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DISSERTATION | DOCTORAL THESIS

Titel | Title

I. Controlling the Fate of Bicyclobutonium Ions by Computation-Aided Reaction Design; II. Synthesis of Difunctionalized Amides by Domino Conjugate Addition-Smiles Rearrangement

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Yi Xiao

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For my late grandfather.

路漫漫其修远兮，

吾将上下而求索。

——[先秦]屈原

The work presented in this doctoral thesis was conducted between January 2022 and September 2025 at the University of Vienna (Austria) under the supervision of Univ. -Prof. Dr. Nuno Maulide.

Herewith I would like to authenticate that I have written this thesis on my own. I have not used other resources, tools or assistance than those reported in this thesis.

Yi Xiao, December 2025

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Abstract (English)

This thesis is divided into two chapters.

The first chapter of the thesis concerns the reactivity of bicyclobutonium (BCB) ions. While previous work has established that an iodine(III)-mediated oxidative Umpolung reaction of a silyl enol ether led to intramolecular cyclization and formation of *trans*-cyclopropylcarbinyl mesylates through a BCB cation intermediate, computational work has suggested that a different substitution pattern can afford cyclobutyl products. In this part of the thesis, silyl enol ethers carrying a terminal, di-substituted alkene were employed as substrates for iodine(III)-mediated Umpolung oxidation. It was discovered that only 1,3-substituted cyclobutanes were formed as the product of this oxidation, with varying diastereomeric ratios depending on the substituents on both the alkene and the silyl enol ether. The regio- and stereoselectivity of this reaction led to a proposed reaction mechanism, in which a highly-strained, bicyclic oxocarbenium ion as a key resting state of the BCB cationic intermediate.

The second chapter describes a domino reaction, in which a conjugate addition-Smiles rearrangement sequence affords α,β-difunctionalized amides from sulfonyl acrylimides in a single step. The reaction progresses under mild, atmospheric conditions and tolerates a range of sulfonyl acrylimides and nucleophiles, including carbon-, phosphorus-, nitrogen- and sulfur-based ones. A one-pot, domino amide coupling-conjugate addition-Smiles rearrangement reaction between acrylic acid derivatives and *N*-methyl nosylamines was also developed to directly afford highly functionalized amides.

Kurzzusammenfassung (Deutsch)

Diese Dissertation besteht aus zwei Kapiteln.

Das erste Kapitel befasst sich mit der Reaktivität von Bicyclobutonium-(BCB-)Ionen. Während frühere Arbeiten gezeigt haben, dass eine durch Iod(III) vermittelte oxidative Umpolung eines Silylenolethers zu einer intramolekularen Cyclisierung und zur Bildung von trans-Cyclopropylcarbinylmesylaten über ein BCB-kationisches Intermediat führt, deuteten computergestützte Untersuchungen darauf hin, dass ein anderes Substitutionsmuster Cyclobutylprodukte liefern kann. In diesem Teil der Dissertation wurden Silylenolether mit einer terminalen, zweifach substituierten Alkengruppe als Substrate für die durch Iod(III) vermittelte Umpolungsoxidation eingesetzt. Es wurde entdeckt, dass ausschließlich 1,3-substituierte Cyclobutane als Produkte dieser Oxidation entstehen, wobei die Diastereomerenverhältnisse je nach Substituenten sowohl am Alken als auch am Silylenolether variieren. Die Regio- und Stereoselektivität dieser Reaktion führte zu einem vorgeschlagenen Reaktionsmechanismus, in dem ein hochgespanntes, bicyclisches Oxocarbeniumion als zentraler Ruhe- bzw. Zwischenzustand des BCB-Kations postuliert wird.

Das zweite Kapitel beschreibt eine Dominoreaktion, bei der eine Sequenz aus konjugierter Addition und Smiles-Umlagerung α,β-difunktionalisierte Amide aus Sulfonylacrylimiden in einem einzigen Schritt liefert. Die Reaktion verläuft unter milden, atmosphärischen Bedingungen und toleriert eine Vielzahl von Sulfonylacrylimiden und Nukleophilen, darunter solche auf Kohlenstoff-, Phosphor-, Stickstoff- und Schwefelbasis. Darüber hinaus wurde eine Eintopf-Dominoreaktion bestehend aus Amidkupplung, konjugierter Addition und Smiles-Umlagerung zwischen Acrylsäurederivaten und N-Methyl-Nosylaminen entwickelt, die direkt zu hochfunktionalisierten Amiden führt.

List of Abbreviations

Å	Angstrom
Ac	acetyl
AIBN	azobisisobutyronitrile
Alk	alkyl
app	apparent
aq.	aqueous
Ar	aryl
BCB	bicyclobutonium
Bn	benzyl
BTMG	2-*tert*-butyl-1,1,3,3-tetramethylguanidine
Bu	butyl
°C	degree Celcius
cat.	catalytic
CB	cyclobutyl
CDI	1,1'-carbonyldiimidazole
CPC	cyclopropylcarbinyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide)
DCM	dichloromethane
DFT	density function theory
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
d.r.	diastereomeric ratio
DTBP	di-*tert*-butyl peroxide
equiv.	equivalent
Et	ethyl
e.r.	enantiomeric ratio
ESI	electron spray ionization
EWG	electron-donating group
g	gram
GC	gas chromatography
h	hour
HA	homoallyl
HAT	hydrogen atom transfer
HMDS	bis(trimethylsilyl)amide
HMPT	tris(dimethylamino)phosphine
HRMS	high-resolution mass spectrometry

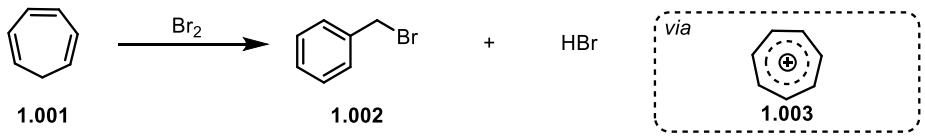
Hz	Hertz
IR	infrared
K	Kelvin
kcal	kilocalorie
L	liter
LB	Lewis base
LDA	lithium diisopropylamide
LED	light-emitting diode
m	multiplet
M	moles per liter
MBH	Morita-Baylis-Hillman
Me	methyl
min	minutes
mol	mole
Ms	methanesulfonyl
MW	molecular weight
m/z	mass-to-charge ratio
n.d.	not detected
NHC	*N*-heterocyclic carbene
n.l.	not located
NMR	nuclear magnetic resonance
Nu	nucleophile
p	pentet
PIDA	iodosobenzene diacetate
PIFA	(bis(trifluoroacetoxy)iodo)benzene
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
RDS	rate-determining step
s	singlet
satd.	saturated
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
t	triplet
TBAI	*tert*-butyl ammonium iodide
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
TOF	time-of-flight
δ	chemical shift
v	wavenumber

Chapter 1. Controlling the Fate of Bicyclobutonium Ions by Computation-Aided Reaction Design

1.1 Introduction

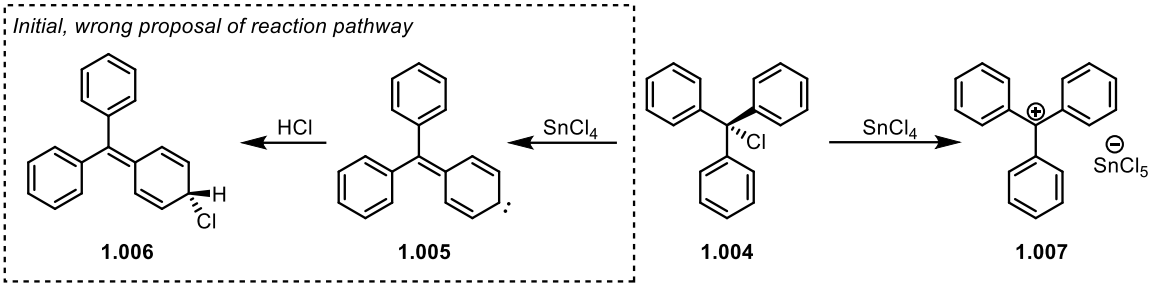
1.1.1 History of Carbocations

Organic chemists have been interested in carbocations for over a century. The first encounter of positively-charged carbon species dates back to 1891, when Merling observed the reaction between tropilidene (**1.001**) and elemental bromine to form hydrobromide and benzyl bromide (**1.002**) (**Scheme 1.01**).[1] Although he did not propose a mechanism at the time, in 1954, Doering and Knox convincingly showed that a tropylium ion (**1.003**) was formed as the intermediate.[2]



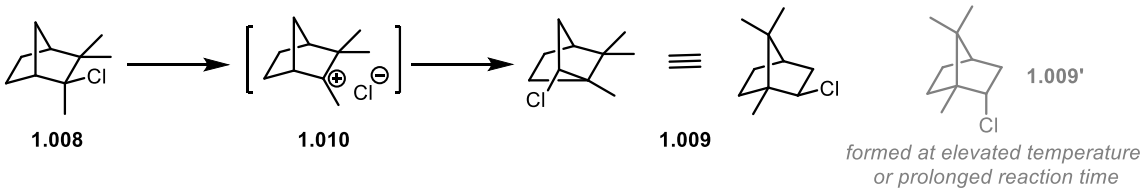
Scheme 1.01. Reaction between tropilidene and bromine reported by Merling, which is believed to be the first encounter of carbocations.

In 1901, Kehrmann and Wentzel noted that the treatment of colourless triphenylmethyl chloride (**1.004**) with tin(IV) chloride led to the formation of a yellow species (**Scheme 1.02**).[3] At the time, this species was mistakenly assigned as a carbene-like structure **1.005**, with considerable basicity on the carbon as it reacts with hydrogen chloride to form an adduct (**1.006**). Only one year later, Gomberg, Baeyer and Villiger proposed that, instead of a carbene, the coloured species was a salt, containing a three-coordinate, positively charged carbon species (**1.007**).[4,5] The charged nature of that intermediate was confirmed in the same year by Walden, who reported its electrical conductivity in solution.[6]



Scheme 1.02. Reaction between Ph_3CCl and $SnCl_4$, with the first experimentally confirmed carbocation.

In 1922, Meerwein and van Emster first proposed a carbocation intermediate (**1.010**) in the acid-catalyzed rearrangement of camphene hydrochloride (**1.008**) into isobornyl chloride (**1.009)** (**Scheme 1.03**).[7] Another isomer, bornyl chloride (**1.009'**), was only formed upon extended reaction time or elevated temperatures. Later identified and confirmed as 2-norbornyl cation,[8] the carbocationic intermediate at play here became the centerpiece of a long-standing scientific debate over the last century and will be described in more detail in section 1.1.2.

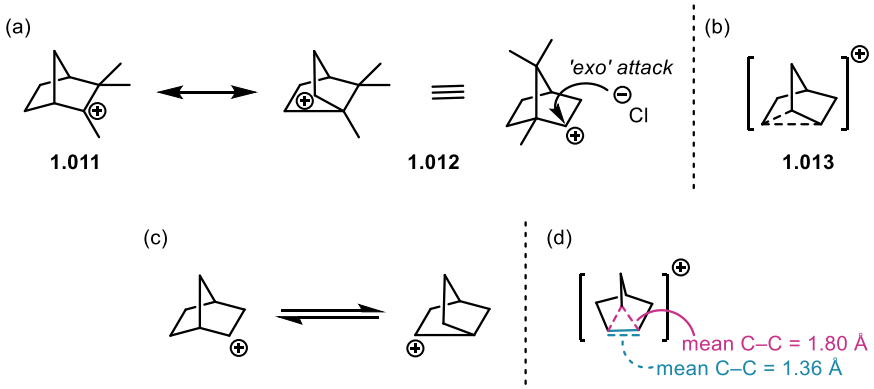


Scheme 1.03. The first proposed carbocationic reaction intermediate in the rearrangement observed by Meerwein and van Emster.

1.1.2. 2-Norbornyl Cation: The Earliest Reported Non-Classical Carbocation

When Meerwein and van Emster observed the rearrangement of **1.008** into **1.009**, they reported that the reaction can be catalyzed either by metal chlorides (such as $FeCl_3$) or hydrochloric acid. At the same time, the reaction rate was also found to be highly solvent-dependent: in nitromethane, a solvent with a high dielectric constant of 35.87[9], the conversion of camphene hydrochloride reached 65% after 3 hours at 20 °C, whereas no conversion was observed after 48 hours at 40 °C in diethyl ether (dielectric constant = 4.34[9]).[7] According to an earlier report by Hantzsch, solvents were deemed to play a role in the ionization to form carbocations;[10] therefore, the authors proposed that the reaction also proceeds through initial dissociation of chloride from the complex, forming a positively charged intermediate **1.011**.

Following their observations, further investigation of this peculiar rearrangement was conducted over the next decades. Importantly, a carbocationic intermediate such as **1.011**, with 6 valence electrons ('open sextet'), should lead to both bornyl chloride (**1.009'**) and isobornyl chloride (**1.009**) in comparable yields. However, that was not the case (see **Scheme 1.03**).[7] Therefore, Bartlett and Pöckel posed that the cationic intermediate must have spatial properties different from the previously proposed 'open sextet'.[11] Shortly after, Nevell, de Salas and Wilson proposed, for the first time, a cationic intermediate with a mesomeric structure between the camphene- (**1.011**) and isobornyl (**1.012**) form (**Scheme 1.04a**). The attack of the chloride ion thus, in agreement with prior stereochemical descriptions, occurs on the *exo*-face.[12]

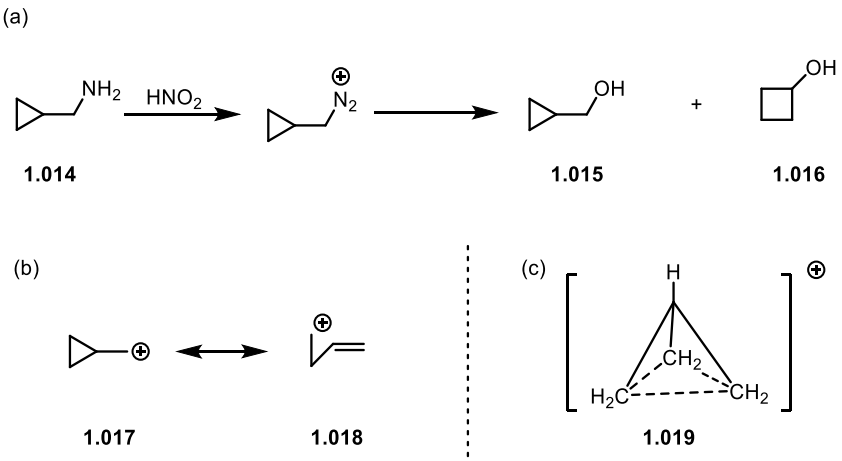


Scheme 1.04. a) Proposed mesomeric structures involved in camphene hydrochloride-isobornyl chloride rearrangement and the *exo*-attack of chloride ion. b) Proposed representation of non-classical 2-norbornyl ion. c) Brown's proposal of 2-norbonyl cation as a pair of equilibrating cations. d) Confirmation of 3-center, 2-electron bond in 2-norbonyl cation by X-ray diffraction. The mean bond length was calculated over 3 different molecules.

In 1949, Winstein and Trifan first represented the abovementioned mesomeric structure with dotted lines representing a 3-center, 2-electron bond (**Scheme 1.04b**, **1.013**), with such structures later referred to by Roberts and Mazur as 'non-classical cations' (although in a different system, described in the next section).[13] However, the nature of this bond was not fully accepted by the scientific community. For many years, Brown disagreed with the proposal of a mesomerically stabilized 'non-classical carbocation' **1.013**, to the point of describing it as a 'spectacle'.[14,15] Instead, he believed that the experimental results involving 2-norbornyl cation can simply be accounted for by a pair of rapidly equilibrating classical cations (**Scheme 1.04c**).[16] The debate continued for many years, until the X-ray crystal structure of a 2-norbornyl ion was obtained in 2013 (**Scheme 1.04d**).[17] The bridging C–C distances (magenta) in these 3-center, 2-electron bonds were determined to exceed the usual C–C single-bond length of 1.54 Å; at the same time, the basal C–C distance (blue) was measured to be close to that in benzene (1.39 Å), suggesting a partial double-bond character and thereby confirming the non-classical carbocation proposal.

1.1.3 Cyclopropylcarbinyl (CPC+) and Bicyclobutonium (BCB+) Cations

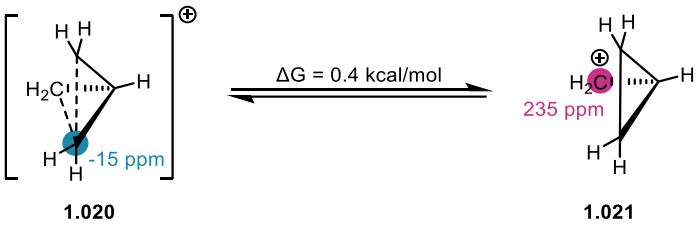
Experimental observations relating to bicyclobutonium (BCB+) ions can be traced back to 1907, when Demjanov reported a rearrangement, now named after him. By treating cyclopropylcarbinylamine (**1.014**) with nitrous acid, a mixture of cyclopropylcarbinol (**1.015**) and cyclobutanol (**1.016**) was formed (**Scheme 1.05b**).[18] In 1951, while investigating the solvolysis rates of cyclopropylcarbinyl, cyclobutyl and homoallyl chlorides, Roberts and Mazur reported the unexpectedly rapid reaction rate of cyclopropylcarbinyl chloride. This led them to propose that the $[C_4H_7]^+$-intermediate formed after solvolytic cleavage of chloride, CPC+ **1.017**, might be stabilized by its mesomeric form, the homoallyl cation (HA+) **1.018**.[19] In the same publication, they also observed that both cyclobutyl chloride and cyclopropylcabinyl chloride rearranged to homoallyl chloride using Lucas' reagent,[20] a solution of zinc chloride in concentrated hydrochloric acid. This observation led them to propose a C_{3V} pyramidal structure (**1.019**) of the $[C_4H_7]^+$ intermediate, in which the three basal methylene groups were considered to be equivalent, and the three carbons were thought to be bonded in a 3-center, 2-electron mode (**Scheme 1.05c**).[19] They described this bonding mode as 'non-classical', the term used by organic chemists ever since.



Scheme 1.05. a) Ring expansion observed by Demjanov in the eponymous rearrangement. b) Proposed stabilization of CPC+ by its mesomeric HA+ form. c) Early proposed C_{3v} structure of BCB+ ions.

However, when Mazur and co-workers later performed ^{14}C labelling experiments on the deamination of cyclopropylcarbinylamine (**1.014**) and its subsequent aqueous quenching, they realized that the unequal distribution of ^{14}C label on the resulting cyclobutanol **1.016** would preclude the earilier proposal of the pyramidal structure of $[C_4H_7]^+$ with a high C_{3v} symmetry.[21] Instead, NMR studies by Olah and co-

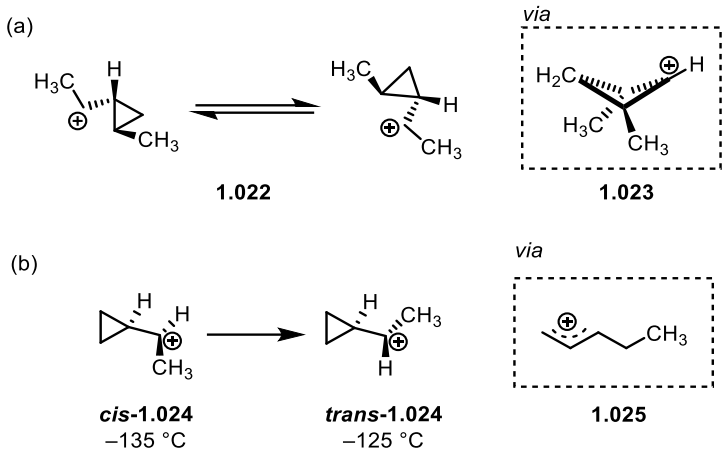
workers revealed a slight temperature dependence of its ^{13}C chemical shifts, suggesting the presence of two rapidly equilibrating structural isomers.[22] Currently, it is generally accepted that the cyclopropylcarbinyl cation $[C_4H_7]^+$ exists in fast equilibrium between a non-classical bicyclobutonium BCB+ ion (**1.020**) and a classical bisected CPC+ cation (**1.021**) (**Scheme 1.06**). The two forms were expected to be very similar energetically, within 0.5–1.5 kcal/mol from each other, as calculated from NMR data.[22] Later, a computational study by the same group reported that **1.021** is 0.4 kcal/mol higher in energy than **1.020**, in good agreement with their earlier experimental results.[23] This pair of structures was also supported by isotope labelling experiments, conducted by Saunders and Siehl, providing strong evidence for a pentacoordinated carbon in **1.020**.[24] This pentacoordinated carbon was identified by ultralow temperature magic angle spinning solid state ^{13}C NMR with a chemical shift of –15 ppm at 60 K. On the other hand, the ^{13}C signal on the positively charged carbon in **1.021** was identified at 235 ppm,[25] both in agreement with the calculated chemical shifts of –24.7 and 245.2 ppm,[26] respectively.



Scheme 1.06. Revised model of $[C_4H_7]^+$ CPC+/BCB+ ions.

However, it is worth noting that not all CPC+ cations exist in an equilibrium (non-static) with a non-classical BCB+ isomer. Their behavior is highly dependent on the substitution pattern.[27] For example, while 1-(2-methylcyclopropyl)ethyl cation (**1.022**) is considered to rearrange rapidly between, and to exist as a mixture of, two isomeric forms in equilibrium via 2,4-dimethylcyclobutyl cation (**1.023**) as an intermediate or a transition state, a non-classical BCB+ isomer has not been reported (**Scheme 1.07a**).[28] In addition, some CPC+ ions may not even exist as an equilibrium of two forms at all: (α–methylcyclopropyl)carbinyl cation (**1.024**) was recognized as static at low temperature (**Scheme 1.07b**). Whereas at –135 °C **1.024** exists in the thermodynamically more stable *cis*-configuration, it rearranges to the *trans*-isomer when the temperature is raised to –125 °C.[29] NMR studies show that the isomerization does not simply involve a rotation around the C–C bond but instead proceeds via a

1-ethylallyl cation (**1.025**).[29] These observations suggest that the substitution pattern on CPC+ ions and their isomers significantly influences their behavior.

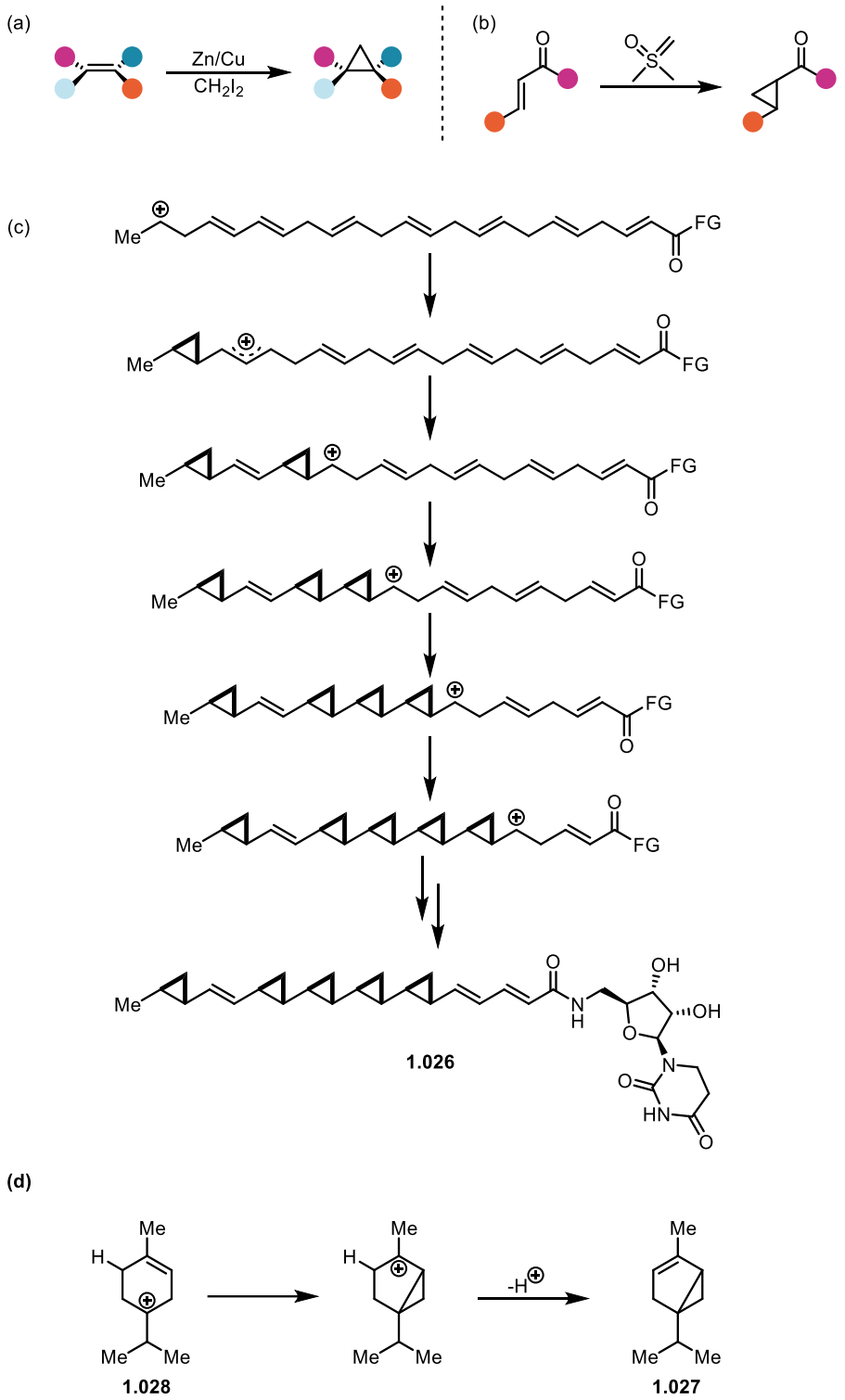


Scheme 1.07. a) A non-static secondary CPC+ ion existing in equilibrium. b) A static secondary CPC+ ion.

1.1.4 Synthetic Methodologies Involving CPC+/BCB+ Systems

Although the reactivity of the CPC+/BCB+ ion system is documented since 1907,[18] its utility in synthetic chemistry remains somewhat underappreciated.[30] Although mesomeric forms provide opportunities for skeletal rearrangements, this reactivity can also be difficult to control, leading to complex product mixtures.[31,32] With the aim of a deeper understanding of this system, extensive studies have been conducted both experimentally and computationally.[31,33,34]

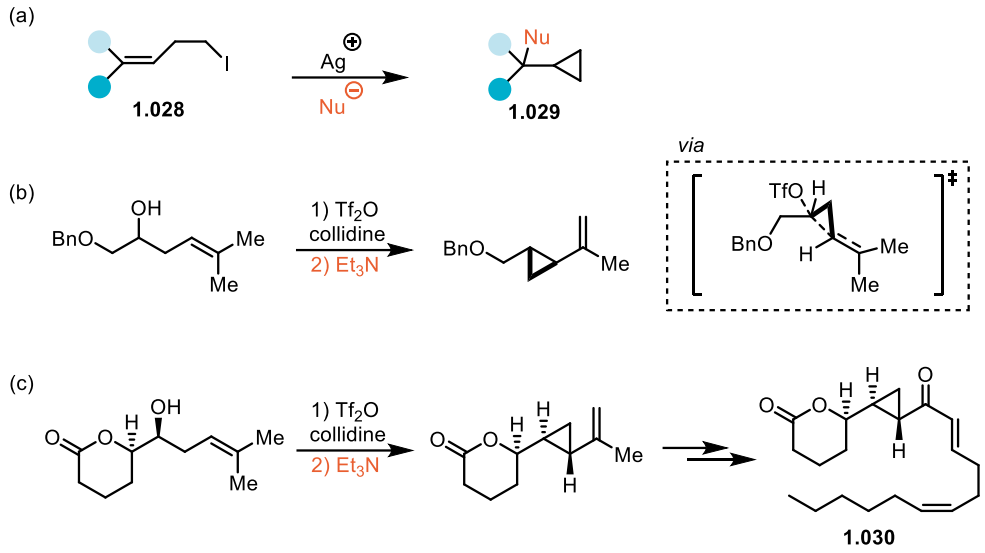
Being the smallest hydrocarbon ring, cyclopropanes possess significant ring strain.[35,36] While this strain often allows cyclopropanes to be used as key synthetic intermediates *en route* to highly functionalized molecules, it also poses challenges for the construction of these rings.[37] Most classical strategies to forge cyclopropanes rely on the use of carbenes or carbenoids, as in the Simmons-Smith[38] and Corey-Chaykovsky[39,40] reactions (**Scheme 1.08a** and **b**); nature, however, has developed different synthetic tools. FR-900848 (**1.026**), a natural antibiotic isolated from the fermentation process of *Streptoverticillium fervens,* contains numerous cyclopropane rings.[41] A possible biosynthetic pathway features a cationic cascade involving HA+/CPC+ cation interconversions (**Scheme 1.08c**).[42] Similarly, the biosynthesis of thujene **1.027** was also proposed to involve a cyclization event from homoallyl cation **1.028** (**Scheme 1.08d**).[43]



Scheme 1.08. Classical cyclopropanations: a) Simmons-Smith reaction. b) Corey-Chaykovsky reaction. Proposed biosynthesis pathways involving HA+/CPC+ interconversions: c) Biosynthesis of FR-900848. d) Biosynthesis of thujene.

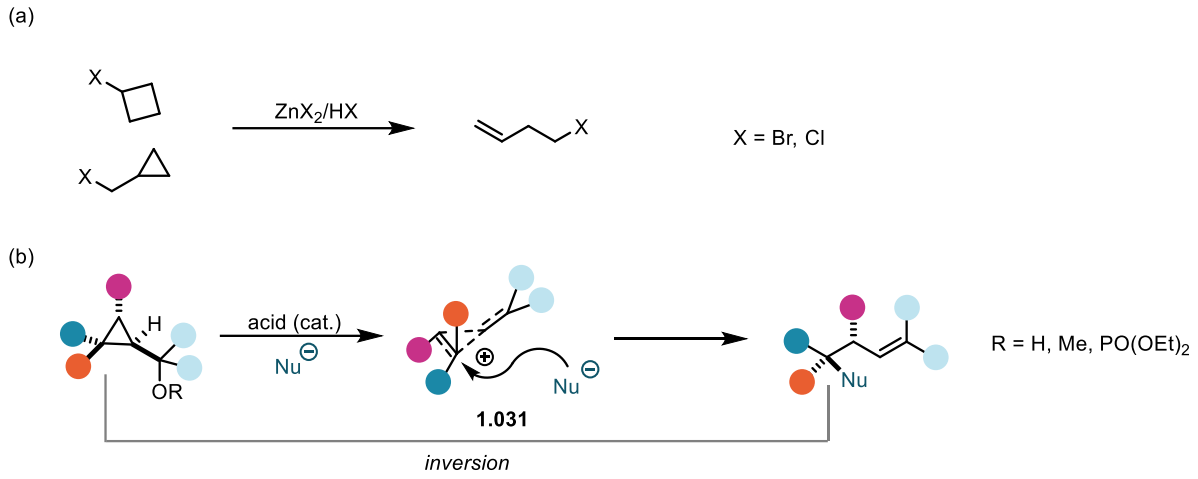
An early synthetic application of HA+ for cyclopropanation was reported by Previtera and co-workers (**Scheme 1.09a**).[44] By treating homoallyl iodide **1.028** with silver salts, cyclopropyl derivatives (**1.029**) can be obtained in near quantitative yields. In the 1990s, Suzuki and co-workers reported the

stereoselective *trans*-cyclopropanation of labile homoallyl triflates,[32] which they later used in the key step of their total synthesis of an eicosanoid natural product (**1.030**) (**Scheme 1.09b** and **c**).[45] Similar strategies are also reported by White and Yamada in their total syntheses of natural products containing cyclopropanes.[46,47]



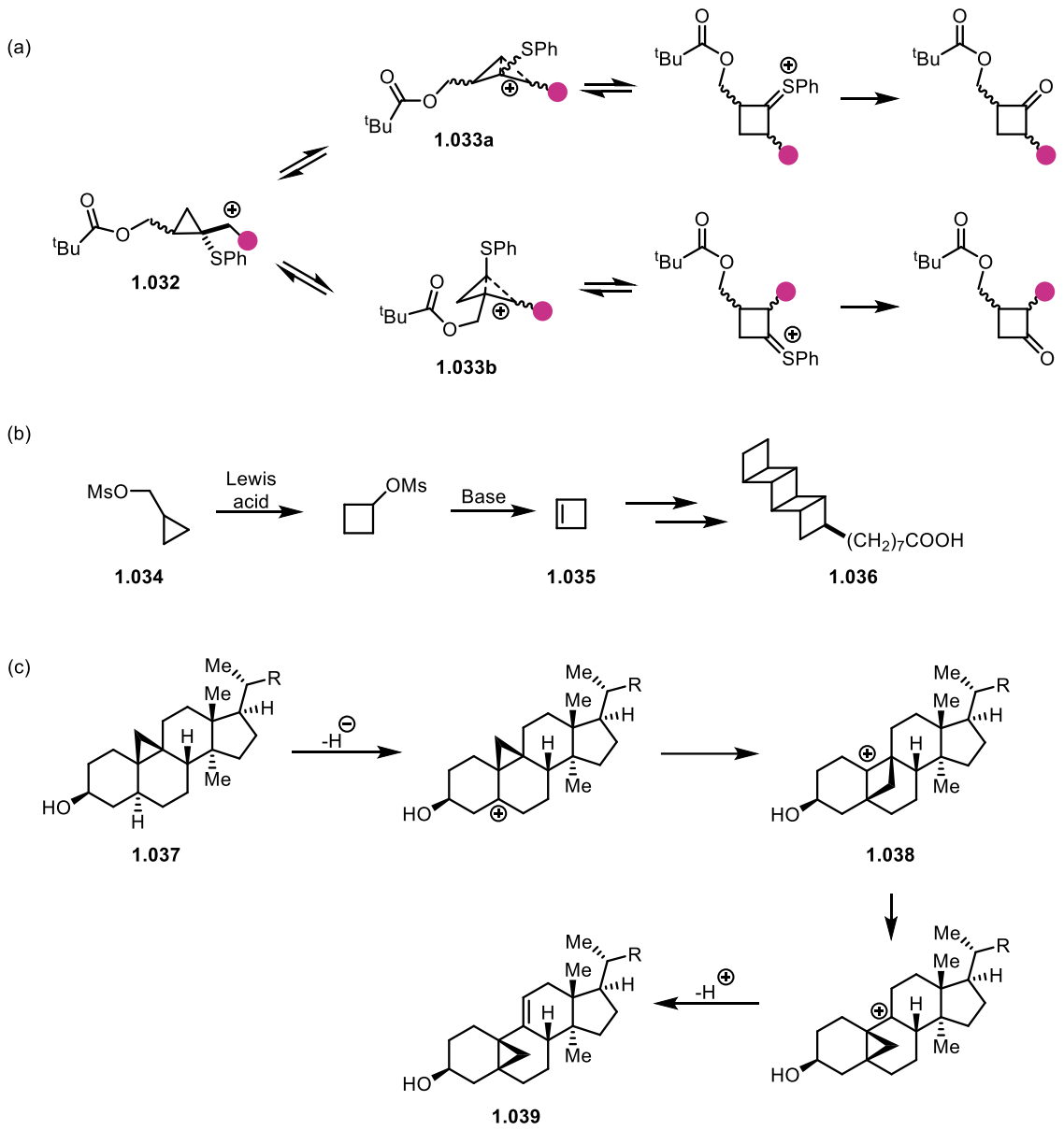
Scheme 1.09. a) Iodide abstraction from homoallyl iodide for cyclopropanation. b) Diastereoselective cyclopropanation and elimination from labile homoallyl triflate. c) Total synthesis of eicosanoid **1.030** with cyclopropanation as a key step.

On the other hand, the reverse ring-opening of cyclopropylcarbinyl precursors into homoallyl products is also well reported. After the seminal work by Roberts and Mazur, in which an equimolar mixture of cyclopropylcarbinyl and cyclobutyl halides rearranged to homoallyl halides (**Scheme 1.10a**),[48] this rearrangement started to gain popularity. Recently, Marek and co-workers reported a series of stereoselective cyclopropane ring-opening reactions leading to homoallyl products (**Scheme 1.10b**).[49–55] Generally, cyclopropylcarbinol derivatives are first treated with a Lewis or Brønsted acid catalyst, forming CPC+ intermediate **1.031**, after which a stereoinvertive nucleophilic attack occurs at the most substituted position of **1.031**.



Scheme 1.10. a) Convergent rearrangement of small-ring halides into homoallyl halides. b) Marek's cyclopropane ring-opening reactions through a CPC+ intermediate.

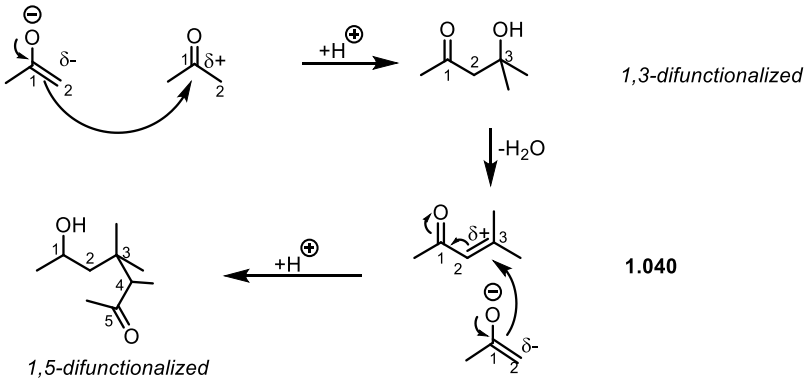
Rearrangements involving cyclobutyl intermediates have been comparably less investigated. Ornstein and Trost reported a rearrangement of CPC+ (**1.032**) into two isomeric BCB+ species (**1.033a**, **1.033b**), which eventually facilitated the synthesis of cyclobutanones (**Scheme 1.11a**).[56] More recently, Mascitti and Corey converted cyclopropylcarbinyl mesylate (**1.034**) into cyclobutene (**1.035**), which was in turn used as a key starting material in their landmark synthesis of pentacycloanammoxic acid (**1.036**).[57] A key cyclobutyl cationic intermediate was also proposed by Tantillo and co-workers in the theoretical study of the interconversion of cyclopropyl-containing sterols (**1.037** to **1.039**) in orchids, suggesting the importance of 4-membered ring cationic intermediate **1.038** in biosynthetic pathways.[58]



Scheme 1.11. a) Rearrangement of a CPC+ ion *via* BCB+ ions to form cyclobutanones. b) Synthesis of cyclobutene, a key starting material in the total synthesis of pentacycloanammoxic acid, by rearrangement of cyclopropylcarbinyl mesylate. c) Proposed biosynthesis pathway of sterol rearrangement through cyclobutyl cation intermediate.

1.1.5 Iodine(III) and Oxidative Umpolung Reaction of Carbonyls

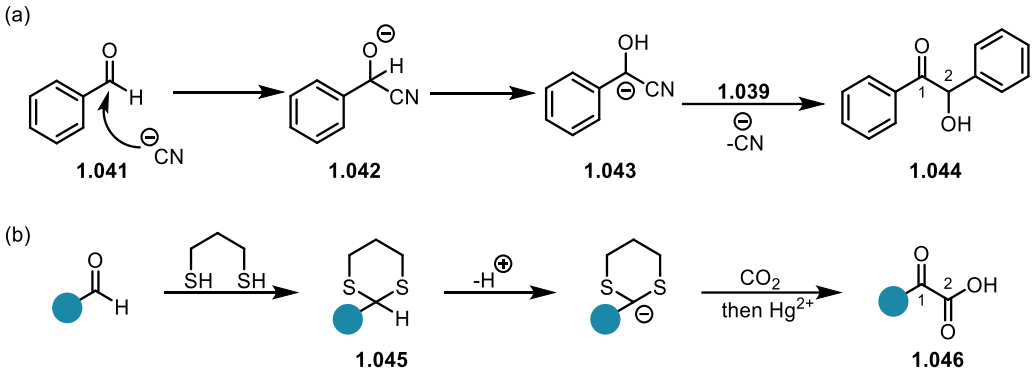
Most reactions used in organic synthesis are polar in nature, involving a nucleophile with a (partial) negative charge and an electrophile with a (partial) positive charge. The polarity of a synthon is often imposed by the position of the heteroatoms. For example, the C_1 position of a carbonyl compound is described as electrophilic, whereas the C_2 position is nucleophilic. Making use of this so-called natural polarity, the aldol reaction is a classic example of the reactivity of carbonyl compounds to construct 1,3-dioxygenated compounds (**Scheme 1.12**). When the product of aldol addition undergoes an elimination, it forms an α,β-unsaturated carbonyl **1.040**, whose C_3 position of is also described as electrophilic. It can in turn be attacked by a nucleophilic enolate in a conjugate addition to construct 1,5-functionalized products. However, the consequence of this natural polarity also poses a challenge to chemists: such addition reactions to carbonyls only lead to 1,3-, 1,5-, …1,(2n+1)-functionalized products with an odd number of carbon atoms between the functional groups. In order to synthesize 1,2- or 1,4-functionalized products, a conceptually different approach is required.[59]



Scheme 1.12. Natural polarity of carbonyls leading to 1,3- and 1,5- difunctionalized products.

Umpolung, a term coined by Dieter Seebach, refers to the reversal of natural polarity.[59] However, the experimental exemplification of this concept far predates the definition of this term. In 1832, von Liebig and Wöhler reported the now classical benzoin condensation (**Scheme 1.13a**), in which the addition of cyanide to the electrophilic C_1 of benzaldehyde (**1.041**) initially forms alkoxide **1.042**.[60] The basicity of this alkoxide, paired with the electron-deficiency of the nitrile, enable subsequent deprotonation of C_1 (forming **1.043**), effectively rendering it as a nucleophile in the construction of a 1,2-difunctionalized product (**1.044**, resulting from addition to a second equivalent of benzaldehyde). Another example of carbonyl C_1 Umpolung, established by Corey and Seebach, relies on the condensation of propane-1,3-

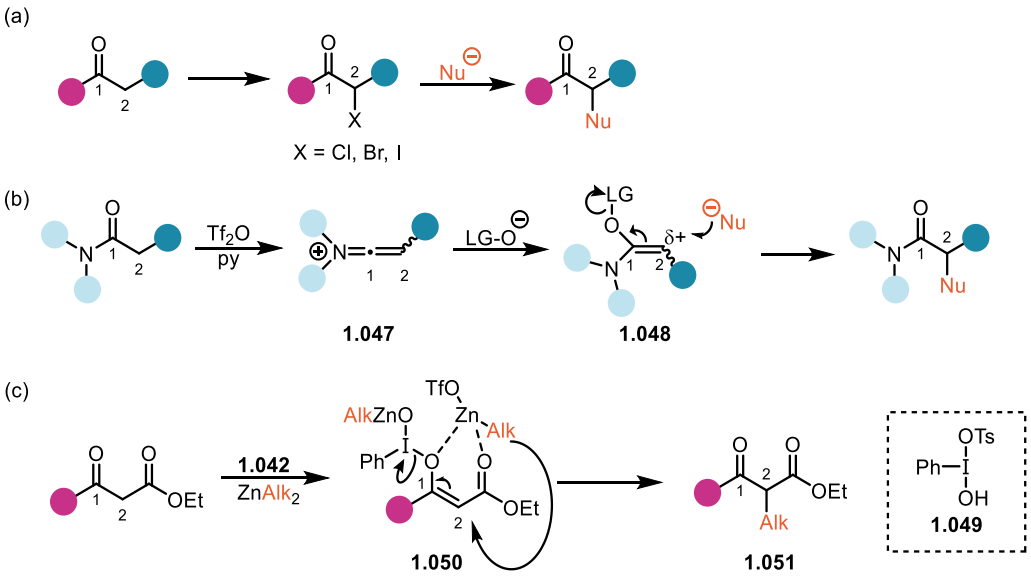
dithiol and an aldehyde (**Scheme 1.13b**). The resulting 1,3-dithiane **1.045** is susceptible to deprotonation at the original carbonyl C_1, enabling its subsequent nucleophilic attack, for example, on solid carbon dioxide to form α-keto carboxylic acids (**1.046**).[61] The chemistry of **1.045** would be extensively developed in the subsequent years for α-functionlization of carbonyls.[62]



Scheme 1.13. Umpolung of aldehyde C_1 into a nucleophile to construct 1,2-difunctionalized products. a) Benzoin condensation catalyzed by cyanide. b) Carbanion from 1,3-diathiane.

While Umpolung of carbonyl C_1 has been well researched, that of carbonyl C_2 (α-position) is less reported.[63,64] Early reports often involve a two-step process (**Scheme 1.14a**), requiring the installation of a leaving group on C_2, as can be achieved, for example, by halogenation, rendering it electrophilic.[65,66] Focussing on the Umpolung of the alpha-position of amides, Maulide and co-workers reported the interception of keteniminium ions (**1.047, Scheme 1.14b**)—generated through Tf_2O-mediated electrophilic activation—with N-oxides. The resulting species **1.048** exhibits electrophilicity on C_2 and can be thus intercepted by nucleophiles to afford α-functionalized products.[67]

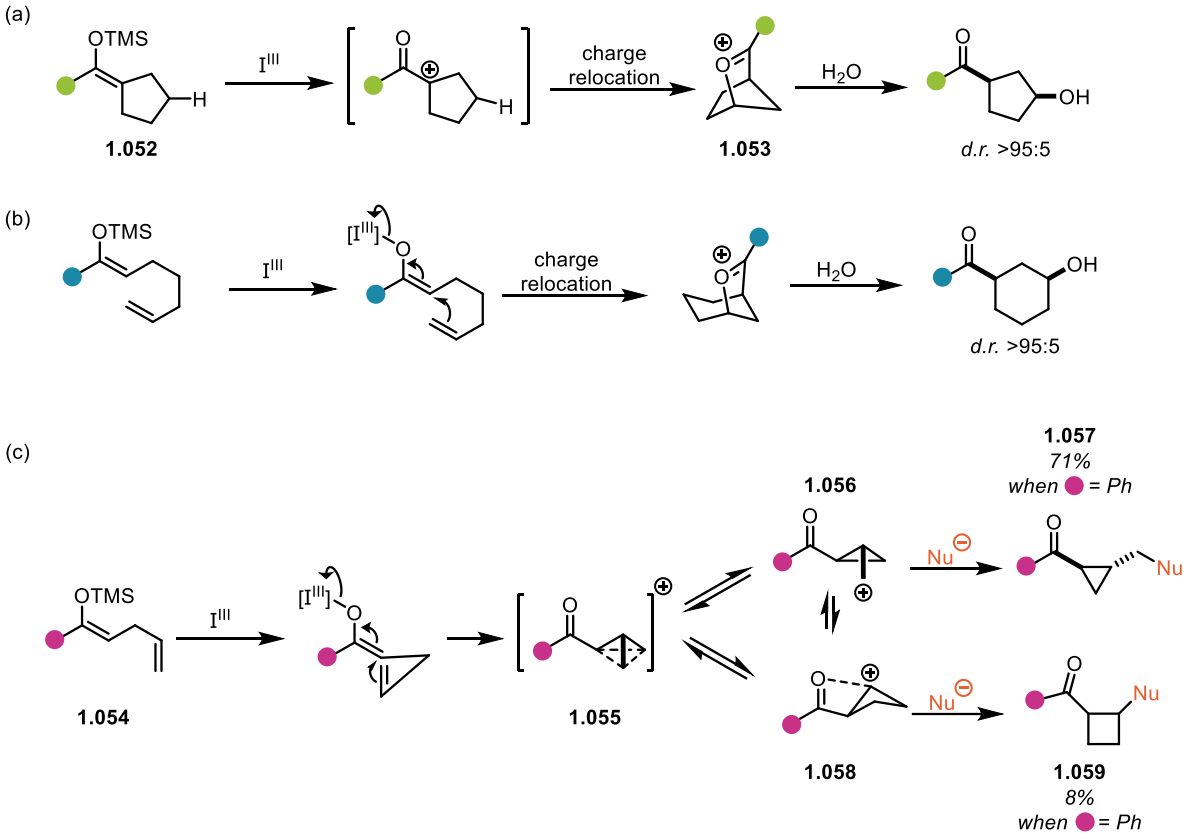
In 2015, Szpilman reported an iodine(III)-facilitated oxidative Umpolung of β-keto esters (**Scheme 1.14c**). Treating β-keto esters with Koser's reagent (**1.049**) forms iodo-enolonium ions (**1.050**), which can then be intercepted by nucleophiles, resulting in formal α-alkylation (**1.051**).[68] Later, they reported α-alkylation, heteroarylation and azidation of ketones from their silyl enol ether derivatives using the same strategy.[69,70] Subsequent extensions by them and other groups include the cross-coupling of silyl enol ethers,[71] halogenation or azidation of 1,3-dicarbonyls[72] and formal 1,2-aryl migrations.[73,74]



Scheme 1.14. Examples of C_2 Umpolung of carbonyls. a) Pre-installation of halogens on C_2 renders it electrophilic. b) Triflic anhydride-mediated electrophilic activation of amides. c) Iodine(III)-mediated oxidative Umpolung of ketones.

Maulide and co-workers recently explored intramolecular processes involving iodine(III)-mediated Umpolung (**Scheme 1.15**). The oxidation of silyl enol ether **1.052** by $(PhI)_2O(SbF_6)_2$ triggered an intramolecular charge-relocation process, leading to a stable [2.2.1] oxocarbenium ion **1.053** in a process that can be viewed as a regioselective remote C–H bond oxidation (**Scheme 1.15a**). Subsequent hydrolysis of **1.053** afforded a β-keto alcohol in good yields and with excellent diastereoselectivity.[75] On acyclic substrates, terminal olefins are also shown to be able to capture umpoled ketones, resulting in intramolecular 6-*endo-trig* cyclization. In a similar sequence of charge relocation and oxocarbenium formation, aqueous work-up led to cyclic β-keto alcohol products (**Scheme 1.15b**).[76]

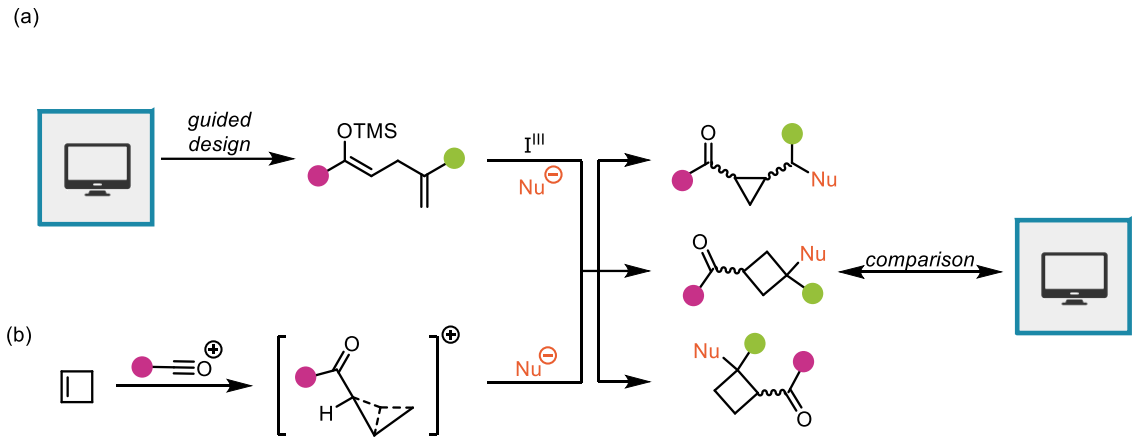
Notably, in acyclic substrates, when the terminal olefin is closer to carbonyl C_2, instead of classical cationic cyclization, non-classical carbocations can be involved. Oxidation of silyl enol ether **1.054** led to a homoallyl-cyclopropylcarbinyl system, in which the iodo-enolonium intermediate **1.055** was transformed into CPC+ ion **1.056**. Capture by external nucleophiles afforded the *trans*-configured cyclopropane derivative **1.057** as the major product. **1.056** is also proposed to be in equilibrium with cyclobutyl cation **1.058** *via* a BCB+ intermediate or transition state **1.055**, leading to *trans*-configured cyclobutanes **1.059** as the minor product**.** (**Scheme 1.15c**).[77]



Scheme 1.15. Maulide and co-worker's iodine(III)-mediated oxidative Umpolung of ketone derivatives: a) Cyclic silyl enol ether leading to remote C–H activation. b) Oxidative cyclization. c) Skeletal rearrangement from a CPC+/BCB+ system forming both cyclopropylcarbinyl products and cyclobutyl products.

1.1.6 Project Aims

Building on the the iodine(III)-mediated oxidative Umpolung of **1.046**, which produced a mixture of major product **1.049** and minor product **1.051**, this work aimed to reroute the reaction to obtain a different product distribution. DFT calculations were first employed to aid in the design of CPC+/BCB+ systems with different substituents, to identify the most stable resonance form. The substrates would then be synthesized and subsequently subjected to iodine(III) oxidation to form the expected CPC+/BCB+ systems (**Scheme 1.16a**). The experimental results would ultimately feed back and inform the computational work.



Scheme 1.16. Two different approaches to CPC+/BCB+ system.

In addition, a different method to access a similar CPC+/BCB+ system was envisaged, involving electrophilic addition of acylium ions to cyclobutene (**Scheme 1.16b**). The product distribution of this reaction would also provide valuable insights into its mechanism.

1.2 Results and Discussion

The results discussed in this section were acquired in collaboration with Dr. Zhi-Jie Niu (experimental), Dr. Philipp Spieß (experimental) and Aymen Benchouche (theoretical), and a part of the work has been submitted for publication.

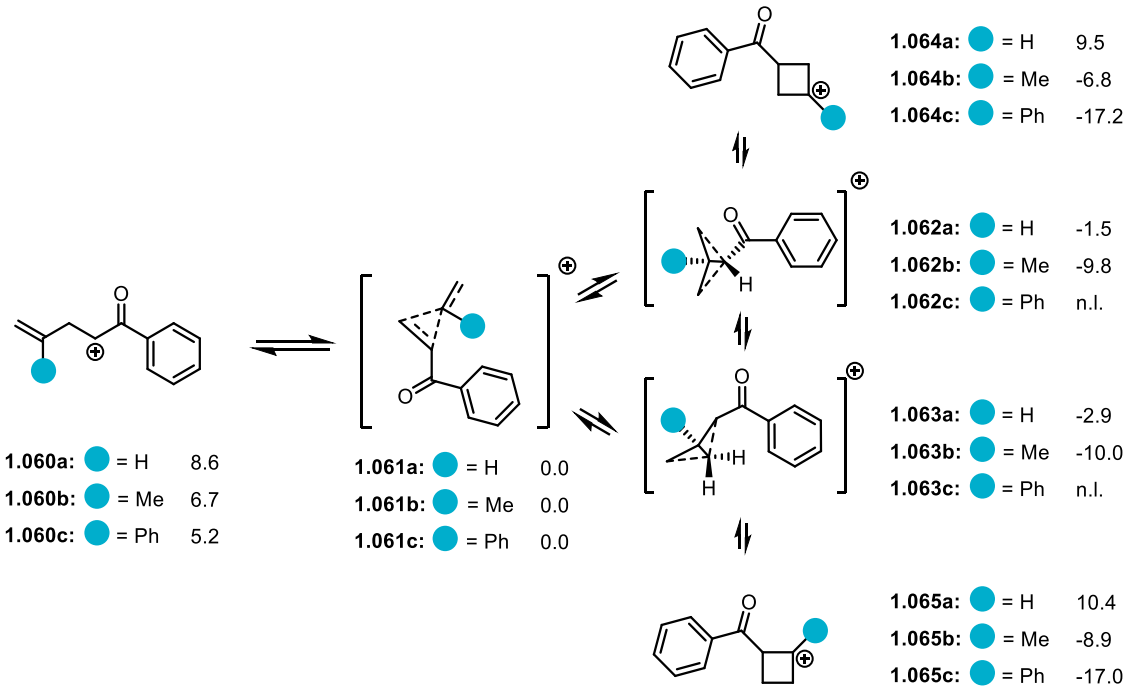
1.2.1 Early Computational Models of BCB+ and Related Cations

Computational work in this section was performed by Aymen Benchouche under the supervision of Prof. Pier Alexandre Champagne, in New Jersey Institute of Technology, United States of America.

Inspired by the work of the Maulide group in 2020 (**Scheme 1.15c**),[77] a computational study was conducted to investigate the energies of HA+ (**1.060**) and the proposed BCB+ key intermediates (**1.062** and **1.063**) together with the isomeric CPC+ (**1.061**) and cyclobutyl (CB+) cations (**1.064** and **1.065**) (**Scheme 1.17**).[1]

For the hydrogen-substituted system, it was found that the BCB+ (**1.062a**, **1.063a**) and CPC+ (**1.061a**) cations are both found as energy minima, less than 3 kcal/mol apart from one another. CB+ (**1.064a**, **1.065a**) ions are energetically unfavourable, consistent with earlier experimental observation of the cyclobutane (**Scheme 1.15c**, **1.059**) being the minor product. However, when a methyl substituent was added, the CPC+ ion (**1.061b**) was no longer a minimum energy species, and the energy gap between **1.061b** and BCB+ (**1.062b** and **1.063b**) ions increased to almost 10 kcal/mol. CB+ ions (**1.064b, 1.065b**) are now also energetically more favourable than CPC+ ions. Even more interestingly, when a phenyl substituent was added, low-lying 1,2- and 1,3-CB+ ions were directly located as minima (**1.064c** and **1.065c**) at -17.0 and-17.2 kcal/mol, respectively.

[1] The energies reported in Scheme 1.17 are early results directly from structure optimization. As no single-point energies were computed at a higher level of theory for optimized structures, these results should be taken with caution. Further computational results will be discussed in later sections.



Scheme 1.17. Computed free energies of the isomeric form of BCB+ ions. Calculations were performed at the ωB97XD/6-31+G(d,p)/SMD(dichloromethane) level of theory. Energies were reported in kcal/mol. n.l. = not located.

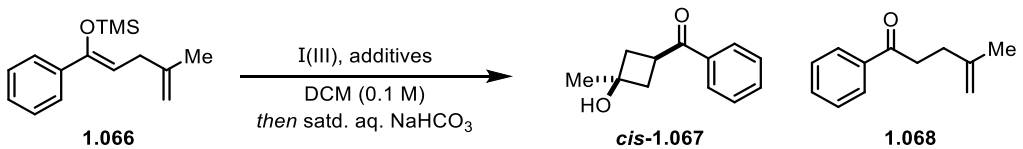
The early computational investigation suggested that the substitution pattern plays a large role in the stability of this BCB+ ion and its isomeric forms. Therefore, by altering the substitution pattern, the I(III)-mediated oxidative Umpolung reaction may be rerouted to produce 1,2- or 1,3-disubstituted cyclobutanes as the major products.

1.2.2 Bicyclobutonium ions formed by iodine(III)-mediated oxidative Umpolung

1.2.2.1 Optimization and Preliminary Results

Following theoretical models, silyl enol ether **1.066** was chosen as the first model substrate for optimization. Several reaction parameters were investigated, including the I(III) source, reaction time and quenching (**Table 1.1**). Initially, iodosylbenzene was chosen as the I(III) source, with methanesulfonic acid as the activator and boron trifluoride etherate to lower the nucleophilicity of the anions in the reaction system. While freshly-synthesized iodosylbenzene[78] (**Entry 1**) resulted in significant hydrolysis of **1.066** to ketone **1.068**, iodosylbenzene dried in a desiccator for 48 hours and longer reaction times triggered only minimal hydrolysis with significant amounts of a cyclized product (**1.067**) (**Entry 2**). To our surprise, while the theoretical study had suggested that both 1,2- and 1,3-disubstituted cyclobutane products can be formed, we only observed 1,3-disubstituted cyclobutanols from the reaction. In the crude NMR, both diastereomers were detected, with a *cis/trans* ratio of approximately 2.6:1; however, only the ***cis*-1.059** could be isolated at this reaction scale (and reported yields refer only to this isomer).

Swapping the additive to tetrabutylammonium iodide led only to hydrolysis (**Entry 3**) and changing the iodine(III) source to $[(PhI)_2O][SbF_6]_2$ was not productive (**Entry 4**), as this iodine source required a much higher temperature to dissolve and led exclusively to unspecific decomposition of **1.066**. Using iodobenzene diacetate (PIDA) (**Entry 5**) or (bis(trifluoroacetoxy)iodo)benzene (PIFA) (**Entry 6**) led to slightly diminished yields.



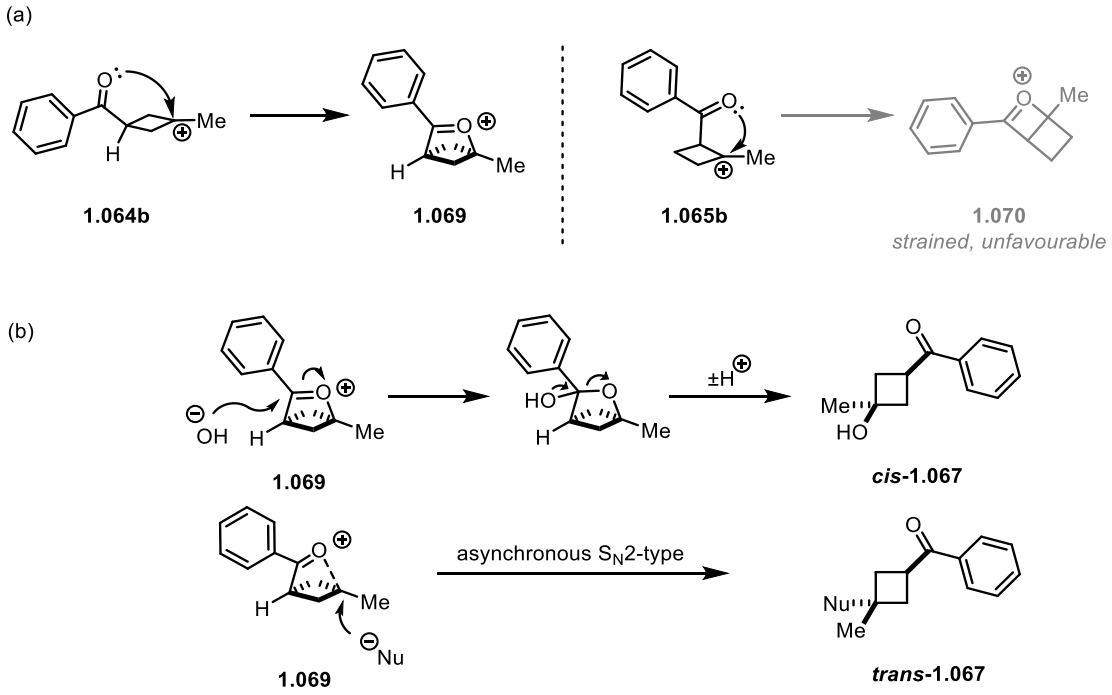
1.066 **cis-1.067** **1.068**

Entry	I(III) source	Equiv.	Additives and equiv.	T/°C	t	Yield ***cis*-1.067**/%	d.r. of **1.067**	Yield **1.068**/%
1	PhIO[a]	1.2	MsOH, 1.3 equiv.; BF_3OEt_2, 1.5 equiv.	-78	15 min	[28]	>20:1	77

2	**PhIO[b]**	**1.2**	**MsOH, 1.3 equiv.; BF_3OEt_2, 1.5 equiv.**	**-78**	**1 h**	**46 [41]**	**2.6:1**	**n.d.**
3	PhIO[b]	1.2	TBAI, 2 equiv.	-78	1 h	n.d.	-	65
4	$[(PhI)_2O][SbF_6]_2$	0.5	N.A.	-10	5 min	Unspecific decomposition		
5	PIDA	1.2	BF_3OEt_2, 1.5 equiv.	-78	1 h	44 [38]	2.1:1	n.d.
6	PIFA	1.2	BF_3OEt_2, 1.5 equiv.	-78	1 h	33	1.4:1	n.d.

Table 1.1. Optimization of I(III)-mediated oxidative Umpolung reaction. All reactions were conducted at 0.20 mmol scale and were performed under argon. Yields and d.r. were determined by quantitative ^{1}H NMR using dibromomethane as the internal standard. Isolated yields in square brackets. a) PhIO dried on high-vaccum for 1 h. b) PhIO dried in evacuated desiccator for 48 h.

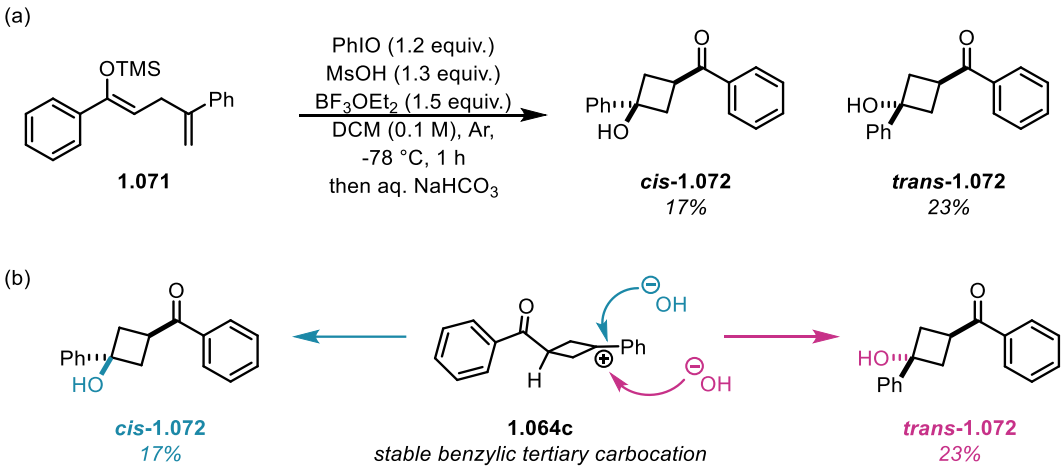
This unexpected regioselectivity suggests an additional stabilization mechanism for 1,3-CB+ **1.064b**. We postulated that, in agreement with recent literature,[75,76,79–81] the carbonyl oxygen can coordinate to the carbocation ion in **1.064b**, forming a bridged-ring [2.1.1] oxocarbenium ion **1.069**. (**Scheme 1.18a**); in contrast, for 1,2-CB+ **1.065b**, stabilization by carbonyl coordination would form a [4,4]-fused ring species **1.070**, expected to be energetically less favourable.



Scheme 1.18. a) Formation of stable oxocarbenium intermediate **1.069** from 1,3-CB+ **1.064b**, and an unstable intermediate (**1.070**) from 1,2-CB+ **1.065b**. b) Hydrolysis of oxocarbenium **1.069**.

Notably, the existence of stable intermediate **1.069** also allows rationalization the observed diastereoselectivity. In line with previous results,[75,76,79] oxocarbenium ions readily hydrolyze through attack of water or hydroxide on the carbonyl carbon (via a hemiacetal intermediate) to yield *cis*-configured products (**Scheme 1.18b, top**). Given the expected strain of the system and the additional carbocation stabilization exerted by the methyl group—rendering the cation tertiary—we postulated an asynchronous S_N2-type attack, displacing the coordinated carbonyl, to be the major pathway leading to the *trans*-configured product (**Scheme 1.18b, bottom**).

The optimized conditions were then applied to the phenyl-substituted substrate **1.071**, another species investigated computationally. Again, only 1,3-disubstituted cyclobutanols (**1.072**) and no other regioisomers were observed. However, the diastereoselectivity was inversed with a *cis/trans* ratio of 0.66:1 by crude NMR, and 17% and 23% isolated yield, respectively (**Scheme 1.19a**). This can be attributed to a better stabilization of the tertiary carbocation by the phenyl substituent, thereby rendering carbonyl coordination non-essential. In this case, the nucleophilic capture of likely follows an S_N1-pathway, where the *anti*-attack is expected to be slightly more favourable for steric reasons (**Scheme 1.19b**).

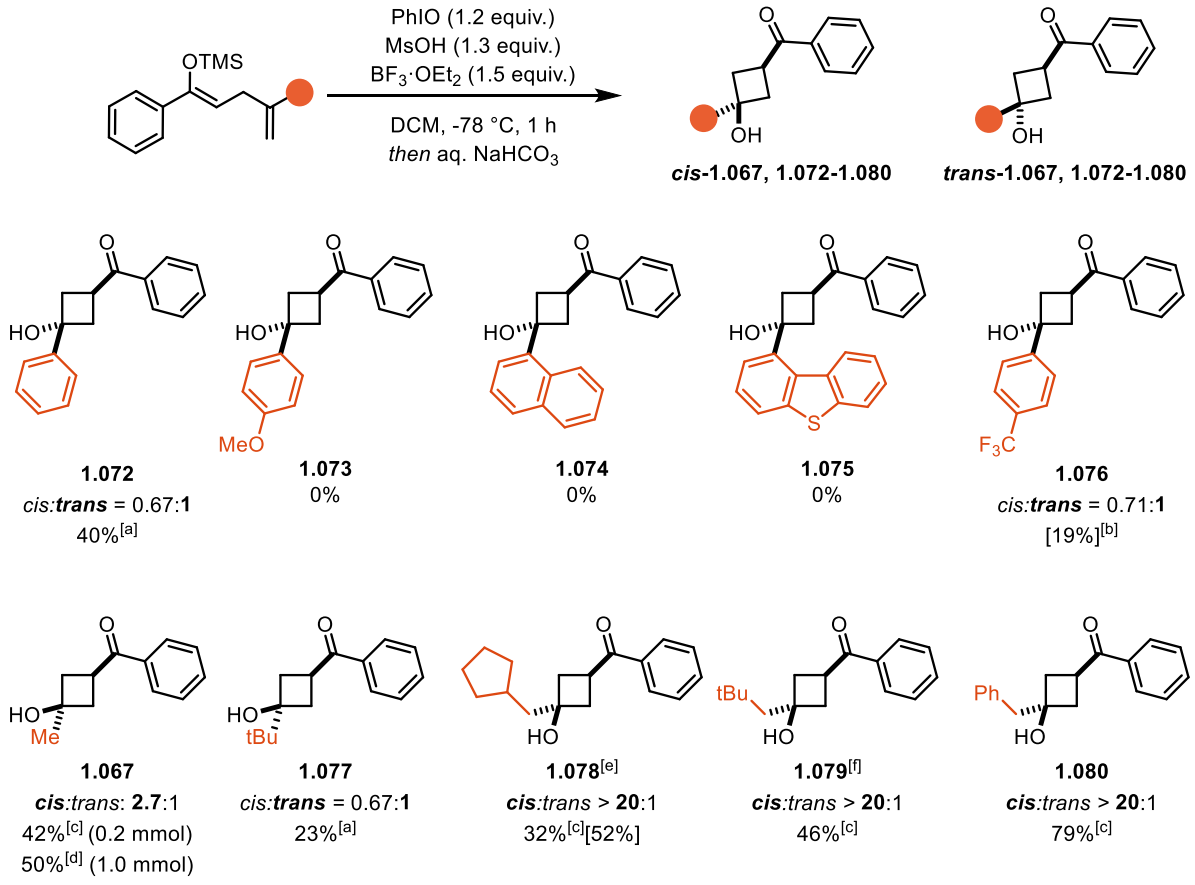


Scheme 1.19. a) Iodine(III)-mediated oxidative Umpolung of **1.071** led to an inversed diastereoselectivity. b) Capture of stable carbocation **1.064c** by hydroxide.

With these initial results in hand, the scope of the reaction was examined. By varying the electronic and steric properties of the ketone and alkene substituents, we aimed to obtain a comprehensive picture of the system at hand.

1.2.2.2 Reaction Scope

First, the effect of alkene substituents was examined. While we expected that aromatic substituents with different electronic properties might modulate the stability of the benzylic tertiary carbocation, to our surprise, all electron-rich aromatic substituents, apart from the phenyl group, afforded no detectable products (**Scheme 1.20**, **1.073–1.075**). We propose that this might be attributed to oxidation of the electron-rich conjugated π system by the strongly oxidative reaction conditions, leading to unspecific decomposition. A low yield of product **1.076** was identified by crude NMR when a substrate bearing an electron-poor *para*-trifluoromethylphenyl group was tested. However, isolation of the products by column chromatography on silica gel was unsuccessful.

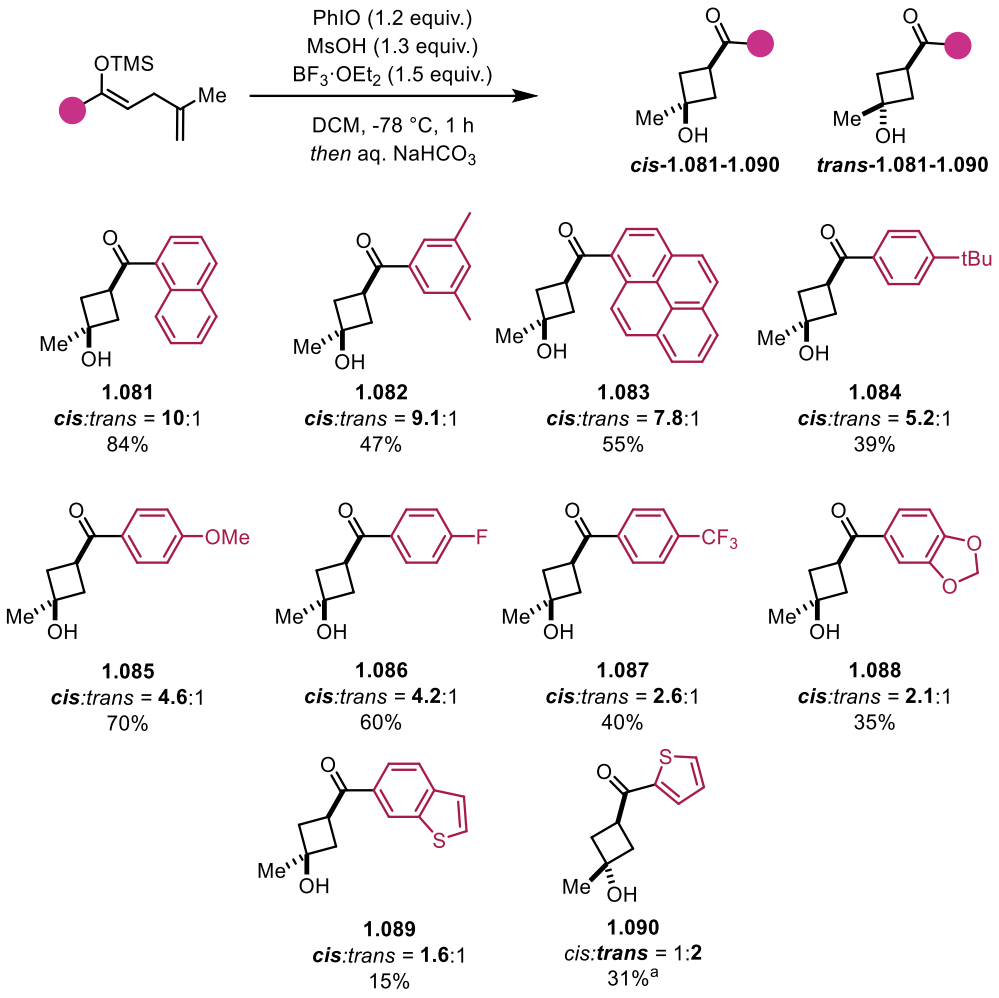


Scheme 1.20. Scope of alkene substituents. All reactions were carried out on 0.20 mmol scale, unless otherwise specified. The *cis/trans* ratio was determined by crude ^{1}H NMR. NMR yields, obtained using dibromomethane as the internal standard, are reported in square brackets. [a] Total isolated yield of both diastereomers. [b] Total NMR yield of both diastereomers. Isolation of products was unsuccessful. [c] Isolated yield of the *cis*-configured product. [d] Isolated yield of the *cis*-configured product. The *trans*-configured product was isolated as a tertiary mesylate in 19% yield. [e] Reaction carried out on 0.10 mmol scale. [f] Reaction carried out on 0.055 mmol scale.

In contrast, aliphatic substituents were better tolerated. A *tert*-butyl substituent, another group known to stabilize adjacent positive charges, behaved similar to a phenyl substituent, leading to a *cis/trans* ratio of 0.67:1 and afforded **1.077** in 23% yield as an inseparable diastereomeric mixture. Furthermore, methylenecyclopentyl (**1.078**), neopentyl (**1.079**) or benzyl (**1.080**) substituents all led to the exclusive formation of *cis*-configured cyclobutanols in moderate to excellent yields. We attribute the excellent diastereoselectivity to the fact that the tertiary carbocation in the corresponding intermediates is inherently less stabilized compared to phenyl and *tert*-butyl substituted ones. This leads to a larger degree of additional stabilization through bridging of the carbonyl oxygen, favoring the cyclic oxocarbenium intermediate, the selective hydrolysis of which (through hemiacetal formation and collapse) leads exclusively to the *cis*-configured isomer. Finally, a scale-up of the reaction leading to **1.067** afforded a similar yield of the *cis*-configured isomer. In addition, the *trans*-diastereomer was isolated from the large-scale reaction as the tertiary mesylate (***trans*-1.067-OMs**), which survived both the basic aqueous work-up and purification by silica column chromatography.

Next, substituents on the ketone moiety were examined (**Scheme 1.21**). Electron-rich aromatic groups such as naphthyl (**1.081**), 3,5-dimethylphenyl (**1.082**), pyrenyl (**1.083**), 4-*tert*-butylphenyl (**1.084**) and 4-methoxyphenyl (**1.085**), owing to their relative electron-richness, were expected to enhance the availability of the lone pair of electrons on the carbonyl oxygen, hence allowing easier formation of the bridged oxocarbenium ion. As expected, cyclobutanols **1.081–1.085** were indeed formed with good to excellent diastereoselectivity. On the other hand, electron-withdrawing aromatic groups, such as 4-fluorophenyl and 4-trifluoromethylphenyl (**1.086, 1.087**) reduce the lone-pair availability on the carbonyl oxygen and hence its bridging ability. We therefore expected a lower degree of formation of the oxocarbenium ion, and hence a lower *cis:trans* ratio. Although methylenedioxy (**1.088**) and 6-benzothiophenyl (**1.089**) groups are expected to be electron-rich and leading to a high *cis:trans* ratio, they only afforded a low diastereoselectivity. We postulate that the oxygen or sulfur atoms may coordinate to the Lewis-acidic BF_3 present in reaction mixture, reducing the electron density and switching them to electron-poor substituents. The most extreme case was seen on 2-thienyl substituent (**1.090**), which, afforded the *trans*-isomer as the major product detected by crude ^{1}H NMR. However, only the minor *cis*-isomer was isolated cleanly as the cyclobutanol. A large proportion of the major *trans*-

product decomposed on column, leaving only 18% to be isolated as the tertiary mesylate ***trans*-1.090-OMs**. The observation of *trans*-tertiary mesylates will be discussed in more detail in the next section.

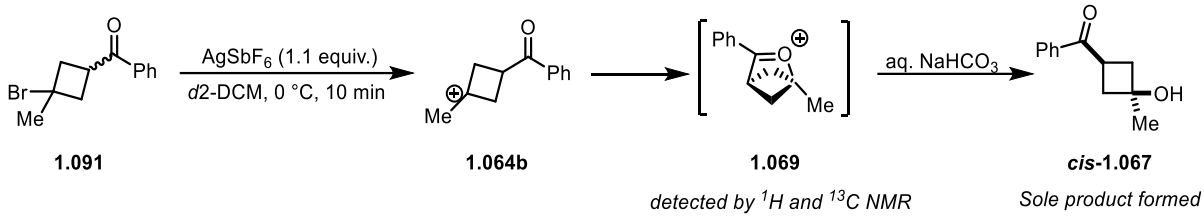


Scheme 1.21. Scope of ketone substituents. All reactions were carried out on 0.20 mmol scale. The *cis/trans* ratio was determined by crude ^{1}H NMR using dibromomethane as the internal standard. Yields refer to isolated yields of the *cis*-configured product. [a] The *trans*-configured product was isolated in 18% as the tertiary mesylate. This observation is discussed in more detail in section 1.2.2.3.3.

1.2.2.3 Mechanistic Discussions and Control Experiments

1.2.2.3.1 Characterisation of the [2.1.1] Bridged Oxocarbenium Intermediate

Given the proposal of an oxocarbenium ion **1.069** as the key intermediate in the reaction, its characterisation would be paramount to prove the proposed mechanism. However, due to the presence of BF_3 and low reaction temperature, obtaining *in-situ* NMR spectra of the reaction mixture was not feasible. Therefore, we aimed to form 1,3-CB+ **1.064b** by bromide abstraction from **1.091** using silver hexafluoroantimonate, hoping that a 'locking' event would occur to form the proposed oxocarbenium intermediate **1.069** (**Scheme 1.22**).[79]



Scheme 1.22. Formation of oxocarbenium **1.061** following bromide abstraction and subsequent hydrolysis to form *cis*-cyclobutanol **1.059**.

Indeed, oxocarbenium **1.069** can be detected by ^{13}C NMR at 0 °C (**Figure 1.1**). The resonance assigned to the quaternary carbon (green) at 82.6 ppm points to a bridged oxocarbenium ion instead of a trivalent carbocation.[76,80] Comparing with the ^{13}C signal at 201.1 ppm (magenta) for *cis*-cyclobutanol **1.067**, the carbonyl signal at 219.7 ppm (yellow) also points to a more deshielded carbonyl involved in bridging.[80]

Furthermore, an aqueous work-up of the reaction solution led to the formation of one single diastereomer, ***cis*-1.067**, consistent with the reported behaviour of oxocarbenium ions.[75,76,79,80] It is also noteworthy that the reactions shown in **Scheme 1.20** and **1.21** have lower diastereoselectivities, which can be attributed to the coordination of Lewis acid BF_3 in reaction medium to carbonyl oxygen, thereby impairing its ability to form the bridged intermediate **1.069**.

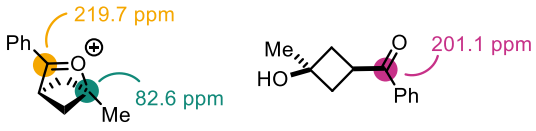


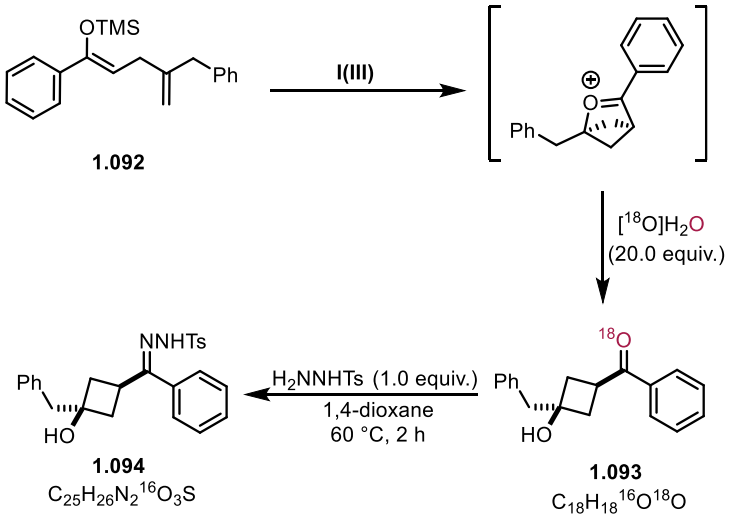
Figure 1.1. Comparison of ^{13}C NMR resonances of oxocarbenium **1.069** and product ***cis*-1.067**.

1.2.2.3.2 ^{18}O Labelling Experiments

In section 1.2.2.1, two different pathways for the formation of the observed products were proposed, depending on the degree of carbonyl oxygen bridging to form a stable oxocarbenium ion.

For tightly bound oxocarbenium ion intermediates, the major product was proposed to be formed during hydrolysis following a pathway in which the incoming nucleophile (hydroxide or water) attacks the carbonyl carbon (see **Scheme 1.18b**). Following the collapse of the tetrahedral intermediate, the carbonyl oxygen would be that of the incoming nucleophile.

To validate the mechanism, we chose substrate **1.092** which afforded the corresponding product with a high yield and a *cis*/*trans* ratio of >20:1, indicating hydrolysis of a closed oxocarbenium intermediate. While the iodine(III)-mediated oxidative Umpolung step was conducted exactly as described in previous sections, the reaction was quenched by the addition of 20 equivalents of $[^{18}O]H_2O$, instead of saturated aqueous sodium bicarbonate (**Scheme 1.23**).



Scheme 1.23. ^{18}O labelling experiment of substrate **1.092**.

While the singly-labelled cyclobutanol **1.093** can be isolated from the reaction and confirmed by HRMS[2] (**Figure 1.2a**), we were unable to ascertain the position of ^{18}O by ^{1}H or ^{13}C NMR. Therefore, the ketone was derivatized into hydrazone **1.094** by condensation with *p*-tosylhydrazide in a neutral, aprotic solvent.

[2] HRMS: ESI$^+$, exact mass calculated for $[M+Na]^+$ ($C_{18}H_{18}Na^{16}O^{18}O^+$) requires *m*/*z* 291.1241, found *m*/*z* 291.1242. The peak at 289.1198 stems from exchange under HRMS measurement conditions, which included non-labelled water.

The oxygen label was no longer detected by HRMS (**Figure 1.2b**) in hydrazone **1.094**[3], pointing to an ^{18}O carbonyl label in **1.093**.

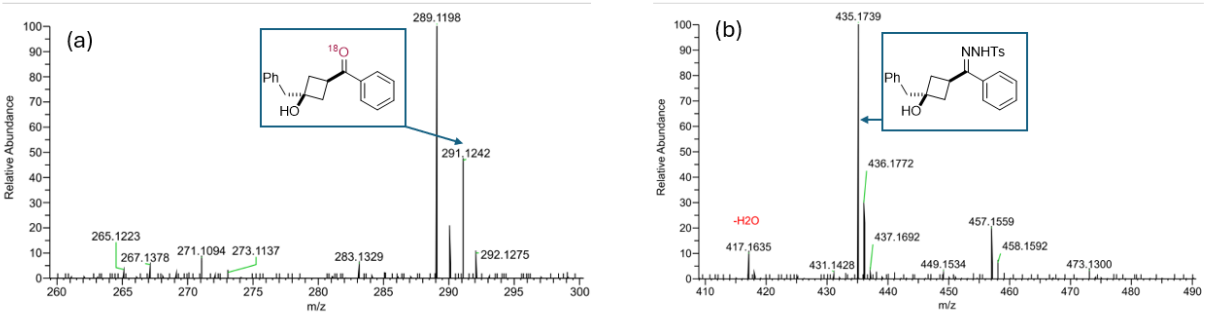


Figure 1.2. a) HRMS spectrum of cyclobutanol **1.093**. b) HRMS spectrum of hydrazone **1.094**.

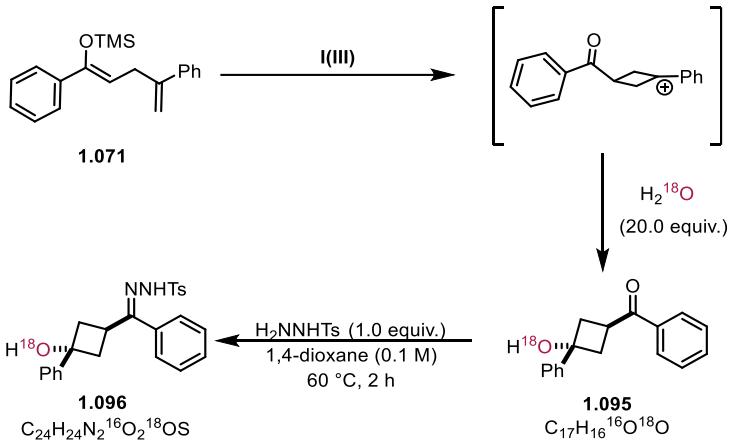
In another reaction pathway, when the open tertiary carbocation is sufficiently stabilized by an aromatic group, the stabilization of carbonyl bridging is proposed to be minimal. In this case, the products can be formed directly by S_N1-type nucleophilic attack from both faces (slightly favoring addition *anti*- to the ketone, see **Scheme 1.18b**). In these products, the hydroxyl oxygen stems from the nucleophile.

To validate this hypothesis, substrate **1.071** (leading to product mixture *cis:trans* = 0.67:1) was chosen for the same labelling experiment (**Scheme 1.24**). A singly-labelled, *trans*-configured product **1.095** was isolated and confirmed by HRMS[4] (Figure 1.3). Upon derivatization to hydrazone **1.096**, the oxygen label was retained[5], proving that cyclobutanol **1.095** was labelled on the hydroxyl position. Therefore, we conclude that ***cis*-1.072** and ***trans*-1.072** was formed by direct, S_N1-type nucleophilic attack on the carbocation.

[3] HRMS: ESI^+, exact mass calculated for $[M+H]^+$ ($C_{25}H_{27}N_2{}^{16}O_3S^+$) requires *m*/*z* 435.1737, found *m*/*z* 435.1739. To avoid scrambling of the potential ^{18}O label in aqueous work-up, the HRMS measurement was done directly from crude reaction mixture.

[4] HRMS: ESI^-, exact mass calculated for $[M-H]^-$ ($C_{17}H_{15}{}^{16}O^{18}O^-$) requires *m*/*z* 253.1120, found *m*/*z* 253.1125.

[5] HRMS: ESI^+, exact mass calculated for $[M+H]^+$ ($C_{24}H_{25}N_2{}^{16}O_2{}^{18}OS^+$) requires *m*/*z* 423.1623, found *m*/*z* 423.1625. To avoid scrambling of ^{18}O label in aqueous work-up, the HRMS measurement was done directly from crude reaction mixture. The peak at 421.1582 stems from exchange under the conditions of the HRMS measurements, which included non-labelled water.



Scheme 1.24. ^{18}O labelling experiment of substrate **1.071**.

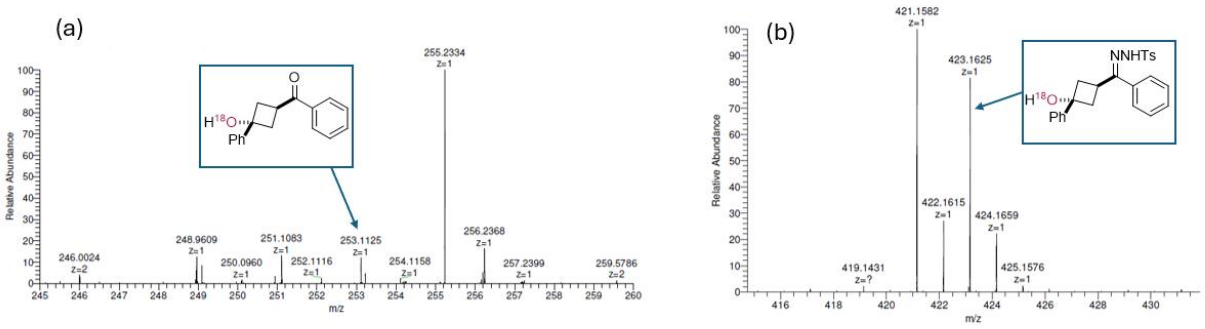
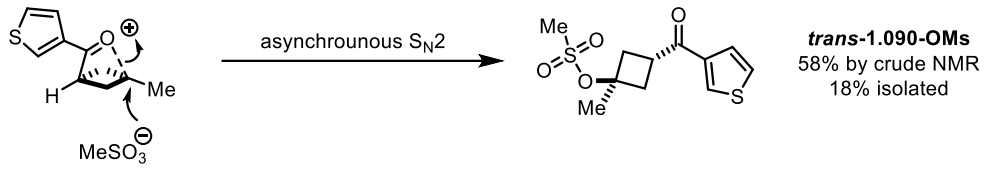


Figure 1.3. a) HRMS spectrum of cyclobutanol **1.095**. b) HRMS spectrum of hydrazone **1.096**.

1.2.2.3.3 Formation of Tertiary Mesylates and Their Stability

For the scope entries in section 1.2.2.2, both *cis*- and *trans*-configured products can be identified by crude NMR. However, except for **1.072** and **1.077**, after column chromatography, only the *cis*-configured cyclobutanol was isolated, which we hypothesize to stem from the hydrolysis of bridged oxocarbenium intermediate.

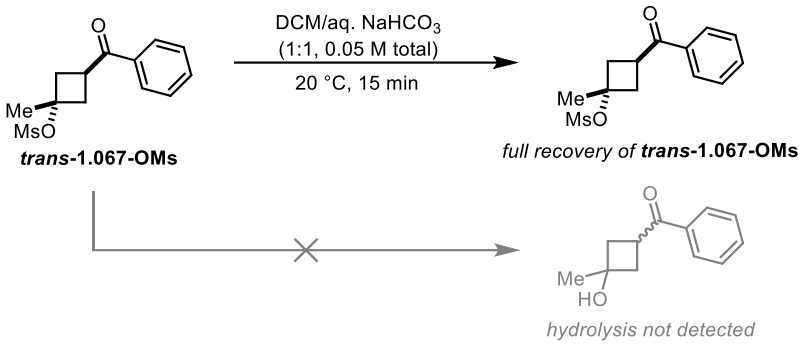
However, in the case of a 2-thienyl-substituted ketone **1.090**, the *trans*-configured tertiary mesylate ***trans*-1.090-OMs** was isolated in 18% yield. It is hypothesized that this product originates from a direct asynchronous S_N2-type attack of mesylate, present in the reaction mixture prior to aqueous work-up (**Scheme 1.25**). The reaction is described as S_N2-like instead of S_N1, as *trans*-mesylate was the sole side product observed, and no *cis*-mesylate was observed. In this case, the carbonyl remains coordinated to a certain extent, thereby preventing the *syn*-mesylate attack.



Scheme 1.25. Formation of ***trans*-1.090-OMs**.

It is also worth noting that, even though ***trans*-1.090-OMs** was observed as the major product in crude NMR, only a small amount was isolated from column chromatography. This can be attributed to the instability of tertiary mesylates on silica.

In a different case, ***trans*-1.067-OMs** was observed as a minor product and subsequently isolated when the reaction was scaled up to 1.0 mmol. To understand whether the mesylate can be hydrolyzed during work-up with a saturated aqueous solution of $NaHCO_3$, the freshly isolated mesylate was subjected again to work-up conditions (**Scheme 1.26**): in this experiment, no hydrolysis of ***trans*-1.067-OMs** was observed by crude ^1H NMR.



Scheme 1.26. Examining stability of ***trans*-1.067-OMs** under aqueous work-up conditions.

Therefore, we are confident that, when the oxocarbenium intermediate is stable enough, the products observed and isolated originate only either from the hydrolysis in which the carbonyl is attacked (*cis*-alcohols) during work-up, or from asynchronous S_N2-type attack of mesylates (*trans*-mesylates) before work-up. The tertiary *trans*-configured mesylates are stable and do not contribute to the formation of *cis*- or *trans*-cyclobutanols upon basic aqueous work-up.

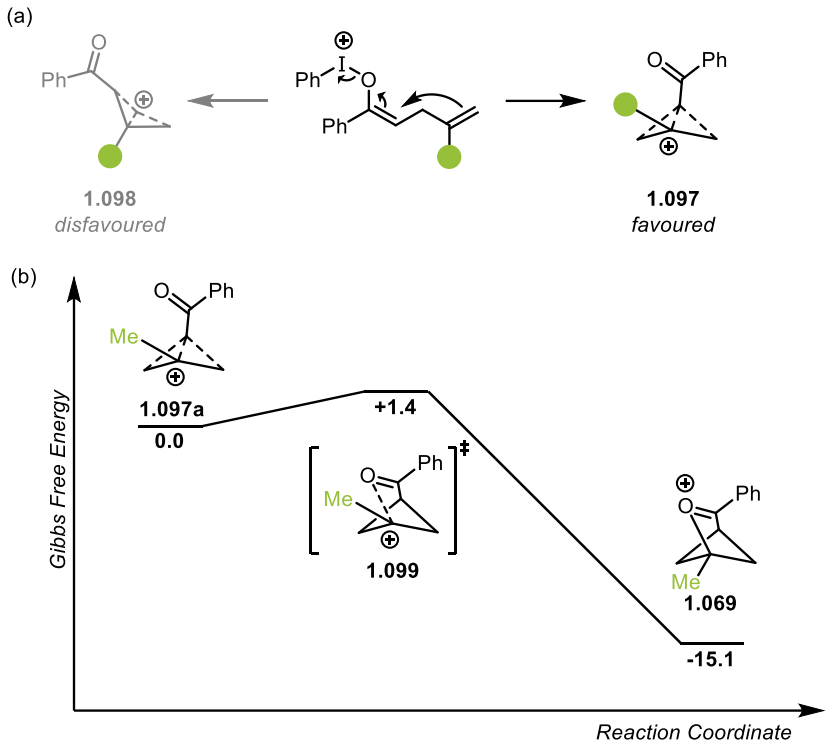
1.2.2.3.4 Computational Study on the Capture of Methyl-Substituted BCB+ and Related Cations

The work in this section was performed by Aymen Benchouche under the supervision of Prof. Pier Alexandre Champagne, in New Jersey Institute of Technology, United States of America. This section provides only a brief discussion of the computational results related to the experimental results presented in previous sections. A full, detailed discussion of the theoretical work is outside of the scope this thesis.

After experimental results revealed the oxocarbenium pathway which was not included in the early models described in 1.2.1, further computational work was carried out to evaluate the relative stability of the oxocarbenium ions and their formation during the reaction.

Firstly, it was shown that the cyclization of the iodo-enolonium ion favors the formation of the *exo*-1,3-BCB+ (**1.097**) over the 1,2-*endo*-BCB+ (**1.098**) by up to 1.2 kcal/mol (**Scheme 1.27a**).

In the case of the methyl-substituted system, after initial formation of the *exo*-1,3-BCB+ ion, the [2.1.1]-bridged ring oxocarbenium ion **1.069** was indeed located as the thermodynamically most stable species (**Scheme 1.27b**, other higher-energy species not shown), with a relative energy of –15.1 kcal/mol compared to the reference species **1.097a**. The energy barrier from **1.097a** to oxocarbenium **1.069** is also the lowest among all transformations at only 1.4 kcal/mol (transition state **1.099**). Computational data correctly predicts the presence of oxocarbenium ion **1.069** as the lowest energy resting state prior to quench, as supported by experimental data presented in previous sections.



Scheme 1.27. Computed reaction pathway of: a) Initial formation of **1.097** and **1.098**, two isomers of BCB+. b) Formation of the lowest-energy intermediate **1.069** through a low-lying transition state **1.099**. Calculations were performed at (ωB97X-D/6-31+G(d,p)/SMD(CH_2Cl_2)//DLPNO-CCSD(T)/Def2TZVPP/SMD(CH_2Cl_2) level of theory. Energies were reported in kcal/mol.

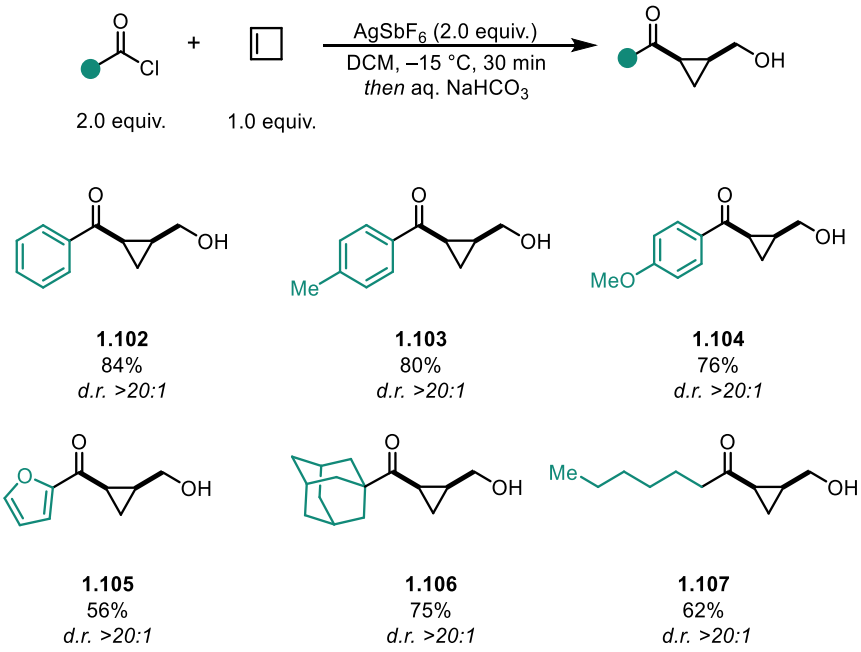
1.2.3 Bicyclobutonium Ions Formed by Cyclobutene and Acylium Ions

1.2.3.1 Reaction Design and Scope

The work presented in this section was carried out by Dr. Zhi-Jie Niu. It is included to provide context to the overall chapter.

As we observed the formation of BCB+ ions and the subsequent 'locking' event to form a stable oxocarbenium intermediate by intramolecular cyclization of iodo-enolonium ions, we were also interested in intermolecular reactions. While the oxidative Umpolung reaction contains multiple reagents which cannot be easily represented in computational studies, computational validation of the reaction mechanism was expected to be more feasible when working on a simpler reaction mixture.

Drawing from previous studies of the reactivity of alkenes and acylium ions, a reaction was designed to use benzoyl chloride and cyclobutene as the precursors to the non-classical BCB+ ion (**Scheme 1.30**).



Scheme 1.30. Acylation of cyclobutene afforded cyclopropylcarbinols. All reactions were carried out on 0.20 mmol scale. The d.r. was determined by crude ^{1}H NMR. Yields refer to isolated yield of the *cis*-configured product. Only selected scope entries are shown.

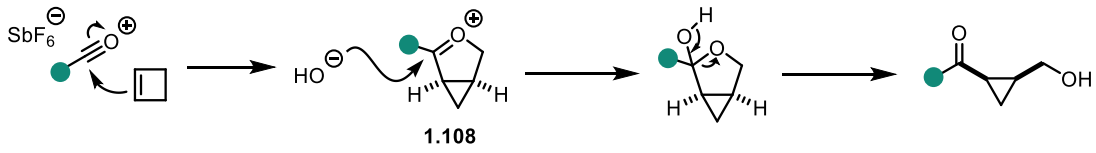
Following basic aqueous work-up, cyclopropylcarbinol **1.102** was isolated in excellent yield (**Scheme 1.29**). When examining the scope of the reaction, it was discovered that a range of aryl (**1.103–1.105**)

and aliphatic acyl chlorides (**1.106**, **1.107**) were well tolerated, all affording the corresponding cyclopropylcarbinols in excellent yield and diastereoselectivity.

1.2.3.2 Reaction Mechanism

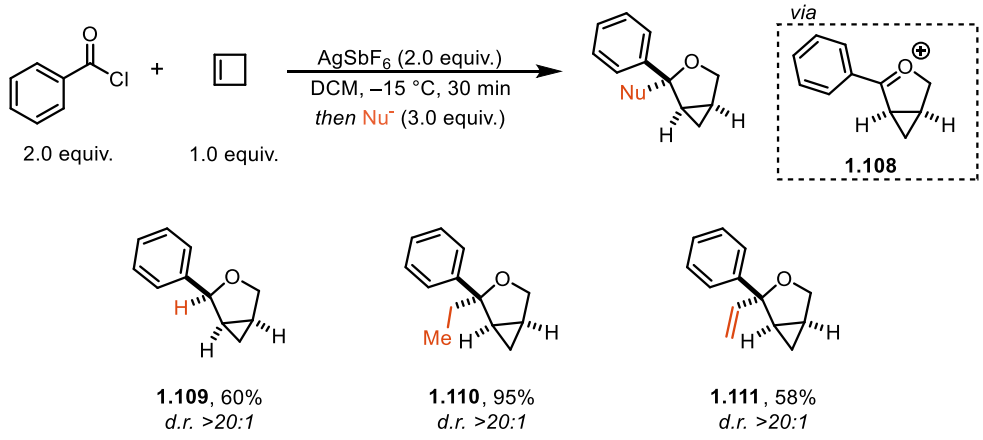
The work presented in this section was carried out by Dr. Zhi-Jie Niu (experimental) and Aymen Benchouche (theoretical).

As all substrates presented in the previous section were synthesized with an excellent diastereomeric ratio of >20:1, we believe that the reaction evolves via a strained oxocarbenium intermediate **1.108**, which sets the cis-configuration. The hydrolysis of **1.108** proceeds through nucleophilic attack at the carbenium carbon, leading to the major product (**Scheme 1.31**).



Scheme 1.31. Proposed reaction mechanism involving key oxocarbenium intermediate **1.108**.

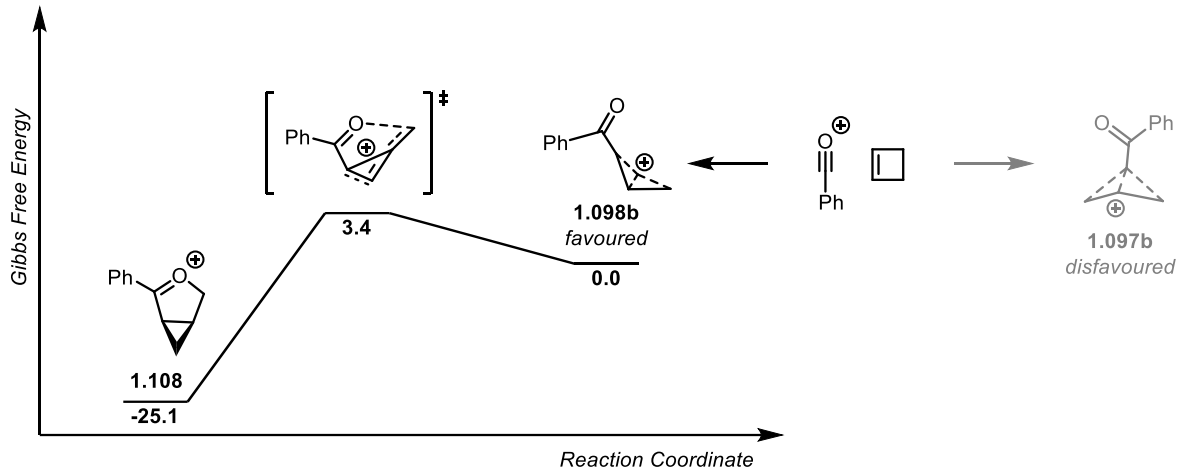
Experimentally, apart from water, the oxocarbenium intermediate was shown to also be susceptible to capture by sodium borohydride, affording a cyclopropane-fused tetrahydrofuran (**Scheme 1.32**, **1.109**). Using Grignard reagents as carbon-based nucleophiles also afforded the corresponding bicyclo [3.1.0] products (**1.110**, **1.111**).



Scheme 1.32. Trapping of the oxocarbenium intermediate by nucleophiles. Reaction carried out on 0.20 mmol scale. The d.r. was determined by crude ^{1}H NMR.

Computational modelling of the intermolecular electrophilic attack of an acylium ion onto cyclobutene leads to the preferential formation of the endo-1,2-BCB+ ion **1.098b** (**Scheme 1.33**), in contrast to **1.097a** formed by the intramolecular reaction (See **Scheme 1.27a**). Among all the possible

rearrangements of this transient intermediate, the pathway leading to the thermodynamically most stable oxocarbenium intermediate, **1.108**, also has the lowest activation barrier of 3.4 kcal/mol, confirming **1.108** as the resting state prior to nucleophilic quench.

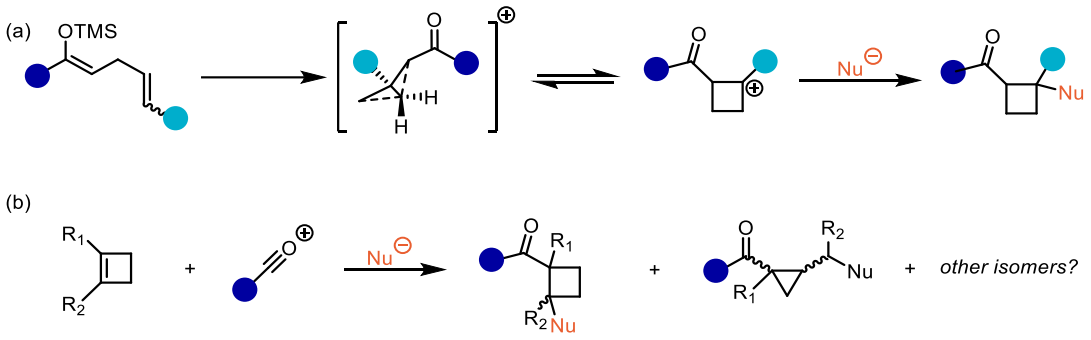


Scheme 1.33. Computed reaction pathway of rearrangement of **1.098b** into **1.108**. Calculations were performed at (ωB97X-D/6-31+G(d,p)/SMD(CH2Cl2)//DLPNO-CCSD(T)/Def2TZVPP/SMD(CH_2Cl_2) level of theory. Energies were reported in kcal/mol.

1.2.4 Summary and outlook

In this chapter, a survey of BCB+ ions formed by intramolecular oxidative Umpolung of silyl enol ethers and intermolecular electrophilic attack of acylium ions on cyclobutene has been presented. Depending on the approach leading to BCB+ ions, the reactions followed completely different pathways, resulting in the formation of either cyclopropane or cyclobutane products. For the first time intermediates in highly strained fused- and bridged-ring systems, we identified oxocarbenium ions as the most thermodynamically stable species, which plays an important role in the excellent regioselectivity and diastereoselectivity of the reactions.

In the future, we can continue to investigate the effects of substituents on the stability of BCB+. Different substrates and reaction pathways could be explored to reroute the reaction to produce 1,2-cyclobutane products, as predicted by the initial computational model (**Scheme 1.34a**).



Scheme 1.34. Outlook. a) Exploring different substrate and reaction pathways which may reroute the reaction to yield 1,2-cyclobutane products. b) Reaction between substituted cyclobutene and acylium ions.

As the substitution pattern has been predicted to be paramount to the energy levels of BCB+ and its related species, examining the reactions between substituted cyclobutenes and acylium ions (**Scheme 1.34b**) could also provide deeper insight into the stability and underlying reactivity of BCB+ ions.

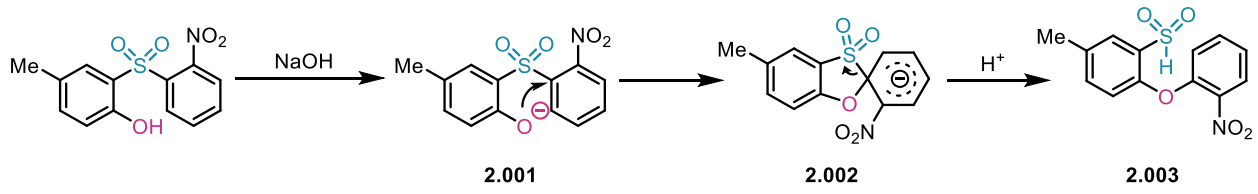
Chapter 2. Synthesis of Difunctionalized Amides by Domino Conjugate Addition-Smiles Rearrangement

2.1 Introduction

2.1.1 Early Examples of the Smiles and Truce-Smiles Rearrangement

Novel methods to construct complex molecular skeletons have been the center of organic chemistry research for decades. Rearrangements are a class of synthetic methods, enabling rapid access to challenging structures from easily synthesized precursors with good atom economy. Numerous named rearrangement reactions have been reported and used in total synthesis of natural products, however, the Smiles rearrangement is arguably underappreciated and underutilized.[82–85]

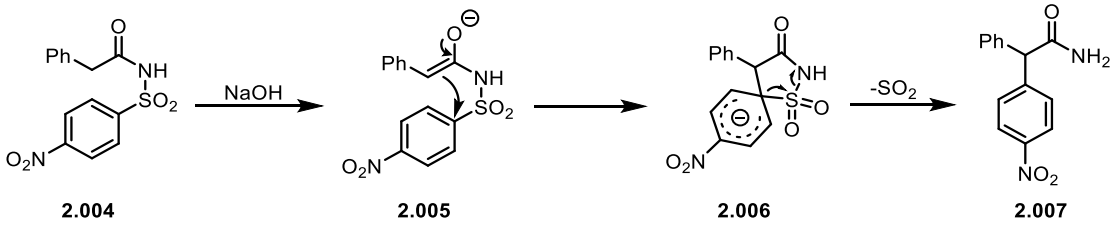
First reported in 1931 by Smiles and co-workers (**Scheme 2.01**), the Smiles rearrangement starts from an intramolecular nucleophilic aromatic substitution (S_NAr) where a nucleophile (magenta phenolic oxygen, **2.001**) attacks the ipso position of a leaving group (blue sulfone, **2.001**) to form a Meisenheimer complex **2.002**. Upon C-S bond cleavage and collapse of **2.002**, a new ether is formed (**2.003**). The reaction can thus be formally described as an S-to-O aryl transfer.[86,87]



Scheme 2.01. Earliest report of Smiles rearrangement, a formal S-to-O aryl transfer.

A sub-class of Smiles rearrangement which utilizes carbon nucleophiles was first reported in the 1950s by Dohmori and co-workers in a series of publications (**Scheme 2.02**).[88–91] Deprotonation of sulfonamide **2.004** with sodium hydroxide leads to enolate **2.005**, and triggers an intramolecular S_NAr reaction to form stabilized Meisenheimer complex **2.006**. Notably, the collapse of **2.006** to form primary

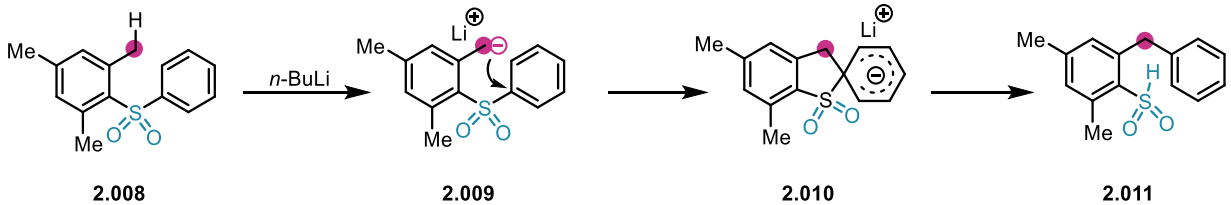
amide **2.007** is accompanied by cleavage of the N-S bond and extrusion of SO_2, the latter the *de facto* driving force of this irreversible reaction.



Scheme 2.02. Smiles rearrangement involving a formal S-to-C aryl transfer reported by Dohmori and co-workers.

It is noteworthy that as an S_NAr reaction, Smiles rearrangements generally require stabilization of the Meisenheimer complex to proceed. The stabilization is classically achieved by installing an electron-withdrawing nitro group at the *ortho*- or *para*- positions.[92] Substrates carrying either a *meta*-nitro substituent or electron-donating *para*-methylthio substituent were both reported to be unreactive.[93,94]

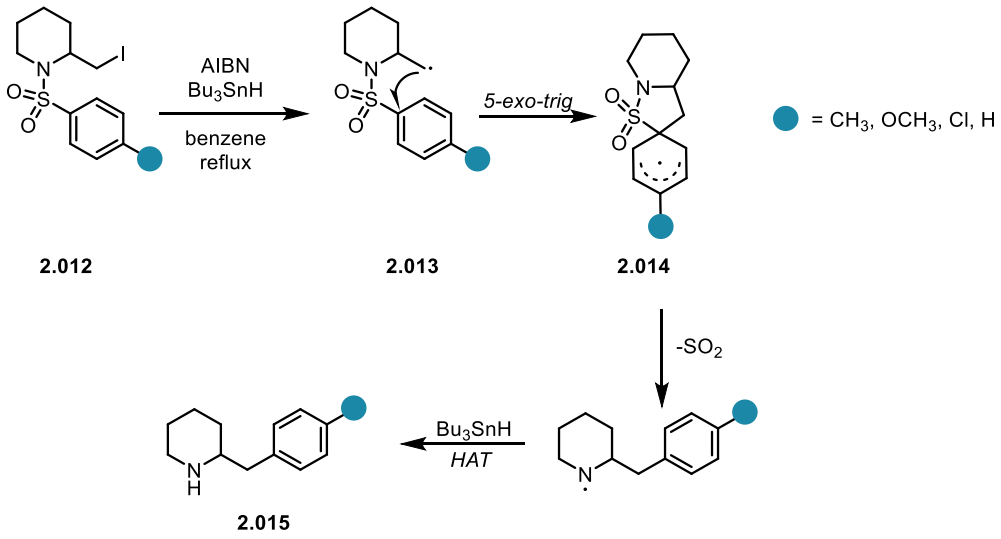
One of the early examples that bypasses this electronic requirement was reported by Truce and co-workers in 1958, also involving a S-to-C aryl transfer (**Scheme 2.03**). This class of reactions were then named Truce-Smiles rearrangements in subsequent literature. Using *n*-butyllithium as a strong base, lithiation of a methyl group (magenta, **2.008**) *ortho*- to a sulfone leads to an *ipso*- S_NAr reaction on the right-hand electron-neutral benzene ring (**2.009**). Collapse of Meisenheimer complex **2.010** furnishes sulfinic acid **2.011**.[95] Despite the lack of an electron-withdrawing substituent, the designed vicinity between nucleophile and aryl group plays a key role in the feasibility of the reaction.[96] In addition, the strong organolithium nucleophile **2.009** favors the formation of intermediate **2.010**, which is inductively stabilized by the *ipso*-sulfonyl group. The release of a sulfonyl group produces a much weaker nucleophile, thereby making the reaction irreversible.



Scheme 2.03. Truce and co-workers reported a variation of the Smiles rearrangement which uses a strong base and pre-organized substrate to bypass the electronic requirements of this class of rearrangements.

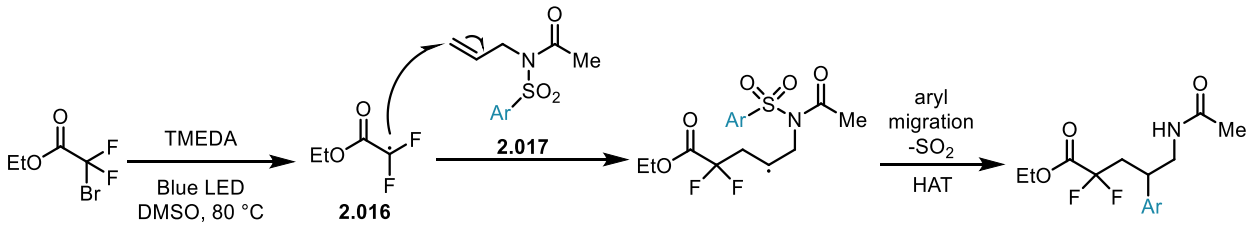
2.1.2 Radical Truce-Smiles Rearrangement

The early examples of Smiles rearrangements discussed in the previous section all fall under the polar regime, where charged nucleophiles are employed to initiate S_NAr reactions. In the 1970s, Speckamp and co-workers reported a radical-initiated aryl migration of sulfonamides (**Scheme 2.04**).[97,98] Upon reflux in benzene under radical chain conditions, sulfonamide **2.012** undergoes a C-I cleavage, forming a methylene radical **2.013**. A *5-exo-trig* cyclization affords intermediate **2.014**, which upon SO_2 extrusion and hydrogen atom transfer (HAT) furnishes amine **2.016** as the rearranged product. In contrast to the polar Smiles rearrangement which often requires an electron-withdrawing substituent on the migrating aryl ring, kinetic studies revealed that the reaction rate was not greatly affected by aryl substituents.



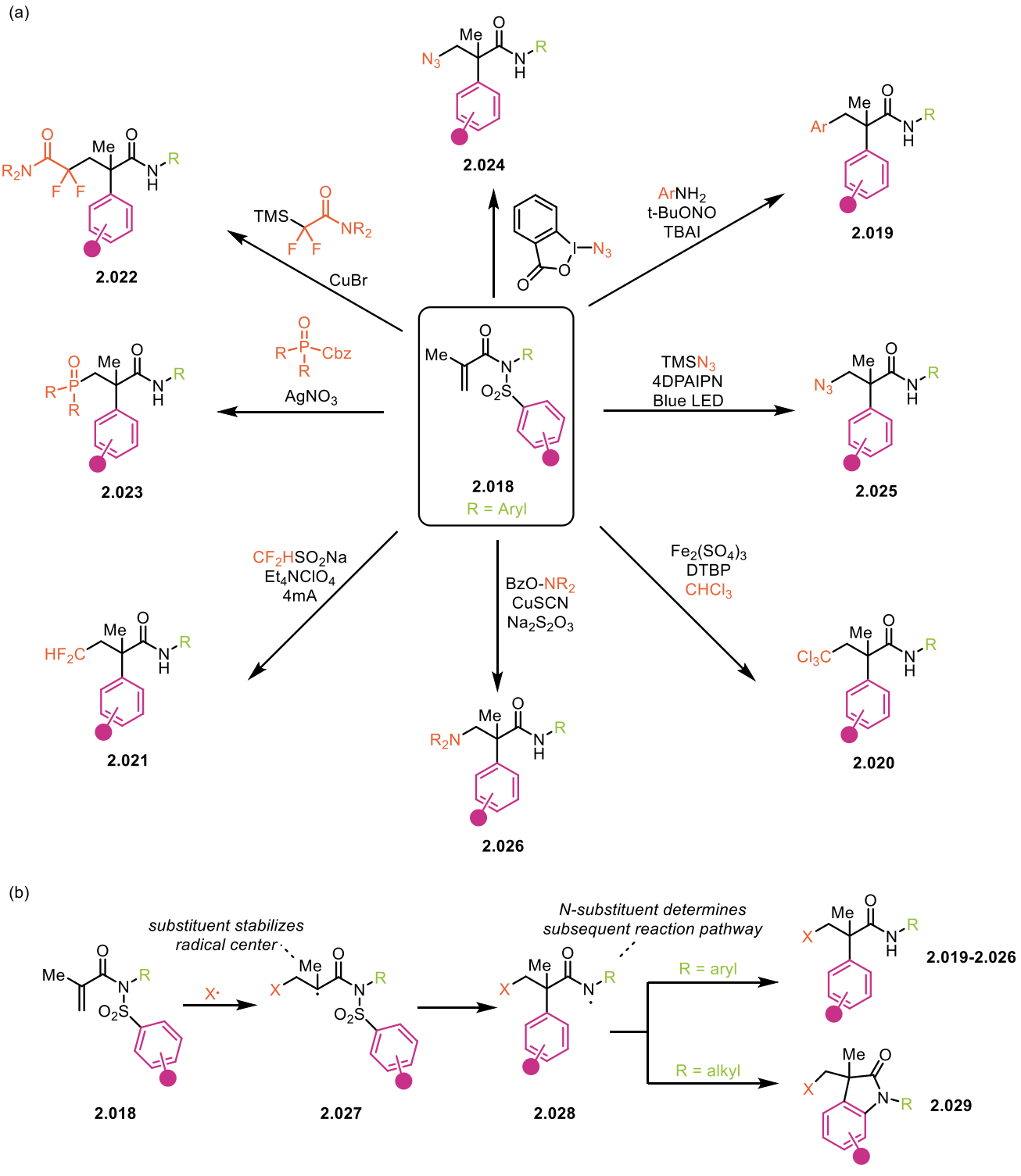
Scheme 2.04. Radical 1,5-aryl migration reported by Speckamp and co-workers, believed to be the first report of radical Truce-Smiles rearrangement.

As the radical Truce-Smiles rearrangement circumvents the electronic restraints of its polar counterpart, this class of reaction has gained wide interest in recent years for C-arylation.[84,99–101] Greaney and co-workers reported a related reaction (**Scheme 2.05**), in which a radical (**2.016**) generated with blue LED at elevated temperatures adds to an unactivated alkene tethered to a sulfonamide (**2.017**), triggering aryl migration.[102]



Scheme 2.05. Metal-free photoredox radical Truce-Smiles rearrangement reported by the Greaney group. TMEDA = tetramethylethylenediamine.

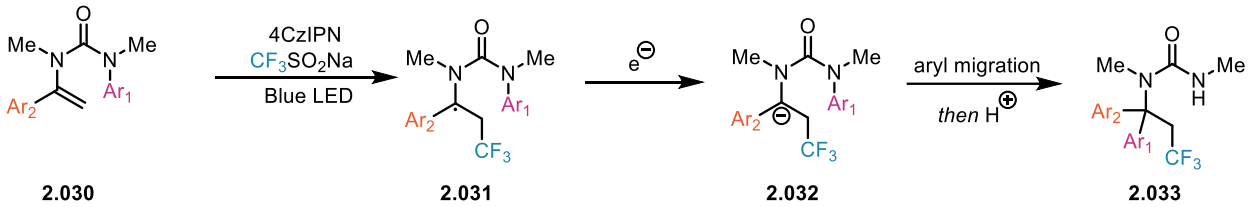
Greaney's report of a photocatalyst-free reaction is rather uncommon, as most radical Truce-Smiles rearrangements require an organic or metal-based catalyst for radical generation. The generated radicals can then undergo Giese-type addition to electron-deficient alkenes[103] to generate the precursor to aryl migration. In recent years, the radical Truce-Smiles rearrangement has seen a revival using sulfonyl acrylamides **2.018** as substrates (**Scheme 2.06a**).[101] Upon Giese-type addition of the radical source, the amidyl radical generated triggers aryl migration. Following desulfonylation and HAT, the reaction furnishes β-functionalized α-aryl amides. Several radical sources have been reported, including carbon-centered (**2.019**-**2.022**),[104–107] phosphonyl (**2.023**),[108] azido (**2.024**, **2.025**)[108,109] and aminyl (**2.026**)[110] precursors. However, each radical precursor requires individually optimized reaction conditions. Moreover, an α-substituent on the sulfonyl acrylamide is required to stabilize the radical intermediate (**Scheme 2.06b**, **2.027**) for high yields, invariably leading to a quaternary center after rearrangement. It is also noteworthy that the nitrogen substituent plays an important role in the reaction pathway after aryl migration. Amidyl radical **2.028** can be stabilized by *N*-aryl substituents until HAT to furnish the amide products exemplified in Scheme **2.07a**. In the case of *N*-alkyl substituents, intermediate **2.038** undergoes an intramolecular cyclization with the migrated aryl group to form oxindole **2.029**.[106,108,109,111,112]



Scheme 2.06. a) Selected examples of radical Truce-Smiles rearrangements utilizing sulfonyl acrylamides as substrates for Giese-type addition. b) Structural requirements of sulfonyl acrylamides for efficient rearrangements. DTBP = di-*tert*-butyl peroxide, 4DPAIPN = 1,3-Dicyano-2,4,5,6-tetrakis(diphenylamino)-benzene.

2.1.3 Recent Advances in Polar Truce-Smiles Rearrangements

In 2020, Clayden's group reported an interesting Truce-Smiles rearrangement. While they initially generated a radical to initiate the reaction and expected the reaction to proceed via the radical pathway, during mechanistic studies, they realized that the migration step was actually a polar process (**Scheme 2.07**).[113] A trifluoromethyl radical generated by oxidation of sodium trifluoromethylsulfinate ($NaSO_2CF_3$) adds to urea **2.030**, and the resulting radical **2.031** is further reduced to the anion **2.032** to initiate a polar rearrangement, affording α-diaryl ureas **2.033**. Interestingly, the scope of the reaction was shown to tolerate electron-rich migrating rings (Ar_1), which was initially thought to be rare under the polar regime. The authors argued that the urea tether provides conformational enhancement of the reactivity,[114–116] which was also thought to be a key factor for the feasibility of electron-neutral polar aryl migration reported by Truce and co-workers (See section 2.1.1, **Scheme 2.03**)

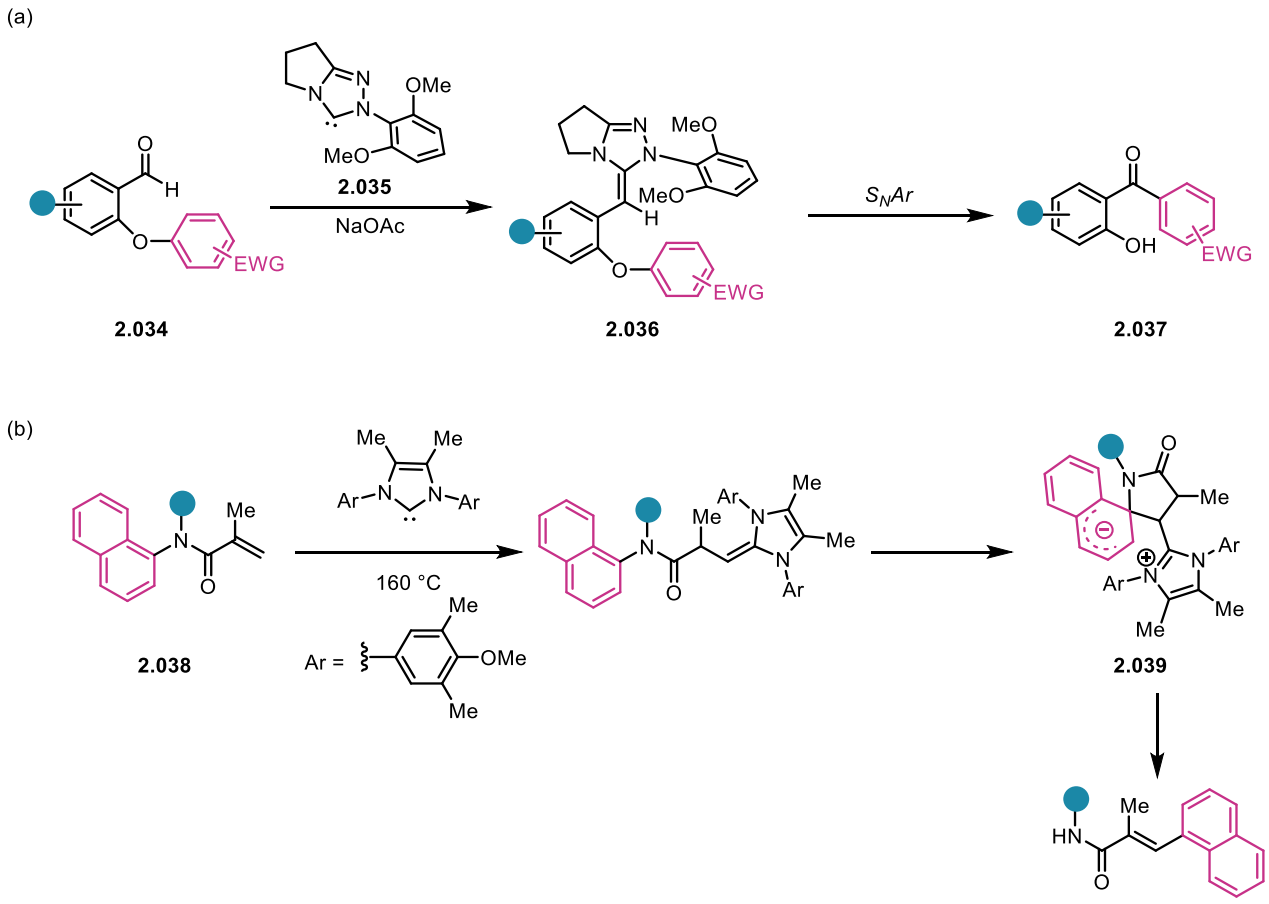


Scheme 2.07. Radical-polar crossover Truce-Smiles rearrangement reported by Clayden and co-workers. 4CzIPN = 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene.

The generation of the rearrangement precursor as reported above is not common in the polar regime. Compared to the radical Truce-Smiles rearrangement which often requires complex and carefully optimized reaction systems including radical initiators and additives (See **Scheme 2.06a**), polar anionic Truce-Smiles rearrangements are operationally simpler, often only requiring a base for initial deprotonation.[100] Similar to the reactions in the radical regime, in recent years, the polar Truce-Smiles rearrangement has also seen a resurgence in literature, in which chemists aim to expand the reaction scope by using novel reagents or smartly designed substrates.

In 2017, Glorius and co-workers reported an X-to-C aryl migration catalyzed by *N*-heterocyclic carbenes (NHC) (**Scheme 2.08a**). As an organocatalyst, NHC **2.035** unlocks the Umpolung reactivity of aryl aldehyde **2.034**, creating acyl anion equivalent **2.036** in the presence of sodium acetate as a weak base.

An intramolecular S_NAr *ipso*- to the substituent on the distal aryl group (magenta) and C-X bond cleavage leads to biaryl ketone products **2.037**.

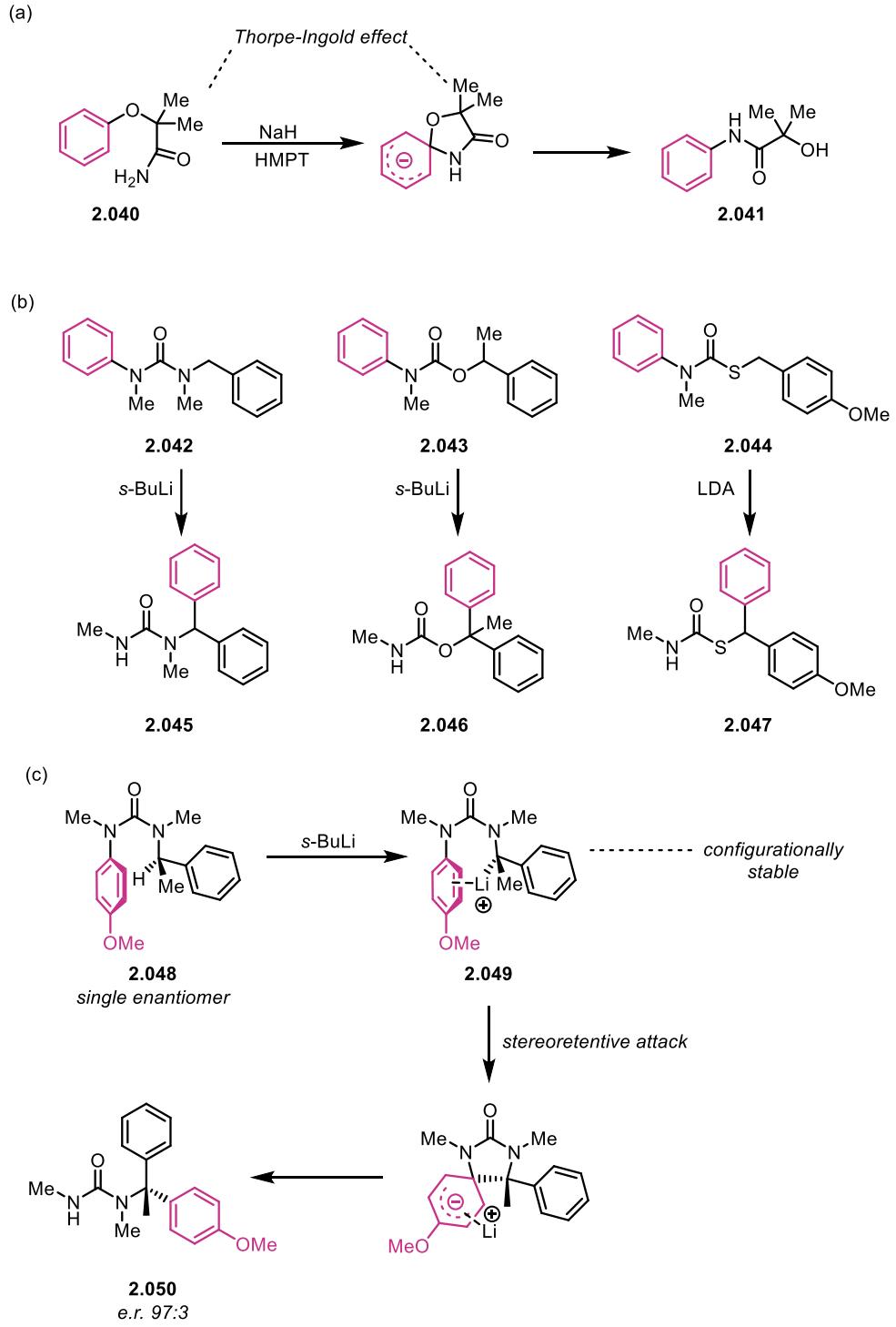


Scheme 2.08. a) NHC-catalyzed aryl migration to afford biaryl ketones. b) Migration of electron-neutral 1-naphthyl group.

On the other hand, Tobisu and co-workers reported an NHC-catalyzed N-to-C migration of electron-neutral aryl groups (**2.038**) at elevated temperature (**Scheme 2.08b**).[117] Although successfully circumventing the electronic requirements, the migrating aryl groups still need extended π systems which mesomerically stabilize the negative charge on the Meisenheimer complex **2.039**.[118]

As briefly discussed in previous sections, manipulation of substrate structure and conformations is key to migration of aryls without electron-withdrawing groups.[96] In a report of electron-neutral and electron-rich aryl migration in 1976, Turner and co-workers pinpointed the Thorpe-Ingold effect exerted by the *gem*-dimethyl linker as the key for successful rearrangement of phenol **2.040** to anilide **2.041** (**Scheme 2.09a**).[119]

Capitalizing on the power of conformational restrains, Clayden and co-workers developed an entire new reaction mode, which was thought to be uncommon for polar Truce-Smiles rearrangements (**Scheme 2.09b**).[120,121] By using tethered substrates such as urea (**2.042**),[122] carbamate (**2.043**)[123] and thiocarbamate (**2.044**),[124] lithiation by LDA or *s*-BuLi leads to the migration of electron-rich and electron-neutral aryl rings to afford the bis-aryl products **2.045**-**2.047**. The lithium cation brings the carbanion and electron-rich aryl ring into close proximity, facilitating the nucleophilic attack to initiate migration (**Scheme 2.09c**). Most notably, when a chiral substrate is used, the reaction has been shown to proceed with stereospecificity. Taking the rearrangement of **2.048** as an example, the authors proposed that the lithiated intermediate **2.049** is configurationally stable, thereby leading to a stereoretentive migration to furnish **2.050**.[122]



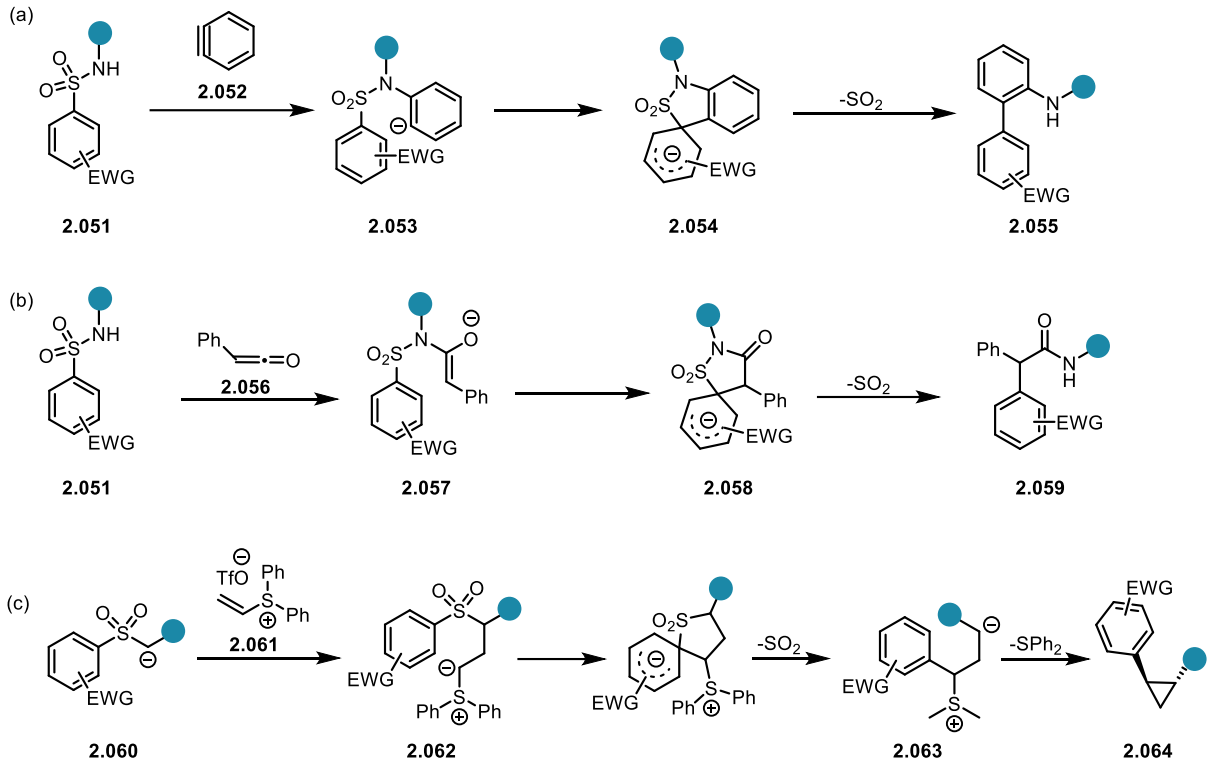
Scheme 2.09. a) Thorpe-Ingold effect provides 'conformational lock' for effective migration of phenyl group. b) Lithiation of urea, carbamate and thiocarbamate sets the stage for electron-neutral aryl migration. c) Lithium brings carbanion and migrating aryl in a proximity to facilitate nucleophilic attack. At the same time, lithiation also leads to retention of stereochemistry during migration.

Already investigated in the early history of polar Truce-Smiles rearrangement (see section 2.1.1), sulfones and sulfonamides have received continued interest from chemists in this type of transformation.

Using highly reactive, *in-situ* generated arynes as electrophiles, Greaney and co-workers developed a novel metal-free strategy to access biaryls (**Scheme 2.10a**).[125] Starting from sulfonamides **2.051** with an electron-withdrawing substituent as often seen in the polar Truce-Smiles rearrangement, its reaction with aryne **2.052** first leads to a highly reactive sp^2 carbanion **2.053**. S_NAr *ipso*- to the sulfonyl group affords Meisenheimer complex **2.054**, which then undergoes desulfonylation to afford biaryl products **2.055**. The high reactivity of arynes allows facile syntheses of sterically hindered biaryls, which is challenging using traditional metal-catalyzed cross-coupling methods.

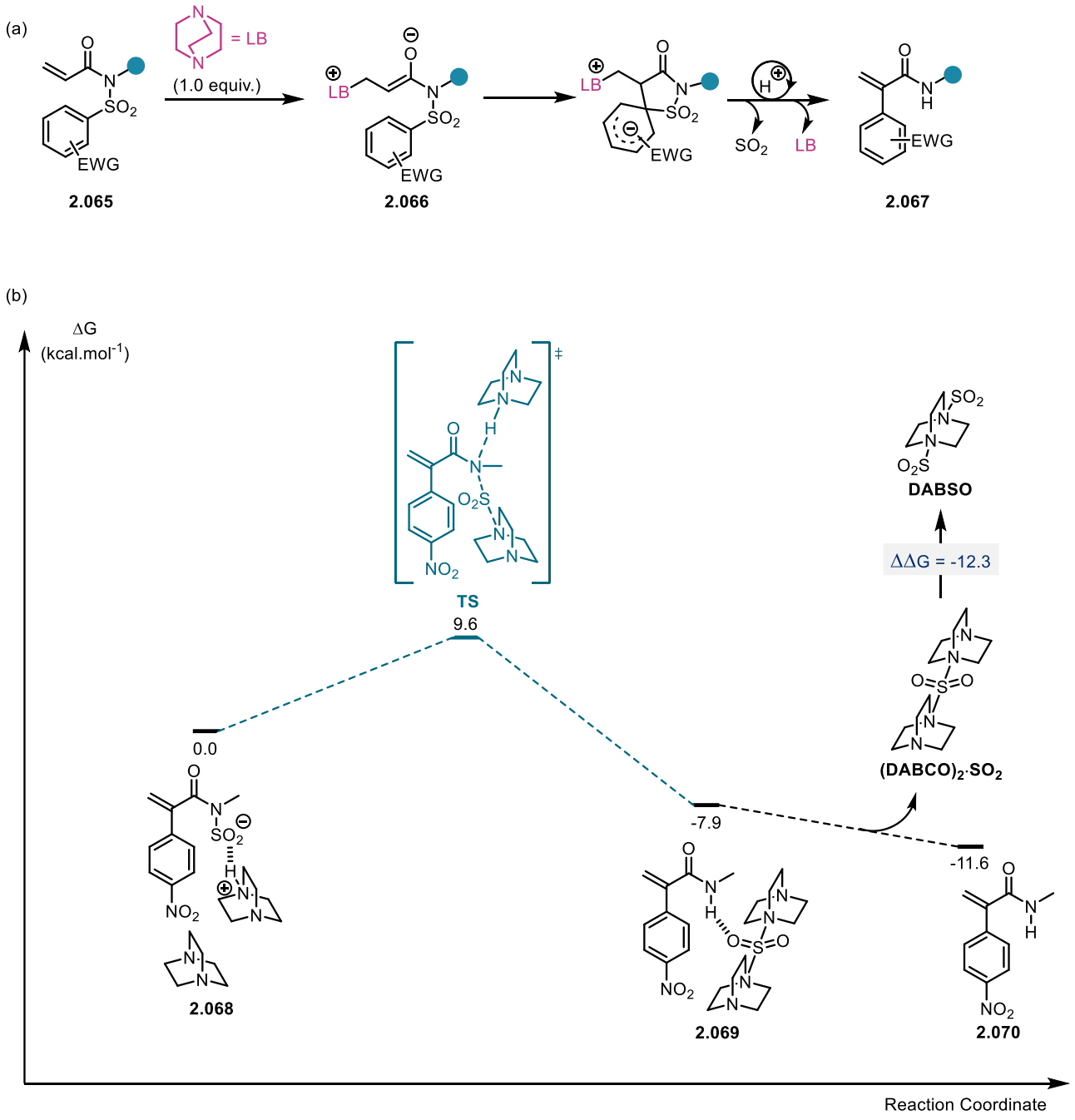
Making use of highly reactive electrophilic intermediates, the same group reported a synthesis of α,α-biaryl amides **2.059** using sulfonamide **2.051** and ketene **2.056** (**Scheme 2.10b**).[126] At elevated temperature, **2.056** is rapidly captured by **2.051** to form enolate intermediate **2.057**. The same rearrangement takes place through Meisenheimer complex **2.058** and subsequent desulfonylation, furnishing the products.

Recently, these authors reported a novel method for cyclopropanation using a Truce-Smiles rearrangement (**Scheme 2.10c**). Nucleophilic attack of deprotonated sulfone **2.060** onto diphenyl(vinyl)sulfonium triflate **2.061** led to the sulfur ylide **2.062**, which then undergoes a Truce-Smiles rearrangement and SO_2 extrusion. Finally, sulfide elimination from **2.063** affords cyclopropane products **2.064**.[127] Despite being a very cleverly designed cascade reaction, it must be noted that this reaction does not have the most commendable atom economy, often the highlight of rearrangement reactions.



Scheme 2.10. Desulfonylative Truce-Smiles rearrangement reactions developed by Greaney and co-workers. a) Reaction between arynes and sulfonamides affords biaryls; b) Capture of ketene by sulfonamides leads to diaryl amides; c) Aryl transfer followed by cyclopropanation.

In 2022, our group reported a Morita-Baylis-Hillman (MBH)-type Truce-Smiles rearrangement to access α-arylated acrylamides (**Scheme 2.11a**).[128] Addition of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a Lewis base (LB) to sulfonyl acrylamide **2.065** generates enolate intermediate **2.066**, which then undergoes 1,4-aryl migration. C-S bond cleavage, SO_2 extrusion and elimination of DABCO furnishes the expected product **2.067** in good to excellent yields. Unlike classical MBH reactions where the nucleophile is often used in catalytic amounts,[129] the optimized reaction requires a stoichiometric amount of DABCO. To further probe the reaction mechanism and the role DABCO plays, DFT studies were performed (**Scheme 2.11b**). Initially, we hypothesized that SO_2 extrusion from **2.068** should be entropically favorable and spontaneous. However, from DFT calculations, it was shown that this process is facilitated by a $[DABCO\text{-}H]^+$ complex, in a formal SO_2-proton exchange. Capture of SO_2 by DABCO forms the observable adduct 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO), removing it from the reaction as a precipitate and furnishing the final product **2.070**.[128]

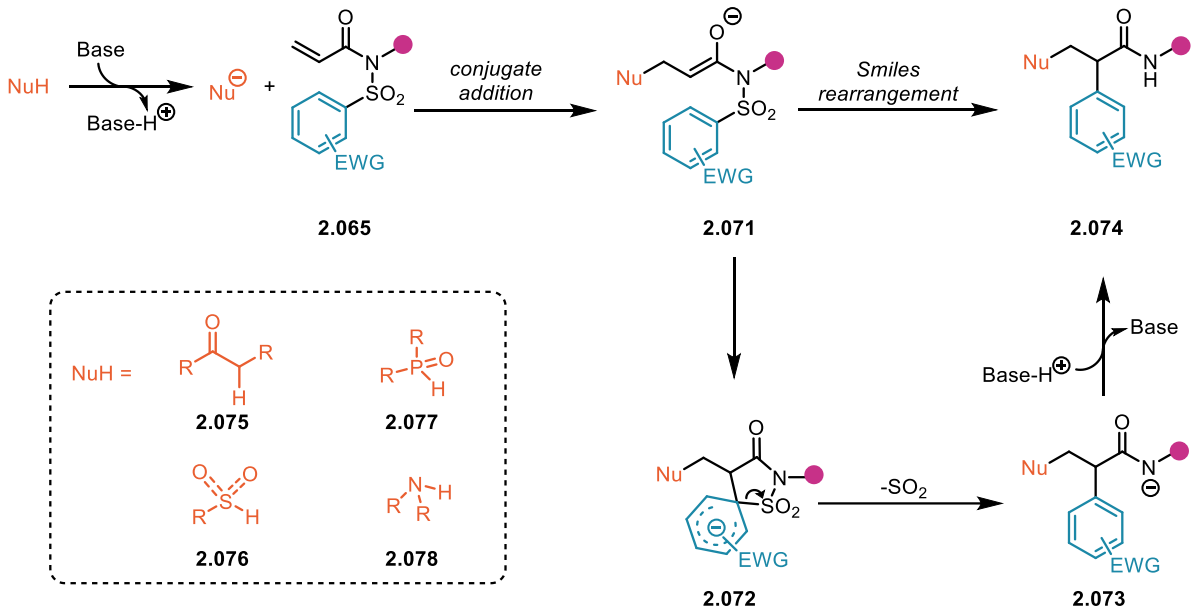


Scheme 2.11. a) Synthesis of α-aryl acrylamide by an MBH-type Truce–Smiles rearrangement of sulfonyl acrylamide. b) Part of DFT calculations showing the energy profile of elimination and desulfonylation in the reaction. Calculations at PBE0-D3(BJ)/def2-TZVP,SMD(MeCN)//PBE0-D3(BJ)/def2-SVP,SMD(MeCN) level of theory.

2.1.4 Project Aims

As shown in section 2.1.2, the radical Truce-Smiles rearrangement provides a powerful method to access β-functionalized, α-aryl amides. However, reaction conditions need to be carefully tailored to each radical source with different methods of radical generation. In addition, there are also restraints on the sulfonyl acrylamide substrates for stabilization of radical intermediates. Drawing inspiration from the earlier work on the synthesis of α-arylated acrylamides,[128] we envisioned an anionic pathway (**Scheme 2.12**), which is complementary to the reactivity of its radical counterpart.

Conjugate addition of a nucleophile to a sulfonyl acrylamide substrate (**2.065**) first would lead to the enolate intermediate **2.071**, followed by S_NAr *ipso*- to SO_2 to form Meisenheimer complex **2.072**. Collapse of **2.072** and desulfonylation would afford the α,β-difunctionalized amide **2.074**. Under a unified set of reaction conditions, we aim to access a wide range of nucleophiles, including carbon- (**2.075**), sulfur- (**2.076**), phosphorus- (**2.077**) and nitrogen-based (**2.078**). In the polar regime, the anionic intermediates are either mesomerically stabilized (**2.072**) or can easily be protonated (**2.073**). Therefore, there will be no additional restraints on the sulfonyl acrylamide substrates as often observed in the radical regime (See section 2.1.2).



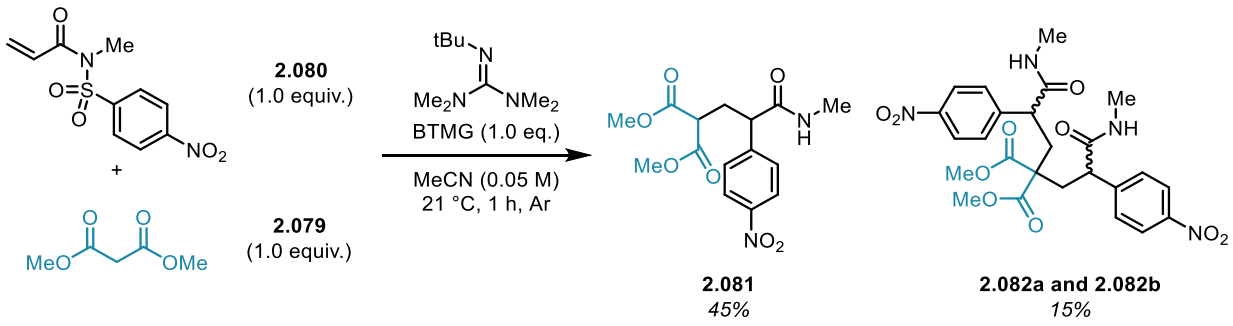
Scheme 2.12. Envisioned polar domino conjugate addition-Smiles rearrangement to afford α,β-difunctionalized amides.

2.2 Results and Discussion

The results discussed in this section were acquired in collaboration with Dr. Haoqi Zhang, Dr. Tommaso Bortolato and Dr. Miran Lemmerer. The work has been partially published in JACS Au ***2024****, 4, 7, 2456–2461.*[130]

2.2.1 Optimization

Initially, dimethyl malonate (**2.079**) was chosen as the pronucleophile in the reaction with sulfonyl acrylamide (**2.080**) (**Scheme 2.13**). 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (BTMG) was selected as a bulky base to avoid direct nucleophilic attack to **2.080**. Taking inspiration from our previous work, acetonitrile was chosen as the polar aprotic solvent. The reaction produced the desired α,β-difunctionalized amide **2.081** in 45% yield. However, we also isolated a pair of diastereomers **2.082a** and **2.082b**, in a combined yield of 15%. We hypothesized that their formation was due to the presence of the second acidic proton on **2.081**, which can be deprotonated again by BTMG to react with a second equivalent of **2.080**.



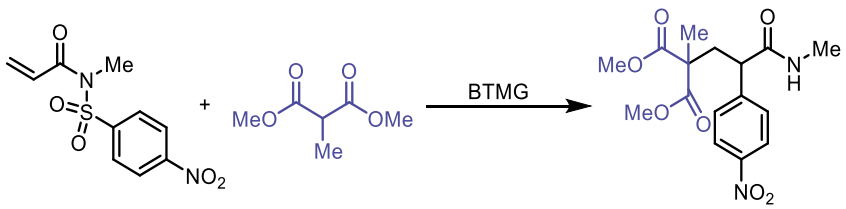
Scheme 2.13. Initial investigation of Conjugate Addition-Smiles Rearrangement between **2.079** and **2.080**.

Encouraged by the initial result, we investigated the effects of the base on the reaction (**Table 2.1**). Although lowering the base loading to 0.5 equivalents (**Entry 2**) only led to a small reduction in conversion, further reduction led to considerably lower conversion (**Entry 1**). Higher base loading (2.0 equivalents, **Entry 4**) was detrimental to the reaction, leading to unspecific decomposition. Weaker bases (**Entry 5-6**) were observed to be unreactive, while KOH (**Entry 7**) and NaH (**Entry 8**) both led to a reduced yield compared to BTMG. Therefore, a BTMG loading of 0.5 equivalents was chosen as the standard for the next step of optimization.

Entry	Base	Base loading/eq.	Conversion[a]
1	**BTMG**	**0.5**	**65%**
2	BTMG	0.1	15%
3	BTMG	1.0	68%
4	BTMG	2.0	decomposition
5	Et_3N	1.0	0%
6	pyridine	1.0	0%
7	KOH	1.0	37%
8	NaH	1.0	51%

Table 2.1 Investigation of base and base loading of the initial reaction. (a) Reaction outcome was reported as conversion of sulfonyl acrylamide **2.080** due to overlap of signals of **2.081** and **2.082** on crude NMR.

In order to avoid the over-reaction described in **Scheme 2.13** and therefore allow a more direct readout of yield of desired product from crude NMR, we decided to use dimethyl methylmalonate **2.083** as the model substrate in the next round of optimization. Several polar solvents were investigated (**Table 2.2**, **Entries 1-4**), and *N,N*-dimethyl acetamide (DMA) (**Entry 4**) was identified as the optimal solvent for the reaction.



2.080 **2.083** **2.084**

Entry	Eq. BTMG	Solvent	Eq. 2.083	Time/h	T/°C	Yield[(c)]
1	0.5	MeCN	1.0[(a)]	5	20	37%
2	0.5	acetone	1.0[(a)]	5	20	22%
3	0.5	DMSO	1.0[(a)]	5	20	31%
4	0.5	DMA	1.0[(a)]	5	20	63%
5	0.5	DMA	1.0[(b)]	5	20	66%

6	0.5	DMA	1.0[(b)]	16	20	73%
7	0.5	DMA	1.0[(b)]	67	20	83%
8	**0.5**	**DMA**	**1.5[(b)]**	**67**	**20**	**89%[(d)]**
9	0.1	DMA	1.5[(b)]	5	20	14%
10	0.2	DMA	1.5[(b)]	5	20	24%
11	0.2	DMA	1.5[(b)]	5	40	30%
12	0.2	DMA	1.5[(b)]	5	60	40%
13	0.2	DMA	1.5[(b)]	5	80	59%

Table 2.2. Optimization of conjugate addition-Smiles rearrangement between **2.080** and **2.083**. (a) **2.080** was mixed with BTMG before addition of **2.083**. (b) **2.083** was mixed with BTMG, followed by addition of sulfonyl acrylamide **2.080**. (c) NMR yield determined using mesitylene as an internal standard. (d) Isolated yield.

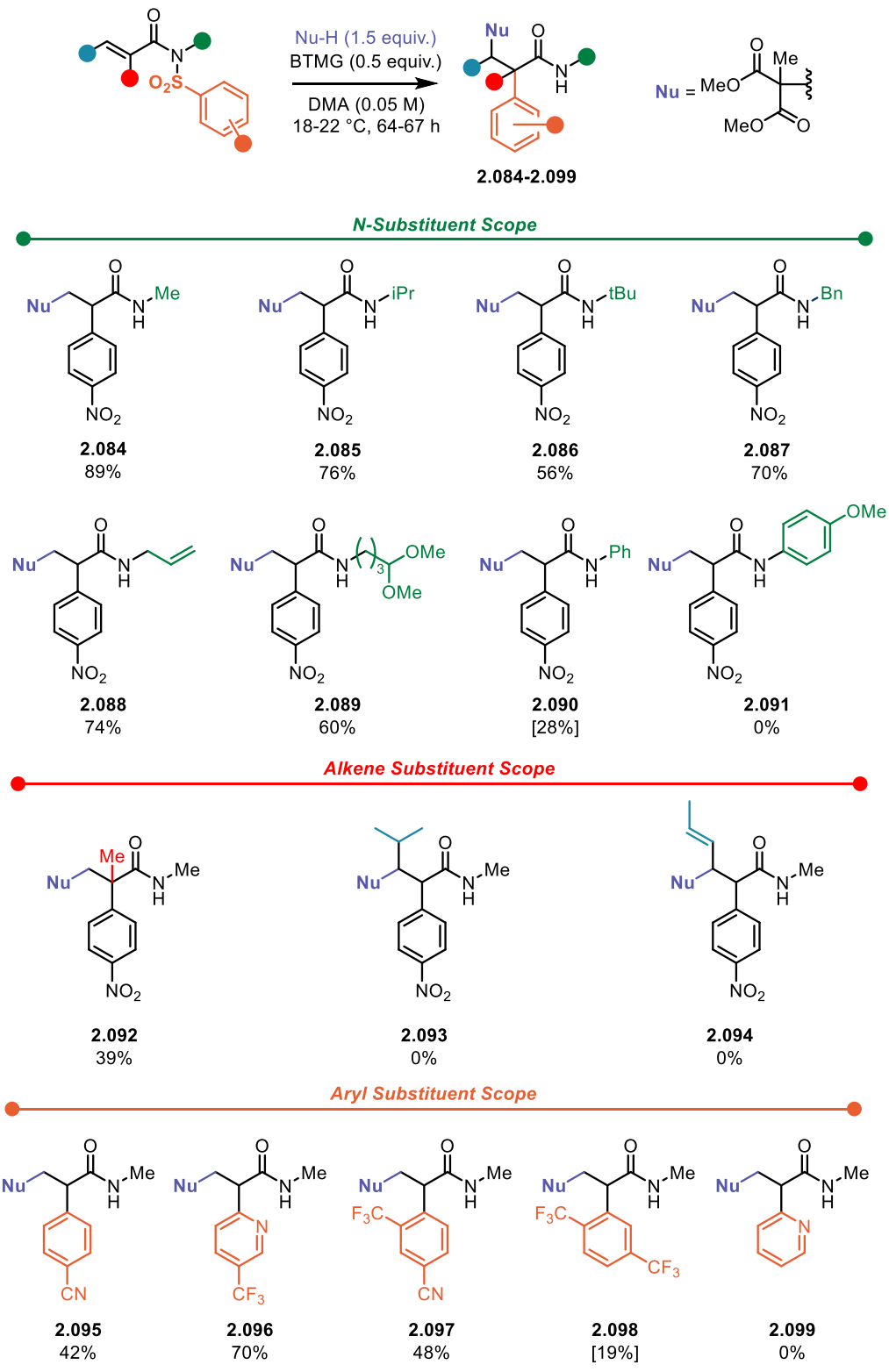
Next, we investigated if the order of reagent addition played a role in the reaction outcome. In all previous experiments (**Table 2.1**, **Entries 1-8**; **Table 2.2**, **Entries 1-4**), base and sulfonyl acrylamide were mixed before addition of the pronucleophile. When base and pronucleophile were mixed first before addition of sulfonyl acrylamide (**Table 2.2**, **Entry 5**), a minor improvement of yield was observed. Prolonging the reaction time from 5 h to 67 h (**Entries 6-7**) led to a significantly higher yield, suggesting that the reaction progress was slow. Finally, increasing the amount of pronucleophile **2.083** to 1.5 equivalents (**Entry 8**) led to the best yield of **2.084** (89% isolated). These conditions were subsequently used for exploration of the reaction scope.

While lowering the base loading to less than 0.5 equivalents in this reaction also led to reduced yield (**Entries 5, 9-10**), we have observed that increasing the reaction temperature can compensate for it (**Entries 10-13**). Drawing parallel from our previous experience, we postulated that SO_2 released may complex with BTMG, therefore rendering it temporarily inactive to deprotonate **2.083** to form the active nucleophile; the release of SO_2 from this complex to free BTMG is a slow step, which can be accelerated by increasing the reaction temperature.

2.2.2 Scope of Sulfonyl Acrylamides

Once the reaction conditions were optimized, we started scope investigations and first focused on the sulfonyl acrylamide reaction partner (**Scheme 2.14**). Benzyl and allyl substituents on nitrogen were both well-tolerated, giving the expected rearrangement products **2.087** and **2.088** in good yields. However, Increasing the bulk on the nitrogen substituent (**2.085**, **2.086**) led to slightly diminished yields compared to the methyl-substituted sulfonyl acrylamide. An acetal group (**2.089**) was also well-tolerated under the reaction and work-up conditions, affording the product in 60% yield. Furthermore, α-methyl sulfonyl acrylamide can also be employed in the reaction, affording a quaternary carbon α-to a carbonyl (**2.092**), despite a much lower yield. We proposed that the increased steric demand of the Meisenheimer complex intermediate formed from this substrate may play a role in diminishing the yield. Notably, aryl groups were not tolerated under these reaction conditions, leading to low yield (**2.090**) or no reaction at all (**2.091**). We hypothesized that the aryl ring may participate in the formation of a molecule-wide conjugated system, thereby lowering the electrophilicity on β-position of acrylamide. Substituents at the β-position were also not permitted (**2.093**, **2.094**), both leading to a complex mixture containing multiple species.

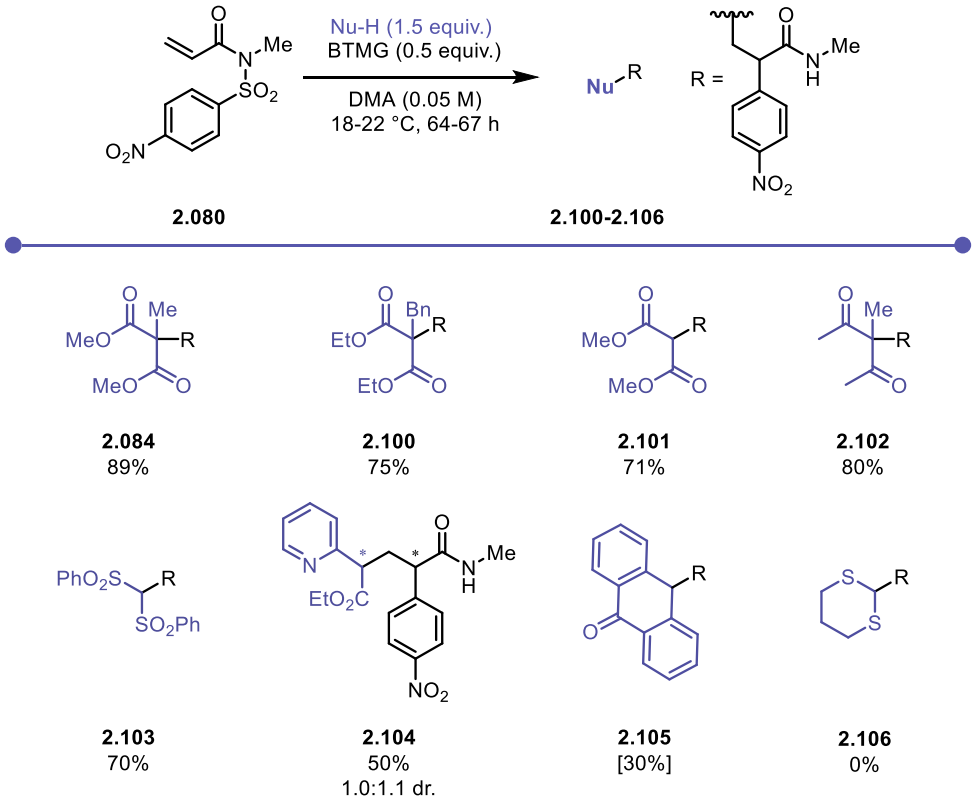
Aryl substituents other than a *p*-nitrophenyl group were also investigated. Both *p*-Cyanophenyl (**2.093**) and *o*-trifluoromethyl-*p*-cyanophenyl groups (**2.097**) readily afforded products in moderate yield. An electron-deficient pyridyl substituent can also be employed as the migrating aryl group, affording the difunctionalized amide in good yield (**2.096**). However, when the aryl substituent is not sufficiently electron deficient, either the yield dropped significantly (**2.098**), or no reaction could be seen (**2.099**).



Scheme 2.14. Scope of sulfonyl acrylamides in conjugate addition-Smiles rearrangement. NMR yields, obtained using dibromomethane as the internal standard, are reported in square brackets.

2.2.3 Scope of Carbon-based Pronucleophiles

We next looked at the scope of carbon-based pronucleophiles that can be used for the conjugate addition to induce aryl migration (**Scheme 2.15**). Increased steric demand posed by a benzyl group (**2.100**) compared to methyl (**2.084**) led to a small loss of yield. To our surprise, when we employed malonate **2.079** again in our optimized conditions, it smoothly afforded product **2.101** with a good yield, with no over-reaction products **2.082a** and **2.082b** as observed in our initial investigations (see section 2.2.1, **Scheme 2.13**). Both 1,3-diketone **2.102** and bis(phenylsulfonyl)methane (**2.103**) can be used as good pro-nucleophiles to afford the expected product. When a prochiral carbon nucleophile is used, we observed the formation of product **2.104** in moderate yield and low diastereoselectivity. Anthracen-9(10*H*)-one can also be used as a pronucleophile (**2.105**), despite a low yield. However, in contrast to **2.101** where the expected product was formed, 1,3-dithiane was identified as an unsuitable pronucleophile (**2.106**) as dimers analogous to **2.082** were detected as major products (see section 2.2.1, **Scheme 2.13**).

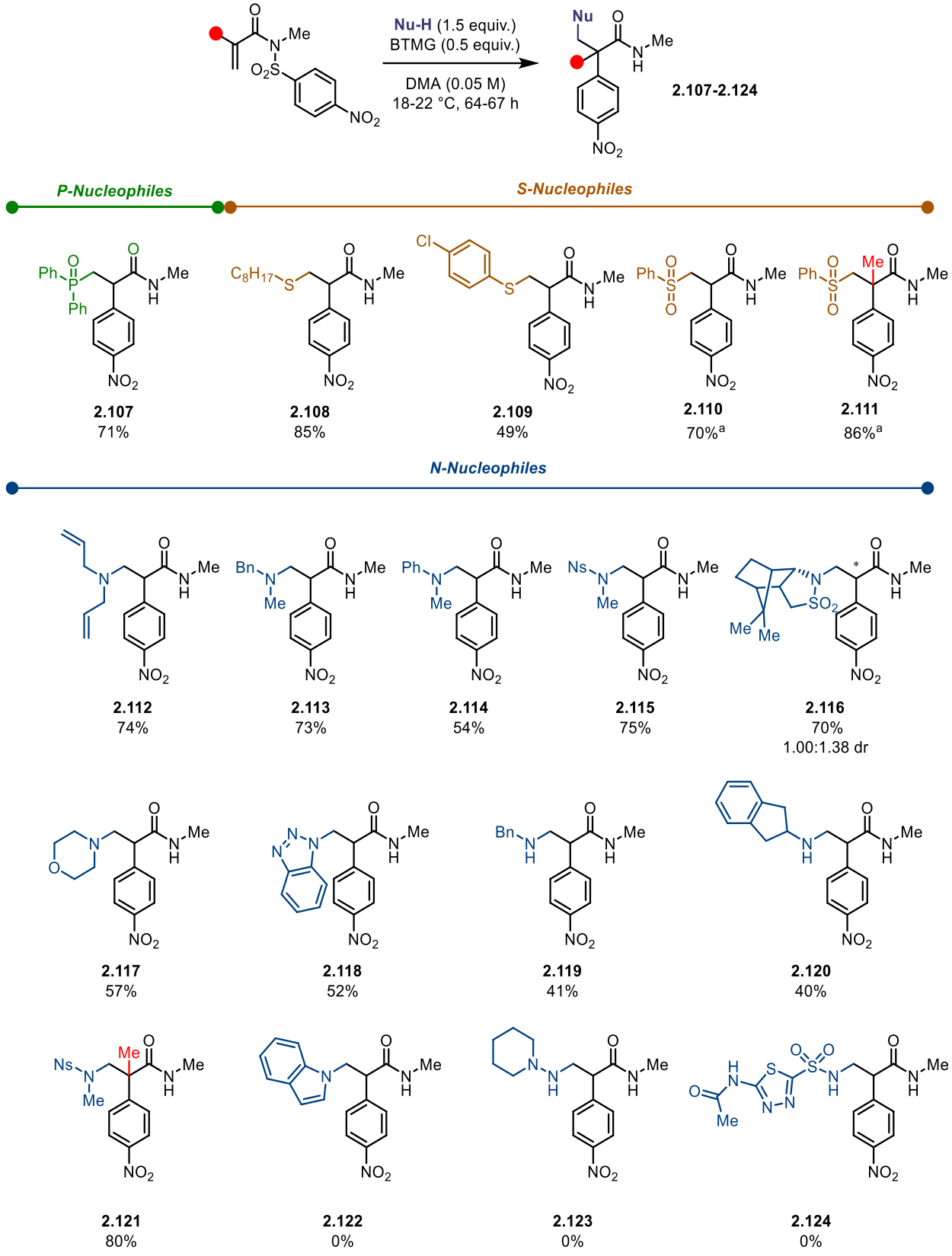


Scheme 2.15. Scope of carbon-based pronucleophiles that can be employed for the conjugate addition-Smiles rearrangement. NMR yields, obtained using dibromomethane as the internal standard, are reported in square brackets.

2.2.4 Scope of Heteroatom-Based Nucleophiles

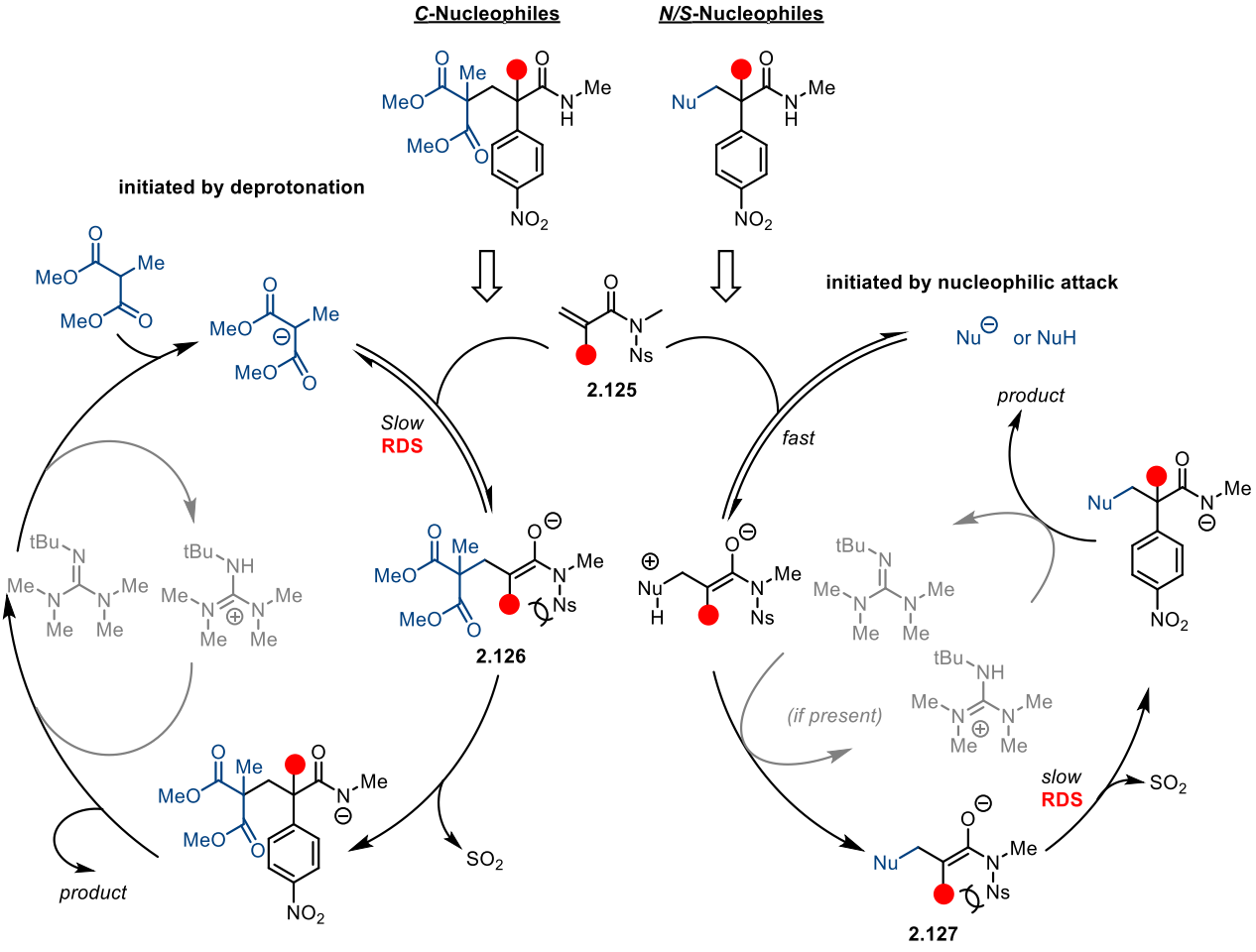
While investigating the possibility of using heteroatoms as nucleophilic centers (**Scheme 2.16**), we first started with diphenylphosphine oxide, which afforded tertiary phosphine oxide **2.107** in 71% yield. Both an aliphatic thiol (**2.108**) and *p*-chloro-thiophenol (**2.109**) were suitable nucleophiles as well, affording products in moderate to excellent yields. Sodium benzenesulfonate, commercially available as a salt, can be directly employed in the reaction without adding BTMG as a base (**2.110**). Intriguingly, when α-methyl sulfonyl acrylamide was coupled with sodium benzenesulfinate, we observe an even higher yield of **2.111** compared to **2.110**, which is opposite to what we observed when a carbon-based pronucleophile was used (see section 2.2.2, **2.084** and **2.092**).

Nitrogen-based nucleophiles are particularly interesting and valuable in this transformation, as a successful rearrangement leads to non-proteogenic α-aryl-β-amino acid derivatives. This transformation cannot be easily achieved by a radical Smiles rearrangement, as nitrogen-based radicals often require carefully chosen substrates and reaction conditions[131,132]. However, a polar regime is much more tolerant for such substrates. Secondary amines such as *N,N*-diallyl amine (**2.112**), *N*-benzylmethyl amine (**2.113**) and *N*-methyl aniline (**2.114**) all afforded the rearranged amide in good yields. In addition, secondary sulfonamides such as *N*-methyl nosyl amine (**2.115**) and the cyclic camphorsultam (**2.116**) were identified as good nucleophiles to induce rearrangement. It is worth mentioning that despite using enantiopure camphorsultam, formation of **2.116** did not exhibit good diastereoselectivity. Nitrogen-containing heterocycles, such as morpholine and benzotriazole, also afforded the β-amino acid derivative in moderate yields (**2.117**, **2.118**). Primary amines can also be employed in the reaction, as demonstrated by benzylamine (**2.119**) and 2,3-dihydro-1*H*-inden-2-amine (**2.120**); the reduced yields are consistent with their reduced nucleophilicity compared to secondary amines. Finally, *N*-methyl nosyl amine can also be coupled with α-methyl sulfonyl acrylamide to afford highly functionalized amide **2.121** in excellent yield, in line with our observations of **2.110** and **2.111**. We also noted that there are limitations in our method and some functional groups cannot be installed on the β-position to induce rearrangement, such as indoles (**2.122**), hydrazides (**2.123**) and primary sulfonamides (**2.124**). We also observed different reactivity with an oxygen-based nucleophile, which will be further elaborated in section 2.2.6.



Scheme 2.16. Scope of heteroatom-based nucleophiles in the conjugate addition-Smiles rearrangement. a) Reaction performed without BTMG.

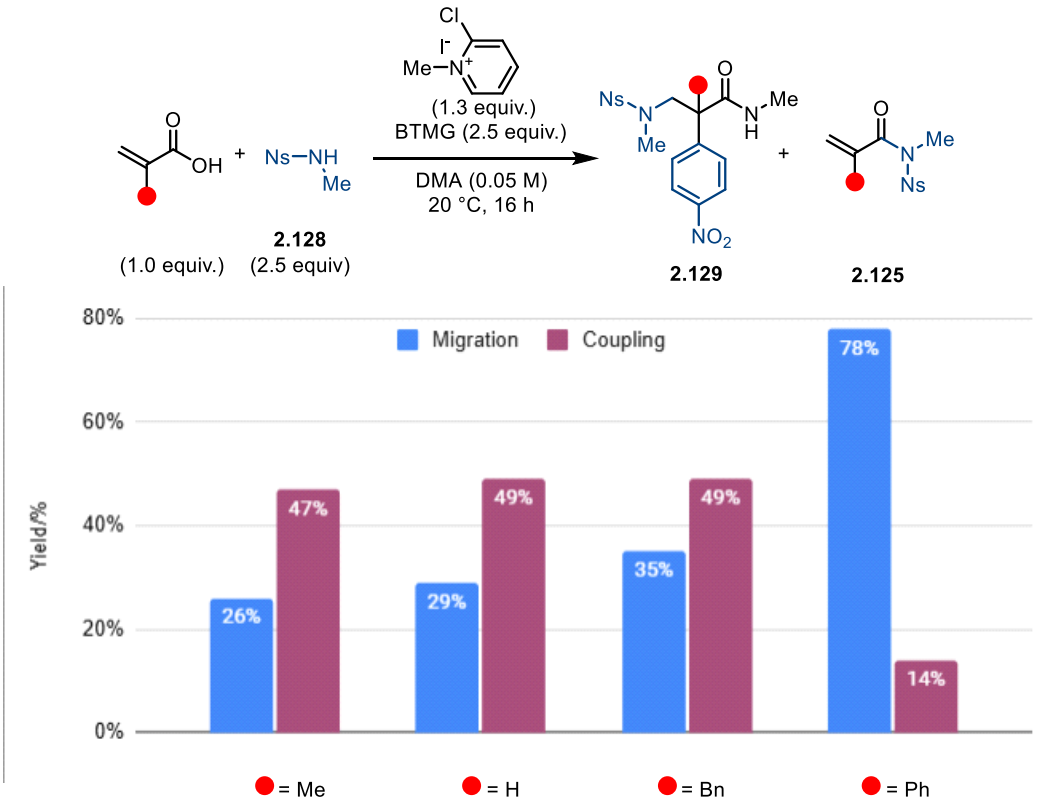
The sharp contrast between the yields of **2.092**, **2.111** and **2.121**, all bearing all-carbon quaternary centers, might be traced back to a different rate-determining step (RDS) in the reaction (**Scheme 2.17**). We hypothesized that for carbon-based nucleophiles, the reaction is initiated by deprotonation of the pronucleophile, and nucleophilic attack is the RDS. Steric hindrance in key intermediate **2.126** in this step plays an important role, leading to its lower yield. On the other hand, for heteroatom-based nucleophiles, the fast initial nucleophilic attack does not require deprotonation.[133] In the rate-determining rearrangement step, release of 1,3-allylic strain is thermodynamically more favored in the α-methyl intermediate **2.127**, thereby leading to a comparable or even higher yields of **2.111** and **2.121** compared to their non-substituted counterparts **2.110** and **2.115**.



Scheme 2.17. Proposal of different rate-determining step (RDS) in the reaction mechanisms.

2.2.5 One-Pot Amide Coupling-Conjugate Addition-Smiles Rearrangement Reaction

Sulfonyl acrylamide starting materials were generally synthesized by amide coupling using activated acrylic acids and secondary sulfonamides. As sulfonamides also proved to be excellent nucleophiles in the domino reaction, we envisioned a two-step, one-pot reaction in which acrylic acids can be directly converted into β-amino acid derivatives (**Scheme 2.18**). When using Mukaiyama's reagent[134] as the activator and BTMG as the base, we observed successful coupling between atropic acid and *N*-methylnosyl amine **2.128**. A second equivalent of **2.128** underwent conjugate addition to the sulfonyl acrylamide intermediate **2.125**, triggering aryl migration to afford rearranged product **2.129** as the major product in 78% yield. However, for α-alkyl acrylic acids, we only observed migration to a limited extent, where the coupling product was isolated as the major product. We hypothesized that this was because an aryl group can better stabilize the charge in the enolate intermediate (**2.127**, see scheme **2.17**) after conjugate addition, thereby facilitating the conjugate addition-aryl migration sequence.

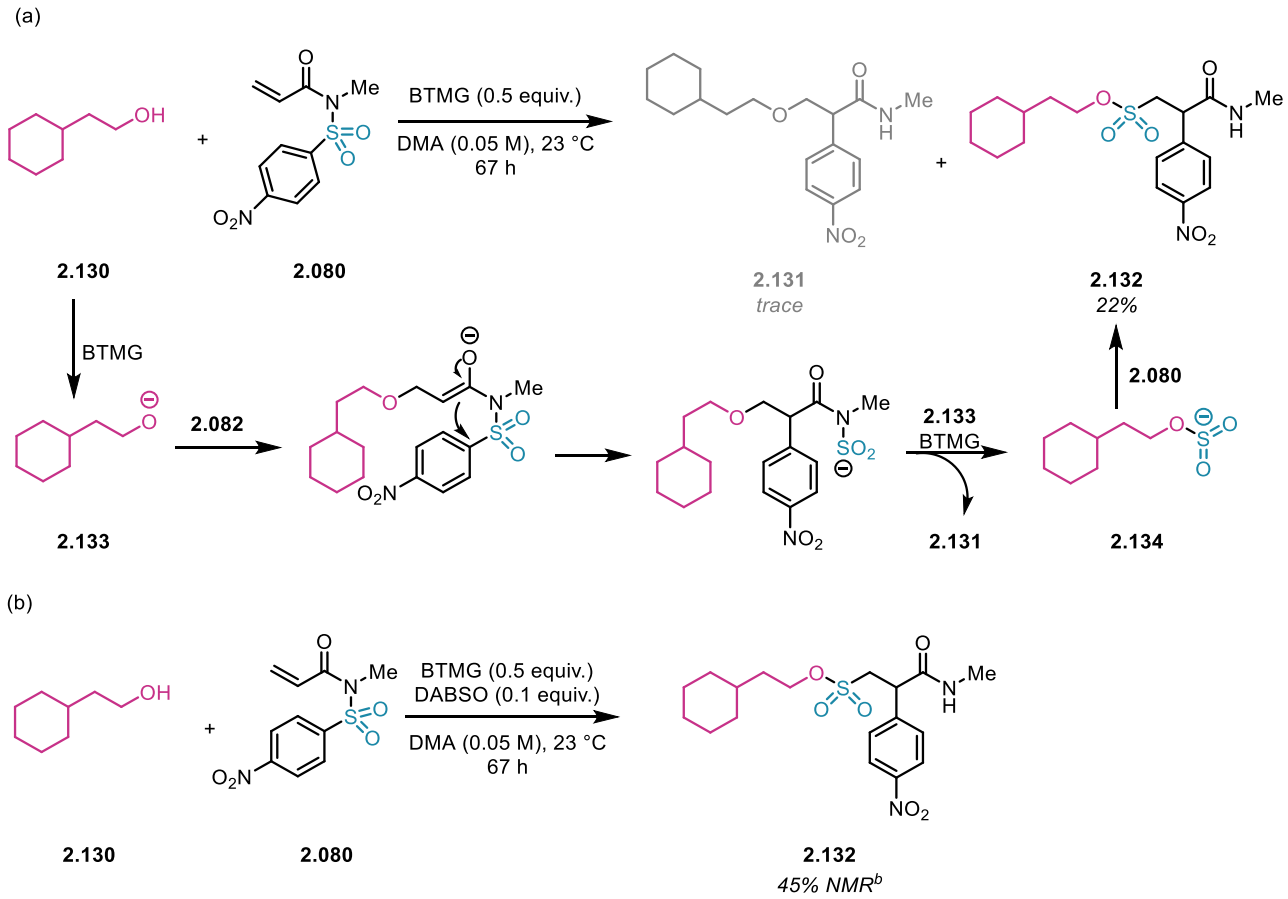


Scheme 2.18. Synthesis of β-amino acid derivatives by one-pot reaction from acrylic acids.

2.2.6 In-Situ Trapping of SO_2

The work presented in this section was carried out by Dr. Haoqi Zhang and Dr. Tommaso Bortolato.

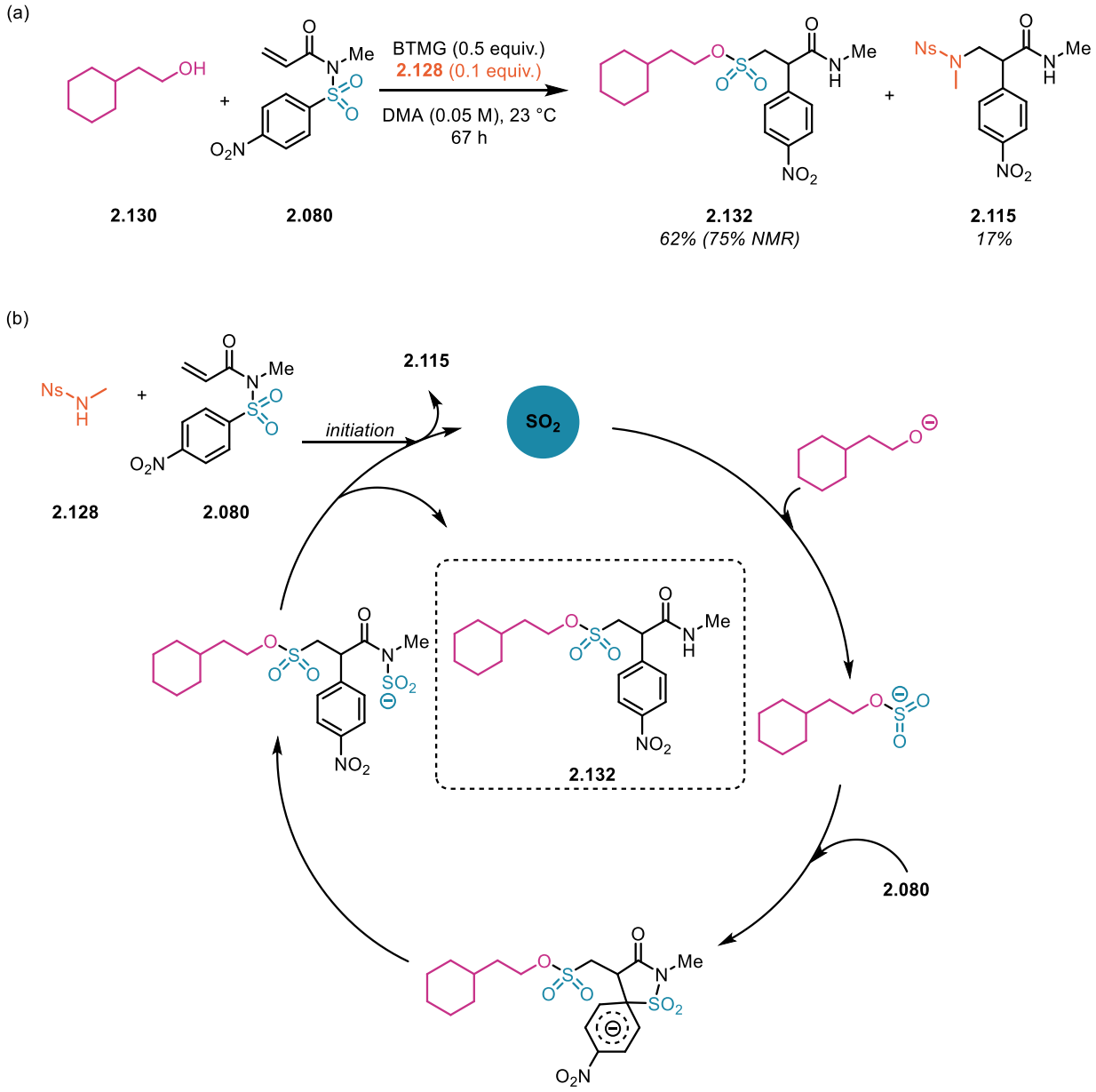
During our study of the scope of heteroatom-based nucleophiles, we came across alcohol **2.130**. While the expected amide **2.131** was only formed in traces, we unexpectedly isolated sulfonic ester **2.132** in 22% yield (**Scheme 2.19a**). Drawing a parallel between this observation and our previous computational study (see section 2.1.3), we hypothesized that during the initial trace formation of **2.131**, released SO_2 can be trapped by alkoxide **2.133** to form sulfonate **2.134,** which then acts as a nucleophile in a conjugate addition to **2.080**, triggering the rearrangement. Compared to **2.130** or **2.133**, sulfonate **2.134** might be a better nucleophile for **2.080** due to its 'softer' nature, thereby producing **2.132** as the major product.



Scheme 2.19. a) Using alcohol **2.130** as nucleophile led to the formation of sulfonic ester **2.132** as the major product. b) Adding DABSO as a catalyst leads to higher yield of **2.132**. b) NMR yield determined using mesitylene as an internal standard.

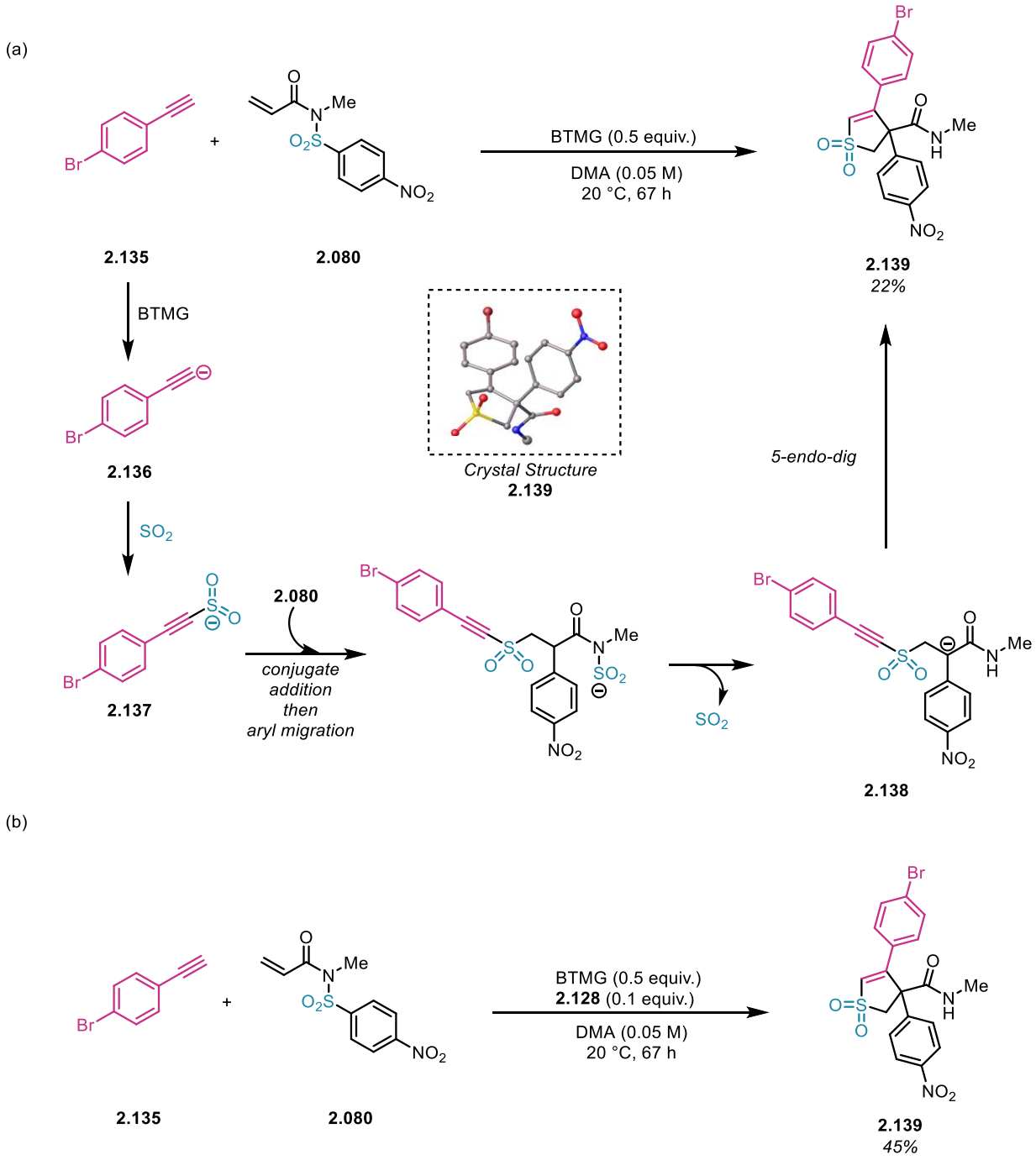
However, the initiation of this mechanistic cycle relies on the initial nucleophilic attack by **2.130** or **2.133** and subsequent aryl migration. In order to accelerate this process, we added DABSO as a catalyst, hoping that SO_2 transfer to alkoxide **2.133** could produce the required nucleophile **2.134** more efficiently. Indeed, an increase in yield of **2.134** was observed (**Scheme 2.19b**). However, it is also worth noting that DABCO can be produced during SO_2 transfer, which will act as a Lewis base to attack **2.080** and trigger aryl migration, as we previously demonstrated.[128]

Therefore, we switched to a catalytic amount (0.1 equiv.) of secondary sulfonamide **2.128**, previously identified as a good nucleophile (**see section 2.2.4**). The initial conjugate addition and aryl migration led to product **2.115**, with concomitant SO_2 capture by alkoxide **2.133**. Sulfonate **2.134** then acts as a nucleophile to start the conjugate addition-aryl migration domino reaction, leading to product **2.132** in a good yield (**Scheme 2.20a** and **b**).



Scheme 2.20. a) Using a catalytic amount of good nucleophile **2.128** led to a good yield of sulfonic ester **2.132**. b) Proposed catalytic cycle.

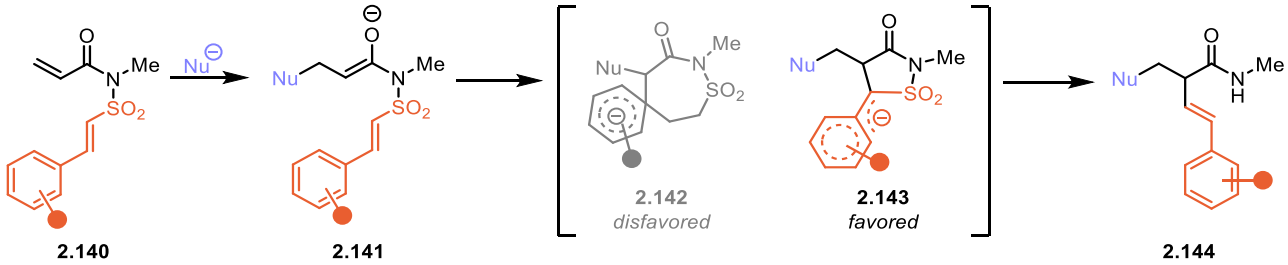
In addition to alcohol **2.130**, we also observed a similar reaction when alkyne **2.135** was used as the pronucleophile (**Scheme 2.21a**). The reaction was initiated by the capture of a trace amount of SO_2 by deprotonated alkyne **2.136**, forming sulfinate **2.137**. **2.137** then acts as the nucleophile to engage in the domino conjugate addition-aryl migration sequence. The release of SO_2 and proton transfer led to intermediate **2.138**, which then engaged in a Baldwin-rule allowed 5-*endo-dig* cyclization to form product **2.139**. In an analogy to sulfonic ester product **2.132**, the yield of cyclic sulfone **2.139** can also be improved by adding a catalytic amount of good nucleophile **2.128** (**Scheme 2.21b**).



Scheme 2.21. a) Using alkyne **2.135** as pronucleophile led to cyclic sulfone **2.139**. b) Adding secondary sulfonamide **2.128** as a catalyst improves yield of **2.139**.

2.2.7 Vinylogous migration

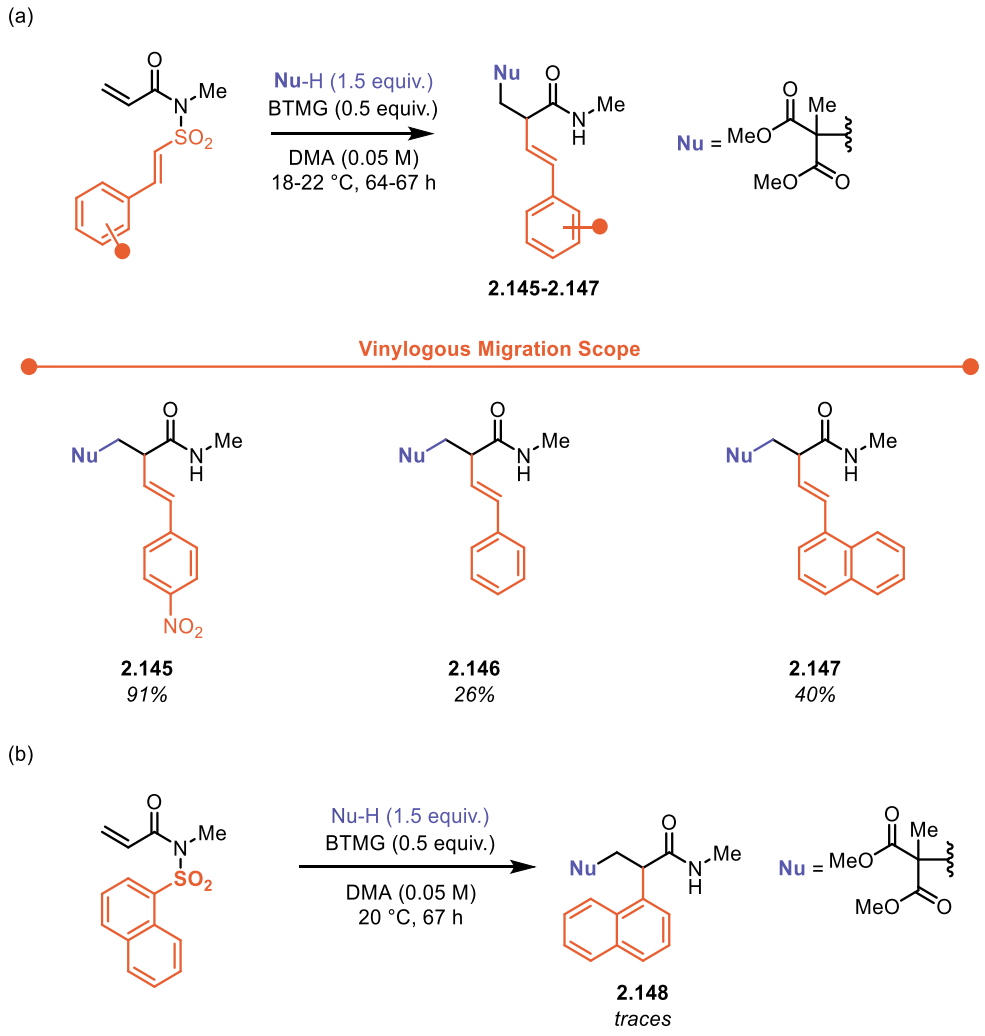
As the polar Truce-Smiles rearrangement involves Meisenheimer complex **2.072** (See **section 2.1.4, Scheme 2.12**) carrying a negative charge as an intermediate or transition state, the aryl group nearly always carries an electron-withdrawing group to stabilize it. In order to overcome this limitation, we envisioned lowering the energy of the Meisenheimer complex by relieving the strain of the spirocyclic ring by extending the conjugate system. Inspired by the work of the Greaney and Clayden groups,[135,136] we chose vinyl sulfonyl acrylamide **2.140** as the substrate. After conjugate addition of the nucleophile to **2.140**, enolate **2.141** can in principle form either spirocyclic Meisenheimer complex **2.142** containing a 7-membered ring, or form intermediate **2.143** with a 5-membered ring. We hypothesized that the latter is kinetically favored, leading to rearranged product **2.144** (**Scheme 2.22**).



Scheme 2.22. Envisioned conjugate addition-vinylogous migration.

We first attempted vinylogous migration on a substrate bearing an electron-withdrawing nitro group (**Scheme 2.23a**). To our delight, migration of the vinyl group led to formation of product **2.145** in an excellent yield 94%, even higher than the related aryl migration product **2.084 (89%, see section 2.2.2)**. As electron-neutral aryl groups were previously thought to be incompatible with polar Truce-Smiles rearrangements, we tested a styryl group to see if we could indeed overcome this limitation. Although the rearrangement product **2.146** was isolated in only 26% yield, it is the first report of migration of an electron-neutral vinyl group in a polar Truce-Smiles rearrangement. Furthermore, the vinyl naphthyl group, with a more extensive conjugate system, migrated successfully to afford **2.147** in 40% yield.

In a control experiment, a substrate bearing only a naphthyl group afforded the rearranged product **2.148** (**Scheme 2.23b**) in only trace amounts. This supported the proposal that only extending the conjugated system in the migrating group is insufficient to allow migration of electron-neutral groups, and a low-strain, non-spirocyclic intermediate **2.143** is the key to our observed migration.



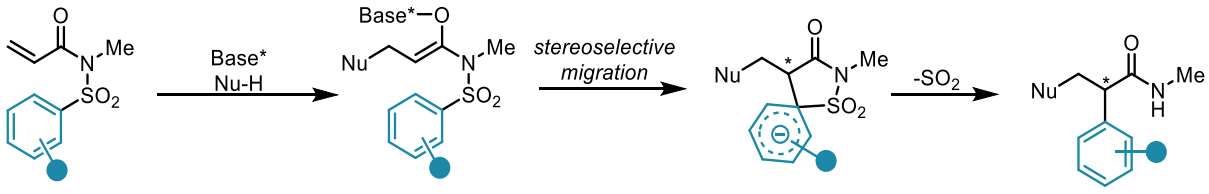
Scheme 2.23 a) Scope of vinylogous migration, including unprecedented migration of electron-neutral groups in a polar Smiles rearrangement. b) Control reaction of naphthyl group migration, highlighting the importance of the non-spirocyclic intermediate in electron-neutral group migration.

2.2.8 Summary and Outlook

In summary, we have developed a conjugate addition-induced polar Smiles rearrangement to access α,β-difunctionalized amides. The protocol is mild and compatible with a range of sulfonyl acrylamides, carbon- and heteroatom-based nucleophiles. In contrast to the radical-based approach, this reaction allows the use of nitrogen-based nucleophiles, allowing direct access to β-amino acid derivatives. A direct two-step, one-pot protocol has also been developed, in which an acryl carboxylic acid can be directly coupled with *N*-methyl nosyl amine to afford β-amino acid derivatives. We have additionally reported that sulfur dioxide released in this rearrangement can be captured by alkoxide or acetylide, effectively functioning as sulfonate or sulfinate nucleophiles in the reaction. Furthermore, by extending the conjugate system and avoiding spirocyclic Meisenheimer complex, an unprecedented migration of electron-neutral vinyl group in polar Truce-Smiles rearrangement was reported.

In the future, the trapping of sulfur dioxide can be further optimized. This provides a novel synthetic approach to sulfonate esters and cyclic sulfones, both with potential in biological applications.[137,138] Knowing that DABSO, a source of SO_2, is beneficial for the reaction, other SO_2 sources can be explored in the next optimizations.

Finally, it might also be of interest to explore a stereoselective modification of the reaction. By using a chiral Brønsted base instead of BTMG, after initial conjugate addition, the ionic interaction between chiral base and enolate intermediate may lead to the aryl migration to happen preferentially on one face (**Scheme 2.24**).[139,140]



Scheme 2.24. Proposed enantioselective domino conjugate addition-Smiles rearrangement.

Chapter 3. Experimental

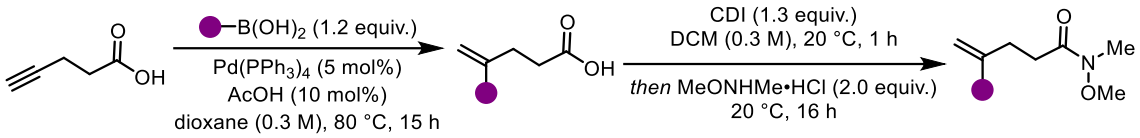
3.1 General Information

Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. All anhydrous solvents were distilled from appropriate drying agents prior to use or, if purchased in anhydrous form under inert atmosphere, used as received. All reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). Neat infrared spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (ν_{max}) are reported in cm^{-1}. Mass spectra were obtained on Agilent 7200B GC-Q-TOF, Bruker amaZon speed ETD spectrometer or Bruker timsTOF Flex spectrometer, using electrospray ionization (ESI) or electron ionization (EI). Details on chromatographic conditions are indicated under each compound. All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400, AV-600 or AV-700 spectrometer at 300 K. Chemical shifts are given in parts per million (ppm, δ), referenced to the solvent peak of $CDCl_3$, defined at δ = 7.26 ppm (^{1}H NMR) and δ = 77.16 ppm (^{13}C NMR). Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) as they appeared in the spectrum. If the appearance of a signal differs from the expected splitting pattern, the observed pattern is designated as apparent (app). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br).

3.2 Controlling the Fate of Bicyclobutonium Ions by Computation-Aided Reaction Design

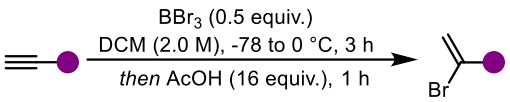
3.2.1 General Procedures

General Procedure A: Synthesis of Weinreb Amides from Boronic Acids



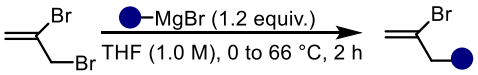
In a dried Schlenk flask under argon, to a solution of 4-pentynoic acid (1.0 equiv.), the appropriate boronic acid (1.2 equiv.), tetrakis(triphenylphosphine)palladium(0) (5 mol%) in anhydrous 1,4-dioxane (0.3 M) at 20 °C was added acetic acid (10 mol%).[141] The reaction was stirred at 20 °C for 15 min before being heated to 80 °C and stirred for further 15 h. After cooling, the reaction was concentrated under reduced pressure, redissolved in ethyl acetate and filtered through a silica pad. The filtrate was concentrated again under reduced pressure, and the crude residue was used directly in the next step without further purification, assuming full conversion. The crude residue was dissolved in dichloromethane (0.3 M) and 1,1'-carbonyldiimidazole (1.3 equiv.) was added portion-wise at 20 °C.[142] The reaction was stirred at the same temperature for 1 h, before *N,O*-dimethylhydroxylamine hydrochloride (2.0 equiv.) was added. After being stirred at 20 °C for 16 h, the reaction was acidified to pH = 1–2 by addition of aq. HCl (1.0 M). The biphasic was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with satd. aq. $NaHCO_3$ and brine. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate/heptanes 0:1–1:0) to afford the Weinreb amide.

General Procedure B: Synthesis of Vinyl Bromides by Hydrobromination of Alkynes



In a dried Schlenk flask under argon, to a solution of the appropriate alkyne (1.0 equiv.) in anhydrous dichloromethane (2.0 M) at -78 °C was added boron tribromide (0.5 equiv.). The reaction was allowed to warm to 20 °C and stirred for 3 h. Acetic acid (16 equiv.) was added slowly and the reaction was stirred for a further 1 h, after which the solution was slowly neutralized by the addition of satd. aq. $NaHCO_3$. The biphasic mixture was separated and the aqueous phase was extracted with pentane. The combined organic phases were washed with satd. aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated carefully under reduced pressure (>500 mbar). The crude residue was filtered through silica, eluting with pentane, and concentrated carefully under reduced pressure (>500 mbar) for 30 min. The yield and final concentration of vinyl bromide were determined by quantitative ^1H NMR analysis, using dibromomethane as the internal standard. ^{13}C NMR spectra were not recorded, as the products were invariably isolated as solutions. The solution of vinyl bromide was used directly in the next step without further purification.

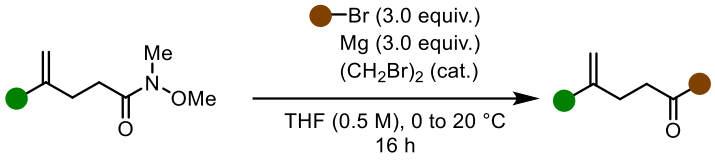
General Procedure C: Synthesis of Vinyl Bromides by Grignard Reaction



In a dried Schlenk flask under argon, to a solution of 2,3-dibromopropene (1.0 equiv.) in anhydrous tetrahydrofuran (1.0 M) at 0 °C was added the Grignard reagent (1.2 equiv.). The reaction was heated to 66 °C and kept at this temperature (at reflux) for 2 h before being decanted into ice. The biphasic mixture was acidified by the addition of aq. HCl (1.0 M) and extracted with diethyl ether. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated carefully under reduced pressure (>500 mbar). The crude residue was filtered through silica, eluting with pentane and concentrated carefully under reduced pressure (>500 mbar) for 30 min. The yield and final concentration of vinyl bromide was determined with quantitative ^1H NMR, using dibromomethane as the internal

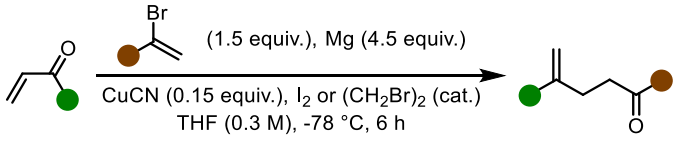
standard. ^{13}C NMR were not recorded due to the solution nature of the product obtained. The solution of vinyl bromide was used directly in the next step without further purification.

General Procedure D: Synthesis of Ketones from Weinreb Amides and Aryl Bromides



To a dried Schlenk flask under argon were added magnesium turnings (3.0 equiv.) and anhydrous tetrahydrofuran (0.5 M) at 20 °C. A few drops of 1,2-dibromoethane were added. The aryl bromide (3.0 equiv.) was then added dropwise. The reaction was stirred at 20 °C for 1 h or until most magnesium had dissolved. The reaction was cooled to 0 °C and the Weinreb amide (1.0 equiv.) was added dropwise, neat or as a solution in anhydrous tetrahydrofuran. The reaction was allowed to warm to 20 °C and stirred for 16 h at that temperature. The reaction was then quenched by addition of aq. HCl (1.0 M), extracted with diethyl ether and washed with brine. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrate under reduced pressure. Purification by column chromatography afforded the desired ketone.

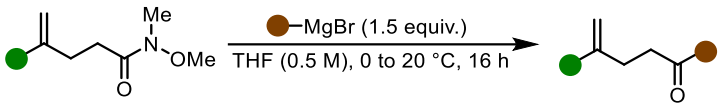
General Procedure E: Synthesis of Ketones by Copper-Mediated Conjugate Addition



To dried Schlenk flask under argon were added magnesium turnings (4.5 equiv.), one grain of iodine or 50 µL of 1,2-dibromoethane and anhydrous tetrahydrofuran (0.3 M) at 20 °C. A solution of the appropriate vinyl bromide (1.5 equiv.) was added dropwise and the reaction was stirred for 1 h at 20 °C. The resulting solution of Grignard reagent was cannulated into a suspension of copper(I) cyanide (0.15 equiv.) in anhydrous tetrahydrofuran prepared in a separate dried Schlenk flask and cooled at -78 °C, after which the reaction was stirred for 10 min. A 1 M solution of the appropriate a,b-unsaturated ketone

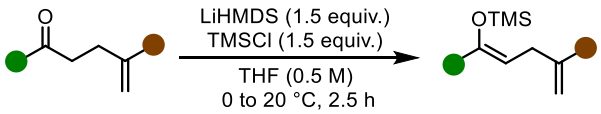
(1.0 equiv.) was subsequently added dropwise. The reaction was stirred for 6 h at -78 °C, before being allowed to warm to 20 °C, after which satd. aq. $NaHCO_3$ was added. The resulting mixture was extracted with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate/heptanes) to afford the ketone. *Minor impurities after column chromatography, if present, were taken into the next step of the synthesis.*

General Procedure F: Synthesis of Ketones from Weinreb Amides and Grignard Reagents



In a dried Schlenk flask under argon at 0°C, to a solution of the Weinreb amide (1.0 equiv.) in anhydrous tetrahydrofuran (0.5 M) was added phenylmagnesium bromide (1 M in tetrahydrofuran, 1.5 equiv.). The reaction was allowed to warm to 20 °C and stirred for 16 h. The reaction was quenched by addition of satd. aq. NH_4Cl, diluted with dichloromethane and the biphasic mixture was separated. The aqueous phase was extracted with dichloromethane, and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate/heptanes) to afford the ketone.

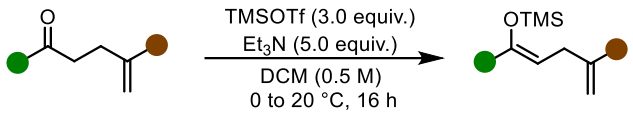
General Procedure G: Synthesis of Silyl Enol Ethers using LiHMDS and TMSCl



In a dried Schlenk flask under argon at 0 °C, to a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.5 equiv.) was added the solution of ketone (1.0 equiv.) in anhydrous tetrahydrofuran (0.5 M) dropwise. The reaction was stirred at 0 °C for 30 min, before chlorotrimethylsilane (1.5 equiv.) was added. The reaction was warmed to 20 °C and stirred for further 2 h, after which it was transferred

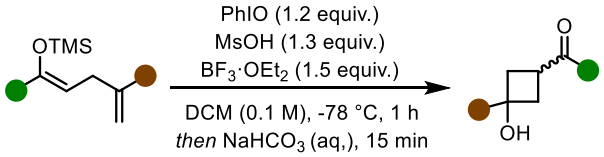
to a round-bottom flask and concentrated under reduced pressure. The crude residue was purified **quickly** by flash column chromatography (SiO_2, ethyl acetate/heptanes) to afford the silyl enol ether. Inseparable TMSOTMS was removed under high vacuum, as much as possible.

General Procedure H: Synthesis of Silyl Enol Ethers using Et_3N and TMSOTf



In a dried Schlenk flask under argon at 0 °C, to a solution of ketone (1.0 equiv.) and triethylamine (5.0 equiv.) in dichloromethane (0.5 M) was added trimethylsilyl trifluoromethanesulfonate (3.0 equiv.) dropwise. The reaction was allowed to warm to 20 °C and stirred for 16 h, after which satd. aq. $NaHCO_3$ was added. The biphasic mixture was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed sequentially with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate/heptanes) to afford the silyl enol ether.

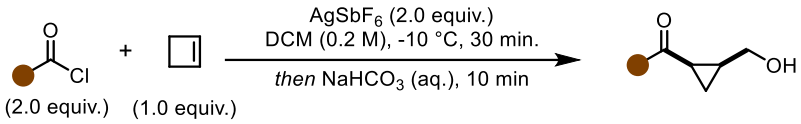
General Procedure I: Umpolung Oxidation of Silyl Enol Ethers



In a dried Schlenk flask under argon at 20 °C, to a suspension of iodosylbenzene (1.2 equiv.) in dichloromethane (0.1 M) was added methanesulfonic acid (1.3 equiv.) and the reaction was stirred for 10 min. After subsequent cooling to -78 °C, boron trifluoride diethyl etherate (1.5 equiv.) was added. The reaction was stirred for another 15 min, before the silyl enol ether (1.0 equiv.) was added and stirring was continued for 1 h. The reaction was allowed to warm to 20 °C, satd. aq. $NaHCO_3$ was added and the resulting biphasic mixture was stirred for 15 min. Following separation of the phases, the aqueous phase was extracted with dichloromethane and the combined organic phases were dried over

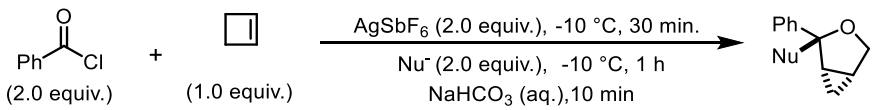
anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was filtered through a silica pad, eluting with ethyl acetate, and concentrated under reduced pressure again. The NMR yield was determined using dibromomethane as the internal standard. The crude residue was purified by flash column chromatography (SiO_2, heptane/ethyl acetate 1:0–1:1) to afford the cyclobutanol.

General Procedure J: Synthesis of Cyclopropylcarbinols



An oven-dried vial was flushed with argon and charged with a magnetic stir bar. A solution of the appropriate acyl chloride (2.0 equiv.) in anhydrous dichloromethane was added to the vial, and the reaction system was cooled to -10 °C (ice/salt bath). Cyclobutene (1 M in dichloromethane, 1.0 equiv.) was added and the solution was treated with silver hexafluoroantimonate ($AgSbF_6$) (2.0 equiv.). The reaction was further stirred at -10 °C for 30 min, after which satd. aq. $NaHCO_3$ was added to the vial and the biphasic system was stirred for 10 min at 20 °C. The reaction was extracted with dichloromethane and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, heptane/ethyl acetate) to afford the cyclopropylcarbinol. *The reactions were performed by Dr. Zhi-Jie Niu, and therefore the product analyses have not been included in this thesis.*

General Procedure K: Synthesis of fused-ring THF products

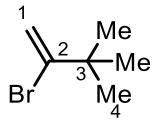


An oven-dried vial was flushed with argon and charged with a magnetic stir bar. A solution of the corresponding acyl chloride (2.0 equiv.) in anhydrous dichloromethane was added to the vial, and the reaction system was cooled to -10 °C (ice/salt bath). Cyclobutene (1M in dichloromethane, 1.0 equiv.)

was added and treated with silver hexafluoroantimonate (2.0 equiv.) under an argon atmosphere. The vial continued stirring in the ice salt bath at -10 °C. After stirring for 30 min, the selected nucleophile (2.0 equiv.) was added. After stirring at -10 °C for 1h, saturated $NaHCO_3$ aqueous solution was added and stirred for 10 min. The reaction was extracted with dichloromethane and the combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (SiO_2, heptane/ethyl acetate) to give the desired compounds. *The reactions were performed by Dr. Zhi-Jie Niu, and therefore the product analyses have not been included in this thesis.*

3.2.2 Characterization of Products

2-Bromo-3,3-dimethylbut-1-ene



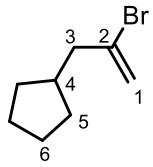
$C_6H_{11}Br$
MW: 163.0580

Following **General Procedure B** using 3,3-dimethyl-1-butyne (2.46 mL, 20.0 mmol, 1.00 equiv.), acetic acid (18.3 mL, 320 mmol, 16.0 equiv.) and boron tribromide (1 M in hexanes, 10.0 mL, 10.0 mmol, 0.500 equiv.). The title compound was obtained as a pale-yellow oil (calculated 794 mg, 4.87 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (d, *J* = 2.1 Hz, 1H, H^{1a}), 5.38 (d, *J* = 2.0 Hz, 1H, H^{1b}), 1.20 (s, 9H, H^4).

The compound was not purified due to its volatility, and used as a solution in pentane directly in the next step. Therefore, complete characterization was not performed.

(2-Bromoallyl)cyclopentane



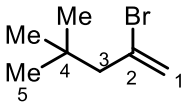
$C_8H_{13}Br$
MW: 189.0960

Following **General Procedure C** using 2,3-dibromopropene (0.98 mL, 10 mmol, 1.0 equiv.) and cyclopentylmagnesium bromide (2 M in ether, 6.0 mL, 12 mmol, 1.2 equiv.) The title compound was obtained as a pale-yellow oil (calculated 1.09 g, 5.76 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 – 5.52 (m, 1H, H^{1a}), 5.38 (d, *J* = 1.4 Hz, 1H, H^{1b}), 2.45 – 2.34 (m, 2H, H^3), 2.18 (tt, *J* = 16.6, 8.3 Hz, 1H, H^4), 1.83 – 1.74 (m, 2H, H^{5a}), 1.60 (m, 2H, H^{5b}), 1.34 – 1.23 (m, 2H,H^{6a}), 1.20 – 1.09 (m, 2H, H^{6b}). *Hydrocarbon impurities were detected on NMR.*

The compound was not purified due to its volatility, and used as a solution in pentane directly in the next step. Therefore, complete characterization was not performed.

2-Bromo-4,4-dimethylpent-1-ene



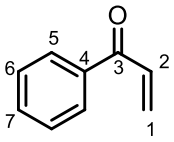
$C_7H_{13}Br$
MW: 177.0850

Following **General Procedure C** using 2,3-dibromopropene (0.49 mL, 5.0 mmol, 1.0 equiv.) and *tert*-butylmagnesium chloride (1 M in tetrahydrofuran, 6.0 mL, 6.0 mmol, 1.2 equiv.) The title compound was obtained as a pale-yellow oil (calculated 603 mg, 3.43 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (s, 1H, H^{1a}), 5.50 (s, 1H, H^{1b}), 2.40 (t, *J* = 4.2 Hz, 2H, H^3), 1.00 (app t, *J* = 4.0 Hz, 9H, H^5).

The compound was not purified due to its volatility, and used as a solution in pentane directly in the next step. Therefore, complete characterization was not performed.

1-Phenylprop-2-en-1-one



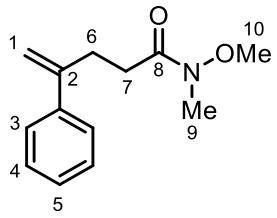
C_9H_8O
MW: 132.1620

The compound was synthesized according to a known literature procedure.[143] The title compound was isolated as a pale-yellow oil (2.53 g, 19.1 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.89 (m, 2H, H^5), 7.62 – 7.54 (m, 1H, H^7), 7.48 (td, *J* = 7.0, 1.5 Hz, 2H, H^6), 7.16 (dd, *J* = 17.1, 10.6 Hz, 1H, H^2), 6.44 (dd, *J* = 17.1, 1.7 Hz, 1H, H^{1a}), 5.94 (dd, *J* = 10.6, 1.7 Hz, 1H, H^{1b}).

The spectroscopic data were consistent with that reported in literature.[144]

N-Methoxy-N-methyl-4-phenylpent-4-enamide



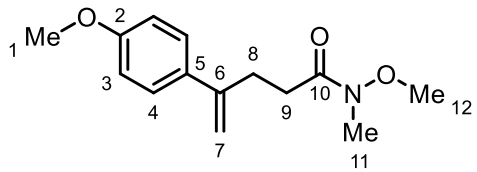
$C_{13}H_{17}NO_2$
MW: 219.2840

Following **General Procedure A** using 4-pentynoic acid (1.00 g, 10.0 mmol, 1.00 equiv.), $Pd(PPh_3)_4$ (578 mg, 0.500 mmol, 5.00 mol%.), phenylboronic acid (1.54 g, 12.0 mmol, 1.20 equiv.), acetic acid (0.057 mL, 1.0 mmol, 0.10 equiv.), 1,1'-carbonyldiimidazole (1.76 g, 10.5 mmol, 1.05 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (1.95 g, 20.0 mmol, 2.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a colourless oil (520 mg, 2.37 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.42 (m, 2H, H^3 or H^4), 7.36 – 7.31 (m, 2H, H^4 or H^3), 7.30 – 7.26 (m, 1H, H^5), 5.33 – 5.30 (m, 1H, H^{1a}), 5.14 – 5.11 (m, 1H, H^{1b}), 3.59 (s, 3H, H^{10}), 3.17 (s, 3H, H^9), 2.89 – 2.83 (m, 2H, H^7), 2.61 – 2.53 (m, 2H, H^6).

The spectroscopic data were consistent with that reported in literature.[145]

N-Methoxy-4-(4-methoxyphenyl)-N-methylpent-4-enamide



$C_{14}H_{19}NO_3$
MW: 249.3100

Following **General Procedure A** using 4-pentynoic acid (1.00 g, 10.0 mmol, 1.00 equiv.), 4-methoxyphenylboronic acid (1.82 g, 12.0 mmol, 1.20 equiv.), $Pd(PPh_3)_4$ (578 mg, 0.500 mmol, 5.00 mol%), acetic acid (0.057 mL, 1.0 mmol, 0.10 equiv.), 1,1'-carbonyldiimidazole (2.17 g, 13.0 mmol, 1.30 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (1.95 g, 20.0 mmol, 2.00 equiv.). Purification

by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a pale-yellow oil (729 mg, 2.92 mmol, 29%).

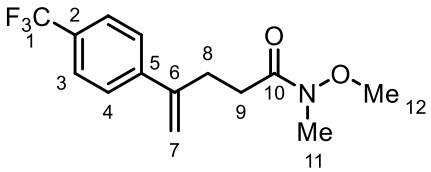
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.45 – 7.30 (m, 2H, H^3 or H^4), 6.93 – 6.72 (m, 2H, H^3 or H^4), 5.25 (d, *J* = 0.5 Hz, 1H, H^{7a}), 5.03 (d, *J* = 1.2 Hz, 1H, H^{7b}), 3.81 (s, 3H, H^1), 3.60 (s, 3H, H^{12}), 3.17 (s, 3H, H^{11}), 2.87 – 2.74 (m, 2H, H^9), 2.64 – 2.50 (m, 2H, H^8).

^{13}C NMR (176 MHz, $CDCl_3$): δ 174.1 (C^{10}), 159.3 (C^2), 146.8 (C^5 or C^6), 133.1 (C^5 or C^6), 127.3 (2C, C^3 or C^4), 113.8 (2C, C^3 or C^4), 111.3 (C^7), 61.3 (C^{12}), 55.4 (C^1), 32.3 (C^{11}), 31.2 (C^8), 30.3(C^9).

IR (neat) ν_{max}: 2936, 2836, 1660, 1511, 1247, 1031, 836.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{29}NO_3Na^+$) requires *m*/*z* 272.1257, found *m*/*z* 272.1253.

N-Methoxy-N-methyl-4-(4-(trifluoromethyl)phenyl)pent-4-enamide



$C_{14}H_{16}NF_3O_2$
MW: 287.2822

Following **General Procedure A** using 4-pentynoic acid (1.00 g, 10.0 mmol, 1.00 equiv.), 4-(trifluoromethyl)phenylboronic acid (2.28 g, 12.0 mmol, 1.20 equiv.), $Pd(PPh_3)_4$ (578 mg, 0.500 mmol, 5.00 mol%), acetic acid (0.057 mL, 1.00 mmol, 0.10 equiv.), 1,1'-carbonyldiimidazole (2.17 g, 13.0 mmol, 1.30 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (1.95 g, 20.0 mmol, 2.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a pale-yellow oil (349 mg, 1.21 mmol, 12%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.3 Hz, 2H, H^3), 7.56 – 7.46 (m, 2H, H^4), 5.38 (app s, 1H, H^{7a}), 5.22 (d, *J* = 0.9 Hz, 1H, H^{7b}), 3.61 (s, 3H, H^{12}), 3.16 (d, *J* = 2.9 Hz, 3H, H^{11}), 2.86 (app. dd, *J* = 8.3, 7.3 Hz, 2H, H^9), 2.68 – 2.46 (m, 2H, H^8).

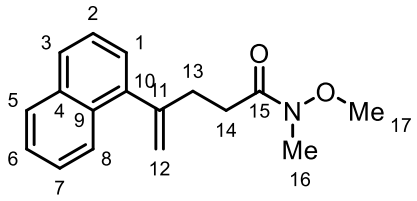
^{13}C NMR (176 MHz, $CDCl_3$): δ 173.7 (C^{10}), 146.5 (C^{6}), 144.4 (C^{5}), 129.7 (q, *J* = 32.5 Hz, C^{2}), 126.6 (2C, C^{4}), 124.4 (q, *J* = 273 Hz, C^{1}), 125.5 (2C, q, *J* = 3.7 Hz, H^{3}), 114.8 (C^{7}), 61.3 (C^{12}), 32.3 (C^{11}), 30.9 (C^{8}), 30.0 (C^{9}).

^{19}F NMR (659 MHz, $CDCl_3$): δ -62.52.

IR (neat) ν_{max}: 2970, 1797, 1666, 1325, 1166, 1117, 1069, 844, 702.

HRMS (GC-TOF): exact mass calculated for $[M\text{-}OMe]^+$ ($C_{13}H_{13}F_3NO^+$) requires *m/z* 256.0944, found *m/z* 256.0939.

N-Methoxy-N-methyl-4-(naphthalen-1-yl)pent-4-enamide



$C_{17}H_{19}NO_2$
MW: 269.3440

Following General **Procedure A** using 4-pentynoic acid (1.00 g, 10.0 mmol, 1.00 equiv.), 1-naphthaleneboronic acid (2.06 g, 12.0 mmol, 1.20 equiv.), $Pd(PPh_3)_4$ (578 mg, 0.500 mmol, 5.00 mol%), acetic acid (0.057 mL, 1.00 mmol, 0.10 equiv.), 1,1'-carbonyldiimidazole (2.17 g, 13.0 mmol, 1.30 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (1.95 g, 20.0 mmol, 2.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a pale-yellow oil (1.43 g, 53.1 mmol, 53%).

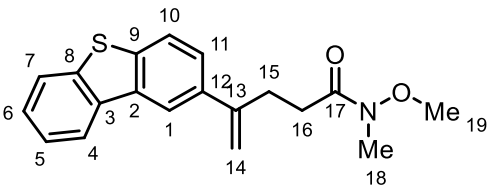
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.09 – 7.98 (m, 1H, H^{Ar}), 7.93 – 7.80 (m, 1H, H^{Ar}), 7.76 (dd, *J* = 14.5, 8.3 Hz, 1H, H^{Ar}), 7.49 – 7.45 (m, 2H, H^{Ar}), 7.43 (dt, *J* = 12.1, 6.0 Hz, 1H, H^{Ar}), 7.31 (dd, *J* = 7.0, 1.1 Hz, 1H, H^{Ar}), 5.50 – 5.42 (m, 1H, H^{12a}), 5.19 – 5.07 (m, 1H, H^{12b}), 3.51 (s, 3H, H^{17}), 3.13 (s, 3H, H^{16}), 2.93 – 2.79 (m, 2H, H^{14}), 2.55 (s, 2H, H^{13}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 174.0 (C^{15}), 147.7 (C^{11}), 140.8 (C^{Ar}), 133.8 (C^{Ar}), 131.5 (C^{Ar}), 128.4 (C^{Ar}), 127.5 (C^{Ar}), 126.0 (C^{Ar}), 125.9(C^{Ar}), 125.8 (C^{Ar}), 125.32 (C^{Ar}), 125.30 (C^{Ar}), 115.9 (C^{12}), 61.2 (C^{17}), 36.3 (C^{12}), 33.3 (C^{13} or C^{14}), 30.6 (C^{13} or C^{14}).

IR (neat) ν_{max}: 2961, 2360, 1660, 1383, 1175, 1102, 992, 803, 779.

HRMS (GC-TOF): exact mass calculated for $[M\text{-}OMe]^+$ ($C_{16}H_{16}NO^+$) requires *m/z* 238.1226, found *m/z* 238.1216.

4-(Dibenzo[b,d]thiophen-2-yl)-N-methoxy-N-methylpent-4-enamide



$C_{19}H_{19}NO_2S$
MW: 325.4260

Following **General Procedure A** using 4-pentynoic acid (1.00 g, 10.0 mmol, 1.00 equiv.), dibenzothiophene-2-boronic acid (2.74 g, 12.0 mmol, 1.20 equiv.), $Pd(PPh_3)_4$ (578 mg, 0.500 mmol, 5.00 mol%), acetic acid (0.057 mL, 1.00 mmol, 0.10 equiv.), 1,1'-carbonyldiimidazole (2.17 g, 13.0 mmol, 1.30 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (1.95 g, 20.0 mmol, 2.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a pale-yellow oil (915 mg, 2.81 mmol, 28%).

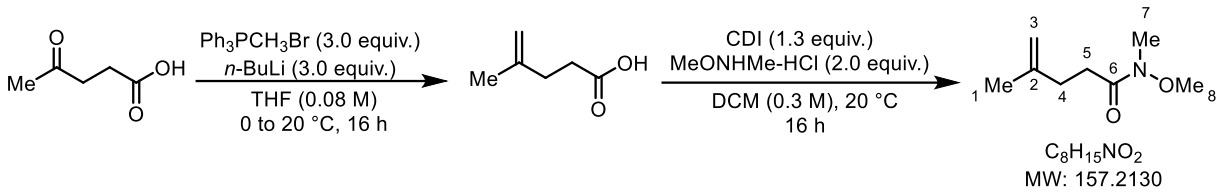
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.21 (d, *J* = 1.5 Hz, 1H, H^{Ar}), 8.20 – 8.16 (m, 1H, H^{Ar}), 7.87 – 7.83 (m, 1H, H^{Ar}), 7.80 (t, *J* = 9.7 Hz, 1H, H^{Ar}), 7.64 – 7.50 (m, 1H, H^{Ar}), 7.50 – 7.35 (m, 2H, H^{Ar}), 5.44 (app. s, 1H, H^{14a}), 5.22 (d, *J* = 0.9 Hz, 1H, H^{14b}), 3.58 (s, 3H, H^{19}), 3.18 (s, 3H, H^{18}), 3.04 – 2.90 (m, 2H, H^{16}), 2.64 (s, 2H, H^{15}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 173.4 (C^{17}, detected by HMBC), 147.5 (C^{13}), 140.0 (C^{Ar}), 138.8 (C^{Ar}), 137.4 (C^{Ar}), 135.9 (C^{Ar}), 135.7 (C^{Ar}), 126.9 (C^{Ar}), 125.3 (C^{Ar}), 124.6 (C^{Ar}), 123.0 (C^{Ar}), 122.7 (C^{Ar}), 121.8 (C^{Ar}), 119.2 (C^{Ar}), 113.1 (C^{14}), 61.4 (C^{19}), 32.4 (C^{18}), 31.2 (C^{15} or C^{16}), 30.6 (C^{15} or C^{16}).

IR (neat) ν_{max}: 3057, 2963, 1659, 1468, 1431, 1176, 994, 764, 732.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{19}H_{19}NO_2S^+$) requires *m/z* 325.1131, found *m/z* 325.1125.

N-Methoxy-N,4-dimethylpent-4-enamide



Following reported procedures,[142,146] methyltriphenylphosphonium bromide (7.50 g, 21.0 mmol, 3.00 equiv.) was suspended in anhydrous tetrahydrofuran (90 mL). The suspension was cooled to 0 °C, and *n*-butyllithium (2.5 M in hexanes, 13.1 mL, 21.0 mmol, 3.00 equiv.) was added dropwise. The resulting suspension was stirred at 0 °C for 1 h, after which levulinic acid (813 mg, 7.00 mmol, 1.00 equiv.) was added. The reaction was allowed to warm to 20 °C and subsequently stirred for 16 h. The excess reagent was then quenched by addition of aqueous 1 M HCl (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was dissolved in dichloroform (20 mL), followed by addition of 1,1'-carbonyldiimidazole (1.47 g, 9.10 mmol, 1.30 equiv.) and stirred at 20 °C for 1 h. *N,O*-Dimethylhydroxylamine hydrochloride (1.37 g, 14.0 mmol, 2.00 equiv.) was added and the reaction was stirred at 20 °C for 16 h. Following this time, aq. HCl (1.0 M, 50 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed with satd. aq. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, eluent heptanes/ethyl acetate 1:0–1:1) afforded the title product as a colourless oil (412 mg, 2.62 mmol, 37%).

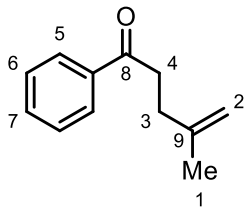
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.74 (d, *J* = 2.6 Hz, 1H, H^{3a}), 4.70 (app s, 1H, H^{3b}), 3.69 (s, 3H, H^8), 3.18 (s, 3H, H^7), 2.57 (t, *J* = 7.9 Hz, 2H, H^5), 2.37 – 2.31 (m, 2H, H^4), 1.76 (s, 3H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8 (detected by HMBC, C^6), 145.1 (C^2), 110.2 (C^3), 61.4 (C^8), 32.40 (2C, C^4 and C^7), 30.40 (C^5), 22.8 (C^1).

IR (neat) ν_{max}: 2969, 2936, 1661, 1465, 1376, 156, 432.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_8H_{16}NO_2^+$) requires *m*/*z* 158.1176, found *m*/*z* 158.1175.

4-Methyl-1-phenylpent-4-en-1-one



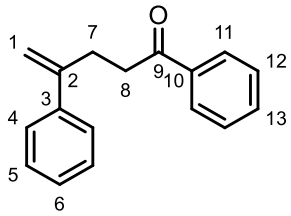
$C_{12}H_{14}O$
MW: 174.2430

The compound was synthesized according to a known literature procedure.[147] The title compound was isolated as a colourless oil (962 mg, 5.52 mmol, 55%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.98 (dt, *J* = 8.4, 1.5 Hz, 2H, H^5), 7.63 – 7.49 (m, 1H, H^7), 7.51 – 7.42 (m, 2H, H^6), 4.93 – 4.58 (m, 2H, H^2), 3.21 – 2.94 (m, 2H, H^3), 2.55 – 2.29 (m, 2H, H^4), 1.79 (app t, *J* = 1.1 Hz, 3H, H^1).

The spectroscopic data is consistent with that reported in literature.[147]

1,4-Diphenylpent-4-en-1-one



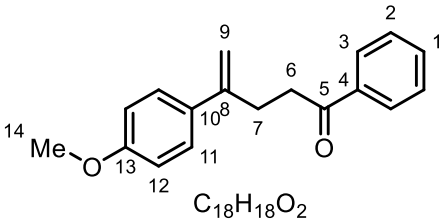
$C_{17}H_{16}O$
MW: 236.3140

Following **General Procedure F** using *N*-methoxy-*N*-methyl-4-phenylpent-4-enamide (520 mg, 2.40 mmol, 1.00 equiv.) and phenylmagnesium bromide (1 M in tetrahydrofuran, 3.60 mL, 3.60 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a colourless oil (447 mg, 1.89 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.90 (m, 2H, H^{Ar}), 7.57 – 7.51 (m, 1H, H^{Ar}), 7.46 – 7.40 (m, 4H, H^{Ar}), 7.38 – 7.31 (m, 2H, H^{Ar}), 7.31 – 7.28 (m, 1H, H^{Ar}), 5.36 – 5.31 (m, 1H, H^{1a}), 5.16 – 5.10 (m, 1H, H^{1b}), 3.16 – 3.08 (m, 2H, H^8), 3.00 – 2.94 (m, 2H, H^7).

The spectroscopic data were consistent with that reported in literature.[148]

4-(4-Methoxyphenyl)-1-phenylpent-4-en-1-one



$C_{18}H_{18}O_2$
MW: 266.3400

Following **General Procedure F** using *N*-methoxy-4-(4-methoxyphenyl)-*N*-methylpent-4-enamide (729 mg, 2.93 mmol, 1.00 equiv.) and phenylmagnesium bromide (1 M in tetrahydrofuran, 4.40 mL, 4.40 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a pale-yellow oil (632 mg, 2.37 mmol, 81%).

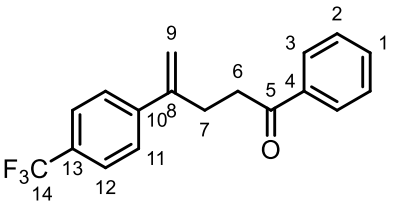
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.96 – 7.89 (m, 2H, H^{Ar}), 7.56 – 7.53 (m, 1H, H^1), 7.48 – 7.41 (m, 2H, H^{Ar}), 7.39 – 7.37 (m, 1H, H^{Ar}), 6.96 – 6.77 (m, 2H, H^{Ar}), 5.26 (d, *J* = 0.6 Hz, 1H, H^{9a}), 5.06 (d, *J* = 1.2 Hz, 1H, H^{9b}), 3.82 (s, 3H, H^{14}), 3.19 – 3.05 (m, 2H, H^6), 3.02 – 2.84 (m, 2H, H^7).

^{13}C NMR (176 MHz, $CDCl_3$): δ 199.8 (C^5), 159.4 (C^{13}), 146.8 (C^{Ar} or C^8), 137.1 (C^{Ar} or C^8), 133.2 (C^1), 133.1 (C^{Ar} or C^8), 128.7 (2C, C^{Ar}), 128.2 (2C, C^{Ar}), 127.4 (2C, C^{Ar}), 113.9 (2C, C^{Ar}), 111.4 (C^9), 55.4 (C^{14}), 37.8 (C^6), 29.9 (C^7).

IR (neat) ν_{max}: 3061, 3002, 2838, 1678, 1624, 1512, 1249, 1185, 840, 745, 687.

HRMS (GC-TOF): exact mass calculated for $[M\text{-}C_7H_5O]^+$ ($C_{11}H_{13}O^+$) requires *m*/*z* 161.0961, found *m*/*z* 161.0958.

1-Phenyl-4-(4-(trifluoromethyl)phenyl)pent-4-en-1-one



$C_{18}H_{15}F_3O$
MW: 304.3122

Following **General Procedure F** using *N*-methoxy-*N*-methyl-4-(4-(trifluoromethyl)phenyl)pent-4-enamide (384 mg, 1.34 mmol, 1.00 equiv.) and phenylmagnesium bromide (1 M in tetrahydrofuran, 2.00 mL, 2.00 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a white solid (348 mg, 1.14 mmol, 85%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.94 – 7.84 (m, 2H, H^{Ar}), 7.59 (t, *J* = 10.3 Hz, 2H, H^{Ar}), 7.55 (m, 3H, H^{Ar}), 7.49 – 7.39 (m, 2H, H^{Ar}), 5.39 (app. s, 1H, H^{9a}), 5.24 (d, *J* = 0.9 Hz, 1H, H^{9b}), 3.17 – 3.06 (m, 2H, H^{6}), 3.01 – 2.93 (m, 2H, H^{7}).

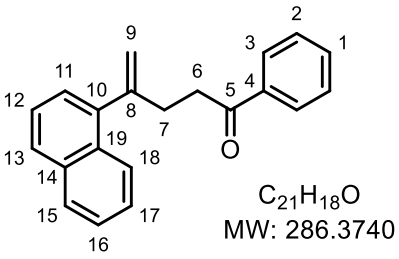
^{13}C NMR (176 MHz, $CDCl_3$): δ 199.3 (C^{5}), 146.5 (C^{Ar} or C^{8}), 144.5 (C^{Ar} or C^{8}), 136.9 (C^{Ar} or C^{8}), 133.3 (C^{1}), 128.8 (2C, C^{Ar}), 128.2 (2C, C^{Ar}), 126.6 (2C, C^{Ar}), 125.6 (2C, q, J = 3.8 Hz, C^{11} or C^{12}), 115.0 (C^{9}), 37.3 (C^{7}), 29.6 (C^{6}). *C^{14} was not detected.*

^{19}F NMR (659 MHz, $CDCl_3$): δ -62.53.

IR (neat) ν_{max}: 2941, 1672, 1627, 1449, 1340, 1119, 849, 745, 686.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{18}H_{15}F_3O^+$) requires *m*/*z* 304.1070, found *m*/*z* 304.1061.

4-(Naphthalen-1-yl)-1-phenylpent-4-en-1-one



$C_{21}H_{18}O$
MW: 286.3740

Following **General Procedure F** using *N*-methoxy-*N*-methyl-4-(naphthalen-1-yl)pent-4-enamide (1.43 g, 5.31 mmol, 1.00 equiv.) and phenylmagnesium bromide (1 M in tetrahydrofuran, 8.00 mL, 8.00 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a pale yellow oil (1.33 g, 4.66 mmol, 88%).

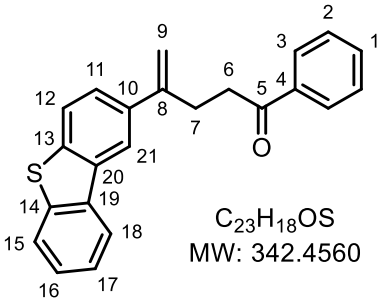
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 – 8.03 (m, 1H, H^{Ar}), 7.86 (d, *J* = 7.4 Hz, 3H, H^{Ar}), 7.77 (t, *J* = 9.9 Hz, 1H, H^{Ar}), 7.54 – 7.39 (m, 6H, H^{Ar}), 7.32 (d, *J* = 6.9 Hz, 1H, H^{Ar}), 5.48 (s, 1H, H^{9a}), 5.15 (s, 1H, H^{9b}), 3.17 – 3.05 (m, 2H, H^6), 2.99 (t, *J* = 7.4 Hz, 2H, H^7).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.5 (C^5), 147.6 (C^8), 140.7 (C^{Ar}), 137.0 (C^{Ar}), 133.9 (C^{Ar}), 133.1 (C^{Ar}), 131.5 (C^{Ar}), 128.7 (2C, C^{Ar}), 128.4 (C^{Ar}), 128.1 (2C, C^{Ar}), 127.6 (C^{Ar}), 126.1 (C^{Ar}), 125.9 (C^{Ar}), 125.8 (C^{Ar}), 125.4 (C^{Ar}), 125.3 (C^{Ar}), 116.2 (C^9), 37.2 (C^7), 33.1 (C^6).

IR (neat) ν_{max}: 3058, 2896, 1684, 1597, 1506, 1204, 803, 779, 745, 689.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{21}H_{18}ONa^+$) requires *m*/*z* 309.1250, found *m*/*z* 309.1250.

4-(Dibenzo[b,d]thiophen-2-yl)-1-phenylpent-4-en-1-one



$C_{23}H_{18}OS$
MW: 342.4560

Following **General Procedure F** using 4-(dibenzo[*b,d*]thiophen-2-yl)-*N*-methoxy-*N*-methylpent-4-enamide (915 mg, 2.81 mmol, 1.00 equiv.) and phenylmagnesium bromide (1 M in tetrahydrofuran, 5.60 mL, 5.60 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0-9:1) gave the title compound as a pale yellow oil (597 mg, 1.74 mmol, 62%).

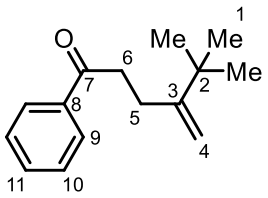
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.25 – 8.13 (m, 2H, H^{Ar}), 7.96 – 7.90 (m, 2H, H^{Ar}), 7.87 – 7.84 (m, 1H, H^{Ar}), 7.82 (d, *J* = 8.3 Hz, 1H, H^{Ar}), 7.57 – 7.51 (m, 2H, H^{Ar}), 7.49 – 7.44 (m, 2H, H^{Ar}), 7.42 (dd, *J* = 10.7, 4.9 Hz, 2H, H^{Ar}), 5.44 (app. s, 1H, H^{9a}), 5.24 (d, *J* = 1.0 Hz, 1H, H^{9b}), 3.27 – 3.15 (m, 2H, H^6), 3.11 (dt, *J* = 15.1, 7.7 Hz, 2H, H^7).

^{13}C NMR (176 MHz, $CDCl_3$): δ 199.7 (C^5), 147.5 (C^8), 140.0 (C^{Ar}), 138.9 (C^{Ar}), 137.5 (C^{Ar}), 137.0 (C^{Ar}), 135.9 (C^{Ar}), 135.6 (C^{Ar}), 133.2 (C^{Ar}), 128.7 (2C, C^{Ar}), 128.2 (2C, C^{Ar}), 127.0 (C^{Ar}), 125.3 (C^{Ar}), 124.6 (C^{Ar}), 123.0 (C^{Ar}), 122.8 (C^{Ar}), 121.8 (C^{Ar}), 119.2 (C^8), 113.3 (C^9), 37.7, 30.2.

IR (neat) ν_{max}: 3059, 2896, 1683, 1203, 979, 821, 763, 689.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{23}H_{18}OS^+$) requires *m*/*z* 342.1073, found *m*/*z* 342.1070.

5,5-Dimethyl-4-methylene-1-phenylhexan-1-one



$C_{15}H_{20}O$
MW: 216.3240

Following **General Procedure E** using 1-phenylprop-2-en-1-one (264 mg, 2.00 mmol, 1.00 equiv.), 1,2-dibromoethane (catalytic), 2-bromo-3,3-dimethylbut-1-ene (489 mg, 3.00 mmol, 1.50 equiv.), magnesium turnings (146 mg, 6.00 mmol, 3.00 equiv.) and copper(I) cyanide (26.9 mg, 0.300 mmol, 0.150 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a pale-yellow oil (38.7 mg, 0.179 mmol, 8.9%). *Hydrocarbon impurities were detected on NMR.*

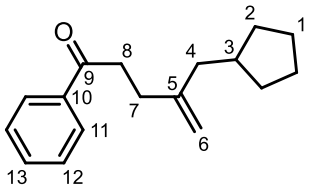
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.00 – 7.95 (m, 2H, H^9), 7.57 – 7.54 (m, 1H, H^{11}), 7.48 – 7.43 (m, 2H, H^{10}), 4.91-4.84 (m, 1H, H^{4a}), 4.74 – 4.66 (m, 1H, H^{4b}), 3.21 – 3.09 (m, 2H, H^6), 2.50 (app ddd, *J* = 49.5, 27.3, 23.7 Hz, 2H, H^5), 1.10 (s, 9H, H^1).

^{13}C NMR (176 MHz, $CDCl_3$): δ 200.1 (C^7), 157.2 (C^3), 137.2 (C^8), 133.1 (C^{11}), 128.7 (2C, C^9 or C^{10}), 128.2 (2C, C^9 or C^{10}), 106.3 (C^4), 41.8 (C^2), 38.3 (C^6), 29.4 (C^7), 25.6 (3C, C^1).

IR (neat) ν_{max}: 3319, 2958, 2895, 1721, 1684, 1448, 1065, 1035, 924, 691.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}ONa^+$) requires *m*/*z* 239.1406, found *m*/*z* 239.1402.

4-(Cyclopentylmethyl)-1-phenylpent-4-en-1-one



$C_{17}H_{22}O$
MW: 242.3620

Following **General Procedure E** using 1-phenylprop-2-en-1-one (264 mg, 2.00 mmol, 1.00 equiv.), 1,2-dibromoethane (catalytic), (2-bromoallyl)cyclopentane (3.18 mmol/g in pentane, 943 mg, 3.00 mmol, 1.50 equiv.), magnesium turnings (146 mg, 6.00 mmol, 3.00 equiv.) and copper(I) cyanide (26.9 mg, 0.300 mmol, 0.150 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a pale-yellow oil (73.9 mg, 0.305 mmol, 15%).

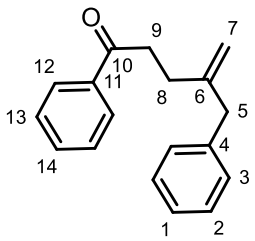
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 – 7.95 (m, 2H, H^{11}), 7.56 (q, *J* = 7.4 Hz, 1H, H^{13}), 7.47 (app t, *J* = 7.7 Hz, 2H, H^{12}), 4.77 (app s, 1H, H^{6a}), 4.75 (d, *J* = 1.1 Hz, 1H, H^{6b}), 3.17 – 3.08 (m, 2H, H^{8}), 2.48 – 2.40 (m, 2H, H^{7}), 2.09 – 2.00 (m, 3H, H^{3} and H^{4}), 1.74 (ddd, *J* = 18.5, 8.9, 3.7 Hz, 2H, H^{2a}), 1.64 – 1.57 (m, 2H, H^{2b}), 1.54 – 1.49 (m, 2H, H^{1a}), 1.12 (td, *J* = 15.2, 7.5 Hz, 2H, H^{1b}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.0 (C^{9}), 148.5 (C^{5}), 137.2 (C^{10}), 133.1 (C^{13}), 128.7 (2C, C^{11} or C^{12}), 128.2 (2C, C^{11} or C^{12}), 109.9 (C^{6}), 43.3 (C^{4}), 38.0 (C^{3}), 37.2 (C^{8}), 32.7 (2C, C^{2}), 30.2 (C^{7}), 25.3 (2C, C^{1}).

IR (neat) ν_{max}: 3229. 2957, 1738, 1552, 1067, 915, 554.

HRMS (GC-TOF): exact mass calculated for $[M\text{-}C_{10}H_{17}]^+$ ($C_7H_5O^+$) requires *m*/*z* 105.0335, found *m*/*z* 105.0343.

4-Benzyl-1-phenylpent-4-en-1-one



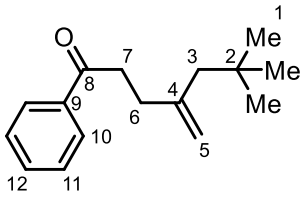
$C_{18}H_{18}O$
MW: 250.3410

The compound was synthesized according to a known literature procedure.[147] The title compound was isolated as a pale-yellow oil (764 mg, 3.05 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.88 (m, 2H, H^{Ar}), 7.58 – 7.52 (m, 1H, H^{Ar}), 7.48 – 7.42 (m, 2H, H^{Ar}), 7.33 – 7.27 (m, 2H, H^{Ar}), 7.24 – 7.18 (m, 3H, H^{Ar}), 4.86 (s, 1H, H^{7a}), 4.83 (s, 1H, H^{7b}), 3.42 (s, 2H, H^5), 3.09 (app dd, *J* = 8.5, 6.8 Hz, 2H, H^9), 2.49 – 2.36 (m, 2H, H^8).

The spectroscopic data were consistent with that reported in literature.[147]

6,6-Dimethyl-4-methylene-1-phenylheptan-1-one



$C_{16}H_{22}O$
MW: 230.3510

Following **General Procedure E** using 1-phenylprop-2-en-1-one (264 mg, 2.00 mmol, 1.00 equiv.), iodine (catalytic), 2-bromo-4,4-dimethylpent-1-ene (525 mg, 3.00 mmol, 1.50 equiv.), magnesium turnings (146 mg, 6.00 mmol, 3.00 equiv.) and copper(I) cyanide (26.9 mg, 0.300 mmol, 0.150 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a pale-yellow oil (41.7 mg, 0.181 mmol, 9.0%).

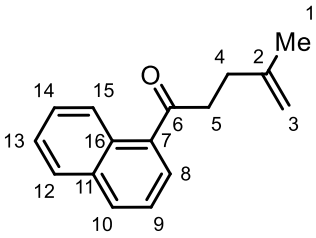
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H, H^{10}), 7.58 – 7.53 (m, 1H, H^{12}), 7.48 – 7.43 (m, 2H, H^{11}), 4.91 – 4.84 (m, 1H, H^{5a}), 4.77 – 4.71 (m, 1H, H^{5b}), 3.16 – 3.05 (m, 2H, H^7), 2.53 – 2.43 (m, 2H, H^6), 1.99 (s, 2H, H^3), 0.94 (s, 9H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.0 (C^8), 146.9 (C^4), 137.2 (C^9), 133.1 (C^{12}), 128.7 (2C, C^{10} or C^{11}), 128.2 (2C, C^{10} or C^{11}), 112.9 (C^5), 55.9 (C^2), 50.2 (C^3), 37.7 (C^7), 32.4 (C^6), 30.1 (3C, C^1).

IR (neat) ν_{max}: 2935, 2839, 1674, 1597, 1253, 1167, 887, 807.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}ONa^+$) requires *m*/*z* 253.1563, found *m*/*z* 253.1562.

4-Methyl-1-(naphthalen-1-yl)pent-4-en-1-one



$C_{16}H_{16}O$
MW: 224.3030

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (314 mg, 2.00 mmol, 1.00 equiv.), 1-bromonaphthalene (1.24 g, 6.00 mmol, 3.00 equiv.) and magnesium turnings (146 mg, 6.00 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a yellow solid (239 mg, 1.07 mmol, 53%).

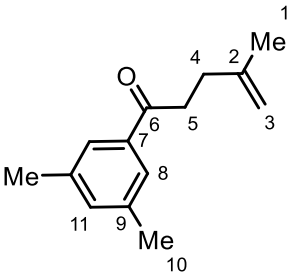
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (app d, *J* = 8.6 Hz, 1H, H^{Ar}), 7.99 (m, 1H, H^{Ar}), 7.88 (m, 2H, H^{Ar}), 7.63 – 7.47 (m, 3H, H^{Ar}), 4.77 (s, 1H, H^{3a}), 4.73 (s, 1H, H^{3b}), 3.23 – 3.18 (m, 2H, H^5), 2.52 (t, *J* = 7.6 Hz, 2H, H^4), 1.80 (s, 3H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 204.3 (C^6), 144.7 (C^2), 136.4 (C^{Ar}), 134.1 (C^{Ar}), 132.6 (C^{Ar}), 130.3 (C^{Ar}), 128.5 (C^{Ar}), 128.0 (C^{Ar}), 127.3 (C^{Ar}), 126.6 (C^{Ar}), 126.0 (C^{Ar}), 124.5 (C^{Ar}), 110.5 (C^3), 40.5 (C^4), 32.5 (C^5), 22.9 (C^1).

IR (neat) ν_{max}: 3049, 2924, 2853, 1680, 1507, 1099, 802, 777.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{16}NaO^+$) requires *m*/*z* 247.1093, found *m*/*z* 247.1093.

1-(3,5-Dimethylphenyl)-4-methylpent-4-en-1-one



$C_{14}H_{18}O$
MW: 202.2970

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (267 mg, 1.70 mmol, 1.00 equiv.), 1-bromo-3,5-dimethylbenzene (944 mg, 5.10 mmol, 3.00 equiv.) and magnesium turnings (124 mg, 5.10 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a pale-yellow oil (114 mg, 0.564 mmol, 33%). *Trace impurities were detected on NMR, and were taken into the next step.*

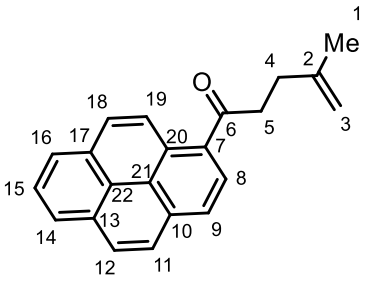
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.59 – 7.55 (m, 2H, H^8), 7.20 (app d, *J* = 0.8 Hz, 1H, H^9), 4.78 – 4.75 (m, 1H, H^{3a}), 4.73 (app dd, *J* = 1.9, 1.0 Hz, 1H, H^{3b}), 3.12 – 3.06 (m, 2H, H^5), 2.46 – 2.41 (m, 2H, H^4), 2.37 (s, 6H, H^{10}), 1.79 (s, 3H, H^1).

^{13}C NMR (176 MHz, $CDCl_3$): 200.3 (C^6), 145.0 (C^2), 138.4 (2C, C^9), 137.2 (C^7), 134.8 (C^{11}), 125.9 (2C, C^8), 110.3 (C^3), 37.1 (C^4), 32.1 (C^5), 22.9 (C^1), 21.2 (2C, C^{10}).

IR (neat) ν_{max}: 2953, 2922, 1714, 1684, 1604, 1443, 1321, 914, 735.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}NaO^+$) requires *m*/*z* 225.1250, found *m*/*z* 225.1245.

4-Methyl-1-(pyren-1-yl)pent-4-en-1-one



$C_{22}H_{18}O$
MW: 298.3850

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (220 mg, 1.40 mmol, 1.00 equiv.), 1-bromopyrene (1.18 g, 4.20 mmol, 3.00 equiv.) and magnesium turnings (102 mg, 4.20 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a pale-yellow solid (110 mg, 0.369 mmol, 26%).

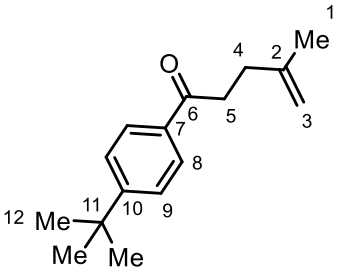
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.87 (d, *J* = 9.3 Hz, 1H, H^{Ar}), 8.35 (dd, *J* = 8.1, 1.4 Hz, 1H, H^{Ar}), 8.26 (dd, *J* = 7.6, 3.7 Hz, 2H, H^{Ar}), 8.23 – 8.16 (m, 3H, H^{Ar}), 8.10 – 8.04 (m, 2H, H^{Ar}), 4.80 (t, *J* = 1.5 Hz, 1H, H^{3a}), 4.78 – 4.75 (m, 1H, H^{3b}), 3.40 – 3.35 (m, 2H, H^5), 2.60 (t, *J* = 7.6 Hz, 2H, H^4), 1.83 (s, 3H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 204.6 (C^6), 144.8 (C^2), 133.8 (C^{Ar}), 132.9 (C^{Ar}), 131.3 (C^{Ar}), 130.7 (C^{Ar}), 129.7 (C^{Ar}), 129.6 (C^{Ar}) , 129.5 (C^{Ar}), 127.3 (C^{Ar}), 126.6 (C^{Ar}), 126.4 (C^{Ar}), 126.2 (C^{Ar}), 126.1 (C^{Ar}), 125.2 (C^{Ar}), 125.0 (C^{Ar}), 124.5 (C^{Ar}), 124.2 (C^{Ar}), 110.6 (C^3), 40.9 (C^4), 32.7 (C^5), 23.0 (C^1).

IR (neat) ν_{max}: 3074, 3040, 2967, 2910, 1675, 1540, 888, 717.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{22}H_{18}O^+$) requires *m*/*z* 298.1358, found *m*/*z* 298.1343.

1-(4-(tert-Butyl)phenyl)-4-methylpent-4-en-1-one



$C_{16}H_{22}O$
MW: 230.3510

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (200 mg, 1.27 mmol, 1.00 equiv.), 1-bromo-4-*tert*-butylbenzene (813 mg, 3.82 mmol, 3.00 equiv.) and magnesium turnings (92.8 mg, 3.82 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a colourless oil (271 mg, 1.18 mmol, 93%).

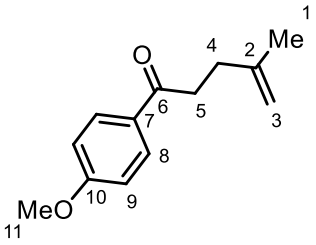
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.5 Hz, 2H, H^8), 7.48 (d, *J* = 8.5 Hz, 2H, H^9), 4.77 (dq, *J* = 2.4, 1.1 Hz, 1H, H^{3a}), 4.72 (dq, *J* = 2.4, 1.1 Hz, 1H, H^{3b}), 3.15 – 2.85 (m, 2H, H^5), 2.55 – 2.32 (m, 2H, H^4), 1.79 (app t, *J* = 1.1 Hz, 3H, H^1), 1.35 (s, 9H, H^{12}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.6 (C^6), 156.9 (C^7), 145.0 (C^2), 134.5 (C^{10}), 128.2 (2C, C^8 or C^9), 125.7 (2C, C^8 or C^9), 110.3 (C^3), 36.9 (C^4), 35.3 (C^{11}), 32.1 (C^5), 31.3 (3C, C^{12}), 22.9 (C^1).

IR (neat) ν_{max}: 2963, 2927, 2869, 1682, 1605, 1108, 887, 842.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{16}H_{22}O^+$) requires *m*/*z* 230.1671, found *m*/*z* 230.1662.

1-(4-Methoxyphenyl)-4-methylpent-4-en-1-one



$C_{13}H_{16}O_2$
MW: 204.2690

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (170 mg, 1.08 mmol, 1.00 equiv.) and 4-methoxyphenylmagnesium bromide (1 M in tetrahydrofuran, 1.50 equiv.). Purification by flash column chromatography (SiO_2, heptanes/ethyl acetate 1:0–9:1) afforded the title product as a pale-yellow oil (112 mg, 0.55 mmol, 51%).

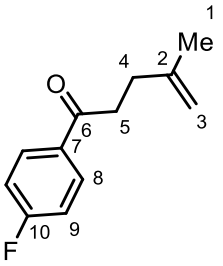
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.9 Hz, 2H, H^8), 6.94 (d, *J* = 8.9 Hz, 2H, H^9), 4.76 (s, 1H, H^{3a}), 4.72 (s, 1H, H^{3b}), 3.87 (s, 3H, H^{11}), 3.10 – 3.04 (m, 2H, H^5), 2.44 (t, *J* = 7.7 Hz, 2H, H^4), 1.79 (s, 3H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 198.5 (C^6), 163.6 (C^{10}), 145.0 (C^2), 130.5 (2C, C^8 or C^9), 130.2 (C^7), 113.9 (2C, C^8 or C^9), 110.2 (C^3), 55.6 (C^{11}), 36.7 (C^4), 32.3 (C^5), 22.9 (C^1).

IR (neat) ν_{max}: 2935, 2839, 1674, 1597, 1253, 1167, 1029, 807.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}NaO_2^+$) requires *m*/*z* 227.1043, found *m*/*z* 227.1044.

1-(4-Fluorophenyl)-4-methylpent-4-en-1-one



$C_{12}H_{13}FO$
MW: 192.2334

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (200 mg, 1.27 mmol, 1.00 equiv.), 1-bromo-4-fluorobenzene (668 mg, 3.82 mmol, 3.00 equiv.) and magnesium turnings (92.8

mg, 3.82 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a pale-yellow oil (201 mg, 1.05 mmol, 82%). *Trace impurities were detected on NMR, and were taken into the next step.*

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.03 – 7.96 (m, 2H, H^8), 7.15 – 7.12 (m, 2H, H^9), 4.77 (app t, *J* = 1.5 Hz, 1H, H^{3a}), 4.71 (app t, *J* = 1.5 Hz, 1H, H^{3b}), 3.11 – 3.07 (m, 2H, H^5), 2.47 – 2.42 (m, 2H, H^4), 1.81 – 1.76 (m, 3H, H^1).

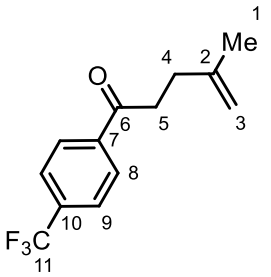
^{13}C NMR (176 MHz, $CDCl_3$): δ 198.2 (C^6), 165.8 (d, *J* = 254.6 Hz, C^{10}), 144.7 (C^2), 133.5 (C^7), 130.8 (2C, d, *J* = 9.3 Hz, C^8), 115.8 (2C, d, *J* = 21.7 Hz, C^9), 110.3 (C^3), 36.8 (C^4), 31.9 (C^5), 22.9 (C^1).

^{19}F NMR (659 MHz, $CDCl_3$): δ -105.49.

IR (neat) ν_{max}: 2963, 2905, 2870, 1684, 1605, 1266, 842.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{12}H_{13}FO^+$) requires *m*/*z* 192.0950, found *m*/*z* 192.0942.

4-Methyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-one



$C_{13}H_{13}F_3O$
MW: 242.2412

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (314 mg, 2.00 mmol, 1.00 equiv.), 4-bromobenzotrifluoride (1.36 g, 6.00 mmol, 3.00 equiv.) and magnesium turnings (146 mg, 6.00 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a yellow oil (262 mg, 1.08 mmol, 54%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.2 Hz, 2H, H^8), 7.74 (d, *J* = 8.2 Hz, 2H, H^9), 4.78 (app s, 1H, H^{3a}), 4.72 (d, *J* = 0.9 Hz, 1H, H^{3b}), 3.18 – 3.12 (m, 2H, H^5), 2.46 (t, *J* = 7.6 Hz, 2H, H^4), 1.79 (s, 3H, H^1).

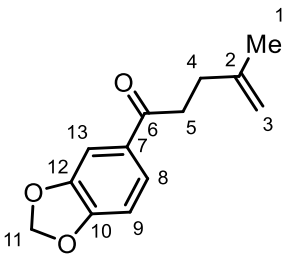
^{13}C NMR (176 MHz, $CDCl_3$): δ 198.8 (C^6), 144.4 (C^2), 139.7 (C^7), 134.5 (q, *J* = 32.7 Hz, C^{10}), 128.4 (2C, C^8), 125.7 (2C, q, *J* = 3.8 Hz, C^9), 123.0 (q, *J* = 272.4 Hz, C^{11}), 110.6 (C^3), 37.2 (C^4), 32.0 (C^5), 22.8 (C^1).

^{19}F NMR (659 MHz, $CDCl_3$): δ -63.11.

IR (neat) ν_{max}: 2972, 2914, 1693, 1324, 1109, 1015, 785.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{13}H_{13}F_3O^+$) requires *m*/*z* 242.0918, found *m*/*z* 242.0907.

1-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-4-en-1-one



$C_{13}H_{14}O_3$
MW: 218.2520

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (170 mg, 1.08 mmol, 1.00 equiv.), 4-bromo-1,2-methylenedioxybenzene (652 mg, 3.24 mmol, 3.00 equiv.) and magnesium turnings (78.9 mg, 3.24 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a pale-yellow oil (142 mg, 0.651 mmol, 60%).

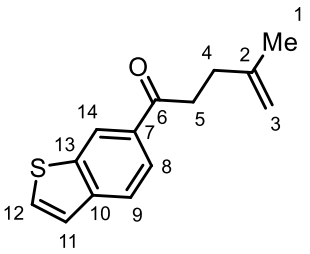
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 8.1, 1.7 Hz, 1H, H^8), 7.45 (d, *J* = 1.7 Hz, 1H, H^{13}), 6.85 (d, *J* = 8.1 Hz, 1H, H^9), 6.04 (s, 2H, H^{11}), 4.78 – 4.74 (m, 1H, H^{3a}), 4.71 (app dd, *J* = 1.8, 1.0 Hz, 1H, H^{3b}), 3.07 – 3.01 (m, 2H, H^5), 2.45 – 2.40 (m, 2H, H^6), 1.78 (app d, *J* = 1.0 Hz, 3H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 197.9 (C^6), 151.8 (C^{10} or C^{11}), 148.3 (C^{10} or C^{11}), 144.9 (C^2), 132.0 (C^7), 124.4 (C^8), 110.3 (C^3), 108.1 (C^9 or C^{13}), 108.0 (C^9 or C^{13}), 101.9 (C^{12}), 36.6 (C^4), 32.3 (C^5), 22.9 (C^1).

IR (neat) ν_{max}: 2967, 2904, 1674, 1503, 1486, 1437, 1342, 1035, 883, 808.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{14}NaO_3^+$) requires *m*/*z* 241.0835, found *m*/*z* 241.0839.

1-(Benzo[b]thiophen-6-yl)-4-methylpent-4-en-1-one



$C_{14}H_{14}OS$
MW: 230.3250

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (220 mg, 1.40 mmol, 1.00 equiv.), 6-bromobenzothiophene (895 mg, 4.20 mmol, 3.00 equiv.) and magnesium turnings (102 mg, 4.20 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a yellow solid (69.3 mg, 0.301 mmol, 22%). *Trace impurities were detected on NMR, and were taken into the next step.*

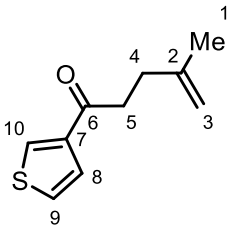
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.55 – 8.52 (m, 1H, H^{Ar}), 7.98 (dd, *J* = 8.4, 1.5 Hz, 1H, H^{Ar}), 7.88 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.67 (d, *J* = 5.4 Hz, 1H, H^{Ar}), 7.40 (d, *J* = 5.4 Hz, 1H, H^{Ar}), 4.79 (app t, *J* = 1.7 Hz, 1H, H^{3a}), 4.76 – 4.67 (m, 1H, H^{3b}), 3.24 – 3.06 (m, 2H, H^4), 2.50 (dd, *J* = 9.2, 6.2 Hz, 2H, H^5), 1.81 (app t, *J* = 1.0 Hz, 3H, H^1). Rotameric effects are seen.

^{13}C NMR (176 MHz, $CDCl_3$): δ 199.4 (C^6), 144.9 (C^2), 143.0 (C^{Ar}), 139.9 (C^{Ar}), 133.3 (C^{Ar}), 130.9 (C^{Ar}), 123.9 (C^{Ar}), 123.9 (C^{Ar}), 123.8 (C^{Ar}), 123.4 (C^{Ar}), 110.4 (C^3), 37.0 (C^4), 32.3 (C^5), 22.9 (C^1). Rotameric effects are seen.

IR (neat) ν_{max}: 3075, 2968, 2908, 1676, 1591, 1233, 887, 698.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{14}H_{14}SO^+$) requires *m*/*z* 230.0765, found *m*/*z* 230.0758.

4-Methyl-1-(thiophen-3-yl)pent-4-en-1-one



$C_{10}H_{12}OS$
MW: 180.2650

Following **General Procedure D** using *N*-methoxy-*N*,4-dimethylpent-4-enamide (267 mg, 1.70 mmol, 1.00 equiv.), 2-bromothiophene (848 mg, 5.10 mmol, 3.00 equiv.) and magnesium turnings (124 mg, 5.10 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–9:1) gave the title compound as a yellow oil (93.4 mg, 0.518 mmol, 31%). *Trace impurities were detected on NMR, and were taken into the next step.*

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 3.7, 1.2 Hz, 1H, H^{Ar}), 7.63 (dd, *J* = 4.9, 1.2 Hz, 1H, H^{Ar}), 7.13 (dd, *J* = 4.9, 3.7 Hz, 1H, H^{Ar}), 4.77 (app t, *J* = 1.6 Hz, 1H, H^{3a}), 4.75 – 4.71 (m, 1H, H^{3b}), 3.08 – 3.02 (m, 2H, H^5), 2.49 – 2.36 (m, 2H, H^6), 1.78 (t, *J* = 1.1 Hz, 3H, H^1).

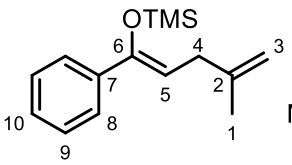
^{13}C NMR (151 MHz, $CDCl_3$): δ 192.8 (C^6), 144.6 (C^2), 133.6 (C^{Ar}), 131.8 (C^{Ar}), 128.2 (C^{Ar}), 110.5 (C^3), 37.6 (C^4), 32.0 (C^5), 22.8 (C^1). *C^7 was not detected.*

IR (neat) ν_{max}: 3076, 2968, 2929, 1663, 1415, 733.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{12}NaSO^+$) requires *m*/*z* 203.0501, found *m*/*z* 203.0498.

E/Z Configuration for all silyl enol ethers were assigned in analogy to previous literature reports.[77]

*(Z)-Trimethyl((4-methyl-1-phenylpenta-1,4-dien-1-yl)oxy)silane (**1.066**)*



$C_{15}H_{22}OSi$
MW: 246.4250

Following **General Procedure H** using 4-methyl-1-phenylpent-4-en-1-one (871 mg, 5.00 mmol, 1.00 equiv.), triethylamine (3.50 mL, 25.0 mmol, 5.00 equiv.) and trimethylsilyl trifluoromethanesulfonate (2.80 mL, 15.0 mmol, 5.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a colourless oil (914 mg, 3.71 mmol, 74%).

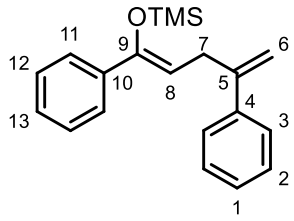
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.52 – 7.44 (m, 2H, H^{8}), 7.32 – 7.28 (m, 2H, H^{9}), 7.25 – 7.22 (m, 1H, H^{10}), 5.30 (app dd, *J* = 9.4, 5.2 Hz, 1H, H^{5}), 4.77 (app dd, *J* = 19.6, 0.8 Hz, 2H, H^{3}), 2.91 (d, *J* = 7.3 Hz, 2H, H^{4}), 1.79 (s, 3H, H^{2}), 0.15 – 0.08 (m, 9H, H^{TMS}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 150.1 (C^{6}), 145.4 (C^{2}), 139.3 (C^{7}), 128.2 (2C, C^{9}), 127.7 (C^{10}), 125.7 (2C, C^{8}), 110.2 (C^{3}), 108.8 (C^{5}), 34.5 (C^{4}), 23.0 (C^{1}), 0.70 (3C, C^{TMS}).

IR (neat) ν_{max}: 3079, 2963, 2906, 1689, 1651, 1492, 1446, 1252, 1051, 876, 844, 756, 696.

HRMS (GC-TOF): *m/z* calculated for $[M^{\cdot}]^{+}$ ($[C_{15}H_{22}OSi]^{+}$) requires 246.1434, found 246.1436.

*(Z)-((1,4-Diphenylpenta-1,4-dien-1-yl)oxy)trimethylsilane (**1.071**)*



$C_{20}H_{24}OSi$
MW: 308.4960

Following **General Procedure H** using 1,4-diphenylpent-4-en-1-one (430 mg, 1.82 mmol, 1.00 equiv.), triethylamine (1.27 mL, 9.10 mmol, 5.00 equiv.) and trimethylsilyl trifluoromethanesulfonate (1.01 mL, 5.46 mmol, 3.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a colorless oil (424 mg, 1.37 mmol, 76%).

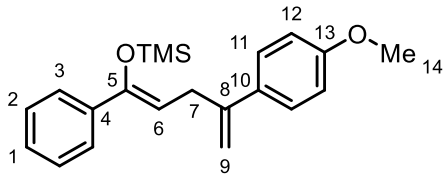
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.45 (m, 4H, H^{Ar}), 7.37 – 7.26 (m, 6H, H^{Ar}), 5.42 – 5.38 (m, 1H, H^{6a}), 5.34 (app t, *J* = 7.0 Hz, 1H, H^{8}), 5.17 (app dd, *J* = 2.8, 1.3 Hz, 1H, H^{6}), 3.40 (d, *J* = 7.0 Hz, 2H, H^{7}), 0.15 (s, 9H, H^{TMS}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3 (C^9), 147.2 (C^5), 141.3 (C^4 or C^{10}), 139.2 (C^4 or C^{10}), 128.4 (2C, C^{Ar}), 128.2 (2C, C^{Ar}), 127.8 (C^1 or C^{13}), 127.6 (C^1 or C^{13}), 126.1 (2C, C^{Ar}), 125.7 (2C, C^{Ar}), 112.5 (C^6), 108.7 (C^8), 32.1 (C^7), 0.8 (3C, C^{TMS}).

IR (neat) ν_{max}: 1682, 1448, 1251, 1226, 1176, 1069, 1025, 1001, 758, 697, 647.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ $(C_{20}H_{25}OSi)^+$ requires *m/z* 309.1669, found *m/z* 309.1667.

(Z)-((4-(4-Methoxyphenyl)-1-phenylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{21}H_{26}O_2Si$
MW: 338.5220

Following **General Procedure H** using 4-(4-methoxyphenyl)-1-phenylpent-4-en-1-one (632 mg, 2.37 mmol, 1.00 equiv.), triethylamine (1.65 mL, 11.9 mmol, 5.00 equiv.) and trimethylsilyl trifluoromethanesulfonate (1.31 mL, 7.12 mmol, 3.00 equiv.), Purification by flash column chromatography (heptanes/ethyl acetate 1:0-19:1) gave the title compound as a pale yellow oil (480 mg, 1.42 mmol, 60%).

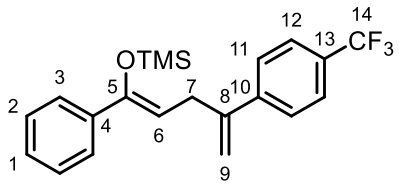
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.5 Hz, 2H, H^{Ar}), 7.46 – 7.42 (m, 2H, H^{Ar}), 7.31 – 7.26 (m, 2H, H^{Ar}), 7.26 – 7.22 (m, 1H, H^{Ar}), 6.95 – 6.84 (m, 2H, H^{Ar}), 5.40 – 5.27 (m, 2H, H^6 and H^{9a}), 5.09 (s, 1H, H^{9b}), 3.82 (s, 3H, H^{14}), 3.38 (d, *J* = 7.0 Hz, 2H, H^7), 0.16 (s, 9H, H^{TMS}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 159.2 (C^{13}), 150.1 (C^5), 146.4 (C^4 or C^{10}), 139.2 (C^4 or C^{10}), 133.7 (C^{10}), 128.2 (2C, C^{Ar}), 127.7 (C^1), 127.2 (2C, C^{Ar}), 125.7 (2C, C^{Ar}), 113.8 (2C, C^{Ar}), 110.7 (C^9), 109.0 (C^6), 55.4 (C^{14}), 32.2 (C^7), 0.8 (3C, C^{TMS}).

IR (neat) ν_{max}: 2956, 2837, 1721, 1511, 1249, 1174, 1026, 836, 699.

HRMS (ESI$^+$): exact mass calculated for $[M\cdot]^+$ ($C_{21}H_{26}O_2Si^+$) requires *m*/*z* 338.1697, found *m*/*z* 338.1698.

(Z)-Trimethyl((1-phenyl-4-(4-(trifluoromethyl)phenyl)penta-1,4-dien-1-yl)oxy)silane



$C_{21}H_{23}F_3OSi$
MW: 376.4942

Following **General Procedure H** using 1-phenyl-4-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (347 mg, 1.14 mmol, 1.00 equiv.), triethylamine (0.80 mL, 5.70 mmol, 5.00 equiv.) and trimethylsilyl trifluoromethanesulfonate (0.53 mL, 3.42 mmol, 3.00 equiv.), Purification by flash column chromatography (heptanes/ethyl acetate 1:0-19:1) gave the title compound as a pale yellow oil (150 mg, 0.398 mmol, 35%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.61 – 7.57 (m, 4H, H^{Ar}), 7.46 (d, *J* = 8.2 Hz, 2H, H^{Ar}), 7.32 – 7.28 (m, 2H, H^{Ar}), 7.25 (d, *J* = 7.0 Hz, 1H, H^1), 5.46 (d, *J* = 7.1 Hz, 1H, H^{9a}), 5.33 – 5.20 (m, 2H, H^6 and H^{9b}), 3.40 (d, *J* = 7.1 Hz, 2H, H^7), 0.16 – 0.11 (m, 9H, H^{TMS}).

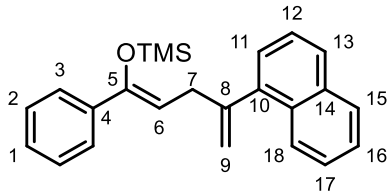
^{13}C NMR (176 MHz, $CDCl_3$): δ 150.7 (C^5), 146.2 (C^6), 144.8 (C^4 or C^{10}), 139.0 (C^4 or C^{10}), 129.53 (q, *J* = 32.2 Hz, C^{13}), 128.3 (2C, C^{Ar}), 128.0 (C^1), 126.4 (2C, C^{Ar}), 125.7 (2C, C^{Ar}), 125.37 (2C, q, *J* = 3.7 Hz, C^{12}), 114.5 (C^9), 108.1 (C^6), 32.0 (C^7), 0.8 (3C, C^{TMS}).

^{19}F NMR (659 MHz, $CDCl_3$): δ -62.49.

IR (neat) ν_{max}: 3068, 1692, 1450,1411, 1323, 1276, 1167, 1124, 1067, 1016, 842, 713, 607.

HRMS (GC-TOF): exact mass calculated for $[M\text{-}TMS]^+$ ($C_{18}H_{15}F_3^+$) requires *m*/*z* 288.1120, found *m*/*z* 288.0748.

(Z)-Trimethyl((4-(naphthalen-1-yl)-1-phenylpenta-1,4-dien-1-yl)oxy)silane



$C_{24}H_{26}OSi$
MW: 358.5560

Following **General Procedure H** using 4-(Naphthalen-1-yl)-1-phenylpent-4-en-1-one (1.33 mg, 4.66 mmol, 1.00 equiv.), triethylamine (3.25 mL, 23.3 mmol, 5.00 equiv.) and trimethylsilyl trifluoromethanesulfonate (2.58 mL, 14.0 mmol, 3.00 equiv.), Purification by flash column chromatography (heptanes/ethyl acetate 1:0-19:1) gave the title compound as a yellow oil (319 mg, 0.89 mmol, 19%).

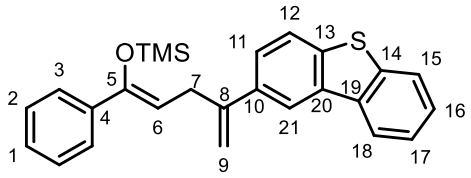
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 – 8.04 (m, 1H, H^{Ar}), 7.88 – 7.80 (m, 1H, H^{Ar}), 7.77 (dd, *J* = 18.5, 6.8 Hz, 1H, H^{Ar}), 7.50 – 7.47 (m, 2H, H^{Ar}), 7.47 – 7.44 (m, 3H, H^{Ar}), 7.34 (dd, *J* = 7.0, 1.2 Hz, 1H, H^{Ar}), 7.32 – 7.28 (m, 2H, H^{Ar}), 7.27 – 7.25 (s, 1H, H^{Ar}), 5.49 (dd, *J* = 3.4, 1.6 Hz, 1H, H^{9a}), 5.37 (t, *J* = 7.2 Hz, 1H, H^{6}), 5.15 – 5.12 (m, 1H, H^{9b}), 3.39 (d, *J* = 7.3 Hz, 2H, H^{7}), 0.08 – 0.06 (m, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.5 (C^{5}), 147.8 (C^{Ar}), 141.8 (C^{8}), 139.3 (C^{Ar}), 133.9 (C^{Ar}), 131.4 (C^{Ar}), 128.4 (C^{Ar}), 128.2 (2C, C^{Ar}), 127.8 (C^{Ar}), 127.3 (C^{Ar}), 126.0 (C^{Ar}), 125.9 (C^{Ar}), 125.82 (2C, C^{Ar}), 125.79 (C^{Ar}), 125.4 (C^{Ar}), 125.1 (C^{Ar}), 115.6 (C^{9}), 108.1 (C^{6}), 35.1 (C^{7}), 0.7 (3C, C^{TMS}).

IR (neat) ν_{max}: 3057, 2896, 1688, 1645, 1446, 1250, 1102, 1061, 841, 776, 696.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{26}H_{26}OSSi^+$) requires *m*/*z* 358.1747, found *m*/*z* 358.1745.

(Z)-((4-(Dibenzo[b,d]thiophen-2-yl)-1-phenylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{26}H_{26}OSSi$
MW: 414.6380

Following **General Procedure H** using 4-(dibenzo[b,d]thiophen-2-yl)-1-phenylpent-4-en-1-one (597 mg, 1.74 mmol, 1.00 equiv.), triethylamine (1.20 mL, 8.72 mmol, 5.00 equiv.) and trimethylsilyl trifluoromethanesulfonate (0.96 mL, 5.23 mmol, 3.00 equiv.), Purification by flash column chromatography (heptanes/ethyl acetate 1:0-19:1) gave the title compound as a yellow oil (476 mg, 1.15 mmol, 66%).

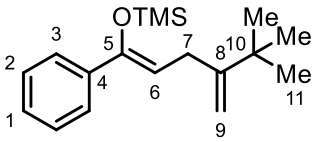
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.31 (s, 1H, H^{Ar}), 8.22 (dd, *J* = 6.6, 2.3 Hz, 1H, H^{Ar}), 7.87 – 7.84 (m, 1H, H^{Ar}), 7.80 (d, *J* = 8.3 Hz, 1H, H^{Ar}), 7.63 (dd, *J* = 8.3, 1.5 Hz, 1H, H^{Ar}), 7.51 – 7.43 (m, 4H, H^{Ar}), 7.29 (t, *J* = 7.6 Hz, 2H, H^{Ar}), 7.24 (t, *J* = 7.3 Hz, 1H, H^{Ar}), 5.53 (d, *J* = 4.6 Hz, 1H, H^{10a}), 5.39 (t, *J* = 7.1 Hz, 1H, H^{7}), 5.29 – 5.19 (m, 1H, H^{10b}), 3.54 (d, *J* = 7.1 Hz, 2H, H^{8}), 0.20 (app. d, *J* = 6.4 Hz, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.3 (C^{5}), 147.0 (C^{Ar}), 140.0 (C^{8}), 139.1 (C^{Ar}), 138.7 (C^{Ar}), 137.6 (C^{8}), 135.9 (C^{Ar}), 135.8 (C^{Ar}), 128.2 (2C, C^{Ar}), 127.8 (C^{Ar}), 126.8 (C^{Ar}), 125.7 (2C, C^{Ar}), 125.1 (C^{Ar}), 124.5 (C^{Ar}), 123.0 (C^{Ar}), 122.6 (C^{Ar}), 121.7 (C^{Ar}), 119.2 (C^{Ar}), 112.6 (C^{9}), 108.9 (C^{6}), 32.6 (C^{7}), 0.8 (3C, C^{TMS}).

IR (neat) ν_{max}: 3058, 2896, 1251, 1092, 1023, 844, 761, 731.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{26}H_{26}OSSi^+$) requires *m*/*z* 414.1468, found *m*/*z* 414.1463.

(Z)-((5,5-Dimethyl-4-methylene-1-phenylhex-1-en-1-yl)oxy)trimethylsilane



$C_{18}H_{28}OSi$
MW: 288.5060

Following **General Procedure G** using 5,5-dimethyl-4-methylene-1-phenylhexan-1-one (38.7 mg, 0.179 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.270 mL, 0.270 mmol, 1.50 equiv.) and chlorotrimethylsilane (34.0 µL, 0.270 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (19.8 mg, 0.0686 mmol, 38%).

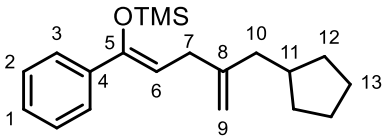
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.50 (dt, *J* = 8.2, 1.7 Hz, 2H, H^{Ar}), 7.32 – 7.29 (m, 2H, H^{Ar}), 7.26 – 7.23 (m, 1H, H^1), 5.35 – 5.29 (m, 1H, H^6), 4.89 (d, *J* = 1.0 Hz, 1H, H^{9a}), 4.82 – 4.77 (m, 1H, H^{9b}), 2.97 (d, *J* = 7.2 Hz, 2H, H^7), 1.12 (s, 9H, H^{11}), 0.14 – 0.11 (m, 9H, H^{TMS}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 157.3 (H^8), 149.7 (C^5), 139.4 (C^4), 128.2 (2C, C^{Ar}), 127.6 (C^1), 125.6 (2C, C^{Ar}), 110.3 (C^6), 107.2 (C^9), 29.5 (3C, C^{11}), 36.1 (C^{10}, detected by HMBC), 0.8 (3C, C^{TMS}).

IR (neat) ν_{max}: 2961, 1685, 1205, 1104, 1045, 878, 845.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{18}H_{28}OSi^+$) requires *m*/*z* 288.1904, found *m*/*z* 288.1901.

(Z)-((4-(Cyclopentylmethyl)-1-phenylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{20}H_{30}OSi$
MW: 314.5440

Following **General Procedure G** using 4-(cyclopentylmethyl)-1-phenylpent-4-en-1-one (75.0 mg, 0.309 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.460 mL, 0.460 mmol, 1.50 equiv.) and chlorotrimethylsilane (59.0 µL, 0.460 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (56.1 mg, 0.178 mmol, 58%).

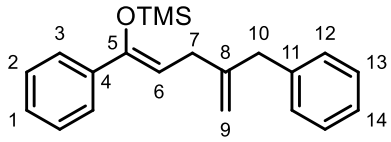
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.49 (m, 2H, H^{Ar}), 7.33 – 7.29 (m, 2H, H^{Ar}), 7.27 – 7.25 (m, 1H, H^1), 5.31 (t, *J* = 7.3 Hz, 1H, H^6), 4.85 – 4.79 (m, 1H, H^{9a}), 4.77 (app dd, *J* = 7.7, 6.9 Hz, 1H, H^{9b}), 2.92 (t, *J* = 7.3 Hz, 2H, H^7), 2.12 – 2.05 (m, 3H, H^{10} and H^{11}), 1.82 – 1.71 (m, 2H, H^{12a}), 1.65 – 1.57 (m, 2H, H^{13a}), 1.57 – 1.47 (m, 2H, H^{13b}), 1.19 – 1.09 (m, 2H, H^{12b}), 0.15 – 0.12 (m, 9H, H^{TMS}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 150.0 (C^5), 148.8 (C^8), 139.3 (C^4), 128.2 (2C, C^{Ar}), 127.6 (C^1), 125.7 (2C, C^{Ar}), 110.0 (C^9), 109.1 (C^6), 43.5 (C^{10}), 38.0 (C^{11}), 32.9 (C^7), 32.8 (2C, C^{12}), 25.3 (2C, C^{13}), 0.7 (3C, C^{TMS}).

IR (neat) ν_{max}: 2950, 2867, 1645, 1251, 917, 873, 840, 754, 695.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{20}H_{30}OSi^+$) requires *m*/*z* 314.2060, found *m*/*z* 314.2052.

*(Z)-((4-Benzyl-1-phenylpenta-1,4-dien-1-yl)oxy)trimethylsilane (**1.092**)*



$C_{21}H_{26}OSi$
MW: 322.5230

Following **General Procedure H** using 4-benzyl-1-phenylpent-4-en-1-one (285 mg, 1.07 mmol, 1.00 equiv.), triethylamine (0.740 mL, 5.35 mmol, 5.00 equiv.) and trimethylsilyl trifluoromethanesulfonate (0.600 mL, 3.21 mmol, 3.00 equiv.), Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (169 mg, 0.499 mmol, 47%).

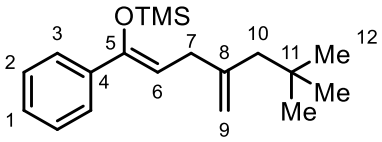
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.40 (m, 2H, H^{Ar}), 7.33 – 7.27 (m, 4H, H^{Ar}), 7.22 (dt, *J* = 15.6, 5.8 Hz, 4H, H^{Ar}), 5.29 (t, *J* = 7.3 Hz, 1H, H^6), 4.91 (s, 1H, H^{9a}), 4.78 (s, 1H, H^{9b}), 3.39 (s, 2H, H^{10}), 2.86 (d, *J* = 7.3 Hz, 2H, H^7), 0.05 (app d, *J* = 3.2 Hz, 9H, H^{TMS}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3 (C^5), 148.5 (C^8), 139.9 (C^4 or C^{11}), 139.3 (C^4 or C^{11}), 129.3 (2C, C^{Ar}), 128.4 (2C, C^{Ar}), 128.2 (2C, C^{Ar}), 127.7 (C^{Ar}), 126.2 (C^{Ar}), 125.7 (2C, C^{Ar}), 111.4 (C^9), 108.5 (C^6), 43.6 (C^{10}), 32.4 (C^7), 0.6 (3C, C^{TMS}).

IR (neat) ν_{max}: 3027, 2956, 2900, 1251, 843, 697.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{21}H_{26}OSi^+$) requires *m*/*z* 322.1747, found *m*/*z* 322.1739.

(Z)-((6,6-Dimethyl-4-methylene-1-phenylhept-1-en-1-yl)oxy)trimethylsilane



$C_{19}H_{30}OSi$
MW: 302.5330

Following **General Procedure G** using 6,6-dimethyl-4-methylene-1-phenylheptan-1-one (41.0 mg, 0.178 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.270 mL, 0.270 mmol, 1.50 equiv.) and chlorotrimethylsilane (34.0 µL, 0.270 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (16.5 mg, 0.0545 mmol, 31%).

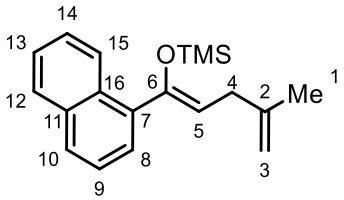
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 – 7.44 (m, 2H, H^{Ar}), 7.33 – 7.28 (m, 2H, H^{Ar}), 7.26 – 7.20 (m, 1H, H^1), 5.29 (t, *J* = 7.1 Hz, 1H, H^6), 4.98 – 4.86 (m, 1H, H^{9a}), 4.77 – 4.60 (m, 1H, H^{9b}), 2.94 (t, *J* = 7.1 Hz, 2H, H^7), 2.00 (s, 2H, H^{10}), 0.95 (d, *J* = 14.6 Hz, 9H, H^{11}), 0.14 – 0.10 (m, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.9 (C^5), 147.1 (C^8), 139.4 (C^4), 128.2 (2C, C^{Ar}), 127.6 (C^1), 125.7 (2C, C^{Ar}), 113.3 (C^9), 109.6 (C^6), 50.4 (C^{10}), 35.0 (C^7), 30.2 (3C, C^{12}), 0.7 (3C, C^{TMS}). *C^{11} was not detected.*

IR (neat) ν_{max}: 3004, 2361, 1713, 1363, 1252,1222, 874, 845.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{19}H_{30}OSi^+$) requires *m*/*z* 302.2066, found *m*/*z* 302.2061.

(Z)-Trimethyl((4-methyl-1-(naphthalen-1-yl)penta-1,4-dien-1-yl)oxy)silane



$C_{19}H_{24}OSi$
MW: 296.4850

Following **General Procedure G** using 4-methyl-1-(naphthalen-1-yl)pent-4-en-1-one (230 mg, 1.03 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (1.54 mL, 1.54 mmol, 1.50 equiv.) and chlorotrimethylsilane (0.20 mL, 1.54 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (260 mg, 0.878 mmol, 86%).

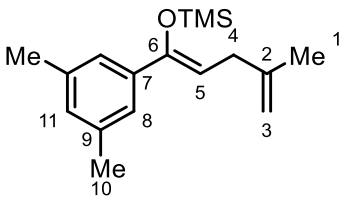
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.28 (dd, *J* = 7.5, 2.0 Hz, 1H, H^{Ar}), 7.86 – 7.74 (m, 2H, H^{Ar}), 7.51 – 7.43 (m, 3H, H^{Ar}), 7.40 (t, *J* = 7.6 Hz, 1H, H^{Ar}), 5.07 (t, *J* = 7.3 Hz, 1H, H^5), 4.84 (d, *J* = 2.4 Hz, 1H, H^{3a}), 4.79 – 4.75 (m, 1H, H^{3b}), 3.01 (d, *J* = 7.3 Hz, 2H, H^4), 1.85 (s, 3H, H^1), 0.12 (s, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.1 (C^6), 145.6 (C^2), 138.0 (C^7), 133.7 (C^{11} or C^{16}), 131.6 (C^{11} or C^{16}), 128.5 (C^{Ar}), 128.2 (C^{Ar}), 126.8 (C^{Ar}), 126.5 (C^{Ar}), 126.0 (C^{Ar}), 125.9 (C^{Ar}), 125.2 (C^{Ar}), 112.0 (C^5), 110.0 (C^3), 34.3 (C^4), 23.0 (C^1), 0.43 (3C, C^{TMS}).

IR (neat) ν_{max}: 3045, 2959, 2925, 2854, 1654, 1251, 1123, 840, 754.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{19}H_{24}OSi^+$) requires *m*/*z* 296.1596, found *m*/*z* 296.1577.

(Z)-((1-(3,5-Dimethylphenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{17}H_{26}OSi$
MW: 274.4790

Following **General Procedure G** using 1-(3,5-dimethylphenyl)-4-methylpent-4-en-1-one (114 mg, 0.570 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (0.860 mL, 0.860 mmol, 1.50 equiv.) and

chlorotrimethylsilane (0.120 mL, 0.860 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (88.5 mg, 0.322 mmol, 57%).

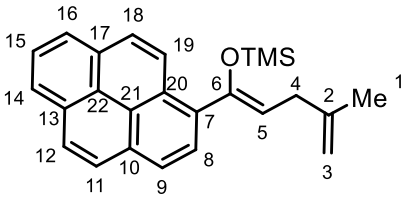
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.12 – 7.10 (m, 2H, H^8), 6.91 – 6.88 (m, 1H, H^{11}), 5.28 (t, *J* = 7.3 Hz, 1H, H^5), 4.81 – 4.76 (m, 2H, H^3), 2.89 (d, *J* = 7.3 Hz, 2H, H^4), 2.31 (app d, *J* = 1.0 Hz, 6H, H^{10}), 1.79 (app t, *J* = 1.2 Hz, 3H, H^1), 0.14 (s, 9H, H^{TMS}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 150.3 (C^6), 145.5 (C^2), 139.1 (C^7), 137.6 (2C, C^9), 129.3 (C^{11}), 123.6 (2C, C^8), 110.0 (C^3), 108.4 (C^5), 34.5 (C^4), 23.0 (C^1), 21.5 (2C, C^{10}), 0.7 (3C, C^{TMS}).

IR (neat) ν_{max}: 2959, 2921, 2856, 1684, 1651, 1601, 1443, 1251, 842.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{17}H_{26}OSi^+$) requires *m*/*z* 274.1753, found *m*/*z* 274.1742.

(Z)-Trimethyl((4-methyl-1-(pyren-1-yl)penta-1,4-dien-1-yl)oxy)silane



$C_{25}H_{26}OSi$
MW: 370.5670

Following **General Procedure G** using 4-methyl-1-(pyren-1-yl)pent-4-en-1-one (110 mg, 0.370 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (0.560 mL, 0.550 mmol, 1.50 equiv.) and chlorotrimethylsilane (70.0 µL, 0.550 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a pale-yellow oil (114 mg, 0.308 mmol, 84%). *Two rotamers or E/Z-isomers are observed, only the major (E)-isomer is reported.*

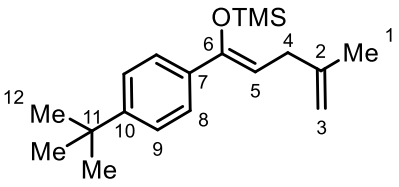
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.56 (d, *J* = 9.1 Hz, 1H, H^{Ar}), 8.21 – 7.97 (m, 8H, H^{Ar}), 5.19 (t, *J* = 7.2 Hz, 1H, H^5), 4.92 – 4.89 (m, 1H, H^{3a}), 4.82 (d, *J* = 1.1 Hz, 1H, H^{3b}), 3.12 (d, *J* = 7.2 Hz, 2H, H^4), 1.90 (d, *J* = 1.2 Hz, 3H, H^1), -0.09 (s, 9H, H^{TMS}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 150.1 (C^6), 145.6 (C^2), 135.3 (C^7), 131.5 (C^{Ar}), 131.2 (C^{Ar}), 131.1 (C^{Ar}), 128.9 (C^{Ar}), 127.6 (C^{Ar}), 127.5 (C^{Ar}), 127.4 (C^{Ar}), 127.0 (C^{Ar}), 126.1 (C^{Ar}), 126.0 (C^{Ar}), 125.2 (C^{Ar}), 125.2 (C^{Ar}), 125.0 (C^{Ar}), 124.9 (C^{Ar}), 124.5 (C^{Ar}), 113.3 (C^5), 110.2 (C^3), 34.6 (C^4), 23.1 (C^1), 0.6 (3C, C^{TMS}).

IR (neat) ν_{max}: 3042, 2962, 2899, 1687, 1652, 1251, 843.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{25}H_{26}OSi^+$) requires *m*/*z* 370.1753, found *m*/*z* 370.1740.

(Z)-((1-(4-(tert-Butyl)phenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{19}H_{30}OSi$
MW: 302.5330

Following **General Procedure G** using 1-(4-(*tert*-butyl)phenyl)-4-methylpent-4-en-1-one (260 mg, 1.13 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (1.70 mL, 1.70 mmol, 1.50 equiv.) and chlorotrimethylsilane (0.220 mL, 1.70 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a pale-yellow oil (171 mg, 0.565 mmol, 50%). *This compound decomposes rapidly and must be used as quickly as possible.*

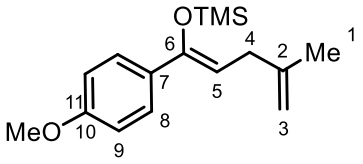
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.5 Hz, 2H, H^{Ar}), 7.31 (d, *J* = 8.5 Hz, 2H, H^{Ar}), 5.27 (t, *J* = 7.3 Hz, 1H, H^5), 5.02 – 4.50 (m, 2H, H^3), 2.89 (d, *J* = 7.3 Hz, 2H, H^4), 1.85 – 1.73 (app m, 3H, H^1), 1.32 (s, 9H, H^{12}), 0.14 (s, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.7 (C^{10} or C^6), 150.1 (C^{10} or C^6), 145.5 (C^2), 136.3 (C^7), 125.3 (2C, C^8 or C^9), 125.1 (2C, C^8 or C^9), 110.1 (C^3), 108.0 (C^5), 41.0 (C^{11}), 34.5 (C^4), 31.4 (3C, C^{12}), 23.0 (C^1), 0.8 (3C, C^{TMS}).

IR (neat) ν_{max}: 2963, 2906, 2363, 1605, 1298, 1108, 843.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{19}H_{30}OSi^+$) requires *m*/*z* 302.2066, found *m*/*z* 302.2048.

(Z)-((1-(4-Methoxyphenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{16}H_{24}O_2Si$
MW: 276.4510

Following **General Procedure G** using 1-(4-methoxyphenyl)-4-methylpent-4-en-1-one (112 mg, 0.550 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (0.820 mL, 0.820 mmol, 1.50 equiv.) and chlorotrimethylsilane (0.110 mL, 0.820 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a pale-yellow oil (50.5 mg, 0.28 mmol, 51%).

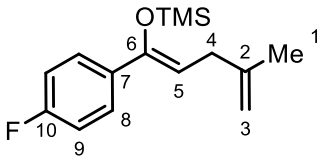
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 6.84 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 5.18 (t, *J* = 7.3 Hz, 1H, H^5), 4.76 (app ddt, *J* = 20.2, 2.5, 1.1 Hz, 2H, H^3), 3.81 (s, 3H, H^{11}), 2.90 – 2.86 (m, 2H, H^4), 1.78 (s, 3H, H^1), 0.12 (s, 9H, H^{TMS}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 159.3 (C^{10}), 149.9 (C^6), 145.6 (C^2), 132.0 (C^7), 126.9 (2C, C^8 or C^9), 113.5 (2C, C^8 or C^9), 110.0 (C^3), 107.2 (C^5), 55.4 (C^{11}), 34.5 (C^4), 23.0 (C^1), 0.71 (3C, C^{TMS}).

IR (neat) ν_{max}: 3461, 3075, 2968, 2936, 2840, 1598, 1510, 1254, 1168, 974, 741.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{16}H_{24}O_2Si^+$) requires *m*/*z* 276.1546, found *m*/*z* 276.1529.

(Z)-((1-(4-Fluorophenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{15}H_{21}FOSi$
MW: 264.4154

Following **General Procedure G** using 1-(4-fluorophenyl)-4-methylpent-4-en-1-one (200 mg, 1.04 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (1.56 mL, 1.56 mmol, 1.50 equiv.) and chlorotrimethylsilane (0.200 mL, 1.56 mmol, 1.50 equiv.). Purification by flash column chromatography

(heptanes/ethyl acetate 1:0–19:1) gave the title compound as a pale-yellow oil (160 mg, 0.605 mmol, 58%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 – 7.38 (m, 2H, H^8), 6.99 (t, *J* = 8.7 Hz, 2H, H^9), 5.22 (t, *J* = 7.3 Hz, 1H, H^5), 4.76 (ddt, *J* = 8.7, 2.5, 1.1 Hz, 2H, H^3), 2.88 (d, *J* = 7.3 Hz, 2H, H^4), 1.78 (s, 3H, H^1), 0.12 (s, 9H, H^{TMS}).

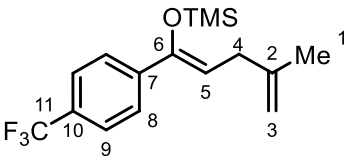
^{13}C NMR (151 MHz, $CDCl_3$): δ 162.5 (d, *J* = 246.6 Hz, C^{10}), 149.3 (C^6), 145.3 (C^2), 135.5 (C^7), 127.3 (d, *J* = 8.0 Hz, 2C, C^8), 115.1 (d, *J* = 21.5 Hz, 2C, C^9), 110.2 (C^3), 108.6 (C^5), 34.5 (C^4), 23.0 (C^1), 0.7 (3C, C^{TMS}).

^{19}F NMR (565 MHz, $CDCl_3$): δ -114.83.

IR (neat) ν_{max}: 2967, 2929, 2363, 1507, 1253, 879, 842, 740.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}FOSi^+$) requires *m*/*z* 265.1419, found *m*/*z* 265.1417.

(Z)-Trimethyl((4-methyl-1-(4-(trifluoromethyl)phenyl)penta-1,4-dien-1-yl)oxy)silane



$C_{16}H_{21}F_3OSi$
MW: 314.4232

Following **General Procedure G** using 4-methyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (262 mg, 1.08 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (1.62 mL, 1.62 mmol, 1.50 equiv.) and chlorotrimethylsilane (0.2 mL, 1.62 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a pale-yellow oil (301 mg, 0.957 mmol, 88%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.61 – 7.53 (m, 4H, H^{Ar}), 5.41 (t, *J* = 7.3 Hz, 1H, H^5), 4.77 (app h, *J* = 1.1 Hz, 2H, H^3), 2.93 – 2.89 (m, 2H, H^4), 1.79 (t, *J* = 1.1 Hz, 3H, H^1), 0.16 (s, 9H, H^{TMS}).

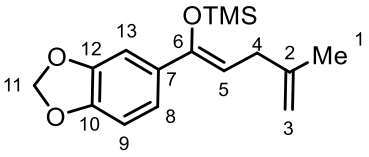
^{13}C NMR (176 MHz, $CDCl_3$): δ 149.0 (C^6), 144.9 (C^2), 142.7 (C^7), 129.6 (q, *J* = 32.4 Hz, C^{10}), 125.67 (2C, C^8), 125.3 (q, *J* = 3.8 Hz, 2C, H^9), 124.3 (q, *J* = 272.1 Hz, C^{11}), 111.0 (C^3), 110.4 (C^5), 34.55 (C^4), 23.0 (C^1), 0.7 (3C, C^{TMS}).

^{19}F NMR (659 MHz, $CDCl_3$): δ -62.46.

IR (neat) ν_{max}: 2923, 2853, 2363, 1694, 1325, 1131, 704.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{16}H_{21}F_3OSi^+$) requires *m*/*z* 314.1314, found *m*/*z* 314.1303.

(Z)-((1-(Benzo[d][1,3]dioxol-5-yl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{16}H_{22}O_3Si$
MW: 290.4340

Following **General Procedure G** using 1-(benzo[*d*][1,3]dioxol-5-yl)-4-methylpent-4-en-1-one (142 mg, 0.650 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (0.980 mL, 0.980 mmol, 1.50 equiv.) and chlorotrimethylsilane (0.140 mL, 0.980 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a pale-yellow oil (127 mg, 0.437 mmol, 67%).

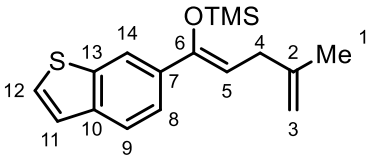
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.01 – 6.95 (m, 2H, H^{Ar}), 6.74 (d, *J* = 8.1 Hz, 1H, H^{Ar}), 5.95 (s, 2H, H^{11}), 5.16 (t, *J* = 7.3 Hz, 1H, H^5), 4.79 – 4.72 (m, 2H, H^3), 2.87 (d, *J* = 7.3 Hz, 2H, H^4), 1.77 (s, 3H, H^1), 0.13 (s, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.8 (C^6), 147.6 (C^{10} or C^{12}), 147.2 (C^{10} or C^{12}), 145.4 (C^2), 133.9 (C^7), 119.4 (C^8), 110.1 (C^3), 108.0 (C^5), 107.7 (C^9 or C^{13}), 106.3 (C^9 or C^{13}), 101.2 (C^{11}), 34.5 (C^4), 23.0 (C^1), 0.7 (3C, C^{TMS}).

IR (neat) ν_{max}: 3076, 2967, 2907, 2854, 1504, 1249, 1038.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{16}H_{22}O_3Si^+$) requires *m*/*z* 290.1138, found *m*/*z* 290.1326.

(Z)-((1-(Benzo[b]thiophen-6-yl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane



$C_{17}H_{22}OSSi$
MW: 302.5070

Following **General Procedure G** using 1-(benzo[*b*]thiophen-6-yl)-4-methylpent-4-en-1-one (69.3 mg, 0.301 mmol, 1.00 equiv.), lithium bis(trimethylsilyl)amide (0.450 mL, 0.450 mmol, 1.50 equiv.) and chlorotrimethylsilane (0.0600 mL, 0.450 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (61.3 mg, 0.202 mmol, 67%).

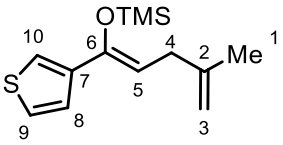
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 1.7, 0.9 Hz, 1H, H^{Ar}), 7.74 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.51 (dd, *J* = 8.4, 1.7 Hz, 1H, H^{Ar}), 7.42 (d, *J* = 5.6 Hz, 1H, H^{Ar}), 7.31 (dd, *J* = 5.6, 0.9 Hz, 1H, H^{Ar}), 5.37 (t, *J* = 7.3 Hz, 1H, H^5), 4.81 – 4.76 (m, 2H, H^3), 2.93 (d, *J* = 7.3 Hz, 2H, H^4), 1.80 (s, 3H, H^1), 0.14 (s, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.1 (C^6), 145.3 (C^2), 140.0 (C^{10} or C^{13}), 139.2 (C^{10} or C^{13}), 135.8 (C^7), 126.8 (C^{Ar}), 123.8 (C^{Ar}), 123.2 (C^{Ar}), 122.5, 119.4 (C^{Ar}), 110.2 (C^3), 109.2 (C^5), 34.6 (C^4), 23.1 (C^1), 0.7 (3C, C^{TMS}).

IR (neat) ν_{max}: 3074, 2963, 1649, 1251, 844.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{17}H_{22}OSSi^+$) requires *m*/*z* 302.1161, found *m*/*z* 302.1151.

(Z)-Trimethyl((4-methyl-1-(thiophen-3-yl)penta-1,4-dien-1-yl)oxy)silane



$C_{13}H_{20}OSSi$
MW: 252.4470

Following **General Procedure G** using 4-methyl-1-(thiophen-3-yl)pent-4-en-1-one (98.4 mg, 0.550 mmol, 1.00 equiv.), LiHMDS (0.820 mL, 0.820 mmol, 1.50 equiv.) and TMSCl (0.120 mL, 0.820 mmol,

1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–19:1) gave the title compound as a yellow oil (69.1 mg, 0.273 mmol, 50%).

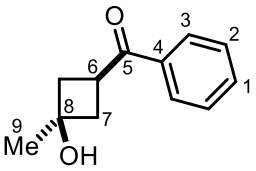
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 4.9, 1.3 Hz, 1H, H^{Ar}), 7.06 (dd, *J* = 3.6, 1.3 Hz, 1H, H^{Ar}), 6.97 – 6.92 (m, 1H, H^{Ar}), 5.30 (t, *J* = 7.4 Hz, 1H, H^5), 4.78 – 4.73 (m, 2H, H^3), 2.86 (d, *J* = 7.4 Hz, 2H, H^4), 1.77 (s, 3H, H^1), 0.21 (s, 9H, H^{TMS}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 144.97 (C^2 or C^6), 144.95 (C^2 or C^6), 143.6 (C^7), 127.2 (C^{Ar}), 124.1 (C^{Ar}), 123.3 (C^{Ar}), 110.4 (C^3), 108.1 (C^5), 34.4 (C^4), 23.0 (C^1), 0.7 (3C, C^{TMS}).

IR (neat) ν_{max}: 2960, 1651, 1413, 1359, 1250, 1097, 919, 839, 694.

HRMS (GC-TOF): exact mass calculated for $[M\cdot]^+$ ($C_{13}H_{20}OSSi^+$) requires *m*/*z* 252.1004, found *m*/*z* 252.0999.

*((1s,3s)-3-Hydroxy-3-methylcyclobutyl)(phenyl)methanone (**cis-1.067**)*



$C_{12}H_{14}O_2$
MW: 190.2420

Following **General Procedure I** using **1.066** (49.3 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (15.5 mg, 0.0816 mmol, 41%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.95 – 7.80 (m, 2H, H^3), 7.60 – 7.50 (m, 1H, H^1), 7.50 – 7.42 (m, 2H, H^2), 3.58 (p, *J* = 8.5 Hz, 1H, H^6), 2.48 – 2.39 (m, 4H, H^7), 1.50 (s, 3H, H^9). *OH was not detected.*

^{13}C NMR (176 MHz, $CDCl_3$): δ 201.1 (C^5), 136.0 (C^4), 133.3 (C^1), 128.8 (2C, C^2 or C^3), 128.5 (2C, C^2 or C^3), 69.6 (C^8), 41.5 (2C, C^7), 32.6 (C^6), 27.5 (C^9).

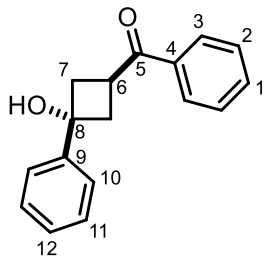
IR (neat) ν_{max}: 3413, 2968, 2933, 1676, 1258, 1223, 698.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ $(C_{12}H_{14}ONa)^+$ requires *m/z* 213.0886, found 213.0884.

*((1r,3r)-3-Hydroxy-3-phenylcyclobutyl)(phenyl)methanone (**trans-1.072**) and ((1s,3s)-3-Hydroxy-3-phenylcyclobutyl)(phenyl)methanone (**cis-1.072**)*

Following **General Procedure I** using **1.071** (49.3 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.30 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the two diastereomers separately.

((1r,3r)-3-Hydroxy-3-phenylcyclobutyl)(phenyl)methanone (***trans*-1.072**)



$C_{17}H_{16}O_2$
MW: 252.3130

The title compound was isolated as a white solid (11.3 mg, 0.0448 mmol, 23%).

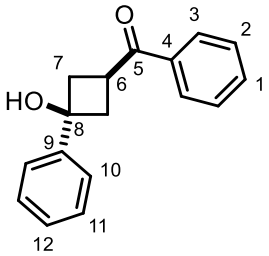
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 – 7.92 (m, 2H, H^{Ar}), 7.59 – 7.54 (m, 1H, H^{Ar}), 7.50 – 7.46 (m, 2H, H^{Ar}), 7.44 – 7.41 (m, 2H, H^{Ar}), 7.38 – 7.34 (m, 2H, H^{Ar}), 7.30 – 7.26 (m, 1H, H^{Ar}), 4.36 (p, *J* = 8.9 Hz, 1H, H^6), 2.95 (ddd, *J* = 10.4, 8.9, 2.8 Hz, 2H, H^{7a}), 2.65 (ddd, *J* = 10.4, 8.9, 2.8 Hz, 2H, H^{7b}), 2.09 (s, 1H, OH).

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.7 (C^5), 146.1 (C^9), 135.7 (C^4), 133.3 (C^{Ar}), 128.8 (2C, C^{Ar}), 128.7 (2C, C^{Ar}), 128.5 (2C, C^{Ar}), 127.6 (C^{Ar}), 124.8 (2C, C^{Ar}), 75.2 (C^8), 39.5 (2C, C^7), 35.9 (C^6).

IR (neat) ν_{max}: 1671, 1447, 1352, 1223, 1113, 913, 778, 758, 695, 669.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ $(C_{17}H_{16}O_2Na)^+$ requires *m/z* 275.1043, found *m/z* 275.1040.

((1s,3s)-3-Hydroxy-3-phenylcyclobutyl)(phenyl)methanone (***cis*-1.072**)



$C_{17}H_{16}O_2$
MW: 252.3130

The title compound was isolated as a white solid (8.5 mg, 0.0337 mmol, 17%).

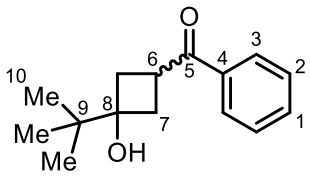
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 – 7.89 (m, 2H, H^{Ar}), 7.64 – 7.55 (m, 3H, H^{Ar}), 7.50 – 7.41 (m, 4H, H^{Ar}), 7.34 (t, *J* = 7.4 Hz, 1H, H^{Ar}), 3.74 (p, *J* = 8.2 Hz, 1H, H^6), 3.01 – 2.93 (m, 2H, H^{7a}), 2.80 – 2.72 (m, 2H, H^{7b}). *OH was not detected.*

^{13}C NMR (151 MHz, $CDCl_3$): δ 201.6 (C^5), 145.3 (C^8), 135.8 (C^4), 133.5 (C^{Ar}), 128.9 (2C, C^{Ar}), 128.8 (2C, C^{Ar}), 128.6 (2C, C^{Ar}), 127.8 (C^{Ar}), 125.3 (2C, C^{Ar}), 73.5 (C^8), 40.8 (2C, C^7), 33.0 (C^6).

IR (neat) ν_{max}: 1677, 1448, 1244, 1223, 698.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ $(C_{17}H_{16}O_2Na)^+$ requires *m/z* 275.1043, found *m/z* 275.1038.

*(3-(tert-Butyl)-3-hydroxycyclobutyl)(phenyl)methanone (**1.077**)*



$C_{15}H_{20}O_2$
MW: 232.3230

Following **General Procedure I** using *(Z)*-((5,5-dimethyl-4-methylene-1-phenylhex-1-en-1-yl)oxy)trimethylsilane (16.8 mg, 0.0583 mmol, 1.00 equiv.), iodosylbenzene (15.4 mg, 0.0700 mmol, 1.20 equiv.), methanesulfonic acid (4.9 µL, 0.0758 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (10.8 µL, 0.0875 mmol, 1.50 equiv.). Purification by flash column chromatography

(heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (3.2 mg, 0.0138 mmol, 24%) as a diasteromeric mixture (*cis:trans* = 0.7:1).

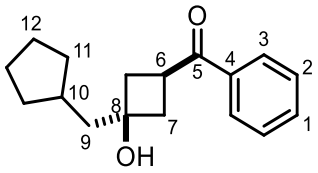
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.00 – 7.96 (m, 2H, *trans*, H^{Ar}), 7.92 – 7.89 (m, 1.4H, *cis*, H^{Ar}), 7.60 – 7.55 (m, 1.7H, *cis* and *trans*, H^{Ar}), 7.50 – 7.45 (m, 3.4H, *cis* and *trans*, H^{Ar}), 4.02 – 3.90 (m, 1H, *trans*, H^{6}), 3.60 – 3.48 (m, 0.7H, *cis*, H^{6}), 3.03 (s, 1H, *trans*, OH), 2.73 – 2.66 (m, 1.4H, *cis*, H^{7a}), 2.27 – 2.24 (m, 2.4H, *cis*,H^{7b} and *trans*, H^{7a}), 2.19 (s, 0.7 H, *cis*, OH), 2.13 (dd, *J* = 14.4, 2.8 Hz, 1H, *trans*, H^{7b}), 1.93 (qd, *J* = 13.1, 9.0 Hz, 2H, *trans*, H^{7c}), 1.22 (s, 3H, *trans*, H^{10a}), 1.04 (s, 3H, *trans*, H^{10b}), 1.00 (app d, *J* = 4.9 Hz, 6.3H, *cis*, H^{10}), 0.99 (s, 3H, *trans*, H^{10c}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 205.7 (*trans*, C^{5}), 201.9 (*cis*, C^{5}), 136.4 (*trans*, C^{4}), 135.8 (*cis*, C^{4}), 133.5 (*trans*, C^{1}), 133.3 (*cis*, C^{1}), 128.9 (2C, *cis* or *trans*, C^{Ar}), 128.82 (2C, *cis* or *trans*, C^{Ar}), 128.79 (2C, *cis* or *trans*, C^{Ar}), 128.6 (2C, *cis* or *trans*, C^{Ar}), 82.0 (*trans*, C^{8}), 77.7 (*cis*, C^{8}), 47.4 (*trans*, C^{9}), 45.0 (*trans*, C^{7a}), 42.1 (*trans*, C^{7b}), 41.2 (*trans*, C^{6}), 35.6 (2C, *cis*, C^{7}), 32.8 (*cis*, C^{6}), 26.2 (*trans*, C^{10a}), 24.0 (3C, *cis*, C^{10}), 21.1 (*trans*, C^{10b}), 20.7 (*trans*, C^{10c}).

IR (neat) ν_{max}: 3474, 2956, 2926, 2869, 2855, 1679, 1256, 1224, 735, 701.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}O_2Na^+$) requires *m*/*z* 255.1356, found *m*/*z* 255.1353.

*((1r,3s)-3-(Cyclopentylmethyl)-3-hydroxycyclobutyl)(phenyl)methanone (**cis-1.078**)*



$C_{17}H_{22}O_2$
MW: 258.3610

Following **General Procedure I** using *(Z)*-((4-(cyclopentylmethyl)-1-phenylpenta-1,4-dien-1-yl)oxy)trimethylsilane (31.5 mg, 0.100 mmol, 1.00 equiv.), iodosylbenzene (26.4 mg, 0.120 mmol, 1.20 equiv.), methanesulfonic acid (8.4 µL, 0.130 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (18.5 µL, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (8.2 mg, 0.317 mmol, 32%).

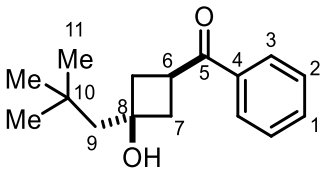
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 – 7.86 (m, 2H, H^3), 7.60 – 7.53 (m, 1H, H^1), 7.53 – 7.33 (m, 2H, H^2), 3.61 (p, *J* = 8.3 Hz, 1H, H^6), 2.54 – 2.43 (m, 2H, H^{7a}), 2.41 – 2.32 (m, 2H, H^{7b}), 2.22 (s, 1H, OH), 2.04 – 1.94 (m, 1H, H^{10}), 1.93 – 1.84 (m, 2H, H^{11a}), 1.79 (d, *J* = 6.5 Hz, 2H, H^9), 1.69 – 1.61 (m, 2H, H^{12a}), 1.57 – 1.47 (m, 2H, H^{12b}), 1.24 – 1.12 (m, 2H, H^{11a}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 201.7 (C^5), 136.0 (C^4), 133.3 (C^1), 128.8 (2C, C^2 or C^3), 128.5 (2C, C^2 or C^3), 72.6 (C^8), 46.0 (C^9), 40.4 (2C, C^7), 36.6 (C^{10}), 34.3 (2C, C^{11}), 33.2 (C^6), 25.0 (2C, C^{12}).

IR (neat) ν_{max}: 3465, 2942, 2865, 1676, 1596, 1222, 698, 660.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}O_2Na^+$) requires *m*/*z* 281.1512, found *m*/*z* 281.1508.

*((1r,3s)-3-Hydroxy-3-neopentylcyclobutyl)(phenyl)methanone (**cis-1.079**)*



$C_{16}H_{22}O_2$
MW: 246.3500

Following **General Procedure I** using *(Z)*-((6,6-dimethyl-4-methylene-1-phenylhept-1-en-1-yl)oxy)trimethylsilane (16.5 mg, 0.0540 mmol, 1.00 equiv.), iodosylbenzene (14.4 mg, 0.0650 mmol, 1.20 equiv.), methanesulfonic acid (5.00 µL, 0.0709 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (10.0 µL, 0.0810 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (6.2 mg, 0.0252 mmol, 46%).

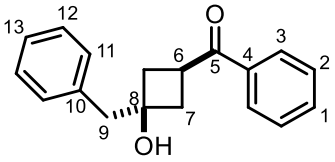
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.99 – 7.88 (m, 2H, H^3), 7.62 – 7.51 (m, 1H, H^1), 7.51 – 7.37 (m, 2H, H^2), 3.79 – 3.64 (m, 1H, H^6), 2.64 – 2.55 (m, 2H, H^{7a}), 2.48 (s, 1H, OH), 2.38 – 2.32 (m, 2H, H^{7b}), 1.69 (s, 2H, H^9), 1.05 (s, 9H, H^{11}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 202.6 (C^5), 135.9 (C^4), 133.4 (C^1), 128.8 (2C, C^2 or C^3), 128.6 (2C, C^2 or C^3), 74.2 (C^8), 52.4 (C^9), 41.8 (2C, C^7), 33.8 (C^6), 31.3 (3C, C^{11}). *C^{10} was not detected.*

IR (neat) ν_{max}: 3473, 2928, 2857, 1767, 1676, 1361, 1222, 698.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{16}H_{22}O_2Na^+$) requires *m*/*z* 269.1512, found *m*/*z* 269.1511.

*((1s,3r)-3-Benzyl-3-hydroxycyclobutyl)(phenyl)methanone (**cis-1.080**)*



$C_{18}H_{18}O_2$
MW: 266.3400

Following **General Procedure I** using **1.092** (64.5 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (42.1 mg, 0.158 mmol, 79%).

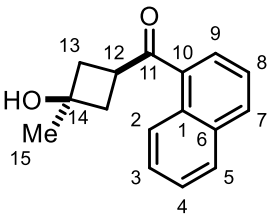
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.74 (m, 2H, H^3), 7.48 (ddd, *J* = 8.5, 2.4, 1.2 Hz, 1H, H^1), 7.37 (dd, *J* = 10.5, 4.7 Hz, 2H, H^2), 7.31 – 7.16 (m, 5H, H^{11}+H^{12}+H^{13}), 3.40 (p, *J* = 8.5 Hz, 1H, H^6), 2.94 (s, 2H, H^9), 2.49 (ddd, *J* = 13.3, 10.5, 9.0 Hz, 2H, H^{7a}), 2.35 – 2.27 (m, 3H, H^{7b} and OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.9 (C^5), 137.2 (C^4 or C^{10}), 135.8 (C^4 or C^{10}), 133.3 (H^{Ar}), 130.2 (2C, H^{Ar}), 128.8 (2C, H^{Ar}), 128.6 (2C, H^{Ar}), 128.5 (2C, H^{Ar}), 126.9 (H^{Ar}), 71.6 (C^8), 45.9 (C^9), 39.2 (2C, C^7), 32.7 (C^6).

IR (neat) ν_{max}: 3456, 2926, 2852, 1673, 1223, 696.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{18}H_{18}O_2Na^+$) requires *m*/*z* 289.1199, found *m*/*z* 289.1191.

*((1s,3s)-3-Hydroxy-3-methylcyclobutyl)(naphthalen-1-yl)methanone (**cis-1.081**)*



$C_{16}H_{16}O_2$
MW: 240.3020

Following **General Procedure I** using *(Z)*-trimethyl((4-methyl-1-(naphthalen-1-yl)penta-1,4-dien-1-yl)oxy)silane (59.3 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (40.2 mg, 0.167 mmol, 84%).

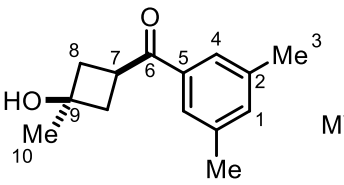
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (dd, *J* = 8.3, 1.2 Hz, 1H, H^{Ar}), 7.98 (d, *J* = 8.2 Hz, 1H, H^{Ar}), 7.90 – 7.85 (m, 1H, H^{Ar}), 7.79 (dd, *J* = 7.2, 1.2 Hz, 1H, H^{Ar}), 7.63 – 7.45 (m, 3H, H^{Ar}), 3.64 (p, *J* = 8.4 Hz, 1H, H^{12}), 2.56 – 2.39 (m, 5H, H^{13} and OH), 1.48 (s, 3H, H^{15}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 205.5 (C^{11}), 135.2 (C^{Ar}), 134.1 (C^{Ar}), 133.0 (C^{Ar}), 130.5 (C^{Ar}), 128.6 (C^{Ar}), 128.1 (C^{Ar}), 127.8 (C^{Ar}), 126.6 (C^{Ar}), 125.9 (C^{Ar}), 124.5 (C^{Ar}), 69.4 (C^{14}), 41.7 (2C, C^{13}), 35.6 (C^{12}), 27.4 (C^{15}).

IR (neat) ν_{max}: 3292, 2971, 2938, 1681, 1323, 1133, 1112, 1015.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}O_2^+$) requires *m*/*z* 241.1223, found *m*/*z* 241.1222.

*(3,5-Dimethylphenyl)((1s,3s)-3-hydroxy-3-methylcyclobutyl)methanone (**cis-1.082**)*



$C_{14}H_{18}O_2$
MW: 218.2960

Following **General Procedure I** using *(Z)*-((1-(3,5-dimethylphenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane (54.9 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol,

1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (20.2 mg, 0.0925 mmol, 46%).

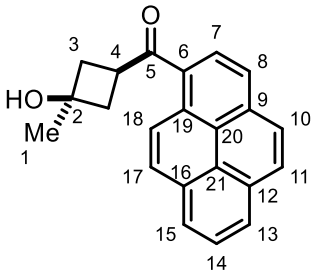
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.52 – 7.49 (m, 2H, H^4), 7.21 – 7.18 (m, 1H, H^1), 3.56 (p, *J* = 8.5 Hz, 1H, H^7), 2.44 – 2.39 (m, 4H, H^8), 2.37 (s, 6H, H^3), 1.49 (s, 3H, H^{10}). *OH was not detected.*

^{13}C NMR (176 MHz, $CDCl_3$): δ 201.6 (C^6), 138.4 (2C, C^2), 136.1 (C^5), 135.0 (C^1), 126.3 (2C, C^4), 69.5 (C^9), 41.6 (2C, C^8), 32.5 (C^7), 27.4 (C^{10}), 21.4 (2C, C^3).

IR (neat) ν_{max}: 3414, 2968, 2931, 1674, 1604, 1289, 1184, 776, 737, 671.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}O_2Na^+$) requires *m*/*z* 241.1199, found *m*/*z* 241.1197.

*((1s,3s)-3-Hydroxy-3-methylcyclobutyl)(pyren-1-yl)methanone (**cis-1.083**)*



$C_{22}H_{18}O_2$
MW: 314.3840

Following **General Procedure I** using *(Z)*-trimethyl((4-methyl-1-(pyren-1-yl)penta-1,4-dien-1-yl)oxy)silane (74.1 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (34.8 mg, 0.111 mmol, 55%).

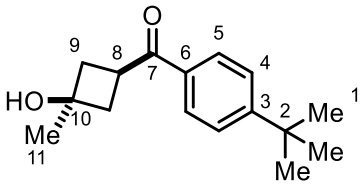
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.93 (d, *J* = 9.3 Hz, 1H, H^{Ar}), 8.28 – 8.20 (m, 4H, H^{Ar}), 8.16 (t, *J* = 7.9 Hz, 2H, H^{Ar}), 8.09 – 8.03 (m, 2H, H^{Ar}), 3.83 (p, *J* = 8.3 Hz, 1H, H^4), 2.63 – 2.56 (m, 2H, H^{3a}), 2.55 – 2.49 (m, 2H, H^{3b}), 1.53 (s, 3H, H^1). *OH was not detected.*

^{13}C NMR (176 MHz, $CDCl_3$): δ 205.8 (C^5), 134.0 (C^{Ar}), 131.6 (C^{Ar}), 131.2 (C^{Ar}), 130.7 (C^{Ar}), 129.9 (C^{Ar}), 129.8 (C^{Ar}), 127.2 (C^{Ar}), 126.6 (C^{Ar}), 126.5 (C^{Ar}), 126.3 (C^{Ar}), 126.3 (C^{Ar}), 125.2 (C^{Ar}), 124.9 (C^{Ar}), 124.4 (C^{Ar}), 124.1 (C^{Ar}), 69.5 (C^2), 42.1 (2C, C^3), 36.0 (C^4), 27.5 (C^1). *One quaternary, aromatic carbon was not detected*.

IR (neat) ν_{max}: 3462, 2928, 2340, 2109, 1646, 1255, 845.

HRMS (MALDI-TOF): exact mass calculated for $[M]^+$ ($C_{22}H_{18}O_2^+$) requires *m*/*z* 314.1301, found *m*/*z* 314.1299.

*(4-(tert-Butyl)phenyl)((1s,3s)-3-hydroxy-3-methylcyclobutyl)methanone (**cis-1.084**)*



$C_{16}H_{22}O_2$
MW: 246.3500

Following **General Procedure I** using *(Z)*-((1-(4-(*tert*-butyl)phenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane (60.5 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a pale-yellow oil (19.0 mg, 0.0771 mmol, 38%).

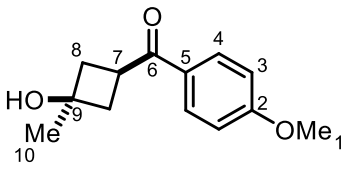
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.6 Hz, 2H, H^5), 7.47 (d, *J* = 8.6 Hz, 2H, H^4), 3.57 (p, *J* = 8.5 Hz, 1H, H^8), 2.54 – 2.26 (m, 5H, H^9 and OH), 1.49 (s, 3H, H^{11}), 1.34 (s, 9H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.9 (C^7), 157.1 (C^3 or C^6), 133.4 (C^3 or C^6), 128.5 (2C, C^4 or C^5), 125.7 (2C, C^4 or C^5), 69.6 (C^{10}), 41.5 (2C, C^9), 35.3 (C^2), 32.5 (C^8), 31.2 (3C, C^1), 27.5 (C^{11}).

IR (neat) ν_{max}: 3424, 2963, 2869, 1670, 1604, 1364, 1258, 1228, 1108, 678, 545.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}O_2^+$) requires *m*/*z* 247.1693, found *m*/*z* 247.1686.

*((1s,3s)-3-Hydroxy-3-methylcyclobutyl)(4-methoxyphenyl)methanone (**cis-1.085**)*



$C_{13}H_{16}O_3$
MW: 220.2680

Following **General Procedure I** using *(Z)*-((1-(4-methoxyphenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane (55.3 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (31.0 mg, 0.141 mmol, 70%).

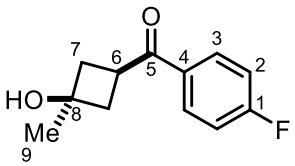
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.8 Hz, 2H, H^3 or H^4), 6.92 (d, *J* = 8.8 Hz, 2H, H^3 or H^4), 3.86 (s, 3H, H^1), 3.53 (p, *J* = 8.5 Hz, 1H, H^7), 2.57 (s, 1H, OH), 2.46 – 2.35 (m, 4H, H^8), 1.48 (s, 3H, H^{10}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.9 (C^6), 163.7 (C^2), 130.8 (2C, C^3 or C^4), 128.9 (C^5), 113.9 (2C, C^3 or C^4), 69.5 (C^9), 55.6 (C^1), 41.6 (2C, C^3), 32.2 (C^7), 27.4 (C^{10}).

IR (neat) ν_{max}: 3408, 2968, 2934, 1664, 1598, 1255, 1231, 1169, 1026, 611.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}O_3Na^+$) requires *m*/*z* 243.0992, found *m*/*z* 243.0995.

*(4-Fluorophenyl)((1s,3s)-3-hydroxy-3-methylcyclobutyl)methanone (**cis-1.086**)*



$C_{12}H_{13}FO_2$
MW: 208.2324

Following **General Procedure I** using *(Z)*-((1-(4-fluorophenyl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane (52.9 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate

(37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a pale-yellow oil (25.0 mg, 0.120 mmol, 60%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.7, 5.4 Hz, 2H, H^{Ar}), 7.12 (t, *J* = 8.7 Hz, 2H, H^{Ar}), 3.52 (p, *J* = 8.5 Hz, 1H, H^{6}), 2.47 – 2.36 (m, 5H, H^{7} and OH), 1.49 (s, 3H, H^{9}).

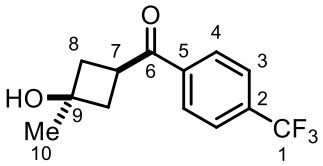
^{13}C NMR (176 MHz, $CDCl_3$): δ 199.6 (C^{5}), 165.92 (d, *J* = 254.9 Hz, C^{1}), 131.14 (C^{4}), 131.12 (d, *J* = 9.3 Hz, 2C, C^{3}), 115.9 (d, *J* = 21.8 Hz, 2C, C^{4}), 69.4 (C^{8}), 41.5 (2C, C^{7}), 32.5 (C^{6}), 27.4 (C^{9}).

^{19}F NMR (659 MHz, $CDCl_3$): δ -105.00.

IR (neat) ν_{max}: 3409, 2969, 2934, 1676, 1596, 1506, 1259, 1225, 1155, 852, 633.

HRMS (GC-TOF): exact mass calculated for $[M\text{-}H_2O\cdot]^+$ ($C_{12}H_{11}OF^+$) requires *m*/*z* 190.0794, found *m*/*z* 190.0782.

*((1s,3s)-3-Hydroxy-3-methylcyclobutyl)(4-(trifluoromethyl)phenyl)methanone (**cis-1.087**)*



$C_{13}H_{13}F_3O_2$
MW: 258.2402

Following **General Procedure I** using *(Z)*-trimethyl((4-methyl-1-(4-(trifluoromethyl)phenyl)penta-1,4-dien-1-yl)oxy)silane (62.9 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (9.2 mg, 0.0356 mmol, 18%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 – 7.99 (m, 2H, H^{Ar}), 7.76 – 7.70 (m, 2H, H^{Ar}), 3.56 (p, *J* = 8.5 Hz, 1H, H^{7}), 2.47 – 2.40 (m, 4H, H^{8}), 1.51 (s, 3H, H^{10}). *OH was not detected.*

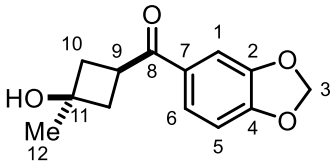
^{13}C NMR (151 MHz, $CDCl_3$): δ 200.0 (C^{6}), 138.6 (C^{5}), 134.64 (q, *J* = 32.7 Hz, C^{2}), 128.8 (2C, C^{4}), 125.89 (q, *J* = 3.8 Hz, 2C, C^{3}), 123.72 (q, *J* = 272.9 Hz, C^{1}), 69.5 (C^{9}), 41.4 (2C, C^{8}), 32.9 (C^{7}), 27.6 (C^{10}).

^{19}F NMR (659 MHz, $CDCl_3$): δ -63.14.

IR (neat) ν_{max}: 3292, 2970, 2365, 1681, 1508, 1326, 1167, 1138, 690.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{13}F_3O_2Na^+$) requires *m*/*z* 281.0760, found *m*/*z* 281.0753.

*Benzo[d][1,3]dioxol-5-yl((1s,3s)-3-hydroxy-3-methylcyclobutyl)methanone (**cis-1.088**)*



$C_{13}H_{14}O_4$
MW: 234.2510

Following **General Procedure I** using *(Z)*-((1-(benzo[*d*][1,3]dioxol-5-yl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane (58.1 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (16.3 mg, 0.0696 mmol, 35%).

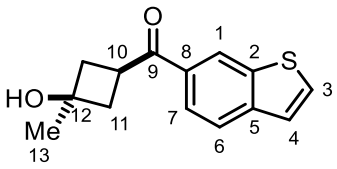
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.2, 1.7 Hz, 1H, H^6), 7.40 (d, *J* = 1.7 Hz, 1H, H^1), 6.84 (d, *J* = 8.2 Hz, 1H, H^5), 6.04 (s, 2H, H^3), 3.49 (p, *J* = 8.5 Hz, 1H, H^9), 2.44 – 2.35 (m, 4H, H^{10}), 2.24 (s, 1H, OH), 1.48 (s, 3H, H^{12}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.3 (C^8), 151.2 (C^2 or C^4), 148.4 (C^2 or C^4), 130.7 (C^7), 124.7 (C^6), 108.3 (C^1 or C^5), 108.1 (C^1 or C^5), 102.0 (C^3), 69.5 (C^{11}), 41.5 (2C, C^{10}), 32.3 (C^9), 27.4 (C^{12}).

IR (neat) ν_{max}: 3414, 2971, 1666, 1603, 1441, 1251, 1037, 740.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{14}O_4Na^+$) requires *m*/*z* 257.0784, found *m*/*z* 257.0786.

*Benzo[b]thiophen-6-yl((1s,3s)-3-hydroxy-3-methylcyclobutyl)methanone (**cis-1.089**)*



$C_{14}H_{14}O_2S$
MW: 246.3240

Following **General Procedure I** using *(Z)*-((1-(benzo[*b*]thiophen-6-yl)-4-methylpenta-1,4-dien-1-yl)oxy)trimethylsilane (60.5 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow oil (7.4 mg, 0.0300 mmol, 15%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.46 (dd, *J* = 1.5, 0.8 Hz, 1H, H^{Ar}), 7.92 (dd, *J* = 8.3, 1.5 Hz, 1H, H^{Ar}), 7.87 (d, *J* = 8.3 Hz, 1H, H^{Ar}), 7.67 (d, *J* = 5.4 Hz, 1H, H^{Ar}), 7.40 (dd, *J* = 5.4, 0.8 Hz, 1H, H^{Ar}), 3.67 (p, *J* = 8.4 Hz, 1H, H^{10}), 2.47 (app d, *J* = 8.5 Hz, 4H, H^{11}), 1.52 (s, 3H, H^{13}). *OH was not detected.*

^{13}C NMR (176 MHz, $CDCl_3$): δ 200.7 (C^9), 143.2 (C^{Ar}), 139.9 (C^{Ar}), 132.1 (C^{Ar}), 131.2 (C^{Ar}), 124.2 (C^{Ar}), 124.0 (C^{Ar}), 123.8 (C^{Ar}), 123.7 (C^{Ar}), 69.7 (C^{12}), 41.5 (2C, C^{11}), 32.7 (C^{10}), 27.5 (C^{13}).

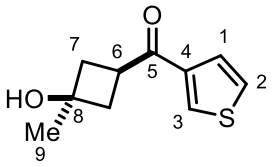
IR (neat) ν_{max}: 3451, 2973, 1714, 1670, 1591, 1260, 1225, 911, 735.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{14}O_2SNa^+$) requires *m*/*z* 269.0607, found *m*/*z* 269.0600.

*((1s,3s)-3-Hydroxy-3-methylcyclobutyl)(thiophen-3-yl)methanone (**cis-1.090**) and (1r,3r)-1-Methyl-3-(thiophene-3-carbonyl)cyclobutyl methanesulfonate (**trans-1.090-OMs**)*

Following **General Procedure I** using *(Z)*-trimethyl((4-methyl-1-(thiophen-3-yl)penta-1,4-dien-1-yl)oxy)silane (50.5 mg, 0.200 mmol, 1.00 equiv.), iodosylbenzene (52.8 mg, 0.240 mmol, 1.20 equiv.), methanesulfonic acid (17.0 µL, 0.260 mmol, 1.30 equiv.) and boron trifluoride diethyl etherate (37.0 µL, 0.300 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the cis-cyclobutanol and trans-cyclobutyl mesylate separately.

((1s,3s)-3-Hydroxy-3-methylcyclobutyl)(thiophen-3-yl)methanone (***cis*-1.090**)



$C_{10}H_{12}O_2S$
MW: 196.2640

The title compound was isolated as a yellow oil (12.2 mg, 0.0622 mmol, 31%).

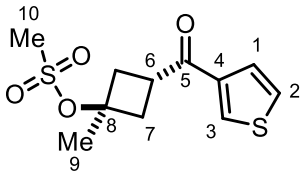
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (m, 2H, H^{Ar}), 7.13 (app dd, *J* = 5.0, 3.8 Hz, 1H, H^{Ar}), 3.48 (p, *J* = 8.3 Hz, 1H, H^6), 2.48 – 2.37 (m, 4H, H^7), 2.31 (s, 1H, OH), 1.47 (s, 3H, H^9).

^{13}C NMR (151 MHz, $CDCl_3$): δ 194.4 (C^5), 143.3 (C^4), 134.0 (C^{Ar}), 132.2 (C^{Ar}), 128.3 (C^{Ar}), 69.6 (C^8), 41.6 (2C, C^7), 33.4 (C^6), 27.4 (C^9).

IR (neat) ν_{max}: 3406, 2969, 2933, 1649, 1515, 1412, 1356, 1256, 1235, 793, 724.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{12}O_2SNa^+$) requires *m*/*z* 219.0450, found *m*/*z* 219.0451.

(1r,3r)-1-Methyl-3-(thiophene-3-carbonyl)cyclobutyl methanesulfonate (***trans*-1.090-OMs**)



$C_{11}H_{14}O_4S_2$
MW: 274.3490

The title compound was isolated as a yellow oil (9.8 mg, 0.0357 mmol, 18%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 – 7.59 (m, 2H, H^{Ar}), 7.19 – 7.10 (m, 1H, H^{Ar}), 4.01 (tt, *J* = 10.2, 6.4 Hz, 1H, H^6), 3.06 (s, 3H, H^{10}), 3.04 – 2.98 (m, 2H, H^{7a}), 2.66 (app dd, *J* = 14.0, 6.4 Hz, 2H, H^{7b}), 1.74 (s, 3H, H^9).

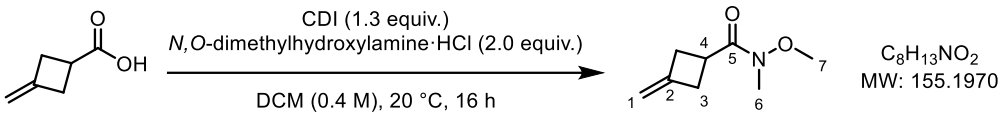
^{13}C NMR (151 MHz, $CDCl_3$): δ 192.7 (C^5), 142.4 (C^4), 134.0 (C^{Ar}), 132.2 (C^{Ar}), 128.2 (C^{Ar}), 88.1 (C^8), 40.8 (C^{10}), 38.6 (2C, C^7), 34.8 (C^6), 26.2 (C^9).

IR (neat) ν_{max}: 3444, 2971, 2934, 1654, 1516, 1414, 1354, 1255, 1236, 1181, 1153, 961, 730.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{14}O_4S_2Na^+$) requires *m*/*z* 297.0226, found *m*/*z* 297.0227.

*Compounds **1.102**–**1.107**, **1.109**–**1.111** were made by Dr. Zhi-Jie Niu, and their analysis were not reported in this thesis.*

N-Methoxy-N-methyl-3-methylenecyclobutane-1-carboxamide

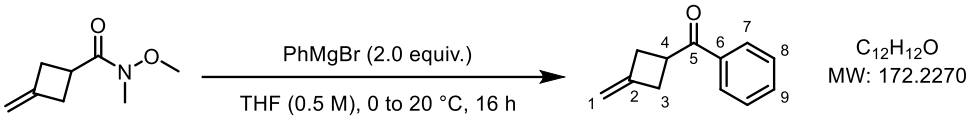


To a solution of 3-methylenecyclobutanecarboxylic acid (561 mg, 5.00 mmol, 1.00 equiv.) in anhydrous dichloromethane (0.4 M) was added 1,1'-carbonyldiimidazole (1.09 g, 6.50 mmol, 1.30 equiv.) at 20 °C.[142] The reaction was stirred at the same temperature for 1 h, before *N,O*-dimethylhydroxylamine hydrochloride (975 mg, 10.0 mmol, 2.00 equiv.) was added. The reaction was stirred at 20 °C for further 16 h before aq. HCl (1.0 M, 50 mL) was added. The biphasic mixture was separated, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with satd. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was obtained as a pale-yellow oil (754 mg, 4.86 mmol, 97%) and used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (m, 2H, H^1), 3.67 (app t, *J* = 2.1 Hz, 3H, H^7), 3.45 (br s, 1H, H^4), 3.19 (app d, *J* = 1.7 Hz, 3H, H^6), 3.08 – 2.98 (m, 2H, H^{2a}), 2.88 – 2.77 (m, 2H, H^{2b}).

The spectroscopic data were consistent with that reported in literature.[149]

(3-Methylenecyclobutyl)(phenyl)methanone

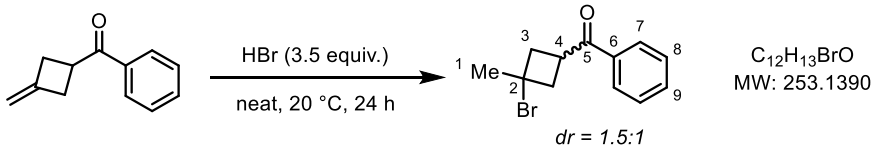


To a solution of *N*-methoxy-*N*-methyl-3-methylenecyclobutane-1-carboxamide (800 mg, 5.15 mmol, 1.00 equiv.) in anhydrous tetrahydrofuran (0.5 M) at 0 °C was added phenylmagnesium bromide (1 M in tetrahydrofuran, 10.3 mL, 10.3 mmol, 2.00 equiv.). The reaction was allowed to warm to 20 °C and stirred for 16 h. The reaction was terminated by addition of satd. aq. NH_4Cl (20 mL), diluted with dichloromethane (20 mL) and the biphasic mixture separated. The aqueous phase was extracted with dichloromethane (3 × 25 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, heptanes/ethyl acetate 1:0–9:1) to afford the title product as a pale-yellow oil (617 mg, 3.58 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 5.2, 3.3 Hz, 2H, H^7), 7.60 – 7.51 (m, 1H, H^9), 7.46 (dd, *J* = 10.4, 4.6 Hz, 2H, H^8), 4.91 – 4.78 (m, 2H, H^1), 4.06 – 3.86 (m, 1H, H^4), 3.23 – 3.07 (m, 2H, H^{3a}), 3.07 – 2.92 (m, 2H, H^{3b}).

The spectroscopic data were consistent with that reported in literature.[149]

*(3-Bromo-3-methylcyclobutyl)(phenyl)methanone (**1.091**)*



To (3-methylenecyclobutyl)(phenyl)methanone (617 mg, 3.58 mmol, 1.00 equiv.) in a vial at 20 °C was added hydrogen bromide (48% in water, 1.42 mL, 12.5 mmol, 3.50 equiv.). The biphasic mixture was stirred at 20 °C for 24 h, before water (5 mL) was added, followed by extraction with diethyl ether (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated

under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, heptanes/ethyl acetate 1:0–19:1) to afford the title product as a yellow oil (536 mg, 2.12 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.78 (m, 5H, H^7, major and minor), 7.62 – 7.51 (m, 2.5H, H^9, major and minor), 7.51 – 7.40 (m, 5H, H^8, major and minor), 4.35 (p, *J* = 8.7 Hz, 1H, H^4, minor), 3.90 – 3.76 (m, 1.5H, H^4, major), 3.26 – 3.12 (m, 3H, H^{3a}, major), 3.00 – 2.89 (m, 2H, H^{3a}, minor), 2.80 – 2.68 (m, 5H, H^{3b}, major and minor), 2.07 (s, 4.5H, H^1, major), 1.88 (s, 3H, H^1, minor).

The spectroscopic data were consistent with that reported in literature.[150]

3.3.3 Computational Details

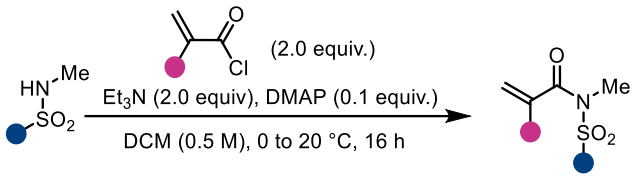
Computational work was performed by Aymen Benchouche under the supervision of Prof. Pier Alexandre Champagne, in New Jersey Institute of Technology, United States of America. The details are included here for the context of the work.

Density functional theory (DFT) calculations were performed using Gaussian 16.[151] Geometry optimizations were carried out with the hybrid ωB97X-D functional,[152] and the 6-31+G(d,p) basis set. For systems containing an iodine, optimizations were instead performed using the hybrid M06-2X functional with the Def2-TZVP basis set.[153] All optimizations employed the SMD implicit solvation model,[154] to account for solvent effects in dichloromethane (CH_2Cl_2), consistent with experimental conditions. Vibrational frequency analyses were performed for all stationary points to confirm their nature as minima (zero imaginary frequencies) or transition structures (TSs, exactly one imaginary frequency). Thermochemical corrections for zero-point energy (ZPE), enthalpy, and Gibbs free energy were obtained at 298.15 K and 1 atm using GoodEVibes v3.2,[155] applying Grimme's quasiharmonic treatment of vibrational frequencies < 100 cm^{-1}.[156] Single-point energy refinements were conducted using ORCA 5.0.4 with the DLPNO-CCSD(T)/Def2-TZVPP level of theory, employing the TightSCF and TightPNO convergence criteria. The SMD solvation model (dichloromethane) was again applied for these single-point calculations. Final Gibbs free energies were obtained by adding the free energy corrections obtained from the frequency analysis to the DLPNO-CCSD(T) single-point electronic energies. Molecular visualizations were prepared using CYLview.[157] Natural bond orbital (NBO)-based HOMO/LUMO analyses,[158] and the distortion-interaction / activation strain model (ASM)[159,160] calculations, were performed at the optimization (DFT) level of theory.

3.3 Synthesis of Difunctionalized Amides by Domino Conjugate Addition-Smiles Rearrangement

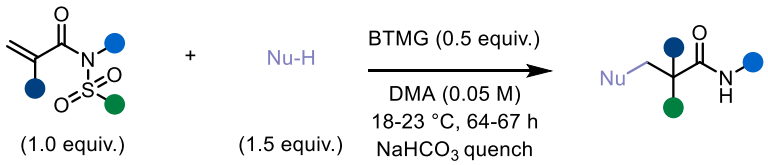
3.3.1 General Procedures

General Procedure L: Synthesis of Sulfonyl Acrylimides



To a flame-dried flask were added sulfonamide (1.0 equiv.), triethylamine (2.0 equiv.), 4-dimethylaminopyridine (DMAP, 0.1 equiv.) and dichloromethane (0.5 M). The solution was cooled to 0 °C and the corresponding acryloyl chloride (2.0 equiv.) was added dropwise. The reaction was allowed to warm to 20 °C and stirred for 16 h. After this time, satd. aq. $NaHCO_3$ was added and the resulting mixture was transferred to a separatory funnel. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, heptanes/ethyl acetate) afforded the sulfonyl acrylimide.

General Procedure M: Synthesis of Difunctionalized Amides

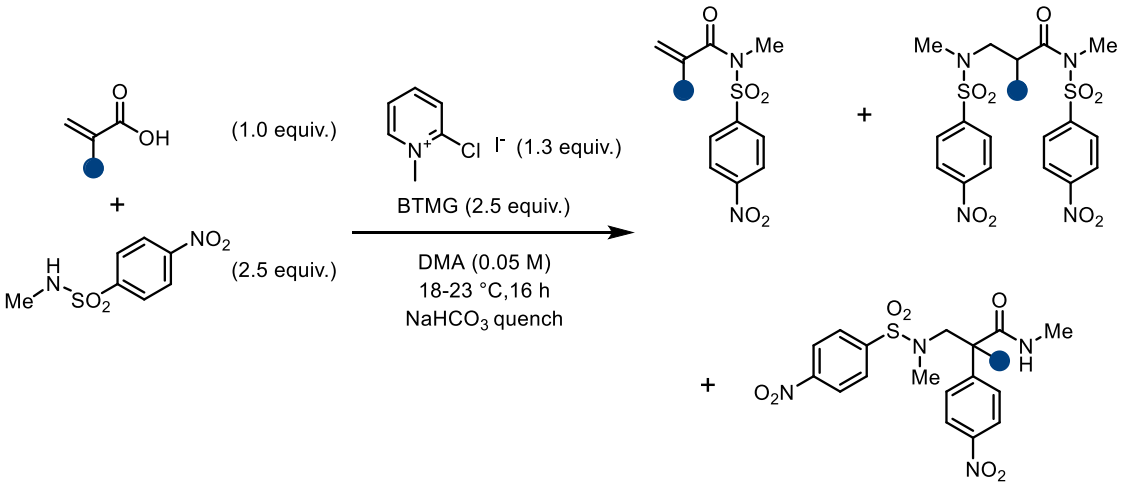


The reaction was performed under air.

An oven-dried vial was charged with the corresponding nucleophile (1.5 equiv.), dimethylacetamide (DMA, 0.05 M) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG, 0.5 equiv.). The reaction was stirred for 10 min at ambient temperature (18–23 °C), before addition of the sulfonyl imide (1.0 equiv.).

The resulting solution was stirred for an additional 64–67 h at ambient temperature. Afterwards, the reaction was transferred to a separation funnel with dichloromethane and satd. aq. $NaHCO_3$. After separation of the phases, the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The NMR yields were taken using two equivalents of mesitylene as internal standard. Purification by flash column chromatography (SiO_2, heptanes/ethyl acetate 9:1–1:1) afforded the difunctionalized amide products.

General Procedure N: One-pot amide coupling/Smiles rearrangement

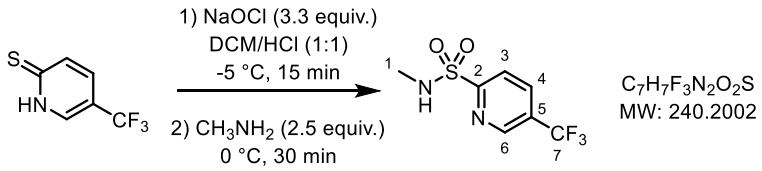


The reaction was performed under air.

To an oven-dried vial at ambient temperature were added *α,β*-unsaturated carboxylic acid (1.0 equiv.), *p*-nosyl methylamide (2.5 equiv.) and 2-chloro-1-methylpyridinium iodide (1.3 equiv.). The reactants were dissolved in dimethylacetamide (0.05 M) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (2.5 equiv.) was added. The solution was stirred at 20 °C for 16 h. The solution was then diluted with dichloromethane, washed sequentially with satd. aq. $NaHCO_3$ and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, heptane/ethyl acetate 9:1–1:1) afforded the products.

3.3.2 Characterisation of Products

N-Methyl-5-(trifluoromethyl)pyridine-2-sulfonamide



The compound is synthesized according to a known literature procecdure.[67] (Trifluormethyl)-2(1*H*)-pyridinethione (896 mg, 5.00 mmol, 1.00 equiv.) was added to an Erlenmeyer flask. Dichloromethane (25 mL) and aqueous HCl (1 M, 25 mL) were then added, and the reaction was cooled to -10 °C. Sodium hypochlorite (13% in H_2O, 7.50 mL, 16.6 mmol, 3.30 equiv.) was added slowly with vigorous stirring, ensuring that the temperature did not exceed -5 °C. The reaction was stirred at -10 to -5 °C for 15 min, after which it was transferred to a pre-cooled separatory funnel. The aqueous phase was collected in an Erlenmeyer flask and cooled to -78 °C. Methylamine (aq. 40%, 1.40 mL, 12.5 mmol, 2.50 equiv.) was added slowly and the reaction was allowed to warm to 20 °C and stirred at that temperature for 14 h. Meanwhile, a light-yellow suspension was formed. The mixture was washed with aqueous HCl (1 M), aqueous saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the title compound as yellow crystals (606 mg, 2.52 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H, H^6), 8.27 – 8.10 (m, 2H, H^3 and H^4), 5.16 (s, 1H, NH), 2.80 (s, 3H, H^1).

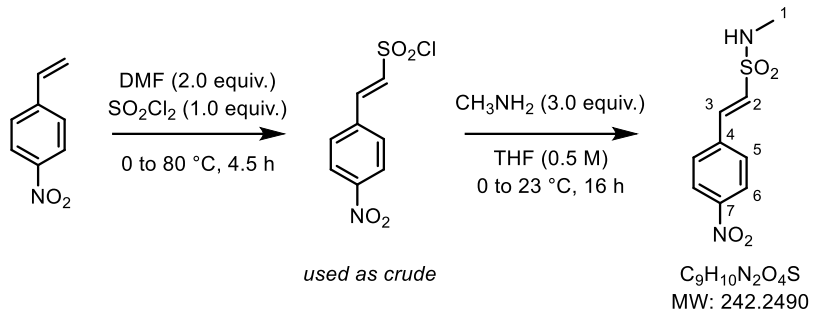
^{13}C NMR (101 MHz, $CDCl_3$): δ 160.2 (C^2), 147.2 (q, *J* = 4.0 Hz, C^6), 135.8 (q, *J* = 3.4 Hz, C^4), 129.5 (q, *J* = 33.9 Hz, C^5), 122.7 (q, *J* = 273.1 Hz, C^7), 122.4 (C^3), 30.0 (C^1).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.63.

IR (neat) ν_{max}: 3299, 3057, 2924, 1322, 1164, 1141, 1105, 1071, 1012, 847, 720.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_7H_7F_3N_2NaO_2S^+$) requires *m*/*z* 263.0073, found *m*/*z* 263.0056.

(E)-N-Methyl-2-(4-nitrophenyl)ethene-1-sulfonamide



The compound was synthesized according to a known literature procedure.[161] Sulfuryl chloride (777 µL, 9.58 mmol, 2.00 equiv.) was added dropwise to anhydrous dimethylformamide (741 µL, 9.58 mmol, 2.00 equiv.) at 0 °C under argon atmosphere. After completion of the addition, the reaction was allowed to warm to 23 °C and stirred for 30 min. 4-Nitrostyrene (614 µL, 4.79 mmol, 1.00 equiv.) was added and the reaction was gradually heated to 80 °C in an oil bath and continued to stir for 16 h. After subsequent cooling to ambient temperature, the reaction was further cooled to 0 °C and quenched by the addition of crushed ice (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue (640 mg), consisting of 60% desired sulfonyl chloride and 40% unreacted alkene, as determined by NMR analysis, was dissolved in tetrahydrofuran (2 mL) under stirring at 23 °C, after which the resulting solution was cooled to 0 °C and methylamine (40% in H_2O, 400 µL, 4.65 mmol, 3.00 equiv.) was added dropwise. The reaction was stirred at 23 °C for 16 h, after which it was acidified with aqueous HCl (1 M) to pH = 2, extracted with ethyl acetate (2 x 20 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (heptanes/ethyl acetate 1:0–0:1) gave the title compound as an orange solid (140 mg, 0.578 mmol, 12% over 2 steps).

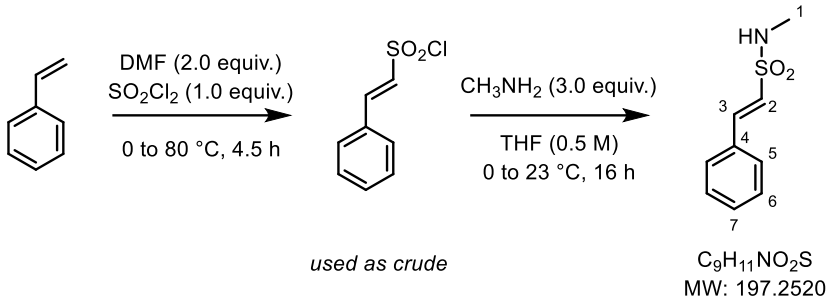
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8 Hz, 2H, H^6), 7.66 (d, *J* = 8.7 Hz, 2H, H^7), 7.54 (d, *J* = 15.5 Hz, 1H, H^2), 6.88 (d, *J* = 15.5 Hz, 1H, H^3), 4.31 (q, *J* = 5.1 Hz, 1H, NH), 2.81 (d, *J* = 5.3 Hz, 3H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.0 (C^7), 139.3 (C^4), 138.8 (C^3), 129.0 (2C, C^5), 128.6 (C^2), 124.5 (2C, C^6), 29.3 (C^1).

IR (neat) ν_{max}: 3297, 3058, 1599, 1519, 1347, 1324, 1310, 1148, 1128, 849, 741, 664.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_9H_{10}N_2O_4SNa^+$) requires *m*/*z* 265.0253, found *m*/*z* 265.0256.

(E)-N-Methyl-2-phenylethene-1-sulfonamide



used as crude

$C_9H_{11}NO_2S$
MW: 197.2520

The compound was synthesized according to a known literature procedure.[161] Sulfuryl chloride (1.62 mL, 20.0 mmol, 2.00 equiv.) was added dropwise to anhydrous dimethylformamide (1.55 mL, 20.0 mmol, 2.00 equiv.) at 0 °C. After completion of the addition, the reaction was allowed to warm to 23 °C and stirred for 30 min. Styrene (1.15 mL, 10.0 mmol, 1.00 equiv.) was added and the reaction was gradually heated to 80 °C in an oil bath and continued to stir for 4 h. The reaction was cooled to 0 °C, quenched by the addition of crushed ice (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue (1.33 g) was dissolved in tetrahydrofuran (6.5 mL) under stirring. Methylamine (40% in H_2O, 1.70 mL, 19.7 mmol, 3.00 equiv.) was added dropwise at 0 °C. The reaction was stirred at room temperature for 16 h, after which it was acidified with aq. HCl (1 M) to pH = 2, extracted with ethyl acetate (2 x 40 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (heptanes/ethyl acetate 1:0–0:1) gave the title compound as a yellow solid (727 mg, 3.69 mmol, 37% over 2 steps).

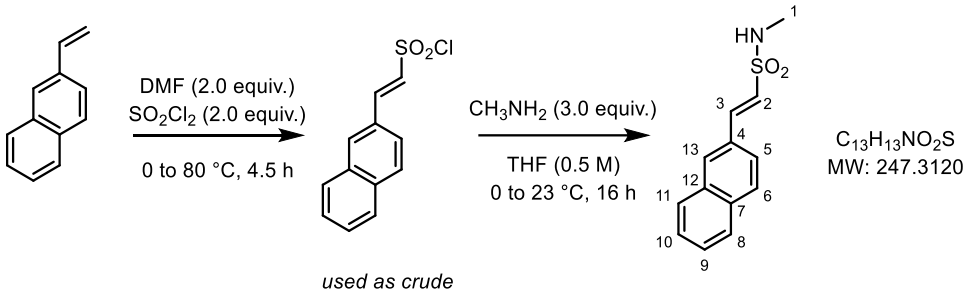
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 – 7.47 (m, 3H, H^3 and H^6), 7.42 – 7.40 (m, 3H, H^5 and H^7), 6.74 (d, *J* = 15.5 Hz, 1H, H^2), 4.59 (q, *J* = 4.9 Hz, 1H, NH), 2.76 (d, *J* = 5.3 Hz, 3H, H^1).

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.5 (C^3), 132.6 (C^4), 131.0 (C^7), 129.2 (2C, C^6), 128.4 (2C, C^5), 124.0 (C^2), 29.2 (C^1).

IR (neat) ν_{max}: 3288, 3057, 2941, 1618, 1315, 1196, 1180, 862, 840, 742, 532.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_9H_{11}NO_2SNa^+$) requires *m*/*z* 220.0403, found *m*/*z* 220.0404.

(E)-N-Methyl-2-(naphthalen-2-yl)ethene-1-sulfonamide



The compound was synthesized according to a known literature procedure.[161] To anhydrous dimethylformamide (0.57 mL, 7.4 mmol, 2.0 equiv.), sulfuryl chloride (0.6 mL, 7.4 mmol, 2.0 equiv.) was added dropwise at 0 °C under argon atmosphere. After the addition was finished, the reaction was allowed to warm to 23 °C and stirred for 30 min. 2-Vinylnaphthalene (0.51 mL, 3.7 mmol, 1.0 equiv.) was added and the reaction was gradually heated to 80 °C in an oil bath and continued to stir for 4 h. The reaction was cooled to 0 °C, quenched by the addition of crushed ice and extracted with ethyl acetate (3 x 20 mL). The organic phase was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue (935 mg) was dissolved in tetrahydrofuran (7.4 mL) under stirring. Methylamine (40% in H_2O, 1.23 mL, 11.1 mmol, 3.00 equiv.) was added dropwise at 0 °C. The reaction was stirred at 23 °C for 16 h, after which it was acidified with aq. HCl (1 M) to pH = 2, extracted with ethyl acetate (2 x 30 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (heptanes/ethyl acetate 1:0–0:1) gave the title compound as a pale-yellow solid (203 mg, 0.813 mmol, 22% over 2 steps).

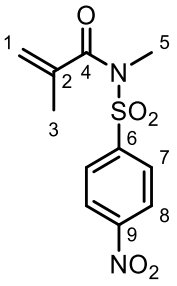
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.94 (s, 1H, H^{13}), 7.91 – 7.80 (m, 3H, H^6, H^8 and H^{11}), 7.67 (d, *J* = 15.4 Hz, 1H, H^3), 7.60 (dd, *J* = 8.6, 1.7 Hz, 1H, H^5), 7.57 – 7.47 (m, 2H, H^9 and H^{10}), 6.83 (d, *J* = 15.4 Hz, 1H, H^2), 4.23 (app d, *J* = 5.2 Hz, 1H, NH), 2.80 (d, *J* = 5.4 Hz, 3H, H^1).

^{13}C NMR (176 MHz, $CDCl_3$): δ 142.7 (C^3), 134.6 (C^7), 133.3 (C^{12}), 130.6 (C^{13}), 130.1 (C^4), 129.2 (C^8), 128.8 (C^{11}), 128.0 (C^6), 127.8 (C^9 or C^{10}), 127.2 (C^9 or C^{10}), 124.1 (C^2), 123.4 (C^5), 29.3 (C^1).

IR (neat) ν_{max}: 3300, 3052, 2921, 2852, 1614, 1319, 1274, 1149, 1129, 1070, 857, 806, 744, 477.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{13}NO_2S^+$) requires *m*/*z* 270.0559, found *m*/*z* 270.0552.

N-Methyl-N-((4-nitrophenyl)sulfonyl)methacrylamide



$C_{11}H_{12}N_2O_5S$
MW: 284.2860

Following **General Procedure L** using *N*-methyl-4-nitrobenzenesulfonamide (1.08 g, 5.00 mmol, 1.00 equiv.) and methacryloyl chloride (1.05 g, 10.0 mmol, 2.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a colourless solid (989 mg, 3.48 mmol, 70%).

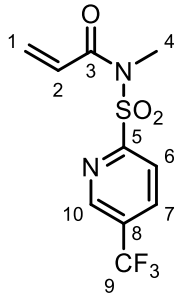
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 9.0 Hz, 2H, H^7), 8.20 (d, *J* = 9.0 Hz, 2H, H^8), 5.47 (d, *J* = 1.5 Hz, 1H, H^{1a}), 5.30 (app s, 1H, H^{1b}), 3.34 (s, 3H, H^5), 1.95 (s, 3H, H^3).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.1 (C^4), 150.8 (C^9), 144.4 (C^6 or C^2), 139.8 (C^6 or C^2) 129.8 (2C, C^7), 124.2 (2C, C^8), 121.3 (C^1), 35.1 (C^8), 19.2 (C^3).

IR (neat) ν_{max}: 3112, 2957, 2930, 2158, 1695, 1533, 1351, 1177, 1027, 936, 856, 610.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{11}H_{12}N_2NaO_5S^+$) requires *m*/*z* 307.0360, found *m*/*z* 307.0354.

N-Methyl-N-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)acrylamide



$C_{10}H_9F_3N_2O_3S$
MW: 294.2482

Following **General Procedure L** using *N*-methyl-5-(trifluoromethyl)pyridine-2-sulfonamide (480 mg, 2.00 mmol, 1.00 equiv.) and acryloyl chloride (434 mg, 4.80 mmol, 2.40 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as colourless crystals (177 mg, 0.602 mmol, 30%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.93 (s, 1H, H^{10}), 8.27 – 8.19 (m, 2H, H^6 and H^7), 6.99 (dd, *J* = 16.7, 10.5 Hz, 1H, H^2), 6.41 (dd, *J* = 16.7, 1.5 Hz, 1H, H^{1a}), 5.83 (dd, *J* = 10.5, 1.5 Hz, 1H, H^{1b}), 3.43 (s, 3H, H^4).

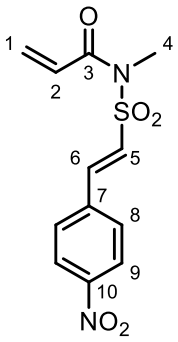
^{13}C NMR (151 MHz, $CDCl_3$): δ 166.5 (C^3), 159.7 (C^5), 147.5 (q, *J* = 3.9 Hz, C^{10}), 136.0 (q, *J* = 3.5 Hz, C^7), 132.0 (C^2), 130.2 (q, *J* = 33.9 Hz, C^8), 128.4 (C^1), 122.9 (C^6), 122.5 (q, *J* = 273.4 Hz, C^9), 34.1 (C^4).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.68.

IR (neat) ν_{max}: 1693, 1366, 1327, 1173, 1138, 1104, 1073, 1013, 730, 621.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{10}H_9F_3N_2NaO_3S^+$) requires *m*/*z* 317.0178, found *m*/*z* 317.0175.

(E)-N-Methyl-N-((4-nitrostyryl)sulfonyl)acrylamide



$C_{12}H_{12}N_2O_5S$
MW: 296.2970

Following **General Procedure L** using (*E*)-*N*-methyl-2-(4-nitrophenyl)ethene-1-sulfonamide (140 mg, 0.578 mmol, 1.00 eq.) and acryloyl chloride (105 mg, 1.16 mmol, 2.00 eq.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a yellow solid (98.0 mg, 0.331 mmol, 57%).

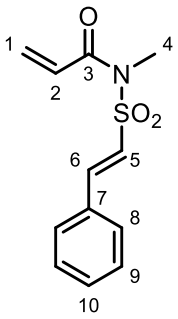
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8 Hz, 2H, H^9), 7.69 (d, *J* = 8.7 Hz, 2H, H^8), 7.66 (d, *J* = 15.5 Hz, 1H, H^6), 7.12 (d, *J* = 15.4 Hz, 1H, H^5), 6.91 (dd, *J* = 16.7, 10.4 Hz, 1H, H^2), 6.49 (dd, *J* = 16.7, 1.5 Hz, 1H, H^{1a}), 5.90 (dd, *J* = 10.5, 1.5 Hz, 1H, H^{1b}), 3.35 (s, 3H, H^4).

^{13}C NMR (176 MHz, $CDCl_3$): δ 166.3 (C^3), 149.4 (C^{10}), 141.0 (C^7), 137.9 (C^6), 132.4 (C^2), 129.5 (2C, C^8), 128.3 (C^1), 128.1 (C^5), 124.5 (2C, C^9), 32.9 (C^4).

IR (neat) ν_{max}: 3113, 3076, 2958, 1687, 1493, 1346, 1147, 847, 742.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}N_2O_5SNa^+$) requires *m*/*z* 319.0359, found *m*/*z* 319.0351.

(E)-N-Methyl-N-(styrylsulfonyl)acrylamide



$C_{12}H_{13}NO_3S$
MW: 251.3000

Following **General Procedure L** using (*E*)-*N*-methyl-2-phenylethene-1-sulfonamide (3.29 g, 16.7 mmol, 1.00 equiv.) and acryloyl chloride (3.02 g, 33.4 mmol, 2.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as a colourless viscous oil (1.16 g, 4.62 mmol, 28%).

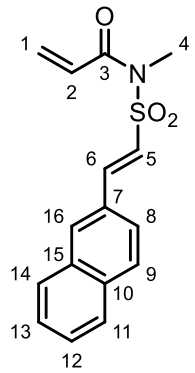
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (d, *J* = 15.4 Hz, 1H, H^6), 7.54 – 7.48 (m, 2H, H^8), 7.48-7.40 (m, 3H, H9 and H^{10}), 7.00 (dd, *J* = 16.7, 10.5 Hz, 1H, H^2), 6.92 (d, *J* = 15.4 Hz, 1H, H^5), 6.46 (dd, *J* = 16.7, 1.6 Hz, 1H, H^{1a}), 5.85 (dd, *J* = 10.4, 1.6 Hz, 1H, H^{1b}), 3.32 (s, 3H, H^4).

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.4 (C^3), 144.2 (C^6), 131.9 (C^7), 131.8 (C^2), 131.6 (C^1), 129.4 (2C, C^9), 128.8 (2C, C^8), 128.6 (C^{10}), 123.8 (C^5), 32.8 (C^4).

IR (neat) ν_{max}: 3060, 2954, 1681, 1613, 1352, 1146, 1014, 908, 817, 743.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{13}NNaO_3S^+$) requires *m*/*z* 274.0508, found *m*/*z* 274.0507.

(E)-N-Methyl-N-((2-(naphthalen-2-yl)vinyl)sulfonyl)acrylamide



$C_{16}H_{15}NO_3S$
MW: 301.3600

Following **General Procedure L** using (*E*)-*N*-methyl-2-(naphthalen-2-yl)ethene-1-sulfonamide (200 mg, 0.808 mmol, 1.00 equiv.) and acryloyl chloride (146 mg, 1.62 mmol, 2.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 1:0–1:1) gave the title compound as an off-white solid (62.0 mg, 0.206 mmol, 25%).

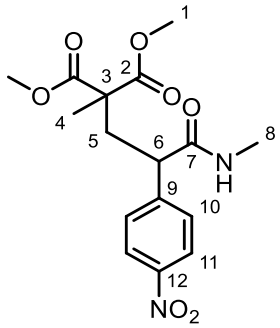
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.97 (s, 1H, H^{16}), 7.90 – 7.85 (m, 3H, H^9, H^{11} and H^{14}), 7.78 (d, *J* = 15.3 Hz, 1H, H^6), 7.62-7.52 (m, 3H, H8, H^{12} and H^{13}), 7.03 (app dd, *J* = 16.1, 10.2 Hz, 2H, H^2 and H^5), 6.47 (dd, *J* = 16.7, 1.6 Hz, 1H, H^{1a}), 5.86 (dd, *J* = 10.4, 1.6 Hz, 1H, H^{1b}), 3.35 (s, 3H, H^4).

^{13}C NMR (176 MHz, $CDCl_3$): δ 166.4 (C^3), 144.3 (C^6), 134.9 (C^{10}), 133.3 (C^{15}), 131.6 (C^1), 131.5 (C^{16}), 129.3 (C^{Ar}), 129.3 (C^{Ar}), 128.9 (C^{Ar}), 128.6 (C^{Ar}), 128.3 (C^2), 128.1 (C^{Ar}), 127.3 (C^{Ar}), 123.8 (C^5), 123.4 (C^8), 32.8 (C^4).

IR (neat) ν_{max}: 3058, 2954, 2922, 1684, 1353, 1149, 910, 745, 733.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{13}NNaO_3S^+$) requires *m*/*z* 324.6057, found *m*/*z* 324.6066.

*Dimethyl 2-methyl-2-(3-(methylamino)-2-(4-nitrophenyl)-3-oxopropyl)malonate (**2.084**)*



$C_{16}H_{20}N_2O_7$
MW: 352.3430

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (31.0 mg, 0.088 mmol, 88%).

Scale up was performed following the same procedure, using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (270 mg, 1.00 mmol, 1.00 equiv.) and dimethyl methylmalonate (219 mg, 1.50 mmol, 1.5 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (267 mg, 0.758 mmol, 76%).

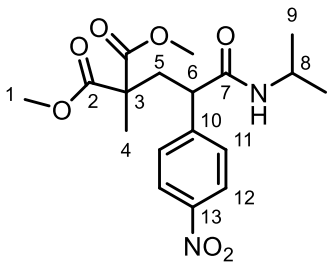
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.7 Hz, 2H, H^{11}), 7.50 (d, *J* = 8.7 Hz, 2H, H^{10}), 5.55 (app d, *J* = 4.1 Hz, 1H, NH), 3.70 (dd, *J* = 7.3, 4.5 Hz, 1H, H^6), 3.65 (s, 3H, H^{1a}), 3.62 (s, 3H, H^{1b}), 2.86 (dd, *J* = 14.5, 7.3 Hz, 1H, H^{5a}), 2.76 (d, *J* = 4.8 Hz, 3H, H^8), 2.20 (dd, *J* = 14.5, 4.5 Hz, 1H, H^{5b}), 1.43 (s, 3H, H^4).

^{13}C NMR (176 MHz, $CDCl_3$): δ 172.4 (C^{2a}, C^{2b} or C^7), 172.2 (C^{2a}, C^{2b} or C^7), 172.0 (C^{2a}, C^{2b} or C^7), 148.1 (C^9 or C^{12}), 147.3 (C^9 or C^{12}), 129.0 (2C, C^{10}), 124.0 (2C, C^{11}), 53.3 (C^3), 52.74 (C^{1a} or C^{1b}), 52.73 (C^{1a} or C^{1b}), 49.3 (C^6), 39.8 (C^5), 26.9 (C^4), 21.4 (C^{21}).

IR (neat) ν_{max}: 3399, 3306, 3080, 3000, 2953, 1731, 1652, 1521, 1382, 1077, 856, 739.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2NaO_7^+$) requires *m*/*z* 375.1163, found *m*/*z* 375.1164.

*Dimethyl 2-(3-(isopropylamino)-2-(4-nitrophenyl)-3-oxopropyl)-2-methylmalonate (**2.085**)*



$C_{18}H_{24}N_2O_7$
MW: 380.3970

Following **General Procedure M** using *N*-isopropyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (29.8 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (28.8 mg, 0.076 mmol, 76%).

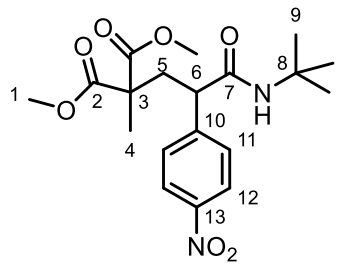
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 – 8.08 (m, 2H, H^{12}), 7.55 – 7.44 (m, 2H, H^{13}), 5.39 (app d, *J* = 7.6 Hz, 1H, NH), 4.04 – 3.91 (m, 1H, H^8), 3.72 – 3.57 (m, 7H, H^1 and H^6), 2.83 (dd, *J* = 14.5, 7.4 Hz, 1H, H^{5a}), 2.18 (dd, *J* = 14.5, 4.4 Hz, 1H, H^{5b}), 1.42 (s, 3H, H^4), 1.15 (d, *J* = 6.6 Hz, 3H, H^{9a}), 1.00 (d, *J* = 6.5 Hz, 3H, H^{9b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4 (C^{2a}), 172.2 (C^{2b}), 170.5 (C^7), 148.4 (C^{13}), 147.2 (C^{10}), 128.9 (2C, C^{12}), 124.0 (2C, C^{11}), 53.4 (C^{1a}), 52.7 (C^{1b}), 49.4 (C^3), 42.0 (C^8), 39.6 (C^6), 22.6 (C^{9a}), 22.5 (C^{9b}), 21.2 (C^5), 14.2 (C^4).

IR (neat) ν_{max}: 3384, 3313, 2973, 1731, 1650, 1605, 1521, 1492, 1347, 1110, 856, 740, 699.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{24}N_2O_7Na^+$) requires *m*/*z* 403.1476, found *m*/*z* 403.1479.

*Dimethyl 2-(3-(tert-butylamino)-2-(4-nitrophenyl)-3-oxopropyl)-2-methylmalonate (**2.086**)*



$C_{19}H_{26}N_2O_7$
MW: 394.4240

Following **General Procedure M** using *N*-(*tert*-butyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (31.2 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (22.0 mg, 0.056 mmol, 56%).

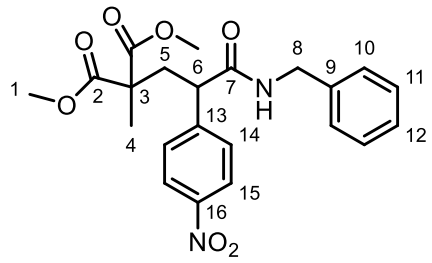
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 – 8.13 (m, 2H, H^{12}), 7.52 – 7.40 (m, 2H, H^{11}), 5.38 (s, 1H, NH), 3.68 (s, 3H, H^{1a}), 3.64 – 3.55 (m, 4H, H^{1b} and H^6), 2.81 (dd, *J* = 14.5, 7.4 Hz, 1H, H^{5a}), 2.14 (dd, *J* = 14.5, 4.2 Hz, 1H, H^{5b}), 1.43 (s,3H, H^4), 1.27 (s, 9H, H^9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5 (C^{2a}), 172.3 (C^{2b}), 170.5 (C^7), 148.7 (C^{13} or C^{10}), 147.2 (C^{10} or C^{13}), 128.8 (2C, C^{12}), 124.0 (2C, C^{11}), 53.5 (C^{1a}), 52.8 (C^{1b}), 52.7 (C^3), 51.7 (C^6), 49.9 (C^8), 39.6 (C^5), 28.7 (3C, C^9), 21.2 (C^4).

IR (neat) ν_{max}: 3392, 2957, 1728, 1679, 1604, 1518, 1454, 1345, 982, 858, 699.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{26}N_2O_7Na^+$) requires *m*/*z* 417.1632, found *m*/*z* 417.1635.

*Dimethyl 2-(3-(benzylamino)-2-(4-nitrophenyl)-3-oxopropyl)-2-methylmalonate (**2.087**)*



$C_{22}H_{24}N_2O_7$
MW: 428.4410

Following **General Procedure M** using *N*-benzyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (34.6 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.15 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (30.0 mg, 0.070 mmol, 70%).

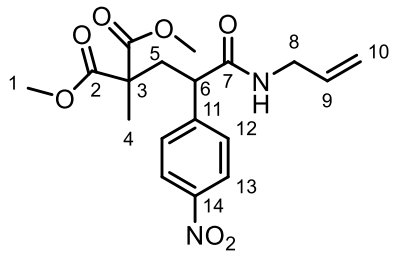
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.6 Hz, 2H, H^{15}), 7.50 (d, *J* = 8.6 Hz, 2H, H^{14}), 7.29 – 7.22 (m, 3H, H^{10} and H^{12}), 7.16 (d, *J* = 7.1 Hz, 2H, H^{11}), 5.92 (t, *J* = 5.3 Hz, 1H, NH), 4.37 (d, *J* = 5.3 Hz, 2H, H^8), 3.76 (dd, *J* = 7.3, 4.3 Hz, 1H, H^6), 3.62 (s, 3H, H^{1a}), 3.61 (s, 3H, H^{1b}), 2.89 (dd, *J* = 14.5, 7.3 Hz, 1H, H^{5a}), 2.22 (dd, *J* = 14.5, 4.3 Hz, 1H, H^{5b}), 1.43 (s, 3H, H^4).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4 (C^{2a}), 172.2 (C^{2b}), 171.3 (C^7), 148.1 (C^{13} or C^{16}), 147.3 (C^{13} or C^{16}), 137.8 (C^9), 128.9 (2C, C^{Ar}), 128.8 (2C, C^{Ar}), 127.9 (2C, C^{Ar}), 127.8 (C^{12}), 124.0 (2C, C^{Ar}), 53.3 (C^8), 52.74 (C^{1a}), 52.72 (C^{1b}), 49.3 (C^3), 44.2 (C^6), 39.6 (C^5), 21.3 (C^4).

IR (neat) ν_{max}: 3302, 2952, 1729, 1650, 1519, 1345, 1108, 855, 738, 699.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{24}N_2O_7Na^+$) requires *m*/*z* 451.1476, found *m*/*z* 451.1477.

*Dimethyl 2-(3-(allylamino)-2-(4-nitrophenyl)-3-oxopropyl)-2-methylmalonate (**2.088**)*



$C_{18}H_{22}N_2O_7$
MW: 378.3810

Following **General Procedure M** using *N*-allyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (29.6 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (28.1 mg, 0.074 mmol, 74%).

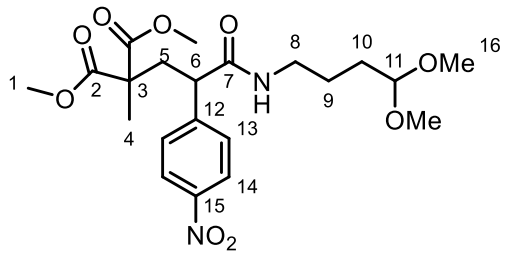
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 2H, H^{13}), 7.50 (d, *J* = 8.5 Hz, 2H, H^{12}), 5.74 (app ddd, *J* = 24.1, 11.9, 6.4 Hz, 2H, NH and H^9), 5.12 – 5.00 (m, 2H, H^{10}), 3.85 – 3.78 (m, 2H, H^8), 3.74 (dd, *J* = 7.1, 4.6 Hz, 1H, H^6),3.65 (s, 3H, H^{1a}), 3.61 (s, 3H, H^{1b}), 2.86 (dd, *J* = 14.5, 7.1 Hz, 1H, H^{5a}), 2.21 (dd, *J* = 14.5, 4.6 Hz, 1H, H^{5b}), 1.43 (s, 3H, H^4).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4 (C^{2a}), 172.2 (C^{2b}), 171.3 (C^7), 148.1 (C^{14} or C^{11}), 147.3 (C^{11} or C^{14}), 133.8 (C^9), 129.0 (2C, C^{13}), 124.0 (2C, C^{12}), 116.9 (C^{10}), 53.3 (2C, C^1), 52.7 (C^8), 49.3 (C^3), 42.4 (C^6), 39.7 (C^5), 21.4 (C^4).

IR (neat) ν_{max}: 3303, 2953, 1730, 1654, 1520, 1346, 1162, 855.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2O_7Na^+$) requires *m*/*z* 401.1319, found *m*/*z* 401.1319.

*Dimethyl 2-(3-((4,4-dimethoxybutyl)amino)-2-(4-nitrophenyl)-3-oxopropyl)-2-methylmalonate (**2.089**)*



$C_{21}H_{30}N_2O_9$
MW: 454.4760

Following **General Procedure M** using *N*-(4,4-dimethoxybutyl)-*N*-((4-nitrophenyl)sulfonyl)acrylamide (37.2 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (27.5 mg, 0.060 mmol, 60%).

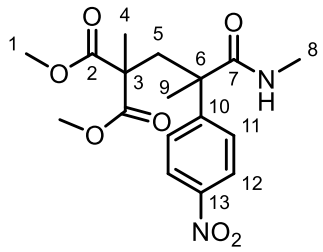
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 – 8.09 (m, 2H, H14), 7.49 (d, *J* = 8.8 Hz, 2H, H13), 5.84 (t, *J* = 5.2 Hz, 1H, H11), 4.28 (t, *J* = 5.2 Hz, 1H, NH), 3.67 (dd, *J* = 7.2, 4.5 Hz, 1H, H6), 3.63 (s, 3H, H1a), 3.61 (s, 3H, H1b), 3.27 (s, 3H, H16a), 3.25 (s, 3H, H16b), 3.22 – 3.15 (m, 2H, H8), 2.89 – 2.80 (m, 1H, H5a), 2.20 (dd, *J* = 14.5, 4.5 Hz, 1H, H5b), 1.55 – 1.46 (m, 4H, H9 and H10), 1.42 (s, 3H, H4).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4 (C^{2a}), 172.2 (C^{2b}), 171.4 (C^7), 148.3 (C^{12} or C^{15}), 147.2 (C^{12} or C^{15}), 128.9 (2C, C^{14}), 124.0 (2C, C^{13}), 104.3 (C^{11}), 53.3 (C^{16a}), 53.2 (C^{16b}), 53.1 (C^6), 52.70 (C^{1a}), 52.67 (C^{1b}), 49.3 (C^3), 39.7 (C^5), 39.5 (C^8), 29.9 (C^9 or C^{10}), 24.3 (C^9 or C^{10}), 21.2 (C^4).

IR (neat) ν_{max}: 3314, 2925, 2854, 1732, 1653, 1522, 1346, 1111, 856, 740.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{21}H_{30}N_2O_9Na^+$) requires *m*/*z* 477.1844, found *m*/*z* 477.1857.

*Dimethyl 2-methyl-2-(2-methyl-3-(methylamino)-2-(4-nitrophenyl)-3-oxopropyl)malonate (**2.092**)*



$C_{17}H_{22}N_2O_7$
MW: 366.3700

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)methacrylamide (28.4 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a yellow solid (14.3 mg, 0.039 mmol, 39%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.9 Hz, 2H, H^{12}), 7.59 (d, *J* = 8.9 Hz, 2H, H^{11}), 5.48 (app d, *J* = 4.2 Hz, 1H, NH), 3.68 (s, 3H, H^{1a}), 3.66 (s, 3H, H^{1b}), 3.06 (d, *J* = 14.9 Hz, 1H, H^{5a}), 2.76 (d, *J* = 4.7 Hz, 3H, H^8), 2.65 (d, *J* = 14.9 Hz, 1H, H^{5b}), 1.61 (s, 3H, H^4 or H^9), 1.32 (s, 3H, H^4 or H^9).

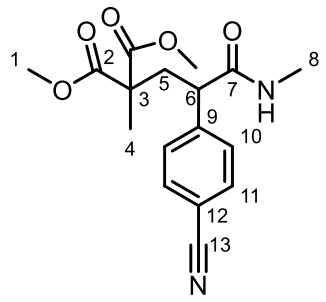
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.7 (C^{2a}, C^{2b} or C^7), 173.0 (C^{2a}, C^{2b} or C^7), 172.5 (C^{2a}, C^{2b} or C^7), 152.2 (C^{10} or C^{13}), 147.0 (C^{10} or C^{13}), 127.6 (2C, C^{12}), 123.8 (2C, C^{11}), 53.2 (C^3), 52.9 (C^{1a}), 52.8 (C^{1b}), 49.8 (C^3), 43.4 (C^6), 27.1 (C^5), 21.8 (C^4 or C^9), 21.6 (C^4 or C^9).

IR (neat) ν_{max}: 3433, 3361, 2998, 2953, 1731, 1668, 1520, 1348, 1267, 1086, 856.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}N_2NaO_7^+$) requires *m*/*z* 389.1320, found *m*/*z* 389.1319.

Dimethyl 2-(2-(4-cyanophenyl)-3-(methylamino)-3-oxopropyl)-2-methylmalonate

(2.095)



$C_{17}H_{20}N_2O_5$
MW: 332.3560

Following **General Procedure M** using *N*-((4-cyanophenyl)sulfonyl)-*N*-methylacrylamide (31.8 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (19.2 mg, 0.048 mmol, 48%).

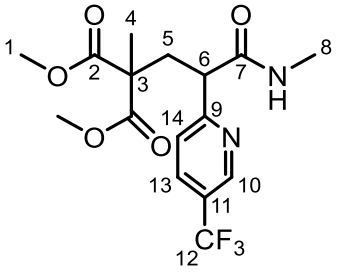
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.3 Hz, 2H, H^{11}), 7.44 (d, *J* = 8.3 Hz, 2H, H^{12}), 5.55 (app d, *J* = 4.5 Hz, 1H, NH), 3.65-3.62 (m, 4H, H^{1a} and H^6), 3.61 (s, 3H, H^{1b}), 2.83 (dd, *J* = 14.5, 7.2 Hz, 1H, H^{5a}), 2.75 (d, *J* = 4.5 Hz, 3H, H^8), 2.19 (dd, *J* = 14.5, 4.7 Hz, 1H, H^{5b}), 1.42 (s, 3H, H^4).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4 (C^{1a}, C^{1b} or C^7), 172.2 (C^{1a}, C^{1b} or C^7), 172.2 (C^{1a}, C^{1b} or C^7), 146.0 (C^9), 132.6 (2C, C^{11}), 128.9 (2C, C^{10}), 118.8 (C^{13}), 111.3 (C^{12}), 53.3 (C^6), 52.7 (C^{1a}), 52.7 (C^{1b}), 49.5 (C^3), 39.6 (C^5), 26.8 (C^8), 21.4 (C^4).

IR (neat) ν_{max}: 3403, 3001, 2955, 2235, 1730, 1674, 1529, 1317, 1057, 666.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2NaO_5^+$) requires *m*/*z* 355.1264, found *m*/*z* 355.1264.

*Dimethyl 2-methyl-2-(3-(methylamino)-3-oxo-2-(5-(trifluoromethyl)pyridin-2-yl)propyl)malonate (**2.096**)*



$C_{16}H_{19}F_3N_2O_5$
MW: 376.3322

Following **General Procedure M** using *N*-methyl-*N*-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)acrylamide (29.4 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a colourless solid (26.5 mg, 0.070 mmol, 70%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.79 (d, *J* = 0.5 Hz, 1H, H^{10}), 7.88 (dd, *J* = 8.2, 2.2 Hz, 1H, H^{13}), 7.46 (d, *J* = 8.2 Hz, 1H, H^{14}), 6.39 (app d, *J* = 4.2 Hz, 1H, NH), 3.87 (t, *J* = 6.2 Hz, 1H, H^6), 3.63 (s, 3H, H^{1a}), 3.57 (s, 3H, H^{1b}), 2.79 (dd, *J* = 14.4, 6.4 Hz, 1H, H^{5a}), 2.75 (d, *J* = 4.9 Hz, 3H, H^8), 2.57 (dd, *J* = 14.4, 6.4 Hz, 1H, H^{5b}), 1.41 (s, 3H, H^4).

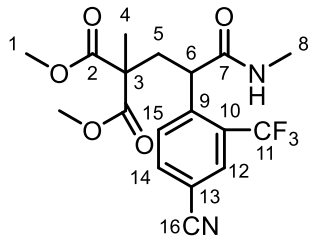
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.3 (C^7), 172.1 (C^{2a}), 171.6 (C^{2b}), 163.4 (C^9), 146.2 (q, *J* = 4.0 Hz, C^{10}), 134.2 (q, *J* = 3.4 Hz, C^{13}), 125.5 (q, *J* = 33.2 Hz, C^{11}), 123.6 (q, *J* = 272.3 Hz, C^{12}), 123.1 (C^{14}), 53.3 (C^6), 52.8 (C^{1a}), 52.6 (C^{1b}), 52.0 (C^3), 38.4 (C^5), 26.7 (C^8), 20.7 (C^4).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.39.

IR (neat) ν_{max}: 3301, 2954, 1732, 1654, 1328, 1163, 1122, 1081.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{19}F_3N_2NaO_5^+$) requires *m*/*z* 399.1138, found *m*/*z* 399.1142.

*Dimethyl 2-(2-(4-cyano-2-(trifluoromethyl)phenyl)-3-(methylamino)-3-oxopropyl)-2-methylmalonate (**2.097**)*



$C_{18}H_{19}F_3N_2O_5$
MW: 400.3542

Following **General Procedure M** using *N*-((4-cyano-2-(trifluoromethyl)phenyl)sulfonyl)-*N*-methylacrylamide (31.8 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (48%, 19.2 mg, 0.048 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.3 Hz, 1H, H^{14}), 7.90 (s, 1H, H^{12}), 7.82 (d, *J* = 8.2 Hz, 1H, H^{15}), 5.65 (d, *J* = 4.2 Hz, 1H, NH), 3.86 (dd, *J* = 9.3, 2.3 Hz, 1H, H^6), 3.70 (s, 3H, H^{1a}), 3.68 (s, 3H, H^{1b}), 3.00 (dd, *J* = 14.4, 9.5 Hz, 1H, H^{5a}), 2.74 (d, *J* = 4.8 Hz, 3H, H^8), 2.12 (dd, *J* = 14.4, 3.0 Hz, 1H, H^{5b}), 1.41 (s, 3H, H^4).

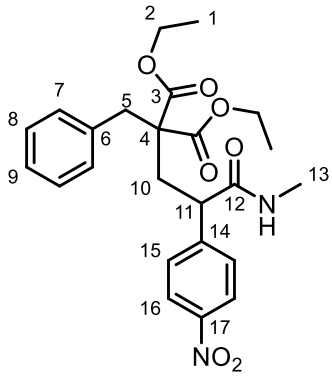
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.1 (C^{2a}), 172.0 (C^{2b}), 170.9 (C^7), 144.4 (C^9), 135.7 (C^{14}), 131.4 (C^{Ar}), 129.7-129.5 (m, C^{Ar}), 128.5 (q, *J* = 30.6 Hz, C^{10}), 123.5 (q, *J* = 274.4 Hz, C^{11}), 122.6 (C^{Ar}), 120.7 (C^{16}), 53.3 (C^3), 52.9 (C^{1a}), 52.8 (C^{1b}), 43.8 (C^6), 39.4 (C^5), 27.0 (C^8), 20.4 (C^4).

^{19}F NMR (565 MHz, $CDCl_3$): δ -58.6.

IR (neat) ν_{max}: 3403, 3001, 2955, 2235, 1730, 1674, 1529, 1317, 1057, 666.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{19}F_3N_2NaO_5^+$) requires *m*/*z* 423.1138, found *m*/*z* 423.1138.

*Diethyl 2-benzyl-2-(3-(methylamino)-2-(4-nitrophenyl)-3-oxopropyl)malonate (**2.100**)*



$C_{24}H_{28}N_2O_7$
MW: 456.4950

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and diethyl benzylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (34.3 mg, 0.075 mmol, 75%).

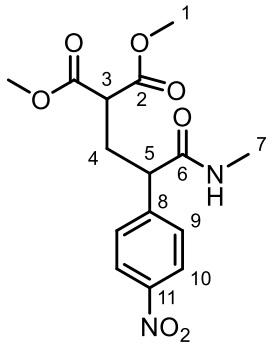
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.6 Hz, 2H, H^{16}), 7.46 (d, *J* = 8.6 Hz, 2H, H^{15}), 7.24 – 7.17 (m, 3H, H^7 and H^9), 7.07 (d, *J* = 6.5 Hz, 2H, H^8), 5.61 (d, *J* = 4.5 Hz, 1H, NH), 4.17 – 4.08 (m, 1H, H^{2a}), 4.05 – 3.91 (m, 3H, H^{2a} and H^{2b}), 3.74 (dd, *J* = 6.8, 4.7 Hz, 1H, H^{11}), 3.28 (app q, *J* = 14.0 Hz, 2H, H^5), 2.79 (dt, *J* = 24.6, 12.3 Hz, 1H, H^{10a}), 2.72 (d, *J* = 4.8 Hz, 3H, H^{13}), 2.12 (dd, *J* = 14.5, 4.5 Hz, 1H, H^{10b}), 1.25 (t, *J* = 7.1 Hz, 3H, H^{1a}), 1.18 (t, *J* = 7.1 Hz, 3H, H^{1b}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.1 (C^{12}), 171.0 (C^{3a} or C^{3b}), 170.9 (C^{3a} or C^{3b}), 148.1 (C^{11} or C^{17}), 147.2 (C^{11} or C^{17}), 135.5 (C^6), 130.1 (2C, C^{Ar}), 129.1 (2C, C^{Ar}), 128.6 (2C, C^{Ar}), 127.4 (C^9), 123.9 (2C, C^{Ar}), 61.7 (C^{2a} or C^{2b}), 61.6 (C^{2a} or C^{2b}), 58.2 (C^4), 49.0 (C^{11}), 40.5 (C^5), 37.0 (C^{10}), 26.8 (C^{13}), 14.0 (C^{1a}), 13.9 (C^{1b}).

IR (neat) ν_{max}: 3387, 3308, 2980, 1725, 1649, 1520, 736, 701.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{24}H_{28}N_2NaO_7^+$) requires *m*/*z* 479.1789, found *m*/*z* 479.1784.

*Dimethyl 2-(3-(methylamino)-2-(4-nitrophenyl)-3-oxopropyl)malonate (**2.101**)*



$C_{15}H_{18}N_2O_7$
MW: 338.3160

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and dimethyl malonate (19.8 mg, 0.15 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (24.2 mg, 0.072 mmol, 72%).

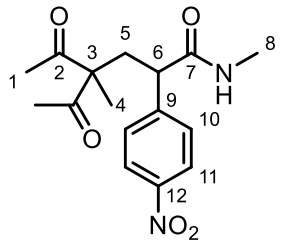
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.26 – 8.12 (m, 2H, H^{10}), 7.55 – 7.44 (m, 2H, H^9), 5.55 (app t, *J* = 14.9 Hz, 1H, NH), 3.73 (s, 3H, H^{1a}), 3.72 (s, 3H, H^{1b}), 3.62 – 3.54 (m, 1H, H^3 or H^5), 3.38 – 3.26 (m, 1H, H^3 or H^5), 2.78 (t, *J* = 6.0 Hz, 3H, H^7), 2.73 – 2.54 (m, 1H, H^{4a}), 2.38 – 2.24 (m, 1H, H^{4b}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 171.4 (C^6), 169.5 (C^{2a}), 169.3 (C^{2b}), 147.6 (C^8 or C^{11}), 146.3 (C^8 or C^{11}), 129.1 (2C, C^9), 124.2 (2C, C^{10}), 52.89 (C^{1a}), 52.87 (C^{1b}), 50.2 (C^3 or C^5), 49.4 (C^5 or C^3), 32.6 (C^4), 26.8 (C^7).

IR (neat) ν_{max}: 3312, 3048, 2853, 1732, 1562, 1604, 1520, 1346, 1156, 856, 740, 698.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_7Na^+$) requires *m*/*z* 361.1006, found *m*/*z* 361.1004.

*4-Acetyl-N,4-dimethyl-2-(4-nitrophenyl)-5-oxohexanamide (**2.102**)*



$C_{16}H_{20}N_2O_5$
MW: 320.3450

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.10 mmol, 1.00 equiv.) and 3-methyl-2,4-pentanedione (17.1 mg, 0.15 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a yellow oil (25.6 mg, 0.080 mmol, 80%).

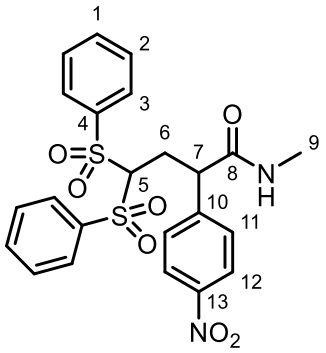
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.6 Hz, 2H, H^{11}), 7.50 (d, *J* = 8.6 Hz, 2H, H^{12}), 5.71 (app d, *J* = 4.2 Hz, 1H, NH), 3.46 (dd, *J* = 8.1, 3.3 Hz, 1H, H^6), 2.80 (dd, *J* = 14.4, 8.2 Hz, 1H, H^{5a}), 2.71 (d, *J* = 4.8 Hz, 3H, H^8), 2.14 (s, 3H, H^{1a}), 2.07 (dd, *J* = 14.4, 3.3 Hz, 1H, H^{5b}), 2.04 (s, 3H, H^{1b}), 1.37 (s, 3H, H^4).

^{13}C NMR (151 MHz, $CDCl_3$): δ 208.8 (C^{2a}), 207.5 (C^{2b}), 172.1 (C^7), 148.5 (C^9 or C^{12}), 147.2 (C^9 or C^{12}), 128.8 (2C, C^{10}), 124.1 (2C, C^{11}), 65.7 (C^3), 48.9 (C^6), 38.4 (C^5), 27.0 (C^{1a}, C^{1b} or C^8), 26.9 (C^{1a}, C^{1b} or C^8), 26.8 (C^{1a}, C^{1b} or C^8), 19.9 (C^4).

IR (neat) ν_{max}: 3307, 2941, 1696, 1652, 1604, 1519, 1345, 856, 740, 561.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2O_5Na^+$) requires *m*/*z* 343.1264, found *m*/*z* 343.1270.

*N-Methyl-2-(4-nitrophenyl)-4,4-bis(phenylsulfonyl)butanamide (**2.103**)*



$C_{23}H_{22}N_2O_7S_2$
MW: 502.5560

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and bis(phenylsulfonyl)methane (44.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a colourless oil (70%, 35.0 mg, 0.070 mmol).

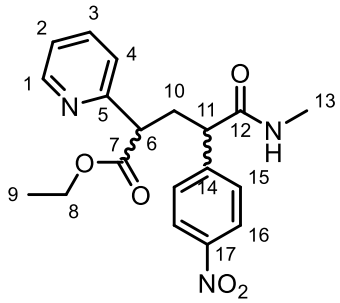
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.7 Hz, 2H, H^{12}), 7.90 (dd, *J* = 8.4, 1.1 Hz, 2H, H^{Ar}), 7.78 (dd, *J* = 8.4, 1.1 Hz, 2H, H^{Ar}), 7.73 – 7.68 (m, 2H, H^{Ar}), 7.58 (dd, *J* = 8.3, 7.6 Hz, 2H, H^{Ar}), 7.52 (dd, *J* = 8.3, 7.6 Hz, 2H, H^{Ar}), 7.34 (d, *J* = 8.7 Hz, 2H, H^{Ar}), 5.79 (app d, *J* = 4.7 Hz, 1H, NH), 4.33 (dd, *J* = 7.4, 5.2 Hz, 1H, H^5 or H^7), 4.28 – 4.22 (m, 1H, H^5 or H^7), 2.87 – 2.81 (m, 1H, H^{6a}), 2.72 (d, *J* = 4.8 Hz, 3H, H^9), 2.64 (ddd, *J* = 15.5, 8.7, 5.1 Hz, 1H, H^{6b}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 170.9 (C^8), 147.6 (C^{10} or C^{13}), 144.8 (C^{10} or C^{13}), 137.7 (C^{4a}), 137.2 (C^{4b}), 135.04 (C^{1a}), 135.00 (C^{1b}), 129.64 (2C, C^{Ar}), 129.58 (2C, C^{Ar}), 129.44 (2C, C^{Ar}), 129.38 (2C, C^{Ar}), 129.2 (2C, C^{Ar}), 124.3 (2C, C^{12}), 80.5 (C^5), 49.4 (C^7), 29.8 (C^6), 26.8 (^{C9}).

IR (neat) ν_{max}: 3399, 3306, 3080, 3000, 2953, 1731, 1652, 1521, 1382, 1077, 856, 739.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{23}H_{22}N_2O_7S_2Na^+$) requires *m*/*z* 525.0761, found *m*/*z* 525.0753.

*Ethyl 5-(methylamino)-4-(4-nitrophenyl)-5-oxo-2-(pyridin-2-yl)pentanoate (**2.104**)*



$C_{19}H_{21}N_3O_5$
MW: 371.3930

1.1 : 1 mixture of diastereoisomers

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and ethyl 2-(pyridin-2-yl)acetate (22.9 µl, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a yellow oil (18.5 mg, 0.050 mmol, 50%). The product consists of a 1.1:1 mixture of diastereoisomers (*di* **A** and **B**).

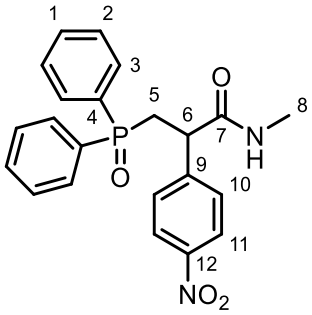
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (q, *J* = 4.6 Hz, 1H, *di* **A** + **B,** H^1), 8.14 (dd, *J* = 10.0, 8.9 Hz, 2H, *di* **A** + **B,** H^{16}), 7.65 (td, *J* = 7.7, 1.5 Hz, 1H, *di* **A** + **B,** H^3), 7.46 (t, *J* = 8.6 Hz, 2H, *di* **A** + **B,** H^2 and H^4), 7.21 (dt, *J* = 12.0, 6.7 Hz, 2H, *di* **A** + **B,** H^{15}), 5.92 (q, *J* = 4.1 Hz, 1H, *di* **B,** NH), 5.64 (d, *J* = 3.9 Hz, 1H, *di* **A,** NH), 4.18 – 4.08 (m, 2H, *di* **A** + **B,** H^8), 3.73 (dt, *J* = 15.0, 7.6 Hz, 1H, *di* **A** + **B,** H^6 or H^{11}), 3.50 (t, *J* = 7.5 Hz, 1H, *di* **A,** H^6 or H^{11}), 3.44 – 3.39 (m, 1H, *di* **B,** H^6 or H^{11}), 2.92 – 2.84 (m, 1H, *di* **B**, H^{10a}), 2.78 (d, *J* = 4.8 Hz, 3H, *di* **B,** H^{13}), 2.77 – 2.71 (m, 1H, *di* **A**, H^{10a}), 2.75 (d, *J* = 4.8 Hz, 3H, *di* **A,** H^{13}), 2.61 – 2.54 (m, 1H, *di* **A**, H^{10b}), 2.41 – 2.34 (m, 1H, *di* **B**, H^{10b}), 1.17 (dt, *J* = 14.5, 7.1 Hz, 3H, *di* **A** + **B,** H^9).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4 (C^7 or C^{12}), 172.3 (C^7 or C^{12}), 172.0 (C^7 or C^{12}), 172.0 (C^7 or C^{12}), 158.1 (C^5), 157.8 (C^5), 149.7 (C^{Ar}), 149.6 (C^{Ar}), 147.4 (C^{Ar}), 147.3 (C^{Ar}), 147.0 (2C, C^{Ar}), 137.2 (C^{Ar}), 137.0 (C^{Ar}), 129.2 (2C, C^{Ar}), 129.1 (2C, C^{Ar}), 124.01 (C^{Ar}), 123.95 (C^{Ar}), 123.4 (C^{Ar}), 122.9 (C^{Ar}), 122.7 (C^{Ar}), 122.6 (C^{Ar}), 61.4 (C^8), 61.3 (C^8), 51.4 (C^6 or C^{11}), 51.3 (C^6 or C^{11}), 50.6 (C^6 or C^{11}), 50.1 (C^6 or C^{11}), 36.1 (C^{10}), 35.8 (C^{10}), 26.7 (C^{13}), 26.7 (C^{13}), 14.2 (C^9), 14.2 (C^9) ppm.

IR (neat) ν_{max}: 3302, 3079, 2939, 1730, 1651, 1590, 1346, 1027, 856, 747, 540.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{21}N_3O_5Na^+$) requires *m*/*z* 394.1373, found *m*/*z* 394.1378.

*3-(Diphenylphosphoryl)-N-methyl-2-(4-nitrophenyl)propanamide (**2.107**)*



$C_{22}H_{21}N_2O_4P$
MW: 408.3938

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and diphenylphosphine oxide (30.3 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (29.1 mg, 0.071 mmol, 71%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.7 Hz, 2H, HAr), 7.79 – 7.72 (m, 2H, H^{Ar}), 7.56 – 7.51 (m, 3H, H^{Ar}) , 7.51 (d, *J* = 8.7 Hz, 2H, H^{Ar}), 7.50 – 7.46 (m, 2H, H^{Ar}), 7.42 (td, *J* = 7.5, 1.1 Hz, 1H, H^{Ar}), 7.32 (td, *J* = 7.7, 2.8 Hz, 2H, H^{Ar}), 7.15 (q, *J* = 4.2 Hz, 1H, NH), 4.39 (dt, *J* = 11.6, 6.8 Hz, 1H, H^6), 3.32 (ddd, *J* = 15.4, 10.4, 7.3 Hz, 1H, H^{5a}), 2.77 – 2.71 (m, 1H, H^{5b}), 2.52 (d, *J* = 4.8 Hz, 3H, H^8).

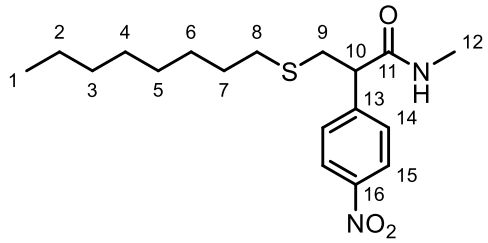
^{13}C NMR (151 MHz, $CDCl_3$): δ 171.4 (d, *J* = 7.5 Hz, C^7), 147.2 (C^{12}), 147.0 (d, *J* = 8.2 Hz, C^9), 132.4 (d, *J* = 99.9 Hz, C^{4a}), 132.4 (d, *J* = 100.2 Hz, C^{4b}), 132.3 (d, *J* = 2.5 Hz, C^{1a}), 132.0 (d, *J* = 3.0 Hz, C^{1b}), 130.8 (d, *J* = 9.8 Hz, 2C, C^{2a}), 130.6 (d, *J* = 9.7 Hz, 2C, C^{2b}), 129.4 (2C, C^{11}), 128.9 (d, *J* = 12.1 Hz, 2C, C^{3a}), 128.7 (d, *J* = 11.6 Hz, 2C, C^{3b}), 123.7 (2C, C^{10}), 45.4 (d, *J* = 1.6 Hz, C^6), 33.8 (d, *J* = 70.0 Hz, C^5), 26.5 (C^8).t

^{31}P NMR (243 MHz, $CDCl_3$): δ 30.43.

IR (neat) ν_{max}: 3427, 3267, 3078, 1666, 1519, 1346, 1176, 695.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{21}N_2O_4NaP^+$) requires *m*/*z* 431.1131, found *m*/*z* 431.1127.

*N-Methyl-2-(4-nitrophenyl)-3-(octylthio)propanamide (**2.108**)*



$C_{18}H_{28}N_2O_3S$
MW: 352.4930

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and 1-octanethiol (21.9 mg, 0.150 mmol, 1.5 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (30.1 mg, 0.085 mmol, 85%).

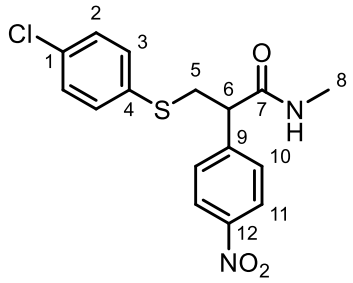
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.8 Hz, 2H, H^{15}), 7.54 (d, *J* = 8.7 Hz, 2H, H^{14}), 5.68 (br s, 1H, NH), 3.59 (t, *J* = 7.4 Hz, 1H, H^{10}), 3.29 (dd, *J* = 13.1, 8.1 Hz, 1H, H^{9a}), 2.87 (dd, *J* = 13.1, 6.8 Hz, 1H, H^{9b}), 2.81 (d, *J* = 4.9 Hz, 3H, H^{12}), 2.52 – 2.44 (m, 2H, H^8), 1.56 – 1.45 (m, 2H, H^7), 1.36 – 1.19 (m, 10H, H^{Alk}), 0.87 (t, *J* = 7.1 Hz, 3H, H^1).

^{13}C NMR (176 MHz, $CDCl_3$): δ 171.4 (C^{11}), 147.5 (C^{13}), 146.3 (C^{16}), 129.0 (2C, C^{15}), 124.1 (2C, C^{14}), 53.9 (C^{10}), 35.8 (C^9), 33.3 (C^8), 31.9 (C^{Alk}), 29.7 (C^7), 29.29 (C^{Alk}), 29.27 (C^{Alk}), 28.9 (C^{Alk}), 26.8 (C^6), 22.8 (C^{Alk}), 14.2 (C^1).

IR (neat) ν_{max}: 3407, 3295, 3081, 2953, 2924, 2854, 1649, 1520, 1345, 855, 695.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{28}N_2NaO_3S^+$) requires *m*/*z* 375.1713, found *m*/*z* 375.1714.

*3-((4-Chlorophenyl)thio)-N-methyl-2-(4-nitrophenyl)propenamide (**2.109**)*



$C_{16}H_{15}ClN_2O_3S$
MW: 350.8170

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and 4-chlorobenzenethiol (21.7 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (17.0 mg, 0.049 mmol, 49%).

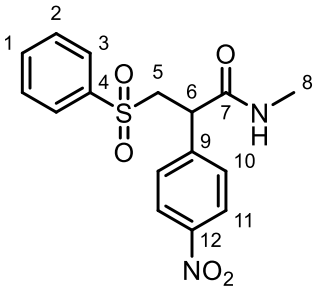
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.6 Hz, 2H, H^{11}), 7.48 (d, *J* = 8.6 Hz, 2H, H^{10}), 7.28 – 7.23 (m, 4H, H^2 and H^3), 5.53 (q, *J* = 3.3 Hz, 1H, NH), 3.70 (dd, *J* = 13.5, 7.8 Hz, 1H, H^{5a}), 3.57 (app t, *J* = 7.4 Hz, 1H, H^6), 3.23 (dd, *J* = 13.5, 6.9 Hz, 1H, H^{5b}), 2.78 (d, *J* = 4.8 Hz, 3H, H^8).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.8 (C^7), 147.7 (C^{12}), 145.6 (C^9), 133.7 (C^4), 133.0 (C^1), 131.4 (2C, C^3), 129.4 (2C, C^2 or C^{11}), 129.0 (2C, C^2 or C^{11}), 124.2 (2C, C^{10}), 52.6 (C^6), 37.5 (C^5), 26.8 (C^8).

IR (neat) ν_{max}: 3403, 3307, 1651, 1519, 1347, 1110, 1012, 1084, 856.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{15}N_2NaO_3SCl^+$) requires *m*/*z* 373.0385, found *m*/*z* 373.0381.

*N-Methyl-2-(4-nitrophenyl)-3-(phenylsulfonyl)propanamide (**2.110**)*



$C_{16}H_{16}N_2O_5S$
MW: 348.3730

Following **General Procedure M** without BTMG, using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and sodium benzenesulfinate (24.6 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a pale-yellow solid (24.2 mg, 0.070 mmol, 70%).

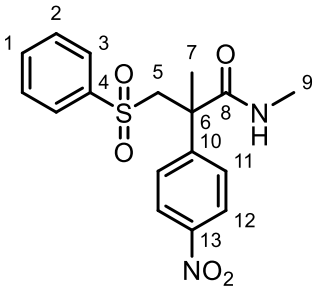
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 – 8.02 (m, 2H, C^{11}), 7.81 – 7.74 (m, 2H, C^3), 7.61 – 7.54 (m, 1H, C^1), 7.45 (app ddt, *J* = 16.7, 9.3, 2.0 Hz, 4H, C^2 and C^{10}), 5.79 (app d, *J* = 4.6 Hz, 1H, NH), 4.23 – 4.12 (m, 2H, H^5), 3.35 (dt, *J* = 10.7, 8.1 Hz, 1H, H^6), 2.66 (d, *J* = 4.6 Hz, 3H, H^8).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.6 (C^7), 147.8 (C^{12}), 144.5 (C^9), 139.2 (C^5), 134.3 (C^1), 129.5 (2C, C^{10} or C^2), 129.1 (2C, C^{10} or C^2), 128.1 (2C, C^3), 124.3 (2C, C^{11}), 58.8 (C^5), 46.6 (C^6), 27.1 (C^8).

IR (neat) ν_{max}: 3318, 3095, 2956, 1684, 1521, 1348, 736.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{16}N_2NaO_5S^+$) requires *m*/*z* 371.0672, found *m*/*z* 371.0667.

*N,2-Dimethyl-2-(4-nitrophenyl)-3-(phenylsulfonyl)propanamide (**2.111**)*



$C_{17}H_{18}N_2O_5S$
MW: 362.4000

Following **General Procedure M** without BTMG, using *N*-methyl-*N*-(4-nitrophenyl)methacrylamide (28.4 mg, 0.100 mmol, 1.00 equiv.) and sodium benzenesulfinate (24.6 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a colourless solid (31.3 mg, 0.086 mmol, 86%).

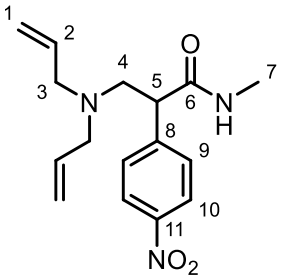
^{1}H NMR (700 MHz, $CDCl_3$): 8.15 – 8.06 (m, 2H, H^{12}), 7.75 – 7.67 (m, 2H, H^3), 7.58 (t, *J* = 7.5 Hz, 1H, H^1), 7.51 – 7.48 (m, 2H, H^{11} or H^2), 7.46 – 7.42 (m, 2H, H^{11} or H^2), 5.39 (app d, *J* = 3.4 Hz, 1H, NH), 4.09 (d, *J* = 14.7 Hz, 1H, H^{5a}), 3.78 (d, *J* = 14.7 Hz, 1H, H^{5b}), 2.78 (d, *J* = 4.8 Hz, 3H, H^9), 2.08 (s, 3H, H^7).

^{13}C NMR (176 MHz, $CDCl_3$): δ 173.5 (C^8), 147.7 (C^{13}), 147.7 (C^4), 141.0 (C^{10}), 133.7 (C^1), 129.3 (2C, C^{11}), 128.1 (2C, C^2 or C^3), 127.7 (2C, C^2 or C^3), 123.9 (2C, C^{12}), 64.0 (C^5), 49.7 (C^6), 27.3 (C^9), 22.5 (C^7).

IR (neat) ν_{max}: 3366, 2921, 1660, 1529, 1316, 1135, 844, 549.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{18}N_2NaO_5S^+$) requires *m*/*z* 385.0829, found *m*/*z* 385.0826.

*3-(Diallylamino)-N-methyl-2-(4-nitrophenyl)propanamide (**2.112**)*



$C_{16}H_{21}N_3O_3$
MW: 303.3620

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and diallylamine (14.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a yellow oil (22.5 mg, 0.074 mmol, 74%).

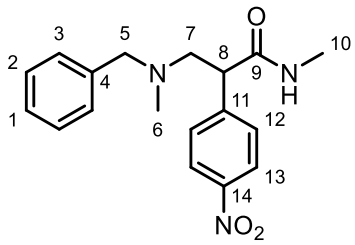
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.6 Hz, 2H, H^{10}), 7.40 (d, *J* = 8.6 Hz, 2H, H^9), 7.37 (br s, 1H, NH), 5.83 – 5.74 (m, 2H, H^2), 5.25 – 5.14 (m, 4H, H^1), 3.71 (dd, *J* = 10.2, 5.0 Hz, 1H, H^5), 3.24 (dd, *J* = 14.1, 6.1 Hz, 2H, H^{3a}), 3.13 (dd, *J* = 13.1, 10.2 Hz, 1H, H^{4a}), 3.07 (dd, *J* = 14.1, 7.0 Hz, 2H, H^{3b}), 2.81 (d, *J* = 4.8 Hz, 3H, H^7), 2.64 (dd, *J* = 13.1, 5.0 Hz, 1H, H^{4b}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.3 (C^6), 147.2 (C^{11}), 146.7 (C^8), 134.6 (2C, C^2), 129.7 (2C, C^{10}), 123.8 (2C, C^9), 118.7 (2C, C^1), 57.2 (2C, C^3), 56.9 (C^5), 50.3 (C^4), 26.3 (C^7).

IR (neat) ν_{max}: 3304, 3078, 2926, 2809, 1646, 1519, 1345, 996, 855, 741, 533.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}N_3O_3^+$) requires *m*/*z* 304.1656, found *m*/*z* 304.1657.

*3-(Benzyl(methyl)amino)-N-methyl-2-(4-nitrophenyl)propanamide (**2.113**)*



$C_{18}H_{21}N_3O_3$
MW: 327.3840

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and *N*-benzylmethylamine (18.2 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a pale-yellow solid (24.0 mg, 0.073 mmol, 73%).

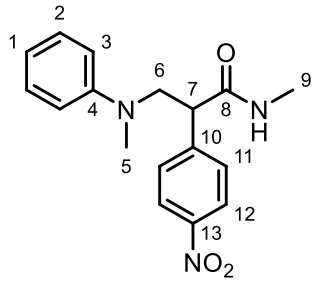
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 – 8.13 (m, 2H, H^{13}), 7.56 (s, 1H, NH), 7.39 – 7.30 (m, 5H, H^{Ar}), 7.26 – 7.21 (m, 2H, H^{Ar}), 3.72 (dd, *J* = 10.1, 5.1 Hz, 1H, H^{8}), 3.65 (d, *J* = 13.0 Hz, 1H, H^{5a}), 3.53 (d, *J* = 13.0 Hz, 1H, H^{5b}), 3.13 (dd, *J* = 12.8, 10.1 Hz, 1H, H^{7a}), 2.82 (d, *J* = 4.8 Hz, 3H, H^{10}), 2.62 (dd, *J* = 12.8, 5.2 Hz, 1H, H^{7b}), 2.33 (s, 3H, H^{6}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.2 (C^{9}), 147.2 (C^{14}), 146.6 (C^{11}), 138.0 (C^{4}), 129.7 (2C, C^{12}), 129.2 (2C, C^{Ar}), 128.6 (2C, C^{Ar}), 127.7 (C^{1}), 123.8 (2C, C^{13}), 62.7 (C^{5}), 60.5 (C^{7}), 49.9 (C^{8}), 42.4 (C^{6}), 26.3 (C^{10}).

IR (neat) ν_{max}: 3335, 2975, 1729, 1651, 1522, 1347, 1050, 881, 739.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{21}N_3NaO_3^+$) requires *m*/*z* 350.1475, found *m*/*z* 350.1473.

*N-Methyl-3-(methyl(phenyl)amino)-2-(4-nitrophenyl)propanamide (**2.114**)*



$C_{17}H_{19}N_3O_3$
MW: 313.3570

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and *N*-methylaniline (16.1 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as an orange solid (17.2 mg, 0.054 mmol, 54%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.6 Hz, 2H, H^{12}), 7.57 (d, *J* = 8.6 Hz, 2H, H^{11}), 7.33 – 7.19 (m, 2H, H^2), 6.75 (t, *J* = 7.2 Hz, 1H, H^1), 6.68 (d, *J* = 8.3 Hz, 2H, H^3), 5.63 (app d, *J* = 3.0 Hz, 1H, NH), 4.12 (dd, *J* = 14.8, 8.4 Hz, 1H, H^{6a}), 3.82 (dd, *J* = 8.4, 5.4 Hz, 1H, H^7), 3.67 (dd, *J* = 14.8, 5.4 Hz, 1H, H^{6b}), 2.86 (s, 3H, H^5), 2.77 (d, *J* = 4.8 Hz, 3H, H^9).

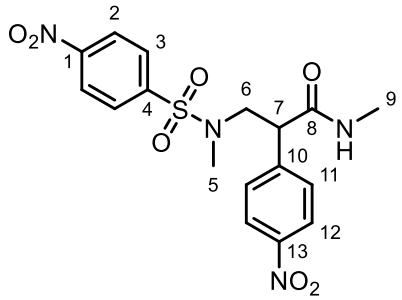
^{13}C NMR (151 MHz, $CDCl_3$): δ 171.5 (C^8), 148.1 (C^5), 147.5 (C^{13}), 145.5 (C^{10}), 129.6 (2C, C^{11}), 129.1 (2C, C^2), 124.0 (2C, C^{12}), 117.1 (C^1), 112.2 (2C, C^3), 56.9 (C^6), 50.9 (C^7), 39.7 (C^5), 26.8 (C^9).

IR (neat) ν_{max}: 3394, 3301, 2939, 1649, 1598, 1518, 1506, 1345, 956, 748, 693.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{19}N_3NaO_3^+$) requires *m*/*z* 336.1319, found *m*/*z* 336.1313.

N-Methyl-3-((N-methyl-4-nitrophenyl)sulfonamido)-2-(4-nitrophenyl)propanamide

(2.115)



$C_{17}H_{18}N_4O_7S$
MW: 422.4120

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and *N*-methyl-4-nitrobenzenesulfonamide (32.4 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (31.8 mg, 0.075 mmol, 75%).

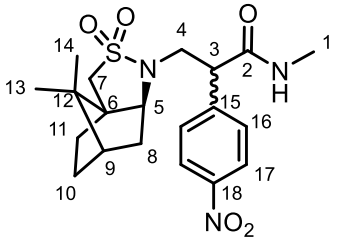
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.7 Hz, 2H, H^2), 8.22 (d, *J* = 8.7 Hz, 2H, H^{12}), 7.95 (d, *J* = 8.7 Hz, 2H, H^3), 7.59 (d, *J* = 8.7 Hz, 2H, H^{11}), 5.67 (app d, *J* = 4.6 Hz, 1H, NH), 3.99 (dd, *J* = 8.4, 6.4 Hz, 1H, H^7), 3.58 (dd, *J* = 14.3, 8.4 Hz, 1H, H^{6a}), 3.40 (dd, *J* = 14.3, 6.4 Hz, 1H, H^{6b}), 2.84 (d, *J* = 4.6 Hz, 3H, H^9), 2.77 (s, 3H, H^5).

^{13}C NMR (151 MHZ, $CDCl_3$): δ 170.6 (C^8), 150.4 (C^1), 147.9 (C^{13}), 144.0 (C^{10}), 142.8 (C^4), 129.3 (2C, C^3), 128.7 (2C, C^{11}), 124.7 (2C, C^2), 124.4 (2C, C^{12}), 54.2 (C^6), 54.0 (C^7), 37.8 (C^5), 26.9 (C^9).

IR (neat) ν_{max}: 3274, 3109, 2923, 2859, 1645, 1516, 1167, 856, 742, 600.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{18}N_4NaO_7S^+$) requires *m*/*z* 445.0788, found *m*/*z* 445.0785.

3-((3aR,6S,7aS)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-N-methyl-2-(4-nitrophenyl)propanamide (2.116)



$C_{20}H_{27}N_3O_5S$
MW: 421.5120

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and (+)-10,2-camphorsultam (32.3 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as two separable diastereomers.

The minor diasteromer was obtained as a white solid (12.3 mg, 0.029 mmol, 29%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.8 Hz, 2H, H^{17}), 7.62 (d, *J* = 8.7 Hz, 2H, H^{16}), 6.04 (q, *J* = 4.6 Hz, 1H, NH), 4.10 (dd, *J* = 12.6, 3.8 Hz, 1H, H^3), 3.42 (t, *J* = 12.7 Hz, 1H, H^{4a}), 3.22 (dd, *J* = 12.7, 3.9 Hz, 1H, H^{4b}), 3.23 – 3.17 (m, 2H, H^7), 3.01 (dd, *J* = 7.9, 4.4 Hz, 1H, H^5), 2.74 (d, *J* = 4.9 Hz, 3H, H^1), 2.16 (ddd, *J* = 12.4, 6.6, 3.8 Hz, 1H, H^{8a}), 1.94 (t, *J* = 3.8 Hz, 1H, H^9), 1.90 – 1.81 (m, 2H, H^{10a} and H^{11a}), 1.66 (dd, *J* = 12.6, 7.8 Hz, 1H, H^{8b}), 1.42 – 1.35 (m, 1H, H^{11b}), 1.29 – 1.22 (m, 1H, H^{10b}), 1.11 (s, 3H, H^{13} or H^{14}), 0.92 (s, 3H, H^{13} or H^{14}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.4 (C^2), 147.6 (C^{18}), 144.0 (C^{15}), 129.2 (2C, C^{16}), 123.9 (2C, C^{17}), 68.4 (C^5), 50.9 (C^3), 50.8 (C^7), 50.3 (C^{12}), 47.7 (C^6), 47.1 (C^4), 44.6 (C^9), 35.3 (C^8), 32.2 (C^{11}), 27.1 (C^{10}), 26.7 (C^1), 20.1 (C^{13} or C^{14}), 20.1 (C^{13} or C^{14}).

IR (neat) ν_{max}: 3386, 2956, 2882, 1661, 1521, 1347, 1301, 1055, 737.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{20}H_{27}N_3NaO_5^+$) requires *m*/*z* 444.1564, found *m*/*z* 444.1567.

The major diasteromer was obtained as a white solid (17.0 mg, 0.040 mmol, 40%).

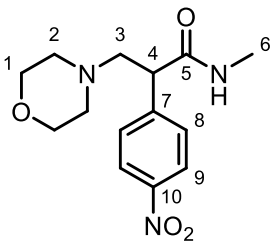
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 2H, H^{17}), 7.66 (d, *J* = 8.7 Hz, 2H, H^{16}), 5.81 (q, *J* = 4.1 Hz, 1H, NH), 4.11 (dd, *J* = 11.1, 5.0 Hz, 1H, H^3), 3.65 (dd, *J* = 14.0, 5.0 Hz, 1H, H^{4a}), 3.28 (dd, *J* = 14.0, 11.2 Hz, 1H, H^{4b}), 3.06 (dd, *J* = 47.4, 13.8 Hz, 2H, H^8), 2.99 (dd, *J* = 7.8, 4.6 Hz, 1H, H^5), 2.77 (d, *J* = 4.8 Hz, 3H, H^1), 1.82 – 1.74 (m, 1H, H^{11a}), 1.72 (t, *J* = 3.7 Hz, 1H, H^9), 1.56 (dd, *J* = 12.6, 7.9 Hz, 1H, H^{8a}), 1.42 – 1.36 (m, 1H, H^{9b}), 1.34 (dd, *J* = 11.4, 6.8 Hz, 1H, H^{12a}), 1.19 (dd, *J* = 9.7, 7.8 Hz, 1H, H^{11b}), 0.77 (s, 3H, H^{14} or H^{15}), 0.39 (s, 3H, H^{14} or H^{15}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.7 (C^2), 147.5 (C^{18}), 145.8 (C^{15}), 129.7 (2C, C^{16}), 123.7 (2C, C^{17}), 67.8 (C^5), 50.3 (C^3), 50.2 (C^7), 50.0 (C^{12}), 47.3 (C^6), 46.8 (C^4), 44.3 (C^{10}), 35.1 (C^8), 32.2 (C^{11}), 26.9 (C^{10}), 26.7 (C^1), 19.9 (C^{14} or C^{15}), 19.5 (C^{14} or C^{15}).

IR (neat) ν_{max}: 3368, 2959, 2882, 1658, 1520, 1347, 1303, 1054, 737.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{20}H_{27}N_3NaO_5^+$) requires *m*/*z* 444.1564, found *m*/*z* 444.1568.

*N-Methyl-3-morpholino-2-(4-nitrophenyl)propenamide (**2.117**)*



$C_{14}H_{19}N_3O_4$
MW: 293.3230

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and morpholine (13.1 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (16.8 mg, 0.057 mmol, 57%).

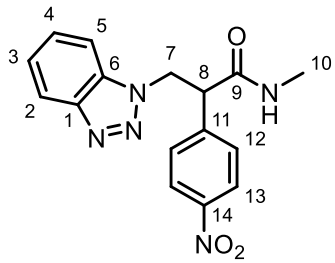
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.7 Hz, 2H, H^9), 7.42 (d, *J* = 8.7 Hz, 2H, H^8), 3.76 – 3.64 (m, 5H, H^1 and H^4), 3.09 (dd, *J* = 12.9, 10.1 Hz, 1H, H^{3a}), 2.83 (d, *J* = 4.8 Hz, 3H, H^6), 2.65 – 2.54 (m, 3H, H^{2a} and H^{3b}), 2.54 – 2.40 (m, 2H, H^{2b}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 172.0 (C^5), 147.3 (C^{10}), 146.4 (C^7), 129.6 (2C, C^8), 123.9 (2C, C^9), 67.1 (2C, C^1), 61.8 (C^3), 53.7 (2C, C^2), 49.3 (C^4), 26.5 (C^6).

IR (neat) ν_{max}: 3304, 3079, 2953, 2854, 2810, 1648, 1516, 1344, 1112, 856, 734, 699.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}N_3O_4^+$) requires *m*/*z* 294.1448, found *m*/*z* 294.1441.

*3-(1H-Benzo[d][1,2,3]triazol-1-yl)-N-methyl-2-(4-nitrophenyl)propanamide (**2.118**)*



$C_{16}H_{15}N_5O_3$
MW: 325.3280

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and 1*H*-benzotriazole (17.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (16.9 mg, 0.052 mmol, 52%).

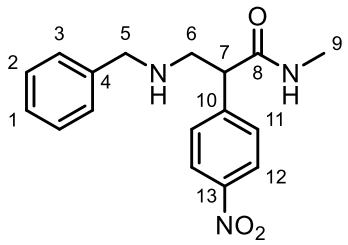
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 2H, H^{13}), 7.98 (d, *J* = 8.4 Hz, 1H, H^2), 7.59 (d, *J* = 8.7 Hz, 2H, H^{14}), 7.52 – 7.42 (m, 2H, H^4 and H^5), 7.34 (dd, *J* = 11.1, 3.9 Hz, 1H, H^3), 5.85 (s, 1H, NH), 5.34 (dd, *J* = 13.9, 8.3 Hz, 1H, H^{7a}), 4.89 (dd, *J* = 13.9, 6.5 Hz, 1H, H^{7b}), 4.54 – 4.39 (m, 1H, H^8), 2.69 (d, *J* = 4.8 Hz, 3H, H^{10}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 169.9 (C^9), 148.0 (C^{14}), 145.7 (C^1), 143.4 (C^7), 133.5 (C^6), 129.2 (2C, C^{12}), 128.0 (C^4), 124.4 (2C, C^{13}), 124.4 (C^3), 119.9 (C^2), 109.70 (C^5), 53.04 (C^7), 50.4 (C^8), 26.9 (C^{10}).

IR (neat) ν_{max}: 3299, 3070, 2948, 1676, 1346, 745.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{15}N_5NaO_3^+$) requires *m*/*z* 348.1067, found *m*/*z* 348.1067.

*3-(Benzylamino)-N-methyl-2-(4-nitrophenyl)propanamide (**2.119**)*



$C_{17}H_{19}N_3O_3$
MW: 313.3570

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and benzylamine (16.1 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (12.8 mg, 0.041 mmol, 41%).

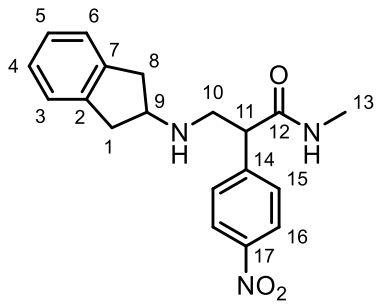
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.20 – 8.13 (m, 2H, H^{12}), 7.46 – 7.40 (m, 2H, H^{11}), 7.35 – 7.30 (m, 2H, H^2 or H^3), 7.29 – 7.26 (m, 2H, H^2 or H^3), 7.25 (m, 1H, H^1), 6.86 (s, 1H, NH), 3.80 (d, *J* = 2.6 Hz, 2H, H^5), 3.69 (dd, *J* = 8.2, 4.8 Hz, 1H, H^7), 3.26 (dd, *J* = 12.2, 8.2 Hz, 1H, H^{6a}), 2.96 (dd, *J* = 12.2, 4.8 Hz, 1H, H^{6b}), 2.81 (d, *J* = 4.8 Hz, 3H, H^9), 1.77 (s, 1H, NH).

^{13}C NMR (176 MHz, $CDCl_3$): δ 172.1 (C^8), 147.4 (C^{13}), 146.0 (C^{10}), 139.4 (C^4), 129.3 (2C, C^{11}), 128.8 (2C, C^{Ar}), 128.3 (2C, C^{Ar}), 127.5 (C^1), 124.1 (2C, C^{Ar}), 54.0 (C^5), 52.8 (C^6), 52.0 (C^7), 26.5 (C^9).

IR (neat) ν_{max}: 3408, 2981, 1653, 1518, 1347, 1051, 737, 648.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}N_3O_3^+$) requires *m*/*z* 314.1499, found *m*/*z* 314.1506.

*3-((2,3-Dihydro-1H-inden-2-yl)amino)-N-methyl-2-(4-nitrophenyl)propenamide (**2.120**)*



$C_{19}H_{21}N_3O_3$
MW: 339.3950

Following **General Procedure M** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide (27.0 mg, 0.100 mmol, 1.00 equiv.) and 2,3-dihydro-1*H*-inden-2-amine (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (13.7 mg, 0.040 mmol, 40%).

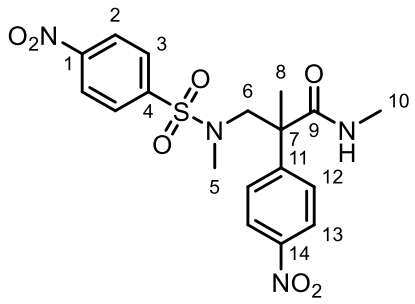
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.24 – 8.16 (m, 2H, H^{16}), 7.51 – 7.42 (m, 2H, H^{15}), 7.19 (dd, *J* = 5.2, 3.5 Hz, 2H, H^4 and H^5), 7.15 (dd, *J* = 5.6, 3.1 Hz, 2H, H^3 and H^6), 6.93 (br.s, 1H, NH), 3.72 (dd, *J* = 8.2, 4.5 Hz, 1H, H^{11}), 3.67 – 3.60 (m, 1H, H^9), 3.31 (dd, *J* = 12.0, 8.3 Hz, 1H, $H1^{0a}$), 3.16 (ddd, *J* = 15.7, 6.9, 2.4 Hz, 2H, H^1 or H^8), 3.02 (dd, *J* = 12.0, 4.6 Hz, 1H, H^{10b}), 2.80 – 2.70 (m, 5H, H^{13} and H^1 or H^8).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.1 (C^{12}), 147.4 (C^{17}), 146.0 (C^{14}), 141.3 (C^2 or C^7), 141.3 (C^2 or C^7), 129.3 (2C, C^{15}), 126.8 (C^3 or C^6), 126.8 (C^3 or C^6), 124.9 (C^4 or C^5), 124.9 (C^4 or C^5), 124.1 (2C, C^{16}), 59.6 (C^9), 52.7 (C^{11}), 50.9 (C^{10}), 39.9 (C^1 or C^8), 39.9 (C^1 or C^8), 26.4 (C^{13}).

IR (neat) ν_{max}: 3297, 3070, 2937, 2843, 1647, 1516, 1343, 735, 698.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{19}H_{22}N_3O_3^+$) requires *m*/*z* 340.1656, found *m*/*z* 340.1648.

*N,2-Dimethyl-3-((N-methyl-4-nitrophenyl)sulfonamido)-2-(4-nitrophenyl)propanamide (2.**121**)*



$C_{18}H_{20}N_4O_7S$
MW: 436.4390

Following **General Procedure N** using *N*-methyl-*N*-(4-nitrophenyl)methacrylamide (28.4 mg, 0.100 mmol, 1.00 equiv.) and *N*-methyl-4-nitrobenzenesulfonamide (32.4 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (35.1 mg, 0.080 mmol, 80%).

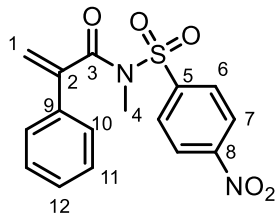
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, *J* = 8.7 Hz, 2H, H^2), 8.22 (d, *J* = 8.9 Hz, 2H, H^{13}), 7.92 (d, *J* = 8.7 Hz, 2H, H^3), 7.59 (d, *J* = 8.9 Hz, 2H, H^{12}), 5.52 (br s, 1H, NH), 3.94 (d, *J* = 14.1 Hz, 1H, H^{6a}), 3.44 (d, *J* = 14.1 Hz, 1H, H^{6b}), 2.81 (d, *J* = 4.8 Hz, 3H, H^{10}), 2.45 (s, 3H, H^5), 1.84 (s, 3H, H^8).

^{13}C NMR (150 MHz, $CDCl_3$): δ 174.3 (C^9), 150.4 (C^1), 149.0 (C^{14}), 147.5 (C^4), 143.2 (C^{11}), 128.8 (2C, C^{12} or C^3), 128.1 (2C, C^{12} or C^3), 124.6 (2C, C^{13} or C^2), 124.1 (2C, C^{13} or C^2), 58.7 (C^6), 51.1 (C^7), 37.4 (C^5), 27.1 (C^{10}), 21.2 (C^5).

IR (neat) ν_{max}: 3340, 2925, 1633, 1606, 1519, 1341, 1154, 975, 849, 600.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}N_4NaO_7S^+$) requires *m*/*z* 459.0954, found *m*/*z* 459.0948.

*N-Methyl-N-((4-nitrophenyl)sulfonyl)-2-phenylacrylamide (**2.125-Ph**)*



$C_{16}H_{14}N_2O_5S$
MW: 346.3570

Following **General Procedure N** using atropic acid (14.8 mg, 0.100 mmol, 1.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (4.8 mg, 0.014 mmol, 14%).

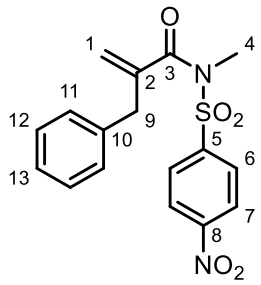
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.8 Hz, 2H, H^7), 8.16 (d, *J* = 8.8 Hz, 2H, H^6), 7.39 – 7.32 (m, 3H, H^{10} and H^{12}), 7.30 – 7.22 (m, 2H, H^{11}), 5.81 (s, 1H, H^{1a}), 5.51 (s, 1H, H^{1b}), 3.22 (s, 3H, H^4).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.4 (C^3), 150.8 (C^8), 144.33 (C^2 or C^5), 144.28 (C^2 or C^5), 134.3 (C^9), 130.1 (2C, C^{Ar}), 129.5 (C^{12}), 129.3 (2C, C^{Ar}), 126.0 (2C, C^{Ar}), 124.2 (2C, C^{Ar}), 119.0 (C^1), 34.8 (C^4).

IR (neat) ν_{max}: 3106, 1690, 1529, 1348, 1173, 854, 738, 682, 637, 578.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{14}N_2NaO_5S^+$) requires *m*/*z* 369.0516, found *m*/*z* 369.0512.

*2-Benzyl-N-methyl-N-((4-nitrophenyl)sulfonyl)acrylamide (**2.125-Bn**)*



$C_{17}H_{16}N_2O_5S$
MW: 360.3840

Following **General Procedure N** using 2-benzylacrylic acid (17.9 mg, 0.100 mmol, 1.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (17.5 mg, 0.049 mmol, 49%).

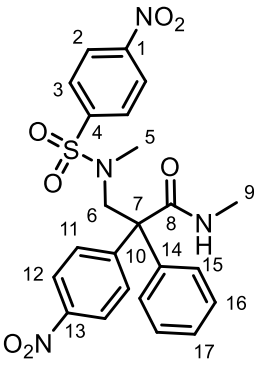
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.33 – 8.28 (m, 2H, H^7), 7.97 – 7.91 (m, 2H, H^6), 7.25 – 7.21 (m, 3H, H^{11} and H^{13}), 7.11 – 7.05 (m, 2H, H^{12}), 5.46 (app t, *J* = 1.4 Hz, 1H, H^{1a}), 5.41 (s, 1H, H^{1b}), 3.61 (s, 2H, H^9), 3.13 (s, 3H, H^4).

^{13}C NMR (176 MHz, $CDCl_3$): δ 171.4 (C^3), 150.7 (C^8), 143.9 (C^5), 143.5 (C^2), 136.9 (C^{10}), 129.8 (2C, C^6), 129.3 (2C, C^{11} or C^{12}), 128.9 (2C, C^{11} or C^{12}), 127.1 (C^{13}), 124.2 (2C, C^7), 120.9 (C^1), 39.9 (C^9), 35.1 (C^4).

IR (neat) ν_{max}: 2922, 2852, 1690, 1531, 1351, 1176, 1012, 742.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{16}N_2NaO_5S^+$) requires *m*/*z* 383.0672, found *m*/*z* 383.0669.

*N-Methyl-3-((N-methyl-4-nitrophenyl)sulfonamido)-2-(4-nitrophenyl)-2-phenylpropanamide (**2.129-Ph**)*



$C_{23}H_{22}N_4O_7S$
MW: 498.5100

Following **General Procedure N** using atropic acid (14.8 mg, 0.100 mmol, 1.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a white solid (39.0 mg, 0.078 mmol, 78%).

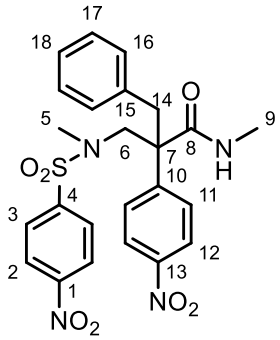
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 – 8.32 (m, 2H, H^2), 8.27 – 8.21 (m, 2H, H^{12}), 7.91 – 7.83 (m, 2H, H^3), 7.61 – 7.54 (m, 2H, H^{11}), 7.46 – 7.36 (m, 3H, H^{15} and H^{17}), 7.31 – 7.26 (m, 2H, H^{16}), 5.62 (d, *J* = 4.8 Hz, 1H, H^9), 4.31 (d, *J* = 13.9 Hz, 1H, H^{6a}), 4.16 (d, *J* = 13.9 Hz, 1H, H^{6b}), 2.81 (d, *J* = 4.8 Hz, 3H, H^9), 2.58 (s, 3H, H^5).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.6 (C^8), 150.3 (C^1), 147.39 (C^{10} or C^{13}), 147.36 (C^{10} or C^{13}), 143.5 (C^4), 139.9 (C^{14}), 130.9 (2C, C^{Ar}), 129.3 (2C, C^{Ar}), 128.9 (2C, C^{Ar}), 128.7 (2C, C^{Ar}), 128.6 (C^{17}), 124.6 (2C, C^{Ar}), 123.5 (2C, C^{Ar}), 61.7 (C^6), 57.0 (C^7), 37.0 (C^5), 27.4 (C^9).

IR (neat) ν_{max}: 3413, 2926, 1663, 1519, 1348, 1165, 741, 600.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{23}H_{22}N_4NaO_7S^+$) requires *m*/*z* 521.1101, found *m*/*z* 521.1092.

*2-Benzyl-N-methyl-3-((N-methyl-4-nitrophenyl)sulfonamido)-2-(4-nitrophenyl)propanamide (**2.129-Bn**)*



$C_{24}H_{24}N_4O_7S$
MW: 512.5370

Following **General Procedure N** using 2-benzylacrylic acid (17.9 mg, 0.100 mmol, 1.00 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a pale-yellow viscous oil (17.9 mg, 0.035 mmol, 35%).

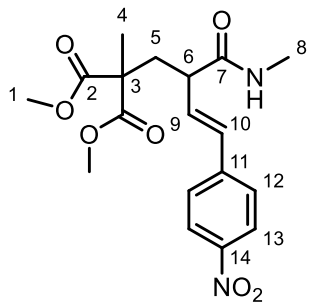
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.40 – 8.35 (m, 2H, H^2), 8.27 – 8.21 (m, 2H, H^{12}), 7.91 – 7.86 (m, 2H, H^{Ar}), 7.65 – 7.59 (m, 2H, H^{Ar}), 7.25 (dd, *J* = 5.8, 3.5 Hz, 3H, H^{Ar}), 7.06 (dd, *J* = 6.6, 2.8 Hz, 2H, H^{Ar}), 5.64 (app d, *J* = 3.8 Hz, 1H, NH), 3.70 – 3.63 (m, 2H, H^{14}), 3.62 (d, *J* = 14.2 Hz, 1H, H^{6a}), 3.39 (d, *J* = 14.2 Hz, 1H, H^{6b}), 2.72 (d, *J* = 4.7 Hz, 3H, H^9), 2.43 (s, 3H, H^5).

^{13}C NMR (176 MHz, $CDCl_3$): δ 172.6 (C^8), 150.5 (C^1), 147.5 (C^4 or C^{13}), 147.4 (C^4 or C^{13}), 142.5 (C^{10}), 135.7 (2C, C^{Ar}), 135.6 (C^{15}), 130.3 (2C, C^{Ar}), 130.1 (C^{Ar}), 128.9 (C^{Ar}), 128.6 (2C, C^{Ar}), 127.7 (C^{18}), 124.6 (2C, C^{Ar}), 123.7 (2C, C^{Ar}), 58.3 (C^6), 57.6 (C^7), 42.4 (C^{14}), 37.8 (C^5), 26.8 (C^9).

IR (neat) ν_{max}: 3411,2930, 1658, 1604, 1527, 1348, 1166, 855, 742.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{24}H_{24}N_4NaO_7S^+$) requires *m*/*z* 535.1258, found *m*/*z* 535.1249.

*Dimethyl (E)-2-methyl-2-(2-(methylcarbamoyl)-4-(4-nitrophenyl)but-3-en-1-yl)malonate (**2.145**)*



$C_{18}H_{22}N_2O_7$
MW: 378.3810

Following **General Procedure M** using (*E*)-*N*-methyl-*N*-((4-nitrostyryl)sulfonyl)acrylamide (29.6 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a yellow oil (34.5 mg, 0.091 mmol, 91%).

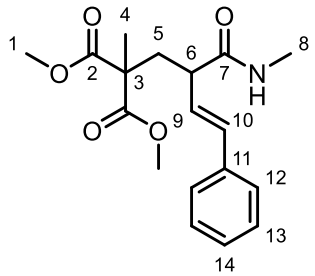
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.8 Hz, 2H, H^{13}), 7.46 (d, *J* = 8.8 Hz, 2H, H^{12}), 6.49 (d, *J* = 15.9 Hz, 1H, H^{10}), 6.37 (dd, *J* = 15.9, 9.0 Hz, 1H, H^{9}), 5.83 (q, *J* = 4.5 Hz, 1H, NH), 3.64 (s, 3H, H^{1a}), 3.63 (s, 3H, H^{1b}), 3.21 (dt, *J* = 9.0, 6.2 Hz, 1H, H^{6}), 2.80 (d, *J* = 4.5 Hz, 3H, H^{8}), 2.58 (dd, *J* = 14.5, 6.2 Hz, 1H, H^{5a}), 2.20 (dd, *J* = 14.5, 6.2 Hz, 1H, H^{5b}), 1.45 (s, 3H, H^{4}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7 (C^{2a}, C^{2b} or C^{7}), 172.5 (C^{2a}, C^{2b} or C^{7}), 172.4 (C^{2a}, C^{2b} or C^{7}), 147.1 (C^{14}), 143.1 (C^{11}), 133.9 (C^{10}), 130.3 (C^{9}), 127.0 (2C, C^{13}), 124.2 (2C, C^{12}), 53.0 (C^{6}), 52.8 (C^{1a}), 52.7 (C^{1b}), 47.4 (C^{3}), 38.0 (C^{5}), 26.7 (C^{8}), 21.1 (C^{4}).

IR (neat) ν_{max}: 3403, 3302, 3084, 2997, 2952, 1731, 1645, 1517, 1343, 1265, 1111, 976, 863, 746.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2O_7Na^+$) requires *m*/*z* 401.1319, found *m*/*z* 401.1319.

*Dimethyl (E)-2-methyl-2-(2-(methylcarbamoyl)-4-phenylbut-3-en-1-yl)malonate (**2.146**)*



$C_{18}H_{23}NO_5$
MW: 333.3840

Following **General Procedure M** using (*E*)-*N*-methyl-2-phenylethene-1-sulfonamide (25.1 mg, 0.10 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a yellow oil (8.8 mg, 0.026 mmol, 26%).

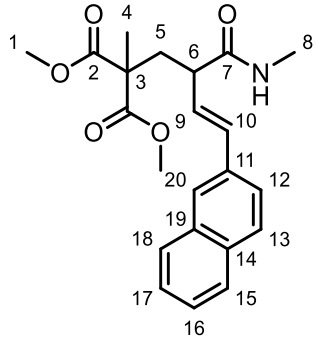
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 2H, H^{12}), 7.30 (dd, *J* = 10.5, 4.9 Hz, 2H, H^{13}), 7.25 – 7.21 (m, 1H, H^{14}), 6.43 (d, *J* = 15.9 Hz, 1H, H^{10}), 6.13 (dd, *J* = 15.9, 9.4 Hz, 1H, H^{9}), 5.69 (app s, 1H, NH), 3.66 (s, 3H, H^{1a}), 3.60 (s, 3H, H^{1b}), 3.14 (ddd, *J* = 9.2, 7.4, 5.3 Hz, 1H, H^{6}), 2.79 (d, *J* = 4.9 Hz, 3H, H^{8}), 2.64 (dd, *J* = 14.5, 5.2 Hz, 1H, H^{5a}), 2.21 (dd, *J* = 14.5, 7.4 Hz, 1H, H^{5b}), 1.47 (s, 3H, H^{4}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 173.2 (C^{2a}, C^{2b} or C^{7}), 172.7 (C^{2a}, C^{2b} or C^{7}), 172.4 (C^{2a}, C^{2b} or C^{7}), 136.5 (C^{11}), 133.0 (C^{10}), 128.8 (2C, C^{13}), 128.5 (C^{9}), 128.0 (C^{14}), 126.5 (2C, C^{12}), 53.0 (C^{6}), 52.8 (C^{1a}), 52.7 (C^{1b}), 47.3 (C^{6}), 37.7 (C^{5}), 26.7 (C^{8}), 20.9 (C^{4}).

IR (neat) ν_{max}: 3391, 3060, 3027, 2999, 2952, 1729, 1642, 1262, 1200, 1160, 1112, 1028, 736, 694.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{23}NNaO_5^+$) requires *m*/*z* 356.1467, found *m*/*z* 356.1461.

*Dimethyl (E)-2-methyl-2-(2-(methylcarbamoyl)-4-(naphthalen-2-yl)but-3-en-1-yl)malonate (**2.147**)*



$C_{22}H_{25}NO_5$
MW: 383.4440

Following **General Procedure M** using (*E*)-*N*-methyl-*N*-((2-(naphthalen-2-yl)vinyl)sulfonyl)acrylamide (30.1 mg, 0.100 mmol, 1.00 equiv.) and dimethyl methylmalonate (21.9 mg, 0.150 mmol, 1.50 equiv.). Purification by flash column chromatography (heptanes/ethyl acetate 9:1–1:1) gave the title compound as a yellow oil (15.2 mg, 0.040 mmol, 40%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.81 – 7.75 (m, *J* = 10.0, 9.3 Hz, 3H, H^{13}, H^{15} and H^{18}), 7.70 (s, 1H, H^{20}), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H, H^{12}), 7.49 – 7.39 (m, *J* = 7.7, 5.4, 1.2 Hz, 2H, H^{16} and H^{17}), 6.59 (d, *J* = 15.8 Hz, 1H, H^{10}), 6.26 (dd, *J* = 15.8, 9.3 Hz, 1H, H^{9}), 5.76 (app d, *J* = 4.0 Hz, 1H, NH), 3.66 (s, 3H, H^{1a}), 3.59 (s, 3H, H^{1b}), 3.20 (ddd, *J* = 9.0, 7.7, 5.1 Hz, 1H, H^{6}), 2.81 (d, *J* = 4.9 Hz, 3H, H^{8}), 2.66 (dd, *J* = 14.5, 5.1 Hz, 1H, H^{5a}), 2.26 (dd, *J* = 14.5, 7.5 Hz, 1H, H^{5b}), 1.49 (s, 3H, C^{4}).

^{13}C NMR (176 MHz, $CDCl_3$): δ 173.2 (C^{2a}, C^{2b} or C^{7}), 172.7 (C^{2a}, C^{2b} or C^{7}), 172.4 (C^{2a}, C^{2b} or C^{7}), 134.0 (C^{11}), 133.7 (C^{19}), 133.2 (C^{14}), 133.1 (C^{10}), 128.9 (C^{16} or C^{17}), 128.5 (C^{9}), 128.1 (C^{16} or C^{17}), 127.8 (C^{13}, C^{15} or C^{18}), 126.6 (C^{13}, C^{15} or C^{18}), 126.5 (C^{13}, C^{15} or C^{18}), 126.2 (C^{20}), 123.4 (C^{12}), 53.0 (C^{6}), 52.8 (C^{1a}), 52.7 (C^{1b}), 47.4 (C^{4}), 37.8 (C^{5}), 26.7 (C^{8}), 21.0 (C^{4}).

IR (neat) ν_{max}: 3297, 3056, 2998, 2952, 1731, 1645, 1557, 1264, 1201, 1115, 743.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{25}NNaO_5^+$) requires *m*/*z* 406.1625, found *m*/*z* 406.1617.

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