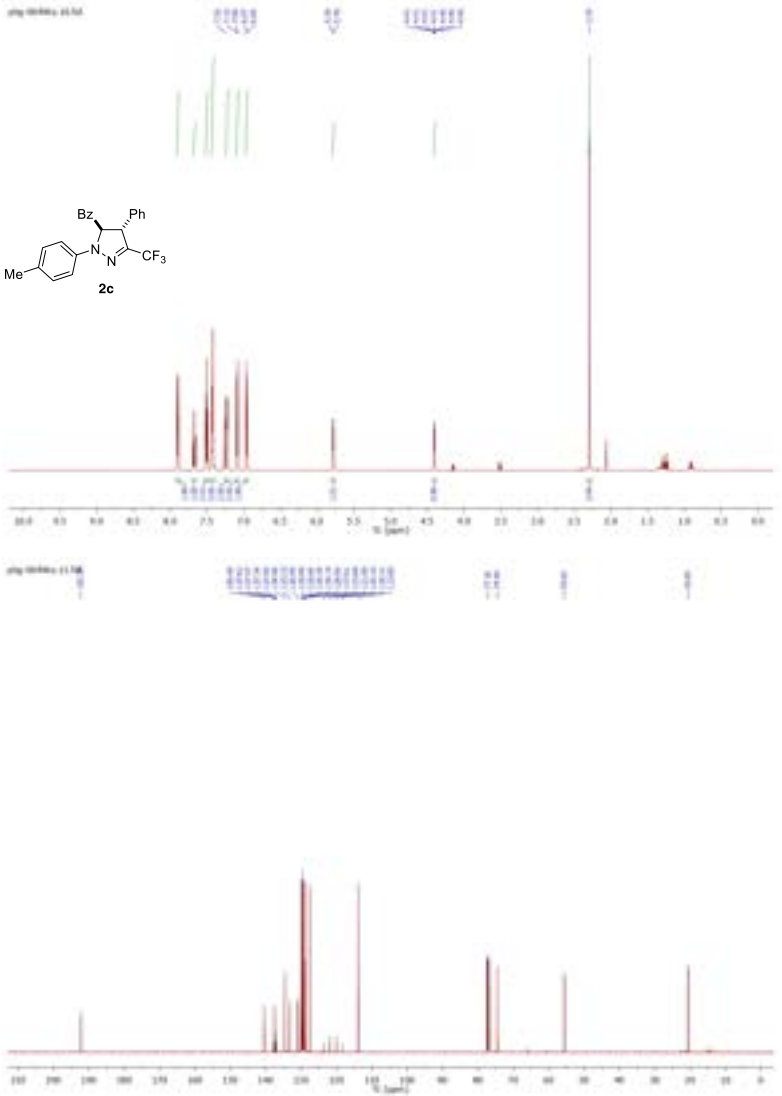


Fig S4. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2c**.

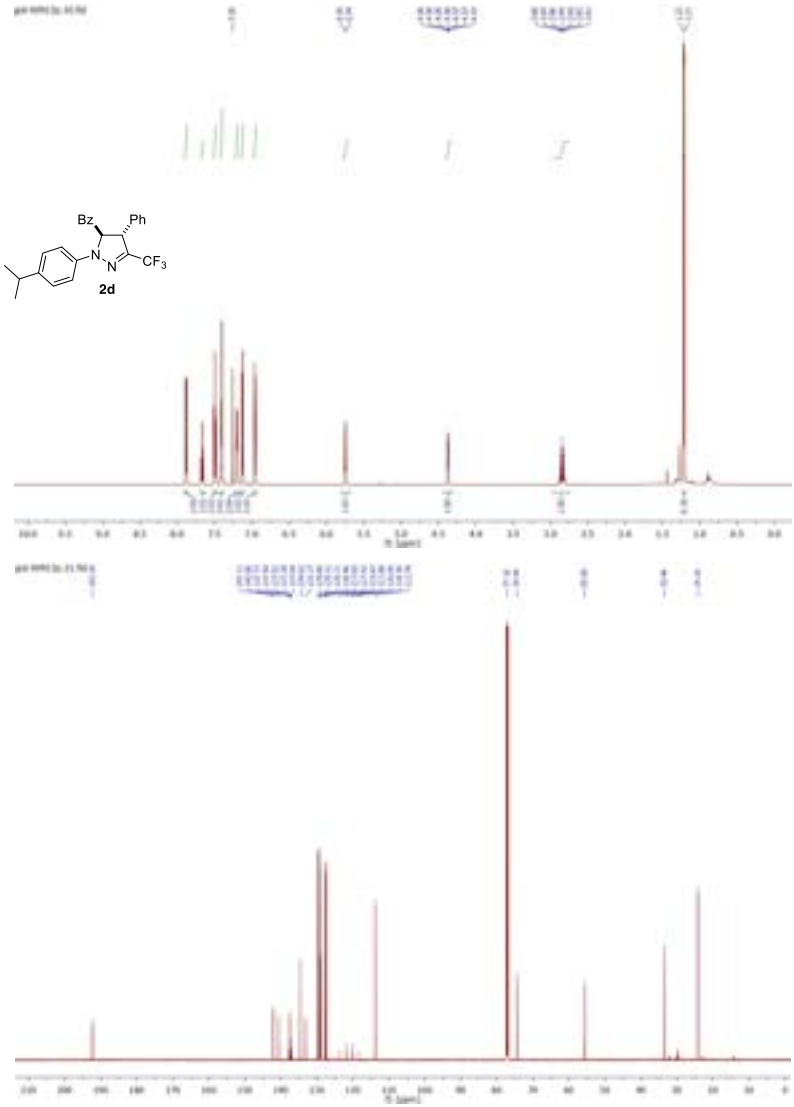


Fig S5. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2d**.

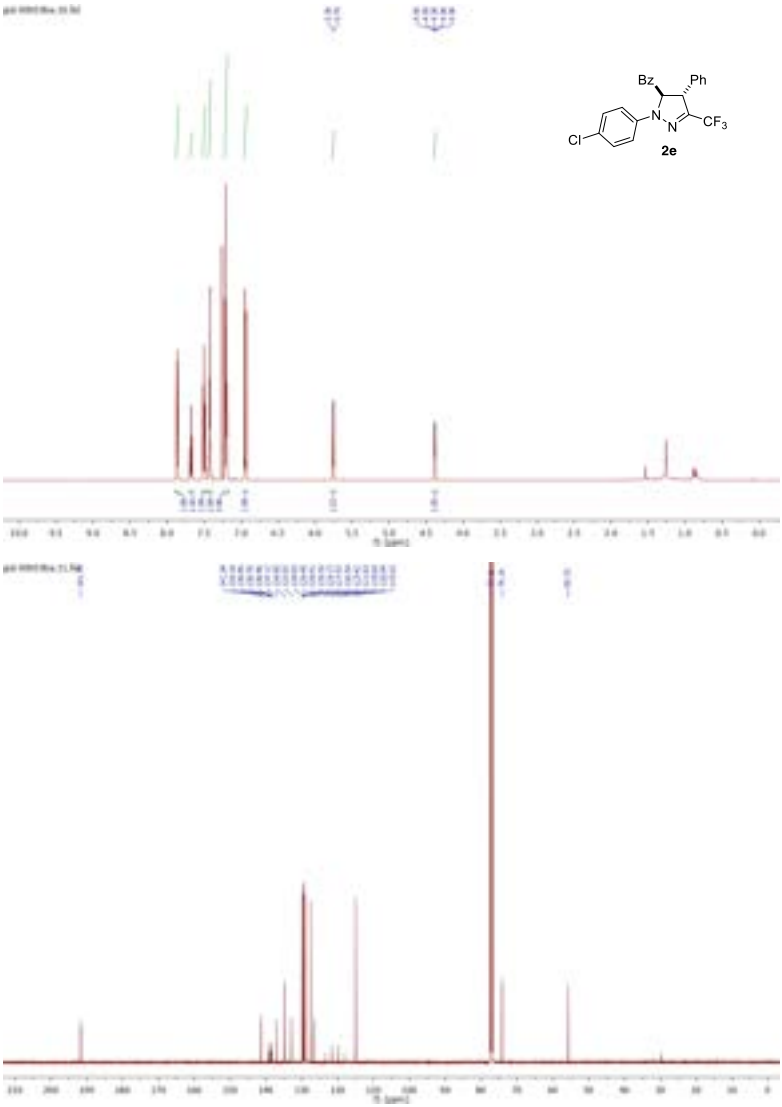


Fig S6. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2e**.

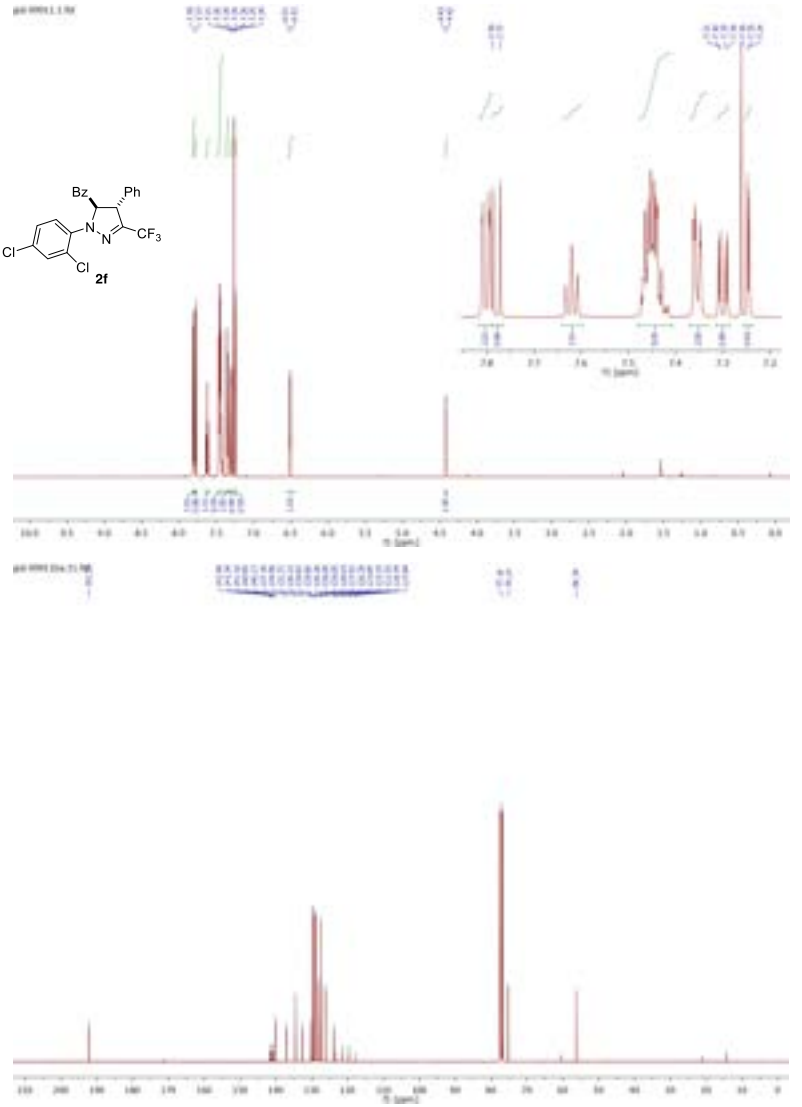


Fig S7. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2f**.

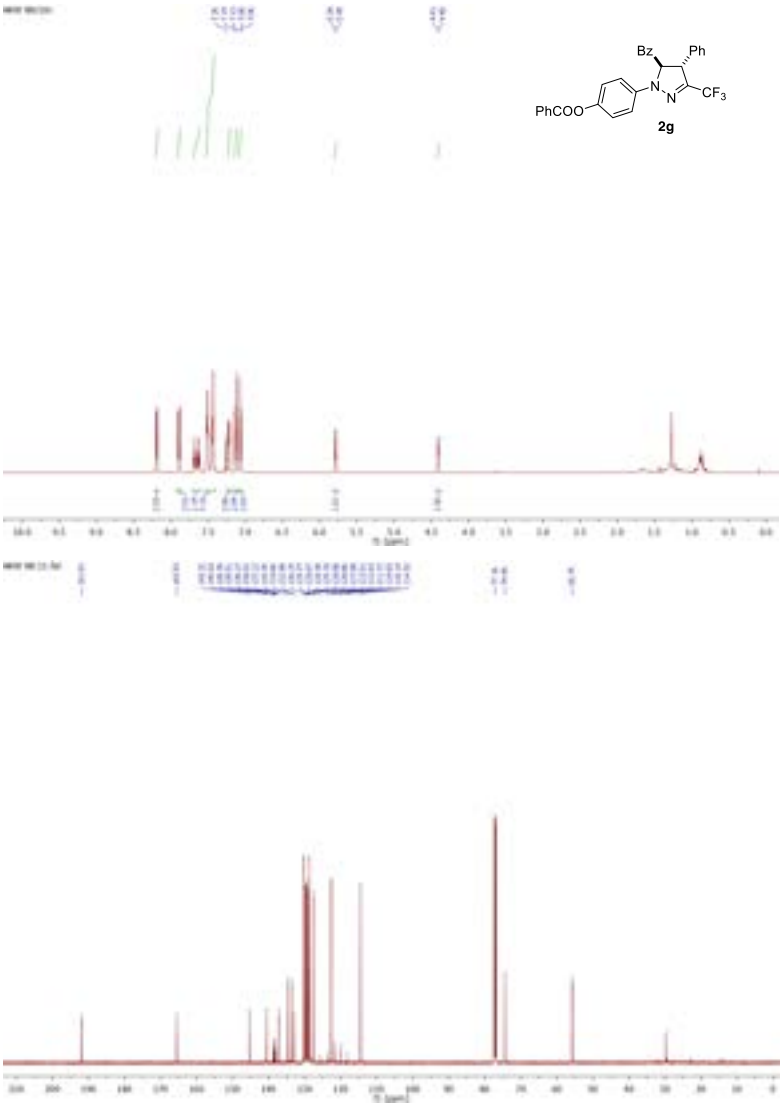


Fig S8. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2g**.

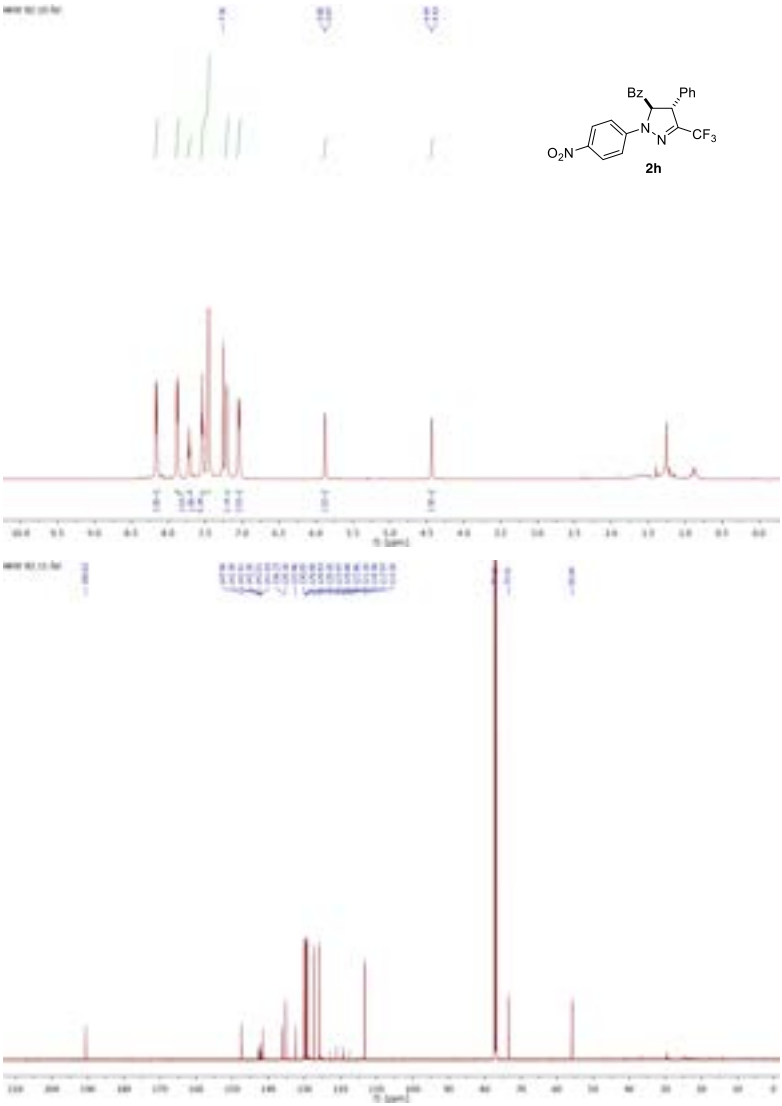


Fig S9. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2h**.

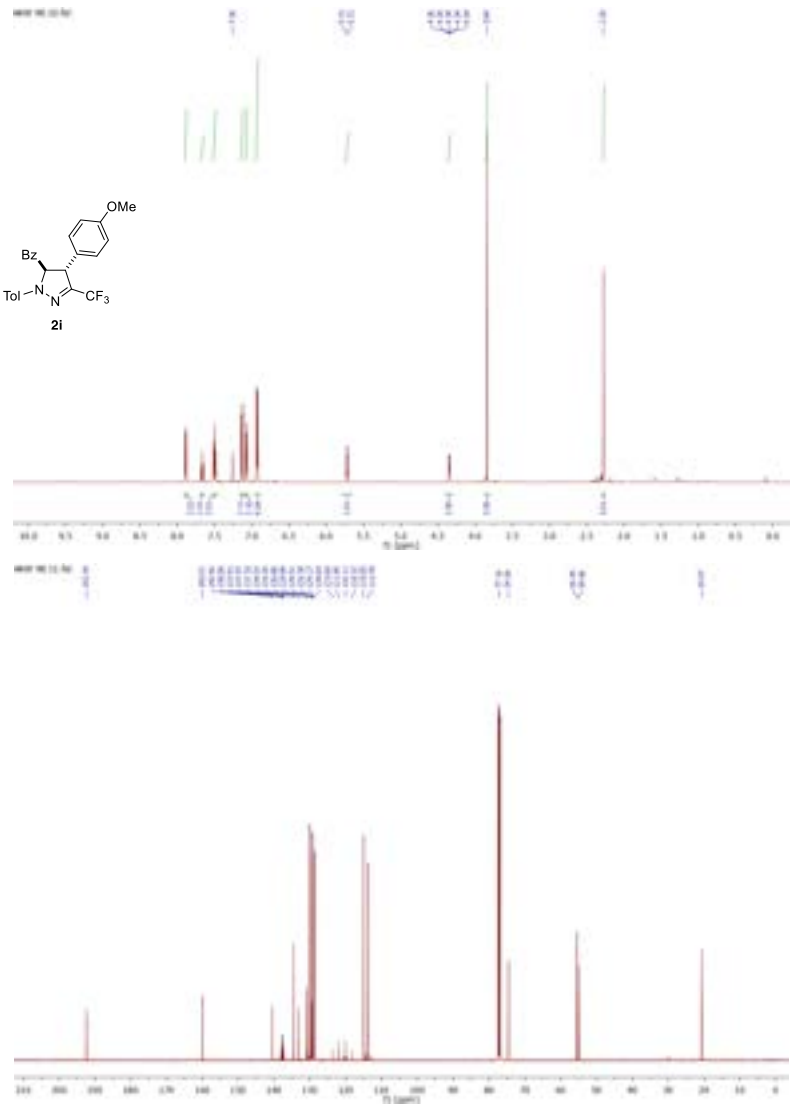


Fig S10. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2i**.

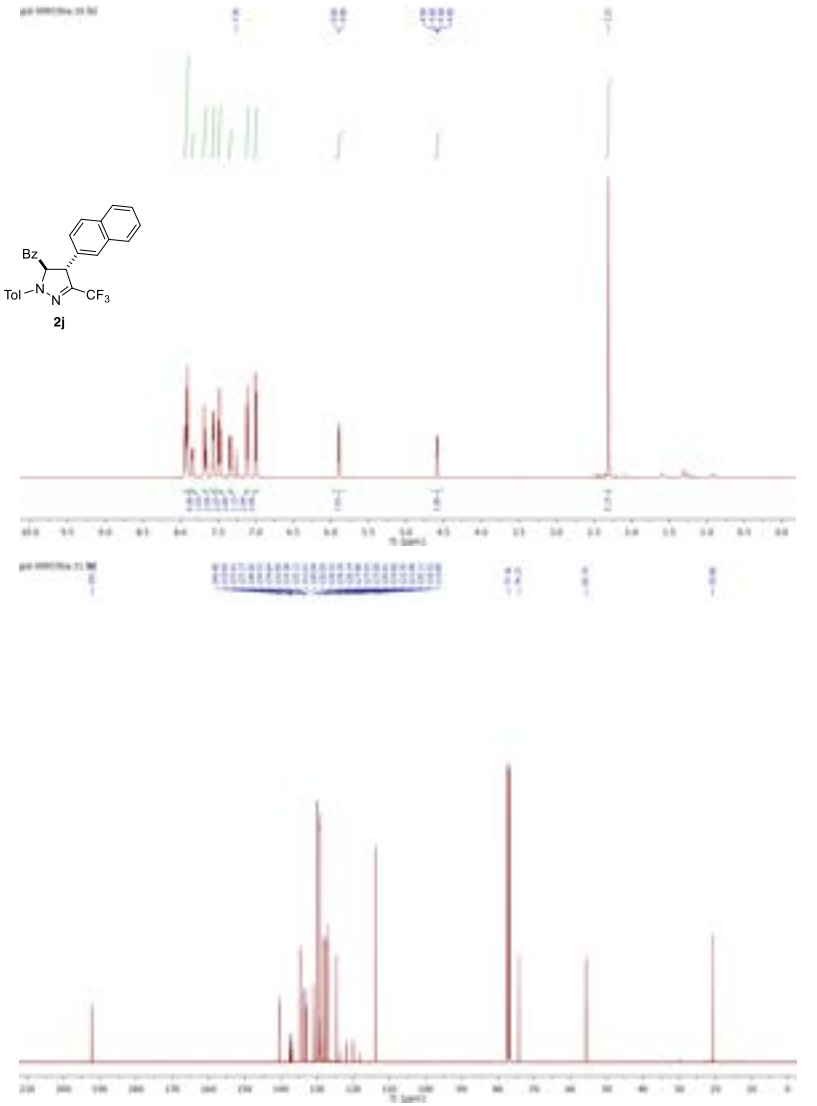


Fig S11. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2j**.

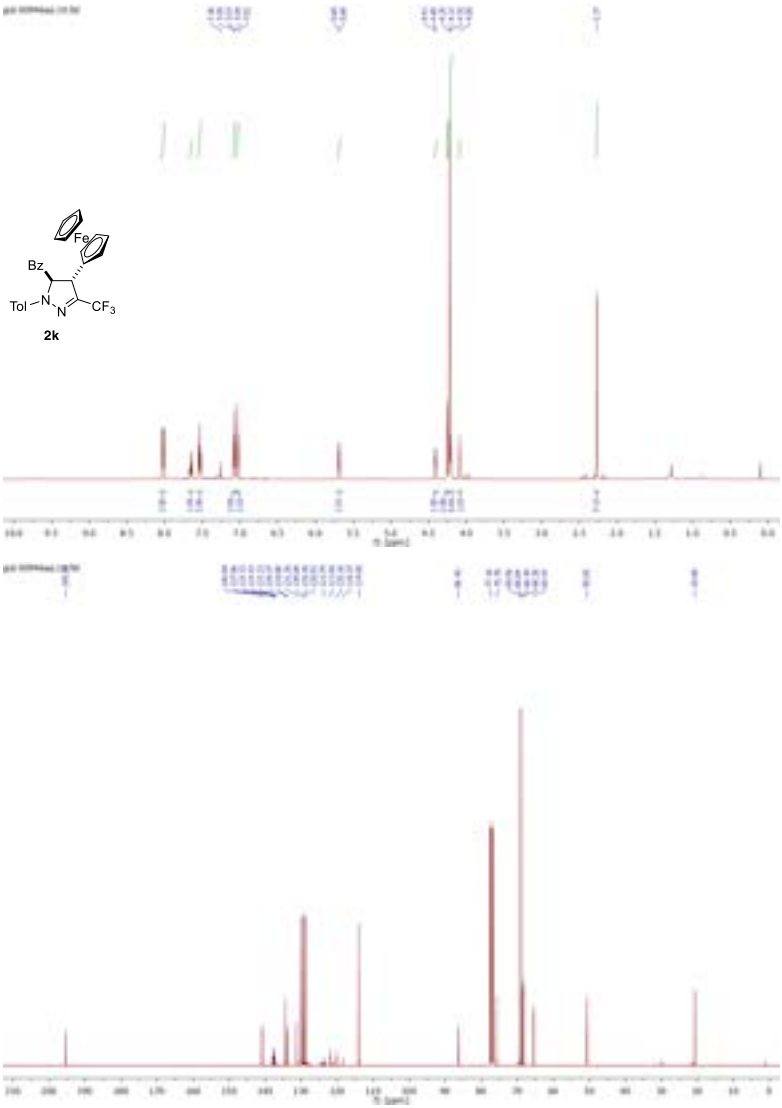


Fig S12. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2k**.

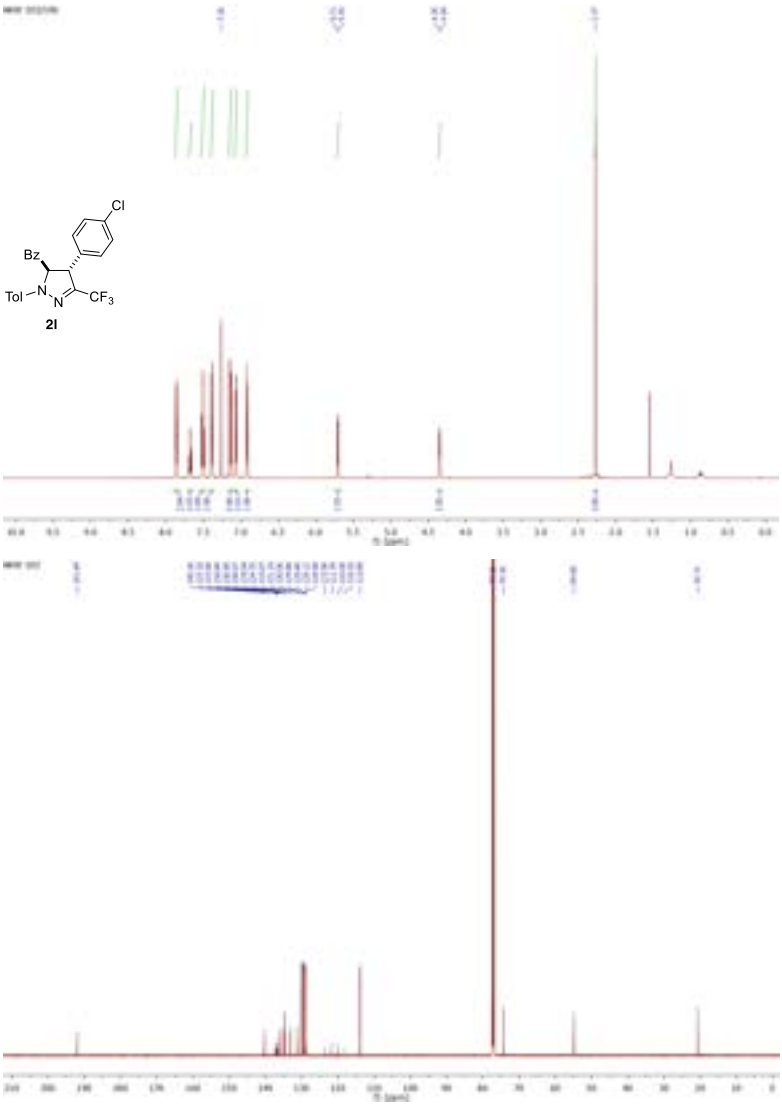


Fig S13. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2l**.

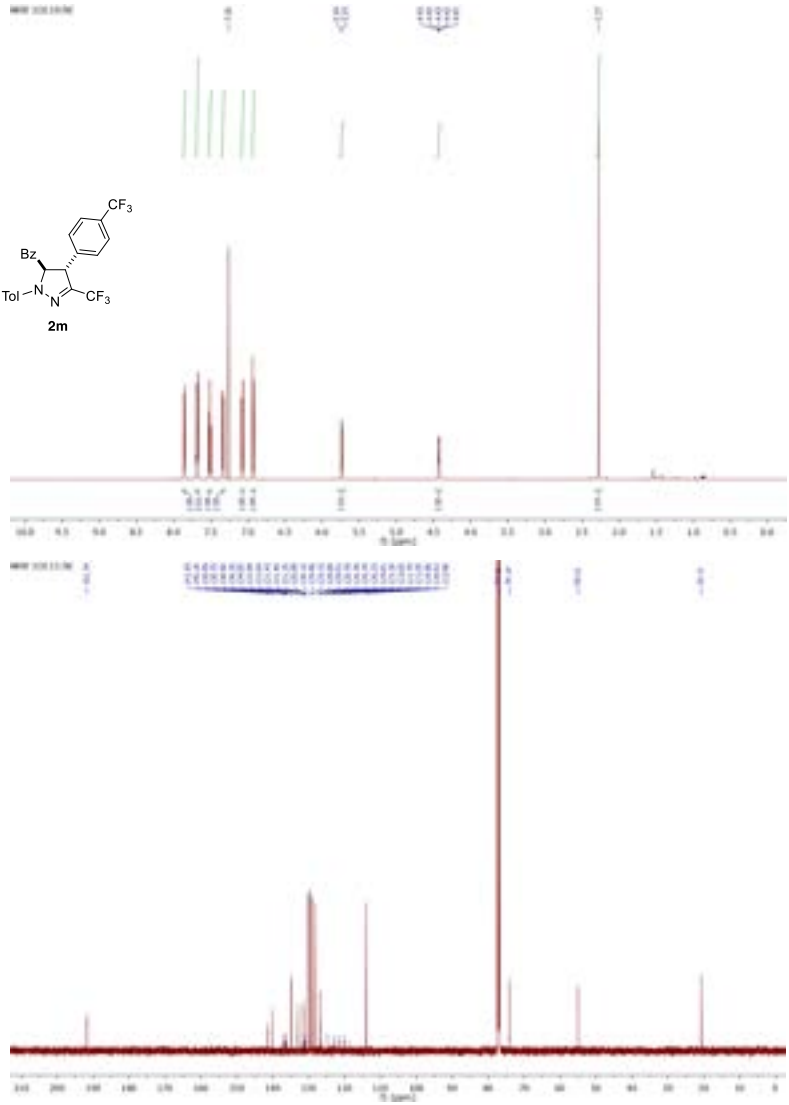


Fig S14. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2m**.

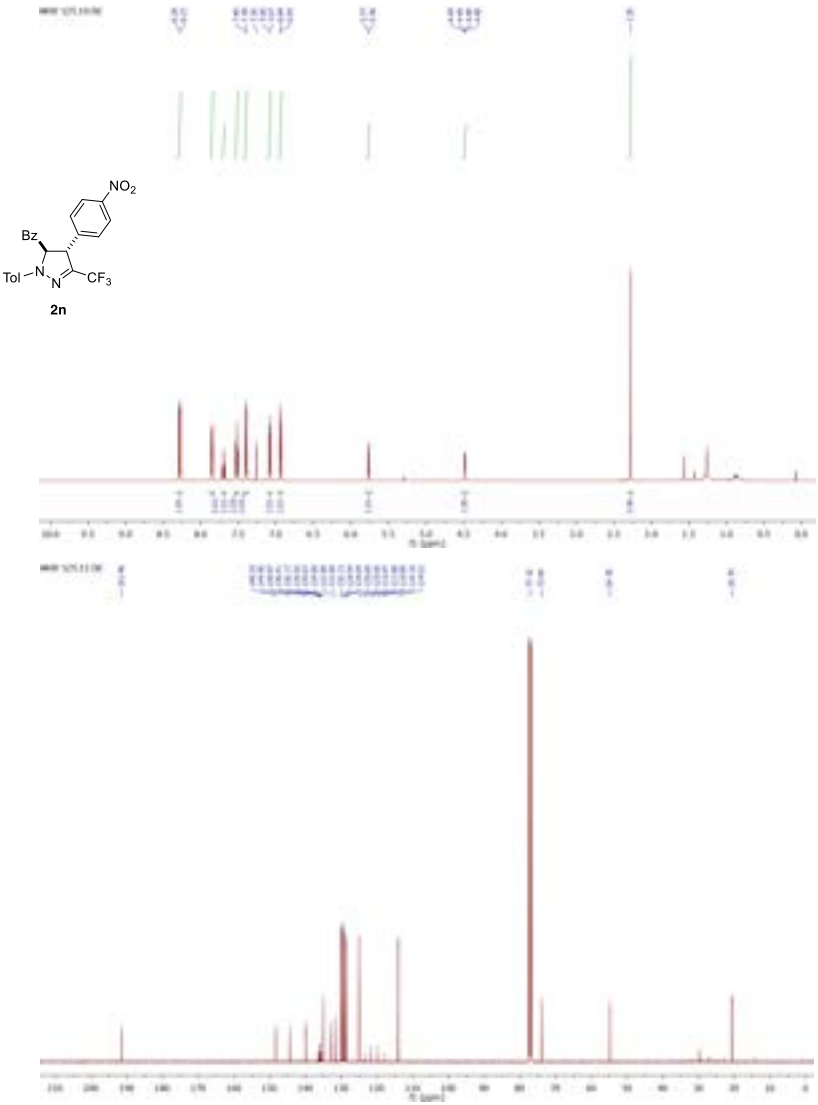


Fig S15. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2n**.

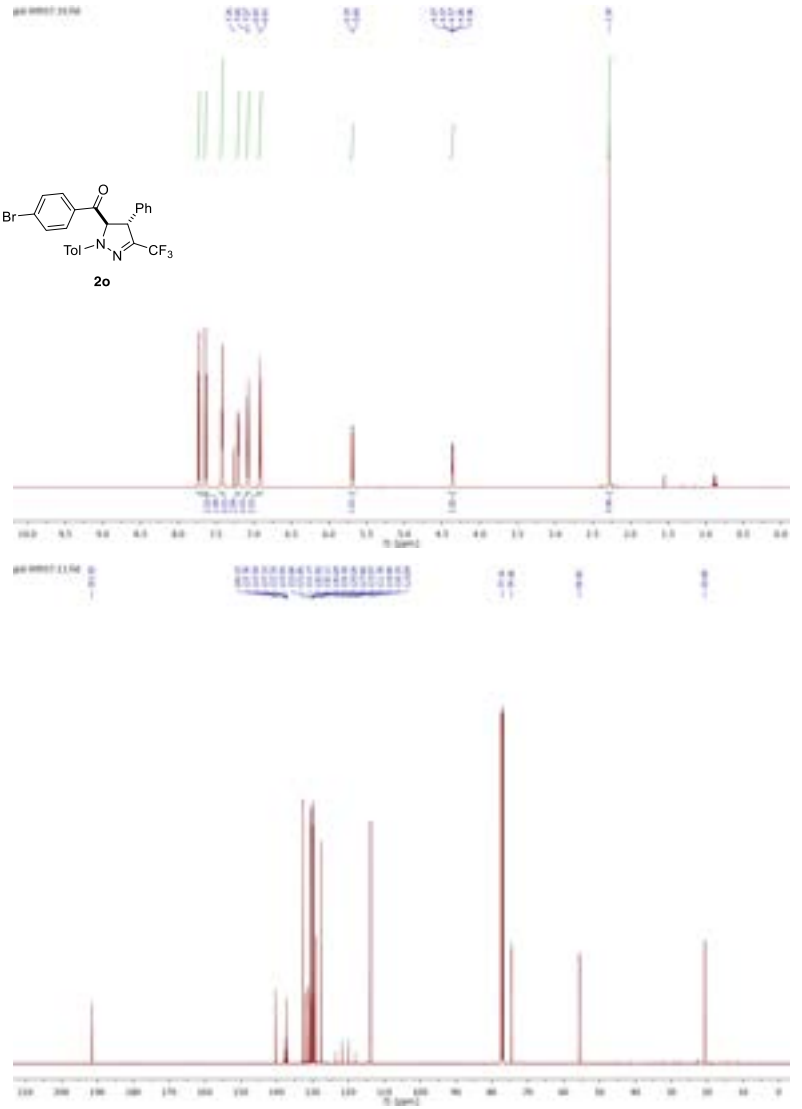


Fig S16. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2o**.

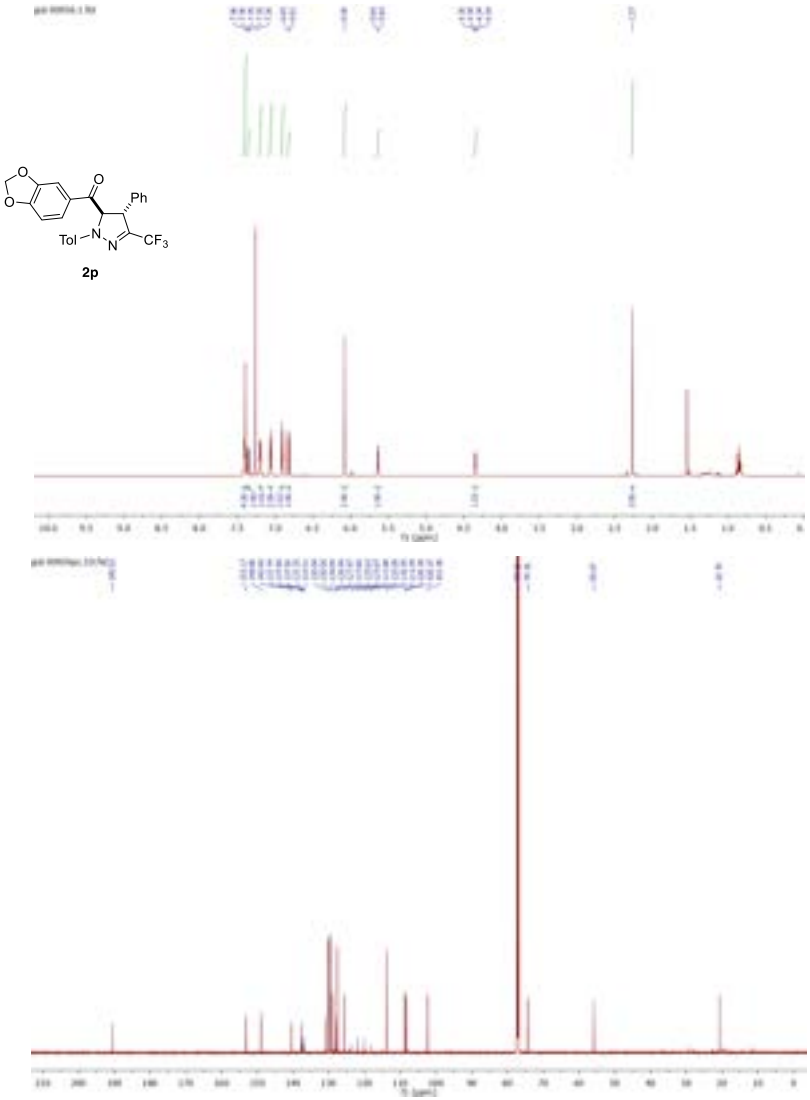


Fig S17. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2p**.

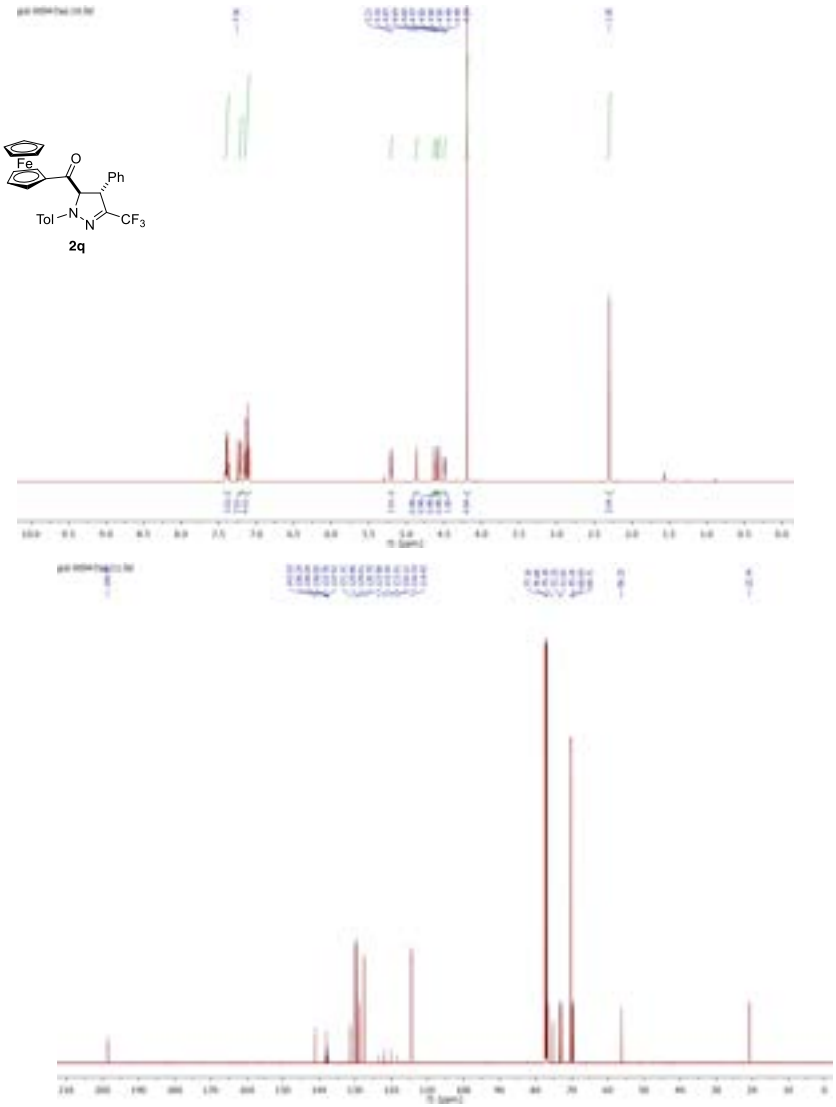


Fig S18. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2q**.

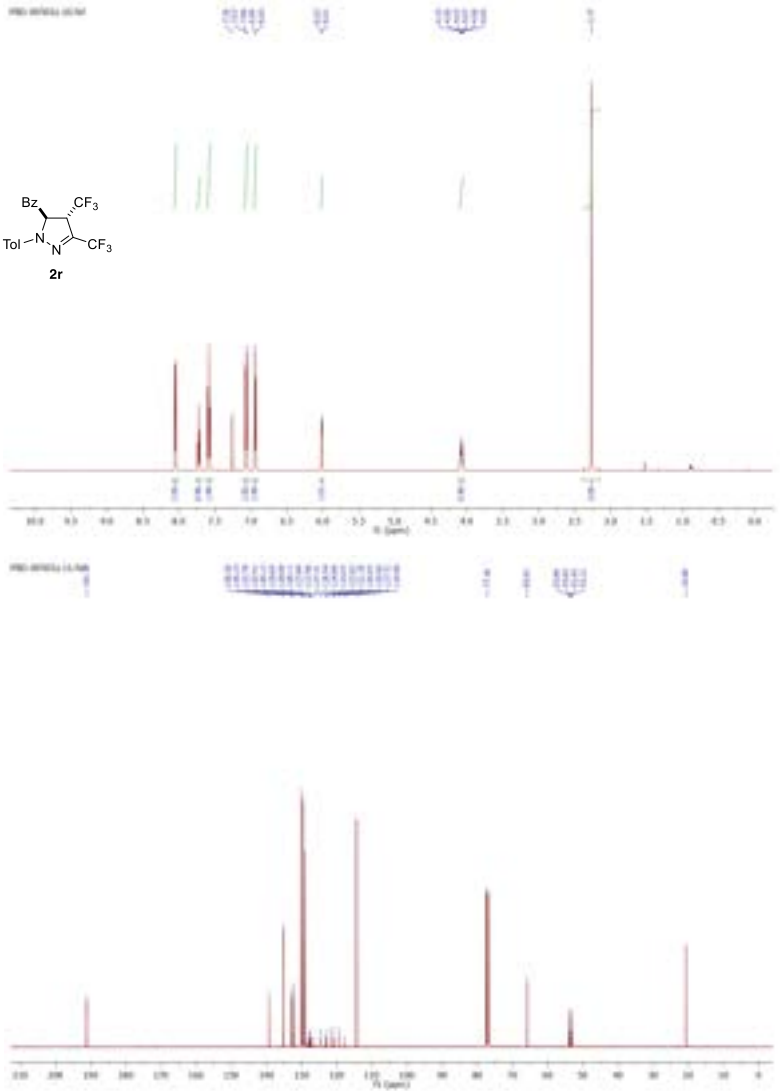


Fig S19. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **2r**.

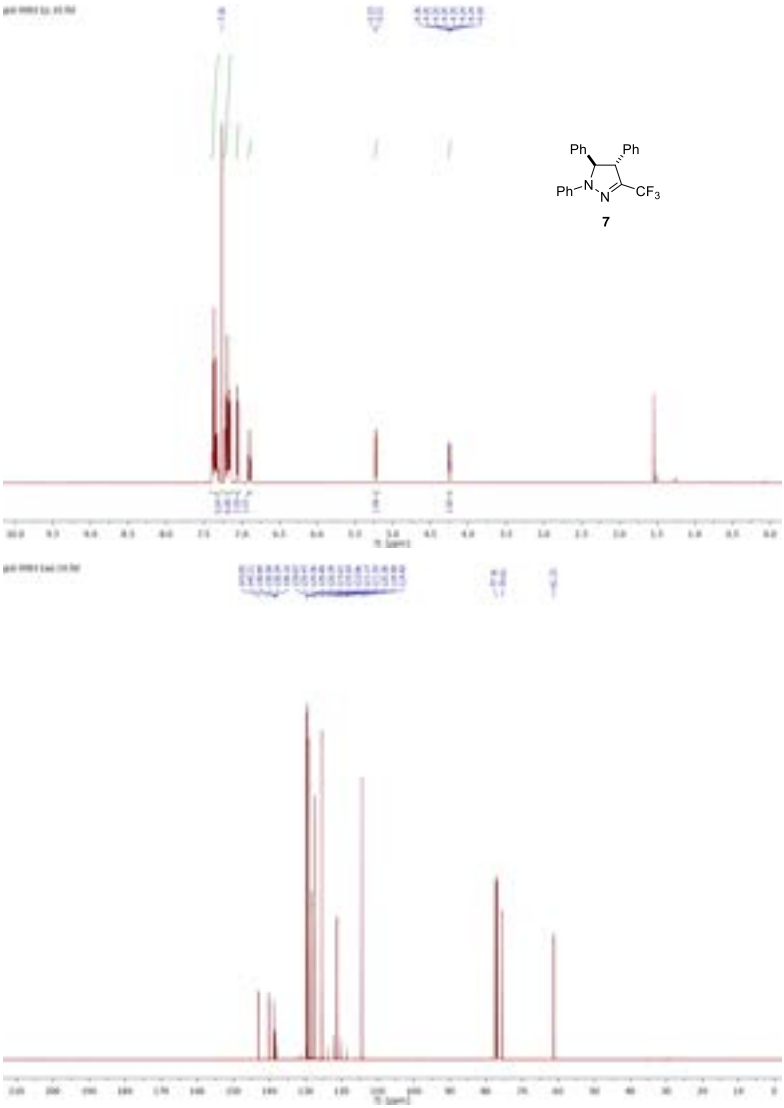


Fig S20. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7**.

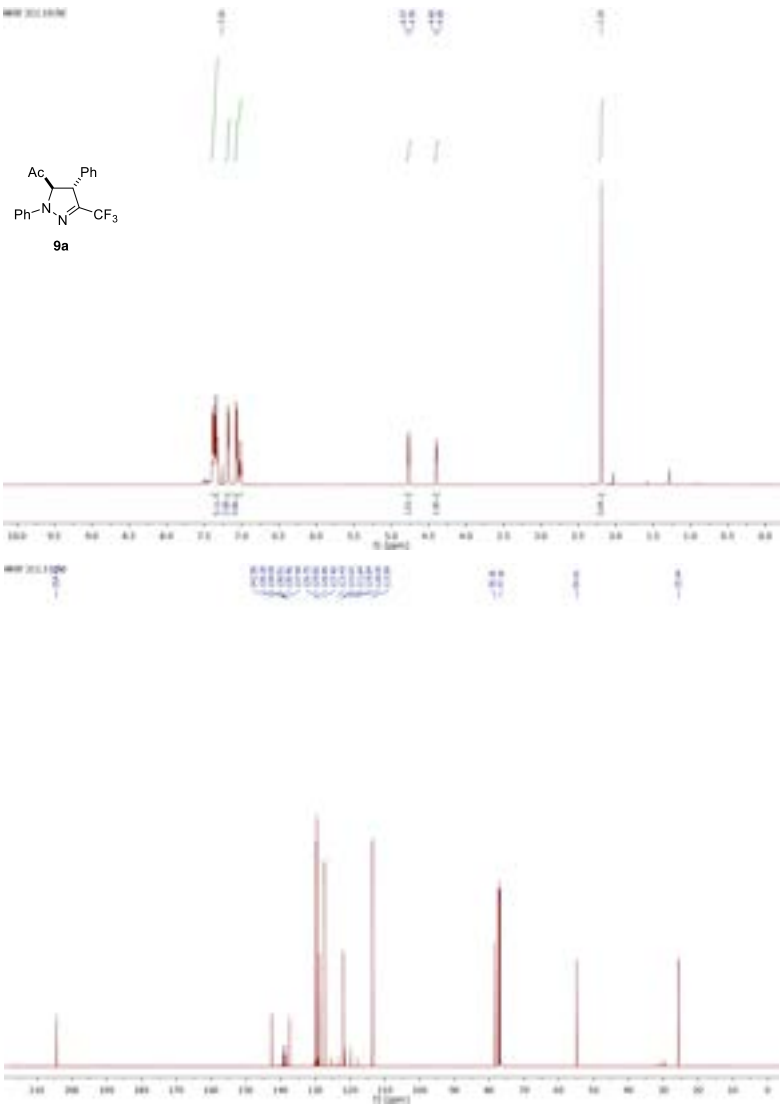


Fig S21. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **9a**.

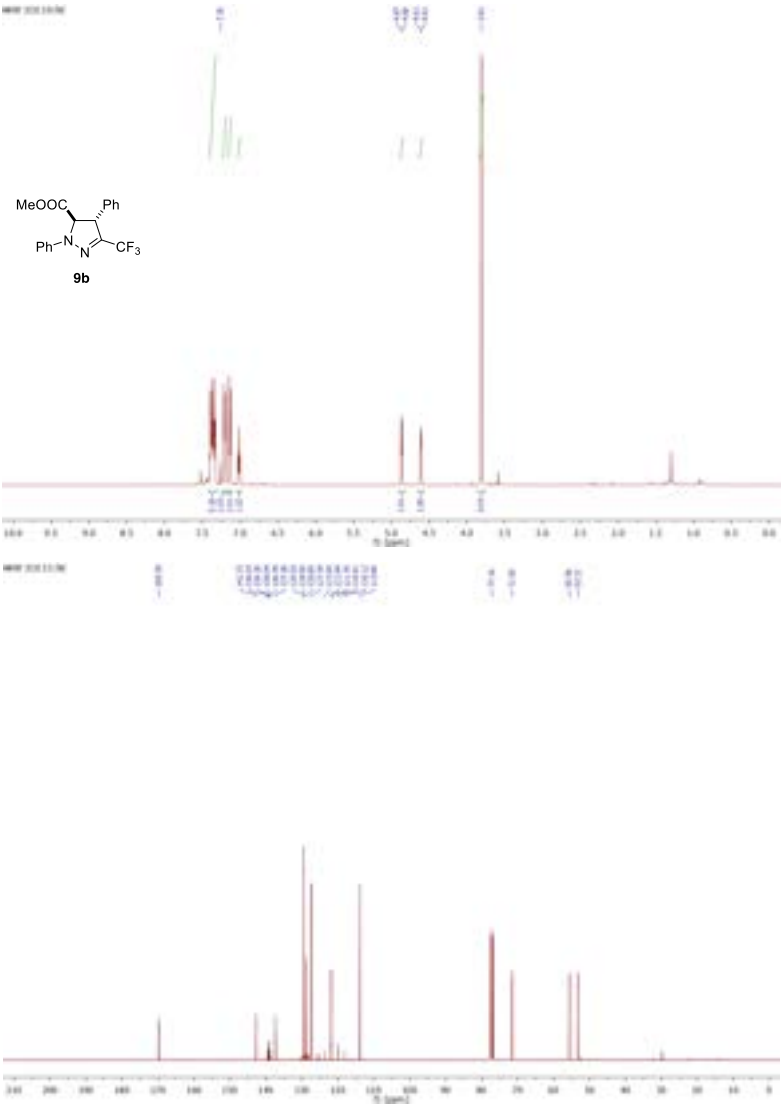


Fig S22. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **9b**.

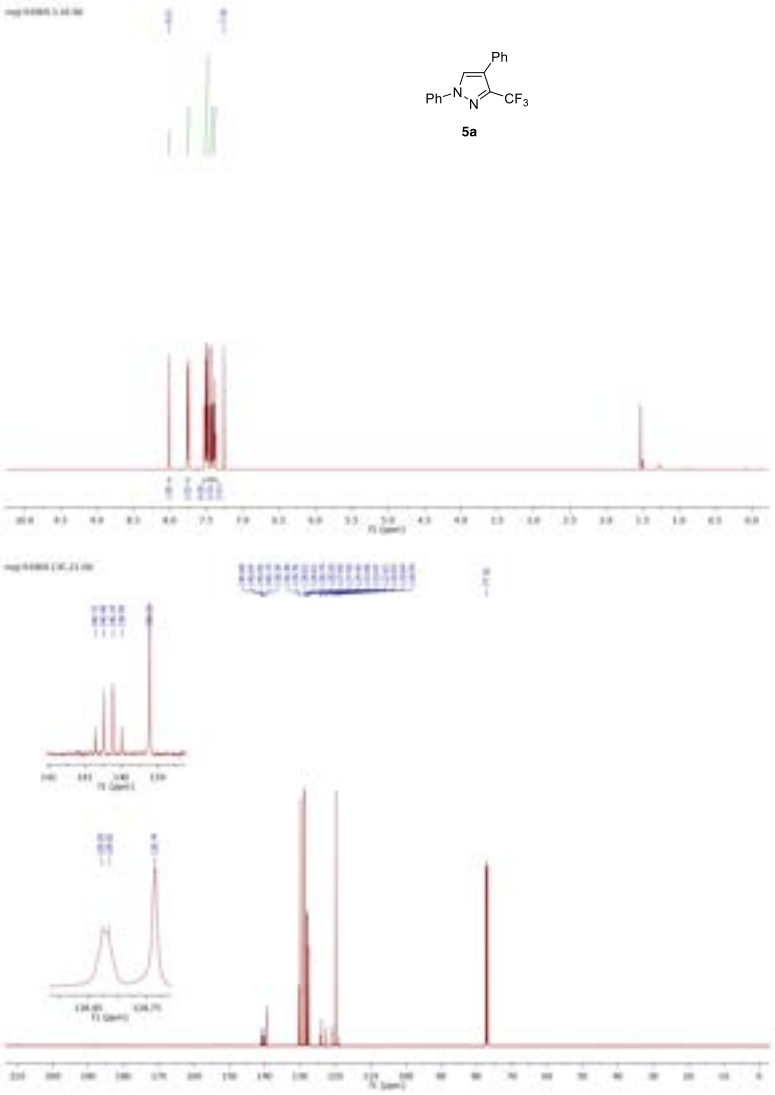


Fig S23. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5a**.

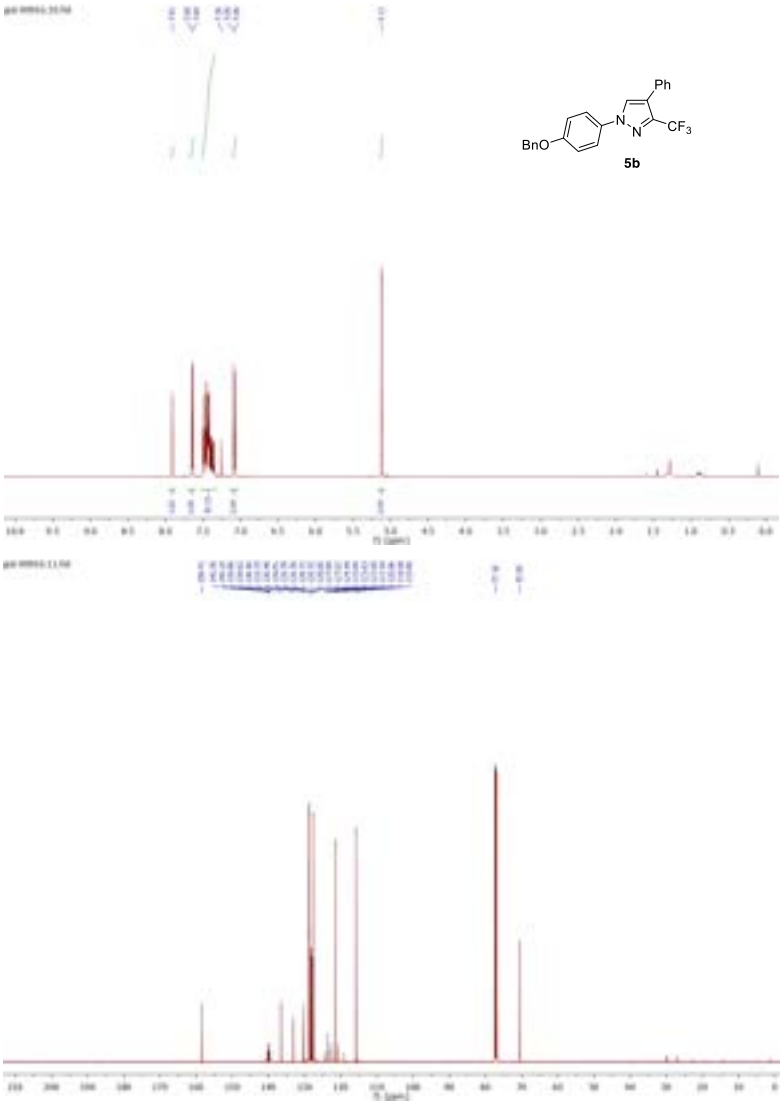


Fig S24. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5b**.

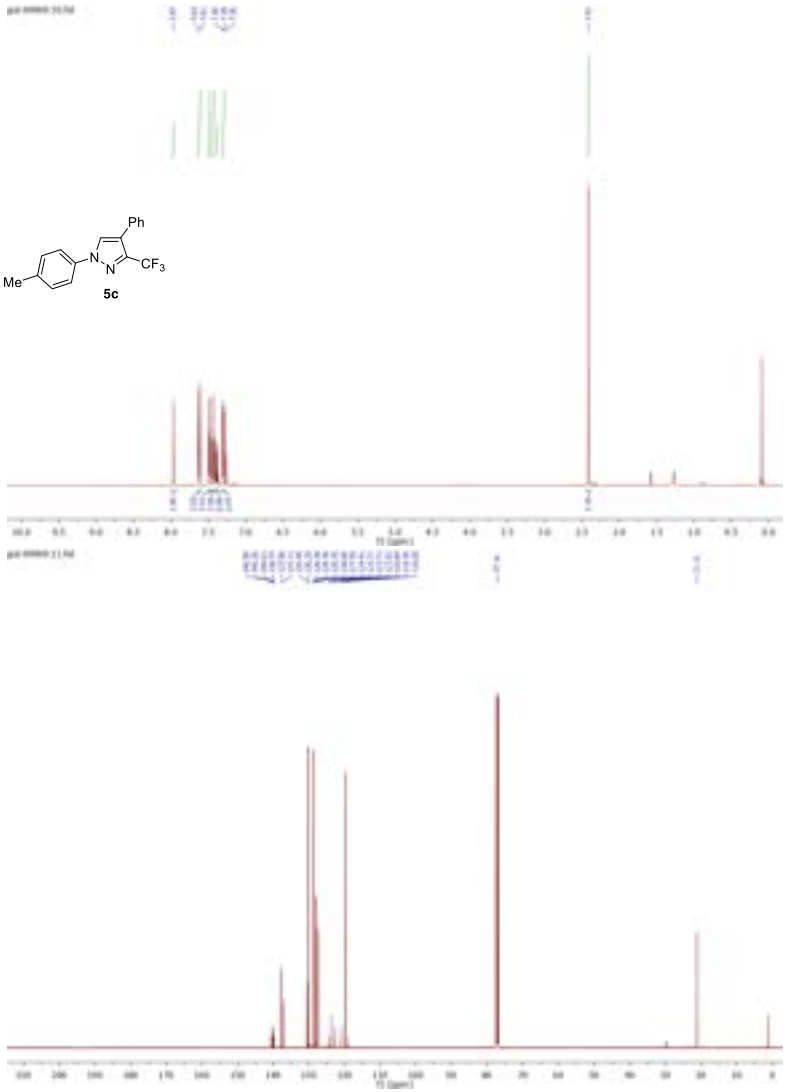


Fig S25. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5c**.

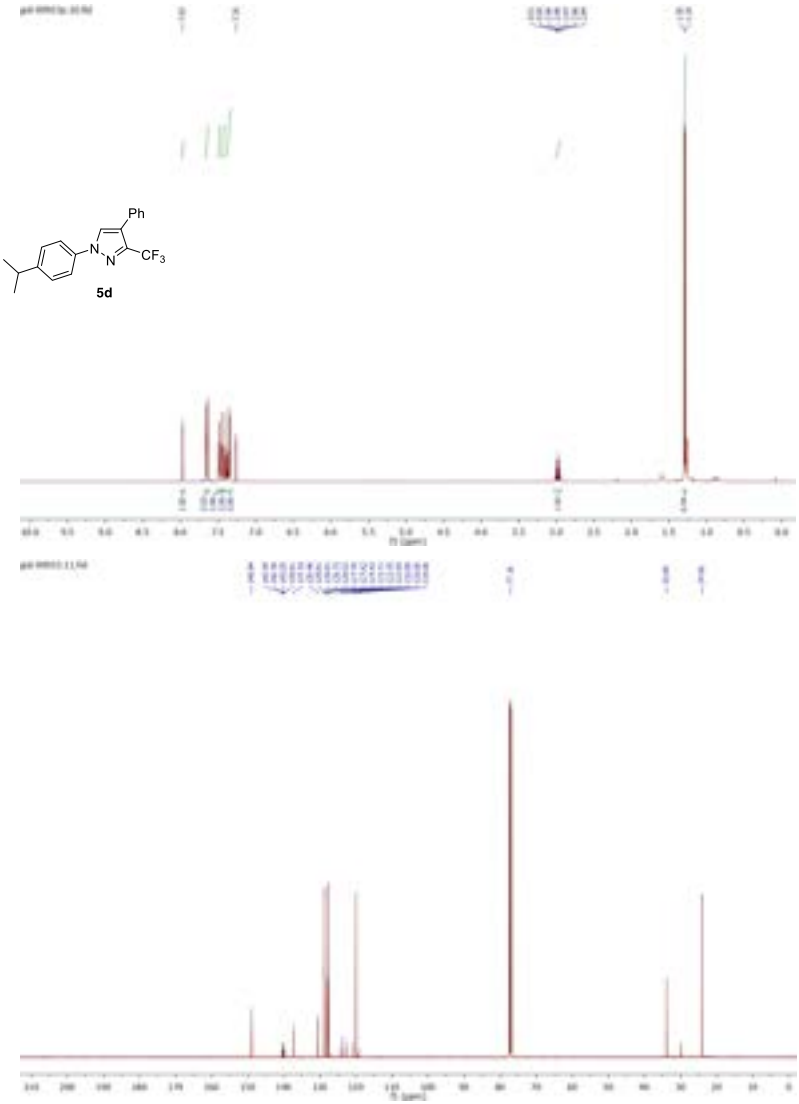


Fig S26. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5d**.

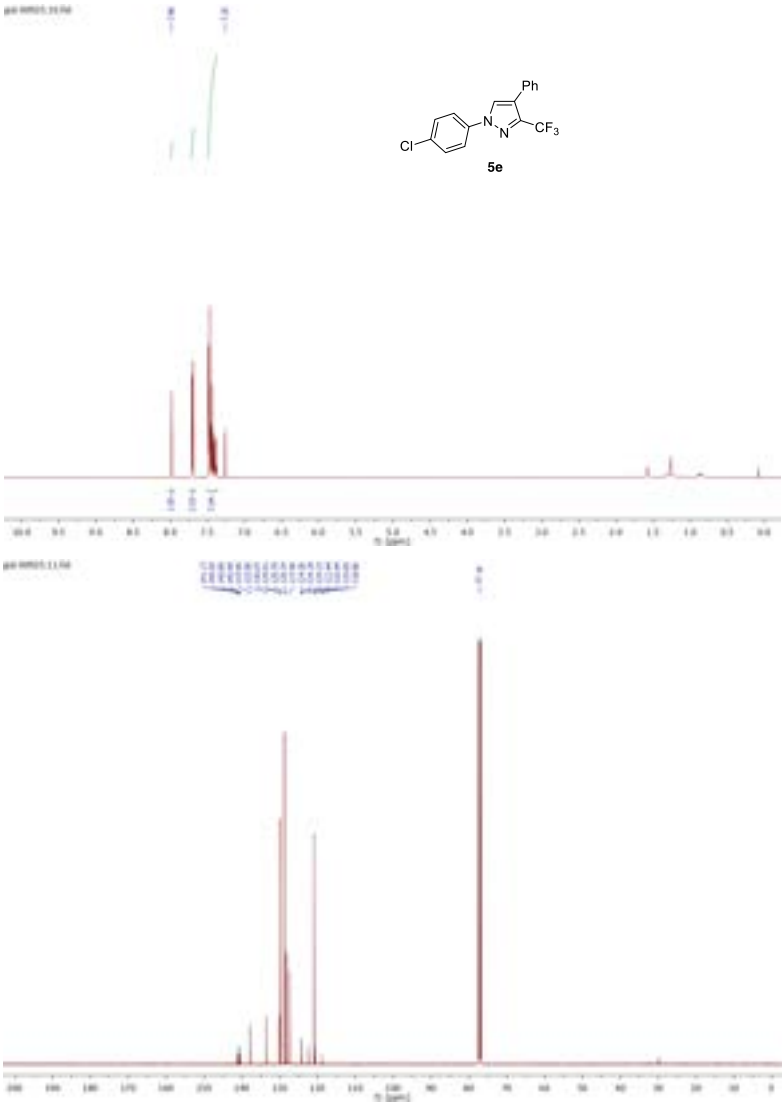


Fig S27. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5e**.

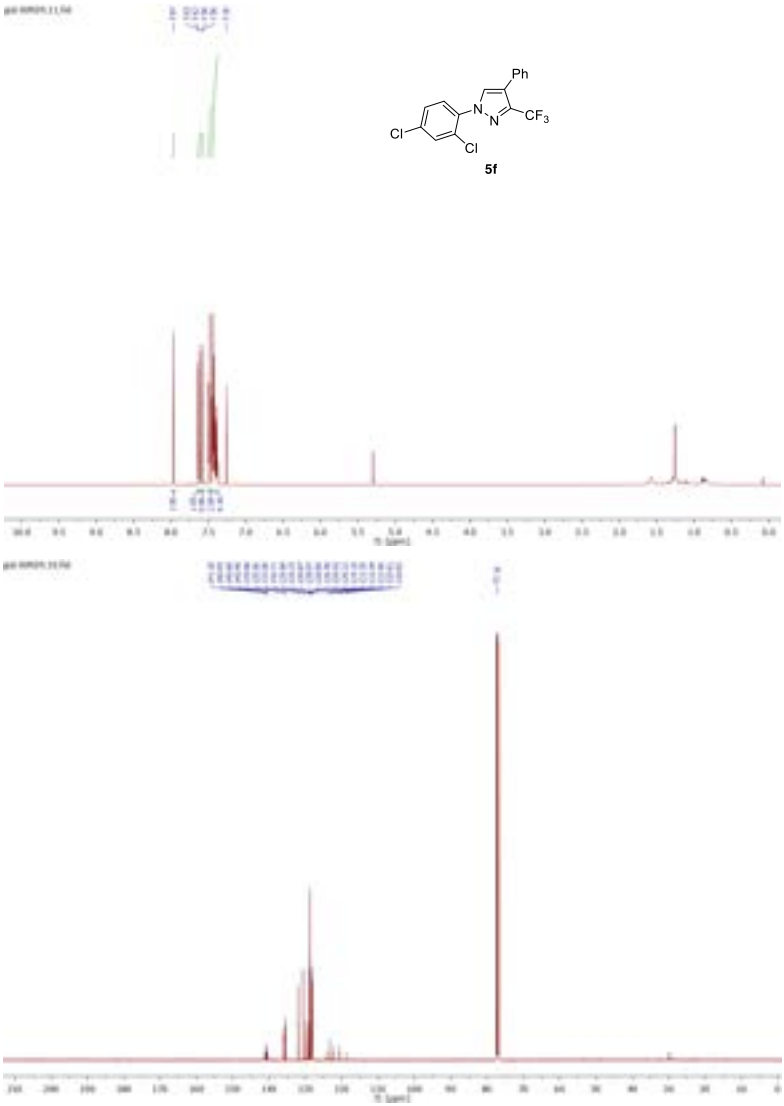


Fig S28. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5f**.

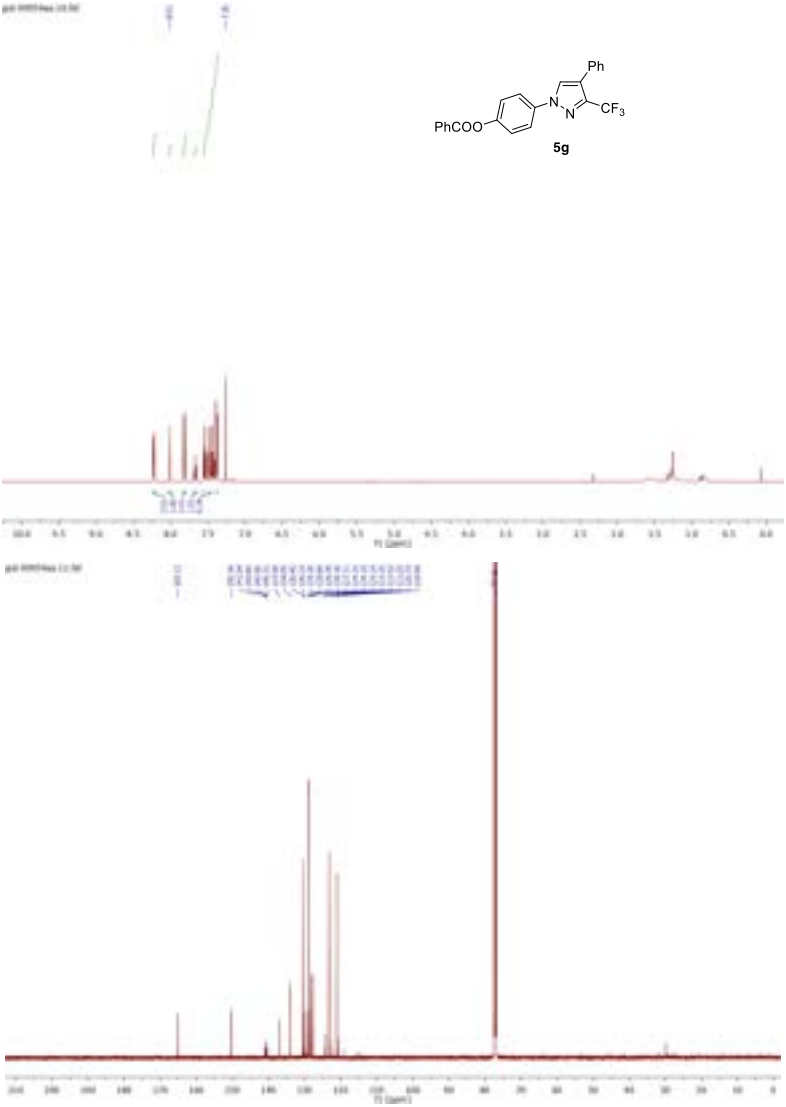


Fig S29. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5g**.

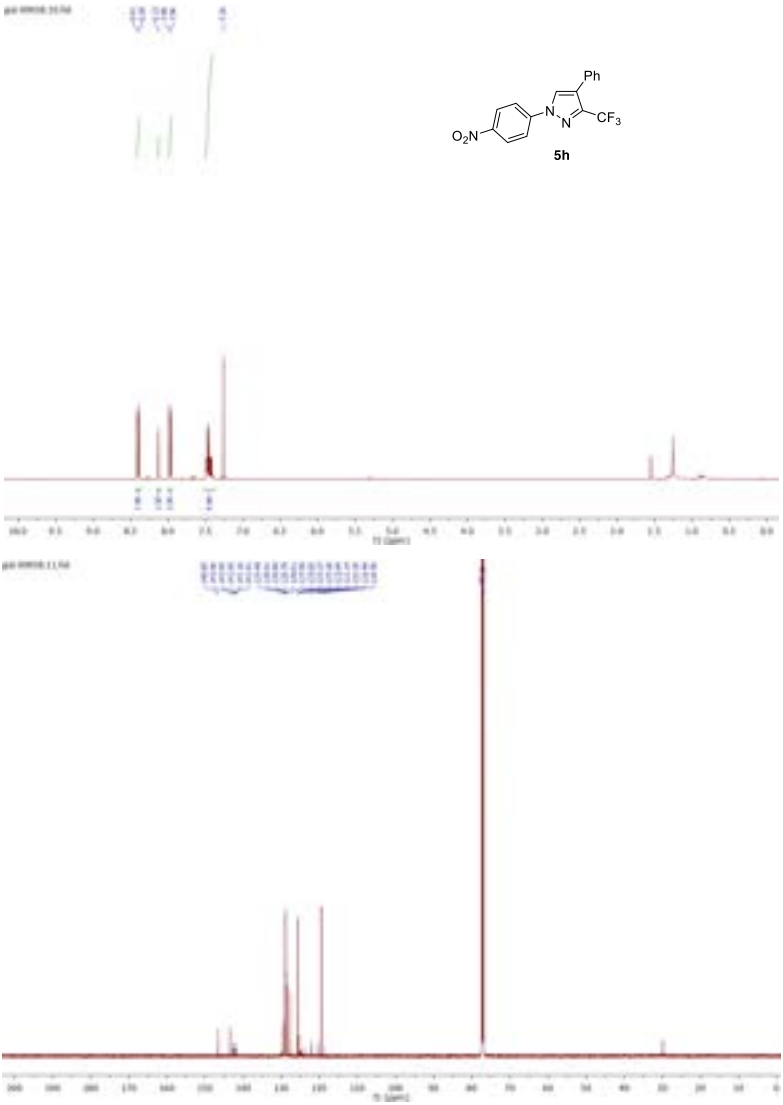


Fig S30. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5h**.

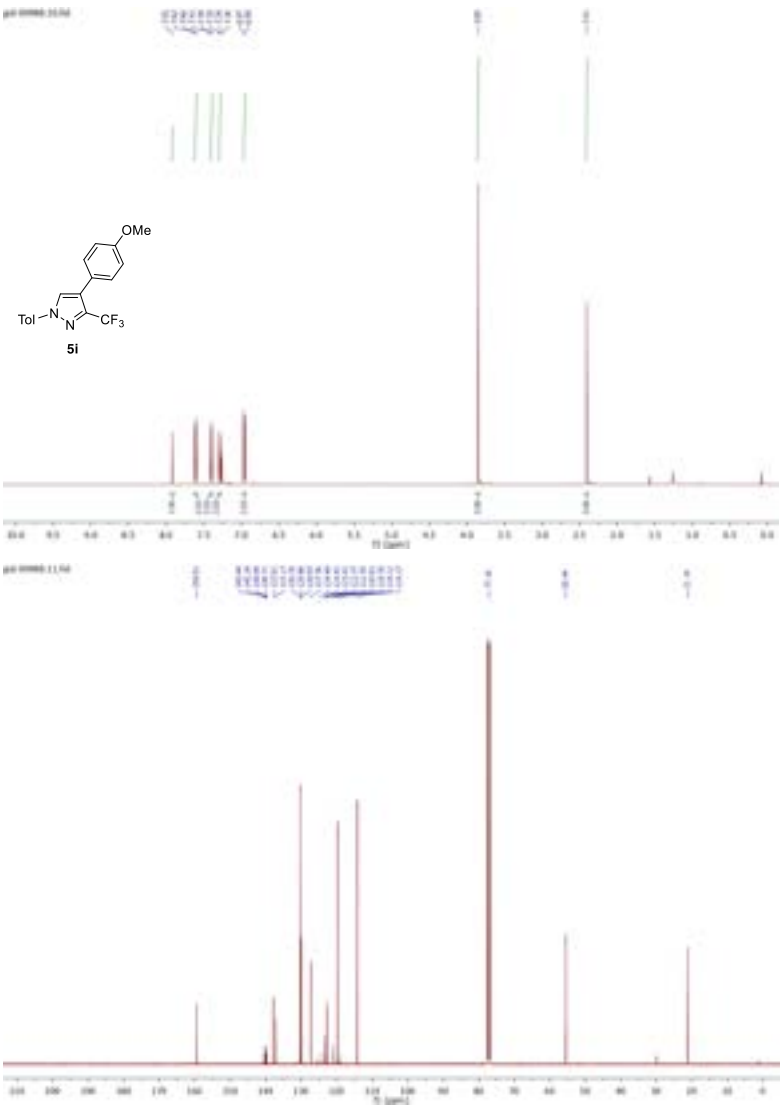


Fig S31. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5i**.

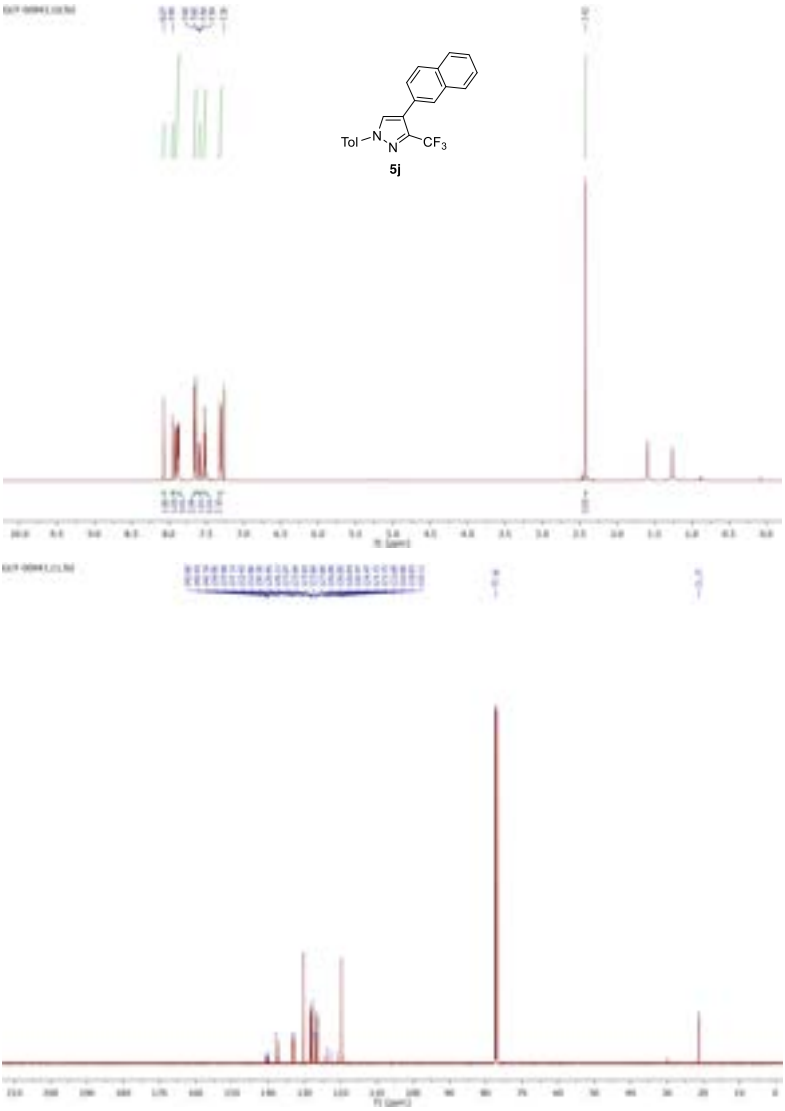


Fig S32. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5j**.

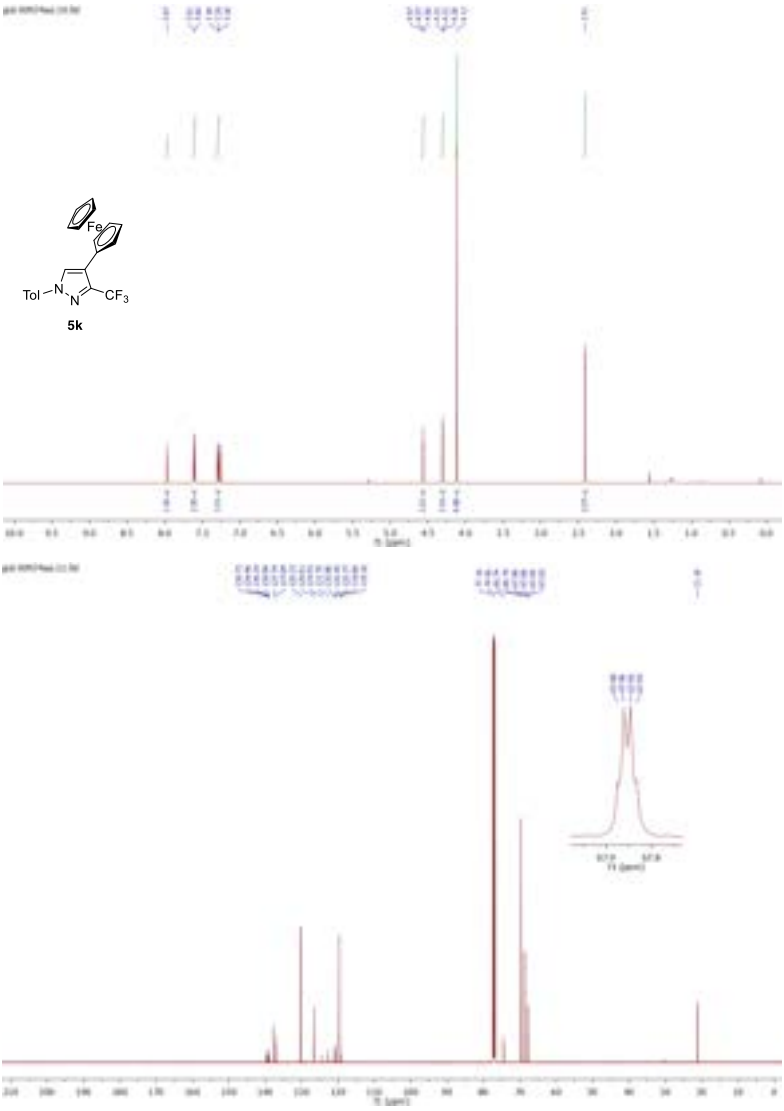


Fig S33. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5k**.

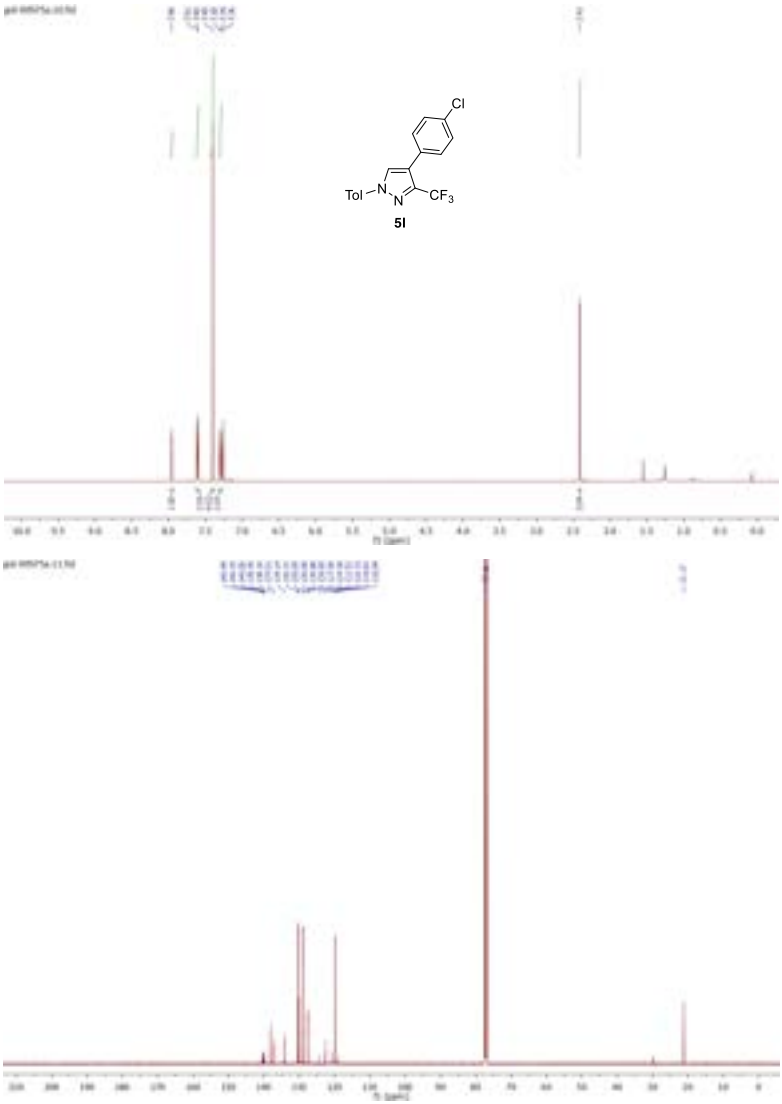


Fig S34. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5l**.

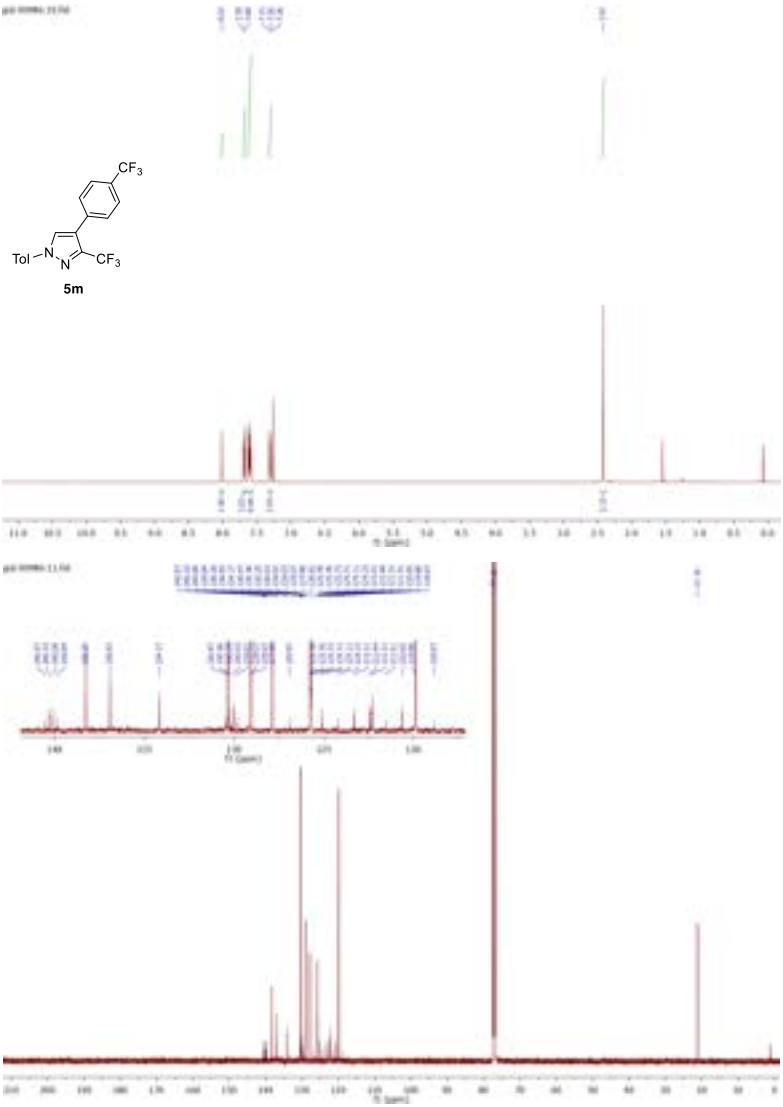


Fig S35. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5m**.

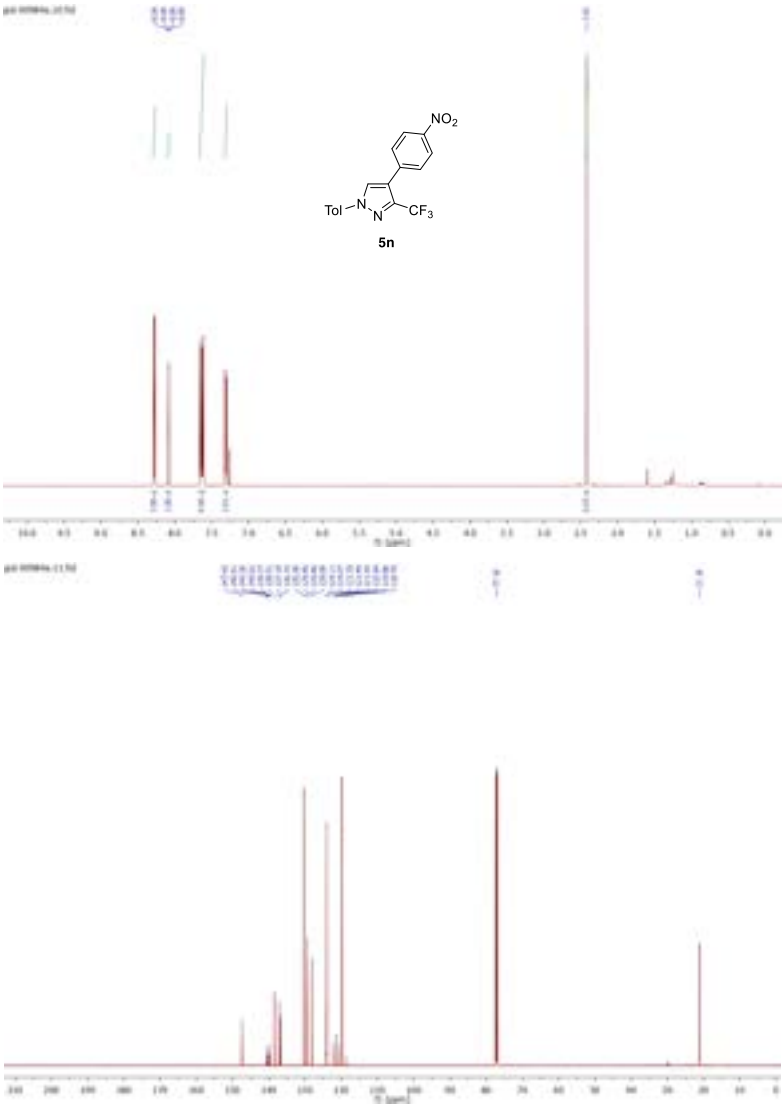


Fig S36. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5n**.

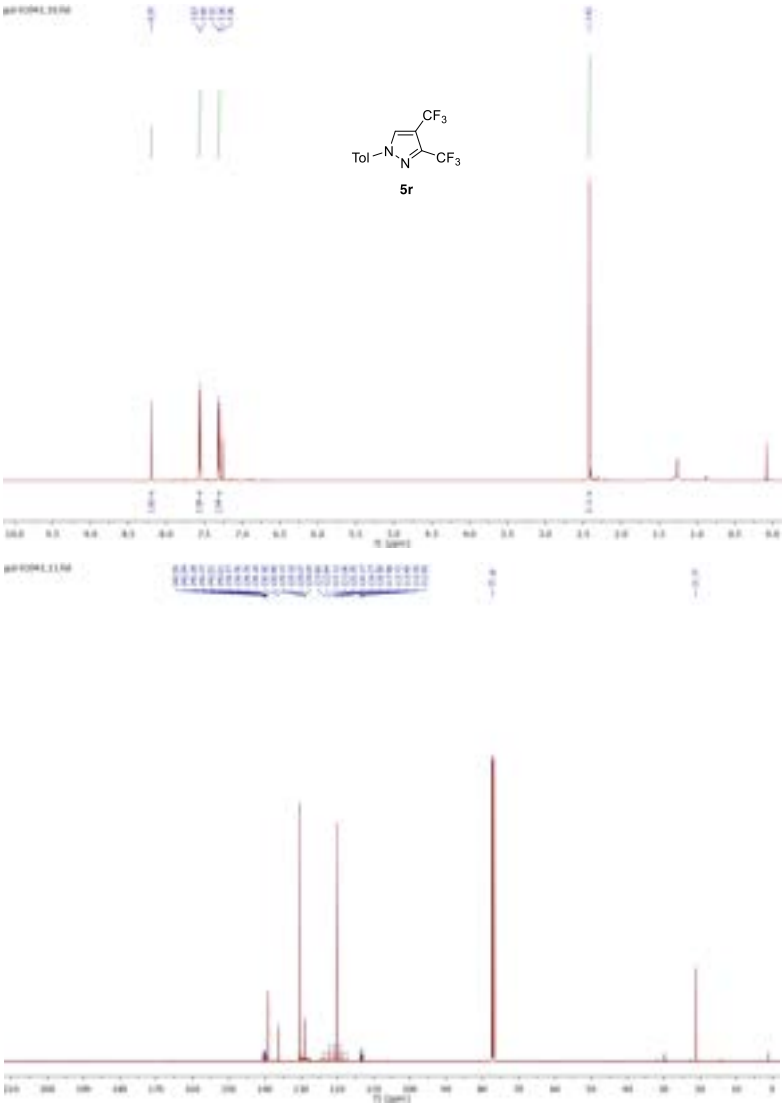


Fig S37. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **5r**.

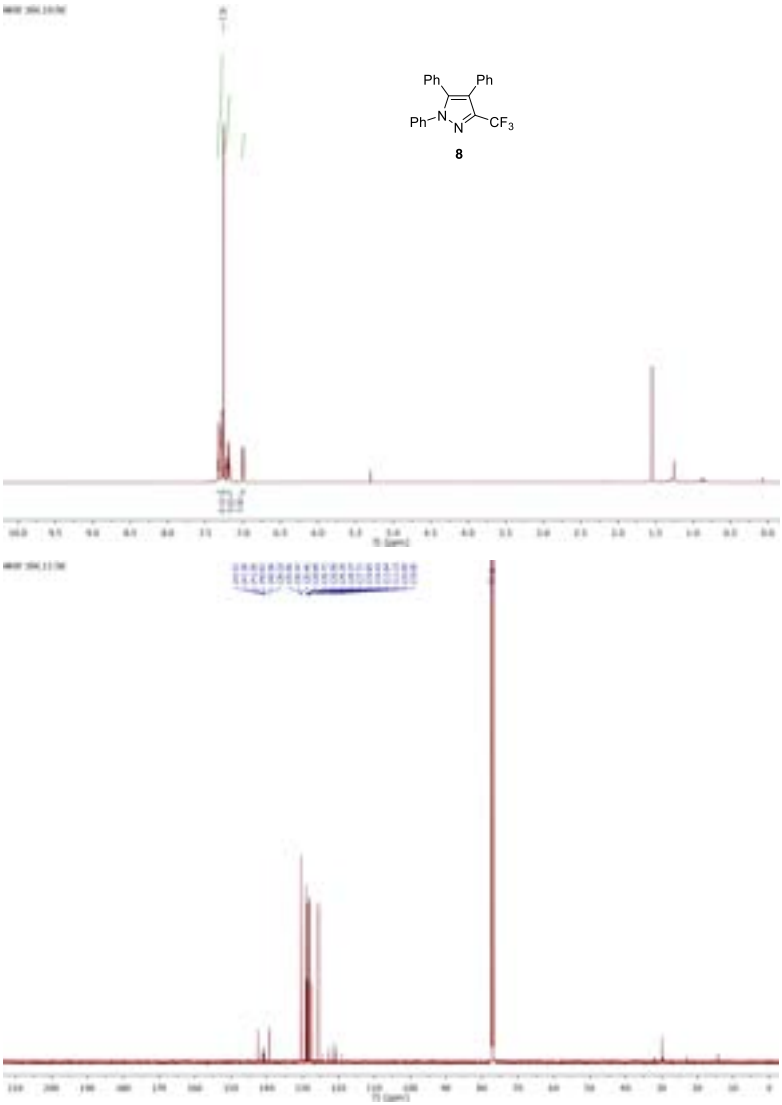


Fig S38. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **8**.

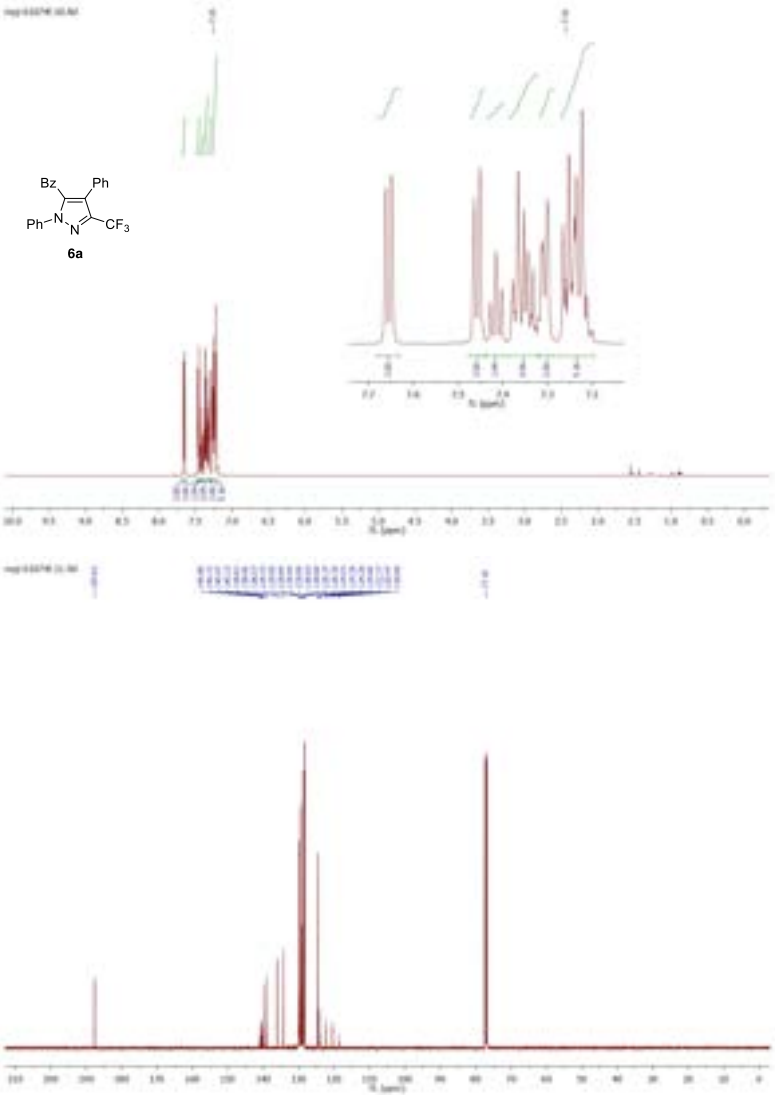


Fig S39. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6a**.

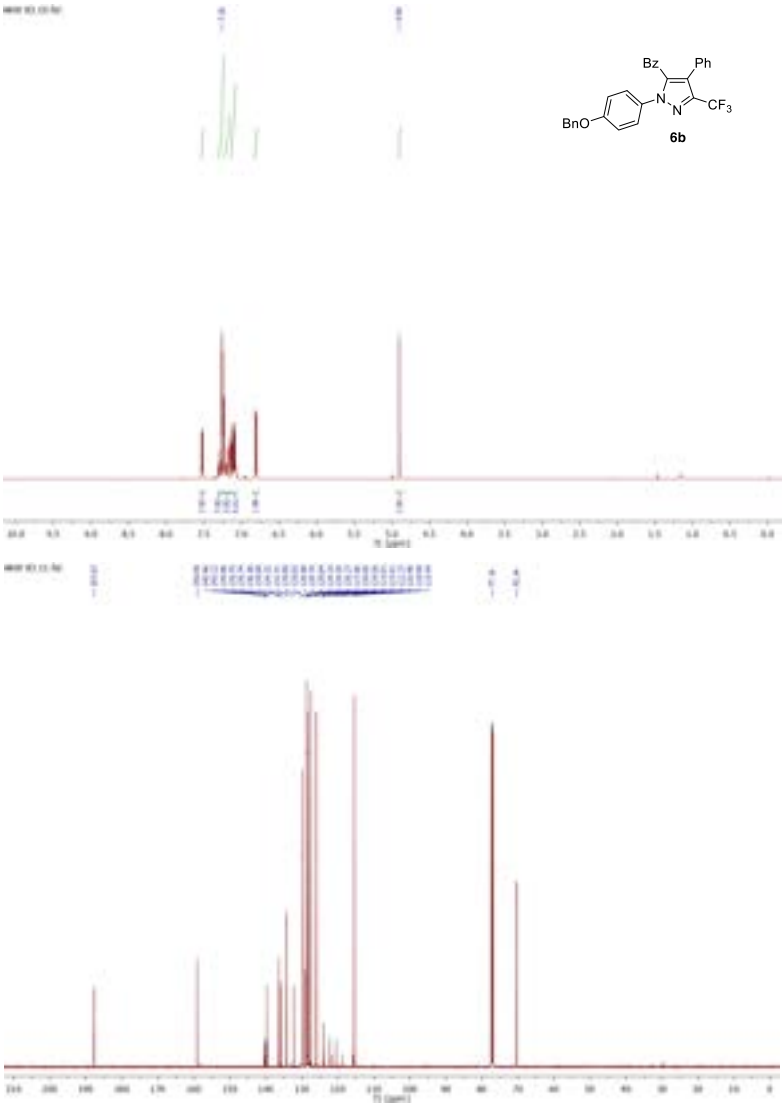


Fig S40. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6b**.

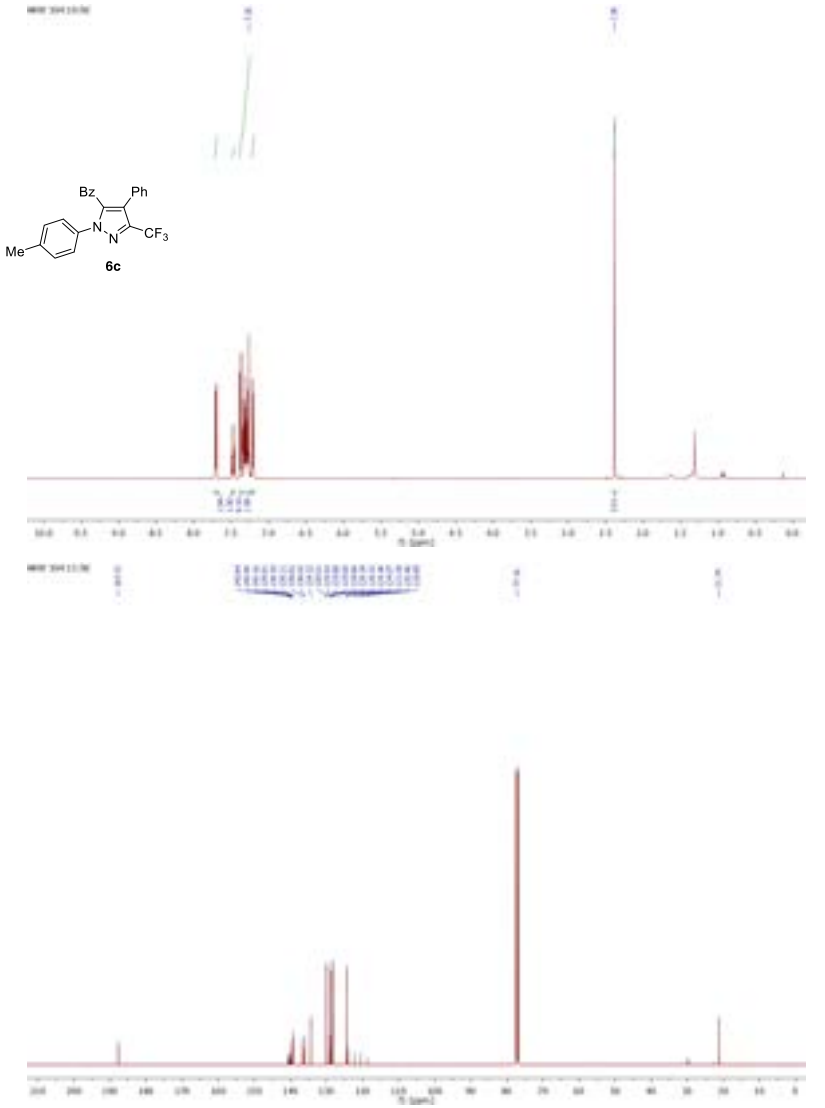


Fig S41. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6c**.

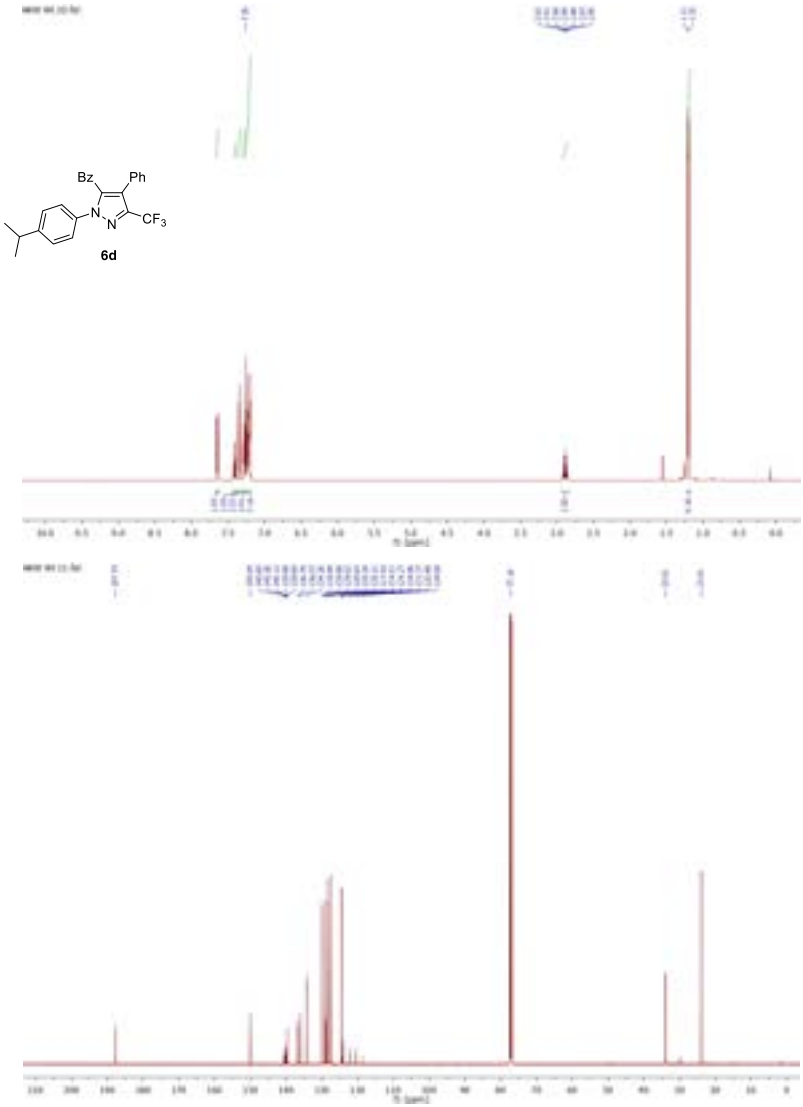


Fig S42. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6d**.

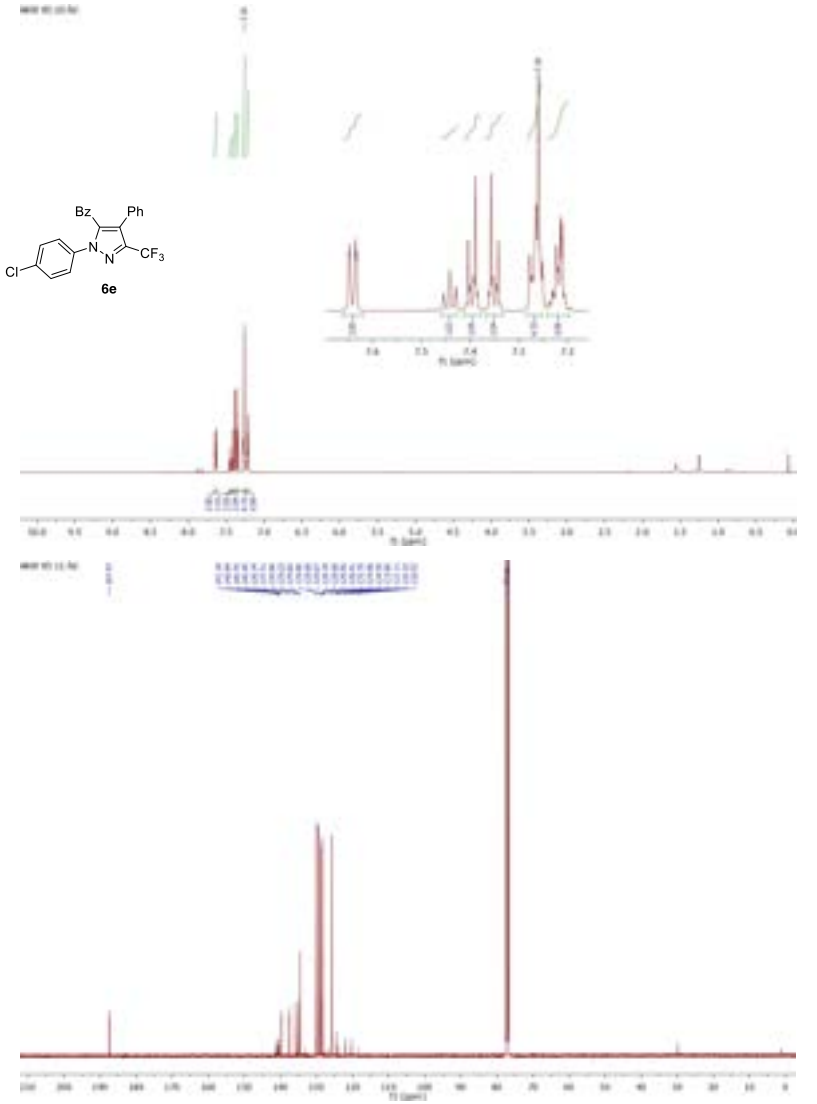


Fig S43. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6e**.

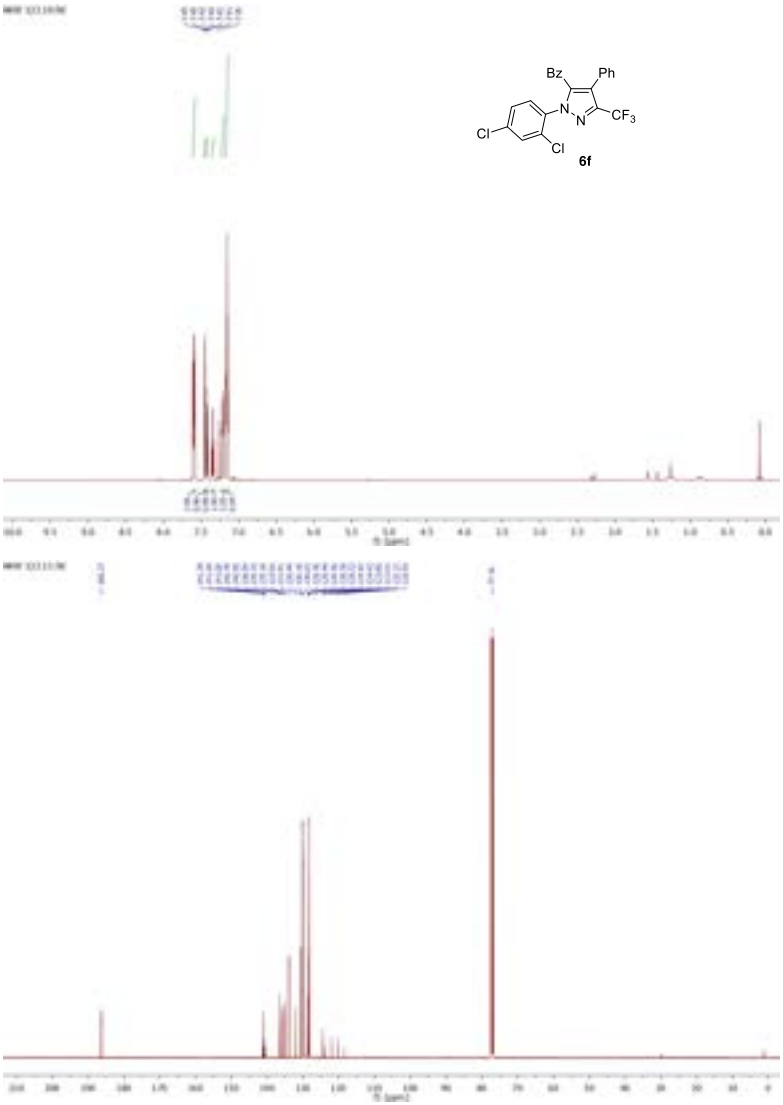


Fig S44. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6f**.

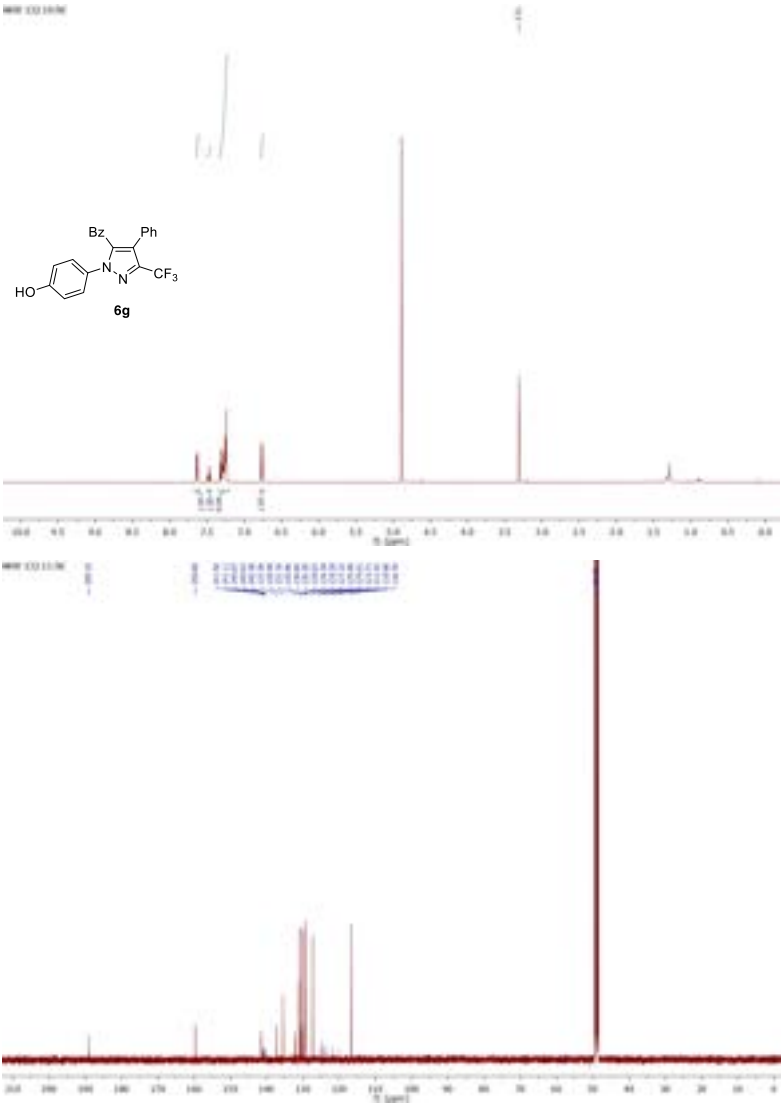


Fig S45. ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (151 MHz, CD_3OD) spectra for compound **6g**.

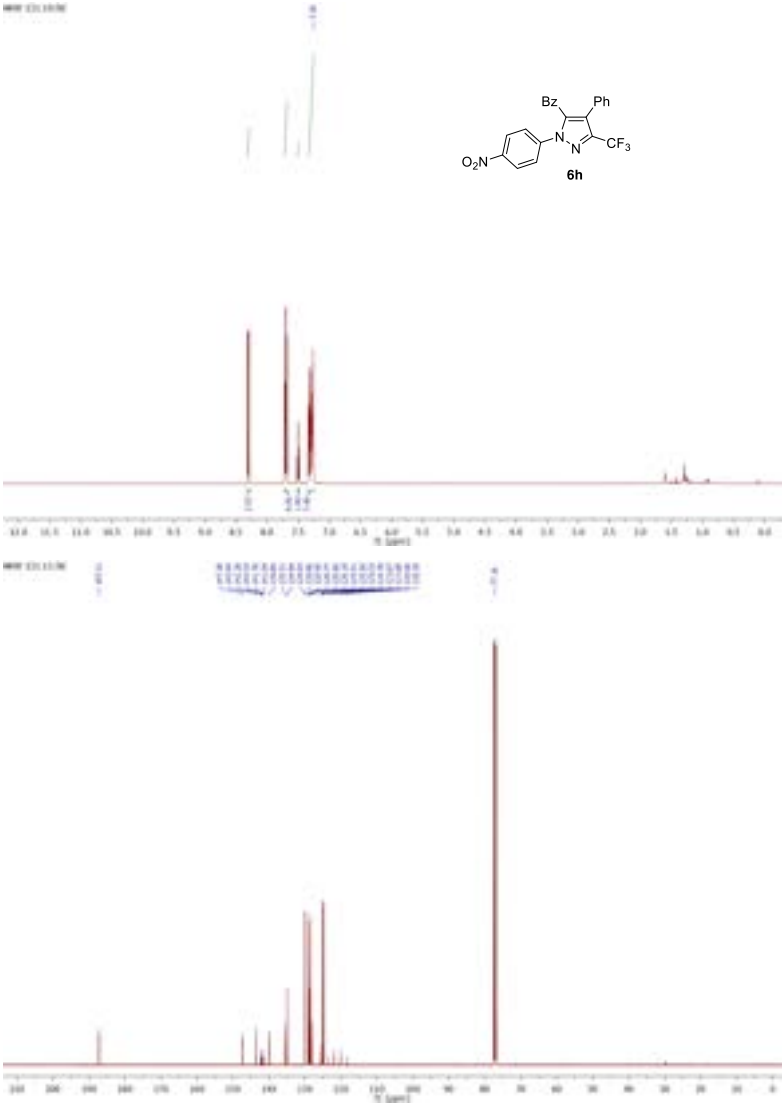


Fig S46. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6h**.

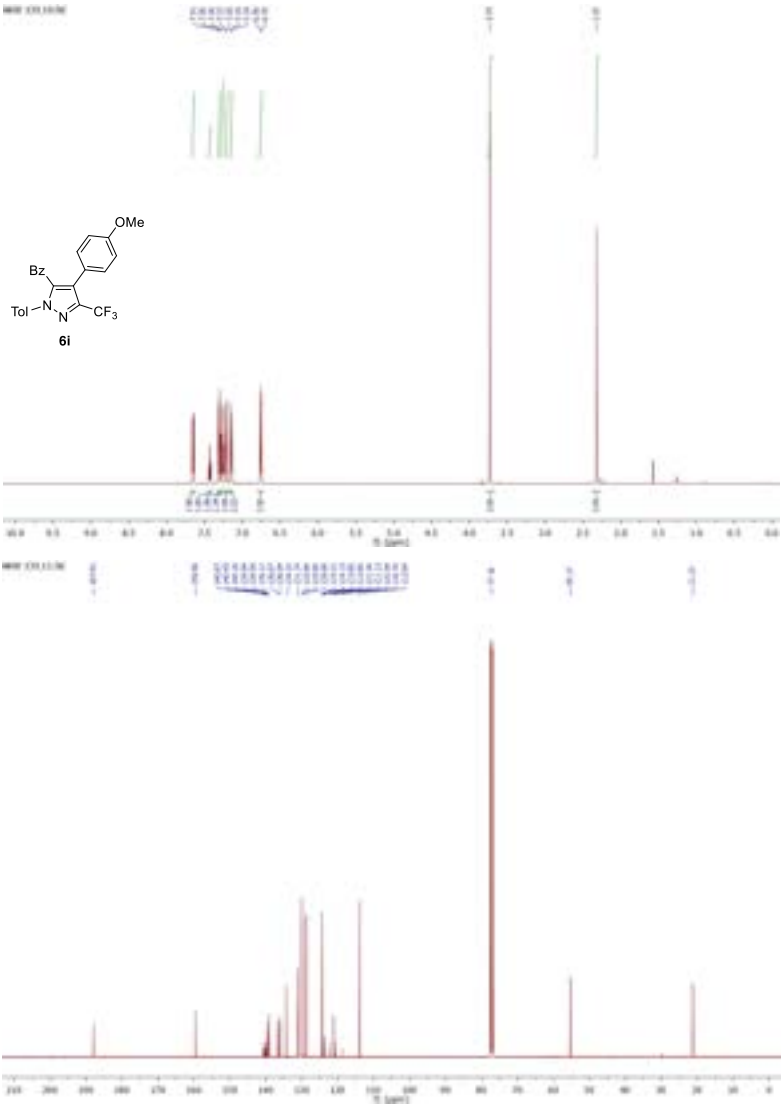


Fig S47. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6i**.

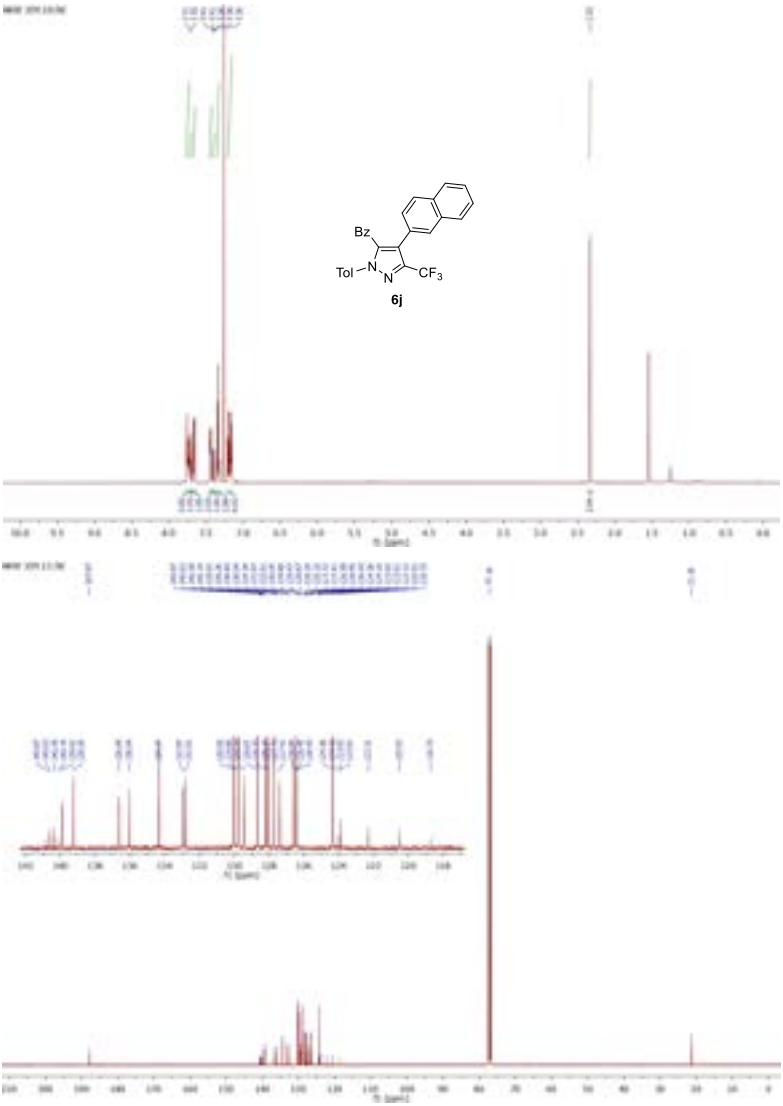


Fig S48. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6j**.

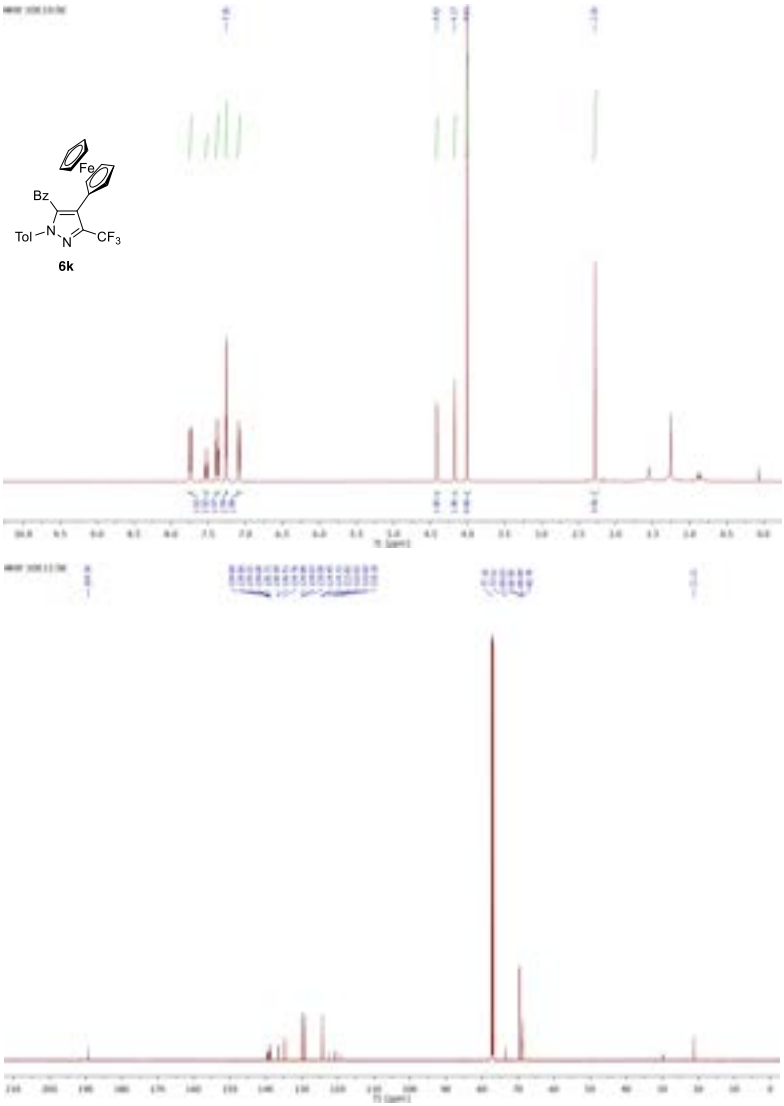


Fig S49. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6k**.

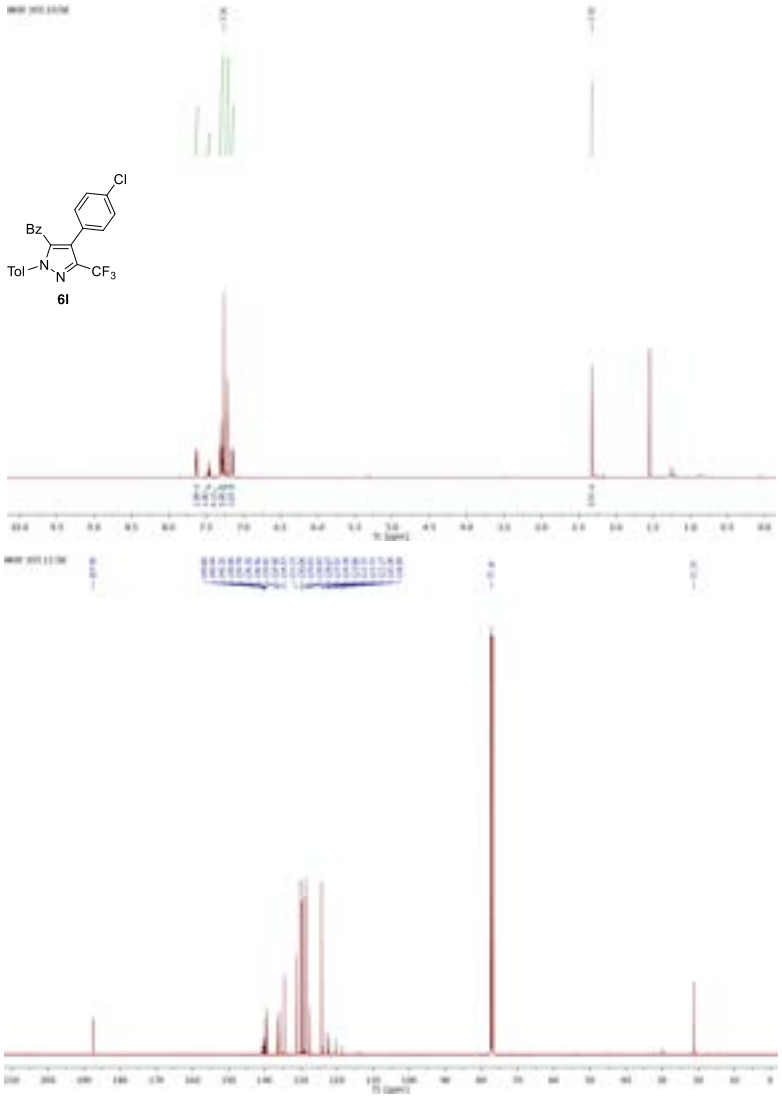


Fig S50. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6l**.

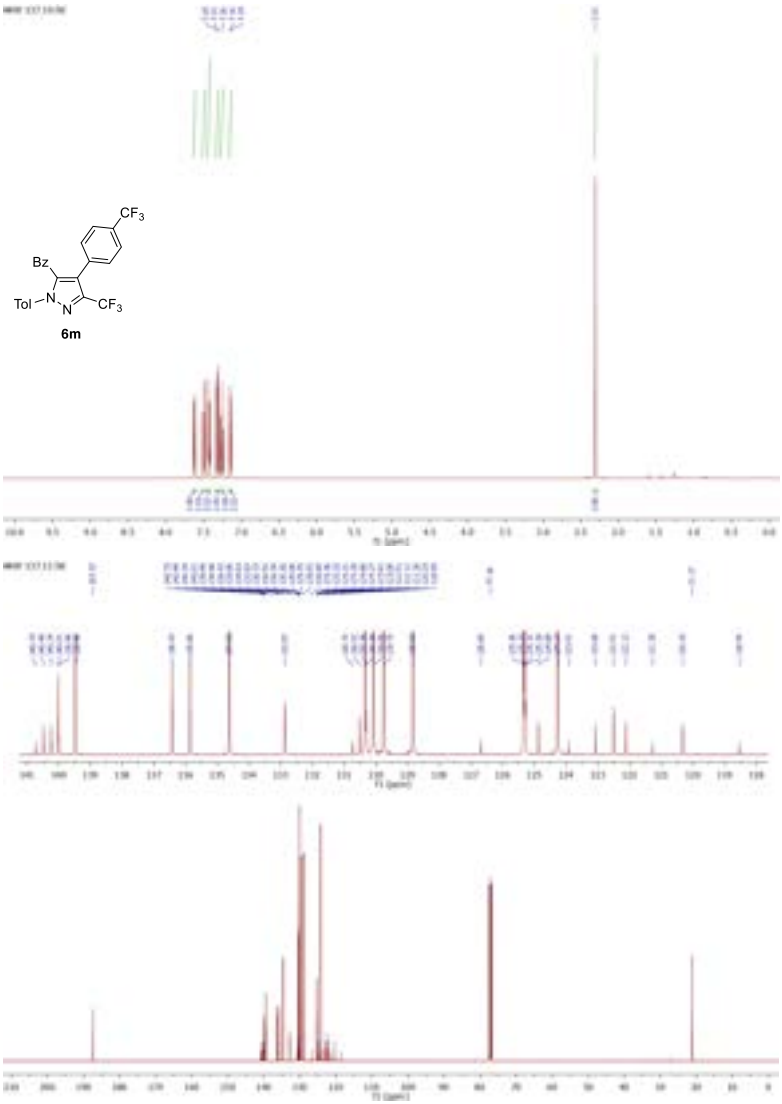


Fig S51. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6m**.

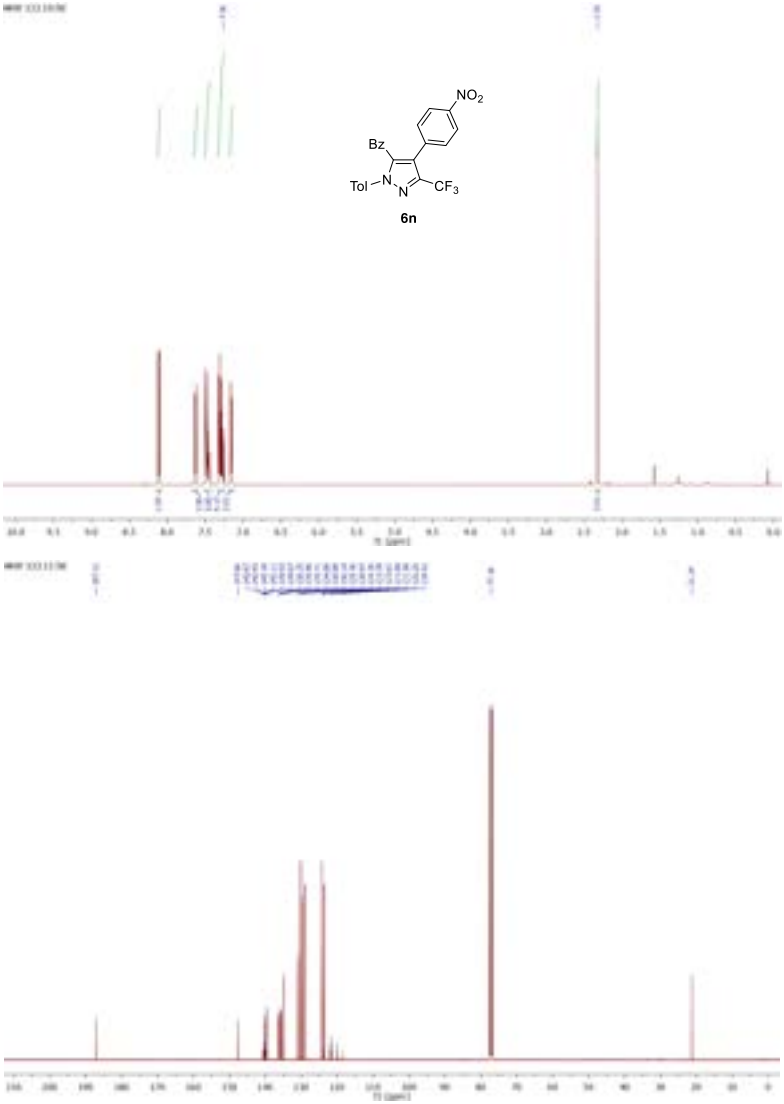


Fig S52. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6n**.

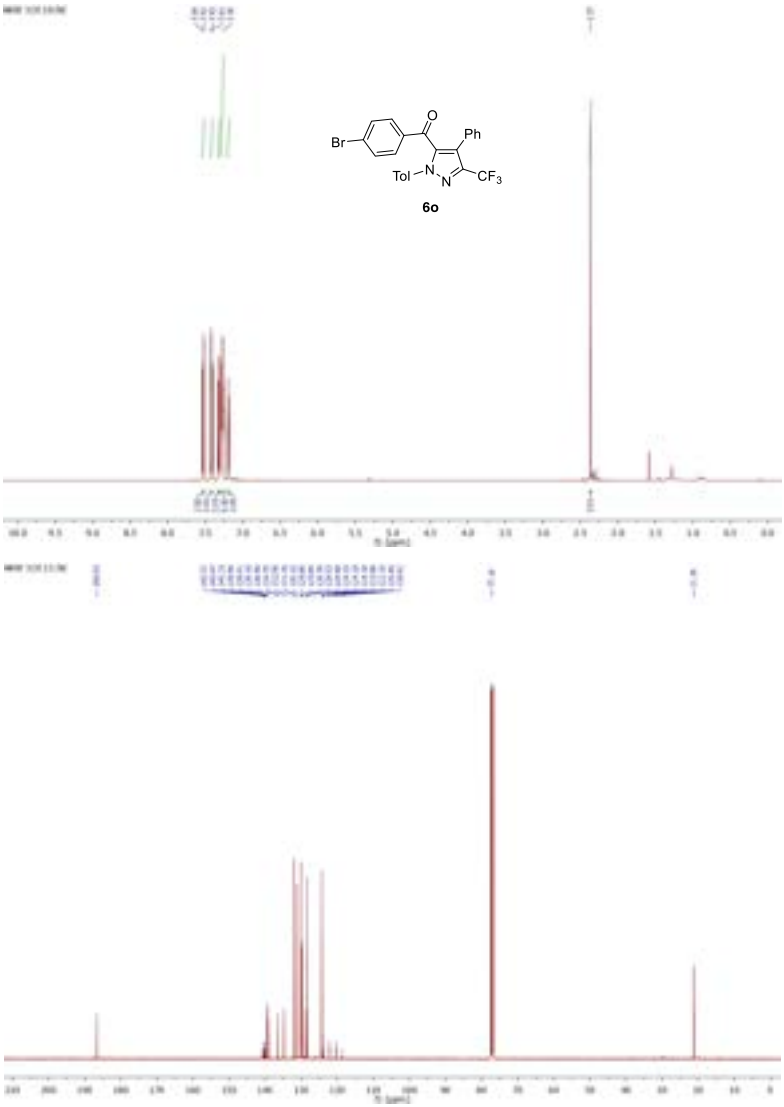
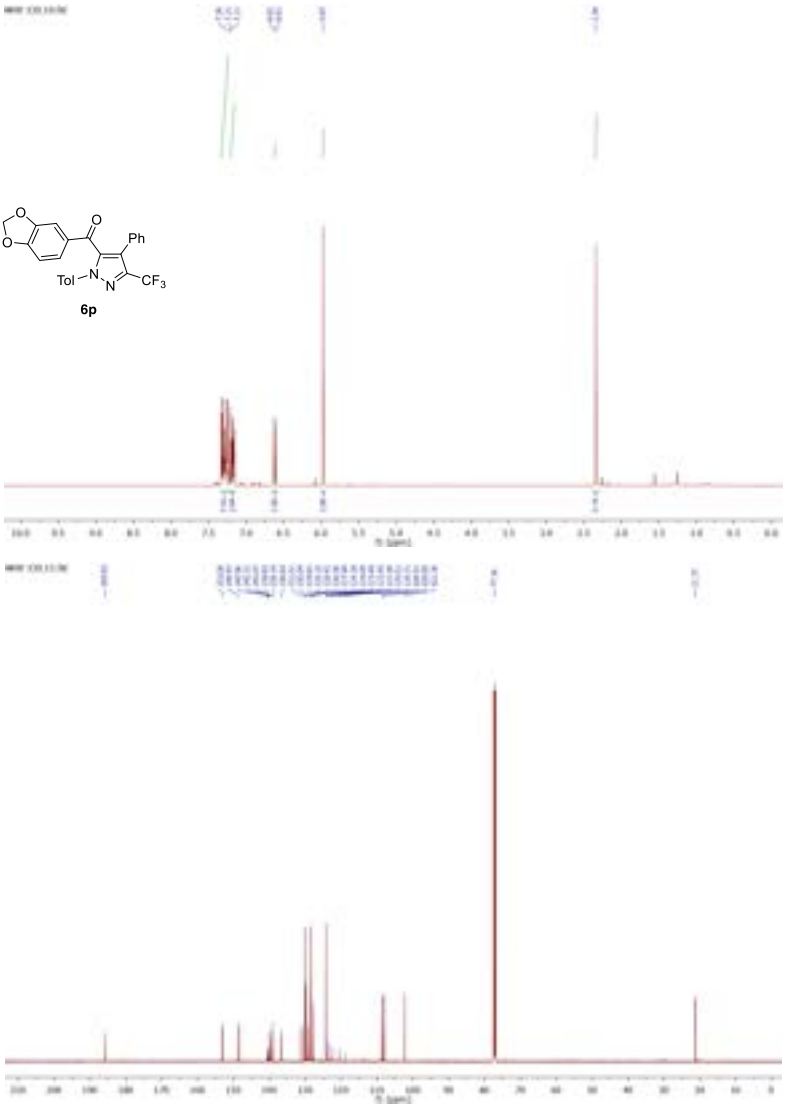
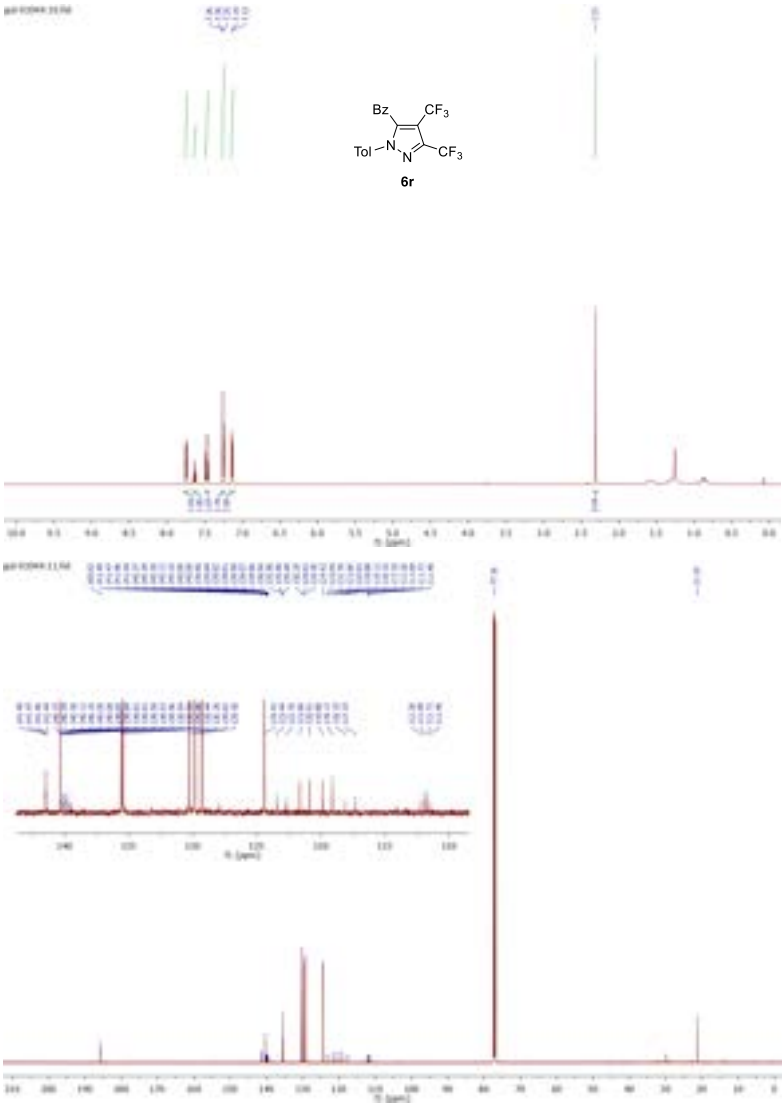


Fig S53. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6o**.



6p

Fig S54. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6p**.



6r

Fig S55. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6r**.

4. Crystallographic analyses

Crystallographic analysis of 2q: A suitable crystal of compound **2q** was selected and measured on a XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer. The crystal was kept at 100.01(10) K during data collection. Using Olex2,[13] the structure was solved with the XT[14] structure solution program using Intrinsic Phasing and refined with the XL[15] refinement package using Least Squares minimization. CCDC-2079231 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via
https://www.ccdc.cam.ac.uk/structures/

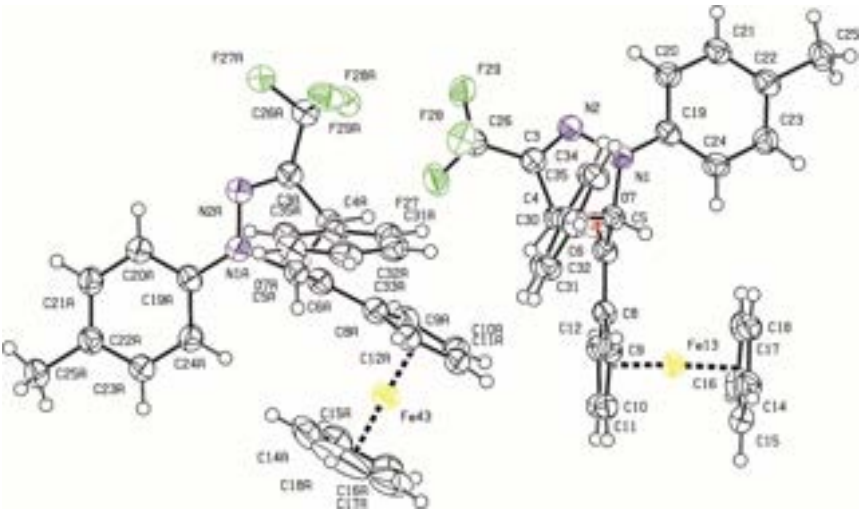


Fig S56. A view of the molecular structure of compound **2q**. Displacement ellipsoids are drawn at the 50% probability level. X-ray data collected at the ambient temperature 100 K.

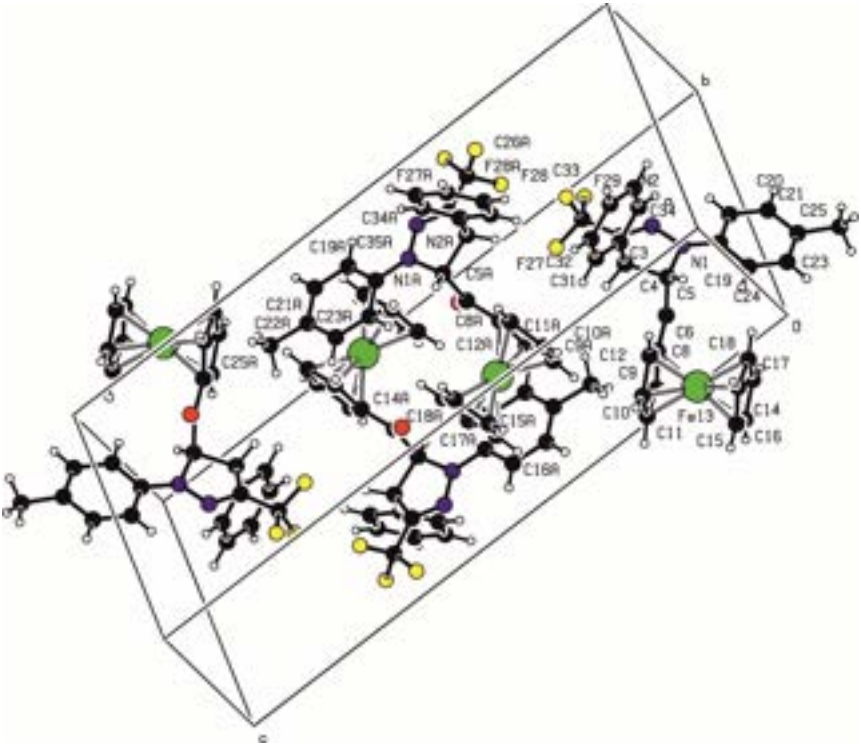


Fig S57. A view of the molecular packing in the structure of compound **2q**.

Table S1 Crystal data and structure refinement for **2q**.

Identification code	GUT_947
Empirical formula	$C_{56}H_{46}F_6Fe_2N_4O_2$
Formula weight	1032.67
Temperature/K	100.01(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.8135(3)
b/Å	10.7419(3)
c/Å	23.2185(4)
α/°	99.306(2)
β/°	90.018(2)
γ/°	104.952(3)

Volume/Å^3	2331.33(11)
Z	2
ρ_{calc}g/cm^3	1.471
μ/mm^{-1}	5.606
F(000)	1064.0
Crystal size/mm^3	0.73 × 0.53 × 0.27
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.724 to 157.652
Index ranges	-12 ≤ h ≤ 12, -10 ≤ k ≤ 13, -26 ≤ l ≤ 29
Reflections collected	27285
Independent reflections	9445 [R_{int} = 0.0567, R_{sigma} = 0.0513]
Data/restraints/parameters	9445/0/633
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0546, wR_2 = 0.1489
Final R indexes [all data]	R_1 = 0.0618, wR_2 = 0.1537
Largest diff. peak/hole / e Å^{-3}	1.02/-0.59

Table S2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2q**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Fe13	3211.7(4)	-1778.0(4)	1449.4(2)	32.39(12)
Fe43	6195.0(5)	2228.5(5)	4014.2(2)	40.31(14)
F28	7748.9(19)	5681.1(17)	1871.7(8)	50.2(4)
F27A	8659(2)	9700.4(17)	3320.6(8)	49.1(4)
F29A	7543(2)	7956.6(19)	2751.4(8)	52.3(4)
F29	5833(2)	6241.8(18)	1760.4(9)	57.9(5)
F27	6058(2)	5148.8(19)	2440.8(7)	52.8(4)
F28A	9798(2)	8593(2)	2740.1(8)	56.2(5)
O7	2657(2)	1654(2)	1472.0(9)	44.4(5)
O7A	6108(2)	5784(2)	4143.8(10)	47.6(5)
N2	4954(2)	3952(2)	1034.0(10)	35.6(5)
N1	4609(2)	2688(2)	748.2(9)	33.9(5)
N2A	8759(3)	8120(2)	4092.0(10)	38.5(5)
N1A	8825(3)	7154(2)	4397.5(10)	38.7(5)
C8	3784(3)	173(3)	1769.5(11)	32.7(5)
C4	6114(3)	2760(3)	1548.6(11)	33.5(5)
C5	4961(3)	1808(3)	1109.3(11)	33.1(5)
C20	3228(3)	3232(3)	-3.8(12)	35.4(5)
C6	3680(3)	1209(3)	1447.8(11)	33.9(5)
C9	4952(3)	-399(3)	1820.4(11)	35.6(5)
C12	2650(3)	-481(3)	2091.3(11)	35.9(5)

Table S2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2q**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C19	3650(3)	2302(3)	264.0(11)	33.6(5)
C11	3117(3)	-1417(3)	2348.5(12)	38.8(6)
C30	7619(3)	2818(3)	1381.2(11)	32.4(5)
C22	1911(3)	1511(3)	-766.6(12)	37.9(6)
C3	5742(3)	4022(3)	1483.8(11)	35.2(5)
C34	9507(3)	3292(3)	717.8(12)	37.9(6)
C18	3285(3)	-2221(3)	560.7(12)	41.2(6)
C35	8127(3)	3254(3)	867.9(11)	35.2(5)
C24A	8655(3)	6308(3)	5306.9(12)	39.2(6)
C31	8513(3)	2433(3)	1744.8(11)	35.2(5)
C5A	8557(3)	5892(3)	4014.0(11)	36.1(5)
C22A	8619(3)	7715(3)	6231.8(12)	39.6(6)
C21	2373(3)	2824(3)	-512.3(12)	38.4(6)
C4A	9039(3)	6318(3)	3416.3(11)	37.1(6)
C6A	6957(3)	5198(3)	3958.0(12)	39.4(6)
C19A	8694(3)	7342(3)	5006.1(12)	37.5(6)
C26	6337(3)	5274(3)	1882.2(12)	39.8(6)
C32	9895(3)	2481(3)	1594.2(12)	37.5(6)
C3A	8838(3)	7683(3)	3548.0(12)	38.0(6)
C24	3157(3)	991(3)	28.2(12)	38.4(6)
C8A	6572(3)	3853(3)	3632.3(12)	39.0(6)
C23A	8610(3)	6503(3)	5912.5(12)	40.3(6)
C23	2300(3)	600(3)	-482.7(12)	39.7(6)
C20A	8675(3)	8553(3)	5317.4(12)	41.0(6)
C25	1055(3)	1082(3)	-1340.2(13)	45.7(7)
C10	4524(3)	-1353(3)	2187.6(12)	38.8(6)
C30A	10549(3)	6275(3)	3297.5(12)	37.3(6)
C33	10389(3)	2904(3)	1081.8(12)	37.9(6)
C21A	8638(3)	8720(3)	5923.6(12)	41.5(6)
C26A	8715(3)	8492(3)	3094.9(12)	40.8(6)
C15	2639(3)	-3760(3)	1156.2(13)	42.4(6)
C11A	6596(4)	1816(3)	3151.7(12)	44.6(7)
C16	1476(3)	-3220(3)	1095.7(13)	45.4(7)
C35A	11663(3)	7013(3)	3684.6(12)	40.1(6)
C17	1876(3)	-2277(3)	724.5(13)	43.6(6)
C10A	5168(4)	1840(3)	3209.6(13)	46.9(7)
C12A	7480(3)	3046(3)	3411.7(12)	41.1(6)
C31A	10826(3)	5446(3)	2816.0(13)	41.6(6)
C14	3746(3)	-3141(3)	831.6(12)	40.6(6)

Table S2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2q**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij} tensor.

Atom	*x*	*y*	*z*	U(eq)
C34A	13027(3)	6887(3)	3600.9(13)	45.1(7)
C25A	8629(4)	7931(3)	6894.8(12)	45.2(7)
C32A	12206(4)	5328(3)	2731.0(14)	46.2(7)
C9A	5142(3)	3091(3)	3510.2(12)	42.6(6)
C33A	13288(3)	6033(3)	3122.7(14)	47.7(7)
C16A	5097(4)	823(4)	4459.7(15)	57.6(9)
C15A	5125(4)	2041(4)	4768.3(14)	54.9(8)
C14A	6501(5)	2738(5)	4896.0(16)	74.8(13)
C17A	6457(6)	711(5)	4393.0(19)	77.8(14)
C18A	7380(5)	1930(8)	4667(2)	112(3)

Table S3 Anisotropic Displacement Parameters (Å^2×10^3) for **2q**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Fe13	34.8(2)	34.6(2)	28.7(2)	3.65(16)	2.57(15)	11.71(16)
Fe43	43.8(3)	44.1(3)	32.8(2)	10.60(18)	3.57(18)	8.64(19)
F28	44.4(9)	45.0(10)	57.0(10)	-1.0(8)	2.7(8)	10.3(7)
F27A	63.3(11)	42.0(10)	44.3(9)	8.4(7)	-2.1(8)	17.2(8)
F29A	54.7(10)	53.9(11)	48.0(9)	10.1(8)	-13.1(8)	12.8(8)
F29	77.7(13)	45.9(10)	55.2(10)	-7.1(8)	-22.4(9)	34.7(9)
F27	62.6(11)	57.5(11)	34.1(8)	0.3(8)	3.5(8)	12.4(9)
F28A	57.9(11)	71.0(13)	53.0(10)	29.8(9)	19.7(9)	28.5(9)
O7	39.9(10)	54.0(12)	49.6(11)	19.9(10)	10.9(9)	23.7(9)
O7A	42.4(11)	49.0(12)	51.8(12)	2.8(10)	6.4(9)	16.0(9)
N2	38.1(11)	37.6(12)	33.6(10)	5.6(9)	2.6(9)	14.4(9)
N1	36.7(11)	36.0(12)	31.3(10)	7.4(9)	-0.1(9)	12.3(9)
N2A	41.8(12)	37.4(12)	37.5(12)	8.8(10)	1.7(9)	10.9(9)
N1A	46.2(13)	35.9(12)	34.4(11)	7.3(9)	2.8(9)	10.6(10)
C8	32.6(12)	36.5(14)	29.4(11)	3.9(10)	-0.1(9)	10.9(10)
C4	35.1(13)	39.1(14)	29.1(11)	5.4(10)	2.5(10)	15.0(10)
C5	33.9(12)	37.4(14)	30.7(11)	6.9(10)	2.1(10)	13.2(10)
C20	36.2(13)	36.9(14)	35.0(12)	7.5(11)	2.5(10)	12.0(10)
C6	32.7(12)	39.7(14)	31.1(12)	6.1(10)	1.5(10)	12.3(10)
C9	35.4(13)	40.1(14)	32.3(12)	0.9(11)	-1.1(10)	14.6(11)
C12	40.1(13)	39.3(14)	29.0(11)	4.4(10)	4.8(10)	12.4(11)
C19	32.3(12)	42.2(14)	28.6(11)	8.1(10)	4.4(9)	12.4(10)
C11	49.0(15)	37.1(14)	32.3(12)	8.6(11)	4.9(11)	13.1(12)
C30	33.7(12)	33.9(13)	30.0(11)	2.7(10)	1.1(9)	11.1(10)

Table S3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **2q**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C22	35.5(13)	47.2(16)	33.5(12)	7.2(11)	0.5(10)	15.1(11)
C3	35.4(13)	39.7(14)	33.6(12)	5.4(11)	2.7(10)	15.8(11)
C34	37.0(13)	43.8(15)	33.6(12)	8.6(11)	6.3(10)	10.4(11)
C18	51.1(16)	43.3(16)	31.8(12)	5.0(11)	2.2(11)	17.9(12)
C35	37.4(13)	36.2(14)	33.4(12)	5.5(10)	1.6(10)	12.5(10)
C24A	45.0(15)	35.3(14)	36.7(13)	3.1(11)	4.8(11)	11.0(11)
C31	38.2(13)	38.8(14)	30.7(12)	6.1(10)	3.0(10)	13.8(11)
C5A	39.2(13)	38.6(14)	30.7(12)	6.0(10)	3.6(10)	10.1(11)
C22A	43.1(14)	40.5(15)	33.7(13)	4.1(11)	4.1(11)	9.7(11)
C21	40.5(14)	44.5(16)	35.0(13)	10.1(11)	2.9(11)	17.7(11)
C4A	38.7(13)	40.6(15)	31.6(12)	6.6(11)	0.5(10)	9.5(11)
C6A	41.5(14)	43.2(16)	34.1(13)	9.1(11)	5.3(11)	10.5(12)
C19A	37.6(13)	42.8(15)	32.4(12)	5.4(11)	4.3(10)	11.4(11)
C26	40.2(14)	45.8(16)	37.2(13)	4.6(12)	-1.6(11)	19.4(12)
C32	36.9(13)	41.8(15)	37.7(13)	7.9(11)	0.4(11)	16.6(11)
C3A	39.4(14)	39.5(15)	35.3(13)	7.0(11)	2.3(11)	10.3(11)
C24	42.1(14)	40.1(15)	37.3(13)	9.9(11)	1.2(11)	16.3(11)
C8A	40.3(14)	43.1(15)	34.0(12)	8.6(11)	3.6(11)	10.2(11)
C23A	45.5(15)	39.8(15)	35.6(13)	7.6(11)	3.6(11)	10.2(12)
C23	41.2(14)	38.6(15)	39.1(14)	2.8(11)	-3.6(11)	12.4(11)
C20A	47.2(15)	38.2(15)	37.8(13)	7.5(11)	2.7(11)	10.9(12)
C25	49.7(16)	51.0(18)	39.0(14)	2.2(13)	-5.8(12)	20.8(14)
C10	47.5(15)	35.5(14)	34.1(13)	1.6(11)	-5.7(11)	14.6(11)
C30A	42.7(14)	39.8(15)	33.1(12)	11.8(11)	5.3(11)	13.6(11)
C33	33.1(13)	41.5(15)	39.7(13)	3.9(12)	5.9(11)	12.3(11)
C21A	46.8(15)	39.2(15)	36.9(14)	1.2(11)	3.5(11)	11.5(12)
C26A	45.1(15)	41.8(15)	36.4(13)	8.4(12)	-1.0(11)	12.0(12)
C15	52.5(16)	35.0(14)	38.4(14)	1.3(11)	0.6(12)	12.1(12)
C11A	58.5(18)	40.7(16)	32.6(13)	7.6(12)	5.0(12)	8.7(13)
C16	40.8(15)	48.2(17)	39.8(14)	-7.2(12)	4.1(12)	7.7(12)
C35A	40.1(14)	47.2(16)	33.9(12)	8.5(11)	5.2(11)	12.1(12)
C17	45.4(15)	48.5(17)	37.3(14)	-4.7(12)	-6.5(12)	20.4(13)
C10A	52.3(17)	42.9(16)	40.4(14)	8.9(12)	-3.4(13)	2.2(13)
C12A	48.3(16)	41.9(16)	32.9(13)	7.5(11)	6.4(11)	10.5(12)
C31A	49.3(16)	41.4(15)	36.9(13)	10.6(12)	6.3(12)	14.0(12)
C14	45.3(15)	46.2(16)	33.1(13)	2.7(11)	2.2(11)	19.8(12)
C34A	40.5(15)	57.2(19)	40.5(14)	17.4(13)	2.2(12)	12.2(13)
C25A	55.7(17)	44.9(16)	32.5(13)	2.2(12)	4.1(12)	11.6(13)
C32A	57.4(18)	45.6(17)	43.0(15)	14.9(13)	17.0(13)	21.8(14)

Table S3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **2q**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C9A	41.8(15)	46.9(16)	36.3(13)	8.4(12)	-2.8(11)	5.3(12)
C33A	45.3(16)	58.8(19)	48.8(16)	24.4(15)	13.3(13)	21.6(14)
C16A	73(2)	52(2)	46.5(17)	18.5(15)	10.9(16)	6.6(16)
C15A	65(2)	62(2)	38.2(15)	16.5(15)	14.6(14)	14.0(16)
C14A	89(3)	79(3)	39.0(17)	21.1(18)	-7.5(18)	-16(2)
C17A	98(3)	100(3)	64(2)	46(2)	35(2)	57(3)
C18A	43(2)	230(8)	87(3)	110(4)	7(2)	27(3)

Table S4 Bond Lengths for **2q**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Fe13	C8	2.036(3)	C19	C24	1.384(4)
Fe13	C9	2.033(3)	C11	C10	1.418(4)
Fe13	C12	2.047(3)	C30	C35	1.396(4)
Fe13	C11	2.067(3)	C30	C31	1.398(4)
Fe13	C18	2.047(3)	C22	C21	1.395(4)
Fe13	C10	2.061(3)	C22	C23	1.392(4)
Fe13	C15	2.056(3)	C22	C25	1.514(4)
Fe13	C16	2.050(3)	C3	C26	1.483(4)
Fe13	C17	2.045(3)	C34	C35	1.391(4)
Fe13	C14	2.047(3)	C34	C33	1.391(4)
Fe43	C8A	2.033(3)	C18	C17	1.423(4)
Fe43	C11A	2.041(3)	C18	C14	1.417(4)
Fe43	C10A	2.052(3)	C24A	C19A	1.397(4)
Fe43	C12A	2.036(3)	C24A	C23A	1.390(4)
Fe43	C9A	2.035(3)	C31	C32	1.391(4)
Fe43	C16A	2.043(3)	C5A	C4A	1.566(4)
Fe43	C15A	2.053(3)	C5A	C6A	1.550(4)
Fe43	C14A	2.033(4)	C22A	C23A	1.388(4)
Fe43	C17A	2.043(4)	C22A	C21A	1.385(4)
Fe43	C18A	2.026(4)	C22A	C25A	1.519(4)
F28	C26	1.342(3)	C4A	C3A	1.511(4)
F27A	C26A	1.334(3)	C4A	C30A	1.519(4)
F29A	C26A	1.341(4)	C6A	C8A	1.472(4)
F29	C26	1.329(3)	C19A	C20A	1.387(4)
F27	C26	1.346(3)	C32	C33	1.385(4)
F28A	C26A	1.338(3)	C3A	C26A	1.492(4)
O7	C6	1.216(3)	C24	C23	1.395(4)
O7A	C6A	1.208(4)	C8A	C12A	1.436(4)

Table S4 Bond Lengths for **2q**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N2	N1	1.367(3)	C8A	C9A	1.432(4)
N2	C3	1.280(3)	C20A	C21A	1.392(4)
N1	C5	1.464(3)	C30A	C35A	1.397(4)
N1	C19	1.403(3)	C30A	C31A	1.385(4)
N2A	N1A	1.363(3)	C15	C16	1.424(4)
N2A	C3A	1.284(4)	C15	C14	1.407(4)
N1A	C5A	1.458(4)	C11A	C10A	1.415(5)
N1A	C19A	1.405(3)	C11A	C12A	1.419(4)
C8	C6	1.461(4)	C16	C17	1.414(5)
C8	C9	1.446(3)	C35A	C34A	1.391(4)
C8	C12	1.434(4)	C10A	C9A	1.417(5)
C4	C5	1.559(4)	C31A	C32A	1.404(4)
C4	C30	1.516(3)	C34A	C33A	1.390(5)
C4	C3	1.521(4)	C32A	C33A	1.375(5)
C5	C6	1.536(4)	C16A	C15A	1.380(5)
C20	C19	1.403(4)	C16A	C17A	1.376(6)
C20	C21	1.390(4)	C15A	C14A	1.371(6)
C9	C10	1.419(4)	C14A	C18A	1.421(8)
C12	C11	1.417(4)	C17A	C18A	1.434(9)

Table S5 Bond Angles for **2q**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C8	Fe13	C12	41.11(10)	C11	C12	Fe13	70.61(16)
C8	Fe13	C11	68.37(11)	C11	C12	C8	108.0(2)
C8	Fe13	C18	114.11(11)	N1	C19	C20	120.9(2)
C8	Fe13	C10	68.27(11)	C24	C19	N1	119.9(2)
C8	Fe13	C15	177.95(11)	C24	C19	C20	119.1(2)
C8	Fe13	C16	140.09(12)	C12	C11	Fe13	69.09(15)
C8	Fe13	C17	113.92(12)	C12	C11	C10	108.1(2)
C8	Fe13	C14	141.17(11)	C10	C11	Fe13	69.65(15)
C9	Fe13	C8	41.63(10)	C35	C30	C4	120.8(2)
C9	Fe13	C12	69.59(11)	C35	C30	C31	119.5(2)
C9	Fe13	C11	68.75(11)	C31	C30	C4	119.7(2)
C9	Fe13	C18	112.85(12)	C21	C22	C25	121.7(3)
C9	Fe13	C10	40.56(11)	C23	C22	C21	117.6(3)
C9	Fe13	C15	137.60(12)	C23	C22	C25	120.7(3)
C9	Fe13	C16	177.66(12)	N2	C3	C4	115.2(2)
C9	Fe13	C17	141.77(12)	N2	C3	C26	121.8(2)
C9	Fe13	C14	111.36(11)	C26	C3	C4	122.8(2)
C12	Fe13	C11	40.29(11)	C33	C34	C35	120.0(2)

Table S5 Bond Angles for **2q**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C12	Fe13	C10	67.93(11)	C17	C18	Fe13	69.59(16)
C12	Fe13	C15	137.56(12)	C14	C18	Fe13	69.77(16)
C12	Fe13	C16	110.82(11)	C14	C18	C17	107.4(3)
C12	Fe13	C14	177.33(11)	C34	C35	C30	120.1(2)
C18	Fe13	C12	141.77(11)	C23A	C24A	C19A	120.0(3)
C18	Fe13	C11	177.51(12)	C32	C31	C30	120.1(2)
C18	Fe13	C10	139.90(12)	N1A	C5A	C4A	101.4(2)
C18	Fe13	C15	67.89(12)	N1A	C5A	C6A	110.8(2)
C18	Fe13	C16	68.36(12)	C6A	C5A	C4A	108.9(2)
C18	Fe13	C14	40.50(11)	C23A	C22A	C25A	121.0(3)
C10	Fe13	C11	40.19(12)	C21A	C22A	C23A	117.5(3)
C15	Fe13	C11	109.63(12)	C21A	C22A	C25A	121.4(3)
C15	Fe13	C10	109.97(12)	C20	C21	C22	122.0(3)
C16	Fe13	C11	109.97(12)	C3A	C4A	C5A	97.4(2)
C16	Fe13	C10	137.25(13)	C3A	C4A	C30A	114.2(2)
C16	Fe13	C15	40.60(12)	C30A	C4A	C5A	112.3(2)
C17	Fe13	C12	112.91(11)	O7A	C6A	C5A	120.2(3)
C17	Fe13	C11	139.06(12)	O7A	C6A	C8A	123.9(3)
C17	Fe13	C18	40.69(12)	C8A	C6A	C5A	115.7(2)
C17	Fe13	C10	177.58(12)	C24A	C19A	N1A	119.4(3)
C17	Fe13	C15	67.82(12)	C20A	C19A	N1A	121.2(3)
C17	Fe13	C16	40.40(13)	C20A	C19A	C24A	119.3(3)
C17	Fe13	C14	68.02(11)	F28	C26	F27	105.5(2)
C14	Fe13	C11	137.38(11)	F28	C26	C3	112.7(2)
C14	Fe13	C10	111.04(11)	F29	C26	F28	106.8(2)
C14	Fe13	C15	40.11(12)	F29	C26	F27	107.5(2)
C14	Fe13	C16	68.12(12)	F29	C26	C3	113.0(2)
C8A	Fe43	C11A	68.59(12)	F27	C26	C3	110.9(2)
C8A	Fe43	C10A	68.67(12)	C33	C32	C31	120.1(2)
C8A	Fe43	C12A	41.32(12)	N2A	C3A	C4A	115.0(2)
C8A	Fe43	C9A	41.22(12)	N2A	C3A	C26A	120.6(3)
C8A	Fe43	C16A	157.15(14)	C26A	C3A	C4A	124.3(2)
C8A	Fe43	C15A	123.81(13)	C19	C24	C23	120.6(3)
C8A	Fe43	C14A	110.32(16)	C6A	C8A	Fe43	124.05(19)
C8A	Fe43	C17A	162.87(17)	C12A	C8A	Fe43	69.44(16)
C11A	Fe43	C10A	40.45(13)	C12A	C8A	C6A	128.8(3)
C11A	Fe43	C16A	122.02(14)	C9A	C8A	Fe43	69.44(17)
C11A	Fe43	C15A	157.50(14)	C9A	C8A	C6A	123.3(3)
C11A	Fe43	C17A	106.83(16)	C9A	C8A	C12A	107.8(3)
C10A	Fe43	C15A	122.07(15)	C22A	C23A	C24A	121.5(3)

Table S5 Bond Angles for **2q**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C12A	Fe43	C11A	40.73(12)	C22	C23	C24	121.1(3)
C12A	Fe43	C10A	68.78(12)	C19A	C20A	C21A	119.4(3)
C12A	Fe43	C16A	159.04(14)	C9	C10	Fe13	68.66(15)
C12A	Fe43	C15A	160.57(14)	C11	C10	Fe13	70.15(16)
C12A	Fe43	C17A	124.57(15)	C11	C10	C9	109.4(2)
C9A	Fe43	C11A	68.40(13)	C35A	C30A	C4A	120.8(2)
C9A	Fe43	C10A	40.57(13)	C31A	C30A	C4A	119.9(3)
C9A	Fe43	C12A	69.41(12)	C31A	C30A	C35A	119.2(3)
C9A	Fe43	C16A	120.04(15)	C32	C33	C34	120.1(2)
C9A	Fe43	C15A	107.45(14)	C22A	C21A	C20A	122.3(3)
C9A	Fe43	C17A	154.1(2)	F27A	C26A	F29A	106.5(2)
C16A	Fe43	C10A	105.38(14)	F27A	C26A	F28A	107.6(2)
C16A	Fe43	C15A	39.39(15)	F27A	C26A	C3A	113.2(2)
C14A	Fe43	C11A	160.92(18)	F29A	C26A	C3A	111.5(2)
C14A	Fe43	C10A	158.33(19)	F28A	C26A	F29A	106.2(2)
C14A	Fe43	C12A	125.74(15)	F28A	C26A	C3A	111.5(2)
C14A	Fe43	C9A	124.23(19)	C16	C15	Fe13	69.48(17)
C14A	Fe43	C16A	66.67(16)	C14	C15	Fe13	69.63(17)
C14A	Fe43	C15A	39.19(17)	C14	C15	C16	108.3(3)
C14A	Fe43	C17A	68.3(2)	C10A	C11A	Fe43	70.19(17)
C17A	Fe43	C10A	119.29(19)	C10A	C11A	C12A	109.1(3)
C17A	Fe43	C16A	39.37(18)	C12A	C11A	Fe43	69.45(16)
C17A	Fe43	C15A	66.70(16)	C15	C16	Fe13	69.91(17)
C18A	Fe43	C8A	126.3(2)	C17	C16	Fe13	69.61(17)
C18A	Fe43	C11A	123.2(2)	C17	C16	C15	107.4(3)
C18A	Fe43	C10A	156.9(3)	C34A	C35A	C30A	120.6(3)
C18A	Fe43	C12A	109.61(15)	C18	C17	Fe13	69.72(16)
C18A	Fe43	C9A	162.2(3)	C16	C17	Fe13	69.99(17)
C18A	Fe43	C16A	67.44(19)	C16	C17	C18	108.5(3)
C18A	Fe43	C15A	67.20(17)	C11A	C10A	Fe43	69.37(17)
C18A	Fe43	C14A	41.0(2)	C11A	C10A	C9A	108.0(3)
C18A	Fe43	C17A	41.3(3)	C9A	C10A	Fe43	69.07(17)
C3	N2	N1	108.0(2)	C8A	C12A	Fe43	69.23(16)
N2	N1	C5	111.4(2)	C11A	C12A	Fe43	69.82(16)
N2	N1	C19	120.4(2)	C11A	C12A	C8A	107.1(3)
C19	N1	C5	125.2(2)	C30A	C31A	C32A	119.9(3)
C3A	N2A	N1A	107.7(2)	C18	C14	Fe13	69.72(16)
N2A	N1A	C5A	111.1(2)	C15	C14	Fe13	70.27(16)
N2A	N1A	C19A	120.1(2)	C15	C14	C18	108.4(3)
C19A	N1A	C5A	125.5(2)	C33A	C34A	C35A	119.6(3)

Table S5 Bond Angles for **2q**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C6	C8	Fe13	125.63(18)	C33A	C32A	C31A	120.4(3)
C9	C8	Fe13	69.05(15)	C8A	C9A	Fe43	69.33(17)
C9	C8	C6	129.0(2)	C10A	C9A	Fe43	70.36(18)
C12	C8	Fe13	69.85(15)	C10A	C9A	C8A	108.0(3)
C12	C8	C6	123.1(2)	C32A	C33A	C34A	120.2(3)
C12	C8	C9	107.9(2)	C15A	C16A	Fe43	70.68(19)
C30	C4	C5	114.6(2)	C17A	C16A	Fe43	70.3(2)
C30	C4	C3	110.8(2)	C17A	C16A	C15A	109.5(4)
C3	C4	C5	97.8(2)	C16A	C15A	Fe43	69.93(19)
N1	C5	C4	102.2(2)	C14A	C15A	Fe43	69.6(2)
N1	C5	C6	110.6(2)	C14A	C15A	C16A	109.1(4)
C6	C5	C4	109.1(2)	C15A	C14A	Fe43	71.2(2)
C21	C20	C19	119.5(3)	C15A	C14A	C18A	107.9(4)
O7	C6	C8	122.0(2)	C18A	C14A	Fe43	69.2(2)
O7	C6	C5	119.9(2)	C16A	C17A	Fe43	70.3(2)
C8	C6	C5	117.9(2)	C16A	C17A	C18A	107.0(4)
C8	C9	Fe13	69.31(15)	C18A	C17A	Fe43	68.7(3)
C10	C9	Fe13	70.77(16)	C14A	C18A	Fe43	69.8(2)
C10	C9	C8	106.7(2)	C14A	C18A	C17A	106.5(4)
C8	C12	Fe13	69.04(15)	C17A	C18A	Fe43	70.0(2)

Table S6 Torsion Angles for **2q**.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
Fe13	C8	C6	O7	93.8(3)	C3	N2	N1	C5	13.0(3)
Fe13	C8	C6	C5	-90.9(3)	C3	N2	N1	C19	174.5(2)
Fe13	C8	C9	C10	-61.26(18)	C3	C4	C5	N1	20.9(2)
Fe13	C8	C12	C11	60.14(19)	C3	C4	C5	C6	-96.2(2)
Fe13	C9	C10	C11	-58.4(2)	C3	C4	C30	C35	-47.0(3)
Fe13	C12	C11	C10	58.93(19)	C3	C4	C30	C31	132.9(3)
Fe13	C11	C10	C9	57.53(19)	C35	C30	C31	C32	-0.2(4)
Fe13	C18	C17	C16	-59.5(2)	C35	C34	C33	C32	-0.1(4)
Fe13	C18	C14	C15	59.8(2)	C24A	C19A	C20A	C21A	0.9(4)
Fe13	C15	C16	C17	59.8(2)	C31	C30	C35	C34	0.6(4)
Fe13	C15	C14	C18	-59.5(2)	C31	C32	C33	C34	0.5(4)
Fe13	C16	C17	C18	59.3(2)	C5A	N1A	C19A	C24A	17.3(4)
Fe43	C8A	C12A	C11A	59.85(19)	C5A	N1A	C19A	C20A	-166.1(3)
Fe43	C8A	C9A	C10A	-60.0(2)	C5A	C4A	C3A	N2A	17.9(3)
Fe43	C11A	C10A	C9A	58.4(2)	C5A	C4A	C3A	C26A	-161.2(3)
Fe43	C11A	C12A	C8A	-59.47(19)	C5A	C4A	C30A	C35A	-58.5(3)

Fe43	C10A	C9A	C8A	59.4(2)	C5A	C4A	C30A	C31A	118.2(3)
Fe43	C16A	C15A	C14A	-58.8(2)	C5A	C6A	C8A	Fe43	97.2(3)
Fe43	C16A	C17A	C18A	59.2(3)	C5A	C6A	C8A	C12A	7.2(4)
Fe43	C15A	C14A	C18A	-59.7(3)	C5A	C6A	C8A	C9A	-176.4(2)
Fe43	C14A	C18A	C17A	-60.7(3)	C21	C20	C19	N1	174.5(2)
Fe43	C17A	C18A	C14A	60.6(3)	C21	C20	C19	C24	-2.6(4)
O7A	C6A	C8A	Fe43	-87.4(3)	C21	C22	C23	C24	-1.9(4)
O7A	C6A	C8A	C12A	-177.4(3)	C4A	C5A	C6A	O7A	-99.9(3)
O7A	C6A	C8A	C9A	-1.0(4)	C4A	C5A	C6A	C8A	75.7(3)
N2	N1	C5	C4	-22.4(2)	C4A	C3A	C26A	F27A	-174.9(2)
N2	N1	C5	C6	93.6(2)	C4A	C3A	C26A	F29A	65.1(4)
N2	N1	C19	C20	11.9(4)	C4A	C3A	C26A	F28A	-53.4(4)
N2	N1	C19	C24	-171.0(2)	C4A	C30A	C35A	C34A	174.5(3)
N2	C3	C26	F28	-113.6(3)	C4A	C30A	C31A	C32A	-175.0(3)
N2	C3	C26	F29	7.5(4)	C6A	C5A	C4A	C3A	92.7(2)
N2	C3	C26	F27	128.3(3)	C6A	C5A	C4A	C30A	-147.3(2)
N1	N2	C3	C4	3.1(3)	C6A	C8A	C12A	Fe43	117.8(3)
N1	N2	C3	C26	178.3(2)	C6A	C8A	C12A	C11A	177.6(3)
N1	C5	C6	O7	-12.6(4)	C6A	C8A	C9A	Fe43	-118.0(3)
N1	C5	C6	C8	171.9(2)	C6A	C8A	C9A	C10A	-178.0(3)
N1	C19	C24	C23	-174.4(2)	C19A	N1A	C5A	C4A	-173.9(2)
N2A	N1A	C5A	C4A	26.5(3)	C19A	N1A	C5A	C6A	70.6(3)
N2A	N1A	C5A	C6A	-88.9(3)	C19A	C24A	C23A	C22A	-0.7(4)
N2A	N1A	C19A	C24A	175.1(3)	C19A	C20A	C21A	C22A	0.0(5)
N2A	N1A	C19A	C20A	-8.2(4)	C3A	N2A	N1A	C5A	-16.2(3)
N2A	C3A	C26A	F27A	6.1(4)	C3A	N2A	N1A	C19A	-177.0(2)
N2A	C3A	C26A	F29A	-114.0(3)	C3A	C4A	C30A	C35A	51.1(3)
N2A	C3A	C26A	F28A	127.5(3)	C3A	C4A	C30A	C31A	-132.2(3)
N1A	N2A	C3A	C4A	-2.6(3)	C23A	C24A	C19A	N1A	176.2(3)
N1A	N2A	C3A	C26A	176.6(2)	C23A	C24A	C19A	C20A	-0.6(4)
N1A	C5A	C4A	C3A	-24.2(2)	C23A	C22A	C21A	C20A	-1.2(5)
N1A	C5A	C4A	C30A	95.8(3)	C23	C22	C21	C20	2.0(4)
N1A	C5A	C6A	O7A	10.8(4)	C25	C22	C21	C20	-176.1(3)
N1A	C5A	C6A	C8A	-173.6(2)	C25	C22	C23	C24	176.2(3)
N1A	C19A	C20A	C21A	-175.8(3)	C30A	C4A	C3A	N2A	-100.7(3)
C8	C9	C10	Fe13	60.31(18)	C30A	C4A	C3A	C26A	80.2(3)
C8	C9	C10	C11	1.9(3)	C30A	C35A	C34A	C33A	0.9(4)
C8	C12	C11	Fe13	-59.15(18)	C30A	C31A	C32A	C33A	-0.1(4)
C8	C12	C11	C10	-0.2(3)	C33	C34	C35	C30	-0.5(4)
C4	C5	C6	O7	98.9(3)	C21A	C22A	C23A	C24A	1.5(4)
C4	C5	C6	C8	-76.5(3)	C15	C16	C17	Fe13	-60.0(2)
C4	C30	C35	C34	-179.5(2)	C15	C16	C17	C18	-0.7(3)

C4	C30	C31	C32	179.9(2)	C11A	C10A	C9A	Fe43	-58.6(2)
C4	C3	C26	F28	61.1(3)	C11A	C10A	C9A	C8A	0.8(3)
C4	C3	C26	F29	-177.7(2)	C16	C15	C14	Fe13	58.9(2)
C4	C3	C26	F27	-56.9(3)	C16	C15	C14	C18	-0.6(3)
C5	N1	C19	C20	170.8(2)	C35A	C30A	C31A	C32A	1.8(4)
C5	N1	C19	C24	-12.2(4)	C35A	C34A	C33A	C32A	0.7(4)
C5	C4	C30	C35	62.5(3)	C17	C18	C14	Fe13	-59.7(2)
C5	C4	C30	C31	-117.6(3)	C17	C18	C14	C15	0.2(3)
C5	C4	C3	N2	-16.0(3)	C10A	C11A	C12A	Fe43	59.1(2)
C5	C4	C3	C26	168.9(2)	C10A	C11A	C12A	C8A	-0.4(3)
C20	C19	C24	C23	2.7(4)	C12A	C8A	C9A	Fe43	59.03(19)
C6	C8	C9	Fe13	-119.5(3)	C12A	C8A	C9A	C10A	-1.0(3)
C6	C8	C9	C10	179.2(3)	C12A	C11A	C10A	Fe43	-58.7(2)
C6	C8	C12	Fe13	120.1(2)	C12A	C11A	C10A	C9A	-0.2(3)
C6	C8	C12	C11	-179.8(2)	C31A	C30A	C35A	C34A	-2.2(4)
C9	C8	C6	O7	-175.3(3)	C31A	C32A	C33A	C34A	-1.1(4)
C9	C8	C6	C5	0.0(4)	C14	C18	C17	Fe13	59.8(2)
C9	C8	C12	Fe13	-58.77(18)	C14	C18	C17	C16	0.3(3)
C9	C8	C12	C11	1.4(3)	C14	C15	C16	Fe13	-59.0(2)
C12	C8	C6	O7	6.0(4)	C14	C15	C16	C17	0.8(3)
C12	C8	C6	C5	-178.6(2)	C25A	C22A	C23A	C24A	-177.5(3)
C12	C8	C9	Fe13	59.27(18)	C25A	C22A	C21A	C20A	177.9(3)
C12	C8	C9	C10	-2.0(3)	C9A	C8A	C12A	Fe43	-59.03(19)
C12	C11	C10	Fe13	-58.59(19)	C9A	C8A	C12A	C11A	0.8(3)
C12	C11	C10	C9	-1.1(3)	C16A	C15A	C14A	Fe43	59.0(2)
C19	N1	C5	C4	177.2(2)	C16A	C15A	C14A	C18A	-0.8(4)
C19	N1	C5	C6	-66.9(3)	C16A	C17A	C18A	Fe43	-60.2(3)
C19	C20	C21	C22	0.2(4)	C16A	C17A	C18A	C14A	0.3(4)
C19	C24	C23	C22	-0.4(4)	C15A	C16A	C17A	Fe43	-60.0(3)
C30	C4	C5	N1	-96.4(2)	C15A	C16A	C17A	C18A	-0.8(4)
C30	C4	C5	C6	146.6(2)	C15A	C14A	C18A	Fe43	61.0(3)
C30	C4	C3	N2	104.1(3)	C15A	C14A	C18A	C17A	0.3(4)
C30	C4	C3	C26	-71.0(3)	C17A	C16A	C15A	Fe43	59.8(3)
C30	C31	C32	C33	-0.3(4)	C17A	C16A	C15A	C14A	1.0(4)

Table S7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **2q**.

Atom	***x***	***y***	***z***	**U(eq)**
H4	5961.27	2568.26	1954.52	40
H5	5337.01	1117.38	871.21	40
H20	3524.77	4132.46	161.11	43
H9	5834.14	-178.79	1642.61	43

Table S7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **2q**.

Atom	*x*	*y*	*z*	U(eq)
H12	1745.74	-315.5	2125.99	43
H11	2580.18	-1987.33	2586.98	47
H34	9848.4	3582.98	366.7	45
H18	3818.95	-1667.46	314.93	49
H35	7527.81	3525.54	620.46	42
H24A	8658.61	5472.33	5097.77	47
H31	8176.49	2138.18	2095.58	42
H5A	9123.64	5327.89	4143.24	43
H21	2094.11	3459.35	-691.88	46
H4A	8379.09	5775.09	3088.57	44
H32	10501.85	2222.83	1843.23	45
H24	3403.96	352.21	215.86	46
H23A	8573.45	5790.79	6112.35	48
H23	1976.48	-304.05	-639.69	48
H20A	8686.96	9262.23	5118.57	49
H25A	795.51	1832.94	-1454.51	69
H25B	197.39	402.75	-1294.87	69
H25C	1618.52	734.34	-1642.59	69
H10	5091.71	-1868.95	2306.9	47
H33	11331.22	2929.93	978.66	46
H21A	8625.76	9553.1	6133.46	50
H15	2664.35	-4424.56	1377.8	51
H11A	6913.63	1091.01	2968.11	53
H16	592.58	-3450.63	1272.16	54
H35A	11485.78	7605.68	4008.15	48
H17	1301.92	-1768.02	604.69	52
H10A	4367.16	1140.79	3071.22	56
H12A	8482.74	3290.62	3435.34	49
H31A	10081.85	4957.95	2543.62	50
H14	4648.49	-3310.32	799.52	49
H34A	13777	7382.14	3869.19	54
H25D	7967.43	7185.45	7023.22	68
H25E	8344.42	8731.6	7037.92	68
H25F	9582.19	8014.07	7050.96	68
H32A	12393.59	4757.75	2401.04	55
H9A	4320.54	3374.53	3612.68	51
H33A	14216.99	5937.07	3066.25	57
H16A	4267.81	163.23	4315.5	69
H15A	4319.36	2347.78	4875.03	66
H14A	6812.26	3608.45	5101.15	90

Table S7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **2q**.

Atom	*x*	*y*	*z*	U(eq)
H17A	6730.96	-31.14	4201.6	93
H18A	8382.54	2151.96	4691.46	134

Crystal structure determination of **2q**

Crystal Data for $C_{56}H_{46}F_6Fe_2N_4O_2$ (*M* =1032.67 g/mol): triclinic, space group P-1 (no. 2), *a* = 9.8135(3) Å, *b* = 10.7419(3) Å, *c* = 23.2185(4) Å, *α* = 99.306(2)°, *β* = 90.018(2)°, *γ* = 104.952(3)°, *V* = 2331.33(11) Å^3, *Z* = 2, *T* = 100.01(10) K, μ(Cu Kα) = 5.606 mm^{-1}, *Dcalc* = 1.471 g/cm^3, 27285 reflections measured (7.724° ≤ 2Θ ≤ 157.652°), 9445 unique (R_{int} = 0.0567, R_{sigma} = 0.0513) which were used in all calculations. The final R_1 was 0.0546 (I > 2σ(I)) and wR_2 was 0.1537 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups
 At 1.5 times of:
  All C(H,H,H) groups
2.a Ternary CH refined with riding coordinates:
 C4(H4), C5(H5), C5A(H5A), C4A(H4A)
2.b Aromatic/amide H refined with riding coordinates:
 C20(H20), C9(H9), C12(H12), C11(H11), C34(H34), C18(H18), C35(H35),
 C24A(H24A), C31(H31), C21(H21), C32(H32), C24(H24), C23A(H23A), C23(H23),
 C20A(H20A), C10(H10), C33(H33), C21A(H21A), C15(H15), C11A(H11A), C16(H16),
 C35A(H35A), C17(H17), C10A(H10A), C12A(H12A), C31A(H31A), C14(H14),
C34A(H34A),
  C32A(H32A), C9A(H9A), C33A(H33A), C16A(H16A), C15A(H15A), C14A(H14A),
 C17A(H17A), C18A(H18A)
2.c Idealised Me refined as rotating group:
 C25(H25A,H25B,H25C), C25A(H25D,H25E,H25F)
```

This report has been created with Olex2, compiled on 2020.11.27 svn.r5f609507 for Rigaku Oxford Diffraction. Please let us know if there are any errors or if you would like to have additional features.

Crystallographic analysis of 6n: A suitable crystal of compound **6n** was selectedand measured on a XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer. The crystal was kept at 99.99(10) K during data collection. Using Olex2,[13] the structure was solved with the XT[14] structure solution program using Intrinsic Phasing and refined with the XL[15] refinement package using Least Squares minimisation. CCDC-2079230 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/

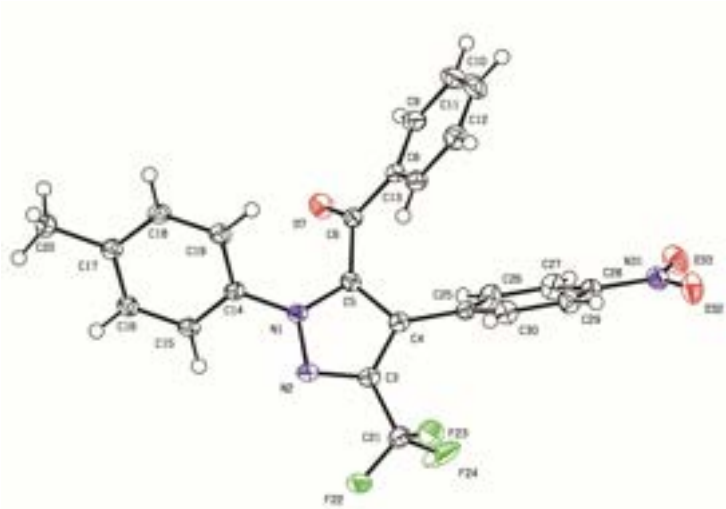


Fig S58. A view of the molecular structure of compound **6n**. Displacement ellipsoids are drawn at the 50% probability level. X-ray data collected at the ambient temperature 100 K.

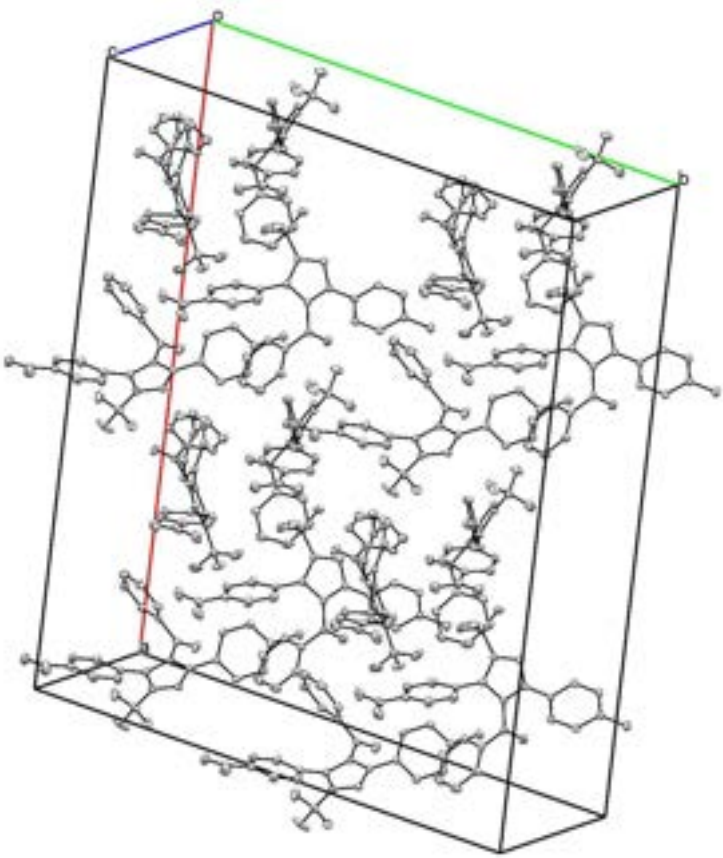


Fig S59. A view of the molecular packing in the structure of compound **6n**.

Table S8 Crystal data and structure refinement for **6n**.

Identification code	GUT-990
Empirical formula	$C_{24}H_{16}F_3N_3O_3$
Formula weight	451.40
Temperature/K	99.99(10)
Crystal system	orthorhombic
Space group	Fdd2

a/Å	33.2382(2)
b/Å	28.8297(2)
c/Å	8.72030(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	8356.20(12)
Z	16
ρ_{calc}g/cm^3	1.435
μ/mm^{-1}	0.975
F(000)	3712.0
Crystal size/mm^3	0.64 × 0.09 × 0.07
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.12 to 157.634
Index ranges	-41 ≤ h ≤ 40, -36 ≤ k ≤ 34, -9 ≤ l ≤ 10
Reflections collected	62799
Independent reflections	4226 [R_{int} = 0.0456, R_{sigma} = 0.0135]
Data/restraints/parameters	4226/1/300
Goodness-of-fit on F^2	1.067
Final R indexes [I>=2σ (I)]	R_1 = 0.0249, wR_2 = 0.0655
Final R indexes [all data]	R_1 = 0.0250, wR_2 = 0.0655
Largest diff. peak/hole / e Å^{-3}	0.18/-0.18
Flack parameter	0.04(3)

Table S9 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **6n**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
F22	4304.6(3)	4034.1(4)	3056.9(15)	31.3(3)
F23	4672.7(4)	4576.6(4)	3969.4(16)	35.2(3)
F24	4423.7(4)	4071.6(6)	5481.4(16)	50.6(4)
O7	5933.0(4)	2833.7(4)	4887.6(17)	27.3(3)
O33	5552.2(4)	4447.2(5)	11824.3(17)	32.8(3)
O32	5481.0(5)	5116.0(5)	10728.7(18)	32.8(3)
N1	5345.2(4)	3335.6(5)	2907.2(17)	16.5(3)
N2	4990.0(4)	3556.2(5)	2682.6(18)	17.7(3)
N31	5495.4(4)	4690.6(5)	10690.2(19)	23.9(3)
C4	5280.0(5)	3796.3(5)	4917(2)	17.4(3)
C3	4951.4(5)	3828.8(5)	3902(2)	17.7(3)
C25	5338.8(5)	4029.0(6)	6414(2)	18.4(3)
C17	5773.2(5)	2446.7(6)	-594(2)	20.1(4)
C14	5493.6(5)	3028.8(5)	1745(2)	16.7(3)

Table S9 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **6n**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C8	6222.9(5)	3572.8(6)	5406(2)	18.7(3)
C5	5528.3(5)	3471.9(5)	4230(2)	17.3(3)
C19	5888.5(5)	3068.6(6)	1237(2)	20.6(4)
C16	5377.0(5)	2418.6(6)	-67(2)	20.4(4)
C6	5906.0(5)	3254.6(6)	4841(2)	18.6(3)
C18	6025.9(5)	2777.4(6)	80(2)	21.9(4)
C28	5444.7(5)	4463.0(6)	9196(2)	20.9(3)
C13	6241.5(5)	4035.8(6)	4938(2)	21.4(4)
C21	4586.1(5)	4125.0(6)	4093(2)	22.8(4)
C15	5234.7(5)	2704.8(6)	1098(2)	19.6(3)
C26	5351.3(6)	3769.6(6)	7760(2)	24.7(4)
C20	5928.6(5)	2130.4(6)	-1829(2)	24.5(4)
C27	5402.6(6)	3986.0(6)	9162(2)	26.1(4)
C30	5383.4(6)	4511.0(6)	6488(2)	22.8(4)
C9	6511.8(5)	3399.4(6)	6419(2)	23.0(4)
C29	5437.2(5)	4730.7(6)	7882(2)	24.2(4)
C12	6544.5(6)	4322.2(7)	5485(2)	27.3(4)
C10	6813.4(6)	3685.4(8)	6961(2)	29.3(4)
C11	6828.7(6)	4146.6(7)	6501(2)	31.4(4)

Table S10 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **6n**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F22	20.0(5)	32.3(6)	41.7(7)	-8.4(5)	-8.1(5)	7.3(4)
F23	34.8(6)	20.4(5)	50.5(8)	-8.2(5)	-9.6(6)	9.1(4)
F24	36.3(7)	82.1(11)	33.3(7)	17.3(7)	17.3(6)	30.4(7)
O7	31.5(7)	15.7(6)	34.7(8)	-1.2(5)	-8.7(6)	3.6(5)
O33	36.8(8)	40.1(8)	21.4(7)	3.4(6)	-3.0(6)	-6.4(6)
O32	43.9(8)	26.9(7)	27.7(8)	-6.6(6)	2.4(6)	-9.9(6)
N1	14.1(6)	14.5(6)	20.9(7)	0.3(5)	-1.1(5)	-0.4(5)
N2	14.0(6)	17.1(6)	22.0(7)	2.7(6)	0.7(5)	0.4(5)
N31	21.3(7)	29.3(8)	21.0(8)	-1.0(6)	1.6(6)	-5.6(6)
C4	18.0(7)	14.0(7)	20.2(9)	1.5(6)	0.9(7)	-0.6(6)
C3	15.3(7)	16.2(7)	21.5(9)	3.7(6)	1.4(6)	-0.3(6)
C25	15.6(7)	17.6(7)	22.1(9)	-0.3(7)	0.4(6)	2.1(6)
C17	19.9(8)	17.3(8)	23.1(9)	0.5(7)	-0.5(7)	1.0(6)
C14	16.1(7)	15.0(7)	18.9(8)	1.4(6)	-1.1(6)	1.0(6)
C8	15.4(7)	21.7(8)	19.1(8)	-2.9(7)	0.6(7)	1.0(6)

Table S10 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **6n**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C5	17.4(7)	14.4(7)	20.0(9)	0.6(6)	-1.6(6)	-1.5(6)
C19	17.9(8)	17.8(7)	26.0(10)	-0.6(7)	-0.2(7)	-3.7(6)
C16	19.3(8)	19.0(8)	23.0(9)	-0.9(7)	-2.2(7)	-2.0(6)
C6	18.9(8)	17.6(8)	19.3(9)	-1.6(6)	-1.3(6)	2.0(6)
C18	16.3(8)	22.2(8)	27.3(10)	-1.3(7)	2.2(7)	-2.2(6)
C28	17.1(7)	24.3(8)	21.3(9)	-1.7(7)	0.3(6)	-0.8(6)
C13	17.9(8)	21.1(8)	25.4(9)	-0.9(7)	0.2(7)	-0.1(6)
C21	20.7(8)	25.3(8)	22.5(10)	-0.2(7)	1.7(7)	4.3(7)
C15	14.5(7)	19.4(8)	25.0(9)	0.7(7)	-0.8(6)	-2.0(6)
C26	31.6(10)	16.8(8)	25.5(10)	1.7(7)	2.6(7)	0.9(7)
C20	23.7(8)	23.8(9)	26.0(9)	-4.8(7)	2.5(7)	-0.9(7)
C27	32.4(10)	22.8(8)	23.1(10)	4.6(7)	1.5(8)	1.3(7)
C30	28.5(9)	17.5(8)	22.6(10)	4.1(7)	-2.5(7)	1.0(7)
C9	19.2(8)	27.0(9)	22.9(9)	2.5(7)	0.2(7)	2.3(7)
C29	27.7(9)	17.5(8)	27.4(10)	-0.7(7)	-2.3(8)	-1.9(7)
C12	26.3(9)	24.2(9)	31.5(11)	-2.6(8)	2.8(8)	-5.2(7)
C10	22.3(9)	40.0(11)	25.5(10)	1.4(8)	-4.7(7)	-0.5(8)
C11	24.7(9)	41.0(11)	28.6(11)	-5.9(9)	-2.1(8)	-10.6(8)

Table S11 Bond Lengths for **6n**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
F22	C21	1.327(2)	C17	C18	1.400(2)
F23	C21	1.338(2)	C17	C20	1.503(3)
F24	C21	1.335(2)	C14	C19	1.390(2)
O7	C6	1.217(2)	C14	C15	1.390(2)
O33	N31	1.227(2)	C8	C6	1.481(2)
O32	N31	1.228(2)	C8	C13	1.397(2)
N1	N2	1.3552(19)	C8	C9	1.397(2)
N1	C14	1.433(2)	C5	C6	1.501(2)
N1	C5	1.362(2)	C19	C18	1.390(3)
N2	C3	1.328(2)	C16	C15	1.391(3)
N31	C28	1.469(2)	C28	C27	1.382(2)
C4	C3	1.409(2)	C28	C29	1.382(3)
C4	C25	1.481(2)	C13	C12	1.387(3)
C4	C5	1.383(2)	C26	C27	1.383(3)
C3	C21	1.494(2)	C30	C29	1.382(3)
C25	C26	1.392(3)	C9	C10	1.381(3)
C25	C30	1.399(2)	C12	C11	1.391(3)

Table S11 Bond Lengths for **6n**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C17	C16	1.397(2)	C10	C11	1.390(3)

Table S12 Bond Angles for **6n**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
N2	N1	C14	119.17(14)	C4	C5	C6	128.87(16)
N2	N1	C5	112.10(14)	C18	C19	C14	119.47(16)
C5	N1	C14	128.56(14)	C15	C16	C17	121.74(16)
C3	N2	N1	104.25(14)	O7	C6	C8	123.63(15)
O33	N31	O32	123.72(17)	O7	C6	C5	119.31(15)
O33	N31	C28	118.50(15)	C8	C6	C5	117.02(14)
O32	N31	C28	117.78(16)	C19	C18	C17	121.26(16)
C3	C4	C25	128.75(15)	C27	C28	N31	118.35(17)
C5	C4	C3	103.64(15)	C29	C28	N31	119.23(15)
C5	C4	C25	127.51(16)	C29	C28	C27	122.42(18)
N2	C3	C4	112.85(14)	C12	C13	C8	120.04(17)
N2	C3	C21	120.40(15)	F22	C21	F23	106.80(15)
C4	C3	C21	126.75(16)	F22	C21	F24	108.04(15)
C26	C25	C4	120.26(15)	F22	C21	C3	112.61(15)
C26	C25	C30	119.45(17)	F23	C21	C3	111.88(14)
C30	C25	C4	120.29(16)	F24	C21	F23	105.80(16)
C16	C17	C18	117.84(16)	F24	C21	C3	111.35(16)
C16	C17	C20	121.63(16)	C14	C15	C16	118.99(16)
C18	C17	C20	120.52(16)	C27	C26	C25	120.43(16)
C19	C14	N1	119.97(15)	C28	C27	C26	118.69(18)
C15	C14	N1	119.28(15)	C29	C30	C25	120.61(17)
C15	C14	C19	120.70(16)	C10	C9	C8	120.09(17)
C13	C8	C6	121.75(16)	C28	C29	C30	118.41(16)
C13	C8	C9	119.73(16)	C13	C12	C11	119.71(18)
C9	C8	C6	118.51(16)	C9	C10	C11	119.94(18)
N1	C5	C4	107.16(14)	C10	C11	C12	120.49(18)
N1	C5	C6	123.63(15)				

Table S13 Torsion Angles for **6n**.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O33	N31	C28	C27	9.6(2)	C25	C30	C29	C28	-0.2(3)
O33	N31	C28	C29	-170.97(16)	C17	C16	C15	C14	0.4(3)
O32	N31	C28	C27	-170.91(16)	C14	N1	N2	C3	-176.49(14)
O32	N31	C28	C29	8.5(2)	C14	N1	C5	C4	175.54(15)

Table S13 Torsion Angles for **6n**.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
N1	N2	C3	C4	0.98(18)	C14	N1	C5	C6	-10.6(3)
N1	N2	C3	C21	-178.60(14)	C14	C19	C18	C17	0.5(3)
N1	C14	C19	C18	-178.26(16)	C8	C13	C12	C11	-0.1(3)
N1	C14	C15	C16	177.83(16)	C8	C9	C10	C11	0.2(3)
N1	C5	C6	O7	-46.7(2)	C5	N1	N2	C3	-0.85(17)
N1	C5	C6	C8	135.22(17)	C5	N1	C14	C19	-44.0(2)
N2	N1	C14	C19	130.80(16)	C5	N1	C14	C15	138.35(17)
N2	N1	C14	C15	-46.8(2)	C5	C4	C3	N2	-0.75(18)
N2	N1	C5	C4	0.42(18)	C5	C4	C3	C21	178.80(16)
N2	N1	C5	C6	174.24(15)	C5	C4	C25	C26	-61.9(2)
N2	C3	C21	F22	8.2(2)	C5	C4	C25	C30	117.9(2)
N2	C3	C21	F23	-112.15(18)	C19	C14	C15	C16	0.2(3)
N2	C3	C21	F24	129.69(18)	C16	C17	C18	C19	0.1(3)
N31	C28	C27	C26	179.46(16)	C6	C8	C13	C12	-179.58(17)
N31	C28	C29	C30	-179.08(16)	C6	C8	C9	C10	179.54(17)
C4	C3	C21	F22	-171.36(16)	C18	C17	C16	C15	-0.5(3)
C4	C3	C21	F23	68.3(2)	C13	C8	C6	O7	160.49(18)
C4	C3	C21	F24	-49.8(2)	C13	C8	C6	C5	-21.6(3)
C4	C25	C26	C27	-179.42(17)	C13	C8	C9	C10	0.3(3)
C4	C25	C30	C29	179.80(16)	C13	C12	C11	C10	0.6(3)
C4	C5	C6	O7	125.7(2)	C15	C14	C19	C18	-0.7(3)
C4	C5	C6	C8	-52.4(3)	C26	C25	C30	C29	-0.4(3)
C3	C4	C25	C26	113.9(2)	C20	C17	C16	C15	178.69(17)
C3	C4	C25	C30	-66.3(2)	C20	C17	C18	C19	-179.16(17)
C3	C4	C5	N1	0.18(17)	C27	C28	C29	C30	0.3(3)
C3	C4	C5	C6	-173.22(16)	C30	C25	C26	C27	0.8(3)
C25	C4	C3	N2	-177.30(16)	C9	C8	C6	O7	-18.8(3)
C25	C4	C3	C21	2.3(3)	C9	C8	C6	C5	159.18(16)
C25	C4	C5	N1	176.79(15)	C9	C8	C13	C12	-0.3(3)
C25	C4	C5	C6	3.4(3)	C9	C10	C11	C12	-0.7(3)
C25	C26	C27	C28	-0.6(3)	C29	C28	C27	C26	0.0(3)

Table S14 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **6n**.

Atom	*x*	*y*	*z*	U(eq)
H19	6063.02	3293.02	1677.04	25
H16	5200.04	2198.17	-515.4	25
H18	6296.54	2803.22	-260.58	26
H13	6046.52	4154.56	4245.04	26
H15	4964.74	2679.16	1445.14	24

Table S14 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **6n**.

Atom	*x*	*y*	*z*	U(eq)
H26	5324.45	3441.81	7715.06	30
H20A	6131.37	1921.28	-1395.81	37
H20B	6050.18	2315.84	-2649.04	37
H20C	5705.57	1947.64	-2248	37
H27	5408.78	3810.42	10083.32	31
H30	5376.61	4689.03	5571.14	27
H9	6500.68	3084.34	6736.11	28
H29	5468.25	5057.85	7934.98	29
H12	6557.81	4637.02	5167	33
H10	7010.19	3566.96	7647.07	35
H11	7034.79	4343.34	6883.96	38

Crystal structure determination of **6n**:

Crystal Data for $C_{24}H_{16}F_3N_3O_3$ (*M* =451.40 g/mol): orthorhombic, space group Fdd2 (no. 43), *a* = 33.2382(2) Å, *b* = 28.8297(2) Å, *c* = 8.72030(10) Å, *V* = 8356.20(12) Å^3, *Z* = 16, *T* = 99.99(10) K, μ(Cu Kα) = 0.975 mm^{-1}, *Dcalc* = 1.435 g/cm^3, 62799 reflections measured (8.12° ≤ 2Θ ≤ 157.634°), 4226 unique (R_{int} = 0.0456, R_{sigma} = 0.0135) which were used in all calculations. The final R_1 was 0.0249 (I > 2σ(I)) and wR_2 was 0.0655 (all data).

Refinement model description

Number of restraints - 1, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups
 At 1.5 times of:
  All C(H,H,H) groups
2.a Aromatic/amide H refined with riding coordinates:
 C19(H19), C16(H16), C18(H18), C13(H13), C15(H15), C26(H26), C27(H27),
 C30(H30), C9(H9), C29(H29), C12(H12), C10(H10), C11(H11)
2.b Idealised Me refined as rotating group:
 C20(H20A,H20B,H20C)
```

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5. References

1. G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.
2. G. Mlostoń, K. Urbaniak, G. Utecht, D. Lentz, M. Jasiński, *J. Fluorine Chem.* **2016**, *192*, 147–154.
3. A. Wojciechowska, M. Jasiński, P. Kaszyński, *Tetrahedron* **2015**, *71*, 2349–2356.
4. (a) L. Claisen, A. Claparede, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2460–2468. (b) J. G. Schmidt, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1459–1461.
5. A. T. Davies, J. E. Taylor, J. Douglas, C. J. Collett, L. C. Morrill, C. Fallan, A. M. Z. Slawin, G. Churchill, and A. D. Smith, *J. Org. Chem.* **2013**, *78*, 9243–9257.
6. H. Xie, J. Zhu, Z. Chen, S. Li, Y. Wu, *Synthesis* **2011**, *17*, 2767–2774.
7. P. Grzelak, G. Utecht, M. Jasiński, G. Mlostoń, *Synthesis* **2017**, *49*, 2129–2137.
8. V. M. Muzalevskiy, Z. A. Sizova, V. V. Panyushkin, V. A. Chertkov, V. N. Khrustalev, V. G. Nenajdenko, *J. Org. Chem.* **2021**, *86*, 2385–2405.
9. K. Tanaka, S. Maeno, K. Mitsuhashi, *Chem. Lett.* **1982**, 543–546.
10. A. Touzot, M. Soufyane, H. Berber, L. Toupet, C. Mirand, *J. Fluorine Chem.* **2004**, *125*, 1299–1304.
11. S. L. Jeon, J. H. Choi, B. T. Kim, I. H. Jeong, *J. Fluorine Chem.* **2007**, *128*, 1191–1197.
12. A. E. Ivanova, Ya. V. Burgart, V. I. Saloutin, *Russ. J. Org. Chem.* **2018**, *54*, 1265–1267.
13. O. V. Dolomanov, L. J. Bourhis, R. J Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339–341.
14. G. M. Sheldrick, *Acta Cryst.* **2015**, *A71*, 3–8.
15. G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

[**D3**]

G. Utecht-Jarzyńska, A. Kowalczyk, M. Jasiński

Fluorinated and non-fluorinated 1,4-diarylpyrazoles via MnO_2-mediated mechanochemical deacylative oxidation of 5-acylpyrazolines

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Fluorinated and Non-Fluorinated 1,4-Diarylpyrazoles via MnO_2-Mediated Mechanochemical Deacylative Oxidation of 5-Acylpyrazolines †

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† Dedicated to Professor Stanisław Leśniak (University of Lodz) on the occasion of his 70th birthday.

Abstract: A solvent-free two-step synthesis of polyfunctionalized pyrazoles under ball-milling mechanochemical conditions was developed. The protocol comprises (3 + 2)-cycloaddition of in situ generated nitrile imines and chalcones, followed by oxidation of the initially formed 5-acylpyrazolines with activated MnO_2. The second step proceeds via an exclusive deacylative pathway, to give a series of 1,4-diarylpyrazoles functionalized with a fluorinated (CF_3) or non-fluorinated (Ph, COOEt, Ac) substituent at C(3) of the heterocyclic ring. In contrast, MnO_2-mediated oxidation of a model isomeric 4-acylpyrazoline proceeded with low chemoselectivity, leading to fully substituted pyrazole as a major product formed via dehydrogenative aromatization. The presented approach extends the scope of the known methods carried out in organic solvents and enables the preparation of polyfunctionalized pyrazoles, which are of general interest in medicine and material sciences.

Keywords: pyrazole; nitrile imine; mechanochemistry; (3 + 2)-cycloaddition; deacylation; oxidation

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1. Introduction

Due to the discovery of a number of practical applications, there is increasing interest in the chemistry of pyrazole-based compounds, and fluorinated analogues are of special significance in medicine, crop protection, as well as material sciences [1–4]. The title heterocycle constitutes a key structural element of pharmaceuticals and agrochemicals; they exhibit a variety of biological activities such as being anti-inflammatory (e.g., Celecoxib, Lonazolac), antibacterial, anticancer (e.g., Crizotinib), anti-obesity (e.g., Rimonabant), antidepressant (e.g., Fezolamine), antiviral (e.g., Lenacapavir), and antifungal (e.g., Penthiopyrad), and have been widely applied as pesticides (Figure 1) [5–13]. In addition, some pyrazoles have been successfully applied in polymer chemistry, as well as for the preparation of advanced liquid crystalline materials [14,15]. Furthermore, polyfunctionalized pyrazoles can efficiently act as ligands in transition metal-catalyzed reactions [1,2,16]. Taking into account the general significance of this class of *N*-heterocycles, the development of new synthetic protocols to access pyrazoles with the desired substitution patterns is of great interest.

Out of the various synthetic methodologies for the preparation of pyrazole derivatives available thus far, condensation of 1,3-dielectrophilic agents (typically 1,3-diketones or their synthetic equivalents) with hydrazines is considered the most versatile and commonly applied strategy [1,2,4,5]. However, this classical method often suffers from regioselectivity issues and leads to isomeric pyrazoles, along with other by-products, which require tedious separation, e.g., using chromatography techniques. Hence, (3 + 2)-cycloaddition processes are an attractive alternative and enable straightforward access to the pyrazole skeleton through simultaneous formation of new carbon–carbon and carbon–nitrogen bonds. In

products, which require tedious separation, e.g., using chromatography techniques. Hence, (3 + 2)-cycloaddition processes are an attractive alternative and enable straightforward access to the pyrazole skeleton through simultaneous formation of new carbon–carbon and carbon–nitrogen bonds. In this context, diazoalkanes, and particularly nitrile imines, have been recognized as readily available and powerful 1,3-dipoles for the construction of the pyrazole ring [1,2,17].

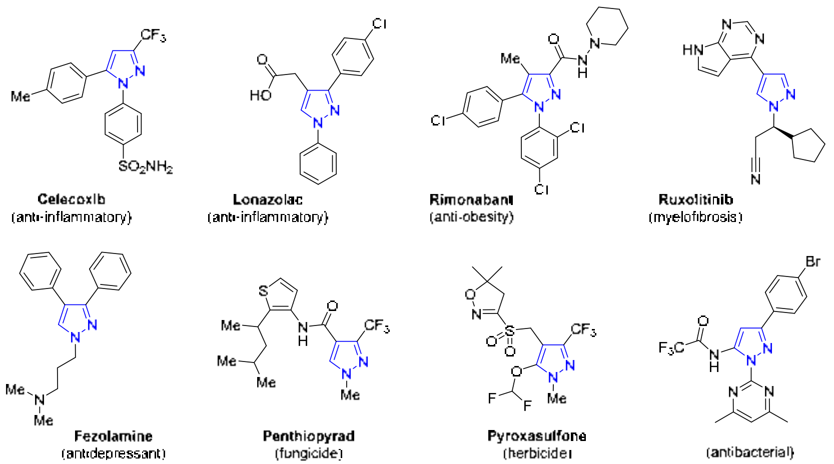

Figure 1. Structures of selected fluorinated and non-fluorinated pyrazole-based pharmaceuticals and agrochemicals.

On the other hand, the negative impact on the environment and public health caused by the large amount of waste solvents produced during classical organic synthesis has to be taken into account. Recently, there has been a rapid development of green and sustainable synthetic protocols based on mechanochemical approaches, in which the reaction is activated by the absorption of mechanical energy originating from collisions of milling balls [18–21]. Moreover, these reactions can be performed either without any solvent or require only small amounts of so-called "liquid assisted grinding" solvents (LAGs), and in many instances the chemo- and regio-selectivity switch, leading to rather unexpected products being observed upon mechanochemical activation. Several interesting applications of mechanochemistry in the synthesis of pharmaceutically relevant N-containing compounds, such as Dantrolene (muscle relaxant), Tolbutamide (antidiabetic), and Axitinib (anticancer) have been reported [22–24]. Furthermore, the presented technique has been successfully applied for preparation of pyrazoles, mainly via condensation reactions starting with 1,3-dicarbonyls [25–30], chalcones [31], or enaminones [32], and appropriate hydrazine derivatives. Notably, to the best of our knowledge, no mechanochemical nitrile imine (3 + 2)-cycloadditions leading to pyrazoles have been reported.

In a series of recent works, we and other groups have demonstrated fluorinated nitrile imines of type **1** and C=C or C≡C dipolarophiles as superior reaction partners for the efficient preparation of fluoroalkylated pyrazole and pyrazoline derivatives. For example, electron-rich enamines [33], vinyl ethers [34], alkoxyallenes [35], and benzynes [36], as well as electron-deficient nitro- [37] and cyanoalkenes [38], isoxazolidinediones [39], quinones [40], and ynone derivatives [41] have served as dipolarophilic agents. Exemplary reactions leading to polysubstituted pyrazoles **2**–**4** and bicyclic analogues **5** (indazoles) are depicted in Scheme 1a. More recently, we disclosed a general two-step protocol for two types of multi-substituted 3-trifluoromethylpyrazoles comprising (3 + 2)-cycloaddition of in situ generated nitrile imines **1** with chalcones, followed by MnO_2-mediated aromatization of the first 5-acylpyrazolines **6** formed [42]. Remarkably, depending on the solvent used, the oxidation step preferentially afforded fully substituted pyrazoles **7** (in polar solvents such as DMF or DMSO) or proceeded via a deacylative pathway (in non-polar solvents, e.g., in

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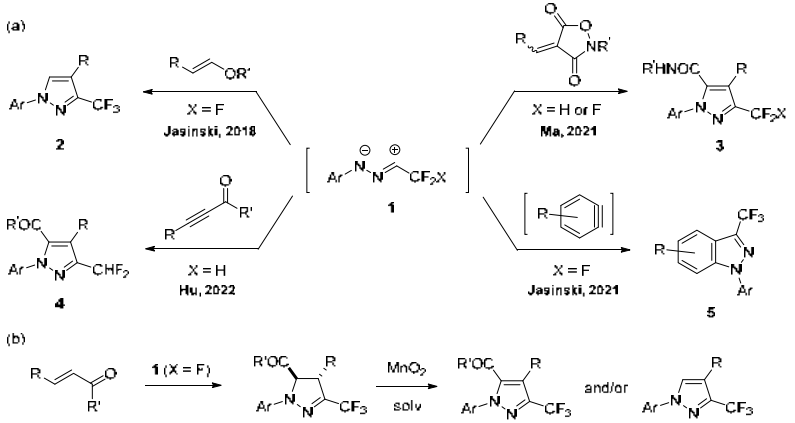


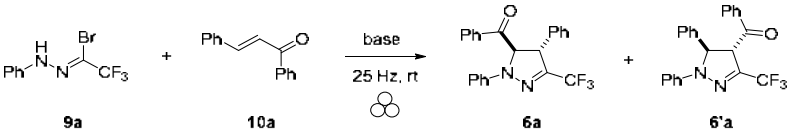
Scheme 1. Synthesis of fluoroalkylated pyrazoles through: (**a**) (3 + 2)-cycloadditions of nitrile imines **1** with selected C=C or C≡C dipolarophiles, leading to monocyclic (**2**–**4**) [34,39,41] and bicyclic (**5**) [36] derivatives and (**b**) trapping of **1** with enones, followed by MnO_2-mediated oxidation of the first 5-acylpyrazolines **6** formed, leading to polysubstituted 3-trifluoromethylpyrazoles **7** and/or **8**.

2. Results and Discussion

The required CF_3-nitrile imines of type **1** are readily available precursors (1,3-dipoles), which can be generated in situ via base-induced dehydrohalogenation of the respective hydrazonoyl halides (or pseudohalides) [37,43]. A series of key precursors, namely hydrazonoyl bromides **9**, were prepared according to the general literature protocols, starting from commercially available substrates, i.e., fluorinated aryl aldehydes [43–46]. According to our previous observations, the reversible generation of trifluoroacetonitrile imines **1** from the corresponding bromide **9** proceeds smoothly upon treatment with excess Et_3N, at room temperature, in anhydrous THF as the solvent of choice. For this reason, initial mechanochemical experiments (steel balls: n = 7, m = 25 Hz, 2 h) were carried out using the known *C*-trifluoromethyl-*N*-phenyl nitrile imine (**1a**) and chalcone (**10a**) selected as model substrates, in the presence of Et_3N (Scheme 2). As evidenced by TLC monitoring, a rapid (3 + 2)-cycloaddition reaction was observed, and after 1 h the expected 3-trifluoromethylpyrazoline **6a** was identified as a major component of the crude reaction mixture, along with small amounts of regioisomeric derivative **6′a** (in ca. 7:1 ratio, respectively), however, in moderate yield (56% conversion estimated based on ^1H NMR spectrum of crude mixture), as unconsumed chalcone **10a** accompanied by unidentified decomposition products of bromide **9a** were also detected. Then, the influence of a series of inorganic bases on the reaction course was briefly checked (Table 1). Whereas application of K_2CO_3 as a base enhanced the conversion significantly (82%), further optimization with respect to the amount of nitrile imine precursor **9a** (1.2 equiv.) and with the volume of the

spectroscopically pure samples of two pyrazolines, **6a** (75%) and **6′a** (13%). The relative orientation of substituents along the C(4)-C(5) bond in **6a** and **6′a** was established based on the ^{1}H NMR spectra and by comparison with the literature data on other *trans*-configured 5-acylpyrazolines [42,47]. For example, in the case of compound **6a,** the diagnostic protons appeared as doublet of quartets ($J_{H\text{-}H}$ = 5.6 Hz, $^4J_{H\text{-}F} \approx 0.9$ Hz) at δ 4.37 (4-H) and as doublet ($J_{H\text{-}H}$ = 5.6 Hz) at δ 5.76 (5-H), thereby confirming the fully diastereoselective addition of 1,3-dipole **1a** onto the C=C bond of the conjugated system of **10a**. The structure of minor isomer **6′a** was elucidated on the basis of ^{1}H and ^{13}C NMR supplemented with 2D NMR measurements (HMQC, HMBC). For example, in the ^{1}H NMR spectrum of **6′a**, two characteristic quartets found at δ 4.37 (4-H) and at δ 5.65 (5-H) nicely matched the proposed structure of **6′a**. Furthermore, in the ^{13}C NMR spectrum of **6′a**, two diagnostic quartets found at δ 120.9 ($^1J_{C\text{-}F}$ = 269.8 Hz) and δ 133.5 ($^2J_{C\text{-}F}$ = 38.0 Hz), attributed to the CF_3 group and C-3 atom, respectively, as well as a low intensity absorption (s) at δ 194.5 attributed to the C=O group, were found.

It should be noted that the reaction of **9a** with **10a** carried out under classical conditions, i.e., in THF solution at room temperature, leads to pyrazoline **6a** (79%) exclusively, although after a rather long reaction time (4 days) [42]. In contrast, the mechanochemical activation of the studied (3 + 2)-cycloaddition provided the desired material **6a** in a comparable yield (75%) after a remarkably shorter reaction time of 3 h, but the competitive formation of small amounts of isomeric product **6′a** was observed.



Scheme 2. Base-catalyzed mechanochemical (3 + 2)-cycloaddition of trifluoromethylated nitrile imine **1a** derived from hydrazonoyl bromide **9a** and chalcone (**10a**), leading to the isomeric benzoylpyrazolines **6a** (major) and **6′a** (minor).

Table 1. Optimization of (3 + 2)-cycloaddition reaction of **9a** and **10a**.

Table 1. Optimization of (3 + 2)-cycloaddition reaction of **9a** and **10a**.

Entry	Base	9a:10a:Base (Ratio)	Time (min)	V_{jar} (mL)	Conversion [1] (%)		Ratio (%) [1] (Isolated Yield)	
							6a	6′a
1	Et_3N	1:1:0.2	60	1.5	56 [2]	56 [2]	87	13
2	CsF	1:1:0.2	60	1.5	27 [2]	27 [2]	72	28
3	KF	1:1:0.2	60	1.5	27 [2]	60 [2]	72	28
4	Cs_2CO_3	1:1:0.2	60	1.5	60 [2]	45 [2]	84	16
5	KF	1:1:0.2	60	1.5	45 [2]	82	79	21
6	Cs_2CO_3	1:1:0.2	60	1.5		84	79	21
7	K_2CO_3	1:1:0.2	90	1.5	82	93	81	19
8	K_2CO_3	1:1:0.2	180	1.5	84	93	82	18
9	K_2CO_3	1:1:0.3	60	1.5	82	93	80 (73)	20 (13)
10	K_2CO_3	1:1:0.3	90	1.5	84	93	82 (75)	18 (13)
11	K_2CO_3	1:1:0.3	180	5	93		80 (73)	20 (13)
12	K_2CO_3	1.2:1.0:1.3	180	5	93		82 (75)	18 (13)

[1] Estimated based on ^{1}H NMR spectra of crude reaction mixtures; [2] Partial decomposition of starting bromide **9a**.

With the optimized conditions in hand, we next turned our attention to the scope and limitations of the developed mechanochemical 1,3-dipolar cycloaddition. A series of nitrile imine precursors of type **9**, bearing either electron-donating (**9b–9d**) or electron-withdrawing (**9e**, **9g**, and **9h**) groups X located at *para* position of the phenyl ring, as well as disubstituted derivative **9f** (2,4-Cl_2), were examined in (3 + 2)-cycloadditions with a model chalcone (**10a**) (Scheme 3). As shown in Table 2, higher chemical yields were observed for reactions carried out with nitrile imine precursors **9b–9d**, i.e., bearing groups increasing the electron density at the negatively charged *N*-termini of the in situ generated dipole

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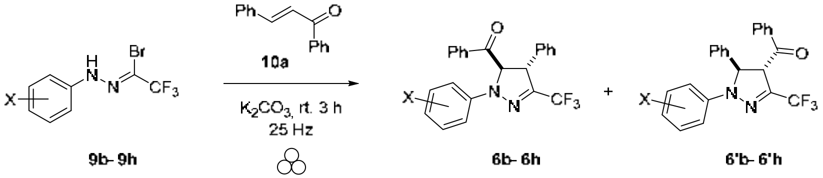


Scheme 3. Mechanochemical synthesis of 5-benzoyl-4-phenyl-3-trifluoromethylpyrazolines **6b**–**6h** derived from chalcone (**10a**); scope of hydrazonoyl bromides **9**.

Table 2. Ball-milling (3 + 2)-cycloadditions of **9b**–**9h** with model chalcone (**10a**).

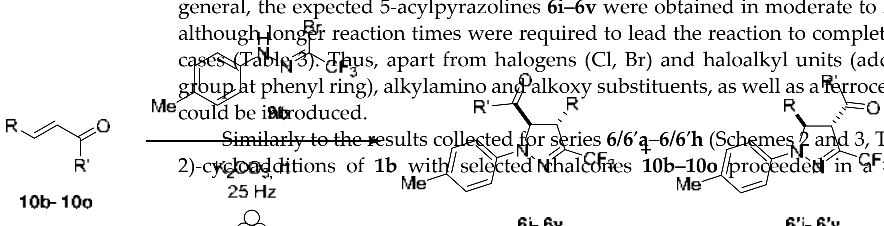
Entry	Substrate	X	6:6′ Ratio [1]	Yield of 6 (%) [2]
1	**9b**	4-Me	81:19	**6b** (70)
2	**9c**	4-*i*-Pr	81:19	**6c** (71)
3	**9d**	4-OBn	83:17	**6d** (58)
4	**9e**	4-Cl	81:19	**6e** (53)
5	**9f**	2,4-Cl_2	77:23	**6f** (54)
6	**9g**	4-NO_2	74:26	**6g** [illegible]
7 [3]	**9g**	4-NO_2	79:21	**6g** (22)
8 [3]	**9h**	4-PhCOO	79:21	**6h** (17)

[1] Estimated on the basis of ^{1}H NMR spectra of crude reaction mixtures; [2] Isolated yield; [3] Grinding time 24 h.

regioselectivity of ca. 4:1 in favor of 5-acylpyrazolines **6**. Again, only *trans*-configur products could be detected in the mother liquors. Interestingly, in the case of 3 methylenedioxy-functionalized chalcone (**10f**) and 3,4-dimethoxy analogue (**10** exceptionally high selectivity (ca. 9:1) or exclusive formation of target 5-acylpyrazolin **6m** and **6l**, respectively, was observed. On the other hand, the reaction of **1b** with anoth electron-rich chalcone, namely 4-(dimethylamino)chalcone (**10g**), provided only t expected (3 + 2)-cycloadducts **6n** and **6′n** as a ca. 2:1 mixture. Possibly, the observ decrease of selectivity resulted from presence of the basic Me_2N group in **10g**, whi can compete with K_2CO_3 in dehydrohalogenation of **9b**, thereby changing the electro properties of chalcone **10g**, due to protonation. The observed moderate yield cycloadditions of **1b** with chalcones **10c** and **10m**, leading to pyrazolines **6j** (38%) and (39%), also deserves a brief comment. Seemingly, the presence of the redox-active group altered the reaction outcome and led to complex mixtures, irrespective of t substituent...

Next, to check the scope of chalcones and to test the functional group tolerance of mechanochemical (3 + 2)-cycloaddition, a series of aryl- and ferrocenyl-functionalized enones **10b**–**10o** were also added to the study and examined in reaction with *N*-(*p*-tolyl) nitrile imine **1b**, selected as a handful ^{1}H NMR-diagnostic representative (Scheme 4). In general, the expected 5-acylpyrazolines **6i**–**6v** were obtained in moderate to high yields, although longer reaction times were required to lead the reaction to completion in most cases (Table 3). Thus, apart from halogens (Cl, Br) and haloalkyl units (additional CF_3 group at phenyl ring), alkylamino and alkoxy substituents, as well as a ferrocenyl moiety, could be introduced.

Similarly to the results collected for series **6/6′a**–**6/6′h** (Schemes 2 and 3, Table 2), (3 + 2)-cycloadditions of **1b** with selected chalcones **10b**–**10o** proceeded in a comparable



Scheme 4. Synthesis of 5-acyl-3-trifluoromethylpyrazolines **6i**–**6v** using *N*-(*p*-tolyl) nitrile imine generated in situ from hydrazonoyl bromide **9b**; scope of chalcones **10**.

Table 3. Mechanochemical (3 + 2)-cycloadditions of **10b**–**10o** with model nitrile imine **1b**.

Entry	Substrate	R	R′	Milling Time (h)	6:6′ Ratio (%) [1]	Yield of 6 (%) [2]

Table 3. Mechanochemical (3 + 2)-cycloadditions of **10b–10o** with model nitrile imine **1b**.

Entry	Substrate	R	R′	Milling Time (h)	6:6′ Ratio (%) [1]	Yield of 6 (%) [2]
1	**10b**	2-Nph [3]	Ph	9	77:23	**6i** (74)
2	**10c**	Fc [3]	Ph	24	85:15	**6j** (38)
3	**10d**	4-$MeOC_6H_4$	Ph	20	76:24	**6k** (59)
4	**10e**	3,4-$(MeO)_2C_6H_3$	Ph	18	100:0	**6l** (74)
5	**10f**	3,4-methylenedioxyphenyl	Ph	12	88:12	**6m** (68)
6	**10g**	4-$(Me_2N)C_6H_4$	Ph	36	65:35	**6n** (46)
7	**10h**	4-ClC_6H_4	Ph	9	79:21	**6o** (70)
8	**10i**	2-ClC_6H_4	Ph	10	77:23	**6p** (57)
9	**10j**	4-$CF_3C_6H_4$	Ph	9	71:29	**6q** (28)
10	**10k**	4-$NO_2C_6H_4$	Ph	28	73:27	**6r** (26)
11	**10l**	3-$NO_2C_6H_4$	Ph	72	79:21	**6s** (65)
12	**10m**	Ph	Fc [3]	24	71:29	**6t** (39)
13	**10n**	Ph	4-BrC_6H_4	16	85:15	**6u** (68)
14	**10o**	Ph	3,4-methylenedioxyphenyl	20	82:18	**6v** (81)

[1] Estimated based on ^{1}H NMR spectra of crude reaction mixtures; [2] Isolated yield; [3] 2-Nph = naphth-2-yl; Fc = ferrocenyl.

Similarly to the results collected for series **6/6′a–6/6′h** (Schemes 2 and 3, Table 2), (3 + 2)-cycloadditions of **1b** with selected chalcones **10b–10o** proceeded in a comparable regioselectivity of ca. 4:1 in favor of 5-acylpyrazolines **6**. Again, only *trans*-configured products could be detected in the mother liquors. Interestingly, in the case of 3,4-methylenedioxy-functionalized chalcone (**10f**) and 3,4-dimethoxy analogue (**10e**), exceptionally high selectivity (ca. 9:1) or exclusive formation of target 5-acylpyrazolines **6m** and **6l**, respectively, was observed. On the other hand, the reaction of **1b** with another electron-rich chalcone, namely 4-(dimethylamino)chalcone (**10g**), provided only the expected (3 + 2)-cycloadducts **6n** and **6′n** as a ca. 2:1 mixture. Possibly, the observed decrease of selectivity resulted from the presence of the basic Me_2N group in **10g**, which can compete with K_2CO_3 in dehydrohalogenation of **9b**, thereby changing the electronic properties of chalcone **10g**, due to protonation. The observed moderate yield in cycloadditions of **1b** with chalcones **10c** and **10m**, leading to pyrazolines **6j** (38%) and **6t** (39%), also deserves a brief comment. Seemingly, the presence of the redox-active Fc group alters the reaction outcome and leads to complex mixtures, irrespective of the substitution pattern in chalcone.

Prompted by the results disclosed in our recent work on the solvent-dependent oxidation of 5-benzoylpyrazolines [42], a series of 3-trifluoromethylated cycloadducts of type **6** were oxidized with an excess of activated MnO_2 under mechanochemical conditions. In a typical experiment, pyrazoline **6a** (1.0 mmol) was reacted with oxidant (activated MnO_2, ca. 85%, <10 μm, 40 equiv.) using zirconium oxide ball-milling equipment (ball, ø 10 mm; jar, 10 mL), at 25 Hz. After the reaction was complete (1.5 h), the resulting material was washed with AcOEt and filtered through a short silica gel pad, to give 1,5-diphenyl-3-trifluoromethylpyrazole (**8a**), isolated as a sole product in excellent purity and a yield of 97% (Scheme 5). The observed result for MnO_2-mediated mechanochemical deacylative oxidation nicely correspond to the recently reported aromatizative debenzoylation of **6a** carried out in non-polar solvents (i.e., hexane solutions). However, the latter protocol provided the final product **8a** after 2 days, by heating the reactants in organic medium at 60 °C [42].

Unfortunately, an attempted one-pot two-step synthesis of pyrazole **8a** was in vain. In the mentioned experiment, hydrazonoyl bromide **9a** and chalcone **10a** were mechanochemically reacted under the developed conditions (in the presence of K_2CO_3), followed by treatment of the resulting crude reaction mixture with excess activated MnO_2. To our surprise, none of the expected pyrazole **8a** was detected in the mixture, thus indicating the necessity of (at least partial) pre-purification of the intermediate 5-benzoylpyrazoline **6a**. Indeed, simple filtration of crude **6a** through a short silica gel pad enabled fast synthesis of desired material **8a**, which was isolated in a high 66% overall yield (for two steps).

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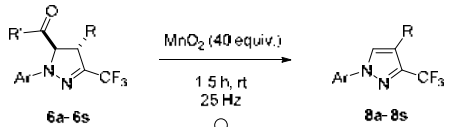
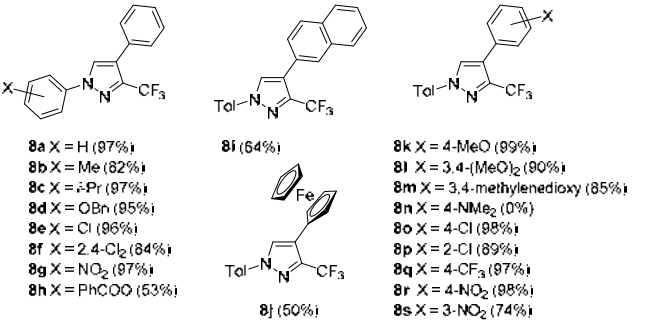
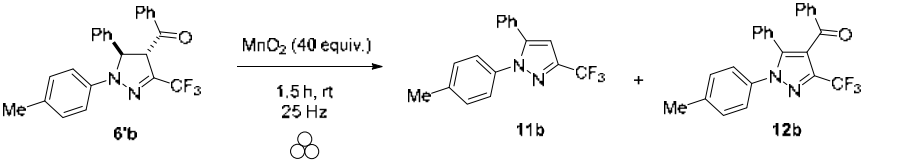




Scheme 5. Mechanochemical MnO_2-mediated deacylative oxidation of 5-acylpyrazolines **6a–6s**, leading to 1,4-diaryl-3-trifluoromethylpyrazoles **8a–8s**.

In continuation, a series of pyrazolines **6b–6s** was examined in reaction with MnO_2 under mechanochemical activation to afford the expected 1,4-diaryl-3-trifluoromethylpyrazoles **8b–8s** identified as the deacylated aromatization products, which were generally isolated in excellent yields. Only in the case of 4-benzoyloxy derivative (**6h**) and ferrocenyl-functionalized analogue (**6j**), either partial decomposition of the starting material or competitive oxidation leading to fully substituted analogue (**6h**, respectively, was observed, and moderate amounts of the final pyrazoles **8h** (53%) and **8j** (50%) were isolated). Surprisingly, the attempted oxidation of pyrazoline **6n** bearing Me_2N group resulted in complete decomposition of the starting material under the applied conditions.

In order to check the reaction outcome in mechanochemical oxidation of isomeric 4-acyl-pyrazolines of type **6′** (available as minor products in (3 + 2)-cycloaddition of nitrile imines **1** and chalcones **10**, a model *trans*-4-benzoyl-5-phenyl-1-*p*-tolyl-3-trifluoromethylpyrazoline (**6′b**) was also examined under analogous reaction conditions. As shown in Scheme 6, treatment of the starting material **6′b** with excess MnO_2 provided, after 1.5 h of milling, a mixture of two pyrazole-based products in ca. 2:3 ratio, and they were identified as 5-phenyl-1-*p*-tolyl-3-trifluoromethylpyrazole (**11b**, 38%) and its 4-benzoylated analogue **12b** (56%). This result indicates that, in contrast to 5-acylpyrazoline **6b**, ball-milling oxidation of its structural isomer 4-acylpyrazoline **6′b** proceeds in low chemoselectivity and leads to dehydrogenative oxidation of product **12b** as a major component of the mixture.



Scheme 6. Synthesis of pyrazoles **11b** and **12b** formed via competitive deacylative vs. dehydrogenative aromatization of 4-benzoylpyrazoline **6′b**.

Finally, to further check the scope, a series of non-fluorinated pyrazolines **13a–13g** were prepared and examined in a mechanochemical oxidation reaction with activated MnO_2. Following the general protocol, five nitrile imine precursors **14a–14e** bearing either phenyl group or selected electron-withdrawing substituents (COOEt, Ac) located at the

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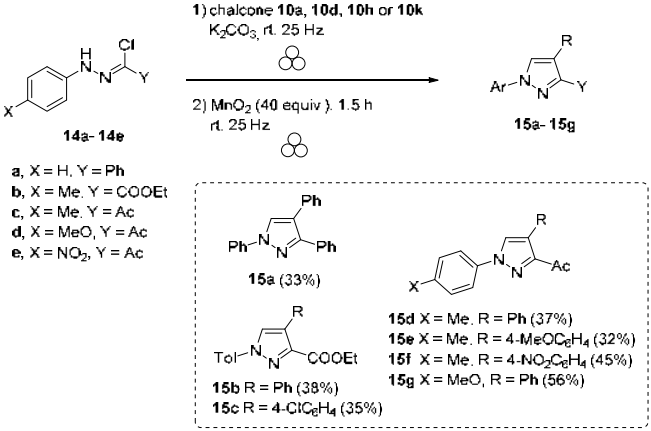

Scheme 7. Two-step synthesis of pyrazoles **15a–15g** using non-fluorinated nitrile imine precursors of type **14**.

It should be pointed out that all the presented deacylative oxidations of benzoyl-pyrazolines were performed using activated MnO_2 (≈85% purity, <10 µm, Sigma Aldrich, St. Louis, MO, USA), which was used as received. In order to gain a greater insight about the studied transformation, non-activated manganese dioxide (Reagent Plus®, ≥99%, Sigma Aldrich) was also tested, but in this case the deacylative aromatization could be observed only using 5-benzoylpyrazoline **6b** as a model compound. To test if hydroxyl radicals were involved in deacylative aromatization of **6b**, the latter experiment was repeated in the presence of trace amounts of water, but the reaction was not triggered. Finally, treatment of the resulting insoluble material formed in deacylative oxidation of **6b** with aqueous methanol released a colorless byproduct identified as benzoic acid. Based on these observations, the mechanism of the studied reaction is tentatively proposed. As depicted in Scheme 8, oxidation of **6b** proceeds preferentially at C(4), leading to fairly stable benzyl-type radical **A**. Then, the acyl group is transferred [48] from **A** onto the activated surface of the heterogeneous oxidant to give the aromatized product **8b** [49]. On the other hand, the presence of the benzoyl group at C(4) in isomeric pyrazoline **6'b** enhances the acidity of this position and thus, the oxidation may possibly be initiated either at C(4) or at C(5), leading to a mixture of products formed via competitive dehydrogenation vs. deacylative aromatization processes.

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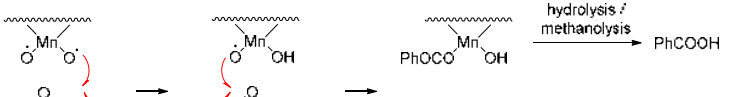

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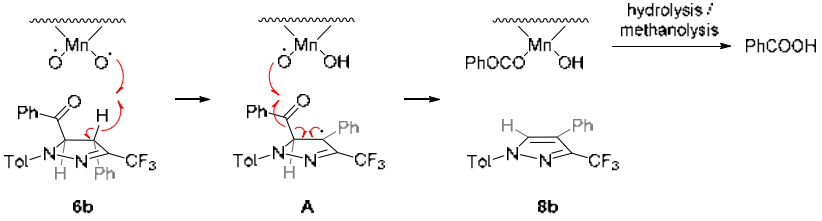

Scheme 5. Proposed mechanism of deacylative oxidation of 5(4*H*)-acylpyrazolines.

3. Materials and Methods

3.1. Chemical Synthesis General Methods

Experimental procedures: The ball-milling apparatus used was a Retsch MM 400 mixer mill (Retsch GmbH, Haan, Germany). Mechanochemical (3 + 2)-cycloadditions were performed in 5 mL stainless steel jars, with three stainless steel balls (7 mm diameter); oxidation reactions were conducted in 10 mL zirconium oxide jars, with one zirconium oxide ball (10 mm diameter). Solvents (hexane, CH_2Cl_2, AcOEt) were purchased and used as received. Products were purified by filtration through a short silica gel plug or by standard column chromatography (CC) on silica gel (230–400 mesh; Merck, Kenilworth, NJ, USA). The NMR spectra were taken on a Bruker AVIII instrument (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz) (Bruker BioSpin AG, Fällanden, Switzerland). Chemical shifts are reported relative to solvent residual peaks; for $CDCl_3$: ^{1}H NMR: δ = 7.26, ^{13}C NMR: δ = 77.16, or to $CFCl_3$ (^{19}F NMR: δ = 0.00) used as an external standard. Multiplicity of the signals in ^{13}C NMR spectra were deduced based on supplementary 2D measurements (HMQC, HMBC). The IR spectra were measured with an Agilent Cary 630 FTIR spectrometer (Agilent Technologies, Santa Clara, CA, USA), in neat. MS (ESI) were performed with a Varian 500-MS LC Ion Trap (Varian, Inc., Walnut Creek, CA, USA), while high resolution MS (ESI-TOF) measurements were taken with a Waters Synapt G2-Si mass spectrometer (Waters Corporation, Milford, MA, USA). Elemental analyses were performed with a Vario EL III (Elementar Analysensysteme GmbH, Langenselbold, Germany) instrument. Melting points were determined in capillaries with a MEL-TEMP apparatus (Laboratory Devices, Holliston, MA, USA) and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra of all new compounds can be found at Supplementary Materials file.

Starting materials: The CF_3-nitrile imine precursors of type **9** were prepared by bromination of the corresponding trifluoroacetaldehyde arylhydrazones with NBS, according to the general protocol [43]. The required fluoral hydrazones were synthesized following the general literature procedure by condensation of aqueous fluoral hydrate (~75% in H_2O) with commercial arylhydrazines [46]. Non-fluorinated hydrazonoyl chlorides **14a**–**14e** were prepared as previously reported [44,45]. Chalcones **10** were purchased or prepared via classical Claisen–Schmidt condensation, starting with appropriate aldehydes and methyl ketones, in ethanol. Activated MnO_2 (ca. 85%, <10 μm, Sigma-Aldrich, product no. 217646-100G), as well as the other commercially available solvents and starting materials, were purchased and used as received.

3.1.1. General Procedure for Mechanochemical Synthesis of Pyrazolines **6**, **6′**, and **13**

Hydrazonoyl halide **9** or **14** (1.2 mmol), chalcone **10** (1.0 mmol), and solid K_2CO_3 (1.3 mmol, 179 mg) were placed in a 5 mL stainless steel grinding jar with three stainless steel balls (7 mm diameter). The jar was closed and ball-milled at 25 Hz until the starting chalcone was fully consumed. Then, CH_2Cl_2 (10 mL) was added, the precipitate was filtered off, washed with CH_2Cl_2 (2 × 10 mL), and the solvent was removed under vacuum. The crude product of type **6** or **13** was purified by standard column chromatography (CC) or pre-purified by flash column chromatography (FCC) on silica. The structures of known pyrazolines **6c**–**6k**, **6o**, **6q**, **6r**, **6t**–**6v** were confirmed based on ^{1}H NMR spectra

supplemented by ESI-MS measurements and by comparison with original samples [42]; the byproducts **6′c–6′v** were not isolated. In the case of non-fluorinated analogues, crude pyrazolines **13a,13d–13g** were pre-purified by FCC and used for the next step, without further purification.

trans-5-Benzoyl-1,4-diphenyl-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6a**) [50]: light yellow solid, 296 mg (75%), mp 159–161 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.37 (dq, $^4J_{H\text{-}F} \approx 0.9$ Hz, $J_{H\text{-}H}$ = 5.6 Hz, 1H, 4-H), 5.76 (d, $J_{H\text{-}H}$ = 5.6 Hz, 1H, 5-H), 6.94–7.06, 7.19–7.29, 7.39–7.44, 7.48–7.52, 7.65–7.68, 7.87–7.89 (6m, 3H, 4H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.6, 74.3, 113.8, 120.9 (q, $^1J_{C\text{-}F}$ = 270.6 Hz, CF_3), 121.6, 127.7, 128.9, 129.2, 129.3, 129.5, 129.7, 133.1, 134.7, 137.5, 138.1 (q, $^2J_{C\text{-}F}$ = 37.0 Hz, C-3), 142.7, 192.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ −63.0 (s_{br}, CF_3). ESI-MS (*m*/*z*) 417.2 (100, $[M + Na]^+$).

trans-4-Benzoyl-1,5-diphenyl-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6′a**): obtained as a minor product in the reaction of **9a** with **10a**; yellow solid, 51 mg (13%), mp 125–126 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.04 (d_{br}, $J_{H\text{-}H} \approx 7.3$ Hz, 1H, 4-H), 5.65 (d, $J_{H\text{-}H}$ = 7.3 Hz, 1H, 5-H), 6.88–6.91, 7.03–7.06, 7.17–7.20, 7.23–7.25, 7.33–7.40, 7.48–7.51, 7.63–7.66, 7.88–7.90 (8m, 1H, 2H, 2H, 2H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 61.2, 71.0, 114.8, 120.9 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 121.7, 126.0, 128.9, 129.14, 129.15, 129.16, 129.8, 133.5 (q, $^2J_{C\text{-}F}$ = 38.0 Hz, C-3), 134.5, 135.5, 139.6, 142.6, 194.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ −63.1 (s, CF_3). IR (neat) υ 1677, 1595, 1577, 1301, 1264, 1208, 1148, 1118, 1066 cm^{-1}. ESI-MS (*m*/*z*) 417.1 (31, $[M + Na]^+$), 395.2 (100, $[M + H]^+$).

trans-5-Benzoyl-1-(p-tolyl)-4-phenyl-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6b**) [51]: light yellow solid, 286 mg (70%), mp 145–147 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30 (s, 3H, Me), 4.38 (dq, $^4J_{H\text{-}F} \approx 1.0$ Hz, $J_{H\text{-}H} \approx 5.7$ Hz, 1H, 4-H), 5.78 (d_{br}, $J \approx 5.7$ Hz, 1H, 5-H), 6.97, 7.09 (2d, J = 8.6 Hz, 2H each), 7.21–7.25, 7.40–7.52, 7.66–7.69, 7.88–7.91 (4m, 2H, 5H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.6, 74.6, 113.9, 121.0 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 127.5, 129.0, 129.1, 129.3, 129.7, 130.0, 130.9, 133.2, 134.6, 137.4 (q, $^2J_{C\text{-}F}$ = 36.8 Hz, C-3), 137.6, 140.5, 192.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ −63.1 (s, CF_3). ESI-MS (*m*/*z*) 431.2 (100, $[M + Na]^+$).

trans-4-Benzoyl-1-(p-tolyl)-5-phenyl-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6′b**): obtained as a minor product in the reaction of **9b** with **10a**; thick yellow oil, 53 mg (13%). ^{1} H NMR (600 MHz, $CDCl_3$) δ 2.23 (s, 3H, Me), 5.04 (dq_{br}, $^4J_{H\text{-}F} \approx 1.6$ Hz, $J_{H\text{-}H} \approx 7.5$ Hz, 1H, 4-H), 5.64 (d, $J_{H\text{-}H} \approx 7.5$ Hz, 1H, 5-H), 6.93–7.00, 7.22–7.25, 7.32–7.39, 7.47–7.50, 7.63–7.66, 7.87–7.90 (6m, 4H, 2H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 61.1, 71.2, 114.8, 121.0 (q, $^1J_{C\text{-}F}$ = 269.5 Hz, CF_3), 126.1, 128.8, 129.12, 129.14, 129.7, 129.8, 131.2, 132.8 (q, $^2J_{C\text{-}F}$ = 37.9 Hz, C-3), 134.5, 135.4, 139.7, 140.3, 194.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ −63.0 (s, CF_3). IR (neat) υ 1752, 1662, 1495, 1446, 1260, 1219, 1163, 1133 cm^{-1}. ESI-MS (*m*/*z*) 431.4 (100, $[M + Na]^+$), 409.5 (39, $[M + H]^+$). Anal. Calcd for $C_{24}H_{19}F_3N_2O$ (408.1): C 70.58, H 4.69, N 6.86; found: C 70.49, H 4.69, N 6.89.

trans-5-Benzoyl-4-(3′,4′-dimethoxyphenyl)-1-(p-tolyl)-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6l**): light yellow solid, 347 mg (74%), mp 122–123 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me), 3.81, 3.91 (2s, 3H each, 2OMe), 4.33 (d_{br}, $J \approx 5.9$ Hz, 1H, 4-H), 5.73 (d, J = 5.9 Hz, 1H, 5-H), 6.65 (d, J = 2.1 Hz, 1H), 6.76 (dd, J = 2.1, 8.2 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1 H), 6.91–6.93, 7.05–7.08, 7.48–7.51, 7.64–7.68, 7.87–7.90 (5m, 2H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.4, 56.1, 56.2, 74.5, 110.4, 111.8, 113.9, 120.2, 121.0 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 129.3 *, 129.8, 130.0, 131.0, 133.2, 134.6, 137.4 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3), 140.5, 149.5, 149.8, 192.4; * higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.2 (s, CF_3). IR (neat) υ 1695, 1595, 1513, 1450, 1293, 1230, 1118 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{24}F_3N_2O_3$ 469.1739, found 469.1743.

trans-5-Benzoyl-4-(3′,4′-methylenedioxyphenyl)-1-(p-tolyl)-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6m**): pale yellow solid, 307 mg (68%), mp 125–126 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 4.31 (d_{br}, $J \approx 5.5$ Hz, 1H, 4-H), 5.73 (d, J = 5.5 Hz, 1H, 5-H), 6.01 (AB system, J = 4.8 Hz, 2H, OCH_2O), 6.66–6.69 (m, 2H), 6.82 (d, J = 7.8 Hz, 1H), 6.92–6.94, 7.07–7.09, 7.50–7.54, 7.66–7.69, 7.90–7.92 (5m, 2H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 55.3, 74.4, 101.7, 107.6, 109.0, 113.8, 121.0 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 121.9, 129.2, 129.3, 130.0, 131.0, 131.2, 133.1, 134.6, 137.5 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, C-3), 140.4, 148.2,

148.9, 192.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s, CF_3). IR (neat) v 1685, 1595, 1517, 1446, 1245, 1118 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{20}F_3N_2O_3$ 453.1426, found 453.1427.

trans-5-Benzoyl-4-(4′-dimethylaminophenyl)-1-(p-tolyl)-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6n**): orange solid, 208 mg (46%), mp 163–165 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me), 2.99 (s, 6H, 2Me), 4.30 (d_{br}, $J \approx 5.5$ Hz, 1H, 4-H), 5.69 (d, J = 5.5 Hz, 1H, 5-H), 6.69–6.72, 6.90–6.92, 7.03–7.07, 7.47–7.51, 7.64–7.66, 7.89–7.91 (6m, 2H, 2H, 4H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 40.5, 55.1, 74.7, 112.9, 113.7, 121.1 (q, $^1J_{C\text{-}F}$ = 270.5 Hz, CF_3), 124.6, 128.5, 129.22, 129.25, 130.0, 130.6, 133.3, 134.4, 138.1 (q, $^2J_{C\text{-}F}$ = 36.2 Hz, C-3), 140.7, 150.7, 192.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.3 (s, CF_3). IR (neat) v 1696, 1595, 1517, 1297, 1230, 1185, 1118, 1066 cm^{-1}. ESI-MS (m/z) 474.4 (100, $[M + Na]^+$), 452.4 (97, $[M + H]^+$). Anal. Calcd for $C_{26}H_{24}F_3N_3O$ (451.2): C 69.17, H 5.36, N 9.31; found: C 69.11, H 5.26, N 9.30.

trans-5-Benzoyl-4-(2′-chlorophenyl)-1-(p-tolyl)-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6p**): thick light orange oil, 252 mg (57%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 5.10 (s_{br}, 1H, 4-H), 5.76 (s_{br}, 1H, 5-H), 6.93–6.95, 7.06–7.09, 7.25–7.36, 7.43–7.50, 7.64–7.67, 7.84–7.88 (6m, 2H, 2H, 3H, 3H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 50.9(br), 74.0(br), 113.9, 120.8 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 128.4(br), 129.1, 129.2 *, 130.0, 130.2, 130.4(br), 131.2, 133.2(br), 136.6, 135.3(br), 136.8 (q_{br}, $^2J_{C\text{-}F} \approx 37.0$ Hz, C-3), 140.4, 192.6; *higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.6 (s, CF_3). IR (neat) v 1692, 1599, 1517, 1297, 1230, 1118, 1066 cm^{-1}. ESI-MS (m/z) 465.4 (100, $[M + Na]^+$), 443.5 (83, $[M + H]^+$). Anal. Calcd for $C_{24}H_{18}F_3N_2O$ (442.1): C 65.09, H 4.10, N 6.33; found: C 65.00, H 4.02, N 6.14.

trans-5-Benzoyl-4-(3′-nitrophenyl)-1-(p-tolyl)-3-trifluoromethyl-4,5-dihydro-1H-pyrazole (**6s**): light yellow solid, 295 mg (65%), mp 170–172 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 4.50 (d_{br}, $J \approx 5.6$ Hz, 1H, 4-H), 5.75 (d, J = 5.6 Hz, 1H, 5-H), 6.93–6.95, 7.07–7.09, 7.50–7.54 (3m, 2H, 2H, 2H), 7.55 (dt, J = 1.4, 7.8 Hz, 1H), 7.62–7.65, 7.68–7.71, 7.85–7.87 (3m, 1H, 1H, 2H), 8.07 (pseudo-t, $J \approx 2.0$ Hz, 1H), 8.28 (ddd, J = 1.1, 2.2, 8.2 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.7, 54.8, 74.1, 114.1, 120.8 (q, $^1J_{C\text{-}F}$ = 270.2 Hz, CF_3), 122.7, 124.1, 129.1, 129.6, 130.1, 131.0, 131.7, 132.9, 133.6, 135.0, 136.1 (q, $^2J_{C\text{-}F}$ = 37.3 Hz, C-3), 139.5, 140.0, 149.0, 191.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.2 (s, CF_3). IR (neat) v 1689, 1595, 1536, 1353, 1297, 1230, 1152, 1122, 1070 cm^{-1}. ESI-MS (m/z) 476.4 (100, $[M + Na]^+$), 454.4 (50, $[M + H]^+$). Anal. Calcd for $C_{24}H_{18}F_3N_3O_3$ (453.1): C 63.58, H 4.00, N 9.27; found: C 63.49, H 4.04, N 9.29.

Ethyl trans-5-benzoyl-4-phenyl-1-(p-tolyl)-4,5-dihydro-1H-pyrazole-3-carboxylate (**13b**): light yellow solid, 234 mg (57%), mp 133–134 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3H, Et), 2.28 (s, 3H, Me), 4.13 (dq, J = 7.1, 10.9 Hz, 1H, Et), 4.20 (dq, J = 7.1, 10.9 Hz, 1H, Et), 4.46 (d, J = 4.9 Hz, 1H, 4-H), 5.79 (d, J = 4.9 Hz, 1H, 5-H), 7.02–7.09, 7.21–7.23, 7.34–7.40, 7.49–7.52, 7.65–7.67, 7.90–7.92 (6m, 4H, 2H, 3H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.2, 20.7, 55.4, 61.2, 74.3, 114.4, 127.5, 128.4, 129.2, 129.3, 129.5, 130.0, 131.4, 133.1, 134.5, 139.4, 139.98, 139.99, 161.8, 192.1. IR (neat) v 1696, 1513, 1279, 1219, 1152, 1100, 1014 cm^{-1}. ESI-MS (m/z) 435.4 (100, $[M + Na]^+$), 413.4 (31, $[M + H]^+$). Anal. Calcd for $C_{26}H_{24}N_2O_3$ (412.2): C 75.71, H 5.86, N 6.79; found: C 75.71, H 6.04, N 6.80.

Ethyl trans-5-benzoyl-4-(4′-chlorophenyl)-1-(p-tolyl)-4,5-dihydro-1H-pyrazole-3-carboxylate (**13c**): yellow solid, 245 mg (55%), mp 157–159 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H, Et), 2.27 (s, 3H, Me), 4.14 (dq, J = 7.1, 10.9 Hz, 1H, Et), 4.21 (dq, J = 7.1, 10.9 Hz, 1H, Et), 4.42 (d, J = 5.0 Hz, 1H, 4-H), 5.74 (d, J = 5.0 Hz, 1H, 5-H), 7.00–7.03, 7.07–7.09, 7.14–7.16, 7.34–7.36, 7.49–7.53, 7.66–7.69, 7.87–7.89 (7m, 2H, 2H 2H, 2H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.3, 20.8, 54.8, 61.3, 74.1, 114.4, 128.9, 129.1, 129.4, 129.7, 130.0, 131.7, 133.0, 134.4, 134.7, 138.0, 139.5, 139.8, 161.7, 191.8. ESI-MS (m/z) 469.4 (100, $[M + Na]^+$), 447.4 (63, $[M + H]^+$). Anal. Calcd for $C_{26}H_{23}ClN_2O_3$ (446.1): C 69.87, H 5.19, N 6.27; found: C 69.72, H 5.04, N 6.01.

3.1.2. General Procedure for Oxidation Reactions with Activated Manganese Dioxide

5-Acylpyrazoline of type **6** or **13** (1.0 mmol) and activated MnO_2 (40 mmol, 4.09 g) were placed in a 10 mL zirconium oxide grinding jar with one zirconium oxide ball (10 mm

diameter). The jar was closed and subjected to grinding for 1.5 h in a vibratory ball-mill operated at 25Hz. After AcOEt (20 mL) was added, the resulting mixture was filtered through a thin pad of silica gel and the solvent was evaporated to give pyrazole **8** or **15**. In the case of 4-benzoylpyrazoline **6′b**, the resulting products **11b** and **12b** were purified using standard column chromatography (SiO_2). The structure of known fluorinated pyrazoles, i.e., **8a**–**8k**, **8n**, **8q**, and **8r** were confirmed based on ^{1}H NMR spectra and by comparison with the original samples [42].

4-(3′,4′-Dimethoxyphenyl)-1-(p-tolyl)-3-trifluoromethylpyrazole (**8l**): colorless solid, 326 mg (90%), mp 129–130 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 3.898, 3.901 (2s, 3H each, 2OMe), 6.88–6.91, 6.99–7.03, 7.25–7.27, 7.58–7.60 (4m, 1H, 2H, 2H, 2H), 7.93 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.0, 55.90, 55.91, 111.3, 112.0, 119.6, 120.9, 121.8 (q, $^1J_{C\text{-}F}$ = 269.7 Hz, CF_3), 122.9, 123.5(br), 127.3, 130.2, 137.0, 137.8, 139.9 (q, $^2J_{C\text{-}F}$ = 36.4 Hz, C-3), 148.9*; *higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.3 (s, CF_3). IR (neat) v 1491, 1241, 1163, 1118 cm^{-1}. (–)-ESI-MS (m/z) 361.4 (100, [M–H]$^-$). Anal. Calcd for $C_{19}H_{17}F_3N_2O_2$ (362.1): C 62.98, H 4.73, N 7.73; found: C 63.00, H 4.69, N 7.44.

4-(3′,4′-Methylenedioxyphenyl)-1-(p-tolyl)-3-trifluoromethylpyrazole (**8m**): colorless solid, 294 mg (85%), mp 99–100 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40 (s, 3H, Me), 6.00 (s, 2H, OCH_2O), 6.85–6.87, 6.93–6.95, 7.27–7.29, 7.59–7.61 (4m, 1H, 2H, 2H, 2H), 7.90 (s_{br}, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.1, 101.4, 108.5, 109.3, 119.7, 121.7 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 122.4(br), 123.4(br), 127.5, 130.2, 137.1, 137.9, 140.0 (q, $^2J_{C\text{-}F}$ = 36.5 Hz, C-3), 147.6, 147.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.4 (s, CF_3). IR (neat) v 1480, 1223, 1167, 1118, 1036 cm^{-1}. ESI-MS (m/z) 369.4 (100, [M + Na]$^+$), 347.4 (76, [M + H]$^+$). Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$ (346.1): C 62.43, H 3.78, N 8.09; found: C 62.60, H 3.92, N 8.08.

4-(2′-Chlorophenyl)-1-(p-tolyl)-3-trifluoromethylpyrazole (**8p**): thick light yellow oil, 299 mg (89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H, Me), 7.29–7.36, 7.40–7.42, 7.48–7.51, 7.62–7.65 (4m, 4H, 1H, 1H, 2H), 7.99 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.1, 119.7(br), 119.8, 121.4 (q, $^1J_{C\text{-}F}$ = 270.1 Hz, CF_3), 126.7, 128.8, 129.5, 129.7, 129.8, 130.3, 132.2(br), 134.1, 137.1, 138.0, 141.3 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3). ^{19}F NMR (565 MHz, $CDCl_3$) δ −60.0 (s, CF_3). IR (neat) v 1521, 1495, 1290, 1223, 1170, 1116, 1062 cm^{-1}. ESI-MS (m/z) 359.3 (23, [M + Na]$^+$), 337.3 (100, [M + H]$^+$). Anal. Calcd for $C_{17}H_{12}ClF_3N_2$ (336.1): C 60.64, H 3.59, N 8.32; found: C 60.51, H 3.39, N 8.47.

4-(3′-Nitrophenyl)-1-(p-tolyl)-3-trifluoromethylpyrazole (**8s**): colorless solid, 257 mg (74%), mp 147–148 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.43 (s, 3H, Me), 7.31–7.33, 7.61–7.64, 7.82–7.84 (3m, 2H, 3H, 1H), 8.08 (s, 1H, 5-H), 8.24 (ddd, J = 1.0, 2.3, 8.2 Hz, 1H), 8.34 (pseudo-t, $J \approx$ 2.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 119.9, 121.3(br), 121.5 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 122.9, 123.6, 128.0, 129.8, 130.4, 132.2, 134.8(br), 136.8, 138.5, 140.2 (q, $^2J_{C\text{-}F}$ = 37.1 Hz, C-3), 148.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ −59.4 (s, CF_3). IR (neat) v 1521, 1349, 1282, 1226, 1170, 1118, 1074 cm^{-1}. ESI-MS (m/z) 370.3 (100, [M + Na]$^+$), 348.3 (70, [M + H]$^+$). Anal. Calcd for $C_{17}H_{12}F_3N_3O_2$ (347.1): C 58.79, H 3.48, N 12.10; found: C 58.85, H 3.51, N 12.08.

5-Phenyl-1-(p-tolyl)-3-trifluoromethylpyrazole (**11b**) [34]: obtained as a minor product in oxidation of **6′b**; light yellow solid, 114 mg (38%), mp 74–76 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H, Me), 6.74 (s_{br}, 1H, 4-H), 7.14–7.24, 7.30–7.36 (2m, 6H, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.3, 105.5, 121.5 (q, $^1J_{C\text{-}F}$ = 268.8 Hz, CF_3), 125.5, 128.8, 128.95, 129.02, 129.5(br), 129.8, 137.0, 138.6, 143.2 (q, $^2J_{C\text{-}F}$ = 38.3 Hz, C-3), 144.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.2 (s, CF_3). IR (neat) v 1454, 1230, 1129, 1073 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{14}F_3N_2$ 303.1109, found 303.1104.

4-Benzoyl-5-phenyl-1-(p-tolyl)-3-trifluoromethylpyrazole (**12b**): colorless solid, 228 mg (56%), mp 139–140 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H, Me), 7.07–7.10, 7.13–7.21, 7.28–7.32, 7.43–7.46, 7.72–7.74 (5m, 2H, 7H, 2H, 1H, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.3, 119.8(br), 121.0 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 125.4, 127.9, 128.4, 128.7, 129.5, 129.8, 129.9, 130.1, 133.5, 136.3, 137.5, 139.0, 141.5 (q, $^2J_{C\text{-}F}$ = 37.9 Hz, C-3), 144.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ −60.3 (s, CF_3). IR (neat) v 1659, 1484, 1443, 1223, 1156, 1129, 1059 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{18}F_3N_2O$ 407.1371, found 407.1369.

1,3,4-Triphenylpyrazole (**15a**) [52]: light yellow solid, 97 mg (33%; for two steps, starting with 1.0 mmol of chalcone **10a** and chloride **14a**), mp 96–98 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29–7.37, 7.47–7.50, 7.60–7.62, 7.80–7.82 (4m, 9H, 2H, 2H, 2H), 8.03 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 119.1, 123.1, 126.6, 126.8, 127.1, 128.1, 128.5, 128.6, 128.7, 128.9, 129.6, 133.0, 133.3, 140.1, 150.6. IR (neat) υ 1722, 1599, 1502, 1401, 1215, 1059 cm^{-1}. ESI-MS (m/z) 297.3 (100, $[M + H]^+$).

Ethyl 4-phenyl-1-(p-tolyl)-pyrazole-3-carboxylate (**15b**): colorless solid, 205 mg (67%), mp 99–102 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H, Et), 2.41 (s, 3H, Me), 4.37 (q, J = 7.1 Hz, 2H, Et), 7.27–7.29, 7.33–7.37, 7.39–7.42, 7.51–7.53, 7.64–7.66 (5m, 2H, 1H, 2H, 2H, 2H), 7.93 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.3, 21.2, 61.2, 120.1, 127.5, 127.7, 127.8, 128.2, 129.5, 130.2, 131.7, 137.4, 137.8, 141.2, 162.7. IR (neat) υ 1722, 1610, 1517, 1465, 1279, 1226, 1141 cm^{-1}. ESI-MS (m/z) 329.2 (25, $[M + Na]^+$), 307.2 (100, $[M + H]^+$). Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306.1): C 74.49, H 5.92, N 9.14; found: C 74.47, H 6.00, N 9.21.

Ethyl 4-(4′-chlorophenyl)-1-(p-tolyl)-pyrazole-3-carboxylate (**15c**): colorless solid, 218 mg (64%), mp 136–137 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H, Et), 2.41 (s, 3H, Me), 4.38 (q, J = 7.1 Hz, 2H, Et), 7.27–7.29, 7.36–7.38, 7.45–7.47, 7.63–7.66 (4m, 2H, 2H, 2H, 2H), 7.92 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.4, 21.2, 61.3, 120.1, 126.4, 127.8, 128.4, 130.18, 130.20, 133.7, 137.2, 138.0, 141.1, 162.5. IR (neat) υ 1707, 1476, 1442, 1349, 1282, 1226, 1156, 1107, 1077, 1033 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}ClN_2O_2$ 341.1057, found 341.1063.

3-Acetyl-4-phenyl-1-(p-tolyl)-pyrazole (**15d**): colorless solid, 102 mg (37%; for two steps, starting with 1.0 mmol of chalcone **10a** and chloride **14c**), mp 137–139 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H, Me), 2.69 (s, 3H, Ac), 7.29–7.35, 7.38–7.41, 7.55–7.57, 7.65–7.67 (4m, 3H, 2H, 2H, 2H), 7.94 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 28.1, 119.6, 126.4, 127.7, 127.9, 128.3, 129.4, 130.3, 131.7, 137.4, 137.8, 137.6, 194.8. IR (neat) υ 1681, 1517, 1349, 1219, 1111 cm^{-1}. ESI-MS (m/z) 299.3 (100, $[M + Na]^+$), 277.3 (87, $[M + H]^+$). Anal. Calcd for $C_{18}H_{16}N_2O$ (276.1): C 78.24, H 5.84, N 10.14; found: C 78.01, H 5.82, N 10.00.

3-Acetyl-4-(4′-methoxyphenyl)-1-(p-tolyl)-pyrazole (**15e**): light brown solid, 98 mg (32%; for two steps, starting with 1.0 mmol of chalcone **10d** and chloride **14c**), mp 108–109 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H, Me), 2.68 (s, 3H, Ac), 3.84 (s, 3H, OMe), 6.92–6.95, 7.29–7.32, 7.49–7.52, 7.64–7.67 (4m, 2H each), 7.89 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 28.1, 55.5, 113.8, 119.6, 124.1, 126.1, 127.5, 130.3, 130.6, 137.5, 137.7, 147.6, 159.3, 194.8. IR (neat) υ 1692, 1551, 1498, 1450, 1387, 1346, 1249, 1182, 1107, 1029 cm^{-1}. ESI-MS (m/z) 329.1 (100, $[M + Na]^+$), 307.2 (71, $[M + H]^+$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1445.

3-Acetyl-4-(4′-nitrophenyl)-1-(p-tolyl)-pyrazole (**15f**): light yellow solid, 144 mg (45%; for two steps, starting with 1.0 mmol of chalcone **10h** and chloride **14c**), mp 191–192 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.44 (s, 3H, Me), 2.72 (s, 3H, Ac), 7.32–7.34, 7.65–7.67, 7.73–7.75 (3m, 2H each), 8.02 (s, 1H, 5-H), 8.23–8.25 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2, 27.9, 119.8, 123.5, 124.2, 128.4, 130.1, 130.4, 137.1, 138.4, 138.7, 147.2, 147.6, 194.7. IR (neat) υ 1692, 1603, 1502, 1334, 1215, 1103, 1073 cm^{-1}. ESI-MS (m/z) 344.9 (100, $[M + Na]^+$). Anal. Calcd for $C_{18}H_{15}N_3O_3$ (321.1): C 67.28, H 4.71, N 13.08; found: C 67.35, H 4.93, N 12.95.

3-Acetyl-1-(4′-methoxyphenyl)-4-phenylpyrazole (**15g**): orange solid, 163 mg (56%; for two steps, starting with 1.0 mmol of chalcone **10a** and chloride **14d**), mp 109–111 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.69 (s, 3H, Ac), 3.87 (s, 3H, OMe), 7.00–7.03, 7.32–7.35, 7.38–7.41, 7.55–7.57, 7.67–7.70 (5m, 2H, 1H, 2H, 2H, 2H), 7.88 (s, 1H, 5-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.0, 55.7, 114.8, 121.3, 126.3, 127.6, 128.0, 128.2, 129.3, 131.7, 133.3, 147.5, 159.2, 194.6. IR (neat) υ 1685, 1513, 1466, 1353, 1260, 1221, 1174, 1118, 1029 cm^{-1}. ESI-MS (m/z) 315.1 (92, $[M + Na]^+$), 293.2 (100, $[M + H]^+$). Anal. Calcd for $C_{18}H_{16}N_2O_2$ (292.1): C 73.95, H 5.52, N 9.58; found: C 73.99, H 5.74, N 9.49.

4. Conclusions

In summary, a solvent-free two-step mechanochemical synthesis of trifluoromethylated and non-fluorinated polysubstituted pyrazoles was developed, starting with simple substrates, i.e., chalcones and hydrazonoyl halides. The latter served as precursors for the K_2CO_3-induced in situ generation of nitrile imines, which were efficiently trapped with chalcones, to give the respective (3 + 2)-cycloadducts in moderate to high regioselectivity and fair yields. The first formed *trans*-configured 5-acylpyrazolines were oxidized with activated manganese dioxide under ball-milling to afford pyrazoles, formed through exclusive deacylative aromatization of the ring. Based on additional experiments, a mechanistic scenario comprising acyl-transfer onto the surface of heterogeneous oxidant was proposed. The presented results extend the scope of the previously reported method for the synthesis of the title compounds in organic solvents [42] and supplements recent developments, both in the synthesis of pyrazoles [2,53–55] and the application of nitrile imines as building blocks for organic synthesis [17,34–45,56–59].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27238446/s1: Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all new compounds.

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References

1. Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to mid-2010: A fruitful decade for the synthesis of pyrazoles. *Chem. Rev.* **2011**, *111*, 6984–7034. [CrossRef] [PubMed]
2. Mykhailiuk, P.K. Fluorinated pyrazoles: From synthesis to applications. *Chem. Rev.* **2021**, *121*, 1670–1715. [CrossRef] [PubMed]
3. Raffa, D.; Maggio, B.; Raimondi, M.V.; Cascioferro, S.; Plescia, F.; Cancemi, G.; Daidone, G. Recent advanced in bioactive systems containing pyrazole fused with a five membered heterocycle. *Eur. J. Med. Chem.* **2015**, *97*, 732–746. [CrossRef]
4. Janin, Y.L. Preparation and chemistry of 3/5-halogenopyrazoles. *Chem. Rev.* **2012**, *112*, 3924–3958. [CrossRef]
5. Li, M.; Zhao, B.X. Progress of the synthesis of condensed pyrazole derivatives (from 2010 to mid-2013). *Eur. J. Med. Chem.* **2014**, *85*, 311–340. [CrossRef]
6. Abrigach, F.; Touzani, R. Pyrazole derivatives with NCN junction and their biological activity: A review. *Med. Chem.* **2016**, *6*, 292–298. [CrossRef]
7. Faria, J.V.; Vegi, P.F.; Miguita, A.G.C.; Silva dos Santos, M.; Boechat, N.; Bernardino, A.M.R. Recently reported biological activities of pyrazole compounds. *Bioorg. Med. Chem.* **2017**, *25*, 5891–5903. [CrossRef]
8. Kumar, V.; Kaur, K.; Gupta, G.K.; Sharma, A.K. Pyrazole containing natural products: Synthetic preview and biological significance. *Eur. J. Med. Chem.* **2013**, *69*, 735–753. [CrossRef]
9. El-Gamal, M.; Zaraei, S.-O.; Madkour, M.M.; Anbar, H.S. Evaluation of substituted pyrazole-based kinase inhibitors in one decade (2011–2020): Current status and future prospects. *Molecules* **2022**, *27*, 330. [CrossRef]
10. Li, X.; Yu, Y.; Tu, Z. Pyrazole scaffold synthesis, functionalization, and applications in Alzheimer's disease and Parkinson's disease treatment (2011–2020). *Molecules* **2021**, *26*, 1202. [CrossRef]
11. Asproni, B.; Murineddu, G.; Corona, P.; Pinna, G.A. Tricyclic pyrazole-based compounds as useful scaffolds for cannabinoid CB1/CB2 receptor interaction. *Molecules* **2021**, *26*, 2126. [CrossRef] [PubMed]
12. Santos, N.E.; Carreira, A.R.F.; Silva, V.L.M.; Braga, S.S. Natural and biomimetic antitumor pyrazoles, a perspective. *Molecules* **2020**, *25*, 1364. [CrossRef] [PubMed]
13. Gomes, P.M.O.; Silva, A.M.S.; Silva, V.L.M. Pyrazoles as key scaffolds for the development of fluorine-18-labeled radiotracers for positron emission tomography (PET). *Molecules* **2020**, *25*, 1722. [CrossRef] [PubMed]

14. Elnagdy, H.M.F.; Chetia, T.; Dehingia, N.; Chetia, B.; Dutta, P.; Sarma, D. Sensing and optical activities of new pyrazole containing polymeric analogues. *Bull. Mater. Sci.* **2022**, *45*, 86. [CrossRef]
15. Cavero, E.; Uriel, S.; Romero, P.; Serrano, J.L.; Giménez, R. Tetrahedral zinc complexes with liquid crystalline and luminescent properties: Interplay between nonconventional molecular shapes and supramolecular mesomorphic order. *J. Am. Chem. Soc.* **2007**, *129*, 11608–11618. [CrossRef] [PubMed]
16. Trofimenko, S. Coordination chemistry of pyrazole-derived ligands. *Chem. Rev.* **1972**, *72*, 497–509. [CrossRef]
17. Jamieson, C.; Livingstone, K. *The Nitrile Imine 1,3-dipole; Properties, Reactivity and Applications*; Springer Nature: Cham, Switzerland, 2020.
18. Howard, J.L.; Cao, Q.; Browne, D.L. Mechanochemistry as an emerging tool for molecular synthesis: What can it offer? *Chem. Sci.* **2018**, *9*, 3080–3094. [CrossRef]
19. Tan, D.; Garcia, F. Main group mechanochemistry: From curiosity to established protocols. *Chem. Soc. Rev.* **2019**, *48*, 2274–2292. [CrossRef]
20. Pickhardt, W.; Grätz, S.; Borchardt, L. Direct mechanocatalysis: Using milling balls as catalysts. *Chem. Eur. J.* **2020**, *26*, 12903–12911. [CrossRef]
21. Leonardi, M.; Villacampa, M.; Menéndez, J.C. Multicomponent mechanochemical synthesis. *Chem. Sci.* **2018**, *9*, 2042–2064. [CrossRef]
22. Pérez-Venegas, M.; Juaristi, E. Mechanochemical and mechanoenzymatic synthesis of pharmacologically active compounds: A green perspective. *ACS Sustain. Chem. Eng.* **2020**, *8*, 8881–8893. [CrossRef]
23. Porcheddu, A.; Delogu, F.; De Luca, L.; Colacino, E. From lossen transposition to solventless "Medicinal Mechanochemistry". *ACS Sustain. Chem. Eng.* **2019**, *7*, 12044–12051. [CrossRef]
24. Yu, J.; Hong, Z.; Yang, X.; Jiang, Y.; Jiang, Z.; Su, W. Bromide-assisted chemoselective Heck reaction of 3-bromoindazoles under high-speed ball-milling conditions: Synthesis of axitinib. *Beilstein J. Org. Chem.* **2018**, *14*, 786–795. [CrossRef]
25. El-Sayed, T.; Aboelnaga, A.; El-Atawy, M.A.; Hagar, M. Ball milling promoted N-heterocycles synthesis. *Molecules* **2018**, *23*, 1348. [CrossRef]
26. Singh, P.; Nath, M. A concise account on eco-friendly synthetic strategies for pyrazole heterocycles. *Curr. Green Chem.* **2019**, *6*, 198–209. [CrossRef]
27. Saeed, A.; Channar, P.A. A green mechanochemical synthesis of new 3,5-dimethyl-4-(arylsulfanyl)pyrazoles. *J. Heterocycl. Chem.* **2017**, *54*, 780–783. [CrossRef]
28. Chowhan, B.; Kour, J.; Gupta, M.; Paul, S. Green synthesis of bis(pyrazol-5-ole) and pyrazolopyranopyrimidine derivatives through mechanochemistry using chitosan as a biodegradable catalyst. *ChemistrySelect* **2021**, *6*, 7922–7930. [CrossRef]
29. Gomes, P.M.O.; Ouro, P.M.S.; Silva, A.M.S.; Silva, V.L.M. Styrylpyrazoles: Properties, synthesis and transformations. *Molecules* **2020**, *25*, 5886. [CrossRef]
30. Howard, J.L.; Nicholson, W.; Sagatov, Y.; Browne, D.L. One-pot multistep mechanochemical synthesis of fluorinated pyrazolone. *Beilstein J. Org. Chem.* **2017**, *13*, 1950–1956. [CrossRef]
31. Zhang, Z.; Tan, Y.-J.; Wang, C.-S.; Wu, H.-H. One-pot synthesis of 3,5-diphenyl-1*H*-pyrazoles from chalcones and hydrazine under mechanochemical ball milling. *Heterocycles* **2014**, *89*, 103–112. [CrossRef]
32. Paveglio, G.C.; Longhi, K.; Moreira, D.N.; München, T.S.; Tier, A.Z.; Gindri, I.M.; Bender, C.R.; Frizzo, C.P.; Zanatta, N.; Bonacorso, H.G.; et al. How mechanical and chemical features affect the green synthesis o 1*H*-pyrazoles in a ball mill. *ACS Sustain. Chem. Eng.* **2014**, *2*, 1895–1901. [CrossRef]
33. Oh, L.M. Synthesis of celecoxib via 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2006**, *47*, 7943–7946. [CrossRef]
34. Utecht, G.; Fruziński, A.; Jasiński, M. Polysubstituted 3-trifluoromethylpyrazoles: Regioselective (3+2)-cycloaddition of trifluoroacetonitrile imines with enol ethers and functional group transformations. *Org. Biomol. Chem.* **2018**, *16*, 1252–1257. [CrossRef] [PubMed]
35. Utecht, G.; Mlostoń, G.; Jasiński, M. A straightforward access to trifluoromethylated spirobipyrazolines through a double (3+2)-cycloaddition of fluorinated nitrile imines with alkoxyallenes. *Synlett* **2018**, *29*, 1753–1758. [CrossRef]
36. Kowalczyk, A.; Utecht-Jarzyńska, G.; Mlostoń, G.; Jasiński, M. A straightforward access to 3-trifluoromethyl-1*H*-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile. *J. Fluorine Chem.* **2021**, *241*, 109691. [CrossRef]
37. Wang, K.-H.; Liu, H.; Liu, X.; Bian, C.; Wang, J.; Su, Y.; Huang, D.; Hu, Y. Regioselective synthesis of 3-trifluoromethyl 4-subtituted pyrazoles by [3+2]-cycloaddition of trifluoroacetonitrile imines and nitroalkenes. *Asian J. Org. Chem.* **2022**, *11*, e202200103-10. [CrossRef]
38. Zhou, Y.; Gao, C.-F.; Ma, H.; Nie, J.; Ma, J.-A.; Zhang, F.-G. Quadruple functionalized pyrazole pharmacophores by one-pot regioselective [3+2]-cycloaddition of fluorinated nitrile imines and dicyanoalkenes. *Chem Asian J.* **2022**, *17*, e202200436. [CrossRef]
39. Tian, Y.-C.; Li, J.-K.; Zhang, F.-G.; Ma, J.-A. Regioselective decarboxylative cycloaddition route to fully substituted 3-CF_3-pyrazoles from nitrilimines and isoxazolidinediones. *Adv. Synth. Catal.* **2021**, *363*, 2093–2097. [CrossRef]
40. Utecht-Jarzyńska, G.; Nagła, K.; Mlostoń, G.; Heimgartner, H.; Palusiak, M.; Jasiński, M. A straightforward conversion of 1,4-quinones into polycyclic pyrazoles via [3+2]-cycloaddition with fluorinated nitrile imines. *Beilstein J. Org. Chem.* **2021**, *17*, 1509–1517. [CrossRef]
41. Han, T.; Wang, K.-H.; Yang, M.; Zhao, P.; Wang, F.; Wang, J.; Huang, D.; Hu, Y. Synthesis of difluoromethylated pyrazoles by the [3+2]-cycloaddition reaction of difluoroacetohydrazonoyl bromides. *J. Org. Chem.* **2022**, *87*, 498–511. [CrossRef]

42. Kowalczyk, A.; Utecht-Jarzyńska, G.; Mlostoń, G.; Jasiński, M. Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions. *Org. Lett.* **2022**, *24*, 2499–2503. [CrossRef] [PubMed]
43. Mlostoń, G.; Urbaniak, K.; Utecht, G.; Lentz, D.; Jasiński, M. Trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles via the regioselective [3+2]-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones. *J. Fluorine Chem.* **2016**, *192*, 147–154. [CrossRef]
44. Al-Hussain, S.A.; Alshehrei, F.; Zaki, M.E.A.; Harras, M.F.; Farghaly, T.A.; Muhammad, Z.A. Fluorinated hydrazonoyl chlorides as precursors for synthesis of antimicrobial azoles. *J. Heterocyclic Chem.* **2021**, *58*, 589–602. [CrossRef]
45. Du, S.; Yang, Z.; Tang, J.; Chen, Z.; Wu, X.-F. Synthesis of 3*H*-1,2,4-triazol-3-ones via $NiCl_2$-promoted cascade annulation of hydrazonoyl chlorides and sodium cyanate. *Org. Lett.* **2021**, *23*, 2359–2363. [CrossRef] [PubMed]
46. Wojciechowska, A.; Jasiński, M.; Kaszyński, P. Tautomeric equilibrium in trifluoroacetaldehyde arylhydrazones. *Tetrahedron* **2015**, *71*, 2349–2356. [CrossRef]
47. Shawali, A.S.; Ezmirly, S.T.; Bukhari, A.M. Nuclear magnetic resonance spectroscopy and the structures of the regioisomeric products of the cycloaddition of C-ethoxycarbonyl-N-arylnitrilimines to α,β-unsaturated ketones. *Spectrochim. Acta Part A* **1992**, *48*, 1165–1171. [CrossRef]
48. Ortega-Martínez, A.; Molina, C.; Moreno-Cabrerizo, C.; Sansano, J.M.; Nájera, C. Deacylative reactions: Synthetic applications. *Eur. J. Org. Chem.* **2018**, 2394–2405. [CrossRef]
49. Fatiadi, A.J. Active manganese dioxide oxidation in organic chemistry—Part I. *Synthesis* **1976**, *1976*, 65–104. [CrossRef]
50. Xie, H.; Zhu, J.; Chen, Z.; Li, S.; Wu, Y. Reaction of a trifluoromethylated N-monosubstituted hydrazone with α,β-ethenyl ketones: A novel synthesis of substituted pyrazolidines and pyrazolines. *Synthesis* **2011**, *17*, 2767–2774. [CrossRef]
51. Grzelak, P.; Utecht, G.; Jasiński, M.; Mlostoń, G. First (3+2)-cycloadditions of thiochalcones as C=S dipolarophiles: Efficient synthesis of 1,3,4-thiadiazoles via reactions with fluorinated nitrile imines. *Synthesis* **2017**, *49*, 2129–2137. [CrossRef]
52. Shi, C.; Ma, C.; Ma, H.; Zhou, X.; Cao, J.; Fan, Y.; Huang, G. Copper-catalyzed synthesis of 1,3,4-trisubstituted and 1,3,4,5-tetrasubstituted pyrazoles via [3+2] cycloadditions of hydrazones and nitroolefins. *Tetrahedron* **2016**, *72*, 4055–4058. [CrossRef]
53. Castillo, J.-C.; Portilla, J. Recent advances in the synthesis of new pyrazole derivatives. In *Targets in Heterocyclic Systems*; Italian Society of Chemistry: Rome, Italy, 2018; Chapter 9; pp. 194–223. [CrossRef]
54. Yet, L. Five-membered ring systems: With more than one N atom (chapter 5.4). In *Progress in Heterocyclic Chemistry*; Elsevier: Amsterdam, The Netherlands, 2020; Volume 31, pp. 325–361. [CrossRef]
55. Ríos, M.-C.; Portilla, J. Recent advances in synthesis and properties of pyrazoles. *Chemistry* **2022**, *4*, 940–968. [CrossRef]
56. Deepthi, A.; Acharjee, N.; Sruthi, S.L.; Meenakshy, C.B. An overview of nitrile imine based [3+2]-cycloadditions over half a decade. *Tetrahedron* **2022**, *116*, 132812. [CrossRef]
57. Utecht-Jarzyńska, G.; Michalak, A.; Banaś, J.; Mlostoń, G.; Jasiński, M. Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: An access to fluorinated 1,3,4-thiadiazine derivatives via (3+3)-annulation. *J. Fluorine Chem.* **2019**, *222−223*, 8–14. [CrossRef]
58. Zhang, Y.; Zeng, J.-L.; Chen, Z.; Wang, R. Base-promoted (3+2)-cycloaddition of trifluoroacetohydrazonoyl chlorides with imidates en route to trifluoromethyl-1,2,4-triazoles. *J. Org. Chem.* **2022**, *87*, 14514–14522. [CrossRef]
59. Ren, Y.; Ma, R.; Feng, Y.; Wang, K.-H.; Wang, J.; Huang, D.; Lv, X.; Hu, Y. Sythesis of difluoroemthyl pyrazolines and pyrazoles by [3+2] cycloaddition reaction of difluoroacetohydrazonoyl bromides with electron-deficient olefins. *Asian J. Org. Chem.* **2022**, *11*, e202200438. [CrossRef]

Supporting Information

for

Fluorinated and non-fluorinated 1,4-diarylpyrazoles via MnO_2-mediated mechanochemical deacylative oxidation of 5-acylpyrazolines

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Content

Copies of ^{1}H and ^{13}C NMR spectra of new compounds S2

Copies of ^{19}F NMR spectra of new pyrazolines and pyrazoles S22

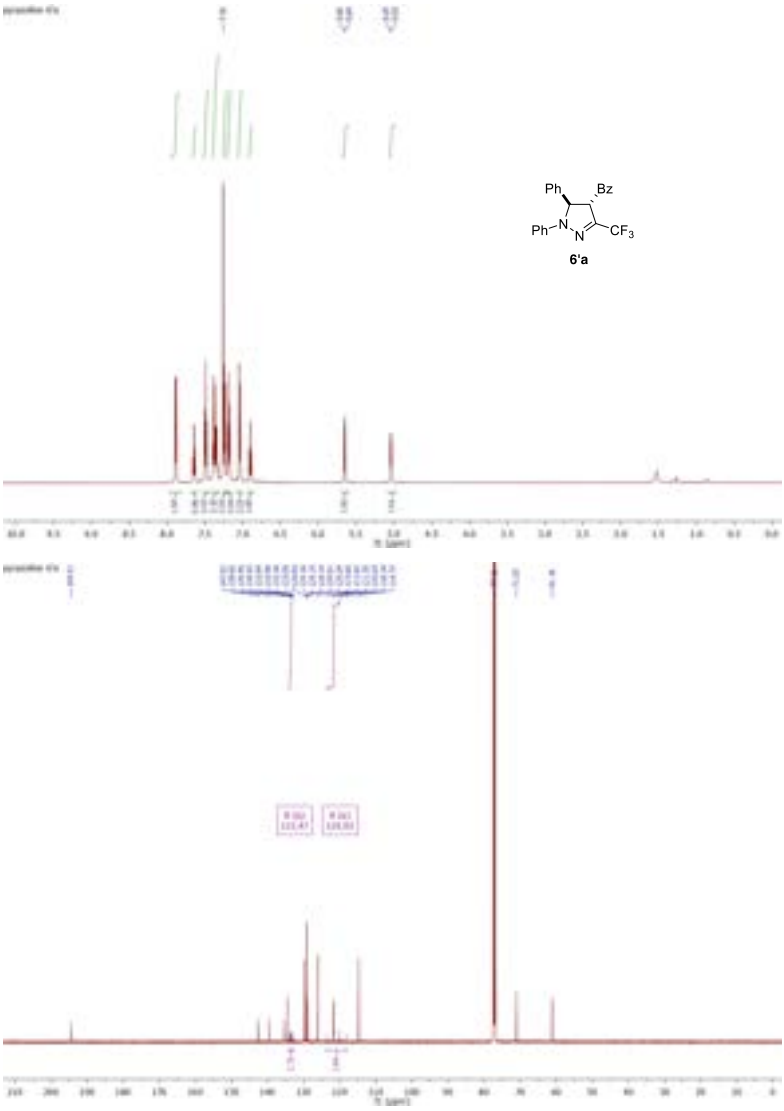


Figure S1. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6'a**.

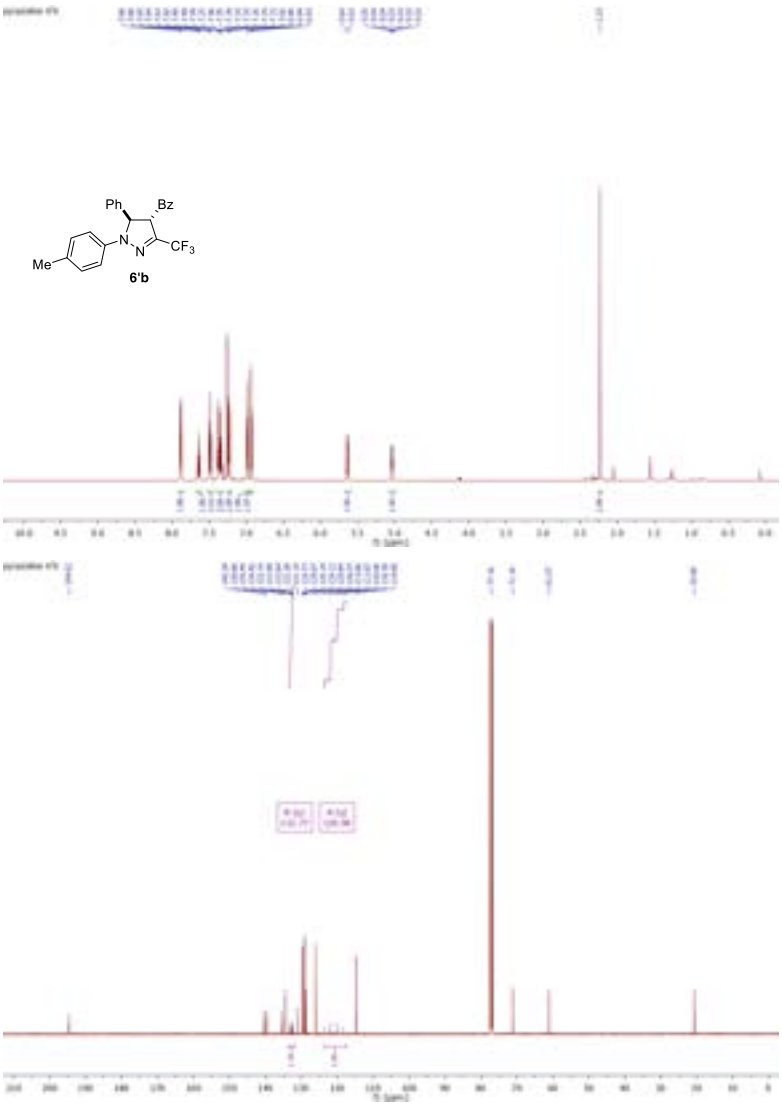


Figure S2. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6'b**.

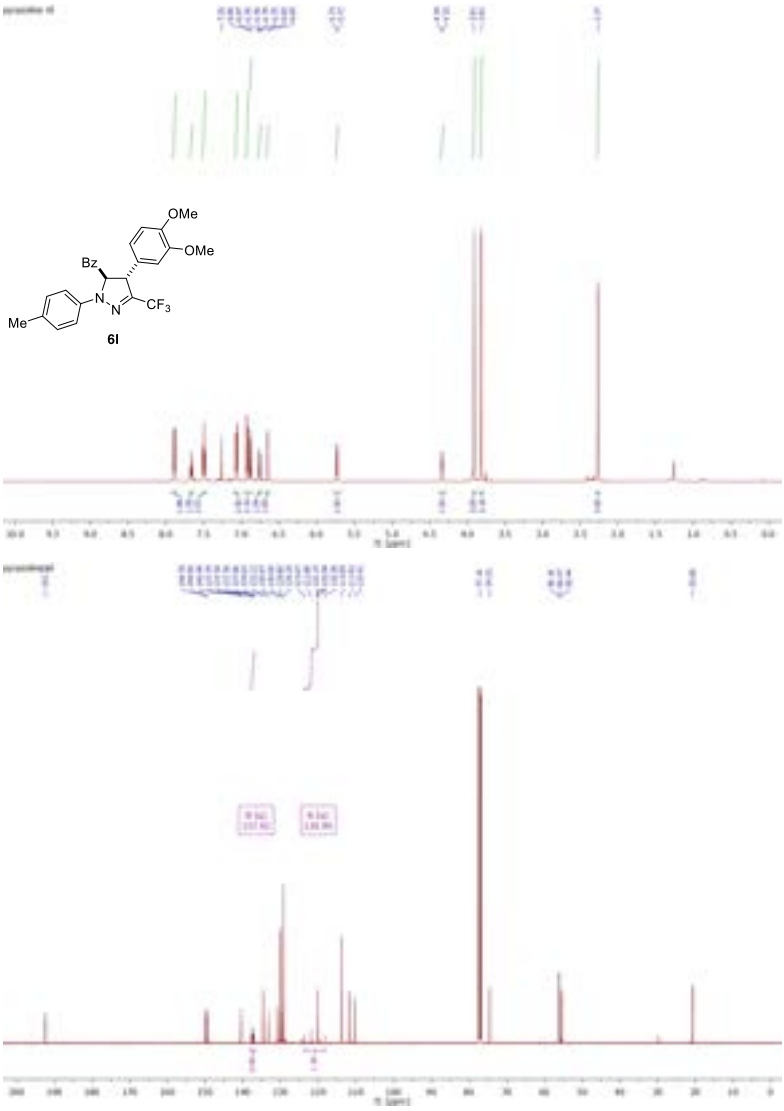


Figure S3. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6l**.

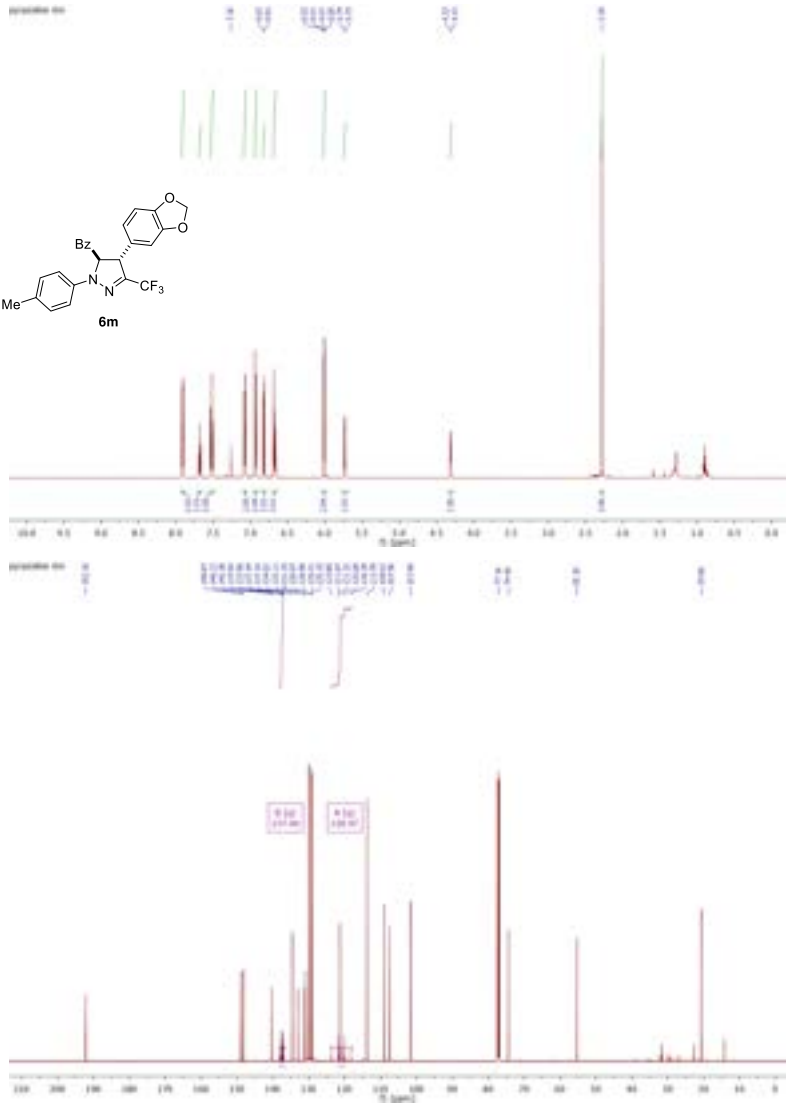


Figure S4. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6m**.

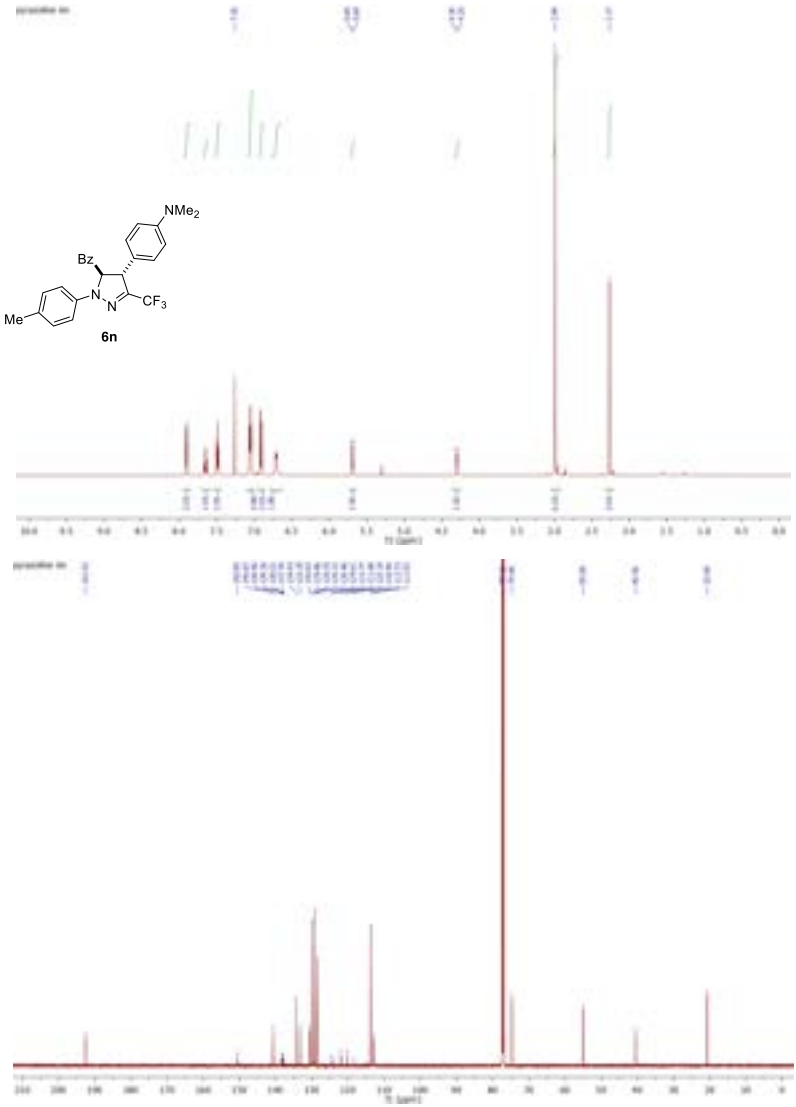


Figure S5. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6n**.

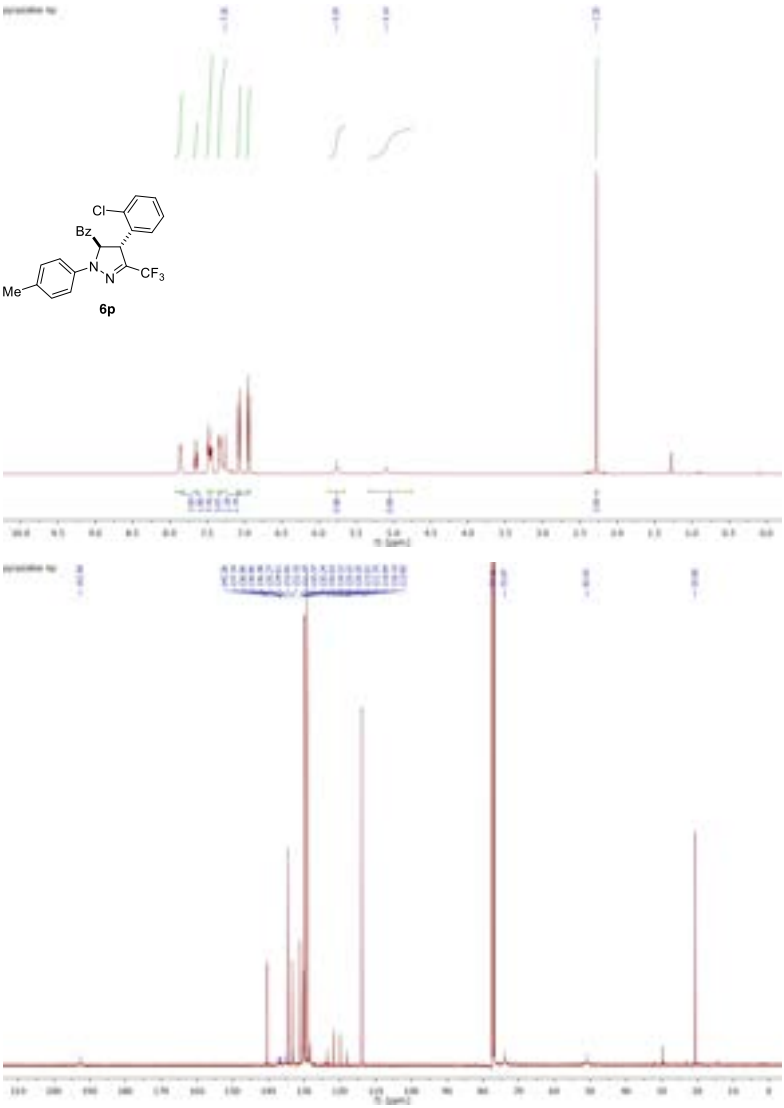


Figure S6. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6p**.

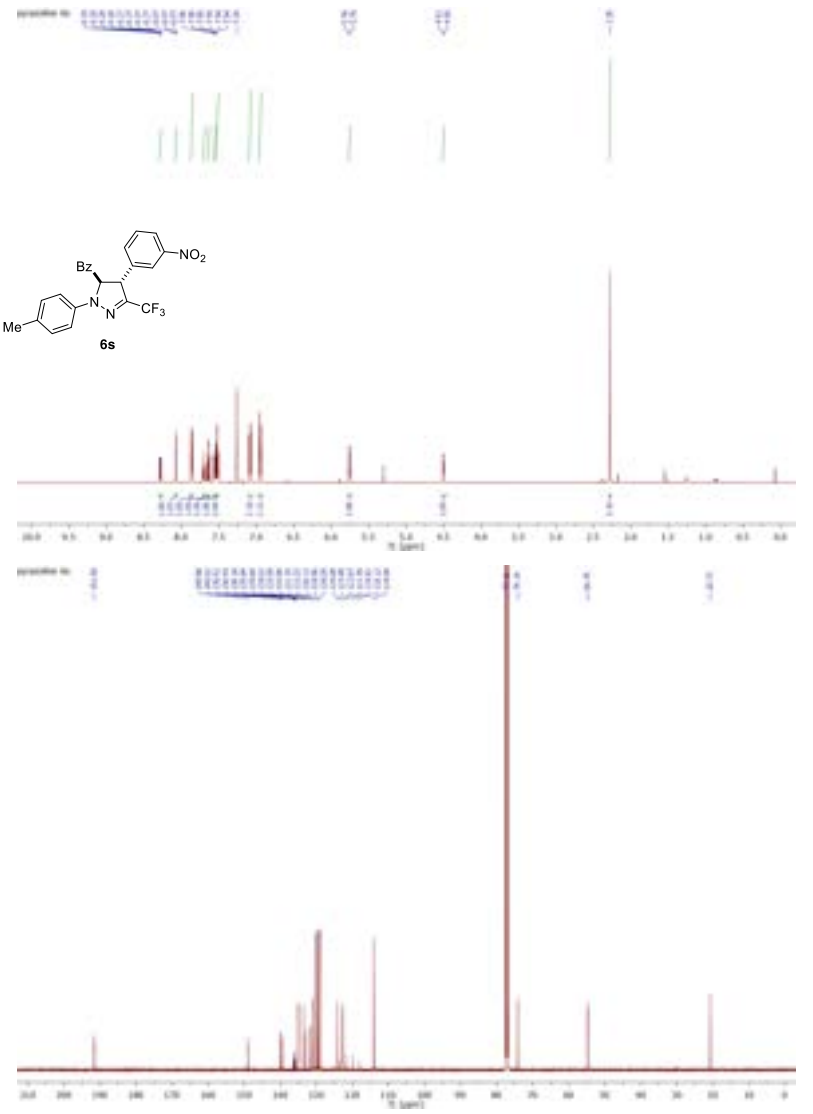


Figure S7. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6s**.

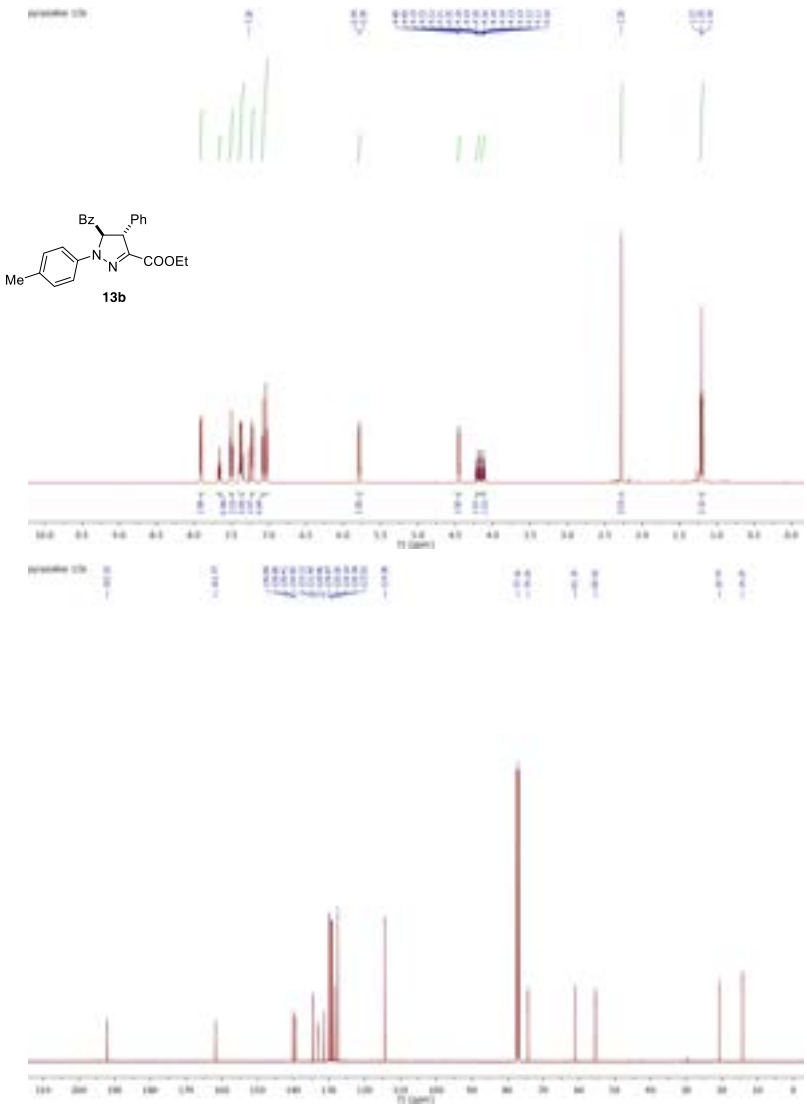


Figure S8. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **13b**.

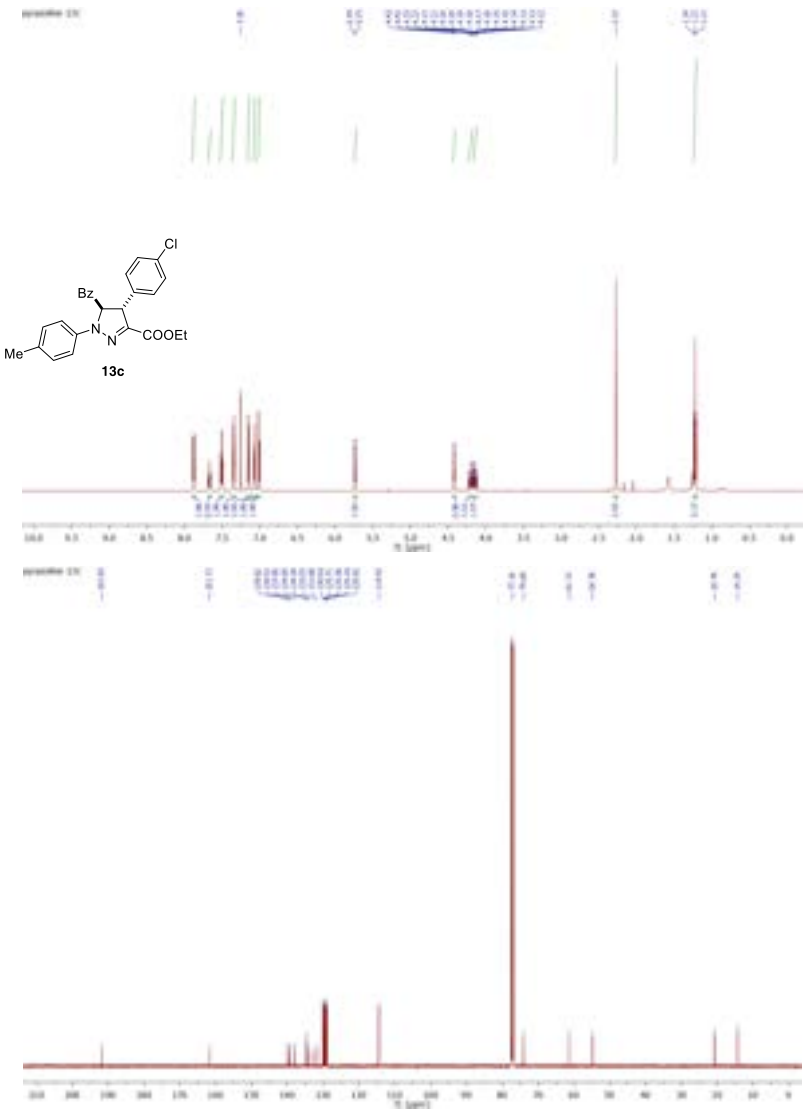


Figure S9. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **13c**.

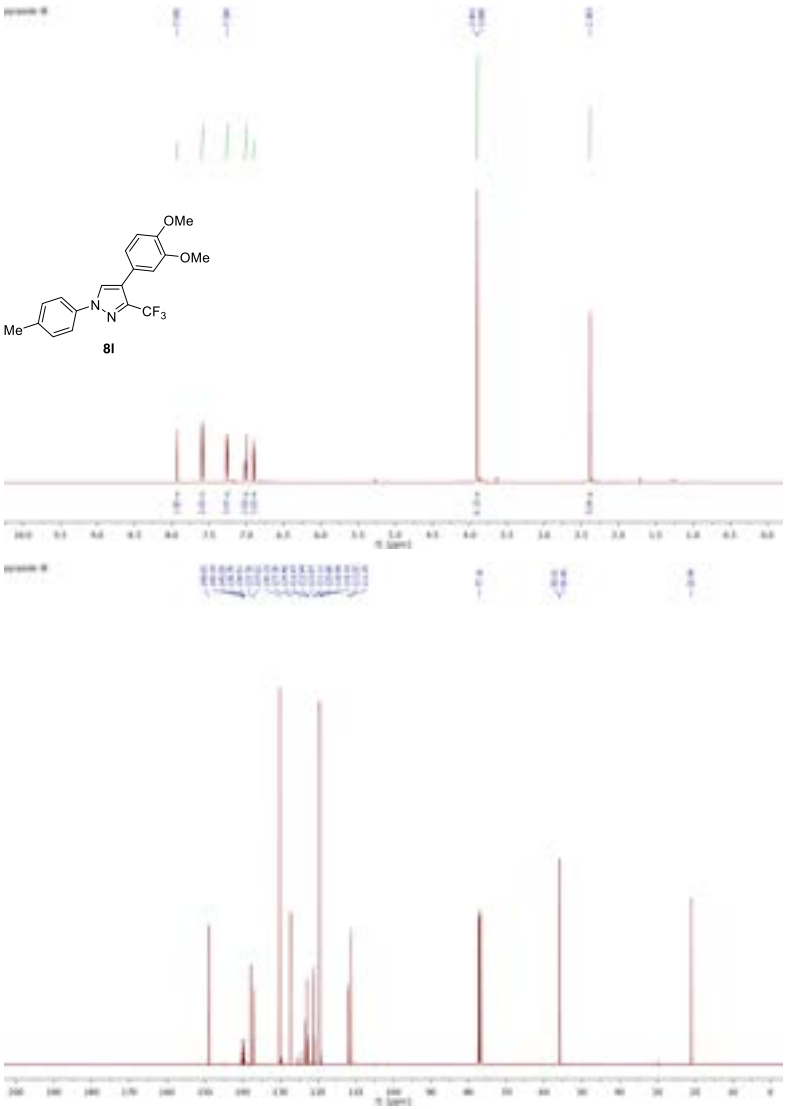


Figure S10. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **8l**.

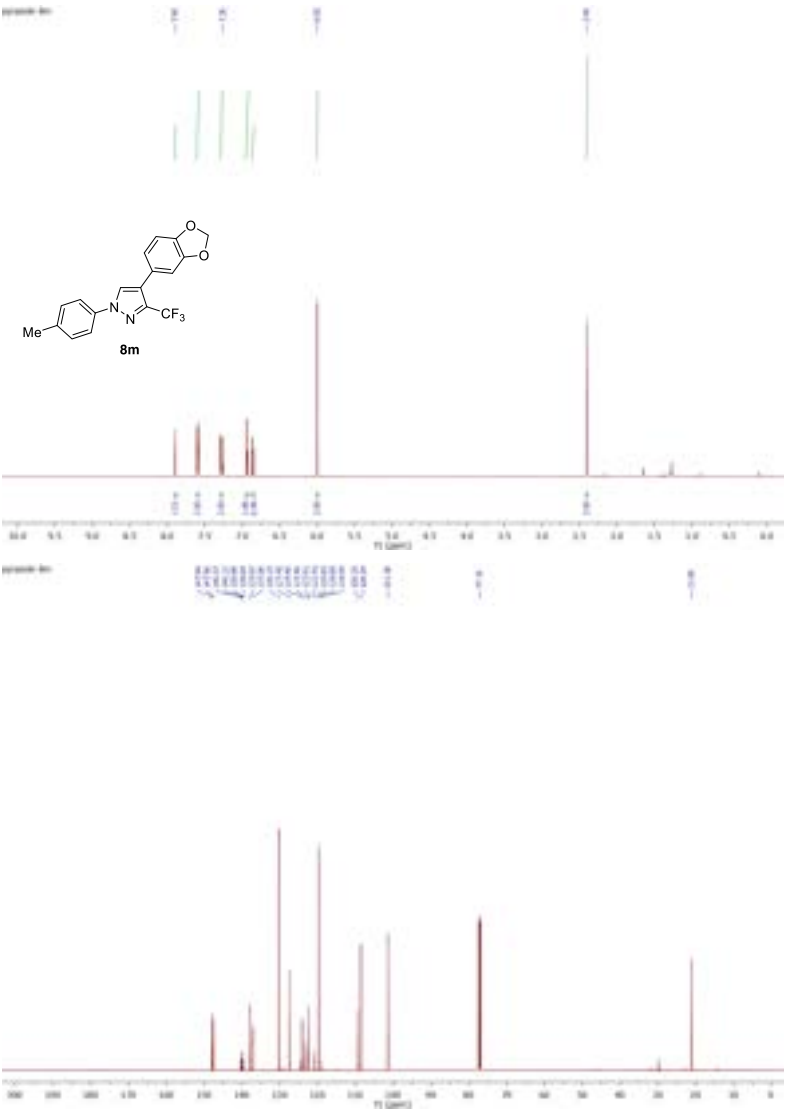


Figure S11. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **8m**.

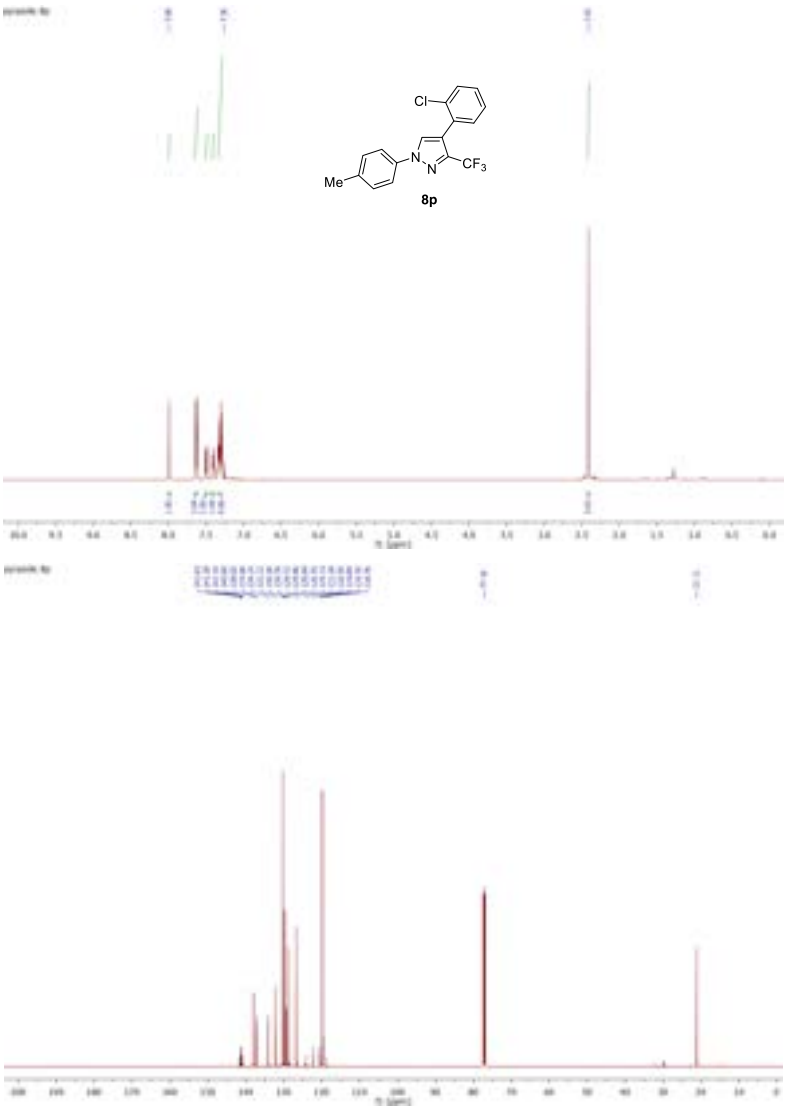


Figure S12. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **8p**.

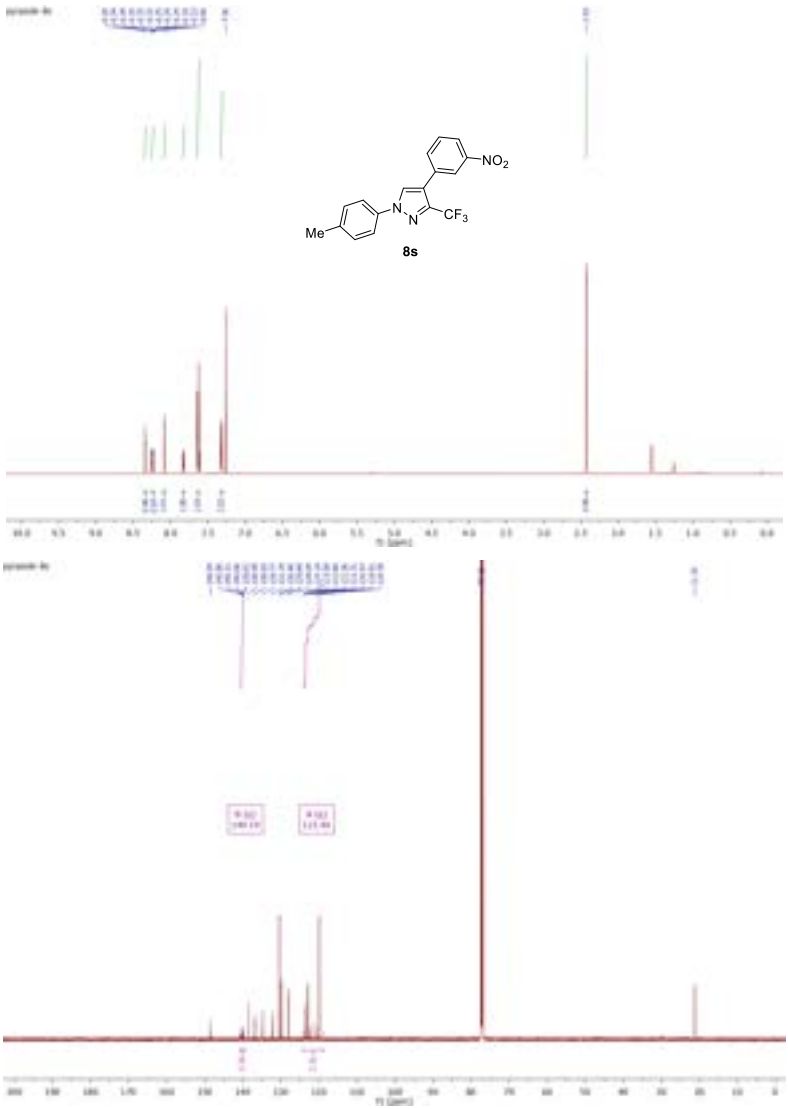
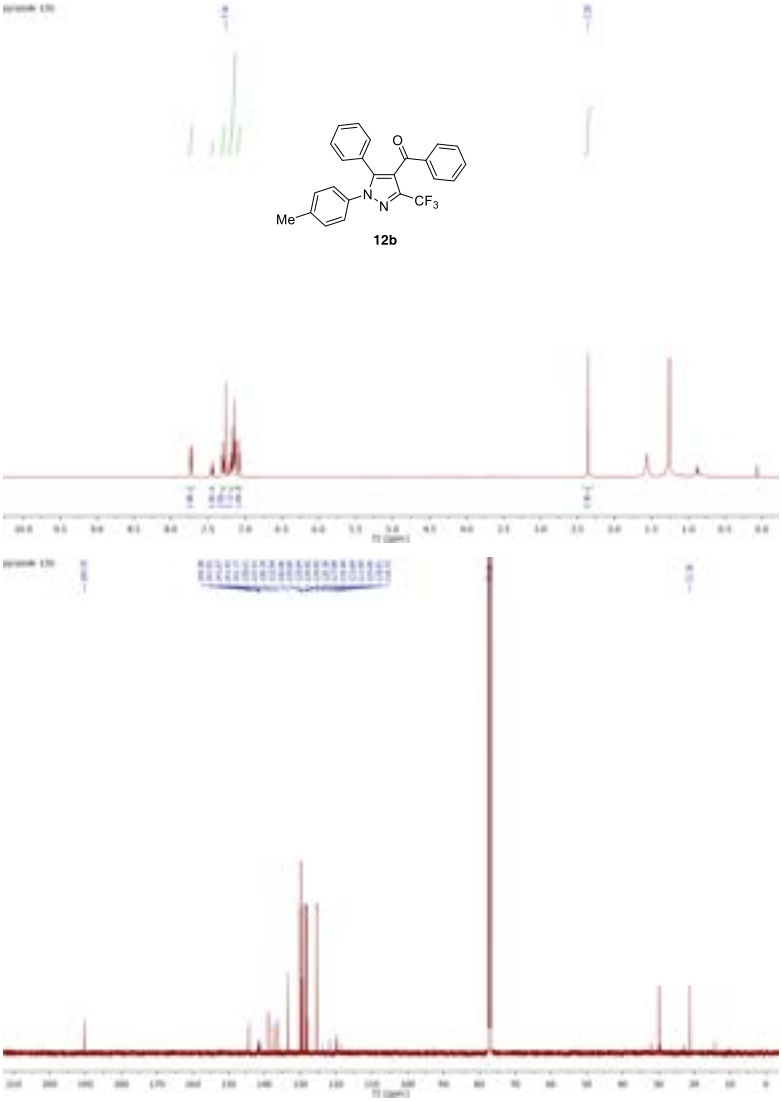
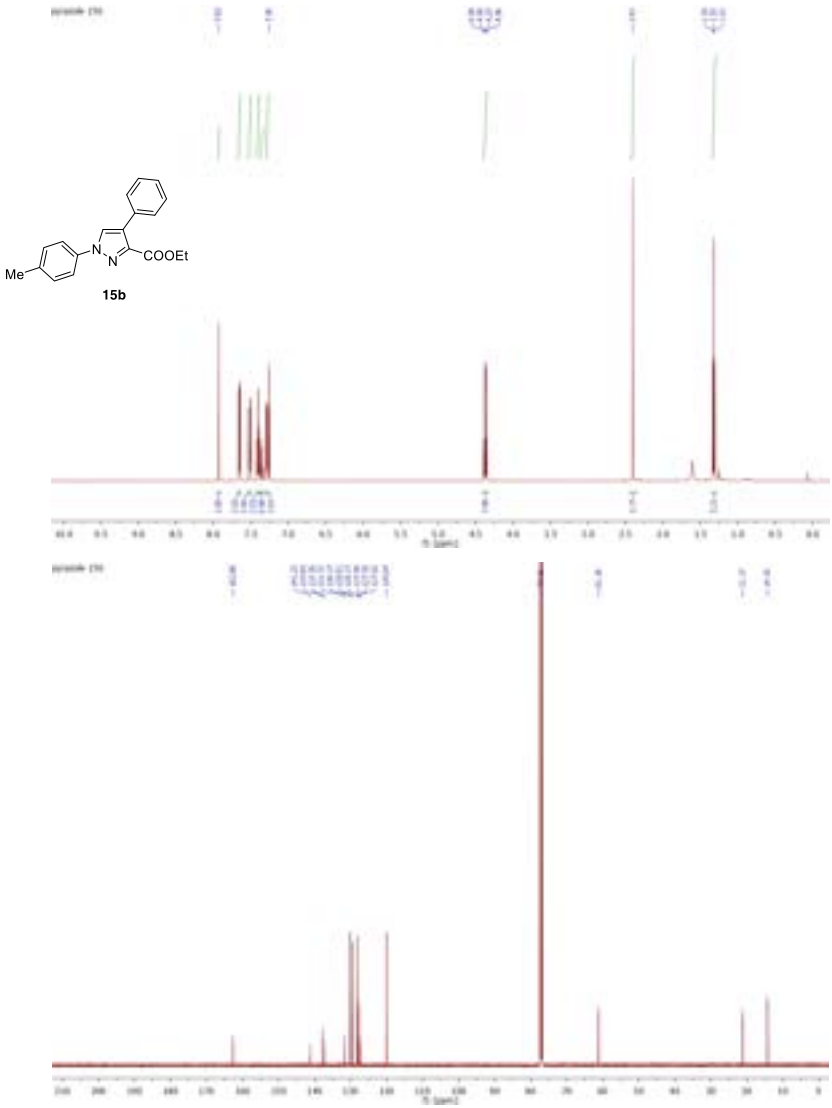


Figure S13. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **8s**.



12b

Figure S14. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **12b**.



15b

Figure S15. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **15b**.

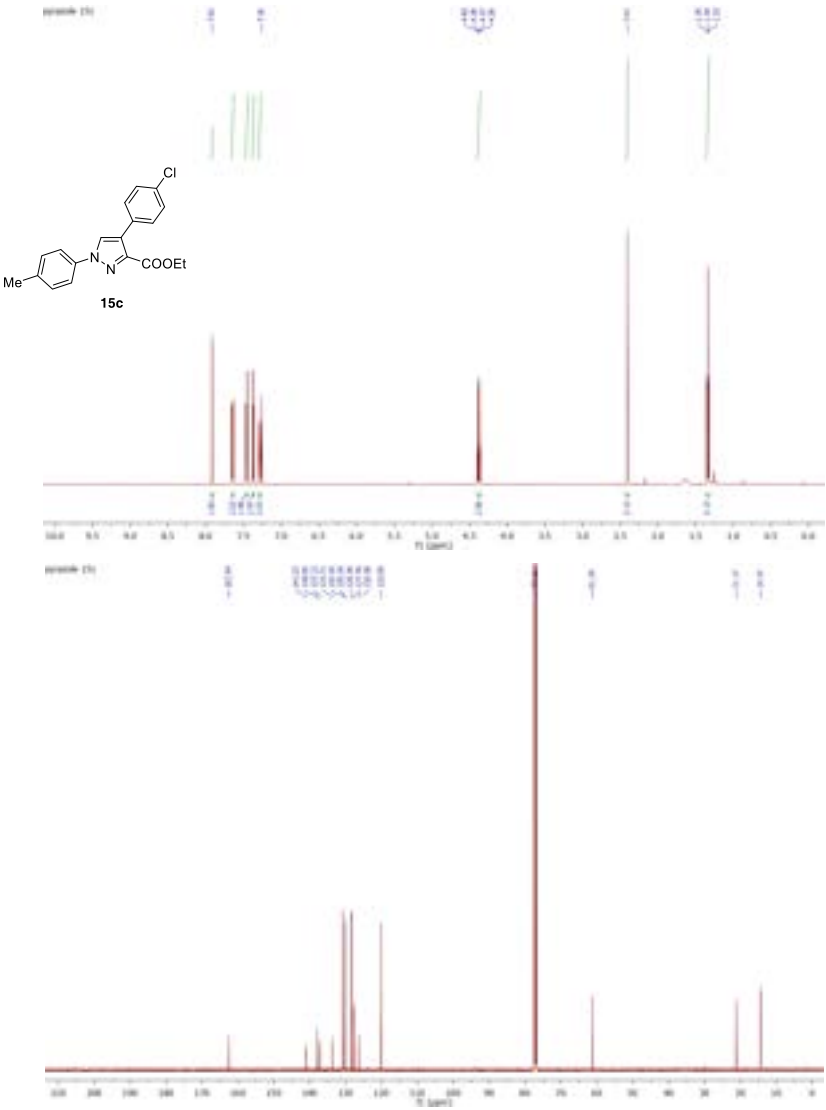


Figure S16. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **15c**.

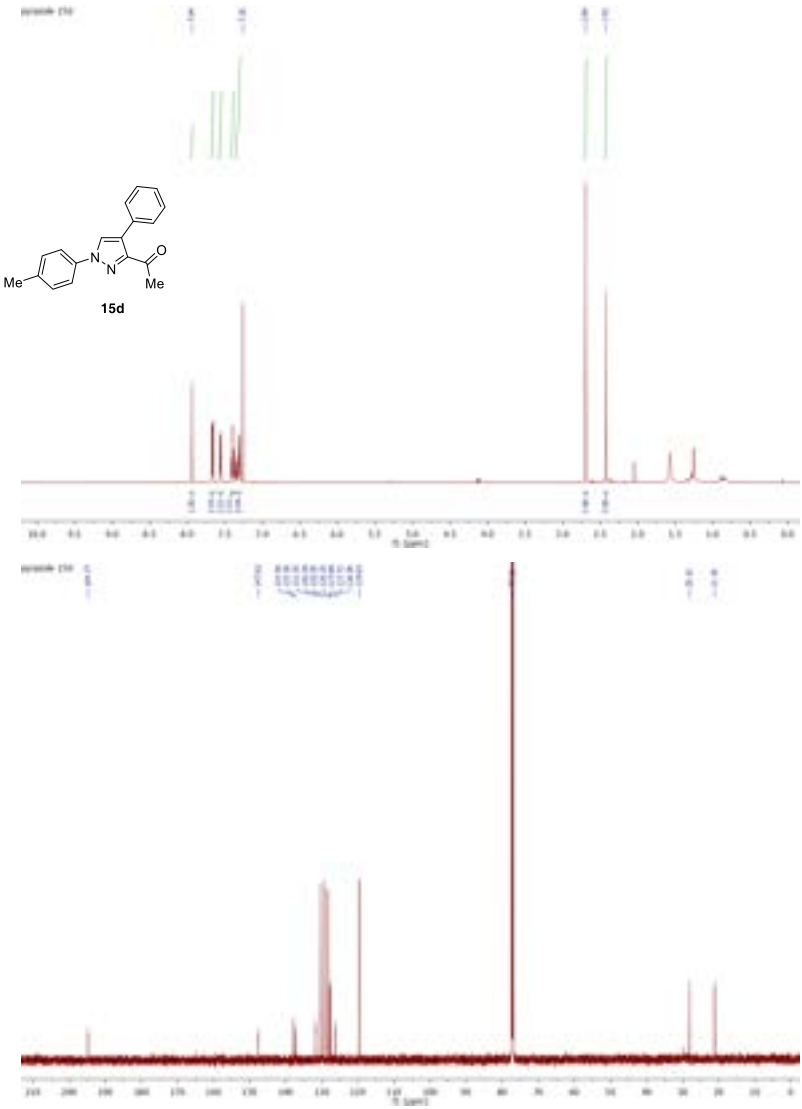


Figure S17. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **15d**.

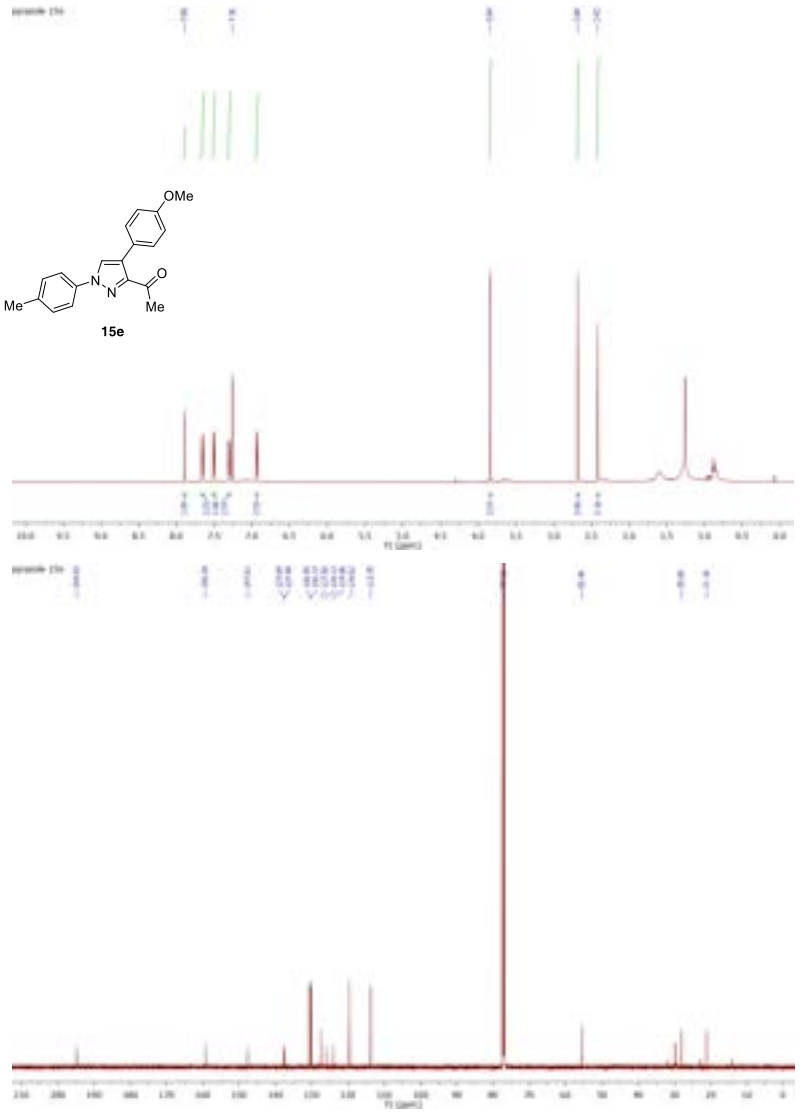


Figure S18. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **15e**.

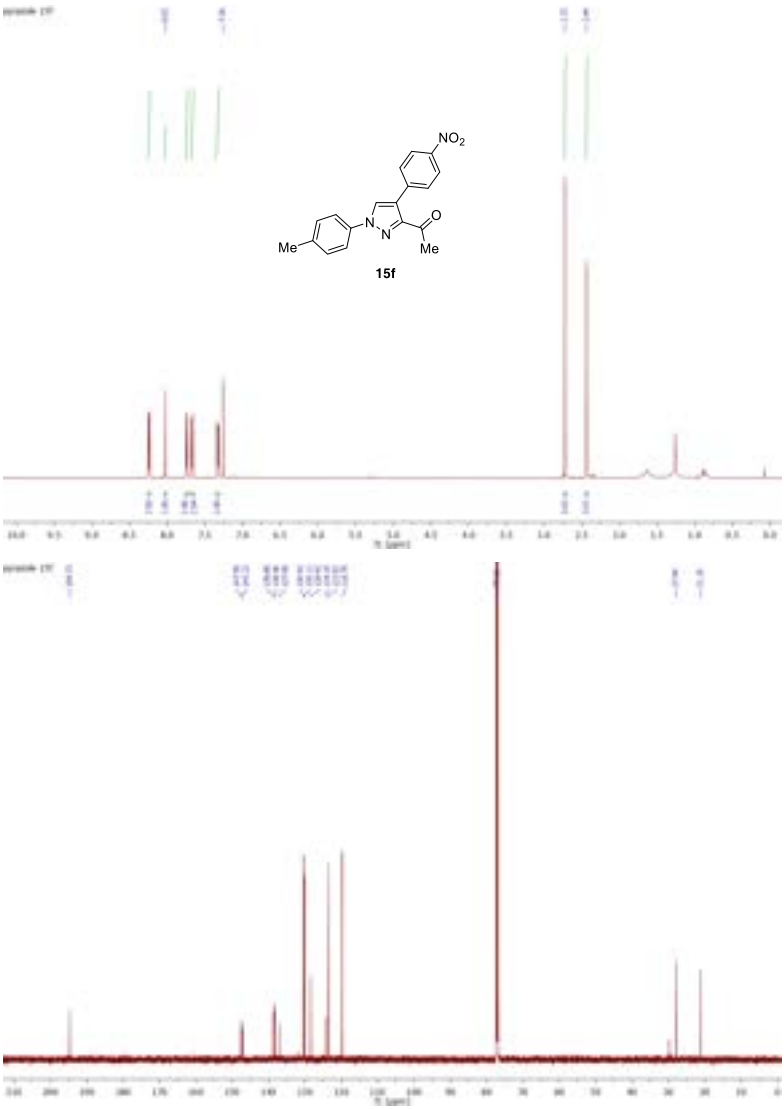
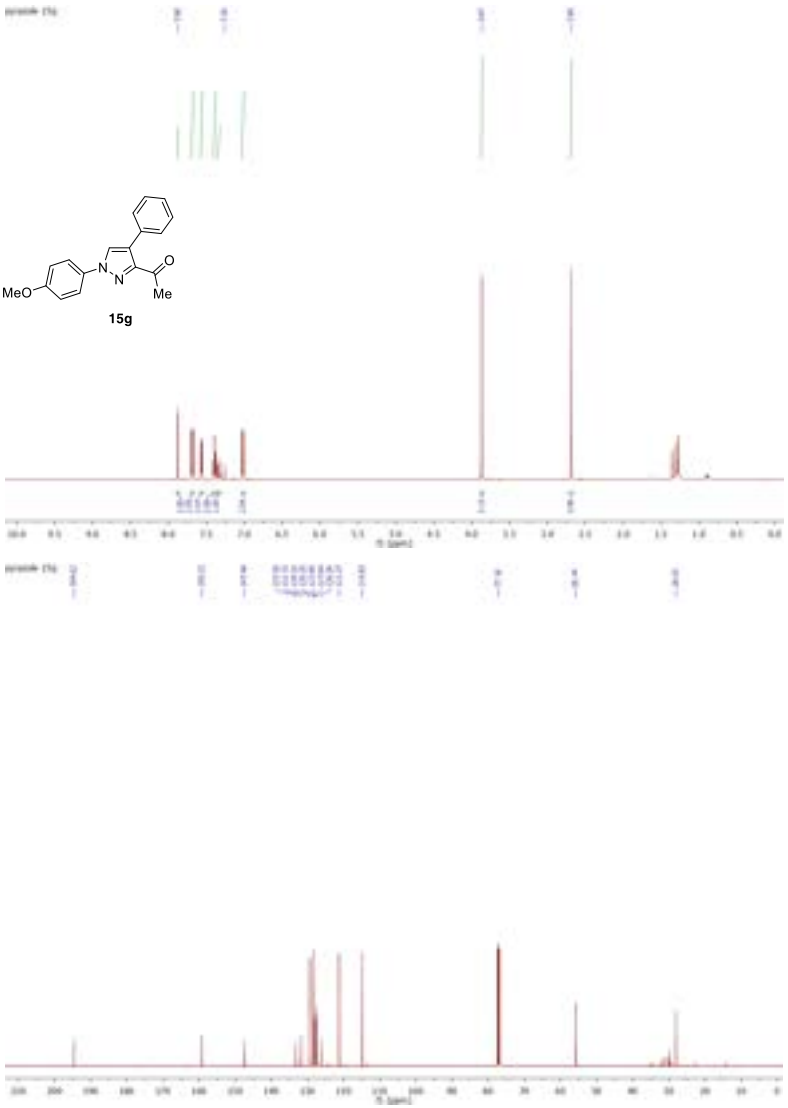


Figure S19. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **15f**.



15g

Figure S20. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **15g**.

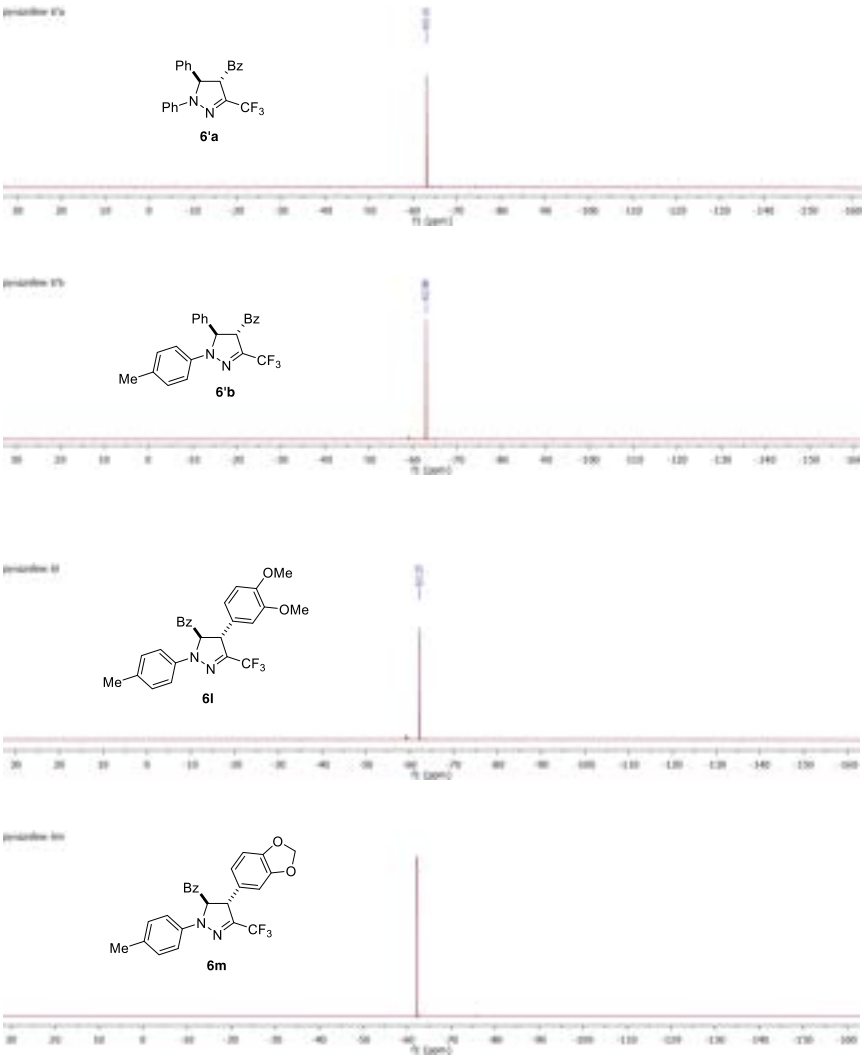


Figure S21. ^{19}F NMR (565 MHz, $CDCl_3$) spectra for pyrazolines **6'a**, **6'b**, **6l** and **6m**.

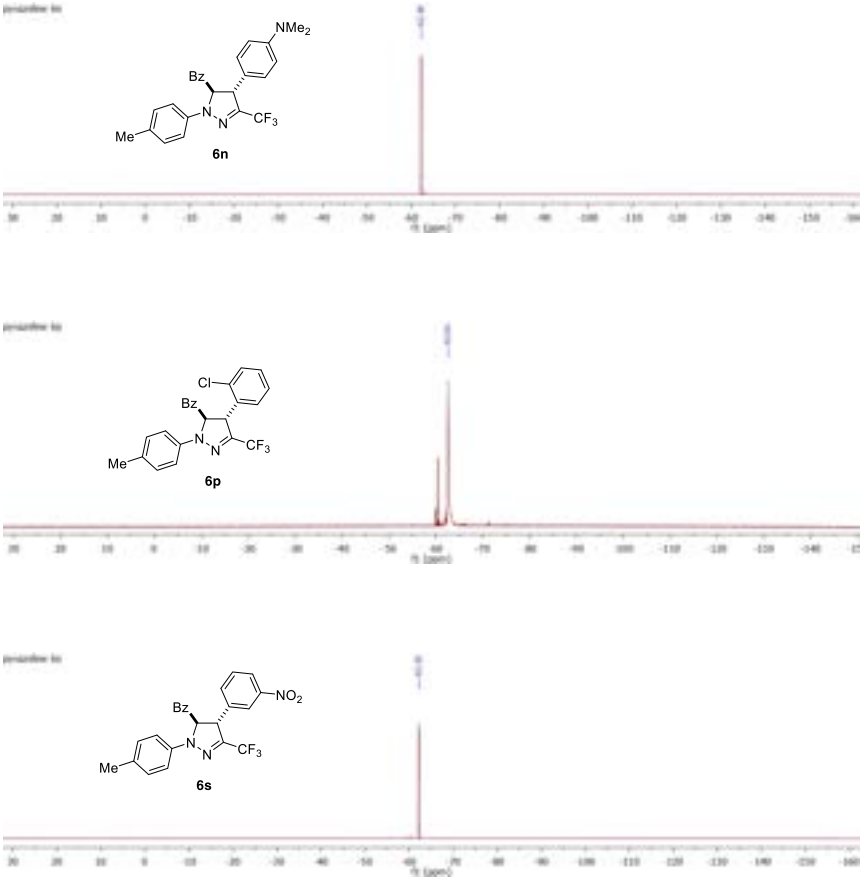


Figure S22. ^{19}F NMR (565 MHz, $CDCl_3$) spectra for pyrazolines **6n**, **6p** and **6s**.

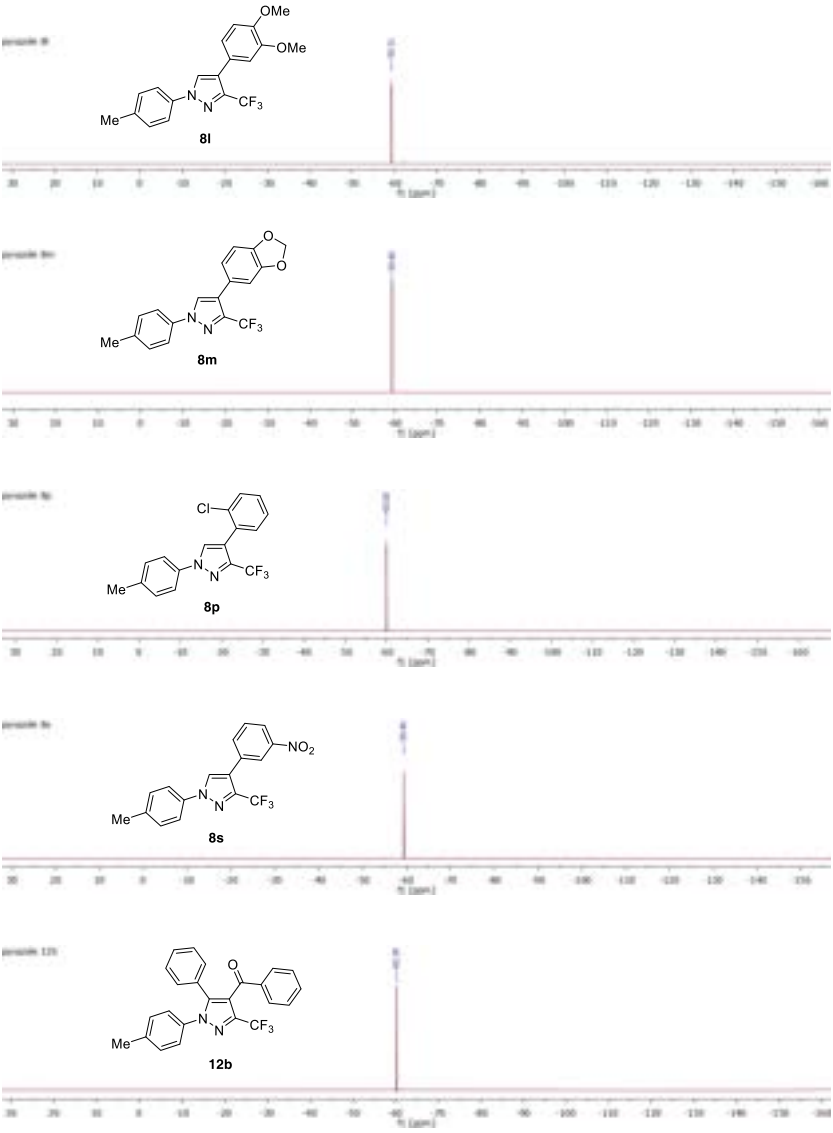


Figure S23. ^{19}F NMR (565 MHz, $CDCl_3$) spectra for pyrazoles **8l**, **8m**, **8p**, **8s** and **12b**.

[**D4**]

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ω-(3-trifluoromethylpyrazol-4-yl)alkanoic acids via (3+2)-cycloaddition of nitrile imines with cyclic enones and deacylative aromatization

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ω-(3-Trifluoromethylpyrazol-4-yl)alkanoic acids via (3 + 2)-cycloaddition of nitrile imines with cyclic enones and deacylative aromatization

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ABSTRACT

A series of ω-substituted alkanoic acids functionalized with 1-aryl-3-trifluoromethylpyrazol-4-yl group was synthesized via two-step protocol using in situ generated CF_3-nitrile imines and cyclic enones as key building blocks. The first 1,3-dipolar cycloaddition step proceeded in a fully selective manner either in solutions or under solvent-free mechanochemical activation. Treatment of the first formed cycloadducts derived from 2-cyclopentenone or 2-cyclohexenone with DDQ afforded corresponding bicyclic pyrazoles formed via dehydrogenative oxidation pathway, whereas MnO_2-mediated deacylative aromatization led to desired propionic or butyric acid derivatives, respectively. In contrast, oxidation of model 2-cycloheptenone-derived (3 + 2)-cycloadduct yielded bicyclic analogue irrespectively to the applied conditions.

1. Introduction

There is increasing interest in pyrazole-functionalized alkanoic acids and their derivatives recognized either as effective non-steroidal anti-inflammatory drugs (NSAIDs) [1] or as agents with remarkable antimicrobial and antifungal properties [2]. For example, *lonazolac* (**1**) is a well-known non-selective, commercially available painkiller and anti-neoplastic agent [3] (Fig. 1). More recently reported pyrazole-functionalized 3-arylpropionic acid derivative **2** exhibits excellent COX-2 inhibitory activity with a high selectivity index [4], whereas 1,3-diarylpyrazole-acylsulfonamide **3** has been identified as a promising antitubercular agent [5].

Although numerous original work have been reported on the synthesis and biological activity of halogenated and non-halogenated (pyrazol-4-yl)alkanoic acids, especially propanoic derivatives, the corresponding trifluoromethylated analogues are little known. Out of three general strategies for the preparation of (pyrazol-4-yl)propionic acids reported to date, the classical approach comprises condensation of hydrazines with an appropriate 1,3-dicarbonyl compound (or its equivalent) functionalized at α position with (alkoxycarbonyl)ethyl group [6]. Another general method is based on post-cyclizative functionalization and typically pyrazole-4-carbaldehydes are applied as key starting materials for the introduction of carboxylate via aldol-like reactions [7]. More recent approach towards (pyrazol-4-yl)propionic acids is based on formic acid-mediated decarboxylative hydrolysis of functionalized pyrano[2,3-c]pyrazole derivatives [8]. Special methods employing less commonly known reagents e.g. alkylenecyclobutanones in a three-component reaction with *N'*-(2-alkynylbenzylidene)hydrazide and water are also known [9]. However, the mentioned routes either suffer from limited access to appropriate CF_3-functionalized precursors and/or require additional synthetic steps (hydrolysis, reduction) to access the target carboxylic acids. Hence, development of new strategies towards fluorinated pyrazole-functionalized alkanoic acids should be of general interest.

In a series of recent work, trifluoromethylated nitrile imines, readily available via base-induced dehydrohalogenation of hydrazonoyl halides, have been demonstrated as powerful building blocks to assembly five- and six-membered heterocycles either via (3 + 2)-cycloaddition reactions or (3 + 3)-annulations, respectively (Scheme 1a). For example, straightforward access to variously functionalized pyrazole [10], 1,2,4-triazole [11], 1,3,4-thiadiazole [12], 1,3,4-thiadiazine [13], and 1,2,4-triazine [14] derivatives has been documented. More recently, Ma and Nie reported on efficient synthesis of a series of 3-difluoro- and 3-trifluoromethylated 5-fluoropyrazoles with potent COX-2 inhibitory activity by using appropriate hydrazonoyl halides and fluorinated nitroalkenes [15]. Soon after, our group disclosed one-pot protocol to access trifluoromethylated 1-arylpyrazoles employing nitrile imines and mercaptoacetaldehyde as a surrogate of acetylene, and the devised method has been applied in the synthesis of well-known anti-inflammatory drug celecoxib [16]. Also, successful trapping of

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trifluoroacetonitrile imines with maleimides opened up access to pyrrolo-pyrazolines, which smoothly aromatized upon treatment with trichloroisocyanuric acid (TCCA), as reported by Hu group [17]. Finally, Wang and Cai communicated on formal (3 + 2)-cycloaddition between fluorinated nitrile imines and 1*H*-benzimidazole-2-thiols leading to fused 3-trifluoromethylated 1,2,4-triazoles [18].

Despite great interest and remarkable progress in the chemistry of trifluoroacetonitrile imines, to the best of our knowledge, the title 1,3-dipole has not been applied for the synthesis of CF_3-functionalized pyrazole-alkanoic acids. Prompted by our previous results on MnO_2-mediated oxidations of 5-acylpyrazolines [19], we envisioned possible pathway towards trifluoromethylated acids of type **A** through deacylative aromatization of the respective bicyclic pyrazolines **B** (Scheme 1b). The latter key precursors should be readily accessible via 1,3-dipolar cycloaddition of in situ generated trifluoroacetonitrile imines and cyclic enones. Thus, the goal of the present study was to examine the scope and limitations of the designed approach.

2. Results and discussion

First experiments on base-promoted (3 + 2)-cycloaddition reactions were carried out using *N*-(*p*-tolyl)-trifluoroacetohydrazonoyl bromide (**4a**) as a precursor of model nitrile imine and 2-cyclopentenone (**5a**) as dipolarophile (Scheme 2). Brief optimization with respect to solvent (DCM, THF, toluene), base (Et_3N, K_2CO_3), stoichiometry and reaction temperature revealed, that the devised cycloaddition proceeds slowly at room temperature, to afford the desired *cis*-bicyclic product **6a** at best in 33 % yield (1.2 equiv. of **4a**, THF, E_3N, 3 days; *Method A*), whereas heating of the reaction results in gradual decomposition of starting materials and lead to complex mixtures. Gratifyingly, solvent-free ball-milling of raw materials **4a** and **5a**, in the presence of K_2CO_3, provided after 4.5 h the expected (3 + 2)-cycloadduct **6a** identified as sole intermolecular product, which was isolated in fair yield of 73 % (*Method B*). The structure of **6a** was established by NMR spectroscopy; for example, in ^{1}H NMR spectrum, taken in $CDCl_3$, two diagnostic absorptions attributed to 3a-H and 6a-H were found at $\delta = 4.24–4.28$ (m) and $\delta = 4.60$ (d, $J_{H\text{-}H} = 11.5$ Hz), respectively, which confirmed regio- (attack of the *N*-termini of 1,3-dipole onto α position of enone) and diastereochemistry (*cis*-fusion) in **6a**. Based on additional 2D measurements, the absorptions found in ^{13}C NMR at $\delta = 46.9$ and $\delta = 68.9$ were assigned to bridgehead carbon atoms C(3a) and C(6a), whereas characteristic quartets located at $\delta = 121.3$ ($^1J_{C\text{-}F} = 269.8$ Hz) and $\delta = 138.3$ ($^2J_{C\text{-}F} = 36.4$ Hz) confirmed the presence of the C(3)-CF_3 moiety. Finally, the elemental analysis supplemented by ESI-MS confirmed the molecular formula of 1-(*p*-tolyl)-3-trifluoromethyl-3a,4,5,6a-tetrahydro-1*H*-cyclopentapyrazol-6-one (**6a**) as $C_{14}H_{13}F_3N_2O$ and analytical purity of the sample.

Next, 2-cyclohexenone (**5b**) and 2-cycloheptenone (**5c**) were examined in reaction with **4a**. Similarly to reactions with **5a**, low conversions were observed in THF solution (46 % and 31 %), whereas remarkably higher chemical yields of desired (3 + 2)-cycloadducts **7a** and **8a** (82 % and 92 %, respectively) were achieved under ball-milling mechanochemical activation (Scheme 2). Noteworthy, both products were accompanied by trace amounts (ca. 5 %) of the corresponding aromatized bicyclic analogues. Finally, two more sterically demanding cyclic enones bearing Me group either at α or β position of the enone unit were also involved into the study. In the reaction of isophorone (**5d**) with **4a** gradual consumption of starting materials was observed both in solution and in a ball-mill reactor leading to a complex mixture of unidentified products, but the expected cycloadduct **9a** could not be detected based on ^{1}H NMR. Attempted isolation of the formed materials by standard column chromatography was in vain. In contrast, the reaction of enantiomerically pure (*S*)-carvone (**5e**) with **4a** proceeded smoothly under mechanochemical activation to afford **10a** (47 %, dr *exo*/*endo* 94:6), formed via the exclusive attack of CF_3-nitrile imine onto the C=C bond of the enone moiety. The observed excellent chemo- and high diastereoselectivity in reaction of trifluoroacetonitrile imine with **5e** is in full agreement with previously reported experimental results as well as computational analysis on (3 + 2)-cycloadditions of carvone with diaryl-nitrile imines [20].

In extension of the study, a series of hydrazonoyl bromides functionalized with selected substituents (i.e. R = Me, OBn, H, Cl, OCOPh, CF_3, and NO_2) located at *para* position of the benzene ring was checked in reactions with cyclic enones **5a** and **5b** under more effective mechanochemical conditions (*Method B*). As shown in Scheme 3, most of nitrile imines smoothly reacted with dipolarophiles **5a** and **5b** leading to the expected (3 + 2)-cycloadducts **6a-6f** (50–73 %) and **7a-7e** (51–83 %), formed in a fully regioselective fashion. Only in the case of strongly electron-deficient nitrile imine derived from NO_2-functionalized hydrazonoyl bromide **4g** no expected (3 + 2)-cycloadduct was formed under the applied conditions. Moreover, in contrast to 2-cyclopentenone-derived products **6a-6f** identified as exclusive products, the first formed pyrazolines **7a-7e** obtained from six-membered enone **5b** suffered partial dehydrogenative air-oxidation, and hence, small amounts (up to 10 %) of the respective aromatized bicyclic cyclohexapyrazol-7-ones were found in crude reaction mixtures.

With new bicyclic α'-acyl-pyrazolines **6–8** in hands, selected representatives were checked in anticipated deacylative oxidation reactions with activated MnO_2 under ball-milling conditions (Scheme 4) [20b]. In a typical experiment, starting pyrazoline was treated with excess activated MnO_2 (85 %; 40 equiv.) and the mixture was ball-milled for 5 h, at room temperature. To our delight, oxidation of **6a** provided, after standard aqueous workup, the desired propionic acid derivative **11a** formed as exclusive product (92 % yield). Similar result was noticed for higher homologue; oxidation of **7a** under analogous conditions afforded the desired trifluoromethylated (pyrazol-4-yl)butyric acid derivative **12a** as major product (71 % yield) accompanied by small amounts of bicyclic pyrazole **13b**. Finally, treatment of 2-heptenone-derived pyrazoline **8a** with MnO_2 resulted in exclusive dehydrogenative aromatization leading to **13c** (95 %). The observed remarkable ring-size dependent mechanochemical MnO_2-mediated oxidation deserve a brief comment. Irrespectively to reaction mechanism, the observed switch of oxidation outcome correspond with the relative torsional strain in the respective bicyclic pyrazoles **13a-13c** [21]. Thus, in the case of **6a**, deacylative oxidation leading to unstrained ring-opened product **11a** is favored over the 1,2-diazabicyclo[3.3.0]octene derivative **13a** with the highly pyramidalized C=C bond. On the other hand, aromatization of highest homologue pyrazoline **8a** proceeds through

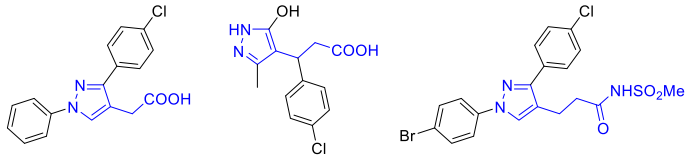


Fig. 1. Structures of *lonazolac* (**1**), selective COX-2 inhibitor **2** derived from 3-(1*H*-pyrazol-yl)propionic acid, and antitubercular acylsulfonamide **3**.

dehydrogenation to give more flexible 1,2-diazabicyclo[5.3.0]decene derivative **13c**, while intermediate bicyclic pyrazoline **7a** undergoes competitive deacylative vs. dehydrogenative oxidation pathways to give a mixture of **12a** (71 %) and **13b** (16 %). Taking into account the observed trend in MnO_2-mediated oxidations, selected propionic acids **11b-11d,11f** were prepared in high yields of 75–85 % following the devised mechanochemical protocol (Scheme 4). Furthermore, the synthesis of bicyclic pyrazole series **13a-13c** was accomplished by treatment of starting pyrazoline precursors with DDQ, in hot EtOAc.

Finally, representative propionic acid derivative **11a** was subjected to functional group transformations on newly formed carboxylic function (Scheme 4). As expected, the standard Fischer esterification carried out in methanol as well as aminolysis of the corresponding in situ generated acid chloride provided methyl ester **14** and amide **15**, respectively, in nearly quantitative yields.

3. Conclusions

The present study showed that the in situ generated electron-deficient trifluoroacetonitrile imines smoothly undergo mechanochemical (3 + 2)-cycloadditions with cyclic enones to give bicyclic pyrazolines in a fully chemo- and regioselective fashion. Oxidation of the first formed cycloadducts with DDQ led to corresponding bicyclic pyrazole derivatives in high yields. In contrast, remarkable ring-size dependent aromatization proceeding through competitive deacylative vs. dehydrogenative pathway was observed upon treatment of the mentioned pyrazolines with activated MnO_2, and the desired trifluoromethylated (pyrazol-4-yl)alkanoic acids derived from 2-cyclopentenone and 2-cyclohexenone were obtained. Subsequent esterification and amidation reactions demonstrated, that the title carboxylic acids can also serve as useful building blocks for the synthesis of more complex analogues of potential practical applications e.g. in medicine and agrochemistry [1–5].

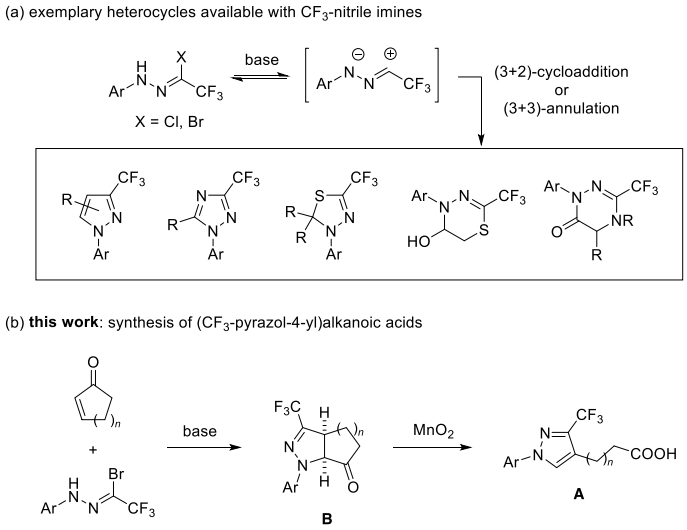
4. Experimental part

4.1. General information

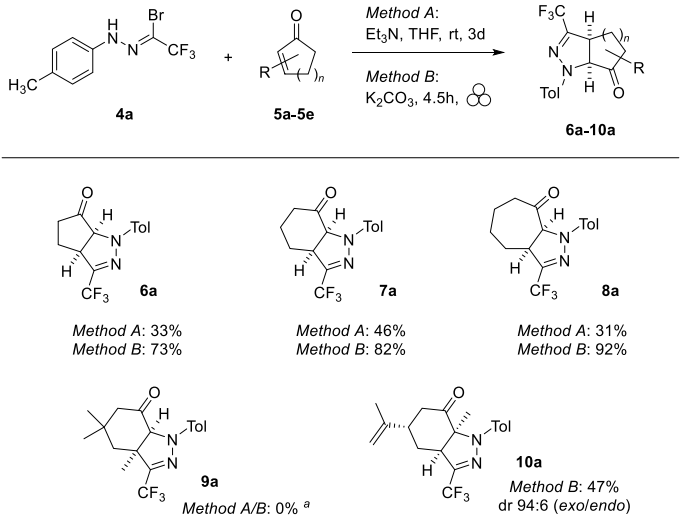
If not stated otherwise, reactions were carried out under inert atmosphere (argon) in a flame-dried flasks with addition of the reactants by using syringes; subsequent manipulations were conducted in air. Products were purified either by standard column chromatography (CC) or by preparative thin-layer chromatography (PTLC) on silica gel (230–400 mesh), using freshly distilled solvents; THF was dried over sodium–benzophenone and freshly distilled before usage. The mechanochemical reactions were performed with a Retsch MM400 mixer mill, using either stainless steel or zirconium oxide jars and grinding balls. Given yields refer to analytically pure samples. NMR spectra were taken on Bruker AVIII 600 MHz spectrometer (^{1}H NMR [600 MHz]; ^{13}C NMR [151 MHz]; ^{19}F NMR [565 MHz]); chemical shifts are reported relative to residual undeuterated solvent peaks (for $CDCl_3$: ^{1}H NMR $\delta = 7.26$, ^{13}C NMR $\delta = 77.16$; for DMSO-d_6: ^{1}H NMR $\delta = 2.50$, ^{13}C NMR $\delta = 39.52$) or to $CFCl_3$ (^{19}F NMR, $\delta = 0.00$) used as external standard. For detailed peak assignments in ^{13}C NMR additional 2D measurements were performed (HMQC). ESI-MS were performed with a Varian 500-MS LC Ion Trap; high resolution measurements were performed with a Waters Synapt G2-Si mass spectrometer. IR spectra were measured with an Agilent Cary 630 FTIR spectrometer, in neat. Elemental analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument. Melting points were determined in capillaries with a Melt-Temp II apparatus, and are uncorrected. The optical rotations were determined with an Anton Paar MCP 500 polarimeter at the temperatures indicated. Starting hydrazonoyl bromides **4** were prepared by NBS-mediated bromination of the respective trifluoroacetaldehyde hydrazones, in analogy to general literature protocols [22,23].

4.2. General procedures for the synthesis of bicyclic pyrazolines *6–10*

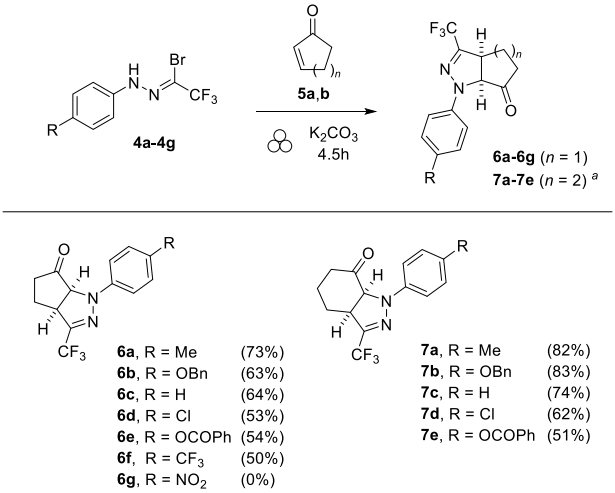
Method A: To a solution of hydrazonoyl bromide **4** (1.2 mmol) and



Scheme 1. Applications of CF_3-nitrile imines in (a) the synthesis of selected five- and six-membered heterocycles, and (b) preparation of trifluoromethylated (pyrazol-4-yl)alkanoic acids **A** through (3 + 2)-cycloaddition/deacylative aromatization route reported herein.



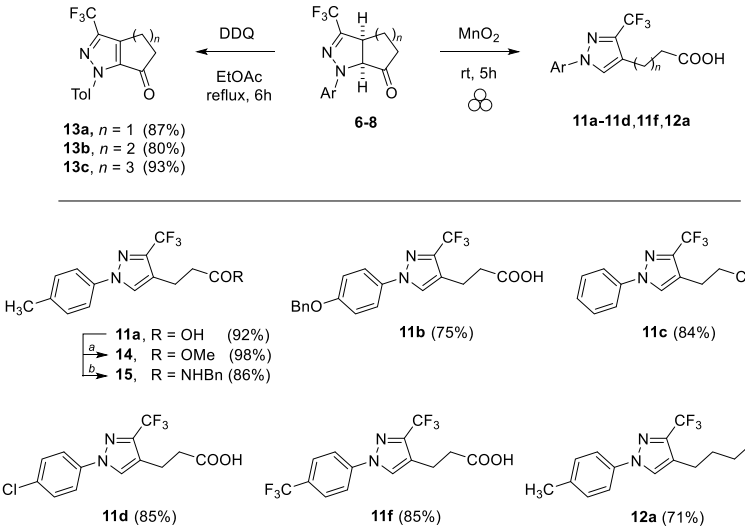
Scheme 2. Synthesis of bicyclic pyrazolines **6a**-**10a** derived from a model hydrazonoyl bromide **4a**; scope of cyclic enones: [a] not detected based on ^{1}H NMR of crude reaction mixture.



Scheme 3. Synthesis of 2-cyclopentenone and 2-cyclohexenone derived pyrazolines of type **6** and **7**; scope of nitrile imines: [a] accompanied by trace amounts of aromatized bicyclic analogues (<10 %).

cyclic enone **5** (1.0 mmol) in dry THF (4 mL) was added Et_3N (129 mg, 1.3 mmol), and the resulting mixture was stirred at room temperature for 3 days. Then, EtOAc (15 mL) was added, the mixture was filtered through short pad of Celite, and the solvents were removed under reduced pressure. Crude product was purified by standard column chromatography (CC) to give pyrazolines **6**–**8**.

Method B: A mixture of hydrazonoyl bromide **4** (2.0 mmol), cyclic enone 5 (1.0 mmol) and solid K_2CO_3 (315 mg, 2.28 mmol) was ball-milled in a 5 mL stainless steel grinding jar with three stainless steel balls (ø 7 mm), at 25 Hz for 4.5 h. Then, EtOAc (15 mL) was added, the mixture was filtered through short pad of Celite, and the solvents were removed in vacuo. Crude products were purified by standard column



13a, *n* = 1 (87%)
13b, *n* = 2 (80%)
13c, *n* = 3 (93%)

6-8

11a-11d,11f,12a

Scheme 4. Synthesis of *ω*-(3-CF_3-pyrazol-4-yl)alkanoic acids **11a**-**11f** and **12a**, preparation of bicyclic pyrazoles **13a**-**13c**, and functional group transformations in carboxylic acid **11a**: [a] MeOH, H_2SO_4 (cat.), rt, 24 h; [b] $SOCl_2$, $BnNH_2$, DMF (cat.), CH_2Cl_2, rt.

chromatography (CC) to give analytically pure pyrazolines **6**–**10**.

*4.2.1. 1-(p-tolyl)-3-trifluoromethyl-3a,4,5,6a-tetrahydro-1H-cyclopentapyrazol-6-one **(6a)***

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1): *Method A*, 93 mg (33 %); *Method B*, 206 mg (73 %); pale yellow solid, mp 88–89 °C. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 2.26–2.37 (m, 3H), 2.30 (s, 3H, Me), 2.41–2.48 (m, 1H), 4.24–4.28 (m, 1H, 3a-H), 4.60 (d, *J* = 11.5 Hz, 1H, 6a-H), 7.10–7.13 (m, 2H), 7.24–7.27 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): *δ* 20.7, 24.8, 35.8, 46.9, 68.9, 114.6, 121.3 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, CF_3), 129.8, 131.6, 138.3 (q, $^2J_{C\text{-}F}$ = 36.4 Hz, C-3), 140.8, 209.2; ^{19}F NMR (565 MHz, $CDCl_3$): *δ* −63.6 (s, CF_3); IR (neat): *ν* 1748, 1603, 1513, 1249, 1178, 1111, 1070, 1048, 1015 cm^{-1}; ESI-MS (*m*/*z*): 283.1 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{14}H_{13}F_3N_2O$ (282.3): C 59.57, H 4.64, N 9.92; found: C 59.51, H 4.65, N 10.14.

*4.2.2. 1-(4-benzyloxyphenyl)-3-trifluoromethyl-3a,4,5,6a-tetrahydro-1H-cyclopentapyrazol-6-one **(6b)***

CC (SiO_2, petroleum ether/CH_2Cl_2 1:4): *Method B*, 236 mg (63 %); colourless solid, mp 82–83 °C. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 2.25–2.48 (m, 4H), 4.22–4.26 (m, 1H, 3a-H), 4.54 (d, *J* = 11.5 Hz, 1H, 6a-H), 5.04 (s, 2H), 6.93–6.96 (m, 2H), 7.29–7.44 (m, 7H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): *δ* 24.9, 35.8, 47.0, 69.5, 70.7, 115.8, 116.1, 121.3 (q, $^1J_{C\text{-}F}$ = 269.7 Hz, CF_3), 127.6, 128.1, 128.7, 137.3, 137.5, 138.3 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3), 154.5, 209.3; ^{19}F NMR (565 MHz, $CDCl_3$): *δ* −63.6 (s, CF_3); IR (neat): *ν* 1748, 1510, 1241, 1178, 1103, 1070 cm^{-1}; ESI-MS (*m*/*z*): 397.3 (100, $[M+Na]^+$), 375.3 (37, $[M+H]^+$); elemental analysis calcd (%) for $C_{20}H_{17}F_3N_2O$ (374.4): C 64.17, H 4.58, N 7.48; found: C 64.11, H 4.62, N 7.40.

*4.2.3. 1-phenyl-3-trifluoromethyl-3a,4,5,6a-tetrahydro-1H-cyclopentapyrazol-6-one **(6c)***

CC (SiO_2, petroleum ether/EtOAc 8:1): *Method B*, 172 mg (64 %); light brown solid, mp 78–79 °C. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 2.26–2.49 (m, 4H), 4.25–4.29 (m, 1H, 3a-H), 4.62 (d, *J* = 11.4 Hz, 1H, 6a-H), 6.98–7.01 (m, 1H), 7.30–7.39 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): *δ* 24.7, 35.7, 47.0, 68.7, 114.6, 121.2 (q, $^1J_{C\text{-}F}$ = 269.9 Hz, CF_3), 122.2, 129.3, 139.0 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, C-3), 143.1, 209.0; ^{19}F NMR (565 MHz, $CDCl_3$): *δ* −63.7 (s, CF_3); IR (neat): *ν* 1744, 1595, 1575, 1502, 1315, 1182, 1126, 1108, 1062 cm^{-1}; (−)-ESI-MS (*m*/*z*): 269.3 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{13}H_{11}F_3N_2O$ (268.2): C 58.21, H 4.13, N 10.44; found: C 58.17, H 4.12, N 10.40.

*4.2.4. 1-(4-chlorophenyl)-3-trifluoromethyl-3a,4,5,6a-tetrahydro-1H-cyclopentapyrazol-6-one **(6d)***

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1): *Method B*, 160 mg (53 %); pale yellow solid, mp 107–109 °C. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 2.28–2.39 (m, 3H), 2.44–2.51 (m, 1H), 4.27–4.30 (m, 1H, 3a-H), 4.59 (d, *J* = 11.4 Hz, 1H, 6a-H), 7.25–7.27 (m, 2H), 7.30–7.32 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): *δ* 24.7, 35.8, 47.2, 68.7, 115.9, 121.1 (q, $^1J_{C\text{-}F}$ = 270.2 Hz, CF_3), 127.3, 129.3, 139.6 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C-3), 141.7, 208.9; ^{19}F NMR (565 MHz, $CDCl_3$): *δ* −63.8 (s, CF_3); IR (neat): *ν* 1744, 1595, 1498, 1316, 1262, 1115, 1074 cm^{-1}; ESI-MS (*m*/*z*): 305.2 (27, $[M\{^{37}Cl\}+H]^+$), 303.2 (100, $[M\{^{35}Cl\}+H]^+$); elemental analysis calcd (%) for $C_{13}H_{10}ClF_3N_2O$ (302.7): C 51.59, H 3.33, N 9.26; found: C 51.78, H 3.25, N 9.04.

*4.2.5. 1-(4-benzoyloxyphenyl)-3-trifluoromethyl-3a,4,5,6a-tetrahydro-1H-cyclopentapyrazol-6-one **(6e)***

CC (SiO_2, CH_2Cl_2): *Method B*, 210 mg (54 %); light orange solid, mp 130–131 °C. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 2.29–2.39 (m, 3H), 2.45–2.51 (m, 1H), 4.27–4.31 (m, 1H, 3a-H), 4.61 (d, *J* = 11.4 Hz, 1H, 6a-H), 7.15–7.18 (m, 2H), 7.41–7.44 (m, 2H), 7.49–7.53 (m, 2H), 7.62–7.65 (m, 1H), 8.18–8.21 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): *δ* 24.8, 35.7, 47.2, 69.0, 115.5, 121.2 (q, $^1J_{C\text{-}F}$ = 270.0 Hz, CF_3), 122.5, 128.7, 129.8, 130.3, 133.7, 139.4 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, C-3), 141.1, 145.9, 165.5, 209.0; ^{19}F NMR (565 MHz, $CDCl_3$): *δ* −63.7 (s, CF_3); IR (neat): *ν* 1733, 1603, 1585, 1510, 1312, 1260, 1200, 1126, 1059, 1014 cm^{-1}; ESI-MS (*m*/*z*): 411.3 (100, $[M+Na]^+$); elemental analysis calcd (%) for $C_{20}H_{15}F_3N_2O_3$ (388.3): C 61.86, H 3.89, N 7.21; found: C 61.88, H 3.86,

N 6.97.

4.2.6. 3-trifluoromethyl-1-(4-trifluoromethylphenyl)-3a,4,5,6a-tetrahydro-1H-cyclopentapyrazol-6-one (6f)

CC (SiO_2, petroleum ether/EtOAc 6:1): *Method B*, 168 mg (50 %); light yellow solid, mp 49–51 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.29–2.42 (m, 3H), 2.45–2.53 (m, 1H), 4.30–4.34 (m, 1H, 3a-H), 4.67 (d, J = 11.4 Hz, 1H, 6a-H), 7.43–7.46 (m, 2H), 7.54–7.57 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 24.5, 35.7, 47.2, 68.0, 114.3(br), 120.9 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 123.9 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, *i*-C), 124.6 (q, $^1J_{C\text{-}F}$ = 271.1 Hz, CF_3), 126.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2CH), 140.7 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C-3), 145.5, 208.7; ^{19}F NMR (565 MHz, $CDCl_3$): δ −64.0, −61.8, (2*s*, 2CF_3); IR (neat): ν 1744, 1618, 1312, 1252, 1185, 1103, 1066, 1014 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{10}F_6N_2O$ (336.2): C 50.01, H 3.00, N 8.33; found: C 49.98, H 3.14, N 8.45.

4.2.7. 1-(p-tolyl)-3-trifluoromethyl-3a,4,5,6,7a-pentahydro-1H-cyclohexapyrazol-7-one (7a)

CC (SiO_2, petroleum ether/CH_2Cl_2 2:1): *Method A*, 136 mg (46 %); *Method B*, 243 mg (82 %); pale yellow solid, mp 123–125 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.77–2.08 (m, 4H), 2.28 (s, 3H, Me), 2.43 (pseudo-dt, $J \approx$ 7.9, 16.4 Hz, 1H), 2.61 (ddd, J = 4.3, 7.8, 16.4 Hz, 1H), 3.96–4.00 (m, 1H, 3a-H), 4.52 (d, J = 11.8 Hz, 1H, 7a-H), 7.00–7.03 (m, 2H), 7.07–7.11 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 20.6, 20.7, 24.1, 37.7, 48.9, 70.7, 114.9, 121.0 (q, $^1J_{C\text{-}F}$ = 270.3 Hz, CF_3), 129.9, 131.9, 140.1 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3), 141.9, 208.0; ^{19}F NMR (565 MHz, $CDCl_3$): δ −63.6 (s, CF_3); IR (neat): ν 1718, 1521, 1301, 1267, 1103, 1036 cm^{-1}; ESI-MS (*m/z*): 297.3 (100, [M+H]$^+$); elemental analysis calcd (%) for $C_{15}H_{15}F_3N_2O$ (296.3): C 60.81, H 5.10, N 9.45; found: C 60.75, H 5.21, N 9.53.

4.2.8. 1-(4-benzoiloxyphenyl)-3-trifluoromethyl-3a,4,5,6,7a-pentahydro-1H-cyclohexapyrazol-7-one (7b)

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): *Method B*, 322 mg (83 %); pale yellow solid, mp 130–132 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.79–1.86 (m, 3H), 2.01–2.09 (m, 1H), 2.41–2.46 (m, 1H), 2.61–2.65 (m, 1H), 3.92–3.97 (m, 1H, 3a-H), 4.45 (d, J = 11.6 Hz, 1H, 7a-H), 5.02 (s, 2H), 6.90–6.93 (m, 2H), 7.05–7.08 (m, 2H), 7.30–7.43 (m, 5H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 20.8, 24.2, 37.9, 48.9, 70.5, 71.2, 115.7, 116.8, 121.0 (q, $^1J_{C\text{-}F}$ = 270.2 Hz, CF_3), 127.6, 128.1, 128.7, 137.2, 138.3, 140.3 (q, $^2J_{C\text{-}F}$ = 36.5 Hz, C-3), 154.7, 207.9; ^{19}F NMR (565 MHz, $CDCl_3$): δ −63.6 (s, CF_3); IR (neat): ν 1715, 1510, 1305, 1238, 1181, 1108, 1014 cm^{-1}; ESI-MS (*m/z*): 411.3 (100, [M+Na]$^+$), 389.3 (73, [M+H]$^+$); elemental analysis calcd (%) for $C_{21}H_{19}F_3N_2O_2$ (388.4): C 64.94, H 4.93, N 7.21; found: C 64.73, H 4.91, N 7.30.

4.2.9. 1-phenyl-3-trifluoromethyl-3a,4,5,6,7a-pentahydro-1H-cyclohexapyrazol-7-one (7c)

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): *Method B*, 209 mg (74 %); pale yellow solid, mp 113–114 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.80–1.85 (m, 1H), 1.90–2.08 (m, 3H), 2.44 (dddd, J = 1.1, 7.8, 8.8, 16.5 Hz, 1H), 2.62 (dddd, J = 1.2, 4.2, 7.9, 16.5 Hz, 1H), 4.00–4.03 (m, 1H, 3a-H), 4.57 (d, J = 11.8 Hz, 1H, 7a-H), 6.97–7.00 (m, 1H), 7.11–7.14 (m, 2H), 7.27–7.30 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 20.5, 24.0, 37.6, 49.0, 70.3, 114.7, 121.0 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 122.3, 129.4, 140.4 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, C-3), 144.2, 207.8; ^{19}F NMR (565 MHz, $CDCl_3$): δ −63.7 (s, CF_3); IR (neat): ν 1722, 1577, 1508, 1320, 1267, 1129, 1092, 1025 cm^{-1}; ESI-MS (*m/z*): 283.4 (100, [M+H]$^+$); elemental analysis calcd (%) for $C_{14}H_{13}F_3N_2O$ (282.3): C 59.57, H 4.64, N 9.92; found: C 59.44, H 4.38, N 9.85.

4.2.10. 1-(4-chlorophenyl)-3-trifluoromethyl-3a,4,5,6,7a-pentahydro-1H-cyclohexapyrazol-7-one (7d)

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): *Method B*, 196 mg (62 %); colourless solid, mp 109–110 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.83–2.06 (m, 4H), 2.42–2.48 (m, 1H), 2.56–2.61 (m, 1H), 4.02–4.05 (m, 1H, 3a-H), 4.56 (d, J = 11.9 Hz, 1H, 7a-H), 7.04–7.07 (m, 2H), 7.22–7.25 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 20.6, 23.9, 37.6, 49.0, 70.1, 115.9, 120.8 (q, $^1J_{C\text{-}F}$ = 270.5 Hz, CF_3), 127.3, 129.3, 140.9 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, C-3), 142.7, 207.3; ^{19}F NMR (565 MHz, $CDCl_3$): δ −63.9 (s, CF_3); IR (neat): ν 1718, 1588, 1498, 1206, 1181, 1111, 1036 cm^{-1}; ESI-MS (*m/z*): 319.3 (42, [M{^{37}Cl}+H]$^+$), 317.2 (100, [M{^{35}Cl}+H]$^+$); elemental analysis calcd (%) for $C_{14}H_{12}ClF_3N_2O$ (316.7): C 53.09, H 3.82, N 8.85; found: C 53.04, H 3.66, N 8.87.

4.2.11. 1-(4-benzoyloxyphenyl)-3-trifluoromethyl-3a,4,5,6,7a-pentahydro-1H-cyclohexapyrazol-7-one (7e)

CC (SiO_2, petroleum ether/EtOAc 3:1): *Method B*, 205 mg (51 %); yellow solid, mp 142–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.84 (dddd, J = 3.1, 6.0, 11.6, 14.6 Hz, 1H), 1.97–2.09 (m, 3H), 2.46 (pseudo-dt, $J \approx$ 7.5, 16.6 Hz, 1H), 2.64 (dddd, J = 1.1, 4.3, 7.8, 16.6 Hz, 1H), 4.02–4.05 (m, 1H, 3a-H), 4.57 (d, J = 11.8 Hz, 1H, 7a-H), 7.12–7.20 (m, 4H), 7.49–7.53 (m, 2H), 7.62–7.65 (m, 1H), 8.17–8.20 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 20.5, 24.0, 37.7, 49.1, 70.5, 115.5, 120.9 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 122.5, 128.7, 129.7, 130.3, 133.7, 140.8 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, C-3), 142.1, 145.9, 165.5, 207.6; ^{19}F NMR (565 MHz, $CDCl_3$): δ −63.8 (s, CF_3); IR (neat): ν 1729, 1712, 1506, 1301, 1267, 1200, 1170, 1126, 1062, 1049 cm^{-1}; ESI-MS (*m/z*): 425.4 (100, [M+Na]$^+$), 403.5 (18, [M+H]$^+$); elemental analysis calcd (%) for $C_{21}H_{17}F_3N_2O_3$ (402.4): C 62.69, H 4.26, N 6.96; found: C 62.70, H 4.36, N 6.80.

4.2.12. 1-(p-tolyl)-3-trifluoromethyl-3a,4,5,6,7,7a-hexahydro-1H-cycloheptapyrazol-7-one (8a)

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): *Method A*, 96 mg (31 %); *Method B*, 286 mg (92 %); pale yellow solid, mp 115–116 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.44–1.68 (m, 3H), 1.80–1.89 (m, 2H), 2.03–2.09 (m, 1H), 2.28 (s, 3H, Me), 2.33–2.38 (m, 1H), 2.64 (pseudo-td, $J \approx$ 4.4, 11.8 Hz, 1H), 3.84–3.88 (m, 1H, 3a-H), 4.83 (d, J = 14.0 Hz, 1H, 8a-H), 6.84–6.87 (m, 2H), 7.07–7.10 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 20.7, 24.7, 25.5, 28.2, 39.7, 45.6, 73.6, 113.6, 121.1 (q, $^1J_{C\text{-}F}$ = 270.2 Hz, CF_3), 130.1, 131.3, 138.2 (q, $^2J_{C\text{-}F}$ = 36.3, C-3), 140.9, 208.9; ^{19}F NMR (565 MHz, $CDCl_3$): δ −63.4 (s, CF_3); IR (neat): ν 1715, 1603, 1517, 1305, 1267, 1148, 1111, 1062 cm^{-1}; ESI-MS (*m/z*): 311.3 (100, [M+H]$^+$); elemental analysis calcd (%) for $C_{16}H_{17}F_3N_2O$ (310.3): C 61.93, H 5.52, N 9.03; found: C 61.75, H 5.53, N 9.09.

4.2.13. (3aS,5S,7aS)-5-isopropenyl-7a-methyl-1-(p-tolyl)-3-trifluoromethyl-3a,4,5,6,7a-pentahydro-1H-cyclohexapyrazol-7-one (10a)

CC (SiO_2, petroleum ether/Et_2O 10:1): *Method B*, 165 mg (47 %, dr: 94:6 *exo/endo*); thick yellow oil; $[\alpha]_D^{20}$ = −15.4 (*c* = 0.21, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$), major isomer: δ 1.33 (s, 3H, Me), 1.55 (ddd, J = 6.2, 12.9, 14.3 Hz, 1H), 1.71 (s, 3H, Me), 1.94–1.98 (m, 1H), 2.29 (s, 3H, Me), 2.40 (dd, J = 9.8, 17.1 Hz, 1H), 2.72–2.78 (m, 1H), 2.88 (ddd, J = 1.8, 8.0, 17.1 Hz, 1H), 3.44 (d_{br}, $J \approx$ 5.9 Hz, 1H), 4.74, 4.80 ($2s_{br}$, 1H each), 6.93–6.96 (m, 2H), 7.06–7.09 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$), major isomer: δ 17.9, 20.5, 20.6, 29.4, 37.8, 43.5, 55.7, 74.4, 110.7, 116.1, 121.3 (q, $^1J_{C\text{-}F}$ = 270.2 Hz, CF_3), 130.0, 132.4, 138.8 (q, $^2J_{C\text{-}F}$ = 36.4, C-3), 139.8, 146.3, 209.4; ^{19}F NMR (565 MHz, $CDCl_3$): δ −62.8 (s, CF_3; major), −64.1 (s, CF_3; minor); IR (neat): ν 1718, 1513, 1260, 1189, 1115, 1062 cm^{-1}; ESI-MS (*m/z*): 351.3 (100, [M+H]$^+$); elemental analysis calcd (%) for $C_{19}H_{21}F_3N_2O$ (350.4): C 65.13, H 6.04, N 8.00; found: C 65.19, H 6.03, N 7.87.

4.3. General procedure for synthesis of alkanoic acids 11–12 via mechanochemical oxidation of pyrazolines 6–7 with activated MnO_2

A mixture of bicyclic pyrazoline derivative **6**–**7** (1.0 mmol) and activated MnO_2 (85 %, 40 mmol) was ball-milled in a 10 mL zirconium oxide jar with three zirconium oxide grinding balls (ø 5 mm), at 23 Hz for 5 h. Then, H_2O (50 mL) was added, the mixture was heated to reflux, filtered, the filtrate was allowed to reach room temperature and acidified with 6 M HCl_{aq} to reach pH~6. After brine (20 mL) was added, the

mixture was extracted with EtOAc (4 × 30 mL), the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give crude product **11**–**12**, which was purified by preparative thin-layer chromatography (PTLC).

4.3.1. 3-[1-(p-tolyl)-3-trifluoromethylpyrazol-4-yl]propionic acid (11a)

PTLC (SiO_2, MeOH/EtOAc/DCM 1:2:16), 272 mg (92 %); colourless solid, mp 136–137 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.34 (s, 3H), 2.61 (t, J = 7.7 Hz, 2H), 2.81 (t, J = 7.7 Hz, 2H), 7.31–7.34 (m, 2H), 7.68–7.72 (m, 2H), 8.50 (s, 1H), 12.24 (s_{br}, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 18.4, 20.4, 33.8, 118.8, 120.5, 121.9 (q, $^1J_{C\text{-}F}$ = 269.2 Hz), 128.8, 130.0, 136.6, 136.9, 139.5 (q, $^2J_{C\text{-}F}$ = 35.8 Hz), 173.3; ^{19}F NMR (565 MHz, DMSO-d_6): δ −59.8 (s, CF_3); IR (neat): ν 1707, 1498, 1439, 1260, 1211, 1159, 1122, 1066 cm^{-1}; HRMS (ESI-TOF) *m/z*: calculated for $C_{14}H_{12}F_3N_2O_2$ ([M−H]$^+$) 297.0851, found 297.0850.

4.3.2. 3-[1-(4-benzyloxyphenyl)-3-trifluoromethylpyrazol-4-yl]propionic acid (11b)

PTLC (SiO_2, MeOH/EtOAc/DCM 1:2:20), 292 mg (75 %); colourless solid, mp 108–109 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.59 (t, J = 7.7 Hz, 2H), 2.80 (t, J = 7.7 Hz, 2H), 5.16 (s, 2H), 7.15–7.18 (m, 2H), 7.33–7.36 (m, 1H), 7.39–7.42 (m, 2H), 7.46–7.48 (m, 2H), 7.71–7.74 (m, 2H), 8.45 (s, 1H), 12.21 (s_{br}, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 18.6, 34.4, 69.6, 115.6, 120.5, 120.6, 121.9 (q, $^1J_{C\text{-}F}$ = 269.2 Hz), 127.7, 127.9, 128.4, 128.9, 132.5, 136.7, 139.2 (q, $^2J_{C\text{-}F}$ = 35.4 Hz), 157.5, 173.6; ^{19}F NMR (565 MHz, DMSO-d_6): δ −59.6 (s, CF_3); IR (neat) ν 1700, 1517, 1301, 1252, 1170, 1129, 1059 cm^{-1}; HRMS (ESI-TOF) *m/z*: calculated for $C_{20}H_{16}F_3N_2O_3$ ([M−H]$^+$) 389.1113, found 389.1120.

4.3.3. 3-[1-phenyl-3-trifluoromethylpyrazol-4-yl]propionic acid (11c)

PTLC (SiO_2, MeOH/EtOAc/DCM 1:2:20), 239 mg (84 %); light brown solid, mp 123–124 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.62 (t, J = 7.7 Hz, 2H), 2.82 (t, J = 7.7 Hz, 2H), 7.38–7.41 (m, 1H), 7.52–7.55 (m, 2H), 7.81–7.84 (m, 2H), 8.57 (s, 1H), 12.25 (s_{br}, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 18.4, 33.8, 118.9, 120.7, 121.8 (q, $^1J_{C\text{-}F}$ = 269.3 Hz), 127.4, 129.1, 129.7, 138.7, 139.8 (q, $^2J_{C\text{-}F}$ = 35.8 Hz), 173.3; ^{19}F NMR (565 MHz, DMSO-d_6): δ −59.8 (s, CF_3); IR (neat) ν 1707, 1498, 1267, 1204, 1167, 1126, 1062 cm^{-1}; HRMS (ESI-TOF) *m/z*: calculated for $C_{13}H_{10}F_3N_2O_2$ ([M−H]$^+$) 283.0694, found 283.0697.

4.3.4. 3-[1-(4-chlorophenyl)-3-trifluoromethylpyrazol-4-yl]propionic acid (11d)

PTLC (SiO_2, MeOH/EtOAc/DCM 1:2:16), 271 mg (85 %); pale yellow solid, mp 109–111 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.61 (t, J = 7.7 Hz, 2H), 2.81 (t, J = 7.7 Hz, 2H), 7.60–7.63 (m, 2H), 7.86–7.89 (m, 2H), 8.61 (s, 1H), 12.26 (s_{br}, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 18.3, 33.7, 119.0, 121.0, 121.7 (q, $^1J_{C\text{-}F}$ = 269.5 Hz), 129.3, 129.6, 131.6, 137.5, 140.1 (q, $^2J_{C\text{-}F}$ = 35.9 Hz), 173.2; ^{19}F NMR (565 MHz, DMSO-d_6): δ −59.9 (s, CF_3); IR (neat): ν 1711, 1491, 1241, 1156, 1118, 1062 cm^{-1}; HRMS (ESI-TOF) *m/z*: calculated for $C_{13}H_9ClF_3N_2O_2$ ([M−H]$^+$) 317.0305, found 317.0308.

4.3.5. 3-[1-(4-trifluoromethylphenyl)-3-trifluoromethylpyrazol-4-yl] propionic acid (11e)

PTLC (SiO_2, MeOH/EtOAc/DCM 1:2:16), 310 mg (88 %); cream solid, mp 127–128 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.63 (t, J = 7.7 Hz, 2H), 2.82 (t, J = 7.7 Hz, 2H), 7.91–7.94 (m, 2H), 8.06–8.10 (m, 2H), 8.74 (s, 1H), 12.26 (s_{br}, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 18.3, 33.5, 119.2, 121.3, 121.6 (q, $^1J_{C\text{-}F}$ = 269.6 Hz), 123.9 (q, $^1J_{C\text{-}F}$ = 272.0 Hz), 127.0 (q, $^3J_{C\text{-}F}$ = 3.5 Hz), 127.5 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 129.6, 140.8 (q, $^2J_{C\text{-}F}$ = 36.1 Hz), 141.4, 173.2; ^{19}F NMR (565 MHz, DMSO-d_6): δ −60.1, −60.9 (2 s, 2CF_3); IR (neat): ν 1711, 1398, 1320, 1245, 1111, 1059 cm^{-1}; HRMS (ESI-TOF) *m/z*: calculated for $C_{14}H_9F_6N_2O_2$ ([M−H]$^+$) 351.0568, found 351.0574.

4.3.6. 4-[1-(p-tolyl)-3-trifluoromethylpyrazol-4-yl]butyric acid (12a)

PTLC (SiO_2, MeOH/CH_2Cl_2 5:85), 222 mg (71 %); colourless solid, mp 83–84 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.84 (quint$_{br}$, $J \approx$ 7.5 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.34 (s, 3H, Me), 2.58 (t, J = 7.6 Hz, 2H), 7.29–7.34 (m, 2H), 7.69–7.74 (m, 2H), 8.50 (s, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 20.4, 22.2, 25.2, 33.7, 118.8, 121.2, 121.9 (q, $^1J_{C\text{-}F}$ = 269.3 Hz), 128.8, 129.9, 136.6, 136.8, 139.5 (q, $^2J_{C\text{-}F}$ = 35.6 Hz), 174.7; ^{19}F NMR (565 MHz, DMSO-d_6): δ −59.6 (s, CF_3); IR (neat): ν 1711, 1521, 1495, 1290, 1241, 1167, 1122, 1059 cm^{-1}; HRMS (ESI-TOF) *m/z*: calculated for $C_{15}H_{16}F_3N_2O_2$ ([M+H]$^+$) 313.1164, found 313.1163.

4.4. Synthesis of bicyclic pyrazoles 13a-13c

To a solution of pyrazoline **6**–**8** (1.0 mmol) in EtOAc (10 mL) was added solid DDQ (341 mg, 1.5 mmol), and the resulting mixture was refluxed for 6 h. The mixture was allowed to reach room temperature, the solvent was removed in vacuo, the resulting was diluted in CH_2Cl_2 (50 mL) and extracted with sat. aqueous solution of Na_2CO_3 (3 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and solvent was removed under reduced pressure. Crude product **13** was purified by standard column chromatography (CC).

4.4.1. 1-(p-tolyl)-3-trifluoromethyl-4,5-dihydro-1H-cyclopentapyrazol-6-one (13a)

CC (SiO_2, petroleum ether/CH_2Cl_2 4:1): 244 mg (87 %); colourless solid, mp 119–120 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.40 (s, 3H, Me), 3.03–3.05 (m, 2H), 3.18–3.20 (m, 2H), 7.27–7.30 (m, 2H), 7.91–7.93 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 17.8, 21.2, 43.6, 118.3, 121.0 (q, $^1J_{C\text{-}F}$ = 269.0 Hz, CF_3), 130.0, 136.3, 137.2 (q, $^2J_{C\text{-}F}$ = 39.6 Hz, C-3), 144.4, 145.9, 188.5; ^{19}F NMR (565 MHz, $CDCl_3$): δ −61.7 (s, CF_3); IR (neat): ν 1715, 1513, 1379, 1260, 1133, 1088, 1051, 1003 cm^{-1}; ESI-MS (*m/z*): 281.4 (100, [M+H]$^+$); elemental analysis calcd (%) for $C_{14}H_{11}F_3N_2O$ (280.3): C 60.00, H 3.96, N 10.00; found: C 60.07, H 4.04, N 9.92.

4.4.2. 1-(p-tolyl)-3-trifluoromethyl-4,5,6-trihydro-1H-cyclohexapyrazol-7-one (13b)

CC (SiO_2, petroleum ether/CH_2Cl_2 2:1): 235 mg (80 %); pale yellow solid, mp 93–95 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.20–2.24 (m, 2H), 2.42 (s, 3H, Me), 2.60–2.63 (m, 2H), 2.95–2.97 (m, 2H), 7.24–7.27 (m, 2H), 7.35–7.37 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 20.8, 21.4, 24.2, 39.8, 121.4 (q, $^1J_{C\text{-}F}$ = 269.5 Hz, CF_3), 125.4, 129.3, 129.4, 136.0, 137.0, 139.47, 139.50 (q, $^2J_{C\text{-}F}$ = 37.9 Hz, C-3), 187.5; ^{19}F NMR (565 MHz, $CDCl_3$): δ −61.4 (s, CF_3); IR (neat): ν 1696, 1510, 1375, 1260, 1197, 1122, 1082 cm^{-1}; ESI-MS (*m/z*): 317.4, (100, [M+Na]$^+$), 295.4 (32, [M+H]$^+$); elemental analysis calcd (%) for $C_{15}H_{13}F_3N_2O$ (294.3): C 61.22, H 4.45, N 9.52; found: C 61.24, H 4.56, N 9.61

4.4.3. 1-(p-tolyl)-3-trifluoromethyl-4,5,6,7-tetrahydro-1H-cycloheptapyrazol-7-one (13c)

CC (SiO_2, petroleum ether/CH_2Cl_2 3:2): 287 mg (93 %); pale yellow solid, mp 97–98 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.93–2.01 (m, 4H), 2.40 (s, 3H, Me), 2.76–2.78 (m, 2H), 2.95–2.98 (m, 2H), 7.20–7.24 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 21.4, 22.1, 22.5, 25.5, 43.0, 121.5 (q, $^1J_{C\text{-}F}$ = 270.0 Hz, CF_3), 125.5, 125.6, 129.6, 137.6, 139.2, 140.4 (q, $^2J_{C\text{-}F}$ = 36.5 Hz, C-3), 140.5, 192.4; ^{19}F NMR (565 MHz, $CDCl_3$): δ −60.9 (s, CF_3); IR (neat): ν 1677, 1502, 1372, 1279, 1245, 1163, 1111, 1082 cm^{-1}; ESI-MS (*m/z*): 331.3 (100, [M+Na]$^+$), 309.3 (32, [M+H]$^+$); HRMS (ESI-TOF) *m/z*: calculated for $C_{16}H_{16}F_3N_2O$ ([M+H]$^+$) 309.1215, found 309.1219.

4.5. Synthesis of 3-[1-(p-tolyl)-3-trifluoromethylpyrazol-4-yl]propanoate (14)

To a solution of carboxylic acid **11a** (298 mg, 1.0 mmol) in methanol (10 mL), concentrated H_2SO_4 (5 drops) was added and the resulting

mixture was stirred for 24 h at room temperature. The resulting was poured into the beaker with iced water (15 mL), the obtained precipitate product was filtered off and dried under vacuum to give methyl ester **14** (291 mg, 93 %) as colorless solid. Mp 96–99 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.38 (s, 3H, Me), 2.64 (t_{br}, $J \approx 7.4$ Hz, 2H), 2.96 (t_{br}, $J \approx 7.4$ Hz, 2H), 3.69 (s, 3H, OMe), 7.22–7.27 (m, 2H), 7.51–7.55 (m, 2H), 7.77 (s 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 18.8, 21.1, 34.7, 51.8, 119.7, 120.4, 122.0 (q, $^{1}J_{C\text{-}F}$ = 269.6 Hz, CF_3), 127.8, 130.2, 137.3, 137.6, 141.3 (q, $^{2}J_{C\text{-}F}$ = 36.5, C-3), 173.1; ^{19}F NMR (565 MHz, $CDCl_3$): δ −61.0 (s, CF_3); IR (neat): ν 1730, 1290, 1260, 1223, 1156, 1111, 1051, 1014 cm^{-1}; ESI-MS (*m/z*): 335.3 (76, $[M+Na]^+$), 313.3 (100, $[M+H]^+$); HRMS (ESI-TOF) *m/z*: calculated for $C_{15}H_{16}F_3N_2O_2$ ($[M+H]^+$) 313.1164, found 313.1162.

4.6. Synthesis of N-benzyl-3-[1-(p-tolyl)-3-trifluoromethylpyrazol-4-yl] propionamide (15)

To a solution of carboxylic acid **11a** (298 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL), $SOCl_2$ (417 mg, 0.25 mL, 3.5 mmol) was added followed by dry DMF (2 drops), and the mixture was stirred overnight under inert atmosphere of argon. The solvents and excess $SOCl_2$ were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (10 mL), Et_3N (2.0 mmol) was added followed by dropwise addition of benzylamine (1.3 mmol), and the mixture was stirred for 3 h at room temperature. After solvents were removed in vacuo, the resulting material was purified by standard column chromatography (SiO_2, CH_2Cl_2 gradient CH_2Cl_2/Et_2O 1:1) to give **15** (333 mg, 86 %) as colorless solid. Mp, 116–117 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.39 (s, 3H, Me), 2.50 (t_{br}, $J \approx 7.1$ Hz, 2H), 3.00 (t_{br}, $J \approx 7.1$ Hz, 2H), 4.40 (d, J = 5.8 Hz, 2H), 5.85 (t_{br}, $J \approx 5.8$ Hz, 1H, NH), 7.14–7.25 (m, 7H), 7.47–7.50 (m, 2H), 7.75 (s, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 19.3, 21.1, 37.1, 43.7, 119.6, 120.4, 122.0 (q, $^{1}J_{C\text{-}F}$ = 269.3 Hz, CF_3), 127.6, 127.7, 128.2, 128.8, 130.1, 137.2, 137.6, 138.3, 141.2 (q, $^{2}J_{C\text{-}F}$ = 36.4, C-3), 171.5; ^{19}F NMR (565 MHz, $CDCl_3$): δ −60.8 (s, CF_3); IR (neat): ν 1715, 1648, 1520, 1488, 1252, 1163, 1115, 1059 cm^{-1}; ESI-MS (*m/z*): 410.3 (100, $[M+Na]^+$), 388.4 (37, $[M+H]^+$); elemental analysis calcd (%) for $C_{21}H_{20}F_3N_3O$ (387.4): C 65.11, H 5.20, N 10.85; found: C 65.07, H 5.10, N 10.69.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

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References

[1] (1a) M.A.H. Ismail, J. Lehmann, D.A.A. El Ella, A. Albohy, K.A.M. Abouzid, Lonazolac analogues: molecular modeling, synthesis and in vivo anti-inflammatory activity, Med. Chem. Res. 18 (2009) 725–744;
(1b) M. Elkady, R. Nieß, A.M. Schaible, J. Bauer, S. Luderer, G. Ambrosi, O. Werz, S.A. Laufer, Modified acidic nonsteroidal anti-inflammatory drugs as dual inhibitors of mPGES-1 and 5-LOX, J. Med. Chem. 55 (2012) 8958–8962;
(1c) M.F. Harras, R. Sabour, O.M. Alkamali, Discovery of new non-acidic lonazolac analogues with COX-2 selectivity as potent anti-inflammatory agents, Med. Chem. Commun. 10 (2019) 1775–1788.

[2] P. Gudimani, N.U. Hebbar, S.L. Shastri, L.A. Shastri, A.K. Shettar, J.H. Hoskeri, S. Joshi, V.A. Sunagar, A new approach for the synthesis of tri-substituted pyrazole propionic acids derivatives: anti-inflammatory, antimicrobial and molecular docking studies, J. Mol. Struct. 1285 (2023), 135405.

[3] (3a) M. Ahmadi, S. Bekeschus, K.-D. Weltmann, T. von Woedtke, K. Wende, Non-steroidal anti-inflammatory drugs: recent advances in the use of synthetic COX-2 inhibitors, RSC Med. Chem. 13 (2022) 471–496;
(3b) D. Priya, P. Gopinath, L.S. Dhivya, A. Vijaybabu, M. Haritha, S. Palaniappan, M.K. Kathiravan, Structural insights into pyrazoles as agents against anti-inflammatory and related disorders, ChemistrySelect 7 (2022), e202104429.

[4] V. Pawar, L.A. Shastri, P. Gudimani, S. Joshi, V. Sunagar, Synthesis, characterization and molecular docking of novel lonazolac analogues 3-(3-hydroxy-5-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives: highly potential COX-1/COX-2, matrix metalloproteinase and protein denaturation inhibitors, J. Mol. Struct. 1260 (2022), 132782.

[5] L.P. Khonde, R. Müller, G.A. Boyle, V. Reddy, A.T. Nchinda, C.J. Eyermann, S. Fienberg, V. Singh, A. Myrick, E. Abay, M. Njoroge, N. Lawrence, Q. Su, T. G. Myers, H.I.M. Boshoff, C.E. Barry III, F.A. Sirgel, P.D. van Helden, L. M. Massoudi, G.T. Robertson, A.J. Lenaerts, G.S. Basarab, S.R. Ghorpade, K. Chibale, 1,3-diarylpyrazolyl-acylsulfonamidesas potent anti-tuberculosis agents targeting cell wall biosynthesis in *Mycobacterium tuberculosis*, J. Med. Chem 64 (2021) 12790–12807.

[6] (6a) G. Blay, I. Fernández, E. Molina, M.C. Muñoz, J.R. Pedro, C. Vila, Diastereoselective Michael addition of (*S*)-mandelic acid enolate to 2-arylidene-1,3-diketones: enantioselective diversity-oriented synthesis of densely substituted pyrazoles, Tetrahedron 62 (2006) 8069–8076;
(6b) M.F.A. Adamo, E.F. Duffy, Multicomponent synthesis of 3-heteroarylpropionic acids, Org. Lett. 8 (2006) 5157–5159;
(6c) B. Çalişkan, S. Luderer, Y. Özkan, O. Werz, E. Banoglu, Pyrazol-3-propanoic acid derivatives as novel inhibitors of leukotriene biosynthesis in human neutrophils, Eur. J. Med. Chem. 46 (2011) 5021–5033;
(6d) K. Tan, C. Jäger, S. Geissler, D. Schlenzig, M. Buchholz, D. Ramsbeck, Synthesis and structure-activity relationships of pyrazole-based inhibitors of meprin α and β, J. Enzyme Inhibit. Med. Chem. 38 (2023), 2165648.

[7] (7a) M.K. Bratenko, V.A. Chornous, M.V. Vovk, Functionally substituted 3-heterylpyrazoles: XI. 3-[3-aryl(hetaryl)pyrazol-4-yl]propenoic and propanoic acids, Russ. J. Org. Chem. 38 (2002) 1223–1229;
(7b) G.J. Reddy, K.S. Rao, A simple and rapid synthesis of 4*H*-4-oxo-1-benzopyran-3-yl and 1,3-diarylpyrazol-4-yl propanoic acids, Heterocycl. Commun. 12 (2006) 423–426;
(7c) M. Deepa, V.H. Babu, R. Parameshwar, B.M. Reddy, Synthesis of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl) propanoic acids using diimide reduction, E-Journal Chem. 9 (2012) 420–424.

[8] (8a) B.M. Chougala, S. Samundeeswari, M. Holiyachi, L.A. Shastri, S. Dodamani, S. Jalalpure, S.R. Dixit, S.D. Joshi, V.A. Sunagar, Synthesis, characterization and molecular docking studies of substituted 4-coumarinylpyrano[2,3-*c*]pyrazole derivatives as potent antibacterial and anti-inflammatory agents, Eur. J. Med. Chem. 125 (2017) 101–116;
(8b) M.K.F. El-Sayed, M.M. El-Shahawi, Y.M. Ali, D.R. Abdel-Haleem, F.S.M.A. El-Azm, Synthesis, larvicidal efficiency and molecular docking studies of novel annulated pyrazno[2,3-*c*]pyrazoles against *Culex pipiens* L. and *Musca domestica* L. larvae, Bioorg. Chem. 130 (2023), 106258.

[9] X. Pan, H. Wang, H.-G. Xia, J. Wu, An unexpected three-component reaction of 2-alkylenecyclobutanone and *N*′-(2-alkynylbenzylidene)hydrazide with water, RSC Adv 5 (2015) 85225–85228.

[10] (10a) G. Utecht, A. Fruziński, M. Jasiński, Polysubstituted 3-trifluoromethylpyrazoles: regioselective (3 + 2)-cycloaddition of trifluoroacetonitrile imines with enol ethers and functional group transformations, Org. Biomol. Chem. 16 (2018) 1252–1257;
(10b) G. Utecht, G. Mlostoń, M. Jasiński, A straightforward access to trifluoromethylated spirobipyrazolines through a double (3 + 2)-cycloaddition of fluorinated nitrile imines with alkoxyallenes, Synlett 29 (2018) 1753–1758;
(10c) Y.-C. Tian, J.-K. Li, F.-G. Zhang, J.-A. Ma, regioselective decarboxylative cycloaddition route to fully substituted 3-CF_3-pyrazoles from nitrilimines and isoxazolidinediones, Adv. Synth. Catal. 363 (2021) 1093–2097;
(10d) A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński, A straightforward access to 3-trifluoromethyl-1*H*-indazoles via (3 + 2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile, J. Fluorine Chem. 241 (2021), 109691;
(10e) G. Utecht-Jarzyńska, K. Nagła, G. Mlostoń, H. Heimgartner, M. Palusiak, M. Jasiński, A straightforward conversion of 1,4-quinones into polycyclic pyrazoles via [3 + 2]-cycloaddition with fluorinated nitrile imines, Beilstein J. Org. Chem. 17 (2021) 1509–1517;
(10f) Y. Zhou, C.-F. Gao, H. Ma, J. Nie, J.-A. Ma, F.-G. Zhang, Quadruple functionalized pyrazole pharmacophores by one-pot regioselective [3 + 2] cycloaddition of fluorinated nitrile imines and dicyanoalkenes, Chem. Asian, J. 17 (2022), e202200436;
(10g) K.-H. Wang, H. Liu, X. Liu, C. Bian, J. Wang, Y. Su, D. Huang, Y. Hu, Regioselective synthesis of 3-trifluoromethyl 4-substituted pyrazoles by [3 + 2] cycloaddition of trifluoroacetonitrile imines and nitroalkenes, Asian J. Org. Chem. 11 (2022), e202200103.

[11] (11a) Y. Zhang, J.-L. Zeng, Z. Chen, R. Wang, Base-promoted (3 + 2) cycloaddition of trifluoroacetohydrazonoyl chlorides with imidates en route to trifluoromethyl-1,2,4-triazoles, J. Org. Chem. 87 (2022) 14514–14522;
(11b) D. Wang, X. Wan, Y. Zhou, J. Liu, J. Cai, G.-J. Deng, Facile synthesis of fully substituted 1,2,4-triazoles via [3 + 2] cycloaddition of nitrileimines with amidines under transition metal-free conditions, Asian J. Org. Chem. 12 (2023), e202200674.

[12] (12a) G. Utecht, J. Sioma, M. Jasiński, G. Mlostoń, Expected and unexpected results in reactions of fluorinated nitrile imines with (cyclo)aliphatic thioketones, J. Fluorine Chem. 201 (2017) 68–75;
(12b) G. Mlostoń, P. Grzelak, G. Utecht, M. Jasiński, First [3 + 2]-cycloadditions of thiochalcones as C=S dipolarophiles in reactions with fluorinated nitrile imines, Synthesis 49 (2017) 2129–2137;
(12c) G. Utecht-Jarzyńska, M. Jasiński, K. Świątek, G. Mlostoń, H. Heimgartner, Novel trifluoromethylated spiro-1,3,4-thiadiazoles via [3 + 2]-cycloaddition of 2,3-diphenylcyclopropenethione with selected in situ-generated nitrile imines derived from trifluoroacetonitrile, Heterocycles 101 (2020) 251–262;
(12d) G. Utecht-Jarzyńska, S.S. Mykhaylychenko, E.B. Rusanov, Y. G. Shermolovich, M. Jasiński, G. Mlostoń, Highly fluorinated 2,3-dihydro-1,3,4-thiadiazole derivatives via [3 + 2]-cycloadditions of tertiary thioamides with nitrile imines derived from trifluoroacetonitrile, J. Fluorine Chem. 242 (2021), 109702.

[13] G. Utecht-Jarzyńska, A. Michalak, J. Banaś, G. Mlostoń, M. Jasiński, Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: an access to fluorinated 1,3,4-thiadiazine derivatives via (3 + 3)-annulation, J. Fluorine Chem. 222–223 (2019) 8–14.

[14] A. Kowalczyk, K. Świątek, M. Celeda, G. Utecht-Jarzyńska, A. Jaskulska, K. Gach-Janczak, M. Jasiński, Trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones via (3 + 3)-annulation of nitrile imines with α-amino esters, Materials 16 (2023) 856.

[15] N. Zhang, H. Ma, C.W. Cheung, F.-G. Zhang, M. Jasiński, J.-A. Ma, J. Nie, Regioselective [3 + 2] cycloadditions of di/trifluoromethylated hydrazonoyl chloride with fluorinated nitroalkanes: a facile access to 3-di/trifluoroalkyl-5-fluoropyrazoles, Org. Biomol. Chem. 21 (2023) 5040–5045.

[16] K. Świątek, G. Utecht-Jarzyńska, M. Palusiak, J.-A. Ma, M. Jasiński, One-pot synthesis of 1-aryl-3-trifluoromethylpyrazoles using nitrile imines and mercaptoacetaldehyde as a surrogate of acetylene, Org. Lett. 25 (2023) 4462–4467.

[17] Y. Feng, B. Chang, Y. Ren, F. Zhao, K.-H. Wang, J. Wang, D. Huang, X. Lv, Y. Hu, Synthesis of trifluoromethylpyrrolopyrazole derivatives via [3 + 2] cycloaddition of trifluoromethyl *N*-acylhydrazones or trifluoroacetohydrazonoyl bromides with maleimides, Tetrahedron 136 (2023), 133353.

[18] K. Cen, J. Wei, Y. Feng, Y. Liu, X. Wang, Y. Liu, Y. Yin, J. Yu, D. Wang, J. Cai, Synthesis of fused 3-trifluoromethyl-1,2,4-triazoles *via* base-promoted [3 + 2] cycloaddition of nitrile imines and 1*H*-benzo[*d*]imidazole-2-thiols, Org. Biomol. Chem. 21 (2023) 7095–7099.

[19] (19a) A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński, Trifluoromethylated pyrazoles via sequential (3 + 2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions, Org. Lett. 24 (2022) 2499–2503;
(19b) G. Utecht-Jarzyńska, A. Kowalczyk, M. Jasiński, Fluorinated and non-fluorinated 1,4-diarylpyrazoles via MnO_2-mediated mechanochemical deacylative oxidation of 5-acylpyrazolines, Molecules 27 (2022) 8446.

[20] (20a) A. Oubella, M.Y.A. Itto, A. Auhmani, A. Riahi, A. Robert, J.-C. Daran, H. Morjani, C.A. Parish, M. Esseffar, Diastereoselective synthesis and cytotoxic evaluation of new isoxazoles and pyrazoles with monoterpenic skeleton, J. Mol. Struct. 1198 (2019), 126924;
(20b) M. Rios-Gutierrez, L.R. Domingo, M. Esseffar, A. Oubella, M.Y.A. Itto, Unveiling the different chemical reactivity of diphenyl nitrilimine and phenyl nitrile oxide in [3 + 2] cycloaddition reaction with (*R*)-carvone through the molecular electron density theory, Molecules 25 (2020) 1085.

[21] S. Vázquez, P. Camps, Chemistry of pyramidalized alkenes, Tetrahedron 61 (2005) 5147–5208.

[22] A. Wojciechowska, M. Jasiński, P. Kaszyński, Tautomeric equilibrium in trifluoroacetaldehyde arylhydrazones, Tetrahedron 71 (2015) 2349–2356.

[23] G. Mlostoń, K. Urbaniak, G. Utecht, D. Lentz, M. Jasiński, Trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles via the regioselective (3 + 2)-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones, J. Fluorine Chem. 192 (2016) 147–154.

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Trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1H)-ones via (3+3)-annulation of nitrile imines with α-amino esters

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Trifluoromethylated 4,5-Dihydro-1,2,4-triazin-6(1*H*)-ones via (3+3)-Annulation of Nitrile Imines with α-Amino Esters

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Abstract: The synthesis of two series of monocyclic and bicyclic trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1*H*)-one derivatives based on (3+3)-annulation of methyl esters derived from natural α-amino acids with in situ generated trifluoroacetonitrile imines has been described. The devised protocol is characterized by a wide scope, easily accessible substrates, remarkable functional group tolerance, and high chemical yield. In reactions with chiral starting materials, no racemization at the stereogenic centers was observed and the respective enantiomerically pure products were obtained. Selected functional group interconversions carried out under catalytic hydrogenation and mild PTC oxidation conditions were also demonstrated.

Keywords: triazinones; nitrile imines; amino acids; (3+3)-annulation; fluorinated heterocycles; anticancer activity

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1. Introduction

The functionalization of organic molecules with fluorine atom(s) and/or with fluoroalkyl groups has been recognized as an efficient method for the tuning of their physicochemical behavior and biological activity [1–4]. The introduction of fluorine atoms into the parent non-fluorinated compound enables control on properties such as the metabolic stability, reactivity, acidity, oleophilicity, and conformational effects, among others, which are of general significance for the search of new advanced materials [5–7], and compounds of potential medicinal [8–10] and agrochemical applications [11]. For this reason, the development of new, efficient synthetic methods leading to fluorinated products, in particular, fluoromethylated *N*-heterocycles [12–14], is highly desirable.

Several synthetic strategies towards F-containing heterocycles, including cycloadditions and cyclocondensation reactions, functional group interconversions, and catalytic C–H functionalizations, have been developed in recent decades and are nicely summarized elsewhere [15–18]. In this context, there is increasing interest in the chemistry of fluoroalkylated 1,3-dipoles, which are recognized as highly useful building blocks for Huisgen (3+2)-cycloaddition reactions [19–24]. For example, despite some limitations and the difficult handling of 2,2,2-trifluorodiazoethane, this highly reactive intermediate has been extensively explored, not only as 1,3-dipolar reagent, but also as a valuable source of the respective carbene employed in (2+1)-annulation reactions [22–24].

On the other hand, a number of more recent publications reported on nitrile imines functionalized at the *C*-termini with either CF_3 [25–30] or CF_2H [31,32] groups. They were successfully applied for the synthesis of various 5-membered *N*-heterocyclic systems formed via (3+2)-cycloadditions, notably, with most of the cases proceeding in a fully

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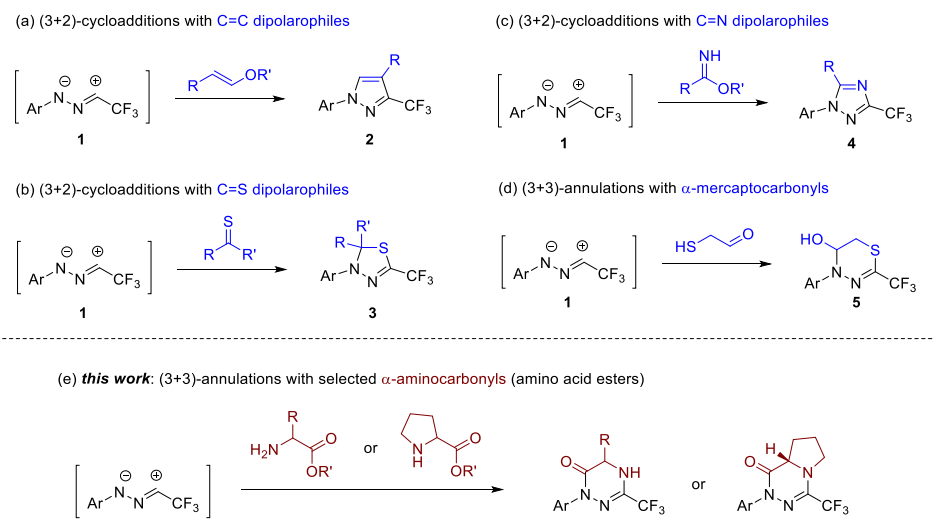
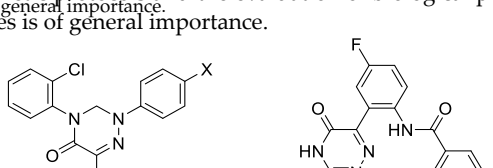
For example, in 2018 we have demonstrated that the trapping of in situ generated trifluoroacetonitrile imines (**1**) with electron-rich vinyl ethers leads to 2-CF_3-pyrazoline derivatives **2** (Scheme 1a) [27]. In this case, the final product is produced via the spontaneous elimination (from an alcohol molecule) of the initially formed (3+2)-cycloadduct. Further studies on 1,3-dipolar cycloadditions of **1** onto C=C and C≡C bonds using nitroolefins [33], cyclic enones [34], olefins [35–37], alkoxyallenes [28], and benzynes [38] as dipolarophiles also evidenced the high synthetic potential of CF_3-nitrile imines in the synthesis of pyrazoline and pyrazole derivatives. The addition of **1** with hetero-dipolarophiles are also known (Scheme 1b); a series of thiocarbonyl compounds including cyclo(aliphatic [26,38], aromatic, and ferrocenyl thioketones [25], as well as thiochalcones [39] and thioamides [40], smoothly reacted with trifluoroacetonitrile imines **1** to afford 1,3,4-thidiazole derivatives of type **3** formed as the exclusive products. More recently, Chen and Wang disclosed an elegant method employing imidates as suitable C=N dipolarophiles en route to 1,2,4-triazoles **4** (Scheme 1c) [41].



Scheme 1. Exemplary applications of in situ generated trifluoroacetonitrile imines (**1**) in synthesis of (**a**–**c**) 5-membered *N*-heterocycles available via (3+2)-cycloadditions with C=C and C≡X dipolarophiles leading to pyrazole, 1,3,4-thiadiazole, and 1,2,4-triazole derivatives **2**–**4**, respectively; (**d**) 1,3,4-thiadiazines available through (3+3)-annulation with α-mercaptoacetaldehyde; (**e**) monocyclic and bicyclic 1,3,4-triazin-6(1*H*)-ones **6** and **7** reported herein.

Despite the remarkable progress in (3+2)-cycloaddition reactions in recent years, the chemistry of higher formal (3+*n*)-cycloadditions of fluorinated nitrile imines, such as **1** bifunctional reagents, are explored to a limited extent. Some time ago, we demonstrated that nitrile imines **1** can be smoothly trapped with α-mercaptoacetaldehyde, and also with other α-mercaptocarbonyl compounds, to give 1,3,4-thiadiazolines **5** as the exclusive products (Scheme 1d) [42]. Nevertheless, to the best of our knowledge, no reports on



8 (X = H or Cl) **9** **10**

Figure 1. Structures of selected biologically active halogenated 1,2,4-triazinones.

Here we report on our results aimed at the application of nitrile imines **1** in the synthesis of a series of monocyclic and bicyclic 1,2,4-triazin-6(1*H*)-ones **6** and **7**, respectively, by using selected natural amino acid esters as suitable reaction partners. Particularly, a group (proline) were examined. Furthermore, the subsequent transformations of the target products, particularly the oxidations of the core heterocyclic ring and interconversions of selected functional group under catalytic hydrogenation conditions, were studied. Finally, taking into account the well-documented biological activity of some fluorinated and non-fluorinated 1,2,4-triazinones and related 1,2,4-triazine-based analogues [43–51], the cytotoxic properties of representative final compounds were examined against MCF-7 and HL-60 cancer cell lines.

2. Materials and Methods

2.1. General Information

All commercially available chemicals (solvents, reagents) were used as received. If not stated otherwise, reactions were performed in flame dried flasks under the atmosphere of inert gas with the addition of the reactants using a syringe; subsequent manipulations were conducted in the air. NMR spectra were measured with Bruker AVIII instrument (^{1}H NMR (600 MHz); ^{13}C NMR (151 MHz); ^{19}F NMR (565 MHz) Bruker BioSpin AG, Fällanden, Switzerland); chemical shifts are given relative to the residual undeuterated solvent peaks (for $CDCl_3$: ^{1}H NMR δ = 7.16, ^{13}C NMR δ = 77.16; for CD_3OD: ^{1}H NMR δ = 3.31, ^{13}C NMR δ = 49.00; for DMSO-d_6: ^{1}H NMR δ = 2.50, ^{13}C NMR δ = 39.52) or to $CHCl_3$ (^{1}H NMR δ = 8.00) as an internal standard. NMR spectra were measured with Bruker AVIII instrument (^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz), ^{19}F NMR(565 MHz) Bruker BioSpin AG, Fällanden, Switzerland); chemical shifts are given relative to the residual undeutera

Ion Trap (Varian Inc., Palo Alto, CA, USA); high resolution measurements were performed with a Waters Synapt G2-Si mass spectrometer (Waters Corporation, Milford, MA, USA). IR spectra were obtained with a Cary 630 FTIR (Agilent Technologies, Santa Clara, CA, USA) spectrometer, in neat. Elemental analyses were performed with a Vario EL III (Elementar Analysensysteme GmbH, Langenselbold, Germany) instrument. The melting points were determined in the capillaries with a Melt-Temp II (Laboratory Devices, Holliston, MA, USA) apparatus or with a polarizing optical microscope (Opta-Tech, Warsaw, Poland), and they are uncorrected. The ball-milling apparatus was a MM 400 mixer mill (Retsch GmbH, Haan, Germany). The mechanochemical reactions were performed in 5 mL stainless steel jars, at 25 Hz, with three stainless steel balls (ø 7 mm). The optical rotations were determined with a MCP 500 (Anton Paar, Graz, Austria) polarimeter at the temperatures indicated. The enantiopurity was analyzed with 1260 Infinity HPLC (Agilent Technology, Germany) using a column with chiral support (CHIRALPAK AD-H). The required known nitrile imine precursors, i.e., hydrazonoyl bromides **11**, were prepared starting with readily available trifluoroacetaldehyde arylhydrazones **14** [52], by NBS-mediated bromination of the latter, as described [25].

2.2. Synthetic Protocols

Synthesis of 1,2,4-triazin-6(1*H*)-ones **6** and **7**: An excess Et_3N (8.0 mmol, 1.12 mL) was added under inert atmosphere to a suspension of amino ester hydrochloride **12** (1.0 mmol) in dry THF (3.0 mL). Then, a solution of hydrazonoyl bromide **11** (1.1 mmol) in dry THF (3.0 mL) was added, and the stirring was continued overnight (the consumption of **11** was confirmed by TLC). The resulting solution was filtered and the precipitate was washed with Et_2O (2 × 4.0 mL). After the filtrates were combined and the solvents were removed under reduced pressure, the crude product **6** or **7** was purified by standard column chromatography (CC). In certain cases of glycine derivatives, the resulting material was additionally recrystallized from hexane-dichloromethane mixtures by the slow evaporation of the solvents.

1-(4-Nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6a**): CC (SiO_2, CH_2Cl_2 gradient CH_2Cl_2/EtOAc 9:1), 216 mg (75%). Colorless solid, m.p. 224–225 °C (CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.30 (d_{br}, $J \approx 1.5$ Hz, 2 H, CH_2), 5.31 (s_{br}, H, NH), 7.92, 8.27 (2 d_{br}, $J \approx 9.2$ Hz, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 44.0 (t, CH_2), 118.2 (q, $^1J_{C\text{-}F}$ = 275.2 Hz, CF_3), 123.7, 124.2 (2 d, 4 CH), 137.3 (q, $^2J_{C\text{-}F}$ = 37.8 Hz, C(3)), 145.0, 145.5 (2 s, 2 *i*-C), 158.1 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.6 (s, CF_3). IR (neat): ν 3295 (NH), 1685 (C=O), 1584, 1487, 1312, 1144 (CF_3), 1059, 854 cm^{-1}. ESI-MS (*m*/*z*): 311.1 (100, [*M*+Na]$^+$), 289.2 (31, [*M*+H]$^+$). $C_{10}H_7F_3N_4O_3$ (288.0): calcd. C 41.68, H 2.45, N 19.44; found: C 41.50, H 2.46, N 19.61.

1-(3-Nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6b**): CC (SiO_2, 3% MeOH in CH_2Cl_2), 248 mg (86%). Yellow crystals, m.p. 144–146 °C (CH_2Cl_2/hexanes). ^{1}H NMR (CD_3OD, 600 MHz): δ 4.19 (s, 2 H, CH_2), 4.61 (s_{br}, 1 H, NH), 7.63 (t, *J* = 8.2 Hz, 1H), 8.04 (ddd, *J* = 1.0, 2.2, 8.2 Hz, 1 H), 8.12 (ddd, *J* = 1.0, 2.2, 8.2 Hz, 1 H), 8.53 (t, *J* = 2.2 Hz, 1 H). ^{13}C NMR (CD_3OD, 151 MHz): δ 44.2 (t, CH_2), 119.9 (q, $^1J_{C\text{-}F}$ = 274.4 Hz, CF_3), 119.8, 121.9, 130.5, 130.8 (4 d, 4 CH), 139.7 (q, $^2J_{C\text{-}F}$ = 37.1 Hz, C(3)), 142.6, 149.4 (2 s, 2 *i*-C), 160.8 (s, C=O). ^{19}F NMR (CD_3OD, 565 MHz): δ −72.2 (s, CF_3). IR (neat): ν 3290 (NH), 1682 and 1647 (C=O), 1536, 1472, 1349, 1271, 1197–1129 (CF_3), 977 cm^{-1}. ESI-MS (*m*/*z*): 289.2 (100, [*M*+H]$^+$). $C_{10}H_7F_3N_4O_3$ (288.0): calcd. C 41.68, H 2.45, N 19.44; found: C 41.44, H 2.36, N 19.48.

4-(3-Trifluoromethyl-4,5-dihydro-6(1*H*)-oxo-1,2,4-triazin-1-yl)benzonitrile (**6c**): CC (SiO_2, 4% MeOH in CH_2Cl_2), 247 mg (92%). Colorless solid, m.p. 212–214 °C. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 4.17 (s, 2 H, CH_2), 7.79, 7.88 (2 d_{br}, $J \approx 8.8$ Hz, 2 H each), 8.67 (s_{br}, 1 H, NH). ^{13}C NMR (DMSO-d_6, 151 MHz): δ 43.0 (t, CH_2), 108.1 (s, CN), 118.4 (q, $^1J_{C\text{-}F}$ = 275.2 Hz, CF_3), 118.7 (s, *i*-C), 123.8, 132.7 (2 d, 4 CH), 137.4 (q, $^2J_{C\text{-}F}$ = 36.2 Hz, C(3)), 143.8 (s, *i*-C), 159.2 (s, C=O). ^{19}F NMR (DMSO-d_6, 565 MHz): δ −69.3 (s, CF_3). IR (neat): ν 3261 (NH), 2236 (CN), 1700 and 1681 (C=O), 1334, 1200–1126 (CF_3), 1066, 839 cm^{-1}. ESI-

MS (*m*/*z*): 291.2 (100, [*M*+Na]$^+$), 269.2 (12, [*M*+H]$^+$). $C_{11}H_7F_3N_4O$ (268.2): calcd. C 49.26, H 2.63, N 20.89; found: C 49.36, H 2.89, N 20.61.

1-(4-Chlorophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6d**): CC (SiO_2, 4% MeOH in CH_2Cl_2), 233 mg (84%). Yellow crystals, m.p. 159–160 °C (CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.18 (d_{br}, $J \approx 1.5$ Hz, 2 H, CH_2), 5.39 (s_{br}, 1 H, NH), 7.36–7.38, 7.51–7.53 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 43.8 (t, CH_2), 118.2 (q, $^1J_{C\text{-}F}$ = 275.2 Hz, CF_3), 125.7, 128.9 (2 d, 4 CH), 132.7 (s, *i*-C), 136.9 (q, $^2J_{C\text{-}F}$ = 37.5 Hz, C(3)), 138.5 (s, *i*-C), 157.8 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.6 (s, CF_3). IR (neat): *ν* 3294 (NH), 1689 and 1655 (C=O), 1491, 1349, 1316, 1194–1133 (CF_3), 1085, 828 cm^{-1}. ESI-MS (*m*/*z*): 278.2 (100, [*M*+H]$^+$), 244.2 (16, [*M*–Cl+H]$^+$). $C_{10}H_7ClF_3N_3O$ (277.6): calcd. C 43.26, H 2.54, N 15.14; found: C 43.30, H 2.53, N 15.24.

1-(2,4-Dichlorophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6e**): The crude reaction mixture was additionally refluxed for 2h in order to accomplish the second cyclization step (see the text), and the product was isolated after the standard work-up; CC (SiO_2, CH_2Cl_2/EtOAc 95:5), 289 mg (93%). Colorless solid, m.p. 138–139 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.24 (s_{br}, 2 H, CH_2), 5.33 (s_{br}, 1 H, NH), 7.34, 7.51 (2 m_c, 2 H, 1 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 43.7 (t, CH_2), 118.2 (q, $^1J_{C\text{-}F}$ = 275.2 Hz, CF_3), 128.3, 130.3, 130.4 (3 d, 3 CH), 133.4, 135.6, 136.3 (3 s, 3 *i*-C), 136.8 (q, $^2J_{C\text{-}F}$ = 37.6 Hz, C(3)), 157.9 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.5 (s, CF_3). IR (neat): *ν* 3284 (NH), 1685 and 1665 (C=O), 1525, 1402, 1357, 1323, 1189–1129 (CF_3), 1103, 1050 cm^{-1}. ESI-MS (*m*/*z*): 312.1 (100, [*M*+H]$^+$). $C_{10}H_6Cl_2F_3N_3O$ (312.1): calcd. C 38.49, H 1.94, N 13.47; found: C 38.72, H 2.19, N 13.54.

Amidrazone **13e**: The spectroscopically pure sample of intermediate **13e** (75 mg, 22%; as ca. 87:13 mixture of *E*/*Z*-isomers) was obtained in reaction of **11e** with **12a** and was isolated from the mother liquor by preparative thin layer chromatography (PTLC; SiO_2, petroleum ether/CH_2Cl_2 3:2) followed by recrystallisation from a hexanes/CH_2Cl_2 mixture. Colorless solid, m.p. 79–81 °C. ^{1}H NMR ($CDCl_3$, 600 MHz); major isomer: δ 3.82 (s, 3 H, Me), 4.05 (d, *J* = 5.7 Hz, 2 H), 4.57 (t_{br}, $J \approx 5.7$ Hz, 1 H, NH), 7.20 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.21 (s_{br}, 1 H, NH), 7.29 (d, *J* = 2.3 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H); diagnostic signals for minor isomer: δ 3.80 (s, 3 H, Me), 4.00 (d, *J* = 5.2 Hz, 2 H), 4.95 (t_{br}, $J \approx 5.2$ Hz, 1 H, NH), absorptions in the aromatic region could not be seen due to overlap of the signals. ^{13}C NMR ($CDCl_3$, 151 MHz); major isomer: δ 44.8 (t, CH_2), 53.0 (q, Me), 116.4 (d, CH), 119.20 (q, $^1J_{C\text{-}F}$ = 274.5 Hz, CF_3), 119.23, 125.7 (2 s, 2 *i*-C), 128.2, 128.7 (2 d, 2 CH), 136.7 (q, $^2J_{C\text{-}F}$ = 34.9 Hz), 140.4 (s, *i*-C), 170.8 (s, C=O); diagnostic signals for minor isomer: δ 43.8 (t, CH_2), 52.6 (q, Me), 114.1 (d, CH), 117.8, 123.8 (2 s, 2 *i*-C), 128.0, 128.6 (2 d, 2 CH), 140.7 (s, *i*-C), 170.4 (s, C=O); absorptions of the CF_3 group and of the neighboring C atom could not be found due to overlap and low intensity, respectively.

1-Phenyl-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6f**): CC (SiO_2, 4% MeOH in CH_2Cl_2), 192 mg (79%). Colorless crystals, m.p. 146–148 °C (CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.13 (d_{br}, $J \approx 1.6$ Hz, 2 H, CH_2), 5.39 (s_{br}, 1 H, NH), 7.28–7.31, 7.40–7.43, 7.52–7.54 (3 m, 1 H, 2 H, 2 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 43.8 (t, CH_2), 118.3 (q, $^1J_{C\text{-}F}$ = 275.1 Hz, CF_3), 124.7, 127.5, 128.9 (3 d, 5 CH), 136.7 (q, $^2J_{C\text{-}F}$ = 37.6 Hz, C(3)), 140.0 (s, *i*-C), 157.9 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.6 (s, CF_3). IR (neat): *ν* 3288 (NH), 1689 and 1655 (C=O), 1495, 1394, 1353, 1320, 1193–1137 (CF_3), 1092, 1057 cm^{-1}. ESI-MS (*m*/*z*): 244.2 (100, [*M*+H]$^+$). $C_{10}H_8F_3N_3O$ (243.2): calcd. C 49.39, H 3.32, N 17.28; found: C 49.23, H 3.47, N 17.30.

1-(4-Tolyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6g**): CC (SiO_2, 5% MeOH in CH_2Cl_2), 195 mg (76%). Colorless crystals, m.p. 153–154 °C (CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.35 (s, 3 H, Me), 4.14 (d_{br}, $J \approx 1.5$ Hz, 2 H, CH_2), 5.37 (s_{br}, 1 H, NH), 7.21, 7.39 (2 d_{br}, $J \approx 8.2$ Hz, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 21.2 (q, Me), 43.8 (t, CH_2), 118.3 (q, $^1J_{C\text{-}F}$ = 275.0 Hz, CF_3), 124.7, 129.5 (2 d, 4 CH), 136.6 (q, $^2J_{C\text{-}F}$ = 37.4 Hz, C(3)), 137.45, 137.53 (2 s, 2 *i*-C), 157.8 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.6 (s, CF_3). IR (neat): *ν* 3243 (NH), 1681 and 1648 (C=O), 1513, 1402, 1357, 1316,

1189–1133 (CF_3), 1085, 820 cm^{-1}. ESI-MS (*m*/*z*): 258.2 (100, $[M+H]^+$). $C_{11}H_{10}F_3N_3O$ (257.2): calcd. C 51.37, H 3.92, N 16.34; found: C 51.33, H 3.93, N 16.80.

1-(4-Benzyloxyphenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6h**): CC (SiO_2, 2% MeOH in CH_2Cl_2), 286 mg (82%). Light orange crystals, m.p. 130–132 °C (CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.15 (d_{br}, $J \approx 1.4$ Hz, 2 H, NCH_2), 5.07 (s, 2 H, OCH_2), 5.33 (s_{br}, 1 H, NH), 6.98–7.01, 7.32–7.34, 7.37–7.43 (3 m, 2 H, 1 H, 6 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 43.8 (t, NCH_2), 70.3 (t, OCH_2), 115.1 (d, 2 CH), 118.3 (q, $^1J_{C\text{-}F}$ = 275.1 Hz, CF_3), 126.3, 127.6, 128.2, 128.7 (4 d, 7 CH), 133.3 (s, *i*-C), 136.5 (q, $^2J_{C\text{-}F}$ = 37.3 Hz, C(3)), 136.8, 157.8, 157.9 (3 s, 2 *i*-C, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.5 (s, CF_3). IR (neat): ν 3276 (NH), 1692–1651 (C=O), 1506, 1349, 1327, 1185–1141 (CF_3), 1081, 1051 cm^{-1}. ESI-MS (*m*/*z*): 372.3 (100, $[M+Na]^+$), 350.4 (52, $[M+H]^+$). $C_{17}H_{14}F_3N_3O_2$ (349.3): calcd. C 58.45, H 4.04, N 12.03; found: C 58.23, H 4.12, N 12.20.

(*S*)-5-Methyl-1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6i**): CC (SiO_2, CH_2Cl_2), 233 mg (77%). Light orange solid, m.p. 132–133 °C. $[\alpha]_D^{20}$ = −31.7 (*c* 0.26, $CHCl_3$). ^{1}H NMR (CD_3OD, 600 MHz): δ 1.51 (d, *J* = 6.8 Hz, 3 H, CH_3), 4.33 (q, *J* = 6.8 Hz, 1 H, 5-H), 7.91–7.93, 8.26–8.28 (2 m, 2 H each). ^{13}C NMR (CD_3OD, 151 MHz): δ 19.2 (q, Me), 50.8 (d, C(5)), 120.0 (q, $^1J_{C\text{-}F}$ = 274.5 Hz, CF_3), 124.8, 125.0 (2 d, 4 CH), 139.7 (q, $^2J_{C\text{-}F}$ = 37.2 Hz, C(3)), 146.5, 147.0 (2 s, 2 *i*-C), 164.2 (s, C=O). ^{19}F NMR (CD_3OD, 565 MHz): δ −68.5 (s, CF_3). IR (neat): ν 3247 (NH), 1685 (C=O), 1588, 1517, 1331, 1197, 1140–1082 (CF_3), 855 cm^{-1}. ESI-MS (*m*/*z*): 325.2 (100, $[M+Na]^+$). $C_{11}H_9F_3N_4O_3$ (302.2): calcd. C 43.72, H 3.00, N 18.54; found: C 43.60, H 3.17, N 18.66.

(*S*)-5-(1-Methylethyl)-1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6j**): CC (SiO_2, petroleum ether/EtOAc 4:1), 271 mg (82%). Pale yellow solid, m.p. 143–144 °C. $[\alpha]_D^{20}$ = −213.4 (*c* 0.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.02 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.07 (d, *J* = 7.0 Hz, 3 H, CH_3), 2.36–2.44 (m, 1 H), 4.14 (dd_{br}, $J \approx 2.4$, 3.9 Hz, 1 H, 5-H), 5.44 (s_{br}, 1 H, NH), 7.88–7.90, 8.24–8.27 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 16.7, 18.3 (2 q, 2 Me), 33.2 (d, $CHMe_2$), 59.5 (d, C(5)), 117.4 (q, $^1J_{C\text{-}F}$ = 275.4 Hz, CF_3), 123.9, 124.2 (2 d, 4 CH), 137.4 (q, $^2J_{C\text{-}F}$ = 37.5 Hz, C(3)), 145.3, 145.4 (2 s, 2 *i*-C), 160.9 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.8 (s, CF_3). IR (neat): ν 3284 (NH), 1689 and 1659 (C=O), 1524, 1495, 1334, 1193, 1148–1111 (CF_3), 1081, 850 cm^{-1}. ESI-MS (*m*/*z*): 353.2 (100, $[M+Na]^+$), 331.3 (20, $[M+H]^+$). $C_{13}H_{13}F_3N_4O_3$ (330.3): calcd. C 47.28, H 3.97, N 16.96; found: C 47.38, H 4.12, N 16.83.

(*S*)-5-(2-Methylpropyl)-1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6k**): CC (SiO_2, petroleum ether/CH_2Cl_2 1:3), 186 mg (54%). Light orange solid, m.p. 107–108 °C (hexanes). $[\alpha]_D^{20}$ = −190.6 (*c* 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.98, 1.01 (2 d, *J* = 6.1 Hz, 3 H each, 2 CH_3), 1.69–1.83 (m, 3 H), 4.27 (ddd, *J* = 2.2, 4.6, 8.4 Hz, 1 H, 5-H), 5.59 (s_{br}, 1 H, NH), 7.88–7.90, 8.23–8.25 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 21.8, 22.9 (2 q, 2 Me), 24.2 (d, $CHMe_2$), 41.9 (t, CH_2), 52.7 (d, C(5)), 118.2 (q, $^1J_{C\text{-}F}$ = 275.3 Hz, CF_3), 123.6, 124.2 (2 d, 4 CH), 137.4 (q, $^2J_{C\text{-}F}$ = 37.5 Hz, C(3)), 145.2, 145.4 (2 s, 2 *i*-C), 161.7 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.8 (s, CF_3). IR (neat): ν 3295 (NH), 1685 and 1659 (C=O), 1521, 1331, 1193–1123 (CF_3), 1081, 849 cm^{-1}. ESI-MS (*m*/*z*): 345.3 (100, $[M+H]^+$). $C_{14}H_{15}F_3N_4O_3$ (344.3): calcd. C 48.84, H 4.39, N 16.27; found: C 48.83, H 4.40, N 16.53.

(*S*)-1-(4-Nitrophenyl)-5-phenyl-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6l**): CC (SiO_2, CH_2Cl_2/hexanes 3:1), 211 mg (58%). Pale yellow solid, m.p. 116–117 °C. $[\alpha]_D^{20}$ = +20.7 (*c* 0.28, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.32 (d_{br}, $J \approx 2.0$ Hz, 1 H, 5-H), 5.83 (s_{br}, 1 H, NH), 7.41–7.46, 7.86–7.89, 8.21–8.24 (3 m, 5 H, 2 H, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 58.2 (d, C(5)), 118.3 (q, $^1J_{C\text{-}F}$ = 275.5 Hz, CF_3), 123.8, 124.2, 126.8, 129.6, 129.8 (5 d, 9 CH), 136.8 (q, $^2J_{C\text{-}F}$ = 37.7 Hz, C(3)), 137.2, 145.2, 145.5 (3 s, 3 *i*-C), 159.6 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.4 (s, CF_3). IR (neat): ν 3291 (NH), 1688 (C=O), 1592, 1517, 1320, 1193–1141 (CF_3), 1081, 854 cm^{-1}. ESI-MS (*m*/*z*): 387.2 (100, $[M+Na]^+$), 365.4 (20, $[M+H]^+$). $C_{16}H_{11}F_3N_4O_3$ (364.3): calcd. C 52.75, H 3.04, N 15.38; found: C 52.69, H 3.13, N 15.21.

(*S*)-5-(Hydroxymethyl)-1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6m**): CC (SiO_2, CH_2Cl_2/EtOAc 6:1), 239 mg (75%). Yellow solid, m.p. 127–128 °C. $[\alpha]_D^{20}$ = −96.5 (*c* 0.28, MeCN). ^{1}H NMR (CD_3OD, 600 MHz): δ 3.72 (dd, *J* = 2.8, 11.6 Hz, 1 H, CH_2), 4.08 (dd, *J* = 3.1, 11.6 Hz, 1 H, CH_2), 4.33 (pseudo-t, *J* ≈ 2.9 Hz, 5-H), 7.93–7.95, 8.25–8.27 (2 m, 2 H each). ^{13}C NMR (CD_3OD, 151 MHz): δ 57.8 (d, C(5)), 64.7 (t, CH_2), 119.9 (q, $^1J_{C\text{-}F}$ = 274.5 Hz, CF_3), 124.7, 125.2 (2 d, 4 CH), 139.7 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, C(3)), 146.5, 147.1 (2 s, 2 *i*-C), 162.5 (s, C=O). ^{19}F NMR (CD_3OD, 565 MHz): δ −72.1 (s, CF_3). IR (neat): ν 3411 (OH), 3198 (NH), 1692 and 1659 (C=O), 1513, 1327, 1193–1088 (CF_3), 1036 cm^{-1}. ESI-MS (*m*/*z*): 341.1 (100, $[M+Na]^+$), 319.2 (13, $[M+H]^+$). $C_{11}H_9F_3N_4O_4$ (318.1): calcd. C 41.52, H 2.85, N 17.61; found: C 41.60, H 3.04, N 17.33.

(*S*)-5-[2-(Methylthio)ethyl]-1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6n**): CC (SiO_2, petroleum ether/EtOAc 3:1), 329 mg (91%). Thick yellow oil. $[\alpha]_D^{20}$ = −93.0 (*c* 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.14 (s, 3 H, Me), 2.15–2.20, 2.32–2.37, 2.68–2.79 (3 m, 1 H, 1 H, 2 H), 4.45 (ddd, *J* = 1.9, 4.1, 7.9 Hz, 1 H, 5-H), 6.07 (s_{br}, 1 H, NH), 7.88–7.90, 8.24–8.27 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 15.3 (q, Me), 30.4, 31.2 (2 t, 2 CH_2), 54.0 (d, C(5)), 118.2 (q, $^1J_{C\text{-}F}$ = 275.5 Hz, CF_3), 123.8, 124.2 (2 d, 4 CH), 137.3 (q, $^2J_{C\text{-}F}$ = 37.5 Hz, C(3)), 145.2, 145.4 (2 s, 2 *i*-C), 161.0 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.8 (s, CF_3). IR (neat): ν 3302 (NH), 1689 and 1657 (C=O), 1592, 1517, 1327, 1193–1108 (CF_3), 1081, 854 cm^{-1}. (-)-ESI-MS (*m*/*z*): 360.9 (100, $[M–H]^-$), 350.1 (13). $C_{13}H_{13}F_3N_4O_3S$ (362.1): calcd. C 43.09, H 3.62, N 15.46, S 8.85; found: C 42.99, H 3.73, N 15.67, S 8.78.

Methyl (*S*)-2-[1-(4-nitrophenyl)-3-trifluoromethyl-6(1*H*)-oxo-4,5-dihydro-1,2,4-triazin-5-yl]acetate (**6o**): CC (SiO_2, petroleum ether/CH_2Cl_2 2:1), 335 mg (93%). Yellow solid, m.p. 114–115 °C (hexanes). $[\alpha]_D^{20}$ = −82.0 (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.90 (dd, *J* = 10.3, 17.6 Hz, 1 H, CH_2), 3.24 (dd, *J* = 2.8, 17.6 Hz, 1 H, CH_2), 3.79 (s, 3 H, Me), 4.66 (ddd, *J* = 1.8, 2.8, 10.3 Hz, 1 H, 5-H), 6.19 (s_{br}, 1 H, NH), 7.90, 8.26 (2 d_{br}, *J* ≈ 9.2 Hz, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 37.1 (t, CH_2), 50.8 (d, C(5)), 52.8 (q, Me), 118.1 (q, $^1J_{C\text{-}F}$ = 275.4 Hz, CF_3), 123.8, 124.2 (2 d, 4 CH), 137.3 (q, $^2J_{C\text{-}F}$ = 37.8 Hz, C(3)), 145.0, 145.6 (2 s, 2 *i*-C), 159.8, 171.6 (2 s, 2 C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.8 (s, CF_3). IR (neat): ν 3396 (NH), 1715 (C=O), 1681 (C=O), 1588, 1521, 1491, 1390, 1323, 1193–1139 (CF_3), 1107, 857 cm^{-1}. ESI-MS (*m*/*z*): 383.2 (100, $[M+Na]^+$). $C_{13}H_{11}F_3N_4O_5$ (360.2): calcd. C 43.34, H 3.08, N 15.55; found: C 43.07, H 2.95, N 15.61.

(*S*)-5-[(Indol-3-yl)methyl]-1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6p**): CC (SiO_2, EtOAc), 346 mg (83%). Pale yellow solid, m.p. 140–141 °C. $[\alpha]_D^{20}$ = −143.6 (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.24 (dd, *J* = 9.4, 14.6 Hz, 1 H, CH_2), 3.53 (dd, *J* = 3.4, 14.6 Hz, 1 H, CH_2), 4.54 (ddd, *J* = 1.7, 3.4, 9.4 Hz, 1 H, 5-H), 5.32 (s_{br}, 1 H, NH), 7.13–7.17, 7.25–7.28 (2 m, 2 H, 1 H), 7.43 (d_{br}, *J* ≈ 8.2 Hz, 1 H), 7.63 (d_{br}, *J* ≈ 7.9 Hz, 1 H), 7.77–7.80, 8.22–8.24 (2 m, 2 H each) °8.24 (s_{br}, 1 H, NH). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 30.1 (t, CH_2), 54.4 (d, C(5)), 108.5 (s, *i*-C), 111.7 (d, CH), 118.2 (q, $^1J_{C\text{-}F}$ = 275.3 Hz, CF_3), 118.6, 120.4, 123.1, 123.8, 123.9, 124.1 (6 d, 8 CH), 126.7, 136.6 (2 s, 2 *i*-C), 137.0 (q, $^2J_{C\text{-}F}$ = 37.6 Hz, C(3)), 145.2, 145.4 (2 s, 2 *i*-C), 161.39 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −70.6 (s, CF_3). IR (neat): ν 3351 (NH), 1689 and 1662 (C=O), 1592, 1517, 1327, 1200–1144 (CF_3), 1085, 854 cm^{-1}. (-)-ESI-MS (*m*/*z*): 416.0 (88, $[M–H]^-$). $C_{19}H_{14}F_3N_5O_3$ (417.3): calcd. C 54.68, H 3.38, N 16.78; found: C 54.43, H 3.49, N 16.74.

(*S*)-5-Phenyl-1-(4-tolyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one ((*S*)-**6q**): CC (SiO_2, CH_2Cl_2), 250 mg (75%). Colorless crystals, m.p. 153–154 °C. $[\alpha]_D^{20}$ = +171.6 (*c* 0.28, $CHCl_3$). ^{1}H NMR (CD_3OD, 600 MHz): δ 2.35 (s, 3 H, CH_3), 5.28 (s_{br}, 1 H, NH), 7.22, 7.32 (d_{br}, *J* ≈ 8.3 Hz, 2 H each), 7.37–7.40, 7.42–7.45 (2 m, 1 H, 4 H). ^{13}C NMR (CD_3OD, 151 MHz): δ 21.1 (q, Me), 58.9 (d, C(5)), 120.1 (q, $^1J_{C\text{-}F}$ = 274.4 Hz, CF_3), 126.1, 127.9, 129.9, 130.1, 130.2 (5 d, 9 CH), 138.5 (s, *i*-C), 138.6 (q, $^2J_{C\text{-}F}$ = 37.0 Hz, C(3)), 139.4, 140.7 (2 s, 2 *i*-C), 161.6 (s, C=O). ^{19}F NMR (CD_3OD, 565 MHz): δ −72.1 (s, CF_3). IR (neat): ν 3336 (NH), 1677 and 1655 (C=O), 1510, 1338, 1189–1144 (CF_3), 1084, 820 cm^{-1}. ESI-MS (*m*/*z*): 372.1 (57, $[M+K]^+$), 356.1 (47, $[M+Na]^+$), 334.2 (100, $[M+H]^+$). $C_{17}H_{14}F_3N_3O$ (333.3): calcd. C 61.26, H 4.23, N 12.61; found: C 61.08, H 4.37, N 12.86. A sample of *rac*-**6q** (276 mg, 83%)

was prepared in an analogous manner starting with hydrazonoyl bromide **11g** and racemic methyl phenylglycinate (*rac*-**12e**). The obtained ^{1}H and ^{13}C NMR data perfectly matched those obtained for (*S*)-**6q**.

(*S*)-2-(4-Nitrophenyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]-triazin-1(2*H*)-one (**7a**): CC (SiO_2, CH_2Cl_2), 269 mg (82%). Yellow solid, m.p. 90–92 °C (CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ = +79.2 (*c* 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.08–2.14 (m, 2 H, 7-H_2), 2.28–2.34 (m, 1 H, 8-H), 2.46–2.51 (m, 1 H, 8-H), 3.75 (t_{br}, $J \approx 7.4$ Hz, 2 H, 6-H_2), 4.17 (dd, *J* = 6.9, 8.9 Hz, 1 H, 8a-H), 7.92–7.94, 8.24–8.26 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.3 (t, C(8)), 48.8 (q, $^{4}J_{C\text{-}F}$ = 2.3 Hz, C(6)), 58.4 (d, C(8a)), 118.5 (q, $^{1}J_{C\text{-}F}$ = 276.0 Hz, CF_3), 123.5, 124.2 (2 d, 4 CH), 138.1 (q, $^{2}J_{C\text{-}F}$ = 36.5 Hz, C(4)), 145.2* (s, 2 *i*-C), 161.5 (s, C=O); *higher intensity. ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.6 (s, CF_3). IR (neat): ν 1698 (C=O), 1519, 1452, 1344, 1191, 1135 (CF_3) cm^{-1}. ESI-MS (*m*/*z*): 329.3 (100, [*M*+H]$^{+}$). $C_{13}H_{11}F_3N_4O_3$ (328.2): calcd. C 47.57, H 3.38, N 17.07; found: C 47.78, H 3.48, N 17.19.

(*S*)-2-(3-Nitrophenyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]-triazin-1(2*H*)-one (**7b**): CC (SiO_2, CH_2Cl_2), 213 mg (65%). Thick yellow oil. $[\alpha]_D^{20}$ = +27.4 (*c* 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.06–2.14 (m, 2 H, 7-H_2), 2.27–2.33 (m, 1 H, 8-H), 2.45–2.51 (m, 1 H, 8-H), 3.71–3.77 (m, 2 H, 6-H_2), 4.17 (dd, *J* = 6.9, 8.9 Hz, 1 H, 8a-H), 7.55 (t, *J* = 8.2 Hz, 1H), 8.01 (ddd, *J* = 1.0, 2.2, 8.2 Hz, 1 H), 8.10 (ddd, *J* = 1.0, 2.2, 8.2 Hz, 1 H), 8.56 (t, *J* = 2.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.3 (t, C(8)), 48.8 (q, $^{4}J_{C\text{-}F}$ = 2.4 Hz, C(6)), 58.3 (d, C(8a)), 118.5 (q, $^{1}J_{C\text{-}F}$ = 276.0 Hz, CF_3), 119.0, 121.2, 129.4, 129.6 (4 d, 4 CH), 138.0 (q, $^{2}J_{C\text{-}F}$ = 36.5 Hz, C(4)), 141.0, 148.4 (2 s, 2 *i*-C), 161.3 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.5 (s, CF_3). IR (neat): ν 1696 and 1648 (C=O), 1528, 1454, 1349, 1193–1118 (CF_3) cm^{-1}. ESI-MS (*m*/*z*): 329.3 (64, [*M*+H]$^{+}$), 327.3 (100, [*M*–H]$^{+}$), 299.2 (36). $C_{13}H_{11}F_3N_4O_3$ (328.2): calcd. C 47.57, H 3.38, N 17.07; found: C 47.75, H 3.43, N 16.84.

(*S*)-4-[4-Trifluoromethyl-1(2*H*)-oxo-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]triazin-2-yl]benzonitrile (**7c**): CC (SiO_2, CH_2Cl_2), 286 mg (93%). Light orange solid, m.p. 103–105 °C. $[\alpha]_D^{20}$ = +68.3 (*c* 0.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.07–2.13 (m, 2 H, 7-H_2), 2.26–2.33 (m, 1 H, 8-H), 2.45–2.50 (m, 1 H, 8-H), 3.71–3.76 (m, 2 H, 6-H_2), 4.16 (d d, *J* = 6.9, 8.9 Hz, 1 H, 8a-H), 7.66–7.69, 7.84–7.86 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.3 (t, C(8)), 48.8 (q, $^{4}J_{C\text{-}F}$ = 2.3 Hz, C(6)), 58.4 (d, C(8a)), 109.7 (s, CN), 118.5 (q, $^{1}J_{C\text{-}F}$ = 275.8 Hz, CF_3), 118.8 (s, *i*-C), 123.8, 132.7 (2 d, 4 CH), 138.0 (q, $^{2}J_{C\text{-}F}$ = 36.3 Hz, C(4)), 143.7 (s, *i*-C), 161.3 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.5 (s, CF_3). IR (neat): ν 2223 (CN), 1690 and 1655 (C=O), 1603, 1452, 1315, 1126 (CF_3) cm^{-1}. ESI-MS (*m*/*z*): 331.3 (29, [*M*+Na]$^{+}$), 309.3 (100, [*M*+H]$^{+}$). $C_{14}H_{11}F_3N_4O$ (308.3): calcd. C 54.55, H 3.60, N 18.18; found: C 54.61, H 3.73, N 18.13.

(*S*)-2-(4-Chlorophenyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]triazin-1(2*H*)-one (**7d**): Reaction time: 2d; CC (SiO_2, petroleum ether/EtOAc 4:1), 219 mg (69%). Pale yellow solid, m.p. 86–87 °C. $[\alpha]_D^{20}$ = +35.1 (*c* 0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.03–2.12 (m, 2 H, 7-H_2), 2.24–2.31 (m, 1 H, 8-H), 2.43–2.48 (m, 1 H, 8-H), 3.68–3.75 (m, 2 H, 6-H_2), 4.13 (dd, *J* = 6.9, 8.9 Hz, 1 H, 8a-H), 7.34–7.36, 7.53–7.55 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.4 (t, C(8)), 48.7 (q, $^{4}J_{C\text{-}F}$ = 2.3 Hz, C(6)), 58.3 (d, C(8a)), 118.6 (q, $^{1}J_{C\text{-}F}$ = 275.7 Hz, CF_3), 125.5, 128.8 (2 d, 4 CH), 132.3 (s, *i*-C), 137.6 (q, $^{2}J_{C\text{-}F}$ = 36.2 Hz, C(4)), 138.7 (s, *i*-C), 160.9 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.5 (s, CF_3). IR (neat): ν 1692 and 1644 (C=O), 1491, 1446, 1331, 1193, 1122 (CF_3) cm^{-1}. ESI-MS (*m*/*z*): 320.3 (31, [*M*{^{37}Cl}+H]$^{+}$), 318.2 (100, [*M*{^{35}Cl}+H]$^{+}$). $C_{13}H_{11}ClF_3N_3O$ (317.7): calcd. C 49.15, H 3.49, N 13.23; found: C 49.22, H 3.68, N 13.10.

(*S*)-2-(2,4-Dichlorophenyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4] triazin-1(2*H*)-one (**7e**): In order to accelerate the second cyclization step, the crude reaction mixture was heated in an oil bath (60 °C) for three days; CC (SiO_2, petroleum ether/EtOAc 4:1), 176 mg (50%). Yellow solid, m.p. 107–108 °C. $[\alpha]_D^{20}$ = −6.8 (*c* 0.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.04–2.12 (m, 2 H, 7-H_2), 2.25–2.32 (m, 1 H, 8-H), 2.43–2.48 (m, 1 H, 8-H), 3.68–3.78 (m, 2 H, 6-H_2), 4.17 (pseudo-t, $J \approx 7.9$ Hz, 1 H, 8a-H), 7.32 (m_c, 2 H), 7.47 (t, *J* = 1.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.0 (t, C(7)), 28.2 (t, C(8)), 48.8 (q,

$^{4}J_{C\text{-}F}$ = 2.5 Hz, C(6)), 58.1 (d, C(8a)), 118.5 (q, $^{1}J_{C\text{-}F}$ = 275.7 Hz, CF_3), 128.2, 130.2, 130.4 (3 d, 3 CH), 133.3, 135.2, 136.5 (3 s, 3 *i*-C), 137.6 (q, $^{2}J_{C\text{-}F}$ = 36.2 Hz, C(4)), 161.0 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.4 (s, CF_3). IR (neat): ν 1689 and 1640 (C=O), 1480, 1443, 1228, 1189, 1160–1118 (CF_3) cm^{-1}. ESI-MS (*m*/*z*): 353.5 (24), 352.4 (100). $C_{13}H_{10}Cl_2F_3N_3O$ (352.1): calcd. C 44.34, H 2.86, N 11.93; found: C 44.42, H 2.96, N 12.04.

(*S*)-2-Phenyl-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]triazin-1(2*H*)-one (**7f**): CC (SiO_2, petroleum ether/EtOAc 4:1), 170 mg (60%). Yellow solid, m.p. 61–63 °C. $[\alpha]_D^{20}$ = +22.6 (*c* 0.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.02–2.11 (m, 2 H, 7-H_2), 2.25–2.32 (m, 1 H, 8-H), 2.42–2.47 (m, 1 H, 8-H), 3.67–3.75 (m, 2 H, 6-H_2), 4.14 (dd, *J* = 6.9, 8.8 Hz, 1 H, 8a-H), 7.25–7.28, 7.38–7.41, 7.54–7.56 (3 m, 1 H, 2 H, 2 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.4 (t, C(8)), 48.7 (q, $^{4}J_{C\text{-}F}$ = 2.3 Hz, C(6)), 58.2 (d, C(8a)), 118.7 (q, $^{1}J_{C\text{-}F}$ = 275.6 Hz, CF_3), 124.5, 127.0, 128.7 (3 d, 5 CH), 137.3 (q, $^{2}J_{C\text{-}F}$ = 36.1 Hz, C(4)), 140.2 (s, *i*-C), 160.9 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.4 (s, CF_3). IR (neat): ν 1685 and 1640 (C=O), 1457, 1312, 1199, 1133 (CF_3), 1102 cm^{-1}. ESI-MS (*m*/*z*): 284.2 (32, [*M*+H]$^+$), 205.2 (100, [*M*–Ph]$^+$). $C_{13}H_{12}F_3N_3O$ (283.2): calcd. C 55.12, H 4.27, N 14.84; found: C 55.41, H 4.44, N 14.59.

(*S*)-2-(4-Tolyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]triazin-1(2*H*)-one (**7g**): CC (SiO_2, petroleum ether/CH_2Cl_2 1:3), 166 mg (56%). Light gray solid, m.p. 78–80 °C. $[\alpha]_D^{20}$ = +22.7 (*c* 0.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.03–2.11 (m, 2 H, 7-H_2), 2.25–2.32 (m, 1 H, 8-H), 2.35 (s, 3 H, Me), 2.42–2.47 (m, 1 H, 8-H), 3.67–3.76 (m, 2 H, 6-H_2), 4.13 (dd, *J* = 6.9, 8.8 Hz, 1 H, 8a-H), 7.18–7.20, 7.39–7.41 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 21.2 (q, Me), 24.1 (t, C(7)), 28.5 (t, C(8)), 48.7 (q, $^{4}J_{C\text{-}F}$ = 2.4 Hz, C(6)), 58.2 (d, C(8a)), 118.7 (q, $^{1}J_{C\text{-}F}$ = 275.6 Hz, CF_3), 124.5, 129.4 (2 d, 4 CH), 137.0 (s, *i*-C), 137.2 (q, $^{2}J_{C\text{-}F}$ = 36.1 Hz, C(4)), 137.7 (s, *i*-C), 160.9 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.4 (s, CF_3). IR (neat): ν 1687 and 1644 (C=O), 1511, 1444, 1198, 1120 (CF_3), 820 cm^{-1}. ESI-MS (*m*/*z*): 299.2 (100, [*M*+2H]$^+$). $C_{14}H_{14}F_3N_3O$ (297.1): calcd. C 56.56, H 4.75, N 14.14; found: C 56.67, H 4.84, N 13.90.

(*S*)-2-(4-Benzyloxyphenyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4] triazin-1(2*H*)-one (**7h**): CC (SiO_2, petroleum ether/EtOAc 4:1), 183 mg (47%). Colorless solid, m.p. 97–99 °C. $[\alpha]_D^{20}$ = +35.0 (*c* 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.02–2.10 (m, 2 H, 7-H_2), 2.24–2.31 (m, 1 H, 8-H), 2.42–2.47 (m, 1 H, 8-H), 3.66–3.74 (m, 2 H, 6-H_2), 4.13 (dd, *J* = 6.9, 8.9 Hz, 1 H, 8a-H), 5.07 (s, 2 H, OCH_2), 6.97–7.00, 7.31–7.34, 7.37–7.39, 7.41–7.44 (4 m, 2 H, 1 H, 2 H, 4 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.5 (t, C(8)), 48.7 (q, $^{4}J_{C\text{-}F}$ = 2.6 Hz, C(6)), 58.2 (d, C(8a)), 70.3 (t, OCH_2), 115.0 (d, 2 CH), 118.7 (q, $^{1}J_{C\text{-}F}$ = 275.6 Hz, CF_3), 126.1, 127.6, 128.1, 128.7 (4 d, 7 CH), 133.5, 137.0 (2 s, 2 *i*-C), 137.2 (q, $^{2}J_{C\text{-}F}$ = 36.2 Hz, C(4)), 157.6 (s, *i*-C), 160.9 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.4 (s, CF_3) ppm. IR (neat): ν 1685 and 1644 (C=O), 1506, 1450, 1338, 1241, 1133 (CF_3), 1018 cm^{-1}. ESI-MS (*m*/*z*): 412.4 (77, [*M*+Na]$^+$), 390.4 (100, [*M*+H]$^+$). $C_{20}H_{18}F_3N_3O_2$ (389.4): calcd. C 61.69, H 4.66, N 10.79; found: C 61.50, H 4.83, N 10.56.

Synthesis of (*S*)-4-Methyl-5-phenyl-1-(4-tolyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one ((*S*)-**6r**)): A solution of 1,2,4-triazin-6(1*H*)-one (*S*)-**6q** (0.5 mmol, 167 mg) in anhydrous MeOH (5.0 mL) was added dropwise to a vigorously stirred solution of sodium methoxide (5.0 mmol, 270 mg) in dry MeOH (25 mL) under argon, at room temperature. Then MeI (5.0 mmol, 705 mg) was added to the resulting mixture and the stirring was continued for 24 **h**. After the solvents were removed in vacuo, the residue was washed with EtOAc (3 × 20 mL). The organic layers were combined, the solvent was removed, and the crude product was purified by CC (SiO_2, DCM) to give (*S*)-**6r** (101 mg, 58%). Colorless solid, m.p. 92–93 °C. $[\alpha]_D^{20}$ = +5.2 (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.34 (s, 3 H, Me), 3.05 (s, 3 H, NMe), 4.94 (s, 1 H, 5-H), 7.17–7.19, 7.36–7.44 (2 m, 2 H, 7 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 21.2 (q, Me), 36.2* (q, $J_{C\text{-}F}$ = 3.4 Hz, NMe), 66.0 (d, C(5)), 118.9 (q, $^{1}J_{C\text{-}F}$ = 275.9 Hz, CF_3), 124.4, 126.9, 129.36, 129.43, 129.5 (5 d, 9 CH), 135.9 (s), 136.5 (q, $^{2}J_{C\text{-}F}$ = 34.3 Hz, C(3)), 137.1, 137.6 (2 s), 158.6 (s, C=O); *through-space C–F coupling observed. ^{19}F NMR ($CDCl_3$, 565 MHz): δ −66.1 (s, CF_3) ppm. IR (neat): ν 1681 and 1655 (C=O), 1513, 1416, 1364, 1238, 1182, 1126 (CF_3), 1077 cm^{-1}. ESI-MS (*m*/*z*): 370.1 (100,

[*M*+Na]$^+$), 348.1 (80, [*M*+H]$^+$), 318.2 (94). $C_{18}H_{16}F_3N_3O$ (347.1): calcd. C 62.24, H 4.64, N 12.10; found: C 61.99, H 4.51, N 12.08. A sample of *rac*-**6r** (111 mg, 64%; 0.5 mmol scale) was obtained in an analogous manner starting with *rac*-**6q**. Colorless crystals, m.p. 93–95 °C. The NMR spectra (^{1}H and ^{13}C) of *rac*-**6r** were in accordance with those of (*S*)-**6r**.

Synthesis of 1-(4-tolyl)-3-trifluoromethyl-1,2,4-triazin-6(1*H*)-one (**6s**): A mixture of 4,5-dihydro-1,2,4-triazinone **6g** (0.5 mmol, 128.5 mg), $K_3Fe(CN)_6$ (3.0 mmol, 987 mg), aqueous solution of Na_2CO_3 (0.5M, 10 mL), and Et_4NBr (15 mol%) in CH_2Cl_2 (10 mL) was vigorously stirred at room temperature for 4 h (monitored on TLC). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over anh. Na_2SO_4, filtered and the solvents were removed under reduced pressure. The crude product was purified by standard CC (SiO_2, CH_2Cl_2) to give **6s** (99 mg, 78%). Colorless solid, m.p. 80–82 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.36 (s, 3 H, Me), 7.25, 7.57 (2 d_{br}, $J \approx$ 8.3 Hz, 2 H each), 8.47 (s, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 21.4 (q, Me), 119.2 (q, $^1J_{C\text{-}F}$ = 273.6 Hz, CF_3), 123.9, 129.9 (2 d, 4 CH), 136.6, 140.2 (2 s, 2 *i*-C), 140.6 (q, $^2J_{C\text{-}F}$ = 39.0 Hz, C(3)), 152.6 (s, C=O), 161.0 (d, C(5)). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −69.7 (s, CF_3). IR (neat): ν 1674 (C=O), 1391, 1346, 1156, 1088 (CF_3) cm^{-1}. ESI-MS (*m*/*z*): 256.1 (100, [*M*+H]$^+$). $C_{11}H_8F_3N_3O$ (255.1): calcd. C 51.77, H 3.16, N 16.47; found: C 51.59, H 3.23, N 16.43.

General procedure for catalytic hydrogenation reactions: A solution of the corresponding triazinone (**7a** or **7h**, 0.5 mmol) in EtOH (10 mL) was added Pd/C (5.0 mmol), and the resulting mixture was vigorously shaken in the atmosphere of H_2 (3 atm) for the required time. The mixture was filtered through Celite, washed with EtOH (5 mL), and the solvents were removed under reduced pressure. The resulting mixture was filtered through a short plug of silica (CC) to give the spectroscopically pure product.

(*S*)-2-(4-Aminophenyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]-triazin-1(2*H*)-one (**7i**): Reaction time: 3 h; CC (SiO_2, silica was washed with 5% Et_3N in EtOAc prior to use; petroleum ether/EtOAc 4:1), 132 mg (89%). Thick light orange oil. $[\alpha]_D^{20}$ = +43.1 (*c* 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.03–2.10 (m, 2 H, 7-H_2), 2.23–2.32 (m, 1 H, 8-H), 2.41–2.46 (m, 1 H, 8-H), 3.65–3.74 (m, 2 H, 6-H_2), 3.70 (s_{br}, 2 H, NH_2), 4.12 (dd, *J* = 6.9, 8.8 Hz, 1 H, 8a-H), 6.66–6.96, 7.24–7.27 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.5 (t, C(8)), 48.7 (q, $^4J_{C\text{-}F}$ = 2.1 Hz, C(6)), 58.2 (d, C(8a)), 115.1 (d, 2 CH), 118.7 (q, $^1J_{C\text{-}F}$ = 275.9 Hz, CF_3), 126.1 (d, 2 CH), 131.5 (s, *i*-C), 137.0 (q, $^2J_{C\text{-}F}$ = 36.1 Hz, C(4)), 145.6 (s, *i*-C), 160.8 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.3 (s, CF_3). IR (neat): ν 3362 (NH), 1674 and 1633 (C=O), 1513, 1446, 1193, 1140–1095 (CF_3) cm^{-1}. ESI-MS (*m*/*z*): 299.3 (100, [*M*+H]$^+$), 279.3 (30).

(*S*)-2-(4-Hydroxyphenyl)-4-trifluoromethyl-6,7,8,8a-tetrahydropyrrolo [1,2-*d*][1,2,4]-triazin-1(2*H*)-one (**7j**): Reaction time: 16 h; CC (SiO_2, hexanes/EtOAc 2:3), 100 mg (67%). Colorless solid, m.p. 94–96 °C. $[\alpha]_D^{20}$ = +23.2 (*c* 0.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.02–2.10 (m, 2 H, 7-H_2), 2.24–2.31 (m, 1 H, 8-H), 2.42–2.47 (m, 1 H, 8-H), 3.67–3.76 (m, 2 H, 6-H_2), 4.15 (dd, *J* = 6.9, 8.9 Hz, 1 H, 8a-H), 5.69 (s_{br}, 1 H, OH), 6.74–6.77, 7.28–7.30 (2 m, 2 H each). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 24.1 (t, C(7)), 28.5 (t, C(8)), 48.7 (q, $^4J_{C\text{-}F}$ = 2.5 Hz, C(6)), 58.2 (d, C(8a)), 115.8 (d, 2 CH), 118.7 (q, $^1J_{C\text{-}F}$ = 275.6 Hz, CF_3), 126.5 (d, 2 CH), 133.0 (s, *i*-C), 137.4 (q, $^2J_{C\text{-}F}$ = 36.1 Hz, C(4)), 155.0 (s, *i*-C), 161.1 (s, C=O). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −68.4 (s, CF_3). IR (neat): ν 3317 (OH), 1666 and 1636 (C=O), 1513, 1446, 1341, 1189–1122 (CF_3), 835 cm^{-1}. ESI-MS (*m*/*z*): 300.2 (100, [*M*+H]$^+$), 298.2 (59).

General procedure for synthesis of hydrazonoyl bromides **11**: Following the general literature protocol [25], arylhydrazone **14** (1.0 mmol) was dissolved in dry DMF (3 mL), the solution was cooled to 0 °C, then solid NBS (1.05 mmol, 187 mg) was added and stirring was continued at this temperature. After the starting hydrazone was fully consumed (TLC monitoring, typically ca. 2 h), the resulting mixture was extracted with H_2O/Et_2O 1:1 mixture (20 mL), the organic layer was washed with H_2O (3 × 10 mL), dried over anh. Na_2SO_4, filtered and the solvents were removed in vacuo. Crude products were purified by column chromatography.

N-(3-Nitrophenyl)-trifluoroacetohydrazonoyl bromide (**11b**): reaction time: 2h; CC (SiO_2, petroleum ether/CH_2Cl_2 3:2), 265 mg (85%). Yellow solid, m.p. 110–111 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49–7.52, 7.87–7.91, 7.99–8.01 (3 m, 2 H, 1 H, 1 H), 8.24 (s_{br}, 1 H, NH). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 107.1 (q, $^2J_{C-F}$ = 44.0 Hz, =CCF_3), 109.2, 117.7 (2 d, 2 CH), 118.2 (q, $^1J_{C-F}$ = 272.1 Hz, CF_3), 120.0, 130.7 (2 d, 2 CH), 142.7, 149.4 (2 s, 2 *i*-C). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −66.6 (s, CF_3). IR (neat): ν 3258 (NH), 1614, 1524, 1346, 1304, 1238, 1121–1075 (CF_3) cm^{-1}. (-)-ESI-MS (*m*/*z*): 311.9 (100, [*M*{^{81}Br}–H]$^-$), 309.9 (99, [*M*{^{79}Br}–H]$^-$). $C_8H_5BrF_3N_3O_2$ (312.0): calcd. C 30.79, H 1.62, N 13.47; found: C 30.95, H 1.88, N 13.65.

N-(2,4-Dichlorophenyl)-trifluoroacetohydrazonoyl bromide (**11e**): Reaction time: 3 h; CC (SiO_2, hexanes), 332 mg (99%). Thick yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.24 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.35 (d, *J* = 2.3 Hz, 1 H), 7.42 (d, *J* = 8.8 Hz, 1 H), 8.52 (s_{br}, 1 H, NH). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 107.8 (q, $^2J_{C-F}$ = 43.9 Hz, =CCF_3), 116.5 (d, CH), 118.3 (q, $^1J_{C-F}$ = 271.9 Hz, CF_3), 119.2, 127.8 (2 s, 2 *i*-C), 128.6, 129.2 (2 d, 2 CH), 136.6 (s, *i*-C). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −66.6 (s, CF_3). IR (neat): ν 3314 (NH), 1595, 1506, 1327, 1282, 1124, 1208, 1133 (CF_3), 969 cm^{-1}. (-)-ESI-MS (*m*/*z*): 336.7 (38), 335.6 (11), 334.7 (100), 332.8 (63). $C_8H_4BrCl_2F_3N_2$ (335.9): calcd. C 28.60, H 1.20, N 8.34; found: C 28.42, H 1.36, N 8.02.

General procedure for synthesis of trifluoroacetaldehyde arylhydrazones **14**: Following the literature protocol [52], a mixture of arylhydrazine hydrochloride (1.0 mmol), excess fluoral hydrate (ca. 3.0 mmol), and freshly activated powdered molecular sieves 4Å (ca. 450 mg) in MeOH (3.5 mL) was heated in a closed ampoule in an oil bath (75 °C) overnight. The solution was cooled to room temperature and filtered through a short pad of Celite, which was washed with several portions of CH_2Cl_2 (4 × 5 mL). The combined organic layers were washed with H_2O (10 mL), then with 5%-aqueous solution of $NaHCO_3$ (10 mL), and dried over Na_2SO_4. The solid inorganics were filtered off and the solvents were removed under reduced pressure (cold bath). The crude products were purified by standard CC to give spectroscopically pure materials, which were used for the next step without further purification.

Trifluoroacetaldehyde 3-nitrophenylhydrazone (**14b**): CC (SiO_2, petroleum ether/CH_2Cl_2 3:2), 152 mg (65%). Yellow solid, m.p. 156–158 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.08 (qd, J_{H-H} = 1.4 Hz, J_{H-F} = 3.9 Hz, 1 H, =$CHCF_3$), 7.43 (ddd, *J* = 1.2, 2.2, 8.2 Hz, 1 H), 7.47 (t_{br}, *J* ≈ 8.0 Hz, 1 H), 7.83 (ddd, *J* = 1.2, 2.2, 7.9 Hz, 1 H), 7.91 (t, *J* = 2.2 Hz, 1 H), 8.18 (s_{br}, 1 H, NH). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 108.3, 116.9, 119.3 (3 d, 3 CH), 120.7 (q, $^1J_{C-F}$ = 269.8 Hz, CF_3), 125.2 (q, $^2J_{C-F}$ = 39.6 Hz, =CCF_3), 130.5 (d, CH), 144.0, 149.4 (2 s, 2 *i*-C). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −65.9 (d, J_{H-F} = 3.9 Hz, CF_3). IR (neat): ν 3302 (NH), 1610, 1558, 1342, 1290, 1245, 1118 (CF_3), 1074 cm^{-1}. (-)-ESI-MS (*m*/*z*): 231.8 (100, [*M*–H]$^-$). $C_8H_6F_3N_3O_2$ (233.0): calcd. C 41.21, H 2.59, N 18.02; found: C 41.21, H 2.72, N 18.03.

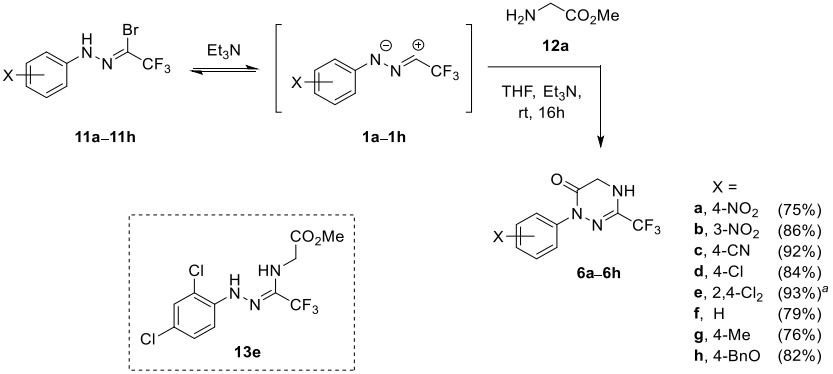
Trifluoroacetaldehyde 2,4-dichlorophenylhydrazone (**14e**): CC (SiO_2, petroleum ether/CH_2Cl_2 3:2), 202 mg (79%). Light orange oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.12 (qd, J_{H-H} = 1.4 Hz, J_{H-F} = 3.8 Hz, 1 H, =*CH*CF_3), 7.22 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.31 (d, *J* = 2.3 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 8.33 (s_{br}, 1 H, NH). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 115.9 (d, CH), 118.2 (s, *i*-C), 120.8 (q, $^1J_{C-F}$ = 269.7 Hz, CF_3), 125.6 (q, $^2J_{C-F}$ = 39.3 Hz, =CCF_3), 126.8 (s, *i*-C), 128.5, 129.0 (2 d, 2 CH), 137.7 (s, *i*-C). ^{19}F NMR ($CDCl_3$, 565 MHz): δ −65.9 (d, J_{H-F} = 3.8 Hz, CF_3). IR (neat): ν 3354 (NH), 1591, 1521, 1357, 1279, 1234, 1115 (CF_3), 1051, 913, 816 cm^{-1}. (-)-ESI-MS (*m*/*z*): 254.8 (100, [*M*–H]$^-$). $C_8H_5Cl_2F_3N_2$ (256.0): calcd. C 37.38, H 1.96, N 10.90; found: C 37.36, H 2.20, N 10.97.

3. Results and Discussion

Based on our experience in the chemistry of (3+2)-cycloaddition reactions of nitrile imines **1**, the first experiments were carried out in dry THF solutions, under inert atmosphere, at room temperature, using hydrazonoyl bromides **11** as the source of nitrile imines and excess Et_3N as a base triggering the dehydrohalogenation reaction [25–28]. For a test experiment, *N*-(4-nitrophenyl)-trifluoroacetohydrazonoyl bromide (**11a**) and methyl glycinate (**12a**, as hydrochloride) were selected as reaction partners, and after the addition

(CH_2Cl_2, toluene) resulted in remarkable change of the chemical yield of the studied reaction. Prompted by the often-observed positive effects of mechanochemical activation on reaction outcomes, (e.g., remarkable shortening of reaction times, higher yields, etc.) [53–55], the (3+3)-annulation reaction of **11a** and **12a** was also tested under ball-mill conditions (steel balls, ø 7 mm, 25 Hz). However, in this case, the formation of viscous mixture was observed upon the reaction progress, which enabled effective ball-milling and the reaction could not be completed. Moreover, the use of three-fold excess of glycinate **12a** (with respect to bromide **11a**) was necessary to obtain the desired product **6a** in a comparable yield (77%) and the remarkably shorter reaction time of 2 h, and for these reasons we waved on the mechanochemical approach.

The structure of the isolated product **6a** was confirmed based on NMR methods; for example, in ^{1}H NMR spectrum, a broadened doublet ($J \approx 1.5$ Hz) attributed to 5-H$_2$ was found at δ 4.30, along with absorption (s_{ex}) of the NH (δ 5.31), and the characteristic set of signals (two d$_m$, located at δ 7.92 and 8.27, $J \approx 9.2$ Hz each) of the C$_6$H$_4$NO$_2$ group. Furthermore, two diagnostic quartets attributed to the CF$_3$ group, and the C-3 atom were found at δ 118.2 ($^1J_{C\text{-}F}$ = 275.2 Hz) and δ 137.3 ($^2J_{C\text{-}F}$ = 37.8 Hz), respectively, whereas the absorption (s) of the amide-type C=O group was found at δ 158.1. Finally, the ^{19}F NMR indicated the presence of a single CF$_3$ group (singlet at δ −70.6), while the ESI-MS, supplemented by combustion analysis, confirmed the molecular formula of $C_{10}H_5F_3N_4O_5$. Based on the collected data, the structure of isolated product was established as the hitherto unknown 1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6a**).



Scheme 2. Synthesis of 1,2,4-triazin-6(1*H*)-ones **6a–6h** derived from methyl glycinate (scope of nitrile imines **1**) and the structure of intermediate **13e**; [a] crude reaction mixture was refluxed for 2 h.

With the optimized reaction conditions in hand, a series of variously substituted nitrile imines **1b–1h** were checked in the reaction with glycinate **12a** (Scheme 2). The required nitrile imine precursors of type **11** were prepared according to the general literature protocols by condensation of arylhydrazines with fluoral hydrate [52], followed by NBS-mediated bromination of the first formed hydrazones **14** (Scheme 3) [25]. As shown in Scheme 2, the expected products were formed in high yields (74–93%), irrespective of the electronic nature of the substituent X. These observations nicely correspond to the previous results reported by Dalinger for reactions of stable perfluoroalkanecarbohydrazonoyl chlorides with methyl glycinate and, the structure of isolated products [56,57] was established as the hitherto unknown 1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6a**).

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of a base (3.0 equiv.), the slow consumption of the nitrile imine precursor was observed (according to TLC monitoring) to give after 16 h the expected (3+3)-cycloadduct **6a**, which was isolated by flash chromatography in a fair 59% yield (Scheme 2). Brief optimization of the reaction conditions revealed that increasing the amount of Et_3N (8.0 equiv.) enhanced the yield of isolated product **6a** (75%) formed as the only product. On the other hand, neither the change of the base (Cs_2CO_3, pyridine, DBU), nor the type of solvent used (CH_2Cl_2, toluene) resulted in remarkable change of the chemical yield of the studied reaction. Moreover, the observed positive effects of mechanochemical activation on reaction outcomes, (e.g., remarkable shortening of reaction times, higher yields, etc.) [53–55], the (3+3)-annulation reaction of **11a** and **12a** was also tested under ball-mill conditions (steel balls, ø 7 mm, 25 Hz). However, in this case, the formation of viscous mixture was observed upon the reaction progress, which enabled effective ball-milling and the reaction could not be completed. Moreover, the use of three-fold excess of glycinate **12a** (with respect to bromide **11a**) was necessary to obtain the desired product **6a** in a comparable yield (77%) and the remarkably shorter reaction time of 2 h, and for these reasons we waved on the mechanochemical approach.

The structure of the isolated product **6a** was confirmed based on NMR methods; for example, in ^{1}H NMR spectrum, a broadened doublet ($J \approx 1.5$ Hz) attributed to 5-H$_2$ was found at δ 4.30, along with absorption (s_{ex}) of the NH (δ 5.31), and the characteristic set of signals (two d$_m$, located at δ 7.92 and 8.27, $J \approx 9.2$ Hz each) of the C$_6$H$_4$NO$_2$ group. Furthermore, two diagnostic quartets attributed to the CF$_3$ group, and the C-3 atom were found at δ 118.2 ($^1J_{C\text{-}F}$ = 275.2 Hz) and δ 137.3 ($^2J_{C\text{-}F}$ = 37.8 Hz), respectively, whereas the absorption (s) of the amide-type C=O group was found at δ 158.1. Finally, the ^{19}F NMR indicated the presence of a single CF$_3$ group (singlet at δ −70.6), while the ESI-MS, supplemented by combustion analysis, confirmed the molecular formula of $C_{10}H_5F_3N_4O_5$. Based on the collected data, the structure of isolated product was established as the hitherto unknown 1-(4-nitrophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**6a**).

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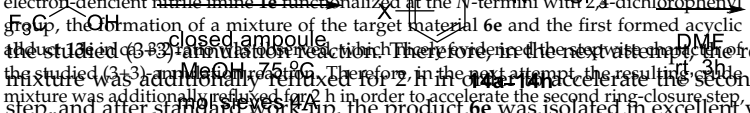
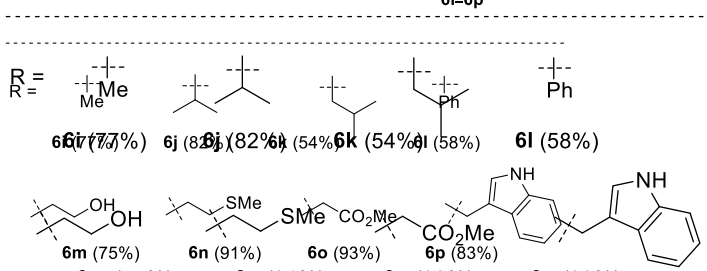
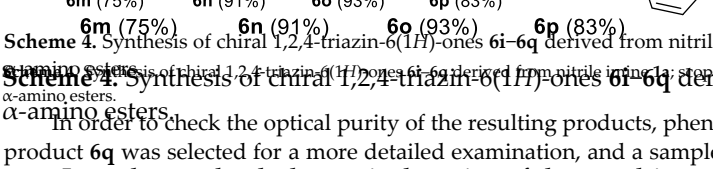
the studied (3+3)-annulation reaction. Therefore, in the next attempt, the resulting
mixture was additionally refluxed for 2 h in order to accelerate the second ring-closure
step, and after standard work-up, the product **6e** was isolated in excellent yield (93%).



Scheme 3. Synthesis of hydrazonoyl bromides **11a–11h**.

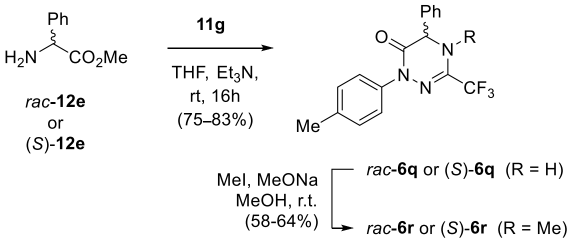
Next, a series of enantiopure α-substituted (*S*)-amino esters **12b–12i** derived from simple alkyl and aryl substituted natural amino acids, namely alanine, valine, leucine, phenylglycine, serine, methionine, aspartic acid and tryptophan's surrogate, respectively, were examined in reaction with selected hydrazonoyl bromides **11a** in the presence of methyl and aspartate (**12h**) of the presence of the additional CO_2Me group did not interfere with the subsequent cyclisation step, and the 6-membered product **6o** was formed exclusively in excellent yield (93%).





Scheme 4. Synthesis of chiral 1,2,4-triazin-6(1*H*)-ones **6i–6q** derived from nitrile imine **1a**; scope of α-amino esters.

In order to check the optical purity of the resulting products, phenylglycine-derived product **6q** was selected for a more detailed examination, and a sample of racemic triazinone *rac*-**6q** was prepared as a reference compound (Scheme 5). Unfortunately, further chiral-HPLC analysis of pure samples of **6q** nor ^{1}H NMR measurements of the stereomeric 1:1 mixtures with (+)-(*S*)-mandelic acid and with (+)-(*R*)-(*tert*-butylphenyl)phosphonothioic acid [58] selected as chiral solvating agents was successful.



Scheme 5. Synthesis of racemic and enantiopure phenylglycine-derived 1,2,4-triazin-6-ones *rac*-**6q** and (*S*)-**6q**, and their transformation into *N*-methylated analogues **6r**.

In order to check the optical purity of the resulting products, phenylglycine-derived product **6q** was selected for a more detailed examination, and a sample of racemic 1,2,4-triazinone *rac*-**6q** was prepared as a reference compound (Scheme 5). Unfortunately, neither chiral-HPLC analysis of pure samples of **6q** nor ^{1}H NMR measurements of their diastereomeric 1:1 mixtures with (+)-(*S*)-mandelic acid and with (+)-(*R*)-(*tert*-butyl)(phenyl) phosphonothioic acid [58] selected as chiral solvating agents was successful. In addition, the attempted derivatization of 1,2,4-triazin-6-ones **6q** using enantiopure acid chloride derived from (*S*)-naproxen was in vain. Nevertheless, the treatment of **6q** with strongly electrophilic MeI under basic conditions enabled fully regioselective methylation at N(4) to afford the expected products (*S*)-**6r** and *rac*-**6r** isolated in 58% and 64% yield, respectively. Subsequent HPLC analysis of both samples proved the optical purity of the product derived from chiral methyl phenylglycinate (*S*)-**12e** (for details, see Supporting Information). Hence, taking into account the high susceptibility for epimerization of the phenylglycine-derived compounds under basic conditions, we assume that other products in the series (**6i**–**6q**) were optically pure as well.

The ^{13}C NMR spectrum of *N*-methylated product **6r** also deserves a brief comment. Along with the expected diagnostic quartets located at δ 118.9 ($^1J_{C\text{-}F}$ = 275.9 Hz) and δ 136.5 ($^2J_{C\text{-}F}$ = 34.3 Hz) attributed to the CF_3 group and the C(3) atom, respectively, an additional quartet of the *N*-Me at δ 36.2 ($J_{C\text{-}F}$ = 3.4 Hz) was found. Apparently, the close proximity of the CF_3 and the Me groups results in the observed C–F through-space coupling.

In addition to a series of experiments performed with the primary *α*-amino esters **12a**–**12i**, (S)-proline methyl ester (**12j**) was also involved in the study as a model secondary amino-compound. As shown in Scheme 6, (3+3)-annulation of **12j** with nitrile imines of type **1** carried out under the analogous reaction conditions provided the expected bicyclic products **7a**–**7h**, which were generally isolated in fair yield (47–93%). Similar to the cyclo-condensation of 2,4-dichlorophenyl-functionalized nitrile imine **1e** with methyl glycinate (Scheme 1), the reaction of **12j** with **1e** also provided the respective amidrazone intermediate, which required prolonged heating in THF (3 d, 60 °C) to afford the target bicyclic material **7e** (50%).

Having in hand two series of 3-trifluoromethylated 1,2,4-triazin-6-ones **6** and **7**, selected functional group interconversions were carried out to demonstrate the robustness of the core heterocycle. Thus, NH_2 and OH groups were easily accessed by medium-pressure (3 atm) catalytic hydrogenation of the NO_2 and BnO groups in **7a** and **7h**, respectively, and the expected products **7i** (89%) and **7j** (67%) were isolated in high yields (Scheme 7). On the other hand, with the treatment of the 4,5-dihydro-1,2,4-triazine derivative **6g** with an aqueous solution of $K_3Fe(CN)_6$, in the presence of tetraethylammonium bromide as a phase transfer catalyst, the smooth oxidation of the N(4)–C(5) bond was observed to yield fairly stable 1,2,4-triazin-6-one **6s** (78%) identified as the only product. The structure of **6s** was confirmed based on ^{1}H and ^{13}C NMR spectra supplemented by 2D measurements (HMQC); particularly, characteristic low-field shifted absorptions attributed to C(5)-H unit, i.e., a singlet at δ 8.47 in ^{1}H NMR and a signal at δ 161.0 in ^{13}C NMR, were observed.

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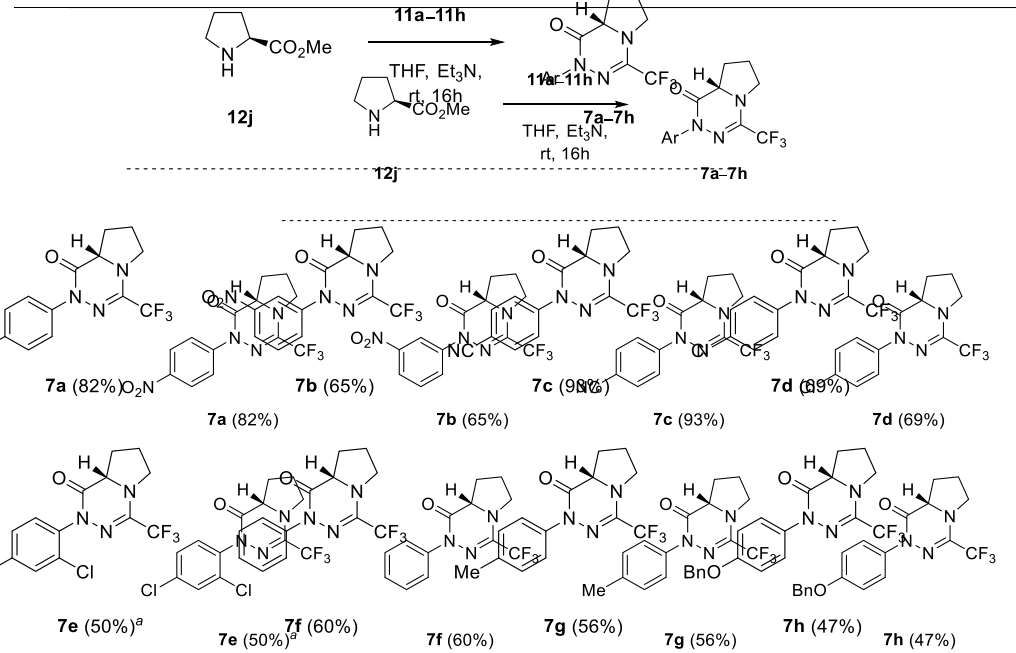

Scheme 6. Synthesis of L-proline-derived bicyclic 1,2,4-triazinones **7a–7h**; crude reaction mixture was heated at 60 °C for 3 d.

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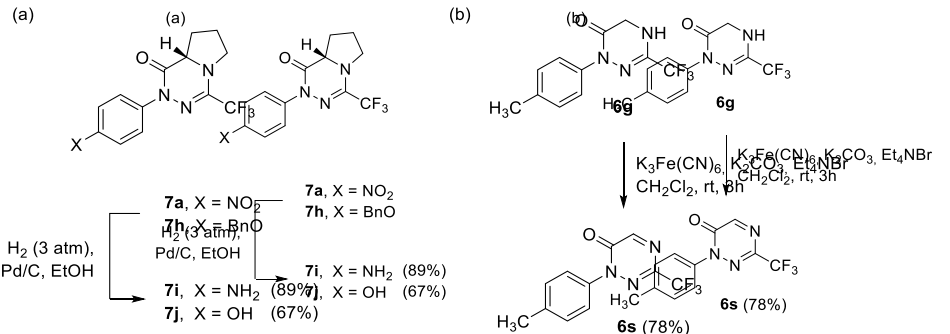

Scheme 7. Selected transformations of title heterocycles: (**a**) synthesis of amino- and hydroxy-functionalized products **7i** and **7j**, starting from nitro- and benzyloxy-containing **7a** and **7h**, respectively; (**b**) selective oxidation of **6g** with $K_3Fe(CN)_6$ under PTC conditions leading to 1,2,4-triazin-6-one **6s**.

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Finally, prompted by recent reports on anticancer properties of some fluorinated and non-fluorinated 1,2,4-triazine-based materials [15–30], the cytotoxicity of 1,2,4-triazin-6(1*H*)-ones **6a–6g** and **7a–7h** obtained in this study was checked against human promyelocytic leukemia (HL-60) and breast cancer adenocarcinoma (MCF-7) cell lines (for details, see Supplementary Materials). However, most of the examined samples showed no mentionable cytotoxicity; for example, all compounds in glycine-derived series **6a–6h** proved inactive irrespective of the type of substituent X, whereas in the case of chiral representatives **6i–6q** only for the analogue functionalized with H-donor/acceptor 2-hydroxyethyl group (compound **6m**), a moderate (IC_{50} = 23.0 μM) activity against HL-60 line was observed. For the analogue functionalized with H-donor/acceptor benzyloxyethyl group (compound **6m**), a moderate (IC_{50} = 23.0 μM) activity against HL-60 line was

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chiral representatives **6i**–**6q** only for the analogue functionalized with H-donor/acceptor 2-hydroxyethyl group (compound **6m**), a moderate (IC_{50} = 23.0 μM) activity against HL-60 line was observed. For the proline-derived analogues **7a**–**7h,** the best result was noticed for benzonitrile-functionalized analogue **7c** with only low cytotoxicity of IC_{50} = 45.4 μM against HL-60 cell line.

4. Conclusions

In the presented study, the synthesis of a series of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones functionalized with the CF_3 group is reported. The devised protocol is based on the (3+3)-annulation of methyl esters derived from natural α-amino acids with in situ generated trifluoroacetonitrile imines applied as reactive 1,3-dipolar reaction partners. Notably, starting with chiral α-amino esters, no racemization occurred under the optimized reaction conditions, and the expected enantiopure materials were isolated as the only products. Furthermore, with the application of methyl L-prolinate as a model secondary amino ester, the respective fused 1,2,4-triazinones were obtained. The selected functional group interconversions performed under catalytic hydrogenation or mild PTC-oxidation conditions demonstrated remarkable stability of the core heterocycle. Thus, the presented method offers straightforward access to the desired heterocyclic system functionalized not only with simple alkyl and aryl substituents, but also with such functional groups as nitro, cyano, hydroxy, amino, methoxycarbonyl, and sulfide, as well as 1*H*-indol-3-yl and halogen(s). Taking into account the easy accessibility of the starting materials and the exceptionally mild reaction conditions, the presented approach can be recommended for the synthesis of title 3-trifluoromethylated heterocycles, and nicely supplements previous reports on the synthesis of 1,2,4-triazin-6(1*H*)-ones exploiting amino acids and their derivatives as key building blocks [56,57,59–64].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ma16020856/s1: Copies of ^{1}H and ^{13}C NMR spectra of all new compounds, HPLC analyses, technical details, and results on biological activity screening. Ref. [65] cited in Supplementary Materials.

Author Contributions: Conceptualization, M.J.; methodology, M.J. and K.G.-J.; investigation, A.K., M.C., K.Ś., G.U.-J. and A.J.; writing—original draft preparation, M.J. and K.G.-J.; writing—review and editing, M.J. and K.G.-J.; supervision, M.J.; funding acquisition, M.J. All authors have read and agreed to the published version of the manuscript.

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References

1. O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **2008**, *37*, 308–319. [CrossRef]
2. Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. [CrossRef]
3. Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2013. [CrossRef]
4. Nenajdenko, V. (Ed.) *Fluorine in Heterocyclic Chemistry, Vol. 1: 5-Membered Heterocycles and Macrocycles*; Springer International Publishing: Manhattan, NY, USA, 2014. [CrossRef]
5. Liu, Y.; Jiang, L.; Wang, H.; Wang, H.; Jiao, W.; Chen, G.; Zhang, P.; Hui, D.; Jian, X. A brief review for fluorinated carbon: Synthesis. Properties and applications. *Nanotechnol. Rev.* **2019**, *8*, 573–586. [CrossRef]

6. Lemoine, K.; Hémon-Ribaud, A.; Leblanc, M.; Lhoste, J.; Tarascon, J.-M.; Maisonneuve, V. Fluorinated materials as positive electrodes for Li- and Na-ion batteries. *Chem. Rev.* **2022**, *122*, 14405–14439. [CrossRef]
7. Chen, X.; Fan, K.; Liu, Y.; Liu, X.; Feng, W.; Wang, X. Recent advances in fluorinated graphene from synthesis to applications: Critical review on functional chemistry and structure engineering. *Adv. Mater.* **2022**, *34*, 2101665. [CrossRef]
8. Wang, J.; Sánchez-Roselló, M.; Aceña, J.L.; del Pozo, C.; Sorochinsky, A.E.; Fustero, S.; Soloshonok, V.A.; Liu, H. Fluorine in pharmaceutical industry: Fluorine-containing drugs introduced to the market in the last decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506. [CrossRef] [PubMed]
9. Zhang, C.; Yan, K.; Fu, C.; Peng, H.; Hawker, C.J.; Whittaker, A.K. Biological utility od fluorinated compounds: From materials design to molecular imaging, therapeutics and environmental remediation. *Chem. Rev.* **2022**, *122*, 167–208. [CrossRef]
10. Tiz, D.B.; Bagnoli, L.; Rosati, O.; Marini, F.; Sancineto, L.; Santi, C. New halogen-containing drugs approved by FDA in 2021: An overview on their syntheses and pharmaceutical use. *Molecules* **2022**, *27*, 1643. [CrossRef]
11. Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current contributions of organofluorine compounds to the agrochemical industry. *iScience* **2020**, *23*, 101467. [CrossRef]
12. Gakh, A.A.; Shermolovich, Y. Trifluoromethylated heterocycles. *Curr. Top. Med. Chem.* **2014**, *14*, 952–965. [CrossRef]
13. Meyer, F. Trifluoromethyl nitrogen heterocycles: Synthetic aspects and potential biological targets. *Chem. Commun.* **2016**, *52*, 3077–3094. [CrossRef] [PubMed]
14. Liu, F.; Sameem, B. Fluorinated *N*-heterocycles as conformationally diverse bioactives for drug discovery. In *Targets in Heterocyclic Systems*; Italian Chemical Society: Rome, Italy, 2021; Volume 25, pp. 502–516. [CrossRef]
15. Petrov, V.A. (Ed.) *Fluorinated Heterocyclic Compound: Synthesis, Chemistry, and Applications*; J. Wiley & Sons, Inc.: Hoboken, NJ, USA, 2009.
16. Luzzio, F.A. Synthesis and reactivity of fluorinated heterocycles. In *Advances in Heterocyclic Chemistry*; Academic Press: Cambridge, MA, USA, 2020; Volume 132, pp. 1–84. [CrossRef]
17. Sap, J.B.I.; Meyer, C.F.; Straathof, N.J.W.; Iwumene, N.; am Ende, C.W.; Trabanco, A.A.; Governeur, V. Late-stage difluoromethylation: Concepts, developments and perspective. *Chem. Soc. Rev.* **2021**, *50*, 8214–8247. [CrossRef] [PubMed]
18. Mlostoń, G.; Shermolovich, Y.; Heimgartner, H. Synthesis of fluorinated and fluoroalkylated heterocycles containing at least one sulfur atom via cyclocondensation reactions. *Materials* **2022**, *15*, 7244. [CrossRef] [PubMed]
19. He, P.; Zhu, S.Z. Preparation of fluorine-containing heterocyclic compounds via cycloaddition reactions. *Mini-Rev. Org. Chem.* **2004**, *4*, 417–435. [CrossRef]
20. Jamieson, C.; Livingstone, K. *The Nitrile Imine 1,3-Dipole; Properties, Reactivity and Applications*; Springer Nature: Cham, Switzerland, 2020.
21. Deepthi, A.; Acharjee, N.; Sruthi, S.L.; Meenakshy, C.B. An overview of nitrile imine based [3+2] cycloadditions over half a decade. *Tetrahedron* **2022**, *116*, 132812. [CrossRef]
22. Mykhailiuk, P.K. 2,2,2-Trifluorodiazoethane (CF_3CHN_2): A long journey since 1943. *Chem. Rev.* **2020**, *120*, 12718–12755. [CrossRef]
23. Kumar, A.; Khan, W.A.; Ahamad, S.; Mohanan, K. Trifluorodiazoethane: A versatile building block to access trifluoromethylated heterocycles. *J. Heterocycl. Chem.* **2022**, *59*, 607–632. [CrossRef]
24. Chandrasekharan, S.P.; Dhami, A.; Kumar, S.; Mohanan, K. Recent advances in pyrazole synthesis employing diazo compounds and synthetic analogues. *Org. Biomol. Chem.* **2022**, *20*, 8787–8817. [CrossRef]
25. Mlostoń, G.; Urbaniak, K.; Utecht, G.; Lentz, D.; Jasiński, M. Trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles via the regioselective [3+2]-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones. *J. Fluor. Chem.* **2016**, *192*, 147–154. [CrossRef]
26. Utecht, G.; Sioma, J.; Jasiński, M.; Mlostoń, G. Expected and unexpected results in reactions of fluorinated nitrile imines with (cyclo)aliphatic thioketones. *J. Fluor. Chem.* **2017**, *201*, 68–75. [CrossRef]
27. Utecht, G.; Fruziński, A.; Jasiński, M. Polysubstituted 3-trifluoromethylpyrazoles: Regioselective (3+2)-cycloaddition of trifluoroacetonitrile imines with enol ethers and functional group transformations. *Org. Biomol. Chem.* **2018**, *16*, 1252–1257. [CrossRef] [PubMed]
28. Utecht, G.; Mlostoń, G.; Jasiński, M. A straightforward access to trifluoromethylated spirobipyrazolines through a double (3+2)-cycloaddition of fluorinated nitrile imines with alkoxyallenes. *Synlett* **2018**, *29*, 1753–1758. [CrossRef]
29. Tian, Y.-C.; Li, J.-K.; Zhang, F.-G.; Ma, J.-A. Regioselective decarboxylative cycloaddition route to fully substituted 3-CF_3-pyrazoles from nitrilimines and isoxazolidinediones. *Adv. Synth. Catal.* **2021**, *363*, 2093–2097. [CrossRef]
30. Kowalczyk, A.; Utecht-Jarzyńska, G.; Mlostoń, G.; Jasiński, M. A straightforward access to 3-trifluoromethyl-1*H*-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile. *J. Fluor. Chem.* **2021**, *241*, 109691. [CrossRef]
31. Han, T.; Wang, K.-H.; Yang, M.; Zhao, P.; Wang, F.; Wang, J.; Huang, D.; Hu, Y. Synthesis of difluoromethylated pyrazoles by the [3+2] cycloaddition reaction of difluoroacetohydrazonoyl bromides. *J. Org. Chem.* **2022**, *87*, 498–511. [CrossRef]
32. Ren, Y.; Ma, R.; Feng, Y.; Wang, K.-H.; Wang, J.; Huang, D.; Lv, X.; Hu, Y. Synthesis of difluoromethyl pyrazolines and pyrazoles by [3+2] cycloaddition reaction of difluoroacetohydrazonoyl bromides with electron-deficient olefins. *Asian J. Org. Chem.* **2022**, *11*, e202200438. [CrossRef]
33. Wang, K.-H.; Liu, H.; Liu, X.; Bian, C.; Wang, J.; Su, Y.; Huang, D.; Hu, Y. Regioselective synthesis of 3-trifluoromethyl 4-subtituted pyrazoles by [3+2]-cycloaddition of trifluoroacetonitrile imines and nitroalkenes. *Asian J. Org. Chem.* **2022**, *11*, e202200103. [CrossRef]

34. Zhou, Y.; Gao, C.-F.; Ma, H.; Nie, J.; Ma, J.-A.; Zhang, F.-G. Quadruple functionalized pyrazole pharmacophores by one-pot regioselective [3+2]-cycloaddition of fluorinated nitrile imines and dicyanoalkenes. *Chem. Asian J.* **2022**, *17*, e202200436. [CrossRef]
35. Utecht-Jarzyńska, G.; Nagła, K.; Młostoń, G.; Heimgartner, H.; Palusiak, M.; Jasiński, M. A straightforward conversion of 1,4-quinones into polycyclic pyrazoles via [3+2]-cycloaddition with fluorinated nitrile imines. *Beilstein J. Org. Chem.* **2021**, *17*, 1509–1517. [CrossRef]
36. Kowalczyk, A.; Utecht-Jarzyńska, G.; Młostoń, G.; Jasiński, M. Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions. *Org. Lett.* **2022**, *24*, 2499–2503. [CrossRef]
37. Utecht-Jarzyńska, G.; Kowalczyk, A.; Jasiński, M. Fluorinated and non-fluorinated 1,4-diarylpyrazoles via MnO_2-mediated mechanochemical deacylative oxidation of 5-acylpyrazolines. *Molecules* **2022**, *27*, 8446. [CrossRef]
38. Utecht-Jarzyńska, G.; Jasiński, M.; Świątek, K.; Młostoń, G.; Heimgartner, H. Novel trifluoromethylated spiro-1,3,4-thiadiazoles via [3+2]-cycloadditions of 2,3-diphenylcyclopropenethione with selected in situ-generated nitrile imines derived from trifluoroacetonitrile. *Heterocycles* **2020**, *101*, 251–262. [CrossRef]
39. Grzelak, P.; Utecht, G.; Jasiński, M.; Młostoń, G. First (3+2)-cycloadditions of thiochalcones as C=S dipolarophiles: Efficient synthesis of 1,3,4-thiadiazoles via reactions with fluorinated nitrile imines. *Synthesis* **2017**, *49*, 2129–2137. [CrossRef]
40. Utecht-Jarzyńska, G.; Mykhaylychenko, S.S.; Rusanov, E.B.; Shermolovich, Y.G.; Jasiński, M.; Młostoń, G. Highly fluorinated 2,3-dihydro-1,3,4-thiadiazole derivatives via [3+2]-cycloadditions of tertiary thioamides with nitrile imines derived from trifluoroacetonitrile. *J. Fluor. Chem.* **2021**, *242*, 109702. [CrossRef]
41. Zhang, Y.; Zeng, J.-L.; Chen, Z.; Wang, R. Base-promoted (3+2)-cycloaddition of trifluoroacetohydrazonoyl chlorides with imidates en route to trifluoromethyl-1,2,4-triazoles. *J. Org. Chem.* **2022**, *87*, 14514–14522. [CrossRef] [PubMed]
42. Utecht-Jarzyńska, G.; Michalak, A.; Banaś, J.; Młostoń, G.; Jasiński, M. Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: An access to fluorinated 1,3,4-thiadiazine derivatives via (3+3)-annulation. *J. Fluor. Chem.* **2019**, *222–223*, 8–14. [CrossRef]
43. Kumar, R.; Sirohi, T.S.; Singh, H.; Yadav, R.; Roy, R.K.; Chaudhary, A.; Pandeya, S.N. 1,2,4-Triazine analogs as novel class of therapeutic agents. *Mini-Rev. Med. Chem.* **2014**, *14*, 168–207. [CrossRef]
44. Cascioferro, S.; Parrino, B.; Spaño, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. An overview on the recent developments of 1,2,4-triazine derivatives as anticancer compounds. *Eur. J. Med. Chem.* **2017**, *142*, 328–375. [CrossRef]
45. Krauth, F.; Dahse, H.-M.; Rüttinger, H.-H.; Frohberg, P. Synthesis and characterization of novel 1,2,4-triazine derivatives with antiproliferative activity. *Bioorg. Med. Chem.* **2010**, *18*, 1816–1821. [CrossRef] [PubMed]
46. Makki, M.S.I.; Abdel-Rahman, R.M.; Khan, K.A. Fluorine substituted 1,2,4-triazinones as potential ani-HIV-1 and CDK2 inhibitors. *J. Chem.* **2014**, *2014*, 430573. [CrossRef]
47. Sweeney, M.; Coyle, R.; Kavanagh, P.; Berezin, A.A.; Lo Re, D.; Zissimou, G.A.; Koutentis, P.A.; Carty, M.P.; Aldabbagh, F. Discovery of anti-cancer activity for benzo[1,2,4]triazin-7-ones: Very strong correlation to pleurotin and thioredoxin reductase inhibition. *Bioorg. Med. Chem.* **2016**, *24*, 3565–3570. [CrossRef] [PubMed]
48. Srinivasa Rao, D.; Pavan Kumar, G.V.; Pooja, B.; Harika, G.; Anil Kumar, Y.; Sadasiva Rao, G. An extensive review on 1,2,3 and 1,2,4-triazines scaffold-valuable lead molecules with potent and diverse pharmacological activities. *Chem. Sin.* **2016**, *7*, 101–130.
49. Zaki, I.; Abdelhameid, M.K.; El-Deen, I.M.; Abdel Wahab, A.H.A.; Ashmawy, A.M.; Mohamed, K.O. Design, synthesis and screening of 1,2,4-triazinone derivatives as potential antitumor agents with apoptosis inducing activity on MCF-7 breast cancer cell line. *Eur. J. Med. Chem.* **2018**, *156*, 563–579. [CrossRef] [PubMed]
50. Saloutina, L.V.; Zapevalov, A.Y.; Kodess, M.I.; Slepukhin, P.A.; Ganebnykh, I.N.; Saloutin, V.I.; Chupakhin, O.N. Trifluoromethyl-containing 1,2,4-triazines. Synthesis on the base of perfluorobiacetyl and reactions with thiosemicarbazide and thiourea. *J. Fluor. Chem.* **2019**, *227*, 109362. [CrossRef]
51. Al-Otaibi, F.A.; Bakhotmah, D.A. Synthesis and biological evaluation of new fluorine compounds bearing 4-amino-1,2,4-triazino[4,3-b]-1,2,4-triazin-8-one and the related derivatives as CDK2 inhibitors of tumor cell. *Polycycl. Aromat. Comp.* **2020**, *42*, 623–634. [CrossRef]
52. Wojciechowska, A.; Jasiński, M.; Kaszyński, P. Tautomeric equilibrium in trifluoroacetaldehyde arylhydrazones. *Tetrahedron* **2015**, *71*, 2349–2356. [CrossRef]
53. Howard, J.L.; Cao, Q.; Browne, D.L. Mechanochemistry as an emerging tool for molecular synthesis: What can it offer? *Chem. Sci.* **2018**, *9*, 3080–3094. [CrossRef]
54. Pickhardt, W.; Grätz, S.; Borchardt, L. Direct mechanocatalysis: Using milling balls as catalysts. *Chem. Eur. J.* **2020**, *26*, 12903–12911. [CrossRef]
55. Młostoń, G.; Celeda, M.; Heimgartner, H.; Duda, D.; Obijalska, E.; Jasiński, M. Synthesis and selected transformations of 2-unsubstituted imidazole *N*-oxides using a ball-milling mechanochemical approach. *Catalysts* **2022**, *12*, 589. [CrossRef]
56. Awadallah, A.M.; Ferwanah, A.-R.S.; El-Sawi, E.; Dalloul, H.M. Cyclocondensation reactions of nitrilimines: Synthesis of 1,2,4-triazin-6-ones and 1,2,4,5-tetrazines. *Heterocycl. Commun.* **2002**, *8*, 369–374. [CrossRef]
57. Dalloul, H.M.M. Synthesis of spiroheterocycles containing thiadiazole thiadiazine and triazine moieties from nitrilimines. *Phosphorus Sulfur Silicon Relat. Elem.* **2011**, *186*, 1876–1884. [CrossRef]

58. Omelańczuk, J.; Mikołajczyk, M. Chiral *t*-butylphenylphosphinothioic acid: A useful chiral solvating agent for direct determination of enantiomeric purity of alcohols, thiols, amines, diols, aminoalcohols and related compounds. *Tetrahedron Asymmetry* **1996**, *7*, 2687–2694. [CrossRef]
59. Kowalczyk, A.; Jasiński, M. 4,5-Dihydro-1,2,4-triazin-6(1*H*)-ones. *Chem. Heterocycl. Comp.* **2022**, *58*, 585–587. [CrossRef]
60. Camparini, A.; Celli, A.M.; Ponticelli, F. Synthesis and structure of dihydro-1,2,4-triazin-6(1*H*)ones. *J. Heterocycl. Chem.* **1978**, *15*, 1271–1276. [CrossRef]
61. Taylor, E.C.; Macor, J.E. Efficient synthesis of 5-substituted-4,5-dihydro-1,2,4-triazin-6-ones and 5-substituted-1,2,4-triazin-6-ones. *J. Heterocycl. Chem.* **1985**, *22*, 409–411. [CrossRef]
62. Boeglin, D.; Cantel, S.; Martinez, J.; Fehrentz, J.-A. Efficient solid-phase synthesis of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones. *Tetrahedron Lett.* **2003**, *44*, 459–462. [CrossRef]
63. Kudelko, A.; Zieliński, W.; Jasiak, K. Synthesis of novel 1-[(1-ethoxymethylene)amino]imidazol-5(4*H*)-ones and 1,2,4-triazin-6(5*H*)-ones from optically active α-aminocarboxylic acid hydrazides. *Tetrahedron Lett.* **2013**, *54*, 4637–4640. [CrossRef]
64. Amin, M.A.; Saad, H.A. Synthesis and biological activity of fused heteropolycyclic systems containing an indole moiety. *Curr. Org. Synth.* **2016**, *13*, 116–125. [CrossRef]
65. Mosmann, T. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. *J. Immunol. Methods* **1983**, *65*, 55–63. [CrossRef]

Supporting Information

for

Trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones *via* (3+3)-annulation of nitrile imines with α-amino esters

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Copies of ^{1}H and ^{13}C NMR spectra of new compounds

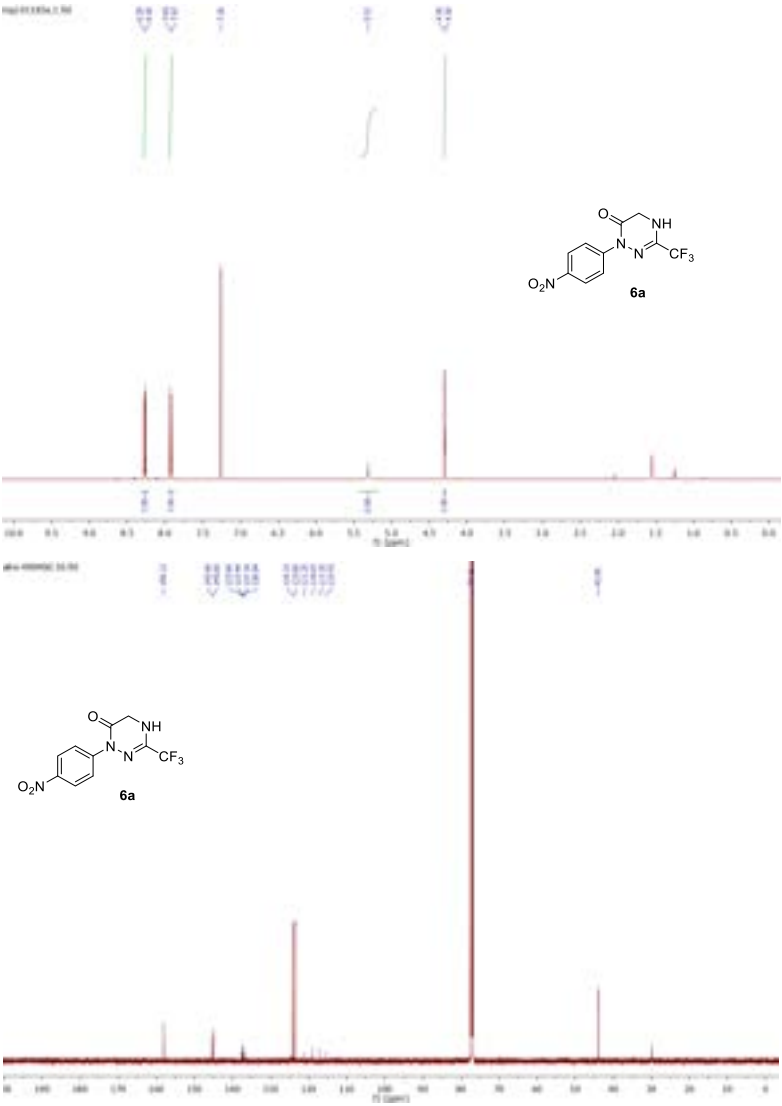


Figure S1. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6a**.

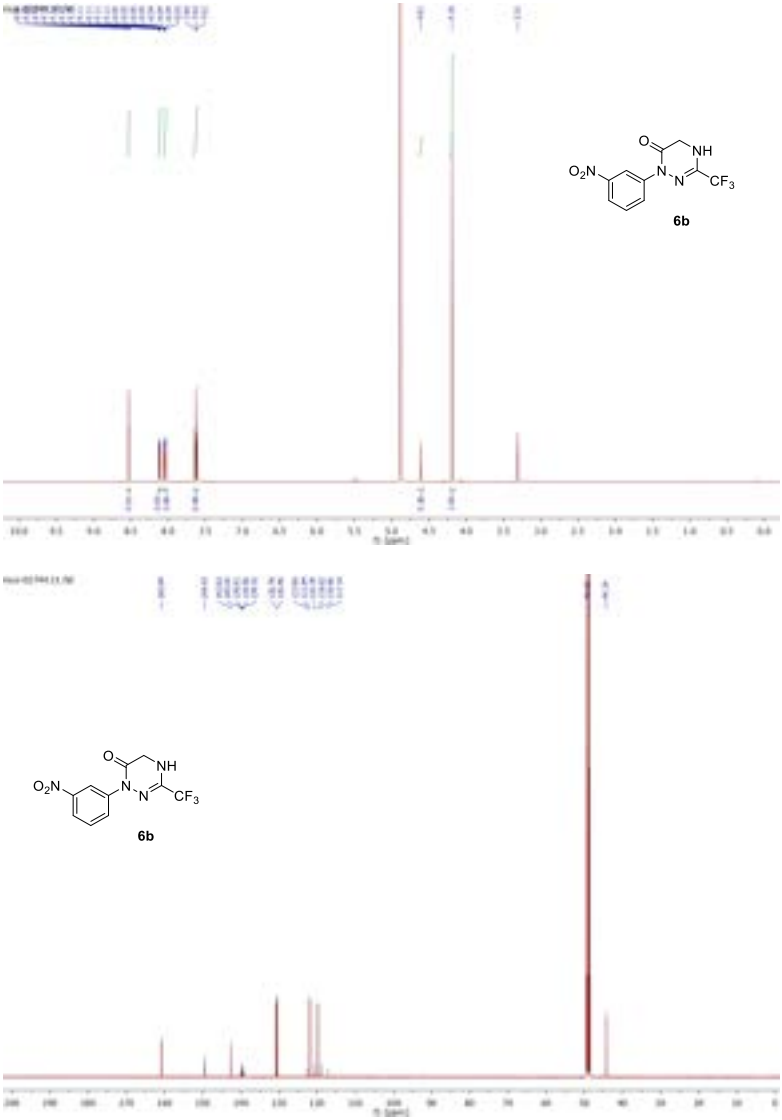


Figure S2. ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (151 MHz, CD_3OD) spectra for compound **6b**.

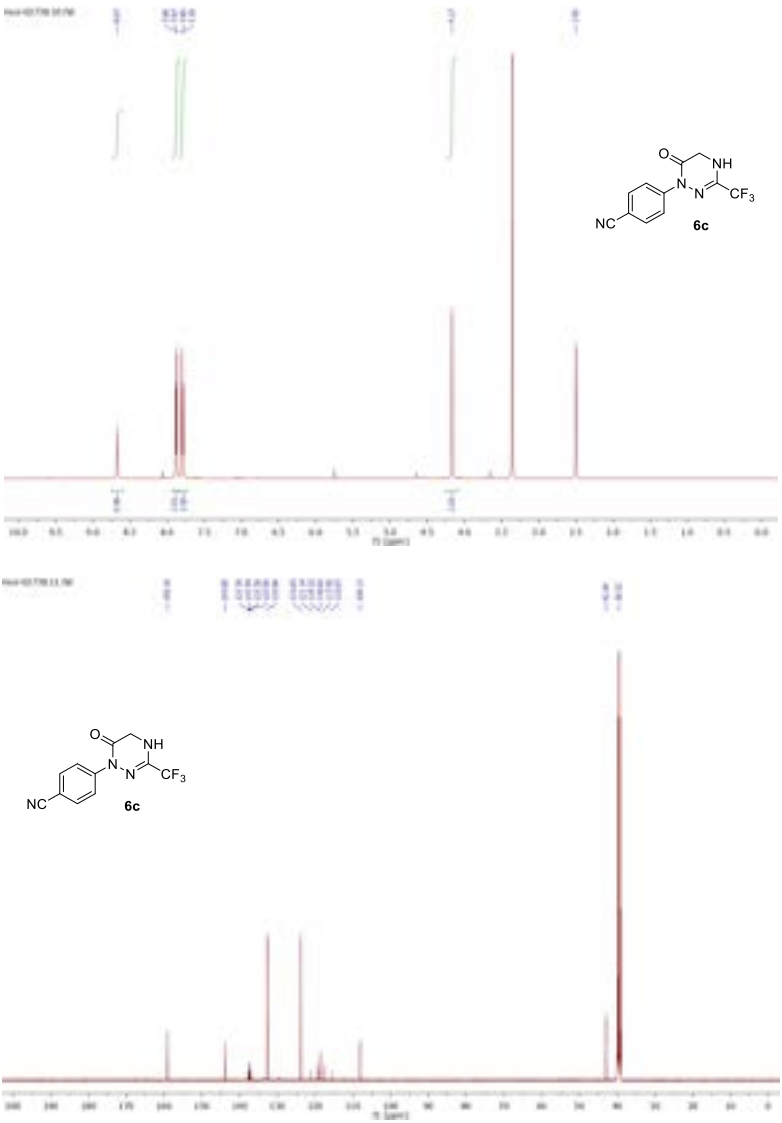


Figure S3. ^{1}H NMR (600 MHz, DMSO-d_6) and ^{13}C NMR (151 MHz, DMSO-d_6) spectra for compound **6c**.

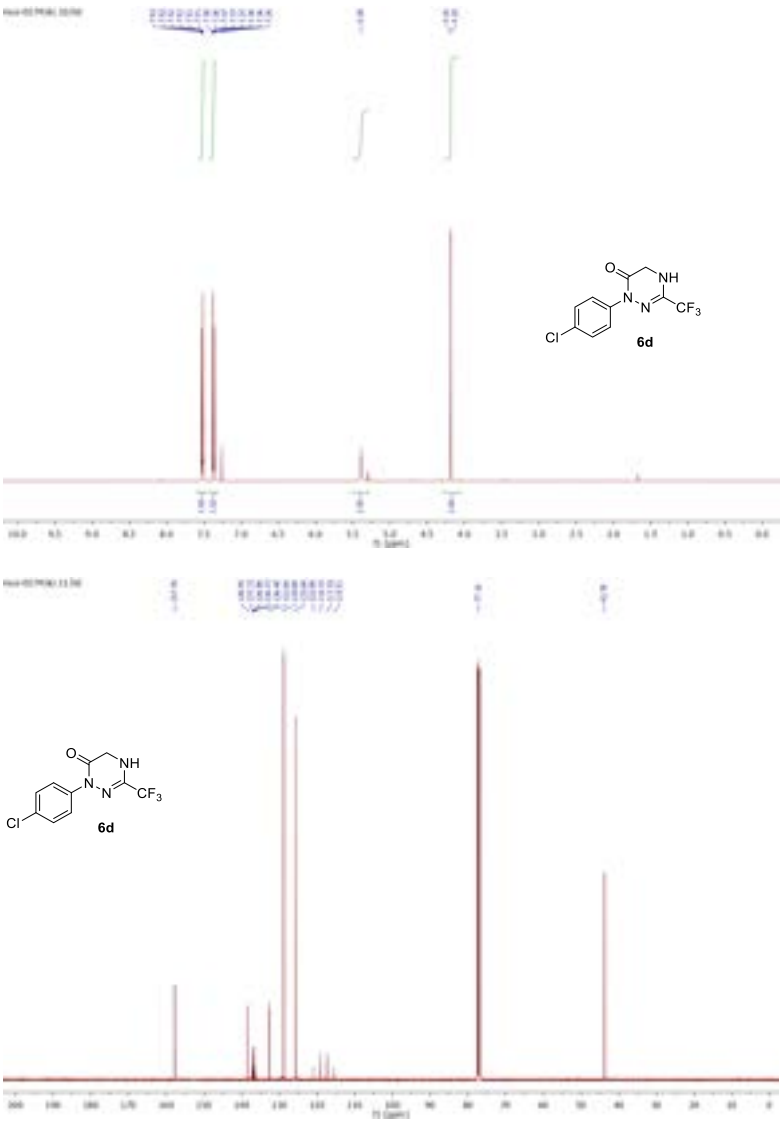


Figure S4. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6d**.

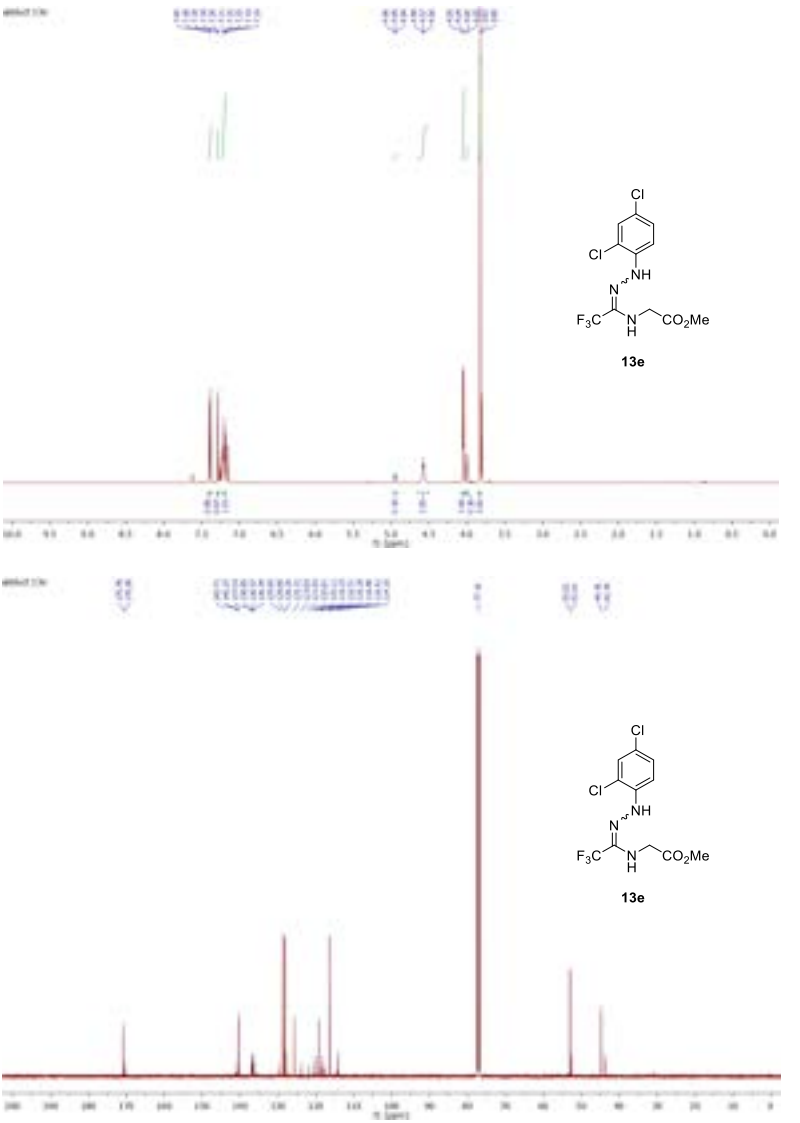


Figure S5. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **13e**.

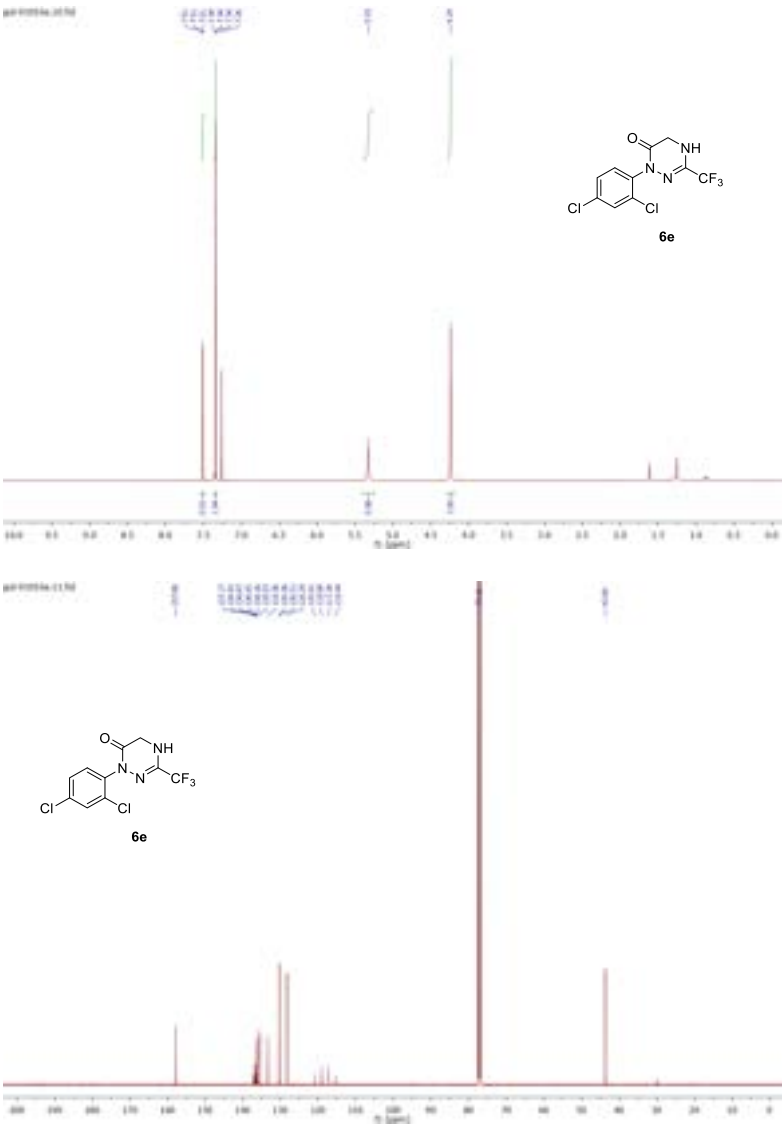


Figure S6. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6e**.

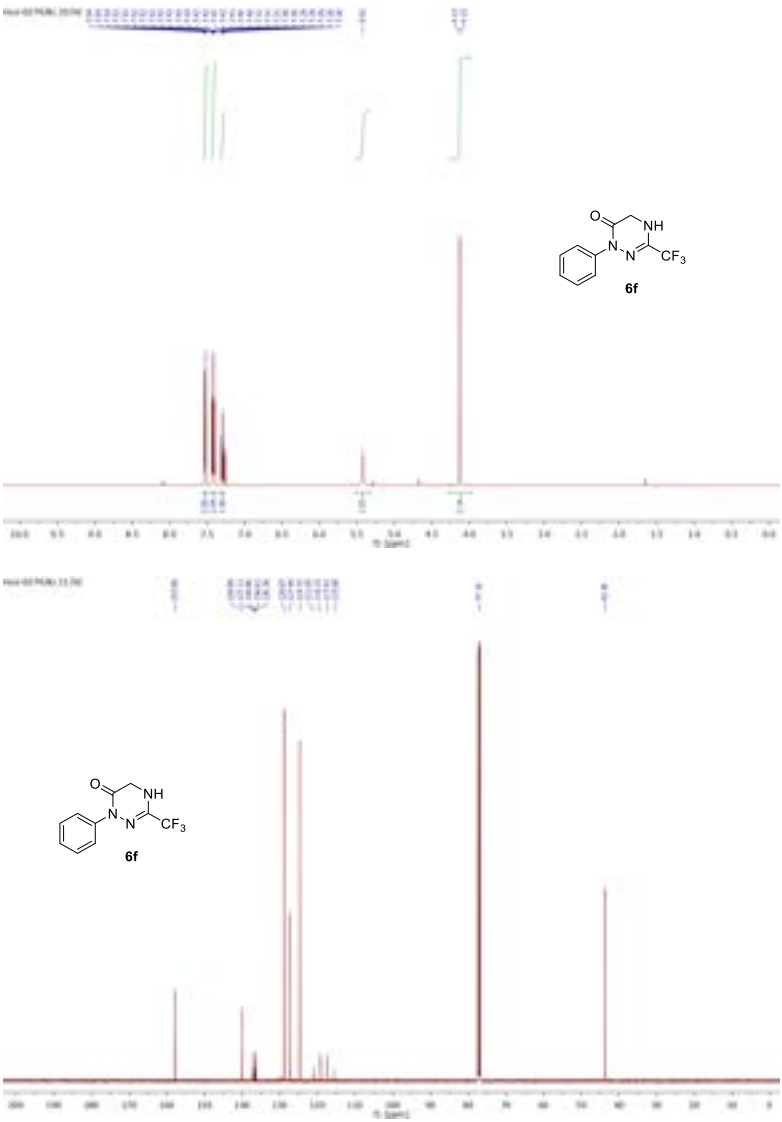


Figure S7. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6f**.

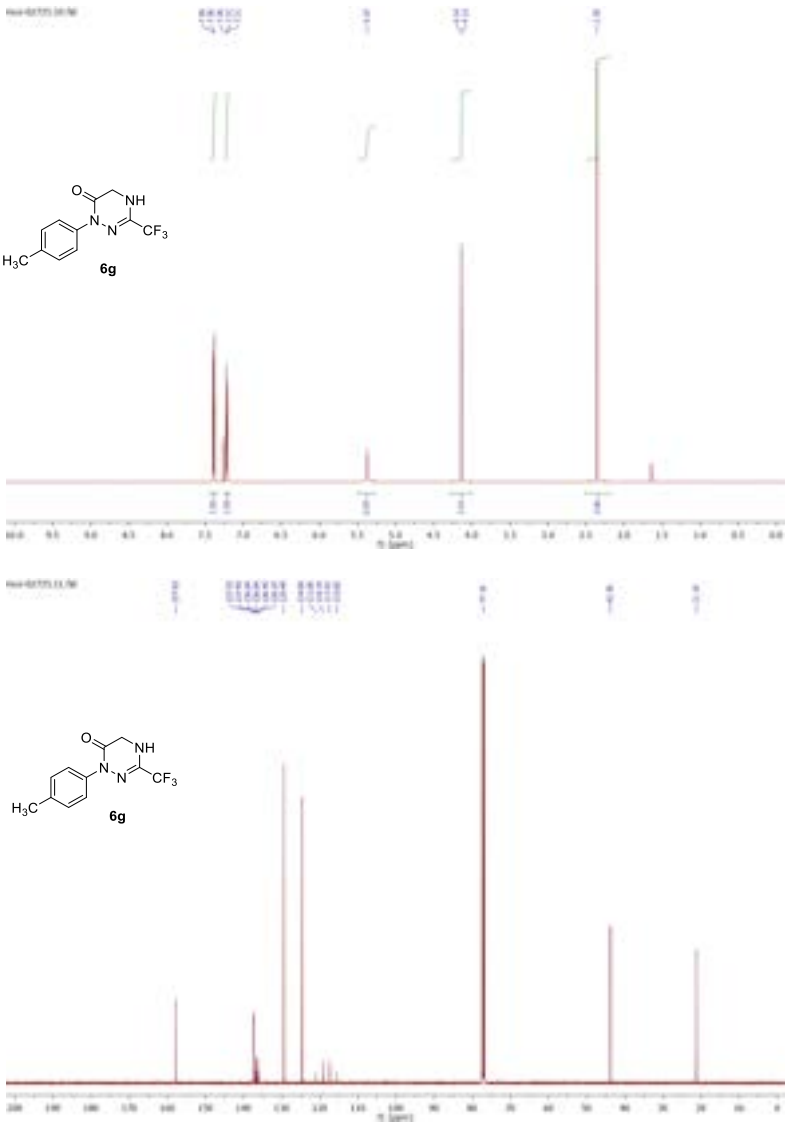


Figure S8. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6g**.

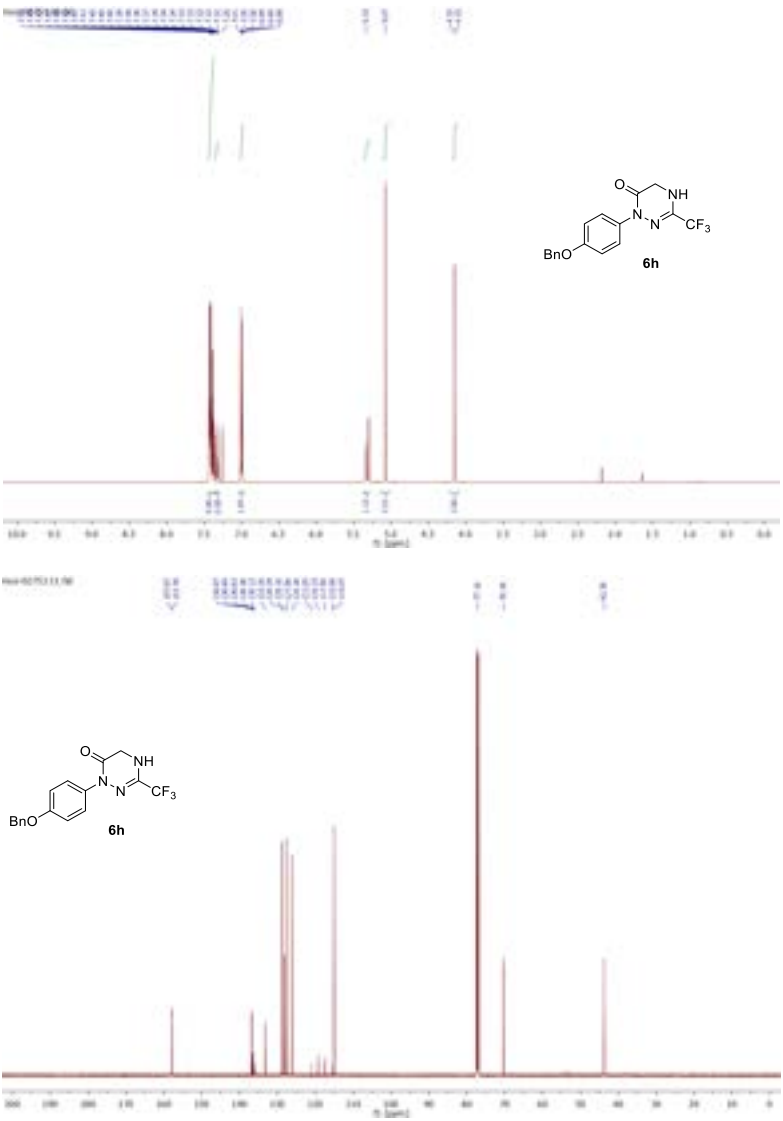


Figure S9. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6h**.

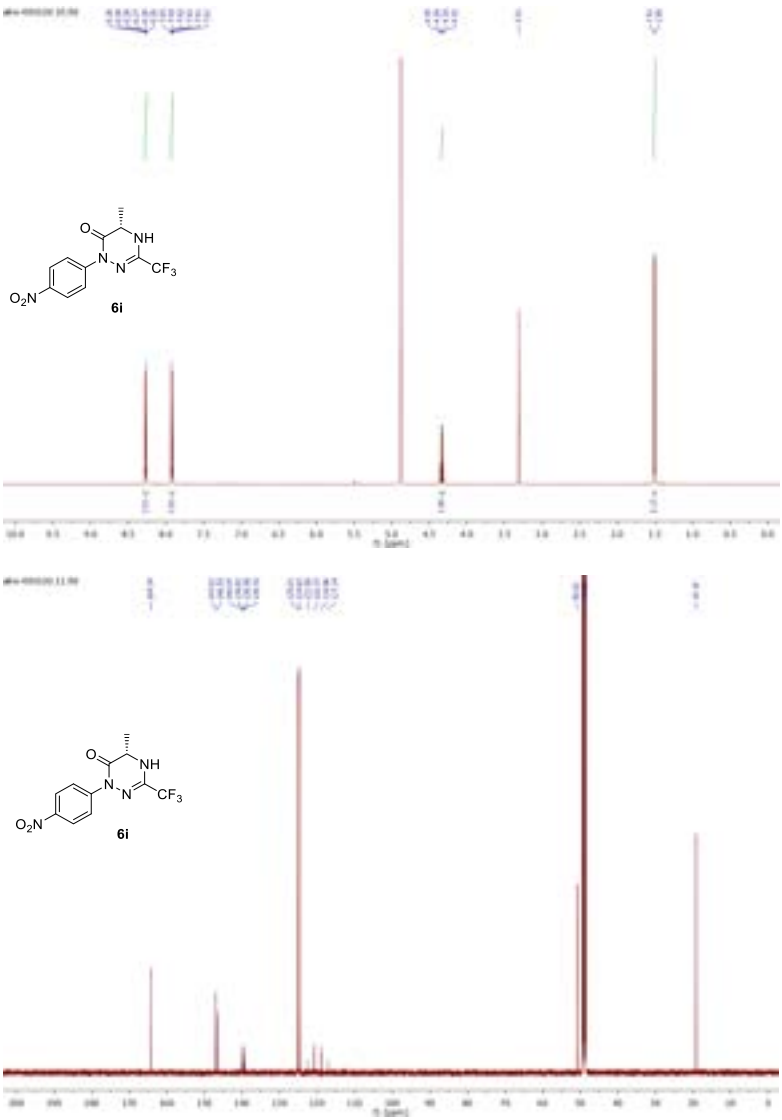


Figure S10. ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (151 MHz, CD_3OD) spectra for compound **6i**.

Figure S11. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6j**.

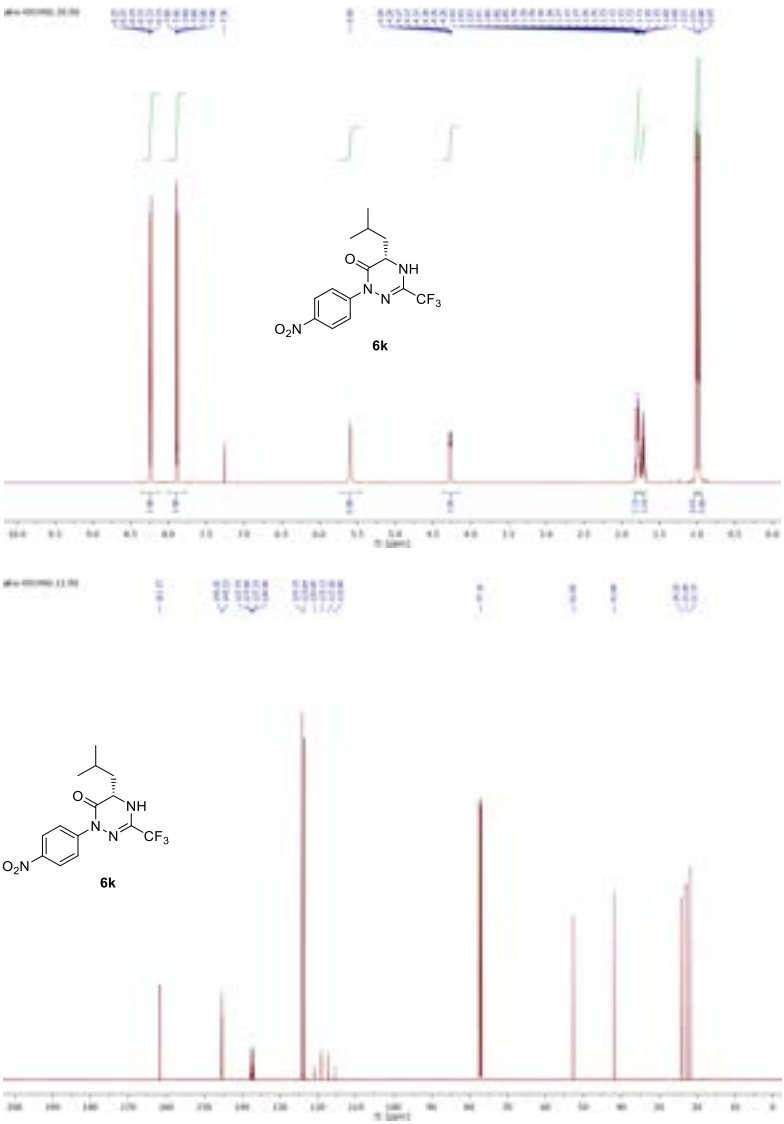


Figure S12. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6k**.

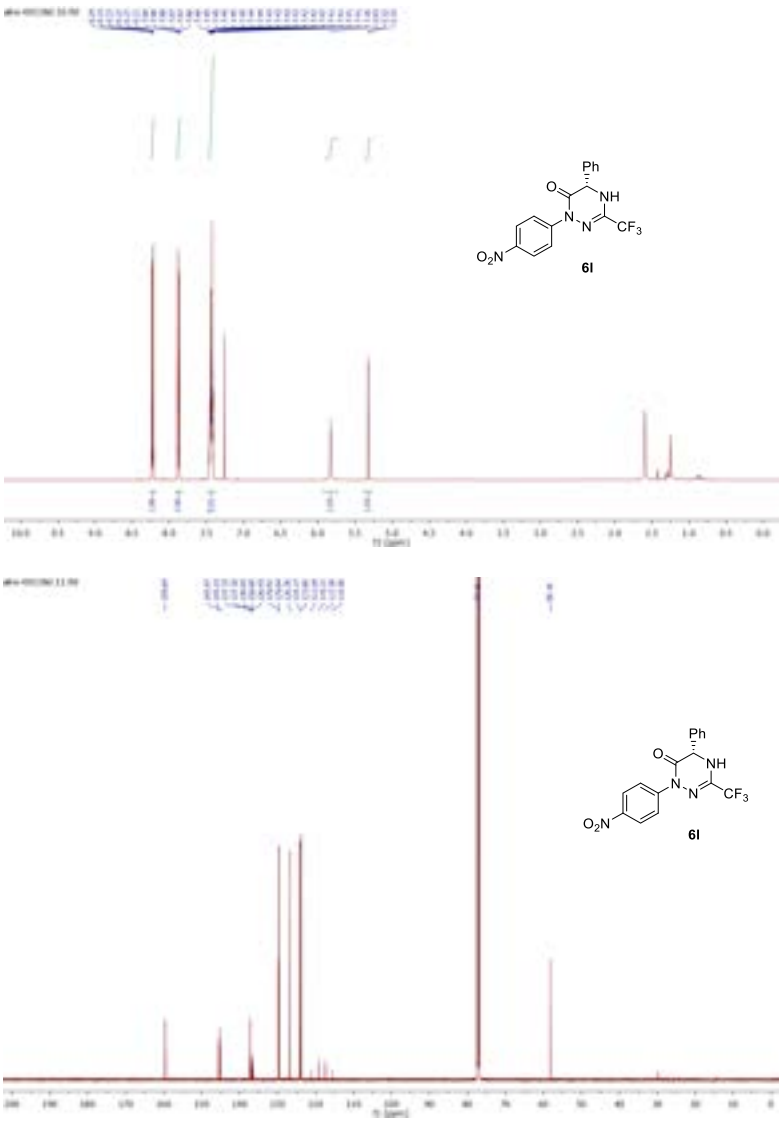


Figure S13. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6l**.

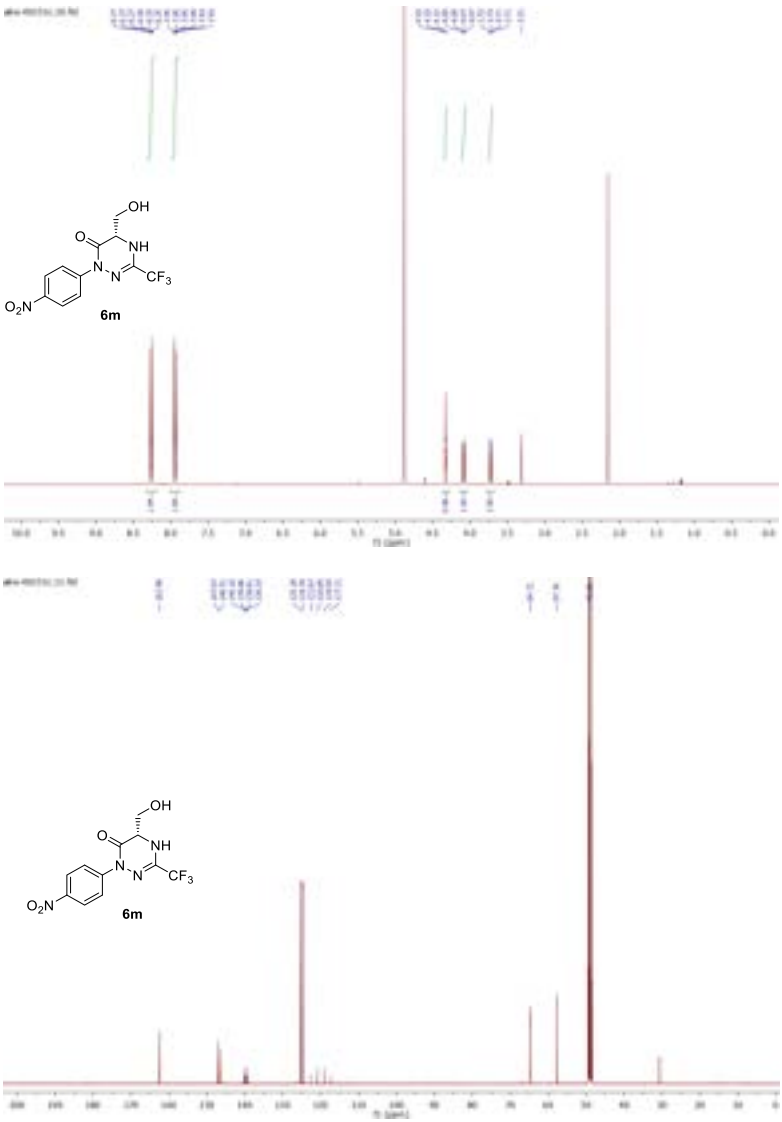


Figure S14. ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (151 MHz, CD_3OD) spectra for compound **6m**.

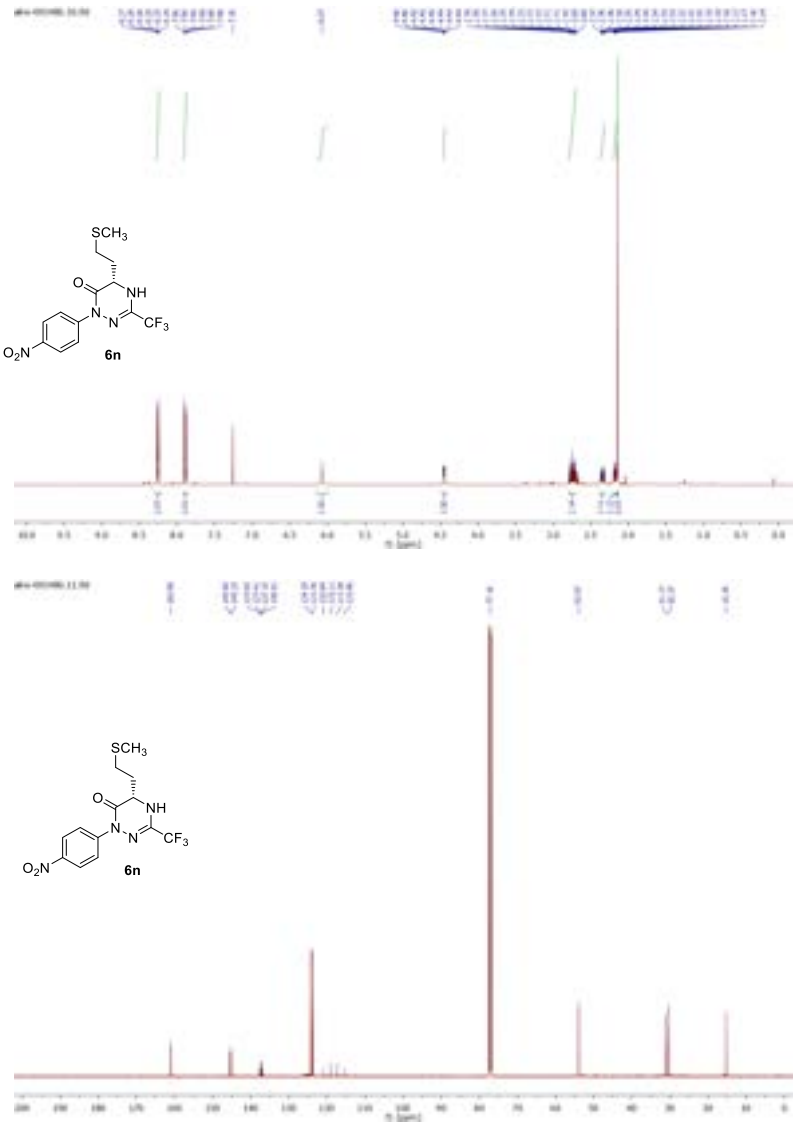


Figure S15. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6n**.

Figure S16. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6o**.

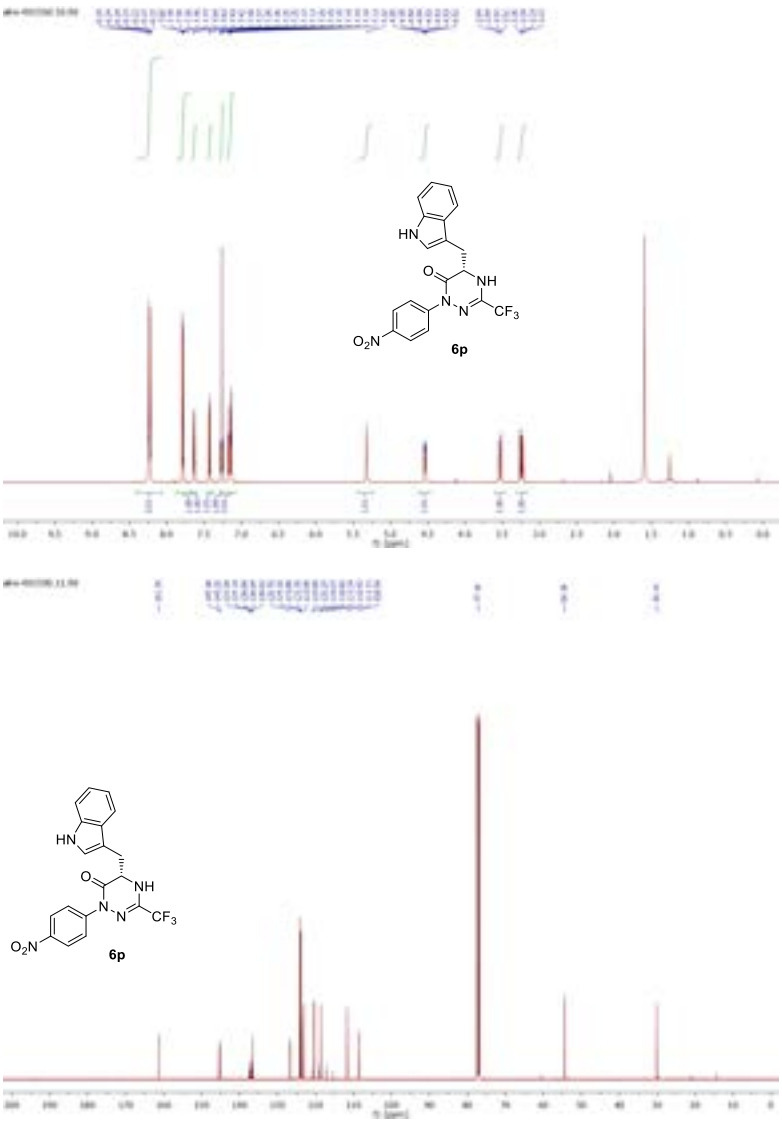


Figure S17. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6p**.

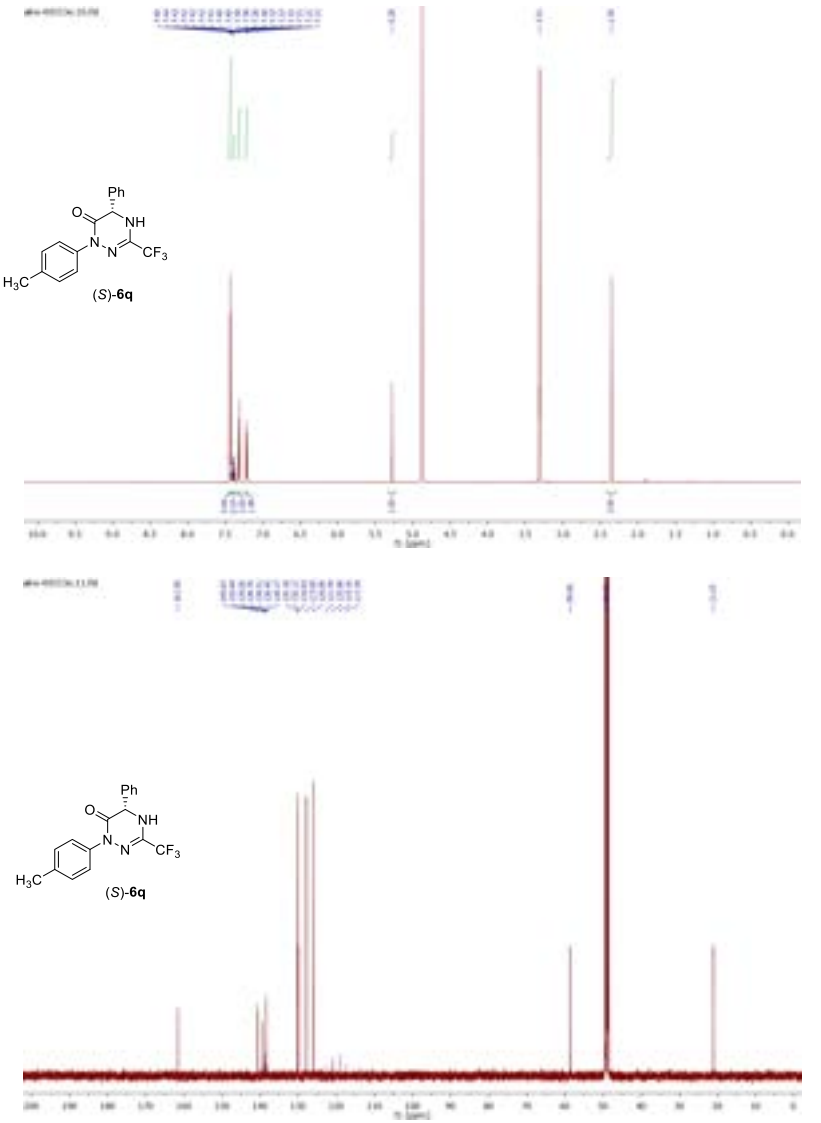


Figure S18. ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (151 MHz, CD_3OD) spectra for compound (*S*)-**6q**.

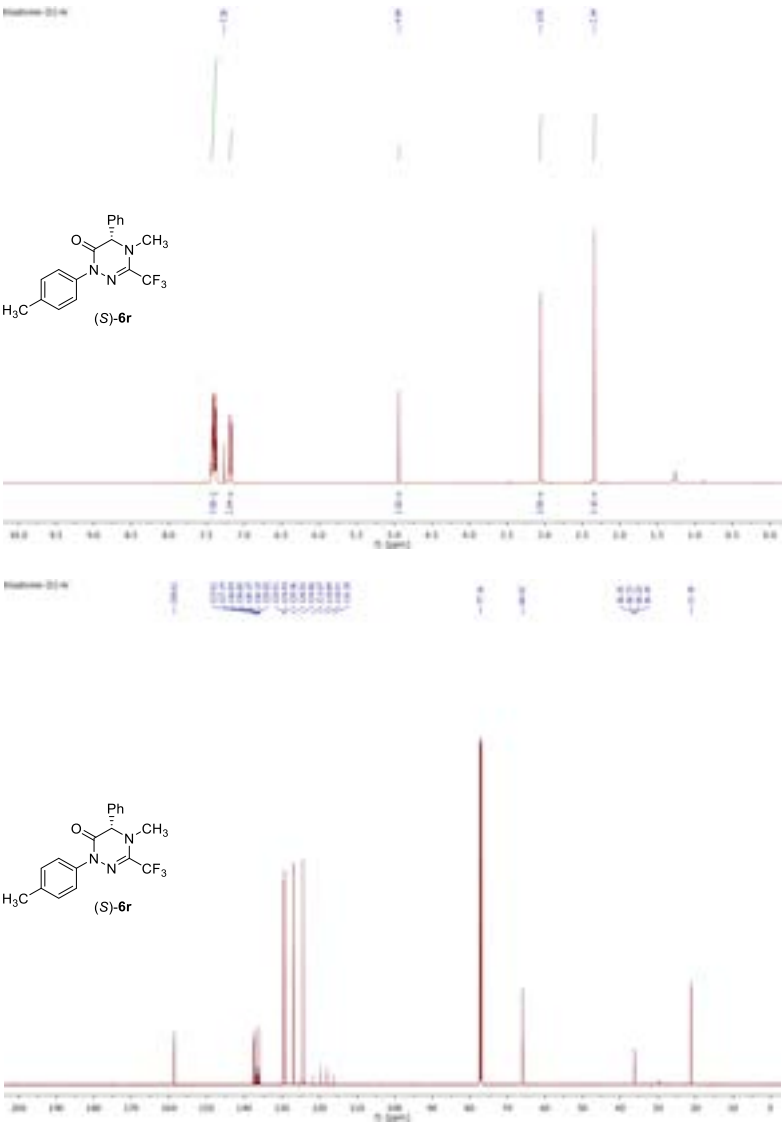


Figure S19. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound (*S*)-**6r**.

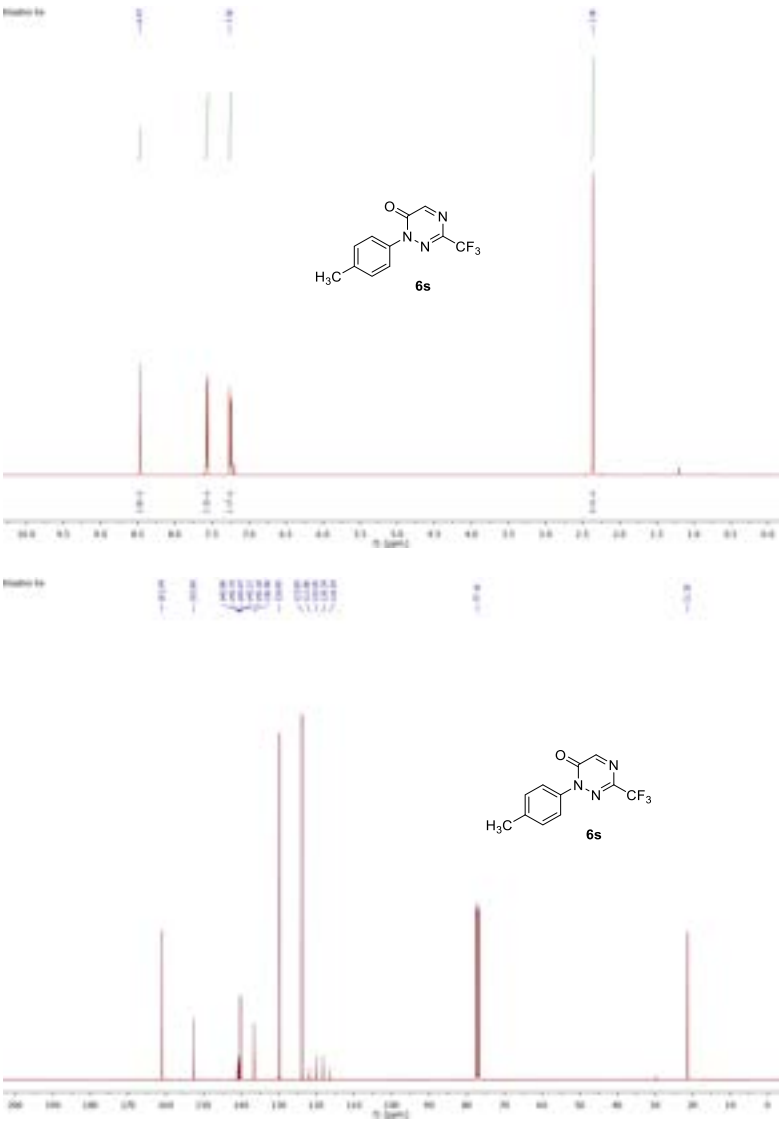


Figure S20. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **6s**.

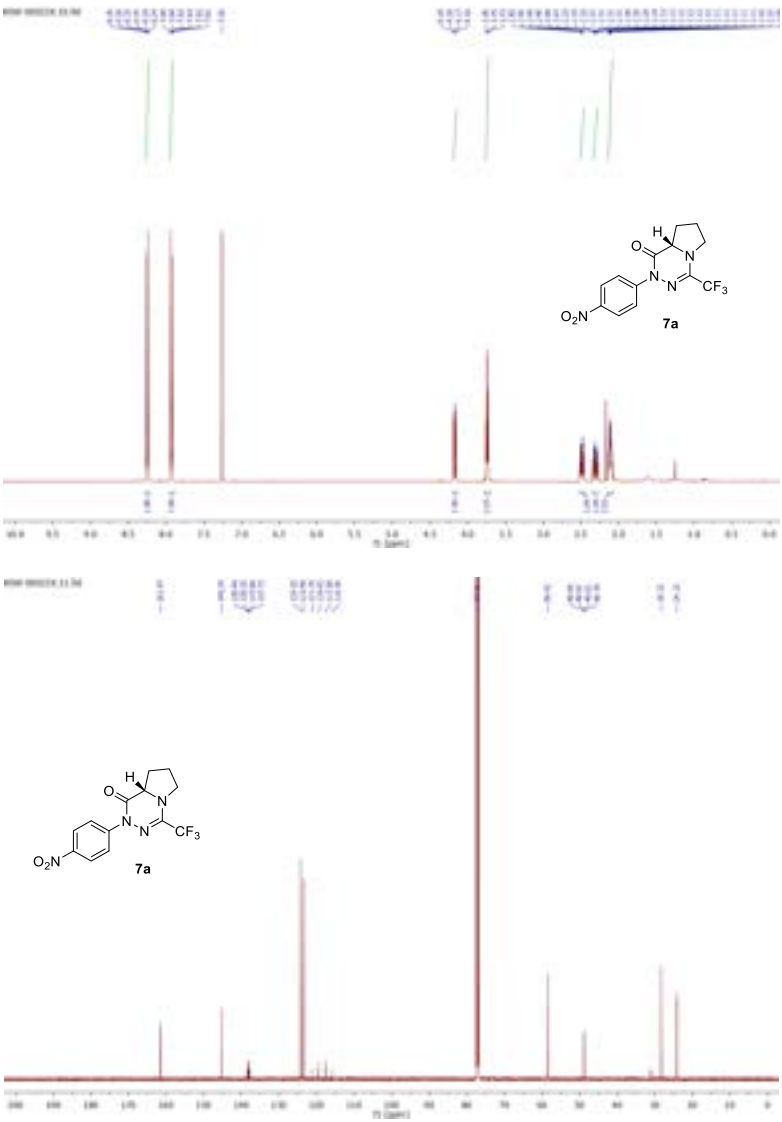


Figure S21. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7a**.

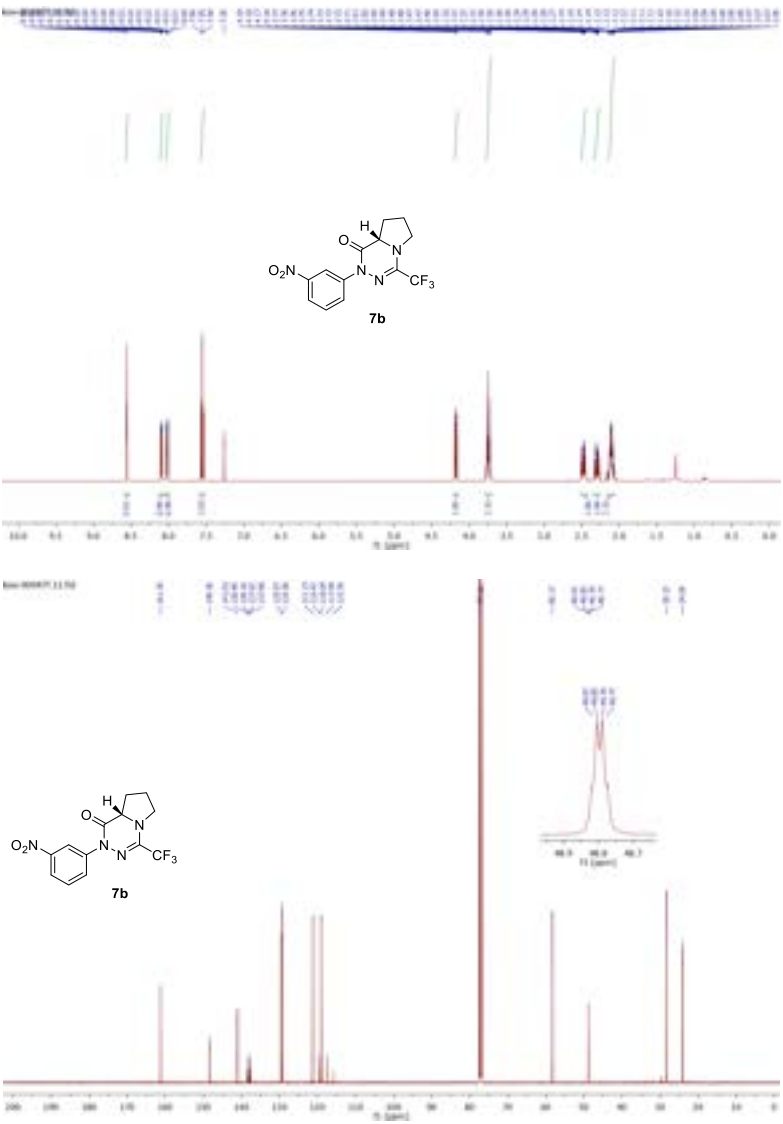


Figure S22. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7b**.

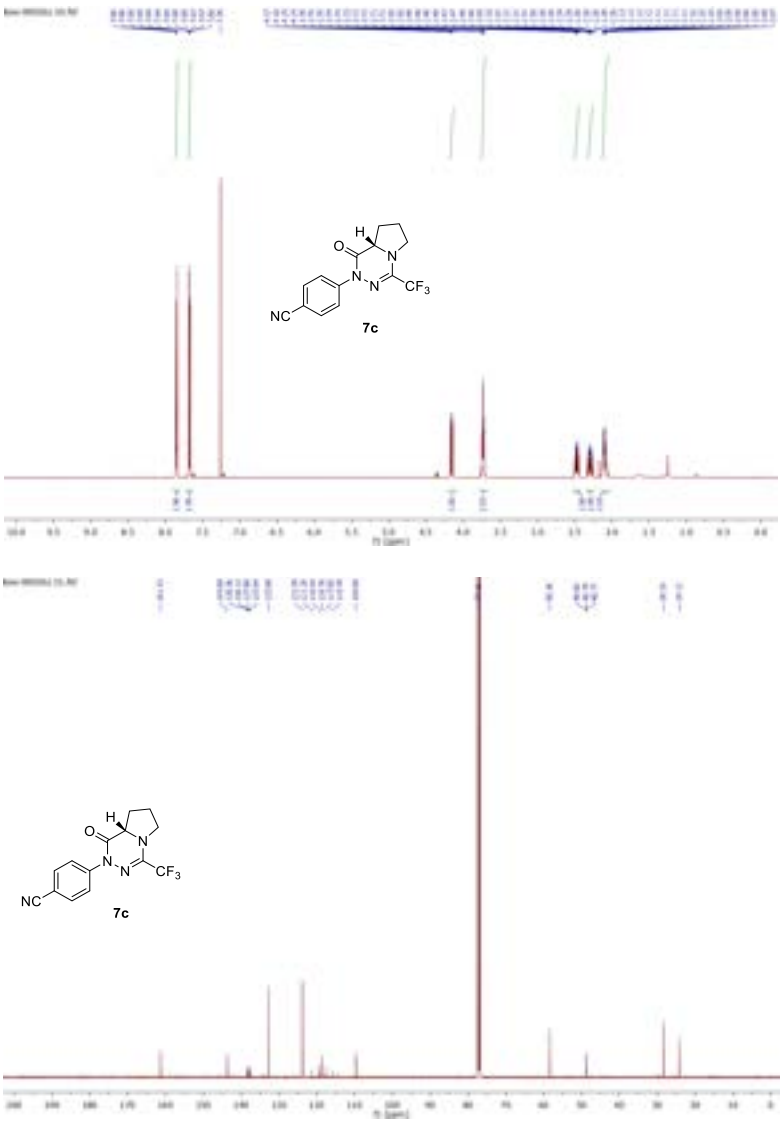


Figure S23. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7c**.

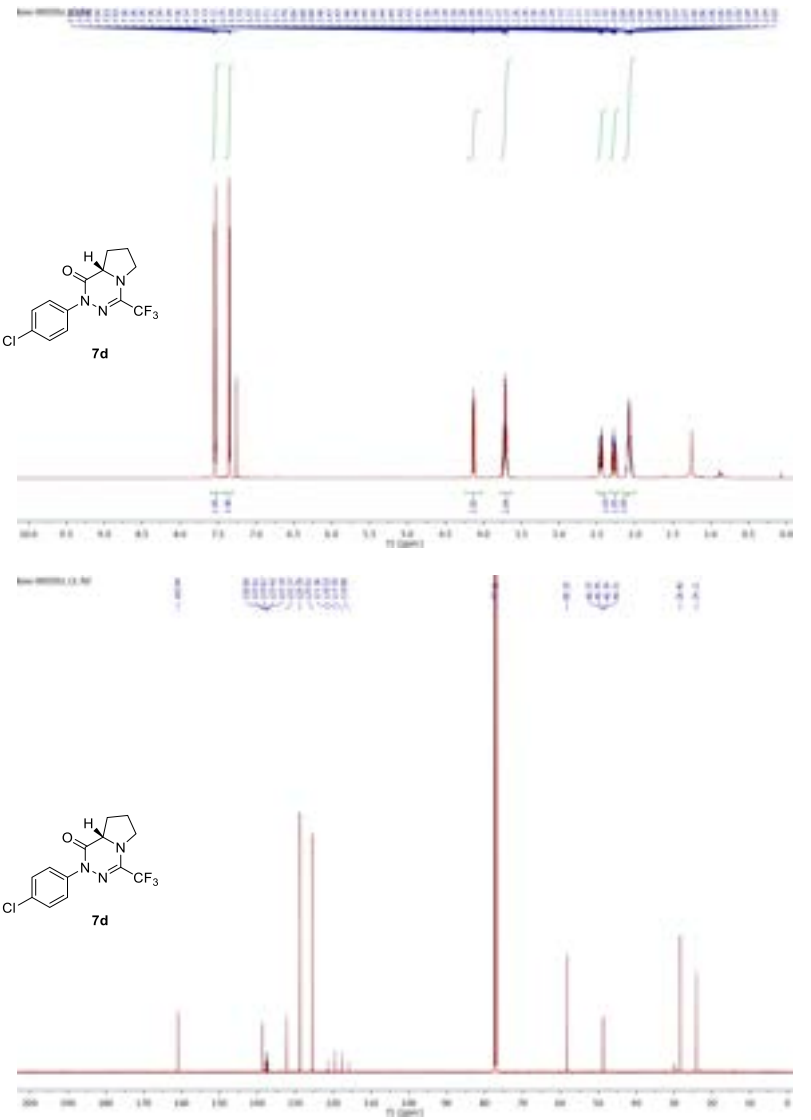


Figure S24. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7d**.

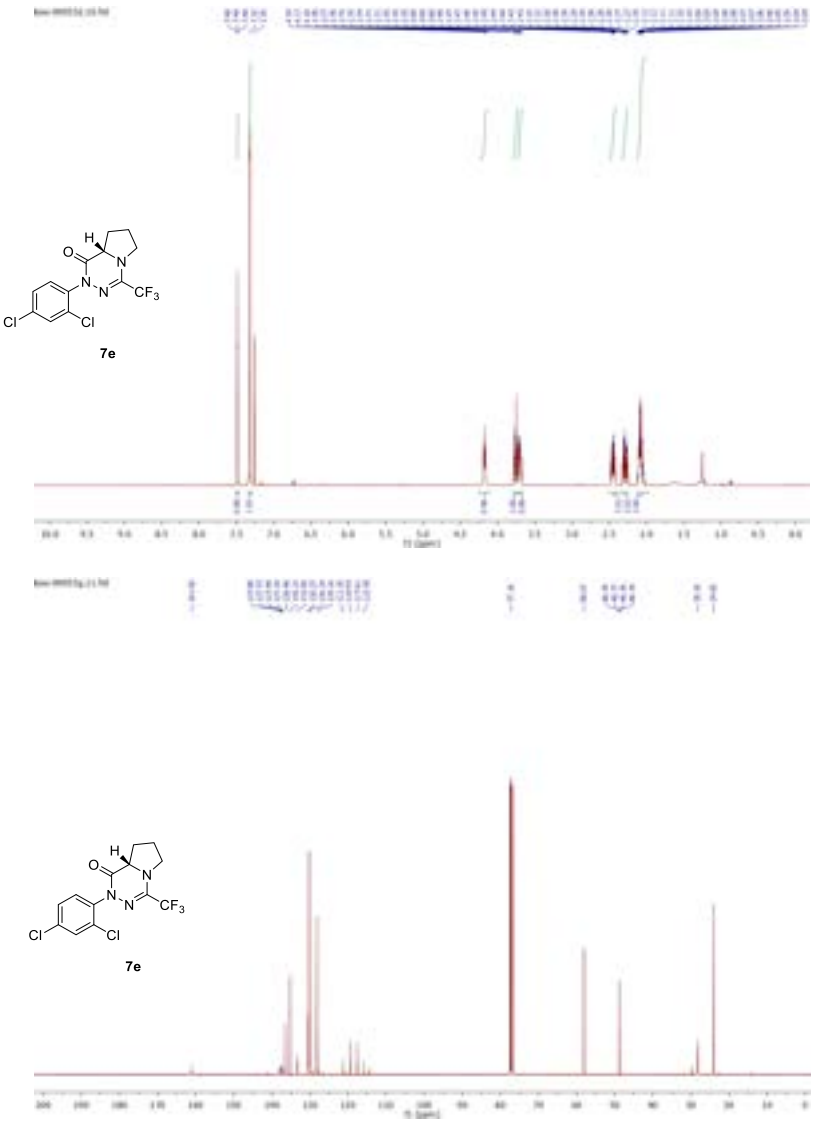


Figure S25. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7e**.

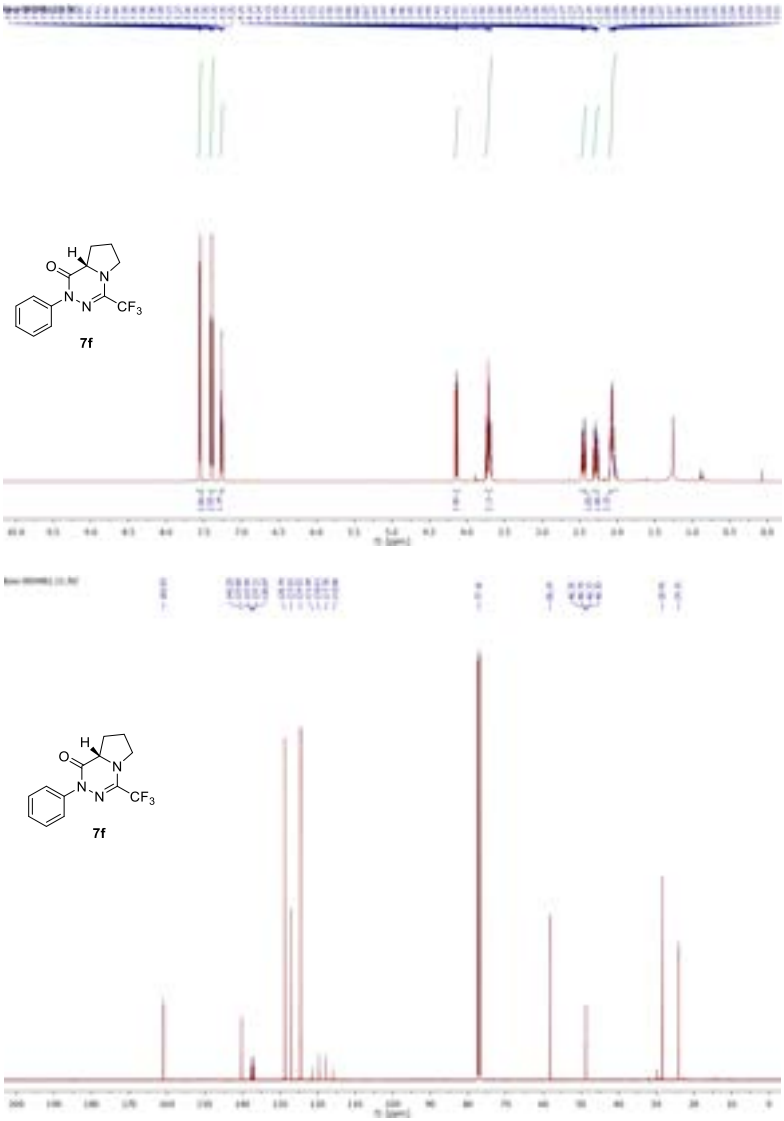


Figure S26. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7f**.

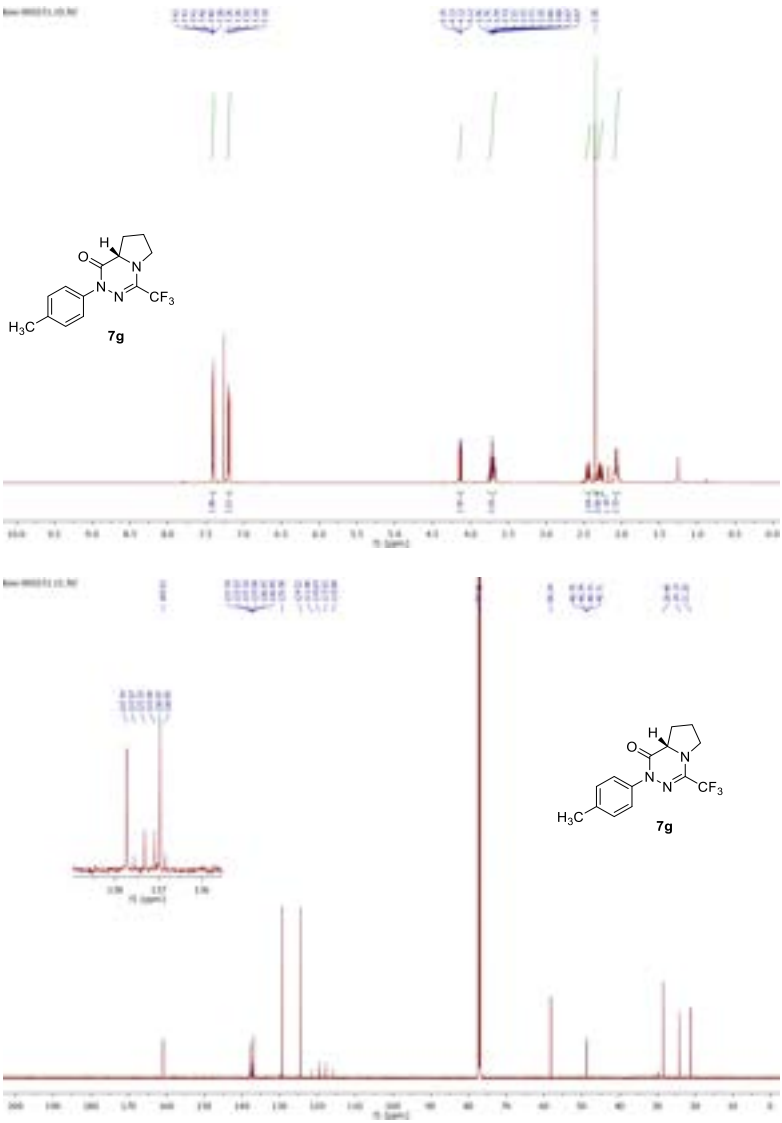


Figure S27. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7g**.

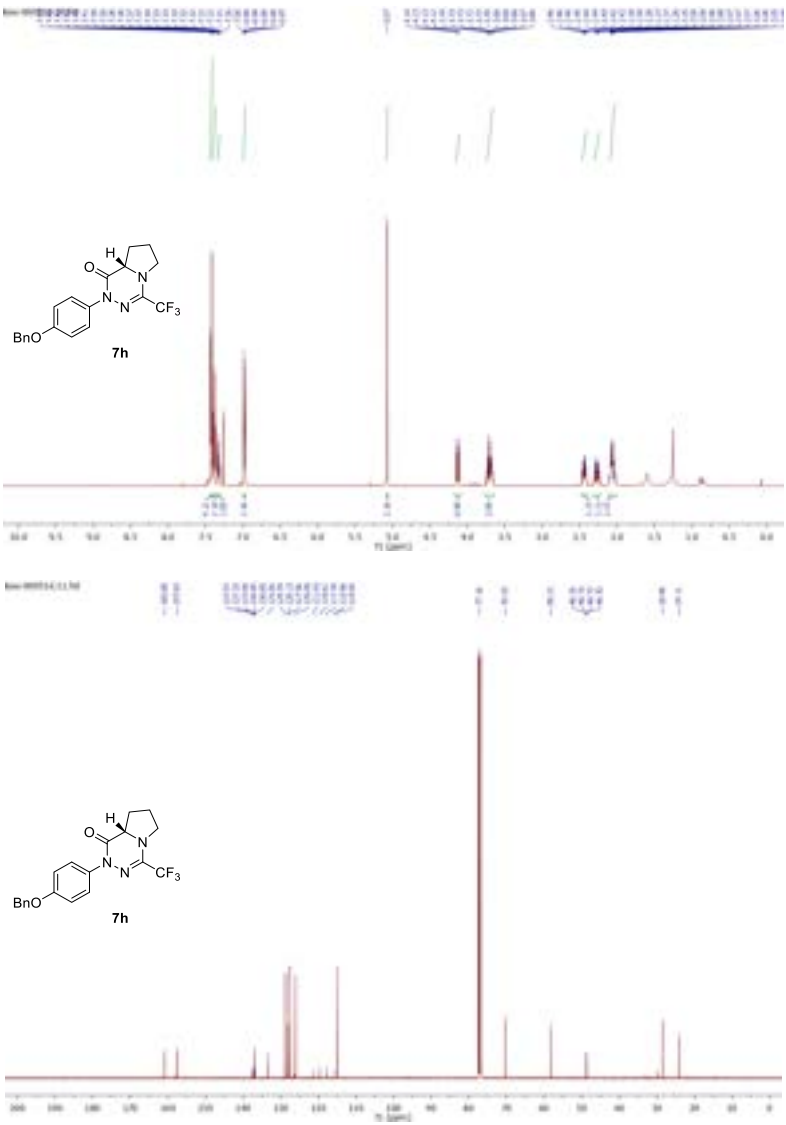


Figure S28. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7h**.

Figure S29. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7i**.

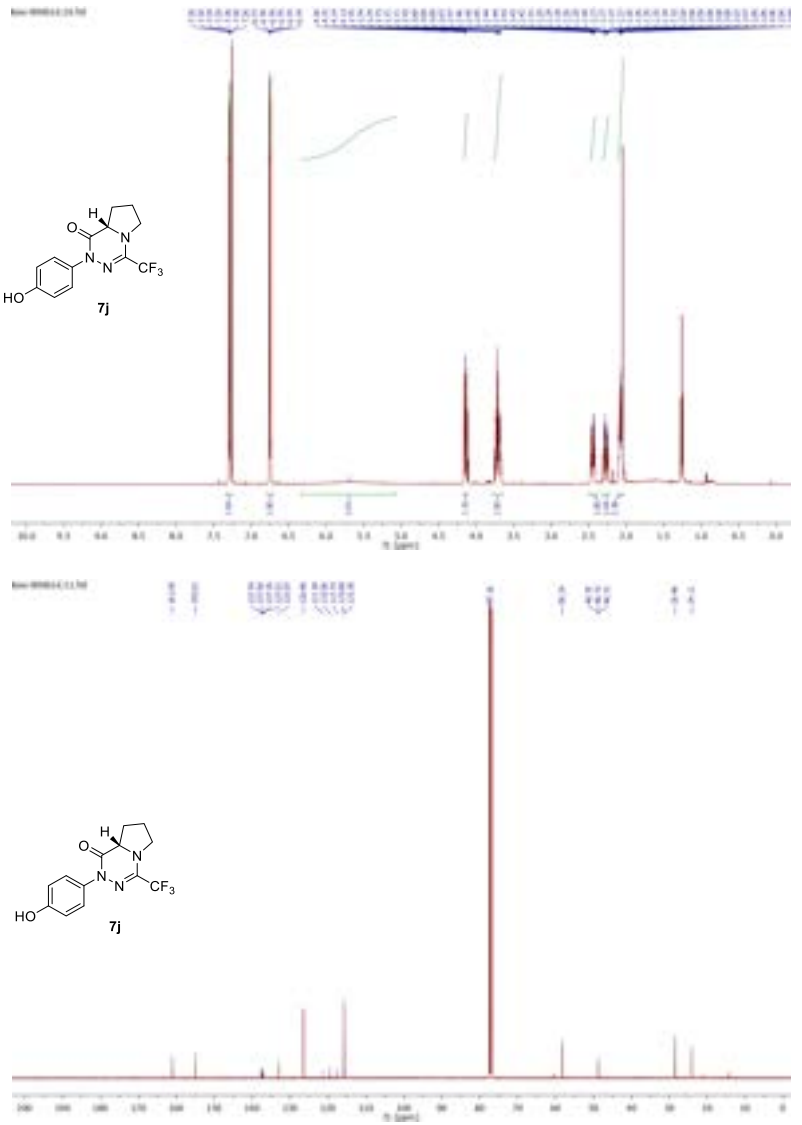


Figure S30. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **7j**.

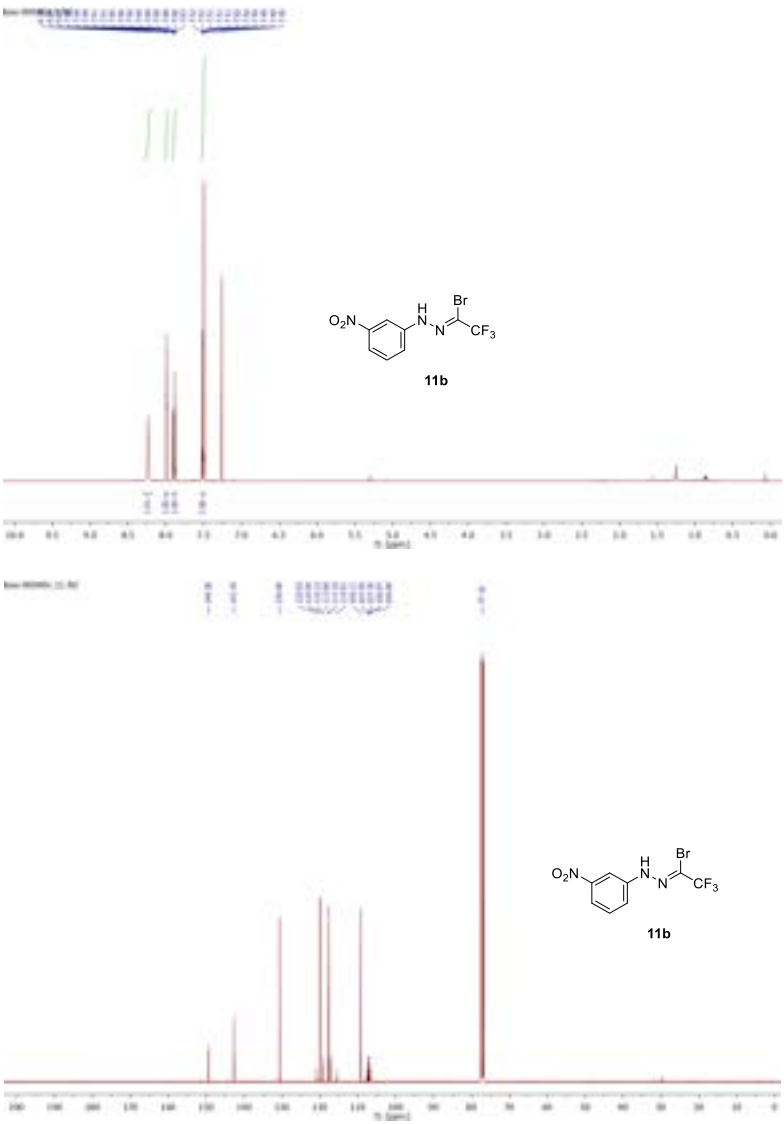


Figure S31. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **11b**.

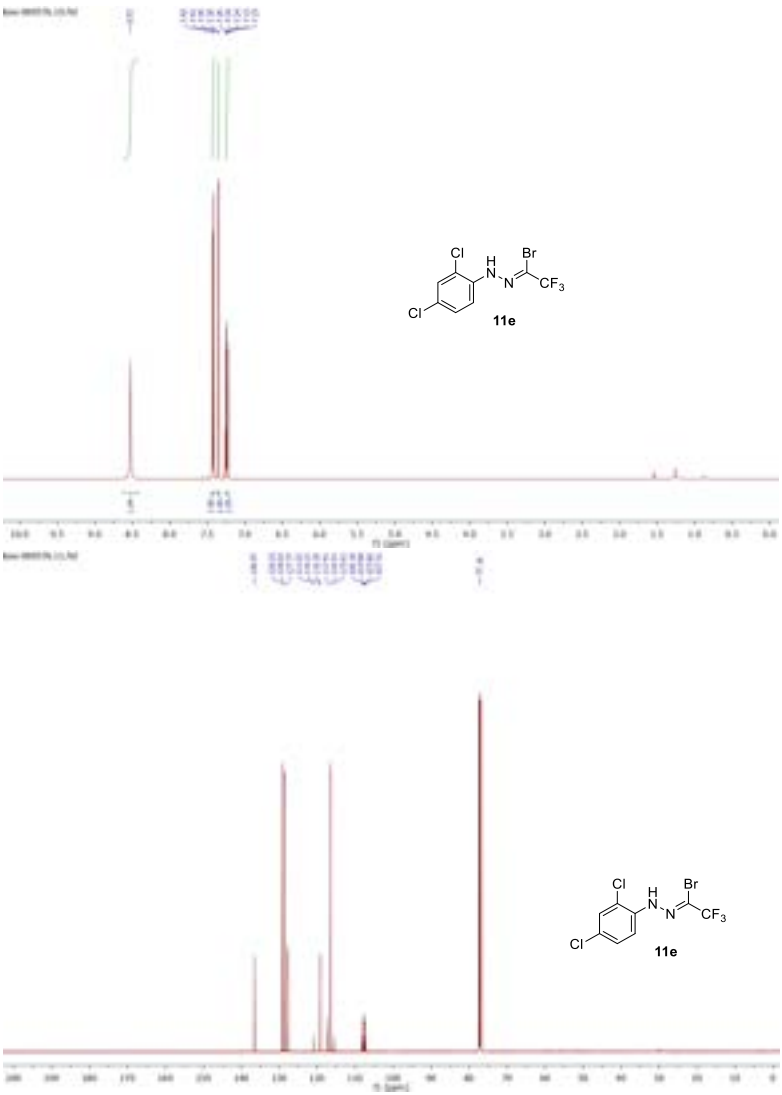


Figure S32. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **11e**.

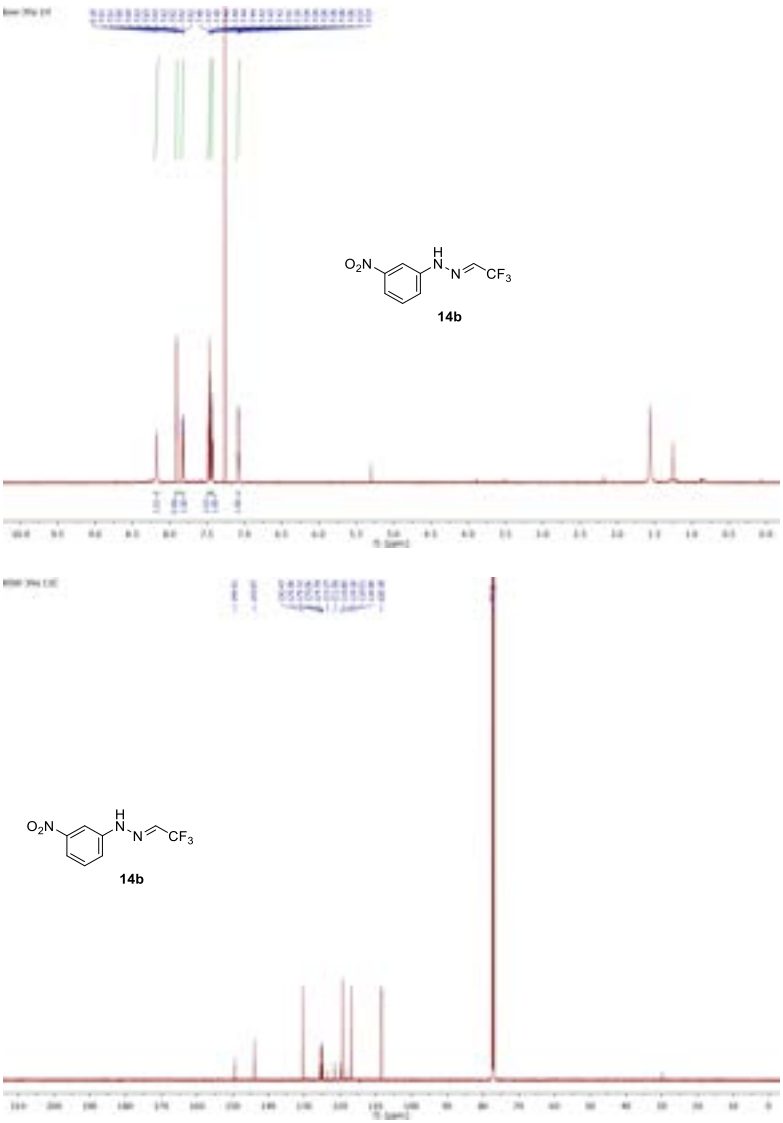


Figure S33. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **14b**.

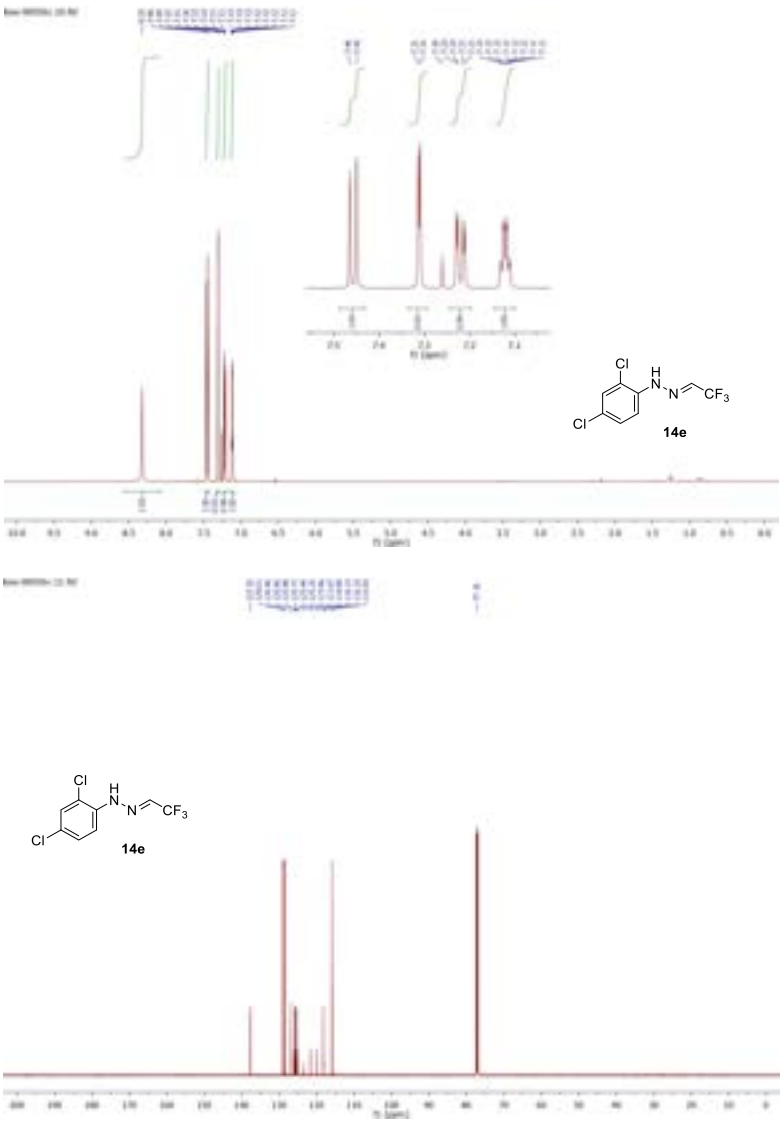
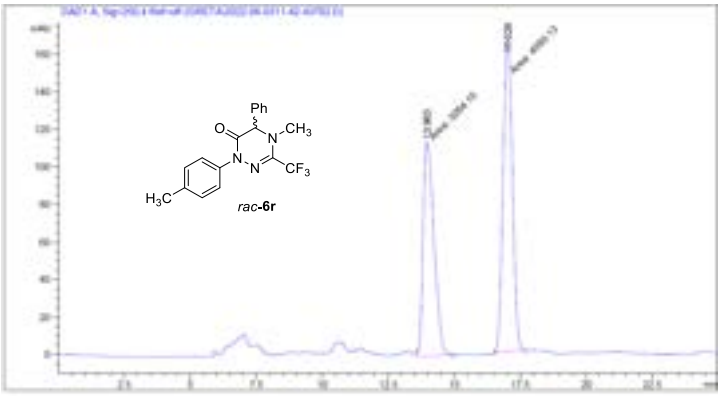
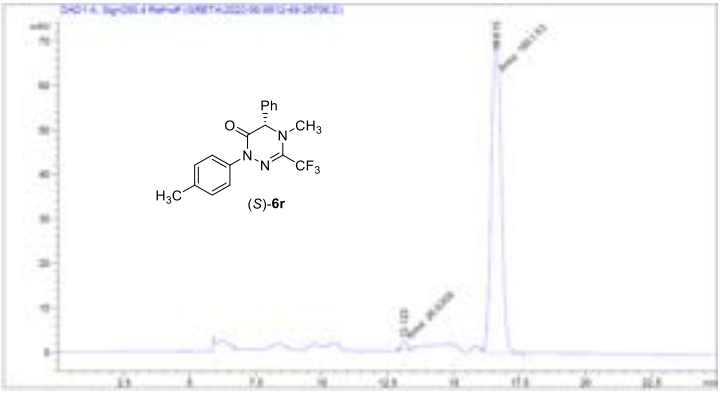


Figure S34. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **14e**.

HPLC analyses

HPLC chromatograms of racemic and *S*-configured 4-methyl-5-phenyl-1-(4-tolyl)-3-trifluoromethyl-4,5-dihydro-1*H*-[1,2,4]triazin-6-one (**6r**): CHIRALPAK® AD-H column {amylose *tris*(3,5-dimethylphenyl-carbamate) coated on 5 µm silica-gel}; hexane:^{i}PrOH = 90:10, flow = 0.5 mL/min, 253 nm.



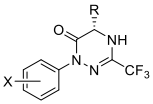


Cytotoxicity tests

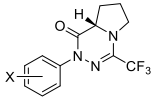
Cell culture and treatment: The promyelocytic leukemia (HL-60) and breast cancer adenocarcinoma (MCF-7) cell lines were purchased from the European Collection of Cell Cultures (ECACC). Leukemia cells were cultured in RPMI 1640 plus GlutaMax I medium (Gibco/Life Technologies, Carlsbad, CA, USA). MCF-7 cells were maintained in Minimum Essential Medium Eagle (Sigma Aldrich, St. Louis, MO, USA) supplemented with 2 mM glutamine and Men Non-essential amino acid solution (Sigma Aldrich, St. Louis, MO, USA). Both media were supplemented with 10% heat-inactivated fetal bovine serum (Biological Industries, Beit-Haemek, Israel) and antibiotics (100 U/mL penicillin and 100 µg/mL streptomycin) (Sigma-Aldrich, St. Louis, MO, USA). Cells were maintained at 37°C in 5% CO_2 atmosphere and grown until 80% confluent. The tested compounds were dissolved in DMSO and further diluted with culture medium. The final concentration of DMSO in cell cultures was less than 0.1% v/v.

In vitro cytotoxicity assay: The MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay was performed according to the known procedure [1]. Cells were seeded into 24-well plates at a density of 8×10^4/mL and left to grow for 24 h. After being cultured for 48 h with various concentrations of the tested compounds, cells were incubated with MTT solution (100 µL, 5 mg/mL in phosphate buffered saline) for 2 h. Then, the plates were centrifuged and the supernatant was discarded. DMSO (1 mL) was added to each well to dissolve the blue formazan product, whose absorbance was measured at 560 nm using FlexStation 3 Multi-Mode Microplate Reader (Molecular Devices, LLC, CA, USA). The untreated cells were used as control. The data were expressed as mean ± SEM of three independent experiments.

Table S1. *In vitro* cytotoxic activity of 1,2,4-triazinones **6** and **7** on selected cancer cell lines.



6a–6q



7a–7h

	X	R	IC_{50} [µM] [1]	
			HL-60	MCF-7
6a	4-NO_2	H	>100	>100
6b	3-NO_2	H	>100	>100
6c	4-CN	H	>100	>100
6d	4-Cl	H	>100	>100
6e	2,4-Cl_2	H	>100	>100
6f	H	H	>100	>100
6g	4-CH_3	H	>100	>100
6h	4-BnO	H	>100	>100
6i	4-NO_2	CH_3	>100	>100
6j	4-NO_2	$CH(CH_3)_2$	93.04±4.52	>100
6k	4-NO_2	$CH_2CH(CH_3)_2$	58.10±3.78	97.50±3.54

6l	4-NO_2	Ph	75.94±5.50	>100
6m	4-NO_2	CH_2CH_2OH	23.04±1.85	>100
6n	4-NO_2	$CH_2CH_2SCH_3$	>100	>100
6o	4-NO_2	CH_2COOCH_3	>100	>100
6p	4-NO_2	1*H*-indol-3-yl	86.33±2.16	99.25±2.05
6q	4-CH_3	Ph	>100	>100
7a	4-NO_2	–	>100	>100
7b	3-NO_2	–	90.58±4.32	>100
7c	4-CN	–	45.44±3.67	>100
7d	4-Cl	–	>100	>100
7e	2,4-Cl_2	–	>100	>100
7f	H	–	>100	>100
7g	4-CH_3	–	>100	>100
7h	4-BnO	–	56.23±1.23	>100

[1] Compound concentration required to inhibit metabolic activity by 50%. Values are expressed as mean ± SEM from concentration-response curves of at least three experiments using a nonlinear estimation (quasi-Newton algorithm) method.

References

[1] Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods* **1983**, *65*, 55–63. [doi: 10.1016/0022-1759(83)90303-4]

[D6]

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4,5-dihydro-1,2,4-triazin-6(1H)-ones

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Chemistry of Heterocyclic Compounds **2022**, *58*(11), 585–587

HETEROCYCLES IN FOCUS

4,5-Dihydro-1,2,4-triazin-6(1*H*)-ones (microreview)

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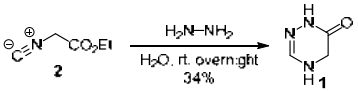
The present microreview highlights key strategies for the synthesis of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones reported up to date. The discussed methods cover (4+2) condensations of both 1,2- and 1,4-binucleophiles, (3+3) and (5+1) annulations, and miscellaneous methods.

Introduction

1,2,4-Triazines and their oxo derivatives have attracted attention as representatives of this class of N-heterocycles exhibit a wide range of bioactivities for potential pharmaceutical and agrochemical applications.[1] The parent compound of the series, namely 4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**1**), has been prepared and characterized for the first time by Leschinsky and Chupp already in 1980.[2] Thus, condensation of ethyl 2-isocyanoacetate (**2**) with hydrazine in water provided single product isolated as a colorless solid (mp 176–178°C) in 34% yield. The structure of compound **1** was elucidated based on ^{1}H NMR and

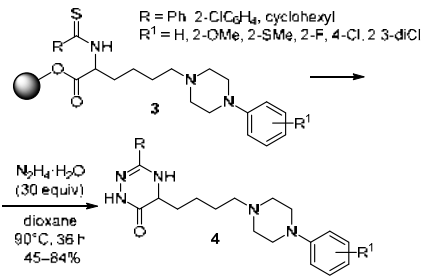


combustion analysis; the former evidenced the presence of a single tautomeric form in DMSO-d_6 solution.

Soon afterward, Lawesson reported a successful synthesis of this heterocycle by using *N*-thioacetylated ethyl glycinate as a suitable reaction partner for hydrazine.[3a] The higher usefulness of amino acid derivatives for the preparation of triazine **1** was further demonstrated by other groups.[3b–e]

(4+2) Annulations

One of the most commonly applied methods for preparation of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones is based on the (4+2) cyclocondensation of hydrazines with appropriate 1,4-bielectrophilic agents. For example, condensation of resin-supported thioamides **3** with excess hydrazine monohydrate in hot dioxane provided a series of *N*-arylpiperazinylbutyl derivatives of type **4** designed as 5-HT$_7$ serotonin receptor antagonists.[4] A similar strategy employing alkoxycarbonyl-functionalized thioamides was also applied for preparation of polycyclic 4,5-dihydro-1,2,4-triazinones demonstrated as efficient protein kinase Cθ inhibitors.[5]

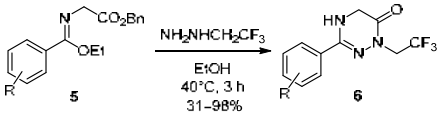


Anna Kowalczyk was born in Kutno, Poland in 1995. In 2019, she graduated as MSc in organic chemistry in the group of Professor J. Lewkowski at the University of Lodz. She is a PhD candidate under the supervision of Professor M. Jasiński at the Department of Organic and Applied Chemistry. She focuses on applications of fluorinated nitrile imines in the synthesis of 5- and 6-membered heterocycles.

Marcin Jasiński received his PhD in chemistry in 2008 under supervision of Professor G. Mlostoń (University of Lodz). After post-doctoral stays at the Freie Universität Berlin (Germany) and the Vanderbilt University (USA), he returned to Łódź. His current scientific activity covers the chemistry of fluoroorganic compounds, S- and N-heterocycles, reactive intermediates, and the synthesis of natural products.

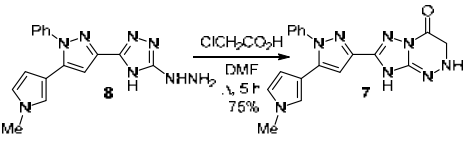
(4+2) Annulations (continued)

A series of fluorinated analogs were prepared by heating an ethanolic mixture of (2,2,2-trifluoroethyl)hydrazine with glycine imidates **5**.[6] The initially formed products **6** were subsequently oxidized with DDQ to afford the respective 1,2,4-triazin-6(1*H*)-ones exhibiting remarkable antifungal activity against several agriculturally relevant plant pathogenic fungi. In addition, efficient condensations of hydrazine(s) with such 1,4-bielectrophilic agents as oxazol-5(4*H*)-ones,[7] as well as amidines derived from *N*,*N*-dimethylformamide and glycinates were also reported.[8]



R = H, 2-F, 2-Cl, 3-F, 3-Cl, 3-Br, 3-Me, 3-CF_3, 4-Cl, 4-F, 4-Me, 4-CF_3, 3,5-Br_2, 3-Br-4-Me, 3-Br-4-Cl, 3-Br-4-F

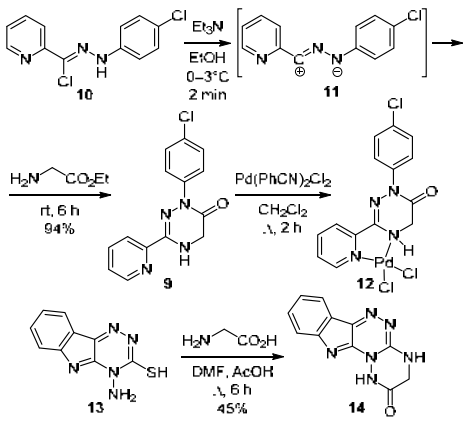
On the other hand, a complementary (2+4) strategy based on the condensation of 1,2-bielectrophiles, such as α-halocarboxylic acids, with aminoguanidine derivatives typically applied as 1,4-binucleophilic reagents is also known.[9] For example, in search for potent antitumor agents against colon cancer cell line HCT-116, a fused 4,5-dihydro-1,2,4-triazinone **7** was synthesized in 75% yield by condensation of 1,2,4-triazol-3-yl hydrazine **8** with chloroacetic acid.[9c] Furthermore, 5-oxo analogs of the title heterocycles were also readily accessed by using amidrazones and oxalates or their synthetic equivalents.[10]



(3+3) Annulations

Another approach toward 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones comprising annulation of amino acid esters with *in situ* generated nitrile imines was developed by Dalloul.[11] The devised protocol was successfully applied for the synthesis of 3-(2-pyridyl)-1,2,4-triazin-6(1*H*)-one derivative **9** by using the respective hydrazonoyl chloride **10** as a precursor of the intermediate 1,3-dipole **11**.[12a] The Pd(II) complex of the resulting product (compound **12**) was demonstrated to smoothly undergo subsequent oxidative coupling with alkanones at the C-5 atom. Similarly, a series of dimeric 5,5'-bi(1,2,4-triazin-6-one) derivatives were readily prepared in an analogous manner.[12b]

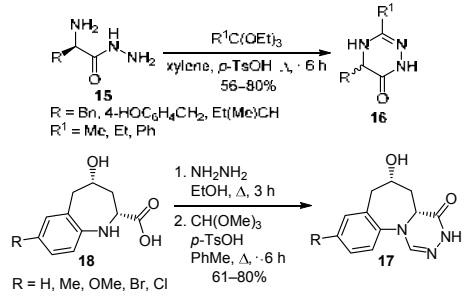
An alternative (3+3) annulation protocol was demonstrated by Amin and Saad.[13] Thus, condensation of 4-amino-1,2,4-triazine-3-thiol derivative **13** with glycine provided polycyclic product **14** in moderate yield under rather harsh reaction conditions (DMF, AcOH, reflux, 6 h). In this case, the SH group played the role of suitable leaving group under Brønsted acid catalysis.



(5+1) Annulations

Yet another general method of practical significance for the synthesis of the 4,5-dihydro-1,2,4-triazin-6(1*H*)-one scaffold is based on cyclocondensation of α-aminocarbohydrazides with orthoesters.[3e,14] Notably, when starting with enantiomerically pure precursors **15** derived from natural amino acids, complete racemization at the asymmetric carbon atom in compound **16** occurred, irrespective of the type of orthoester used.[14a]

More recently, Palma et al. reported on the one-pot approach toward [*a*]-fused 1-benzazepine derivatives **17** by using cyclic α-aminocarbohydrazides **18** as key building blocks.[14b] In this case, treatment of the initially formed *cis*-configurated carbohydrazides with trimethyl orthoformate, under acid catalysis provided the expected products **17** isolated as single diastereoisomers. The structure of a selected derivative (R = Cl) was unambiguously confirmed by X-ray analysis.



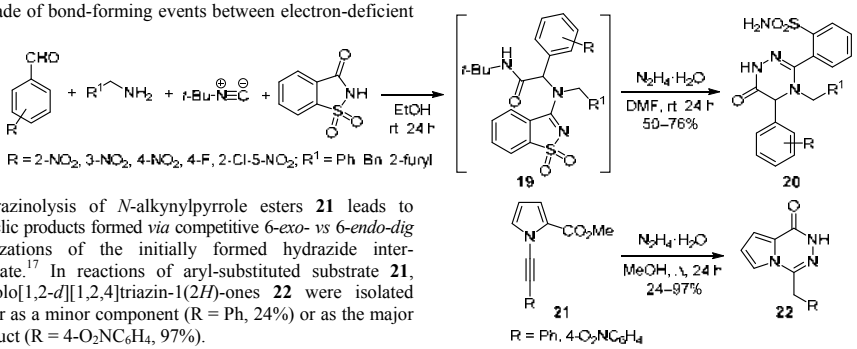
R = H, Me, OMe, Br, Cl

R = Bn, 4-$HOC_6H_4CH_2$, Et(Me)CH
R^1 = Me, Et, Ph

Following the methods described above, various 4,5-dihydro-1,2,4-triazin-6(1*H*)-one derivatives have been synthesized and evaluated as antimicrobial and/or antifungal agents.[15]

Miscellaneous reactions

In 2018, Rominger reported on the synthesis of polysubstituted 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones through a sequential Ugi–Smiles type multicomponent addition and cyclization reaction.[16] The developed approach involves a cascade of bond-forming events between electron-deficient benzaldehydes, primary amines, saccharin, and isocyanates, followed by ring closure of the initially formed adduct **19** with hydrazine. A small library of products **20** was prepared in moderate to good yield.



Hydrazinolysis of *N*-alkynylpyrrole esters **21** leads to bicyclic products formed *via* competitive 6-*exo*- *vs* 6-*endo*-*dig* cyclizations of the initially formed hydrazide intermediate.[17] In reactions of aryl-substituted substrate **21**, pyrrolo[1,2-*d*][1,2,4]triazin-1(2*H*)-ones **22** were isolated either as a minor component (R = Ph, 24%) or as the major product (R = 4-$O_2NC_6H_4$, 97%).

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References

1. (a) Hashem, H. E. *Mini-Rev. Org. Chem.* **2021**, *18*, 1127. (b) Verma, T.; Sinha, M.; Bansal, N. *Curr. Bioact. Compd.* **2020**, *16*, 1116. (c) Cascioferro, S.; Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. *Eur. J. Med. Chem.* **2017**, *142*, 328.
2. Leschinsky, K. L.; Chupp, J. P. *J. Heterocycl. Chem.* **1980**, *17*, 1621.
3. (a) Andersen, T. P.; Ghattas, A.-B. A. G.; Lawesson, S.-O. *Tetrahedron* **1983**, *39*, 3419. (b) Taylor, E. C.; Macor, J. E. *J. Heterocycl. Chem.* **1985**, *22*, 409. (c) Smodiš, J.; Zupet, R.; Petrič, A.; Stanovnik, B.; Tisler, M. *Heterocycles* **1990**, *30*, 393. (d) Lobanov, P. S.; Grebelkin, A. L.; Zaitsev, D. I.; Gindin, V. A.; Potekhin, A. A. *Chem. Heterocycl. Compd.* **1991**, *27*, 1116. (e) Neunhoeffer, H.; Klein-Cullmann, B. *Liebigs Ann. Chem.* **1992**, 1271.
4. Grychowska, K.; Masurier, N.; Verdié, P.; Satała, G.; Bojarski, A. J.; Martinez, J.; Pawłowski, M.; Subra, G.; Zajdel, P. *Chem. Biol. Drug Des.* **2015**, *86*, 697.
5. George, D. M.; Breinlinger, E. C.; Argiriadi, M. A.; Zhang, Y.; Wang, J.; Bansal-Pakala, P.; Duignan, D. B.; Honore, P.; Lang, Q.; Mittelstadt, S.; Rundell, L.; Schwartz, A.; Sun, J.; Edmunds, J. J. *J. Med. Chem.* **2015**, *58*, 333.
6. Owen, W. J.; Sullenberger, M. T.; Loso, M. R.; Meyer, K. G.; Slanec, T. J. *Pest. Manag. Sci.* **2015**, *71*, 83.
7. (a) Atta-Allah, S. R.; Gouhar, R. S.; Hemdan, M. M.; Abou-Elmagd, W. S. I.; Haneen, D. S. A.; Kandeel, K. A. A.; Youssef, A. S. A. *Synth. Commun.* **2017**, *47*, 299. (b) Salem, M. S.; El-Helw, E. A. E.; Derbala, H. A. Y. *Russ. J. Bioorg. Chem.* **2020**, *46*, 77.
8. Zhan, P.; Li, X.; Li, Z.; Chen. X.; Tian, Y.; Chen, W.; Liu, X.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7155.
9. (a) El-Mahdy, K. M. *J. Sulfur Chem.* **2013**, *34*, 539. (b) Magtoof, M. S.; Kumari, A.; Bari, S. S.; Banik, B. K.; Bhalla, A. *Heterocycl. Lett.* **2017**, *7*, 287. (c) Abdelrehim, E. M. *ACS Omega* **2021**, *6*, 1687.
10. (a) Aly, A. A.; Ramadan, M.; Morsy, N. M.; Elkanzi N. A. A. *J. Heterocycl. Chem.* **2017**, *54*, 2067. (b) Tsizorik, N. M.; Hrynyshyn, Y. V.; Musiychuk, A. R.; Bol'but, A. V.; Panasenko, N. V.; Vovk, M. V. *Chem. Heterocycl. Compd.* **2018**, *54*, 710.
11. Dalloul, H. M. M. *Phosphorus*, *Sulfur Silicon Relat. Elem.* **2011**, *186*, 1876.
12. (a) El-Abedelah, M. M.; Hodali, H. A.; Zreid, M. S.; Awwadi, F. F. *Polyhedron* **2018**, *139*, 201. (b) Mohammad, H. H.; El-Abadelah, M. M.; Sabri, S. S.; Awwadi, F. F.; Voelter, W. *Z. Naturforsch. B*: *J. Chem. Sci.* **2018**, *73*, 965.
13. Amin, M. A.; Saad, H. A. *Curr. Org. Synth.* **2016**, *13*, 116.
14. (a) Kudelko, A.; Zieliński, W.; Jasiak, K. *Tetrahedron Lett.* **2013**, *54*, 4637. (b) Guerrero, S. A.; Ramírez, J. E.; Sanabria, C. M.; Acosta, L. M.; Cobo, J.; Nogueras, M.; Palma, A. *Synthesis* **2021**, *53*, 1315.
15. (a) Zemanová, I.; Gašparová, R.; Kraic, F.; Kružlicová, D.; Maliar, T.; Boháč, A.; Addová, G. *ARKIVOC* **2017**, (iv), 184. (b) Jebamani, J.; Pranesh, S.; Shivalingappa, J.; Narayanarao, M.; Pasha, M. *Synth. Commun.* **2021**, *51*, 921.
16. Ramezanpour, S.; Rezaei, M. N.; Vaezghaemi, A.; Rominger, F. *New. J. Chem.* **2018**, *42*, 17533.
17. Yenice, I.; Basceken, S.; Balci, M. *Beilstein J. Org. Chem.* **2017**, *13*, 825.

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OŚWIADCZENIE

Oświadczam, że mój wkład w powstanie poniższych publikacji:

1. A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *'A straightforward access to 3-trifluoromethyl-1H-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile' J. Fluorine Chem.* **2021**, *241*, 109691
2. A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *'Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions' Org. Lett.* **2022**, *24*, 2499-2503
3. G. Utecht-Jarzyńska, A. Kowalczyk, M. Jasiński *'Fluorinated and non-fluorinated 1,4-diarylpyrazoles via MnO_2-mediated mechanochemical deacylative oxidation of 5-acylpyrazolines' Molecules* **2022**, *27*, 8446
4. A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński *'ω-(3-trifluoromethylpyrazol-4-yl)alkanoic acids via (3+2)-cycloaddition of nitrile imines with cyclic enones and deacylative aromatization' J. Fluorine Chem.* **2023**, *272*, 110206
5. A. Kowalczyk, K. Świątek, M. Celeda, G. Utecht-Jarzyńska, A. Jaskulska, K. Gach-Janczak, M. Jasiński *'Trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1H)-ones via (3+3)-annulation of nitrile imines with α-amino esters' Materials* **2023**, *16*, 856
6. A. Kowalczyk, M. Jasiński *'4,5-Dihydro-1,2,4-triazin-6(1H)-ones' Chem. Heterocycl. Compd.* **2022**, *58*, 585-587

polegał na stworzeniu ogólnej koncepcji i planu badań, zapewnieniu finansowania na realizację części prac, udziału w analizie danych eksperymentalnych, współpracy w przygotowaniu manuskryptów publikacji, prowadzeniu korespondencji z Edytorami wydawnictwa oraz opracowaniu finalnych wersji prac i odpowiedzi na uwagi recenzentów.

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[**D1**] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *'A straightforward access to 3-trifluoromethyl-1H-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile' J. Fluorine Chem.* **2021**, *241*, 109691

współpracy nad koncepcją badań, syntezą i analizą wyników oraz udziale w redakcji tekstu manuskryptu.

[**D2**] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *'Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions' Org. Lett.* **2022**, *24*, 2499-2503

współpracy w zakresie optymalizacji metod utleniania i syntezy wyjściowych pochodnych pirazoliny, wykonaniu utleniań w wariancie deacylującym oraz syntez bis-trifluorometylowanych pirazoli, współpracy nad analizą wyników oraz udziale w redakcji tekstu manuskryptu.

[**D3**] G. Utecht-Jarzyńska, A. Kowalczyk, M. Jasiński *'Fluorinated and non-fluorinated 1,4-diarylpyrazoles via MnO_2-mediated mechanochemical deacylative oxidation of 5-acylpyrazolines' Molecules* **2022**, *27*, 8446

współtworzeniu koncepcji i planu badań, wykonaniu optymalizacji procesu utleniania w młynie kulowym, współpracy w zakresie syntezy produktów i analizy wyników, przygotowaniu pierwszej wersji manuskryptu i udziale w jego redakcji.

[**D4**] A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński *'ω-(3-trifluoromethylpyrazol-4-yl)alkanoic acids via (3+2)-cycloaddition of nitrile imines with cyclic enones and deacylative aromatization' J. Fluorine Chem.* **2023**, *272*, 110206

współpracy nad analizą wyników oraz udziale w redakcji tekstu manuskryptu.

[**D5**] A. Kowalczyk, K. Świątek, M. Celeda, G. Utecht-Jarzyńska, A. Jaskulska, K. Gach-Janczak, M. Jasiński *'Trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1H)-ones via (3+3)-annulation of nitrile imines with α-amino esters' Materials*, **2023**, *16*, 856

współpracy w optymalizacji warunków reakcji i syntezy pochodnych L-proliny, wykonaniu analiz HPLC, udziale w analizie wyników i redakcji tekstu manuskryptu.

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(podpis)

Newark, NJ, 25.02.2024r.
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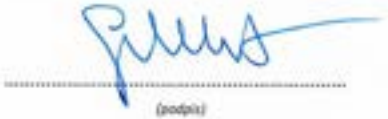
Udział w dyskusji uzyskanych wyników, interpretacja mechanizmu reakcji oraz współpraca przy redagowaniu manuskryptu i autorskiej kontroli wersji galley proofs.

[**D2**] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *'Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions' Org. Lett.* **2022**, *24*, 2499-2503

Udział w dyskusji uzyskanych wyników, interpretacja mechanizmu reakcji oraz współpraca przy redagowaniu manuskryptu i autorskiej kontroli wersji galley proofs.



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(podpis)

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Oświadczam, że mój wkład w powstanie poniższej publikacji polegał na:

A. Kowalczyk, K. Świątek, M. Celeda, G. Utecht-Jarzyńska, A. Jaskulska, K. Gach-Janczak, M. Jasiński *'Trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1H)-ones via (3+3)-annulation of nitrile imines with α-amino esters' Materials*, **2023**, *16*, 856

przeprowadzeniu badań *in vitro* aktywności cytotoksycznej serii triazyn na linii komórkowej MCF-7 oraz interpretacji otrzymanych wyników.

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Jaskulska Agata
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otrzymaniu bromków hydrazonoilowych **1a**, **b**, **e** i **h**, współpracy w optymalizacji ogólnych warunków prowadzenia omawianych eksperymentów, syntezie pochodnych *L*-proliny **7a-h**, oraz przeprowadzeniu transformacji pochodnych **7a** i **7h**.

.....
(podpis)

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synteza prekursorów 1,3-dipoli.

13.03.2024 Celeda Małgorzata

(podpis)

Łódź, 13.03.2024

(data)

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Oświadczam, że mój wkład w powstanie poniższej publikacji polegał na:

[**D1**] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *'A straightforward access to 3-trifluoromethyl-1H-indazoles via (3+2)-cycloaddition of arynes with nitrile imines derived from trifluoroacetonitrile' J. Fluorine Chem.* **2021**, *241*, 109691

[**D2**] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński *'Trifluoromethylated pyrazoles via sequential (3+2)-cycloaddition of fluorinated nitrile imines with chalcones and solvent-dependent deacylative oxidation reactions' Org. Lett.* **2022**, *24*, 2499-2503

[**D3**] G. Utecht-Jarzyńska, A. Kowalczyk, M. Jasiński *'Fluorinated and non-fluorinated 1,4-diarylpyrazoles via MnO_2-mediated mechanochemical deacylative oxidation of 5-acylpyrazolines' Molecules* **2022**, *27*, 8446

[**D4**] A. Kowalczyk, G. Utecht-Jarzyńska, M. Jasiński *'ω-(3-trifluoromethylpyrazol-4-yl)alkanoic acids via (3+2)-cycloaddition of nitrile imines with cyclic enones and deacylative aromatization' J. Fluorine Chem.* **2023**, *272*, 110206

współtworzeniu koncepcji i planu badań, wykonaniu większości syntez, współudziale w analizie wyników, udziale w redakcji manuskryptu.

[**D5**] A. Kowalczyk, K. Świątek, M. Celeda, G. Utecht-Jarzyńska, A. Jaskulska, K. Gach-Janczak, M. Jasiński *'Trifluoromethylated 4,5-dihydro-1,2,4-triazin-6(1H)-ones via (3+3)-annulation of nitrile imines with α-amino esters' Materials*, **2023**, *16*, 856

współtworzeniu koncepcji i planu badań, optymalizacji oraz opracowaniu metody syntezy 4,5-dihydro-1,2,4-triazin-6(1*H*)-onów, syntezy serii pochodnych glycinaniu metylu oraz α-podstawionych (*S*)-aminoestrów, badań nad udowodnieniem czystości optycznej otrzymanych związków oraz dalszymi transformacjami układów, współpracy nad analizą wyników oraz udział w redakcji tekstu manuskryptu.

[**D6**] A. Kowalczyk, M. Jasiński *'4,5-Dihydro-1,2,4-triazin-6-(1H)-ones' Chem. Heterocycl. Compd.* **2022**, *58*, 585-587

zebraniem literatury, współpracy w przygotowaniu manuskryptu oraz jego redakcji.

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(podpis)

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(data)