Instytut Chemii Organicznej
Polskiej Akademii Nauk

Karbokationy i rodniki alkilowe jako komplementarne bloki budulcowe w reakcjach z nukleofilami i elektrofilami

Jakub Durka

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Chciałbym serdecznie podziękować wszystkim,

którzy wspierali mnie podczas powstawania niniejszej pracy:

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Mariana for the way my life has changed since the day we met

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Spis treści

1. Spis publikacji wchodzących w skład rozprawy doktorskiej

Publikacje oryginalne:

1) J. Turkowska ‡, J. Durka ‡, M. Ociepa, D. Gryko *Chem. Commun.*, **2022**, *58*, 509-512

Reversal of regioselectivity in reactions of donor–acceptor cyclopropanes with electrophilic olefins

2) J. Durka, B. Zielińska, D. Gryko *Angew. Chem. Int. Ed.* **2025**, *64* (7)

Aliphatic Amines Unlocked for Selective Transformations through Diazotization

Publikacje przeglądowe:

1) J. Durka, J. Turkowska, D. Gryko *ACS Sustainable Chem. Eng.* **2021**, *9*, 8895−8918

Lightening Diazo Compounds?

2. Spis publikacji niewchodzących w skład rozprawy doktorskiej

Publikacje oryginalne:

1) Ł. W. Ciszewski, J. Durka, D. Gryko *Org. Lett.* **2019**, *2117*, 7028-7032

Photocatalytic Alkylation of Pyrroles and Indoles with α-Diazo Esters

2) D. Walaszek, M. Jawiczuk, J. Durka, O. Drapała, D. *Beilstein J. Org. Chem*. **2019**, *15*, 2076–2084

α-Photooxygenation of chiral aldehydes with singlet oxygen

Publikacje przeglądowe:

1) J. Turkowska, J. Durka, D. Gryko *Chem. Commun.* **2020***, 56,* 5718-5734

Strain release – an old tool for new transformations

3. Spis wystąpień konferencyjnych

Wyniki przedstawione w niniejszej pracy zostały zaprezentowane na konferencjach:

1) *Thinking out of the ring. Present and future of small cyclic compounds*; Lejda, Holandia 27-31.05.2024

Prezentacja posterowa: *Cobalt catalyst enables new reactivity of strained, small molecules*

2) *Summer School on Organic Synthesis under Non-classical Conditions*; Warszawa 2-6.09.2024

Prezentacja ustna: *Aliphatic amines unlocked as efficient carbocation precursors*

4. Streszczenie w języku polskim

Karbokationy oraz rodniki alkilowe stanowią jedne z najważniejszych aktywnych indywiduów stosowanych w syntezie organicznej. Ze względu na ich dużą reaktywność, w reakcjach z reguły stosowane są odpowiednio stabilizowane pochodne. Dzięki temu odpowiednie indywidua łatwiej jest wygenerować, a procesy z ich udziałem zachodzą bardziej selektywnie. Co ważne, za stabilizację zarówno karbokationów jak i rodników odpowiadają te same podstawniki – najczęściej są to grupy alkilowe, arylowe bądź heteroatomy. A zatem te ważne indywidua bardzo często łączy budowa. Z kolei najważniejszą różnicę między nimi stanowi reaktywność. Karbokationy mają jednoznacznie elektrofilowy charakter. Z kolei stabilizowane, a więc posiadające podstawniki elektronodonorowe, rodniki alkilowe są nukleofilami. Teoretycznie więc, ten sam blok budulcowy można rozbudować o fragment pochodzący od substratów o przeciwnych filowościach, modyfikując sposób prowadzenia procesu. **Celem mojej pracy było opracowanie nowych, użytecznych przekształceń w chemii organicznej, wykorzystujących stabilizowane karbokationy bądź rodniki alkilowe.**

W pierwszej części badań skupiłem się na opracowaniu nowej metody otwierania pierścienia cyklopropanów donorowo-akceptorowych, odwracającej ich standardową reaktywność. Często znajdują one zastosowanie w syntezach związków aktywnych biologicznie. Wykorzystanie katalizy witaminą B_{12} lub jej pochodnymi, pozwoliło na wygenerowanie rodnika na atomie węgla z podstawnikiem elektronodonorowym, początkowo obdarzonym cząstkowym ładunkiem dodatnim. Wstępował on następnie w reakcje z elektrofilowymi alkenami, a następcza redukcja prowadziła do klasycznych, nasyconych produktów addycji. Opracowane, łagodne warunki reakcji pozwoliły na obecność w ich strukturach niemal wszystkich najważniejszych grup elektronoakceptrowych, oraz pierścieni heteroaromatycznych. Badania wykazały duży wpływ ligandów obecnych w katalizatorze kobaltowym na przebieg procesu.

W dalszych badaniach podjąłem się opracowania metody selektywnego prowadzenia procesu diazowania amin alifatycznych. Mimo upływu prawie półtora wieku od jego odkrycia, reakcja ta stosowana jest niemal wyłącznie do funkcjonalizacji substratów aromatycznych. Jej wydajne zastosowanie również dla amin alifatycznych uczyniłoby je ważnym prekursorem karbokationów. Podjąłem się próby rozwiązania tego problemu, a najważniejsze okazało się zastosowanie 1,1,1,3,3,3-heksafluoroizopropanolu (HFIP) jako rozpuszczalnika. Dzięki swoim właściwościom pozwolił on na bardziej selektywny przebieg samego diazowania oraz umożliwił przekształcenie produktów pośrednich w pożądane po dodaniu silnego kwasu. W ten sposób z wysokimi wydajnościami otrzymałem ok. 70 produktów, głównie alkilowania związków aromatycznych w reakcji typu Friedela-Craftsa, ale także przekształcenia grupy aminowej w atomy chloru, bromu czy grupę karboksylową. Poza pokonaniem wieloletniego wyzwania, opracowany proces odznacza się bardzo dobrą ekonomią atomową, a stosowane aminy nie wymagają prefunkcjonalizacji. Prowadzenie reakcji jest bardzo proste, nie wymaga skomplikowanej aparatury, a mieszanina nie jest wrażliwa na wodę ani składniki powietrza.

5. Streszczenie w języku angielskim / Abstract in English

Carbocations and alkyl radicals represent some of the most important reactive intermediates in organic synthesis. Due to their high reactivity, reactions typically employ appropriately stabilized derivatives, which facilitates their generation and improves selectivity. Notably, both species are stabilized by the same types of substituents—typically alkyl, aryl, or heteroatom-containing groups—resulting in common structural motifs. The key distinction between them lies in their philicity: carbocations exhibit strong electrophilic character, whereas stabilized alkyl radicals, bearing electron-donating substituents, behave as nucleophiles. Theoretically, the same molecular scaffold can be functionally diversified by introducing fragments of opposite philicity, provided by the suitable reaction conditions. **The objective of my work was to develop synthetically valuable transformations involving either stabilized carbocations or alkyl radicals.**

In the first part of the study, I focused on developing a new method for the ring-opening of donor–acceptor cyclopropanes by reversing their standard reactivity. These strained molecules are commonly used in the synthesis of biologically active compounds. The application of vitamin B_{12} (or its derivatives) catalysis enabled the generation of a carbon-centered radical at the donor-substituted position, initially bearing a partial positive charge. It then reacted with electrophilic olefins, followed by reduction to afford classical saturated addition products. The mild reaction conditions were compatible with a wide range of electron-accepting groups and heteroaromatic systems. Importantly, the nature of the ligands on the cobalt catalyst was found to significantly influence the reaction outcome.

Subsequent efforts were directed at developing a selective diazotization protocol for aliphatic amines. Although this reaction was discovered nearly 150 years ago, it has remained largely confined to the functionalization of aromatic compounds. Its efficient application also for aliphatic amines would make them an important precursor of carbocations. The key breakthrough was the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the reaction medium. Its unique properties enabled both a more selective diazotization step and acid-promoted conversion of intermediates into the desired products. This strategy afforded approximately 70 distinct products in high yields, including Friedel–Crafts-type alkylation of arenes, as well as transformations of the amine group into chloro, bromo, or carboxylic acid functionalities. Beyond addressing a longstanding synthetic challenge, the process offers good atom economy, uses amines without prefunctionalization, and proceeds under operationally simple, air- and moisture-tolerant conditions without the need for complex equipment.

6. Wykaz stosowanych skrótów

1-bpp	2,6-bis(pirazol-1-ilo)pirydyna
4,4’-diOMebpy	4,4’-dimetoksy-2,2’-bipirydyna
4CzIPN	4,6-dicyjano-1,2,3,5-tetrakis(karbazol-9-ilo)benzen
9-BBN	9-borabicyklo(3.3.1)nonan
A	grupa elektronoakceptorowa
Ac	acetyl
acac	acetyloacetonian
Ar	aryl
Bn	benzyl
Boc	*tert*-butoksykarbonyl
Bphen	batofenantrolina (4,7-difenylo-1,10-fenantrolina)
bpy	2,2’-bipirydyna
Bu	butyl
cod	cyklookta-1,5-dien
D	grupa elektronodonorowa
DABCO	1,4-diazabicyklo[2.2.2]oktan
DBU	1,8-diazabicyklo(5.4.0)undek-7-en
DCE	1,2-dichloroetan
dF(CF_3)ppy	2-(2,4-difluorofenylo)-5-(trifluorometylo)pirydyna
DIPEA	*N*,*N*-diizopropyloetyloamina
DMA	*N*,*N*-dimetyloacetamid
DME	1,2-dimetoksyetan
DMF	*N*,*N*-dimetyloformamid
DMSO	dimetylosulfotlenek
dmbpy	5,5’-dimetylo-2,2’-bipirydyna
dppf	1,1'-bis(difenylofosfino)ferrocen
dtbbpy	4,4’-di-*tert*-butylo-2,2’-bipirydyna
EDA kompleks	kompleks elektronodonorowo-elektronoakceptorowy
EDG	grupa elektronodonorowa
ee	nadmiar enancjomeryczny

ekwiw.	ekwiwalent
EWG	grupa elektronoakceptorowa
E	elektrofil
Et	etyl
GC-MS	chromatografia gazowa sprzężona ze spektrometrią mas
HME	ester heptametylowy kwasu kobyrynowego
HFIP	1,1,1,3,3,3-heksafluoroizopropanol (1,1,1,3,3,3-heksafluoropropan-2-ol)
hν	światło
LED	dioda elektroluminescencyjna
Me	metyl
Ms	mesyl (metanosulfonyl)
NHC	karben *N*-heterocykliczny
NHPI	*N*-hydroksyftalimid
NMP	*N*-metylopirolidon
NMR	magnetyczny rezonans jądrowy
Ns	nosyl (4-nitrobenzenosulfonyl)
Nu	nukleofil
PC	fotokatalizator
Ph	fenyl
phen	1,10-fenantrolina
pin	grupa pinakolowa
Piv	piwaloil (trimetyloacetyl)
pK_a	ujemny logarytm ze stałej dysocjacji kwasu
ppy	2-fenylopirydyna
T	ogrzewanie
^{t}Bu	*tert*-butyl
Tf	trifluorometanosulfonyl
THF	tetrahydrofuran
TMHD	2,2,6,6-tetrametyloheptano-3,5-dionian
TMS	trimetylosilil
Ts	tosyl (4-metylobenzenosulfonyl)
ttbtpy	2,6-bis[4-(*tert*-butylo)pirydyn-2-ylo)-4-(*tert*-butylo)pirydyna

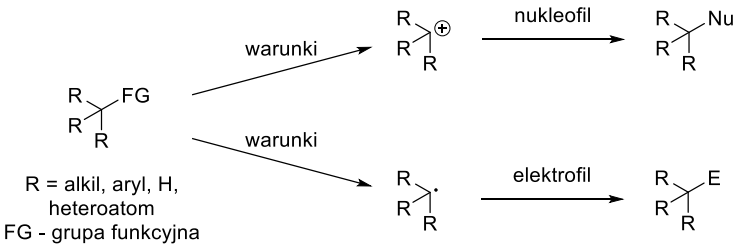
7. Przewodnik po rozprawie doktorskiej

7.1. Założenia i cel pracy

W syntezie organicznej wielokrotnie stosuje się strategie prowadzenia reakcji oparte na wykorzystaniu aktywnych indywiduów. Cząstki te, często tworzone w wyniku działania katalizatora, posiadają wysoką energię i aby ją obniżyć wchodzą w reakcje z innymi związkami obecnymi w mieszaninie reakcyjnej. Oczywiście, kluczowe znaczenie ma energia posiadana przez takie indywidua. Jeśli jest ona zbyt niska może nie stanowić wystarczającej siły napędowej dla zajścia reakcji chemicznej. Natomiast indywidua o bardzo wysokiej energii mogą wstępować w bardzo wiele konkurencyjnych reakcji, prowadząc do nieselektywnych przemian. Wyzwanie może także stanowić samo ich wytworzenie. Jak to często zatem bywa, optymalne właściwości znajdują się gdzieś po środku.

Jako, że chemia organiczna stanowi naukę o związkach węgla, przeanalizujmy aktywne indywidua zlokalizowane na tym atomie. Trzy najważniejsze i najpopularniejsze w syntezie stanowią: karbokation (cząstka z ładunkiem dodatnim zlokalizowanym na atomie węgla), karboanion (obdarzony ładunkiem ujemnym), oba formalnie utworzone poprzez heterolityczny rozpad wiązania C-X, oraz rodnik, produkt jego rozpadu homolitycznego. Oczywiście nawet indywidua tego samego rodzaju mogą znacznie różnić się energią. Zależy ona od wielu czynników, wśród których wymienić należy przede wszystkim efekty indukcyjny i rezonansowy podstawników czy zatłoczenie steryczne. Grupy zlokalizowane w pobliżu aktywnego atomu węgla mogą zarówno podwyższać jak i obniżać jego energię. Z reguły przy projektowaniu reakcji chemicy zainteresowani są tym drugim rozwiązaniem. Stabilizacja aktywnego indywiduum ułatwia bowiem jego wytworzenie oraz może prowadzić do bardziej selektywnej reakcji.

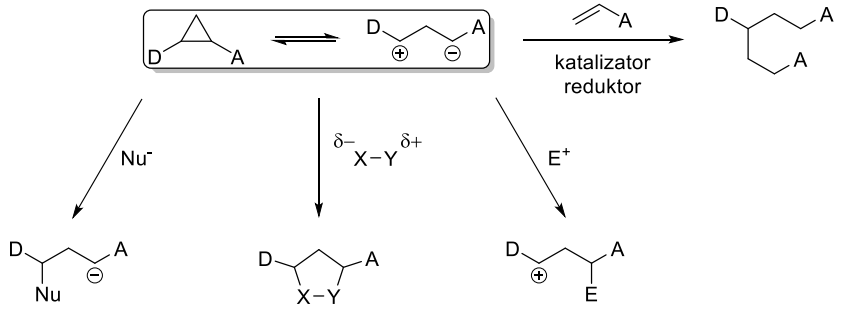
Co ciekawe te same grupy funkcyjne odpowiadają za stabilizację zarówno karbokationów jak i rodników alkilowych. Jest to bardzo istotne, gdyż oba indywidua wykazują przeciwną reaktywność. Karbokationy stanowią klasyczne i jedne z najpopularniejszym elektrofili, na takich właściwościach opiera się ich wykorzystanie w syntezie organicznej. Z kolei rodniki alkilowe mają charakter nukleofilowy.[1] Oznacza to, że stosując te dwa indywidua alternatywnie można przyłączyć tę samą strukturę zarówno do nukleofila jak i elektrofila. Reakcje takie są komplementarne i umożliwiają uzyskanie bardzo wielu różnych produktów posiadających ten samym motyw strukturalny. Do najchętniej wykorzystywanych stabilizowanych karbokationów i rodników zalicza się te posiadające kilka podstawników alkilowych, szczególnie trzeciorzędowe, a także benzylowe czy allilowe.



Schemat 1.1. Funkcjonalizacja tego samego fragmentu strukturalnego przez manipulacje warunkami kationowymi i rodnikowymi.

Celem mojej pracy jest opracowanie nowych, użytecznych przekształceń w chemii organicznej, wykorzystujących stabilizowane karbokationy bądź rodniki alkilowe.

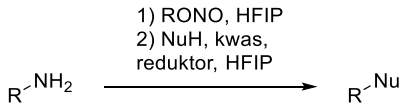
W pierwszej części badań skupiłem się na opracowaniu nowej metody otwierania pierścienia cyklopropanów donorowo-akceptorowych, odwracającej ich standardową reaktywność. Substancje te są często wykorzystywane do otrzymywania związków aktywnych biologicznie, w tym w syntezach totalnych.[2–6] Atom węgla cyklopropanu połączony z grupą elektronodonorową, np. fenylową, wykazuje cząstkowy ładunek dodatni, a zatem podobnie do karbokationów ulega reakcjom z nukleofilami.[7] Założyłem, że zastosowanie katalizy witaminą B_{12} w warunkach redukujących, pozwoli wygenerować w tym miejscu cząsteczki rodnik benzylowy. Takie indywidua z powodzeniem wstępują w reakcje z akceptorami Michaela, a więc typowymi elektrofilami. A zatem zmiana mechanizmu na rodnikowy powinna pozwolić na odwrócenie standardowej reaktywności cyklopropanów donorowo-akceptorowych i przyłączyć elektrofilowy alken do tej samej struktury (Schemat 1.2).



Schemat 1.2. Standardowa reaktywność cyklopropanów donorowo-akceptorowych oraz cel projektu.

W dalszych badaniach skupiłem się na procesach wykorzystujących aminy jako substraty. Choć ta klasa substancji ma ogromne znaczenie w chemii organicznej, to jednak modyfikacjom podlega z reguły sama grupa $-NR_2$. Ilość znanych procesów deaminatywnych jest bardzo ograniczona, gdyż jest ona bardzo słabą grupą odchodzącą.[8] Jednym z procesów uznawanych do tej pory za niemożliwy do wydajnego przeprowadzenia było wykorzystanie amin jako wydajnego źródła karbokationów. Choć te łatwo tworzą się w wyniku diazowania amin alifatycznych, ulegają wielu konkurencyjnym procesom prowadząc do mieszanin produktów.[9,10] **Postanowiłem podjąć się próby rozwiązania tego prawie stupięćdziesięcioletniego problemu i uczynić diazowanie amin alifatycznych również użytecznym w syntezie organicznej.** Jako rozwiązania upatrywałem zastosowania 1,1,1,3,3,3-heksafluoroizopropanolu (HFIP) w charakterze rozpuszczalnika. Ze względu na swoje szczególne właściwości może on zapewnić bardziej selektywny przebieg diazowania,

a także umożliwić przekształcenie produktów pośrednich w oczekiwane, w drugim, katalizowanym kwasem, etapie reakcji.[11] Taka strategia umożliwiłaby dodanie amin do zbioru substratów używanych w najważniejszych procesach zachodzących z wykorzystaniem karbokationów.



Schemat 1.3. Wykorzystanie amin alifatycznych jako wydajnych źródeł karbokationów.

7.2. Wstęp literaturowy

7.2.1 Najważniejsze aktywne indywidua w syntezie organicznej i ich stabilizacja

Mechanizmy reakcji organicznych bardzo często zakładają tworzenie aktywnych indywiduów. Są to wysokoenergetyczne produkty pośrednie generowane z substratów reakcji, które umożliwiają dalsze przemiany. Do najważniejszych należą trzy indywidua, które formalnie można rozpatrywać jako powstałe w wyniku rozpadu wiązania C-X w różny sposób:

- karbokation – dodatnio naładowana cząstka z ładunkiem ulokowanym na atomie węgla. Formalnie utworzony przez heterolityczny rozpad wiązania C-X z przejściem pary elektronowej tworzącej to wiązanie na atom X. Najczęściej generowany poprzez działanie kwasu Brønsteda lub Lewisa na odpowiedni substrat.
- rodnik – cząstka obojętna elektrycznie, z pojedynczym niesparowanym elektronem ulokowanym na atomie węgla. Produkt homolitycznego rozerwania wiązania C-X.
- karboanion - ujemnie naładowana cząstka z ładunkiem ulokowanym na atomie węgla. Formalnie utworzony przez heterolityczny rozpad wiązania C-X z przejściem pary elektronowej tworzącej to wiązanie na atom węgla. Najczęściej generowany poprzez deprotonowanie C-H kwasu wystarczająco silną zasadą.

Aby dany produkt pośredni mógł być efektywnie wykorzystany w syntezie organicznej musi charakteryzować się odpowiednią energią. Jeśli będzie ona niska, może okazać się niewystarczająca, aby indywiduum wchodziło w dalsze, pożądane reakcje. Zbyt stabilizowany produkt pośredni wykazuje się dużą trwałością, a w konsekwencji zbyt małą reaktywnością. Pożądaną sytuacją nie jest również produkt pośredni o zbyt wysokiej energii. Taka cząstka jest bardzo niestabilna, a zgromadzona energia pozwala przekroczyć barierę aktywacji wielu możliwych procesów. Zatem reakcje z jej udziałem będą wysoce nieselektywne, prowadząc do wielu produktów. Ponadto, istotnym problemem jest wygenerowanie takiego produktu pośredniego z substratu. Procesowi temu towarzyszy wysoka energia aktywacji, której przekroczenie wiąże się niejednokrotnie z koniecznością zastosowania ostrych warunków reakcji, co dodatkowo nie sprzyja jej selektywności oraz ogranicza zakres kompatybilnych grup funkcyjnych.

Z wymienionych względów, zastosowanie produktów pośrednich o odpowiedniej energii jest kluczowe dla powodzenia reakcji. Jednocześnie najprostsze możliwe przykłady wszystkich wymienionych indywiduów tj. pochodne metanu: CH_3^+, $CH_3^{\cdot}$ i CH_3^- są bardzo niestabilnymi, a przez to reaktywnymi cząstkami. Dlatego też do efektywnego zastosowania ich w syntezie konieczne jest obniżenie energii produktów pośrednich. Najczęściej spowodowane jest to obecnością odpowiednich grup funkcyjnych, które stabilizują kation, rodnik bądź anion w odpowiednim miejscu cząsteczki. Co ciekawe, dwa pierwsze wymienione indywidua stabilizowane są przez podstawniki należące do tej samej grupy.

7.2.2 Karbokationy

Generalnie można stwierdzić, że owe obdarzone dodatnim ładunkiem cząstki stabilizowane są przez grupy elektronodonorowe. Do najważniejszych z nich zaliczają się:

- grupy alkilowe – stabilność karbokationów wzrasta w szeregu metylowy < pierwszo- < drugo- < trzeciorzędowy.
- podstawniki z wiązaniami **π** - szczególnie fenylowe i winylowe, które silnie stabilizują karbokation przez rezonans.
- heteroatomy posiadające wolne pary elektronowe – w ich przypadku istnieje możliwość wytworzenia wiązania **π** z przeniesieniem ładunku na heteroatom.

Oczywiście zwiększenie ilości wymienionych podstawników przekłada się na dalsze zwiększenie stabilizacji karbokationu. Najtrwalsze z nich zostały wyizolowane w postaci jonów w kryształach soli np. $(C_6H_5)_3C^+$ PF_6^-.[12] Stabilizacja heteroatomami bardzo często występuje w strukturach z wiązaniami wielokrotnymi C=X np. w jonie acylowym. A zatem do najczęściej stosowanych, stabilizowanych karbokationów typowo alkilowych zaliczymy benzylowe, allilowe oraz wysoko podstawione, szczególnie trzeciorzędowe.

Oczywiście za reaktywność tych indywiduów odpowiada zlokalizowany na atomie węgla ładunek dodatni. W związku z tym mają one jednoznacznie elektrofilowy charakter. Zatem, to właśnie reakcje z nukleofilami stały się podstawą ich zastosowania w syntezie organicznej. Ich znaczenie jest ogromne i wniosło cenny wkład w rozwój chemii organicznej już od XIX wieku. Stąd wiele reakcji wykorzystujących karbokationy znana jest obecnie pod nazwiskami swoich odkrywców m.in.: Friedla-Craftsa, Rittera, Kocha itd. Mimo upływu wielu lat od ich odkrycia niektóre z nich wciąż wykorzystywane są w przemyśle, nierzadko na wielką skalę. Odpowiada za to m.in. prostota prowadzenia części z tych procesów. Do wytworzenia stabilizowanego karbokationu wystarczy bowiem działanie kwasu Brønsteda lub Lewisa na odpowiedni prekursor. Najczęściej w tej roli wykorzystywane są alkeny, alkohole i halogenki alkilowe. Najtrwalsze karbokationy nie wymagają nawet dodatku kwasu i tworzą się na drodze reakcji S_N1.

7.2.3 Rodniki

Dokładnie te same grupy funkcyjne odpowiadają też za stabilizację rodników. W przypadku podstawników z wiązaniami **π** stabilizacja opiera się teraz na delokalizacji, a nie rezonansie. Podobnie jak w przypadku karbokationów, zwiększenie liczby stabilizujących podstawników prowadzi do dalszego zwiększenia trwałości. Dlatego też rodnikowy analog kationu trifenylometylowego, który może być wyizolowany w postaci soli, został jednym z pierwszych odkrytych indywiduów tego typu.[13] Podobnie jak w przypadku karbokationów, najczęściej stosowanymi stabilizowanymi rodnikami alkilowymi będą te wyżej rzędowe czy benzylowe.

Przez większość czasu reakcje rodnikowe postrzegane były jako bardziej wymagające i trudniejsze do kontroli, a przez to opracowanych zostało mniej takich metod. Jednakże pierwsza syntetycznie użyteczna reakcja, w której rodniki generowano w wyniku elektrolizy kwasów karboksylowych, odkryta została już w 1847 r. przez Kolbego.[14] Duże znaczenie zyskały procesy rodnikowego halogenowania jak również możliwość zastosowania tych reaktywnych indywiduów w reakcjach katalizowanych metalami przejściowymi. Ostatnie dwie dekady przyniosły znaczny wzrost zainteresowania chemików organików metodami wykorzystującymi rodniki dzięki odkryciu łagodnych i selektywnych sposobów ich generowania, zwłaszcza opartych na katalizie fotoredoks czy elektrochemii.[1]

Duże znaczenie ma fakt, że choć stabilizowane są tymi samymi podstawnikami, rodniki alkilowe mają odmienny od karbokationów charakter chemiczny. Gdy bowiem grupy alkilowe czy fenylowe przyłączone są do atomu węgla posiadającego niesparowany elektron ma on charakter nukleofilowy. Dopiero zastąpienie ich jedną (dla rodników pierwszorzędowych) lub dwiema (dla drugo- i trzeciorzędowych) grupami elektronoakceptorowymi zmienia właściwości rodnika na elektrofilowe.[1]

Stabilizowane karbokationy i rodniki mają zatem podobne struktury i występujące w nich podstawniki, ale przeciwne właściwości chemiczne. **Można zatem domniemywać, że umiejętne projektowanie procesów pozwala wykorzystać te różnice i zastosować korzystniejszy wariant prowadzenia reakcji do wprowadzenia pożądanego elementu strukturalnego.**

7.2.4 Zastąpienie reakcji jonowych rodnikowymi

Jako, że przez zdecydowaną większość czasu przypadającego na rozwój chemii organicznej reakcje wykorzystujące karbokationy były lepiej poznane, skupię się na omówieniu powodów, dla których zastąpienie ich procesami rodnikowymi może być korzystne.

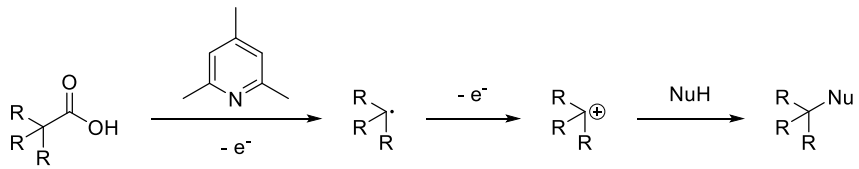
Po pierwsze, nowoczesne metody generowania rodników nierzadko wykorzystują bardzo łagodne warunki reakcji. Są zatem możliwe do zastosowania w syntezie bardziej złożonych produktów, zawierających wiele grup funkcyjnych, często na ostatnich etapach funkcjonalizacji. Jest to bardzo istotne, biorąc pod uwagę złożoność wielu cząsteczek leków i innych środków aktywnych biologicznie. Metody z udziałem rodników mają tu zatem znaczną przewagę nad procesami przebiegającymi przez stadium karbokationu. Te bowiem często charakteryzują się ostrymi warunkami, chociażby, ze względu na konieczność zastosowania kwasów do generowania tych aktywnych indywiduów.[15] Dobrym przykładem zmiany specyfiki procesu, mimo wprowadzania tej samej grupy funkcyjnej, są reakcje fluorowania, również zyskujące ostatnio na znaczeniu. Często, ze względu na konieczność generowania karbokationów, niską nukleofilowość jonu fluorkowego oraz silne wiązanie H-F, do syntez fluorków alkilowych stosowano odczynniki oparte na silnie toksycznym fluorowodorze.[16] Jednakże odkrycia ostatnich lat doprowadziły do opracowania metod pozwalających na wprowadzenie atomu fluoru w łagodnych, niemal obojętnych warunkach.

W procesach tych, ze względu na charakter chemiczny rodników alkilowych, konieczne jest stosowanie elektrofilowych czynników fluorujących np. Selectfluor.[17,18]

Karbokationy, szczególnie te mniej stabilizowane, ulegają całej gamie potencjalnych reakcji ubocznych. Gdy przy sąsiednim atomie węgla dostępny jest atom wodoru, możliwy jest proces eliminacji. Dodatkowo, utworzony w ten sposób alken jest świetnym akceptorem karbokationu, a proces prowadzi do utworzenia kolejnej cząstki tego typu. W efekcie możliwa jest oligomeryzacja substratu. Jeśli istnieje taka możliwość, przeniesienie atomu wodoru czy grupy alkilowej prowadzi do przegrupowania produktu pośredniego w bardziej trwały karbokation co stanowi reakcję charakterystyczną dla tej grupy związków. Ponadto, ze względu na swoją aktywność, większość indywiduów tego typu będzie wstępowała w reakcję z każdym nukleofilem obecnym w roztworze. Dobrym przykładem ilustrującym opisane reakcje uboczne jest diazowanie amin alifatycznych, gdzie to właśnie one odpowiadają za brak syntetycznego znaczenia tego prostego procesu (Schemat 2.4).[9,10]

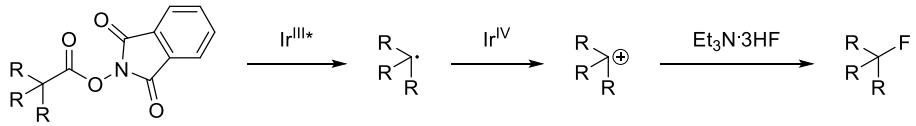
Kolejnym powodem, dla którego zamiana mechanizmu kationowego na rodnikowy może być warta rozważenia jest wspomniany już różny charakter chemiczny tych indywiduów. Dzięki temu wykorzystując karbokationy można rozbudować strukturę o fragment pochodzący od typowego nukleofila np. bogaty w elektrony pierścień aromatyczny. Z kolei wybierając przekształcenie rodnikowe do cząsteczki wprowadzić można nukleofil np. akceptor Michaela. Teoretycznie więc umiejętny balans warunkami procesu pozwoli rozbudować benzylową czy trzeciorzędową strukturę o większość motywów strukturalnych dostępnych w syntezie organicznej.

Bliską relację między stabilizowanymi kationami a rodnikami podkreśla fakt, że jedne mogą powstawać z drugich nawet w warunkach reakcji. Anodowe utlenianie anionów kwasów karboksylowych jest znaną od dawna metodą generowania rodników.[14] Jednakże w przypadku pochodnych trzeciorzędowych, benzylowych czy allilowych możliwe jest ich następcze utlenienie do karbokationów w warunkach reakcji. W ten sposób te aktywne indywidua zostały wygenerowane bez użycia silnego kwasu, a nawet w zasadowym środowisku. Oczywiście przejawiały one typową dla karbokationów reaktywność, i z powodzeniem tworzyły produkty z całą gamą nukleofili, w tym nawet bardzo zatłoczone sterycznie i trudno dostępne etery trzeciorzędowych alkoholi (Schemat 2.1).[15]



Schemat 2.1. Elektrochemiczne utlenianie kwasów karboksylowych do karbokationów.

Niedługo później podobne przekształcenie zostało opublikowane z wykorzystaniem katalizy fotoredoks.[19] Redukcja aktywnych estrów *N*-hydroksyftalimidu (NHPI) typowo prowadzi do utworzenia rodników. Jednakże dobór odpowiedniego fotokatalizatora irydowego umożliwił ich następcze utlenienie do stabilizowanych karbokationów. Te następnie wydajnie tworzyły fluorki alkilowe w reakcji z trifluorowodorkiem trietyloaminy ($Et_3N{\cdot}3HF$, schemat 2.2).



Schemat 2.2. Synteza fluorków alkilowych z estrów NHPI w warunkach katalizy fotoredoks.

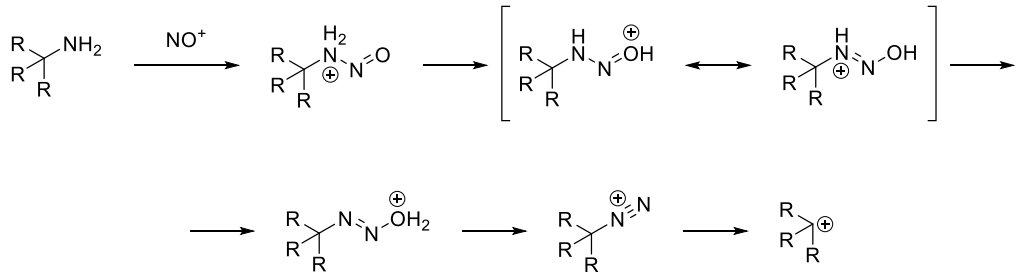
7.2.5 Deaminatywne reakcje przebiegające z wykorzystaniem karbokationów i rodników

Reakcje przebiegające przez stadium karbokationów lub wolnych rodników stanowią znaczny procent procesów wykorzystywanych w chemii organicznej. Jako wydajne prekursory tych indywiduów zastosowanie znalazły niemal wszystkie najważniejsze grupy funkcyjne. Wartym odnotowania wyjątkiem pozostają tu jednak aminy. Mimo ich ogromnego znaczenia w chemii organicznej, bardzo rzadko znajdują one zastosowanie w celu tworzenia nowych wiązań C-C. Zdecydowana większość wykorzystania amin opiera się bowiem na nuklofilowych i zasadowych właściwościach atomu azotu i reakcjach z jego udziałem. Wiązanie C-N jest silne i trudne do rozerwania. W związku z tym, w przeciwieństwie do alkoholi czy halogenopochodnych, aminy bardzo rzadko wykorzystywane są jako alifatyczne bloki budulcowe. Jednakże potencjał tego typu reakcji, spowodowany przede wszystkim przez znaczenie i dostępność związków z grupą NH_2, powoduje, że chemicy organicy od dawna starają się opracowywać warunki umożliwiające deaminatywne przekształcenia. Znaczny wzrost zainteresowania nimi widać w ostatnich latach. Opracowane niedawno przemiany pokazują też trend zastępowania reakcji kationowych rodnikowymi.[8]

7.2.5.1 Deaminatywne procesy wykorzystujące karbokationy

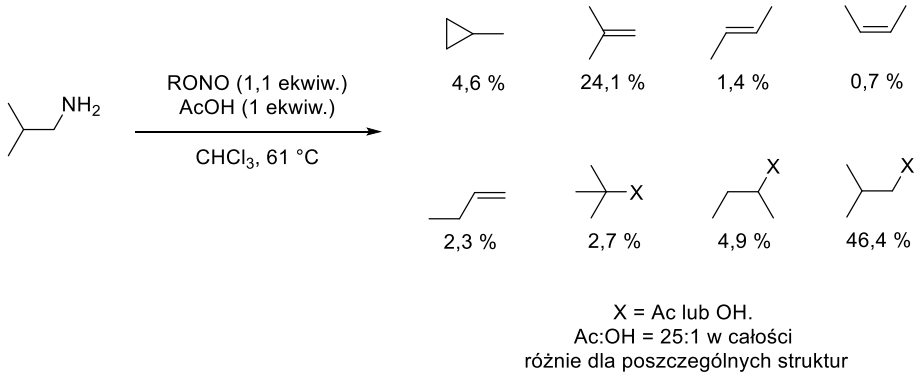
Znaną od niemal półtora wieku reakcją posiadającą trudny do przecenienia wkład w rozwój chemii organicznej jest diazowanie. Ten jakże ważny i chlubny wyjątek wśród procesów deaminatywnych ma bardzo istotne ograniczenie. Jego syntetyczne zastosowanie opiera się niemal wyłącznie na przekształceniach wykorzystujących aminy aromatyczne i stanowi jedną z podstawowych przemian wykorzystywanych do funkcjonalizacji arenów.

Diazowaniu ulegają również aminy alifatyczne, prawdopodobnie nawet łatwiej, ze względu na znacznie większą nukleofilowość atomu azotu niesprzężonego z pierścieniem aromatycznym. Podobnie jak w przypadku anilin prowadzi ono do utworzenia soli diazoniowej, jednakże tutaj pojawia się istotna różnica – pozbawiona sprzężenia z pierścieniem aromatycznym alifatyczna sól diazoniowa jest bardzo nietrwała. Ulega ona niemal natychmiastowej reakcji S_N1 z wydzieleniem prawdopodownie najlepszej grupy odchodzącej w chemii organicznej – cząsteczki azotu N_2. Drugim produktem tego procesu jest karbokation (Schemat 2.3).[9]



Schemat 2.3. Mechanizm diazowania amin alifatycznych.

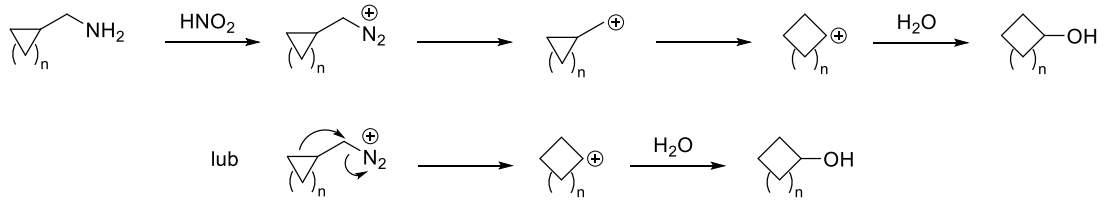
Proces ten ma też szereg dalszych, potencjalnych zalet. Po pierwsze, do wygenerowania aktywnego indywiduum w reakcji diazowania, jonu nitrozoniowego NO^+, nie jest potrzebny silny kwas, wystarczający jest już kwas octowy. Ponadto proces ten zachodzi dla dowolnej aminy alifatycznej. W związku z tym, w tych samych, stosunkowo łagodnych warunkach, możliwe jest wygenerowanie bardzo wysokoenergetycznych kationów jak metylowego czy nawet posiadających niektóre grupy wyciągające elektrony. Uzyskanie takich indywuów jest niemal niemożliwe innymi metodami, ze względu na bardzo wysoką energię aktywacji procesów ich tworzenia. Można by w związku z tym uznać, że diazowanie amin alifatycznych to jedna z najlepszych metod generowania karbokationów. Tak jednak nie jest. W rzeczywistości jest jedną z najgorszych, niemal pozbawiona znaczenia syntetycznego. Proces diazowania amin alifatycznych skupia w sobie większość wad związanych z wykorzystaniem karbokationów. Powstają one w reakcji szybko, w niekontrolowanych warunkach i pozbawione są stabilizacji. W związku z tym obserwowane są niemal wszystkie reakcje uboczne, jakim karbokationy ulegają. Po pierwsze, w obecności atomów wodoru w pozycji β następuje eliminacja prowadząca do alkenu(ów). Z kolei przeniesienie jonu wodorkowego lub grupy alkilowej prowadzi do przekształcenia utworzonego karbokationu w stabilniejszy. Oczywiście przegrupowanie to zachodzi, jeśli występuje możliwość utworzenia indywiduum o niższej energii. Niestabilizowane karbokationy są cząstkami wysoce reaktywnymi i atakują dowolny nukleofil obecny w roztworze. Z reguły jest ich bardzo wiele, szczególnie w przypadku prowadzenia procesu diazowania w wodzie. Wówczas już sam rozpuszczalnik posiada silne właściwości nukleofilowe, a obok niego występują jon azotynowy (azotanowy(III)), stanowiący prekursor HNO_2, czy przeciwjon używanego kwasu, często chlorkowy. Poza tym, nawet przy próbie skrupulatnego dobierania warunków reakcji, całkowita eliminacja niepożądanych nukleofili z roztworu jest niemożliwa. Jeden ekwiwalent wody powstaje w procesie diazowania, zaś drugi ekwiwalent nukleofila pochodzi od zastosowanego prekursora jonu NO^+ (NO_2^- lub RONO). Wpływ wymienionych czynników na selektywność procesu diazowania dobitnie podkreśla mieszanina produktów tej reakcji dla izobutyloaminy (Schemat 2.4).[10]



Schemat 2.4. Diazowanie izobutyloaminy w warunkach możliwie pozbawionych nukleofili.

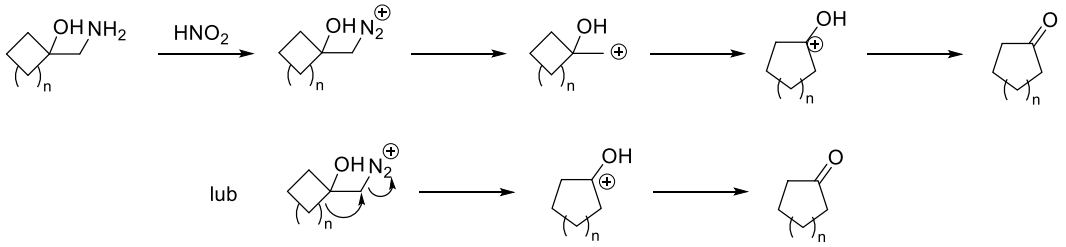
Chemicy organicy już od czasu odkrycia procesu diazowania amin aromatycznych próbowali przenieść jego skuteczność również na pochodne alifatyczne. Jednakże mimo prawie półtora wieku, które upłynęło oraz wielu podejmowanych prób dobrania odpowiednich warunków, proces ten wciąż uznawany jest za bezużyteczny w syntezie dla standardowej aminy alifatycznej. Istnieją jednakże szczególne przypadki reakcji, gdzie ze względu na budowę substratu udało się uzyskać produkty z wysokimi wydajnościami. Zwykle zawdzięczane jest to obecności odpowiedniego ugrupowania w bliskim sąsiedztwie karbokationu, jako że procesy wewnątrzcząsteczkowe są szybsze od tych angażujących większą liczbę molekuł.

Jedną z takich reakcji, która zyskała nawet miano nazwiskowej jest przegrupowanie Demjanowa. Ulegają mu cykloalkilometyloaminy w typowych warunkach diazowania. Utworzony w tym procesie karbokation ulega typowemu dla tych indywiduów przegrupowaniu, które prowadzi do powiększenia pierścienia (Schemat 2.5). Zastosowanie tej metody umożliwiło otrzymanie pierścieni od cztero- do dziewięcioczłonowych.[20]



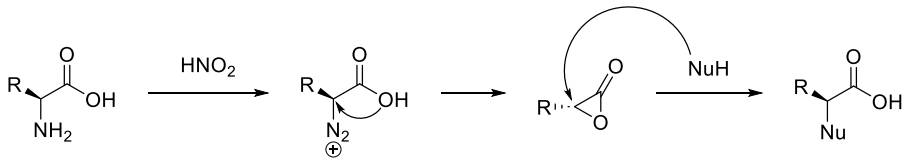
Schemat 2.5. Przegrupowanie Demjanowa.

Podobnym procesem jest odkryte blisko dwie i pół dekady później przegrupowanie Tiffeneau-Demjanowa. Jego substraty stanowią 1-(aminometylo)-cykloalkanole, a reakcja pozwala na uzyskanie odpowiednich ketonów o powiększonym pierścieniu (Schemat 2.6). Zakres otrzymywanych pierścieni jest mniejszy niż w przypadku przegrupowania Demjanowa, gdyż reakcję tę zastosowano do syntezy pierścieni od cyklopentanowego do cyklononanowego, z niewielkim spadkiem wydajności towarzyszącym zwiększaniu pierścienia. Jednakże przegrupowanie Tiffeneau-Demjanowa cechuje się wyższymi wydajnościami.[20]



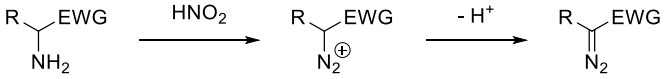
Schemat 2.6. Przegrupowanie Tiffeneau-Demjanowa.

Istotnym procesem, którego wydajne prowadzenie umożliwia bliskość centrów reakcyjnych jest diazowanie aminokwasów. Reakcja ta klasycznie rozpoczyna się od przekształcenia grupy aminowej w sól diazoniową. Ta jednak nie ulega rozpadowi do karbokationu, który byłby zresztą bardzo niestabilny, zamiast tego następuje atak pobliskiej grupy karboksylowej na atom węgla z grupą N_2. Zachodząca w ten sposób reakcja S_N2 prowadzi do utworzenia bardzo nietrwałego α-laktonu, a proces ten zachodzi z inwersją konfiguracji. Ze względu na naprężenie występujące w trójczłonowym pierścieniu posiadającym dodatkowo grupę karbonylową, łatwo ulega on otwarciu, co następuje w wyniku kolejnego nukleofilowego ataku. Jeśli zastosowany do diazowania kwas posiada wystarczająco silnie nukleofilowy anion np. HCl czy HBr, produkt reakcji powstaje w efekcie jego addycji.[21] Z kolei w przypadku nieobecności takiego anionu, rolę nukleofila spełnia rozpuszczalnik, czyli woda, prowadząc do utworzenia hydroksykwasu.[22] Warto podkreślić, że proces ten zachodzi również w myśl mechanizmu S_N2, a więc z inwersją konfiguracji. Sumarycznie więc proces diazowania aminokwasów pozwala na syntezę α-chloro-, bromo- czy hydroksykwasów z retencją konfiguracji (Schemat 2.7).



Schemat 2.7. Diazowanie aminokwasów.

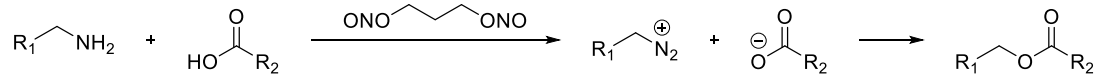
Oczywiście reakcja ta ma szansę zajść jedynie dla aminokwasów z wolną grupą karboksylową. W przypadku ich estrów, podobnie jak i innych amin z silną grupą elektronoakceptorową przy tym samym atomie węgla, sól diazoniowa ulega deprotonowaniu tworząc stabilizowany diazozwiązek (Schemat 2.8). Jest to opisana w literaturze metoda otrzymywania diazoestrów, które mogą być wyekstrahowane do fazy organicznej.[23] Stabilizowane diazozwiązki stanowią bardzo ważną grupę reagentów stosowaną w syntezie organicznej, a badania nad ich wykorzystaniem stały się bardzo intensywne w ostatnich latach, dzięki zastosowaniu reakcji fotochemicznych. Porównaniu metod wykorzystujących diazozwiązki w tych warunkach, z klasycznymi, poświęciłem artykuł przeglądowy, który również stanowi część pracy doktorskiej.[24]



Schemat 2.8. Synteza stabilizowanych diazozwiązków z amin.

Zaledwie kilka lat temu opublikowana została metoda bardzo podobna chemicznie oraz mechanistycznie do diazowania aminokwasów. Wykazano, że wydajna substytucja soli

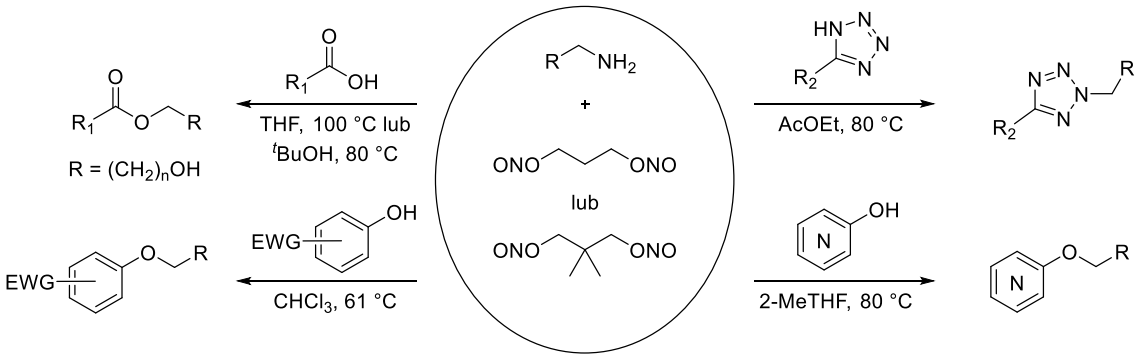
diazoniowej karboksylanem może zachodzić również międzycząsteczkowo. Choć autorzy wskazują, że odkrycie to inspirowane było estryfikacją kwasów karboksylowych z użyciem diazometanu, w procesie tym widoczne jest spore podobieństwo do mechanizmu tworzenia α-laktonu. Opisana metoda opiera się bowiem na estryfikacji kwasów karboksylowych nadmiarem aminy oraz azotynu alkilu w aprotycznym, słabo nukleofilowym rozpuszczalniku. Mechanizm procesu zakłada oczywiście diazowanie aminy. Fakt, iż reakcja ta wymaga udziału kwasu oznacza, że w niewielkiej odległości od centrum reakcyjnego powstaje anion kwasu karboksylowego. W zasadzie stanowi on przeciwjon kationu diazoniowego utworzonego z aminy. Bliskość tych dwóch indywiduów skutkuje stosunkowo wydajną reakcją typu S_N2 z wytworzeniem estru (Schemat 2.9).[25]



Schemat 2.9. Estryfikacja kwasów karboksylowych nadmiarem aminy w warunkach diazowania.

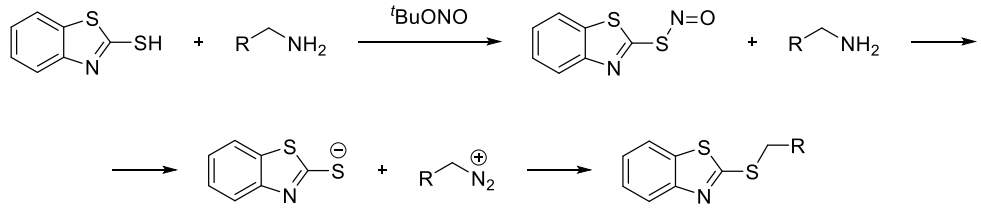
Warto jednak zauważyć konieczność stosowania dużego nadmiaru aminy (2 ekwiw.) i azotynu (3,2 ekwiw.). Wynika on z faktu niewielkiej selektywności reakcji względem interesującego nas substratu, czyli aminy. Utworzona z niej sól diazoniowa może ulegać ubocznym procesom substytucji innym nukleofilem np. cząsteczką wody czy eliminacji. W takich przypadkach kwas karboksylowy zostaje odtworzony, katalizuje diazowanie następnej cząsteczki aminy, aż do momentu wydajnego ataku na sól diazoniową. Teorię tę potwierdzają obniżone wydajności dla amin, ze zwiększoną możliwością eliminacji czy brak klasycznego estru trzeciorzędowego w produktach. Metoda zatem sprawdza się jako wydajny i łatwy sposób estryfikacji kwasów karboksylowych, jednakże nie stanowi zbyt wydajnego sposobu funkcjonalizacji amin poprzez diazowanie.

Wobec sukcesu w opracowaniu metody autorzy postanowili poszerzyć jej stosowanie. Okazało się, że do wydajnej estryfikacji kwasów karboksylowych nadają się niezabezpieczone aminoalkohole, mimo potencjalnych reakcji ubocznych powodowanych obecnością grupy -OH.[26] Choć w reakcji najlepiej sprawdzał się 3-aminopropan-1-ol, wydajnie zastosowano nawet aminoetanol (etanoloaminę). W innych publikacjach wykazano, że w reakcji tego typu sprawdzają się również inne substraty o kwasowości zbliżonej do kwasów karboksylowych. Do takich związków należą nitro- i cyjanofenole. Brak substratu pozbawionego grup elektronoakceptorowych pozwala oszacować jaka kwasowość wymagana jest do wydajnego przebiegu reakcji diazowania.[27] Zastosowanie 5-podstawionych tetrazoli pozwoliło na alkilowanie atomu azotu w pozycji 2, wraz z niewielką ilością produktu 1-alkilowania.[28] W przypadku użycia 2-hydroksypirydyn, produkt *O*-alkilowania dominował, jednakże konkurencyjny proces reakcji na atomie azotu odpowiadał za powstawanie znacznej ilości produktu ubocznego. Lepiej w charakterze substratów sprawdziły się 4-hydroksypirydyny, 2-hydroksychinoliny i 2-hydroksypirymidiny (Schemat 2.10).[29]



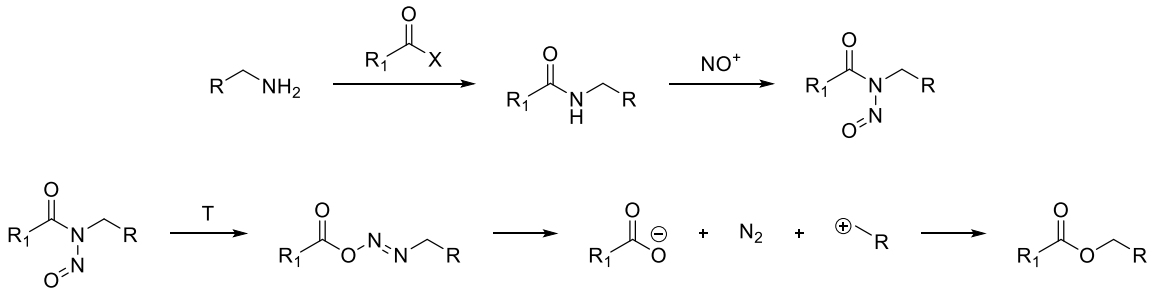
Schemat 2.10. Diazowanie jako metoda alkilowanie O-H i N-H kwasów aminami.

Proces bardzo podobny w swej naturze opisano już w 1984. Wówczas jako nukleofil zastosowano 2-merkaptobenzotiazol. Związek ten nie ulegał typowemu dla tioli utlenieniu do dwusiarczku w tych warunkach, lecz pozwalał na otrzymanie produktu S-H alkilowania. Ze względu na niewielkie wartości nadmiarów enancjomerycznych, które pozostały w reakcjach z użyciem czystych optycznie α-metylobenzyloamin, autorzy założyli inny mechanizm procesu. Według nich proces rozpoczynało przeniesienie jonu nitrozoniowego z wyjściowego azotynu na tiol, i dopiero z niego na cząsteczkę aminy, co umożliwia proces diazowania. Końcowy fragment mechanizmu odpowiada już znanemu dla *O* i *N*-nukleofili (Schemat 2.11). Warto zwrócić uwagę, że mimo zastosowania substratów w stosunku stechiometrycznym (1:1) metoda ta pozwalała na uzyskanie wysokich wydajności, dla większości produktów zawierających się w przedziale 60 – 80%. [30]



Schemat 2.11. *S*-alkilowanie 2-merkaptobenzotiazolu aminami.

Wieloetapowa synteza estrów z amin została opisana wiele lat wcześniej. Wymaga ona otrzymania amidu, a następnie jego nitrozowania. Uzyskany w ten sposób *N*-nitrozoamid ulega w podwyższonej temperaturze przegrupowaniu, w wyniku którego powstaje anion kwasu karboksylowego i karbokation. Te dwa indywidua łatwo rekombinują tworząc ester (Schemat 2.12), choć obserwowane są też reakcje uboczne charakterystyczne dla kationów, jak eliminacja.[31] Jednakże bliskość w jakiej tworzą się oba jony powoduje, że karbokation praktycznie nie wstępuje w typowe dla siebie reakcje z innymi nukleofilami, nawet użytymi w dużym nadmiarze.[32] Aby było to możliwe, konieczne okazało się zastosowanie układu o wiele większej ilości wiązań dzielących oba powstające jony.[33]



Schemat 2.12. Otrzymywanie estrów przez przegrupowanie *N*-nitrozoamidów.

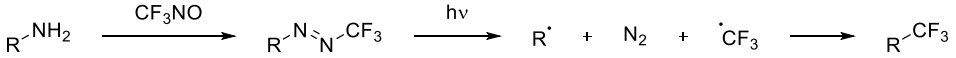
Oczywiście otrzymany ester można poddać hydrolizie, co oznacza sumaryczną, czteroetapową przemianę aminy w alkohol. Proces ten wspomagają grupy wyciągające elektrony w części pochodzącej od kwasu, np. dichlorooctowego.[34]

Podsumowując, zastosowanie reakcji deaminatywnych opartych na karbokationowym mechanizmie jest bardzo niewielkie, szczególnie porównując do ich znaczenia w syntezie organicznej w przypadku zastosowania innych prekursorów. Ogranicza się ono w zasadzie do kilku użytecznych przekształceń zachodzących wydajnie jedynie dla substratów o określonej budowie. Dlatego też opracowane w XX wieku protokoły procesów deaminatywnych skupiały się głównie na reakcjach nukleofilowych. Z reguły opierały się one na przekształceniu grupy aminowej w lepszą grupę odchodzącą, a przez to umożliwienie reakcji substytucji nukleofilowej lub eliminacji. Do trzech najważniejszych metod należą: wyczerpujące metylowanie,[35] ditosylowanie[36] oraz przekształcenie w sól pirydyniową.[37]

7.2.5.2 Deaminatywne procesy rodnikowe

Obecnie metodologia rodnikowych procesów deaminatywnych jest rozbudowana dużo lepiej niż reakcji opartych o mechanizm kationowy. Większość metod związana jest z rozwojem katalizy fotoredoks czy procesów rodnikowych katalizowanych metalami przejściowymi w ostatnich latach.

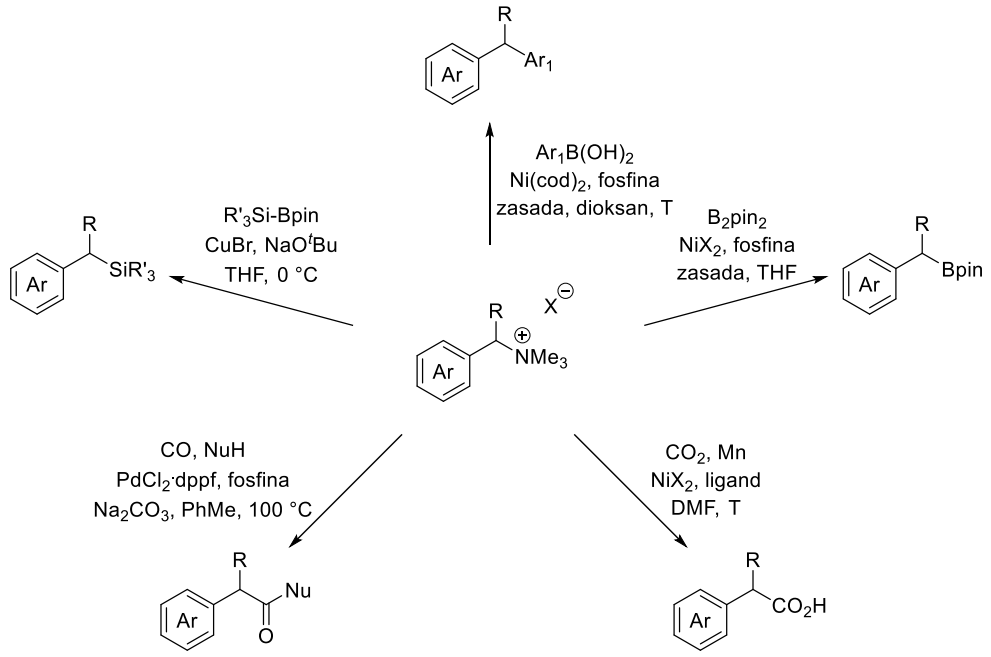
Mimo to, niektóre procesy zostały opracowane już w XX wieku. Do wartych wspomnienia należy z pewnością metoda przekształcenia grupy aminowej w trifluorometylową w wyniku reakcji z trifluoronitrozometanem (CF_3NO). Produktem przejściowym reakcji jest dość trwały azozwiązek, który w wyniku naświetlania promieniowaniem z zakresu ultrafioletowego ulega rozpadowi na rodniki. Ich następcza rekombinacja prowadzi do produktu (Schemat 2.13). Oczywistą wadą metody jest konieczność pracy z toksycznym gazem CF_3NO.[38]



Schemat 2.13. Deaminatywne, rodnikowe trifluorometylowanie.

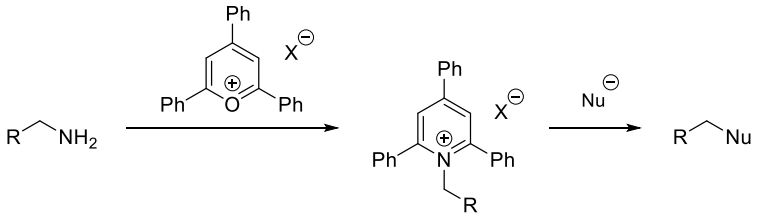
Prawdziwy przełom w opracowywaniu deaminatywnych przekształceń wykorzystysujących rodniki przyniosło odkrycie, że te reaktywne indywidua można generować z substratów używanych w XX w. w reakcjach substytucji nukleofilowej.

Wyczerpujące alkilowanie pierwszorzędowych amin jodkiem metylu prowadzi do uzyskania czwartorzędowych soli amoniowych. Działanie na nie zasadą np. tlenkiem srebra prowadzi do eliminacji Hoffmana.[35] Jednakże w 2013 r. wykazano, że stanowią one również użyteczne substraty do reakcji sprzęgania katalizowanych kompleksami metali przejściowych. Zastosowanie $Ni(cod)_2$ pozwoliło na bardzo wydajne sprzęganie soli uzyskanych z benzyloamin z arylowymi kwasami boronowymi. Co ważne, w przypadku zastosowania czystego enancjomerycznie substratu warunki pozwalają na uzyskanie produktu z ee dochodzącym do 99% i z inwersją konfiguracji.[39] Później autorzy wykazali, że reakcja ta nie wymaga nawet zastosowania liganda fosfinowego.[40] Użycie B_2pin_2, w bardzo podobnych warunkach, pozwala na formalne przekształcenie aminy w kwas boronowy.[41] Z kolei zastosowanie sililowych estrów boronowych prowadzi do analogicznego procesu, umożliwiając wprowadzenie grupy sililowej do cząsteczki w łagodnych warunkach.[42] Opracowane zostały również dwa protokoły przesztalcania benzylowych, czwartorzędowych soli amoniowych w kwasy karboksylowe lub ich pochodne. Proces katalizowany kompleksami niklu, w redukującym środowisku, umożliwia bezpośrednie zastosowanie dwutlenku węgla, jako prekursora grupy karboksylowej.[43] Z kolei w wariancie katalizowanym palladem wykorzystuje się zwykle stosowany do karbonylowania rodników tlenek węgla, a w zależności od zastosowanego nukleofila możliwe jest otrzymanie amidu, estru alkoholu bądź fenolu (Schemat 2.14).[44]



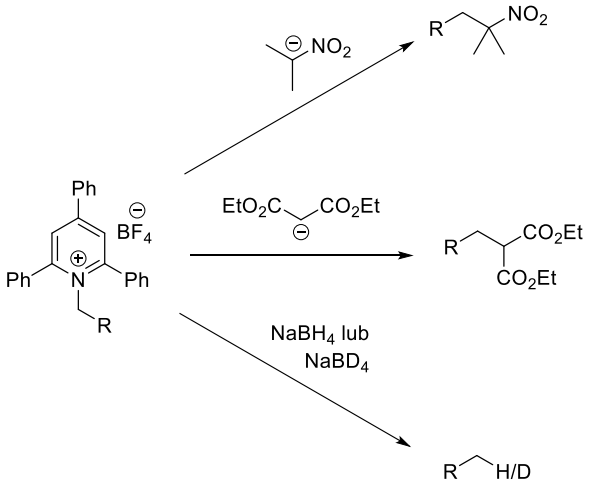
Schemat 2.14. Czwartorzędowe sole amoniowe jako substraty w procesach katalizowanych metalami przejściowymi.

Najważniejsze do tej pory okazało się jednak wykorzystanie soli pirydyniowych. Związki te powstają bardzo łatwo w wyniku kondensacji pierwszorzędowych amin z solami piryliowymi. Metodologia ich zastosowania została opracowana na przełomie lat 70 i 80 w grupie Alana Katritzky'ego i dlatego też obecnie sole te często nazywane są jego imieniem. Większość opracowanych metod opierała się na substytucji nukleofilowej, z obojętną, zatłoczoną sterycznie pirydyną jako grupą odchodzącą (Schemat 2.15).[37]



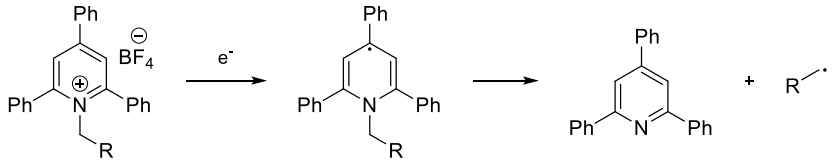
Schemat 2.15. Wykorzystanie soli pirydyniowych do prowadzenia reakcji deaminatywnych.

Jednakże już kilka procesów opracowanych wówczas okazało się mieć mechanizm rodnikowy. Badania mechanistyczne, głównie kinetyczne wskazały, że należą do nich reakcje substytucji z udziałem anionów nitrozwiązków oraz malonianowych,[45,46] jak również redukcje soli pirydyniowych z wytworzeniem alkanów przy użyciu $NaBH_4$ (Schemat 2.16).[47,48]



Schemat 2.16. Reakcje soli pirydyniowych z nukleofilami o rodnikowym mechaniźmie.

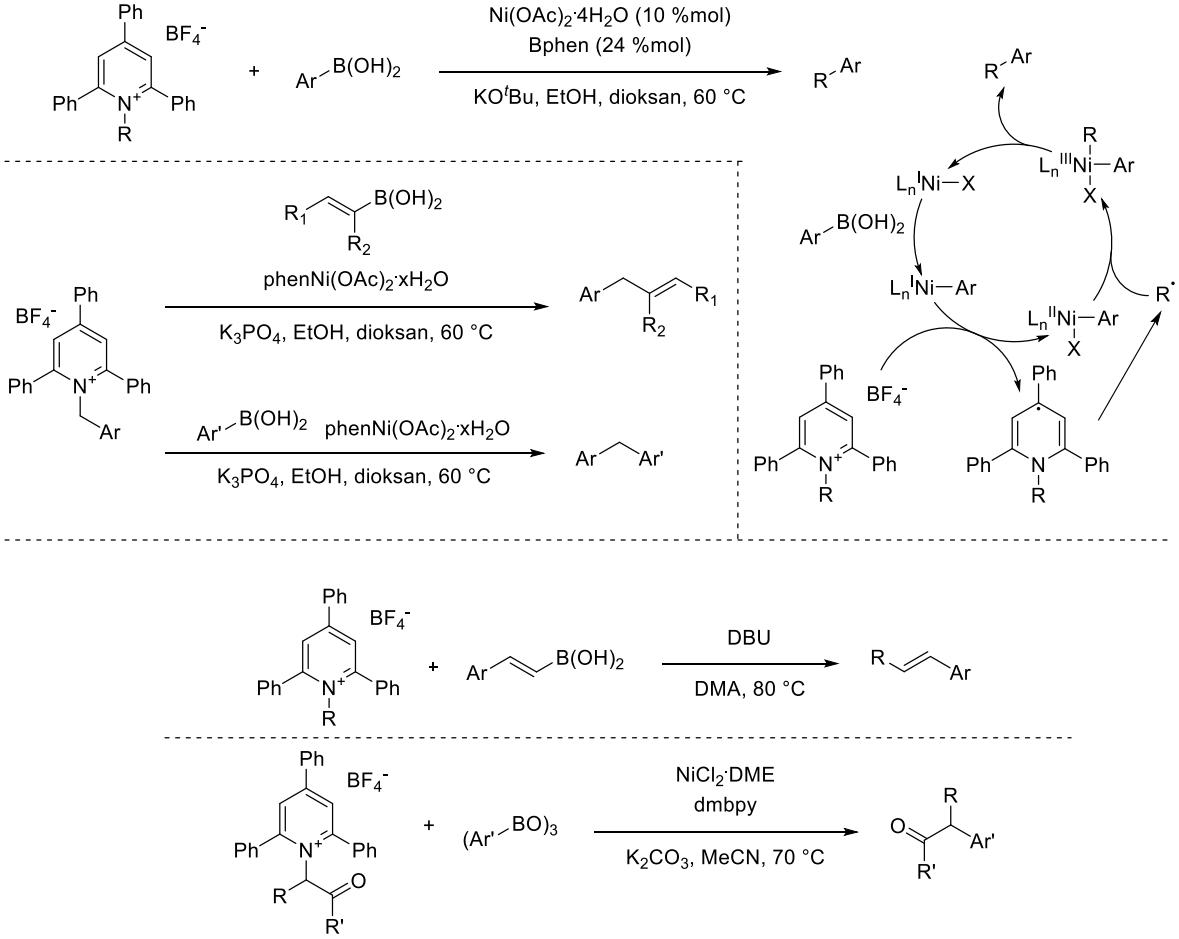
Odkrycia te mają głównie charakter mechanistyczny, gdyż stosowane reagenty uważane są zwykle za typowe nukleofile. Prawdziwy przełom przyniosło wykorzystanie soli pirydyniowych w reakcjach z użyciem metali przejściowych czy katalizy fotoredoks. Okazało się bowiem, że związki te stosunkowo łatwo ulegają jednoelektronowej redukcji, a jej nietrwały produkt przejściowy łatwo rozpada się tworząc obojętną pirydynę i rodnik alkilowy (Schemat 2.17).



Schemat 2.17. Generowanie rodników alkilowych przez redukcję soli pirydyniowych.

Źródło elektronu może stanowić typowy reduktor np. cynk czy mangan lub wzbudzona forma fotokatalizatora, natomiast wytworzony rodnik oprócz typowych dla tych indywiduów reakcji, łatwo ulega addycji utleniającej do kompleksów np. niklu. Te i wiele innych opracowanych procesów pozwoliły wykorzystać sole pirydyniowe do formalnej przemiany funkcji $-NH_2$ w inne grupy funkcyjne czy zastosowania amin jako bloków budulcowych na drodze sprzęgań czy addycji.[49] Pierwszym przykładem wykorzystania tej reaktywności było, podobnie jak w przypadku czwartorzędowych soli amoniowych, katalizowane niklem

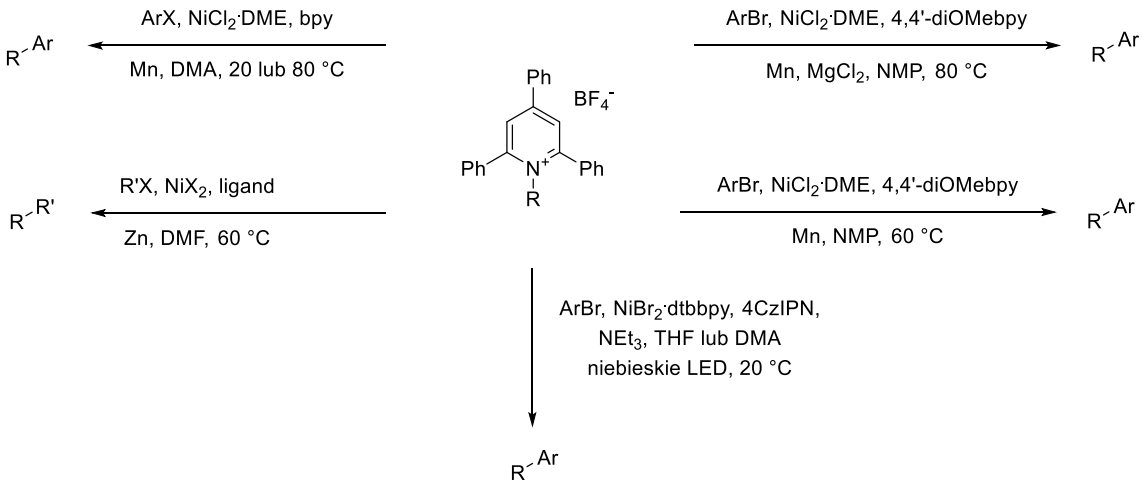
sprzęganie z aromatycznymi kwasami boronowymi (Schemat 2.18).[50] W tym przypadku rolę reduktora pełnił kompleks na najniższym (I) stopniu utlenienia, a sole pirydyniowe stanowiły prekursory różnych pierwszo- i drugorzędowych grup alkilowych.



Schemat 2.18. Sprzęganie rodników generowanych z soli pirydyniowych z kwasami boronowymi.

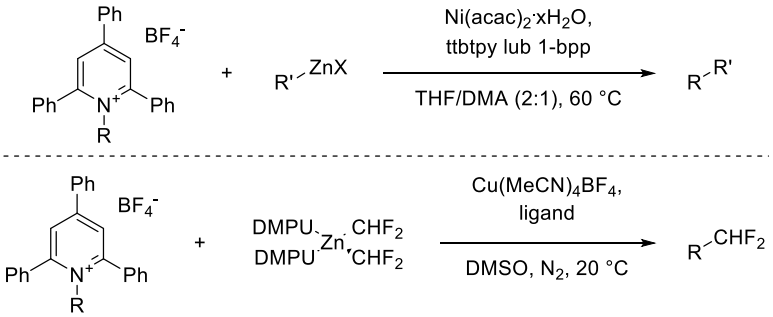
W następnych latach opublikowano modyfikacje tego procesu: wykorzystujące pochodne benzyloamin[51,52] czy aminokwasów[53], winylowe kwasy boronowe[52,54] a nawet niewymagające katalizy metalami przejściowymi.[54]

Następnie opracowano szereg warunków reakcji sprzęgania z łatwiej dostępnymi substratami – halogenkami arylowymi. W tym przypadku konieczne było zastosowanie dodatkowego reduktora, najczęściej metalicznego manganu.[55–58] Opracowano również fotokatalityczny wariant tej przemiany, stosując 4CzIPN i trietyloaminę jako donor elektronów (Schemat 2.19).[59]



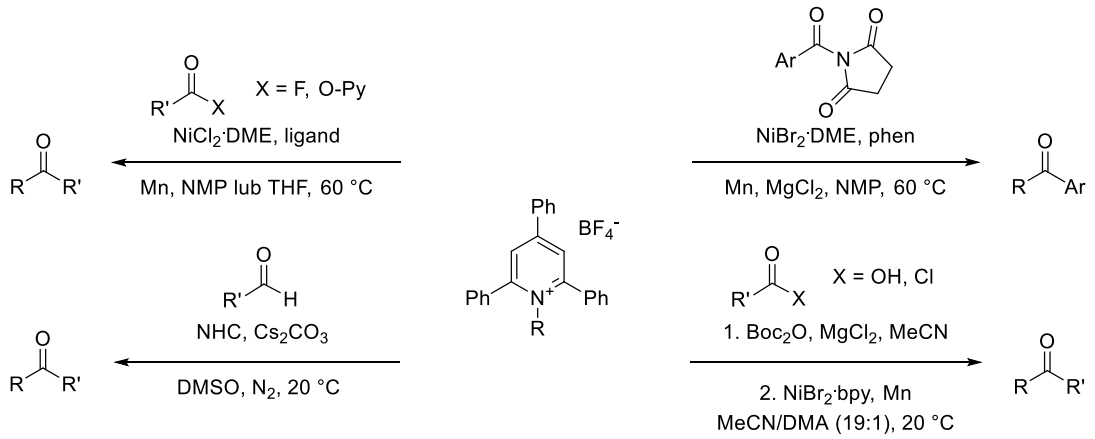
Schemat 2.19. Sprzęganie rodników generowanych z soli pirydyniowych z halogenkami arylowymi.

Użytecznymi substratami do sprzęgań okazały się również związki metaloorganiczne. W przypadku użycia ich jako prekursorów grupy alkilowej klasycznie zastosowano katalizę niklem.[60] Możliwe jest również wprowadzenie, ważnej przy projektowaniu związków biologicznie czynnych, grupy difluorometylowej przy użyciu katalizatora opartego na miedzi (Schemat 2.20).[61]



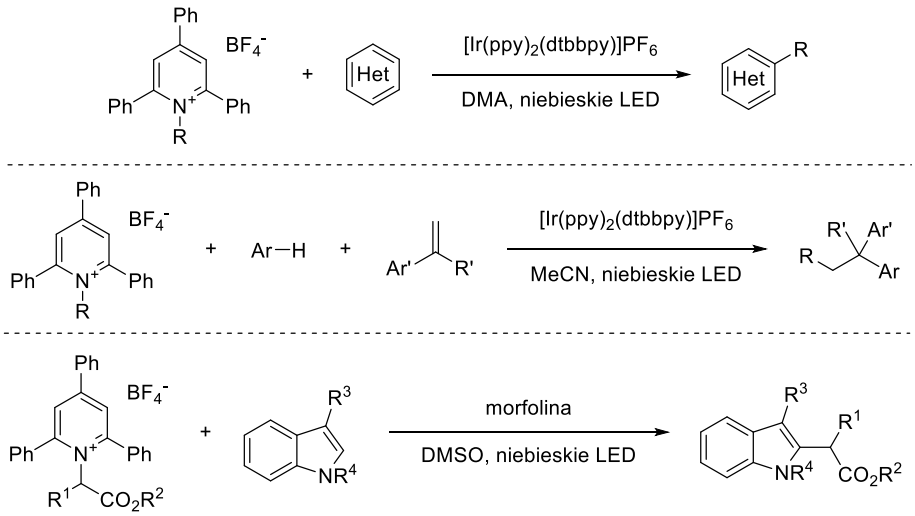
Schemat 2.20. Sprzęganie rodników generowanych z soli pirydyniowych ze związkami cynkoorganicznymi.

Wiele warunków opracowano również dla sprzęgania z aktywowanymi pochodnymi kwasów karboksylowych celem otrzymania ketonów (Schemat 2.21). Uwagę zwraca, że wszystkie prace dotyczące tego tematu zostały opublikowane w tym samym roku, co dowodzi zainteresowania i znaczenia badań wykorzystania soli pirydyniowych w tamtym okresie.[62–65]



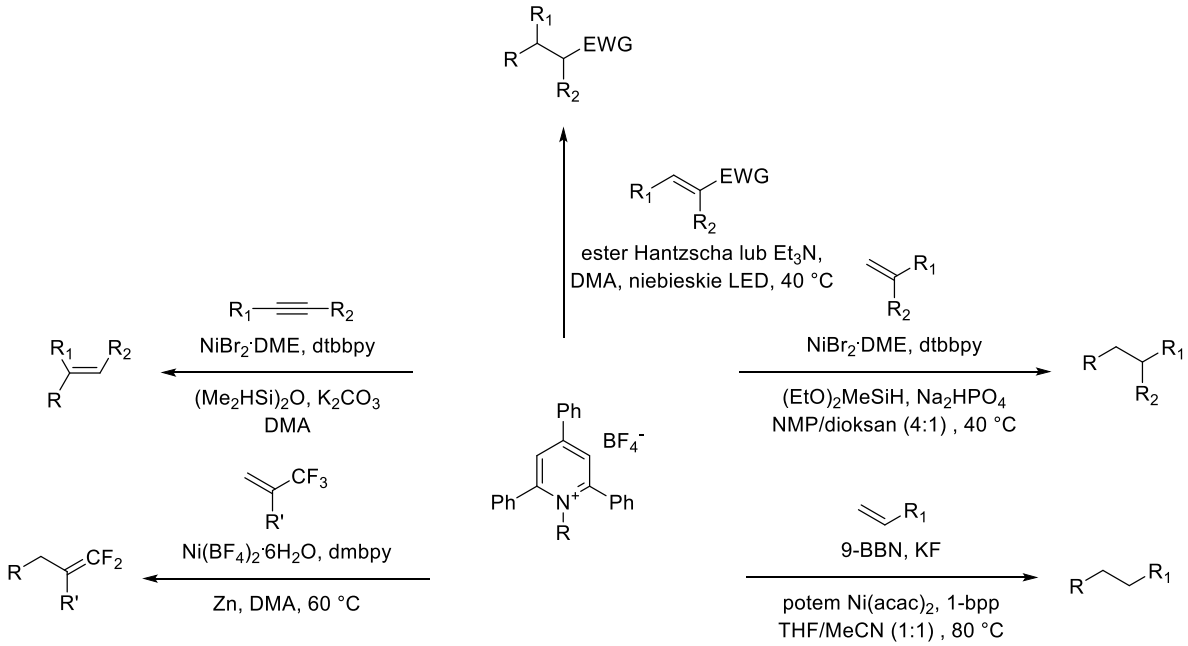
Schemat 2.21. Zastosowanie rodników generowanych z soli pirydyniowych do otrzymywania ketonów.

Rodniki generowane z soli pirydyniowych zostały zastosowane również do alkilowania pierścieni aromatycznych. Jednakże ze względu na nukleofilowy charakter tych indywiduów w reakcji uczestniczą ubogie w elektrony, heteroaromatyczne związki azotowe. Z kolei rodniki generowane z pochodnych aminokwasów, o elektrofilowych właściwościach, zostały zastosowane do funkcjonalizacji indoli i piroli.[66] Prowadzenie podobnej reakcji z dodatkiem alkenu powoduje jego wbudowanie w strukturę produktu.[67] Sole pirydyniowe stanowiące pochodne aminokwasów zostały zastosowane do alkilowania bogatych w elektrony pierścieni heteroaromatycznych także w metodzie niewymagającej stosowania fotokatalizatora. Oba substraty tworzą bowiem ze sobą EDA kompleks, po naświetleniu którego następuje przeniesienie elektronu rozpoczynające ciąg pożądanych przemian (Schemat 2.22).[68]



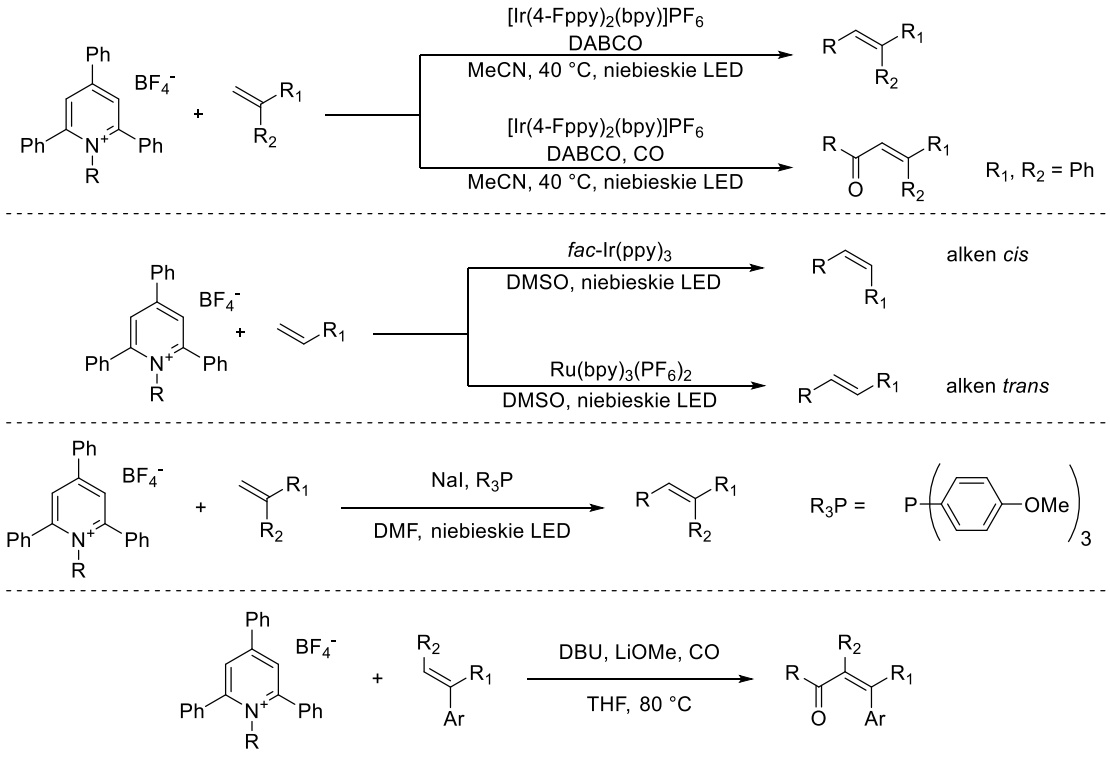
Schemat 2.22. Zastosowanie rodników generowanych z soli pirydyniowych do alkilowania pierścieni heteroaromatycznych.

Wiele z opracowanych przekształceń wykorzystuje alkeny jako substraty. Typowo dla nukleofilowych rodników alkilowych, ulegały one addycji do akceptrów Michaela w myśl reakcji Giesego.[69] Zastosowanie katalizy kompleksami niklu wraz z dodatkiem reduktora pozwoliło poszerzyć zakres o alkeny bogate w elektrony.[70,71] Analogicznej przemianie ulegają również alkiny,[72] natomiast obecność grupy trifluorometylowej skutkuje eliminacją jednego atomu fluoru i utworzenie $=CF_2$ (Schemat 2.23).[73]



Schemat 2.23. Addycja rodników generowanych z soli pirydyniowych do wiązań wielokrotnych.

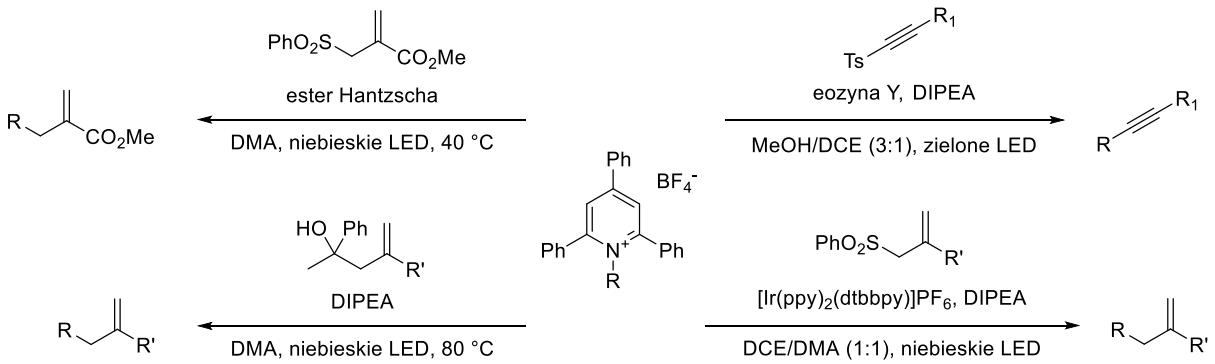
Opracowano również kilka wariantów reakcji typu Hecka. W wyniku zastosowania katalizy fotoredoks udało się selektywnie otrzymać izomery *cis* i *trans* alkenów, jak również wbudować w strukturę cząsteczkę tlenku węgla prowadząc do uzyskania nienasyconych ketonów.[74,75] Następnie podobne produkty uzyskano na drodze reakcji prowadzonych w bardziej klasycznych warunkach (Schemat 2.24).[76,77]



Schemat 2.24. Reakcje typu Hecka z użyciem rodników generowanych z soli pirydyniowych.

Zastosowanie substratów z wiązaniami wielokrotnymi, posiadających odpowiednie grupy odchodzące, pozwalało uzyskać produkty formalnej substytucji. Najczęściej rolę tę spełniały

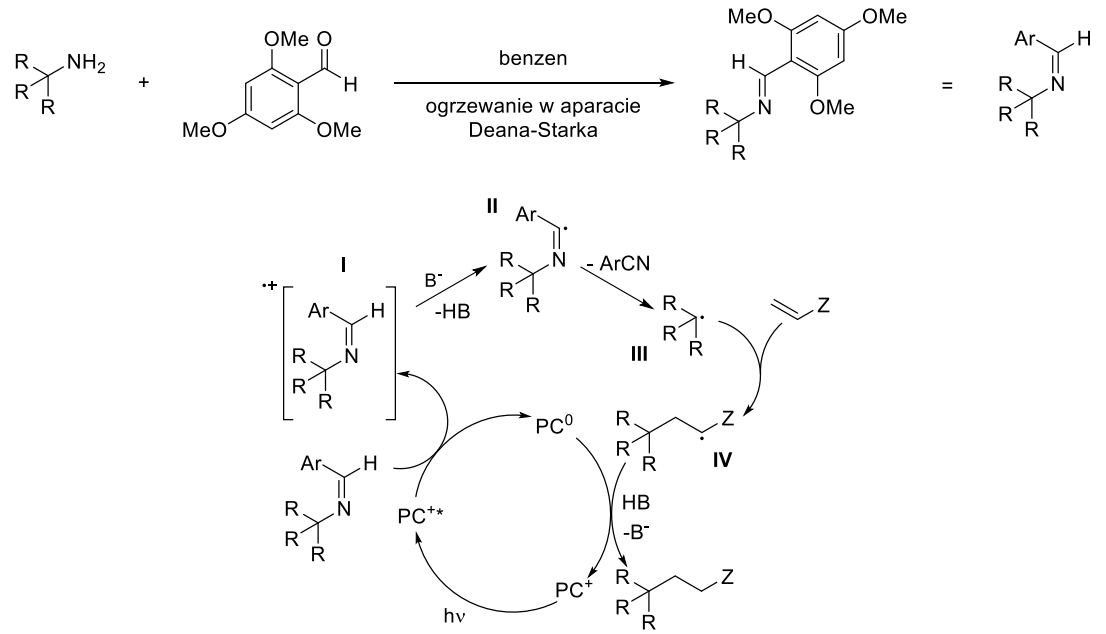
podstawniki sulfonowe,[69,78,79] jednakże wykorzystanie alkoholi homoallilowych prowadziło do wydzielania aromatycznych ketonów z ich struktury (Schemat 2.25).[80]



Schemat 2.25. Reakcje formalnej substytucji z użyciem rodników generowanych z soli pirydyniowych.

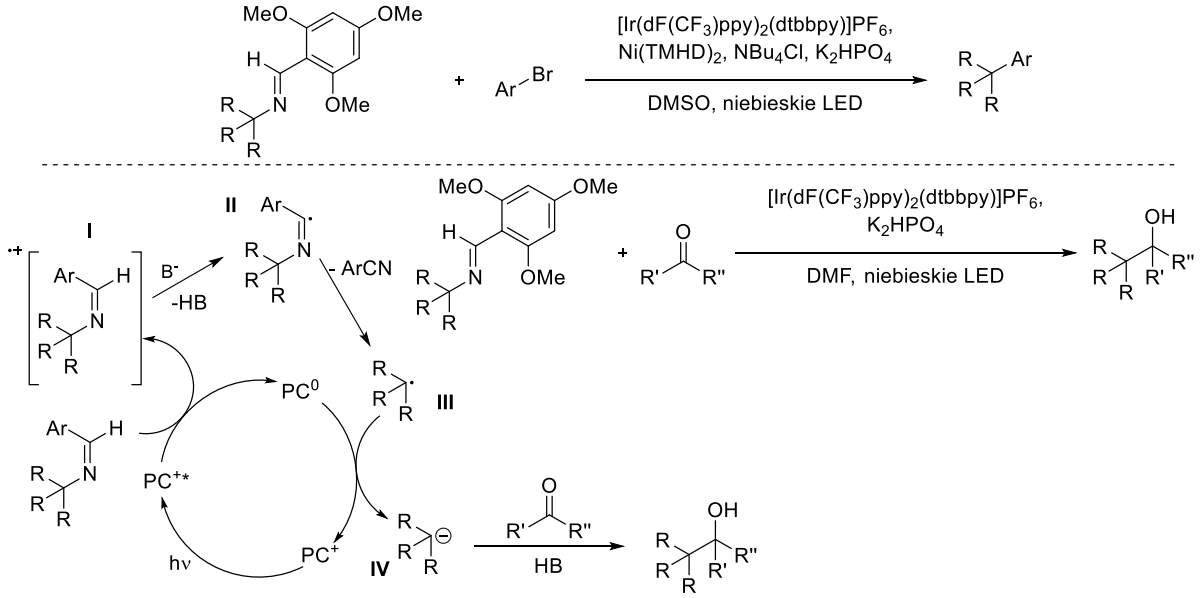
Duża liczba prac dotyczących zastosowania soli pirydyniowych jako prekursorów rodników, opisanych powyżej jak i tych niewspomnianych w tym wstępie, stawia tę metodologię jako jedną z najważniejszych dających dostęp do tych reaktywnych indywiduów. Nie oznacza to jednak, że procesy te nie mają ograniczeń. Najważniejsze z nich dotyczy dostępnych substratów. Metoda ta nie pozwala bowiem na generowanie rodników trzeciorzędowych. Stanowiące ich prekursor aminy cechują się zbyt dużą zawadą steryczną by kondensować z solami piryliowymi.[81] Ponadto, redukujące warunki konieczne do generowania rodników z soli pirydyniowych uniemożliwiają zastosowanie silnych utleniaczy w tych procesach, gdyż te zostałyby zredukowane jako pierwsze. Właściwości takie często posiadają silne czynniki elektrofilowe, stosowane do reakcji z nukleofilowymi rodnikami alkilowymi.

Rozwiązanie obu tych niedogodności przyniosła nowa metoda deaminatywnego generowania rodników.[82] Wykorzystuje ona substraty, w których grupa aminowa połączona jest właśnie z trzeciorzędowym atomem węgla. W ramach prefunkcjonalizacji poddaje się je kondensacji z bogatymi w elektrony aldehydami aromatycznymi. Utworzone w ten sposób iminy podatne są na utlenienie, np. przy pomocy fotokatalizatora o odpowiednio wysokim potencjale. Powstaje wówczas kationorodnik **I**, którego tworzeniu towarzyszy znaczne zwiększenie kwasowości benzylowego atomu wodoru. Wobec stosowanej w reakcji zasady następuje zatem deprotonowanie prowadzące do rodnika iminoilowego **II**. W obecności rozbudowanej przestrzennie grupy trzeciorzędowej indywidua te ulegają łatwo procesowi β-rozszczepienia, czyli rozpadowi z wytworzeniem nitrylu aromatycznego i rodnika alkilowego **III**. Ten oczywiście ulegać może całej gamie procesów charakterystycznych dla tych indywiduów. W oryginalnej publikacji autorzy przeprowadzili ich addycję do akceptorów Michaela, uzyskując po redukcji nasycone produkty (Schemat 2.26).



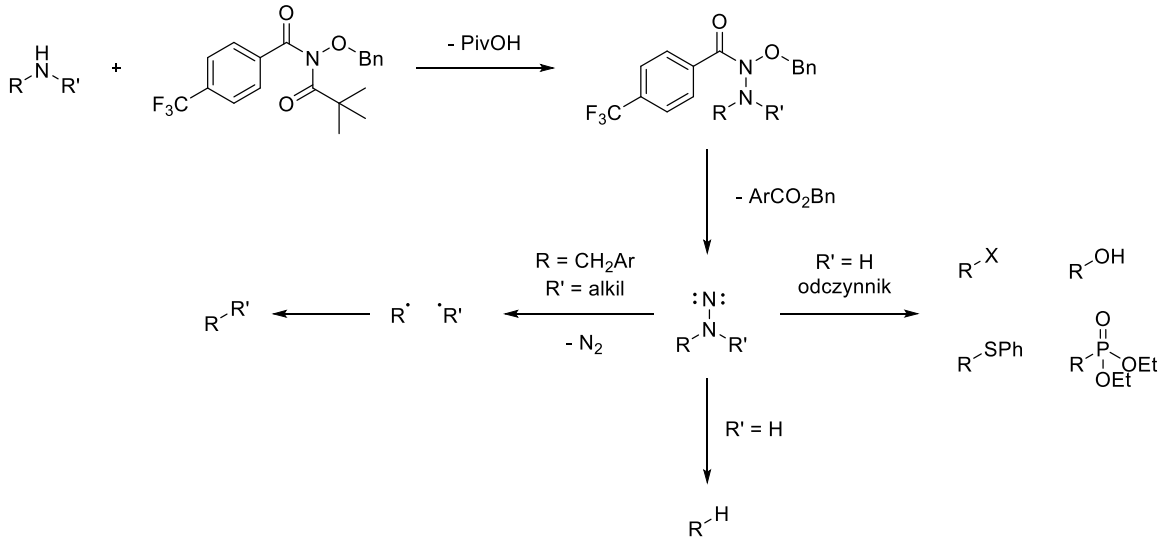
Schemat 2.26. Metoda generowania trzeciorzędowych rodników alkilowych z amin.

Klasycznie, opracowanie nowej metody generowania rodników skutkowało dalszymi pracami rozszerzającymi jej zastosowania. Niedługo później autorzy opracowali metodę sprzęgania otrzymywanych rodników z halogenkami arylowymi. Wymagało to zastosowania kompleksów niklu z ligandami lepiej sprawdzającymi się ze stanowiącymi znaczną zawadę steryczną grupami trzeciorzędowymi.[83] Niedawno odkryto, że wobec odpowiednich podstawników otrzymywane rodniki trzeciorzędowe mogą zostać przekształcone w karboaniony przy udziale zredukowanej formy fotokatalizatora. Chociaż substrat musi zawierać co najmniej jedną grupę arylową bądź estrową, metoda ta pozwala w łagodnych warunkach generować trudno dostępne trzeciorzędowe karboaniony. Oczywiście ulegają one reakcjom z obecnymi w układzie elektrofilami, najczęściej związkami karbonylowymi (Schemat 2.27).[84]



Schemat 2.27. Zastosowanie rodników generowanych z imin.

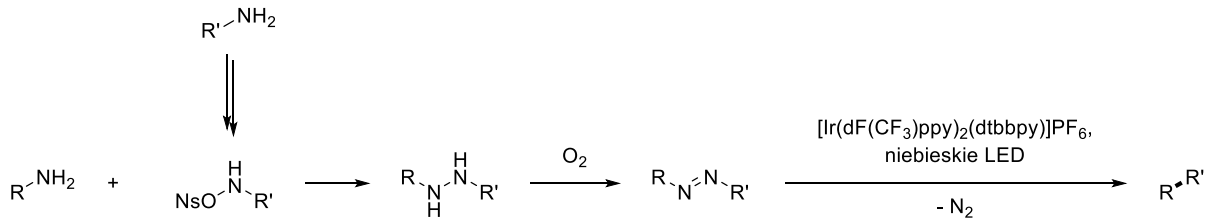
Omówione metody pozwalają zatem na generowanie rodników alkilowych z amin o dowolnej rzędowości atomu węgla. Wymagają one jednak ich prefunkcjonalizacji – dodatkowego etapu w syntezie, który przekształca substrat w formę aktywną w procesie. Jednakże w 2021 r. opracowano rozwiązanie umożliwiające zastosowanie amin bezpośrednio w reakcji. Odpowiednio zaprojektowany anomeryczny amid wchodzi z nimi w cykl przemian prowadzący do generowania rodników. Początkowo, amina podstawia anion kwasu piwalowego w wyniku substytucji nukleofilowej. Utworzony produkt przejściowy ulega następnie reduktywnej eliminacji estru z atomu azotu. W jej wyniku tworzy się niestabilny izodiazen, którego reaktywność bardzo zależy od podstawników alkilowych. Może on bowiem dimeryzować lub, w wariancie bardziej interesującym, ulec rozpadowi na rodniki z wydzieleniem cząsteczki azotu. Ten scenariusz wymaga pewnej stabilizacji tych reaktywnych indywiduów, np. przez sąsiednie grupy arylowe. Może jednak prowadzić do bardzo ciekawych przekształceń. Najważniejszym z nich wydaje się rekombinacja dwóch tworzonych w sąsiedztwie rodników. Formalnie więc, jest to proces prowadzący do usunięcia atomu azotu z aminy drugorzędowej i połączenia grup alkilowych.[85] Z kolei aminy pierwszorzędowe, nawet te niepozwalające na utworzenie stabilizowanych rodników, ulegają w tych warunkach redukcji do alkanu.[86] Zastosowanie w środowisku reakcji odpowiednich odczynników pozwala jednak wyłapać tworzące się z nich rodniki i utworzenie halogenków alkilowych, alkoholi, tioeterów czy fosfonianów (Schemat 2.28).[87] Synteza anomerycznego amidu pozwalającego na przeprowadzenie wszystkich tych użytecznych przekształceń została zoptymalizowana i opisana na łamach *Organic Synthesis*.[88]



Schemat 2.28. Procesy deaminatywne z użyciem anomerycznego amidu.

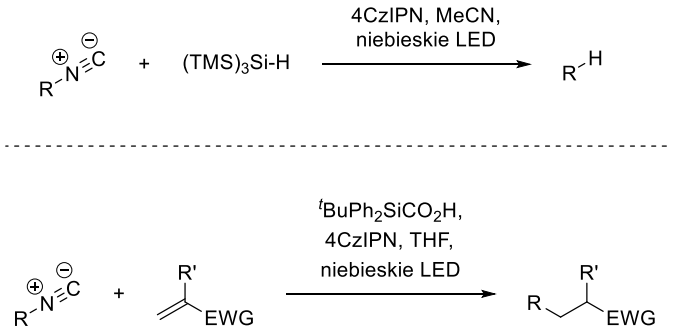
W 2023 r. została opublikowana kolejna metoda wykorzystująca sprzęganie rodników utworzonych z diazenów, którą można uznać za formalne sprzęganie grup alkilowych pochodzących z dwóch amin. W tym celu jedną z nich trzeba przekształcić w sól nosylohydroksyloaminy. Jest ona aktywna w reakcjach substytucji nukleofilowej, w tym ulega podstawieniu grupy nosylowej przez inną aminę. Utworzona w tym procesie pochodna hydrazyny ulega utlenieniu tlenem atmosferycznym do diazenu. W celu jego rozpadu na rodniki autorzy zastosowali transfer energii z fotokatalizatora irydowego. Utworzone w tym procesie indywiua ulegają rekombinacji z utworzeniem nowego wiązania C-C (Schemat

2.29). Znaczącą wadą metody jest aż czteroetapowy proces syntezy pochodnej nosylohydroksyloaminy z wyjściowej aminy.[89]



Schemat 2.29. Formalne sprzęganie rodników generowanych z amin.

Rodniki alkilowe wygenerowano również z izonitryli w warunkach fotokatalitycznych. W przypadku uwodornienia z użyciem silanów substrat ulegał bezpośredniej redukcji wzbudzoną formą katalizatora do jonu cyjankowego i rodnika. Ten z kolei przyłączał atom wodoru. [90] W przypadku drugiej reakcji, przemianę rozpoczynało utlenienie i dekarboksylacja kwasu skutkujące generowaniem rodnika sililowego. Ten ulegał addycji do izonitrylu, a powstały addukt ulegał następczemu β-rozpadowi. Utworzony rodnik alkilowy zastosowano do addycji do akceptorów Michaela (Schemat 2.30).[91]



Schemat 2.30. Reakcje wykorzystujące generowanie rodników alkilowych z izonitryli.

7.2.6 Podsumowanie

Stabilizowane karbokationy oraz rodniki stanowią bardzo ważne i często wykorzystywane indywidua w chemii organicznej. Badania nad nimi mają długą historię, która doprowadziła do zastosowania ich w wielu procesach, w tym tych prowadzonych w skali wielkotonażowej. Mimo to wciąż możliwe do znalezienia są obszary tych metodologii, które wydają się niedostatecznie zbadane.

Do najważniejszych na pewno można zaliczyć przemiany deaminatywne. Zastosowanie amin jako alifatycznych bloków budulcowych jest ogólnie bardzo ograniczone i tyczy się to również przemian przebiegających przez stadium karbokationów czy rodników. Szczególnie ta pierwsza grupa reakcji jest bardzo rzadko wykorzystywana. Do niedawna znane były niemal wyłącznie specjalne przypadki reakcji diazowania zachodzące jedynie dla substratów o specyficznej budowie. Ostatnie lata przyniosły zastosowanie karbokationów generowanych z amin do alkilowania kilku grup związków posiadających wiązanie X-H o odpowiedniej kwasowości. Jednakże reakcje te nie pozwalają np. tworzyć nowych wiązań C-C.

Dużo lepiej reprezentowane są procesy deaminatywne przebiegające przez stadium rodników. Szczególnie ostatnia dekada przyniosła ogromny postęp w tej dziedzinie. Opracowano wówczas kilka sposobów pozwalających na uzyskanie rodnika z aminy oraz ich dalsze, liczne zastosowania. Mimo rozbudowanej metodologii oraz często bardzo łagodnych warunków przemiany, podstawową wadą tych procesów wydaje się ekonomia atomowa. Szczególnie w dzisiejszych czasach, staje się to istotnym zagadnieniem. Niestety opracowane metody wymagają prefunkcjonalizacji aminy rozbudowanymi reagentami bądź zastosowania ich w środowisku reakcji. Często konieczne jest również zastosowanie wielu odczynników w tych procesach.

Niemal idealnym rozwiązaniem wspomnianych reakcji wydaje się opracowanie syntetycznie użytecznego wariantu diazowania amin alifatycznych. Choć prace tego typu prowadzono już niemal półtora wieku temu, wciąż nie przyniosły one pożądanego rozwiązania, a reakcje tego typu traktowane są jako nieselektywne. Jednakże ich wydajne prowadzenie dałoby bardzo łatwy dostęp do karbokationów z amin oraz posiadałoby szereg dalszych zalet. Wśród nich wymienić należy chociażby stosunkowo wysoką ekonomię atomową procesu diazowania.

Ponadto istnieją pojedyncze przekształcenia, które wydają się niedostatecznie zbadane mimo swojego potencjału. Często wiąże się ono z potrzebami chemii medycznej, biorąc pod uwagę biologiczną aktywność amin. Inną grupą ważnych związków bioaktywnych są fluoropochodne. Jednakże mimo potencjału przekształcenia grupy aminowej we fluorek znane są jedynie pojedyncze metody to umożliwiające.

Zagadnieniem o dużej wartości wydaje się być również zastąpienie procesów przebiegających przez stadium karbokationów rodnikowymi i odwrotnie. Przeciwne właściwości tych indywiduów dają potencjał do rozbudowy tej samej cząsteczki o fragment pochodzący od nukleofila bądź elektrofila w zależności od wybranej drogi.

7.3. Badania własne

Celem mojej pracy było opracowanie nowych, użytecznych przekształceń w chemii organicznej, wykorzystujących stabilizowane karbokationy bądź rodniki alkilowe. Choć historia badań nad tymi indywiduami trwa już przeszło sto lat wciąż istnieją możliwości opracowania ważnych metod syntetycznych. Pewne przekształcenia wciąż pozostają nieznane, lub mogą być rozszerzone na nowe grupy substratów bądź produktów. Coraz większe skomplikowanie struktur środków aktywnych biologicznie wymusza opracowywanie selektywnych reakcji prowadzonych w łagodnych warunkach. Optymalnie powinny one tolerować wiele grup funkcyjnych i być możliwe do zastosowania w ostatnich etapach syntezy pożądanego związku. Z kolei trend dążenia ku zielonej chemii ogranicza ilość i właściwości używanych odczynników. Ważna jest też jak najlepsza ekonomia atomowa opracowywanych przemian. Z kolei możliwość przyłączenia różnych syntonów do tej samej struktury poprzez umiejętne manipulowanie procesami rodnikowymi i kationowymi wydaje się użytecznym narzędziem o niezbadanym jeszcze potencjale.

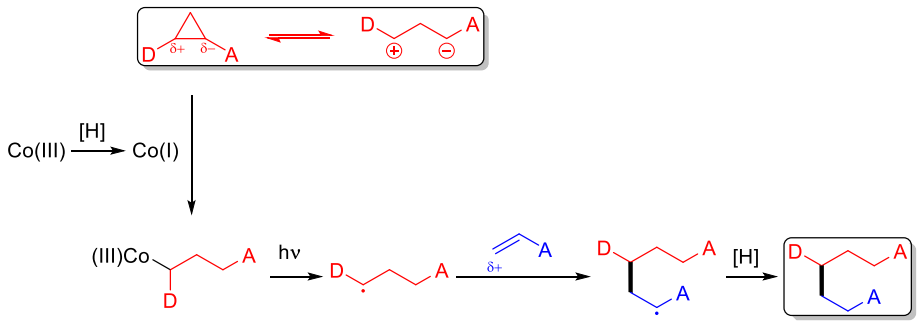
W prowadzonych badaniach pomogło mi napisanie wraz z dr Joanną Turkowską artykułu przeglądowego porównującego reaktywność diazo związków w metodach klasycznych np. z wykorzystaniem kompleksów metali przejściowych i w wyniku ich naświetlania. Ta klasa związków daje łatwy dostęp do wielu aktywnych indywiduów. Oprócz karbenów, mogą to być również rodniki i karbokationy. Szczególnie te ostatnie są blisko związane z diazo związkami. Ich protonowanie prowadzi do alkilowej soli diazoniowej, która natychmiast wydziela cząsteczkę azotu tworząc kation. Często taki właśnie mechanizm mają reakcje C-H insercji.

J. Durka, J. Turkowska, D. Gryko *ACS Sustainable Chem. Eng.* **2021**, *9*, 8895−8918

Lightening Diazo Compounds?

7.3.1 Odwrócenie standardowej reaktywności cyklopropanów donorowo-akceptorowych

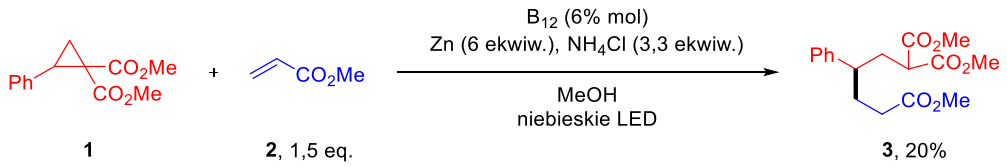
Cyklopropany donorowo-akceptorowe posiadają szczególnie słabe wiązanie C-C ze względu na kombinację dwóch czynników: naprężenia oraz obecności podstawników o przeciwstawnych właściwościach. Powodują one silną polaryzację, której skrajność przedstawia struktura rezonansowa, w której wiązanie jest rozerwane z przeniesieniem pary elektronowej na atom z podstawnikami elektronoakceptorowymi. Wobec tego na drugim atomie węgla powstaje stabilizowany karbokation. Choć w rzeczywistości centralne wiązanie C-C jest obecne w strukturach substratów, to jednak atom węgla z podstawnikami elektronodonorowymi posiada cząstkowy ładunek dodatni, a zatem jednoznacznie elektrofilowy charakter. Wspólnie z dr Joanną Turkowską podjęliśmy się próby opracowania metody funkcjonalizacji cyklopropanów donorowo-akceptorowych odwracających ich standardową reaktywność. Naszym celem było przyłączenie typowego elektrofila, jakim jest akceptor Michaela, do atomu węgla z podstawnikiem elektronodonorowym. Kluczem do odwrócenia tej standardowej reaktywności okazało się zastosowanie katalizy witaminą B_{12}. W środowisku redukującym przechodzi ona w formę z atomem kobaltu na I stopniu utlenienia, o silnych właściwościach nukleofilowych. Zatem reakcja z cyklopropanem donorowo-akceptorowym prowadzi do ataku na atom węgla z grupą EDG, otwarcia pierścienia i utworzenia wiązania Co-C. Pod wpływem światła lub ciepła ulega ono następczemu, homolitycznemu rozerwaniu. Wobec tego na atomie połączonym z grupą elektronodonorową tworzy się rodnik. W ten sposób następuje odwrócenie reaktywności początkowo elektrofilowego centrum cząsteczki. Wchodzi ono zatem w reakcję addycji do akceptora Michaela, a następcza redukcja rodnika prowadzi do utworzenia pożądanego produktu (Schemat 3.1).



Schemat 3.1. Odwrócenie reaktywności cyklopropanów donorowo-akceptorowych.

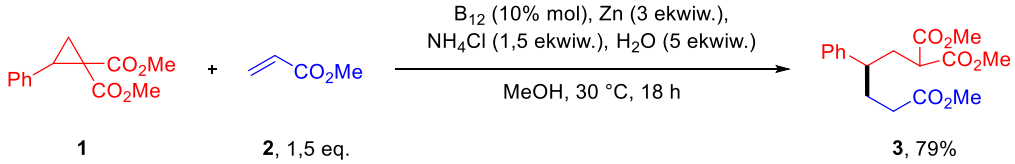
Badania rozpoczęliśmy od wstępnych eksperymentów, które potwierdziły, że założony proces ma szansę sprawdzić się w rzeczywistości. Już w pierwszej reakcji cyklopropanu **1** z akrylanem metylu **2**, udało się uzyskać pożądany produkt **3** z wydajnością 20% (Schemat 3.2). Zastosowaliśmy witaminę B_{12} jako katalizator oraz standardowo stosowany układ cynku i chlorku amonu do jej redukcji. Reakcja prowadzona była w metanolu i naświetlana niebieskim światłem. Eksperymenty kontrolne wykazały, że w przeciwieństwie do pozostałych, ten ostatni czynnik nie jest konieczny do zajścia procesu. Choć reakcja

nienaświetlana cechowała się wydajnością zaledwie 9%, oznacza to, że wiązanie Co-C ulega rozerwaniu również pod wpływem energii pobieranej jako ciepło.



Schemat 3.2. Eksperyment wstępny.

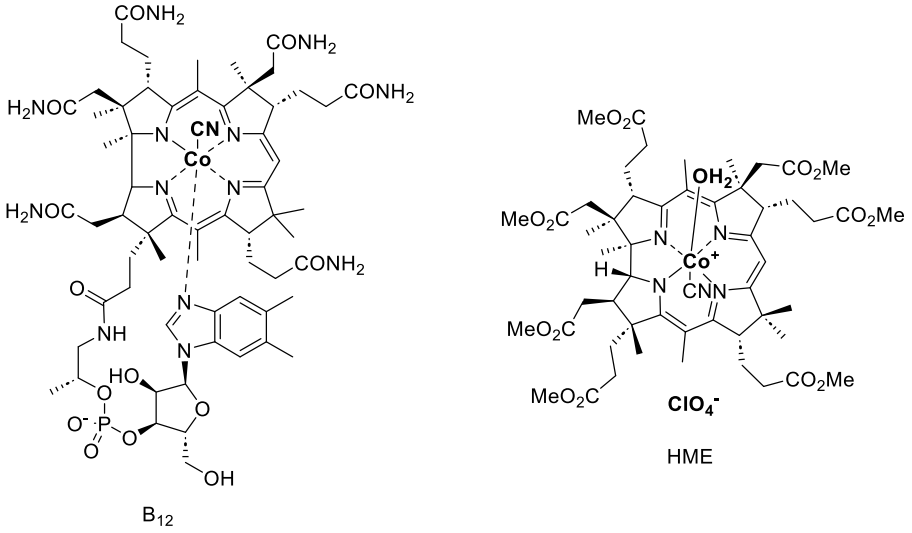
Następnie zajęliśmy się optymalizacją warunków prowadzenia procesu, wybierając opisaną reakcję jako modelową. Stosowane już w pierwszych eksperymentach reagenty okazały się najlepiej sprawdzać w swoich rolach, zmianie uległy jedynie ich ilości. Duży wzrost wydajności przyniosło zastosowanie większej ilości akrylanu metylu. Korzystniejsze względem naświetlania reakcji okazało się prowadzenie jej w temperaturze podwyższonej do zaledwie 30 °C. Znaczący wpływ okazał się mieć również dodatek niewielkiej ilości wody, prawdopodobnie ze względu na ułatwienie protonowania koniecznego do utworzenia produktu. W zoptymalizowanych warunkach produkt udało się uzyskać z wydajnością 79% (Schemat 3.3).



Schemat 3.3. Zoptymalizowana reakcja modelowa.

Następnie przystąpiłem do zbadania zakresu stosowalności metody pod kątem akceptorów Michaela. Niestety, większość zbadanych w początkowym etapie substratów nie wykazywała pożądanej reaktywności. Spośród 6 związków, oczekiwane produkty udało się uzyskać jedynie w przypadku dwóch pochodnych z grupą amidową. Co istotne, w przypadkach, gdzie nie udało się otrzymać produktu, cyklopropan pozostawał nieprzereagowany. Poczynione obserwacje wyglądu reakcji w trakcie jej trwania wraz z wykryciem w mieszaninie poreakcyjnej adypinianu dimetylu pozwoliły mi zdiagnozować potencjalny problem. Zgodnie z proponowanym mechanizmem cyklopropan powinien ulegać reakcji szybciej niż akceptor Michaela, którego przyłączenie następować ma w końcowym etapie. Jednakże obecność nieprzereagowanego substratu oraz adypinianu dimetylu, produktu redukcyjnej dimeryzacji akrylanu metylu, w mieszaninie poreakcyjnej świadczyły, że jest wręcz odwrotnie. Akceptory Michaela, w przypadku których nie udało mi się uzyskać produktów, ulegały reakcji ze zredukowaną witaminą B_{12} szybciej niż cyklopropan. W związku z tym sprawdziłem kilka czynników mogących mieć wpływ na wydajność przemiany, takich jak aktywność cynku, katalizatora czy rodzaj rozpuszczalnika, pochodną witaminy B_{12} – heptametyloester (HME) w roli katalizatora. Okazało się, że reakcja z metakrylanem metylu w obecności tego związku daje produkt z wydajnością aż 78%. Wyjaśnienie powodów takiej różnicy w aktywności katalitycznej przynosły badania kinetyczne przeprowadzone wraz z dr Turkowską. Wykazały one, że dla wszystkich zbadanych akceptorów Michaela reakcja zachodziła szybciej, gdy jako katalizator zastosowany został HME, a więc pochodna witaminy B_{12} posiadająca grupy estrowe zamiast amidowych oraz pozbawiona pętli nukleotydowej. (Rysunek 3.1). Jak

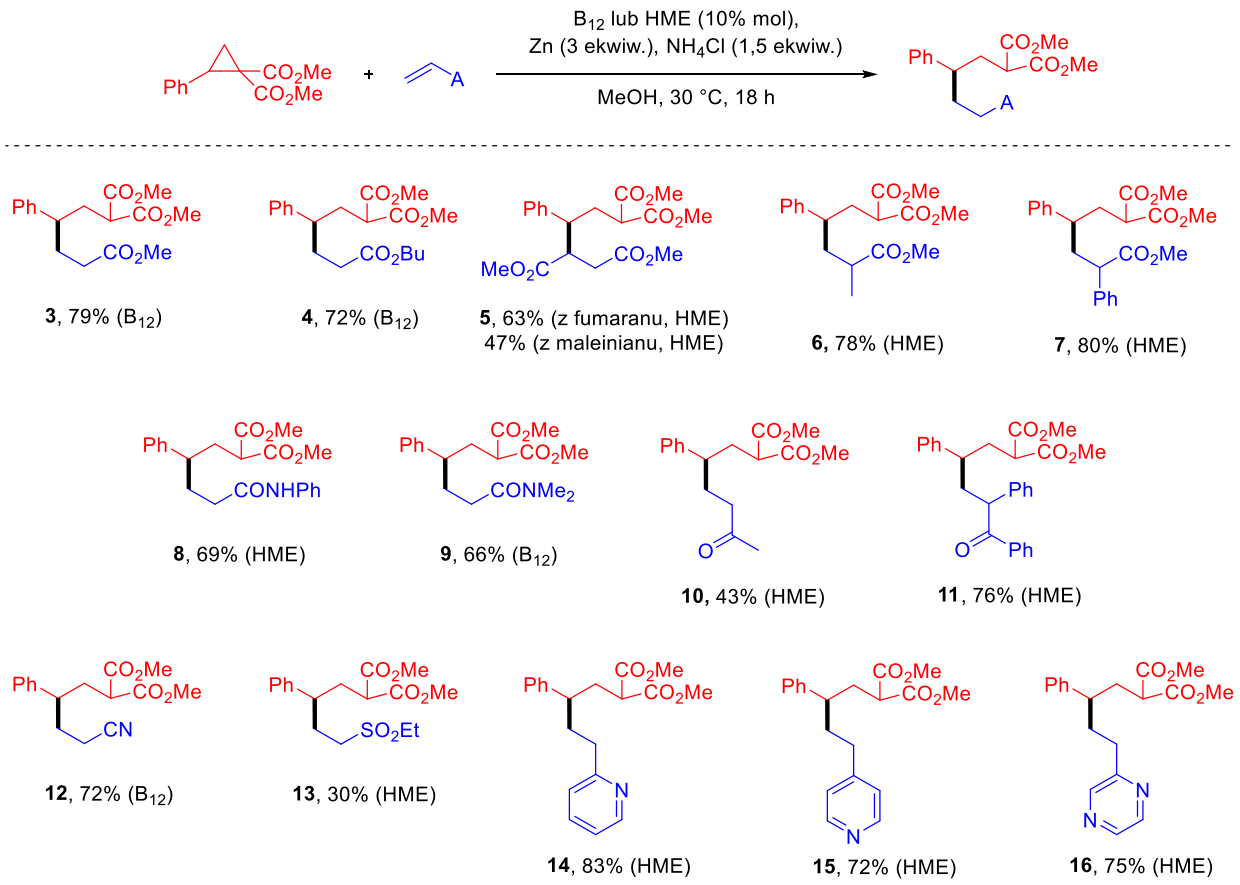
wykazano, różnice w kompleksowaniu centralnego atomu kobaltu mogą mieć duży wpływ na wynik reakcji. Często katalizatory pozbawione pętli nukleotydowej pozwalają na lepszą kontrolę procesu i ograniczenie reakcji ubocznych.[92]



Rysunek 3.1. Witamina B_{12} i jej pochodna heptametyloester (HME).

Wobec powodzenia procesu z użyciem HME sprawdziłem inne, poprzednio testowane akceptory. We wszystkich przypadkach produkt tworzył się, ale z różną efektywnością. Reakcje z akceptorami Michaela o większej masie cząsteczkowej wykazywały podobny przebieg reakcji jak metakrylan metylu - bardzo dobre wydajności przy użyciu HME, natomiast całkowity brak konwersji cyklopropanu w przypadku katalizy witaminą B_{12}. Dodatkowo sprawdziłem butenon, który również pozwolił na uzyskanie produktu. Bardzo dobre wyniki uzyskałem dla winylowych pochodnych azotowych związków heteroaromatycznych. Produkt zawierający pierścień pirydyny uzyskałem z wydajnością 83%, a więc przekraczającą wartość uzyskaną dla reakcji modelowej.

Sumarycznie udało mi się otrzymać 14 produktów z różnymi akceptorami Michaela z dobrymi wydajnościami (Schemat 3.4). Posiadają one w swojej strukturze większość najważniejszych ugrupowań elektronoakceptorowych.



Schemat 3.4. Zakres stosowalności akceptorów Michaela. Katalizator: B_{12} – witamina B_{12}, HME – heptametyloester (HME). W reakcjach z użyciem witaminy B_{12} stosowano dodatek 5 ekwiw. wody.

Uzyskane wyniki zostały opisane w artykule naukowym:

J. Turkowska ‡, J. Durka ‡, M. Ociepa, D. Gryko *Chem. Commun.*, **2022**, *58*, 509-512

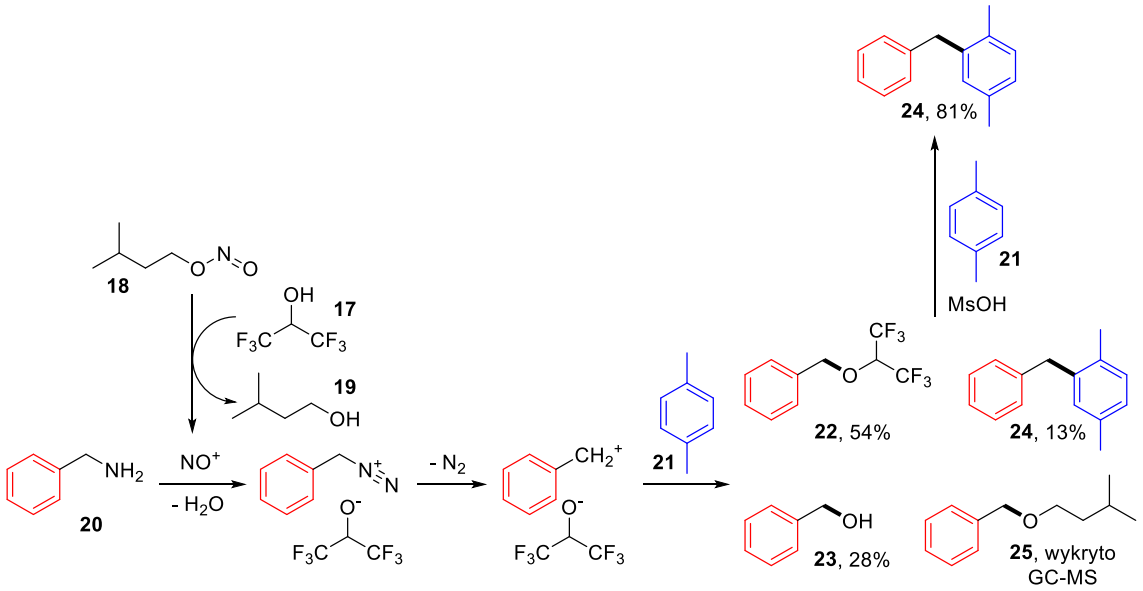
Reversal of regioselectivity in reactions of donor–acceptor cyclopropanes with electrophilic olefins

7.3.2 Użyteczna syntetycznie metoda diazowania amin alifatycznych

W dalszej części swoich badań zainteresowałem się zastosowaniem amin jako alifatycznych bloków budulcowych. Po wielomiesięcznych badaniach nad różnymi wariantami deaminatywnego halogenowania, moją uwagę przyciągnęło diazowanie. We wstępie literaturowym opisałem powody, dla których reakcja ta nie znalazła syntetycznego znaczenia.

Dobrze udokumentowano, że fluorowane alkohole mogą dramatycznie wpływać na wyniki reakcji chemicznych, działając między innymi jako łagodne katalizatory kwasowe lub stabilizując pośrednie karbokationy.[11] Efekty ich działania okazały się bardzo zbieżne z warunkami poprawy selektywności procesu diazowania. Założyłem zatem, że efektywność tej reakcji można znacznie poprawić stosując 1,1,1,3,3,3-heksafluoroizopropanol (HFIP, **17**), jako rozpuszczalnik. Zapewnia on bardzo dobrą stabilizację karbokationów,[11] dlatego był on często stosowany w reakcjach wykorzystujących te reaktywne indywidua.[93–97] Ze względu na kwasowość HFIP (pK_a = 9,3) powinien ułatwić generowanie kationu nitrozoniowego z azotynu alkilu (**18**). W konsekwencji byłby on jedynym odczynnikiem w reakcji, oprócz aminy, ograniczając w ten sposób liczbę nukleofili obecnych w roztworze. HFIP nie tylko sam w sobie wykazuje bardzo niską nukleofilowość, ale jest także zdolny do zmniejszania nukleofilowości innych związków obecnych w roztworze, z którymi tworzy wiązania wodorowe.[98] Jest to szczególnie istotne, ponieważ całkowita eliminacja nukleofili z reakcji diazowania jest niemożliwa z definicji: alkohol jest produktem ubocznym powstającym z azotynu, a podczas reakcji uwalnia się 1 ekwiwalent wody. Ponadto wiadomo, że HFIP ułatwia katalizowane kwasem rozszczepianie wiązania C-O, prowadzące do utworzenia karbokationu.[94,99,100] Przywidywałem, że cecha ta okaże się istotna aby przekształcić produkty uboczne, powstałe w reakcji z tlenowymi nukleofilami (HFIP, alkohol, woda), w pożądany, po dodaniu kwasu.

Aby zweryfikować postawioną hipotezę, przeprowadziłem reakcję modelową benzyloaminy (**20**) z azotynem izopentylu (**18**) i *p*-ksylenem (**21**) w HFIP, która pozwoliła otrzymać, zgodnie z przewidywaniem, pożądany produkt alkilowania Friedela-Craftsa (**24**), ale z niską wydajnością (13%). Eter benzylowy HFIP (**22**, 54%) i alkohol benzylowy (**23**, 28%) powstały w większych ilościach (Schemat 3.5). Przytoczone wyniki eksperymentalne wskazują, że kwasowość samego HFIP jest wystarczająca do całkowitej konwersji aminy bez konieczności dodawania nawet katalitycznej ilości kwasu. W konsekwencji diazowanie można przeprowadzić w łagodnych warunkach, ograniczając powstawanie produktów ubocznych, takich jak nitrozoareny.



Schemat 3.5. Reakcja modelowa.

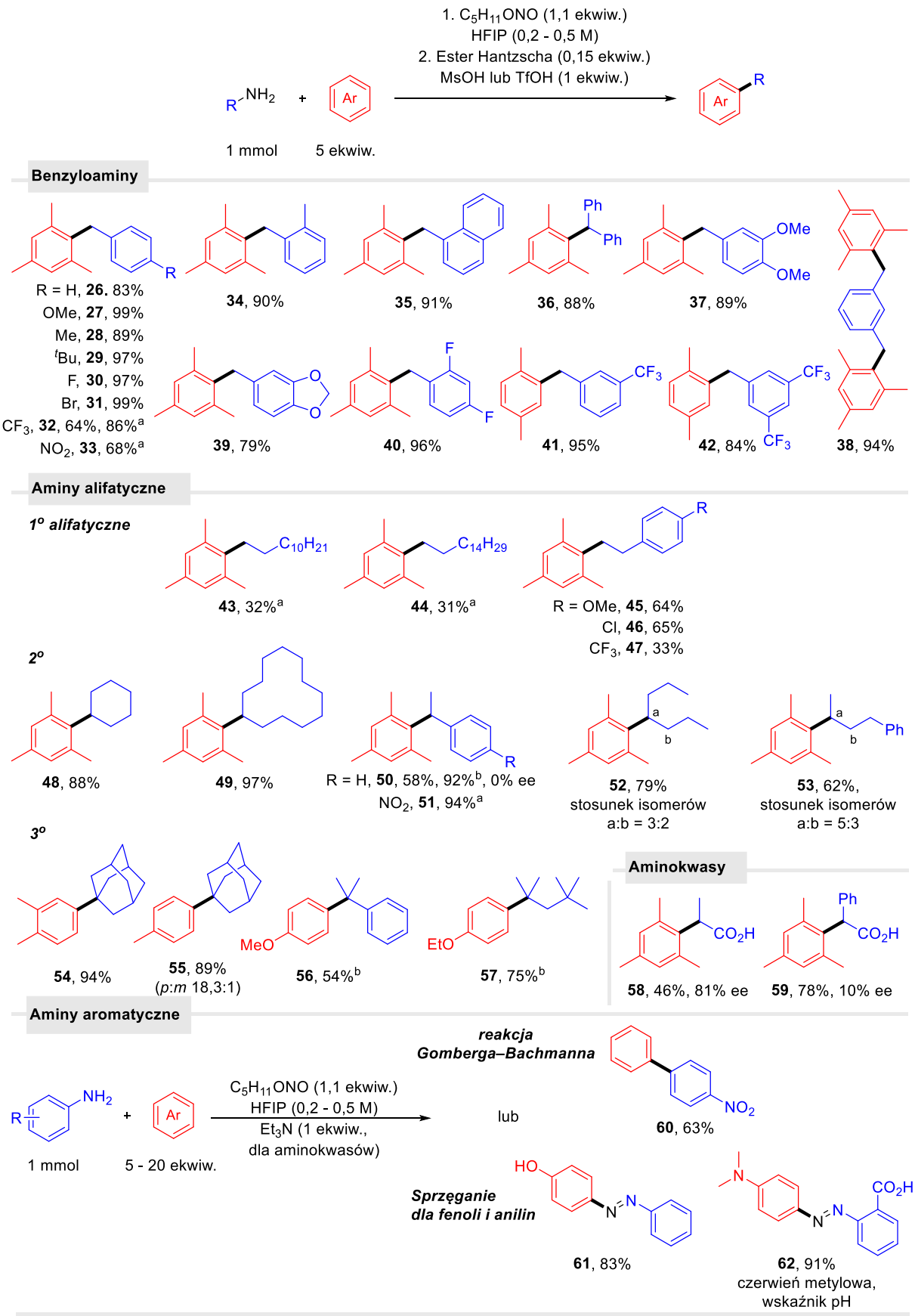
Ponadto, znaczenie kwasowości HFIP potwierdzają wyniki uzyskane dla reakcji modelowej w innych alkoholach. Po czasie, gdy reakcja w HFIP zakończyła się, nie zaobserwowano praktycznie żadnej konwersji w mniej kwaśnym trifluoroetanolu (pK_a = 12,5), podczas gdy diazowanie w etanolu w ogóle nie zachodzi.

Powstałe produkty są stabilne w środowisku reakcji, jak wykazały przeprowadzone badania kinetyczne. Jednakże dobrze udokumentowany jest fakt, że HFIP znaczenie ułatwia katalizowane kwasowo procesy wykorzystujące alkohole i etery. Zatem, aby umożliwić alkilowanie Friedela-Craftsa z użyciem powstałych eterów, konieczne wydawało się dodanie kwasu. Rzeczywiście, dodanie kwasu metanosulfonowego zwiększyło wydajność do 70%.

W następnym etapie badań, podjąłem się krótkiej optymalizacji reakcji modelowej. Największy wpływ na uzyskiwaną wydajność miał stosowany nadmiar związku aromatycznego. Typowo dla reakcji Friedela-Craftsa odpowiada on za eliminację reakcji następczego alkilowania produktu.

Następnie zbadałem zakres stosowalności alkilowania Friedela-Craftsa z użyciem amin (Schemat 3.6). Najlepszą grupę substratów stanowiły benzyloaminy. Produkty z bardzo dobrymi wydajnościami udało się uzyskać nawet dla bardzo zubożonych w elektrony pochodnych (**33**, **42**).

Co ważne, produkty udało się uzyskać nawet z amin będących prekursorami niestabilizowanych, pierwszorzędowych karbokationów (**43**, **44**). W ich przypadku do diazowania zastosowano kwas octowy. Znacznie większa nukleofilowość anionu octanowego względem HFIP pozwoliła uniknąć eliminacji i przegrupowań bardzo niestabilnego kationu pierwszorzędowego, a produkt dużo łatwiej odtwarza to reaktywne indywiduum po dodaniu kwasu niż eter HFIP. Dużo lepiej sprawdziły się fenyloetyloaminy, tworząc odpowiednie produkty z dobrymi wydajnościami. Przewagę generowania karbokationów w wyniku diazowania potwierdza synteza produktu **47** z grupą wyciągającą elektrony w pierścieniu fenylowym, który nie jest dostępny w metodach wykorzystujących alkohole jako substraty.[100]



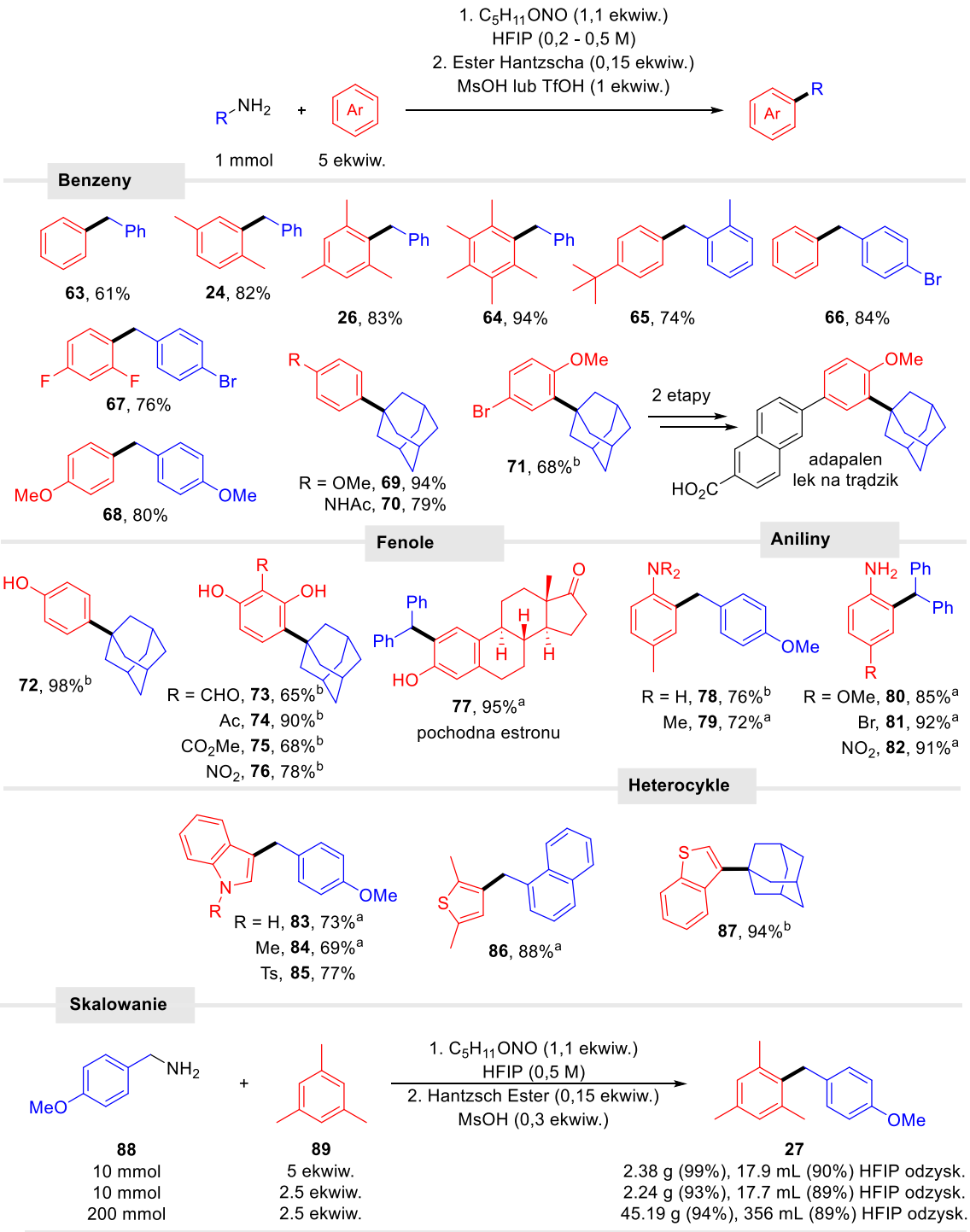
Schemat 3.6. Zakres stosowalności amin. a - diazowanie z użyciem AcOH zamiast HFIP. b - dodatek 1 ekwiw. Et_3N.

Aminy α-drugorzędowe również dobrze się sprawdziły w roli substratów, szczególnie te cykliczne. Ponadto, funkcjonalizacja arenów trzeciorzędowymi karbokationami jest również możliwa, co ilustrują reakcje z adamantyloaminą. Substraty liniowe wymagały dodania NBu_4Br (1 ekwiw.), aby uzyskać dobre wydajności produktów alkilowania poprzez zatrzymanie reakcji ubocznej oligomeryzacji alkenu.

Choć dla aminokwasów reakcje diazowania można przeprowadzić z syntetycznie użytecznymi wydajnościami, opracowane warunki umożliwiły zastosowanie ich w reakcji z nienaładowanymi, niepolarnymi, węglowymi nukleofilami. Ten sposób umożliwia syntezę kwasów 2-arylokarboksylowych, analogów niesteroidowych leków przeciwzapalnych, z użytecznymi wydajnościami, w jednym etapie. Jednocześnie badania skręcalności optycznej uzyskanych produktów stanowią dowód zmiany mechanizmu tej reakcji w zależności od poziomu stabilizacji generowanego kationu.

Nie ograniczając się do przykładów wymienionych powyżej, przedstawiony sposób diazowania umożliwia przeprowadzenie przemian znanych dla aromatycznych soli diazoniowych w jednym etapie. W zależności od aktywności arenu zachodzi reakcja Gomberga-Bachmanna lub sprzęganie, prowadzące do odpowiednich barwników diazowych.

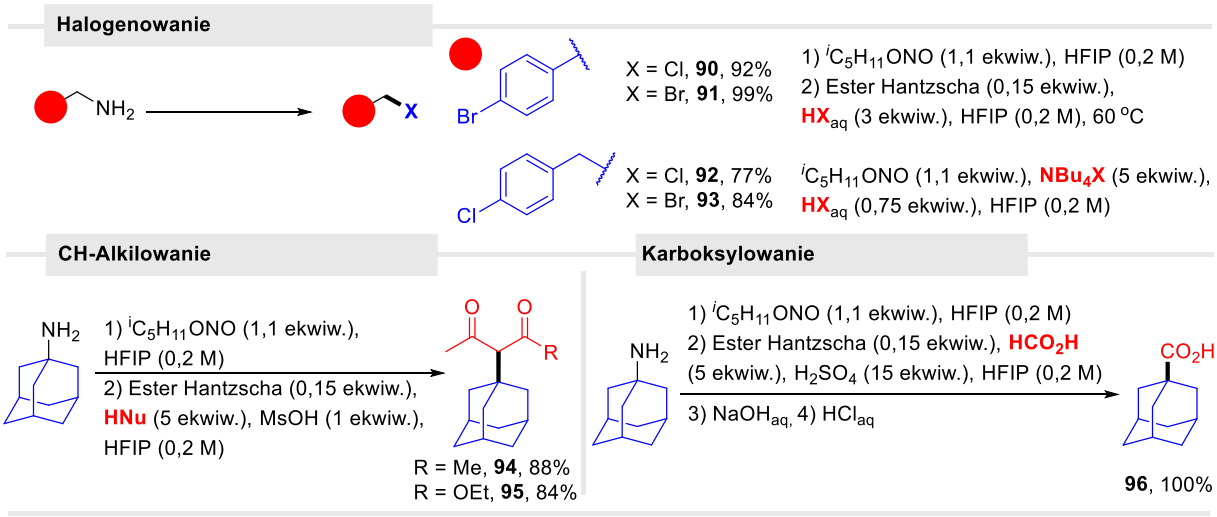
Zbadałem też zakres stosowalności substratów aromatycznych (Schemat 3.7). Typowo dla elektrofilowej substytucji aromatycznej, wraz ze spadkiem nukleofilowości arenu, zmniejsza się skuteczność alkilowania. W tym przypadku jednak nawet dezaktywowany 1,3-difluorobenzen jest wystarczająco reaktywny, aby uzyskać produkt **67**. Obecność dwóch grup hydroksylowych skutecznie neutralizuje dezaktywujący efekt grup wyciągających elektrony, umożliwiając w ten sposób wykorzystanie szerszej grupy arenów. Reakcja jest możliwa w obecności wszystkich głównych grup EWG, nawet wysoce reaktywnej grupy aldehydowej. Ponadto zastosowanie HFIP umożliwia skuteczne alkilowanie anilin pomimo ich zasadowej natury i podatności na diazowanie. Tutaj wykorzystałem możliwość dodawania arenu po etapie diazowania. Oprócz pochodnych benzenu, z powodzeniem zastosowałem również związki heteroaromatyczne. Zarówno *N*-podstawiony, jak i N-H indol dają produkty **83-85** z dobrą wydajnością. Pochodne tiofenu reagują znakomicie.



Schemat 3.7. Zakres stosowalności arenów. a - diazowanie z użyciem AcOH zamiast HFIP. b – aren dodany po diazowaniu.

Aby zademonstrować syntetyczną użyteczność opisywanej metody, syntezę związku **27** przeskalowałem dziesięcio- a następnie dwustukrotnie. Eksperyment w skali 10 mmol wykazał, że zmniejszenie ilości arenu do 2,5 ekwiw. nie wpłynęło znacznie na wydajność reakcji (93% w porównaniu do 99%). Z reakcji w skali 200 mmol pożądany produkt został wyizolowany przez krystalizację (45,2 g, wydajność 94%, czystość 95%) bez pogorszenia selektywności i wydajności. Cenny rozpuszczalnik HFIP został odzyskany przez destylację (89%) i ponownie zastosowany w procesie. Pomimo wydzielania azotu reakcja na taką skalę była słabo egzotermiczna.

Opracowana metodologia nie ogranicza się do alikowania związków aromatycznych, w tę reakcję wchodzą również inne nukleofile (Schemat 3.8). Pochodne acetyloacetonu i acetylooctanu etylu **94**, **95** uzyskano z wysoką wydajnością. Powróciłem też do badanych wcześniej procesów deaminatywnego halogenowania. Dzięki opracowanej metodzie aminy są przekształcane w klasyczne alifatyczne bloki budulcowe przy użyciu najtańszych możliwych środków halogenujących - wodnych kwasów halogenowodorowych. Fenyloetyloaminy dają organiczne halogenki z wysokimi wydajnościami już na etapie diazowania. Karboksylowanie w warunkach reakcji Kocha zostało również pomyślnie przeprowadzone, uzyskując kwas adamantanokarboksylowy (**96**) z ilościową wydajnością po hydrolizie estru heksafluoroizopropylowego. Metoda ta pozwala zatem na przekształcenie aminy w kwas karboksylowy w prosty sposób przy użyciu bardzo tanich substratów.



Schemat 3.8. Dalsze zastosowania procesu.

Podsumowując, opracowałem metodę selektywnego prowadzenia procesu diazowania amin alifatycznych. Poza rozwiązaniem przeszło stuletniego problemu opracowane rozwiązanie niesie za sobą szereg dalszych zalet. Reakcja wykorzystuje aminy, jedne z najbardziej rozpowszechnionych związków organicznych, bez konieczności ich prefunkcjonalizacji. Odznacza się zatem bardzo dobrą ekonomią atomową, co jest bardzo ważne w czasach dążenia do zielonej chemii. Jedynymi produktami ubocznymi opracowanej przemiany są nietoksyczne, małe cząsteczki wody i azotu oraz niewielka ilość utlenionego estru Hantzscha. Reakcja nie wymaga do przeprowadzenia skomplikowanej aparatury, nie jest wrażliwa na wodę ani składniki powietrza. Nie powstają w niej szkodliwe czy żrące gazy, a proces oczyszczania produktu jest prosty. Co również bardzo ważne, opracowana metoda nie wymaga zastosowania żadnych związków metali, które często są toksyczne, drogie, a ich resztki ciężko jest usunąć z produktów farmaceutycznych.

Ze względu na potencjał aplikacyjny opisanego procesu został on objęty zgłoszeniem patentowym. Jednocześnie **uzyskane wyniki zostały opisane w artykule naukowym:**

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Aliphatic Amines Unlocked for Selective Transformations through Diazotization

7.3.3 Podsumowanie

Celem mojej pracy było opracowanie nowych, użytecznych przekształceń w chemii organicznej, wykorzystujących stabilizowane karbokationy bądź rodniki alkilowe. W ramach przeprowadzonych przeze mnie badań:

1) **Opracowałem metodę funkcjonalizacji cyklopropanów donorowo akceptorowych odwracających ich standardową reaktywność.**
   Dzięki temu do dotychczasowego centrum elektrofilowego cząsteczki z powodzeniem przyłączony został cały szereg akceptorów Michaela. Zakres stosowalności metody pozwala na obecność w ich strukturze większości najważniejszych grup elektronoakceptorowych.
2) **Opracowałem użyteczną syntetycznie metodę diazowania amin alifatycznych, która dodaje tę ważną grupę związków do wydajnych prekursorów karbokationów.**
   Mimo upływu niemal półtora wieku od odkrycia reakcji diazowania takie przekształcenie było do tej pory uważane za bezużyteczne w syntezie, jako skutkujące otrzymaniem skomplikowanej mieszaniny produktów. Było to uznane status quo, opisywane w klasycznych podręcznikach do syntezy organicznej. Mi natomiast z powodzeniem udało się uzyskać ok. 70 produktów różnych reakcji deaminatywnych, w większości z bardzo dobrymi wydajnościami. Największą część badań stanowił projekt, w którym aminy były stosowane do alkilowania związków aromatycznych w reakcji typu Friedela-Craftsa. Opracowałem także warunki deaminatywnego chlorowania, bromowania czy karboksylowania.

Uzyskane wyniki znacząco poszerzają zakres wiedzy oraz możliwości wykorzystania stabilizowanych karbokationów i rodników w syntezie organicznej. Stanowią też dobry punkt wyjścia dla opracowywania dalszych procesów wykorzystujących aminy jako alifatyczne bloki budulcowe czy pozwalających na wprowadzenie grup o przeciwnych właściwościach poprzez umiejętne manipulowanie mechanizmem reakcji.

7.4. Bibliografia

(1) Parsaee, F.; Senarathna, M. C.; Kannangara, P. B.; Alexander, S. N.; Arche, P. D. E.; Welin, E. R. *Nat. Rev. Chem.* **2021**, *5* (7), 486–499.

(2) Kreuzer, A.; Kerres, S.; Ertl, T.; Rücker, H.; Amslinger, S.; Reiser, O. *Org. Lett.* **2013**, *15* (13), 3420–3423.

(3) Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3* (9), 1315–1318.

(4) Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem. Int. Ed.* **2007**, *46* (33), 6361–6363.

(5) Sanders, S. D.; Ruiz-Olalla, A.; Johnson, J. S. *Chem. Commun.* **2009**, *34*, 5135.

(6) Leduc, A. B.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2008**, *47* (41), 7945–7948.

(7) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53* (22), 5504–5523.

(8) Berger, K. J.; Levin, M. D. *Org. Biomol. Chem.* **2021**, *19* (1), 11–36.

(9) Smith, M.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley, 2007.

(10) Bayless, J. H.; Mendicino, F. D.; Friedman, L. *J. Am. Chem. Soc.* **1965**, *87* (24), 5790–5791.

(11) Pozhydaiev, V.; Power, M.; Gandon, V.; Moran, J.; Lebœuf, D. *Chem. Commun.* **2020**, *56* (78), 11548–11564.

(12) Olah, G.; Svoboda, J.; Olah, J. *Synthesis* **1972,** *10*, 544–544.

(13) Tidwell, T. T. In *Stable Radicals*; Wiley, 2010; pp 1–31.

(14) Yan, M.; Kawamata, Y.; Baran, P. S. *Chem. Rev.* **2017**, *117* (21), 13230–13319.

(15) Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S. H.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M. R.; Davies, A.; et al. *Nature* **2019**, *573* (7774), 398–402.

(16) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44* (22), 3872–3881.

(17) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137* (17), 5654–5657.

(18) González-Esguevillas, M.; Miró, J.; Jeffrey, J. L.; MacMillan, D. W. C. *Tetrahedron* **2019**, *75* (32), 4222–4227.

(19) Webb, E. W.; Park, J. B.; Cole, E. L.; Donnelly, D. J.; Bonacorsi, S. J.; Ewing, W. R.; Doyle, A. G. *J. Am. Chem. Soc.* **2020**, *142* (20), 9493–9500.

(20) Smith, P. A. S.; Baer, D. R. In *Organic Reactions*; Wiley, 2011; pp 157–188.

(21) *Org. Synth.* **1998**, *75*, 37.

(22) Cohen-Arazi, N.; Katzhendler, J.; Kolitz, M.; Domb, A. J. *Macromolecules* **2008**, *41*

(20), 7259–7263.

(23) *Org. Synth.* **1956**, *36*, 25.

(24) Durka, J.; Turkowska, J.; Gryko, D. *ACS Sustain. Chem. Eng.* **2021**, *9* (27), 8895–8918.

(25) Audubert, C.; Lebel, H. *Org. Lett.* **2017**, *19* (16), 4407–4410.

(26) Reynard, G.; Joseph-Valcin, E.-M.; Lebel, H. *Chem. Commun.* **2020**, *56* (74), 10938–10941.

(27) Reynard, G.; Mayrand, H.; Lebel, H. *Can. J. Chem.* **2020**, *98* (9), 480–484.

(28) Reynard, G.; Lebel, H. *J. Org. Chem.* **2021**, *86* (17), 12452–12459.

(29) Reynard, G.; Lai, C.; Azek, E.; Lebel, H. *Tetrahedron Lett.* **2025**, *155*, 155396.

(30) Ueno, Y.; Tanaka, C.; Okawara, M. *Tetrahedron Lett.* **1984**, *25* (25), 2675–2678.

(31) White, E. H. *J. Am. Chem. Soc.* **1955**, *77* (22), 6011–6014.

(32) Darbeau, R. W.; White, E. H. *J. Org. Chem.* **2000**, *65* (4), 1121–1131.

(33) Darbeau, R. W.; Trahan, G. A.; Siso, L. M. *Org. Biomol. Chem.* **2004**, *2* (5), 695–700.

(34) MacArthur, N. S.; Wang, L.; McCarthy, B. G.; Jakobsche, C. E. *Synth. Commun.* **2015**, *45* (17), 2014–2021.

(35) *Philos. Trans. R. Soc. London* **1851**, *141*, 357–398.

(36) Curtis, V. A.; Knutson, F. J.; Baumgarten, R. J. *Tetrahedron Lett.* **1981**, *22* (3), 199–202.

(37) Katritzky, A. R.; Marson, C. M. *Angew. Chem. Int. Ed.* **1984**, *23* (6), 420–429.

(38) Gölitz, P.; de Meijere, A. *Angew. Chem. Int. Ed.* **1977**, *16* (12), 854–855.

(39) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135* (1), 280–285.

(40) Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P. *Tetrahedron* **2014**, *70* (27–28), 4257–4263.

(41) Basch, C. H.; Cobb, K. M.; Watson, M. P. *Org. Lett.* **2016**, *18* (1), 136–139.

(42) Scharfbier, J.; Gross, B. M.; Oestreich, M. *Angew. Chem. Int. Ed.* **2020**, *59* (4), 1577–1580.

(43) Moragas, T.; Gaydou, M.; Martin, R. *Angew. Chem. Int. Ed.* **2016**, *55* (16), 5053–5057.

(44) Yu, W.; Yang, S.; Xiong, F.; Fan, T.; Feng, Y.; Huang, Y.; Fu, J.; Wang, T. *Org. Biomol. Chem.* **2018**, *16* (17), 3099–3103.

(45) Katritzky, A. R.; Thind, S. S. *J. Chem. Soc. Perkin Trans. 1* **1981**, 661.

(46) Katritzky, A. R.; De Ville, G.; Patel, R. C. *Tetrahedron* **1981**, *37*, 25–30.

(47) Katritzky, A. R.; Horvath, K.; Plau, B. *J. Chem. Soc. Chem. Commun.* **1979**, No. 6, 300.

(48) Katritzky, A. R.; Horvath, K.; Plau, B. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2554.

(49) He, F.-S.; Ye, S.; Wu, J. *ACS Catal.* **2019**, *9* (10), 8943–8960.

(50) Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. *J. Am. Chem. Soc.* **2017**, *139* (15), 5313–5316.

(51) Liao, J.; Guan, W.; Boscoe, B. P.; Tucker, J. W.; Tomlin, J. W.; Garnsey, M. R.; Watson, M. P. *Org. Lett.* **2018**, *20* (10), 3030–3033.

(52) Guan, W.; Liao, J.; Watson, M. *Synthesis* **2018**, *50* (16), 3231–3237.

(53) Hoerrner, M. E.; Baker, K. M.; Basch, C. H.; Bampo, E. M.; Watson, M. P. *Org. Lett.* **2019**, *21* (18), 7356–7360.

(54) Hu, J.; Cheng, B.; Yang, X.; Loh, T. *Adv. Synth. Catal.* **2019**, *361* (21), 4902–4908.

(55) Liao, J.; Basch, C. H.; Hoerrner, M. E.; Talley, M. R.; Boscoe, B. P.; Tucker, J. W.; Garnsey, M. R.; Watson, M. P. *Org. Lett.* **2019**, *21* (8), 2941–2946.

(56) Martin-Montero, R.; Yatham, V. R.; Yin, H.; Davies, J.; Martin, R. *Org. Lett.* **2019**, *21* (8), 2947–2951.

(57) Yue, H.; Zhu, C.; Shen, L.; Geng, Q.; Hock, K. J.; Yuan, T.; Cavallo, L.; Rueping, M. *Chem. Sci.* **2019**, *10* (16), 4430–4435.

(58) Ni, S.; Li, C.-X.; Mao, Y.; Han, J.; Wang, Y.; Yan, H.; Pan, Y. *Sci. Adv.* **2019**, *5* (6), eaaw9516.

(59) Yi, J.; Badir, S. O.; Kammer, L. M.; Ribagorda, M.; Molander, G. A. *Org. Lett.* **2019**, *21* (9), 3346–3351.

(60) Plunkett, S.; Basch, C. H.; Santana, S. O.; Watson, M. P. *J. Am. Chem. Soc.* **2019**, *141* (6), 2257–2262.

(61) Zeng, X.; Yan, W.; Zacate, S. B.; Cai, A.; Wang, Y.; Yang, D.; Yang, K.; Liu, W. *Angew. Chem. Int. Ed.* **2020**, *59* (38), 16398–16403.

(62) Yu, C.-G.; Matsuo, Y. *Org. Lett.* **2020**, *22* (3), 950–955.

(63) Pulikottil, F. T.; Pilli, R.; Suku, R. V.; Rasappan, R. *Org. Lett.* **2020**, *22* (8), 2902–2907.

(64) Wang, J.; Hoerrner, M. E.; Watson, M. P.; Weix, D. J. *Angew. Chem.* **2020**, *132* (32), 13586–13591.

(65) Kim, I.; Im, H.; Lee, H.; Hong, S. *Chem. Sci.* **2020**, *11* (12), 3192–3197.

(66) Klauck, F. J. R.; James, M. J.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**, *56* (40), 12336–12339.

(67) Klauck, F. J. R.; Yoon, H.; James, M. J.; Lautens, M.; Glorius, F. *ACS Catal.* **2019**, *9* (1), 236–241.

(68) James, M. J.; Strieth-Kalthoff, F.; Sandfort, F.; Klauck, F. J. R.; Wagener, F.; Glorius, F. *Chem. – A Eur. J.* **2019**, *25* (35), 8240–8244.

(69) Wu, J.; Grant, P. S.; Li, X.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2019**, *58* (17), 5697–5701.

(70) Sun, S.-Z.; Romano, C.; Martin, R. *J. Am. Chem. Soc.* **2019**, *141* (41), 16197–16201.

(71) Baker, K. M.; Lucas Baca, D.; Plunkett, S.; Daneker, M. E.; Watson, M. P. *Org. Lett.* **2019**, *21* (23), 9738–9741.

(72) Zhu, Z.-F.; Tu, J.-L.; Liu, F. *Chem. Commun.* **2019**, *55* (76), 11478–11481.

(73) Jin, Y.; Wu, J.; Lin, Z.; Lan, Y.; Wang, C. *Org. Lett.* **2020**, *22* (14), 5347–5352.

(74) Jiang, X.; Zhang, M.-M.; Xiong, W.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2019**, *58* (8), 2402–2406.

(75) Yang, Z.; Xu, N.; Wang, C.; Uchiyama, M. *Chem. – A Eur. J.* **2019**, *25* (21), 5433–5439.

(76) Fu, M.-C.; Shang, R.; Zhao, B.; Wang, B.; Fu, Y. *Science* **2019**, *363* (6434), 1429–1434.

(77) Zhao, F.; Li, C.-L.; Wu, X.-F. *Chem. Commun.* **2020**, *56* (64), 9182–9185.

(78) Ociepa, M.; Turkowska, J.; Gryko, D. *ACS Catal.* **2018**, *8* (12), 11362–11367.

(79) Zhang, M.-M.; Liu, F. *Org. Chem. Front.* **2018**, *5* (23), 3443–3446.

(80) Lübbesmeyer, M.; Mackay, E. G.; Raycroft, M. A. R.; Elfert, J.; Pratt, D. A.; Studer, A. *J. Am. Chem. Soc.* **2020**, *142* (5), 2609–2616.

(81) Ni, Q.; Zhou, Y.; Chen, L.; Liu, Y. *Org. Chem. Front.* **2025**, *12* (3), 975–1000.

(82) Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2020**, *142* (43), 18310–18316.

(83) Dorsheimer, J. R.; Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2021**, *143* (46), 19294–19299.

(84) Marchese, A. D.; Dorsheimer, J. R.; Rovis, T. *Angew. Chem. Int. Ed.* **2024**, *63* (6).

(85) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, *593* (7858), 223–227.

(86) Berger, K. J.; Driscoll, J. L.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143* (42), 17366–17373.

(87) Dherange, B. D.; Yuan, M.; Kelly, C. B.; Reiher, C. A.; Grosanu, C.; Berger, K. J.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2023**, *145* (1), 17–24.

(88) J. Berger, K. *Org. Synth.* **2023**, *100*, 113–135.

(89) Steiniger, K. A.; Lamb, M. C.; Lambert, T. H. *J. Am. Chem. Soc.* **2023**, *145* (21), 11524–11529.

(90) Quirós, I.; Martín, M.; Gomez-Mendoza, M.; Cabrera-Afonso, M. J.; Liras, M.; Fernández, I.; Nóvoa, L.; Tortosa, M. *Angew. Chem. Int. Ed.* **2024**, *63* (7).

(91) Pérez-Sánchez, C.; Rigotti, T.; Tortosa, M. *Org. Lett.* **2025**, *27* (2), 583–587.

(92) Karczewski, M.; Ociepa, M.; Gryko, D. *European J. Org. Chem.* **2019**, *2019* (2–3), 469–477.

(93) Tang, R.-J.; Milcent, T.; Crousse, B. *J. Org. Chem.* **2018**, *83* (22), 14001–14009.

(94) Bering, L.; Jeyakumar, K.; Antonchick, A. P. *Org. Lett.* **2018**, *20* (13), 3911–3914.

(95) Qin, Q.; Xie, Y.; Floreancig, P. E. *Chem. Sci.* **2018**, *9* (45), 8528–8534.

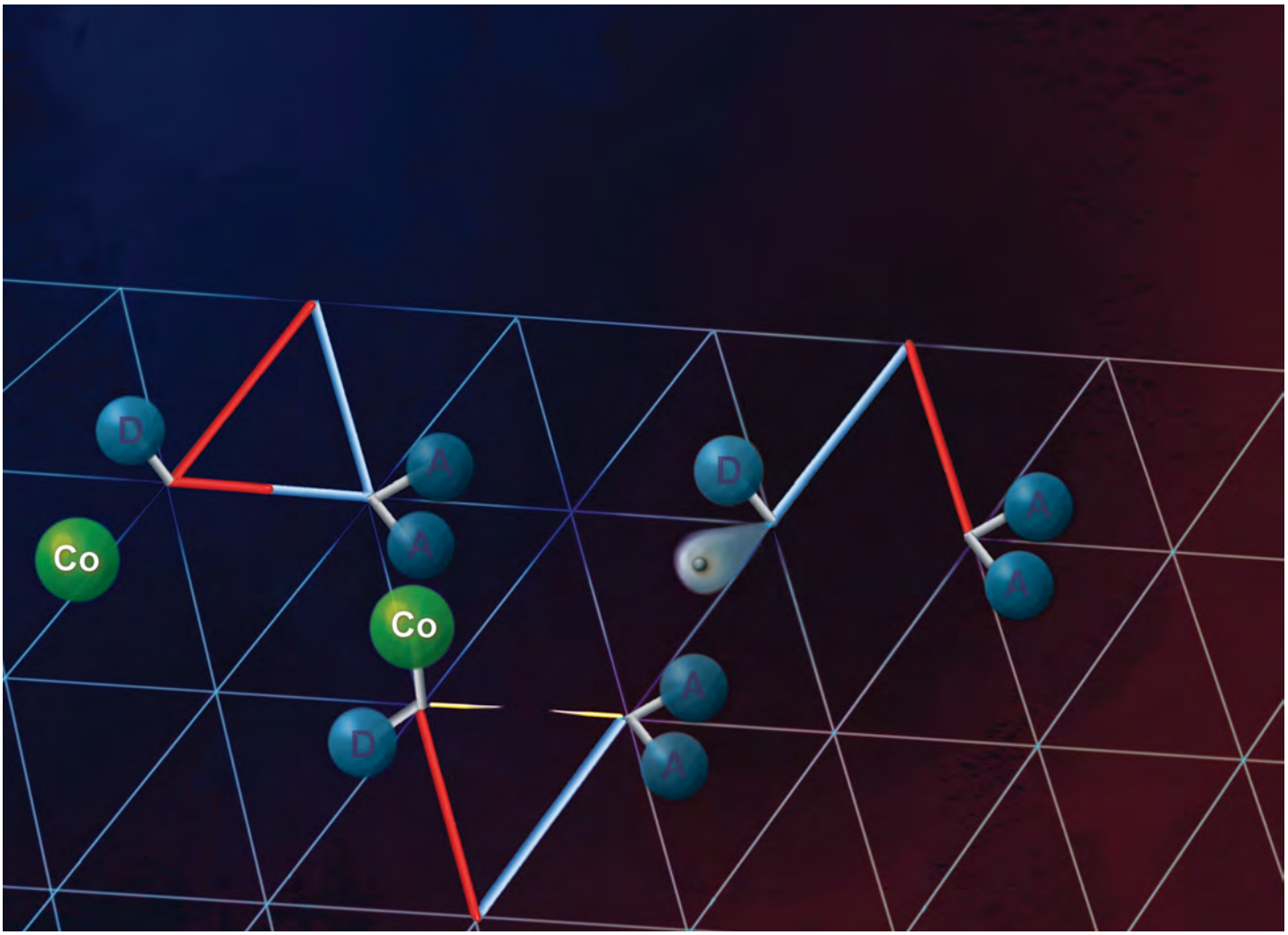
(96) Meng, S.-S.; Tang, X.; Luo, X.; Wu, R.; Zhao, J.-L.; Chan, A. S. C. *ACS Catal.* **2019**, *9* (9), 8397–8403.

(97) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137* (30), 9694–9703.

(98) Ammer, J.; Mayr, H. *J. Phys. Org. Chem.* **2013**, *26* (1), 59–63.

(99) Zeidan, N.; Bicic, S.; Mayer, R. J.; Lebœuf, D.; Moran, J. *Chem. Sci.* **2022**, *13* (28), 8436–8443.

(100) Zhang, S.; Vayer, M.; Noël, F.; Vuković, V. D.; Golushko, A.; Rezajooei, N.; Rowley, C. N.; Lebœuf, D.; Moran, J. *Chem* **2021**, *7* (12), 3425–3441.



Showcasing research from Prof. Dorota Gryko's group, Institute of Organic Chemistry, Polish Academy of Sciences. Image designed and illustrated by Joanna Turkowska.

Reversal of regioselectivity in reactions of donor–acceptor cyclopropanes with electrophilic olefins

Vitamin B_{12}– a natural Co-complex catalyzes generation of alkyl radicals from donor–acceptor cyclopropanes. The developed methodology reverses the reactivity of cyclopropanes, enabling regioselective installation of electrophilic reagents at the originally electrophilic carbon atom.

As featured in:

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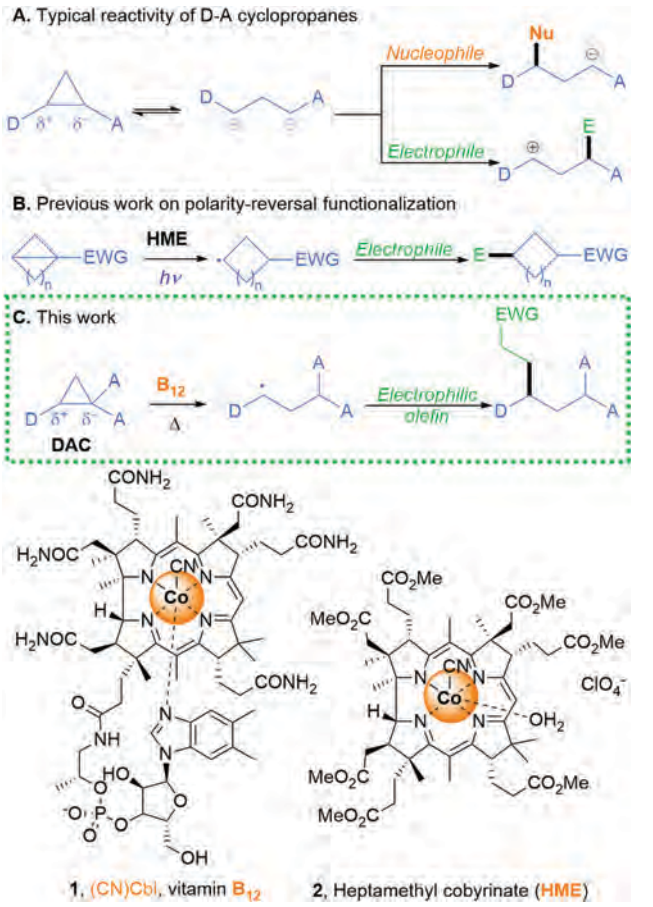
Reversal of regioselectivity in reactions of donor–acceptor cyclopropanes with electrophilic olefins†

Joanna Turkowska,‡ Jakub Durka,‡ Michał Ociepa and Dorota Gryko *

Reactivity of donor–acceptor cyclopropanes towards nucleophiles and electrophiles is determined by the specific philicity of the carbon atoms originating from the strong polarization of the central C–C bond. Herein, we report that vitamin B_{12} catalysis enables the transformation of an initially electrophilic center into a nucleophilic radical that reacts with SOMOphiles. This radical-based strategy reverses the standard regioselectivity and thus complements the classical approaches.

The chemistry of donor–acceptor (D–A) cyclopropanes (**DAC**) has experienced a well-deserved revival over the last few years. These compounds are appreciated building blocks offering multifaceted reactivity.[1] Being the smallest cycloalkanes, cyclopropanes are characterized by high ring strain resulting in increased energy;[2] this, however, is not the only factor affecting their chemical properties. An additional activation stems from strong polarization of the C–C bond vicinally substituted with donor and acceptor groups.[1b] The zwitterionic relationship between two substituted carbon atoms makes D–A cyclopropanes perfect substrates for cycloadditions,[1,3] rearrangements,[1,4] and ring opening[1,5] reactions. The latter provides convenient access to mono- or 1,3-difunctionalized compounds.

Because of the dipole-like nature of **DAC**s, their transformations are highly regioselective. The nucleophilic attack occurs on the donor-substituted carbon atom with a partial positive charge leading to the ring-opening (Scheme 1A).[1b] Subsequently, the negative charge on the carbon bearing the acceptor is neutralized by an electrophile, often a proton, though a number of 1,3-bifunctionalization reactions have also been reported in the last few years.[6] Exclusively installing an electrophile in the regioselective ring-opening is highly underdeveloped and typically occurs on the acceptor-substituted carbon atom. The only exception to this rule is transition-metal catalyzed addition of C-electrophiles on the donor-substituted carbon atom resulting from the formation of nucleophilic π-allyl-metal complex.[7,8] The scope of this method is, however, limited only to a few vinylcyclopropanes. Consequently, the range of such functionalized derivatives is restricted. To expand synthetic possibilities, we wondered whether it is possible to establish a general method for reversal of the reactivity of the



Scheme 1 Reactivity of D–A cyclopropanes.

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland. E-mail: dorota.gryko@icho.edu.pl

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‡ These authors contributed equally.

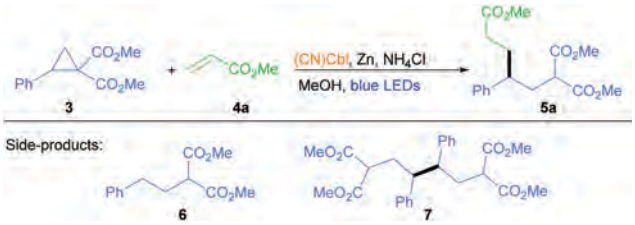
substituted C–C bond and hence enable the regioselective reaction with electrophilic reagents at the donor-substituted carbon atom. Based on our experience in Co-catalysis, we thought that it should be an excellent tool for that purpose (Scheme 1B and C). Among cobalt catalysts, vitamin B_{12} (**1**, cobalamin) offers some exceptional features. In the Co(I) form, it acts as a 'super-nucleophile' inclined to react with carbon electrophiles, typically *via* the S_N2 mechanism. The newly formed Co(III)–C bond is prone to homolytic cleavage under both photolytic and thermal conditions giving radicals that subsequently may engage in numerous transformations.[9] In this line, we have employed vitamin B_{12} for the generation of cyclobutyl and cyclopentyl radicals from bicyclo[1.1.0]butanes and bicyclo[2.1.0]pentanes respectively, involving cleavage of their central C–C bond.[10] This polarity reversal strategy enables reactions with electrophiles and SOMOphiles on the originally electrophilic carbon atom (Scheme 1B). That is possible due to a set of features typical of small bicyclic compounds. They are characterized by high ring strain and their central bridging bonds are polarized when substituted with at least an electron-withdrawing group on one of the bridgehead carbons.[1,11] These properties are also relevant to D–A cyclopropanes, therefore we envisaged that the B_{12}-based methodology can be employed to generate C-centered radicals from these cyclic compounds and achieve the addition of SOMOphiles on the donor-substituted carbon atom. The use of electrophilic coupling partner would enable formal electrophile–electrophile coupling expanding the scope of scaffolds accessible from **DAC**. Scattered information on the ring-opening of cyclopropanes and formation of alkyl-cobalamin derivatives support our hypothesis.[12,13] Recently, we have also used this approach for regioselective ring-opening arylation of epoxides.[14] Our approach would also contribute to the radical chemistry of D–A cyclopropanes which has been recently explored by Werz group.[6f]

Herein, we report a polarity-reversal ring-opening alkylation of donor–acceptor cyclopropanes with electrophilic olefins.

We initiated our studies by reacting D–A cyclopropane **3** with Michael acceptor **4a** in the presence of vitamin B_{12} (**1**) as a cobalt catalyst and Zn/NH_4Cl as a reducing system under blue light irradiation (455 nm, Table 1). The initial conditions afforded product **5a** in 24% yield (entry 1). Control experiments revealed the crucial role of cobalamin (**1**) (entry 2). Interestingly, without irradiation, the reaction was not completely halted which suggested thermal conditions might be also suitable for the generation of alkyl radicals (entry 3).

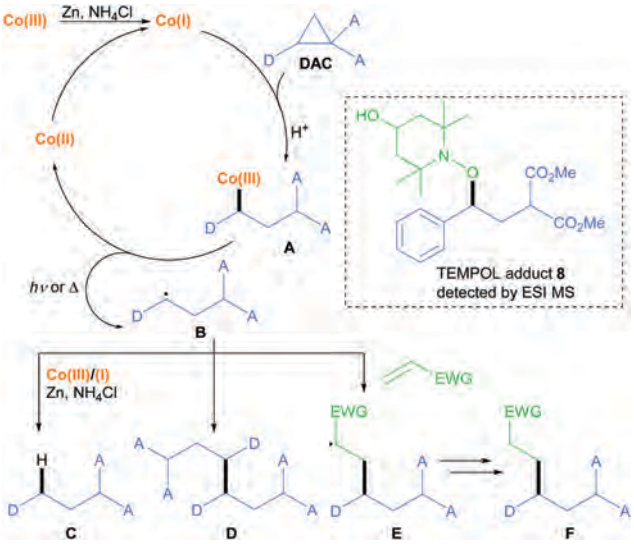
Based on our[10,14] and others[15] previous experience, it can be reasonably assumed that under the applied conditions, the Co(III) form of the catalyst is reduced to the 'supernucleophilic' Co(I) species that attacks the donor-substituted carbon atom of **DAC** generating alkyl radical **B** (trapped with TEMPOL, see ESI†) (Scheme 2). In the desired scenario, it reacts with activated olefin affording intermediate **E** that after reduction forms desired alkylated product **F** (Scheme 2). In our preliminary experiments, we identified two side products **6** and **7**, which presumably originate from the same radical **B**. In the first scenario, it is reduced to side-product **C**. The second option involves dimerization of radical B leading to dimer **D**. To

Table 1 Background studies for the model reaction[a]



Entry	Deviation from standard conditions	Yield of **5a**[b] [%]
1	None	24
2	No catalyst **1**	0[c]
3	No light	9
4	No olefin	0[d]

[a] Reaction conditions: **DAC 3** (0.1 mmol), olefin **4a** (1.5 equiv.), (CN)Cbl (**1**) (6 mol%), Zn (6 equiv.), NH_4Cl (3 equiv.), MeOH (c = 0.1 M), blue LEDs (455 nm, 9 W), 18 h, rt, degassed. (see ESI). [b] GC yield. [c] Product **6** was observed. [d] Products **6** and **7** were observed.



Scheme 2 Plausible pathway of the polarity-reversal alkylation of **DAC**.

corroborate the radical pathway, we performed the model reaction with the addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). When added at the beginning of the reaction, it suppressed the formation of product **5a** completely while its addition after 4 hours diminished yield of product **5a** (31%, see ESI†).

From the beginning of our optimization studies, it became clear that the choice of a solvent is crucial (Table 2). MeOH gave significantly better results than any other tested, presumably because of the excellent solubility of vitamin B_{12} (**1**), whilst simultaneously being a source of protons. Since cyanocobalamin (**1**) and cobalamin-based catalysts **2**, **9** were similarly effective (entries 1–3), commercially available, native vitamin B_{12} (**1**) was further explored. Possible dimerization of a radical derived from cyclopropane **3** called for an excess of acceptor **4a**

Table 2 Optimization studies[a]

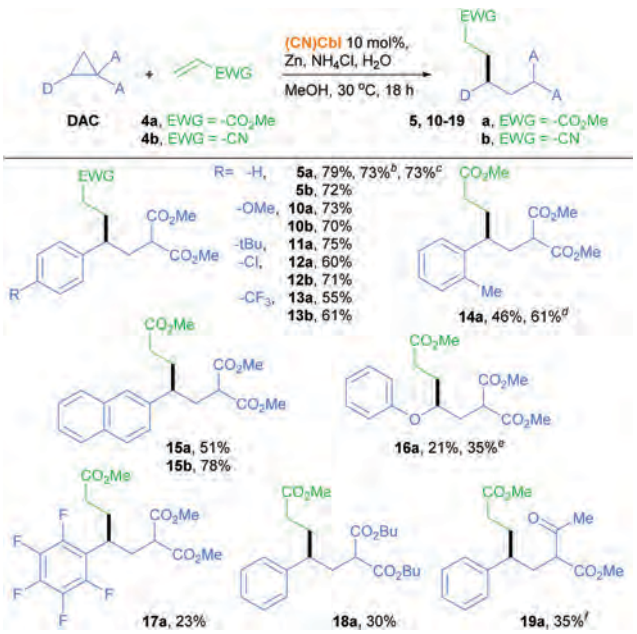
Entry	Deviation from standard conditions	Yield of **5a**[b] [%]
1	None	77 (79%)[c]
2[d]	HME (**2**)	66
3[d]	$Cbl(OH_2)^+Cl^-$ **9** (see ESI)	74
4	3 equiv. of **5a**	63
5	No H_2O	61
6[e]	Blue LEDs instead of heating	73
7	Room temperature (23 °C)	62

[a] Reaction conditions: **DAC3** (0.1 mmol), **4a** (5 equiv.), (CN)Cbl (**1**) (10 mol%), Zn (3 equiv.), NH_4Cl (1.5 equiv.), MeOH (c = 0.2 M), 18 h, 30 °C, degassed. [b] GC yields. [c] Isolated yield. [d] No water was added. [e] Blue LEDs: 455 nm, 9 W.

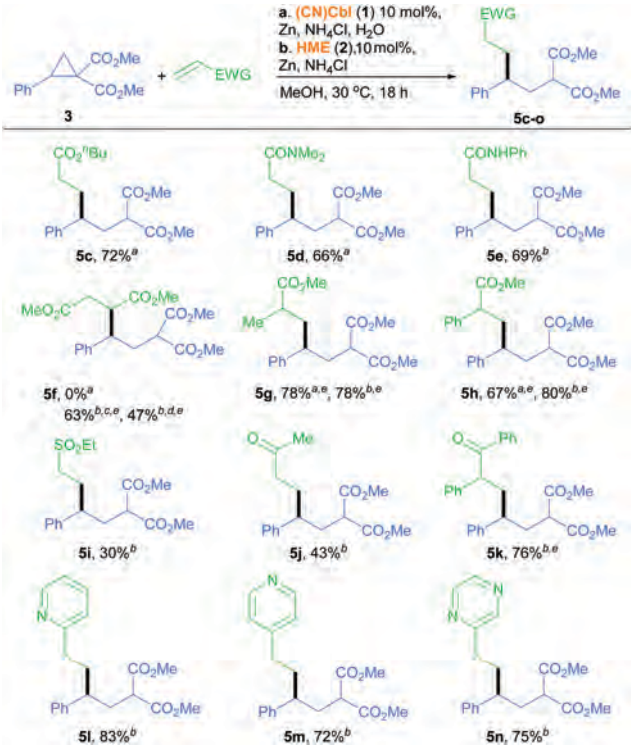
to be used (entry 4). The yield of the reaction appreciably increased by the addition of water (5 equiv.). One of the most important factors we analyzed was the driving force for the cleavage of the Co–C bond with the concominat formation of C-radicals. Light sources differing in wavelength and power were tested but photochemical conditions, at best gave similar results to those obtained without any irradiation (entry 6). The reaction at slightly elevated temperature (30 °C) was the most effective (entry 1, 79%).

With the optimized conditions in hand, we explored the substrate scope of the ring-opening polarity-reversal alkylation of **DAC** (Scheme 3). A range of cyclopropanes differing in donor and acceptor groups were reacted with methyl acrylate (**4a**).

Our method worked well for the substrates bearing aryl substituents at the donor position and the best results were achieved for these with both weakly and strongly electron-donating groups



Scheme 3 Scope of reaction: donor–acceptor cyclopropanes.[a] [a]Reaction conditions: **DAC** (0.2 mmol), olefin **4a** or **4b** (5 equiv.), (CN)Cbl (**1**, 10 mol%), Zn (3 equiv.), NH_4Cl (1.5 equiv.), H_2O (5 equiv.), MeOH (c = 0.2 M), 30 °C, 18 h, degassed. [b]1 mmol scale, reaction time – 24 h. [c]3 mmol scale, reaction time – 24 h. [d]Reaction time – 48 h. [e]Catalyst: HME (**2**, 10 mol%) (see ESI†). [f]A mixture of diastereomers.



Scheme 4 Scope of reaction: electrophilic alkenes. [a,b]Reaction conditions: cyclopropane **3** (0.2 mmol), olefin (5 equiv.), catalyst: **a**: (CN)Cbl (**1**, 10 mol%), **b**: HME (**2**, 10 mol%), Zn (3 equiv.), NH_4Cl (1.5 equiv.), H_2O (5 equiv.), MeOH (c = 0.2 M), 30 °C, 18 h, degassed; [c]from dimethyl fumarate; [d]from dimethyl maleate; [e]a mixture of diastereomers.

such as phenyl (**5a**, 79%), 4-*t*Bu-phenyl (**11a**, 75%) and 4-OMe-phenyl (**10a**, 73%). Substitution at the position 2 of the phenyl ring hinders the attack of the Co(I) catalyst thus slowing down the desired reaction and diminishing the yield of product **14a** (46%). This problem was, however, easily solved, simply by prolonging the reaction time (61%). On the other hand, for cyclopropanes bearing electron-deficient aromatic groups the yields of the products **12a, 13a** slightly diminished. In these cases, the presence of a strong electron-withdrawing group at the aromatic ring raises the reduction potential of **DAC** (see ESI† for more information) and consequently accelerates side-reactions (ring-opening and reduction of the cyclopropane). These processes should be suppressed for more reactive SOMOphiles. Indeed, the use of acrylonitrile, particularly in the case of **DAC** bearing electron-deficient aromatic substituents, appreciably increased yields of products (Scheme 3, **12b**, **13b**). To emphasize utility of the method, the model reaction was performed on a preparative scale (3 mmol) giving compound **4a** in 73% yield.

Next, a set of electrophilic alkenes were tested (Scheme 4). Various olefins bearing electron-withdrawing groups, including esters (**5c**, **5g–h**), amides (**5d and e**), and nitrile (**5b**) are well tolerated. Only traces of product **5f**, however, were observed in the case of dimethyl fumarate, which we associated with fast, partial reduction of the olefin under the developed conditions. Hence, changing the kinetics of the desired reaction should eliminate the problem. Our previous studies indicated that the

rate of reactions catalyzed by HME (**2**) are significantly higher than those catalyzed by native vitamin B_{12} (**1**).[16] Indeed, kinetic studies performed for the HME-catalyzed formation of product **5a** indicated a significant acceleration of the reaction rate compared to (CN)Cbl-catalyzed transformations (see ESI†). Consequently, the change of a catalyst from vitamin **1** to HME (**2**) enabled the formation of product **5f** in a satisfactory yield (63%). These modified conditions proved also more efficient for 1,1-disubstituted olefins (**5h**, **5k**) as well as for vinyl ethyl sulfone (**5i**) or vinyl pyridines and 2-vinylpyrazine giving products **5l, m** and **5n** in high yields.

In summary, we have developed a strategy that reverses the reactivity of D–A substituted cyclopropanes, enabling regioselective installation of electrophilic reagent at the originally electrophilic carbon atom. In particular, vitamin B_{12} (**1**) as a catalyst reacts with **DAC**s giving alkyl cobalamins. Homolytic cleavage of the Co–C bond leads to C-centered radicals that engage in reactions with SOMOphiles. The outcome of the reaction stems from the subtle balance between three competing transformations of the generated radical.

Importantly, the presented strategy complements the existing activation modes for the generation of radicals from donor–acceptor cyclopropanes. Only recently the Werz group reported that the electrocatalytic activation enables generation of a radical on the acceptor-substituted carbon atom in contrast to our B_{12}-catalysis.[6f] As a consequence new molecular scaffolds can be accessed complementing the library of compounds derived from cyclopropanes. These can undergo subsequent transformations, for instance to 1,7-dicarbonyl compounds which in turn can be converted *via* Dieckmann condensation to cyclic β-ketoesters, a class of building-blocks highly prized in organic synthesis.[17] Therefore we believe our methodology will make a meaningful contribution to expanding the currently available chemical space.

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Conflicts of interest

The authors declare no conflict of interest.

Notes and references

1 For reviews see: (*a*) H. U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (*b*) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504; (*c*) M. A. Cavitt, L. H. Phun and S. France, *Chem. Soc. Rev.*, 2014, **43**, 804; (*d*) H. K. Grover, M. R. Emmett and M. A. Kerr, *Org. Biomol. Chem.*, 2015, **13**, 655; (*e*) N. R. O'Connor, J. L. Wood and B. M. Stoltz, *Isr. J. Chem.*, 2016, **56**, 431; (*f*) E. M. Budynina, K. L. Ivanov, I. D. Sorokin and M. Y. Melnikov, *Synthesis*, 2017, 3035; (*g*) O. A. Ivanova and I. V. Trushkov, *Chem. Rec.*, 2019, **19**, 2189; (*h*) K. Ghosh and S. Das, *Org. Biomol. Chem.*, 2021, **19**, 965.

2 K. B. Wiberg, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 312.

3 For selected examples see: (*a*) T. P. Lebold and M. A. Kerr, *Pure Appl. Chem.*, 2010, **82**, 1797; (*b*) P. D. Pohlhaus and J. S. Johnson, *J. Am. Chem. Soc.*, 2005, **127**, 16014; (*c*) L. K. B. Garve, M. Pawliczek, J. Wallbaum, P. G. Jones and D. B. Werz, *Chem. – Eur. J.*, 2016, **22**, 521; (*d*) A. O. Chagarovskiy, V. S. Vasin, V. V. Kuznetsov, O. A. Ivanova, V. B. Rybakov, A. N. Shumsky, N. N. Makhova and I. V. Trushkov, *Angew. Chem., Int. Ed.*, 2018, **57**, 10338; (*e*) M. Petzold, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2019, **58**, 6225; (*f*) A. U. Augustin, J. L. Merz, P. G. Jones, G. Mlostoń and D. B. Werz, *Org. Lett.*, 2019, **21**, 9405; (*g*) A. Jacob, P. G. Jones and D. B. Werz, *Org. Lett.*, 2020, **22**, 8720; (*h*) G. Nie, X. Huang, Z. Wang, D. Pan, J. Zhang and Y. R. Chi, *Org. Chem. Front.*, 2021, **8**, 5105–5111.

4 For selected examples see: (*a*) E. Wenkert, M. E. Alonso, B. L. Buckwalter and K. J. Chou, *J. Am. Chem. Soc.*, 1977, **99**, 4778; (*b*) C. Brückner and H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 588; (*c*) D. R. Wenz and J. R. De Alaniz, *Org. Lett.*, 2013, **15**, 3250; (*d*) H. Chen, J. Zhang and D. Z. Wang, *Org. Lett.*, 2015, **17**, 2098–2101.

5 For selected examples see: (*a*) O. Lifchits and A. B. Charette, *Org. Lett.*, 2008, **10**, 2809; (*b*) M. R. Emmett and M. A. Kerr, *Org. Lett.*, 2011, **13**, 4180; (*c*) D. Gladow and H.-U. Reissig, *Synthesis*, 2013, 2179; (*d*) Q. K. Kang, L. Wang, Q. J. Liu, J. F. Li and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 14594; (*e*) A. A. Akaev, M. Y. Melnikov and E. M. Budynina, *Org. Lett.*, 2019, **21**, 9795.

6 For selected examples see: (*a*) L. K. B. Garve, P. Barkawitz, P. G. Jones and D. B. Werz, *Org. Lett.*, 2014, **16**, 5804; (*b*) S. Das, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2016, **18**, 5576; (*c*) L. K. B. Garve, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2017, **56**, 9226; (*d*) A. U. Augustin, P. G. Jones and D. B. Werz, *Chem. – Eur. J.*, 2019, **25**, 11620; (*e*) A. Guin, T. Rathod, R. N. Gaykar, T. Roy and A. T. Biju, *Org. Lett.*, 2020, **22**, 2276; (*f*) S. Kolb, M. Petzold, F. Brandt, P. G. Jones, C. R. Jacob and D. B. Werz, *Angew. Chem., Int. Ed.*, 2021, **60**, 15928.

7 N. Selander and K. J. Szabó, *Chem. Commun.*, 2008, 3420.

8 J. Moran, A. G. Smith, R. M. Carris, J. S. Johnson and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 18618.

9 (*a*) M. Giedyk, K. Goliszewska and D. Gryko, *Chem. Soc. Rev.*, 2015, **44**, 3391; (*b*) K. L. Brown, *Chem. Rev.*, 2005, **105**, 2075; (*c*) M. Hapke and G. Hilt, *Cobalt Catalysis in Organic Synthesis*, Wiley-VCH, 2020.

10 M. Ociepa, A. J. Wierzba, J. Turkowska and D. Gryko, *J. Am. Chem. Soc.*, 2020, **142**, 5355.

11 J. Turkowska, J. Durka and D. Gryko, *Chem. Commun.*, 2020, **56**, 5718.

12 Y. Hisaeda, T. Nishioka, Y. Inoue, K. Asada and T. Hayashi, *Coord. Chem. Rev.*, 2000, **198**, 21.

13 T. Troxler and R. Scheffold, *Helv. Chim. Acta*, 1994, **77**, 1193.

14 (*a*) A. Potrząsaj, M. Musiejuk, W. Chaładaj, M. Giedyk and D. Gryko, *J. Am. Chem. Soc.*, 2021, **143**, 9368; (*b*) A. Potrząsaj, M. Ociepa, O. Baka, G. Spólnik and D. Gryko, *Eur. J. Org. Chem.*, 2020, 1567.

15 (*a*) G. N. Schrauzer and E. Deutsch, *J. Am. Chem. Soc.*, 1969, **91**, 3341; (*b*) R. Scheffold, S. Abrecht, R. Orlinski, H.-R. Ruf, P. Stamouli, O. Tinembart, L. Walder and C. Weymuth, *Pure Appl. Chem.*, 1987, **59**, 363; (*c*) Y. Hisaeda, T. Nishioka, Y. Inoue, K. Asada and T. Hayashi, *Coord. Chem. Rev.*, 2000, **198**, 21; (*d*) J. Shey, C. M. McGinley, K. M. McCauley, A. S. Dearth, B. T. Young and W. A. van der Donk, *J. Org. Chem.*, 2002, **67**, 837; (*e*) H. Shimakoshi and Y. Hisaeda, *Angew. Chem., Int. Ed.*, 2015, **127**, 15659.

16 M. Karczewski, M. Ociepa, K. Pluta, K. ó. Proinsias and D. Gryko, *Chem. – Eur. J.*, 2017, **23**, 7024.

17 S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto and V. Zanirato, *Chem. Rev.*, 1995, **4**, 1065.

Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

Reversal of regioselectivity in the reactions of donor-acceptor cyclopropanes with electrophilic alkenes

J. Turkowska,[a] J. Durka,[a] M. Ociepa, and D. Gryko*

Abstract: Cyclopropanes bearing donor and acceptor groups at the opposite ends of the C-C bond should react with both nucleophiles and electrophiles. Their reactivity towards nucleophilic reagents is well explored while only few specific electrophiles give desired products. The methods are limited by the specific philicity of the carbon atoms resulting from the strong polarization of the central C-C bond. Herein, we report a strategy that reverses the standard regioselectivity of these methods and thus complements the classical approach. The use of vitamin B_{12} catalysis enables the transformation of initially electrophilic center into a radical that as such reacts with electrophilic SOMOphiles.

a - these authors contributed equally

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1. General Information

All solvents and commercially available reagents were purchased as reagent grade and were used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC), using 0.20 mm Merck silica plates (60F-254) and visualized using UV-light, anisaldehyde or cerium molybdate stain, with heat as a developing agent. Colum chromatography was performed on Merck silica gel 60 (230-400 mesh). Yields refer to spectroscopically (^{1}H NMR) homogeneous materials. NMR spectra were recorded on Bruker 400 MHz or Varian 500 MHz and calibrated using residual undeuterated solvent ($CHCl_3$ – 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR) or TMS as an internal reference. Low-resolution mass spectra (LRMS) were recorded on an Applied Biosystems API 365 mass spectrometer using electrospray ionization (ESI) technique. High-resolution mass spectra (HRMS) were recorded on a Waters AutoSpec Premier instrument using electron ionization (EI) or a Waters SYNAPT G2-S HDMS instrument using electrospray ionization (ESI) with time of flight detector (TOF). Elemental analysis (C, H, N) were performed using a PERKIN-ELMER 240 Elemental Analyzer. Cyclic voltammograms were recorded using Bio-Logic SP-50 potentiostat. GC-MS analyses were performed using Shimadzu GCMS-QP2010 SE gas chromatograph with FID detector and Zebron ZB 5MSi column. Melting points were recorded on a Marienfeld MPM-H2 melting point apparatus and are uncorrected.

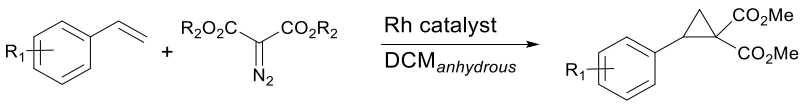
2. General synthetic procedures

2.1 Starting materials

Dimethyl diazomalonate,[1] dibutyl diazomalonate,[1] 2-diazo-3-oxo-butyric acid methyl ester,[2] 2-phenyl-acrylic acid methyl ester,[3] 1,2-diphenylprop-2-en-1-one,[4] $(CN)(H_2O)Cby(OMe)_7$ (**HME**, **2**),[5] $Co(dmgH)_2py^iPr$ (x)[6] were synthesized according to the literature procedures.

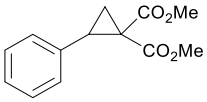
2.2 Preparation of donor-acceptor cyclopropanes 3, S1-S.

Donor-acceptor cyclopropanes **1a-k** were prepared according to slightly modified literature procedure:[7]



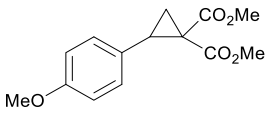
A solution of the corresponding styrene (1.0 equiv.), Rh catalyst (0.5 mol%) in anhydrous dichloromethane was stirred under argon atmosphere at 0 °C. Diazomalonate (1.3 equiv.) in dichloromethane was added dropwise over 30 min via syringe. Cooling bath was removed and the mixture was stirred overnight at ambient temperature. The solvent was removed *in vacuo* and crude product was purified by column chromatography.

Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (3)



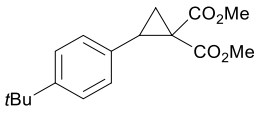
Synthesized according to general procedure from 520 mg (5.0 mmol) of styrene and 1 g (6.5 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 11 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 702 mg of **3** (3.0 mmol, 60%) as a white solid. All analytical data were consistent with that previously reported.

Dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (S1)



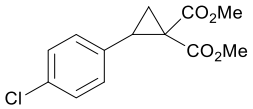
Synthesized according to general procedure from 268 mg (2.0 mmol) of 4-methoxystyrene and 411 mg (2.6 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 4.4 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 343 mg of **S1** (1.3 mmol, 67%) as a white solid. All analytical data were consistent with that previously reported.

Dimethyl 2-(4-(tert-butyl)phenyl)cyclopropane-1,1-dicarboxylate (S2)



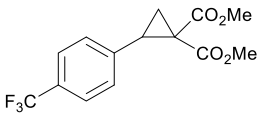
Synthesized according to general procedure from 400 mg (2.5 mmol) of 4-*tert*-butylstyrene and 514 mg (3.25 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 5.5 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 645 mg of **S2** (2.2 mmol, 89%) as a white solid. All analytical data were consistent with that previously reported.[8]

Dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (S3)



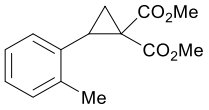
Synthesized according to general procedure from 276 mg (2.0 mmol) of 4-chlorostyrene and 411 mg (2.6 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 4.4 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 440 mg of **S3** (1.6 mmol, 82%) as a white solid. All analytical data were consistent with that previously reported.[9]

Dimethyl 2-(4-(trifluoromethyl)phenyl)cyclopropane-1,1-dicarboxylate (S4)



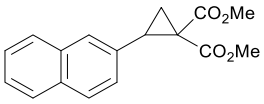
Synthesized according to general procedure from 344 mg (2.0 mmol) of 4-trifluoromethyl styrene and 411 mg (2.6 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 4.4 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 441 mg of **S4** (1.5 mmol, 73%) as colorless oil. All analytical data were consistent with that previously reported.[9]

Dimethyl 2-(o-tolyl)cyclopropane-1,1-dicarboxylate (S5)



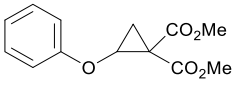
Synthesized according to general procedure from 295 mg (2.5 mmol) of 2-methylstyrene and 514 mg (3.25 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 5.5 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 533 mg of **S5** (2.2 mmol, 86%) as a white solid. All analytical data were consistent with that previously reported.[10]

Dimethyl 2-(naphthalene-2-yl)cyclopropane-1,1-dicarboxylate (S6)



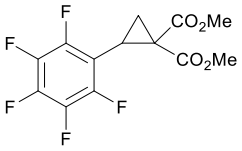
Synthesized according to general procedure from 770 mg (5 mmol) of 2-vinylnaphthalene and 1 g (6.5 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 11 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 284 mg of **S6** (1 mmol, 20%) as a white solid. All analytical data were consistent with that previously reported.[11]

2-Phenoxycyclopropane-1,1-dimethylester (S7)



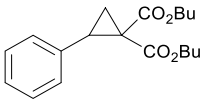
Synthesized according to general procedure from 300 mg (2.5 mmol) of vinyloxybenzene and 514 mg (3.25 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 5.5 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 363 mg of **S7** (1.5 mmol, 58%) as colorless oil. All analytical data were consistent with that previously reported.[12]

Dimethyl 2-(perfluorophenyl)cyclopropane-1,1-dicarboxylate (S8)



Synthesized according to general procedure from 295 mg (2 mmol) of perfluorostyrene and 411 mg (2.6 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 4.4 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 395 mg of **S8** (1.2 mmol, 61%) as colorless oil. All analytical data were consistent with that previously reported.[9]

Dibutyl 2-phenylcyclopropane-1,1-dicarboxylate (S9)



Synthesized according to general procedure from 416 mg (4 mmol) of styrene and 1.3 g (5.2 mmol, 1.3 equiv.) of dibutyl 2-diazomalonate using 8.8 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 712 mg of **S9** (2.2 mmol, 56%) as colorless oil.

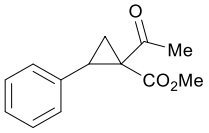
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.25 (m, 1H), 7.25 – 7.17 (m, 4H), 4.22 (dt, J = 10.8, 6.6 Hz, 1H), 4.14 (dt, J = 10.8, 6.5 Hz, 1H), 3.77 (t, J = 6.6 Hz, 2H), 3.20 (t, J = 8.6 Hz, 1H), 2.15 (dd, J = 8.0, 5.1 Hz, 1H), 1.69 (dd, J = 9.2, 5.1 Hz, 1H), 1.67 – 1.60 (m, 2H), 1.45 – 1.35 (m, 2H), 1.28 – 1.20 (m, 2H), 1.15 – 1.04 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H), 0.77 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 166.8, 134.8, 128.5, 128.1, 127.3, 65.5, 65.1, 37.6, 32.1, 30.6, 30.3, 19.1, 18.81, 18.77, 13.6, 13.5.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{26}O_4Na$: 341.1729, found: 341.1731.

Elemental analysis (%) calculated for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23, found: C, 71.66; H, 8.40.

Methyl 1-acetyl-2-phenylcyclopropanecarboxylate (S10)

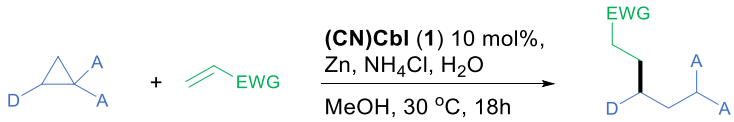


218 Synthesized according to general procedure from 208 mg (2 mmol) of styrene and 369 mg (2.6 mmol, 1.3 equiv.) of dimethyl 2-diazomalonate using 4.4 mg (0.5 mol%) of $Rh_2(OAc)_4$ as a catalyst (*c* = 1M). Column chromatography (10:90 AcOEt/Hexanes) afforded 288 mg of **S10** (1.3 mmol, 66%, mixture of diastereomers 20:80) as colorless oil. All analytical data were consistent with that previously reported.[13]

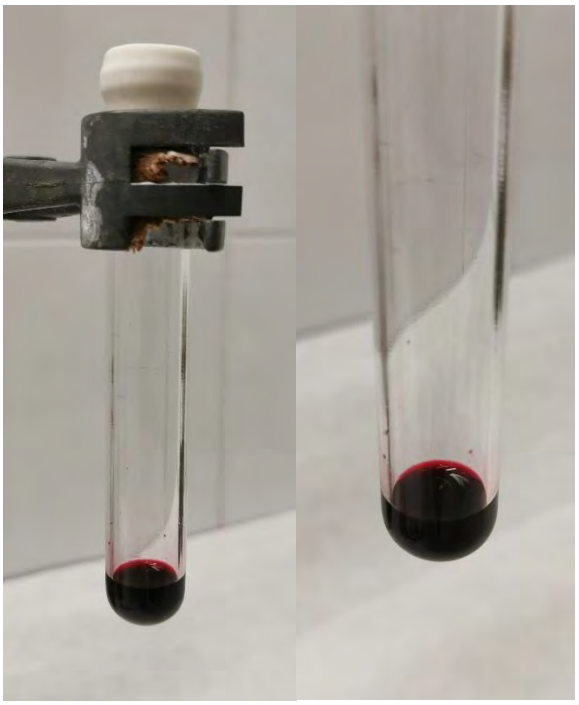
2.3 Procedure for zinc activation[5]

Zinc powder (5.0 g) was suspended in 10% aq. HCl (50 ml) and grinded in mortar for 2 – 3 min. Subsequently, the solution was filtered and the zinc precipitate was washed successively with water (50 ml), acetone (50 ml), MeOH (50 ml), and Et_2O (50 ml). The resulting precipitate was transferred to the mortar, grinded and dried *in vacuo* to afford light grey powder which was then stored under argon atmosphere and used for maximum 1 month.

2.4 General procedure A for the opening and alkylation of D-A cyclopropanes



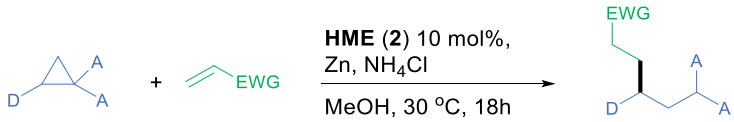
A glass reaction tube (inner diameter = 18 mm) equipped with a magnetic bar and sealed with a septum was charged with a donor-acceptor cyclopropane (0.2 mmol, 1.0 equiv.), vitamin B_{12} (27 mg, 0.02 mmol, 10 mol%), NH_4Cl (16 mg, 0.3 mmol, 1.5 equiv.), and activated zinc 39 mg, 0.6 mmol, 3.0 equiv.). Subsequently, MeOH (1.0 ml) was added and the resulting mixture was degassed 3x by a simplified freeze-thaw method using dry ice as a cooling agent. Then, an electrophilic alkene (1 mmol, 5 equiv.) and H_2O (20 µl) were added under argon. The reaction tube was placed in ultrasonic bath for 30 s in order to break up zinc lumps. Subsequently, it was transferred into oil bath set on 30 °C for 18 h. After that time, the mixture was diluted with AcOEt, filtered through a cotton pad, and concentrated *in vacuo*. A crude product was purified using column chromatography.



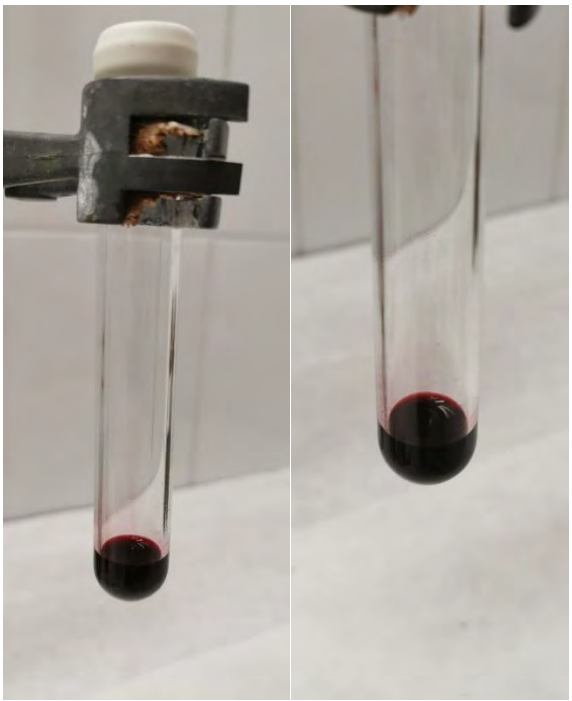
Reaction mixture before reduction of (CN)Cbl (**1**) – Co(III) form

Reaction mixture after reduction of (CN)Cbl (**1**) to the Co(I) form

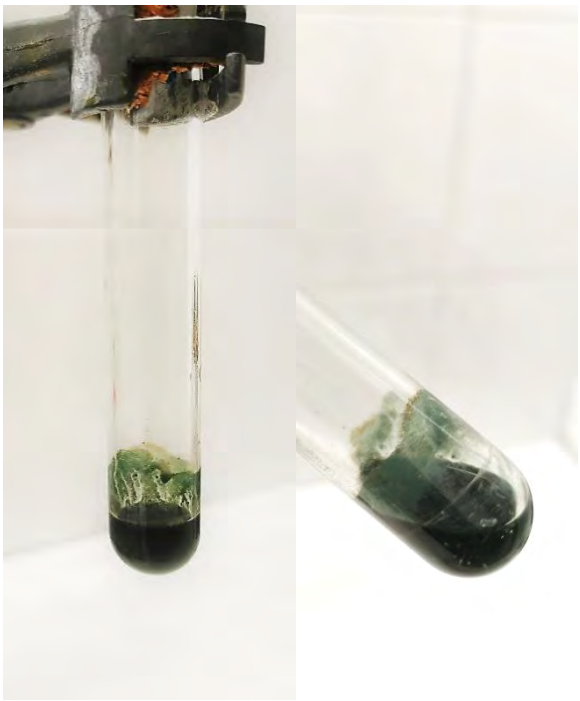
2.5 General procedure B for the opening and alkylation of D-A cyclopropanes



A glass reaction tube (inner diameter = 18 mm) equipped with a magnetic bar and sealed with a septum was charged with a donor-acceptor cyclopropane (0.2 mmol, 1.0 equiv.), HME (x) (24 mg, 0.02 mmol, 10 mol%), NH_4Cl (16 mg, 0.3 mmol, 1.5 equiv.), and activated zinc 39 mg, 0.6 mmol, 3.0 equiv.). Subsequently, MeOH (1.0 ml) was added and the resulting mixture was degassed 3x by simplified freeze-thaw method using dry ice as a cooling agent. Then, an electrophilic alkene (1 mmol, 5 equiv.) was added under argon. The reaction tube was placed in ultrasonic bath for 30 s in order to break up zinc lumps. Subsequently, it was transferred into oil bath set on 30 °C for 18 h. After that time, the mixture was diluted with AcOEt, filtered through a cotton pad, and concentrated *in vacuo*. A crude product was purified using column chromatography.



Reaction mixture before reduction of HME (**2**) – Co(III) form



Reaction mixture after reduction of HME (**2**) to the Co(I) form

3. Optimization details

3.1 Optimization of substrates ratio[a]

Entry	DAC **3** [mmol]	Michael acceptor **4a** [mmol]	Ratio **3**:**4a**	Yield of 5**a** [%][b]
1	0.1	0.15	1:1.5	14
2	0.1	0.3	1:3	24
3	0.1	0.5	1:5	50
4	0.1	1	1:10	71

[a] (CN)Cbl **1** (6 mol%), Zn (6 equiv), NH_4Cl (3 equiv), MeOH (c = 0.1 M), 18 h under Argon atmosphere, rt, blue LEDs (455 nm, 9 W). [b] GC yield.

3.2 Optimization of solvent

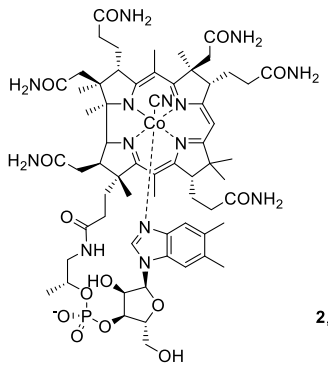
Entry	solvent	c of substrate **3** [M]	Yield of **5a** [%][b]
1	MeOH	0.03	37
2	MeOH	0.1	50
3	**MeOH**	**0.2**	**65**
4	MeOH	0.4	58
5	$MeOH_{anhydrous}$	0.2	61
6	**MeOH + H_2O (5 equiv.)**	**0.2**	**70**
7	MeOH + H_2O (10 equiv.)	0.2	64
8	MeOH + H_2O (25 equiv.)	0.2	54
9	*i*PrOH	0.2	0
10	DMF	0.2	11
11	EtOH	0.2	8
12	CF_3CH_2OH	0.2	7

[a] DAC **3** (0.10 mmol, 1 equiv.), alkene **4a** (0.5 mmol, 5 equiv.), (CN)Cbl **1** (6 mol%), Zn (3 equiv.), NH_4Cl (1.5 equiv.), 18 h under Argon atmosphere, rt, blue LEDs (455 nm, 9 W). [b] GC yield.

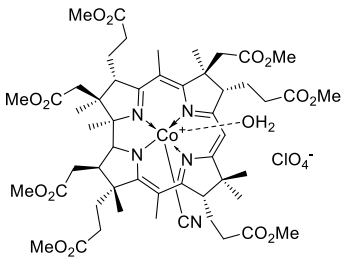
3.2 Cobalt catalysts screening[a]

Entry	Catalyst	Catalyst loading [mol%]	Yield of **5a** [%][b]
1	(CN)Cbl (**1**)	3	46
2	(CN)Cbl (**1**)	6	65
3	(CN)Cbl (**1**)	**10**	**73**
4	HME (**2**)	10	66
5	$Cbl(OH_2)^+Cl^-$ (**9**)	10	74
6	$Co(dmgH)_2py^iPr$ (**S11**)	10	0
7	HME Co(II) (**S12**)[c]	10	0

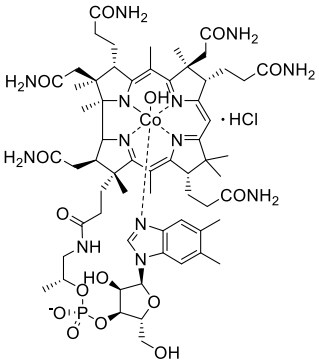
[a] DAC **3** (0.10 mmol, 1 equiv.), alkene **4a** (0.5 mmol, 5 equiv.), Zn (3 equiv.), NH_4Cl (1.5 equiv), MeOH (*c* = 0.1 M), 18 h under Argon atmosphere, rt, blue LEDs (455 nm, 9 W). [b] GC yield. [c] No zinc added.



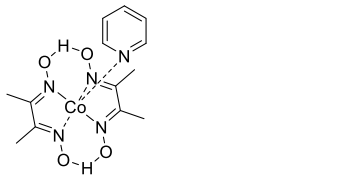
1, **(CN)Cbl**, Cyanocobalamin, **Vitamin B_{12}**



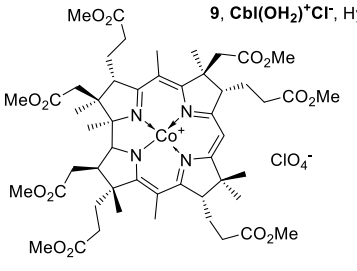
2, Aqua(cyano)heptamethyl cobyrinate (**HME**)



9, **$Cbl(OH_2)^+Cl^-$**, Hydroxocobalamin hydrochloride



S11, Chloro(pyridine)bis (dimethylglyoximato)cobalt(III)



S12, Heptamethyl cobyrinate(II)

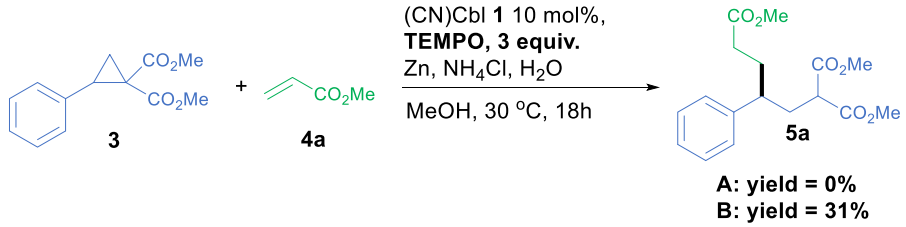
3.4 Activation mode for the cleavage of Co-C bond[a]

Entry	Activation mode for the cleavage of Co-C bond	Yield of **5a** [%][b]
1	Blue LEDs	73
2	No light, room temperature	62
3	**Heating: 30 °C**	**77**
4	Heating: 40 °C	59

[a] DAC **3** (0.10 mmol, 1 equiv.), alkene **4a** (0.5 mmol, 5 equiv.), (CN)Cbl **1** (10 mol%), Zn (3 equiv), NH_4Cl (1.5 equiv), MeOH (*c* = 0.1 M), 18 h under Argon atmosphere, rt, blue LEDs (455 nm, 9 W). [b] GC yield.

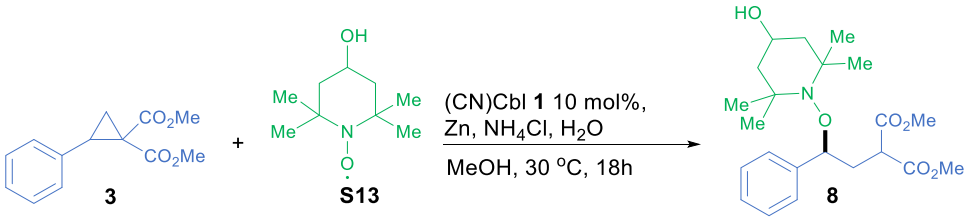
4. Mechanistic experiments

4.1 Experiment with radical trap



Experiment A: The reaction was set up according to general procedure A. Subsequently, 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO, 3 equiv.) was added and the reaction was stirred at 30 °C for 18 h. The reaction was then worked up as usual and analyzed with GC/FID with dodecane as a standard. In this case **we did not observe formation of a product**.

Experiment B: The reaction was set up according to general procedure A and it was stirred at 30 °C for 3 h. Subsequently, TEMPO (3 equiv.) was added and the reaction was stirred at 30 °C for another 15 h. The reaction was then worked up as usual and analyzed with GC/FID with dodecane as a standard. In this case **we observed formation of a product 5a in diminished yield (31%)**.



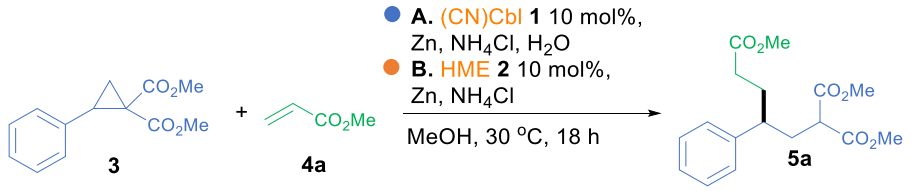
Experiment C: The reaction was set up according to general procedure A. Subsequently, TEMPOL (3 equiv.) was added and the reaction was stirred at 30 °C for 18 h. The reaction was then worked up as usual and analyzed with GC/FID with dodecane as a standard. In this case **we did not observe formation of a product**. The reaction was further investigated with ESI MS. HRMS ESI(+) analysis indicates formation of TEMPO adduct **8**.

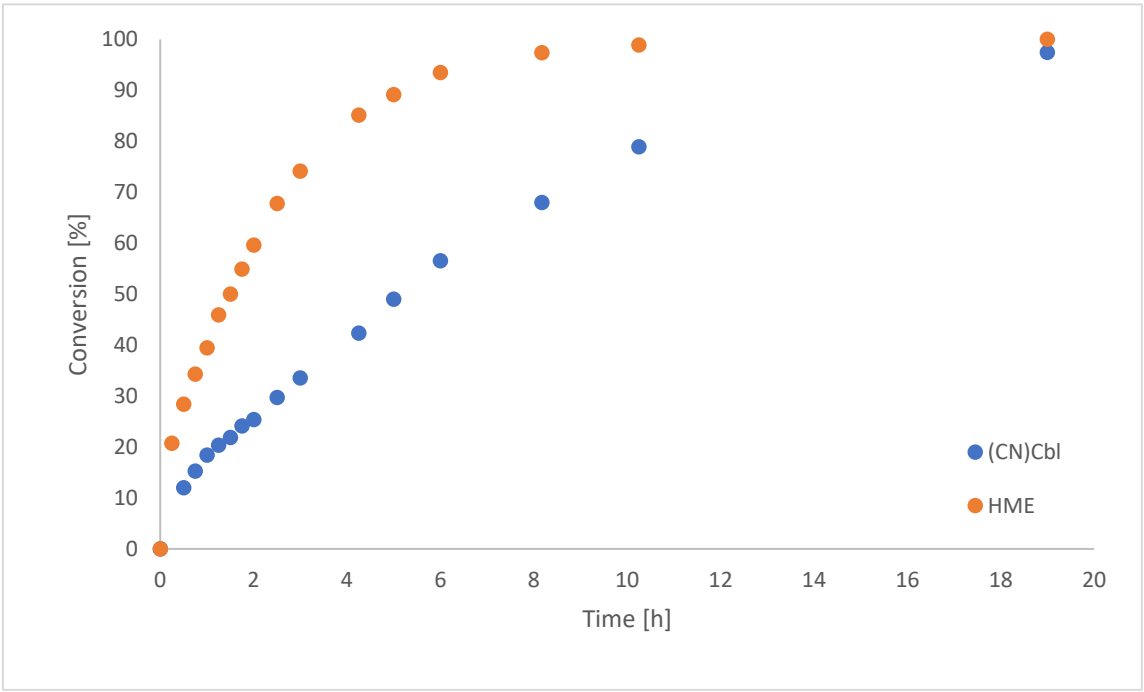
HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{34}NO_6$: 408.2378, found: 408.2386.

4.2 Kinetic studies

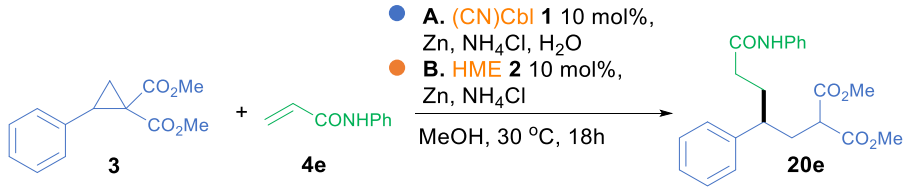
The reactions for individual compounds were set up following general procedures A or B on a 0.3 mmol scale with the addition of 1,3,5-trimetoxybenzene as an internal standard. The reactions were conducted for 18 – 20 hours and monitored by GC/FID.

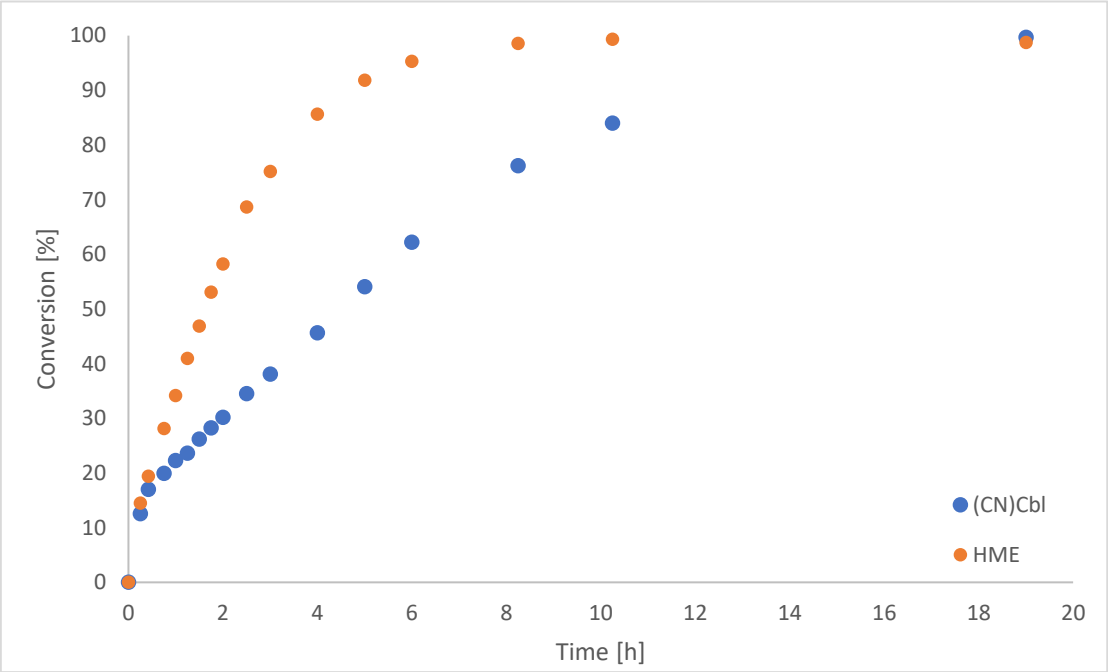
A. Kinetic studies of model reaction



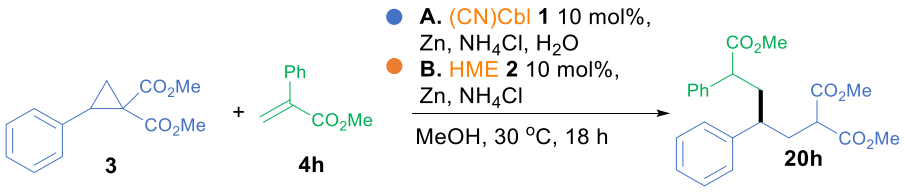


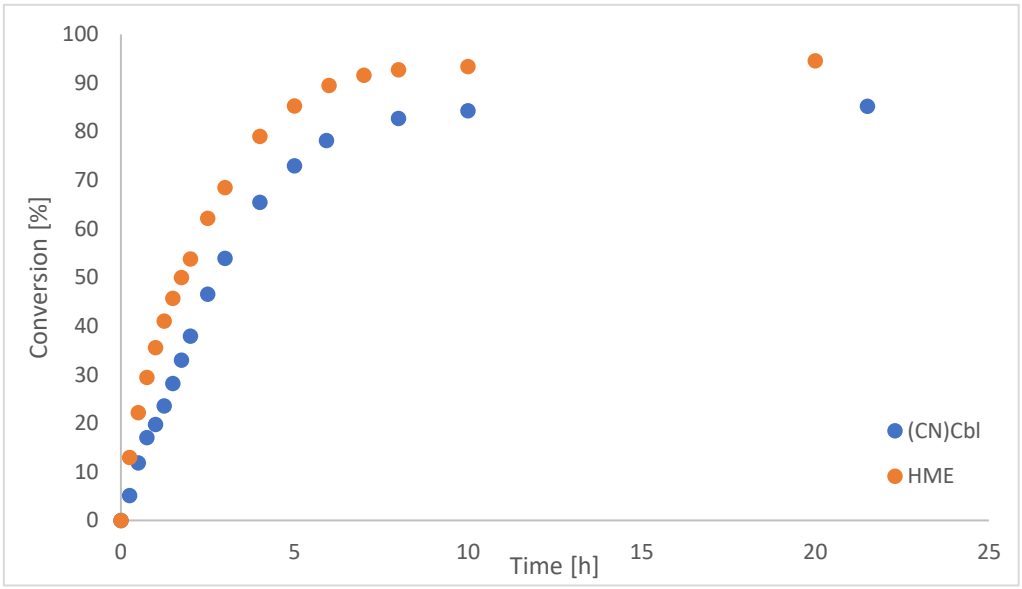
B. Kinetic studies of reaction of D-A cyclopropane 3 and olefin 4e.





C. Kinetic studies of reaction of D-A cyclopropane 3 and olefin 4h.

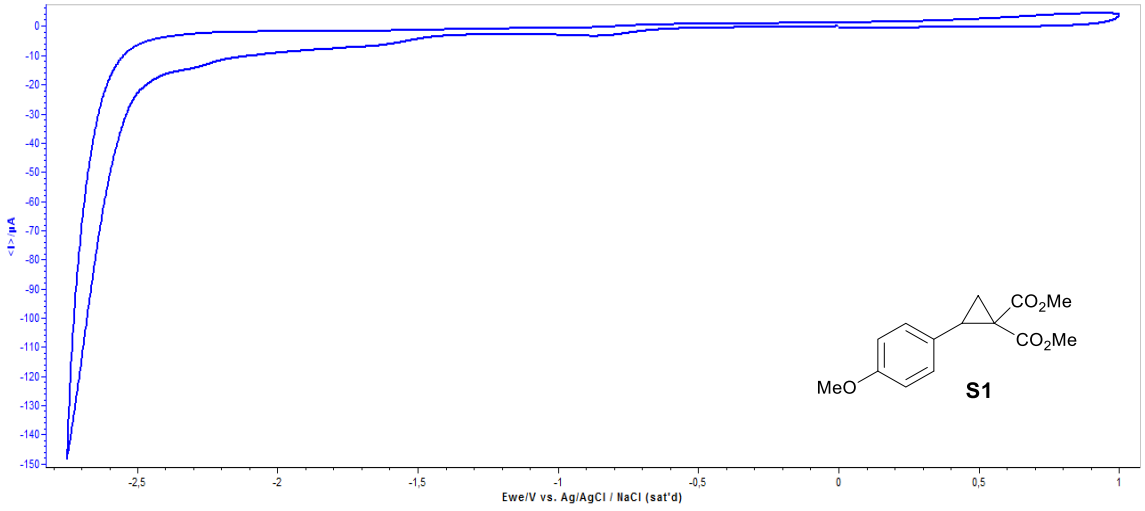


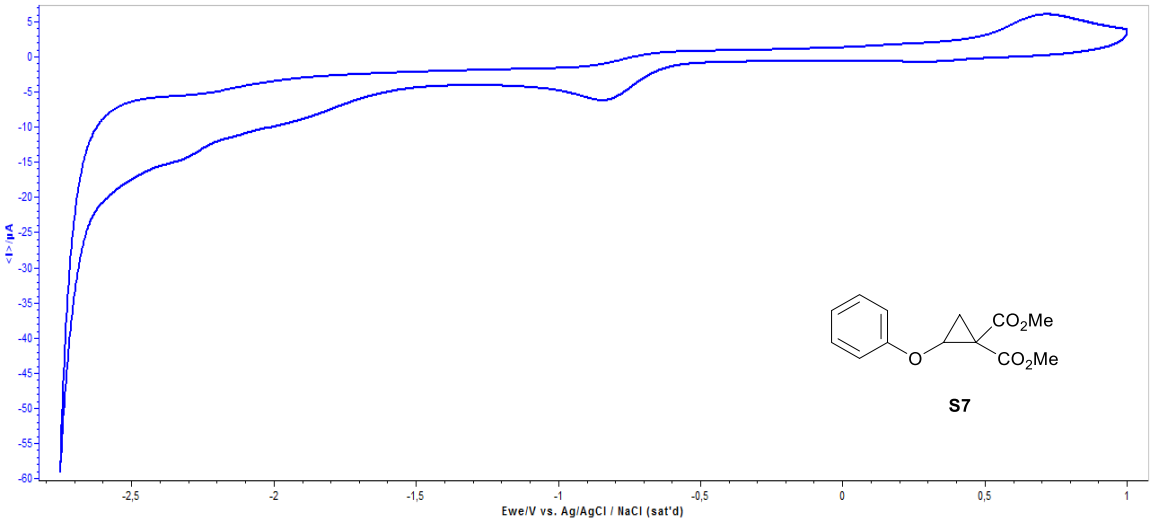


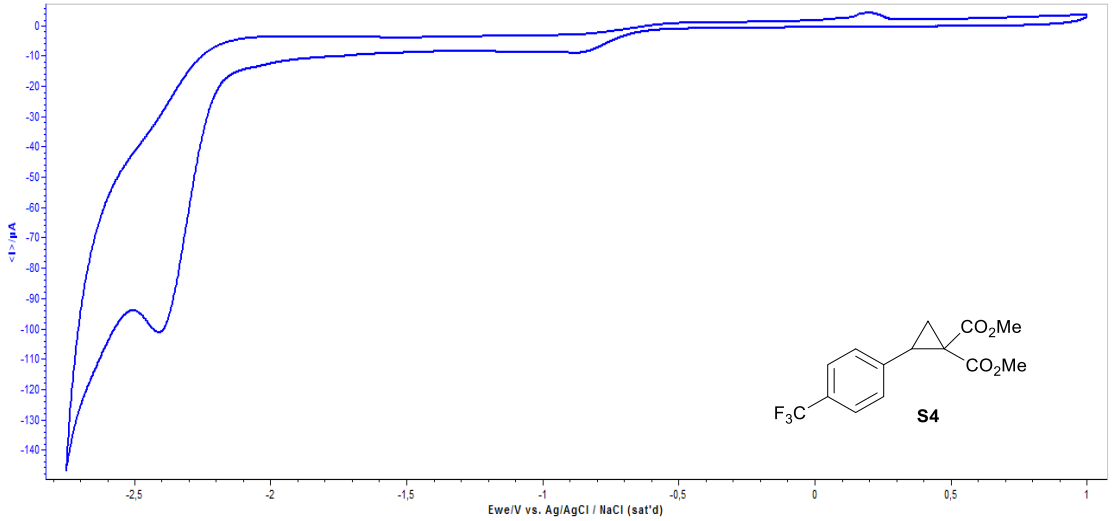
In all studied reactions the conversion rate of the substrate was higher for the ones catalyzed by HME (**2**). This observation is in accordance with our previous studies.

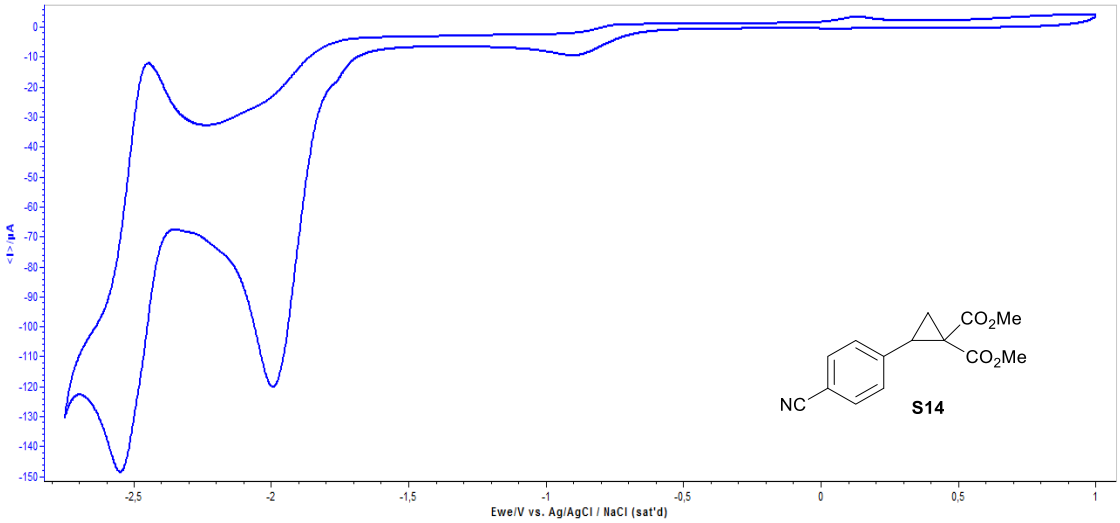
4.3 CV studies

A cylindrical three-electrode cell was equipped with a glassy carbon working electrode, a 25 mm platinum wire as the counter electrode and Ag/AgCl (3.0 M NaCl) electrode as the reference electrode. The scan rate for a typical experiment was 100 $mV \cdot s^{-1}$. The solution of donor-acceptor cyclopropane ($1.0 \cdot 10^{-2}$ M) and *n*-Bu_4NClO_4 (0.1 M) in dry MeCN was deaerated by Ar gas bubbling before the measurement, and the cyclic voltammetry was carried out under an Ar gas atmosphere at room temperature.



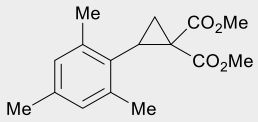
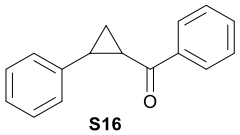
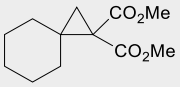
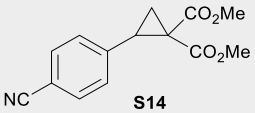
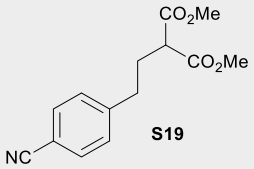
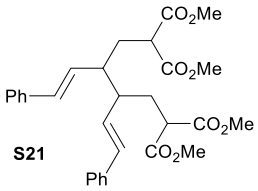
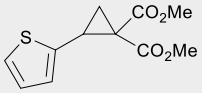
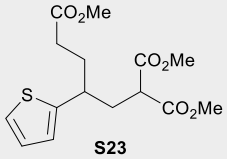






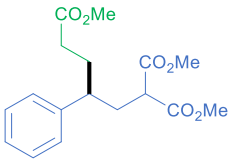
CV studies show correlation between the reaction performance and reduction potentials of selected D-A cyclopropanes. In the reaction of cyclopropane **S4** we observed significant amount of side-product being the result of opening and reduction of cyclopropane. In case of cyclopropane **S14**, the easiest to reduce, the product of opening and reduction reaction exclusively formed.

4.4 Unsuccessful examples

Entry	Substrate	Outcome	Product
1	 **S15**	No conversion	-
2	 **S16**	No conversion	-
3	 **S17**	No conversion	-
4	 **S18**	No conversion	-
5	 **S14**	DAC opened and reduced	 **S19**
6	 **S20**	Radical dimer **S21** as the only product	 **S21**
7	 **S22**	<10% of product **S23**	 **S23**

5. Scope and characterization of new compounds

Trimethyl 3-phenylpentane-1,1,5-tricarboxylate (5a)



Following General Procedure A, compound **5a** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 20:80 AcOEt/Hexanes) to afford 51 mg of compound **5a** as colorless oil. (**Yield = 79%**)

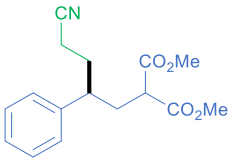
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.24 – 7.19 (m, 1H), 7.12 – 7.09 (m, 2H), 3.73 (s, 3H), 3.60 (s, 3H), 3.60 (s, 3H), 3.14 (dd, *J* = 9.8, 5.2 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.36 – 2.29 (m, 1H), 2.22 – 2.08 (m, 3H), 2.09 – 1.95 (m, 1H), 1.96 – 1.82 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 169.67, 169.65, 142.2, 128.7, 127.8, 127.0, 52.43, 52.43, 51.4, 49.8, 43.3, 35.4, 32.0, 31.8.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{22}O_6Na$: 345.1314, found: 345.1318.

Elemental analysis (%) calculated for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88, found: C, 63.54; H, 6.98.

Dimethyl 2-(4-cyano-2-phenylbutyl)malonate (5b)



Following General Procedure A, compound **5b** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and acrylonitrile (**4b**) (53 mg, 1.0 mmol). The crude product was purified by column chromatography (20:80 AcOEt/Hexanes) to afford 42 mg of compound **5b** as colorless oil. (**Yield = 72%**)

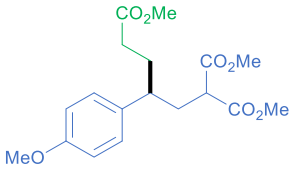
^{1}H NMR (400 MHz, $CDCl_3$) 1H NMR δ 7.38 – 7.29 (m, 2H), 7.29 – 7.22 (m, 1H), 7.17 – 7.08 (m, 2H), 3.75 (s, 3H), 3.60 (s, 3H), 3.14 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.68 (tt, *J* = 10.8, 4.3), 2.33 (ddd, *J* = 14.2, 9.8, 4.4 Hz, 1H), 2.24 – 2.11 (m, 2H), 2.11 – 1.98 (m, 2H), 1.95 – 1.81 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.44, 169.40, 140.5, 129.1, 127.7, 127.5, 119.1, 52.6, 52.5, 49.6, 42.8, 35.1, 32.3, 15.3.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{19}NO_4$: 312.1213, found: 312.1212.

Elemental analysis (%) calculated for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84, found: C, 66.39; H, 6.69; N, 4.84.

Trimethyl 3-(4-methoxyphenyl)pentane-1,1,5-tricarboxylate (10a)



Following General Procedure A, compound **10a** was obtained from D-A cyclopropane **S1** (47 mg, 0.20 mmol) (and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 20:80 AcOEt/Hexanes) to afford 51 mg of compound **10a** as colorless oil. (**Yield = 73%**)

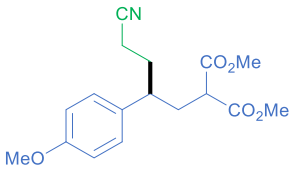
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.99 (m, 2H), 6.86 – 6.81 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.60 (s, 3H), 3.59 (s, 3H), 3.14 (dd, *J* = 9.9, 5.0 Hz, 1H), 2.50 (tt, *J* = 9.9, 4.6 Hz, 1H), 2.29 (ddd, *J* = 14.2, 9.9, 4.4 Hz, 1H), 2.21 – 2.03 (m, 3H), 2.05 – 1.92 (m, 1H), 1.89 – 1.79 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.8, 169.7, 158.5, 134.0, 128.7, 114.1, 55.2, 52.4, 51.4, 49.8, 42.4, 35.6, 32.1, 31.9.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{24}O_7Na$: 375.1418, found: 375.1420.

Elemental analysis (%) calculated for $C_{18}H_{24}O_7$: C, 61.35; H, 6.87, found: C, 61.13; H, 7.06.

Dimethyl 2-(4-cyano-2-(4-methoxyphenyl)butyl)malonate (10b)



Following General Procedure A, compound **10b** was obtained from D-A cyclopropane **S1** (53 mg, 0.20 mmol) and acrylonitrile (**4b**) (53 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 20:80 AcOEt/Hexanes) to afford 45 mg of compound **10b** as colorless oil. (**Yield = 70%**)

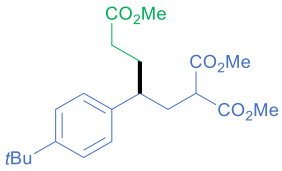
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 7.01 (m, 2H), 6.90 – 6.84 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.61 (s, 3H), 3.14 (dd, *J* = 9.9, 4.9 Hz, 1H), 2.69 – 2.56 (m, 1H), 2.30 (m, 1H), 2.24 – 2.09 (m, 2H), 2.09 – 1.97 (m, 2H), 1.93 – 1.76 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.52, 169.45, 158.9, 132.3, 128.6, 119.2, 114.5, 55.2, 52.6, 52.5, 49.6, 42.0, 35.3, 32.4, 15.3.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{21}NO_5Na$: 342.1321, found: 342.1317.

Elemental analysis (%) calculated for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39, found: C, 64.00; H, 6.66; N, 4.55.

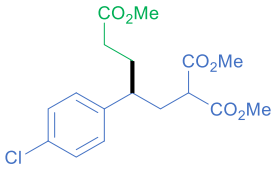
Trimethyl 3-(4-(*tert*-butyl)phenyl)pentane-1,1,5-tricarboxylate (11a)



Following General Procedure A, compound **11a** was obtained from D-A cyclopropane **S2** (58 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (20:80 AcOEt/Hexanes) to afford 57 mg of compound **11a** as colorless oil. (**Yield = 75%**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.3 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 3.73 (s, 3H), 3.59 (s, 6H), 3.17 (dd, *J* = 9.7, 5.3 Hz, 1H), 2.51 (tt, *J* = 9.9, 4.7 Hz, 1H), 2.30 (ddd, *J* = 14.0, 9.7, 4.5 Hz, 1H), 2.22 – 2.06 (m, 3H), 2.06 – 1.94 (m, 1H), 1.94 – 1.81 (m, 1H), 1.30 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.75, 169.73, 149.6, 138.9, 127.4, 125.5, 52.41, 52.39, 51.4, 49.8, 42.8, 35.5, 34.4, 32.1, 31.8, 31.3.
HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{30}O_6Na$: 401.1941, found: 401.1940.
Elemental analysis (%) calculated for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99, found: C, 66.42; H, 8.00.

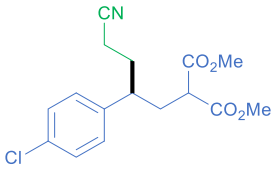
Trimethyl 3-(4-chlorophenyl)pentane-1,1,5-tricarboxylate (12a)



Following General Procedure A, compound **12a** was obtained from D-A cyclopropane **S3** (54 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 20:80 AcOEt/Hexanes) to afford 43 mg of compound **12a** as colorless oil. (**Yield = 60%**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.07 – 7.03 (m, 2H), 3.73 (s, 3H), 3.61 (s, 3H), 3.60 (s, 3H), 3.11 (dd, *J* = 9.8, 5.2 Hz, 1H), 2.55 (tt, *J* = 10.0, 4.7 Hz, 1H), 2.31 (ddd, *J* = 14.2, 9.8, 4.5 Hz, 1H), 2.19 – 2.06 (m, 3H), 2.05 – 1.97 (m, 1H), 1.89 – 1.81 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 169.52, 169.50, 140.7, 132.7, 129.1, 128.9, 52.53, 52.51, 51.5, 49.6, 42.7, 35.3, 31.9, 31.7.
HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{21}ClO_6Na$: 379.0923, found: 379.0924.
Elemental analysis (%) calculated for $C_{17}H_{21}ClO_6$: C, 57.23; H, 5.93, found: C, 57.12; H, 6.05.

Dimethyl 2-(4-cyano-2-(4-chlorophenyl)butyl)malonate (12b)



Following General Procedure A, compound **12b** was obtained from D-A cyclopropane **S3** (54 mg, 0.20 mmol) (and acrylonitrile (**4b**) (53 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 20:80 AcOEt/Hexanes) to afford 46 mg of compound **12b** as colorless oil. (**Yield = 71%**)

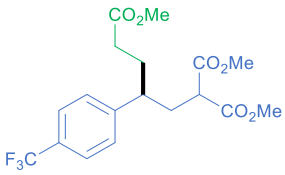
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.73 (s, 3H), 3.60 (s, 3H), 3.09 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.68 (tt, *J* = 10.6, 4.1 Hz, 1H), 2.31 (ddd, *J* = 14.1, 9.9, 4.3 Hz, 1H), 2.24 – 2.08 (m, 2H), 2.09 – 1.98 (m, 2H), 1.88 – 1.81 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.23, 169.19, 139.0, 133.3, 129.2, 129.0, 118.8, 52.6, 52.5, 49.4, 42.1, 35.0, 32.0, 15.2.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{18}NO_4NaCl$: 346.0826, found: 346.0822.

Elemental analysis (%) calculated for $C_{16}H_{18}ClNO_4$: C, 59.35; H, 5.60; N, 4.33, found: C, 59.18; H, 5.57; N, 4.40.

Trimethyl 3-(4-(trifluoromethyl)phenyl)pentane-1,1,5-tricarboxylate (13a)



Following General Procedure A, compound **13a** was obtained from D-A cyclopropane **S4** (60 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 20:80 AcOEt/Hexanes) to afford 43 mg of compound **13a** as colorless oil. (**Yield = 55%**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.73 (s, 3H), 3.60 (s, 6H), 3.10 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.66 (tt, *J* = 9.7, 4.6 Hz, 1H), 2.34 (ddd, *J* = 14.1, 9.6, 4.6 Hz, 1H), 2.21 – 2.00 (m, 4H), 1.96 – 1.85 (m, 1H).

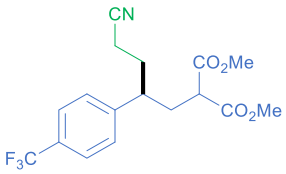
^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 169.40, 169.39 146.5, 129.3 (q, *J* = 32.6 Hz), 128.2, 125.7 (q, *J* = 3.8 Hz), 124.1 (q, *J* =271.9 Hz), 52.56, 52.51, 51.54, 49.61, 43.08, 35.16, 31.79, 31.53.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.6.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{21}F_3O_6Na$: 413.1184, found: 413.1188.

Elemental analysis (%) calculated for $C_{18}H_{21}F_3O_6$: C, 55.38; H, 5.42, found: C, 55.36; H, 5.32.

Dimethyl 2-(4-cyano-2-(4-(trifluoromethyl)phenyl)butyl)malonate (13b)



Following General Procedure A, compound **13b** was obtained from D-A cyclopropane **S4** (60 mg, 0.20 mmol) and acrylonitrile (**4b**) (53 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 20:80 AcOEt/Hexanes) to afford 44 mg of compound **13b** as colorless oil. (**Yield = 61%**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H)., 3.75 (s, 3H), 3.60 (s, 3H), 3.09 (dd, *J* = 9.7, 5.2 Hz, 1H), 2.80 (tt, *J* = 10.6, 4.6 Hz, 1H), 2.36 (ddd, *J* = 14.1, 9.7, 4.4 Hz, 1H), 2.27 – 2.15 (m, 2H), 2.14 – 2.00 (m, 2H), 1.96 – 1.85 (m, 1H).

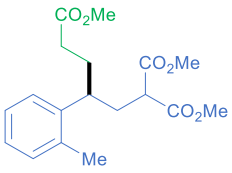
^{13}C NMR (125 MHz, $CDCl_3$) δ 169.16, 169.15, 144.9, 129.95 (q, *J* = 32.7 Hz), 128.1, 126.06 (q, *J* = 3.8 Hz), 123.90 (q, *J* = 272.1 Hz), 118.7, 52.7, 52.6, 49.4, 42.6, 34.8, 31.9, 15.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.65.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{18}NO_4Na\ F_3$: 380.1090, found: 380.1086.

Elemental analysis (%) calculated for $C_{17}H_{18}F_3NO_4$: C, 57.14; H, 5.08; N, 3.92, found: C, 57.09; H, 5.08; N, 3.73.

Trimethyl 3-(2-methylphenyl)pentane-1,1,5-tricarboxylate (14a)



A: Following General Procedure A, compound **14a** was obtained from D-A cyclopropane **S5** (50 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (15:85 AcOEt/Hexanes) to afford 31 mg of compound **14a** as colorless oil. (**Yield = 46%**) After the reaction, substrate could be seen on TLC and GC chromatogram. Therefore, additional reaction was conducted:

B: Following General Procedure A compound **14a** was obtained from D-A cyclopropane **S5** (50 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The reaction time was prolonged from 18 to 48 h. The crude product was purified by column chromatography (gradually from 5:95 to 15:85 Acetone/Hexanes) to afford 41 mg of compound **14a** as colorless oil. (**Yield = 61%**)

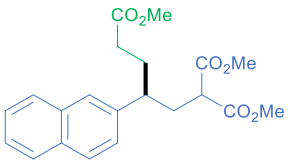
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.04 (m, 4H), 3.71 (s, 3H), 3.61 (s, 3H), 3.59 (s, 3H), 3.17 (dd, *J* = 9.2, 5.7 Hz, 1H), 2.97 (tt, *J* = 10.0, 5.2 Hz, 1H), 2.31 (ddd, *J* = 14.3, 9.2, 5.2 Hz, 1H), 2.22 (s, 3H), 2.21 – 2.08 (m, 3H), 2.08 – 1.95 (m, 1H), 1.94 – 1.80 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.73, 169.67, 140.5, 136.6, 130.5, 126.6, 126.4, 125.7, 52.44, 52.42, 51.4, 49.7, 35.2, 31.8, 31.6, 19.5.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{24}O_6Na$: 359.1469, found: 359.1471.

Elemental analysis (%) calculated for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19, found: C, 64.31; H, 7.29.

Trimethyl 3-naphthylpentane-1,1,5-tricarboxylate (15a)



Following General Procedure A, compound **15a** was obtained from D-A cyclopropane **S6** (57 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 10:90 to 20:80 AcOEt/Hexanes) to afford 38 mg of compound **15a** as colorless oil. (**Yield = 51%**)

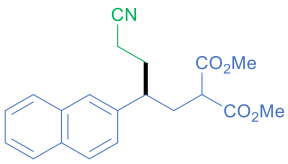
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.73 (m, 3H), 7.54 (s, 1H), 7.52 – 7.40 (m, 2H), 7.28 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.74 (s, 3H), 3.57 (s, 3H), 3.54 (s, 3H), 3.18 (dd, *J* = 9.7, 5.2 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.41 (ddd, *J* = 14.2, 9.7, 4.5 Hz, 1H), 2.33 – 2.22 (m, 1H), 2.21 – 2.07 (m, 3H), 2.07 – 1.94 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 169.65, 169.64, 139.5, 133.5, 132.6, 128.7, 127.6, 127.1, 126.1, 125.7, 125.2, 52.44, 52.38, 51.4, 49.8, 43.4, 35.4, 32.0, 31.6.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{24}O_6Na$: 395.1469, found: 395.1471.

Elemental analysis (%) calculated for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50, found: C, 67.46; H, 6.47.

Dimethyl 2-(4-cyano-2-naphthylbutyl)malonate (15b)



Following General Procedure A, compound **15b** was obtained from D-A cyclopropane **S6** (57 mg, 0.20 mmol) and acrylonitrile (**4b**) (53 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 10:90 to 20:80 AcOEt/Hexanes) to afford 53 mg of compound **15b** as colorless oil. (**Yield = 78%**)

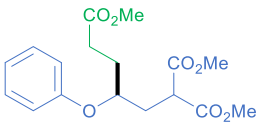
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.75 (m, 3H), 7.59 (s, 1H), 7.53 – 7.43 (m, 2H), 7.29 – 7.24 (m, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 3.16 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.41 (ddd, *J* = 14.1, 9.8, 4.4 Hz, 1H), 2.33 – 2.25 (m, 1H), 2.24 – 1.96 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 137.8, 133.4, 132.8, 129.1, 127.6, 127.3, 126.4, 126.0, 124.5, 119.1, 52.6, 52.4, 49.6, 42.9, 35.0, 32.1, 15.3.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{20}H_{21}NO_4Na$: 362.1360, found: 362.1368.

Elemental analysis (%) calculated for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13, found: C, 70.52; H, 6.21; N, 4.16.

Trimethyl 3-phenoxypentane-1,1,5-tricarboxylate (16a)



A: Following General Procedure A, compound **16a** was obtained from D-A cyclopropane **S7** (50 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 10:90 to 20:80 AcOEt/Hexanes) to afford 14 mg of compound **16a** as colorless oil. (**Yield = 21%**)

B: Following General Procedure B, compound **16a** was obtained from D-A cyclopropane **S7** (57 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 10:90 to 20:80 AcOEt/Hexanes) to afford 24 mg of compound **16a** as colorless oil. (**Yield = 35%**)

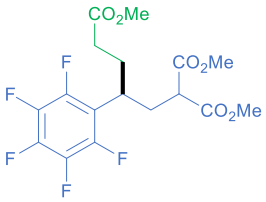
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.24 (m, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 2H), 4.43 (p, *J* = 5.9 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.66 – 3.61 (m, 3H + 1 H), 2.47 – 2.40 (m, 2H), 2.31 – 2.24 (m, 2H), 2.07 – 1.92 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 169.7, 169.5, 157.8, 129.6, 121.2, 115.7, 73.9, 52.6, 52.6, 51.6, 48.1, 33.1, 29.3, 28.8.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{22}O_7Na$: 361.1262, found: 361.1263.

Elemental analysis (%) calculated for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55, found: C, 60.11; H, 6.51.

Trimethyl 3-(perfluorophenyl)pentane-1,1,5-tricarboxylate (17a)



Following General Procedure A, compound **17a** was obtained from D-A cyclopropane **S8** (65 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 10:90 Acetone/Hexanes) to afford 19 mg of compound **17a** as colorless oil. (**Yield = 23%**)

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 3.16 – 3.12 (m, 2H), 2.41 – 2.33 (m, 2H), 2.25 – 2.16 (m, 2H), 2.13 – 2.04 (m, 2H).

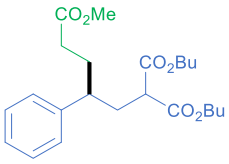
^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 168.95, 168.93, 146.6 – 146.4 (m), 144.6 – 144.4 (m) (from: 145.5, d, J = 246.1 Hz, C-F), 141.2 – 141.0 (m), 139.2 – 139.0 (m) (from: 140.1, d, J = 253.7 Hz, C-F), 138.7 – 138.5 (m), 136.7 – 136.5 (m) (from: 137.6, d, J = 252.0 Hz, C-F), 115.0 (t, J = 15.4 Hz, C), 52.71, 52.68, 51.7, 49.9, 33.3, 32.3, 32.0, 28.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ -141.59, -155.27 (t, J = 20.8 Hz), -161.42 (td, J = 21.8, 7.8 Hz).

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{17}F_5O_6Na$: 435.0846, found: 435.0843.

Elemental analysis (%) calculated for $C_{17}H_{17}F_5O_6$: C, 49.52; H, 4.16, found: C, 49.53; H, 4.14.

1,1-di-*n*-Butyl 5-methyl 3-phenylpentane-1,1,5-tricarboxylate (18a)



Following General Procedure A, compound **18a** was obtained from D-A cyclopropane **S9** (64 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (10:90 AcOEt/Hexanes) to afford 24 mg of compound **18a** as colorless oil. (**Yield = 30%**)

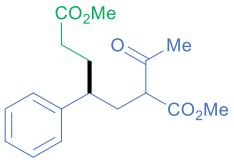
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.18 (m, 1H), 7.12 – 7.08 (m, 2H), 4.13 (t, J = 6.5 Hz, 2H), 4.06 – 3.94 (m, 2H), 3.59 (s, 3H), 3.10 (dd, J = 9.9, 5.0 Hz, 1H), 2.56 (tt, J = 9.9, 4.7 Hz, 1H), 2.30 (ddd, J = 14.3, 9.9, 4.6 Hz, 1H), 2.21 – 2.09 (m, 3H), 2.07 – 1.96 (m, 1H), 1.95 – 1.83 (m, 1H), 1.65 – 1.56 (m, 2H), 1.56 – 1.49 (m, 2H), 1.40 – 1.27 (m, 4H), 0.93 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.39, 169.36, 142.3, 128.7, 127.8, 126.9, 65.2, 65.1, 51.4, 50.1, 43.2, 35.4, 32.1, 31.8, 30.5, 30.4, 19.00, 18.94, 13.6.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{23}H_{34}O_6Na$: 429.2255, found: 429.2253.

Elemental analysis (%) calculated for $C_{23}H_{34}O_6$: C, 67.96; H, 8.43, found: C, 68.23; H, 8.67.

Dimethyl 2-acetyl-4-phenylheptanedioate (19a)



Following General Procedure A, compound **19a** was obtained from D-A cyclopropane **S10** (44 mg, 0.20 mmol) and methyl acrylate (**4a**) (86 mg, 1.0 mmol). The crude product was purified by column chromatography (20:80 AcOEt/Hexanes) to afford 21 mg of compound **19a** as colorless oil (mixture of diastereomers, ratio = 48:52). (**Yield = 35%**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.75 (s, 1H from enolate) 7.31 – 7.28 (m, 2H + 2H +2H), 7.25 – 7.19 (m, 1H + 1H + 1H), 7.09 – 7.07 (m, 2H + 2H +2H), 3.73 (s, 3H), 3.69 (s, 3H from enolate) 3.60 (s, 3H from enolate) 3.59 (s, 3H), 3.58 (s, 3H), 3.26 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.18 (dd, *J* = 10.0, 4.4 Hz, 1H), 2.55 – 2.45 (m, 1H + 1H), 2.35 – 2.22 (m, 1H = 1H), 2.20 – 1.94 (m, 4H + 4H), 2.13 (s, 3H), 2.03 (s, 3H), 1.93 – 1.81 (m, 1H + 1H).

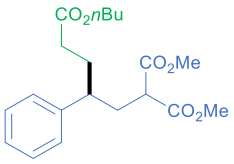
*Most of the enolate protons could not be clearly specified, therefore they are not listed above.

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 202.7, 173.66, 173.66, 170.1, 169.9, 142.35, 142.32, 128.78, 128.76, 127.73, 127.71, 126.98, 126.95, 57.6, 57.0, 52.37, 52.34, 51.5, 43.4, 43.1, 34.6, 34.5, 32.02, 31.97, 31.9, 31.8, 29.7, 28.7.

HRMS (ESI) $[M-H]^-$ calculated for $C_{17}H_{21}O_5$: 305.1383, found: 305.1389.

Elemental analysis (%) calculated for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24, found: C, 66.39; H, 7.31.

5-*n*-Butyl 1,1-dimethyl 3-phenylpentane-1,1,5-tricarboxylate (5c)



Following General Procedure A, compound **5c** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and *n*-butyl acrylate (**4c**) (128 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 10:90 AcOEt/Hexanes) to afford 52 mg of compound **5c** as colorless oil. (**Yield = 72%**)

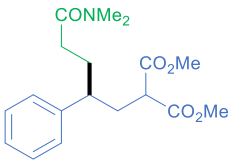
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 1H), 7.13 – 7.09 (m, 2H), 4.09 – 3.94 (m, 2H), 3.73 (s, 3H), 3.60 (s, 3H), 3.15 (dd, *J* = 9.8, 5.2 Hz, 1H), 2.56 (tt, *J* = 9.8, 4.6 Hz, 1H), 2.32 (ddd, *J* = 14.2, 9.8, 4.4 Hz, 1H), 2.23 – 1.96 (m, 4H), 1.95 – 1.82 (m, 1H), 1.64 – 1.45 (m, 2H), 1.42 – 1.28 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 169.67, 169.64, 142.2, 128.7, 127.8, 126.9, 64.2, 52.4, 49.8, 43.3, 35.5, 32.3, 31.8, 30.6, 19.1, 13.6.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{20}H_{28}O_6Na$: 387.1784, found: 387.1782.

Elemental analysis (%) calculated for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74, found: C, 66.01; H, 7.84.

Dimethyl 2-(5-(dimethylamino)-5-oxo-2-phenylpentyl)malonate (5d)



Following General Procedure A, compound **xa** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and *N,N*-dimethylacrylamide (**4d**) (99 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 40:60 to 80:20 AcOEt/Hexanes) to afford 45 mg of compound **5d** as yellowish oil. (**Yield = 66%**)

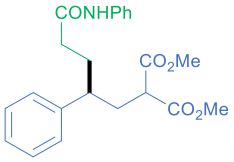
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 1H), 7.16 – 7.10 (m, 2H), 3.73 (s, 3H), 3.59 (s, 3H), 3.17 (dd, *J* = 9.5, 5.4 Hz, 1H), 2.88 (s, 3H), 2.81 (s, 3H), 2.65 – 2.52 (m, 1H), 2.33 (ddd, *J* = 14.2, 9.6, 4.6 Hz, 1H), 2.22 – 2.00 (m, 4H), 1.95 – 1.85 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 169.75, 169.74, 142.7, 128.7, 127.8, 126.8, 52.42, 52.39, 49.8, 43.4, 37.0, 35.6, 35.3, 31.9, 31.1.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{25}NO_5Na$: 358.1630, found: 358.1632.

Elemental analysis (%) calculated for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18, found: C, 64.43; H, 7.66; N, 4.23.

Dimethyl 2-(5-oxo-2-phenyl-5-(phenylamino)pentyl)malonate (5e)



Following General Procedure B, compound **5e** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and *N*-phenylacrylamide (**4e**) (147 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 20:80 to 25:75 AcOEt/Hexanes) to afford 53 mg of compound **5e** as yellowish oil. (**Yield = 69%**)

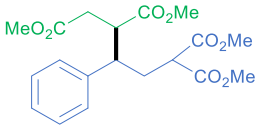
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.36 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 7.14 (d, *J* = 7.0 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.00 (s, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 3.18 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.67 – 2.55 (m, 1H), 2.37 (ddd, *J* = 14.0, 9.8, 4.3 Hz, 1H), 2.23 – 2.11 (m, 4H), 2.07 – 1.92 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.75, 169.68, 142.4, 137.9, 128.9, 128.8, 127.8, 127.0, 124.1, 119.7, 52.5, 52.4, 49.7, 43.2, 35.4, 32.1.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{25}NO_5Na$: 406.1630, found: 406.1633.

Elemental analysis (%) calculated for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65, found: C, 68.91; H, 6.64; N, 3.65.

Tetramethyl 3-phenylpentane-1,1,4,5-tetracarboxylate (5f)



A: Following General Procedure B, compound **5f** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and dimethyl fumarate (**4f**) (144 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 15:85 to 25:75 AcOEt/Hexanes) to afford 48 mg of compound **xa** in dimethyl fumarate reaction as colorless oil (mixture of diastereomers, ratio = 40:60). (**Yield = 63%**)

B: Following General Procedure B, compound **5f** was obtained 0 D-A cyclopropane **3** (47 mg, 0.20 mmol) and dimethyl maleate (**4f'**) (144 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 15:85 to 25:75 AcOEt/Hexanes) to afford 36 mg of compound **5f** as colorless oil (mixture of diastereomers, ratio = 40:60). (**Yield = 47%**)

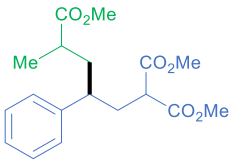
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 3H + 3H), 7.14 – 7.06 (m, 2H + 2H), 3.75 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.62 (s, 3H), 3.61 (s, 3H), 3.56 (s, 3H), 3.54 (s, 3H), 3.49 (s, 3H), 3.18 – 3.06 (m, 2H), 3.06 – 2.99 (m, 2H), 2.96 – 2.86 (m, 1H), 2.84 – 2.68 (m, 1H + 1H), 2.62 – 2.47 (m, 1H + 1H), 2.44 – 2.18 (m, 2H + 2H), 2.13 (dd, *J* = 16.8, 3.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.5, 172.2, 172.0, 169.44, 169.37, 169.2, 169.1, 139.3, 139.0, 129.0, 128.6, 128.3, 128.2, 127.6, 127.5, 52.5, 52.5, 52.4, 52.0, 51.8, 51.7, 49.7, 49.6, 47.5, 47.4, 45.8, 45.3, 35.1, 33.5, 32.8, 30.9.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{24}O_8Na$: 403.1369, found: 403.1366.

Elemental analysis (%) calculated for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36, found: C, 60.08; H, 6.40.

Trimethyl 3-phenylhexane-1,1,5-tricarboxylate (5g)



Following General Procedure A, compound **5g** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and methyl methacrylate (**4g**) (100 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually 5:95 to 10:90 Acetone/Hexanes) to afford 52 mg of compound **5g** as colorless oil (mixture of diastereomers, ratio = 32:68). (**Yield = 78%**)

Following General Procedure B, compound **5g** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and methyl methacrylate (**4g**) (100 mg, 1.0 mmol). The crude product was purified by column chromatography (15:85 AcOEt/Hexanes) to afford 52 mg of compound **5g** as colorless oil (mixture of diastereomers, ratio = 33:67). (**Yield = 78%**)

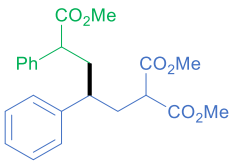
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H + 2H), 7.24 – 7.18 (m, 1H + 1H), 7.14 – 7.06 (m, 2H + 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H), 3.59 (s, 3H), 3.58 (s, 3H), 3.52 (s, 3H), 3.18 – 3.08 (m, 1H + 1H), 2.67 – 2.52 (m, 1H + 1H), 2.36 – 2.17 (m, 2H + 2H), 2.16 – 1.98 (m, 2H + 2H), 1.78 – 1.59 (m, 1H + 1H), 1.10 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 176.7, 169.7, 169.6, 142.6, 142.0, 128.7, 128.6, 127.81, 127.79, 126.9, 126.8, 52.42, 52.39, 51.5, 49.8, 49.7, 41.7, 41.4, 41.0, 40.1, 37.3, 37.2, 35.8, 35.5, 17.8, 16.6.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{24}O_6Na$: 359.1471, found: 359.1475.

Elemental analysis (%) calculated for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19, found: C, 64.08; H, 7.22.

Trimethyl 3,5-diphenylpentane-1,1,5-tricarboxylate (5h)



Following General Procedure A, compound **5h** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and methyl 2-phenylacrylate (**4h**) (162 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 10:90 to 15:85 AcOEt/Hexanes) to afford 54 mg of compound **5h** as yellowish oil (mixture of diastereomers, ratio = 45:55). (**Yield = 67%**)

Following General Procedure B, compound **5h** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and methyl 2-phenylacrylate (**4h**) (162 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 10:90 to 15:85 AcOEt/Hexanes) to afford 64 mg of compound **5h** as yellowish oil (mixture of diastereomers, ratio = 45:55). (**Yield = 80%**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 6H + 6H), 7.19 – 7.14 (m, 2H + 2H), 7.09 – 7.01 (m, 2H + 2H), 3.69 (s, 3H), 3.64 (s, 3H), 3.61 (s, 3H), 3.59 (s, 3H), 3.53 (s, 3H), 3.51 (s,

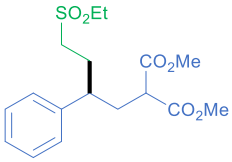
3H), 3.38 (dd, J = 9.5, 5.4 Hz, 1H), 3.30 (dd, J = 9.7, 5.2 Hz, 1H), 3.15 (dd, J = 9.4, 5.5 Hz, 1H), 3.09 (dd, J = 9.0, 5.8 Hz, 1H), 2.61 – 2.44 (m, 2H), 2.42 – 2.07 (m, 7H), 2.02 – 1.90 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 173.9, 169.6, 169.5, 169.52, 169.46, 142.4, 141.9, 139.1, 138.2, 128.74, 128.67, 128.6, 128.2, 128.0, 127.73, 127.69, 127.4, 127.2, 126.99, 126.96, 52.39, 52.38, 52.32, 52.30, 51.9, 51.9, 49.81, 49.77, 49.1, 49.0, 41.8, 41.1, 40.7, 39.4, 35.9, 35.3.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{23}H_{26}O_6Na$: 421.1627, found: 421.1631.

Elemental analysis (%) calculated for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58, found: C, 69.00; H, 6.71.

Dimethyl 2-(4-(ethylsulfonyl)-2-phenylbutyl)malonate (5i)



Following General Procedure B, compound **5i** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and ethyl vinyl sulfone (**4i**) (120 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 20:80 to 40:60 AcOEt/Hexanes) to afford 21 mg of compound **5i** as colorless oil. (**Yield = 30%**)

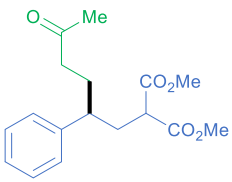
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 7.4 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.15 – 7.10 (m, 2H), 3.74 (s, 3H), 3.61 (s, 3H), 3.14 (dd, J = 9.9, 5.0 Hz, 1H), 2.89 (q, J = 7.5 Hz, 2H), 2.80 (ddd, J = 13.8, 11.3, 5.3 Hz, 1H), 2.72 – 2.61 (m, 2H), 2.35 (ddd, J = 14.2, 9.9, 4.4 Hz, 1H), 2.29 – 2.14 (m, 2H), 2.14 – 2.02 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.46, 169.42, 140.9, 129.1, 127.6, 127.5, 52.56, 52.53, 50.0, 49.5, 47.1, 42.7, 35.4, 28.60, 6.5.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{24}O_6S$: 379.1191, found: 379.1194.

Elemental analysis (%) calculated for $C_{17}H_{24}O_6S$: 57.29; H, 6.79, found: C, 57.45; H, 7.04.

Dimethyl 2-(5-oxo-2-phenylhexyl)malonate (5j)



Following General Procedure B, compound **5j** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and methyl vinyl ketone (**4j**) (70 mg, 1.0 mmol). The crude product was purified by column chromatography (20:80 AcOEt/Hexanes) to afford 26 mg of compound **5j** as colorless oil. (**Yield = 43%**)

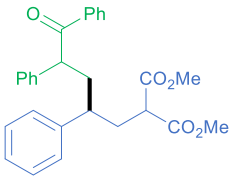
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.26 – 7.17 (m, 1H), 7.13 – 7.06 (m, 2H), 3.73 (s, 3H), 3.60 (s, 3H), 3.14 (dd, J = 9.8, 5.2 Hz, 1H), 2.52 (tt, J = 10.0, 4.8 Hz, 1H), 2.36 – 2.07 (m, 4H), 2.01 (s, 3H), 2.01 – 1.91 (m, 1H), 1.88 – 1.76 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 169.7, 142.5, 128.7, 127.7, 126.9, 52.42, 52.40, 49.8, 43.1, 41.4, 35.6, 30.4, 29.9.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{22}O_5Na$: 329.1365, found: 329.1375.

Elemental analysis (%) calculated for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24, found: C, 66.49; H, 7.30.

Dimethyl 2-(5-oxo-2,4,5-triphenylpentyl)malonate (5k)



Following General Procedure B, compound **5k** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and 1,2-diphenyl-2-propen-1-one (**4k**) (208 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 5:95 to 10:90 AcOEt/Hexanes) to afford 67 mg of compound **5k** as yellowish oil (mixture of diastereomers, ratio = 40:60). (**Yield = 77%**)

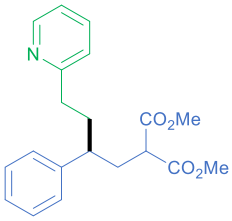
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 2H + 2H), 7.46 – 7.38 (m, 1H + 1H), 7.37 – 7.10 (m, 12H + 10H), 7.05 – 7.00 (m, 2H), 4.37 – 4.27 (m, 1H + 1H), 3.71 (s, 3H), 3.58 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H), 3.19 (dd, J = 9.1, 5.7 Hz, 1H), 3.12 (dd, J = 8.9, 6.1 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.58 (tt, J = 10.1, 4.8 Hz, 1H), 2.45 – 2.11 (m, 5H + 2H), 1.96 (ddd, J = 13.9, 9.7, 4.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 169.7, 169.6, 169.54, 169.46, 142.8, 142.5, 139.6, 138.5, 136.9, 136.4, 132.8, 132.7, 128.9, 128.8, 128.73, 128.65, 128.54, 128.50, 128.4, 128.3, 128.11, 128.0, 127.9, 127.1, 126.98, 126.89, 52.43, 52.36, 52.30, 52.26, 50.92, 50.90, 49.90, 49.84, 41.84, 41.2, 41.0, 39.8, 36.1, 35.6.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{28}O_5Na$: 467.1834, found: 467.1833.

Elemental analysis (%) calculated for $C_{28}H_{28}O_5$: C, 75.66; H, 6.35, found: C, 75.70; H, 6.40.

Dimethyl 2-(2-phenyl-4-(pyridin-2-yl)butyl)malonate (5l)



Following General Procedure B, compound **5l** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and 2-vinylpyridine (**4l**) (105 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 30:70 to 40:60 AcOEt/Hexanes) to afford 57 mg of compound **5l** as colorless oil. (**Yield = 83%**)

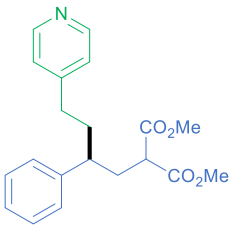
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.0 Hz, 1H), 7.52 (td, *J* = 7.7, 1.9 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 1H), 7.17 – 7.11 (m, 2H), 7.05 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 3.70 (s, 3H), 3.58 (s, 3H), 3.15 (dd, *J* = 9.8, 5.2 Hz, 1H), 2.71 – 2.52 (m, 3H), 2.36 (ddd, *J* = 14.2, 9.8, 4.5 Hz, 1H), 2.21 – 2.08 (m, 2H), 2.07 – 1.96 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.72, 169.69, 161.6, 149.1, 142.9, 136.3, 128.6, 127.8, 126.7, 122.8, 121.0, 52.3, 49.8, 43.6, 36.7, 36.1, 35.6.

HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{24}NO_4$: 342.1705, found: 342.1704.

Elemental analysis (%) calculated for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10, found: C, 70.14; H, 6.70; N 4.16.

Dimethyl 2-(2-phenyl-4-(pyridin-4-yl)butyl)malonate (5m)



Following General Procedure B, compound **5m** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and 4-vinylpyridine (**4m**) (105 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 30:70 to 40:60 AcOEt/Hexanes) to afford 49 mg of compound **5m** as yellowish oil. (**Yield = 72%**)

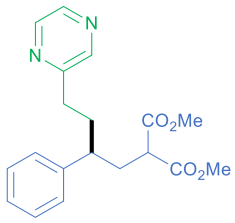
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.9 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.0 Hz, 2H), 7.00 (d, *J* = 5.1 Hz, 2H), 3.70 (s, 3H), 3.58 (s, 3H), 3.12 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.57 – 2.48 (m, 1H), 2.48 – 2.39 (m, 2H), 2.34 (ddd, *J* = 14.2, 9.9, 4.3 Hz, 1H), 2.14 (ddd, *J* = 13.9, 10.9, 5.0 Hz, 1H), 2.04 – 1.86 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 150.9, 149.6, 142.5, 128.7, 127.7, 126.9, 123.8, 52.4, 49.7, 43.2, 37.2, 35.5, 32.9.

HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{24}NO_4$: 342.1705, found: 342.1708.

Elemental analysis (%) calculated for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10, found: C, 69.96; H, 6.91; N, 3.96.

Dimethyl 2-(2-phenyl-4-(pyrazin-2-yl)butyl)malonate (5n)



Following General Procedure B, compound **5n** was obtained from D-A cyclopropane **3** (47 mg, 0.20 mmol) and 2-vinylpyrazine (**4n**) (106 mg, 1.0 mmol). The crude product was purified by column chromatography (gradually from 25:75 to 40:60 AcOEt/Hexanes) to afford 52 mg of compound **5n** as an off-white solid. (**Yield = 75%**)

m.p. 77.0 – 77.9 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.34 (d, *J* = 2.5 Hz, 1H), 8.30 (s, 1H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.26 – 7.17 (m, 1H), 7.17 – 7.11 (m, 2H), 3.71 (s, 3H), 3.60 (s, 3H), 3.17 (dd, *J* = 9.5, 5.3 Hz, 1H), 2.74 – 2.58 (m, 3H), 2.37 (ddd, *J* = 14.1, 9.6, 4.6 Hz, 1H), 2.23 – 2.01 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.66, 169.64, 157.3, 144.6, 144.0, 142.8, 142.1, 128.8, 127.9, 126.9, 52.3, 49.9, 43.7, 36.0, 35.7, 33.3.

HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{22}N_2O_4Na$: 365.1477, found: 365.1482.

Elemental analysis (%) calculated for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18, found: C, 66.85; H, 6.49; N; 8.05.

6. References

[1] F. De Simone, T. Saget, F. Benfatti, S. Almeida, J. Waser, *Chem. - A Eur. J.* **2011**, *17*, 14527–14538.

[2] X. Wang, J. Zhang, Y. He, D. Chen, C. Wang, F. Yang, W. Wang, Y. Ma, M. Szostak, *Org. Lett.* **2020**, *22*, 5187–5192.

[3] F. Shi, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *Chem. - A Eur. J.* **2012**, *18*, 6885–6894.

[4] J. E. Laudenschlager, L. A. Combee, M. K. Hilinski, *Org. Biomol. Chem.* **2019**, *17*, 9413–9417.

[5] M. Ociepa, A. J. Wierzba, J. Turkowska, D. Gryko, *J. Am. Chem. Soc.* **2020**, *142*, 5355–5361.

[6] M. E. Weiss, L. M. Kreis, A. Lauber, E. M. Carreira, *Angew. Chemie Int. Ed.* **2011**, *50*, 11125–11128.

[7] A. U. Augustin, M. Busse, P. G. Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 820–823.

[8] S. R. Goudreau, D. Marcoux, A. B. Charette, *J. Org. Chem.* **2009**, *74*, 470–473.

[9] F. González-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillant, *Adv. Synth. Catal.* **2008**, *350*, 813–816.

[10] D. A. Dias, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3694–3697.

[11] R. Talukdar, D. P. Tiwari, A. Saha, M. K. Ghorai, *Org. Lett.* **2014**, *16*, 3954–3957.

[12] J. Wallbaum, L. K. B. Garve, P. G. Jones, D. B. Werz, *Org. Lett.* **2017**, *19*, 98–101.

[13] P. Müller, A. Ghanem, *Org. Lett.* **2004**, *6*, 4347–4350.

7. NMR spectra

Widma NMR dostępne są w pełnej wersji pliku Supporting Information.

https://www.rsc.org/suppdata/d1/cc/d1cc05330b/d1cc05330b1.pdf

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Diazonium Ions | Hot Paper

Aliphatic Amines Unlocked for Selective Transformations through Diazotization

Jakub Durka, Barbara Zielińska, and Dorota Gryko**

Abstract: While aromatic diazonium salts are important reagents in organic synthesis, *'Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits.'*[1] In this work, we report that this statement is no longer valid, and it is now possible to control diazotization of aliphatic amines by utilizing isopentyl nitrite in HFIP. This transformation enabled electrophilic aromatic substitution with these highly abundant and commercially available alkyl reagents, as well as transforming them into building blocks typically employed in organic synthesis. The methodology opens an avenue for reactions involving aliphatic amines, even such demanding substrates as amino acids, as a source of carbocations thus expanding the degree of chemical space.

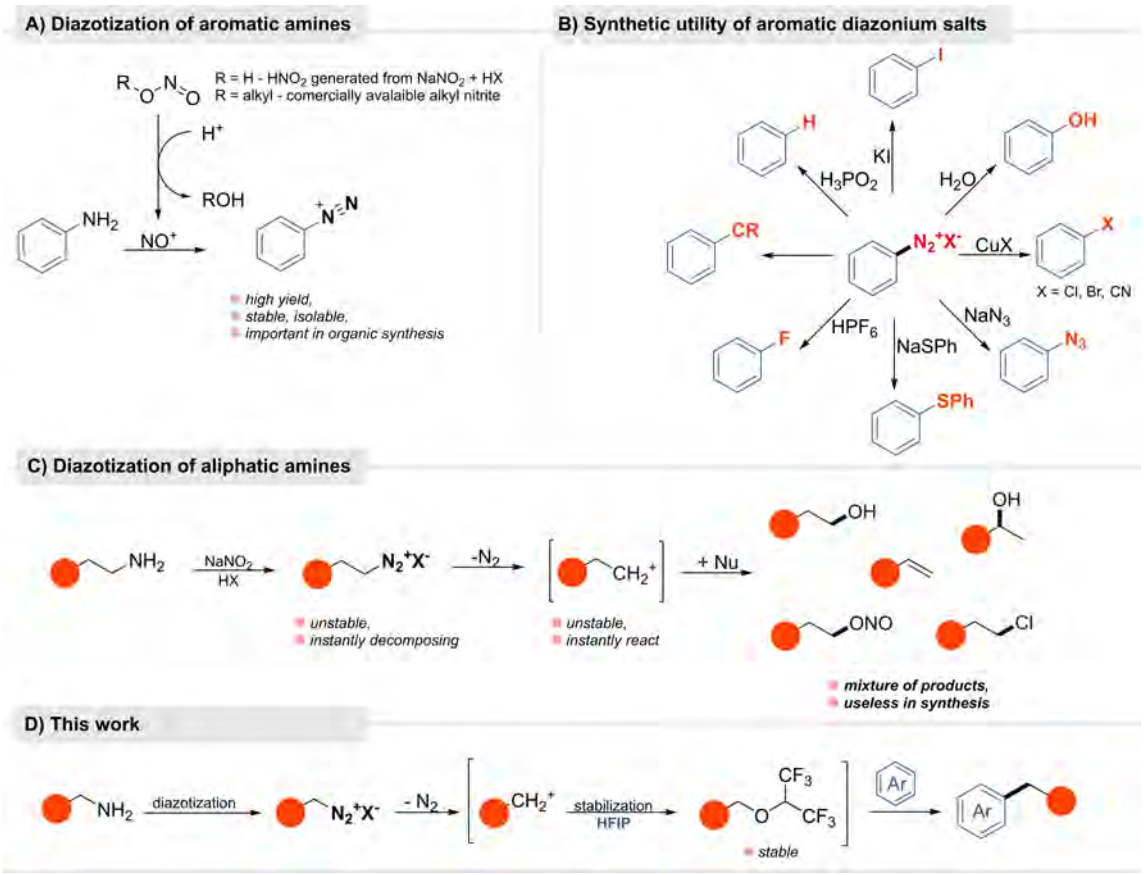
Introduction

Amines play a vital role in nature and have found numerous applications in the chemical industry.[1,2] Although they are produced on a large scale, they are mainly utilized in C–N bond forming reactions and rarely serve for the primary purpose of organic synthesis, which is to create new C–C bonds.[3] By expanding the scope of these transformations, these highly abundant and bench-stable reagents would immensely enhance the pool of available building blocks. Along these lines, several methods have been developed, but the most studied and widely applied is diazotization.[4,5] Developed in the 19th century, this reaction transforms aromatic amines into stable diazonium salts that are widely used as synthetic intermediates since N_2 is such a great leaving group (Scheme 1A).[6] A diazotization/dediazotization strategy allows for the replacement of the -NH_2 functionality with other substituents like –H, –F, –Cl, –Br, –I, –CN, –OH, –SPh, alkyl, aryl, etc (Scheme 1B).[5,6] Such reactions are, however, limited to aromatic amines. For aliphatic analogs, these reactions are commonly considered nonselective.[3,7] Aliphatic diazonium salts lack stabilization and therefore immediately release a nitrogen molecule generating a carbocation which captures any nucleophile present in the reaction medium (water, nitrite, the anion of the acid used, etc., Scheme 1C) to give a mixture of products, loses proton in elimination processes, or rearranges.[8,9] Consequently, this reaction is regarded as non-practical in organic synthesis; instead, other sources of carbocations that include alkenes, alcohols, or alkyl halides in the presence of acidic catalysts are employed.[10]

Diazotization reactions of aliphatic amines typically result in complex mixtures of products but over the last 140 years, isolated examples of selective reactions have been reported, usually involving intramolecular transformations. For example, aminomethyl-cycloalkanes undergo the Demjanov rearrangement leading to alcohols. Enlarged rings, ranging from cyclobutane to cyclononane, have been successfully obtained using this method. The Tiffeneau-Demjanov rearrangement proceeds similarly, diazotization of 1-(aminomethyl)-cycloalkanols gives access to ring-expanded ketones.[11] Furthermore, diazonium salts derived from α-amino acids do not decompose into a carbocation, but instead intramolecular nucleophilic attack by the neighboring carboxylate furnishes α-lactone. The subsequent S_N2 reaction with the concomitant strain-release gives access to optically pure 2-halo- and 2-hydroxy acids. Due to the non-cationic mechanism, the reaction is stereoselective and occurs with retention of configuration.[12,13] For diazonium salts with other electron-withdrawing groups, the intramolecular nucleophilic substitution cannot occur, instead deprotonation (if a hydrogen atom is present at the α-position), leading to the formation of stabilized diazo compounds, is taking place.[14,15] These compounds have gained huge importance in organic synthesis, commonly used in reactions catalyzed by transition metals, or induced by light.[16] While, in general, diazotization reactions in the presence of thiols resulted in the formation of disulfides, there are exceptions, as in the case of 2-mercaptobenzothiazole that selectively gives sulfides.[17]

Although isolated examples for selective diazotization of aliphatic amines do exist,[10–13,17] a general method for simple

[*] J. Durka, B. Zielińska, Prof. D. Gryko
Institute of Organic Chemistry Polish Academy of Sciences
Kasprzaka 44/52, 01-224 Warsaw, Poland
E-mail: jakub.durka@icho.edu.pl
dorota.gryko@icho.edu.pl
B. Zielińska
Department of Chemistry
Warsaw University of Technology
Noakowskiego 3, 00-664 Warsaw, Poland



Scheme 1. Diazotization of amines.

aliphatic amines remains to be found. With this goal in mind, we challenged ourselves to develop a system enabling selective deaminative transformations of aliphatic amines via a diazotization/dediazotization strategy. We hypothesized that this transformation could be realized if the carbocation generated from a diazonium salt is transiently transformed into an intermediate that subsequently can participate in the electrophilic aromatic substitution in the reaction system/ environment. We have found that the use of HFIP for the diazotization step assures the selectivity of the Friedel–Crafts alkylation, halogenation, carboxylation reactions (Scheme 1D). This method extends the diazonization strategy to aliphatic amines.

Results and Discussion

Reaction Design and Optimization of the Reaction Conditions

Aliphatic amines easily form diazonium salts. These are extremely reactive species and thus are challenging to handle and utilize in controlled synthetic procedures. The diazotization/dediazotization selectivity could potentially be enhanced by a) stabilization of the carbocation, b) limiting the number of available nucleophiles,and/ or c) reducing the nucleophilicity of the system. It is well-documented that fluorinated alcohols can dramatically influence the outcomes of chemical reactions by, among many effects, acting as mild acid catalysts or stabilizing cationic intermediates.[18] This proved to be particularly crucial in reactions with alcohols.[19,20] Recently, Lebauf, Moran, and co-workers have shown that in the Friedel–Crafts arylation with primary aliphatic alcohols and epoxides, a protonated cluster of HFIP molecules acts as a Brønsted acid and lowers the kinetic barriers associated with dearomatization and assures selectivity.[21] We thus anticipated that by stabilizing carbocations, hexafluoroisopropanol (HFIP, **1**)[22] might also have a beneficial effect on reactions of aliphatic amines involving diazonium salts.

HFIP should impart the selective diazotization/dediazotization of aliphatic amines because:

a) due to it is high polarity and mild acidity ($pK_a = 9.3$), it serves as an excellent hydrogen bond donor providing extensive stabilization of carbocations.[18] It has been frequently employed in reactions involving these reactive intermediates, for example in Friedel–Crafts type transformations with alcohols,[23–27]
b) due to its acidity, the generation of highly stabilized carbocations obviates the need for the addition of classically used Brønsted or Lewis acids, hence, ensuring milder reaction conditions.[19,28] For example, polymerization of styrenes in this solvent occurs without any stimuli.[29] In our case, it should facilitate the generation of the nitrosonium cation from alkyl nitrites. Conse-

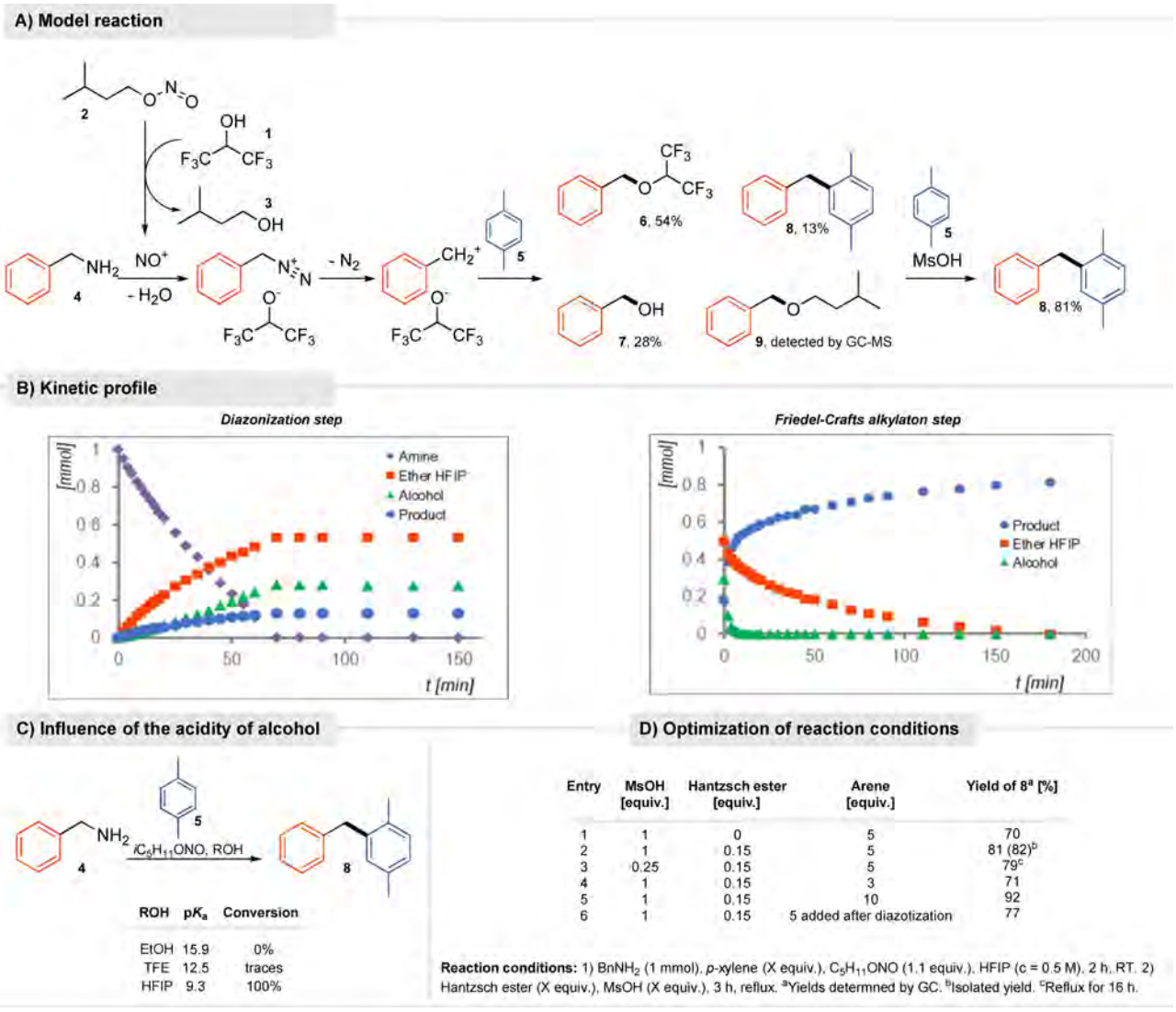
quently, the alkyl nitrite would be the sole reagent in the reaction, in addition to amine, thereby limiting the number of nucleophiles present in the solution,

c) due to its exceptionally low nucleophilicity; the inductive effect of the two $-CF_3$ groups renders HFIP much less nucleophilic than alcohol or water,[18] typically used in diazotization reactions, thus side reactions (related to solvent) should be limited,

d) according to the data available in the Mayr's Database of Reactivity Parameters, not only does HFIP itself exhibit low nucleophilicity, but also it is capable of reducing the nucleophilicity of other molecules present in the solution with which it forms hydrogen bonds.[30] This is particularly significant as the complete elimination of nucleophiles from the diazotization reaction is impossible; by definition, 1) the respective alcohol is a byproduct formed from the nitrite, 2) during the reaction an equivalent of water is released,

e) once the carbocation is generated from a diazonium salt, it may react with nucleophilic species (HFIP, alcohol, water) affording by-products (hexafluoroisopropyl ether, alkyl ether, and alcohol). However, HFIP is known to facilitate acid-catalyzed C–O bond cleavage regenerating carbocationic intermediates from such species.[21,24,31] Therefore, we anticipated that the addition of an acid would assure their transformation to the desired product.

To verify our hypothesis, we performed the model reaction of benzylamine (**4**) with isopentyl nitrite (**2**) and *p*-xylene (**5**) in HFIP which gave, the desired Friedel–Crafts derivative but as a minor product **8**, (13%), instead, benzyl HFIP ether **6** (54%), and benzyl alcohol (**7**, 28%) were observed (Scheme 2A). The GC-MS analysis additionally revealed the formation of benzyl isopentyl ether **9** though in traces. Of course, this ratio of primary products depends on the amine used and the arene activity – for example, for 4-



Scheme 2. Reaction design and optimization studies.

methoxybenzylamine, the Friedel–Crafts alkylation was already the main process. These experimental data indicate that the acidity of HFIP itself is sufficient for complete conversion of the amine without the need for the addition of an acid. As a consequence, diazotization can be conducted under mild conditions, limiting the formation of by-products, such as nitroso arenes.

Furthermore, the impact of the HFIP acidity is corroborated by the results obtained for the model reaction in other alcohols (Scheme 2C). Practically no conversion was observed for less acidic trifluoroethanol ($pK_a = 12.5$), while diazotization does not occur at all in ethanol.

The kinetic profile of the diazotization shows that hexafluoroisopropyl ether and the alkylated xylene are produced proportionally over time, while the rate of the benzyl alcohol formation slightly accelerates as the concentration of water increases during the reaction course (Scheme 2B).

The resulting products are stable in the reaction medium. Along this line, Lebauf, Moran, and co-workers reported that hexafluoro isopropyl ethers form rapidly during hydroarylation of enamides and serve as a slow-release reservoir for cations.[31] Waldvogel regarded benzyl hexafluoro isopropyl ether as a molecular mask for the benzylic cation.[32] Acid catalysis in HFIP has been documented to trigger transformations with alcohols and ethers. Thus, to push forward the Friedel-Crafts alkylation with transient ethers, the addition of an acid seemed required. In fact, the addition of MsOH (1 equiv.) increased the yield up to 70%. Kinetic studies revealed that electrophilic aromatic substitution is much faster for alcohol than for the electron deficient hexafluoro isopropyl ether (Scheme 2B). Indeed, the results corroborate our hypothesis that under the appropriate conditions aliphatic amines can serve as a useful source of carbocations, thus giving a solution to the problem that has drawn the interest of many groups over the years. The reaction developed proceeds in a two-step one-pot sequence with one purification step.

Next, efforts were made to increase the reaction yield and optimize its conditions (Scheme 2D, for details see Supplementary Section 3.9, page 8). Among the nitrosating agents (*t*BuONO, NBu_4NO_2, NMe_4NO_2, $NaNO_2$), *iso*pentyl nitrite proved to be the most versatile when used in a slight excess. The GC analysis of the crude reaction mixture revealed the formation of benzaldehyde. Presumably, after the addition of the acid, the remaining RONO oxidizes the alcohol formed. As a remedy to this issue, the addition of a reducing agent was foreseen. The Hantzsch ester (0.15 equiv., entry 2) acted most effectively. From now, the only side products observed in the model reaction resulted from subsequent benzylation of **8**, a known side reaction in electrophilic aromatic substitution. Typically, for Friedel–Crafts alkylation, it is beneficial to use an excess of the aromatic substrate. The yield gradually increased from 71% to 92% as the amount of *p*-xylene (**5**) increased (from 3 to 10 equivalents, entries 4–5). Importantly, the reaction yield remained almost the same regardless of whether the aromatic substrate was added before or after the diazotization reaction (entries 2, 6). This feature enables the use of highly active aromatic substrates, which are susceptible to nitrosation or oxidation under such mild conditions. It was observed that for generating less stabilized carbocations it is beneficial to use TfOH over MsOH.

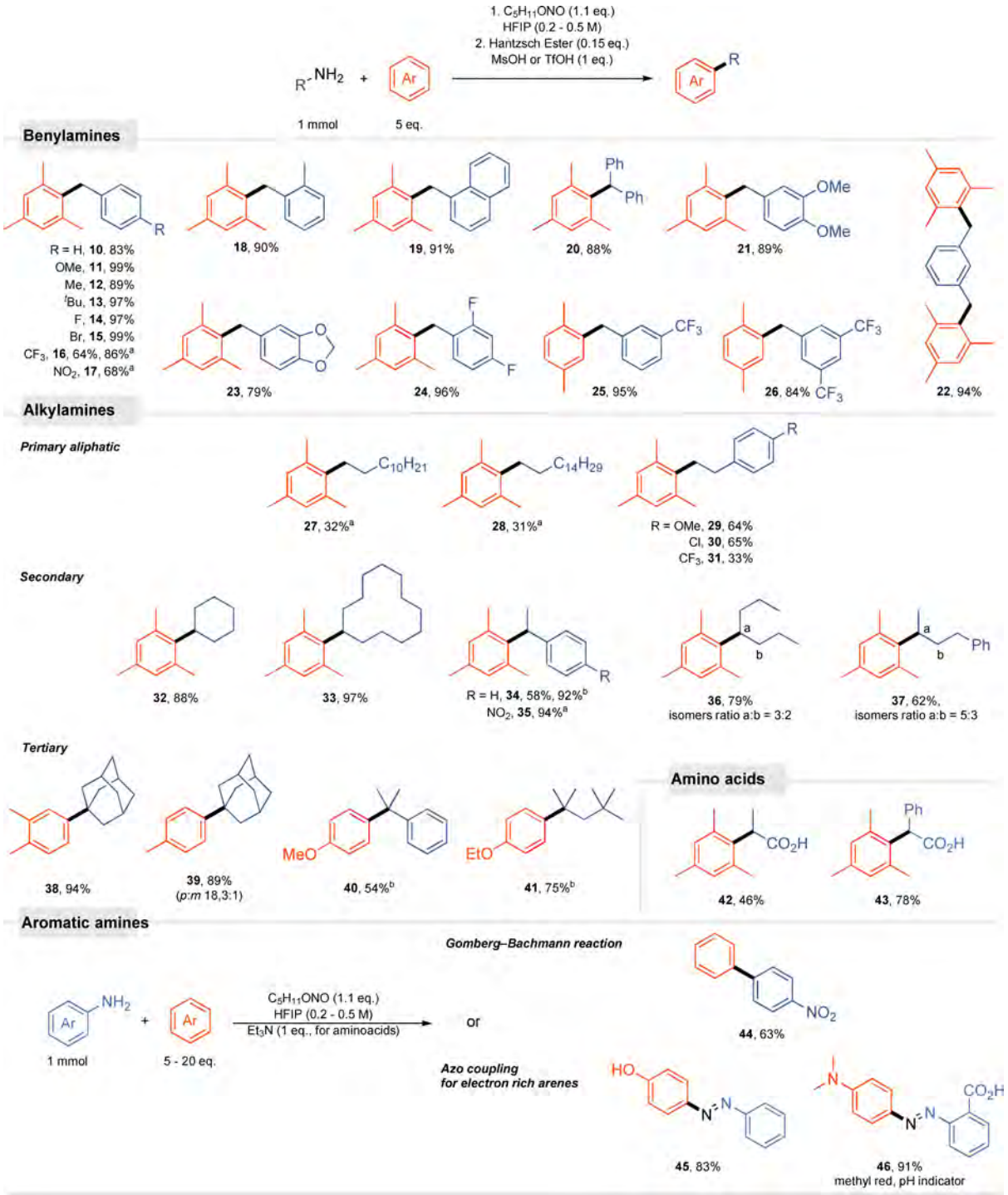
Optimized Conditions: Reaction conditions: 1) $BnNH_2$ (**4**, 1 mmol), *p*-xylene (**5**, 5 equiv.), $C_5H_{11}ONO$ (**2**, 1.1 equiv.), HFIP (**1**, $c = 0.5$ M), 2 h, RT. 2) Hantzsch ester (0.15 equiv.), MsOH (1 equiv.), 3 h, reflux.

Scope and Limitations

With the optimized conditions in hand, the scope of the Friedel–Crafts alkylation was evaluated. Electron-rich and electron-deficient benzylamines give desired products in good to excellent yields regardless of the substitution pattern. Even 3,5-bisCF_3- or 4-CF_3-benzylamines react efficiently with alkyl benzenes (Scheme 3). Product **16** degrades with time under the reaction conditions but the replacement of HFIP with AcOH in the diazotization step mitigates this issue. The acetate formed in this process generates a cation more easily compared to HFIP ether. Furthermore, steric hindrance imposed by the methyl group at the *ortho* position of benzylamine does not interfere with the process. Despite acidic conditions and alcoholic solvent, the acetal group is not cleaved (**23**).

Importantly, unstabilized linear alkylamines are suitable starting materials in the developed method. Under the optimized diazotization conditions, hexadecylamine gives a complex mixture of products; the modified protocol (AcOH in the place of HFIP for diazotization), however, ensures the formation of the desired product **28** in serviceable yield (31%). Here, significantly higher nucleophilicity of the acetate anion compared to HFIP ensures the formation of a transient intermediate ester before side rearrangements take place. Phenylethylamines performed much better, forming the corresponding products in good yields, presumably because of the mechanism involving the stabilized phenonium cation postulated by Lebauf and Moran as an intermediate in the dehydroxylative arylation of phenylethanols.[21] The use of the diazotization process enabled the synthesis of products with an electron withdrawing group at the phenyl ring **31**, which is not accessible via methods using alcohols as substrates.[21] In this case, a by-product resulting from the rearrangement to the stabilized benzyl cation forms. α-Secondary amines are also effective as alkylating reagents in the developed Friedel–Crafts alkylation.

Cycloalkyl reagents furnish products **32**, **33** in high yields whilst for linear secondary amines, a mixture of compounds forms due to a classical carbocation rearrangement. For 1-phenylethylamine, formation of styrene, a great electrophile acceptor leading to oligomerization, competes with the desired reaction pathway. In this case, the yield of 58% improves significantly upon the addition of NBu_4Br (1 equiv.). Assumingly, it prevents styrene oligomerization by transforming it into benzylic bromide that subsequently reacts via the S_N1 mechanism to give the final product. Furthermore, the Friedel–Crafts functionalization of arenes



Scheme 3. Friedel–Crafts alkylation with various aliphatic amines–scope and limitations. [a]Reaction conditions: 1) amine (1 mmol), AcOH (1.5 equiv.), $C_5H_{11}ONO$ (1.1 equiv.), DCE (c = 0.5 M). 2) Hantzsch ester (0.15 equiv.), HFIP (4 mL), arene (5 equiv.), MsOH or TfOH (1 equiv.). [b]NBu_4Br (1 equiv.) also added to the second step. Amino acids reaction conditions: amino acid (1 mmol), arene (20 equiv.), $C_5H_{11}ONO$ (1.1 equiv.), Et_3N (1 equiv.), HFIP (c = 0.17 M).

with tertiary alkyl carbocations is also possible as represented by reactions with adamantylamine. Non-cyclic substrates also required the addition of bromide, as previously described, to achieve alkylated arenes in good yields (**40**, **41**).

As mentioned earlier, amino acids are unique substrates for which diazotization reactions can be carried out with synthetically useful yields. The reaction is, however, usually performed in water, severely limiting its scope to simple, usually ionic nucleophiles. Although amino acids are insoluble in HFIP, the addition of base (NEt_3) to the

developed protocol proved to be beneficial, thus allowing uncharged, non-polar, carbon nucleophiles to be employed. Along this line, we have used alanine for the synthesis of an analogue of a nonsteroidal anti-inflammatory drugs (**42**).

This protocol gives access to 2-arylcarboxylic acids in synthethically useful yields in one-step, while the reported ibuprofen synthesis requires 3 steps and use of highly toxic hydrogen fluoride and carbon monoxide.[33]

An interesting trend can be observed for optically active substrates. Product **34** derived from (*R*)-α-methylbenzylamine was obtained as a racemic mixture, evidencing that the reaction proceeds via the assumed carbocation intermediate. When the methyl substituent was replaced with the carboxyl group, e.g. (*S*)-phenylglycine was used as a starting material, acid **43** formed with 10% ee. For (*S*)-alanine the ee increased to 81%. These results suggests the change in the reaction mechanism for amino acids, where the formation of chiral α-lactone governs the enantioselectivity of the transformation, hence the retention of configuration can be observed.[34] The low enantioselectivity for the reaction with (*S*)-phenylglycine indicates that the competitive mechanism through the phenyl-stabilized carbocation still dominates in contrast to (*S*)-alanine.

Not limited to the examples mentioned above, the diazotization protocol also enables the synthesis of aromatic diazonium salts. They can be obtained in situ from anilines and reacted with the aromatic compound present in the system. For weakly nucleophilic arenes, the Gomberg-Bachmann reaction takes place (**44**), while for phenol or aniline, diazo coupling occurs, leading to the corresponding dyes. In this way, methyl red **46**, a well-known pH indicator, was synthesized in an excellent yield of 91%. It is worth noting that this reaction occurs in one step, immediately after the addition of the alkyl nitrite, and thus, utilizing two-step procedures involving neutralization of nitrous acids in between, as in an aqueous environment, is not required.

Subsequently, the set of aromatic substrates was examined. Typically for Fiedel-Crafts type reactions, the yield increased with the nucleophilicity of the arene (**47**, **8**, **10**, **48**), but even 1,3-difluorobenzene was used efficiently benzylated (**51**) (Scheme 4). Alkylation of anisole, phenol, or acetanilide works well as represented by the synthesis of a substrate for the production of adapalene **55**. In electrophilic aromatic substitution, as the nucleophilicity of the arene decreases, the efficacy of the alkylation decreases. In our case, however, benzene or even deactivated 1,3-difluorobenzene is sufficiently reactive to afford product **51**. The presence of two hydroxyl groups effectively neutralizes the deactivating effect of electron-withdrawing groups, thus enabling exploration of a broader group of arenes. Along this line, the reaction tolerates all major EWGs, even the highly reactive aldehyde group (**57** - **60**). Furthermore, the use of HFIP allows for efficient alkylation of anilines despite their basic nature and susceptibility to diazotization. Here, we took advantage of the fact that the arene can be added after the diazonization step. Moreover, even the presence of a strongly deactivating nitro group does not interrupt the reaction, providing excellent yields (**66**). In addition to benzene derivatives, heteroaromatic compounds are also successfully employed. Both *N*-substituted and *N*-H indole give products **67** - **69** in good yields. Thiophene derivatives react excellently. Note that for most anilines and heteroaromatic compounds, diazotization employing acetic acid is more efficient.

To demonstrate the synthetic impact of our method, we chose the synthesis of compound **11** as a test reaction that was scaled by a factor of 10 and then 200. The experiment on a 10 mmol scale showed that reducing the amount of arene to 2.5 equiv. did not affect the efficacy of the reaction (99% versus 93%). From the 200 mmol scale, the desired product was isolated by crystallization (45.2 g, 94% yield,95% purity) with no erosion of selectivity or yield. HFIP was recovered by distillation (89%) and can thus be reused, which makes the protocol possible for technical applications. Despite the evolution of nitrogen, the reaction on such a scale was weakly exothermic.

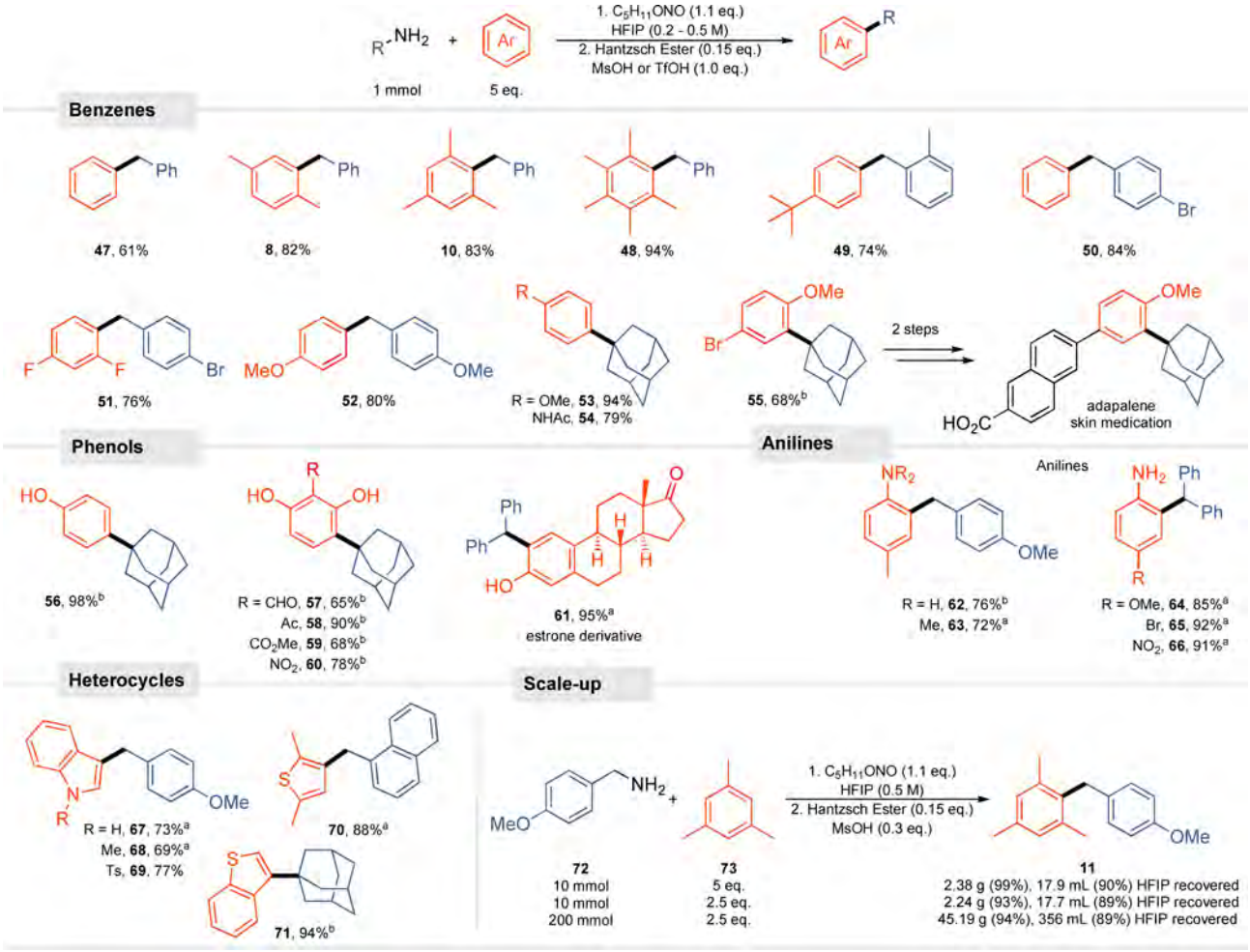
The developed methodology is not limited to alkylation, other nucleophiles engage in this transformation as well (Scheme 5). C-nucleophiles can be used providing they possess a significant partial negative charge on the carbon atom. Derivatives of acetylacetone and ethyl acetoacetate **78**, **79** were obtained in high yields. Deaminative halogenations transform amines into classical aliphatic building blocks using the cheapest possible halogenating agents–aqueous hydrohalic acids without the need for modifying the conditions. Phenylethylamines give organic halides step in high yields already at diazotization, potential side reactions of oxidation of halide ions are negligible. Carboxylation under Koch reaction conditions was also successfully employed, obtaining adamantane carboxylic acid (**80**) in quantitative yield after hydrolysis of the hexafluoroisopropyl ester. The method therefore allows for the transformation of an amine functionality into a carboxylic acid in a simple way using very cheap substrates.

Conclusions

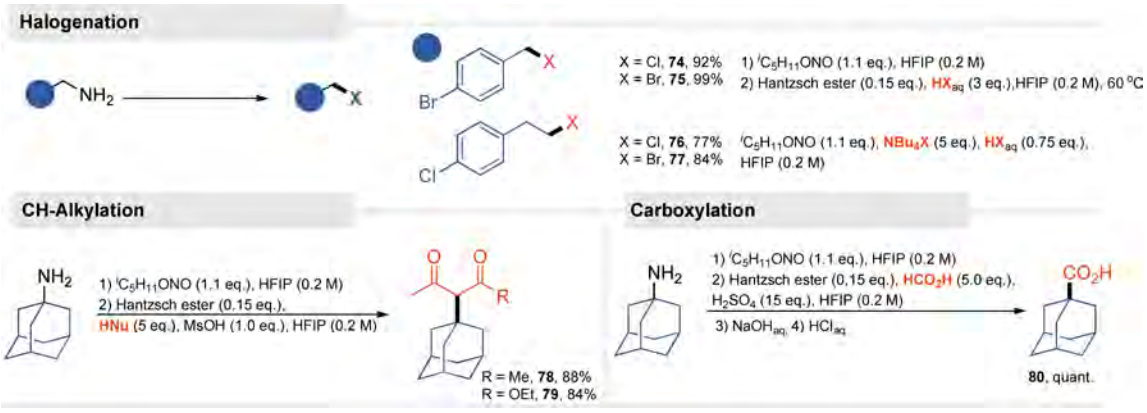
We have demonstrated that diazotization of aliphatic amines, contrary to what is believed, can serve preparative purposes. The key to success in utilizing this transformation lies in the use of HFIP as a reaction medium that enables application of these reagents as precursors of carbocations. Here, these reactive intermediates are trapped by HFIP in a less reactive state thus enabling selective reactions to take place.

The diazotization process followed by subsequent acid-catalyzed alkylation of aromatic compounds enables Friedel–Crafts-type reactions in yields reaching quantitative. The described method stands out among deamination reactions because of its operational simplicity. It also allows for the generation of alkylated products involving highly destabilized carbocations, which are inaccessible from traditionally used alcohols or alkyl halides.

In addition to solving a long-standing issue, the two-step sequence procedure brings several additional benefits. Given the ready availability of the amine, from natural or commercial sources in wide structural varieties, and no need



Scheme 4. Scope and limitations functionalizations of arenes. [a]Reaction conditions: 1) amine (1 mmol), AcOH (1.5 equiv.), $C_5H_{11}ONO$ (1.1 equiv.), DCE (c = 0.5 M). 2) Hantzsch ester (0.15 equiv.), HFIP (4 mL), arene (5 equiv.), MsOH or TfOH (1 equiv.). [b]Reaction conditions: 1) amine (1 mmol), $C_5H_{11}ONO$ (1.1 equiv.), HFIP (c = 0.2 - 0.5 M). 2) Hantzsch ester (0.15 equiv.), arene (5 equiv.), MsOH or TfOH (1 equiv.). [c]Contains 8% *ortho* isomer.



Scheme 5. The developed methodology enable the transformation of amines into valuable building blocks–organohalides and carboxylic acids.

for prefunctionalization it also exhibits a very good atom economy compared to other deamination approaches. The only byproducts of the developed transformation are oxidized Hantzsch ester and innocuoussmall molecules of water and nitrogen (the alcohol, formed from alkyl nitrite, is used as a substrate for the synthesis of this reagent). No harmful or corrosive gases are produced, the purification process is straightforward and reaction is easily scalable.

We believe that our methodology lays ground for further exploration of other reactions involving aliphatic diazonium salts.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Aliphatic amines · Alkylation · Diazotization · Synthetic methods

[1] S. Plunkett, C. H. Basch, S. O. Santana, M. P. Watson, *J. Am. Chem. Soc.* **2019**, *141*, 2257–2262.
[2] M. Ociepa, J. Turkowska, D. Gryko, *ACS Catal.* **2018**, *8*, 11362–11367.
[3] K. J. Berger, M. D. Levin, *Org. Biomol. Chem.* **2021**, *19*, 11–36.
[4] B. D. Dherange, M. Yuan, C. B. Kelly, C. A. Reiher, C. Grosanu, K. J. Berger, O. Gutierrez, M. D. Levin, *J. Am. Chem. Soc.* **2023**, *145*, 17–24.
[5] F. Mo, G. Dong, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1582–1593..
[6] F. Mo, D. Qiu, L. Zhang, J. Wang, *Chem. Rev.* **2021**, *121*, 5741–5829.
[7] Y. Li, F. Xiao, Y. Guo, Y. Zeng, *Eur. J. Org. Chem.* **2021**, *2021*, 1215–1228.
[8] M. B. Smith, J. March, *March's Advanced Organic Chemistry Reactions, Mechanisms, and Structure*, Wiley, **2007**, pp. 500.
[9] J. H. Bayless, F. D. Mendicino, L. Friedman, *J. Am. Chem. Soc.* **1965**, *87*, 5790–5791.
[10] R. R. Naredla, D. A. Klumpp, *Chem. Rev.* **2013**, *113*, 6905–6948.
[11] S. M. Kohlbacher, V.-S. Ionasz, L. Ielo, V. Pace, *Monatshefte für Chemie - Chem. Mon.* **2019**, *150*, 2011–2019.
[12] N. Cohen-Arazi, J. Katzhendler, M. Kolitz, A. J. Domb, *Macromolecules* **2008**, *41*, 7259–7263.
[13] Y. Petit, M. Larchevêque *Org. Synth.* **1998**, *75*, 37.
[14] N. E. Searle *Org. Synth.* **1956**, *36*, 25.
[15] G. Wu, Y. Deng, C. Wu, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 10510–10514.
[16] J. Durka, J. Turkowska, D. Gryko, *ACS Sustainable Chem. Eng.* **2021**, *9*, 8895–8918.
[17] Y. Ueno, C. Tanaka, M. Okawara, *Tetrahedron Lett.* **1984**, *25*, 2675–2678.
[18] V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebauf, *Chem. Commun.* **2020**, *56*, 11548–11564.
[19] Y. Chen, Y. Wang, R. Zhong, J. Li, *J. Org. Chem.* **2020**, *85*, 10638–10647.
[20] V. D. Vuković, E. Richmond, E. Wolf, J. Moran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3085–3089.
[21] S. Zhang, M. Vayer, F. Noël, V. D. Vuković, A. Golushko, N. Rezajooei, C. N. Rowley, D. Lebauf, J. Moran, *Chem* **2021**, *7*, 3425–3441.
[22] H. F. Motiwala, A. M. Armaly, J. G. Cacioppo, T. C. Coombs, K. R. K. Koehn, V. M. Norwood, J. Aubé, *Chem. Rev.* **2022**, *122*, 12544–12747.
[23] R.-J. Tang, T. Milcent, B. Crousse, *J. Org. Chem.* **2018**, *83*, 14001–14009.
[24] L. Bering, K. Jeyakumar, A. P. Antonchick, *Org. Lett.* **2018**, *20*, 3911–3914.
[25] Q. Qin, Y. Xie, P. E. Floreancig, *Chem. Sci.* **2018**, *9*, 8528–8534.
[26] S.-S. Meng, X. Tang, X. Luo, R. Wu, J.-L. Zhao, A. S. C. Chan, *ACS Catal.* **2019**, *9*, 8397–8403.
[27] X. Mo, J. Yakiwchuk, J. Dansereau, J. A. McCubbin, D. G. Hall, *J. Am. Chem. Soc.* **2015**, *137*, 9694–9703.
[28] P. A. Champagne, Y. Benhassine, J. Desroches, J. Paquin, *Angew. Chem. Int. Ed.* **2014**, *53*, 13835–13839.
[29] D. M. Kuznetsov, V. V. Tumanov, W. A. Smit, *J. Polym. Res.* **2013**, *20*, 128–133..
[30] J. Ammer, H. Mayr, *J. Phys. Org. Chem.* **2013**, *26*, 59–63.
[31] N. Zeidan, S. Bicic, R. J. Mayer, D. Lebauf, J. Moran, *Chem. Sci.* **2022**, *13*, 8436–8443.
[32] Y. Imada, J. L. Röckl, A. Wiebe, T. Gieshoff, D. Schollmeyer, K. Chiba, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 12136–12140.
[33] M. A. Murphy, *Found. Chem.* **2018**, *20*, 121–165.
[34] P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, P. A. D. S. Rao, *Nature* **1950**, *166*, 179–180.

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Supporting Information

Aliphatic Amines Unlocked for Selective Transformations through Diazotization

J. Durka, B. Zielińska, D. Gryko**

Supporting Information

ALIPHATIC AMINES UNLOCKED FOR SELECTIVE TRANSFORMATION VIA DIAZOTIZATION

Jakub Durka,* Barbara Zielińska, and Dorota Gryko*

Institute of Organic Chemistry Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

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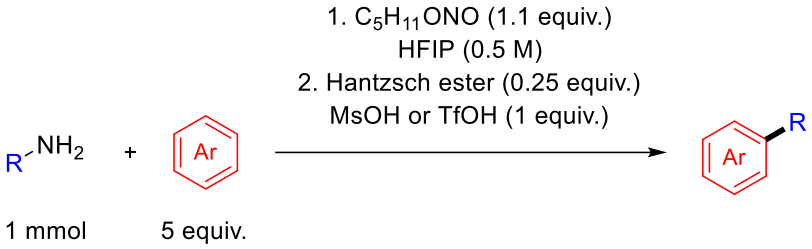
1. General information

All solvents and commercially available reagents were purchased as reagent grade and used without further purification, unless otherwise stated. Reactions were performed without the exclusion of air or moisture. They were monitored by gas chromatography (GC, Shimadzu GCMS-QP2010 SE gas chromatograph with FID detector and Zebron ZB 5MSi column) and thin layer chromatography (TLC), using 0.20 mm Merck silica plates (60F-254) and visualized using UV-light, anisaldehyde or bromocresol green stain, with heat as a developing agent. Colum chromatography was performed on Merck silica gel 60 (230-400 mesh). GC yields were calibrated using dodecane as an internal standard.

NMR spectra were recorded on Bruker 400 MHz and calibrated using residual undeuterated solvent ($CHCl_3$ – 7.26 ppm ^1H NMR, 77.16 ppm ^{13}C NMR) or TMS as internal reference. Low-resolution mass spectra (LRMS) were recorded on an Applied Biosystems API 365 mass spectrometer using an electrospray ionisation (ESI) technique. High resolution mass spectra (HRMS) were recorded on a Waters AutoSpec Premier instrument using electron ionisation (EI) or a Waters SYNAPT G2-S HDMS instrument using electrospray ionization (ESI) with time of flight detector (TOF). Melting points were recorded on a Marienfeld MPM-H2 melting point apparatus and are uncorrected.

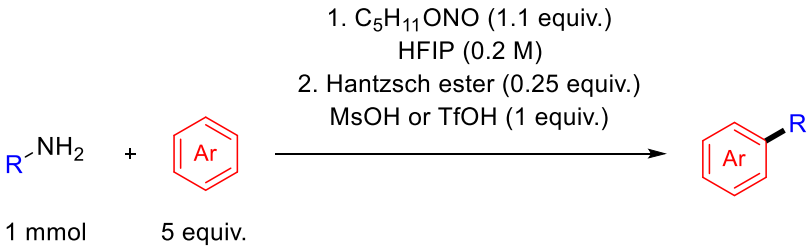
2. General procedures

2.1 General procedure A for the alkylation of arenes with amines



A 25 mL round-bottom flask equipped with a magnetic bar was charged with an amine (1.00 mmol, 1.00 equiv.), arene (5.00 mmol, 5.00 equiv.), HFIP (2.0 mL), and *iso*-pentyl nitrite (148 µL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred at room temperature for 2 h. Then, Hantzsch ester (38 mg, 0.15 mmol, 0.15 equiv.), and MsOH or TfOH (65 µL or 88 µL, 1.0 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at the indicated temperature for the indicated time. If the required temperature exceeded the boiling point of the solvent, the reaction mixture was transferred to a screw-cap vial. Upon completion, the reaction mixture was quenched with triethylammonium acetate (161 mg, 1.00 mmol) and concentrated *in vacuo*. A crude product was purified using column chromatography.

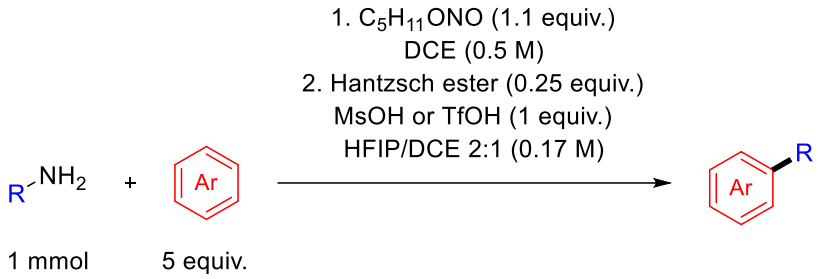
2.2 General procedure B for the alkylation of arenes with amines



A 25 mL round-bottom flask equipped with a magnetic bar was charged with an amine (1.00 mmol, 1.00 equiv.), HFIP (5.0 mL), and *iso*-pentyl nitrite (148 µL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred at room temperature for 2 h. Then, Hantzsch ester (38 mg, 0.15 mmol, 0.15 equiv.), arene (5.00 mmol, 5.00 equiv.) and MsOH or TfOH (65 µL or 88 µL, 1.0 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at the indicated temperature for the indicated time. If the required temperature exceeded the boiling point of the solvent, the reaction mixture was transferred to a screw-cap vial. Upon completion, the reaction mixture

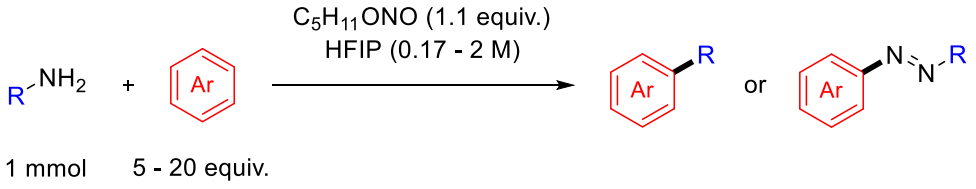
was quenched with triethylammonium acetate (161 mg, 1.00 mmol) and concentrated *in vacuo*. A crude product was purified using column chromatography.

2.3 General procedure C for the alkylation of arenes with amines



A 25 mL round-bottom flask equipped with a magnetic bar was charged with an amine (1.00 mmol, 1.00 equiv.), acetic acid (86 µL, 1.5 mmol, 1.5 equiv.), DCE (2.0 mL), and *iso*-pentyl nitrite (148 µL, 1.10 mmol, 1.10 equiv.). The reaction mixture was brought to reflux and stirred for 30 minutes. Then, after cooling, Hantzsch ester (38 mg, 0.15 mmol, 0.15 equiv.), HFIP (4.0 mL), arene (5.00 mmol, 5.00 equiv.) and MsOH or TfOH (65 µL or 88 µL, 1.0 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at the indicated temperature for the indicated time. If the required temperature exceeded the boiling point of the solvent, the reaction mixture was transferred to a screw-cap vial. Upon completion, the reaction mixture was quenched with triethylammonium acetate (161 mg, 1.0 mmol) and concentrated *in vacuo*. A crude product was purified using column chromatography.

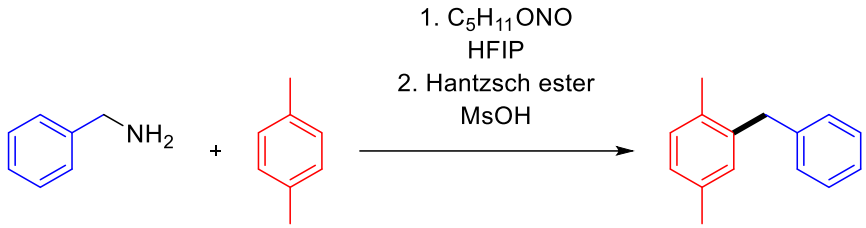
2.4 General procedure D for the alkylation, arylation, or azo coupling of arenes with amines



A 25 mL round-bottom flask equipped with a magnetic bar was charged with an amine (1.00 mmol, 1.00 equiv.), arene (5 – 20 equiv.), HFIP (0,5 – 6 mL), and *iso*-pentyl nitrite (148 µL, 1.10 mmol, 1.10 equiv.). The reaction mixture was stirred at room temperature for 16 h. Upon completion, the reaction mixture was quenched with triethylammonium acetate (161 mg, 1.0 mmol) and concentrated *in vacuo*. A crude product was purified using column chromatography.

3. Optimisation of reaction parameters

Model reaction



Reaction conditions: according to the general procedure A: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) Hantzsch ester (0.15 equiv.), MsOH (1.0 equiv.), 3 h, reflux.

3.1 Background experiments

Entry	Deviation from the standerd conditions	Yield of X [%]
1	none	81
2	no MsOH	13
3	no Hantzsch ester	70
4	TFE instead of HFIP	0
5	*p*-xylene added to 2. step	77

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) Hantzsch ester (0.15 equiv.), MsOH (1.0 equiv.), 3 h, reflux.

3.2 Different reducing agents

Entry	Reducing agent	Added to step	Yield of X [%]
1	none	-	70
2	urea	1	63
3	urea	2	69
4	hexanal	1	46
5	hexanal	2	75
6	$BuNH_2$	2	73
7	NH_4HCO_3	2	69
8	Hantzsch ester	1	58
9	Hantzsch ester	2	81

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) reducing agent (0.15 equiv.), MsOH (1.0 equiv.), 3 h, reflux.

3.3 Optimisation of the amount of nitrite

Entry	$C_5H_{11}ONO$ (equiv.)	Yield of X [%]
1	1.00	74
2	1.05	78
3	1.10	81
4	1.15	81

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (X equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) Hantzsch ester (0.25 equiv.), MsOH (1.0 equiv.), 3 h, reflux.

3.4 Optimisation of the amount of arene

Entry	*p*-xylene (equiv.)	Yield of X [%]
1	3.00	71
2	5.00	81
3	10.00	92

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (X equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) Hantzsch ester (0.15 equiv.), MsOH (1.0 equiv.), 3 h, reflux. The use of 5 mmol was chosen as a compromise between the excess of arene and the efficiency.

3.5 Optimisation of the amount of Hantzsch ester

Entry	Hantzsch ester (equiv.)	Yield of X [%]
1	0.05	71
2	0.10	74
3	0.15	81
4	0.25	81

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) Hantzsch ester (X equiv.), MsOH (1.0 equiv.), 3 h, reflux.

3.6 Optimisation of the amount of acid

Entry	MsOH (equiv.)	Yield of X [%]
1	0.25[a]	78
2	0.50	79
3	1.00	81

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) Hantzsch ester (0.15 equiv.), MsOH (X equiv.), 3 h, reflux. [a]Reflux for 16h. Although the amount of acid used had no effect on the yield of the model reaction, 1 equiv. was used for scope evaluation due to the occasional acid-binding side reactions.

3.7 Optimisation of the amount of HFIP

Entry	c of $BnNH_2$ (M)	Yield of X [%]
1	2.0	70
2	1.0	81
3	0.5	81
4	0.33	81

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = X M), 2 h, RT. 2) Hantzsch ester (0.15 equiv.), MsOH (1.0 equiv.), 3 h, reflux.

3.8 The influence of reaction time and temperature

Entry	Conditions of the 2. step	Yield of X [%]
1	24 h, room temperature	76
2	3 h, reflux	81
3	1.5 h, 140 °C	81

Reaction conditions: 1) $BnNH_2$ (1.00 mmol), *p*-xylene (5.00 equiv.), $C_5H_{11}ONO$ (1.10 equiv.), HFIP (c = 0.5 M), 2 h, RT. 2) Hantzsch ester (0.15 equiv.), MsOH (1.0 equiv.), X h, X °C.

3.9 Optimisation of the nitrite reagent

The choice of nitrite reagent was based on the experience gained while developing the project, not only by optimising the model reaction. We tested 5 different sources of nitrite:

Sodium nitrite $NaNO_2$ – while being the cheapest and easiest accesible, it is not soluble in HFIP and therefore was found innefective, even after the addition of phase transfer catalyst.

Tetrabutylammonium nitrite NBu_4NO_2 – although the reagent is commercially available it is expensive, hygroscopic, and very non-atom economical.

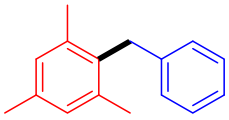
Tetramethylammonium nitrite NMe_4NO_2 – this reagent was desired to adress both solubility and atom economy issues. It was synthesised in a simple salt metathesis reaction between $NaNO_2$ and NMe_4Cl in 95% ethanol, after evaporation of the solvent. It is less hygroscopic than the tetrabutylammonium salt, has lower solubility in HFIP and, nevertheless, enables the reaction to proceed. The problem associated with the use of ionic nitrites under these conditions is the side reaction of nitration of aromatic rings, which is not detected in the case of nitrous acid esters.

***tert*-Butyl nitrite C_4H_9ONO** – is cheap, commercially available, and enables the diazotization reaction to proceed smoothly. However, in the second reaction step, stable tertiary carbocations are generated from the leftover *t*-butanol, leading to products of the undesired Friedel-Crafts reaction.

***iso*-Pentyl nitrite $C_5H_{11}ONO$** – is similarly cheap, available, and useful in the diazotization process as *tert*-butyl ester. It has a significant advantage over it in the second stage of the reaction because the products of undesirable alkylation are observed only at very high reaction temperatures. Moreover, due to the lack of steric hindrance, it more easily attacks substituted rings of substrates, e.g. mesitylene, and not the reaction product.

4. Scope and characterization of products

2-Benzylmesitylene (10)[1]

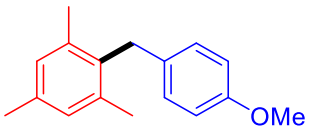


Following General Procedure A, compound **10** was obtained from benzylamine (107 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 174 mg of compound **10** as colorless oil. **(Yield = 83%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 2H), 7.25 – 7.16 (m, 1H), 7.13 – 7.04 (m, 2H), 6.96 (s, 2H), 4.09 (s, 2H), 2.37 (s, 3H), 2.28 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 137.1, 135.7, 133.9, 129.0, 128.4, 127.9, 125.7, 34.8, 21.0, 20.2.

2-(4-Methoxybenzyl)mesitylene (11)[2]

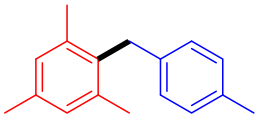


Following General Procedure A, compound **11** was obtained from 4-methoxybenzylamine (137 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 239 mg of compound **11** as a white solid. **(Yield = 99%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, J = 8.7 Hz, 2H), 6.89 (s, 2H), 6.80 – 6.76 (m, 2H), 3.95 (s, 2H), 3.77 (s, 3H), 2.28 (s, 3H), 2.21 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 136.9, 135.5, 134.2, 132.1, 128.9, 128.7, 113.8, 55.2, 33.8, 20.9, 20.1.

2-(4-Methylbenzyl)mesitylene (12)[1]

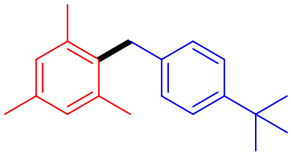


Following General Procedure A, compound **12** was obtained from 4-methylbenzylamine (121 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 200 mg of compound **12** as colorless oil. **(Yield = 89%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.8 Hz, 2H), 7.02 – 6.89 (m, 4H), 4.04 (s, 2H), 2.36 (s, 6H), 2.27 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 137.0, 135.6, 135.1, 134.0, 129.1, 128.9, 127.8, 34.3, 21.0, 20.9, 20.2.

2-(4-*tert*-Butylbenzyl)mesitylene (13)[1]

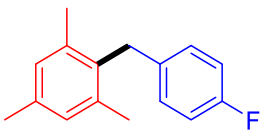


Following General Procedure A, compound **13** was obtained from 4-*tert*-butylbenzylamine (163 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 258 mg of compound **13** as a white solid. **(Yield = 97%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.22 (m, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.88 (s, 2H), 3.98 (s, 2H), 2.29 (s, 3H), 2.22 (s, 6H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 137.0, 137.0, 135.5, 134.2, 128.9, 127.6, 125.2, 34.3, 34.3, 31.5, 20.9, 20.2.

2-(4-Fluorobenzyl)mesitylene (14)[1]



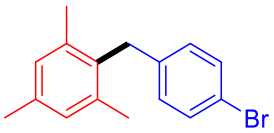
Following General Procedure A, compound **14** was obtained from 4-fluorobenzylamine (125 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with

MsOH for 4 h. Purified by column chromatography (petroleum ether) to afford 222 mg of compound **14** as colorless oil. **(Yield = 97%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.89 (m, 6H), 3.99 (s, 2H), 2.31 (s, 3H), 2.21 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, *J* = 243.3 Hz), 136.9, 135.8, 135.7 (d, *J* = 3.2 Hz), 133.6, 129.1 (d, *J* = 7.7 Hz), 129.0, 115.1 (d, *J* = 21.1 Hz), 33.9, 20.9, 20.0.

2-(4-Bromobenzyl)mesitylene (15)[1]

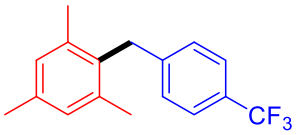


Following General Procedure A, compound **15** was obtained from 4-bromobenzylamine (223 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 4 h. Purified by column chromatography (petroleum ether) to afford 287 mg of compound **15** as a white solid. **(Yield = 99%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H), 6.97 – 6.89 (m, 4H), 4.00 (s, 2H), 2.33 (s, 3H), 2.23 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 136.9, 136.0, 133.2, 131.4, 129.6, 129.1, 119.5, 34.2, 20.9, 20.1.

2-(4-Trifluoromethylbenzyl)mesitylene (16)[1]



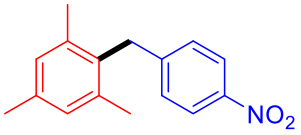
Following General Procedure A, compound **16** was obtained from 4-trifluoromethylbenzylamine (175 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 48 h. Purified by column chromatography (petroleum ether) to afford 177 mg of compound **16** as colorless oil. **(Yield = 64%)**

Following General Procedure C, compound **16** was obtained from 4-trifluoromethylbenzylamine (175 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with TfOH at 100 °C for 16 h. Purified by column chromatography (petroleum ether) to afford 240 mg of compound **16** as colorless oil. **(Yield = 86%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.90 (s, 2H), 4.06 (s, 2H), 2.30 (s, 3H), 2.18 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 136.9, 136.6, 132.8, 129.1, 128.3, 128.1, 125.3 (q, *J*= 3.7 Hz), 123.0, 34.6, 20.9, 20.1.

2-(4-Nitrobenzyl)mesitylene (17)[3]

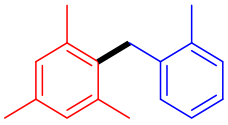


Following General Procedure C, compound **17** was obtained from 4-nitrobenzylamine (152 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with TfOH at 100 °C for 16 h. Purified by column chromatography (0:100 to 3:97 AcOEt/hexanes) to afford 174 mg of compound **17** as a yellowish solid. **(Yield = 68%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.05 (m, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.91 (s, 2H), 4.11 (s, 2H), 2.30 (s, 3H), 2.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 146.4, 136.8, 136.5, 132.1, 129.2, 128.6, 123.7, 34.8, 20.9, 20.1.

2-(2-Methylbenzyl)mesitylene (18)[1]

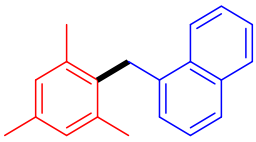


Following General Procedure A, compound **18** was obtained from 2-methylbenzylamine (121 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 202 mg of compound **18** as a white solid. **(Yield = 90%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.98 (s, 2H), 6.59 (d, *J* = 7.6 Hz, 1H), 3.95 (s, 2H), 2.49 (s, 3H), 2.38 (s, 3H), 2.22 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.2, 136.2, 135.6, 133.6, 129.7, 128.9, 126.3, 126.1, 125.8, 32.1, 21.0, 19.9, 19.8.

2-(Naphthalen-1-ylmethyl)mesitylene (19)[2]

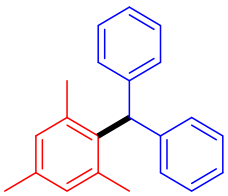


Following General Procedure A, compound **19** was obtained from 1-naphthylmethylamine (157 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (petroleum ether) to afford 237 mg of compound **19** as a white solid. **(Yield = 91%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.5 Hz, 1H), 8.00 – 7.93 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.64 – 7.57 (m, 1H), 7.36 – 7.29 (m, 1H), 7.04 (s, 2H), 6.77 (dd, *J* = 7.1, 1.1 Hz, 1H), 4.49 (s, 2H), 2.43 (s, 3H), 2.24 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.9, 135.4, 133.8, 133.2, 132.4, 129.0, 128.9, 126.6, 126.0, 125.8, 125.6, 123.6, 123.2, 31.5, 21.1, 19.9.

2-Benzhydrylmesitylene (20)[2]

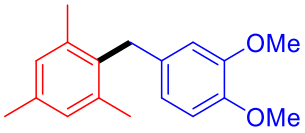


Following General Procedure A, compound **20** was obtained from benzhydrylamine (183 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (petroleum ether) to afford 252 mg of compound **20** as a white solid. **(Yield = 88%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 4H), 7.27 – 7.22 (m, 2H), 7.19 – 7.14 (m, 4H), 6.92 (s, 2H), 6.07 (s, 1H), 2.33 (s, 3H), 2.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 137.6, 137.2, 136.0, 130.2, 129.4, 128.2, 126.0, 51.1, 22.0, 20.9.

2-(3,4-Dimethoxybenzyl)mesitylene (21)[2]

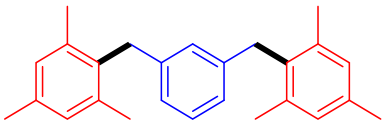


Following General Procedure A, compound **21** was obtained from 3,4-dimethoxybenzylamine (167 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 241 mg of compound **21** as a yellowish solid. **(Yield = 89%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 2H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 1.3 Hz, 1H), 6.52 – 6.45 (m, 1H), 3.98 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.31 (s, 3H), 2.24 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 147.2, 137.0, 135.6, 133.9, 132.7, 128.9, 119.5, 111.6, 111.3, 55.9, 55.8, 34.2, 20.9, 20.1.

1,3-Bis(2,4,6-trimethylbenzyl)benzene (22)[4]

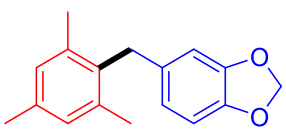


Following General Procedure A, compound **22** was obtained from 1,3-bis(aminomethyl)-benzene (136 mg, 1.00 mmol) and mesitylene (1202 mg, 10.0 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 323 mg of compound **22** as a white solid. **(Yield = 94%).**

^{1}H NMR (400 MHz, $CDCl_3$) 7.11 – 7.03 (m, 1H), 6.88 (s, 4H), 6.78 – 6.73 (m, 3H), 3.95 (s, 4H), 2.31 (s, 6H), 2.18 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 136.9, 135.5, 133.9, 128.8, 128.3, 127.9, 125.0, 34.7, 20.9, 20.1.

2-Piperonylmesitylene (23)



Following General Procedure A, compound **23** was obtained from piperonylamine (151 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with MsOH

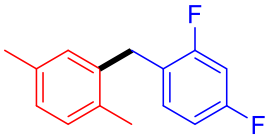
at room temperature for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 200 mg of compound **23** as yellowish oil. **(Yield = 78%)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.54 (s, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 3.97 (s, 2H), 2.33 (s, 3H), 2.25 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 145.6, 137.0, 135.7, 134.0, 134.0, 129.0, 120.6, 108.4, 108.1, 100.8, 34.3, 20.9, 20.1.

HRMS (m/z) (EI) [M] calculated for $C_{17}H_{18}O_2$: 254.1307, found: 254.1305.

1,4-Dimethyl-2-(2,4-difluorobenzyl)benzene (24)[5]

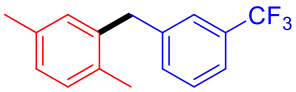


Following General Procedure A, compound **24** was obtained from 2,4-difluorobenzylamine (143 mg, 1.00 mmol) and *p*-xylene (531 mg, 5.00 mmol).The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 224 mg of compound **24** as colorless oil. **(Yield = 96%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.97 – 6.88 (m, 2H), 6.87 – 6.81 (m, 1H), 6.81 – 6.74 (m, 1H), 3.93 (s, 2H), 2.32 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (dd, *J* = 74.3, 12.1 Hz), 159.9 (dd, *J* = 75.2, 12.1 Hz), 137.0, 135.6, 133.4, 131.0 (dd, *J* = 9.4, 6.2 Hz), 130.5, 130.3, 127.4, 123.3 (dd, *J* = 16.1, 3.8 Hz), 111.0 (dd, *J* = 20.8, 3.8 Hz), 103.5 (t, *J* = 25.3 Hz), 31.4, 31.4, 20.9, 18.9.

1,4-Dimethyl-2-(3-trifluoromethylbenzyl)benzene (25)[5]

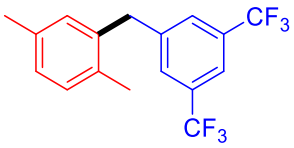


Following General Procedure A, compound **25** was obtained from 3-trifluoromethylbenzylamine (175 mg, 1.00 mmol) and *p*-xylene (531 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 252 mg of compound **25** as colorless oil. **(Yield = 95%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.95 (s, 1H), 4.03 (s, 2H), 2.33 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 137.6, 135.7, 133.4, 132.0, 130.9, 130.8, 130.6, 130.4, 128.8, 127.6, 124.1 (dq, *J* = 256.0, 3.8 Hz), 39.3, 21.0, 19.2.

1,4-Dimethyl-2-(3,5-bis(trifluoromethyl)benzyl)benzene (26)[6]

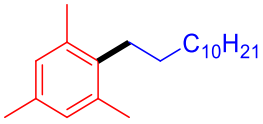


Following General Procedure A, compound **26** was obtained from 3,5-bis(trifluoromethyl)benzylamine (243 mg, 1.00 mmol) and *p*-xylene (531 mg, 5.00 mmol). The reaction mixture was stirred with TfOH at 140 °C for 40 h. Purified by column chromatography (petroleum ether) to afford 277 mg of compound **26** as colorless oil. **(Yield = 83%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.56 (s, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.90 (s, 1H), 4.06 (s, 2H), 2.31 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 136.4, 136.0, 133.3, 131.7 (q, *J* = 33.0 Hz), 130.7, 130.7, 128.8 – 128.6 (m), 128.0, 123.4 (q, *J* = 272.6 Hz), 120.1 (sep, *J* = 3.9 Hz), 39.1, 20.9, 19.1.

2-Dodecylmesitylene (27)[7]

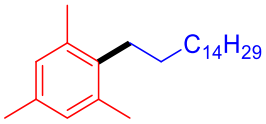


Following a slightly modified General Procedure C, compound **27** was obtained from dodecylamine (185 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). DCE was carefully evaporated after diazotization so that the second step could proceed in pure HFIP. The reaction mixture was stirred with TfOH at 70 °C for 30 min and then at 140 °C for 16 h. Purified by column chromatography (petroleum ether) to afford 92 mg of compound **27** as colorless oil. **(Yield = 32%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2H), 2.61 – 2.52 (m, 2H), 2.29 (s, 6H), 2.25 (s, 3H), 1.48 – 1.39 (m, 4H), 1.32 – 1.25 (m, 16H), 0.93 – 0.87 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.8, 134.7, 128.8, 31.9, 30.3, 29.7, 29.7, 29.7, 29.5, 29.5, 29.4, 22.7, 20.8, 19.7, 14.1.

2-Hexadecylmesitylene (28)[7]

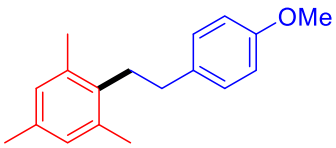


Following a slightly modified General Procedure C, compound **28** was obtained from hexadecylamine (241 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). DCE was carefully evaporated after diazotization so that the second step could proceed in pure HFIP. The reaction mixture was stirred with TfOH at 70 °C for 30 min and then at 140 °C for 16 h. Purified by column chromatography (petroleum ether) to afford 107 mg of compound **28** as colorless oil. **(Yield = 31%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 2.59 – 2.52 (m, 2H), 2.28 (s, 6H), 2.24 (s, 3H), 1.46 – 1.39 (m, 4H), 1.26 (s, 24H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.8, 134.7, 128.8, 31.9, 30.3, 29.7, 29.7, 29.7, 29.5, 29.4, 29.3, 29.3, 22.7, 20.8, 19.7, 14.1.

2-(4-Methoxyphenethyl)mesitylene (29)[7]

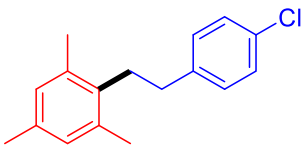


Following General Procedure A, compound **29** was obtained from 4-methoxyphenethylamine (151 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 162 mg of compound **29** as yellowish oil. **(Yield = 64%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.95 – 6.89 (m, 4H), 3.86 (s, 3H), 2.92 (dd, *J* = 10.5, 6.3 Hz, 2H), 2.75 (dd, *J* = 10.4, 6.3 Hz, 2H), 2.37 (s, 6H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 136.0, 135.6, 135.2, 134.5, 129.2, 129.0, 113.9, 55.3, 34.7, 32.0, 20.9, 19.7.

2-(4-Chlorophenethyl)mesitylene (30)[7]

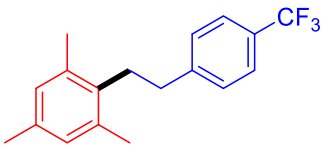


Following General Procedure A, compound **30** was obtained from 4-chlorophenethylamine (156 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 169 mg of compound **30** as colorless oil. **(Yield = 65%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.21 – 7.15 (m, 2H), 6.90 (s, 2H), 2.90 (dd, *J* = 10.8, 5.8 Hz, 2H), 2.76 (dd, *J* = 10.7, 5.8 Hz, 2H), 2.33 (s, 6H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 136.0, 135.3, 135.0, 131.7, 129.7, 129.1, 128.5, 34.9, 31.6, 20.9, 19.7.

2-(4-Trifluoromethylphenethyl)mesitylene (31)[8]

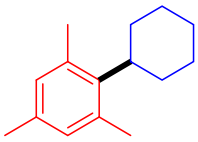


Following General Procedure A, compound **31** was obtained from 4-trifluoromethylphenethylamine (189 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 97 mg of compound **31** as a white solid. **(Yield = 33%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.87 (s, 2H), 2.94 – 2.86 (m, 2H), 2.84 – 2.77 (m, 2H), 2.31 (s, 6H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 146.3, 136.0, 135.5, 134.8, 129.1, 128.6, 128.6, 128.3, 127.9, 125.8, 125.4, 125.4, 125.3, 125.3, 123.1, 35.4, 31.4, 20.8, 19.6.

2-Cyclohexylmesitylene (32)[9]

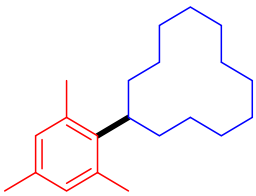


Following General Procedure A, compound **32** was obtained from cyclohexylamine (99 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 178 mg of compound **32** as colorless oil. **(Yield = 88%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.94 (s, 1H), 6.87 – 6.81 (m, 2H), 3.05 – 2.94 (m, 1H), 2.73 – 2.63 (m, 1H), 2.51 – 2.32 (m, 6H), 2.30 – 2.28 (m, 3H), 2.26 (s, 6H), 2.23 – 2.21 (m, 3H), 2.00 – 1.75 (m, 10H), 1.50 – 1.24 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.2, 136.1, 134.7, 133.9, 133.4, 132.3, 131.7, 128.2, 126.8, 123.9, 41.4, 39.8, 33.9, 33.9, 30.6, 27.8, 27.3, 27.3, 26.4, 26.4, 20.6, 19.4, 19.1, 18.7.

2-Cyclododecylmesitylene (33)[7]

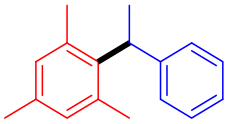


Following General Procedure A, compound **33** was obtained from cyclododecylamine (183 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 277 mg of compound **33** as a yellowish solid. **(Yield = 97%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 2H), 3.23 (p, J = 6.7 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.27 (s, 3H), 2.04 – 1.93 (m, 2H), 1.75 – 1.27 (m, 20H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 136.7, 136.4, 134.6, 131.3, 128.9, 34.1, 29.8, 24.8, 24.6, 24.5, 23.2, 22.3, 21.9, 21.7, 20.6.

2-(1-Phenylethyl)mesitylene (34)[2]



Following General Procedure A, compound **34** was obtained from (*R*)-(+)-α-methylbenzylamine (121 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 129 mg of compound **34** as colorless oil. **(Yield = 58%)**

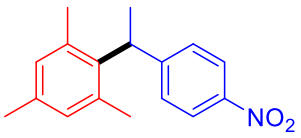
Following General Procedure A, compound **34** was obtained from (*R*)-(+)-α-methylbenzylamine (121 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with NBu_4Br (322 mg, 1.00 mmol, added before the acid) and MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 207 mg of compound **34** as colorless oil. **(Yield = 92%).**

$[\alpha]D_{20}$ = 0.00 (*c* = 0.67 in $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.18 (m, 3H), 6.88 (s, 2H), 4.70 (q, *J* = 7.3 Hz, 1H), 2.32 (s, 3H), 2.20 (s, 6H), 1.72 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 140.1, 136.5, 135.4, 130.0, 128.2, 126.9, 125.3, 37.9, 21.1, 20.8, 16.9.

2-(1-(4-Nitrophenyl)ethyl)mesitylene (35)[10]

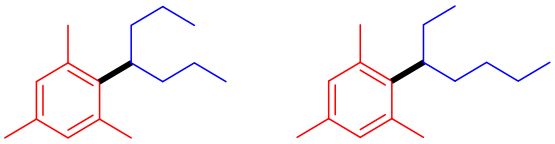


Following General Procedure C, compound **35** was obtained from 1-(4-nitrophenyl)ethylamine (166 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was stirred with TfOH at 100 °C for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 254 mg of compound **35** as a yellowish solid. **(Yield = 94%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.05 (m, 2H), 7.41 – 7.28 (m, 2H), 6.86 (s, 2H), 4.67 (q, *J* = 7.2 Hz, 1H), 2.28 (s, 3H), 2.10 (s, 6H), 1.72 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 145.9, 138.6, 136.2, 136.2, 130.3, 127.6, 123.4, 38.3, 21.0, 20.7, 16.9.

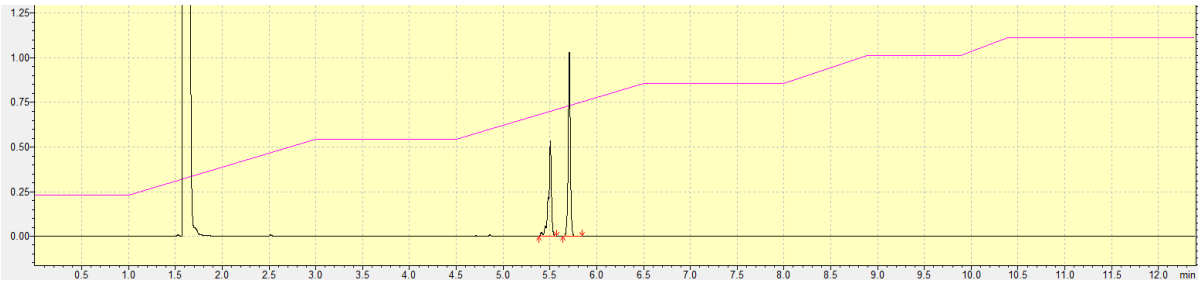
2-(4-Heptyl)mesitylene (36A), 2-(3-heptyl)mesitylene (36B)



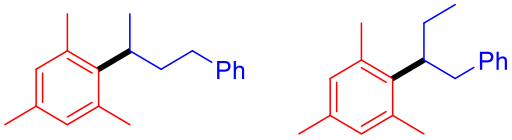
Following General Procedure A, compounds **36A** and **36B** was obtained from 4-heptylamine (115 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 173 mg of compounds **36A** and **36B** 3:2 as colorless oil. **(Yield = 79%)**

HRMS (m/z) (EI) [M] calculated for $C_{16}H_{26}$: 218.2035, found: 218.2031.

GC Chromatogram: purity: 98%, peak ratio: 2:3



3-Mesityl-1-phenylbutane (37A)[7]**, 2-mesityl-1-phenylbutane (37B)**

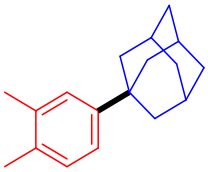


Following General Procedure A, compounds **37A** and **37B** was obtained from 4-phenyl-2-butylamine (149 mg, 1.00 mmol) and mesitylene (601 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (petroleum ether) to afford 156 mg of compounds **37A** and **37B** 5:3 as colorless oil. **(Yield = 62%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.09 (m, 8H), 6.82 (m, 3H), 3.36 – 3.20 (m, 1.6H), 3.11 – 2.95 (m, 1.2H), 2.70 – 2.53 (m, 2.2H), 2.51 (s, 1.8H), 2.40 (s, 3H), 2.29 (s, 3H), 2.28 (s, 1.8H), 2.25 – 1.74 (m, 8.4H), 1.37 (d, J = 7.3 Hz, 3H), 0.81 (t, J = 7.4 Hz, 1.8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 142.0, 139.7, 137.8, 137.3, 136.1, 134.9, 131.2, 129.1, 128.5, 128.3, 128.1, 125.7, 77.4, 77.1, 76.8, 45.0, 40.9, 37.3, 34.7, 34.2, 26.3, 21.9, 21.6, 21.5, 20.7, 20.7, 19.1, 13.0.

1-(3,4-Dimethylphenyl)adamantane (38)[11,12]

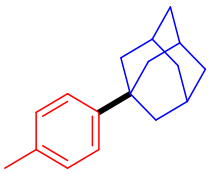


Following General Procedure A, compound **38** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and o-xylene (531 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (petroleum ether) to afford 225 mg of compound **38** as a white solid. **(Yield = 94%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.17 – 7.10 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.16 – 2.10 (m, 3H), 1.95 (d, *J* = 2.7 Hz, 6H), 1.87 – 1.76 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 136.0, 133.6, 129.4, 126.2, 122.2, 43.3, 36.9, 35.8, 29.1, 20.1, 19.2.

1-(4-Methylphenyl)adamantane (39)[13]

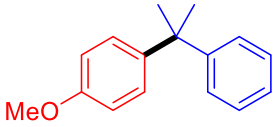


Following General Procedure A, compound **39** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and toluene (461 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (petroleum ether) to afford 202 mg of compound **39** as a white solid. **(Yield = 89%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.20 – 7.14 (m, 2H), 2.36 (s, 3H), 2.17 – 2.09 (m, 3H), 1.95 (d, *J* = 2.8 Hz, 6H), 1.85 – 1.77 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 134.9, 128.8, 124.7, 43.3, 36.9, 35.9, 29.1, 20.9.

4-Cumylanisole (40)[14]



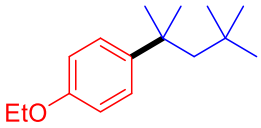
Following General Procedure A, compound **40** was obtained from cumylamine (135 mg, 1.00 mmol) and anisole (541 mg, 5.00 mmol). The reaction mixture was refluxed with NBu_4Br (322

mg, 1.00 mmol, added before the acid) and MsOH for 3 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 123 mg of compound **40** as yellowish oil. **(Yield = 54%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 3H), 7.23 – 7.16 (m, 3H), 6.88 – 6.81 (m, 2H), 3.81 (s, 3H), 1.72 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.0, 142.9, 128.0, 127.8, 126.8, 125.6, 113.3, 55.2, 42.3, 30.9.

1-Ethoxy-4-(2,4,4-trimethylpentan-2-yl)benzene (41)[15]

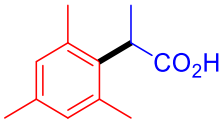


Following General Procedure A, compound **41** was obtained from *tert*-octylamine (129 mg, 1.00 mmol) and ethoxybenzene (611 mg, 5.00 mmol). The reaction mixture was refluxed with NBu_4Br (322 mg, 1.00 mmol, added before the acid) and MsOH at room temperature for 3 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 176 mg of compound **41** as yellowish oil. **(Yield = 75%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 2H), 6.88 – 6.78 (m, 2H), 4.03 (q, J = 7.0 Hz, 2H), 1.72 (s, 2H), 1.41 (t, J = 7.0 Hz, 2H), 1.36 (s, 6H), 0.74 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 142.1, 127.0, 113.7, 63.3, 57.0, 37.9, 32.3, 31.8, 31.7, 14.9.

2-Mesitylpropanoic acid (42)[31]



Following General Procedure D, compound **42** was obtained from alanine (89 mg, 1.00 mmol) and mesitylene (2404 mg, 20.00 mmol) with HFIP (6 mL) with Et_3N (140 µL, 1.00 mmol, 1.00 equiv.). Purified by column chromatography (DCM) to afford 89 mg of compound **42** as a yellowish solid. **(Yield = 46%).**

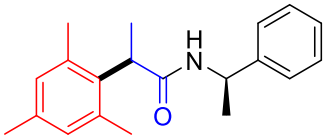
$[\alpha]D_{20}$ = −81.55 (c = 0.75 in $CHCl_3$). 81% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (s, 1H), 6.89 (s, 2H), 4.14 (q, J = 7.2 Hz, 1H), 2.32 (s, 6H), 2.29 (s, 3H), 1.47 (d, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 136.4, 136.0, 134.7, 129.8, 40.1, 20.8, 20.3, 15.3.

To determine the ratio of enantiomers the compound was transformed into a mixture of diasteromeric amides in the reaction with (*R*)-(+)-α-methylbenzylamine.

_N_-((_R_)-1-phenylethyl)-2-mesitylpropanamide (42a)



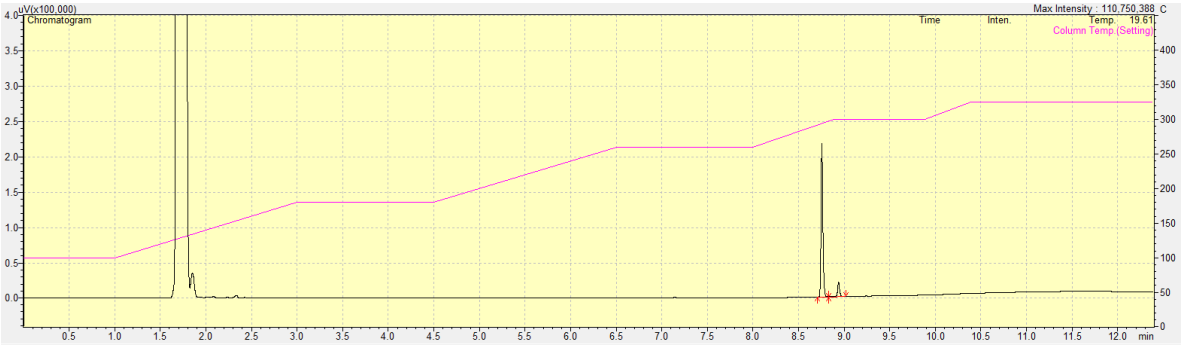
A 25 mL round-bottom flask equipped with a magnetic bar was charged with compound **42** (58 mg, 0.3 mmol, 1.0 equiv.), (R)-(+)-α-methylbenzylamine (121 mg, 1.00 mmol, 3.33 equiv.) and dry THF (1.0 mL). Then 4-dimethylaminopyridine (6.1 mg, 0.05 mmol, 0.17 equiv.) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (192 mg, 1.00 mmol, 3.33 equiv.) were added and flask was flushed with argon. The reaction mixture was stirred at room temperature for 4 h. Upon completion, the reaction mixture was transferred to separatory funnel with 40 mL Et_2O. Ethereal solution was washed with 3 x 25 mL 0.5 M HCl, 2 x 25 mL saturated $NaHCO_3$. The organic phase was dried with Na_2SO_4, filtered, and evaporated. A crude product **42a** was purified via column chromatography (AcOEt/hexanes, gradually from 10:90 to 30:70) to afford 60 mg of mixture of diastereoisomers (9.7:1) of compound **42a** as a yellowish oil. **(Yield = 68%).**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, $2H_{major}$ + $2H_{minor}$), 7.22 – 7.18 (m, $1H_{major}$ + $1H_{minor}$), 7.16 – 7.10 (m, $2H_{major}$ + $2H_{minor}$), 6.86 (s, $1H_{minor}$), 6.81 (s, $1H_{major}$), 5.52 – 5.42 (m, $1H_{major}$ + $1H_{minor}$), 5.19 – 5.09 (m, $1H_{major}$ + $1H_{minor}$), 3.98 – 3.91 (m, $1H_{major}$ + $1H_{minor}$), 2.30 – 2.05 (m, $6H_{major}$ + $6H_{minor}$), 1.43 (d, J = 7.2 Hz, $3H_{minor}$), 1.40 (d, J = 7.2 Hz, $3H_{major}$), 1.38 – 1.34 (m, $3H_{major}$ + $3H_{minor}$).

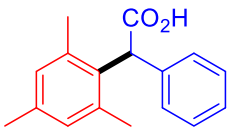
^{13}C NMR (151 MHz, $CDCl_3$, major diastereoisomer) δ 173.8, 143.2, 136.7, 136.5, 135.0, 130.0, 128.4, 127.1, 126.2, 48.7, 40.8, 21.8, 20.8, 20.3, 14.7.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{20}H_{26}NO$: 296.2014, found: 296.2016.

GC Chromatogram: diastereoisomer peak ratio: 9.7:1.



2-Mesityl-2-phenylacetic acid (43)



Following General Procedure D, compound **43** was obtained from phenylglycine (151 mg, 1.00 mmol) and mesitylene (2404 mg, 20.00 mmol) with HFIP (6 mL) with Et_3N (140 µL, 1.00 mmol, 1.00 equiv.). Purified by column chromatography (DCM) to afford 197 mg of compound **43** as a white solid. **(Yield = 78%).**

$[\alpha]D_{20}$ = 1.10 (*c* = 0.47 in $CHCl_3$). 10% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (s, 1H), 7.32 – 7.21 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 2H), 6.93 (s, 2H), 5.46 (s, 1H), 2.31 (s, 3H), 2.22 (s, 6H).

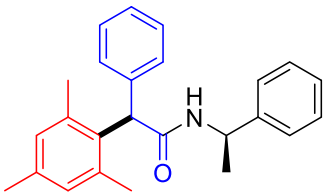
^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 137.5, 137.1, 136.1, 131.7, 130.0, 128.7, 128.2, 126.9, 50.7, 20.9.

HRMS (m/z) (ESI) $[M+Na]^+$ calculated for $C_{17}H_{18}O_2Na$: 277.1204, found: 277.1206.

mp: 170.4 – 171.8 °C

To determine the ratio of enantiomers the compound was transformed into a mixture of diasteromeric amides in the reaction with (R)-(+)-α-methylbenzylamine.

***N*-((*R*)-1-phenylethyl)-2-mesityl-2-phenylacetamide (43a)**



A 25 mL round-bottom flask equipped with a magnetic bar was charged with compound **43** (77 mg, 0.3 mmol, 1.0 equiv.), (R)-(+)-α-methylbenzylamine (121 mg, 1.00 mmol, 3.33 equiv.) and dry THF (1.0 mL). Then 4-dimethylaminopyridine (6.1 mg, 0.05 mmol, 0.17 equiv.) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (192 mg, 1.00 mmol, 3.33 equiv.) were added and flask was flushed with argon. The reaction mixture was stirred at room temperature for 4 h. Upon completion, the reaction mixture was transferred to separatory funnel with 40 mL Et_2O. Ethereal solution was washed with 3 x 25 mL 0.5 M HCl, 2 x 25 mL saturated $NaHCO_3$. The organic phase was dried with Na_2SO_4, filtered, and evaporated. A crude product was purified using column chromatography (AcOEt/hexanes gradually from 10:90 to 30:70) to

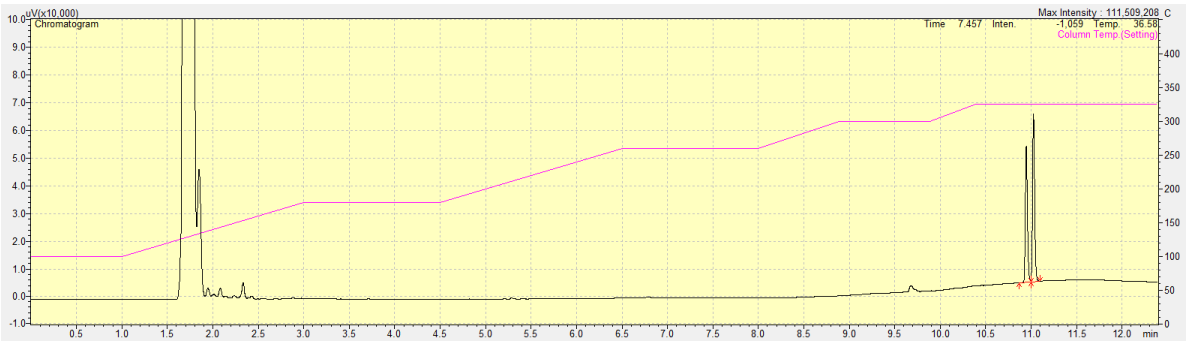
afford 49 mg of mixture of diastereoisomers (1.2:1) of compound **43a** as a yellowish oil. **(Yield = 46%).**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.14 (m, $10H_{major}$ + $10H_{minor}$), 6.90 – 6.86 (m, $2H_{major}$ + $2H_{minor}$), 5.74 – 5.67 (m, $1H_{major}$ + $1H_{minor}$), 5.28 (s, $1H_{minor}$), 5.26 (s, $1H_{major}$), 5.23 – 5.16 (m, $1H_{major}$ + $1H_{minor}$), 2.30 – 2.27 (m, $3H_{major}$ + $3H_{minor}$), 2.14 (s, $6H_{major}$), 2.10 (s, $6H_{minor}$), 1.40 (t, J = 6.5 Hz, $3H_{major}$ + $3H_{minor}$).

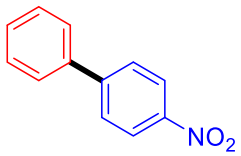
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 171.2, 143.1, 143.0, 137.6, 137.6, 137.2, 137.2, 136.9, 136.9, 132.8, 132.8, 130.1, 130.1, 129.3, 129.3, 128.6, 128.5, 128.3, 128.3, 127.2, 127.2, 126.7, 126.7, 126.1, 126.1, 52.8, 52.7, 48.9, 48.8, 21.7, 21.6, 21.1, 21.0, 20.9, 20.9.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{25}H_{28}NO$: 358.2171, found: 358.2176.

GC Chromatogram: diastereoisomer peak ratio: 1.2:1.



4-Nitrobiphenyl (44)[28]

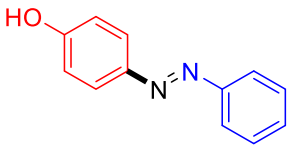


Following General Procedure D, compound **44** was obtained from 4-nitroaniline (138 mg, 1.00 mmol) and benzene (1564 mg, 20.0 mmol) with HFIP (0,5 mL). Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 126 mg of compound **44** as a yellow solid. **(Yield = 63%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.24 (m, 2H), 7.77 – 7.70 (m, 2H), 7.66 – 7.59 (m, 2H), 7.53 – 7.41 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 147.1, 138.8, 129.2, 128.9, 127.8, 127.4, 124.1.

4-Hydroxyazobenzene (45)[29]

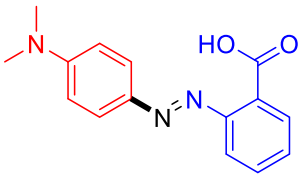


Following General Procedure D, compound **45** was obtained from aniline (93 mg, 1.00 mmol) and phenol (471 mg, 5.00 mmol) with HFIP (2 mL). Purified by column chromatography (AcOEt/hexanes gradually from 5:95 to 10:90) to afford 164 mg of compound **45** as orange solid. **(Yield = 83%).**

^{1}H NMR (400 MHz, DMSO) δ 10.26 (s, 1H), 7.85 – 7.73 (m, 4H), 7.58 – 7.49 (m, 2H), 7.49 – 7.36 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR (100 MHz, DMSO) δ 161.4, 152.6, 145.7, 130.9, 129.8, 125.3, 122.6, 116.4.

Methyl red (46)[30]

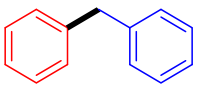


Following General Procedure D, compound **46** was obtained from anthranilic acid (137 mg, 1.00 mmol) and *N*,*N*-dimethylaniline (606 mg, 5.00 mmol) with 2 mL HFIP. Purified by column chromatography (AcOEt/hexanes gradually from 60:40 to 80:20) to afford 245 mg of compound **46** as a dark red solid. **(Yield = 91%).**

^{1}H NMR (400 MHz, CDCl$_3$) δ 14.23 (s, 1H), 8.40 – 8.31 (m, 1H), 8.02 – 7.93 (m, 1H), 7.82 – 7.72 (m, 2H), 7.64 – 7.56 (m, 1H), 7.52 – 7.44 (m, 1H), 6.78 – 6.67 (m, 2H), 3.13 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 167.3, 154.1, 150.4, 142.1, 133.5, 132.6, 129.9, 127.0, 125.2, 115.6, 111.9, 40.3.

Diphenylmethane (47)[2]



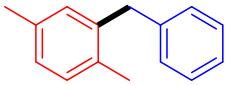
Following General Procedure A, compound **47** was obtained from benzylamine (107 mg, 1.00 mmol) and benzene (391 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for

4.5 h. Purified by column chromatography (petroleum ether) to afford 102 mg of compound **47** as colorless oil. **(Yield = 61%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 4H), 7.30 – 7.23 (m, 6H), 4.06 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 129.0, 128.5, 126.1, 42.0.

2-Benzyl-1,4-dimethylbenzene (8)[16]

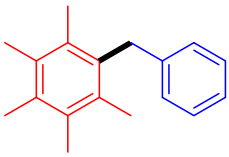


Following General Procedure A, compound **8** was obtained from benzylamine (107 mg, 1.00 mmol) and *p*-xylene (531 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 160 mg of compound **8** as colorless oil. **(Yield = 82%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 7.27 – 7.21 (m, 1H), 7.21 – 7.15 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 7.07 – 6.97 (m, 2H), 4.02 (s, 2H), 2.36 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 138.7, 135.4, 133.5, 130.8, 130.3, 128.8, 128.4, 127.2, 125.9, 39.5, 21.0, 19.2.

Benzylpentamethylbenzene (48)[17]

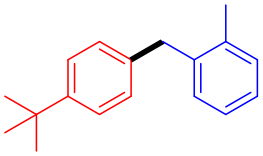


Following General Procedure A, compound **48** was obtained from benzylamine (107 mg, 1.00 mmol) and pentamethylbenzene (741 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 224 mg of compound **48** as a yellowish solid. **(Yield = 94%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 3H), 7.14 – 7.08 (m, 2H), 4.19 (s, 2H), 2.35 (s, 3H), 2.32 (s, 6H), 2.25 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 133.9, 133.2, 132.9, 132.5, 128.4, 128.0, 125.6, 36.2, 17.0, 16.9, 16.9.

4-(2-Methylbenzyl)-*tert*-butylbenzene (49)[18]

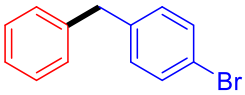


Following General Procedure A, compound **49** was obtained from 2-methylbenzylamine (121 mg, 1.00 mmol) and *tert*-butylbenzene (671 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 3 h. Purified by column chromatography (petroleum ether) to afford 182 mg of compound **49** as colorless oil. **(Yield = 76%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.22 – 7.16 (m, 4H), 7.13 – 7.09 (m, 2H), 4.01 (s, 2H), 2.31 (s, 3H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 139.2, 137.3, 136.6, 130.3, 130.0, 128.4, 126.4, 126.0, 125.30, 38.9, 34.4, 31.5, 19.7.

(4-Bromobenzyl)benzene (50)[5]

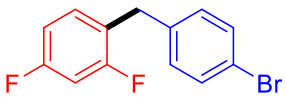


Following General Procedure A, compound **50** was obtained from 4-bromobenzylamine (186 mg, 1.00 mmol) and benzene (391 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 4.5 h. Purified by column chromatography (petroleum ether) to afford 207 mg of compound **50** as colorless oil. **(Yield = 84%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.36 – 7.30 (m, 2H), 7.28 – 7.22 (m, 1H), 7.22 – 7.17 (m, 2H), 7.12 – 7.05 (m, 2H), 3.96 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 140.1, 131.6, 130.7, 128.9, 128.6, 126.4, 120.0, 41.4.

4-(4-Bromobenzyl)-1,3-difluorobenzene (51)[2]

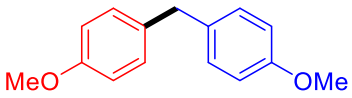


Following General Procedure A, compound **51** was obtained from 4-bromobenzylamine (186 mg, 1.00 mmol) and 1,3-difluorobenzene (570 mg, 5.00 mmol). The reaction mixture with MsOH was refluxed for 21 h. Purified by column chromatography (petroleum ether) to afford 214 mg of compound **51** as colorless oil. **(Yield = 76%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.15 – 7.04 (m, 3H), 6.85 – 6.76 (m, 2H), 3.91 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (dd, *J* = 100.9, 11.8 Hz), 160.1 (dd, *J* = 101.8, 11.9 Hz), 138.6, 131.7, 131.4 (dd, *J* = 9.5, 6.1 Hz), 130.4, 123.3 (dd, *J* = 16.0, 3.9 Hz), 120.3, 111.2 (dd, *J* = 21.0, 3.8 Hz), 103.9 (t, *J* = 25.6 Hz), 33.8 (d, *J* = 2.6 Hz).

4,4'-Dianisylmethane (52)[2] (containing 8% ortho isomer)

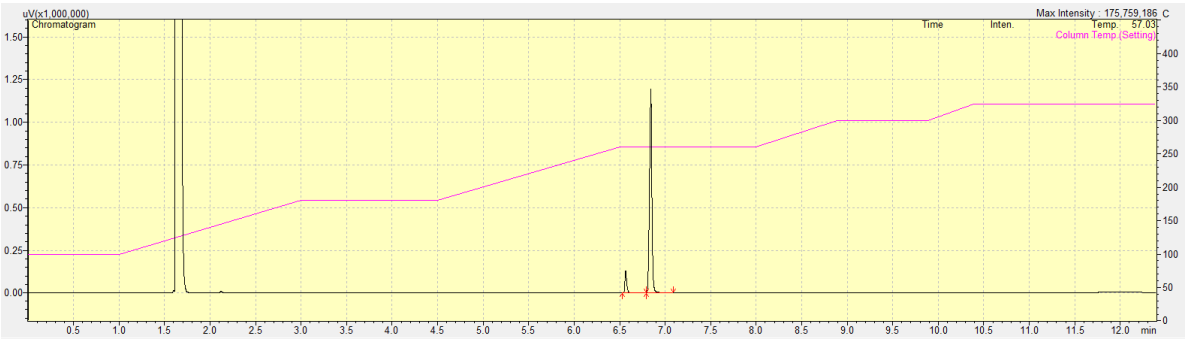


Following General Procedure A, compound **52** was obtained from 4-methoxybenzylamine (137 mg, 1.00 mmol) and anisole (541 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 182 mg of compound **52** (containing 8% *ortho* isomer) as yellowish oil. **(Yield = 80%).**

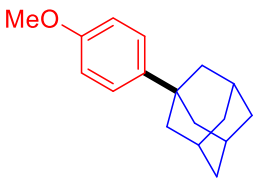
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 4H), 6.89 – 6.82 (m, 4H), 3.90 (s, 2H), 3.80 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 133.8, 129.9, 129.8, 113.9, 113.6, 55.3, 40.2.

GC Chromatogram: peak ratio: 11.5:1 (8% *ortho* isomer).



1-(4-Methoxyphenyl)adamantane (53)[19]



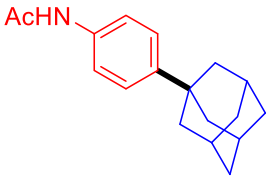
Following General Procedure A, compound **53** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and anisole (541 mg, 5.00 mmol). The reaction mixture was stirred at room temperature for 16 h with MsOH. Purified by column chromatography (AcOEt/hexanes

gradually from 0:100 to 3:97) to afford 240 mg of compound **53** as a white solid. **(Yield = 99%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 6.90 – 6.85 (m, 2H), 3.80 (s, 3H), 2.13 – 2.06 (m, 3H), 1.94 – 1.88 (m, 6H), 1.83 – 1.71 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 143.7, 125.8, 113.4, 77.3, 77.0, 76.7, 55.2, 43.4, 36.8, 35.6, 29.0.

4-(Adamantan-1-yl)acetanilide (54)[20]

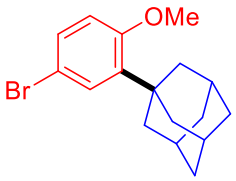


Following General Procedure A, compound **54** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and acetanilide (676 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from:70 to 50:50) to afford 214 mg of compound **54** as a white solid. **(Yield = 79%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.22 (s, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 1.91 – 1.85 (m, 6H), 1.81 – 1.70 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 147.6, 135.3, 125.4, 119.8, 43.2, 36.8, 35.9, 28.9, 24.5.

2-(Adamantan-1-yl)-4-bromoanisole (55)[27]

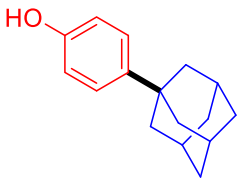


Following General Procedure B, compound **55** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and 4-bromoanisole (935 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 36 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 3:97) to afford 219 mg of compound **55** as a white solid. **(Yield = 68%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ (d, J = 2.5 Hz, 1H), 7.26 (dd, J = 8.6, 2.5 Hz, 1H), 6.73 (d, J = 8.6 Hz, 1H), 3.81 (s, 3H), 2.06 (s, 9H), 1.77 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 140.8, 129.8, 129.3, 113.3, 113.3, 55.2, 40.4, 37.2, 37.0, 29.0.

1-(4-Hydroxyphenyl)adamantane (56)[12,21]

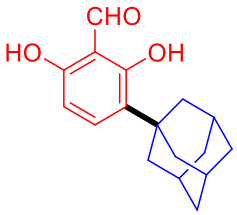


Following General Procedure B, compound **56** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and phenol (471 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. The reaction mixture was quenched with water (15 mL), the resulting precipitate was filtered and washed with water/MeOH (4:1, 50 mL) to afford 219 mg of compound **56** as a white solid. **(Yield = 96%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 4.72 (s, 1H), 2.18 – 1.99 (m, 3H), 1.98 – 1.84 (m, 6H), 1.83 – 1.67 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 144.0, 126.0, 114.8, 43.4, 36.8, 35.6, 29.0.

3-(Adamantan-1-yl)-2,6-dihydroxybenzaldehyde (57)



Following General Procedure B, compound **57** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and 2,6-dihydroxybenzaldehyde (691 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 30 min. Purified by column chromatography (AcOEt/toluene gradually from 0:100 to 5:95) to afford 177 mg of compound **57** as a yellow solid. **(Yield = 65%)**

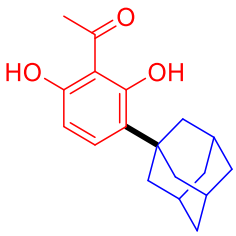
^{1}H NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 10.60 (s, 1H), 10.21 (s, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 6.33 (d, *J* = 8.7 Hz, 1H), 1.99 (s, 9H), 1.69 (s, 6H).

^{13}C NMR (100 MHz, DMSO) δ 195.6, 162.0, 160.3, 136.6, 127.4, 110.3, 105.9, 37.0, 36.1, 28.8.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{17}H_{21}O_3$: 273.1491, found: 273.1490.

mp: – decomposes before melting

3-(Adamantan-1-yl)-2,6-dihydroxyacetophenone (58)



Following General Procedure B, compound **58** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and 2,6-dihydroxyacetophenone (761 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (AcOEt/toluene gradually from 0:100 to 5:95) to afford 257 mg of compound **58** as a yellow solid. **(Yield = 90%)**

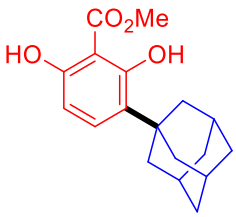
^{1}H NMR (400 MHz, DMSO) δ 13.96 (s, 1H), 10.54 (s, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 8.6 Hz, 1H), 2.63 (s, 3H), 1.99 (s, 9H), 1.68 (s, 6H).

^{13}C NMR (100 MHz, DMSO**)** δ 206.6, 163.2, 159.2, 134.1, 127.6, 110.2, 106.0, 37.1, 36.2, 33.9, 28.9.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{18}H_{23}O_3$: 287.1647, found: 287.1644.

mp: – decomposes before melting

Methyl 3-(adamantan-1-yl)-2,6-dihydroxybenzoate (59)



Following General Procedure B, compound **59** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and methyl 2,6-dihydroxybenzoate (841 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (30:70 toluene/hexanes) to afford 204 mg of compound **59** as a white solid. **(Yield = 67%)**

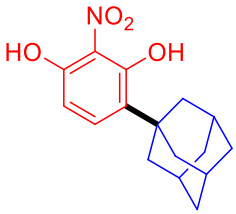
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 9.18 (s, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 6.43 (d, *J* = 8.8 Hz, 1H), 4.07 (s, 3H), 2.08 (s, 9H), 1.76 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 160.5, 158.2, 134.3, 128.6, 107.0, 99.9, 52.8, 40.4, 37.1, 36.5, 29.1.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{18}H_{23}O_4$: 303.1596, found: 303.1600.

mp: 151.9 – 152.6 °C

4-(Adamantan-1-yl)-2-nitroresorcinol (60)



Following General Procedure B, compound **60** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and 2-nitroresorcinol (776 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (10:90 toluene/hexanes) to afford 226 mg of compound **60** as an orange solid. **(Yield = 78%)**

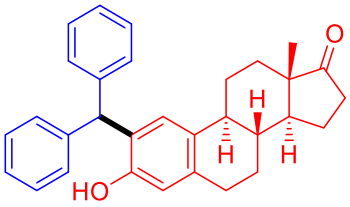
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 10.53 (s, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 6.55 (d, *J* = 9.0 Hz, 1H), 2.08 (s, 9H), 1.77 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 154.2, 137.0, 129.9, 124.3, 107.9, 40.3, 36.9, 29.0.

HRMS (m/z) (APCI) $[M-H]^-$ calculated for $C_{16}H_{18}NO_4$: 288.1236, found: 288.1237.

mp: 147.4 – 148.8 °C

(8*R*,9*S*,13*S*,14*S*)-2-Benzhydryl-3-hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (61)[2]

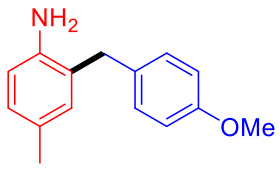


Following General Procedure C, compound **61** was obtained from benzhydrylamine (183 mg, 1.00 mmol) and estrone (811 mg, 3.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 15 min. Purified by column chromatography (DCM/hexanes gradually from 80:20 to 100:0) to afford 415 mg of compound **61** as white solid. **(Yield = 95%).**

^{1}H NMR (400 MHz, DMSO) δ 9.08 (s, 1H), 7.32 – 7.22 (m, 4H), 7.22 – 7.13 (m, 2H), 7.06 (t, *J* = 7.7 Hz, 4H), 6.68 (s, 1H), 6.52 (s, 1H), 5.80 – 5.73 (m, 1H), 2.84 – 2.66 (m, 2H), 2.41 (dd, *J* = 18.8, 8.4 Hz, 1H), 2.17 – 1.83 (m, 5H), 1.69 – 1.60 (m, 1H), 1.60 – 1.12 (m, 6H), 0.79 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ 152.9, 144.5, 144.4, 135.4, 129.9, 129.5, 129.5, 128.5, 128.5, 127.9, 127.1, 126.3, 115.4, 50.0, 49.7, 47.8, 44.0, 38.4, 35.8, 31.7, 29.2, 26.6, 26.0, 21.6, 14.0.

2-(4-Methoxybenzyl)-4-methylaniline (62)



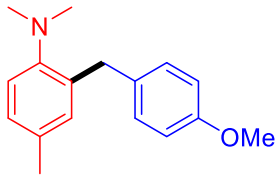
Following General Procedure B, compound **62** was obtained from 4-methoxybenzylamine (137 mg, 1.00 mmol) and 4-methylaniline (536 mg, 5.00 mmol). The reaction mixture was stirred with TfOH at 140 °C for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 5:95 to 15:85) to afford 173 mg of compound **62** as yellowish oil. **(Yield = 76%)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 2H), 6.97 – 6.90 (m, 2H), 6.89 – 6.84 (m, 2H), 6.62 (d, *J* = 7.8 Hz, 1H), 3.85 (s, 2H), 3.80 (s, 3H), 3.42 (s, 2H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 142.2, 131.6, 131.4, 129.5, 128.1, 127.9, 125.7, 116.1, 114.1, 55.3, 37.3, 20.5.

HRMS (m/z) (EI) [M] calculated for $C_{15}H_{17}NO$: 227.1310, found: 227.1313.

2-(4-Methoxybenzyl)-4,*N*,*N*-trimethylaniline (63)



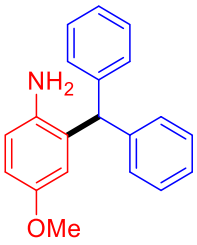
Following General Procedure C, compound **63** was obtained from 4-methoxybenzylamine (137 mg, 1.00 mmol) and 4,*N*,*N*-trimethylaniline (676 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 96 h. Purified by column chromatography (AcOEt/toluene gradually from 0:100 to 10:90) to afford 184 mg of compound **63** as yellowish oil. **(Yield = 72%)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.11 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.88 – 6.85 (m, 1H), 6.85 – 6.80 (m, 2H), 4.02 (s, 2H), 3.79 (s, 3H), 2.65 (s, 6H), 2.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 150.4, 136.3, 133.9, 132.8, 131.3, 120.0, 127.4, 119.5, 113.7, 55.2, 45.4, 35.6, 20.8.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{17}H_{22}NO$: 256.1701, found: 256.1702.

2-Benzhydryl-4-methoxyaniline (64)[22]

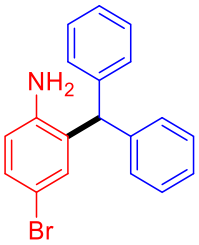


Following General Procedure C, compound **64** was obtained from benzhydrylamine (183 mg, 1.00 mmol) and 4-methoxyaniline (616 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (AcOEt/toluene gradually from 0:100 to 10:90) to afford 245 mg of compound **64** as a brown solid. **(Yield = 85%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.28 – 7.22 (m, 2H), 7.20 – 7.12 (m, 4H), 6.73 – 6.62 (m, 2H), 6.39 – 6.30 (m, 1H), 5.53 (s, 1H), 3.64 (s, 3H), 3.21 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 142.4, 137.9, 131.2, 129.5, 128.6, 126.7, 117.3, 116.8, 112.1, 55.5, 52.4.

2-Benzhydryl-4-bromoaniline (65)



Following General Procedure C, compound **65** was obtained from benzhydrylamine (183 mg, 1.00 mmol) and 4-bromoaniline (860 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (toluene/hexanes gradually from 50:50 to 100:0) to afford 310 mg of compound **65** as a brown solid. **(Yield = 92%)**

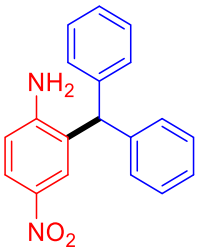
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 6H), 7.19 (dd, J = 8.4, 2.3 Hz, 1H), 7.15 – 7.10 (m, 4H), 6.77 (d, J = 2.1 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 5.42 (s, 1H), 3.47 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 141.6, 132.5, 131.3, 130.3, 129.4, 128.8, 127.0, 117.8, 110.7, 52.2.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{19}H_{17}NBr$: 338.0544, found: 338.0543.

mp: 94.4 – 96.1 °C

2-Benzhydryl-4-nitroaniline (66)



Following General Procedure C, compound **66** was obtained from benzhydrylamine (183 mg, 1.00 mmol) and 4-nitroaniline (691 mg, 5.00 mmol). The reaction mixture was refluxed with TfOH for 16 h. Purified by column chromatography (toluene) to afford 275 mg of compound **66** as a yellow solid. **(Yield = 91%)**

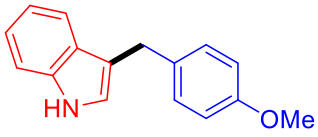
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.62 (d, *J* = 2.6 Hz, 1H), 7.41 – 7.23 (m, 6H), 7.20 – 7.06 (m, 4H), 6.64 (d, *J* = 8.8 Hz, 1H), 5.38 (s, 1H), 4.24 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 140.7, 139.3, 129.2, 129.0, 127.9, 127.4, 126.5, 124.4, 114.7, 52.2.

HRMS (m/z) (APCI) $[M+H]^+$ calculated for $C_{19}H_{17}N_2O_2$: 305.1290, found: 305.1289.

mp: 179.8 – 181.1 °C

3-(4-Methoxybenzyl)indole (67)[23]

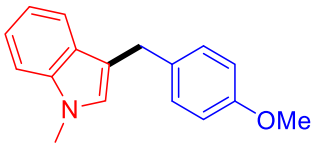


Following General Procedure C, compound **67** was obtained from 4-methoxybenzylamine (137 mg, 1.00 mmol) and indole (586 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 1 h. Purified by column chromatography (AcOEt/hexanes gradually from 5:95 to 15:85) to afford 173 mg of compound **67** as a red solid. **(Yield = 73%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.82 (m, 1H), 7.57 – 7.52 (m, 1H), 7.38 – 7.32 (m, 1H), 7.25 – 7.17 (m, 3H), 7.14 – 7.07 (m, 1H), 6.91 – 6.88 (m, 1H), 6.88 – 6.83 (m, 2H), 4.09 (s, 2H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 136.5, 133.4, 129.6, 127.5, 122.2, 122.0, 119.3, 119.2, 116.3, 113.8, 111.1, 55.3, 30.7.

3-(4- Methoxybenzyl)-1-methylindole (68)[24]

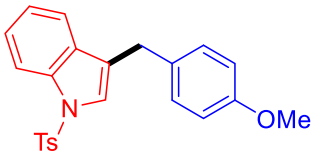


Following General Procedure C, compound **68** was obtained from 4-methoxybenzylamine (137 mg, 1.00 mmol) and 1-methylindole (656 mg, 5.00 mmol). The reaction mixture was refluxed with MsOH for 1 h. Purified by column chromatography (AcOEt/hexanes gradually from 5:95 to 15:85) to afford 174 mg of compound **68** as brown oil. **(Yield = 69%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.28 – 7.21 (m, 3H), 7.13 – 7.07 (m, 1H), 6.89 – 6.84 (m, 2H), 6.76 (s, 1H), 4.08 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 137.2, 133.6, 129.6, 127.9, 127.0, 121.6, 119.2, 118.8, 114.8, 113.8, 109.2, 55.3, 32.6, 30.7.

3-(4- Methoxybenzyl)-1-tosylindole (69)[25]

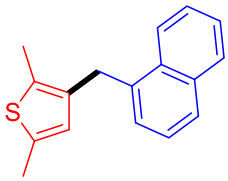


Following General Procedure A, compound **69** was obtained from 4-methoxybenzylamine (137 mg, 1.00 mmol) and 1-tosylindole (1357 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (50:50 toluene/hexanes) to afford 300 mg of compound **69** as a yellowish solid. **(Yield = 77%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.75 (s, 1H), 7.73 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 7.14 (s, 1H), 7.12 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.95 (s, 2H), 3.80 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 144.7, 135.6, 135.4, 131.0, 130.9, 129.8, 129.6, 126.8, 124.7, 123.9, 123.1, 123.0, 119.8, 114.0, 113.8, 55.3, 30.5, 21.5.

2,5-Dimethyl-3-(naphthalen-1-ylmethyl)thiophene (70)



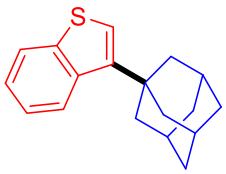
Following General Procedure C, compound **70** was obtained from 1-naphthylmethylamine (157 mg, 1.00 mmol) and 2,5-dimethylthiophene (561 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 1 h. Purified by column chromatography (petroleum ether) to afford 222 mg of compound **70** as yellowish oil. **(Yield = 88%)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 1H), 7.92 – 7.87 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.46 – 7.39 (m, 1H), 7.24 – 7.19 (m, 1H), 6.32 (s, 1H), 4.26 (s, 2H), 2.41 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.3, 135.2, 133.8, 132.1, 131.0, 128.7, 127.6, 126.9, 126.2, 126.0, 125.7, 125.6, 123.8, 31.5, 15.2, 13.1.

HRMS (m/z) (EI) [M] calculated for $C_{17}H_{16}S$: 252.0973, found: 252.0979.

3-(Adamantan-1-yl)benzothiophene (71)[26]

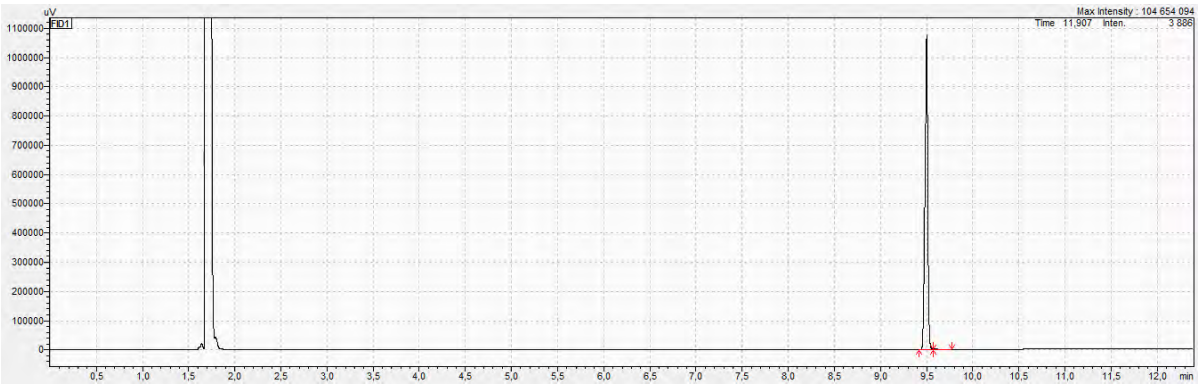


Following General Procedure B, compound **71** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and benzothiophene (671 mg, 5.00 mmol). The reaction mixture was stirred with MsOH at room temperature for 15 min. Purified by column chromatography (petroleum ether) to afford 254 mg of compound **71** as white solid. **(Yield = 94%).**

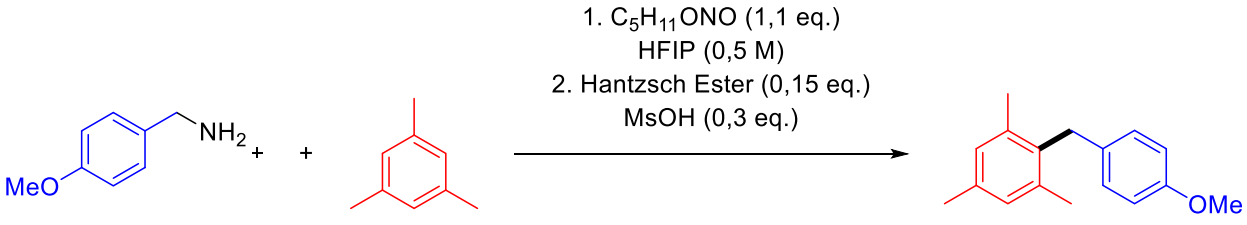
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.18 (m, 1H), 7.91 – 7.86 (m, 1H), 7.39 – 7.27 (m, 2H), 7.08 (s, 1H), 2.24 – 2.14 (m, 9H), 1.92 – 1.85 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 141.8, 137.5, 124.7, 123.4, 123.4, 123.0, 119.8, 42.1, 37.1, 37.0, 28.9.

GC Chromatogram: purity: 99.6%



Reaction scale up



10 mmol	5.0 eq.	11.
10 mmol	2.5 eq.	2.38 g (99%), 17.9 mL (90%) HFIP recovered
200 mmol	2.5 eq.	2.24 g (93%), 17.7 mL (89%) HFIP recovered 45.19 g (94%), 356 mL (89%) HFIP recovered

10 mmol scale

A 50 mL round-bottom flask equipped with a magnetic bar was charged with 4-methoxybenzylamine (1.37 g, 10.0 mmol, 1.00 equiv.), mesitylene (7.0 mL, 50 mmol, 5.0 equiv.), HFIP (20 mL), and *iso*-pentyl nitrite (1.5 mL, 11 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 2 h. No significant increase in temperature was observed. Then, Hantzsch ester (380 mg, 1.50 mmol, 0.150 equiv.), and MsOH (195 µL, 3.00 mmol, 0.300 equiv.) were added. The reaction mixture was stirred for 1 h at room temperature. Then, triethylamine (0.42 mL, 3.0 mmol, 0.3 equiv.) was added to quench the reaction. The distillation kit was assembled and HFIP was distilled directly from the reaction flask, obtaining 17.9 mL (90%) of the solvent used. The rest of the reaction mixture was evaporated under high vacuum, removing most of the mesitylene. Methanol:water:concentared HCl solution (5:1.5:1, 7.5 mL) was added to the remaining oil and left in the cold to crystallize. The resulting crystals were filtered, washed with a water:methanol solution (1:1) and dried to afford 2.38 g of compound **11** as an off-white solid. **(Yield = 99%).**

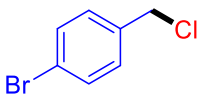
The reaction with 2.5 equiv. (3.5 mL, 25 mmol) of mesitylene was performed similarly. The same workup allowed recovery of HFIP (17.7 mL, 89%) of used and afforded 2.38 g of off-white solid product, which was 94% pure (GC). To further purify, the solid was subjected to a short silica plug and was eluted with hexane to afford 2.24 g of pure, white product. **(Yield = 93%).**

200 mmol scale

A 1000 mL round-bottom flask equipped with a magnetic bar was charged with 4- methoxybenzylamine (27.4 g, 200 mmol, 1.0 equiv.), mesitylene (70 mL, 500 mmol, 2.5 equiv.), HFIP (400 mL, including the recycled from previous runs), and isopentyl nitrite (30 mL, 220 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 2 h. The flask was placed in a vessel of water to absorb the heat of the reaction, but this procedure did not appear to have been necessary. Then, Hantzsch ester (7.6 g, 30 mmol, 0.15 equiv.), and MsOH (3.9 mL, 60 mmol, 0.3 equiv.) were added. The reaction mixture was stirred for 1 h at room temperature. Then, triethylamine (8.4 mL, 60 mmol, 0.3 equiv.) was added to quench the reaction. The distillation kit was assembled and HFIP was distilled directly from the reaction flask, obtaining 356 mL (89%) of the solvent used. The rest of the reaction mixture was evaporated under high vacuum, removing most of the mesitylene. Methanol:water:concentared HCl solution (5:1.5:1, 150 mL) was added to the remaining oil and left in the cold to crystallize. The resulting crystals were filtered, washed with a water:methanol solution (1:1) and dried to afford 47.5 g of off-white solid product, which was 95% pure (GC). **(Yield = 94%).**

Other nucleophiles

4-Bromobenzyl chloride (74)[32]

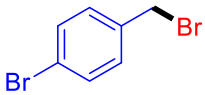


Following General Procedure B, compound **74** was obtained from 4-bromobenzylamine (223 mg, 1.00 mmol) using concentrated hydrochloric acid (36%, 258 µL, 3.00 mmol, 3.00 equiv.) as both a chloride source and an acid, instead of an arene and MsOH. HCl was added after diazotization and the reaction mixture was stirred at 60 °C for 16 h in a screw-cap vial. Purified by column chromatography (petroleum ether) to afford 189 mg of compound **74** as a white solid. **(Yield = 92%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.29 – 7.23 (m, 2H), 4.53 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 131.9, 130.2, 122.5, 45.4.

4-Bromobenzyl bromide (75)[33]

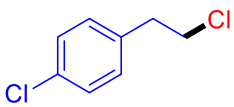


Following General Procedure B, compound **75** was obtained from 4-bromobenzylamine (223 mg, 1.00 mmol) using concentrated hydrobromic acid (48%, 339 µL, 3.00 mmol, 3.00 equiv) as both bromide source and an acid, instead of an arene and MsOH. HBr was added after diazotization and the reaction mixture was stirred at 60 °C for 16 h in a screw-cap vial. Purified by column chromatography (petroleum ether) to afford 247 mg of compound **75** as a white solid. **(Yield = 99%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H), 7.30 – 7.23 (m, 2H), 4.43 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 132.0, 130.7, 122.5, 32.4.

2-(4-Chlorophenyl)ethyl chloride (76)[34]



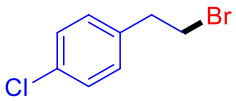
Following General Procedure D, compound **76** was obtained from 4-chlorophenethylamine (156 mg, 1.00 mmol) using concentrated hydrochloric acid (36%, 64 µL, 0.75 mmol, 0.75

equiv.) and tetraethylammonium chloride (829 mg, 5.00 mmol, 5.00 equiv.) as chloride sources, instead of an arene, with HFIP (5 mL). Purified by column chromatography (petroleum ether) to afford 135 mg of compound **76** as colourless oil. **(Yield = 77%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 2H), 7.20 – 7.01 (m, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 132.8, 130.2, 128.7, 44.7, 38.4.

2-(4-Chlorophenyl)ethyl bromide (77)[35]

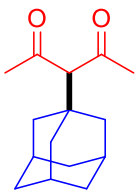


Following General Procedure D, compound **77** was obtained from 4-chlorophenethylamine (156 mg, 1.00 mmol) using concentrated hydrobromic acid (48%, 85 µL, 0.75 mmol, 0.75 equiv.) and tetrabutylammonium bromide (1612 mg, 5.00 mmol, 5.00 equiv.) as bromide sources, instead of an arene, with HFIP (5 mL). Purified by column chromatography (petroleum ether) to afford 184 mg of compound **77** as colourless oil. **(Yield = 84%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 2H), 7.22 – 7.11 (m, 2H), 3.54 (t, *J* = 7.4 Hz, 2H), 3.13 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 132.8, 130.0, 128.7, 38.6, 32.6.

3-(1-Adamantyl)pentane-2,4-dione (78)[36]

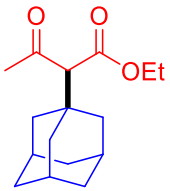


Following General Procedure B, compound **78** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and acetylacetone (501 mg, 5.00 mmol), used instead of an arene, added after diazotization. The reaction mixture was stirred with MsOH at room temperature for 16 h. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 5:95) to afford 206 mg of compound **78** as a white solid. **(Yield = 88%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 1H), 2.13 (s, 6H), 1.91 (s, 3H), 1.70 – 1.52 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 78.1, 40.3, 38.4, 36.5, 33.0, 28.5.

Ethyl 2-(adamantan-1-yl)-3-oxobutanoate (79)[37]

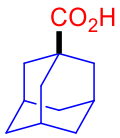


Following General Procedure B, compound **79** was obtained from 1-adamantylamine (151 mg, 1.00 mmol) and ethyl acetoacetate (651 mg, 5.00 mmol), used instead of an arene, added after diazotization. The reaction mixture was stirred with MsOH at room temperature for a week. Purified by column chromatography (AcOEt/hexanes gradually from 0:100 to 5:95) to afford 219 mg of compound **79** as yellowish oil. **(Yield = 83%).**

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.2 Hz, 2H), 3.16 (s, 1H), 2.20 (s, 3H), 1.99 – 1.91 (m, 3H), 1.81 – 1.57 (m, 12H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 168.6, 69.9, 60.7, 40.0, 36.9, 36.6, 32.1, 28.6, 14.2.

1-Adamantanecarboxylic acid (80)[38]



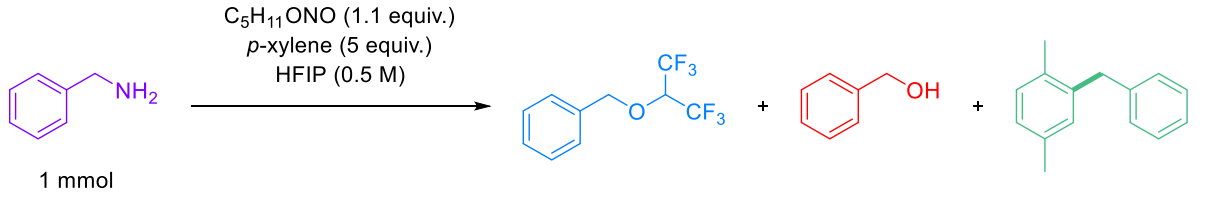
A 10 mL vial equipped with a magnetic bar was charged with 1-adamantylamine (151 mg, 1.00 mmol), HFIP (5.0 mL), and isopentyl nitrite (148 µL, 1.1 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 2 h. Then, Hantzsch ester (38 mg, 0.15 mmol, 0.15 equiv.), formic acid (189 µL, 5.00 mmol, 5.00 equiv.) and H_2SO_4 (98%, 820 µL, 15.0 mmol, 15.0 equiv.) were added. The vial was sealed with a cup and the reaction mixture was stirred at room temperature for 16 h. Then, the reaction mixture was transfered to 100 mL round bottom flask and stirred with 25 mL 2 M aqueous NaOH solution for 16 h. The mixture was then acidified with 2 M HCl, and extracted with 3 x 25 mL DCM. The organic phase was dried with Na_2SO_4, filtered, and evaporated to afford 180 mg of compound **80** as a yellowish solid. **(Yield = 100%).**

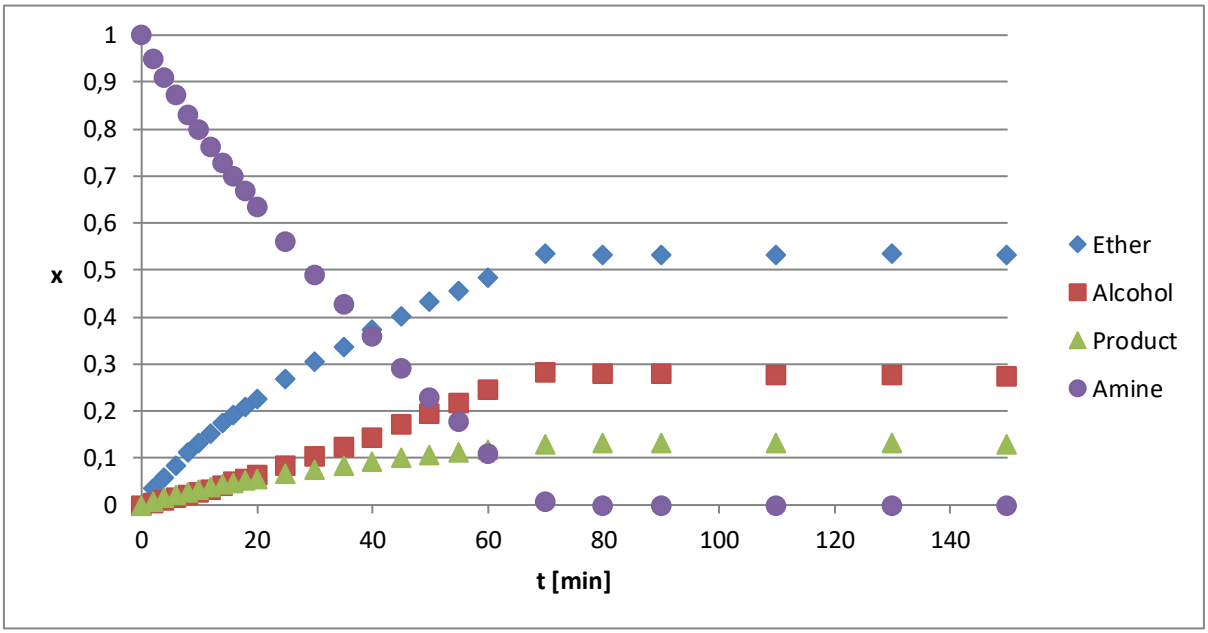
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.90 (s, 1H), 2.06 – 1.97 (m, 3H), 1.94 – 1.86 (m, 6H), 1.78 – 1.65 (m, 6H).

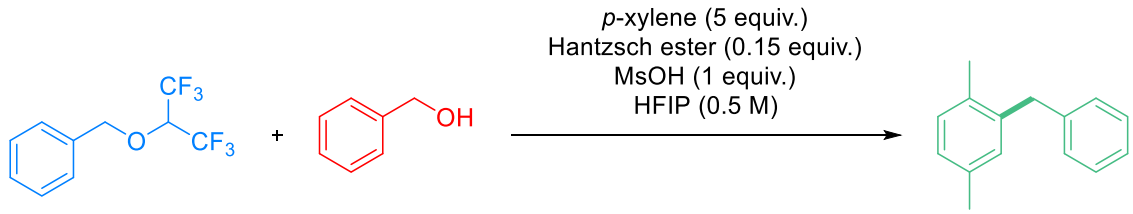
^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 40.5, 38.6, 36.4, 27.8.

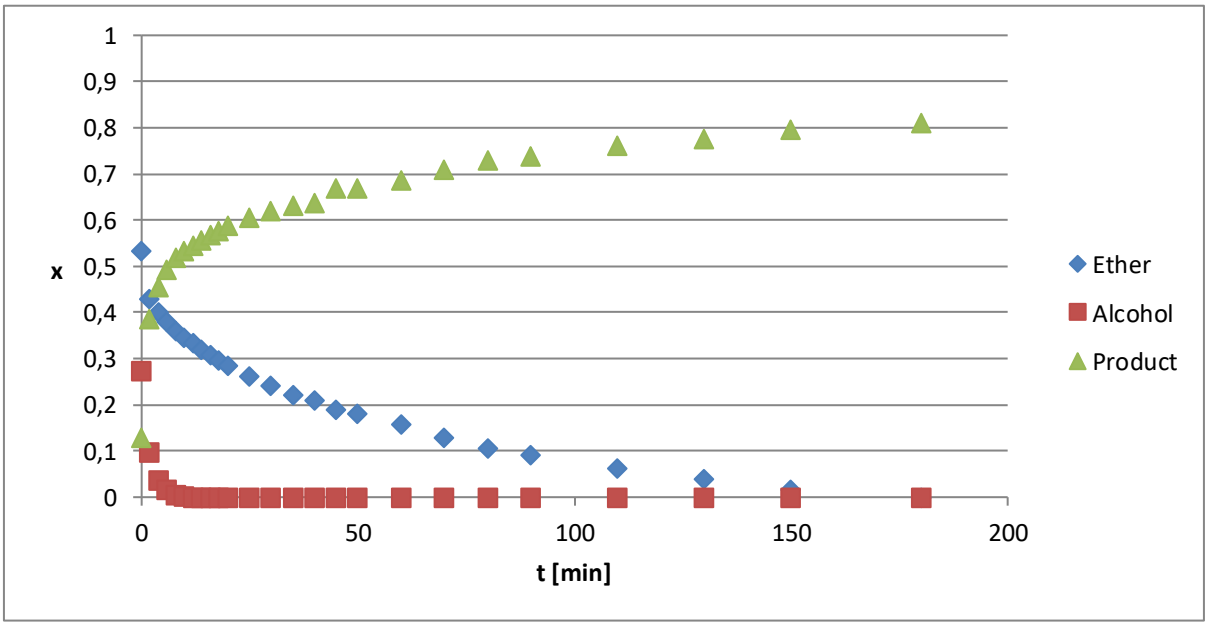
5. Mechanistic studies

5.1 Kinetic studies









The kinetic profile of the diazotization shows that hexafluoro *iso*-propyl ether and the alkylated xylene are produced proportionally over time, while the rate of the benzyl alcohol formation slightly accelerates as the concentration of water increases during the reaction course. The resulting products are stable in the reaction medium. Thus, to push forward the Friedel-Crafts alkylation with transient ethers, the addition of an acid seemed required. Kinetic studies revealed that electrophilic aromatic substitution is much faster for alcohol than for electron deficient hexafluoro isopropyl ether. This fact explains why, in the case of some substrates, the use of acetates obtained in the diazotization reaction with the addition of acetic acid proved beneficial over ethers formed in the typical reaction carried out in HFIP.

5.2 Influence of the acidity of alcoholic solvent

Entry	Alcoholic solvent	pK_a	Conversion of the amine
1	EtOH	15.9	None
2	TFE	12.5	Traces
3	HFIP	9.3	Full

Reaction conditions: 1) $BnNH_2$ (1 mmol), p-xylene (5 equiv.), $C_5H_{11}ONO$ (1.1 equiv.), alcohol (c = 0.5 M), 2 h, RT.

These experiments prove that the appropriate acidity of the solvent is necessary for the diazotization process to occur.

6. NMR spectra

Widma NMR dostępne są w pełnej wersji pliku Supporting Information.

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fanie.202419450&file=anie202419450-sup-0001-misc_information.pdf

7. References

(1) Lv, F.; Xiao, J.; Xiang, J.; Guo, F.; Tang, Z.-L.; Han, L.-B. *J. Org. Chem.* **2021**, *86* (3), 3081–3088.

(2) Bering, L.; Jeyakumar, K.; Antonchick, A. P. *Org. Lett.* **2018**, *20* (13), 3911–3914.

(3) Khodaei, M. M.; Nazari, E. *Tetrahedron Lett.* **2012**, *53* (38), 5131–5135.

(4) Sun, H.-B.; Li, B.; Chen, S.; Li, J.; Hua, R. *Tetrahedron* **2007**, *63* (41), 10185–10188.

(5) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137* (30), 9694–9703.

(6) Qin, Q.; Xie, Y.; Floreancig, P. E. *Chem. Sci.* **2018**, *9* (45), 8528–8534.

(7) Zhang, S.; Vayer, M.; Noël, F.; Vuković, V. D.; Golushko, A.; Rezajooei, N.; Rowley, C. N.; Lebœuf, D.; Moran, J. *Chem* **2021**, *7* (12), 3425–3441.

(8) Yang, X.-W.; Li, D.-H.; Song, A.-X.; Liu, F.-S. *J. Org. Chem.* **2020**, *85* (18), 11750–11765.

(9) Mannschreck, A.; Ernst, L. *Chem. Ber.* **1971**, *104* (1), 228–247.

(10) Pallikonda, G.; Chakravarty, M. *J. Org. Chem.* **2016**, *81* (5), 2135–2142.

(11) Stepakov, A. V.; Molchanov, A. P.; Kostikov, R. R. *Russ. J. Org. Chem.* **2007**, *43* (4), 538–543.

(12) Khusnutdinov, R. I.; Shchadneva, N. A.; Khisamova, L. F. *Russ. J. Org. Chem.* **2015**, *51* (11), 1545–1550.

(13) Akram, M. O.; Tidwell, J. R.; Dutton, J. L.; Martin, C. D. *Angew. Chemie Int. Ed.* **2022**, *61* (46).

(14) He, Y.; Liu, C.; Yu, L.; Zhu, S. *Angew. Chemie Int. Ed.* **2020**, *59* (23), 9186–9191.

(15) Liu, W.; Li, J.; Querard, P.; Li, C.-J. *J. Am. Chem. Soc.* **2019**, *141* (16), 6755–6764.

(16) Tang, R.-J.; Milcent, T.; Crousse, B. *J. Org. Chem.* **2018**, *83* (22), 14001–14009.

(17) Fujita, H.; Kakuyama, S.; Fukuyoshi, S.; Hayakawa, N.; Oda, A.; Kunishima, M. *J. Org. Chem.* **2018**, *83* (8), 4568–4580.

(18) Sha, S.-C.; Tcyrulnikov, S.; Li, M.; Hu, B.; Fu, Y.; Kozlowski, M. C.; Walsh, P. J. *J. Am. Chem. Soc.* **2018**, *140* (39), 12415–12423.

(19) Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2017**, *139* (29), 9847–9850.

(20) Zurabishvili, D. S.; Lomidze, M. O.; Samsoniya, S. A.; Wesquet, A.; Kazmaier, U. *Chem. Heterocycl. Compd.* **2008**, *44* (8), 941–949.

(21) Huang, H.-M.; Bellotti, P.; Pflüger, P. M.; Schwarz, J. L.; Heidrich, B.; Glorius, F. *J.*

Am. Chem. Soc. **2020**, *142* (22), 10173–10183.

(22) Meng, S.-S.; Tang, X.; Luo, X.; Wu, R.; Zhao, J.-L.; Chan, A. S. C. *ACS Catal.* **2019**, *9* (9), 8397–8403.

(23) Su, J.; Li, C.; Hu, X.; Guo, Y.; Song, Q. *Angew. Chemie Int. Ed.* **2022**, *61* (52).

(24) Wang, Z.-H.; Wei, L.; Jiao, K.-J.; Ma, C.; Mei, T.-S. *Chem. Commun.* **2022**, *58* (59), 8202–8205.

(25) Yang, L.; Chen, X.; Ni, K.; Li, Y.; Wu, J.; Chen, W.; Ji, Y.; Feng, L.; Li, F.; Chen, D. *Tetrahedron Lett.* **2020**, *61* (29), 152123.

(26) Sämann, C.; Dhayalan, V.; Schreiner, P. R.; Knochel, P. *Org. Lett.* **2014**, *16* (9), 2418–2421.

(27) Wang, N.; Wang, R.; Shi, X.; Zou, G. *Beilstein J. Org. Chem.* **2012**, *8*, 227–233.

(28) Bao, Z.; Zou, J.; Mou, C.; Jin, Z.; Ren, S.-C.; Chi, Y. R. *Org. Lett.* **2022**, *24* (48), 8907–8913.

(29) Tang, Y.; Zhang, Y.; Chen, X.; Xie, X.; Zhou, N.; Dai, Z.; Xiong, Y. *Angew. Chemie Int. Ed.* **2023**, *62* (4).

(30) Basu Baul, T. S.; Dutta, D.; Duthie, A.; Guedes da Silva, M. F. C. *Inorganica Chim. Acta* **2017**, *455*, 627–637.

(31) Reed, J. H.; Cramer, N. *ChemCatChem* **2020**, *12* (17), 4262–4266.

(32) Ramachandran, P. V.; Alawaed, A. A.; Hamann, H. J. *Org. Lett.* **2023**, *25* (25), 4650–4655.

(33) Nair, A.; Tiwari, V.; Rath, S.; Saini, P.; Verma, A.; Elias, A. J. *Chem. Commun.* **2023**, *59* (74), 11117–11120.

(34) Miele, M.; Citarella, A.; Langer, T.; Urban, E.; Zehl, M.; Holzer, W.; Ielo, L.; Pace, V. *Org. Lett.* **2020**, *22* (19), 7629–7634.

(35) Ai, H.; Leidecker, B. N.; Dam, P.; Kubis, C.; Rabeah, J.; Wu, X. *Angew. Chemie Int. Ed.* **2022**, *61* (43).

(36) Khusnutdinov, R. I.; Kislitsina, K. S.; Shchadneva, N. A. *Russ. J. Org. Chem.* **2014**, *50* (10), 1409–1411.

(37) Vil', V. A.; dos Passos Gomes, G.; Bityukov, O. V.; Lyssenko, K. A.; Nikishin, G. I.; Alabugin, I. V.; Terent'ev, A. O. *Angew. Chemie Int. Ed.* **2018**, *57* (13), 3372–3376.

(38) Yu, Y.; Zhai, D.; Zhou, Z.; Jiang, S.; Qian, H.; Ma, S. *Chem. Commun.* **2023**, *59* (35), 5281–5284.

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Perspective

Lightening Diazo Compounds?

Jakub Durka, Joanna Turkowska, and Dorota Gryko*

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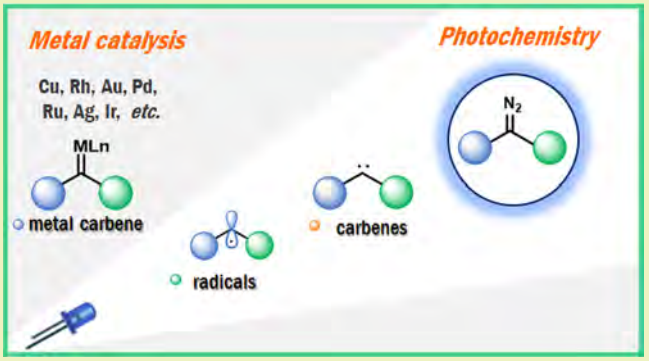
ABSTRACT: The development of new sustainable reactions and protocols is essential to fulfill the growing demands of every branch of organic chemistry for greener synthetic methodologies. In this context, the use of visible light as the only source of energy is highly appealing. Since diazo compounds are valuable reagents in organic synthesis, their transformations realized in a sustainable manner are of interest. High reactivity and easy availability make them suitable for solar-driven transformations. Indeed, photochemical reactions of diazo compounds have recently proven a valuable alternative to transition metal catalysis. In this perspective, we highlight applications of these reagents under visible irradiation, particularly focusing on recent advancements. These include photochemical generation of carbenes and radicals which involve many relevant reactions, [2+1]-cycloadditions, X−H and C−H insertions, Wolff rearrangement, and more. Mechanistic aspects of these processes are briefly addressed to give readers a deeper understanding of rules underlying photoreactivity of diazo compounds. We conclude by emphasizing significant advancements and discussing challenges for future developments in the photochemistry of these valuable reagents.

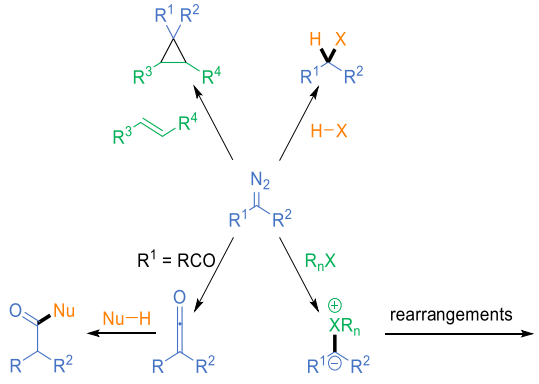


KEYWORDS: *Diazo compounds, Carbenes, Radicals, Photochemistry, Photoredox catalysis*

INTRODUCTION

Diazo compounds occupy a very important position in the methodology of organic chemistry, and their synthesis, as well as reactivity, have been studied since the end of the 19th century. These reagents are mainly used in cyclopropanation reactions, insertions into C−H and X−H bonds, the Wolff rearrangement, and transformations related to rearrangements of ylides generated via the addition of carbene intermediates to the lone pair of a heteroatom (e.g., Doyle−Kirmse reaction or Sommelet−Hauser rearrangement) (Scheme 1).[1]

Scheme 1. Established Reactivity of Diazo Compounds



The vast majority of these reactions involve diazo compounds as precursors of carbenes. Three main methods for generating these reactive intermediates are known. The earliest developed thermal method has, however, a limited range of applicability due to harsh reaction conditions. Therefore, transition metal catalysis giving access to metal carbenes proved an important alternative. In this case, transformations often occur at ambient temperature, but sometimes the very nature of catalysts is problematic. Transition metals are generally expensive and harmful to the environment and their traces are usually difficult to remove, which represents an important issue for the pharmaceutical industry. In pursuit of greener strategies, photochemical methods emerged; however, in the early development, highly energetic ultraviolet light was used.[1,2] As a consequence, the selectivity of these processes was greatly affected. In the few last years, intensified development of visible-light-driven photocatalysis enabled utilizing diazo compounds as precursors of radicals.[1,3] Generation of carbenes, however, has long remained unreachable. In this context, Jurberg and Davies

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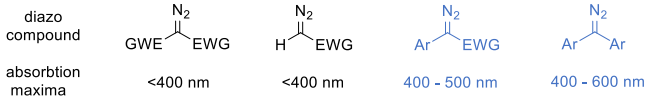
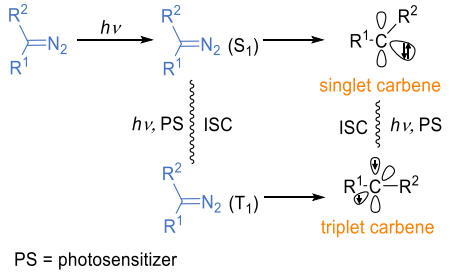
made a momentous discovery.[4] In 2018, they observed that aryl diazoacetates absorb visible light in the blue region, which distinguishes them from other diazo compounds requiring ultraviolet for direct excitation. Since then, we have witnessed the revival of interest in aryl diazoacetates, particularly in their reactivity under very mild conditions—blue light as the only source of energy, ambient temperature, and no catalyst added. Very recently, Koenigs et al. reported on the successful photogeneration of carbenes from another type of diazo compounds—diaryl diazoalkanes and their use in reactions with alkynes (Scheme 2).[5]

Scheme 2. Absorption Maxima of Diverse Diazo Compounds



The spin state of carbenes greatly impacts their reactivity. In general, under light irradiation, diazo compounds undergo photoexcitation to the singlet state. From this point, different pathways lead to carbenes in either singlet or triplet states.[6,7] In the first scenario, the excited diazo compound undergoes photolysis to a singlet carbene (Scheme 3). In this case, two

Scheme 3. Possible Pathways for Generation of Carbenes under Light Irradiation



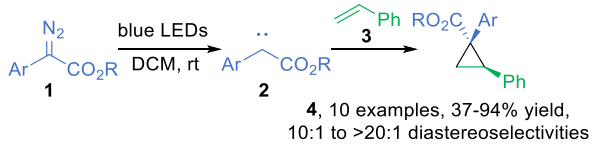
nonbonding electrons on divalent carbon having antiparallel spins occupy one hybridized orbital, leaving one p-orbital empty. Therefore, depending on the character of adjacent groups, singlet carbenes can react as both electrophiles and nucleophiles. As such, they can engage or be involved in many transformations including C−H and X−H insertion reactions and stereospecific addition to alkenes as the most representative. The second scenario implies the generation of the triplet carbene which can occur in two ways: either the singlet carbene undergoes intersystem crossing to the triplet carbene or the excited diazo compound in its singlet state also undergoes intersystem crossing to its triplet form followed by decomposition to the triplet carbene (Scheme 3). Both pathways leading to triplet carbenes are usually driven by energy transfer from a photosensitizer added to the reaction. In contrast to the singlet state, triplet carbenes have nonbonding electrons with parallel spins distributed on two different orbitals. Thereby, they are commonly considered as diradicals and typically are involved in the abstraction of hydrogen atoms or nonstereospecific addition to alkenes.[6,7]

Diazo compounds that absorb only in the UV region can also be transformed under visible light, provided that an appropriate photocatalyst is added. In terms of reactivity, photoredox catalysis offers new opportunities, giving access to a plethora of radical transformations, for example, the use of diazo compounds as radical rather than carbene precursors as initially demonstrated by Gryko et al.[8] and Meggers et al.[3] These catalytic methods have numerous advantages typical for photochemical reactions, such as the use of the most ecological and practically inexhaustible source of energy or very mild conditions. Many of the photocatalysts used are organic dyes; hence, problems associated with the use of expensive and toxic transition metals are eliminated. All these factors and discoveries contributed to a significant increase of interest in visible light-mediated reactions of diazo compounds.[1,2] In this perspective, we put recent advances in this area in a broader context and discuss challenges and future directions.

[2+1]-CYCLOADDITIONS

Noncatalyzed Reactions. Cyclopropanation is definitely one of the most important reactions related to diazo compounds. Therefore, it is not surprising that the seminal work by Davies and Jurberg on visible light-induced generation of carbenes **2** from aryl diazoacetates **1** reports this transformation as an example (Scheme 4).[4] Advantageously, this

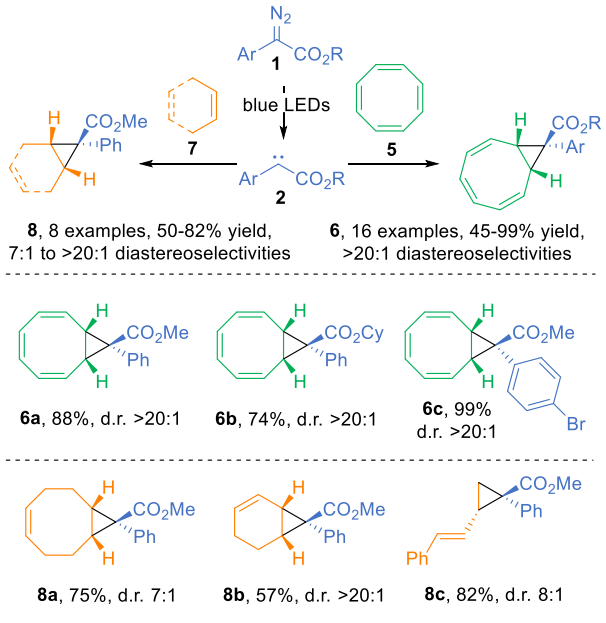
Scheme 4. Visible Light-Mediated Cyclopropanation of Styrene 3 with Aryldiazoacetates 1



reaction can be carried out at room temperature, under air, and without the need to thoroughly remove water from the reaction mixture. Unsubstituted styrene **3** provided cyclopropanes **4** in high yields, as well as high diastereoselectivities.

Recently, Koenigs et al. have reported selective monocyclopropanation of polyunsaturated hydrocarbons **5** and **7** (Scheme 5). A range of products **6** was obtained from cyclooctatetraene (**5**) and various EDG/EWG diazo compounds **1** in good yields

Scheme 5. Monocyclopropanation of (Poly-)unsaturated hydrocarbons



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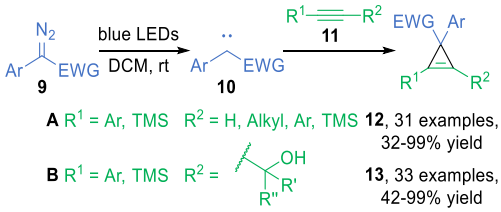
and very high stereoselectivities. Other (poly-)unsaturated cyclic hydrocarbons **7** furnished products with similar efficiency. The monoselectivity of this reaction, despite the presence of multiple double bonds being present in starting materials, is ensured by the use of high excess of an alkene **5** and **7**.[9]

The photolytic approach was also applied to the efficient synthesis of cyclopropenes **12** from alkynes **11** (Scheme 6A).[10]

Scheme 6. Synthesis of Cyclopropenes from Alkynes 11: 11A, Alkynes with Different Substituents; 11B, Unprotected Propargylic Alcohols)

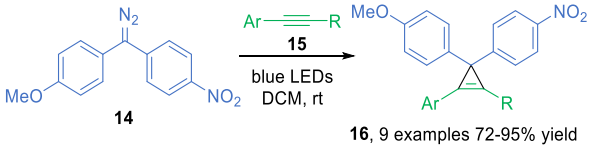


In this case, the use of a syringe pump for the addition of reactive aryl diazoacetates significantly limited side reactions. Furthermore, a usual problem with the scalability of photochemical methods was overcome by performing this reaction in flow.[10]

The scope of blue light-induced [2+1]-cycloadditions with aryl diazoacetates is very broad—even unprotected propargylic alcohols **11B** are well tolerated (Scheme 6B). Such procedure allows for the synthesis of structurally complex cyclopropenes **13** in high yields and under very mild conditions. In contrast to metal-catalyzed reactions, neither O−H insertion nor products of further rearrangements were observed.[11]

In addition, Koenigs et al. have recently reported that the substitution pattern strongly influences absorption properties of diaryl diazo compounds and, consequently, their reactivity under light irradiation.[5] In the case of electron-poor aryl/aryl diazoalkanes, a cyclopropenation reaction occurs via singlet carbenes. The scope was, however, tested only for (4-methoxyphenyl)(4-nitrophenyl) diazomethane (**14**) and several acetylene derivatives **15** (Scheme 7). Interestingly, for aliphatic

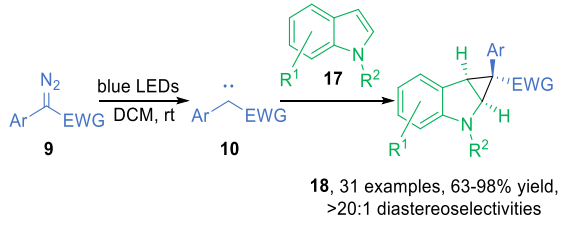
Scheme 7. Cyclopropenation of Alkynes 15 with Diaryl Diazo Compound 14



alkynes, C−H functionalization of the triple bond is preferred.[5] Alternatively, cyclopropenes were synthesized from EDG-EDG diazo compounds and acetylenedicarboxylates. In the first step, 1,3-dipolar cycloaddition leads to the formation of a five-membered product which photochemically decomposes with nitrogen evolution to give the desired cyclopropene.[12]

In their seminal paper, Jurberg and Davies showed that singlet carbenes **10** generated from EDG/EWG diazo compounds **9** under light irradiation undergo [2+1]-cycloaddition to *N*-Boc-protected indoles **17** and pyrrole.[4] This method was then extended by Song et al. who synthesized a series of cyclopropane-fused indolines **18** in excellent yields and diastereoselectivities (Scheme 8).[13] Both electron-donating and electron-withdrawing groups are well tolerated on both indoles

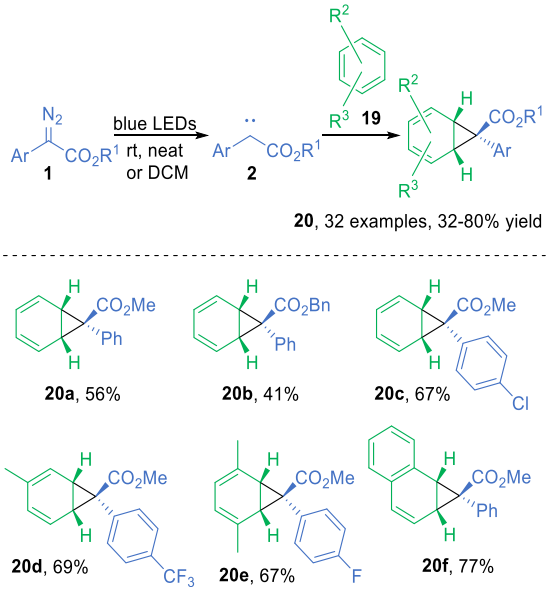
Scheme 8. [2+1]-Cycloaddition of EDG/EWG Diazo Compounds 9 to protected indoles 17



17 and aryl moieties of diazo compounds **9**. The main limitation of this process is the need to use *N*-protected indole.

Also, functionalization of aromatic hydrocarbons **19** is possible with this strategy (Scheme 9). The reaction is efficient

Scheme 9. Cyclopropanation of Aromatic Hydrocarbons 19



provided that carbene acceptors (benzene, toluene, xylenes, and *p*-cymene) are used as solvents. Only the polyaromatic hydrocarbons' (10 equiv) reaction can be carried out in DCM.[14]

To avoid free diazo compounds handling, Koenigs et al. tested the possibility of using their precursors, namely, tosyl hydrazones.[15] In the presence of cesium carbonate, they transform into diazo compounds which upon photolysis undergo [2+1]-cycloaddition reactions, for example, to heteroaromatic compounds. The slow conversion of tosyl hydrazone to diazo compound mimics high-dilution conditions; consequently, side reactions (for example dimerization) are suppressed. Carbene **23** can also be generated from pyridotriazole **21**, the tautomer of 2-(aryldiazomethyl)pyridine **22**. This reactive intermediate readily adds to alkene **24** to yield cyclopropane **25** (Scheme 10).[16]

Catalyzed Reactions. Probably, the most important advantage of catalysts in photochemical transformations of diazo compounds is the possibility to control their stereoselectivity apart from accessing new reactivity modes. In this line, at the boundary of centuries, Katsuki and co-workers developed stereoselective photochemical [2+1]-cycloaddition of alkenes **26** to diazo esters **27** (Scheme 11).[17−21] Application of a chiral ruthenium complex assures the formation of a series of cyclopropanes **28** with high enantiomeric excesses.[19−21] The

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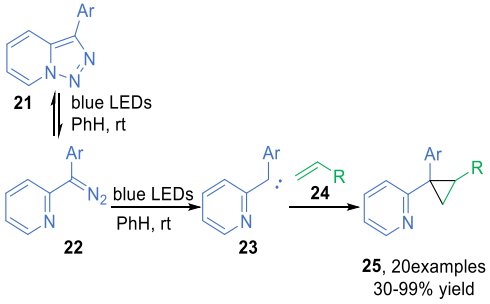
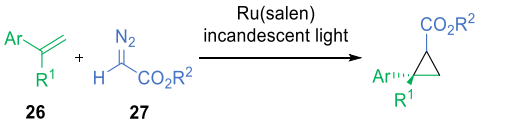
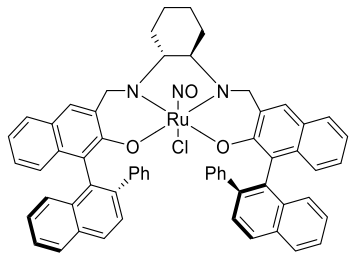
Scheme 10. [2+1]-Cycloaddition of Styrenes 24 to Pyridotriazoles 21



Scheme 11. Stereoselective Photochemical [2+1]-Cycloaddition of Alkenes 26 to Diazo Esters 27



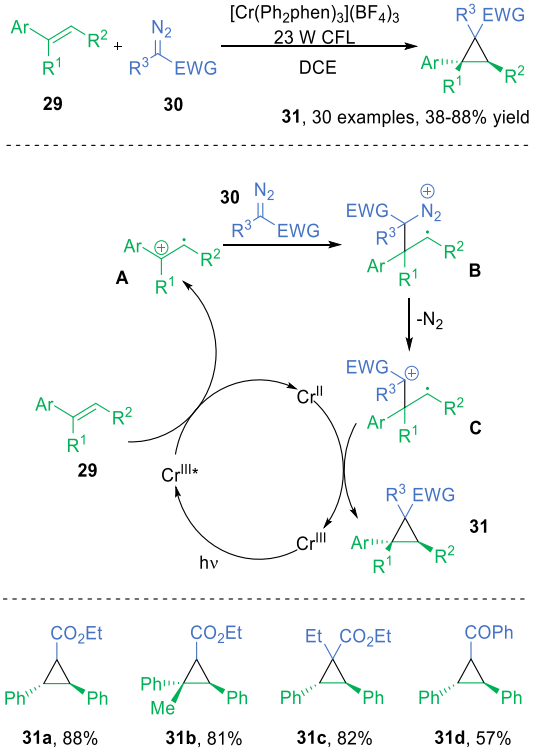


authors explain that the role of light is to activate the catalyst by inducing dissociation of ligands, which creates a free coordination site for attaching a molecule of the diazo compound and initiating the catalytic cycle.[17]

In the presence of $Cr(Ph_2phen)_3BF_4$, the cyclopropanation with diazo compounds **30** involves neither carbenes nor metal carbenes (Scheme 12). Here, alkene **29** is first oxidized to a radical cation **A** by the excited chromium(III) complex, and this intermediate reacts with diazo compound **30** releasing nitrogen. The generated Cr(II) complex reduces intermediate **C** to cyclopropane **31**, thus completing the catalytic cycle. As a consequence, the scope of this method is limited to alkenes with reduction potentials between 1.11 and 1.80 V, within the calculated range accessible to Cr(III) complexes.[22] The reaction is compatible with not only α-diazoacetates but also alkyl/EWG diazoalkanes because it is $Cr(Ph_2phen)_3BF_4$ that absorbs light and induces the catalytic cycle.

Remarks. Classical, metal-catalyzed [2+1]-cycloadditions of alkenes to diazo compounds have been known for decades. This methodology is very well established and often applied even for the synthesis of complex natural products.[23−25] Depending on the type of desired chemoselectivity and substituents present in a diazo compound structure, a whole range of metal complexes of groups 8−11 with different ligands may be used. Catalysts based on copper and rhodium are the most commonly applied but others, such as ruthenium, cobalt, gold, silver, or iridium, are also effective.[24,26−29] Nevertheless, the main focus is currently put on developing stereoselective cyclopropanation reactions.

Scheme 12. Chromium-Photocatalyzed Cyclopropanation of Olefins 29 with diazo compounds 30



This challenge was successfully addressed with methods utilizing chiral rhodium or iron complexes catalysis.[24,26,30−35] Their effectiveness, expressed in TON, often exceeds one million.[30]

In this context, it must be admitted that the development of photochemical cyclopropanation reactions, particularly stereoselective, is only in its infancy. It is yet worth emphasizing that already established methods have the advantage of often being metal free and performed under mild conditions—under air, without the need for dry solvents, and at ambient temperature. Gratifyingly, photoredox catalysis helps to solve the problem of the limited scope of substrates as alternative mechanisms of these reactions involving radical intermediates allow the use of diazo compounds which do not absorb visible light.

X−H INSERTIONS

X−H carbene insertion reactions represent a branch of elegant chemistry that leads to the straightforward formation of new C−C and C-heteroatom bonds with high atom economy. Until only recently, this field was almost exclusively dominated by transition metal-catalyzed reactions[36] with rare examples of thermal transformations.[37,38] This monopoly was broken by light-driven reactions, and at present, it is possible to construct all types of bonds accessible via transition metal catalysis, i.e., C−C, C−N, C−O, C−Si, and C−S in a photochemical manner. Obviously, currently, it is not possible to measure up to an enormous number of transformations involving metal carbenes and carbenoids, yet the need for mild and more ecofriendly conditions drives the development of photochemical reactions. What is equally important is that transition metal-catalyzed and light-driven transformations, in some cases, complement each other in terms of their scope and limitations.

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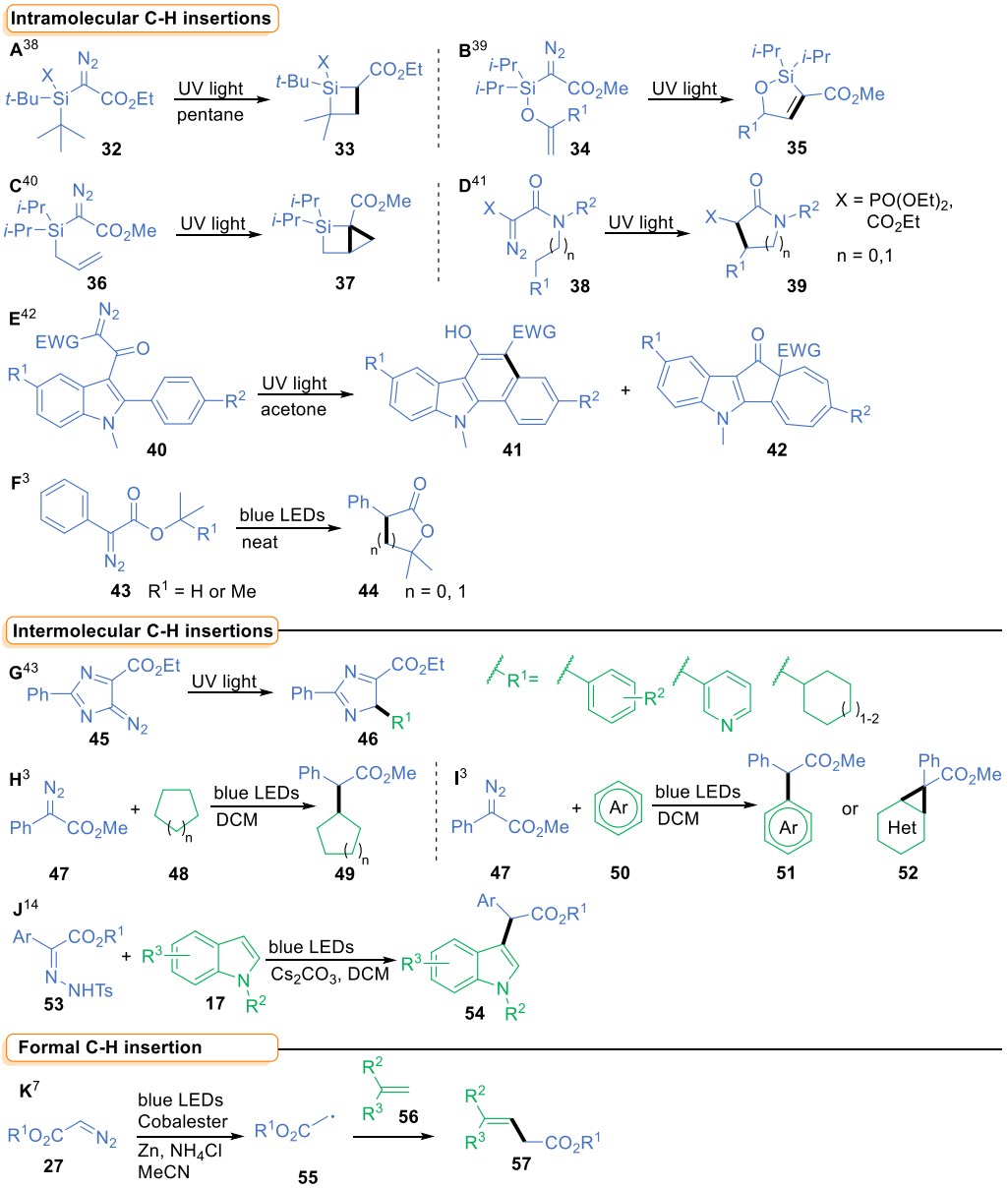
Scheme 13. Previous Advancements in C−H Insertions with Diazo Compounds[a]



[a]Intramolecular insertions: **A**, with the formation of the cyclobutane ring; **B**, with the formation of the cyclopentene ring; **C**, with the formation of the cyclopropane ring; **D**, with the formation of lactams; **E**, with the formation of an additional aromatic ring; **F**, with the formation of lactones. Intermolecular insertions: **G**, using specific diazo compound **45** and various hydrocarbons; **H**, using aryldiazo esters and cycloalkanes; **I**, using aryldiazo esters and arenes; **J**, using tosylhydrazones as diazo precursors and indoles; **K**, formal C−H insertions of diazo esters into alkenes. The number next to the letter indicates that the reaction corresponds to the reference number.

In this section, not only X−H insertions are described, but we also included *formal insertions* which, while they seem to be insertion reactions, proceed via utterly distinct mechanisms.

C−H Insertion Reactions. Over the years of studies on light-induced reactions of diazo compounds, many C−H insertions were developed (Scheme 13).[8,15,39−44] Most of them are exhaustively described in previous reviews;[1,2] therefore, here we focus only on the most recent advancements.

In the last years, the field of C−C bond-forming reactions was dominated by *formal* C−H insertions. Photochemical processes offer much more than a simple generation of carbenes from diazo compounds. Instead, radicals can form in a single-electron reduction event in the presence of a photocatalyst or in a reaction of diazo compounds with intermediates generated in a photocatalytic cycle.

In 2019, Gryko et al. developed selective alkylation of pyrroles and indoles **59** with α-diazo esters **58** (Scheme 14).[45] This strategy is based on the unique reduction of α-diazo ester **58** to alkyl radical **B** via single-electron transfer from an excited Ru photocatalyst. This is possible because in aqueous conditions protonation of diazo esters lowers their reduction potential making them accessible for $Ru(bpy)_3Cl_2$. Subsequently, alkyl radical **B** reacts with heterocycle **59** to give radical **C**. After oxidation and deprotonation, desired product **60** is formed (Scheme 14). This method enables the synthesis of a wide range of indole and pyrrole derivatives, in most cases alkylated at the C2 position. Protected and unprotected indoles as well as

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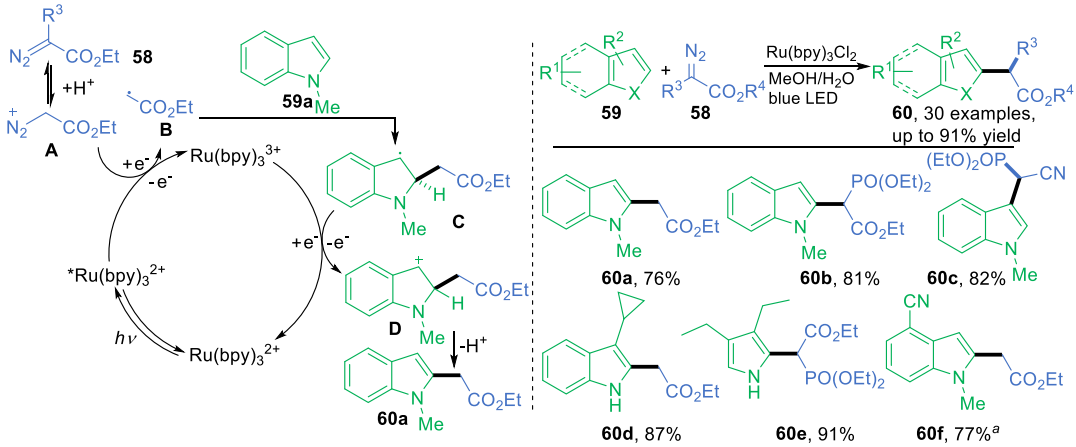
Scheme 14. C-2 Alkylation of Indoles with A-Diazo Esters[a]



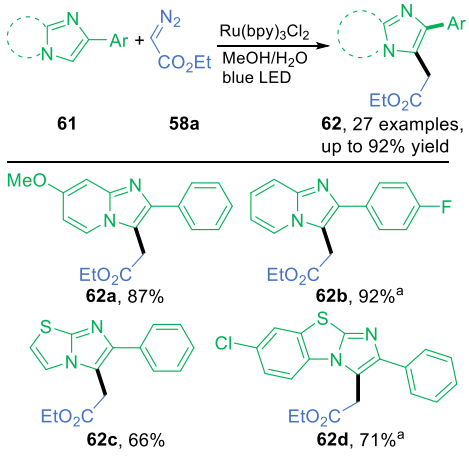
[a]With the use of *N*,*N*-dimethyl-*m*-toluidine added.

pyrroles bearing alkyl substituents are obtained in moderate to very good yields. When electron-deficient substrates are applied, the addition of *N*,*N*-dimethyl-*m*-toluidine as a sacrificial reductant is required. Both monosubstituted and disubstituted diazo compounds are well tolerated with the best results being obtained for acceptor−acceptor substituted ones.

This method complements existing thermal or transition metal-catalyzed procedures usually leading to C3-alkylated products.[46−48] However, for diazo compounds absorbing within the blue region, C3 functionalization also predominates as a consequence of photochemical carbene generation instead of radical **B**. Admittedly, C2 alkylation is also achievable with the use of transition metal catalysis; however, the presence of a directing group at the nitrogen atom is a prerequisite.[47−49]

A similar strategy was also utilized for C−H functionalization of imidazoheterocycles **61** with ethyl diazoacetate **58a**.[50] Various imidazopyridines and other imidazoheterocycles furnish products **62** in high to excellent yields (Scheme 15). The mechanism of this reaction is in analogy to the one described by Gryko et al.[45] Shortly afterward, Deng et al. further expanded the scope of diazo compounds suitable for this transformation to other α-diazo esters.[51]

Scheme 15. C−H Functionalization of Imidazoheterocycles 61 with ethyl diazoacetate 58a[a]



[a]With the use of *N*,*N*-dimethyl-*m*-toluidine.

Nicewicz et al. took advantage of the nucleophilic reactivity of diazo compounds and applied them in a photocatalytic C−H alkylation of arenes (Scheme 16).[52] In this approach, arene **19** is first oxidized to radical cation **A** via photoinduced electron transfer and then directly reacts with diazo compound **27**. The resulting intermediate **B** is reduced by an acridinium-derived radical leading to norcaradiene **C** which subsequently opens to distonic radical cation **D**. In the final step, intermediate **D** is reduced and deprotonated to form the desired product **63** (Scheme 16). This unprecedented methodology enables the construction of a series of alkylated arenes, providing that arenes are electron rich while diazo compounds are highly nucleophilic, which is behind only poor to good yields of products.

In comparison to similar strategies based on transition metal catalysis, the light-driven methodology has certain advantages which cannot be underestimated. First, it avoids the use of a high excess of an arene which is necessary due to the enhanced reactivity of metal carbenes. Second, it requires no directing groups, typical for transition metal-catalyzed reactions. Notably, no additives that are a sacrificial reductant or oxidant, often indispensable in photoredox catalysis, are needed.

Reactivity of aryl/EWG diazo compounds under light irradiation is already quite well established; over the years, a variety of diverse compounds were applied as partners in C−H insertions with diazoacetates leading to predictable products. However, only recently, Koenigs et al. took an interest in the photochemical properties of aryl/aryl diazoalkanes.[5] They discovered that, depending on the substituents on the phenyl rings, these compounds differ not only in absorption range but also in reactivity. While electron-poor aryl/aryl diazo compounds react with alkynes to give cyclopropenes (see [2+1]-Cycloadditions) and electron-neutral aryl/aryl diazoalkanes form indene products, electron-rich aryl/aryl diazoalkanes **64** undergo C(sp)−H or C(sp^3)−H insertion. This phenomenon was rationalized by two overlapping effects. First, singlet−triplet splitting energy calculated for bis(4-methoxyphenyl)carbene is low, which facilitates intersystem crossing and enables the coexistence of singlet and triplet carbenes. The second factor is an increased electron density at the carbene atom of diazoalkane **64** which increases its nucleophilicity and thus promotes C−H insertion. Importantly, despite the existence of the carbene intermediate, the mechanism is assumed to be *formal* C−H insertion proceeding via different pathways depending on the alkyne partner. The scope of this reaction was investigated; a

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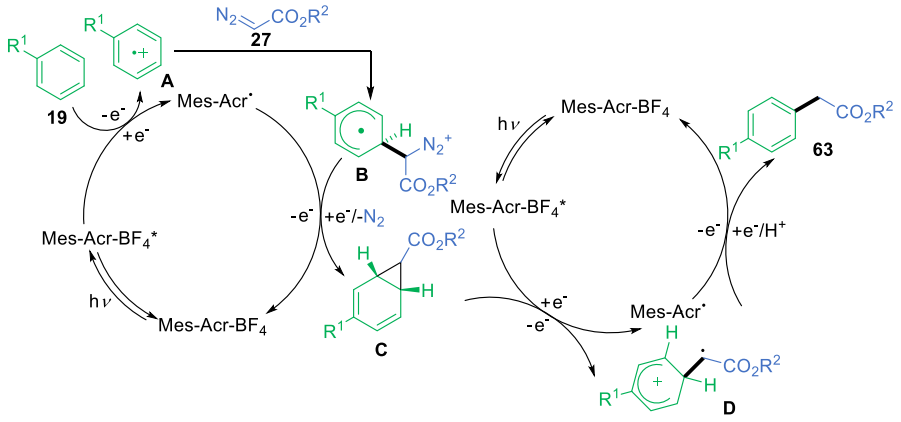
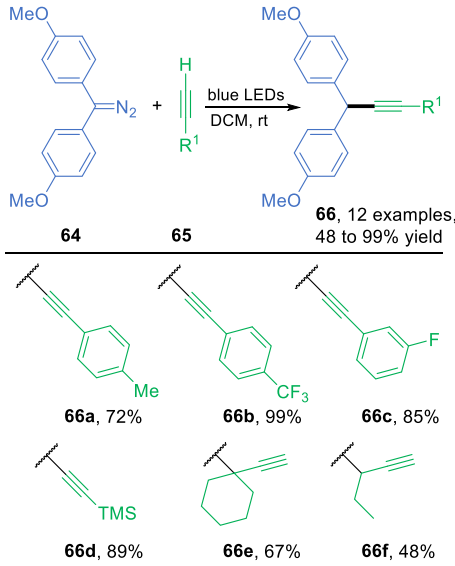
Scheme 16. Plausible Mechanism of Photocatalytic C−H Alkylation of Arenes



range of terminal alkynes **65** gives products **66** in good to high yields (Scheme 17). It should be noticed that aryl alkynes undergo C(sp)−H insertion, while for aliphatic alkynes C(sp^3)−H products functionalized at the propargylic position are formed.[5]

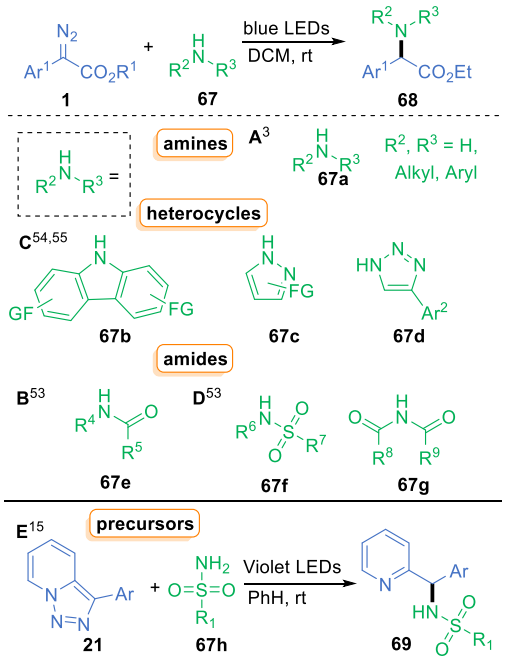
Scheme 17. C−H Functionalization of Alkynes 65 with Electron-Rich Aryl/Aryl Diazoalkane 64



N−H Insertion Reactions. The ground-breaking discovery of Jurberg and Davies which enables the generation of carbenes under blue light irradiation led to the development of *N*-alkylation of amines **67** with diazo compounds **1** (Scheme 18A).[4] Further studies expanded the scope of this reaction giving access to various *N*-alkylated amides, sulfonamides, and heterocycles (Scheme 18B−D).[53−55] The already mentioned work of Gevorgyan et al. enabled the generation of *N*-alkylated sulfonamide **67h** with carbenes derived from pyridotriazoles **21** (Scheme 18E).[16]

In 2020, Yang et al. found that under light irradiation also N^1-alkylation of benzotriazoles **70** with *α*-diazoacetates **58** is possible (Scheme 19).[56] Their studies served as a response to the problem of site selectivity often encountered in such transformations. This issue was earlier approached by Sun et al., who developed a strategy for N^2-selective N−H insertion of diazo compounds into benzotriazoles using rhodium catalysts.[57]

Scheme 18. Previous Advancements in N−H Insertions of Diazo Compounds[a]



[a]**A**, insertions into alkyl or aryl amines; **B**, insertions into amides; **C**, insertions into nitrogen heterocycles; **D**, insertions into imides and sulfonamides; **E**, reactions using pyridotriazoles as diazo compounds. The number next to the letter indicates that the reaction variant corresponds to the reference number.

However, N^1-selectivity seemed to be out of reach via a standard carbene insertion. But the reaction of a carbene with a N^1-benzotriazole radical, readily accessible via visible-light catalysis, leads to the desired product. Due to the enhanced stability of a N^1-radical this, in fact, *formal* N−H insertion allows for the selective alkylation of a wide range of benzotriazoles and other *N*-heteroaromatics **71** in good to high yields (Scheme 19).[56] The scope of diazo compounds **58** is similar in both rhodium and visible-light-mediated methods, although transition metal catalysis enables the use of not only aryl but also alkyl diazoacetates.

Photochemical generation of carbenes from diazo compounds proved also useful in *N*-alkylation of indoles **72**. This strategy has been lately developed by Sen et al. who studied this reaction in both batch and flow conditions.[58] The above transformation

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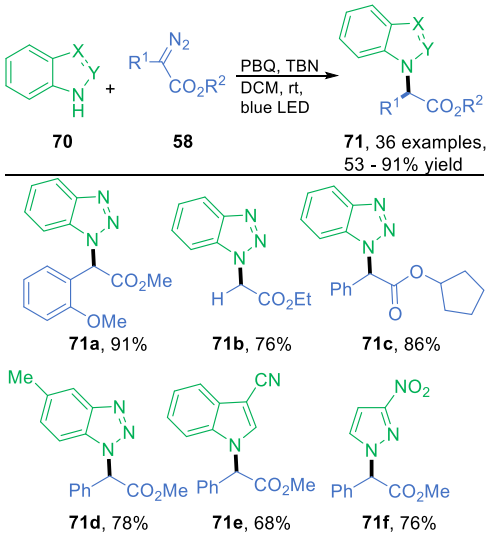
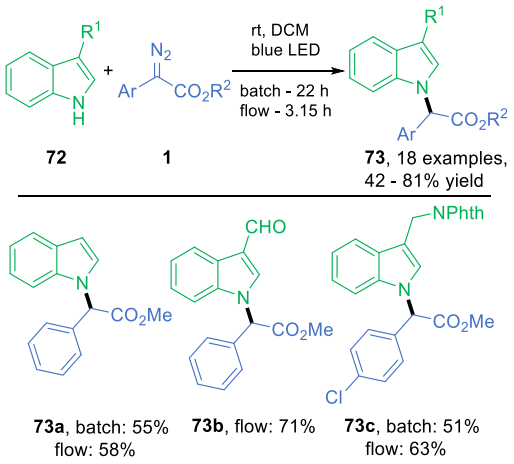
Scheme 19. N^1-Alkylation of Benzotriazoles 70 with α-diazoacetates 58[a]



[a]PBQ, 1,4 benzoquinone; TBN, tert-butyl nitrite.

is feasible for several indoles **72** and diazo compounds **1** simply under blue light irradiation with yields of products being usually higher under flow conditions (Scheme 20). Importantly, typical

Scheme 20. *N*-Alkylation of Indoles 72

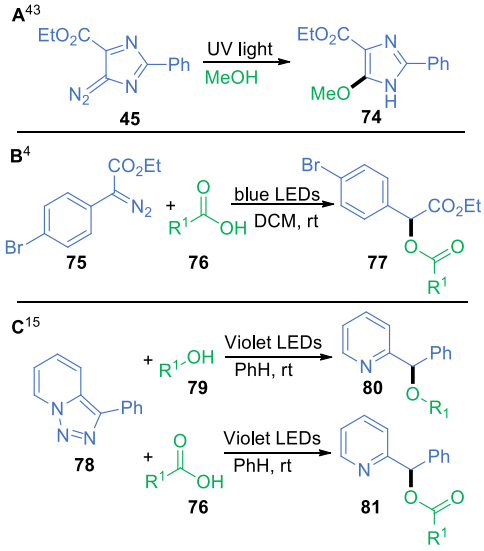


side reactions, such as cyclopropanation and C3-alkylation, are not observed. This strategy is closely related to the earlier work by Van Vranken et al. who accomplished *N*-alkylation with the use of palladium catalysis.[59] In this context, avoiding the use of a metal as toxic as palladium is an obvious advantage of Sen's work. However, it is impossible to miss that transition metal catalysis, also in this case, may enable enantioselective transformations.

O−H Insertion Reactions. Until recently, the only reported visible-light-mediated O−H insertions accompanied photochemical N−H insertions (Scheme 21).[4,16,44] In the last years, however, the scope of this transformation was significantly broadened, with *formal* O−H insertions standing out.

Selectivity is a common problem in many transformations. For example, this obstacle arises in the functionalization of 2-pyridones, for which both *O*- and *N*-alkylations usually occur simultaneously. Under light irradiation, however, the selective

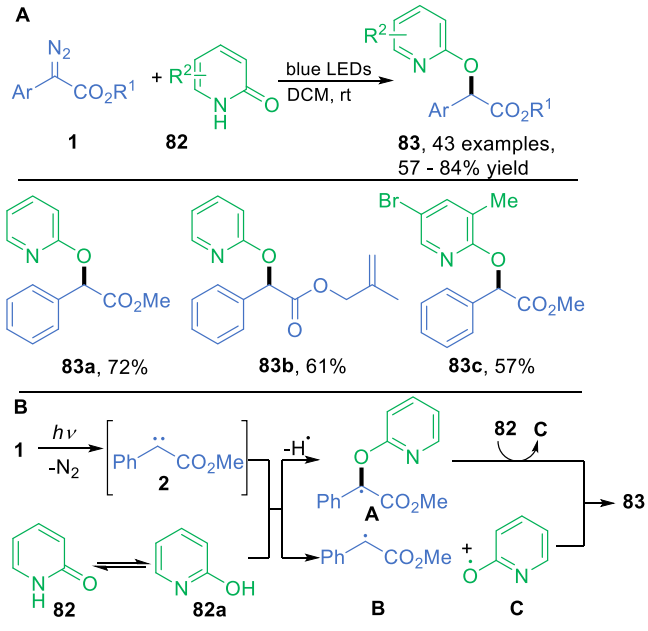
Scheme 21. Previous Advancements in O−H Insertions of Diazo Compounds[a]



[a]**A**, insertions into methanol; **B**, insertions into carboxylic acids; **C**, reactions using pyridotriazoles as diazo compounds and carboxylic acids and alcohols as O−H bond source. The number next to the letter indicates that the reaction variant corresponds to the reference number.

O−H insertion of carbenes derived from α-aryl diazoacetates **1** into 2-pyridones **82** proceeds smoothly giving *O*-alkylated products **83** in high yields (Scheme 22A).[60] Two mechanistic pathways were proposed for this transformation. In the first scenario, photodecomposition of diazoacetate **1** provides carbene **2** that subsequently adds to 2-pyridone **82** generating radical **A** which affords desired product **83** upon addition of hydrogen. Alternatively, carbene **1** is first transformed into radical **B** and as such couples with an *O*-radical generated from

Scheme 22. O−H Insertion of 2-Pyridones 82 into α-Aryl Diazoacetates 1[a]



[a]**A**, reaction scheme and products; **B**, mechanistic proposal.

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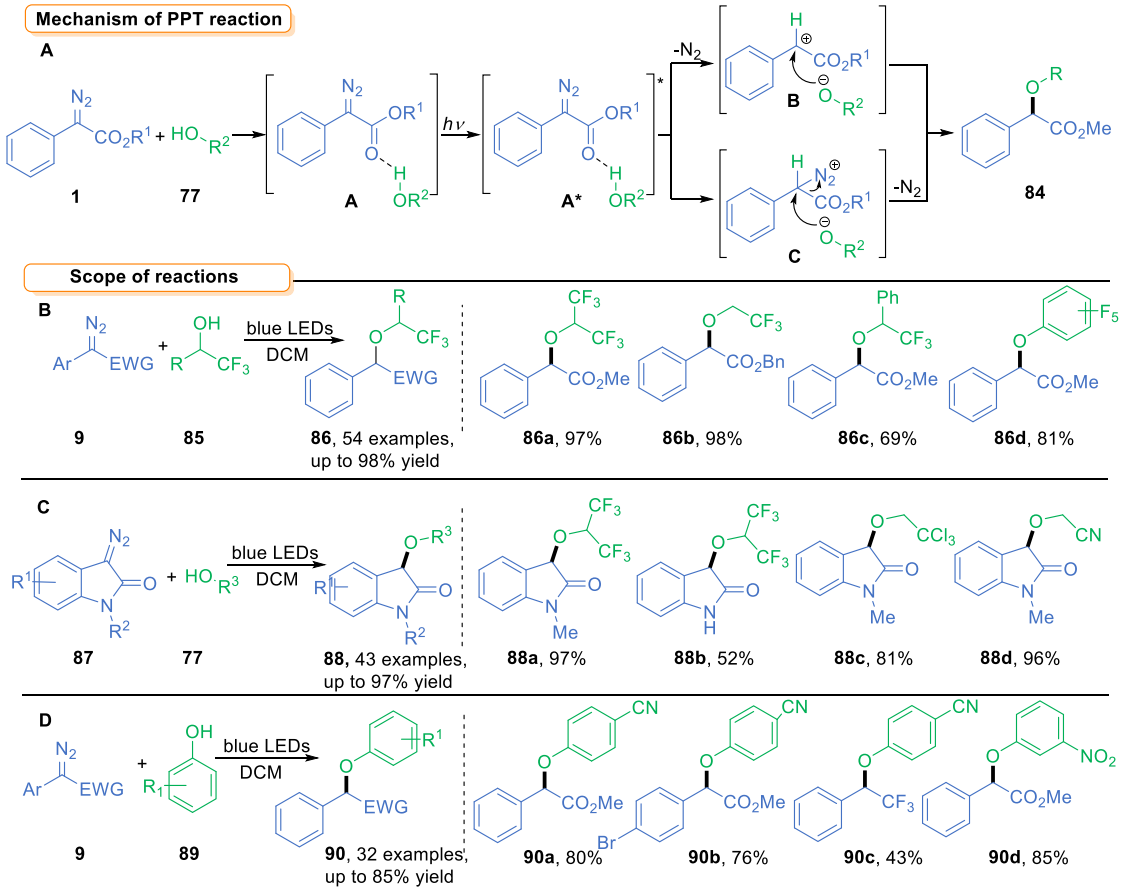
Scheme 23. Photoexcited Proton Transfer Reactions for O−H Formal Insertions into Diazo Compounds[a]



[a]**A**, proposed mechanism for PPT reaction; **B**, scope of aryldiazo esters insertion into polyfluorinated alcohols; **C**, scope of cyclic diazo amide insertion into alcohols; **D**, scope of aryldiazo esters insertion into phenols.

2-pyridone **C** (Scheme 22B). Although the reason for site selectivity is not entirely clear, the authors suggest that the lower bond dissociation energy of the O−H bond compared to that of the N−H bond favors the formation of an O radical, thus facilitating the second pathway.[60]

Formal O−H Insertions. As mentioned before, light irradiation opens a way for diversified mechanistic pathways leading to products unavailable via other transformations. The photoexcited proton transfer (PPT) reaction is one of the exciting new strategies which emerged in recent years. Koenigs et al. adapted it for O−H functionalization of diazo compounds with unreactive and weakly acidic alcohols (Scheme 23).[61] The reaction involves photoexcitation of complex **A** formed from diazo compound **1** and alcohol **77** via a hydrogen bond (Scheme 23A). Within photoexcited complex **A***, a proton from the O−H partner is transferred to the diazo group (carbon) leading to ion pair **C**. Subsequent nucleophilic substitution gives desired product **84**. The first report on this topic concerns the reaction of aryl/EWG diazo compounds **9** with fluorinated alcohols **85**, but it works well also for chlorinated and brominated compounds (Scheme 23B),[61] as well as for cyclic diazo amides **87** (Scheme 23C).[62] This transformation gives access to a range of halogenated, mainly fluorinated, ethers **88** which are formed in high to excellent yields. Importantly, the same reaction was examined in the dark in the presence of Cu and Rh catalysts, typically used to generate metal carbene species, but no product formation was observed.

Photochemical conditions tolerate also phenols **89** and a broad range of aryl/EWG diazo compounds **9** (Scheme 23D).[63] The highest yields of products are obtained for phenols substituted with electron-withdrawing groups at the *meta*-position emphasizing the significance of two factors: acidity of the phenol and strength of the hydrogen bonding between substrates.

The above examples clearly demonstrate one of the key advantages of light-induced reactions of diazo compounds. Photochemistry enables the use of not only new substrates which may react with diazo compounds under mild conditions but above all gives access to new pathways in which we can modulate their reactivity according to our needs. As evidenced by mechanistic experiments, the formation of ethers from cyclic diazo amides would not be possible via a carbenoid intermediate. It is only the excitation of this complex and formation of photobase **A*** that facilitates crucial deprotonation and the following steps leading to the desired product.

O−H functionalizations of diazo compounds with acids often proceed without any additive driven by an elevated temperature. Even in such cases, light irradiation offers some advantages—an increase in the reaction rates or yields of products. For instance, this effect was observed for the recently reported reaction of (2-diazo-1,1-difluoroethyl)phosphonates **91** with sulfonic acids **92** (Scheme 24).[64] Remarkably, due to decreased stability of these diazo derivatives, they were generated *in situ* from corresponding amines.

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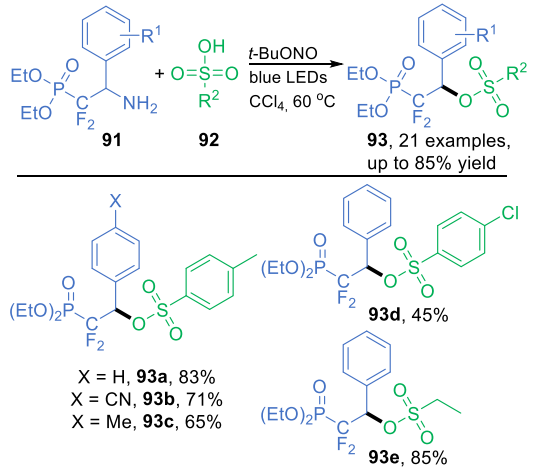
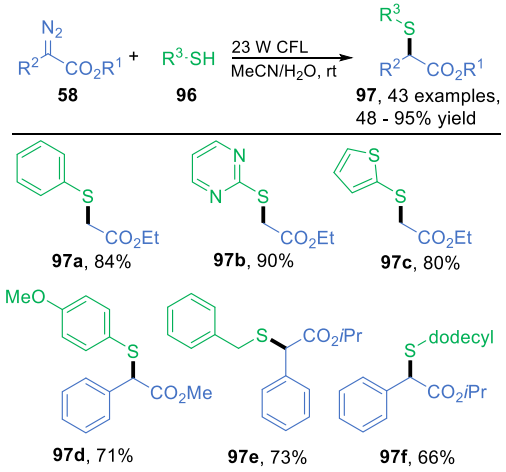
Scheme 24. Visible-Light-Promoted Coupling Reaction of *In Situ*-Generated Diazo Compounds with Sulfonic Acids

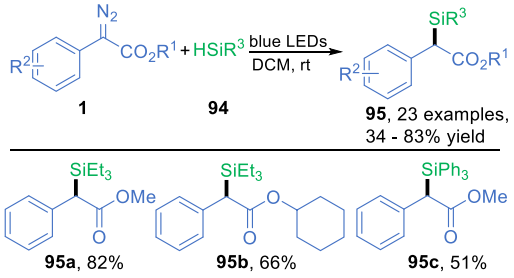


Scheme 26. S−H Insertion Reaction of Thiols 96 with α-Diazoesters 58



Si−H Insertion Reactions. Si−H insertions are convenient and effective reactions enabling the construction of C−Si bonds. Until recently, it was only possible to perform such transformations with the use of metal catalysis. In 2020, Koenigs et al. reported a method for a visible-light-driven insertion reaction of silanes **94** with aryl diazoacetates **1** (Scheme 25).[65] This strategy enables the formation of a vast array of products in moderate to good yields, even for such demanding substrates as triphenyl silane (product **95**).

Scheme 25. Visible-Light-Driven Insertion Reaction of Silanes 94 with Aryl Diazoacetates 1



Previous Si−H insertion methods usually required transition metals such as iridium, ruthenium, and rhodium.[66] Despite obvious advantages such as the possibility of enantioselective transformations and a wide range of applicable diazo compounds, such methods are less and less desirable in synthetic chemistry due to the high price and, above all, the toxicity of used metals. A very important contribution to this subject was the recently developed method relying on iron catalysis. Heme-containing enzymes allowed for enantioselective Si−H insertion to diazo compounds.[67] Alas, enzymatic reactions may still be problematic in terms of set up, price, and availability of enzyme catalysts. Remarkably, the nonenantioselective transformation is also achievable with simple iron salt $Fe(OTf)_2$.[68] Yet, even in that light, it is hard to overlook the main advantages of the visible-light-based method which is the simplicity of set up, low price, and excellent atom economy.

S−H Insertion Reactions. Harnessing light-induced activation proved effective in the S−H insertion reaction of thiols **96** with α-diazo esters **58** (Scheme 26).[69] Even though in this case the intensity of light has to be quite high (23 W compact fluorescent lamps), it is rewarded by the absence of any other additive. The scope of the reaction is broad, furnishing a wide range of thioethers **97**. Both aryl and heteroaryl thiols, as well as ethyl diazoacetate and various α-phenyl diazoacetates, are well tolerated. Alkyl thiols form products, however, only in the reaction with α-phenyl diazoacetate which absorbs visible light. The latter observation raised questions concerning the mechanism of this reaction. The authors proposed that under light irradiation a thiyl radical is formed which subsequently reacts with either a carbene generated from a diazo compound or with a diazo compound itself. In both cases, the consequent transformations lead to the same product.

Remarks. C−H and X−H insertions are among the most useful tools in organic synthesis as they allow for straightforward construction of new bonds with high atom economy. This feature is particularly important in modern chemistry which puts emphasis on practical and cost-effective strategies. Over the years, transition metal catalysis allowed for building a substantial toolbox for these transformations with the use of diazo compounds and metals such as rhodium, ruthenium, copper, and iron.[36,70] The already advanced methodologies provide high selectivity and a generally broad scope of reactions with some of them available in enantioselective variants. Some disadvantages, however, cannot be overlooked. High selectivity often requires the use of directing groups in one of the substrates, which implies additional steps in the synthetic route. Furthermore, many of the most studied transition metals are toxic (e.g., rhodium). Naturally, there are already developed methods based on less harmful metals such as iron; nevertheless, their applications are far more limited. Another disadvantage is the occurrence of side reactions; for example, insertions catalyzed by rhodium complexes often compete with β-elimination.[70]

In this context, visible-light-driven methods are a perfect alternative. As shown above, in this case, selectivity may be achieved without any additional groups. The conditions are mild, and side reactions are rarely problematic. Interestingly, in terms of selectivity, photochemical methods often complement transition metal-catalyzed transformations as was shown for alkylation of benzotriazoles or C−H insertion of diazo esters to indoles. However, the most important benefit offered by light-driven reactions is the possibility to introduce new pathways for diazo compound transformations. In this line, many new formal C−H and X−H insertion methods were developed.

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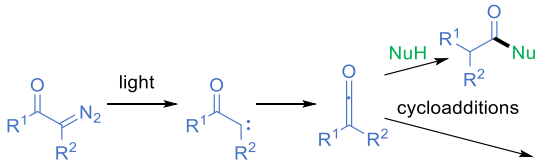
WOLFF REARRANGEMENT

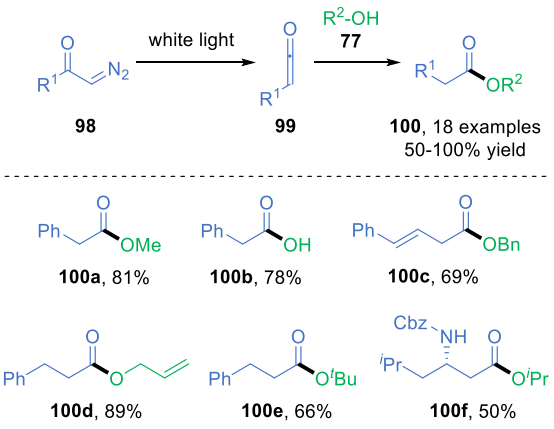
The Wolff rearrangement, one of the most widely studied reactions of α-ketodiazo compounds, involves nitrogen extrusion followed by [1,2]-rearrangement to ketene which can proceed via carbene intermediates or in a concerted manner. The resulting ketene reacts with nucleophiles furnishing carboxylic acid derivatives, or it can also undergo cycloadditions (Scheme 27). Here, we discuss only recent advancements in this area; for a more detailed review, see ref 70.

Scheme 27. Photochemical Wolff Rearrangement



Reactions with Nucleophiles. Unlike most of the photochemical reactions described, the use of light for the Wolff rearrangement is well established. However, classically, rather high energy light sources, such as xenon or mercury lamps, were used.[71] In contrast, Burtoloso et al. have recently utilized white LEDs instead, which were sufficient for the synthesis of esters **100** from a couple of α-diazomethyl ketones **98** and primary, secondary, and tertiary alcohols **77**, phenols, and water as a nucleophilic partner (Scheme 28).[72] Advantageously, the use of optically pure, protected amino-ketones leads to β-aminoesters with preserved configurations.

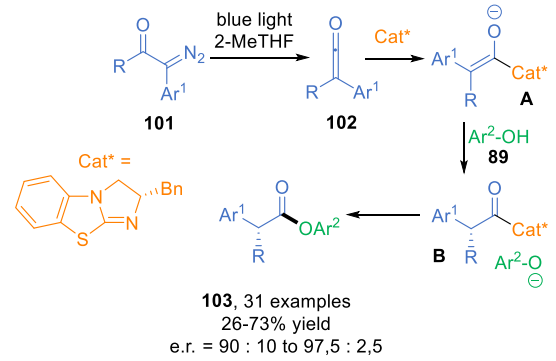
Scheme 28. Photochemical Synthesis of Esters via Wolff Rearrangement



The asymmetric, photochemical Wolff rearrangement was developed quite recently by Han et al. (Scheme 29).[73] A readily available chiral benzotetramisole catalyzes the formation of esters **103** from ketene **102** generated photochemically. The catalyst reacts with ketene **102** generating chiral anionic intermediate **A** which is subsequently protonated in a stereo-specific manner. Then, benzotetramisole moiety **B** is substituted with a phenoxide anion, furnishing product **103**. The method allows for the diastereoselective formation of a series of aryl esters of α,α-disubstituted carboxylic acids **103** in high e.r. > 9:1, including several bioactive derivatives, for example, *(R)*-ibuprofen ester.

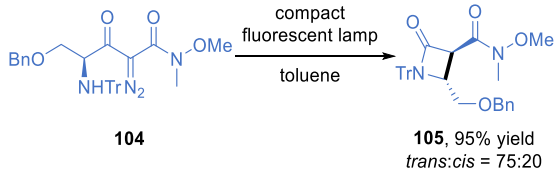
In addition, the photochemical Wolff rearrangement is suitable for the functionalization of complex amino acid

Scheme 29. Photochemical Stereoselective Synthesis of Esters via Wolff Rearrangement



derivatives. The intramolecular reaction of enantiomerically pure α-diazo-*N*-methoxy-*N*-methyl-β-ketoamide (**104**) gives corresponding β-lactam **105** in high yield (Scheme 30).

Scheme 30. Photochemical Functionalization of Diazo Amino Acid Derivatives



Notably, the activation with a compact fluorescent lamp is as effective as in the case of irradiation with highly energetic UV light. For scaling up, flow conditions were employed.[74]

Carbon nucleophiles can also be used as reaction partners for ketenes generated via Wolff rearrangement, although this requires the addition of an appropriate catalyst. In this line, Lu et al. reported formal acylation of β-ketoesters with diazo ketones as ketene precursors.[75] The role of applied $NiCl_2$·glyme as a Lewis acid is the activation of β-ketoester molecule **108** which promotes *C*-selectivity. The use of a Lewis base, on the other hand, leads to *O*-acylation of the carbonyl group of the β-ketoester due to activation of a ketene instead (Scheme 31).

Cycloadditions Involving Ketene. In recent years, photochemically generated ketenes were engaged in cycloadditions catalyzed by palladium complexes. For example, [3+2]-cycloaddition of these reactive intermediates to vinyl cyclopropanes gives highly substituted tetrahydrofurans with the exocyclic double bond in moderate to excellent yields (Scheme 32).[76]

The use of 3-alkenyloxindoles (**113**) enables, on the other hand, [4+2]-cycloaddition leading to δ-lactones. Chiral *N*-heterocyclic carbene assures highly enantioselective and diastereoselective reactions. Mechanistically, photolytically generated ketene **102** reacts with NHC carbene giving enolate **A** which ensures stereoselectivity of the subsequent [4+2]-annulation. The following elimination affords desired product **114** and regenerates the catalyst (Scheme 33).[77]

The synthesis of quinolones **116** from ketenes **107** and vinyl benzoxazinanones **115** also relies on [4+2]-cycloaddition. In this case, the reaction begins with the oxidative addition of an allyl ester of the vinylbenzoxazinanone molecule to the palladium complex followed by decarboxylation. The resulting intermediate **C** acts as a nucleophile in the reaction with photochemically generated ketene **107**, and the process ends

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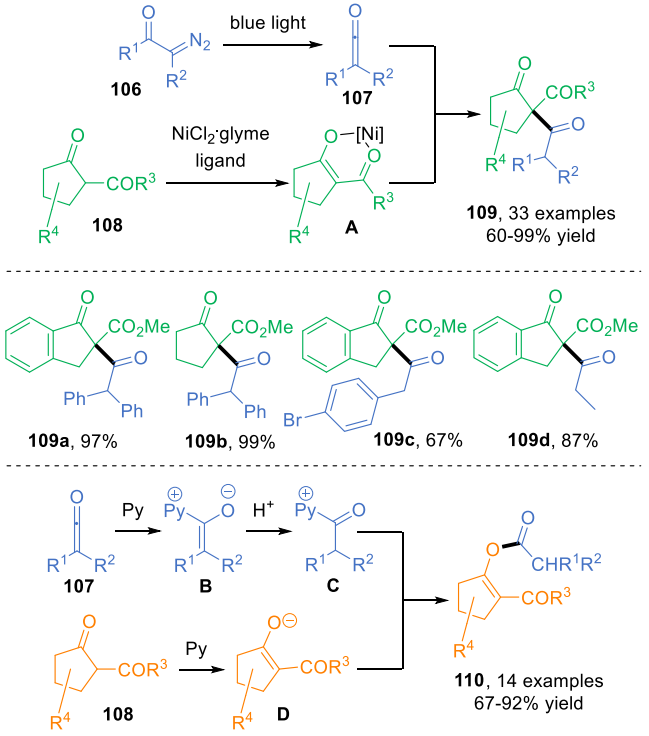
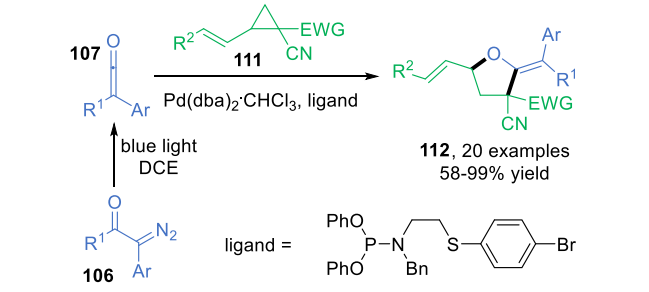
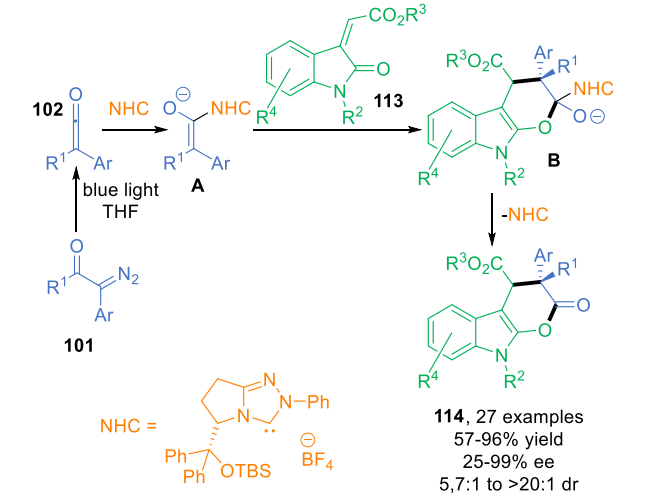
Scheme 31. Catalyst-Dependent *C*- or *O*-Selective Reactions of α-Ketoesters with Ketenes



Scheme 32. [3+2]-Cycloaddition of Ketenes to Vinyl Cyclopropanes

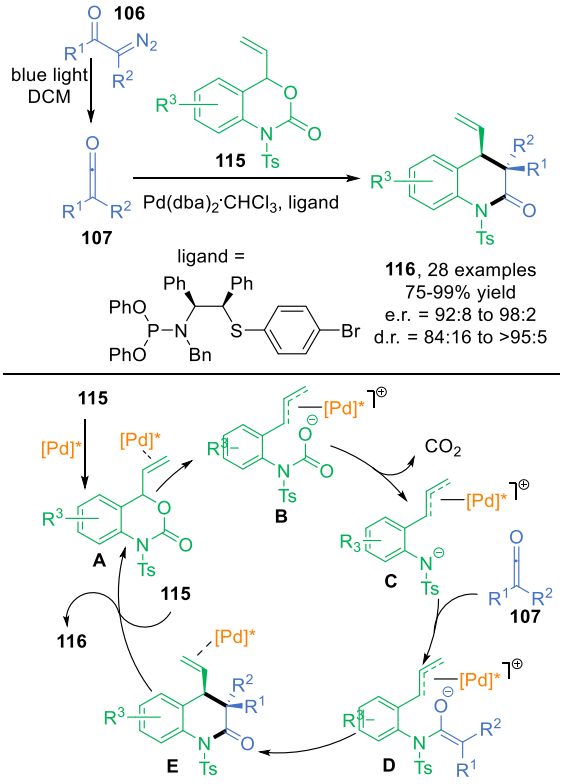


Scheme 33. [4+2]-Cycloaddition of Ketenes to Indole Derivatives



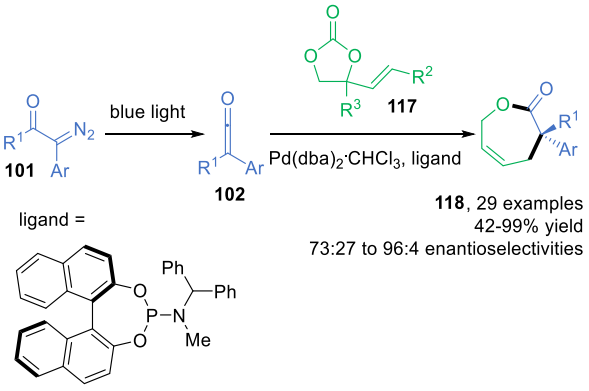
with catalyzed cyclization to yield quinolinone **116** (Scheme 34). Highly enantioselective and diastereoselective reactions are provided by a palladium catalyst with a chiral ligand.[78]

Scheme 34. Palladium-Mediated [4+2]-Cycloaddition of Ketenes to Vinyl Benzoxazinanones



Vinylethylene carbonates **117** react with ketenes **102** in [5+2]-cycloaddition (Scheme 35). In fact, carbonates first undergo catalytic decarboxylation and then react with the ketene giving 7-membered lactones in good yields and with high enantioselectivities induced by chiral ligands.[79]

Scheme 35. [5+2]-Cycloaddition of Ketenes to Vinyl Ethylene Carbonates



Remarks. The Wolff rearrangement itself was discovered in 1902 and is therefore very well studied. On the 100th anniversary of its discovery, a review was published describing advances made during that time.[71] Apart from the photochemical activation of this reaction, the most important methods for ketene generation include thermolysis or catalysis with silver

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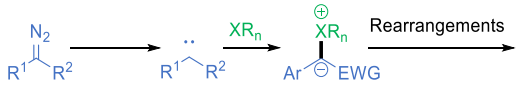
salts (most commonly AgOBz). The reactive intermediates undergo not only reactions with nucleophiles or cycloadditions but can be involved in other types of transformations as well. Among them, the Arndt–Eistert reaction is definitely worth mentioning as it is frequently used in the conversion of α-amino acids to β-amino acids.[23] The rearrangement methodology was often used in the synthesis of biologically active substances. This is, of course, mainly due to the availability of strategies for the highly stereoselective Wolff rearrangement.[71]

Contrary to other types of photochemical reactions, this activation mode for the Wolff rearrangement has been utilized for a long time. Nevertheless, several significant discoveries have been recently made in this field, for instance, the use of visible-light sources instead of highly energetic UV proved sufficient. As a result, the generation of ketenes does not require basic amines, hence opening possibilities that palladium catalysis offers. It is also worth emphasizing that, in contrast to other photochemical transformations of diazo compounds developed so far, most of the Wolff rearrangement reactions can be performed in a stereoselective manner.

REARRANGEMENT REACTIONS INVOLVING YLIDES

Carbenes generated from diazo compounds are known to react with various heteroatoms possessing lone electron pairs forming ylides which as reactive intermediates are prone to further rearrangements, mainly [2,3]- and [1,2]-sigmatropic rearrangements (Scheme 36).[80]

Scheme 36. Formation and Rearrangements of Ylides

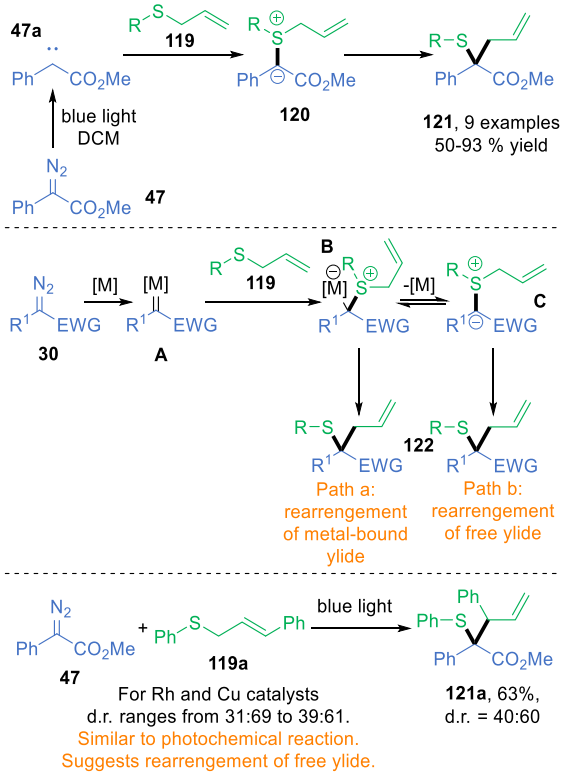


[2,3]-Sigmatropic Rearrangements. The [2,3]-sigmatropic rearrangement has been known for over 50 years,[81] but a metal-free, photocatalyzed process was reported by Koenigs et al. only in 2019.[10] Under blue light irradiation homoallyl sulfides **121** are obtained from allyl sulfides **119** and methyl phenyldiazoacetate (**47**) in very good yields (Scheme 37). Furthermore, the authors later showed that the transformation can be successfully performed under flow conditions facilitating the scale-up process.[82] Apart from being synthetically useful, this work also contributed to mechanistic considerations. It is still unresolved whether the key rearrangement step for metal-catalyzed reactions involves free ylide **B** or a ylide bounded to catalyst **C**. Since the photochemical approach is metal free, it supports the first option. The more important evidence for free ylide being predominant intermediate is a similar diastereoselectivity observed in both metal-catalyzed and photochemical reactions.[83]

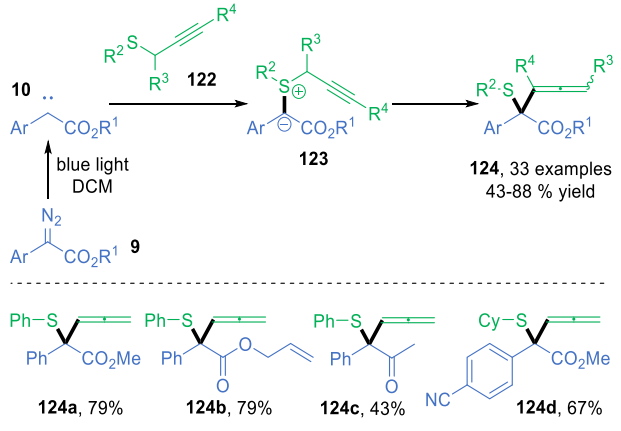
The use of propargyl sulfides **122** instead of allyl derivatives leads to the formation of allenes **124** via [2,3]-sigmatropic rearrangement. This useful transformation can be conducted also in a photochemical manner for aryl diazo carbonyl compounds **9** without the need for a catalyst as shown by Gryko et al. (Scheme 38).[84] The reaction tolerates various substituents on the aromatic ring and ester groups of aryldiazoacetates as well as structurally diversified sulfides—alkyl, aryl, and heteroaryl.

Fluorine is an extremely essential element in the construction of bioactive molecules,[85] with difluoromethylene being one of

Scheme 37. Photochemical Doyle–Kirmse Reaction



Scheme 38. Photochemical Synthesis of Allenes via the Doyle–Kirmse Reaction



the most important functional groups containing this atom.[86−88] On the basis of the photochemical strategy for the Doyle–Kirmse reaction, Xiao et al. developed a high yielding process of EDG/EWG diazoalkanes **1** with specifically designed 2-bromo-3,3-difluoroallyl sulfides **125** leading to highly functionalized products suitable for further transformations (Scheme 39).[89]

Similarly α-mercaptoesters **128** are known to form ylides that undergo the Sommelet–Hauser rearrangement. The originally formed ylide **129** is in equilibrium with its tautomeric form **130** whose subsequent sigmatropic rearrangement leads to formal aromatic substitution. Please note that both the mechanism and structure of products differ significantly from the Doyle–Kirmse reaction (Scheme 40).[90]

Ammonium ylides generated from EDG/EWG diazo compound **1** and aniline derivatives **132** undergo the [2,3]-sigmatropic rearrangement (Scheme 41).[91] It is an important

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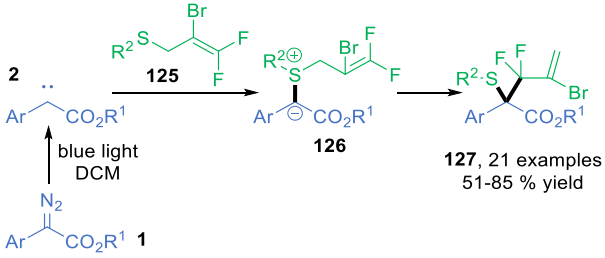
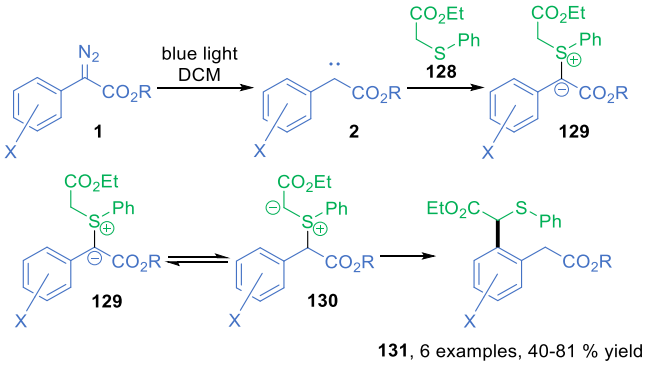
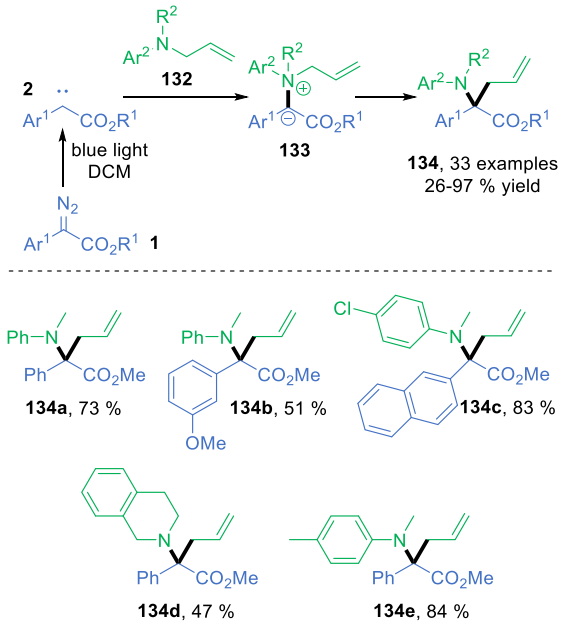
Scheme 39. Doyle−Kirmse Reaction of Aryldiazoacetates with 2-Bromo-3,3-difluoroallyl Sulfides



Scheme 40. Photochemical Sommelet−Hauser Rearrangement



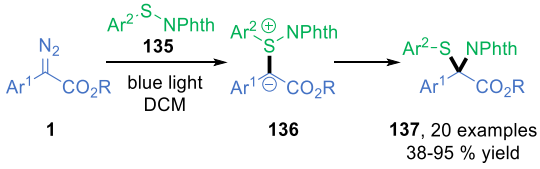
Scheme 41. Photochemical Doyle−Kirmse Reaction of Ammonium Ylides



discovery as traditional methods for this transformation work almost exclusively for acceptor-substituted diazoalkanes[92,93] or has a very limited range of applicability.[37,94] The reported photochemical reaction gives access to α,α-disubstituted α-amino acids under mild conditions, featuring a mechanism identical to that of the Doyle−Kirmse reaction for allyl sulfides. Here, photochemically generated carbene **2** adds to amine **132** affording ylide **133**. This reactive intermediate then undergoes [2,3]-sigmatropic rearrangement forming desired product **134**. The reaction has a wide tolerance for variously substituted aryl diazoacetates and allylanilines as well as allylbenzylamines. However, a significant limitation of the method is the possibility of using the only ester as an electron-withdrawing group in the structure of a diazo reagent and the sensitivity to the steric hindrance imposed by an amine. In addition, only tertiary allylamines can be used, which is typical for a [2,3]-sigmatropic rearrangement.

[1,2]-Sigmatropic Rearrangements. A photochemical [1,2]-sigmatropic rearrangement was reported for sulfides lacking multiple bonds in their structure. In this line, carbenes generated from aryl diazoacetetes **1** react with *N*-sulfenyl phthalimides **135** to form ylides **136** that rearrange to the product of formal N−S carbene insertion (Scheme 42). This

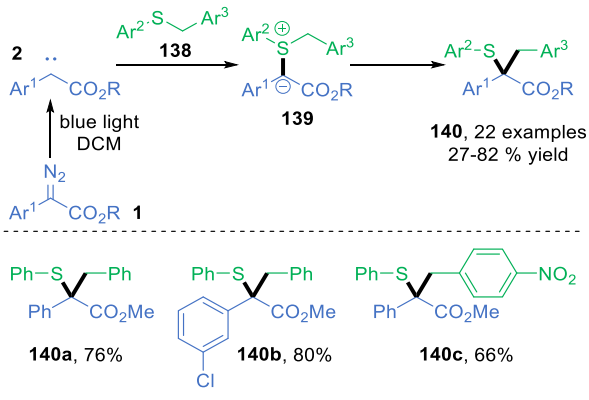
Scheme 42. Formal *N*−*S* Insertion via Photochemical [1,2]-Sigmatropic Rearrangement



method enables the synthesis of protected, fully substituted α-amino-α-mercaptoesters **137** in good yields. The scope includes mostly variously substituted aromatic rings within aryl diazoester as well as sulfide structures.[90]

Depending on the substrate structure, the reaction leads either to formal insertion of carbene into the heteroatom−heteroatom bond or carbon−heteroatom bond when only those are present. In the latter case, the process is known as the Stevens rearrangement, which is more common for ammonium ylides than for sulfur ones. However, the photochemical reaction of aryl-benzyl sulfides **138** and EDG/EWG diazo compounds **1** takes advantage of their ability to absorb photons from the blue region of the light spectrum.[90] Importantly, this method enables the regioselective formation of quaternary-substituted carbon atoms, the preparation of which is often challenging (Scheme 43).

Scheme 43. Photochemical Stevens Rearrangement



In 2019, Hock and Koenigs utilized this valuable strategy for the diastereoselective synthesis of tetrahydrofurans and thiolanes **144** via the ring expansion reaction of oxetanes or thietanes **141** with donor−acceptor diazo compounds **1** (Scheme 44).[95] DFT calculations proved important in the discussion on differences in mechanisms of processes involving

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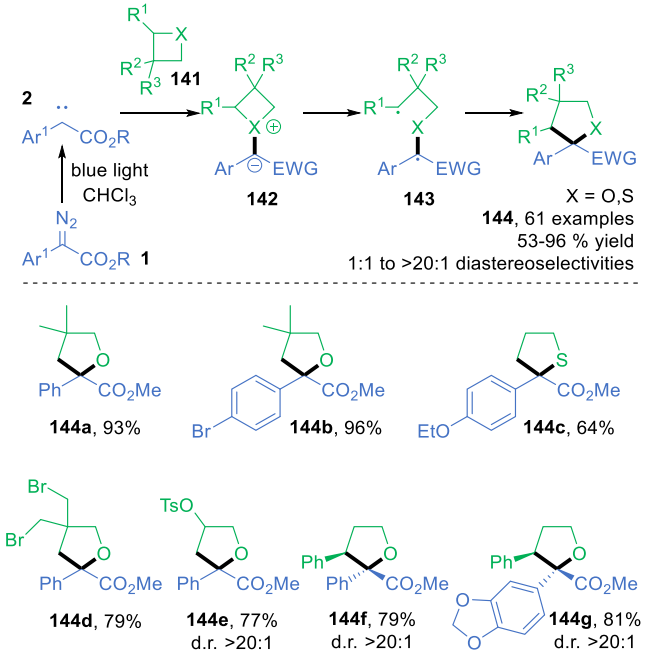
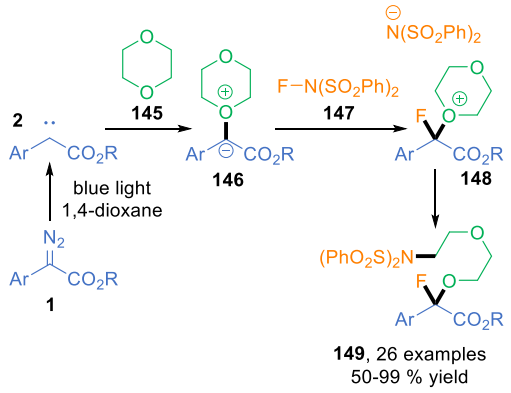
Scheme 44. Photochemical Ring Expansion of Oxetanes and Thietanes



oxygen and sulfur ylides,[96] showing that regardless of a heteroatom the reaction proceeds through the biradical stage.

Other Photochemical Rearrangements. The importance of fluorine compounds in medicinal chemistry is well established.[85] In this line, Koenigs et al. developed a photochemical, three-component reaction of donor/acceptor diazo compounds (**1**) with cyclic ethers **145** and NFSI (**147**) efficiently affording highly functionalized esters **149** (Scheme 45).[97] The mechanism for this transformation, supported by

Scheme 45. Multicomponent Photochemical Reaction of Diazo Esters



DFT calculations, starts with the formation of ylide **146** from intermediate carbene **2** and dioxane **145** which then reacts with NFSI (**147**), leading to the fluorination of the negatively charged carbon atom. The released $N(SO_2Ph)_2^-$ anion cleaves the dioxane ring to form a short polyether chain.

Remarks. Rearrangements of reactive ylides have been known for years. For example, [2,3]-sigmatropic rearrangement of ylide generated from diazo compounds and allyl sulfides was discovered by Kirmse et al. in 1968[81] and then rediscovered 13 years later by Doyle et al.[98] Since then, it has become an important tool in organic synthesis. This reaction is usually catalyzed by rhodium or copper complexes, but other metals like palladium, gold, or iron are also applicable.[99] Advances in photochemistry contributed to the development of the light-induced Doyle−Kirmse allene reaction and the Sommelet−Hauser, [1,2]-sigmatropic, and Stevens rearrangements. Both intramolecular and multicomponent reactions have been reported and proved effective in the synthesis of biologically active substances. Stereoselective methods do exist, but at present, they require chiral metal complexes as catalysts.[100,101]

Despite the short research period, studies on rearrangements of photochemically generated ylides have contributed significantly to this very extensively explored topic, particularly to the understanding of mechanistic aspects of ylides rearrangements. Metal-free experiments indicate that the [2,3]-sigmatropic rearrangement occurs through free ylides and that radical rearrangements occur identically for oxygen and sulfur ylides. Photochemical methods allow for the synthesis of unexplored, structurally complex derivatives with numerous functional groups (the Doyle−Kirmse reaction with 2-bromo-3,3-difluoroallyl sulfides and three-component reaction of donor−acceptor diazo compounds, dioxane, and NFSI) or the use of so far underexplored types of substrates (EDG/EWG diazo compounds in rearrangements of ammonium ylides) but at present are limited to diazo compounds absorbing in the visible region of the electromagnetic spectrum.

OTHER PHOTOCHEMICAL REACTIONS

Noncatalyzed Reactions. Due to the dimerization of diazo compounds, it is difficult to overcome common side reactions. However, recently, it was turned into an advantage. The selective preparation of alkenes from two diazo compounds, of which only one (EDG/EWG diazo alkane **9**) photolyzes with the formation of carbene **10**, while EWG-only substituted diazo alkane **27** remains untouched. Carbene **10** then reacts with other diazo compounds **27** forming zwitterion **150** which after elimination of dinitrogen results in trisubstituted alkenes **151**. The reaction gives products in very high yields and, in many cases, with high diastereoselectivities *trans*:*cis* product ratios exceeding 20:1 (Scheme 46).[102]

Alkenes with the same pattern of substituents can also be obtained using sulfur ylides **152** as acceptors for carbenes **2** generated photochemically from aryl diazoacetates **1** (Scheme 47). In this case, the elimination of dimethyl sulfide from intermediate **153** gives desired product **154** in decent yields and excellent diastereoselectivity.[103]

Photochemically generated carbenes react with *β*-ketothioamides affording heterocyclic compounds via a cascade of transformations enabling synthesis of substituted thiazolines in very good yields.[104]

In their very recent work, Koenigs et al. described the formation of carbenes from aryl/aryl diazo compounds and their reactivity with alkynes **65**.[5] The reaction is dependent on the type of substituents on the aromatic rings and can lead to cyclopropenation or C−H insertion. When unsubstituted benzene rings are used, a cascade of reactions occurs leading to substituted indenes **157** in good yields (Scheme 48).

Catalyzed Reactions. Photoredox catalysis has opened up a number of pathways to reactive intermediates inaccessible by other means. This also applies to diazo compounds chemistry. In general, direct photolysis of diazo reagents leads to carbenes, while photoredox catalysis gives access to radical transformations. Diazoalkanes can also be converted into alkyl

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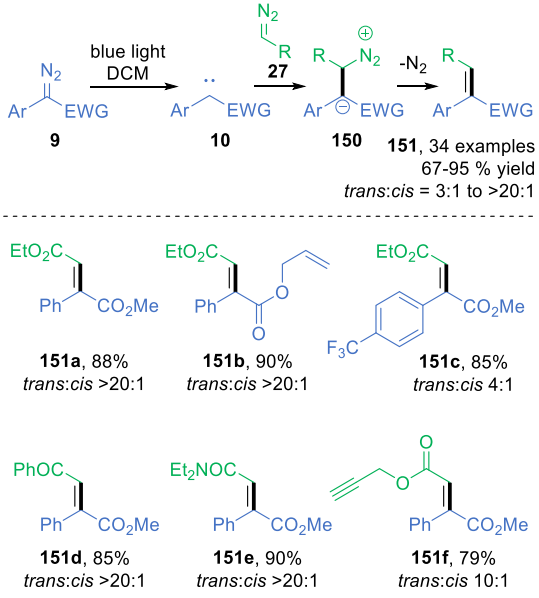
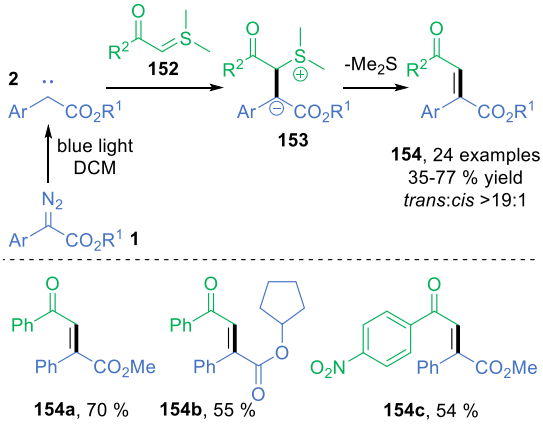
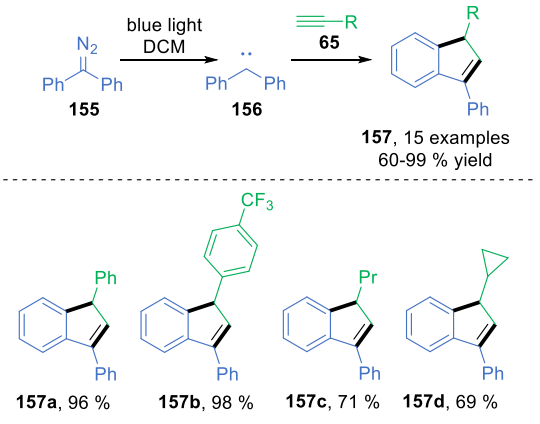
Scheme 46. Synthesis of Alkenes via Cross-Coupling of Two Types of Diazo Compounds



Scheme 47. Polysubstituted Olefin Synthesis from Diazo Esters and Sulfur Ylides

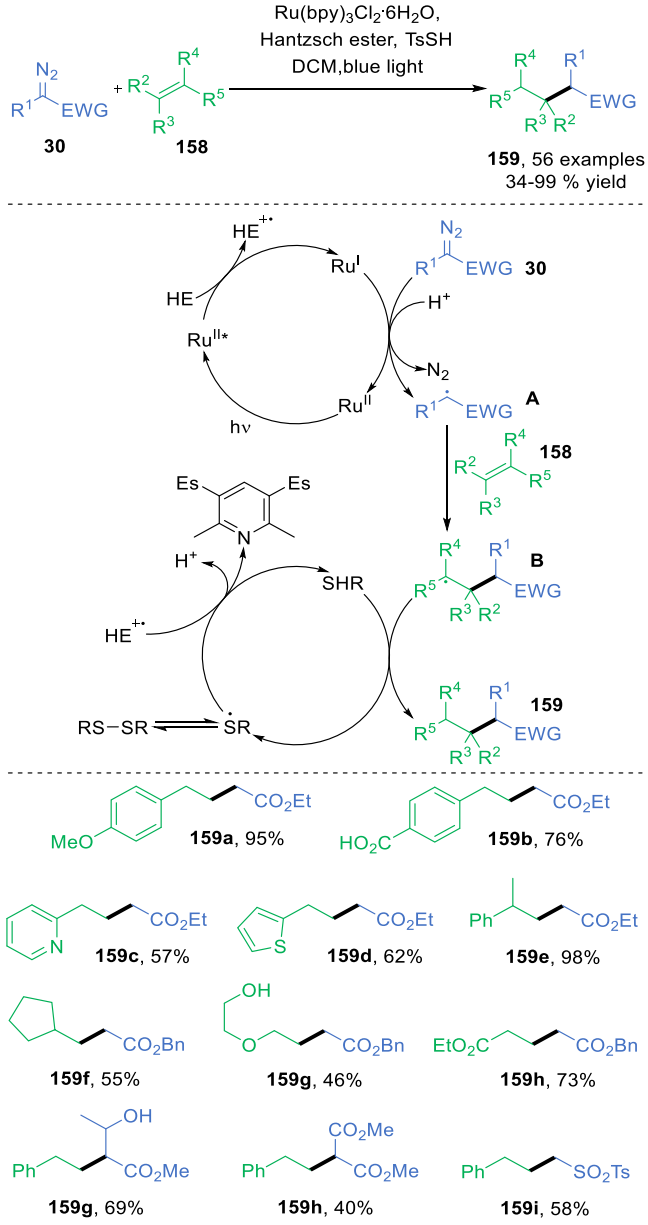


Scheme 48. Photochemical Reaction of Diphenyl Diazomethane with Alkynes



radical **A** as a result of the proton-coupled electron transfer (PCET). These active species react with alkenes **158** to form radical **B** that after hydrogen atom transfer (HAT) leads to alkanes **159**. Several EWG-substituted alkanes were efficiently synthesized using this strategy.[105] The common and well-known reaction of diazo compounds with alkenes leads to cyclopropane, while photoredox catalysis facilitates hydroalkylation of alkenes in the Giese-type reaction instead (Scheme 49).

Scheme 49. Giese-Type Hydroalkylation of Alkenes with Radicals Generated from Diazo Compounds



Photochemical radical benzannulation of diazo ketones **160** with alkynes **65** has been developed as a method for the synthesis of polysubsituted naphthols **161** (Scheme 50). The first step involves the generation of zwitterionic species **A** from diazo compound **160** that upon photochemical reduction gives radical **B**. This reactive intermediate adds to alkyne **65** forming radical **C** that intramolecularly attacks the aryl ring. Cyclohexadiene radical **D** is then oxidized, which completes the catalytic cycle, generating final product **161** after cation exchange. In addition to an interesting mechanistic aspect, this reaction allows for the introduction of a large alkyne substituent

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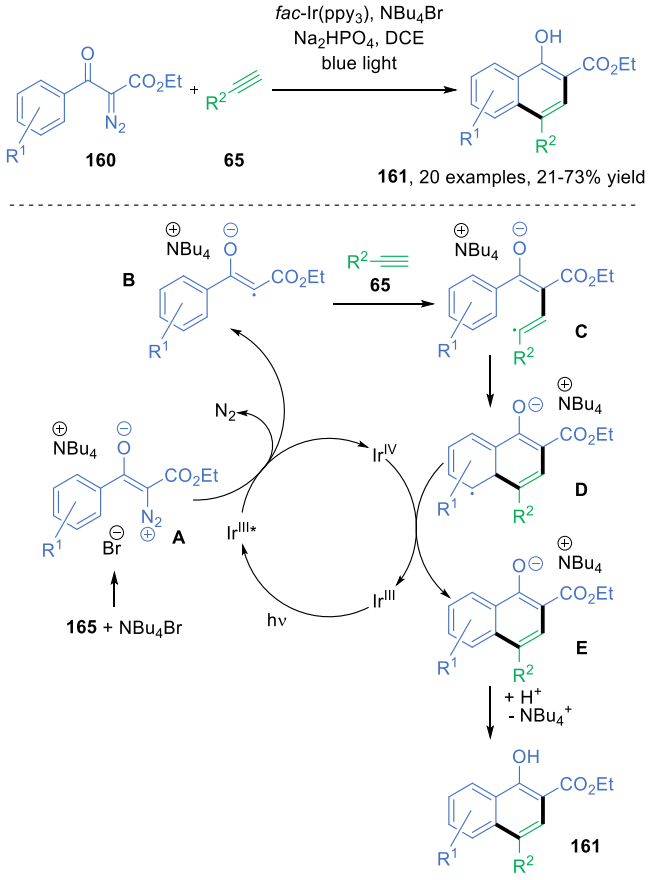
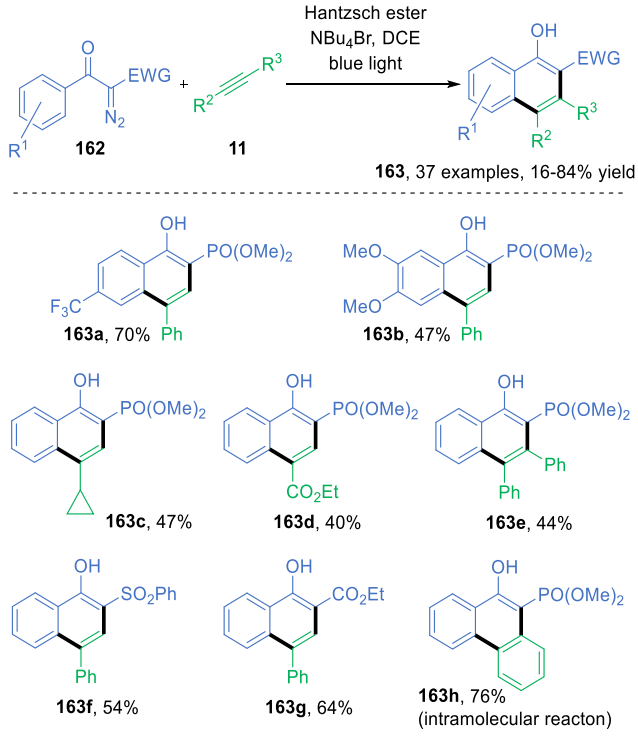
Scheme 50. Photochemical Radical Benzannulation of Diazo Ketones with Alkynes



Scheme 51. Hantzsch Ester-Mediated Benzannulation of Diazoketones with Alkynes



in the *para* position, in contrast to conventional procedures in which an *ortho* product is formed.[106]

Another approach to benzannulation engaging diazo compounds **162** utilizes the Hantzsch ester addition (Scheme 51). After excitation, this readily available reagent fulfills a very similar function to that of a photocatalyst; thus, mechanisms of both methods for obtaining naphthols **163** are very similar. Here, as well, the sterically hindered substituent is situated *para* to the hydroxyl group. This approach extended the scope of substrates with, among others, other electron-withdrawing groups and effective use of alkyl alkynes. Moreover, the use of o-aryl-α-diazophosphonates makes it possible to obtain substituted phenanthrene-1-ol (**163h**) under the same conditions.[107]

Suero et al. described a completely new reactivity of unique, specifically designed diazo compounds under photochemical conditions that is not associated with the release of nitrogen.[108] Under white light irradiation and in the presence of a ruthenium photocatalyst, hypervalent iodine reagents with diazo functionality **164** decompose to release diazo radical **A** which can be regarded as the carbyne equivalent (Scheme 52). This reactive intermediate reacts with aromatic compounds **19** giving radical **B** which, upon oxidation, yields aryl diazoacetates **165**. A series of diazo compounds **165** were obtained in good yields, even complex derivatives of biologically active compounds. Some of these diazo compounds are difficult to synthesize by other methods. Worth mentioning is the fact that many reactive functional groups like hydroxyl, ketone, or borane do not interfere with the reaction course. Thanks to the discovery of such an important new reactivity, it is now possible to introduce diazo functionality, which can then be further transformed into other functional groups. White light does not carry sufficient energy to decompose EDG/EWG diazo compounds to carbenes within 2 h. Under blue light irradiation, however, hypervalent iodine reagents with diazo functionality generate reactive species which exhibit dual radical−carbene reactivity allowing for double site-selective functionalizations.

Unique diazo reagent **166** has also been exploited in the preparation of heterocyclic compounds with two nitrogen atoms, which originate from the diazo functionality. The reaction of α-oxocarboxylic acids **167** as precursors of acyl radical **B** with iodonium salt **166** in the presence of 4CzPN dye as a photocatalyst gives 2,5-disubstituted 1,3,4-oxadiazoles **168** in good yields (Scheme 53).[109]

In the presented transformations, it is the diazo compound that quenches the luminescence of a photocatalyst generating reactive intermediates. Alternatively, a diazo reagent can react with active species formed in a photocatalytic cycle. In this line, photoredox catalysis enables cross-dehydrogenative coupling of tertiary amines **169** with α-diazo carbonyl compounds (**98**) leading to a formal hydrogen substitution by α-diazo carbonyl functionality (Scheme 54). This transformation involves the oxidation of amine **169** to radical cation **A** by the excited rose bengal which forms the radical anion. This, in turn, reduces molecular oxygen to superoxide species, which abstracts the hydrogen atom from amine radical cation **A** affording imine cation **B** that reacts with diazo compound **98**. Then, a hydroperoxide anion deprotonates generated intermediate **C** to yield the final product **170**. The use of an organic dye as the photocatalyst enables the functionalization of diazo compounds in good yields in a metal-free manner (Scheme 54).[110] This strategy was later applied to the photochemical Mannich reaction of tertiary amines with silyl diazoenolates.[111]

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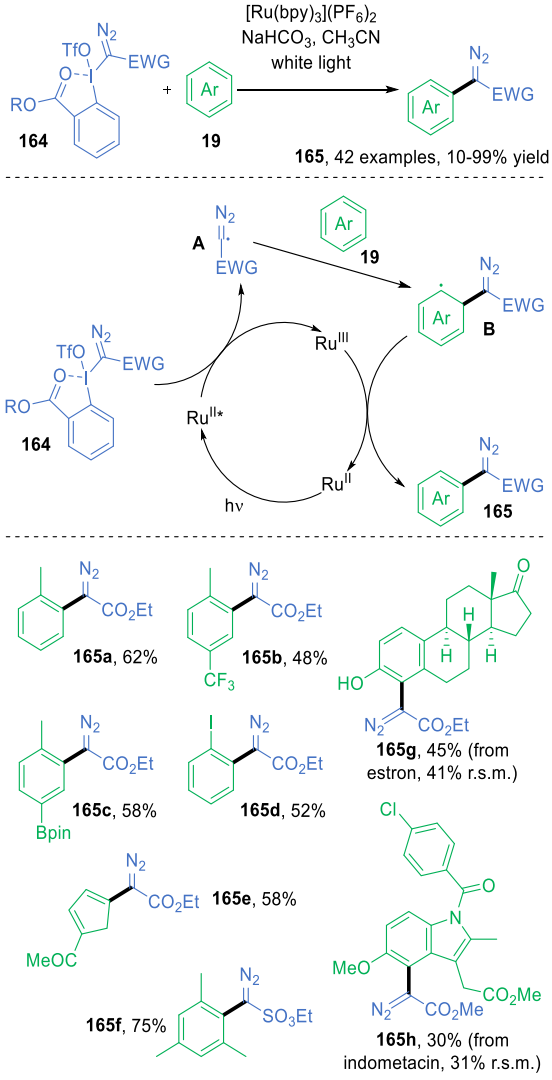
Scheme 52. Introducing Diazo Functionality via Carbyne Equivalents

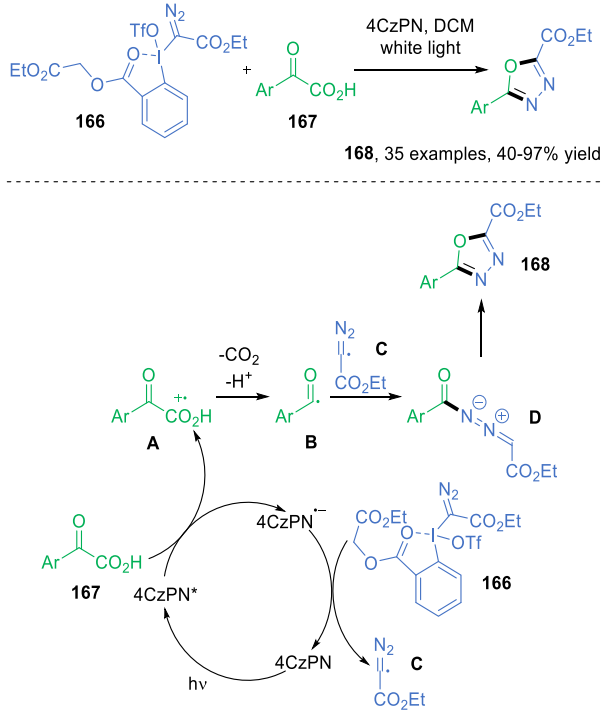


For aryl glycines (**171**), the reaction with diazo compounds **98** gives aziridines **172** via the aza-Darzens reaction (Scheme 55). In this case, radical cation **A** undergoes decarboxylation to yield radical **B** which after oxidation and deprotonation gives imine **D**. The following reaction of **D** with diazo compound **98** leads to zwitterionic species **E**. The subsequent intramolecular nucleophilic substitution with the loss of nitrogen yields aziridine **172**.[112]

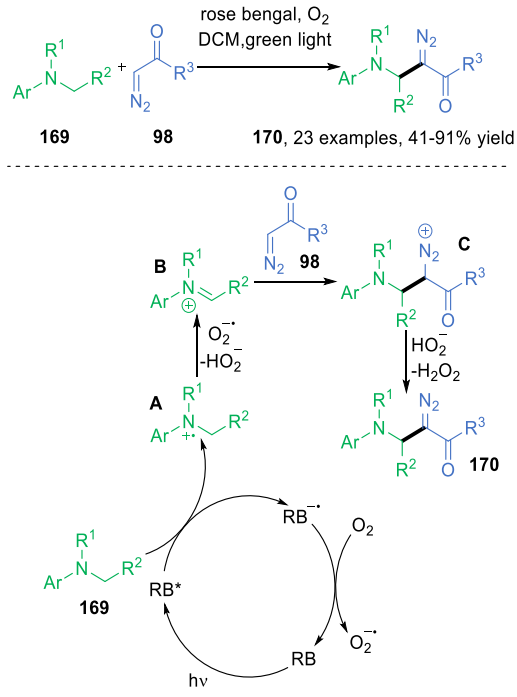
A photocatalytic method for [3+2]-cycloaddition of vinyl diazo compounds **173** and alkenes **158** was also developed by yielding substituted cyclopentenes **174** (Scheme 56). Classically, this type of reaction catalyzed by transition metal complexes proceeds via the metal carbene stage, while the photochemical approach is based on a radical process. Interestingly, both chromium and ruthenium complexes with different *N*,*N*-heterocyclic ligands can be effectively used as photocatalysts. In the first step, they oxidize alkene molecule **158** to cation radical **A**, which then reacts with diazo compound **173**. Subsequent cyclization and reduction yield the final product **174**. The method is highly diastereoselective; almost all cyclopentenes **174** are formed with high 19:1 d.r.[113]

Diazo compounds react also with free radicals generated in a photoredox catalytic cycle. Utilizing this strategy for the

Scheme 53. 2,5-Disubstituted 1,3,4-Oxadiazoles Synthesis via Carbyne Equivalents



Scheme 54. Cross-Dehydrogenative Coupling of Tertiary Amines with Diazo Compounds



synthesis of substituted hydrazones **176** from EDG/EWG diazo compounds **9** and NHPI esters **175** was accomplished (Scheme 57). In this transformation, photoredox catalysis facilitates the generation of alkyl radical **B** from NHPI esters **175**. The crucial step leading to hydrazone involves its reaction with diazo alkane **9**.[114]

The use of organic dyes in the presence of oxygen opens the possibility of converting diazoacetates **27** into oxalic acid esters

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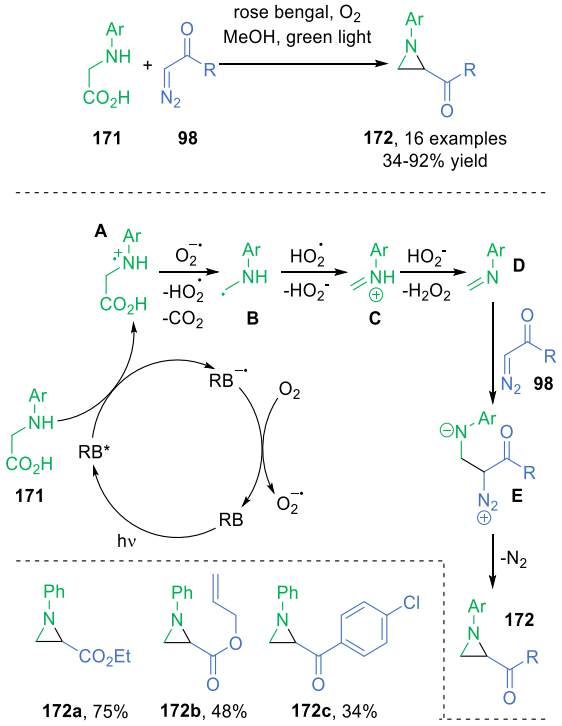
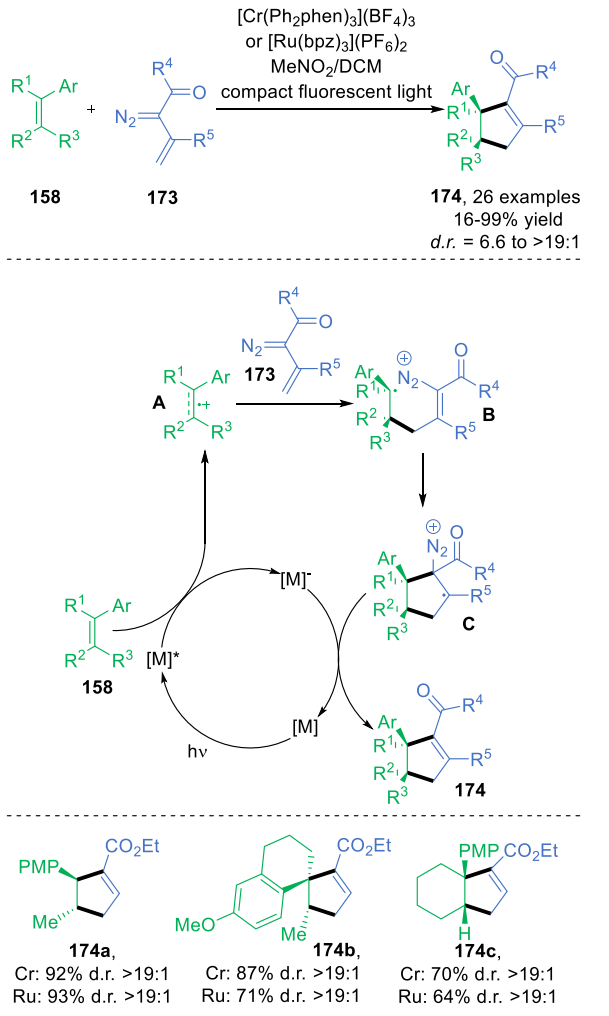
Scheme 55. Synthesis of Aziridines from Diazo Compounds via Aza-Darzens Rreaction



Scheme 56. [3+2] Cycloaddition of Vinyl Diazo Compounds and Alkenes



178 (Scheme 58). This three-component reaction is a radical process initiated with the photocatalytic one-electron reduction of α-bromoacetophenone **177** to radical **A** by eosin in the excited state. In the presence of oxygen, it transforms into oxyradical **B**, which then in a key step reacts with diazo ester **27** with the release of nitrogen. The resulting radical **C** attaches another oxygen molecule, and expected oxalate **178** is formed after rearrangement and oxidation of oxy radical **D**.[115]

Remarks. The vast majority of the above-mentioned transformations represent new reactivity modes of diazo compounds. They are accessible by the photochemical decomposition of specifically designed diazoalkanes or, above all, by the possibilities offered by photoredox catalysis. The use of a redox-active photocatalyst opens the way to a whole set of radical reactions which, when applied to diazo compounds, resulted in the discovery of transformations inaccessible by the classical reactivity associated with carbenes and metal carbenes. In most cases, diazo compounds act as radical acceptors but can also serve as a radical source. Importantly, the described processes are characterized by mild conditions (light irradiation instead of heating) and very often the use of organic, metal-free catalysts or no need for them at all (direct photolysis of diazo compounds).

CONCLUSIONS/PERSPECTIVES

In summary, recent years have witnessed significant discoveries in the field of visible-light-mediated reactions of diazo compounds. They encompass many significant advantages over classical, metal-catalyzed methods. First of all, the use of light is a very ecological/sustainable choice. In practice, it is a nonconsumable source of energy that does not generate any pollution. Therefore, research on light-mediated processes is very advanced, and it seems to be the future for chemical processes. Mild reaction conditions are another great asset of photochemical reactions. Most of the uncatalyzed processes take place at room temperature, often in air atmosphere, and without the need for stringent removal of moisture from the reaction mixture. The possibility of carrying out transformations in such mild conditions often allows one to increase the selectivity and avoid side reactions typical for thermal reactions or those induced with higher-energy UV radiation. In addition, for reactions catalyzed by organic dyes, or those that do not require the use of toxic transition metal complexes, the costly process of removing their traces is avoided, a feature particularly prized by the pharmaceutical industry. In turn, the use of photoredox catalysis enables radical processes involving diazo compounds. This opens up many possibilities related to the new reactivity modes of these compounds, previously regarded as carbene equivalents only.

It should be emphasized, however, that research on visible-light-mediated reactions of diazo compounds is only in the phase of intensive development. For this reason, they are still behind classical methods in terms of the number of available transformations and their applicability. Noncatalyzed reactions are limited mostly to EDG/EWG and aryl/aryl diazo compounds, as only these are known to absorb light in the visible range. For this reason, catalyzed reactions seem to provide a broader range of transformations. Properly designed transition metal complexes allow for highly stereoselective

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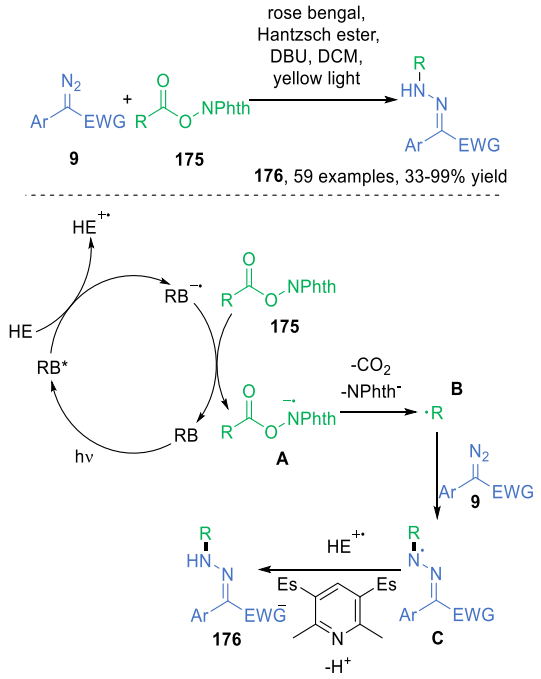
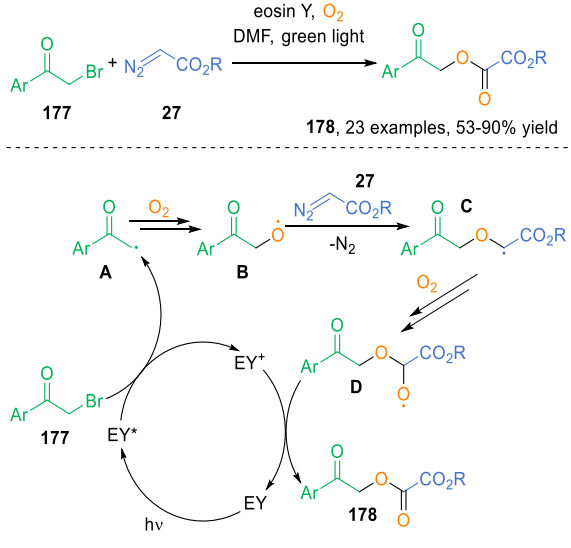
Scheme 57. Synthesis of Substituted Hydrazones from Diazo Compounds and NHPI Esters



Scheme 58. Oxidative Synthesis of Oxalate Esters with Diazo Compounds



transformations of diazo compounds. However, most of the methods induced by visible light developed so far are devoid of this aspect. Properly designed catalysts also significantly increase the selectivity of these processes. Furthermore, this strategy allows the use of near-stoichiometric amounts of reagents. This is not the case with direct, photochemical transformations, where the generation of highly reactive carbenes *in situ* necessitates the use of large excesses of their acceptor for the reaction to be selective.

However, taking into account the intensity of research on light-mediated processes, it can be assumed that the advantages of metal-catalyzed methods will be gradually reduced. Their environmentally friendly photocatalytic variants will be developed, and those already existing will be successively improved. The main challenge seems to be the possibility of conducting light-mediated processes in a stereoselective manner. Only such a discovery would fully enable broader applications of photochemical processes of diazo compounds in the pharmaceutical industry. We perceive extending the scope of applicability of this type of reaction, especially in its non-catalyzed variant, beyond EDG/EWG diazo alkanes as a second challenge. It is necessary to look for new chromophores capable of absorbing visible light and find synthetic methods to install them in the diazo compound structure. Variously substituted aromatic and heteroaromatic rings are considered the main hope in this regard. Furthermore, a solvent selection is also an important issue, as most photochemical reactions involving diazo compounds are carried out in dichloromethane (DCM) or dichloroethane (DCE). This presents a significant obstacle to considering these processes as green, despite the use of light. Also, there is a common problem with the scalability of photochemical reactions. Among them are those including diazo compounds, although, in some of the above-mentioned reactions, flow conditions were used successfully for this purpose. We expect some of these challenges to be solved in the coming years.

AUTHOR INFORMATION

Corresponding Author

Dorota Gryko − *Institute of Organic Chemistry Polish Academy of Sciences, 01-224 Warsaw, Poland;* orcid.org/0000-0002-5197-4222; Email: dorota.gryko@icho.edu.pl

Authors

Jakub Durka − *Institute of Organic Chemistry Polish Academy of Sciences, 01-224 Warsaw, Poland*

Joanna Turkowska − *Institute of Organic Chemistry Polish Academy of Sciences, 01-224 Warsaw, Poland*

Complete contact information is available at: https://pubs.acs.org/10.1021/acssuschemeng.1c01976

Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Jakub Durka was born in Poniatowa, Poland, in 1996. In 2016, he obtained a Master of Science degree in chemical technology at the Warsaw University of Technology and started his Ph.D. studies under

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the supervision of Prof. Gryko in the same year. His current research interests include photoredox catalysis and radical transformations.

Joanna Turkowska joined the research group of Prof. Gryko in 2016. In 2017, she obtained a Master of Science degree in chemistry at Warsaw University. Currently, she is working toward her Ph.D. degree at the Institute of Organic Chemistry of the Polish Academy of Sciences. Her research interests include cobalt catalysis in organic synthesis and biomimetic chemistry.

Dorota Gryko obtained her Ph.D. degree from the Institute of Organic Chemistry at the Polish Academy of Sciences in 1997, under the supervision of Prof. J. Jurczak. After a postdoctoral stay with Prof. J. Lindsey at North Carolina State University (1998−2000), she started an independent career in Poland. In 2009 and 2018, she received the prestigious TEAM grants from the Foundation for Polish Science. Her current research interests are focused on light-induced processes with particular attention being paid to porphyrinoid catalysis as well as on vitamin B_{12} chemistry.

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■ REFERENCES

(1) Ciszewski, Ł. W.; Rybicka-Jasińska, K.; Gryko, D. Recent Developments in Photochemical Reactions of Diazo Compounds. *Org. Biomol. Chem.* **2019**, *17*, 432−448.
(2) Yang, Z.; Stivanin, M. L.; Jurberg, I. D.; Koenigs, R. M. Visible Light-Promoted Reactions with Diazo Compounds: A Mild and Practical Strategy towards Free Carbene Intermediates. *Chem. Soc. Rev.* **2020**, *49*, 6833−6847.
(3) Huang, X.; Webster, R. D.; Harms, K.; Meggers, E. Asymmetric Catalysis with Organic Azides and Diazo Compounds Initiated by Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2016**, *138*, 12636−12642.
(4) Jurberg, I. D.; Davies, H. M. L. Blue Light-Promoted Photolysis of Aryldiazoacetates. *Chem. Sci.* **2018**, *9*, 5112−5118.
(5) Jana, S.; Pei, C.; Empel, C.; Koenigs, R. M. Photochemical Carbene Transfer Reactions of Aryl/Aryl Diazoalkanes - Experiment and Theory. *Angew. Chem., Int. Ed.* **2021**, *60*, 13271−13279.
(6) Roth, H. D.; Manion, M. L. Photosensitized Decomposition of Methyl Diazoacetate. Triplet Carbomethoxycarbene via Energy Transfer. *J. Am. Chem. Soc.* **1975**, *97*, 779−783.
(7) Roth, H. D. Chemically Induced Nuclear Spin Polarization in the Study of Carbene Reaction Mechanisms. *Acc. Chem. Res.* **1977**, *10*, 85−91.
(8) Giedyk, M.; Goliszewska, K.; óProinsias, K.; Gryko, D. Cobalt-Catalysed CH-Alkylation of Terminal Olefins, and Beyond. *Chem. Commun.* **2016**, *52*, 1389−1392.
(9) Guo, Y.; Empel, C.; Pei, C.; Atodiresei, I.; Fallon, T.; Koenigs, R. M. Photochemical Cyclopropanation of Cyclooctatetraene and (Poly-)Unsaturated Carbocycles. *Org. Lett.* **2020**, *22*, 5126−5130.
(10) Hommelsheim, R.; Guo, Y.; Yang, Z.; Empel, C.; Koenigs, R. M. Blue-Light-Induced Carbene-Transfer Reactions of Diazoalkanes. *Angew. Chem., Int. Ed.* **2019**, *58*, 1203−1207.
(11) He, F.; Koenigs, R. M. Visible Light Mediated, Metal-Free Carbene Transfer Reactions of Diazoalkanes with Propargylic Alcohols. *Chem. Commun.* **2019**, *55*, 4881−4884.
(12) Hashmi, A. S. K.; Grundl, M. A.; Nass, A. R.; Naumann, F.; Bats, J. W.; Bolte, M. Photochemical Synthesis of Prochiral Dialkyl 3,3-Dialkylcyclopropene-1,2-Dicarboxylates with Facial Shielding Substituents and Related Substrates. *Eur. J. Org. Chem.* **2001**, *2001*, 4705−4732.
(13) Zhang, X.; Du, C.; Zhang, H.; Li, X.-C.; Wang, Y.-L.; Niu, J.-L.; Song, M.-P. Metal-Free Blue-Light-Mediated Cyclopropanation of Indoles by Aryl(Diazo)Acetates. *Synthesis* **2019**, *51*, 889−898.
(14) Guo, Y.; Nguyen, T. V.; Koenigs, R. M. Norcaradiene Synthesis via Visible-Light-Mediated Cyclopropanation Reactions of Arenes. *Org. Lett.* **2019**, *21*, 8814−8818.
(15) Jana, S.; Li, F.; Empel, C.; Verspeek, D.; Aseeva, P.; Koenigs, R. M. Stoichiometric Photochemical Carbene Transfer by Bamford-Stevens Reaction. *Chem. - Eur. J.* **2020**, *26*, 2586−2591.
(16) Zhang, Z.; Yadagiri, D.; Gevorgyan, V. Light-Induced Metal-Free Transformations of Unactivated Pyridotriazoles. *Chem. Sci.* **2019**, *10*, 8399−8404.
(17) Uchida, T.; Irie, R.; Katsuki, T. Chiral (ON)Ru-Salen Catalyzed Cyclopropanation: High Cis - and Enantioselectivity. *Synlett* **1999**, *1999*, 1163−1165.
(18) Uchida, T.; Irie, R.; Katsuki, T. Highly Cis - and Enantioface-Selective Cyclopropanation Using (R, R)-Ru-Salen Complex: Solubility Dependent Enantioface Selection. *Synlett* **1999**, *1999*, 1793−1795.
(19) Uchida, T.; Irie, R.; Katsuki, T. Cis- and Enantio-Selective Cyclopropanation with Chiral (ON+)Ru-Salen Complex as a Catalyst. *Tetrahedron* **2000**, *56*, 3501−3509.
(20) Saha, B.; Uchida, T.; Katsuki, T. Intramolecular Asymmetric Cyclopropanation with (Nitroso)(Salen)Ruthenium(II) Complexes as Catalysts. *Synlett* **2001**, *2001*, 0114−0116.
(21) Saha, B.; Uchida, T.; Katsuki, T. Highly Enantioselective Intramolecular Cyclopropanation of Alkenyl Diazo Ketones Using Ru(Salen) as Catalyst. *Chem. Lett.* **2002**, *31* (8), 846−847.
(22) Sarabia, F. J.; Ferreira, E. M. Radical Cation Cyclopropanations via Chromium Photooxidative Catalysis. *Org. Lett.* **2017**, *19*, 2865−2868.
(23) Ye, T.; McKervey, M. A. Organic Synthesis with. Alpha.-Diazo Carbonyl Compounds. *Chem. Rev.* **1994**, *94*, 1091−1160.
(24) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α-Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981−10080.
(25) Davies, H. M. L.; Denton, J. R. Application of Donor/Acceptor-Carbenoids to the Synthesis of Natural Products. *Chem. Soc. Rev.* **2009**, *38*, 3061−3071.

https://doi.org/10.1021/acssuschemeng.1c01976
ACS Sustainable Chem. Eng. 2021, 9, 8895−8918

(26) Zhang, Z.; Wang, J. Recent Studies on the Reactions of α-Diazocarbonyl Compounds. *Tetrahedron* **2008**, *64*, 6577−6605.
(27) Prieto, A.; Fructos, M. R.; Mar Díaz-Requejo, M.; Pérez, P. J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A. M. Gold-Catalyzed Olefin Cyclopropanation. *Tetrahedron* **2009**, *65*, 1790−1793.
(28) Thompson, J. L.; Davies, H. M. L. Enhancement of Cyclopropanation Chemistry in the Silver-Catalyzed Reactions of Aryldiazoacetates. *J. Am. Chem. Soc.* **2007**, *129*, 6090−6091.
(29) Anding, B. J.; Ellern, A.; Woo, L. K. Olefin Cyclopropanation Catalyzed by Iridium(III) Porphyrin Complexes. *Organometallics* **2012**, *31*, 3628−3635.
(30) Pelphrey, P.; Hansen, J.; Davies, H. M. L. Solvent-Free Catalytic Enantioselective C-C Bond Forming Reactions with Very High Catalyst Turnover Numbers. *Chem. Sci.* **2010**, *1*, 254−257.
(31) Sambasivan, R.; Ball, Z. T. Screening Rhodium Metallopeptide Libraries "On Bead": Asymmetric Cyclopropanation and a Solution to the Enantiomer Problem. *Angew. Chem., Int. Ed.* **2012**, *51*, 8568−8572.
(32) Adly, F. G.; Gardiner, M. G.; Ghanem, A. Design and Synthesis of Novel Chiral Dirhodium(II) Carboxylate Complexes for Asymmetric Cyclopropanation Reactions. *Chem. - Eur. J.* **2016**, *22*, 3447−3461.
(33) Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. D 2 -Symmetric Dirhodium Catalyst Derived from a 1,2,2-Triarylcyclopropanecarboxylate Ligand: Design, Synthesis and Application. *J. Am. Chem. Soc.* **2011**, *133*, 19198−19204.
(34) Shen, J.-J.; Zhu, S.-F.; Cai, Y.; Xu, H.; Xie, X.-L.; Zhou, Q.-L. Enantioselective Iron-Catalyzed Intramolecular Cyclopropanation Reactions. *Angew. Chem., Int. Ed.* **2014**, *53*, 13188−13191.
(35) Xu, H.; Li, Y.-P.; Cai, Y.; Wang, G.-P.; Zhu, S.-F.; Zhou, Q.-L. Highly Enantioselective Copper- and Iron-Catalyzed Intramolecular Cyclopropanation of Indoles. *J. Am. Chem. Soc.* **2017**, *139*, 7697−7700.
(36) Xia, Y.; Qiu, D.; Wang, J. Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chem. Rev.* **2017**, *117*, 13810−13889.
(37) Hansen, S. R.; Spangler, J. E.; Hansen, J. H.; Davies, H. M. L. Metal-Free N-H Insertions of Donor/Acceptor Carbenes. *Org. Lett.* **2012**, *14*, 4626−4629.
(38) Tortoreto, C.; Rackl, D.; Davies, H. M. L. Metal-Free C-H Functionalization of Alkanes by Aryldiazoacetates. *Org. Lett.* **2017**, *19*, 770−773.
(39) Maas, G.; Bender, S. Synthesis and Ring Enlargement of 2-Ethoxycarbonyl-1-Silacyclobutanes. *Chem. Commun.* **2000**, 437−438.
(40) Daucher, B.; Gettwert, V.; Striegler, R.; Maas, G. Intramolecular Carbene and Carbenoid Reactions of α-(Vinyloxy)Silyl-α-Diazoacetates. *Z. Naturforsch., B: J. Chem. Sci.* **2004**, *59*, 1444−1450.
(41) Maas, G.; Daucher, B.; Maier, A.; Gettwert, V. Synthesis and Ring Opening Reactions of a 2-Silabicyclo[2.1.0]Pentane. *Chem. Commun.* **2004**, 238−239.
(42) Candeias, N. R.; Gois, P. M. P.; Veiros, L. F.; Afonso, C. A. M. C-H Carbene Insertion of α-Diazo Acetamides by Photolysis in Non-Conventional Media. *J. Org. Chem.* **2008**, *73*, 5926−5932.
(43) Yang, J.; Zhang, Q.; Zhang, W.; Yu, W. Synthesis of Benzo[a]Carbazoles and Indolo[2,3-a]Carbazoles via Photoinduced Carbene-Mediated C-H Insertion Reaction. *RSC Adv.* **2014**, *4*, 13704−13707.
(44) Smith, M. R.; Blake, A. J.; Hayes, C. J.; Stevens, M. F. G.; Moody, C. J. Carbene Reactivity of 4-Diazo-4 H -Imidazoles toward Nucleophiles and Aromatic Compounds. *J. Org. Chem.* **2009**, *74*, 9372−9380.
(45) Ciszewski, L. W.; Durka, J.; Gryko, D. Photocatalytic Alkylation of Pyrroles and Indoles with α-Diazo Esters. *Org. Lett.* **2019**, *21*, 7028−7032.
(46) Jackson, R. W.; Manske, R. H. The Reaction Products of Indols with Diazoesters. *Can. J. Res.* **1935**, *13b*, 170−174.
(47) Gibe, R.; Kerr, M. A. Convenient Preparation of Indolyl Malonates via Carbenoid Insertion. *J. Org. Chem.* **2002**, *67*, 6247−6249.
(48) Li, Z.; Shi, Z.; He, C. Addition of Heterocycles to Electron Deficient Olefins and Alkynes Catalyzed by Gold(III). *J. Organomet. Chem.* **2005**, *690*, 5049−5054.
(49) Li, Y.-P.; Li, Z.-Q.; Zhu, S.-F. Recent Advances in Transition-Metal-Catalyzed Asymmetric Reactions of Diazo Compounds with Electron-Rich (Hetero-) Arenes. *Tetrahedron Lett.* **2018**, *59*, 2307−2316.
(50) Bhattacharjee, S.; Laru, S.; Samanta, S.; Singsardar, M.; Hajra, A. Visible Light-Induced Photocatalytic C-H Ethoxycarbonylmethylation of Imidazoheterocycles with Ethyl Diazoacetate. *RSC Adv.* **2020**, *10*, 27984−27988.
(51) Xiao, Y.; Yu, L.; Yu, Y.; Tan, Z.; Deng, W. Visible-Light-Mediated C3-Ethoxycarbonylmethylation of Imidazo[1,2-a]Pyridines and Convenient Access to Zolpidem. *Tetrahedron Lett.* **2020**, *61*, 152606−152609.
(52) Holmberg-Douglas, N.; Onuska, N. P. R.; Nicewicz, D. A. Regioselective Arene C-H Alkylation Enabled by Organic Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 7425−7429.
(53) Okada, C. Y.; dos Santos, C. Y.; Jurberg, I. D. Blue Light-Promoted N-H Insertion of Amides, Isatins, Sulfonamides and Imides into Aryldiazoacetates: Synthesis of Unnatural α-Aryl Amino Acid Derivatives. *Tetrahedron* **2020**, *76*, 131316−131325.
(54) Stivanin, M. L.; Fernandes, A. A. G.; da Silva, A. F.; Okada, C. Y.; Jurberg, I. D. Blue Light-Promoted N-H Insertion of Carbazoles, Pyrazoles and 1,2,3-Triazoles into Aryldiazoacetates. *Adv. Synth. Catal.* **2020**, *362*, 1106−1111.
(55) Empel, C.; Patureau, F. W.; Koenigs, R. M. Visible Light Induced Metal-Free Carbene N -Carbazolation. *J. Org. Chem.* **2019**, *84*, 11316−11322.
(56) Yang, J.; Duan, J.; Wang, G.; Zhou, H.; Ma, B.; Wu, C.; Xiao, J. Visible-Light-Promoted Site-Selective N1-Alkylation of Benzotriazoles with α-Diazoacetates. *Org. Lett.* **2020**, *22*, 7284−7289.
(57) Wang, K.; Chen, P.; Ji, D.; Zhang, X.; Xu, G.; Sun, J. Rhodium-Catalyzed Regioselective N 2 -Alkylation of Benzotriazoles with Diazo Compounds/Enynones via a Nonclassical Pathway. *Angew. Chem., Int. Ed.* **2018**, *57*, 12489−12493.
(58) Maiti, D.; Das, R.; Sen, S. Blue LED-Mediated N-H Insertion of Indoles into Aryldiazoesters at Room Temperature in Batch and Flow: Reaction Kinetics, Density Functional Theory, and Mechanistic Study. *J. Org. Chem.* **2021**, *86*, 2522−2533.
(59) Arredondo, V.; Hiew, S. C.; Gutman, E. S.; Premachandra, I. D. U. A.; Van Vranken, D. L. Enantioselective Palladium-Catalyzed Carbene Insertion into the N-H Bonds of Aromatic Heterocycles. *Angew. Chem., Int. Ed.* **2017**, *56*, 4156−4159.
(60) Yang, J.; Wang, G.; Zhou, H.; Li, Z.; Ma, B.; Song, M.; Sun, R.; Huo, C. Visible-Light-Promoted Selective: O -Alkylation of 2-Pyridones with α-Aryldiazoacetates. *Org. Biomol. Chem.* **2021**, *19*, 394−398.
(61) Jana, S.; Yang, Z.; Li, F.; Empel, C.; Ho, J.; Koenigs, R. M. Photoinduced Proton-Transfer Reactions for Mild O-H Functionalization of Unreactive Alcohols. *Angew. Chem., Int. Ed.* **2020**, *59*, 5562−5566.
(62) Empel, C.; Verspeek, D.; Jana, S.; Koenigs, R. M. Photochemical O-H Functionalization Reactions of Cyclic Diazoamides. *Adv. Synth. Catal.* **2020**, *362*, 4716−4722.
(63) Empel, C.; Jana, S.; Pei, C.; Nguyen, T. V.; Koenigs, R. M. Photochemical O-H Functionalization of Aryldiazoacetates with Phenols via Proton Transfer. *Org. Lett.* **2020**, *22*, 7225−7229.
(64) Mei, H.; Liu, J.; Pajkert, R.; Wang, L.; Röschenthaler, G.-V.; Han, J. Design of (β-Diazo-α,α-Difluoroethyl)Phosphonates and Their Application as Masked Carbenes in Visible Light-Promoted Coupling Reactions with Sulfonic Acids. *Org. Chem. Front.* **2021**, *8*, 767−772.
(65) He, F.; Li, F.; Koenigs, R. M. Metal-Free Insertion Reactions of Silanes with Aryldiazoacetates. *J. Org. Chem.* **2020**, *85*, 1240−1246.
(66) Keipour, H.; Carreras, V.; Ollevier, T. Recent Progress in the Catalytic Carbene Insertion Reactions into the Silicon-Hydrogen Bond. *Org. Biomol. Chem.* **2017**, *15*, 5441−5456.
(67) Khade, R. L.; Chandgude, A. L.; Fasan, R.; Zhang, Y. Mechanistic Investigation of Biocatalytic Heme Carbenoid Si-H Insertions. *ChemCatChem* **2019**, *11*, 3101−3108.

https://doi.org/10.1021/acssuschemeng.1c01976
ACS Sustainable Chem. Eng. 2021, 9, 8895−8918

(68) Keipour, H.; Ollevier, T. Iron-Catalyzed Carbene Insertion Reactions of α-Diazoesters into Si-H Bonds. *Org. Lett.* **2017**, *19*, 5736−5739.
(69) Yang, J.; Wang, G.; Chen, S.; Ma, B.; Zhou, H.; Song, M.; Liu, C.; Huo, C. Catalyst-Free, Visible-Light-Promoted S-H Insertion Reaction between Thiols and α-Diazoesters. *Org. Biomol. Chem.* **2020**, *18*, 9494−9498.
(70) Gillingham, D.; Fei, N. Catalytic X-H Insertion Reactions Based on Carbenoids. *Chem. Soc. Rev.* **2013**, *42*, 4918−4931.
(71) Kirmse, W. 100 Years of the Wolff Rearrangement. *Eur. J. Org. Chem.* **2002**, *2002*, 2193−2256.
(72) Bernardim, B.; Hardman-Baldwin, A. M.; Burtoloso, A. C. B. LED Lighting as a Simple, Inexpensive, and Sustainable Alternative for Wolff Rearrangements. *RSC Adv.* **2015**, *5*, 13311−13314.
(73) Meng, J.; Ding, W.-W.; Han, Z.-Y. Synthesis of Chiral Esters via Asymmetric Wolff Rearrangement Reaction. *Org. Lett.* **2019**, *21*, 9801−9805.
(74) Vaske, Y. S. M.; Mahoney, M. E.; Konopelski, J. P.; Rogow, D. L.; McDonald, W. J. Enantiomerically Pure Trans -β-Lactams from α-Amino Acids via Compact Fluorescent Light (CFL) Continuous-Flow Photolysis. *J. Am. Chem. Soc.* **2010**, *132*, 11379−11385.
(75) Liu, D.; Ding, W.; Zhou, Q.-Q.; Wei, Y.; Lu, L.-Q.; Xiao, W.-J. Catalyst-Controlled Regioselective Acylation of β-Ketoesters with α-Diazo Ketones Induced by Visible Light. *Org. Lett.* **2018**, *20*, 7278−7282.
(76) Liu, J.; Li, M.-M.; Qu, B.-L.; Lu, L.-Q.; Xiao, W.-J. A Photoinduced Wolff Rearrangement/Pd-Catalyzed [3+2] Cycloaddition Sequence: An Unexpected Route to Tetrahydrofurans. *Chem. Commun.* **2019**, *55*, 2031−2034.
(77) Wang, C.; Wang, Z.; Yang, J.; Shi, S.-H.; Hui, X.-P. Sequential Visible-Light and N -Heterocyclic Carbene Catalysis: Stereoselective Synthesis of Tetrahydropyrano[2,3- b]Indoles. *Org. Lett.* **2020**, *22*, 4440−4443.
(78) Li, M.-M.; Wei, Y.; Liu, J.; Chen, H.-W.; Lu, L.-Q.; Xiao, W.-J. Sequential Visible-Light Photoactivation and Palladium Catalysis Enabling Enantioselective [4 + 2] Cycloadditions. *J. Am. Chem. Soc.* **2017**, *139*, 14707−14713.
(79) Wei, Y.; Liu, S.; Li, M.-M.; Li, Y.; Lan, Y.; Lu, L.-Q.; Xiao, W.-J. Enantioselective Trapping of Pd-Containing 1,5-Dipoles by Photogenerated Ketenes: Access to 7-Membered Lactones Bearing Chiral Quaternary Stereocenters. *J. Am. Chem. Soc.* **2019**, *141*, 133−137.
(80) Jana, S.; Guo, Y.; Koenigs, R. M. Recent Perspectives on Rearrangement Reactions of Ylides via Carbene Transfer Reactions. *Chem. - Eur. J.* **2021**, *27*, 1270−1281.
(81) Kirmse, W.; Kapps, M. Reaktionen Des Diazomethans Mit Diallylsulfid Und Allyläthern Unter Kupfersalz-Katalyse. *Chem. Ber.* **1968**, *101*, 994−1003.
(82) Empel, C.; Koenigs, R. M. Continuous-Flow Photochemical Carbene Transfer Reactions. *J. Flow Chem.* **2020**, *10*, 157−160.
(83) Zhang, X.; Qu, Z.; Ma, Z.; Shi, W.; Jin, X.; Wang, J. Catalytic Asymmetric [2,3]-Sigmatropic Rearrangement of Sulfur Ylides Generated from Copper(I) Carbenoids and Allyl Sulfides. *J. Org. Chem.* **2002**, *67*, 5621−5625.
(84) Orłowska, K.; Rybicka-Jasińska, K.; Krajewski, P.; Gryko, D. Photochemical Doyle-Kirmse Reaction: A Route to Allenes. *Org. Lett.* **2020**, *22*, 1018−1021.
(85) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633−10640.
(86) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons, Ltd: Chichester, UK, 2009. DOI: 10.1002/9781444312096.
(87) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529−2591.
(88) O'Hagan, D.; Wang, Y.; Skibinski, M.; Slawin, A. M. Z. Influence of the Difluoromethylene Group (CF2) on the Conformation and Properties of Selected Organic Compounds. *Pure Appl. Chem.* **2012**, *84*, 1587−1595.
(89) Yang, J.; Wang, J.; Huang, H.; Qin, G.; Jiang, Y.; Xiao, T. Gem -Difluoroallylation of Aryl Diazoesters via Catalyst-Free, Blue-Light-Mediated Formal Doyle-Kirmse Reaction. *Org. Lett.* **2019**, *21*, 2654−2657.
(90) Yang, Z.; Guo, Y.; Koenigs, R. M. Photochemical, Metal-Free Sigmatropic Rearrangement Reactions of Sulfur Ylides. *Chem. - Eur. J.* **2019**, *25*, 6703−6706.
(91) Li, F.; He, F.; Koenigs, R. M. Catalyst-Free [2,3]-Sigmatropic Rearrangement Reactions of Photochemically Generated Ammonium Ylides. *Synthesis* **2019**, *51*, 4348−4358.
(92) Sweeney, J. B. Sigmatropic Rearrangements of 'Onium' Ylids. *Chem. Soc. Rev.* **2009**, *38*, 1027−1038.
(93) Roiser, L.; Zielke, K.; Waser, M. Ammonium Ylide Mediated Cyclization Reactions. *Asian J. Org. Chem.* **2018**, *7*, 852−864.
(94) Sharma, A.; Guénée, L.; Naubron, J.-V.; Lacour, J. One-Step Catalytic Asymmetric Synthesis of Configurationally Stable Tröger Bases. *Angew. Chem., Int. Ed.* **2011**, *50*, 3677−3680.
(95) Jana, S.; Yang, Z.; Pei, C.; Xu, X.; Koenigs, R. M. Photochemical Ring Expansion Reactions: Synthesis of Tetrahydrofuran Derivatives and Mechanism Studies. *Chem. Sci.* **2019**, *10*, 10129−10134.
(96) Hock, K. J.; Koenigs, R. M. Enantioselective [2,3]-Sigmatropic Rearrangements: Metal-Bound or Free Ylides as Reaction Intermediates? *Angew. Chem., Int. Ed.* **2017**, *56*, 13566−13568.
(97) He, F.; Pei, C.; Koenigs, R. M. Photochemical Fluoro-Amino Etherification Reactions of Aryldiazoacetates with NFSI under Stoichiometric Conditions. *Chem. Commun.* **2020**, *56*, 599−602.
(98) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. Highly Effective Catalytic Methods for Ylide Generation from Diazo Compounds. Mechanism of the Rhodium- and Copper-Catalyzed Reactions with Allylic Compounds. *J. Org. Chem.* **1981**, *46*, 5094−5102.
(99) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. Toward a Symphony of Reactivity: Cascades Involving Catalysis and Sigmatropic Rearrangements. *Angew. Chem., Int. Ed.* **2014**, *53*, 2556−2591.
(100) Sheng, Z.; Zhang, Z.; Chu, C.; Zhang, Y.; Wang, J. Transition Metal-Catalyzed [2,3]-Sigmatropic Rearrangements of Ylides: An Update of the Most Recent Advances. *Tetrahedron* **2017**, *73*, 4011−4022.
(101) Neuhaus, J. D.; Oost, R.; Merad, J.; Maulide, N. Sulfur-Based Ylides in Transition-Metal-Catalysed Processes. *Top. Curr. Chem.* **2018**, *376*, 429−479.
(102) Xiao, T.; Mei, M.; He, Y.; Zhou, L. Blue Light-Promoted Cross-Coupling of Aryldiazoacetates and Diazocarbonyl Compounds. *Chem. Commun.* **2018**, *54*, 8865−8868.
(103) Ye, C.; Cai, B.-G.; Lu, J.; Cheng, X.; Li, L.; Pan, Z.-W.; Xuan, J. Visible-Light-Promoted Polysubstituted Olefins Synthesis Involving Sulfur Ylides as Carbene Trapping Reagents. *J. Org. Chem.* **2021**, *86*, 1012−1022.
(104) Ansari, M. A.; Yadav, D.; Singh, M. S. Visible-Light-Driven Photocatalyst- and Additive-Free Cross-Coupling of B-Ketothioamides with A-Diazo 1,3-Diketones: Access to Highly Functionalized Thiazolines. *Chem. - Eur. J.* **2020**, *26*, 8083−8089.
(105) Su, Y.-L.; Liu, G.-X.; Liu, J.-W.; Tram, L.; Qiu, H.; Doyle, M. P. Radical-Mediated Strategies for the Functionalization of Alkenes with Diazo Compounds. *J. Am. Chem. Soc.* **2020**, *142*, 13846−13855.
(106) He, Y.; Chen, H.; Li, L.; Huang, J.; Xiao, T.; Anand, D.; Zhou, L. Visible Light-Promoted Radical Benzannulation of Diazoketones with Alkynes Leading to Polysubsituted Naphthols. *J. Photochem. Photobiol., A* **2018**, *355*, 220−225.
(107) Nagode, S. B.; Kant, R.; Rastogi, N. Hantzsch Ester-Mediated Benzannulation of Diazo Compounds under Visible Light Irradiation. *Org. Lett.* **2019**, *21*, 6249−6254.
(108) Wang, Z.; Herraiz, A. G.; del Hoyo, A. M.; Suero, M. G. Generating Carbyne Equivalents with Photoredox Catalysis. *Nature* **2018**, *554*, 86−91.
(109) Li, J.; Lu, X.-C.; Xu, Y.; Wen, J.-X.; Hou, G.-Q.; Liu, L. Photoredox Catalysis Enables Decarboxylative Cyclization with Hypervalent Iodine(III) Reagents: Access to 2,5-Disubstituted 1,3,4-Oxadiazoles. *Org. Lett.* **2020**, *22*, 9621−9626.
(110) Xiao, T.; Li, L.; Lin, G.; Mao, Z.; Zhou, L. Metal-Free Visible-Light Induced Cross-Dehydrogenative Coupling of Tertiary Amines with Diazo Compounds. *Org. Lett.* **2014**, *16*, 4232−4235.

https://doi.org/10.1021/acssuschemeng.1c01976
ACS Sustainable Chem. Eng. 2021, 9, 8895−8918

(111) Pramanik, M. M. D.; Nagode, S. B.; Kant, R.; Rastogi, N. Visible Light Catalyzed Mannich Reaction between Tert-Amines and Silyl Diazoenolates. *Org. Biomol. Chem.* **2017**, *15*, 7369−7373.
(112) Liu, Y.; Dong, X.; Deng, G.; Zhou, L. Synthesis of Aziridines by Visible-Light Induced Decarboxylative Cyclization of N-Aryl Glycines and Diazo Compounds. *Sci. China: Chem.* **2016**, *59*, 199−202.
(113) Sarabia, F. J.; Li, Q.; Ferreira, E. M. Cyclopentene Annulations of Alkene Radical Cations with Vinyl Diazo Species Using Photocatalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 11015−11019.
(114) Chan, C.-M.; Xing, Q.; Chow, Y.-C.; Hung, S.-F.; Yu, W.-Y. Photoredox Decarboxylative C(Sp 3)-N Coupling of α-Diazoacetates with Alkyl N -Hydroxyphthalimide Esters for Diversified Synthesis of Functionalized N -Alkyl Hydrazones. *Org. Lett.* **2019**, *21*, 8037−8043.
(115) Ma, M.; Hao, W.; Ma, L.; Zheng, Y.; Lian, P.; Wan, X. Interception of Radicals by Molecular Oxygen and Diazo Compounds: Direct Synthesis of Oxalate Esters Using Visible-Light Catalysis. *Org. Lett.* **2018**, *20*, 5799−5802.

https://doi.org/10.1021/acssuschemeng.1c01976
ACS Sustainable Chem. Eng. 2021, 9, 8895−8918

Instytut Chemii Organicznej
Polskiej Akademii Nauk

mgr inż. Jakub Durka
doktorant
+48 22 343 2113
jakub.durka@icho.edu.pl

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- J. Turkowska [‡], J. Durka [‡], M. Ociepa, D. Gryko *Chem. Commun.*, **2022**, *58*, 509-512
Reversal of regioselectivity in reactions of donor–acceptor cyclopropanes with electrophilic olefins

polegał na dyskusji koncepcji badań, współuczestnictwie w optymalizacji warunków reakcji modelowej, zbadaniu zakresu stosowalności i ograniczeń metody w odniesieniu do akceptorów Michaela (związki **5a-5n**), współuczestnictwie w przeprowadzeniu badań kinetycznych, interpretacji otrzymanych wyników i przygotowaniu manuskryptu.

- J. Durka, B. Zielińska, D. Gryko *Angew. Chem. Int. Ed.* **2025**, *64* (7)
Aliphatic Amines Unlocked for Selective Transformations through Diazotization

polegał na opracowaniu koncepcji badań, optymalizacji warunków reakcji modelowej oraz innych reakcji, które tego wymagały, zbadaniu całego zakresu stosowalności i ograniczeń metody z wyjątkiem związków **23**, **27**, **28**, **31**, **61**, **68**, **70**, **71**, przeprowadzeniu badań mechanistycznych, interpretacji otrzymanych wyników i przygotowaniu manuskryptu.

- J. Durka, J. Turkowska, D. Gryko *ACS Sustainable Chem. Eng.* **2021**, *9*, 8895−8918
Lightening Diazo Compounds?

polegał na współopracowaniu koncepcji artykułu, dokonaniu przeglądu literaturowego i przygotowaniu artykułu z wyjątkiem rozdziału poświęconego C-X insercjom.

Potwierdzam zgodność z prawdą Dorota Gryko Digitally signed by Dorota Gryko Date: 2025.05.30 07:31:42 +02'00' .....

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Jakub Durka
30.05.2025
5:07:08 +02'00'

.....

Instytut Chemii Organicznej
Polskiej Akademii Nauk

prof. dr hab. Dorota Gryko
kierownik Zespołu XV
+48 22 343 2051
dorota.gryko@icho.edu.pl

Warszawa 30 maja 2025 r.

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- J. Turkowska [‡], J. Durka [‡], M. Ociepa, D. Gryko *Chem. Commun.*, **2022**, *58*, 509-512
Reversal of regioselectivity in reactions of donor–acceptor cyclopropanes with electrophilic olefins

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polegał na interpretacji otrzymanych wyników i przygotowaniu manuskryptu.

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Lightening Diazo Compounds?

polegał na współopracowaniu koncepcji artykułu i udziale w przygotowaniu artykułu

Dorota Gryko
Digitally signed by Dorota Gryko
Date: 2025.05.30 07:30:40 +02'00'

Dr Joanna Turkowska

Kraków, 30.05.2025 r.

Oświadczenie

Oświadczam, że mój wkład w powstanie poniższych publikacji:

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polegał na opracowaniu koncepcji badań, współuczestnictwie w optymalizacji warunków reakcji modelowej, zbadaniu zakresu stosowalności i ograniczeń metody w odniesieniu do cyklopropanów donorowo akceptorowych (związki **10a-19a**), przeprowadzeniu badań mechanistycznych, interpretacji otrzymanych wyników i przygotowaniu manuskryptu.

- J. Durka, J. Turkowska, D. Gryko *ACS Sustainable Chem. Eng.* **2021**, *9*, 8895−8918

Lightening Diazo Compounds?

polegał na współopracowaniu koncepcji artykułu, dokonaniu przeglądu literaturowego i przygotowaniu rozdziału o C-X insercjach.

Joanna Turkowska

.....

Instytut Chemii Organicznej
Polskiej Akademii Nauk

dr Michał Ociepa
kierownik Zespołu XVa
+48 22 343 21 08
michal.ociepa@icho.edu.pl

Warszawa 30 maja 2025 r.

Oświadczam, że mój wkład w powstanie poniższych publikacji:

- J. Turkowska [‡], J. Durka [‡], M. Ociepa, D. Gryko *Chem. Commun.*, **2022**, *58*, 509-512
Reversal of regioselectivity in reactions of donor–acceptor cyclopropanes with electrophilic olefins

polegał na współopracowaniu koncepcji badań.

Podpisuję z CenCert

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Inż. Barbara Zielińska

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Oświadczenie

Oświadczam, że mój wkład w powstanie poniższej publikacji:

- J. Durka, B. Zielińska, D. Gryko *Angew. Chem. Int. Ed.* **2025**, *64* (7)

Aliphatic Amines Unlocked for Selective Transformations through Diazotization

polegał współuczestnictwie w badaniu zakresu stosowalności i ograniczeń metody (synteza związków **23**, **27**, **28**, **31**, **61**, **68**, **70**, **71**).

Barbara Zielińska