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DISSERTATION / DOCTORAL THESIS

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„Reactions of alkenes mediated by
(I) counterion, (II) solvent or (III) Lewis base“

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The work presented in this doctoral thesis was conducted between 2018 and 2023 at the University of Vienna (Austria) under the supervision of 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 the thesis.

Miran Lemmerer, 2023

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“Wer zu intensiv in sich selbst hineindenkt,

dem wird alles Bekannte rätselhaft.”

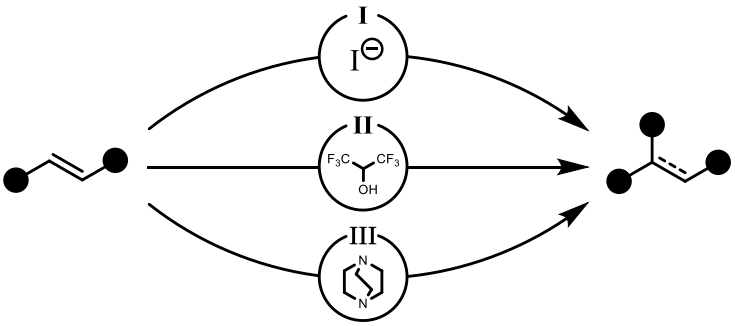
- Josef Hader

Abstract

Alkenes are readily available organic compounds containing a C=C double bond. Depending on the electronic nature of the double bond, different classes of reactions can be employed to transform alkenes into new types of chemicals. In this thesis, three different approaches are developed, each allowing for the selective modification of alkenes.

First, the reaction of alkenes with iminium ions in the presence of redox active iodide counterion and strong acid is investigated, leading to the regioselective, reductive synthesis of tertiary amines from electron-rich alkenes (and even other types of electrophiles). Second, a formal C–H aminomethylenation of electron-deficient alkenes, akin to the *aza*-Morita–Baylis–Hillman reaction, is described. This transformation utilises iminium iodides and relies on the specific counterion and solvent interactions. Third, α-arylation of acrylamides is achieved through a Lewis base-induced, anionic Smiles rearrangement of sulfonyl acrylimides.

In all three approaches, the reaction scope and mechanism are studied in detail using a variety of synthetic, spectroscopic and quantum computational methods. Furthermore, the novel compounds are applied in the synthesis of more complex organic molecules, showing their utility to the synthesis community.

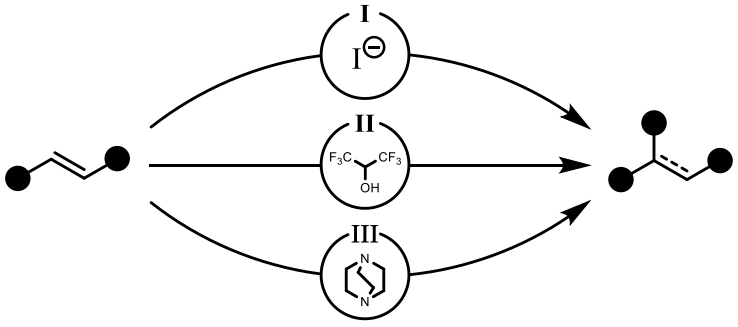


Zusammenfassung

Alkene sind leicht verfügbare Verbindungen mit einer C=C-Doppelbindung, die, in Abhängigkeit von ihrer elektronischen Beschaffenheit, durch verschiedene Reaktionsklassen in neue Chemikalien umgewandelt werden können. In dieser Arbeit werden drei verschiedene Ansätze entwickelt, die eine selektive Modifizierung von Alkenen ermöglichen.

Im ersten Teil wird ihre Reaktivität mit Iminiumionen in Gegenwart von redoxaktivem Iodid-Gegenion und starker Säure untersucht. Diese Methode erlaubt die regioselektive und reduktive Synthese von tertiären Aminen aus elektronenreichen Alkenen oder verschiedenen Elektrophilen. Im zweiten Teil wird eine formale C–H-Aminomethylenierung elektronenarmer Alkene ähnlich der *aza*-Morita-Baylis-Hillman-Reaktion mit Iminiumiodid beschrieben, die auf den spezifischen Wechselwirkungen zwischen Gegenion und Lösungsmittel beruht. Drittens wird die α-Arylierung von Acrylamiden durch Lewis-Base-induzierte, anionische Smiles-Umlagerung von Sulfonylacrylimiden erreicht.

In den drei Ansätzen werden der Umfang der Reaktion und ihr Mechanismus mit einer Vielzahl von synthetischen, spektroskopischen und quantenchemischen Methoden im Detail untersucht. Darüber hinaus werden die neuen Verbindungen bei der Synthese komplexerer organischer Moleküle angewendet, um ihre Nützlichkeit für die Synthesegemeinschaft aufzuzeigen.



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Abbreviations

Ar	aryl
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
cod	cyclooctadiene
Cy	cyclohexyl
d	doublet
δ	chemical shift
DABCO	diazabicyclo-[2,2,2]-octane
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMA-MIX	DCM:MeOH:NH_4OH (aq. 25%) = 90:10:1
DMF	*N*,*N*-dimethylformamide
d.r.	diastereomeric ratio
ee	enantiomeric excess
HE	Hantzsch ester
HFIP	hexafluoro isopropanol
^{i}Pr	*iso*-propyl
J	coupling constant
LG	leaving group
m	multiplet
MBH	Morita–Baylis–Hillman
MeCN	acetonitrile
ν	wave number
NHC	*N*-heterocyclic carbene
Ns	nosyl, 4-nitrobenzenesulfonyl
Nu	nucleophile
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PMP	*p*-methoxyphenyl
q	quartet
s	singlet
SET	single electron transfer
t	triplet
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
^{t}Bu	*t*ert-butyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	triflyl, trifluoromethylsulfonyl
TFA	trifluoro acetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl, toluensulfonyl
xyl	3,5-$Me_2C_6H_3$

1 General Introduction into the Reactivity of Alkenes

The availability and utility of alkenes, being hydrocarbons containing C=C double bonds, makes them pivotal structural motifs in different fields of chemistry, allowing for a wide range of functionalisation reactions. Industrially, alkenes, often also referred to as olefins, are mainly produced by steam cracking of fossil fuels, making them cheap building blocks to synthesise more complex, value-added compounds. The reactivity of alkenes usually revolves around cleavage of one of the higher-energy bonds, the π-bond. Formation of two new σ-bonds to the still connected carbon atoms allows for rapid buildup of complexity, as well as allowing the installation of three-dimensional structures. Under certain conditions, an elimination reaction can follow, regenerating the C=C double bond, now substituted with a new moiety (Figure 1). Such addition processes are possible by a myriad of methods, however, with sheer endless possibilities, many approaches, thus far, remain unexplored. Importantly, the electronic properties of an alkene govern its preferred mode of reaction: they can be more prone to interact with radicals in open shell processes or with two-electron species in formal π-acid/base reactions. The latter can again be subclassified into reactions of electron-rich alkenes with electrophiles or the complementary process where electron-deficient olefins react with nucleophiles. In this thesis, all three pathways will be explored within the development of addition and addition/elimination reactions for the synthesis of novel, complexity-added chemicals.

Figure 1: Addition and elimination reactions of alkenes.

2 Reductive Aminomethylenation Mediated by Iodide

2.1 Introduction

This chapter will revolve around iminium iodides, in particular Eschenmoser's salt, and their use in aminomethylenation reactions, acting as both a source of aminomethylene group and a reductant (iodide counterion). This reaction is performed using an array of starting materials including diazonium salts, vinyl arenes, benzylic alcohols and benzylic halides, offering a novel approach to the synthesis of tertiary amines.

2.1.1 Iodine in Redox Reactions – an Underexplored Reductant

The element iodine has for long been used as a disinfectant. This property is due to the oxidation power of the I_2 molecule in solution. Being a halogen, iodine is readily reduced by accepting an electron to complete its octet and form an iodide anion (Figure 2a). Iodine in oxidation state 0 (I_2) is widely used in organic chemistry for iodination reactions or as a sacrificial oxidant. Also, reagents containing iodine in higher oxidation states as the pivotal atom are being developed up to this day (Figure 2b). For example, iodine (III) reagents like iodosobenzene (**2.1**) are widely used for the umpolung of carbonyl groups,[1] and Dess-Martin periodinane (**2.2**, oxidation state V) is a common oxidant for alcohols.[2]

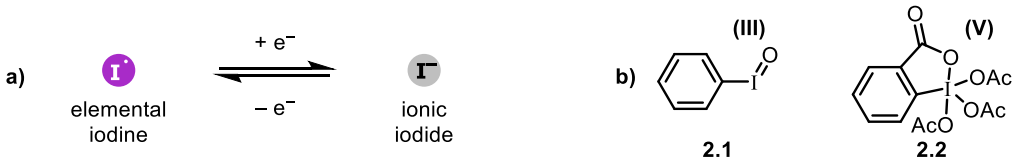
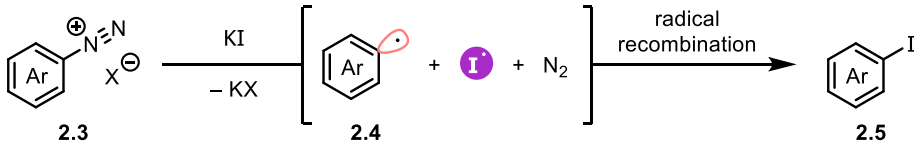


Figure 2: a) Iodine in its oxidation states 0 and -1. b) Examples of commonly used reagents containing iodine in the oxidation states III and V.

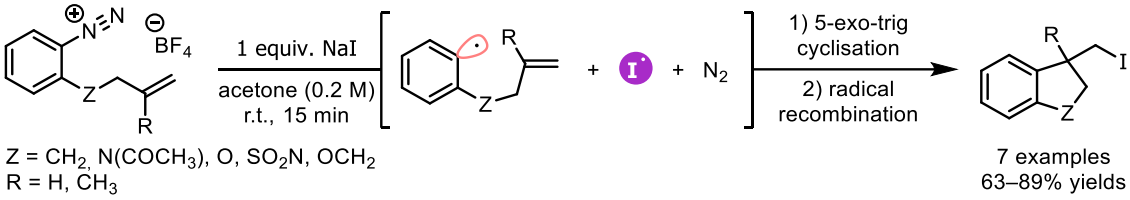
Less explored is the use of iodide anion itself as a reductant, despite its abundance in an array of different inorganic and organic salts. In the early 20th century, Kaufler *et al.* reported the direct reduction of aryl diazonium salts to aryl iodides after simple treatment with potassium iodide.[3] This reactivity displays similarities to the copper-mediated transformation of diazonium salts to chlorides or bromides, named after its developer, Sandmeyer.[4,5] In both

transformations, an N_2 group is displaced by a halide, however, in the case of chloride and bromide, copper is needed for the reaction to proceed, while with iodide, no additional components are required. This is attributed to the property of the iodide anion to undergo a direct single-electron transfer (SET) to the diazonium cation **2.3** generating a highly reactive aryl radical **2.4** and an iodine atom (Scheme 1).[6] Rapid radical recombination affords the aryl iodide **2.5**.



Scheme 1: Proposed general mechanism of diazonium salts iodination via single electron transfer (SET). X = BF_4, Cl, HSO_4.

If slow enough, this process can be exploited by interception of the carbon-based radical prior to C–I recombination, via reaction with a pendant alkene. Such a process was reported by Meijs *et al.* with substrates that can undergo efficient radical cyclisation, in an overall intramolecular iodoarylation of unactivated alkenes (Scheme 2).[7] Depending on the substitution pattern, 5- (5-exo-trig) or 6-membered (6-endo-trig) rings, formed in generally high yields.

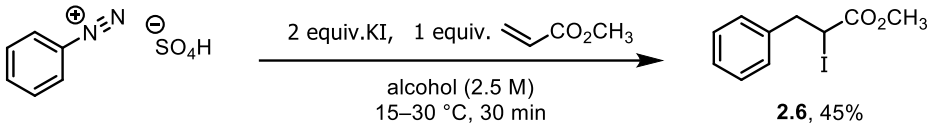


Scheme 2: Application of the reduction of ArN_2BF_4 with iodide in radical cyclisation cascades.

The process depicted in Scheme 2 demonstrates that carbon-iodine radical recombination is slow enough to allow further reaction with radical acceptors prior to C–I bond formation, opening a new avenue for the formation of C–C-bonds.

A general method for the arylation of electron-deficient alkenes (Meerwein arylation) involves the use of aryl diazonium salts and an appropriate reagent to decompose/reduce the salt to

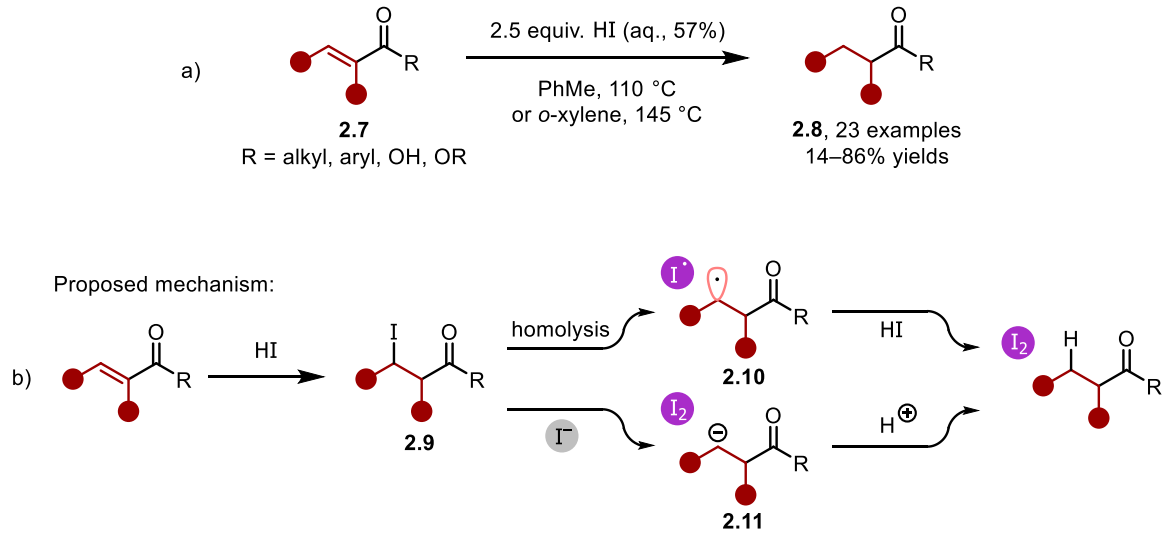
an aryl radical and N_2 gas.[8,9] While these reagents are usually transition metal salts, in 1984 Ganushchak *et al.* have shown how simple iodide can be used, whereby the resulting aryl radical is intercepted by an olefin yielding α-iodo ester **2.6** (Scheme 3).[10,11] Crucial for the transformation is the use of electron-deficient alkenes to outcompete terminating radical recombination.[9]



Scheme 3: Iodoarylation of an electron deficient olefin.

As these few examples show, iodide offers a unique and atom-economical path to aryl radical generation from diazonium salts and is not limited to Sandmeyer-type halogenation, but can rather be used for synthesis of complex structures.

A different mode of reduction is observed when α,β-unsaturated carbonyls **2.7**, such as ketones, carboxylic acids or esters are treated with HI at elevated temperature (Scheme 4a). In this case a formal hydrogenation leads to the saturated products **2.8**. As reported by Matsumoto *et al.,*[12] the reaction proceeds via a β-iodo carbonyl intermediate **2.9**, which can either form radical **2.10** through C–I-bond homolysis, or be protonated via an ionic pathway (anion **2.11**) (Scheme 4b). Two key factors render the first option likely: 1) the enol tautomer stabilises the β-radical, and 2) presumably the use of an apolar solvent means the C–I bond is unpolarised. Additional indication of a radical intermediate is the requirement of an aromatic group either in α- or more commonly in β-position for the reaction to proceed.

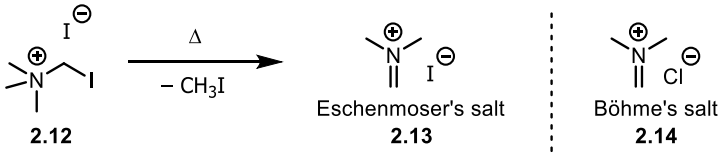


Scheme 4: a) Reduction of α,β-unsaturated carbonyls with iodide. b) Two possible mechanistic pathways proposed by the authors.

In this chapter, we aim to use the reductive property of iodide counterions for the first time as a two-in-one reagent (electrophile + reductant) for intermolecular C–C-bond formation. Iminium iodides allow for the aminomethylenation of diazonium salts employing a simple procedure, as described below in section 2.2.1.

2.1.2 Eschenmoser's Salt

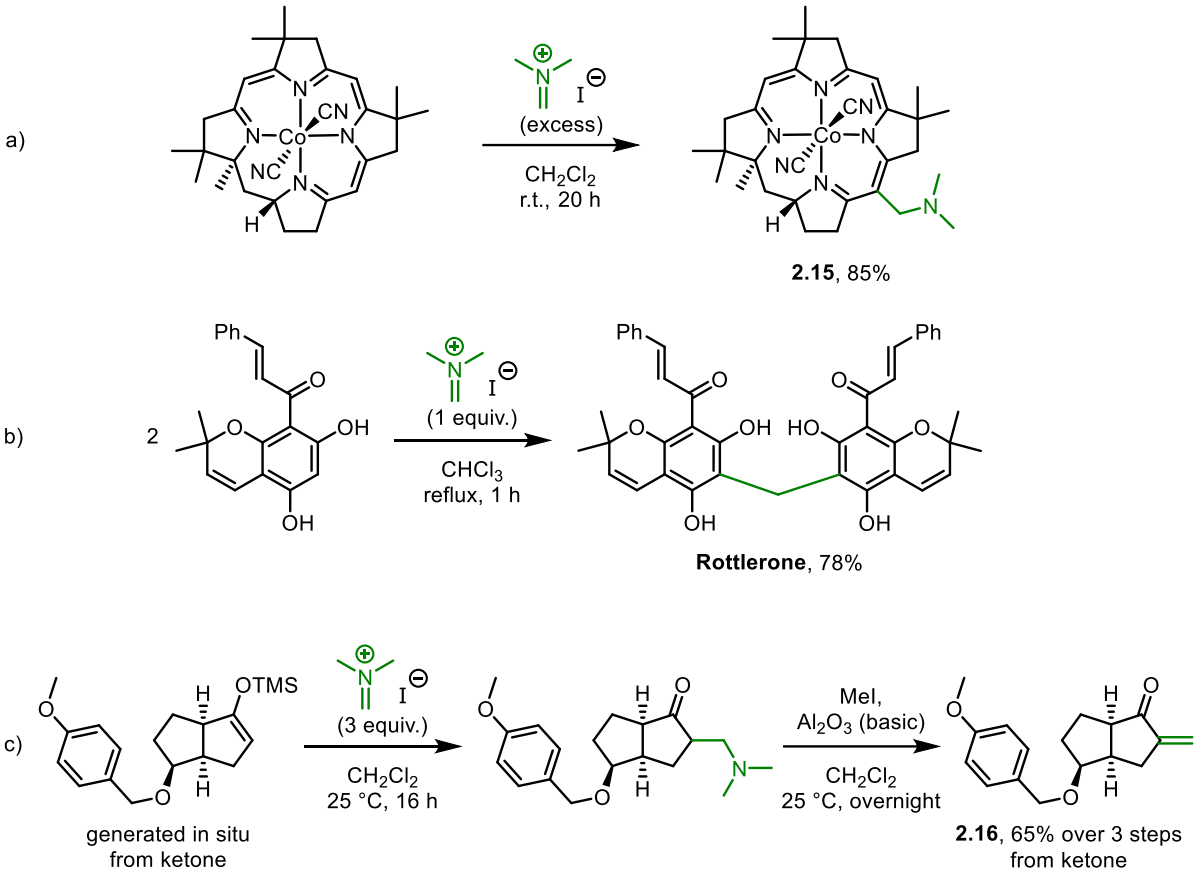
Iminium iodides have found broad applications in organic chemistry as intermediates in catalytic cycles or as stoichiometric reagents.[13,14] While generally susceptible to hydrolysis and therefore often generated *in situ*, some iminium salts are sufficiently bench-stable to be isolated using simple setups and are even commercially available. The simple compound dimethylmethyleneiminium iodide (**2.13**) was originally described by Eschenmoser *et al.* in the context of their well-known study on the synthesis of cobalamin.[15] The salt is prepared by thermolysis of iodomethyl trimethylammonium iodide (**2.12**) releasing methyl iodide as a by-product (Scheme 5). A similar reagent (**2.14**) was reported over a decade earlier by Böhme *et al.* featuring a chloride instead of iodide as the counterion.[16]



Scheme 5: Two iminium salts commonly used in organic syntheses.

Eschenmoser's salt is a simple and convenient reagent for the aminomethylenation of various organic molecules. Electron-rich aromatic compounds, such as simplified cobalamin derivative **2.15**, can be modified easily by simple mixing with the salt at ambient temperature (Scheme 6a).[15] Additionally, dimethylamine can act as a leaving group precursor, enabling the reagent to be deployed as a methylene linker for double electrophilic aromatic substitution, such as in the last step of the total synthesis of Rottlerone by Wang *et al.* (Scheme 6b).[17] Enolates derived from various carbonyl groups also react readily with this iminium. The resulting β-*N*,*N*-dimethylamino carbonyls can be further *N*-alkylated to trigger elimination and generate α-methylenated carbonyls **2.16** as depicted in Scheme 6c, illustrating an intermediate step in the total synthesis of Pepluanol B.[18]

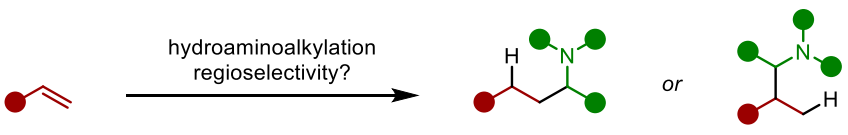
These selected examples showcase the broad utility of this simple salt for aminomethylenation or as a "C_1^{++}" synthon. In the following two chapters, additional synthetic methods will be presented which specifically rely on the iodide counterion.



Scheme 6: Selected examples employing Eschenmoser's salt in organic synthesis.

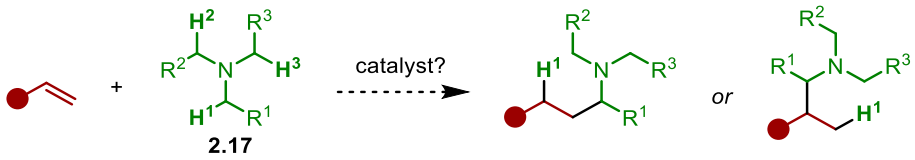
2.1.3 Aminoalkylation of Alkenes

An ever-growing area of amine synthesis consists of hydroaminoalkylation of alkenes.[19,20] In an often highly atom-economical sequence, C=C double bonds are functionalised with hydrogen and carbon, breaking a π-bond and forming two σ-bonds (C–H and C–C) in the process (not taking into account any broken bonds in the reagents). As olefins are commonly not symmetric, this raises the potential for regioselectivity issues to be overcome in the desired aminoalkylation reaction (Scheme 7).



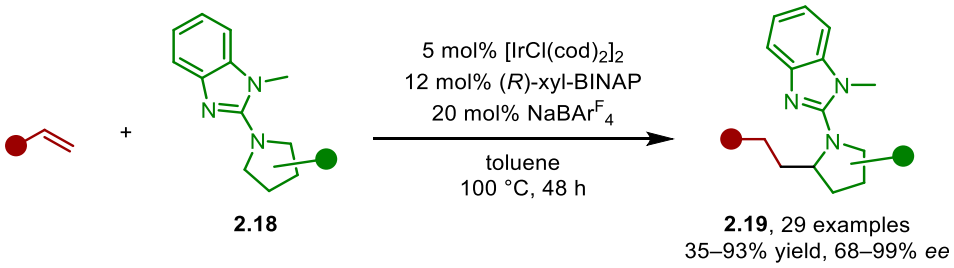
Scheme 7: A question of regioselectivity in a hypothetic hydroaminoalkylation reaction.

This challenge can be approached from multiple angles, depending on the available starting materials. It would be desirable, for example, to use simple alkylamines and formally insert an alkene into the α-C–H bond (Scheme 8). Such a sequence would not generate any waste products; however, it may present additional problems to tackle such as, the requirement to overcome the strong bond dissociation energy of alkyl amine α-C–H-bonds. Additionally, achieving regioselectivity on unsymmetrical trialkyl amines could be challenging, particularly if all alkyl groups are electronically and sterically similar (**2.17**).



Scheme 8: The additional challenge of regioselective amine activation.

A way to address both challenges is the use of directing groups for transition metal-catalysed C–H activation. Using such a strategy, Nishimura *et al.* prepared a variety of benzimidazole-containing amines (**2.18**) in high yields and *ee* values using iridium catalysis (Scheme 9).[21] Strikingly, the method delivers exclusively the linear product **2.19**. Other related approaches rely on pyridine or benzoxazole directing groups.[22–27]



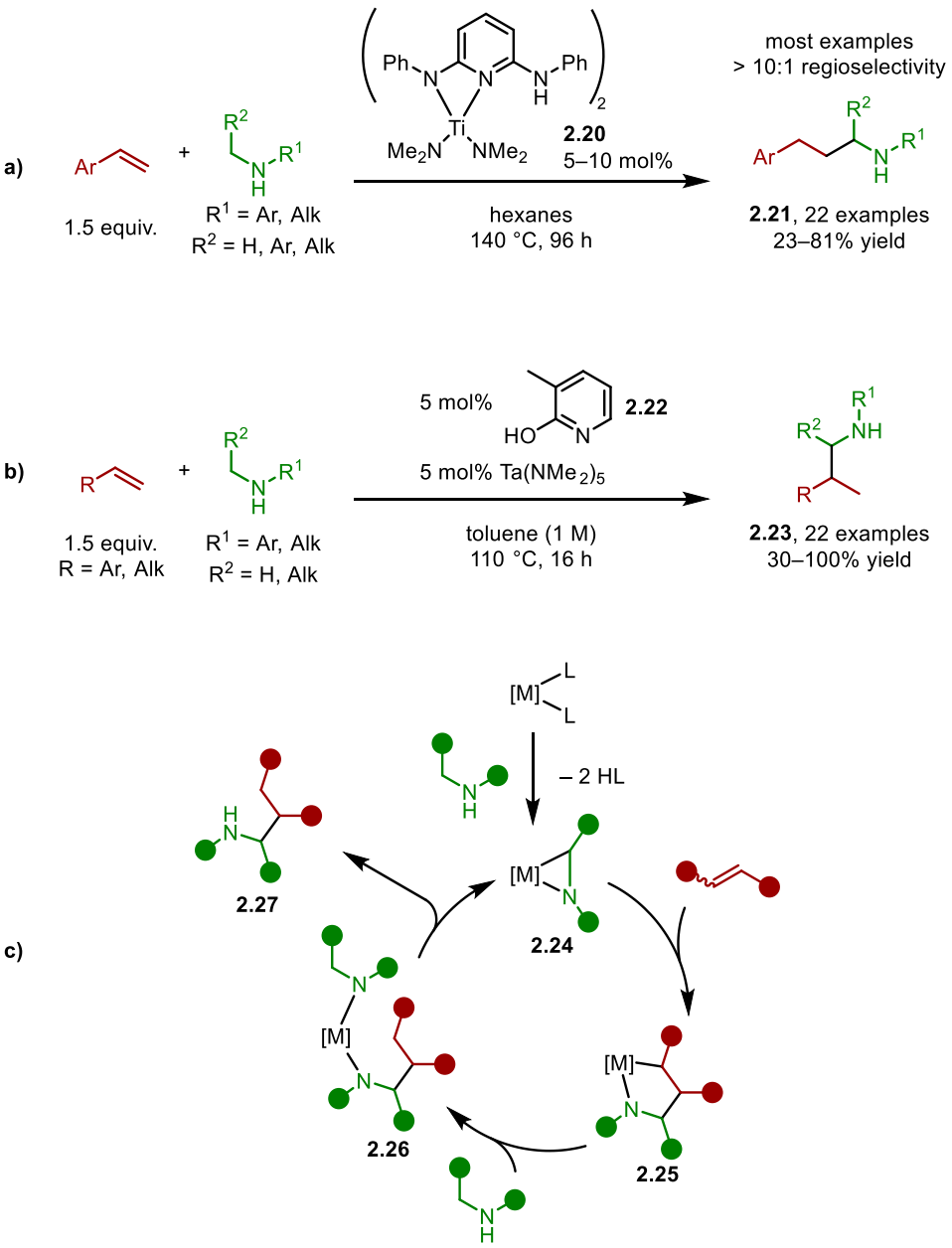
*Scheme 9: Iridium-catalysed enantioselective hydroaminoalkylation of alkenes with 2-amino benzimidazoles **2.18**. cod = cyclooctadiene; Ar^F = 3,5-$(CF_3)_2C_6H_3$; xyl = 3,5-$Me_2C_6H_3$.*

While this method is highly efficient for a special class of amines, broader scope can be achieved using titanium or tantalum catalysis.[28] Similar reactions are also reported using other transition metals, however, the effective use of titanium and tantalum is particularly

noteworthy.[19] Multiple research groups have developed catalytic systems which are highly selective for linear or branched regioisomers.

Using Titanium amide complex **2.20**, Doye *et al.* have described the hydroaminoalkylation of styrenes with excellent selectivity for the linear product **2.21** (Scheme 10a).[29] This is especially remarkable as previous titanium-catalysed processes delivered mixtures or only gave the linear product for specific substrates.[30–32] They also reported one aliphatic alkene substrate which delivered the desired amine with opposite selectivity of 1:10 (linear:branched).

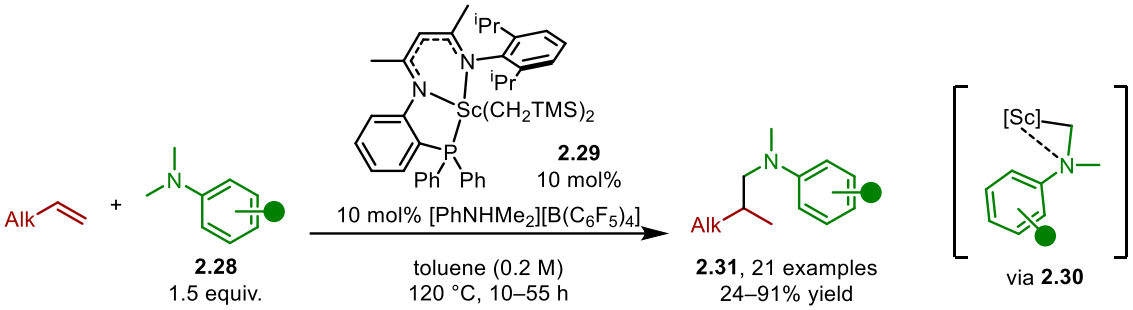
Tantalum catalysis has been heavily developed over recent years to achieve branched (over linear) selectivity. For example, Schafer *et al.* have developed a method using commercial ligand **2.22** as a ligand and tantalum complex $Ta(NMe_2)_5$ as a metal source (Scheme 10b).[33] The process displays high selectivity for the branched product **2.23**.



Scheme 10: Selected examples for a) linear selective and b) branched selective hydroaminoalkylation. c) A general catalytic cycle for early transition metal catalysed hydroaminoalkylation of alkenes.

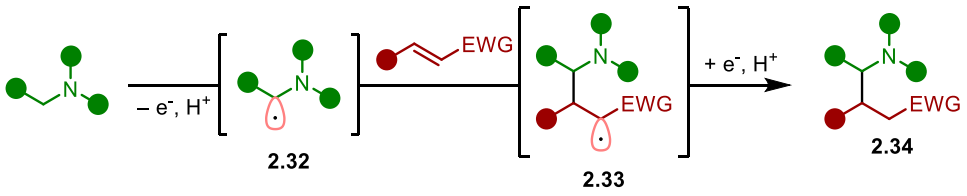
From a mechanistic standpoint, the examples described in Scheme 10a and b involve the formation of metallaziridine **2.24** which adds to the olefin partner forming metallapyrolidine **2.25** (Scheme 10c). This addition step effectively sets the regioselectivity of the transformation. Reaction with the next amine molecule leads to formal proto de-metallation (**2.26**) followed by C–H insertion, reforming **2.24** and releasing product **2.27**. Accordingly, this approach limits the hydroaminalkylation to primary and secondary amines.

In 2018, Xu *et al.* disclosed a method which incorporates tertiary amines **2.28** using scandium catalyst **2.29** (Scheme 11).[34] This complex allows for L-type bonding of the amine via intermediate **2.30** in an intermediate as metallaziridine **2.24** (Scheme 10c). The specific process highlighted in Scheme 11 is highly selective for branched products **2.31**, but limited to aniline derivatives (**2.28**).



Scheme 11: A reaction with N,N-dimethyl anilines as an example for tertiary amines.

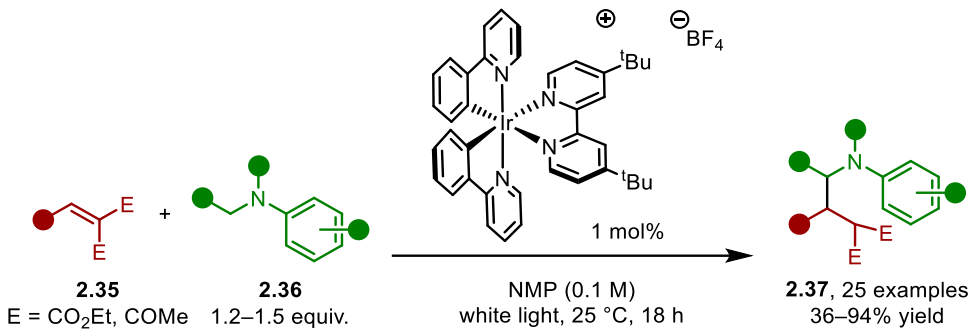
The α-position of amines is not only susceptible to heterolytic C–H activation by transition metal catalysts as described above, but also suitable for radical generation by tamed homolytic pathways (Scheme 12). Oxidation of tertiary amines allows for formal α-hydrogen atom abstraction (HAT) generating carbon-centred radical **2.32**, which can add to (electron-deficient) alkenes forming **2.33**. Reduction of this newly formed radical (**2.34**) completes the redox cycle potentially rendering the process redox-neutral.



Scheme 12: A general redox catalysed hydroaminoalkylation mechanism involving α-amino radicals.

As one of the first groups to explore this approach, Nishibayashi *et al.* employed photoredox catalysis to synthesise γ-amino carbonyls.[35] Unsaturated esters **2.35** were coupled to Anilines **2.36** using homogeneous iridium visible light photocatalysis, yielding products **2.37** (Scheme

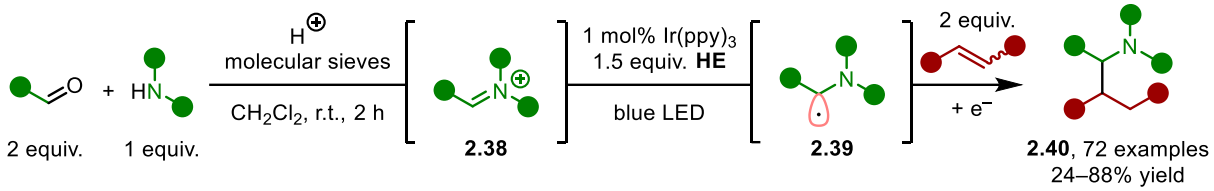
13). Reiser *et al.* concurrently reported a similar approach deploying tetrahydroisoquinolines as amine components.[36] Over the last decade, several more reports on related amine oxidation-initiated radical addition reactions have been disclosed.[37,38] While this concept has significant appeal for the use of electron-deficient alkenes, it lacks generality for unbiased or electron-rich olefins as efficient polarity pairing is needed.



Scheme 13: A photoredox catalysed hydroamaminoalkylation method developed by Nishibayashi et.al.

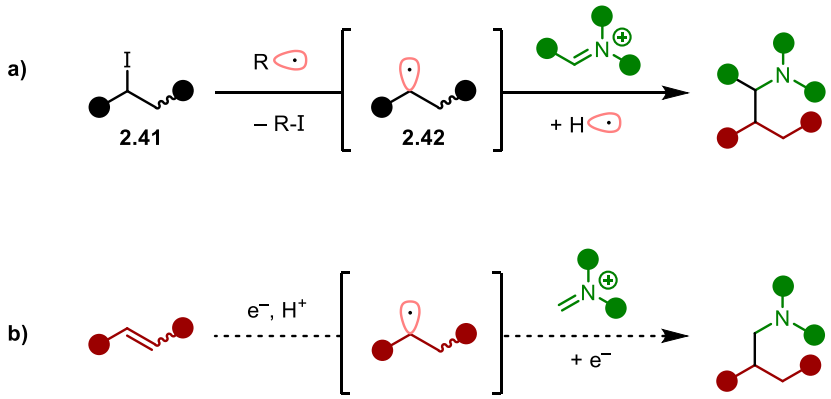
In every aforementioned hydroaminoalkylation method, all atoms of the amine product were derived from the alkene and starting amine precursors. A different approach would be the combination of olefins with iminium ions. However, in this case, an additional stoichiometric reagent is needed to provide an external source of hydride or H atom.

An alternative path to generate pivotal α-amino radicals, besides the oxidation of amines, is the single electron reduction of iminium ions. This can be achieved through reduction with an appropriate photocatalyst, as reported by Gaunt *et al.* (Scheme 14).[39] Iminium ions **2.38**, prepared *in situ* from aldehydes and amines, were reduced with an Ir-photocatalyst affording the α-amino radicals **2.39**. These react further with electron-deficient alkenes or other olefins to generate stablised radicals, similarly to methods described before. In this case, Hantzsch ester (HE) is used as a reductive scavenger delivering amines **3.40**.



Scheme 14: Photoredox-catalysed reductive assambly of aldehydes, amines and alkenes. HE = Hantzsch ester.

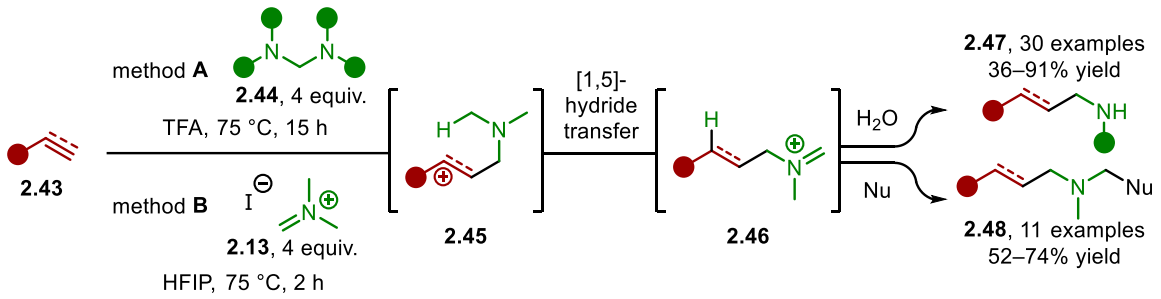
A different radical approach involves the homolytic π-bond cleavage of the alkene coupling partner as depicted in Scheme 15. Addition of C-centred radicals **2.42** (generated through halogen atom abstraction of alkyl iodides **2.41**) to iminium ions is a fast emerging method for amine synthesis (Scheme 15a).[40–42] In principle, the formation of a transient alkyl iodide, through the formal addition of hydrogen iodide to an alkene for example, would allow the direct use of olefins and therefore a complementary alternative to the established methods (Scheme 15b). However, to the best of our knowledge, such a process for the aminoalkylation of alkenes has not yet been described (our efforts will be discussed in part 2.2.2).



Scheme 15: a) Established strategy involving radical generation via halogen atom abstraction followed by addition to iminium ions. b) A hypothetical amine synthesis through reduction of alkenes followed by addition to an iminium ion and SET.

A redox-neutral approach involving a 1,5-hydride transfer step was explored by Maulide *et al.* in 2019 (Scheme 16).[43,44] Alkenes (or alkynes) **2.43** were treated with iminium ions under two possible conditions. Either the iminium ion was generated in situ from aminals **2.44** under strongly acidic conditions (using trifluoroacetic acid (TFA) as a solvent, method A), or Eschenmoser's salt **2.12** was deployed in hexafluoro isopropanol (HFIP), a highly polar protic solvent (method B). The reaction is initiated by nucleophilic attack of the alkene to the

iminium (*aza*-Prins reaction), forming a new carbocation (**2.45**). A hydride adjacent to the newly generated amine then participates in 1,5-hydride transfer, leading to the more stable iminium ion **2.46**. Prior related studies had proposed a concerted ene-reaction as an alternative pathway.[45–47] It was shown that this new electrophile could either be hydrolysed to generate secondary amines **2.47**, or be trapped with an appropriate nucleophile to synthesise functionalised tertiary amines **2.48**.



Scheme 16: A redox-neutral hydroaminomethylenation method of alkenes and alkynes involving a 1,5-hydride transfer step. TFA = trifluoroacetic acid; HFIP = hexafluoro isopropanol.

The number of concepts for the synthesis of α-branched teriary amides is large and many methods have been developed over the last decades. Yet, starting from simple alkenes and iminium salts, metal-free approaches often rely on complicated reductants producing large amounts of waste. In the next section, we present a novel approach employing a particularly simple (and versatile) reductant.

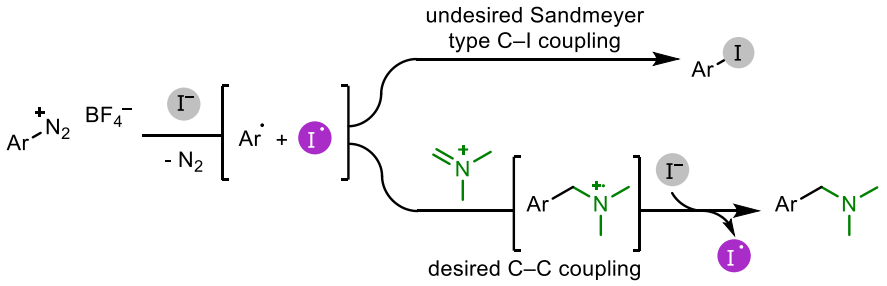
2.2 Results and Discussion

The results described in this chapter were obtained together with Dr. Veronica Tona, Dr. David Just and Miloš Vavrík. Dr. Giovanni di Mauro performed quantum chemical calculations under the guidance of Dr. Boris Maryasin which will be briefly discussed.

In this chapter, the reductive aminomethylation of transient radicals exploiting the reducing power of iodide will be covered.

2.2.1 Reductive Aminomethenylation of Diazonium Salts

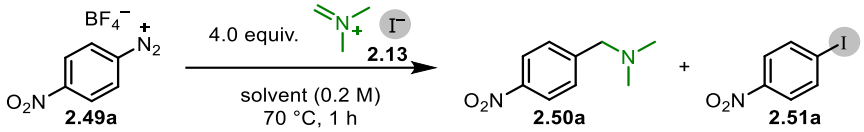
As discussed in section 2.1.2, aryldiazonium salts are an easily accessible source of aryl radicals in presence of iodide. Using Eschenmoser's salt, we hoped to achieve a reductive coupling of two electrophiles, diazonium and iminium, without the need for additional reductants such as titanium reagents (Scheme 17).[48] However, this would only be possible if we could find conditions where the recombination of aryl- and iodine radicals was slower than an attack on the iminium salt. Furthermore, reduction of the resulting aminium radical cation by iodide would be challenging. However, if overall successful, the only by-products of such a reaction would be the salt dimethylmethyleneiminium tetrafluoroborate and I_2.



Scheme 17: Our hypothesised direct reductive coupling of diazonium- and Eschenmoser's salts.

At the outset, we chose *p*-nitrophenyldiazonium tetrafluoroborate **2.49a** and Eschenmoser's salt as model substrates (Table 1). Initial survey of different solvents at 70 °C revealed that polar solvents delivered the desired benzylic amine **2.50a**, albeit with low yield. Aryl iodide **2.51a** was the major product of the reaction in all cases. While a variety of polar solvents led to desired amine formation, HFIP (entry 4), gave the highest yield of 24%.

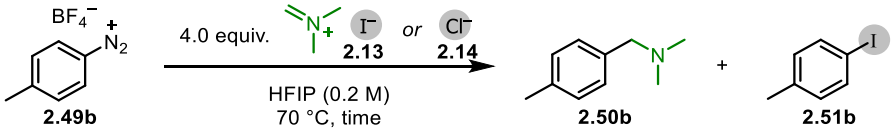
*Table 1: Screening of different solvents for the reductive coupling of diazonium salt xx with Eschenmoser's salt. * Yield determined by quantitative ^{1}H-NMR. ** not determined due to peak overlap.*



entry	solvent	yield 2.50*	yield 2.51*
1	H_2O	0%	88%
2	MeCN	0%	n.d.[2]
3	DCE	6%	82%
4	**HFIP**	**24%**	**72%**
5	AcOH	8%	85%
6	PhMe	0%	72%
7	DMF	6%	73%
8	THF	0%	45%
9	hexane	9%	78%
10	TFE	17%	75%
11	^{i}PrOH	0%	53%
12	TFA	6%	58%
13	DMSO	8%	n.d.**
14	pyridine	0%	58%
15	acetone	9%	78%

Since the electron deficient diazonium salt **2.49a** generally delivered high amounts of undesired recombination product **2.51a**, further parameter screening was performed with electron-neutral tolyl derivative **2.49b** (Table 2) and led to improved yields (59%) of the desired product (entry 1). The methyl substituent was chosen to increase the boiling point of the benzylic amine and therefore decrease the chance of loss during solvent removal under vacuum. Decreasing the equivalents of **2.13** led to lower yield of **2.50b** (entries 2 and 3), and a switch to **2.14** in combination with KI further decreased the yield, potentially due to the low solubility of KI (entries 4 and 5). This highlights the benefit of having iodide and iminium in one salt. Encouragingly, the mode of addition led to a slight increase in yield (entries 6–8).

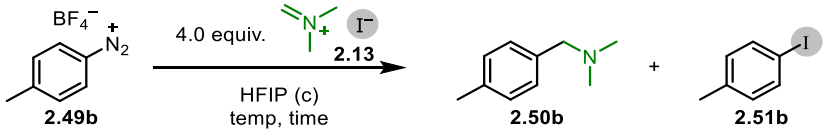
*Table 2: Second set of optimisation of the reaction conditions. * Yield determined by quantitative ^{1}H-NMR.*



entry	time (h)	other deviations	yield 2.50b*	yield 2.51b*
1	1	-	59	16
2	1	3 equiv. **2.13**	53	17
3	1	2 equiv. **2.13**	50	15
4	2.5	**2.14** instead **2.13** + 4 eq. KI	19	n.d.
5	2.5	**2.14** instead **2.13** + 2 eq. KI	15	n.d.
6	1	solids mixed before HFIP addition	50	25
7	**1**	**2.49b dissolved before addition of 2.13**	**63**	**21**
8	1	**2.13** added in 4 equal portions after 5 min each	46	20

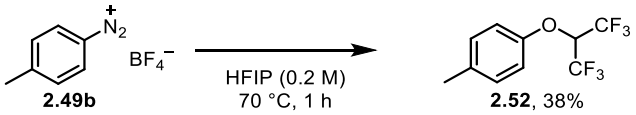
Next, we investigated concentration and temperature variations, together with alternative energy sources and additives (Table 3). Since longer reaction time resulted in a slight decrease in yield, we sought for milder conditions. However, running the reaction at ambient temperature offered no improvement (entries 1 vs 2). Concentration played a significant role in the outcome of the reaction (entries 3–10), with lower concentrations providing reduced yields, whereas higher concentrations were beneficial. In particular, a concentration of 0.66 M appeared to be optimal, affording **2.53** in 70% yield (entry 8). Screening different temperatures did not improve the yield (entries 11–14), and the influence of light at longer reaction times was negligible (entries 15 and 16). However, this result showed that the reaction could also be performed at ambient temperature with longer reaction times to give comparable yields. Interestingly, if again conducted at 70 °C, the reaction time could also be lowered to 10 min with only a slight loss in yield, highlighting how fast the process really is (entry 17). Further changes in work up condition or additives did not lead to an increase in efficiency (entries 18–21). Finally, $AgBF_4$ was added in an attempt to partially sequester the iodide counterion and lower the amount of aryl iodide **2.51b**; however, it had no beneficial effect (entry 22).

*Table 3: Further optimisation of the reaction conditions. * Yield determined by quantitative 1H-NMR.*



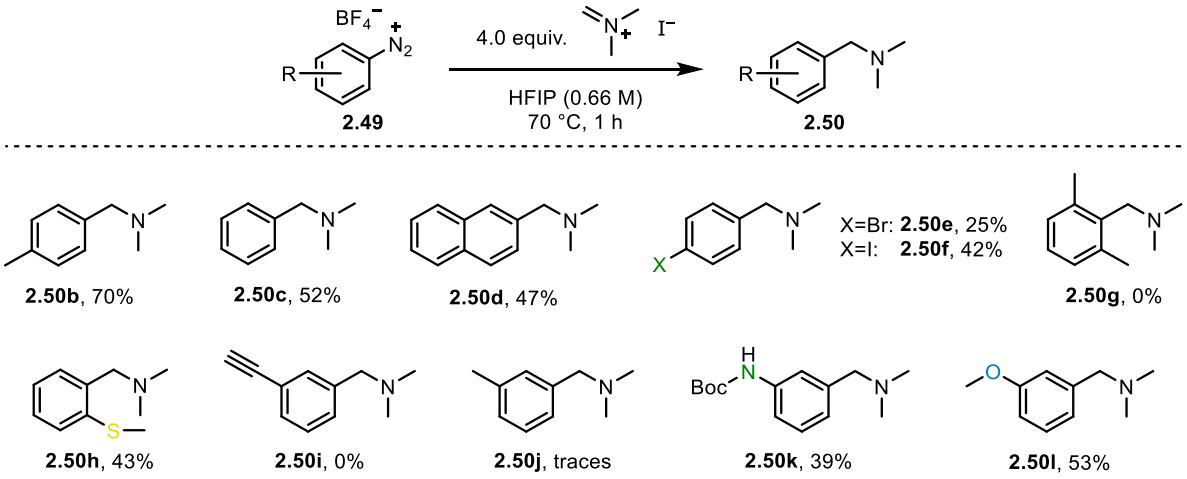
entry	C (M)	temp (°C)	time (h)	other deviations	yield 2.50b*	yield 2.51b*
1	0.2	70	16	-	52	17
2	0.2	20–25	14	-	52	7
3	0.1	70	1	-	43	13
4	0.02	70	1	-	43	14
5	0.4	70	1	-	65	22
6	0.5	70	1	-	68	24
7	0.6	70	1	-	67	25
8	**0.66**	**70**	**1**	**-**	**70**	**25**
9	1	70	1	-	67	24
10	2	70	1	-	62	33
11	0.66	100	1	-	41	24
12	0.6	40	1	-	66	25
13	0.6	20–25	1	-	63	24
14	0.6	0	1	-	48	11
15	0.66	20–25	14	blue LED irradiation	70	15
16	0.66	20–25	14	light exclusion	69	27
17	0.66	70	10 min	-	66	25
18	0.66	70	1	$Na_2S_2O_3$+NaOH work up	68	25
19	0.66	70	1	+ 2.0 equiv. TFA	68	29
20	0.66	70	1	+ 2.0 equiv. Hantzsch ester	61	16
21	0.66	70	1	+ 2.0 equiv. Cs_2CO_3	60	19
22	0.66	70	1	**2.13** premixed with 1.5 equiv. $AgBF_4$	63	23

The lower combined yield in the reactions with decreased concentration can partially be explained by solvolysis of the diazonium salt. While HFIP is generally considered non-nucleophilic, given that the reaction is run at elevated temperature, substitution of the diazonium presumably takes place as shown in a control experiment without Eschenmoser's salt (Scheme 18).



*Scheme 18: Background solvolysis reaction of diazonium salts **2.49b** with HFIP.*

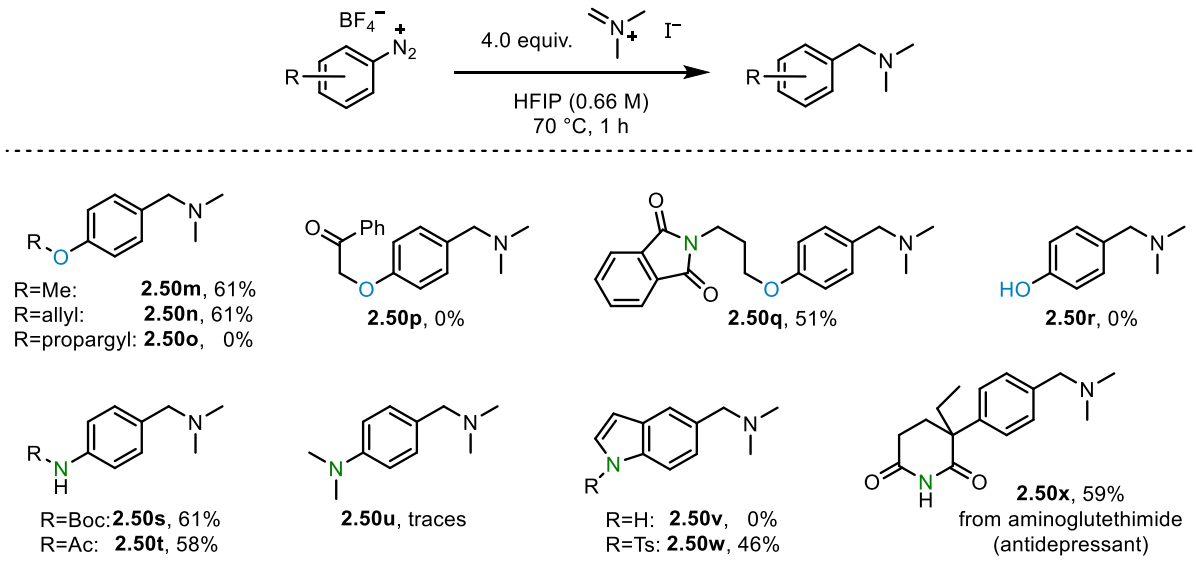
Satisfied with the yield and simplicity of the reaction conditions, we turned our focus towards different diazonium tetrafluoroborate derivatives. A brief investigation of simple diazonium salts revealed mixed applicability of the method, limited primarily by competitive iodination of the aryl group (Scheme 19). Simple benzene (**2.50c**) and naphthalene (**2.50d**) benzylamides were obtained in moderate yields. Two *p*-halides, bromide **2.50f** and iodide **2.50f** revealed iodide to be most effective. Sterically shielded *o*,*o*'-dimethyl product **2.50g** was not obtained, while an *o*-sulfide substituted diazonium salt engaged effectively to form amine **2.50h** in 43% isolated yield. Meta-substituted diazonium tetrafluoroborates showed no significant product formation for alkyne (**2.50i**) or methyl (**2.50j**) substituents. The first can be explained through side reactions of the alkyne,[43] however, it is not clear why **2.50j** did not form. Boc-protected amine **2.50k** and methoxy substituted **2.50l** both delivered the corresponding products with reasonable efficiency.



Scheme 19: Substrate Scope for the reaction with substituted-diazonium salts.

This simple aminomethylation method delivers amines in high yield, especially for aryl diazonium salts bearing an electron-donating group in the para-position (Scheme 20). One can speculate that this is due to better matching of reactive intermediates with the electron-deficient iminium ion. Generally, *p*-oxygen bearing benzylamines were synthesized in 51–61% yield (**2.50m,n**). As described previously, an alkyne was not tolerated (**2.50o**), ketone substrate **2.50p** was also not observed. A tethered phthalimide was well tolerated (**2.50q**),

however, unprotected phenol derivative **2.50r** could not be obtained. We further explored the functional group tolerance on this transformation with more challenging substrates. Amines, protected as carbamates (**2.50s**), carboxamides (**2.50t**) or sulfonamides (**2.50w**), display similar reactivity to the ethereal substrates discussed above. However, simple dimethylamine (**2.50u**) did not form the product effectively, and in the case of indoles, nitrogen protection was required (**2.50v,w**). Finally, aminoglutethimide, an antidepressant representing a more complex molecular structure, could be derivatised using our method, providing **2.50x** in 59% yield.

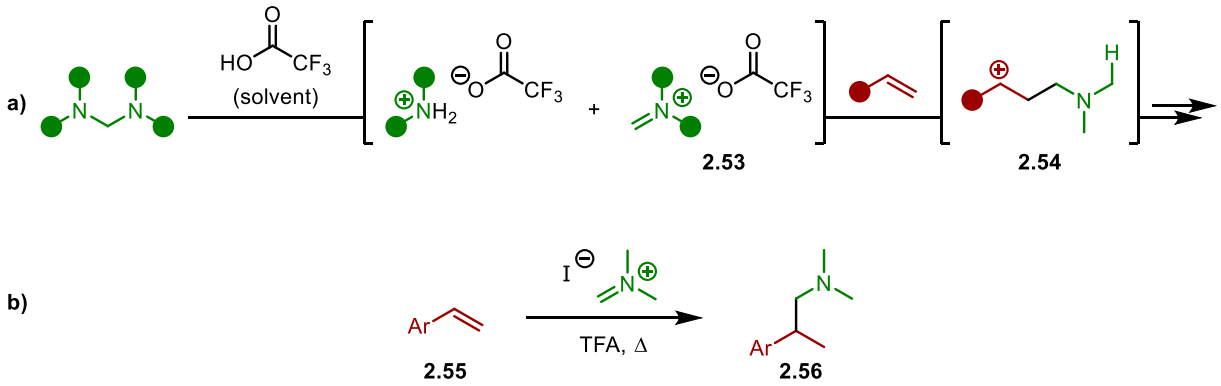


Scheme 20: Substrate scope electron-rich aryl diazonium salts.

While this method certainly has its limits in terms of functional group tolerance and electronic requirements of the aromatic group, it highlights the possibility for interrupted Sandmeyer type reactions via intermolecular C–C bond formation. The reduction of organic molecules by iodide to generate carbon-centred radicals and subsequent reactivity beyond simple C–I-bond formation is certainly an underdeveloped area of research.

2.2.2 Reductive Aminomethenylation of Benzyl Cation Sources

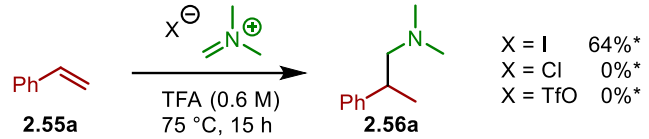
The previous chapter discussed the possibility of benzyl amine synthesis from aryldiazonium salts using iminium ions as aminomethene source where their iodide counterion acts as the reductant. A similar effect was observed during the study on redox-neutral aminomethylenation by Maulide *et al.* (Scheme 16).[43] Alkenes were treated with aminals using TFA as solvent to form linear amines. The aminal reacts with the highly acidic solvent and heterolyses to an amine (which rapidly gets protonated in the acidic environment) and an iminium trifluoroacetate **2.53**. Subsequent attack of the alkene onto the iminium forms a carbon-centred cation **2.54**. Trapping of this cation with trifluoroacetate can occur, but due to its reversible nature, the cation can undergo 1,5-hydride transfer leading to stabilised iminium **2.46** (Scheme 16). This stable intermediate was either hydrolysed to form secondary amines or treated with nucleophiles generating functionalised products (Scheme 16 and Scheme 21a).



Scheme 21: a) Maulide et al.'s previously reported method for the redox-neutral synthesis of linear amines and b) reductive synthesis of branched amines from alkenes and Eschenmoser's salt.

During the study, it was found that Eschenmoser's salt behaved differently than the *in situ* generated iminium trifluoroacetate (Scheme 21b). Using styrenes **2.55** led, instead of linear amines, to reduced branched products **2.56**. Presumably, the iodide had unexpectedly acted as a reductant. This hypothesis was tested by exchanging the counterion of the iminium salt (Scheme 22). When styrene **2.55a** was treated with Eschenmoser's salt (iodide counterion) in TFA at elevated temperatures, the reduced α-branched amine **2.56a** formed in 64% yield.

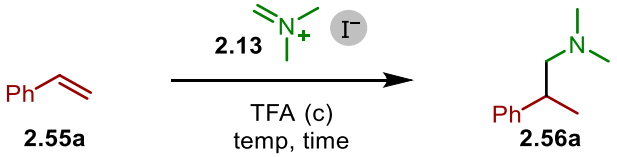
However, using chloride or triflate as counterions saw no formation of **2.56a,** highlighting the need for iodide to promote this particular reaction pathway.



*Scheme 22: Effect of counterions in Eschenmoser's salt in the synthesis of α-branched amines. *Reaction performed by V. Tona.*

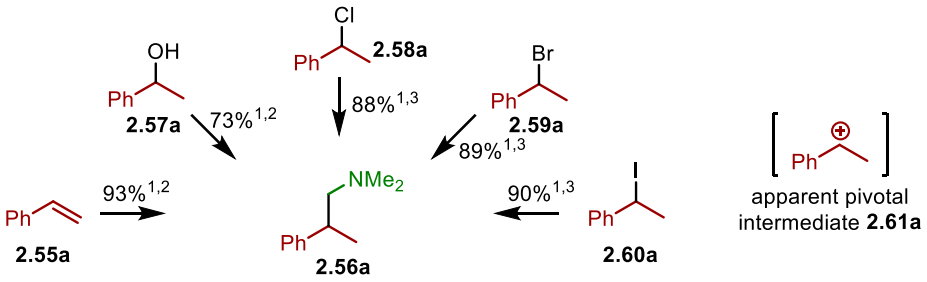
To achieve higher yields, several experiments were carried out investigating different reaction parameters (Table 4). The influence of light and air was deemed negligible (entries 1 and 2), however high reaction temperature (75 °C) was crucial (entry 3). The reaction time could be lowered (entries 4 and 5) with no influence on the yield, and a high loading of **2.13** was important to achieve good yields (entries 6 and 7). Significantly, higher concentration provided a significant improvement in yield (93%, entry 8). Lowering the amount of acid led to a dramatic decrease in the formation of **2.56a** (entries 9 and 10).

*Table 4: Optimisation of the reaction conditions as performed by V. Tona. *Yield determined by quantitative ^{1}H-NMR.*



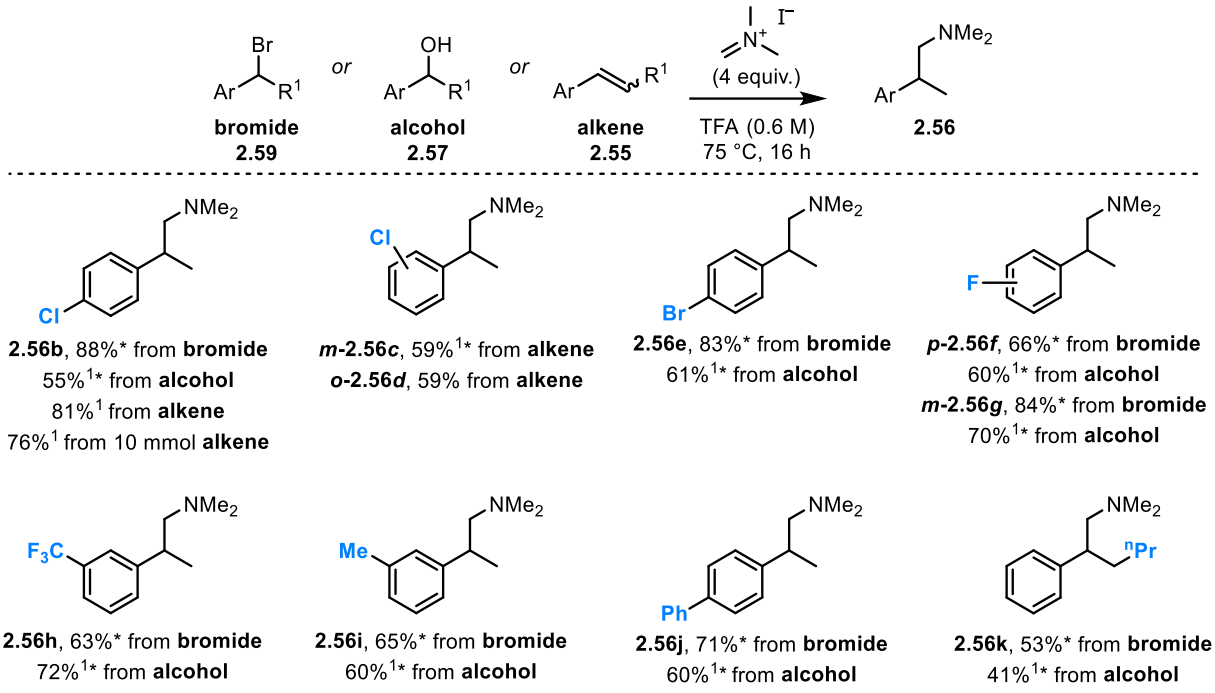
entry	equiv. 2.13	temp (°C)	TFA (M)	time (h)	notes	yield*
1	4	75	0.6	16	under light	76%
2	4	75	0.6	16	under air	73%
3	4	r.t.	0.6	16	-	28%
4	4	75	0.6	1	-	53%
5	4	75	0.6	2	-	75%
6	1	75	0.6	2	-	15%
7	2	75	0.6	2	-	37%
8	**4**	**75**	**1.2**	**2**	**-**	**93%**
9	4	75	4 equiv.	2	-	40%
10	4	75	4 equiv. + DCE (0.6)	2	-	<15%

The need for strongly acidic conditions is in agreement with previously reported results as solvents with lower acidity, like HFIP, deliver the linear product.[43] We presumed the formation of the branched product might involve initial protonation of the alkene leading to a benzylic carbocation **2.61a** as an intermediate. Therefore, we investigated different carbocation precursors such as benzylic alcohol **2.57a** and halides **2.58a**–**2.60a**. Strikingly, all starting materials converge to the α-branched amines in excellent yields (Scheme 23). The presumed *modus operandi* for the different staring materials will be explained later in this chapter.



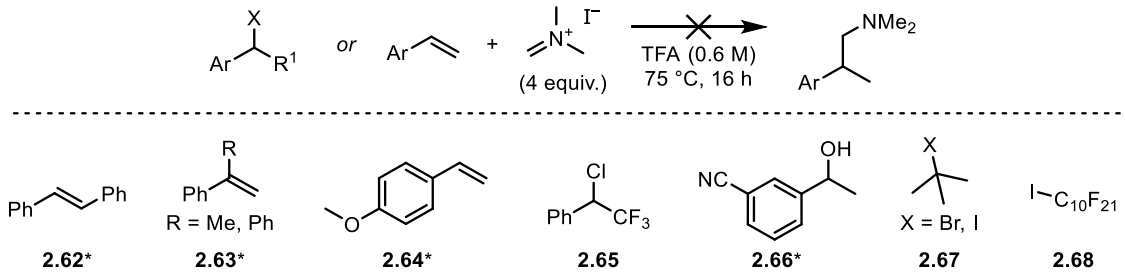
*Scheme 23: Different benzylic cation sources for the synthesis of **2.56a** using 4 equiv. of **2.13** at 75 °C for 16 h. 1) Yield determined by quantitative ^{1}H-NMR. 2) At 1.2 M concentration. 3) At 0.6 M concentration. Reactions performed by V. Tona.*

A scope of different amines revealed broad applicability of the method, starting from either benzylic bromides, alcohols or vinyl arenes (Scheme 24). A scale-up experiment (10 mmol) worked smoothly (**2.56b**) with comparable yield, and different halides on the aromatic system were well tolerated (**2.56c**–**g**). Similarly, alkyl (**2.56h**,**i**) and aryl (**2.56j**) functionality did not interfere with the reaction, and neither did a longer alkyl chain (**2.56k**).



Scheme 24 Scope of different benzylic cation sources. 1) Reaction run at 1.2 M concentration.
** Reaction performed by V. Tona.*

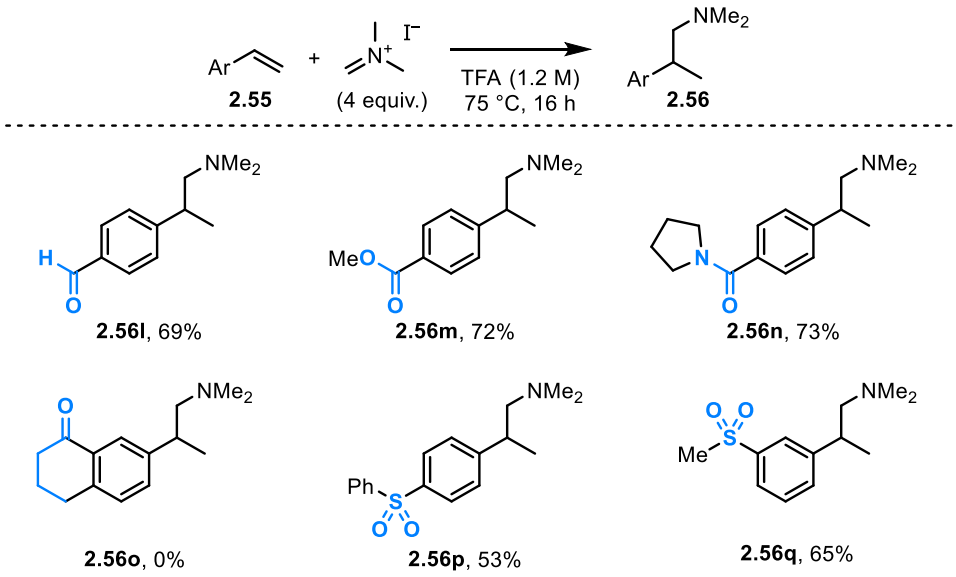
Initial limitations were met with stilbenes (**2.62**), α-substituted styrenes (**2.63**), electron-rich alkenes like **2.64**, electron-deficient trifluoroalkyl chloride **2.65,** and nitrile **2.66** for which no product formation was observed. Unfortunately, alkyl halides (**2.67**, **2.68**) were also unsuccessful under the reaction conditions (Scheme 25).



*Scheme 25: Selected initially found limitation of the described method. * Reaction performed by V. Tona.*

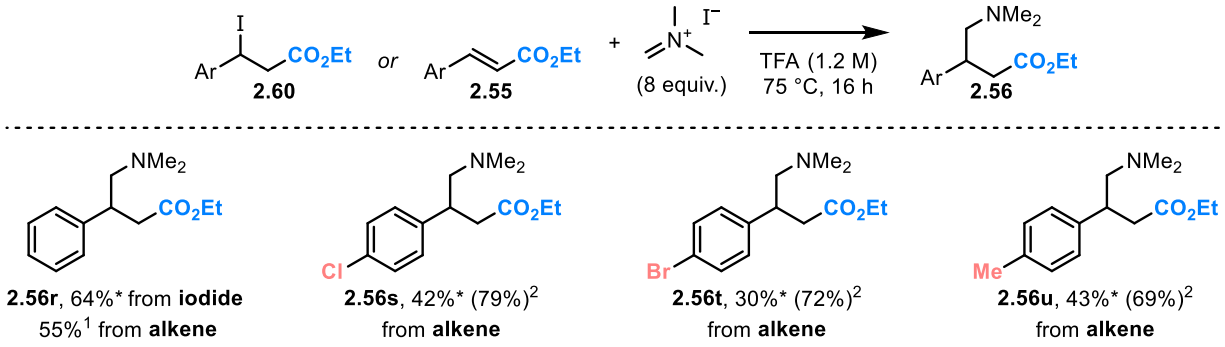
Next, we investigated different electron-withdrawing groups on the aromatic ring of the styrene component (Scheme 26). Carbonyl groups such as aldehydes (**2.56l**), esters (**2.56m**) and pyrrolidine carboxamides (**2.56n**) participated effectively. Notably, reaction with ketone

(**2.56o**) was unsuccessful. In the case of sulfones (**2.56p**,**q**), the desired amines were obtained in good yields.



Scheme 26: A survey of different electron withdrawing groups on the vinyl arene reactants.

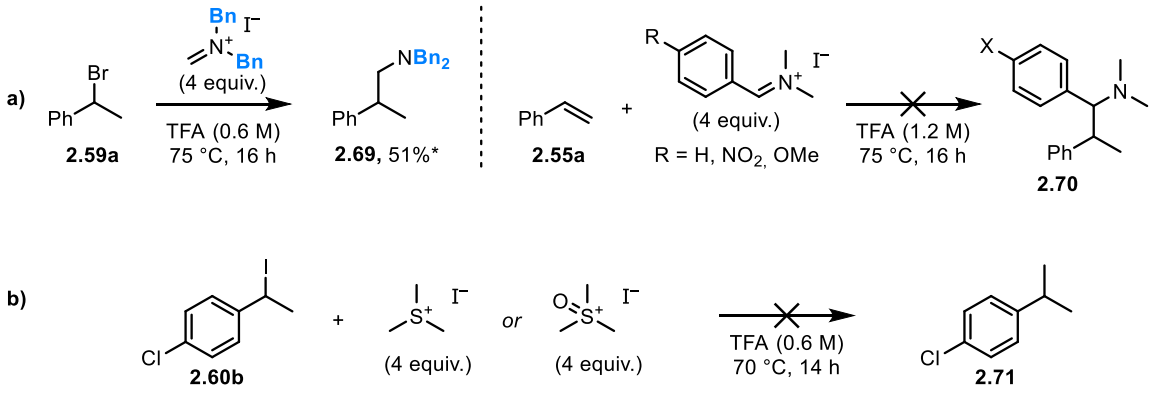
Styrenes bearing esters in the β-position (cinnamates) turned out to be competent substrates for the reaction. They reacted much slower compared to their unsubstituted counterparts, and required 8 equivalents of **2.13** to reach reasonable conversion. Despite these forcing conditions, a large amount of starting material was recovered, as shown in Scheme 27. Nevertheless, several β-aminomethylenated esters could be obtained (**2.56r**–**u**). Exchange of the ester group to a carboxamide, ketone or nitro group was not tolerated under these reaction conditions. The regioselectivity of cinnamates is especially noteworthy since conventional reactivity would lead to the other regioisomer (discussed in more detail in chapter 3).



*Scheme 27: Synthesis of γ-amino esters using with cinnamate precursors. 1) Yield determined by quantitative ^{1}H-NMR. 2) Based on recovered starting material. * Reaction performed by D. Just.*

The reaction with different iminium ions gave mixed results (Scheme 28a). While dibenzylmethylene iminium iodide reacted with a benzyl bromide as desired (**2.69** formed in 51% yield), another three dimethyliminium iodides derived from benzaldehyde derivatives did not deliver the expected amines **2.70** and only the corresponding aldehydes could be identified as reaction products.

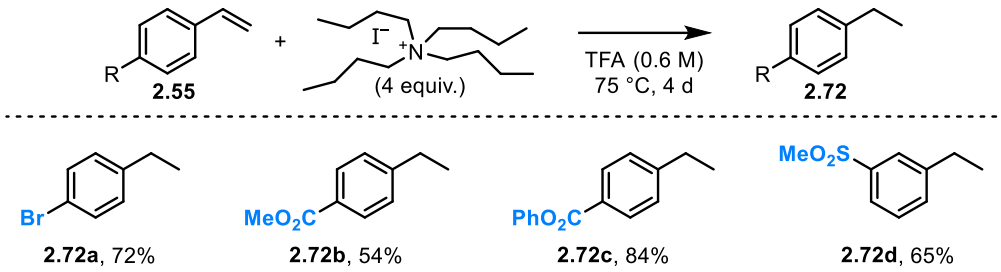
As other organic iodide salts are common reagents in synthesis, we employed sulfonium or sulfoxonium iodide attempting to perform a methylation reaction of benzyl iodide **2.60b**. However, no desired product **2.71** was observed (Scheme 28b).



*Scheme 28: A survey of different a) iminium iodides and b) sulfur-based salts. *Reaction performed by V. Tona.*

A commonly observed side reaction during this study was the formal hydrogenation of the alkene.[12] In the absence of an electrophilic iminium ion, the formation of alkanes took place. Tetrabutylammonium iodide (TBAI) is an excellent, affordable salt to mirror the reducing

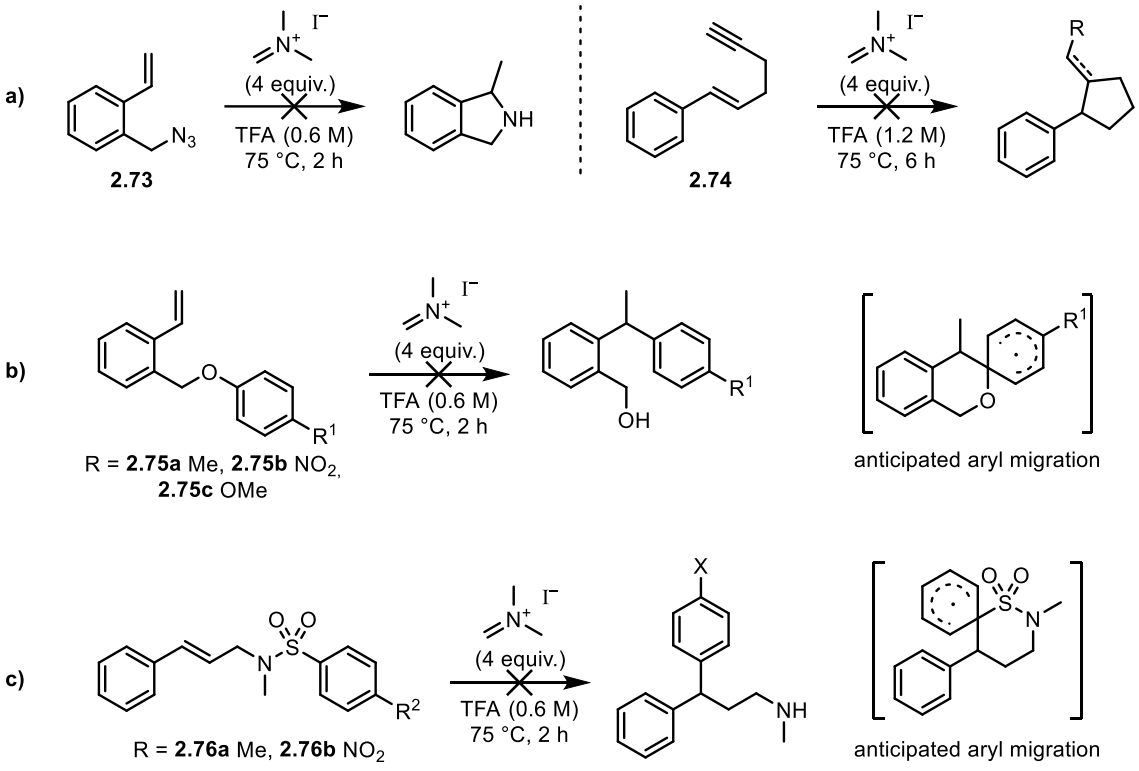
reactivity of Eschenmoser's salt without the electrophilic component. The ammonium cation is inert under the reaction conditions, but mimics other physical aspects of the iminium such as solubility. Using TBAI in TFA, several styrene derivatives could be formally hydrogenated even in the presence of carbonyls (**2.72a**–**d**, Scheme 29). The reaction is rather slow, and requires four days to reach completion. Noteworthy, the corresponding benzylic iodides were observed as intermediates.



Scheme 29: Reduction of vinyl arenes using tetrabutylammonium iodide and TFA.

With the observed reactivity of the iodide-TFA system, we speculated the involvement of benzylic radicals. As reported above, under the reaction conditions a benzylic carbon-iodide bond is formed, which presumably undergoes thermal homolysis to form a stabilised secondary and benzylic radical, as well as an iodine atom. To investigate this idea further, we conducted the reaction of styrenes in the presence of different radical acceptors (Scheme 30). First, compounds (**2.73**, **2.74**) which could potentially cyclise were assessed (Scheme 30a). No cyclisation was observed, which probably stems from the high reactivity of the involved functional groups (azide, alkyne) under the acidic conditions at high temperature.

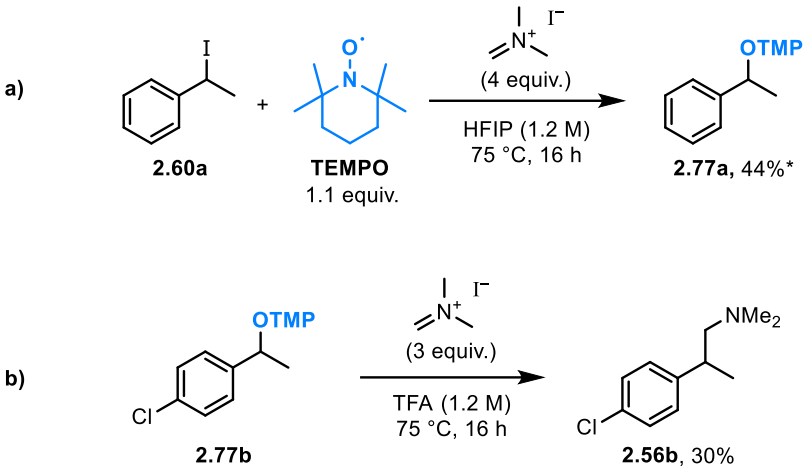
Next, alkenes bearing aryl groups (**2.75a**–**c** and **2.76a**,**b**) with the potential to migrate onto a benzylic radical were tested (Scheme 30b and c). No migration to was observed, which might indicate that the proposed benzyl radical is either more stable compared to the one formed after migration, or reacts through other pathways with lower reaction barriers. The reactions in Scheme 30b led to undefined decomposition, while in Scheme 30c only cleaved sulfonamide was observed after the reaction.



Scheme 30: Attempts towards intermolecular trapping of the putative benzylic radical via a) cyclisation or b) and c) radical aryl migration.

To capture the putative radical intermediate, we attempted to perform the reaction in the presence of TEMPO. However, as TEMPO is known to decompose in acidic media,[49] we decided to conduct the experiment starting from known benzylic iodide intermediate **2.60a** using HFIP as a solvent (Scheme 31a). Under these conditions, TEMPO adduct **2.77a** formed in 44% yield, indicating radical formation during the reaction.

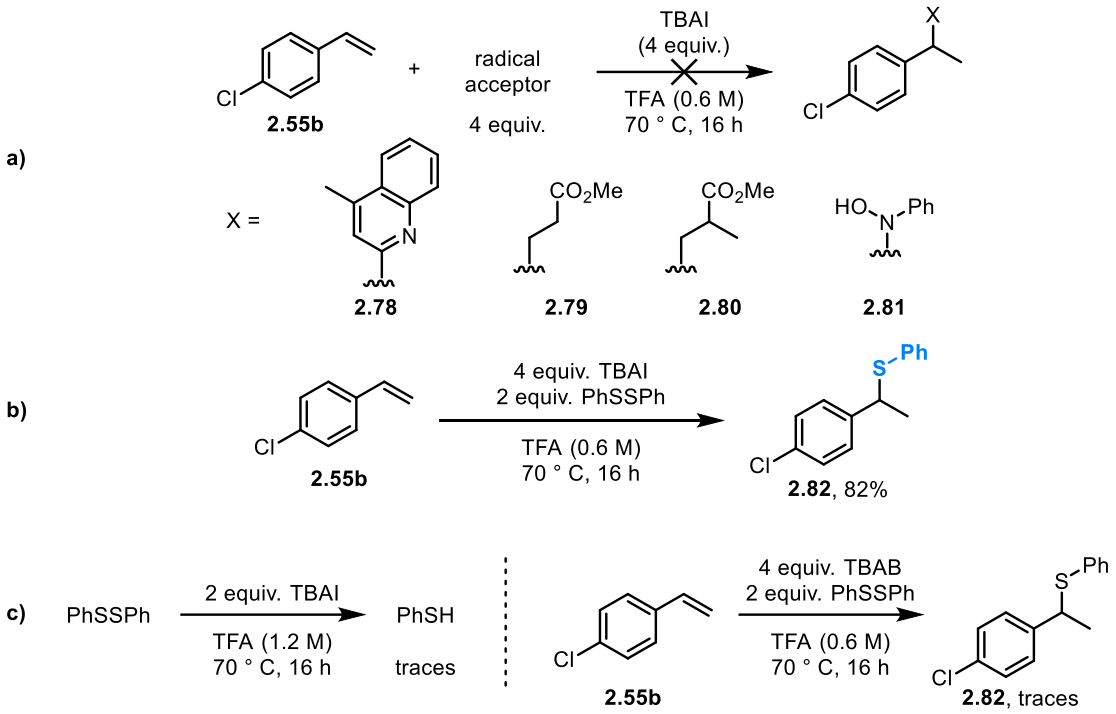
Since adduct formation is reportedly reversible at elevated temperatures,[50] we also conducted the reaction starting from precursor **2.77b** (Scheme 31b). Interestingly, amine **2.56b** was formed albeit in low yield.



Scheme 31: Reactions involving the persistent radical TEMPO clarifying the presence of benzylic radicals.
** Reaction performed by D. Just.*

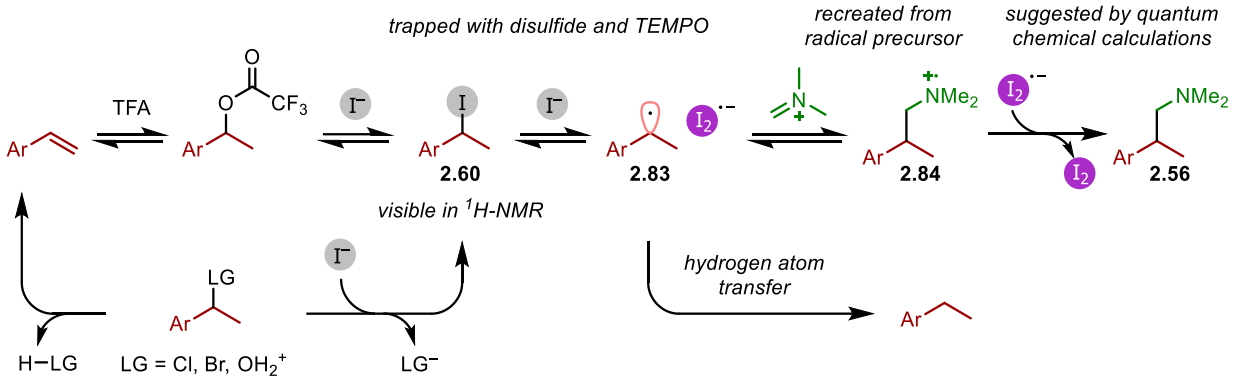
These two experiments not only indicate the formation of a benzylic radical, but also showcase the ability of a radical to form the branched aminomethylenated products using just Eschenmoser's salt.

Using TBAI as a reductant, other intermolecular radical functionalisations were tested (Scheme 32a). The heterocycle lepidine, as well as acrylates or nitroso benzene, did not lead to formation of an isolable adduct (**2.78**–**2.81**). However, diphenyl disulfide reacted successfully to produce benzyl sulfide **2.82** in high yield (Scheme 32b). At this point it was not clear if the product stems from radical trapping or initial disulfide cleavage (reduction) followed by simple nucleophilic attack on the benzylic cation. To exclude this possibility of a polar C–S bond formation, we tested the decomposition of disulfide under the reaction conditions and found no significant reduction to the thiol (Scheme 32c). Furthermore, the comparison with the bromide salt TBAB showed the need for iodide as a reductant. This thioether synthesis highlights the possibility of iodide to act as a general reductant in electrophile-electrophile coupling reactions beyond amine synthesis.



Scheme 32: a) Unsuccessful attempts to trap benzyl radicals. b) Successful trap with disulfide. c) Control reactions of the disulfide trapping indicating a radical mechanism.

Overall, the conducted experiments indicate a benzylic iodide as a common intermediate, irrespective of the starting material employed. Alkenes experience the formal addition of HI, while compounds with leaving groups such as a protonated alcohol or halides undergo substitution by the iodide counterion of Eschenmoser's salt (**2.60**, Scheme 33). During heating, this common intermediate forms benzylic radical **2.83,** with concomitant liberation of an iodine atom. It was calculated that the iodine atom readily combines with an iodide ion to form a diatomic I_2 radical anion with an energy gain of ΔG = -6.7 kcal/mol (computed by G. di Mauro on a M06-2X-D3/def2-TZVP,SMD(TFA) level of theory). Secondary benzyl radical **2.83** then reacts with the iminium cation in the key event of this process to generate aminium radical cation **2.84**. It finally undergoes a single electron transfer from the I_2 radical anion generating neutral I_2 and the desired amine **2.56**.

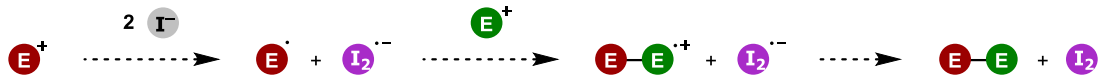


Scheme 33: Proposed mechanism of the investigated reductive aminomethylenation reaction based on experimental observations and computed energies.

2.3 Conclusion and Perspectives

In conclusion, we have developed a method for the reductive synthesis of tertiary amines starting from simple materials such as diazonium salts, styrenes, benzylic halides or alcohols. Iminium iodides served as both the amine source and the reductant. This new type of electrophile-electrophile coupling is enabled through the highly acidic solvent (TFA) and its interplay with the iodide salt. Further investigations to uncover the mechanism have shown that other electrophiles can be coupled, leading to formal hydrogenation of alkenes and to a novel thioether synthesis.

We anticipate that iodide could be used as a highly atom economical reductant (a single atom providing an electron) for other reductive, radical based couplings in the future (Scheme 34). One could also speculate that such reactions can be designed in a way to use the iodine by-product for a downstream oxidation reaction, potentially regenerating iodide ions.



Scheme 34: A general description of a hypothetic electrophile-electrophile coupling enabled by iodide.

Cooperative effects of fluorinated solvents, which are able to form hydrogen bridged complexes, together with iminium iodide salts will be further explored in the next chapter.

2.4 Experimental Data

2.4.1 General Information

Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. Hexafluoro isopropanol (HFIP) was purchased from Fluorochem and trifluoroacetic acid (TFA) from ABCR and used without any particular precaution. All reagents were used as received from commercial suppliers unless otherwise stated. Eschenmoser's salt was purchased from TCI, stored in smaller containers when received (ca. 5 g each) and used as such. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F_{254} with 0.2 mm thickness. Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed on an Isolera 4 or Select medium pressure chromatography system (Biotage) using silica gel 60 (230-400 mesh, Merck and co.) or aluminium oxide 90 active neutral (70-230 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 using a Bruker maXis UHR-TOF (Qq-TOF) spectrometer, using electrospray ionization (ESI). All ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Bruker AV-400, AV-500, AV-600 or AV-700 spectrometer at 300K. 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 (^{13}C-NMR), or DMSO-d_6, defined at δ = 2.50 ppm (^{1}H-NMR) and δ = 39.52 (^{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) 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 visualised are designated as multiplet (m) or broad (br).

2.4.2 Preparation of starting materials and their characterisation

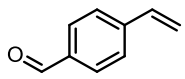
Diazonium salts

All aryl diazonium salts were prepared according to the procedure reported by Shen *et al.*[51] and used directly without any further purification or characterisation. Their synthesis has been previously described in detail in the bachelor thesis of Miloš Vavrík.[52]

General procedure for the synthesis of styrenes

In a vial, aryl bromide (2.35 mmol, 1.00 equiv.), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (543 mg, 3.53 mmol, 1.50 equiv.), $Pd(OAc)_2$ (42.2 mg, 0.188 mmol, 0.08 equiv.), KF (165 mg, 7.05 mmol, 3.00 equiv.) and dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane (XPhos, 134 mg, 0.282 mmol, 0.12 equiv.) were mixed. The mixture was suspended in 5 mL THF and stirred at 40 °C for 70 h. The solvent was removed under reduced pressure and the mixture was purified by flash column chromatography.

2.55l: 4-Vinylbenzaldehyde

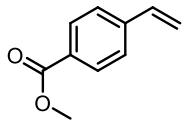


The styrene **2.55l** was synthesised according to the procedure described by Scheidt et al.[53]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 6.78 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.92 (d, *J* = 17.6 Hz, 1H), 5.44 (d, *J* = 10.9 Hz, 1H) ppm.

Experimental Data

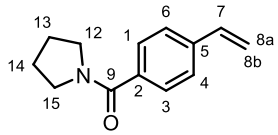
2.55l: Methyl 4-vinylbenzoate



The styrene **2.55l** was synthesised according to the procedure described by Scheidt et al.[54]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.93 (m, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.86 (dd, *J* = 17.6, 0.4 Hz, 1H), 5.43 – 5.31 (m, 1H), 3.91 (s, 3H) ppm.

2.55n: Pyrrolidin-1-yl(4-vinylphenyl)methanone



To 4-vinylbenzoic acid (148 mg, 1 mmol, 1.00 equiv.) was added pyrrolidine (71.1 mg, 1.00 mmol, 1.00 equiv.), Et_3N (101 mg, 1.00 mmol, 1.00 equiv), HOBt (135 mg, 1.00 mmol, 1.00 equiv.) and EDCI (192 mg, 1.00 mmol, 1.00 equiv.) in 5 mL DCM (0.2 M). The reaction was stirred for 16 h, before being diluted with EtOAc and washed sequentially with 1 M HCl (aq.), saturated $NaHCO_3$ (aq.), and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford compound **2.55n** in quantitative (201 mg) yield as a yellow solid.

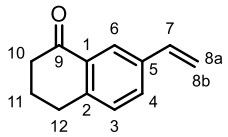
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 2H^{1,3}), 7.42 (d, *J* = 8.3 Hz, 2H^{4,6}), 6.72 (dd, *J* = 17.5, 10.9 Hz, 1H^{7}), 5.79 (d, *J* = 17.5 Hz, 1H^{8b}), 5.30 (d, *J* = 10.9 Hz, 1H^{8a}), 3.64 (t, *J* = 6.9 Hz, 2H^{12}), 3.43 (t, *J* = 6.9 Hz, 2H^{15}), 2.00–1.81 (m, 4H^{13,14}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C^{9}), 139.1 (C^{Ar}), 136.6 (C^{Ar}), 136.3 (CH^{7}), 127.6 (2CH^{Ar}), 126.1 (2CH^{Ar}), 115.2 (CH_2^{8}), 49.7 (CH_2^{12}), 46.3 (CH_2^{15}), 26.5 (CH_2^{13}), 24.5 (CH_2^{14}) ppm.

IR (neat) ν_{max}: 2970, 2873, 1608, 1413, 907, 851, 775, 726 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{15}NNaO^+$) requires 224.1046, found 224.1043.

2.55o: 7-Vinyl-3,4-dihydronaphthalen-1(2H)-one



Was prepared from 7-Bromo-1-tetralone (450 mg, 2 mmol). Purification by flash column chromatography on silica gel (0% to 40% EtOAc in heptane) afforded compound 2.55o in 69% (238 mg) yield as a white solid.

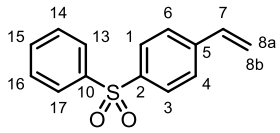
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 1.5 Hz, 1H^{6}), 7.53 (dd, *J* = 7.9, 1.5 Hz, 1H^{4}), 7.22 (d, *J* = 7.9 Hz, 1H^{3}), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H^{7}), 5.80 (d, *J* = 17.6 Hz, 1H^{8b}), 5.28 (d, *J* = 10.9 Hz, 1H^{8a}), 2.96 (t, *J* = 6.0 Hz, 2H^{Al}), 2.66 (t, *J* = 6.3 Hz, 2H^{Al}), 2.18 – 2.09 (m, 2H^{11}) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 198.6 (C^{9}), 144.1 (C^{Ar}), 136.3 (C^{Ar}), 136.0 (CH^{7}), 132.8 (C^{Ar}), 130.9 (CH^{Ar}), 129.2 (CH^{Ar}), 125.0 (CH^{Ar}), 114.7 (CH^{8}), 39.3 (CH_2^{Al}), 29.7 (CH_2^{Al}), 23.4 (CH_2^{Al}) ppm.

IR (neat) ν_{max}: 2938, 2867, 1679, 1605, 1493, 1431, 1348, 1321, 1295, 1266, 1168, 989, 907, 825 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}NaO^+$) requires 195.0780, found 195.0780.

2.55p: 1-(Phenylsulfonyl)-4-vinylbenzene



Following procedure was adapted from Wang *et al*.[55]: To a Schlenk flask was added 1-bromo-4-(phenylsulfonyl)benzene (594 mg, 2.00 mmol, 1.00 equiv.), dicyclohexyl(2',6'-dimethoxy[1,1'-biphenyl]-2-yl)phosphane (SPhos, 82.1 mg, 0.2 mmol, 0.1 equiv.), anhydrous potassium phosphate (1.27 g, 6 mmol, 3.00 equiv.), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (509 µL, 3.00 mmol, 1.50 equiv), 15 mL dioxane and 3 mL H_2O (0.11 M). The mixture was degassed by bubbling argon through the solution. Then, palladium acetate (22.5 mg, 0.1 mmol, 0.05 equiv.) was added and the mixture heated to 80 °C for 14 h. After cooling to room temperature, the mixture was diluted with 10 mL EtOAc and filtered through a short

silica pad. The solution was washed with brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (0% to 40% EtOAc in heptane) afforded compound **2.55p** in 99% (486 mg) yield as a yellow solid.

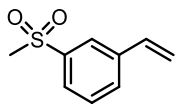
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.87 (m, 4H^{1,3,13,17}), 7.59 – 7.47 (m, 5H$^{4,6,14–16}$), 6.71 (dd, *J* = 17.5, 10.8 Hz, 1H^{7}), 5.85 (d, *J* = 17.5 Hz, 1H^{8cis}), 5.42 (d, *J* = 10.8 Hz, 1H^{8trans}) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 142.5 (C^{Ar}), 141.9 (C^{Ar}), 140.5 (C^{Ar}), 135.4 (CH^{7}), 133.3 (CH^{Ar}), 129.4 ($2CH^{Ar}$), 128.2 ($2CH^{Ar}$), 127.7 ($2CH^{Ar}$), 127.1 ($2CH^{Ar}$), 117.9 (CH_2^{8}) ppm.

IR (neat) ν_{max}: 1594, 1446, 1308, 1156, 1105, 924, 846, 719, 648 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{12}NaO_2S^+$) requires 267.0450, found 267.0447.

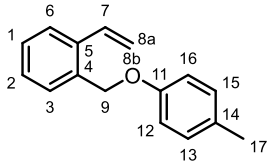
2.55q: 1-(Methylsulfonyl)-3-vinylbenzene



The styrene **2.55q** was synthesised according to the procedure described by Scheidt et al.[53]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.53 (app.t, *J* = 7.8 Hz, 1H), 6.76 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.88 (d, *J* = 17.6 Hz, 1H), 5.42 (d, *J* = 10.9 Hz, 1H), 3.06 (s, 3H) ppm.

2.75a: 1-((*p*-Tolyloxy)methyl)-2-vinylbenzene



Purification by flash column chromatography on silica gel (0% to 5% EtOAc in heptane) afforded compound **2.75a** in 92% (486 mg) yield as a yellow semisolid.

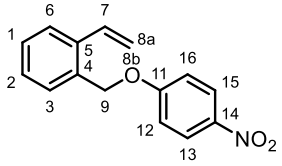
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1H^{Ar}), 7.44 (d, *J* = 7.4 Hz, 1H^{Ar}), 7.35 (t, *J* = 7.5 Hz, 1H^{Ar}), 7.30 (t, *J* = 7.3 Hz, 1H^{Ar}), 7.12 (d, *J* = 8.3 Hz, 2H^{13,15}), 7.01 (dd, *J* = 17.3, 11.1 Hz, 1H^{7}), 6.91 (d, *J* = 8.3 Hz, 2H^{12,16}), 5.71 (d, *J* = 17.3 Hz, 1H^{8b}), 5.35 (d, *J* = 11.1 Hz, 1H^{8a}), 5.08 (s, 2H^{9}), 2.32 (s, 3H^{17}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 156.8 (C^{11}), 137.3 (C^{Ar}), 134.0 (CH^{7}), 130.4 (2C^{Ar}), 130.1 (2CH^{13,15}), 129.3 (CH^{Ar}), 128.6 (CH^{Ar}), 128.0 (CH^{Ar}), 126.2 (CH^{Ar}), 116.7 (CH_2^{8}), 114.8 (2CH^{12,16}), 68.5 (CH_2^{9}), 20.64 (CH_3^{17}) ppm.

IR (neat) ν_{max}: 2922, 1612, 1509, 1379, 1233, 1013, 817, 768 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+Na]^{+}$ ($C_{16}H_{16}NaO^{+}$) requires 247.1093, found 247.1092.

2.75b: 1-((4-Nitrophenoxy)methyl)-2-vinylbenzene



Purification by flash column chromatography on silica gel (0% to 10% EtOAc in heptane) afforded compound **2.x** in 66% (396 mg) yield as a white foam.

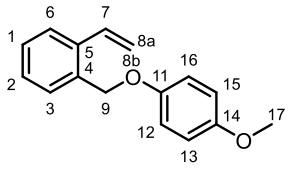
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (dt, *J* = 9.2, 3.4, Hz, 2H^{13,15}), 7.58 (d, *J* = 7.6 Hz, 1H^{Ar}), 7.43–7.36 (m, 2H^{Ar}), 7.32 (td, *J* = 7.5, 1.2 Hz, 1H^{Ar}), 7.04 (dt, *J* = 9.2, 3.4 Hz, 2H^{12,16}), 6.95 (dd, *J* = 17.3, 11.0 Hz, 1H^{7}), 5.72 (dd, *J* = 17.3, 1.1 Hz, 1H^{8b}), 5.39 (dd, *J* = 11.0, 1.1 Hz, 1H^{8a}), 5.20 (s, 2H^{9}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 163.8 (C^{14}), 141.9 (C^{11}), 137.5 (C^{Ar}), 133.6 (CH^{7}), 132.3 (C^{Ar}), 129.3 (CH^{Ar}), 129.2 (CH^{Ar}), 128.2 (CH^{Ar}), 126.5 (CH^{Ar}), 126.1 ($2CH^{13,15}$), 117.5 (CH_2^{8}), 115.0 ($2CH^{12,16}$), 69.1 (CH_2^{9}) ppm.

IR (neat) ν_{max}: 3111, 1591, 1341, 1259, 1112, 990, 846, 752 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{13}NNaO_3^+$) requires 278.0788, found 278.0785.

2.75c: 1-((4-Methoxyphenoxy)methyl)-2-vinylbenzene



Purification by flash column chromatography on silica gel (0% to 10% EtOAc in heptane) afforded compound **2.x** in 86% (488 mg) yield as a white solid.

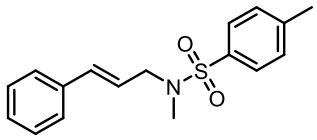
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.6, 1.4 Hz, $1H^{Ar}$), 7.42 (dd, *J* = 7.2, 1.2 Hz, $1H^{Ar}$), 7.36–7.26 (m, $2H^{Ar}$), 7.01 (dd, *J* = 17.3, 11.1 Hz, $1H^{7}$), 6.93 (dt, *J* = 9.2, 3.5 Hz, $2H^{12,16}$), 6.85 (dt, *J* = 9.2, 3.5 Hz, $2H^{13,15}$), 5.70 (dd, *J* = 17.3, 1.3 Hz, $1H^{8b}$), 5.34 (dd, *J* = 11.1, 1.3 Hz, $1H^{8a}$), 5.05 (s, $2H^{9}$), 3.78 (s, $3H^{17}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3 (C^{14}), 153.1 (C^{11}), 137.3 (C^{Ar}), 134.1 (CH^{sp2}), 134.0 (CH^{sp2}), 129.3 (CH^{Ar}), 128.6 (CH^{Ar}), 128.0 (CH^{Ar}), 126.2 (CH^{Ar}), 116.7 (CH_2^{8}), 116.1 ($2CH^{Ar}$), 114.8 ($2CH^{Ar}$), 69.2 (CH_2^{9}), 55.9 (CH_3^{17}) ppm.

IR (neat) ν_{max}: 2930, 1507, 1227, 1039, 824, 769 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{16}NaO_2^+$) requires 263.1043, found 263.1048.

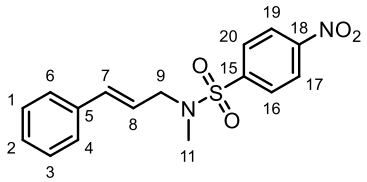
2.76a: *N*-Cinnamyl-*N*,4-dimethylbenzenesulfonamide



The styrene **2.76a** was synthesised according to the procedure described by Yoshida et al.[56]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.29 (m, 4H), 7.28 – 7.22 (m, 1H), 6.53 – 6.42 (m, 1H), 6.06 (dt, *J* = 15.8, 6.7 Hz, 2H), 3.80 (app.dd, *J* = 6.6, 1.0 Hz, 2H), 2.72 (s, 3H), 2.44 (s, 3H) ppm.

2.76b: *N*-Cinnamyl-*N*-methyl-4-nitrobenzenesulfonamide



To *N*-*p*-nosyl-*N*-methyl (519 mg, 2.40 mmol, 1.20 equiv.) amine in 4 mL DMF under argon was added sodium hydride (96 mg, 2.40 mmol, 1.20 equiv.) and the mixture was stirred for 30 min. Then, cinnamyl bromide (394 mg, 2.00 mmol, 1.00 equiv.) was added and the solution was heated to 50 °C for 70 h. The reaction was diluted with EtOAc, washed with NaOH (aq., 1 M), 2 x H_2O, brine and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to afford compound **2.76b** in quantitative (678 mg) yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dt, *J* = 9.2, 2.3 Hz, 2H^{17,19}), 8.01 (dt, *J* = 9.2, 2.3 Hz, 2H^{16,20}), 7.35–7.27 (m, 5H^{1,2,3,4,6}), 6.51 (d, *J* = 15.8, 1H^{7}), 6.04 (dt, *J* = 15.8, 6.7 Hz, 1H^{8}), 3.89 (dd, *J* = 6.7, 1.0 Hz, 2H^{9}), 2.81 (s, 3H^{11}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 150.2 (C^{Ar}), 144.0 (C^{Ar}), 135.9 (C^{Ar}), 135.1 ($2CH^{Ar}$), 128.9 ($2CH^{Ar}$), 128.7 ($2CH^{Ar}$), 128.5 (CH^{sp2}), 126.6 ($2CH^{Ar}$), 124.5 ($2CH^{Ar}$), 122.7 (CH^{sp2}), 52.8 (CH_2^{9}), 34.5 (CH_2^{11}) ppm.

IR (neat) ν_{max}: 2920, 1529, 1349, 1311, 1164, 925, 761, 741, 601 cm^{-1}.

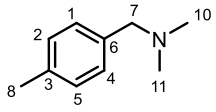
HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{16}N_2NaO_4S^+$) requires 355.0723, found 355.0719.

2.4.3 Products syntheses and characterisation

General Procedure A: Aminomethylation of diazonium salts

To a flame dried Schlenk tube was added the diazonium salt (0.2 mmol unless otherwise stated, 1.00 equiv.) under argon. Then, 0.3 mL (0.66 M) HFIP was added, followed by Eschenmoser's salt (148 mg, 0.8 mmol, 4.00 equiv.). The tube was sealed with a rubber septum and placed in an oil bath preheated to 70 °C. The mixture was stirred at this temperature for 1 h, after which it was allowed to cool to room temperature. DCM (10 mL) was added and the solution was poured into a separation funnel containing 5 mL aqueous NaOH (1 M) and 3 mL aqueous NaS_2O_5 (10%). The funnel was vigorously shaken until the colouration caused by molecular iodine disappeared. The phases were separated and the aqueous solution was extracted three times with 10 mL DCM. The combined organic phases were dried over K_2CO_3 and the solvent was removed under reduced pressure. The crude product was purified by medium pressure chromatography on silica gel using DCM and a stock solution of [DCM:MeOH:NH_4OH (aq. 25%) = 90:10:1], termed DMA-MIX .

2.50b: *N*,*N*-Dimethyl-1-(p-tolyl)methanamine

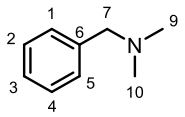


2.50b was prepared according to general procedure **A**. Purification by flash column chromatography on silica gel (20% DMA-MIX in DCM to 100% DMA-MIX) afforded compound **2.50b** in 70% (20.8 mg) yield as a yellow liquid.

The spectroscopic data is in accordance with those reported.[57]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.17 (m, 2H^{1,4}), 7.15 – 7.11 (m, 2H^{2,5}), 3.40 (s, 2H^7), 2.34 (s, 3H^8), 2.24 (s, 6H^{10,11}) ppm.

2.50c: *N*,*N*-Dimethyl-1-phenylmethanamine

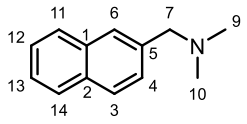


2.50c was prepared according to general procedure **A**. Purification by flash column chromatography on silica gel (10% DMA-MIX to 75% DMA-MIX in DCM) afforded compound **2.50c** in 52% (14.1 mg) yield as a pale-yellow liquid.

The spectroscopic data is in accordance with those reported.[58]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 5H$^{1\text{-}5}$), 3.40 (s, 2H^{7}), 2.21 (s, 6H^{9,10}) ppm.

2.50d: *N*,*N*-Dimethyl-1-(naphthalen-2-yl)methanamine

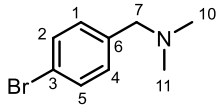


2.50d was prepared according to general procedure **A**. Purification by flash column chromatography on silica gel (0% DMA-MIX to 50% DMA-MIX in DCM) afforded compound **2.50d** in 47% (17.4 mg) yield as a pale-yellow liquid.

The spectroscopic data is in accordance with those reported.[57]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 3H^{Ar}), 7.75 (br s, 1H^{Ar}), 7.51 – 7.44 (m, 3H^{Ar}), 3.64 (s, 2H^{7}), 2.22 (s, 6H^{9,10}) ppm.

2.50e: 1-(4-Chlorophenyl)-*N*,*N*-dimethylmethanamine

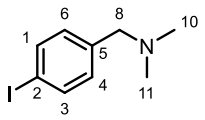


2.50e was prepared according to general procedure **A**. Purification by flash column chromatography on silica gel (20% DMA-MIX in DCM to 100% DMA-MIX) afforded compound **2.50e** in 25% (10.8 mg) yield as a yellow liquid.

The spectroscopic data is in accordance with those reported.[59]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H^{1,4}), 7.20 (t, J = 6.6 Hz, 2H^{2,5}), 3.39 (s, 2H^{7}), 2.23 (s, 6H^{10,11}) ppm.

2.50f: 1-(4-Iodophenyl)-*N*,*N*-Dimethylmethanamine



2.50f was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (0% DMA-MIX to 40% DMA-MIX in DCM) afforded compound **2.50f** in 42% (21.7 mg) yield as a pale-yellow liquid.

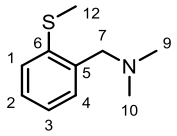
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 2H^{1,3}), 7.08 – 7.04 (m, 2H^{4,6}), 3.36 (s, 2H^{8}), 2.22 (s, 6H^{10,11}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 138.8 (C^{5}), 137.5 (2CH^{1,3}), 131.2 (2CH^{4,6}), 92.5 (C^{2}), 63.9 (CH_2^{8}), 45.5 (2$CH_3^{10,11}$) ppm.

IR (neat) ν_{max}: 3377, 2956, 1661, 1586, 1477, 1406, 1060, 1008, 850, 795, 726 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_9H_{13}IN^+$) requires 262.0087, found 262.0094.

2.50h: *N*,*N*-Dimethyl-1-(2-(methylthio)phenyl)methanamine



2.50h was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (20% DMA-MIX to 70% DMA-MIX in DCM) afforded compound **2.50h** in 43% (15.7 mg) yield as a yellow liquid.

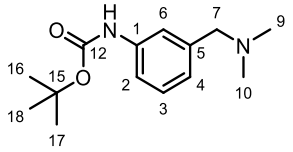
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, $3H^{Ar}$), 7.13 – 7.08 (dt, *J* = 7.2, 1.6 Hz, $1H^{Ar}$), 3.48 (s, $2H^{7}$), 2.46 (s, $3H^{12}$), 2.27 (s, $6H^{9,10}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 138.9 (C^5), 136.8 (C^6), 129.9 (CH^{Ar}), 127.9 (CH^{Ar}), 125.3 (CH^{Ar}), 124.5 (CH^{Ar}), 62.1 (CH_2^7), 45.5 ($2CH_3^{9,10}$), 15.8 (CH_3^{12}) ppm.

IR (neat) ν_{max}: 2939, 2852, 2813, 2761, 1437, 1361, 1251, 1173, 1023, 845, 744 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{10}H_{16}NS^+$) requires 182.0998, found 182.1000.

2.50k: *tert*-Butyl (3-((dimethylamino)methyl)phenyl)carbamate



2.50k was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (10% DMA-MIX to 70% DMA-MIX in DCM) afforded compound **2.50k** in 39% (19.6 mg) yield as a pale-yellow solid.

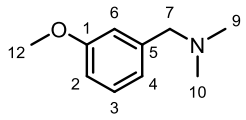
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, $2H^{Ar}$), 7.26 – 7.21 (m, $1H^{Ar}$), 7.01 – 6.97 (m, $1H^{Ar}$), 6.47 (br s, $1H^{NH}$); 3.42 (s, $2H^{7}$), 2.26 (s, $6H^{9,10}$), 1.51 (s, $9H^{16,17,18}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 152.9 (C^{12}), 139.6 (C^{Ar}), 138.6 (C^{Ar}), 129.1 (C^{Ar}), 124.0 (C^{Ar}), 119.4 (C^{Ar}), 117.6 (C^{Ar}), 80.6 (C^{15}), 64.3 (CH_2^7), 45.4 ($2CH_3^{9,10}$), 28.5 ($3CH_3^{16,17,18}$) ppm.

IR (neat) ν_{max}: 2976, 2819, 2777, 1717, 1608, 1542, 1366, 1238, 1155, 1053, 738, 697 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}N_2O_2^+$) requires 251.1754, found 251.1755.

2.50l: 1-(3-Methoxyphenyl)-*N*,*N*-dimethylmethanamine

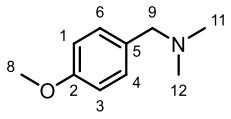


2.50l was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (20% DMA-MIX to 60% DMA-MIX in DCM) afforded compound **2.50l** in 53% (17.4 mg) yield as a pale-yellow liquid.

The spectroscopic data is in accordance with those reported.[57]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.0 Hz, 1H^3), 6.91 – 6.87 (m, 2H^{Ar}), 6.83 – 6.78 (m, 1H^{Ar}), 3.81 (s, 3H^{12}), 3.42 (s, 2H^7), 2.26 (s, 6H^{9,10}) ppm.

2.50m: 1-(4-Methoxyphenyl)-*N*,*N*-dimethylmethanamine

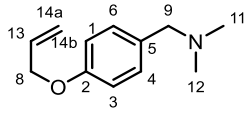


2.50m was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (20% DMA-MIX to 75% DMA-MIX in DCM) afforded compound **2.50m** in 25% (10.8 mg) yield as a pale-yellow liquid.

The spectroscopic data is in accordance with those reported.[57]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (app. dt, *J* = 9.4, 2.8 Hz, 2H^{4,6}), 6.86 (app. dt, *J* = 9.4, 2.8 Hz, 2H^{1,3}), 3.80 (s, 3H^8), 3.37 (s, 2H^9), 2.23 (s, 6H^{11,12}) ppm.

2.50n: 1-(4-(Allyloxy)phenyl)-*N*,*N*-dimethylmethanamine



2.50n was prepared according to the general procedure **A** on a 0.17 mmol scale. Purification by flash column chromatography on silica gel (10% DMA-MIX to 75% DMA-MIX in DCM) afforded compound **2.50n** in 61% (19.7 mg) yield as a pale-yellow liquid.

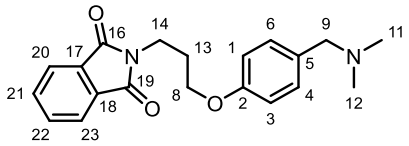
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (app. dt, *J* = 9.5, 2.8 Hz, $2H^{4,6}$), 6.87 (app. dt, *J* = 9.5, 2.8 Hz, $2H^{1,3}$), 6.11 – 6.00 (m, $1H^{13}$), 5.41 (dd, *J* = 17.4, 1.5 Hz, $1H^{14b}$), 5.28 (qd, *J* = 10.5, 1.5 Hz, $1H^{14a}$), 4.53 (dt, *J* = 4.0, 1.4 Hz, $2H^{8}$), 3.36 (s, $2H^{9}$), 2.23 (s, $6H^{11,12}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9 (C^{2}), 133.6 (CH^{13}), 131.2 (C^{5}), 130.4 ($2CH^{4,6}$), 117.7 ($CH_2{}^{14}$), 114.6 ($2CH^{1,3}$), 69.0 ($CH_2{}^{8}$), 63.8 ($CH_2{}^{9}$), 45.3 ($2CH_3{}^{11,12}$) ppm.

IR (neat) ν_{max}: 2939, 2860, 2813, 2768, 1611, 1509, 1457, 1240, 1175, 1023, 927, 853, 819 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{18}NO^+$) requires 192.1383, found 192.1385.

2.50q: 2-(3-(4-((Dimethylamino)methyl)phenoxy)propyl)isoindoline-1,3-dione



2.50q was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (10% DMA-MIX to 75% DMA-MIX in DCM) afforded compound **2.50q** in 51% (34.5 mg) yield as a pale-yellow liquid.

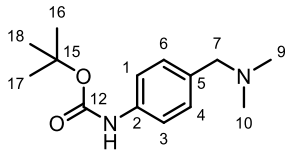
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, $2H^{20,23}$), 7.73 – 7.68 (m, $2H^{21,22}$), 7.16 (app. dt, *J* = 9.5, 2.8, $2H^{4,6}$), 6.86 (app. dt, *J* = 9.5, 2.8 Hz, $2H^{1,3}$), 4.02 (t, *J* = 6.0 Hz, $2H^{14}$), 3.91 (t, *J* = 6.9 Hz, $2H^{8}$), 3.35 (s, $2H^{9}$), 2.22 (s, $6H^{11,12}$), 2.20 – 2.14 (m, $2H^{13}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5 ($2C^{16,19}$), 158.1 (C^{2}), 134.1 ($2CH^{Ar}$), 132.3 ($3CH^{Ar}$), 130.4 ($2CH^{Ar}$), 123.4 ($2CH^{20,23}$), 114.4 ($2CH^{1,3}$), 65.8 (CH_2^{8}), 63.8 (CH_2^{9}), 45.3 ($2CH_3^{11,12}$), 35.7 (CH_2^{14}), 28.5 (CH_2^{13}) ppm.

IR (neat) ν_{max}: 2941, 2816, 2772, 1772, 1708, 1510, 1395, 1240, 1038, 906, 717, 647 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}N_2O_3^+$) requires 339.1703, found 339.1712.

2.50s: *tert*-Butyl (4-((dimethylamino)methyl)phenyl)carbamate



2.50s was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (10% DMA-MIX to 50% DMA-MIX in DCM) afforded compound **2.50s** in 61% (31.3 mg) yield as a pale-yellow solid.

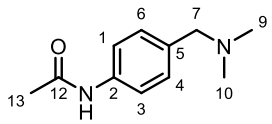
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, $2H^{1,3}$), 7.22 (d, *J* = 8.5 Hz, $2H^{4,6}$), 6.05 (br s, $1H^{NH}$), 3.38 (s, $2H^{7}$), 2.23 (s, $6H^{9,10}$), 1.51 (s, $9H^{16,17,18}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 152.9 (C^{12}), 137.5 (C^{2}), 133.3 (C^{5}), 129.9 ($2CH^{4,6}$), 118.6 ($2CH^{1,3}$), 80.6 (C^{15}), 63.9 (CH_2^{7}), 45.3 ($2CH_3^{9,10}$), 28.5 ($3CH_3^{16,17,18}$) ppm.

IR (neat) ν_{max}: 2976, 2816, 2775, 1700, 1597, 1522, 1410, 1365, 1312, 1235, 1155, 1050, 906, 731 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}N_2O_2^+$) requires 251.1754, found 251.1757.

2.50t: *N*-(4-((Dimethylamino)methyl)phenyl)acetamide



2.50t was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (10% DMA-MIX to 50% DMA-MIX in DCM) afforded compound **2.50t** in 58% (22.3 mg) yield as a pale-yellow oil.

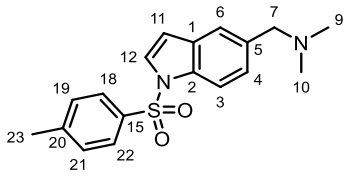
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, $2H^{1,3}$), 7.35 (br s, $1H^{NH}$), 7.24 (d, *J* = 8.4 Hz, $2H^{4,6}$), 3.37 (s, $2H^{7}$), 2.21 (s, $6H^{9,10}$), 2.15 (s, $3H^{13}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4 (C^{12}), 137.0 (C^{2}), 135.1 (C^{5}), 129.8 ($2CH^{4,6}$), 119.9 ($2CH^{1,3}$), 64.0 (CH_2^{7}), 45.4 ($2CH_3^{9,10}$), 24.7 (CH_3^{13}) ppm.

IR (neat) ν_{max}: 3257, 3190, 2942, 2818, 2777, 1665, 1602, 1537, 1513, 1410, 1367, 1314, 1272, 1012, 857, 824 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{11}H_{17}N_2O^+$) requires 193.1335, found 193.1337.

2.50w: *N*,*N*-Dimethyl-1-(1-tosyl-1H-indol-5-yl)methanamine



2.50w was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (10% DMA-MIX to 40% DMA-MIX in DCM) afforded compound **2.50w** in 46% (30.5 mg) yield as a pale-yellow liquid.

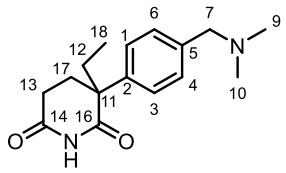
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, $1H^{Ar}$), 7.76 (d, *J* = 8.3 Hz, $2H^{18,22}$), 7.54 (d, *J* = 3.6 Hz, $1H^{Ar}$), 7.45 (br s, $1H^{Ar}$), 7.30 – 7.24 (m, $1H^{Ar}$), 7.21 (d, *J* = 8.0 Hz, $2H^{19,21}$), 6.61 (d, *J* = 3.6 Hz, $1H^{Ar}$), 3.48 (s, $2H^{7}$), 2.33 (s, $3H^{23}$), 2.24 (s, $6H^{9,10}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0 (C^{20}), 135.5 (C^{Ar}), 134.3 (C^{Ar}), 133.8 (C^{15}), 131.0 (C^{Ar}), 130.0 ($2CH^{19,21}$), 127.0 ($2CH^{18,22}$), 126.7 (C^{Ar}), 126.1 (C^{Ar}), 121.9 (C^{Ar}), 113.5 (C^{Ar}), 109.1 (C^{Ar}), 64.4 (CH_2^7), 45.4 ($2CH_3^{9,10}$), 21.7 (CH_3^{23}) ppm.

IR (neat) ν_{max}: 2940, 2815, 2771, 1596, 1456, 1367, 1273, 1170, 1123, 995, 812, 764, 677 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}N_2O_2S^+$) requires 329.1318, found 329.1317.

2.50x: 3-(4-((Dimethylamino)methyl)phenyl)-3-ethylpiperidine-2,6-dione



2.50x was prepared according to the general procedure **A**. Purification by flash column chromatography on silica gel (10% DMA-MIX to 60% DMA-MIX in DCM) afforded compound **2.50x** in 59% (32.5 mg) yield as a pale-yellow solid.

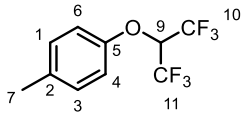
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (br s, $1H^{NH}$), 7.30 (d, *J* = 8.4 Hz, $2H^{1,3}$), 7.21 (app. dt, *J* = 8.4, 2.0 Hz, $2H^{4,6}$), 3.41 (s, $2H^7$), 2.61 – 2.54 (m, $1H^{Al}$), 2.45 – 2.33 (m, $2H^{Al}$), 2.26 – 2.16 (m, $1H^{Al}$), 2.22 (s, $6H^{9,10}$), 2.09 – 2.00 (m, $1H^{Al}$), 1.96 – 1.86 (m, $1H^{Al}$), 0.87 (t, *J* = 7.5 Hz, $3H^{18}$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 175.4 (C^{14}), 172.5 (C^{16}), 138.5 (C^{Ar}), 137.7 (C^{Ar}), 129.8 ($2CH^{4,6}$), 126.2 ($2CH^{1,3}$), 63.8 (CH_2^7), 51.1 (C^{11}), 45.5 ($2CH_3^{9,10}$), 33.0 (CH_2^{Al}), 29.5 (CH_2^{Al}), 27.2 (CH_2^{Al}), 9.2 (CH_3^{18}) ppm.

IR (neat) ν_{max}: 2966, 2817, 2774, 1695, 1457, 1351, 1267, 1190, 1016, 915, 858, 808, 730 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2O_2^+$) requires 275.1754, found 275.1764.

2.52: 1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-4-methylbenzene



4-Methylbenzenediazonium tetrafluoroborate (41.2 mg, 0.20 mmol, 1.00 equiv.) was dissolved in 1 mL HFIP (0.2 M) and the resulting solution was stirred at 70 °C for 1 h. After it was allowed to cool to room temperature, the solution was diluted with 10 mL DCM and washed with 5 mL aqueous NaOH (1 M). The layers were separated and the aqueous phase extracted with 3x10 mL DCM. The combined organic phases were dried over K_2CO_3 and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (pentane) afforded compound **2.52** in 38% (19.7 mg) yield as a colourless liquid.

^{1}H NMR (600 MHz, $CDCl_3$): **δ** 7.15 (d, *J* = 8.7 Hz, $2H^{1,3}$), 6.97 (d, *J* = 8.7 Hz, $2H^{4,6}$), 4.76–4.70 (m, $1H^9$), 2.33 (s, $3H^7$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): **δ** 155.9 (C^5), 134.5 (C^2), 130.6 ($2CH^{Ar}$), 121.1 (q, *J* = 284.3 Hz, $2C^{10,11}$), 117.4 ($2CH^{Ar}$), 76.8 (hep, *J* = 33.2 Hz, CH^9), 20.8 (C^7) ppm.

^{19}F NMR (564 MHz, $CDCl_3$): **δ** = -73.6 ppm.

IR (neat): 1509, 1368, 1289, 1230, 1190, 1100, 893, 818, 685 cm^{-1}.

HRMS (EI): exact mass calculated for $[M]^+$ ($C_{10}H_8F_6O^+$) requires 258.0474, found 258.0474.

Hydroaminomethylation of styrenes and aminomethylation of benzylic halides or alcohols

General Procedure B: Aminomethylation of benzylic halides

An oven-dried vial containing a stirring bar was charged with Eschenmoser's salt (**2.13**) (148 mg, 0.8 mmol, 4.00 equiv.), followed by addition of the benzyl halide (0.2 mmol, 1.00 equiv.) and trifluoroacetic acid (TFA, 0.33 mL, 22.4 equiv., 0.6 M with respect to the halide). After complete addition of TFA, the flask was sealed and placed in an oil bath at 75 °C. The reaction was vigorously stirred at this temperature for 16 h, after which it was allowed to cool to room

temperature. The crude mixture was then treated with aqueous sodium hydroxide (until pH = 12) and extracted with DCM (4 x 15 mL). The combined organic phases were dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with DCM/DMA-MIX 2:1 (DMA-MIX = DCM:MeOH:NH_4OH (aq. 25%) = 90:10:1) to afford the pure product.

General Procedure C: Aminomethylation of benzylic alcohols

An oven-dried vial containing a stirring bar was charged with Eschenmoser's salt (**2.13**) (148 mg, 0.8 mmol, 4.00 equiv.), followed by addition of the benzyl alcohol (0.2 mmol, 1.00 equiv.) and trifluoroacetic acid (TFA, 0.17 mL, 11.2 equiv., 1.2 M with respect to the alcohol). After complete addition of TFA, the flask was sealed and placed in an oil bath at 75 °C. The reaction was vigorously stirred at this temperature for 12 h, after which it was allowed to cool to room temperature. The crude mixture was then treated with aqueous sodium hydroxide (until pH = 12) and extracted with DCM (4 x 15 mL). The combined organic phases were dried over anhydrous K_2CO_3, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with DCM/DMA-MIX 2:1 (DMA-MIX = DCM:MeOH:NH_4OH (aq. 25%) = 90:10:1) to afford the pure product.

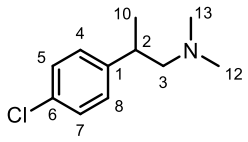
General Procedure D: Hydroaminomethylation of styrenes

An oven-dried vial containing a stirring bar was charged with Eschenmoser's salt (**2.13**) (148 mg, 0.8 mmol, 4.00 equiv.). After this, trifluoroacetic acid (TFA, 0.33 mL, 22.4 equiv., 0.6 M with respect to the alkene) was added, followed by the alkene (0.2 mmol, 1.00 equiv.) in one portion. The flask was sealed and placed in an oil bath at 75 °C. The reaction was vigorously stirred at this temperature for 16 h, after which it was allowed to cool to room temperature. The crude mixture was then treated with aqueous sodium hydroxide (until pH = 12) and extracted with DCM (4 x 15 mL). The combined organic phases were dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with DCM /DMA-MIX 2:1 (DMA-MIX = DCM:MeOH:NH_4OH (aq. 25%) = 90:10:1) to afford the pure product.

General Prodecure E: Hydroaminomethylation of cinnamates

An oven-dried vial containing a stirring bar was charged with Eschenmoser's salt (296 mg, 1.6 mmol, 8.00 equiv.). The ethyl cinnamate (0.2 mmol, unless stated otherwise, 1.00 equiv.) was then added, followed by trifluoroacetic acid (0.17 mL, 11.2 equiv., 1.2 M with respect to the alkene). After complete addition of TFA, the flask was sealed and placed in pre-heated oil bath and vigorously stirred at 75 °C for 16 h. Upon completion, the mixture was allowed to cool to room temperature and diluted with DCM. The mixture was then washed with 1 M aqueous sodium hydroxide (15 mL) and the aqueous phase was extracted with dichloromethane (4 x 15 mL). The combined organic phases were dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (DCM/DMA-MIX 1:0 to 2:1 gradient; DMA-MIX = DCM:MeOH:NH_4OH (aq. 25%) = 90:10:1) to afford the β-substituted γ-aminoacid ester.

2.56b: 2-(4-Chlorophenyl)-*N,N*-dimethylpropan-1-amine



4.2 was prepared according to general procedures **B**, **C**, and **D** using bromide **2.59b**, alcohol **2.57b**, and styrene **2.55b** (at 1.2 M concentration), respectively. Purification by flash column chromatography on silica gel (10% DMA-MIX to 75% DMA-MIX in DCM, Rf = 0.23 in 40% DMA-MIX) afforded compound **4.2** in 88% (35 mg, procedure **B**), 52% (20.5 mg, procedure **C**), and 76% (30 mg, procedure **D**; 81%, 1.60 g on a 10 mmol scale) yields as a yellow liquid.

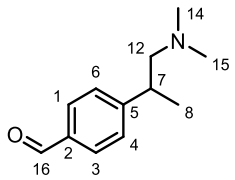
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H^{5,7}), 7.15 – 7.13 (m, 2H^{4,8}), 2.92 – 2.83 (m, 1H^3), 2.41 (app. dd, *J* = 12.2, 7.3 Hz, 1H^2), 2.37 – 2.32 (m, 1H^3), 2.21 (s, 6H^{12,13}), 1.23 (d, *J* = 6.9 Hz, 3H^{10}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (C^{Ar}), 131.9 (C^{Ar}), 128.7 (2CH^{Ar}), 128.6 (2CH^{Ar}), 67.5 (CH_2^3), 46.0 ($2CH_3^{12,13}$), 37.7 (CH^2), 20.4 (CH_3^{10}) ppm.

IR (neat) ν_{max}: 2928, 2816, 2766, 1492, 1459, 1092, 1035, 1012, 855, 820 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{11}H_{17}NCl$) requires 198.1044, found 198.1044.

2.56l: 4-(1-(Dimethylamino)propan-2-yl)benzaldehyde



2.56l was prepared according to general procedure **D** using styrene **2.55l** at 1.2 M concentration. Purification by flash column chromatography on silica gel (0% DMA-MIX to 50% DMA-MIX in DCM, Rf = 0.20 in 50% DMA-MIX) afforded compound **2.56l** in 69% (26.3 mg) yield as a pale-yellow liquid.

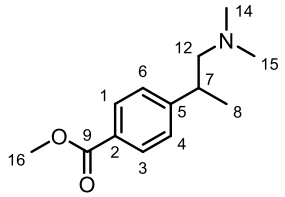
^{1}H NMR (400 MHz, $CDCl_3$): **δ** 9.97 (s, 1H^{16}), 7.82 (d, *J* = 8.1 Hz, 2H^{1,3}), 7.37 (d, *J* = 8.1 Hz, 2H^{4,6}), 3.06 – 2.95 (m, 1H^{7}), 2.50 (dd, *J* = 12.2, 7.6 Hz, 1H^{12}), 2.40 (dd, *J* = 12.2, 7.6 Hz, 1H^{12}), 2.22 (s, 6H^{14,15}), 1.27 (d, *J* = 6.9 Hz, 3H^{8}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.1 (C^{16}), 153.7 (C^{2}), 135.0 (C^{5}), 130.2 (2CH^{Ar}), 128.0 (2CH^{Ar}), 67.1 (CH_2^{12}), 46.0 ($2CH_3$^{14,15}), 38.6 (CH^{7}), 20.3 (CH_3^{8}) ppm.

IR (neat) ν_{max}: 2963, 2940, 2817, 2766, 1699, 1605, 1458, 1306, 1212, 1169, 1036, 841, 825 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{18}NO^+$) requires 192.1383, found 192.1384.

2.56m: Methyl 4-(1-(dimethylamino)propan-2-yl)benzoate



2.56m was prepared according to general procedure **D** using styrene **2.55m** at 1.2 M concentration. Purification by flash column chromatography on silica gel (0% DMA-MIX to 50% DMA-MIX in DCM, Rf = 0.20 in 50% DMA-MIX) afforded compound **2.56m** in 72% (32.0 mg) yield as a pale-yellow liquid.

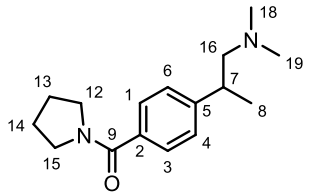
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 2H^{1,3}), 7.27 (d, *J* = 8.3 Hz, 2H^{4,6}), 3.89 (s, 3H^{16}), 3.03 – 2.89 (m, 1H^7), 2.50–2.33 (m, 2H^{12}), 2.21 (s, 6H^{14,15}), 1.26 (d, *J* = 6.9 Hz, 3H^8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C^9), 151.8 (C^2), 130.0 ($2CH^{Ar}$), 128.2 (C^5), 127.3 ($2CH^{Ar}$), 67.3 (CH_2^{12}), 52.1 (CH_3^{16}), 46.0 ($2CH_3^{14,15}$), 38.4 (CH^7), 20.2 (CH_3^8) ppm.

IR (neat) ν_{max}: 2950, 2768, 1721, 1610, 1435, 1277, 1181, 1111, 1016, 773, 707 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{20}NO_2^+$) requires 222.1489, found 222.1490.

2.56n: (4-(1-(Dimethylamino)propan-2-yl)phenyl)(pyrrolidin-1-yl)methanone



2.56n was prepared according to general procedure **D** using styrene **2.55n** at 1.2 M concentration. Purification by flash column chromatography on silica gel (0% DMA-MIX to 50% DMA-MIX in DCM, Rf = 0.20 in 50% DMA-MIX) afforded compound **2.56n** in 73% (37.9 mg) yield as a pale-yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 2H^{1,3}), 7.21 (d, *J* = 8.1 Hz, 2H^{4,6}), 3.63 (t, *J* = 6.8 Hz, 2H^{12}), 3.45 (t, *J* = 6.8 Hz, 2H^{15}), 2.97–2.85 (m, 1H^7), 2.44–2.32 (m, 2H^{16}), 2.21 (s, 6H^{18,19}), 2.01–1.78 (m, 4H^{13,14}), 1.24 (d, *J* = 6.9 Hz, 3H^8) ppm.

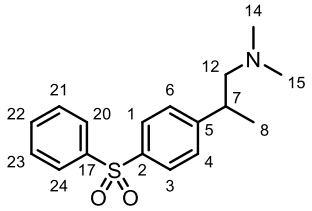
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C^9), 148.3 (C^2), 135.2 (C^5), 127.5 ($2CH^{Ar}$), 127.1 ($2CH^{Ar}$), 67.5 (CH_2^{16}), 49.8 (CH_2^{12}), 46.3 (CH_2^{15}), 46.0 ($2CH_3^{18,19}$), 38.1 (CH^7), 26.6 (CH_2^{13}), 24.6 (CH_2^{14}), 20.2 (CH_3^8) ppm.

IR (neat) ν_{max}: 2966, 2872, 2765, 1619, 1420, 1033, 841, 766 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{16}H_{25}N_2O^+$) requires 261.1961, found 261.1961.

Experimental Data

2.56p: *N*,*N*-Dimethyl-2-(4-(phenylsulfonyl)phenyl)propan-1-amine



2.56p was prepared according to general procedure **D** using styrene **2.55p** at 1.2 M concentration. Purification by flash column chromatography on silica gel (0% DMA-MIX to 50% DMA-MIX in DCM, Rf = 0.20 in 50% DMA) afforded compound **2.56p** in 53% (32.0 mg) yield as a pale-yellow liquid.

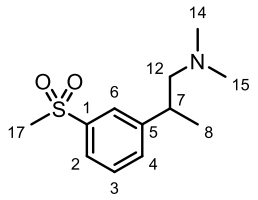
^{1}H NMR (400 MHz, $CDCl_3$): **δ** 7.97 – 7.92 (m, 2H^{20,24}), 7.86 (d, *J* = 8.4 Hz, 2H^{1,3}), 7.59 – 7.46 (m, 3H$^{21–23}$), 7.33 (d, *J* = 8.4 Hz, 2H^{4,6}), 3.01 – 2.89 (m, 1H^{7}), 2.46 (dd, *J* = 12.3, 7.8 Hz, 1H^{12}), 2.33 (dd, *J* = 12.3, 7.8 Hz, 1H^{12}), 2.19 (s, 6H^{14,15}), 1.21 (d, *J* = 6.9 Hz, 3H^{8}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3 (C^{Ar}), 142.0 (C^{Ar}), 139.4 (C^{Ar}), 133.2 (CH^{22}), 129.4 ($2CH^{Ar}$), 128.2 ($2CH^{Ar}$), 128.1 ($2CH^{Ar}$), 127.8 ($2CH^{Ar}$), 66.9 ($CH_2{}^{12}$), 46.0 ($2CH_3{}^{14,15}$), 38.3 (CH^{7}), 20.4 ($CH_3{}^{8}$) ppm.

IR (neat) ν_{max}: 1596, 1446, 1307, 1155, 1107, 717, 688, 589 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}NO_2S^+$) requires 304.1366, found 304.1369.

2.56q: *N*,*N*-Dimethyl-2-(3-(methylsulfonyl)phenyl)propan-1-amine



2.56q was prepared according to general procedure **D** using styrene **2.55q** at 1.2 M concentration. Purification by flash column chromatography on silica gel (0% DMA-MIX to 50% DMA-MIX in DCM, Rf = 0.20 in 50% DMA) afforded compound **2.56q** in 65% (31.2 mg) yield as a pale-yellow liquid.

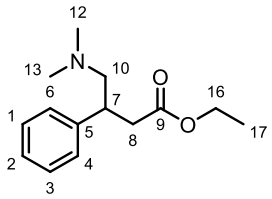
^{1}H NMR (400 MHz, $CDCl_3$): **δ** 7.81 – 7.73 (m, 2H^{Ar}), 7.53 – 7.47 (m, 2H^{Ar}), 3.06 (s, 3H^{17}), 3.05 – 2.87 (m, 1H^{7}), 2.52 – 2.36 (m, 2H^{12}), 2.23 (s, 6H^{14,15}), 1.28 (d, *J* = 6.9 Hz, 3H^{8}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1 (C^{Ar}), 140.7 (C^{Ar}), 132.7 (CH^{Ar}), 129.6 (CH^{Ar}), 126.1 (CH^{Ar}), 125.3 (CH^{Ar}), 67.0 (CH_2^{12}), 45.9 ($2CH_3^{14,15}$), 44.7 (CH_3^{17}), 38.2 (CH^{7}), 20.3 (CH_3^{8}) ppm.

IR (neat) ν_{max}: 2860, 2817, 2767, 1460, 1297, 1141, 1088, 1033, 958, 756, 696 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{20}NO_2S^+$) requires 242.1209, found 242.1211.

2.56r: Ethyl 4-(dimethylamino)-3-phenylbutanoate



2.56r was prepared according to general procedures **B** and **E** using iodide **2.60r** with 8 equiv. of **1** at 1.2 M concentration on 0.15 mmol scale and cinnamate **2.55r**, respectively. Purification by flash column chromatography on silica gel (0% DMA-MIX to 80% DMA-MIX in DCM) afforded compound **2.56r** in 64% (22.5 mg, procedure **B**) and 55% (NMR, procedure **E**) yields as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H^{Ar}), 7.23 – 7.17 (m, 3H^{Ar}), 4.09 – 3.93 (m, 2H^{16}), 3.39 – 3.27 (m, 1H^{7}), 2.82, (dd, *J* = 15.4, 6.2 Hz, 1H^{8}), 2.56 – 2.34 (m, 3H^{8,10}), 2.23 (s, 6H^{12,13}), 1.13 (t, *J* = 7.1 Hz, 3H^{17}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8 (C^{9}), 143.0 (C^{5}), 128.6 (2CH^{Ar}), 127.6 (2CH^{Ar}), 126.8 (CH^{2}), 65.7 (CH_2^{10}), 60.3 (CH_2^{16}), 45.9 ($2CH_3^{12,13}$), 40.6 (CH^{7}), 39.6 (CH_2^{8}), 14.3 (CH_3^{17}) ppm.

IR (neat) ν_{max}: 2941, 2767, 1729, 1455, 1371, 1263, 1181, 1138, 1026, 855, 759, 699 cm^{-1}.

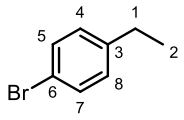
HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{22}NO_2^+$) requires 236.1645, found 236.1643.

2.4.4 Reduction of styrenes by tetrabutylammonium iodide

Procedure F: Formal hydrogenation of styrenes

Styrene (0.300 mmol, 1.00 equiv.) and TBAI (443 mg, 1.20 mmol, 4.00 equiv.) were added to an oven-dried vial containing a magnetic stirrer bar. Then, 0.50 mL TFA (0.60 M) was added, and the solution was stirred in a preheated oil bath at 75 °C for 4 days. Upon completion, the reaction was allowed to cool to room temperature and was diluted with Et_2O and washed with sat. $NaHCO_3$ (aq.) solution. The organic phase was dried over $MgSO_4$, and the solvents were removed under reduced pressure to give the crude product which was purified by flash column chromatography on silica gel.

2.72a: 1-Bromo-4-ethylbenzene

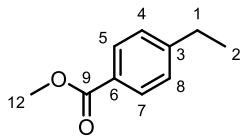


2.72a was prepared according to general procedure **F** using styrene **2.55e**. The product was purified via column chromatography on silica gel (pentane) to afford compound **2.72a** in 72% (40.0 mg) yield as a colourless oil.

The spectroscopic data is in accordance with the reported one.[60]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 2H^{5,7}), 7.07 (d, *J* = 8.3 Hz, 2H^{4,8}), 2.60 (q, *J* = 7.6 Hz, 2H^1), 1.22 (t, *J* = 7.6 Hz, 3H^2) ppm.

2.72b: Methyl 4-ethylbenzoate

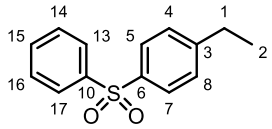


2.72b was prepared according to general procedure **F** using styrene **2.55m**. The product was purified via column chromatography on silica gel (0–10% EtOAc in heptane) to afford a compound **2.72b** in 54% (26.4 mg) yield as a colorless oil.

The spectroscopic data is in accordance with the reported one.[61]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 2H^{5,7}), 7.26 (d, *J* = 8.2 Hz, 2H^{4,8}), 3.90 (s, 3H^{12}), 2.70 (q, *J* = 7.6 Hz, 2H^{1}), 1.25 (t, *J* = 7.6 Hz, 3H^{2}) ppm.

2.72c: 1-Ethyl-4-(phenylsulfonyl)benzene

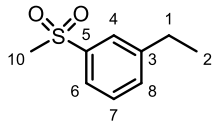


2.72c was prepared according to general procedure **F** using styrene **2.55p**. The product was purified via column chromatography on silica gel (0–20% EtOAc in heptane) to afford compound **2.72c** in 84% (62.3 mg) yield as a colourless oil.

The spectroscopic data is in accordance with the reported one.[62]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H^{Ar}), 7.88 – 7.81 (m, 2H^{Ar}), 7.58 – 7.45 (m, 3H^{Ar}), 7.32 (d, *J* = 8.5 Hz, 2H^{4,8}), 2.69 (q, *J* = 7.6 Hz, 2H^{1}), 1.23 (t, *J* = 7.6 Hz, 3H^{2}) ppm.

2.72d: 1-Ethyl-3-(methylsulfonyl)benzene



2.72d was prepared according to general procedure **F** using styrene **2.55q**. The product was purified via column chromatography on silica gel (0–30% EtOAc in heptane) to afford compound **2.72d** in 65% (35.7 mg) as a colourless oil.

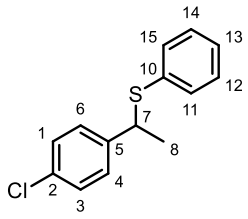
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 2H^{4,6}), 7.51 – 7.44 (m, 2H^{7,8}), 3.05 (s, 3H^{10}), 2.75 (q, *J* = 7.6 Hz, 2H^{1}), 1.28 (q, *J* = 7.6 Hz, 3H^{2}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 146.1 (C^{Ar}), 140.7 (C^{Ar}), 133.5 (CH^{Ar}), 129.5 (CH^{Ar}), 126.7 (CH^{Ar}), 124.8 (CH^{Ar}), 44.7 (CH_3^{10}), 28.8 (CH_2^{1}), 15.4 (CH_3^{2}) ppm.

IR (neat) ν_{max}: 2967, 2929, 1295, 1139, 956, 752, 691, 533 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_9H_{12}NaO_2S^+$) requires 207.0450, found 207.0442.

2.82: (1-(4-Chlorophenyl)ethyl)(phenyl)sulfane



Diphenyl disulfide (87.3 mg, 0.4 mmol, 2.00 equiv.) and TBAI (295 mg, 0.8 mmol, 4.00 equiv.) were added to an oven-dried vial containing a magnetic stirrer bar. Then, 0.33 mL TFA (0.6 M) was added followed by styrene **2.55b** (28.6 mg, 0.2 mmol, 1.00 equiv.), and the solution was stirred in a preheated oil bath at 70 °C for 16 h. Upon completion, the reaction was allowed to cool to room temperature and was diluted with Et_2O and washed with sat. $NaHCO_3$ (aq.) solution. The organic phase was dried over $MgSO_4$, and the solvents were removed under reduced pressure. Purification by flash column chromatography on silica gel (heptane) afforded compound **2.82** in 82% (41.0 mg) yield as a white solid.

The spectroscopic data is in accordance with the reported one.[63]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.18 (m, $9H^{Ar}$), 4.29 (q, *J* = 7.0 Hz, $1H^7$), 1.60 (d, *J* = 7.0 Hz, $3H^8$) ppm.

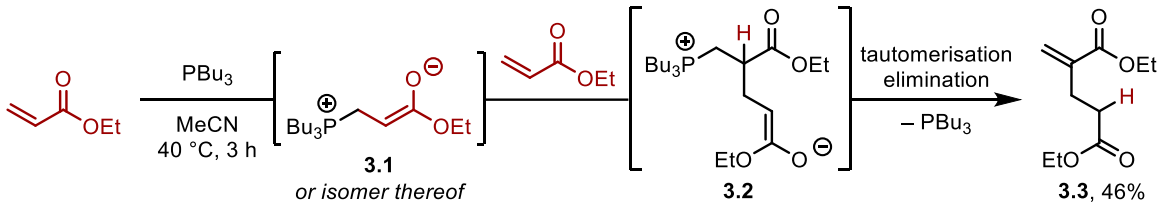
3 Direct Aminomethylenation of Electron-Deficient alkenes Enabled by Counterion-Solvent Interplay

3.1 Introduction

The interplay of Eschenmoser's salt with polar solvents allows for direct C–C coupling with electron deficient alkenes. This reactivity resembles the heavily studied *aza*-Morita–Baylis–Hillman reaction, however, does not require any additives like the usual Lewis base catalysts. This discovery and an in-depth study of the reaction will be described in this chapter.[64]

3.1.1 *aza*-Morita–Baylis–Hillman Reaction

The Morita–Baylis–Hillman (MBH) reaction is formally an aldol reaction between an α,β-unsaturated carbonyl and an aldehyde, catalysed by a Lewis base. Its conceptually simpler vinylogous version, the dimerisation of two α,β-unsaturated carbonyls, is commonly referred to as the Rauhut–Currier reaction (Scheme 35).[65] Generally, electron deficient alkenes can react with tributyl phosphine to form betaine **3.1**. This reactive intermediate can then attack a second equivalent of alkene generating intermediate **3.2**. Subsequent elimination affords product **3.3** and releases the catalyst.

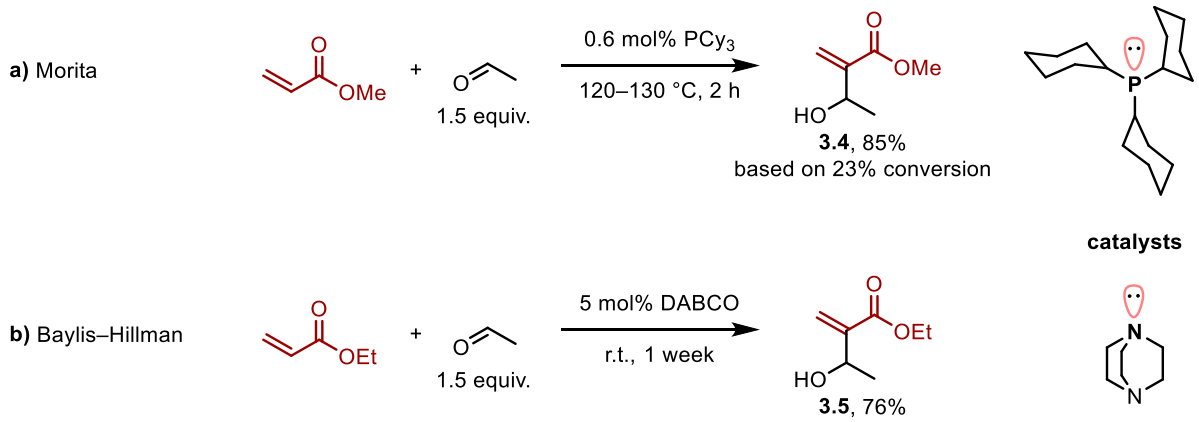


Scheme 35: The tributyl phosphine catalysed dimerization process of ethyl acrylate as reported by Rauhut and Currier.

The mechanistic details of this reaction have been investigated in detail over the last decades. For example, the phosphine/alkene adduct has been computationally studied to exist as a

mixture of several isomers including a closed five-membered oxaphosphole derivative.[66] The population of the different conformers or double bond isomers presumably highly depends on the starting alkene, Lewis base, and solvent.

A similar oxaphosphole intermediate was proposed by Morita *et al.* in a slightly different context.[67] If the second molecule of acrylate in the Rauhut–Currier dimerisation is exchanged with an aldehyde, allyl alcohols are formed instead and the reaction is termed Morita–Baylis–Hillman reaction. The name is derived from the two research groups (Morita[67] and Baylis/Hillman[68]) who independently described the reaction, in 1968 and 1970 respectively (Scheme 36).[69]

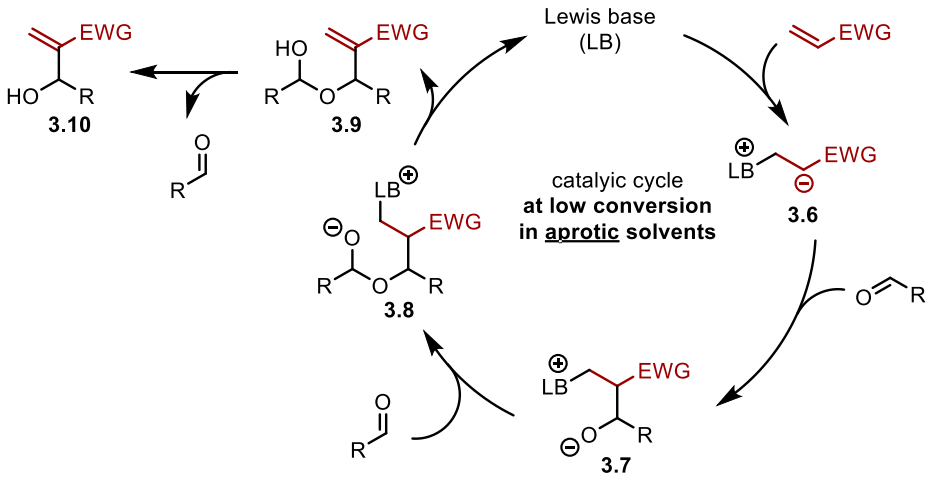


Scheme 36: The synthesis of allyl alcohols as described with a) a phosphine catalyst by Morita et al. or b) an amine catalyst by Baylis and Hillman. Cy = cyclohexyl; DABCO = diazabicyclo-[2,2,2]-octane

Morita used a phosphine catalyst similar to the reaction reported by Rauhut and Currier while Baylis and Hillman employed the highly nucleophilic bridgehead amine diazabicyclo-[2,2,2]-octane (DABCO). Immediately apparent is the long reaction time needed to achieve high conversion under neat conditions. Morita's reaction resulted in only 23% conversion after two hours (**3.4**) whereas Baylis and Hillman's required one week to complete (**3.5**).

The mechanism has been extensively studied and is believed to change in presence or absence of protic solvents or additives. Aggarwal *et al.* have conducted quantum chemical computations, with the conclusion that the final proton transfer step is rate-determining.[70] If it would happen intramolecularly, this process would involve a high energy four-membered transition state which is not reachable at the reaction temperatures. Therefore, the proton

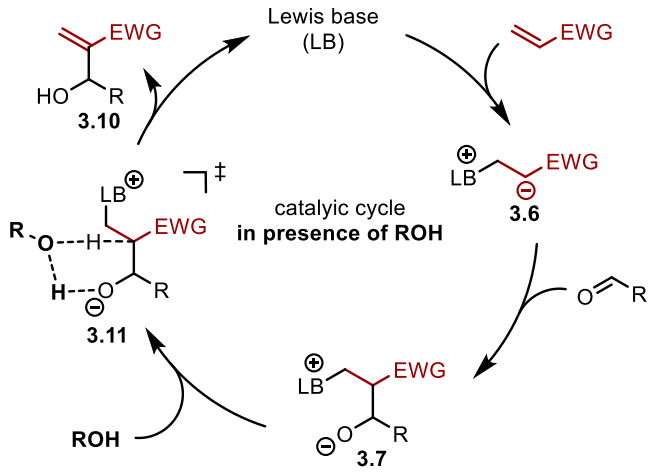
transfer must either be catalysed by an alcoholic additive/solvent or proceed through another mechanism. The simple additive-free process in aprotic solvents is shown in Scheme 37. After formation of a Lewis base/Michael acceptor adduct **3.6**, an aldol-like process occurs with the employed aldehyde to generate alkoxide **3.7**. At this stage, in absence of any species containing an OH moiety, a second molecule of aldehyde reacts to form hemiacetalate **3.8**. This intermediate undergoes an intramolecular proton transfer via a six-membered transition state liberating the Lewis base through elimination. Hemiacetal **3.9** further decomposes to product **3.10** and aldehyde.



Scheme 37: Proposed reaction mechanism relying on a second aldehyde equivalent to aid in the proton transfer step.

The dependence of the reaction rate was second-order in aldehyde concentration at the reaction start, which supported this proposal.[71] Furthermore, the proton transfer was identified as the rate determining step at the start of the reaction through a study of the kinetic isotope effect (KIE) of α-D-acrylonitrile at low conversion (<20%).[70] However, as the reaction progresses, autocatalysis was observed. The allylic alcohol product **3.10** acts as a proton shuttle within a new mechanistic pathway via transition state **3.11** (Scheme 38).

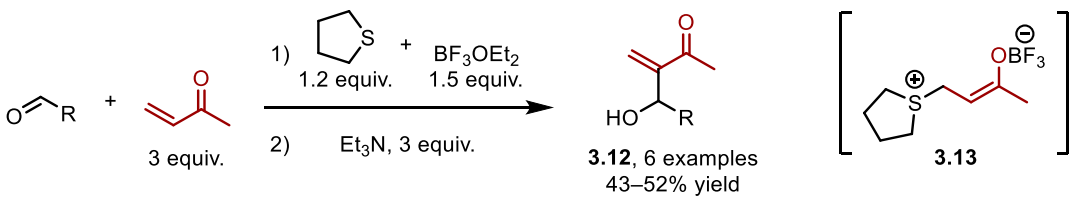
Other protic additives or solvents hence allow for an increase in overall reaction rate.[72] Therefore, the reaction is nowadays often conducted in methanol, isopropanol or even octanol.[73,74] It should be noted that other (KIE) studies indicated that under certain conditions the proton transfer can still be rate-determining, even in the presence of water.[71]



Scheme 38: Proposed mechanism of the MBH reaction co-cataylsed by an alcohol additive or product.

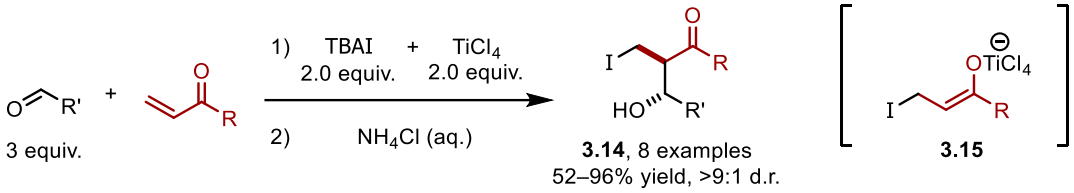
Over the years, many new catalysts for the MBH reaction have been identified based on different Lewis basic main group elements.[69] Beyond a plethora of pnictogen catalysts, carbon, chalcogen[75] and even halogen bases[76] (in combination with Lewis acids) have been reported to mediate such C–C couplings. In most methods, the highly nucleophilic DABCO,[68] its close derivative quinuclidine or simple Me_3N[74] as well as electron-rich pyridine iron complex[77] are employed as efficient catalysts. Phosphines such as triaryl[78] or trialkyl phosphines[67] are similarly easily accessible and reactive Lewis bases.

Several conditions using other Lewis basic molecules have been discovered. For instance, a sulphide-catalysed transformation reported by Goodman *et al.* delivers allyl alcohols **3.12** (Scheme 39).[75] Importantly, additional Lewis acid (BF_3OEt_2) is needed for the reaction to proceed followed by treatment with a base. If the mixture is treated with acid instead, a sulfonium salt derived from intermediate **3.13** can be isolated instead of the MBH-adducts.



Scheme 39: A selected example of an MBH reactions catalysed by tetrahydrothiophene and BF_3.

When the strong Lewis acid $TiCl_4$ is used, even weak nucleophiles such as iodide may react in an MBH-like transformation (Scheme 40).[76] Oshima *et al.* reported the diastereoselective synthesis of β-iodo carbonyls **3.14**, using a mixed reagent composed of TBAI and $TiCl_4$, via titanium enolate intermediate **3.15**.

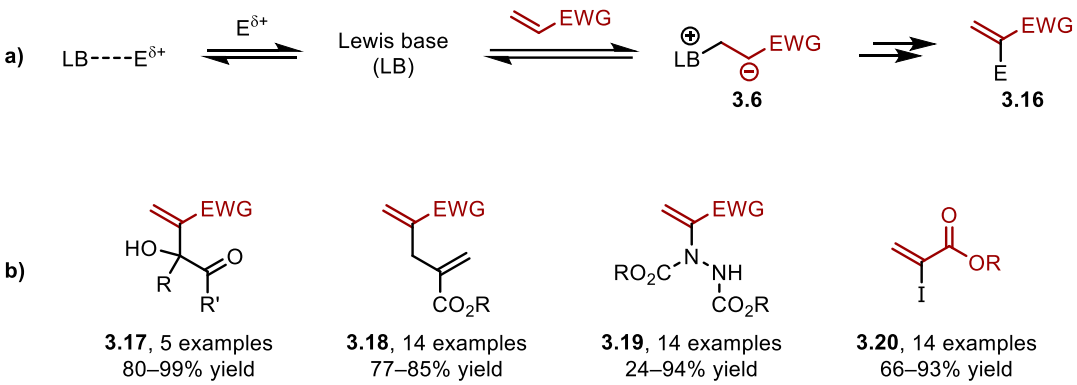


Scheme 40: Iodide as a nucleophile in combination with $TiCl_4$ for an MBH like aldol reaction.

The chemical diversity of other electrophilic coupling partners towards generic products **3.16** is, despite extensive studies, somewhat limited. One reason might be the specific requirements for the electrophile. Undesired interactions with the Lewis base need to be reversible or to lead to a constructive reaction intermediate (Scheme 41a). Scheme 41b shows selected examples of products formed through an MBH-like transformation. Certain ketones such as α-keto carbonyls fall in that category by reacting similar as aldehydes to form α-hydroxy carbonyls **3.17**.[72]

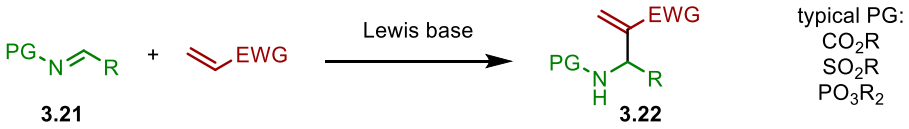
Allylation (**3.18**), as an example for non-carbonyl carbon electrophiles, can be achieved in a similar process using allyl bromides which themselves can be produced in an MBH/deoxybromination sequence.[79] In this case, the catalyst (DABCO) presumably first forms an ammonium allyl bromide salt which then gets attacked by the enolate (generated transiently with a second equivalent of amine). Additionally, great excess of the alkene is needed. In a recent report, catalytically generated allyl-palladium complexes served as electrophiles.[80]

Besides carbon-based electrophiles not many other examples have been reported. Electrophilic amination using azodicarboxylates (**3.19**) is an illustration of these Lewis base-catalysed alkene functionalisations.[81] Iodination in α-position of α,β-unsaturated carbonyls (**3.20**) can also be achieved with an amine catalyst and a source of electrophilic iodine.[82]



Scheme 41: a) The required reversibility of Lewis base–electrophile adduct formation. b) Selected examples of different MBH-style alkene–electrophile coupling products.

The *aza*-Morita–Baylis–Hillman (*aza*-MBH) reaction is a variation which typically employs imines bearing an electron-withdrawing group nitrogen (**3.21**).[83] The resulting products are *N*-protected allyl amines **3.22**. Commonly used electron-withdrawing groups include carbamates, sulfonamides and phosphoramidates (Scheme 42).

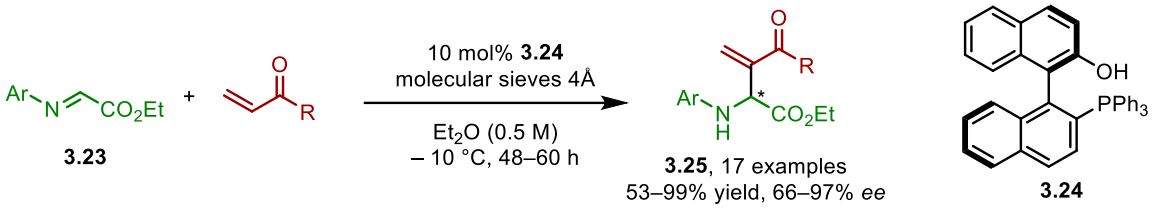


Scheme 42: General illustration for an aza-Morita–Baylis–Hillman reaction.

Analogously to the MBH reaction, the *aza*-MBH usually requires long reaction times which can be lowered in the presence of protic additives, catalysts or solvent. In a three-component coupling of protected amine, aldehyde and alkene the transformation benefits from the addition of a Lewis acid to facilitate imine formation.

To the best of our knowledge, there are no reports on unprotected and unbiased *N*-alkyl imines as coupling partners for the *aza*-MBH reaction. This might be due to their lower electrophilicity. With appropriate electron withdrawing groups, however, the reaction can proceed.[84] Shi *et al.* have successfully employed α-imino esters **3.23** under classic MBH conditions using chiral phosphine catalyst **3.24** (Scheme 43).[85] This reaction is an example how the Lewis base can induce enantioselectivity and also contain a protic moiety to facilitate

the proton transfer step as well, producing allyl amines **3.25** in high yields and with very good enantiomeric excesses.

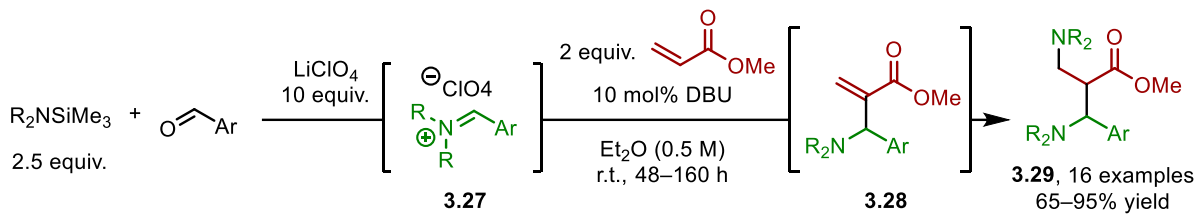


Scheme 43: An aza-MBH-reaction using unprotected imines exemplifying the induction of enantioselectivity and use of a protic catalyst.

Electron-withdrawing aromatic groups connected to the imine nitrogen also allow for a smooth *aza*-MBH process. Zhu *et al.* have demonstrated the synthesis of perfluorinated aryl amines **3.26** using acrylonitrile (Scheme 44).[86] Exchange of even one fluorine atom to a chlorine in *para* position lowered the yield from 98% to 50%, highlighting the stringent electronic requirement. Interestingly, triphenylphosphine did not deliver the desired product, while the amine DABCO did.

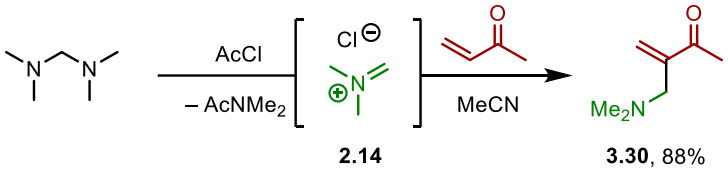
Scheme 44: Perfluorinated aryl substituents on nitrogen allow for this aza-MBH reaction to proceed.

The use of iminium ions in the context of these reactions is rather scarce. One report by Saidi *et al.* employed *in situ* generated aryl iminium perchlorates **3.27** (Scheme 45).[87] Through DBU (1,8-diazabicyclo(5.4.0)undec-7-ene) catalysis, an *aza*-MBH occurs with methyl acrylate, to transiently generate unprotected amines **3.28** (which could also be isolated under slightly modified conditions, using the iminium salt **3.27**). Under the standard conditions, addition of a second silylamine forms diamines **3.29** in good yields.



Scheme 45: In situ generation of iminium salts in an aza-MBH reaction. DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.

This example demonstrates the feasibility of an iminium *aza*-MBH reaction, even if the products were directly further functionalised through 1,4-addition. In comparison, a similar reaction using in situ generated Böhme's salt **2.14** and methyl vinyl ketone led to the formation of dimethyl allylic amine **3.30** as reported by Koldovski *et al.* in 1992 (Scheme 46).[88] While only a single example was reported, the reaction is remarkable as no immediately apparent catalyst was added. Later on, this transformation was found to be irreproducible and the authors speculated that remaining aminal acted as the required Lewis base.[89]



Scheme 46: An aza-MBH like reaction between in situ generated Böhme's salt and methyl vinyl ketone.

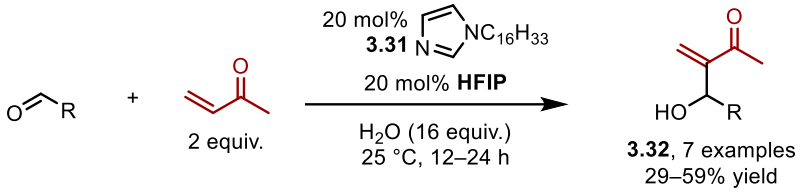
In this chapter, a similar iminium salt (Eschenmoser's salt **2.13**) will serve as coupling partner to electron-deficient alkenes in an *aza*-MBH style reaction, but without the need for any additional Lewis base catalysts.

3.1.2 Hexafluoroisopropanol – an Emerging Privileged Solvent

Hexafluoroisopropanol (HFIP) is a highly polar protic solvent which greatly increased in popularity over the last decades. In comparison to its structurally related derivative isopropanol (^{i}PrOH) it has increased acidity, higher resistance towards oxidation, and reduced nucleophilicity. The physical and chemical properties have been summarised in detail by

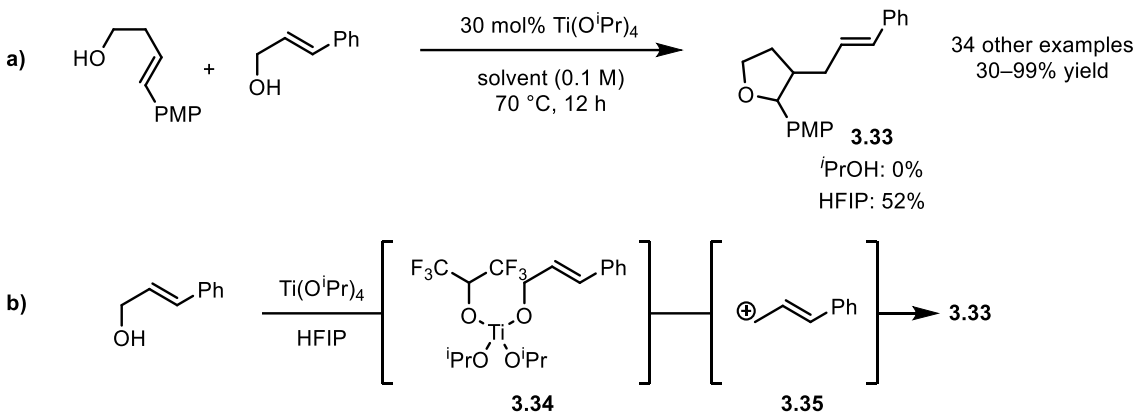
Donohoe *et al.* as well as Motiwala *et al.* a few years later.[90,91] Its exceptional ability to engage in hydrogen bonding makes it an excellent additive or solvent to stabilise polar reaction intermediates.

In the context of the Morita–Baylis–Hillman reaction, HFIP can be used as a protic additive. Matsubara *et al.* have conducted the reaction between aldehydes and methyl vinyl ketone on a water surface using *N*-alkyl-imidazole **3.31** as a catalyst and observed that the addition of 20 mol% of HFIP led to an increase in the yield of allyl alcohols **3.32** (Scheme 47).[92]



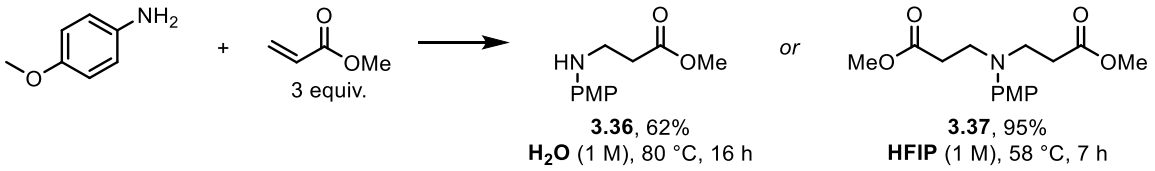
Scheme 47: Effect of HFIP as an additive in an MBH reaction.

Carbocation formation can be facilitated by HFIP as it is weakly nucleophilic on the one hand and forms clusters with the corresponding counterions to stabilise the ionic form on the other hand. For example, Donohoe *et al.* reported an alkylation/cyclisation sequence forming 2,3 disubstituted tetrahydrofurans **3.33** (Scheme 48a).[93] HFIP was found to be crucial for the reaction, as other solvents (including ^{i}PrOH) did not deliver the desired product **3.33**. The proposed mechanism includes the formation of a HFIP/allyl alcohol titanium-centred co-complex **3.34**, which subsequently generates an HFIP-solvated allylic carbocation **3.35** (Scheme 48b). The authors have detected and characterised complex **3.34** and state that it probably undergoes dynamic ligand exchange in solution.



Scheme 48: HFIP as a key solvent in the generation of carbocations in the synthesis of tetrahydrofurane derivatives. PMP = p-methoxyphenyl

This example demonstrates the effect of HFIP in stabilising reactive ionic intermediates such as carbocations. Additionally, this solvent can also promote proton-transfer steps, e. g. in *aza*-Michael additions of amines and electron-deficient alkenes. Legros *et al.* have compared the solvent-effects of water and HFIP in the reaction of anilines with acrylates (Scheme 49).[94] In water, mono alkylation product **3.36** was exclusively formed, whereas HFIP led to the formation of tertiary amine **3.37** in 95% yield even at lower temperatures and shorter reaction times. The authors speculate this selectivity arises from an interaction, and therefore activation towards nucleophiles, of HFIP with the acrylate.



Scheme 49: A distinct solvent effect of water versus HFIP in an aza-Michael addition.

These three discussed examples clearly highlight unique properties of HFIP in comparison to other protic solvents. In particular, pronounced effects on the reaction rate of processes which involve carbocation formation and addition of nucleophiles are observed. In this chapter, these properties will be further explored in the context of an *aza*-MBH-like reaction between Eschenmoser's salt and Michael acceptors.

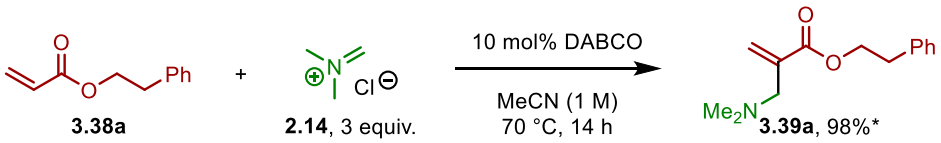
3.2 Results and Discussion

The results described in this chapter were obtained in collaboration with Dr. Margaux Riomet. Ricardo Meyrelles performed quantum chemical calculations under the supervision of Dr. Boris Maryasin which will be briefly discussed. The crystal structures were measured and analysed by the team of the centre for X-ray structure analysis at the University of Vienna. The results of this chapter have been partly published in Angewandte Chemie International Edition.[64]

This chapter revolves around the interaction of Eschenmoser's salt with HFIP, enabling direct C–C bond formation with electron-deficient alkenes (Michael acceptors) without the need for any additives. The reaction was discovered during the investigations described in chapter 2.

While the majority of reported *aza*-MBH processes employ protected imines as coupling partners, the use of iminium ions is less explored.[87,88] This might partially be due to the instability of iminium salts towards hydrolysis and the need to generate them *in situ*, while protected imines can be isolated and are bench stable. As discussed in the previous chapter, Eschenmoser's salt is an iminium iodide which is both bench stable and commercially available. Because of these attributes, we investigated the use of this salt in the context of an *aza*-MBH like reaction, circumventing the use of additional Lewis bases and similar to the work of Koldovski *et al.*, employing highly reactive methyl vinyl ketone (Scheme 46).[88]

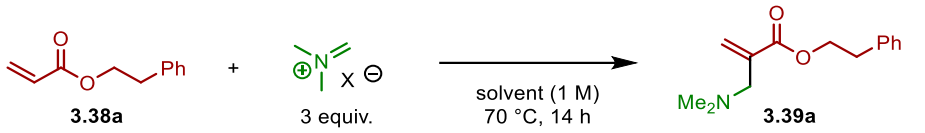
We started our investigations with the less electrophilic (and thus more challenging) acrylate **3.38a**. To verify whether the reaction proceeds at all, a catalytic amount of DABCO was added to a mixture of Böhme's salt and **3.38a** (Scheme 50). As expected, novel amine **3.39a** was obtained in high yield.



*Scheme 50: The aza-MBH between acrylate **3.38a** and Böhme's salt catalysed by DABCO.*
** Yield determined by quantitative ^{1}H-NMR.*

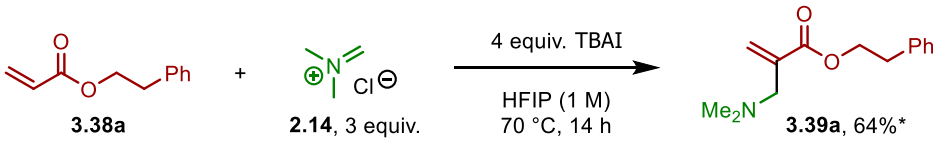
In order to investigate the possibility to achieve this transformation in the absence of Lewis base, further optimisation was performed. We immediately saw a large dependency on counterion as neither chloride nor bromide delivered the product while iodide formed 3.39a in 31% yield using acetonitrile as a solvent (Table 5, entries 1–3). Encouraged by this finding, we sought to increase the yield by a change to a protic solvent as these commonly increase reaction rates in *aza*-MBH like processes (see section 3.1.1). While simple ^{i}PrOH decreased the yield, presumably through solvolysis of the iminium ion, HFIP greatly improved the yield of **3.39a** to 82% (entries 4–7). Again, a pronounced counterion effect was observed between the different halides with iodide giving the best results.

*Table 5: Investigation of counterion and solvents for a Lewis base-free aminomethylenation reaction. * Yield determined by quantitative ^{1}H-NMR.*



entry	X	solvent	yield*
1	Cl	MeCN	0%
2	Br	MeCN	0%
3	I	MeCN	31%
4	I	^{i}PrOH	15%
5	Cl	HFIP	0%
6	Br	HFIP	5%
7	**I**	**HFIP**	**82%**

The clear effect of iodide in comparison to chloride was again confirmed by the addition of TBAI to the reaction between acrylate **3.38a** and Böhme's salt (Scheme 51). The additional iodide in solution promoted the reaction yielding amine **3.39a** in 64% instead of the previous 0% (Table 5, entry 5).



*Scheme 51: Dramatic effect of added external iodide as a promoter when employing **2.14**. * Yield determined by quantitative ^{1}H-NMR.*

Intrigued by this high-yielding reaction but puzzled by the strong solvent and counterion effects, we investigated this new reaction further. Quantum chemical calculations by R. Meyrelles indicate a difference in the degree of ionisation of Eschenmoser's and Böhme's salt. The dissociated structure (C–I bond distance 3.120 Å, Figure 3) of the iodide salt is 7.2 kcal/mol lower in Gibbs free energy than the covalently bound ICH_2NMe_2 molecule (C–I bond distance 2.280 Å), when computed as a complex with 3 HFIP molecules which form a hydrogen-bond network. The same calculations with chloride instead of iodide showed only a marginal lower free Gibbs energy for the ionic state of 0.5 kcal/mol in comparison to the covalent state. The number of HFIP molecules in the model was chosen to mimic the ratio of salt to solvent in the investigated reaction. From this, we conclude that the higher reactivity of iodide over chloride salt (Table 5, entries 5 and 7) might, in part, stem from a larger concentration of the ionic iminium form in solution stabilised by the HFIP hydrogen bond network.

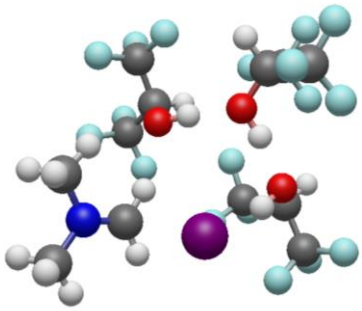
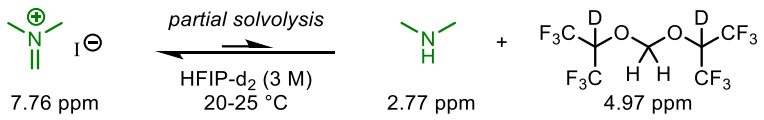


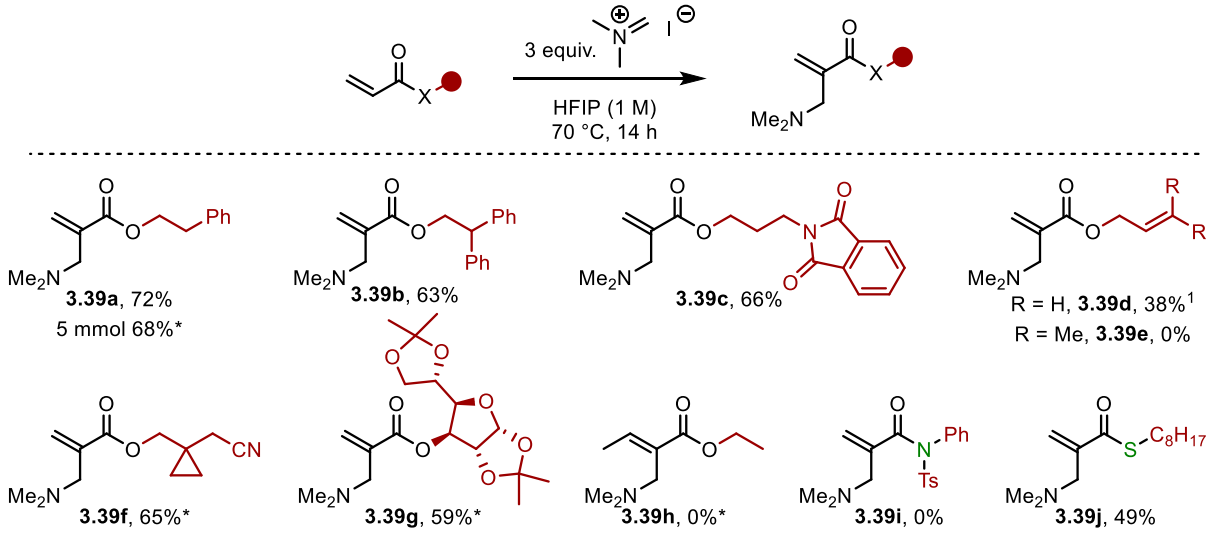
Figure 3: Eschenmoser's salt and 3 discrete molecules of HFIP in its dissociated, ionic form as computed on a PBE0-D3BJ/def2-TZVP//PBE0-D3BJ/def2-SVP level of theory by R. Meyrelles.

To further study the behaviour of the iminium salts in solution we recorded ^{1}H-NMR spectra of both dimethylmethyleneiminium iodide (**2.13**) and chloride (**2.14**) in HFIP-d_2 at the same concentration as employed in the reactions in Table 5. In the spectrum of Eschenmoser's salt a partial solvolysis to dimethylamine was noted together with formation of the formacetal of HFIP (Scheme 52). On the one hand, the measured iminium signal at 7.76 ppm is in agreement with the computed preference of an ionic form of Eschenmoser's salt. The partially liberated dimethylamine suggested its possible involvement as a Lewis base in the, at first glance uncatalysed, reaction with a Michael acceptor.



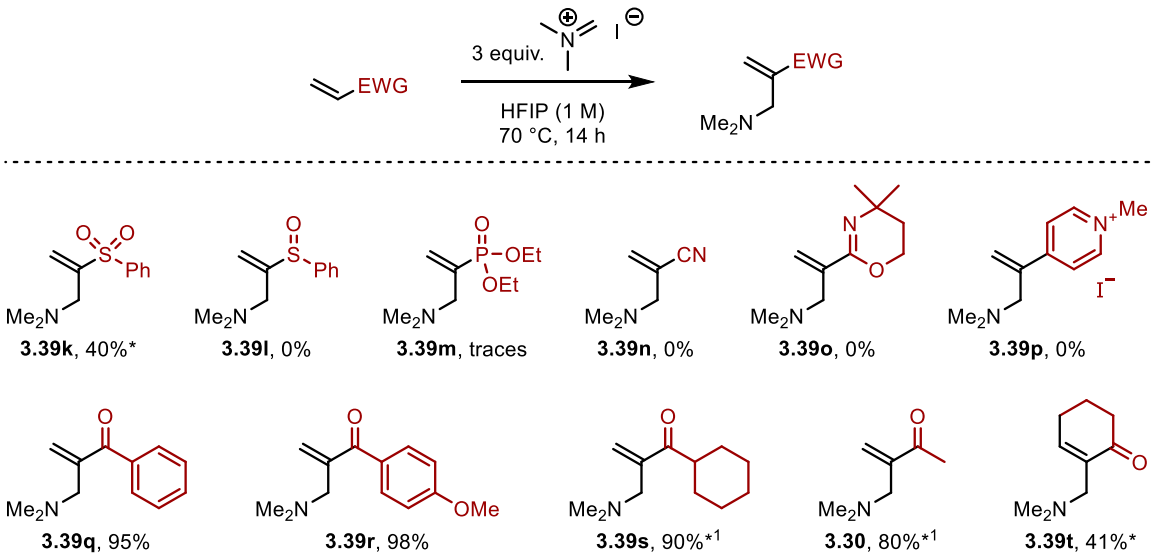
Scheme 52: Observed ^{1}H-NMR signals of Eschenmoser's salt in HFIP-d_2.

Next, we explored the scope of the reaction with regard to the electron-deficient alkene partner to obtain deeper insights into the mechanism and additionally to test the applicability of this operationally simple setup in the synthesis of *aza*-MBH products. Different acrylates were suitable substrates in this transformation (Scheme 53, **3.39a**–**3.39c**). A scale up to 5 mmol of acrylate **3.39a** only slightly decreased the yield to 68%. An allyl group led to lower yield (38%, **3.39d**), whereas a prenyl derivative was not tolerated (**3.39e**), presumably due to the intrinsic nucleophilicity of this moiety and ability to engage in side-reactions with Eschenmoser's salt itself.[43] Interestingly, a nitrile, bearing potentially acidic α-protons, was tolerated (**3.39f**) and an acetal-protected glucose moiety remained intact despite the acidic environment and high temperatures (**3.39g**). Substitution in β-position did not afford **3.39h**, presumably due to steric hindrance. Surprisingly, acrylimide did not afford product **3.39i**, while thioester **3.39j** was successfully synthesised albeit in a moderate yield of 49%.



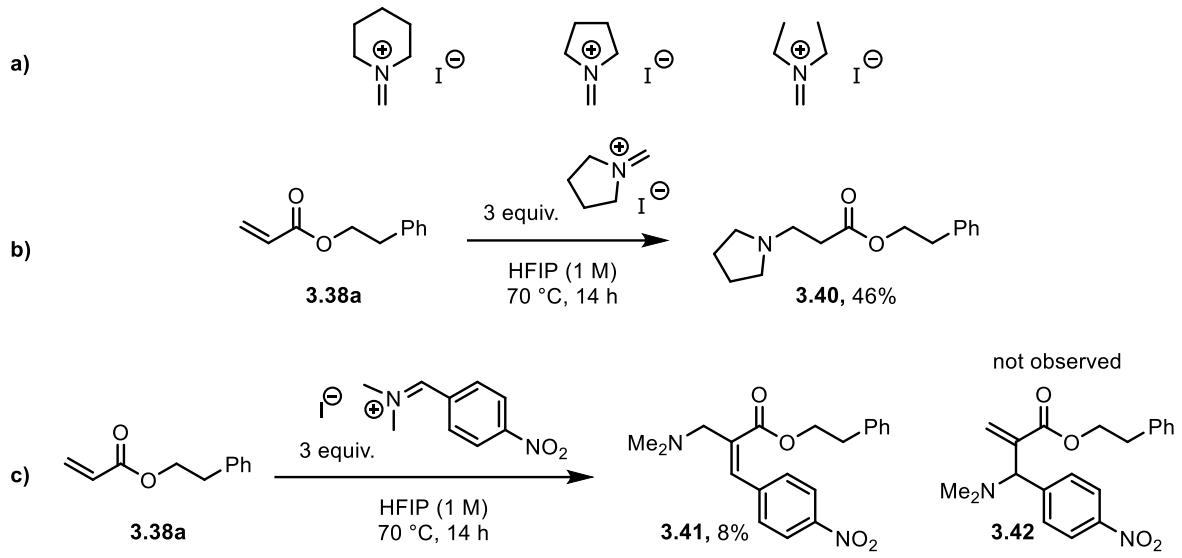
*Scheme 53: Selected reaction scope of different acrylates in the external Lewis base-free aza-MBH like reaction. *Reaction performed by M. Riomet. 1) 4 equiv. **2.13**.*

To further examine the boundaries of reactivity, we turned our attention to other electron-deficient alkenes (Scheme 54). Apparently, the olefin must bear a strong enough electron-withdrawing group for the reaction to occur. While a sulfone still delivered the desired amine **3.39k** in 40% yield, a sulfoxide derivative was not reactive (**3.39l**). Similarly, phosphonate (**3.39m**), nitrile (**3.39n**), oxazine (**3.39o**) and pyridinium iodide (**3.39p**) did not yield the expected products. In contrast, vinyl ketones were highly reactive forming amines **3.39q**–**3.39t** in high yields of up to 98%. Surprisingly, alkyl vinylketones did not react in a classic Mannich reaction[89] but rather formed the *aza*-MBH type allyl amines instead (products **3.39s** and **3.30**). Furthermore, **3.39t** is the first example in this reaction of not only a β-substituted product but also a cyclic alkene. Again, the lower electrophilicity might be the reason for the decreased yield (41%). For further examples synthesised by M. Riomet see the corresponding publication.[64]



*Scheme 54: Investigation of different electron deficient alkene in the external Lewis base-free aza-MBH like reaction. *Reaction performed by M. Riomet. 1) at 20–25 °C.*

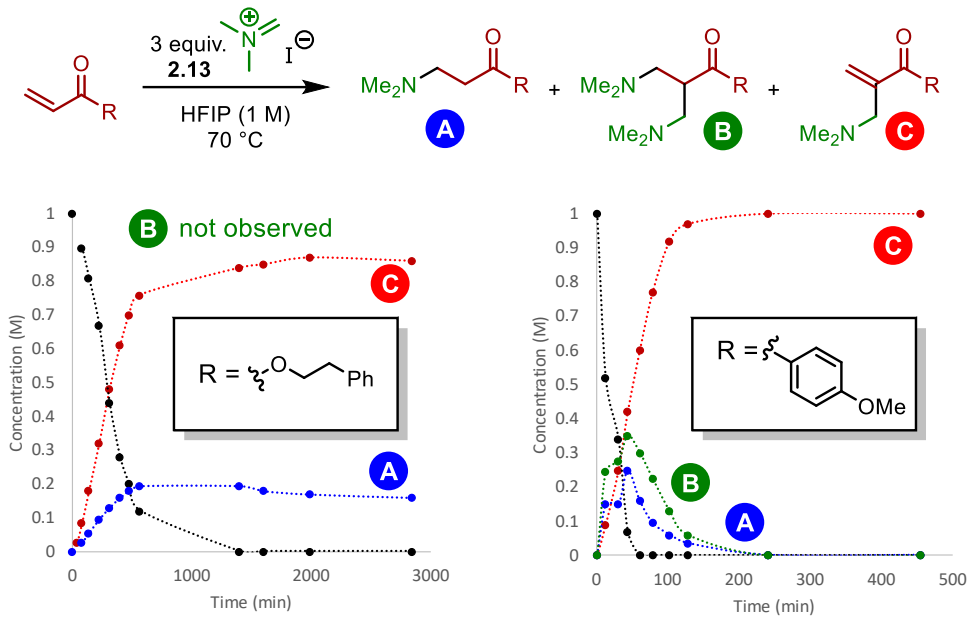
Besides Eschenmoser's salt, other iminium iodide salts (Scheme 55a) did not deliver the *aza*-MBH products. Only, Michael addition products (**3.40**), from an *in situ* decomposed iminium salt, were observed (Scheme 55b).



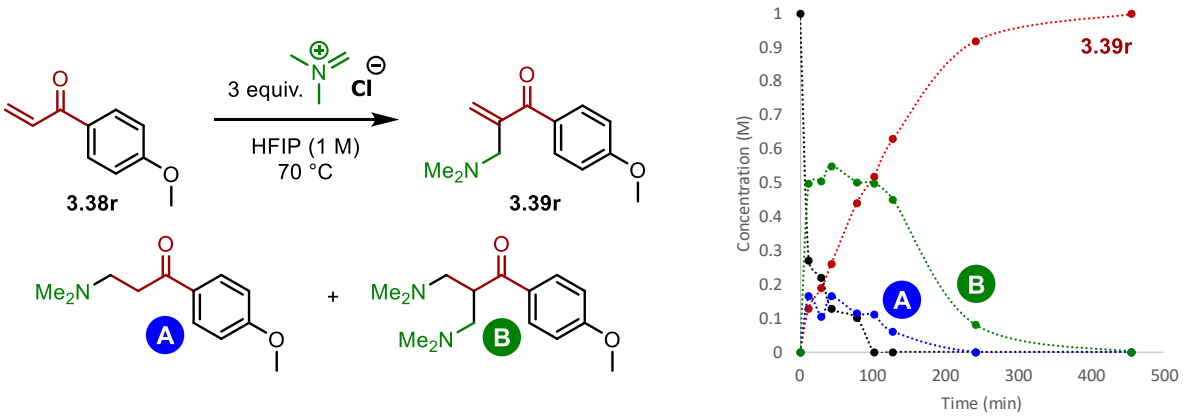
Scheme 55: Reactions using different salts performed by M. Riomet.
a) Unsuccessful iminium iodide salts. b) Observed 1,4-amination. c) Observed formal amine migration.

We attribute this limitation to the delicate equilibrium between iminium ion, α-iodo amine and solvolysed secondary amine needed for a constructive *aza*-MBH reaction in absence of additional Lewis base. We speculate, that while this equilibrium is beneficial for Eschenmoser's salt at these conditions, other iminium iodides would require further optimisation. Scheme 55c shows the reaction with an aryl substituted iminium salt delivering β-amino C–C coupling product **3.41** (8% yield) instead of expected amine **3.42**. The mechanism of this formal migration will be discussed later in this chapter.

To get further insight into the mechanism, we monitored the transformation using ^{1}H-NMR (Scheme 56). Both acrylate **3.38a** and aryl vinylketone **3.38r** formed product **C** as well as 1,4-aminated by-product **A**. However, in the case of the ketone, **A** was consumed over the course of the reaction. Additionally, another intermediate (diamine **B**) was detected and we observed how Böhme's salt can engage with aryl vinyl ketones to furnish *aza*-MBH product **3.39r**, nevertheless at a slower rate (estimated t½ of 100 min, Scheme 57) than Eschenmoser's salt (estimated t½ of 50 min, Scheme 56). This reaction was by ^{1}H-NMR as well, again revealing the formation of intermediates **A** and **B** (Scheme 57).



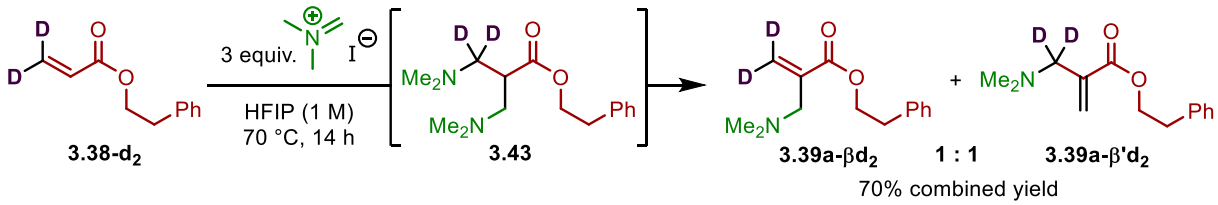
Scheme 56: The investigated aza-MBH like reaction was monitored via ^{1}H-NMR by M. Riomet.



*Scheme 57: The aza-MBH like reaction using vinyl ketone **3.38r** and iminium chloride **2.14** was monitored via ^{1}H-NMR by M. Riomet.*

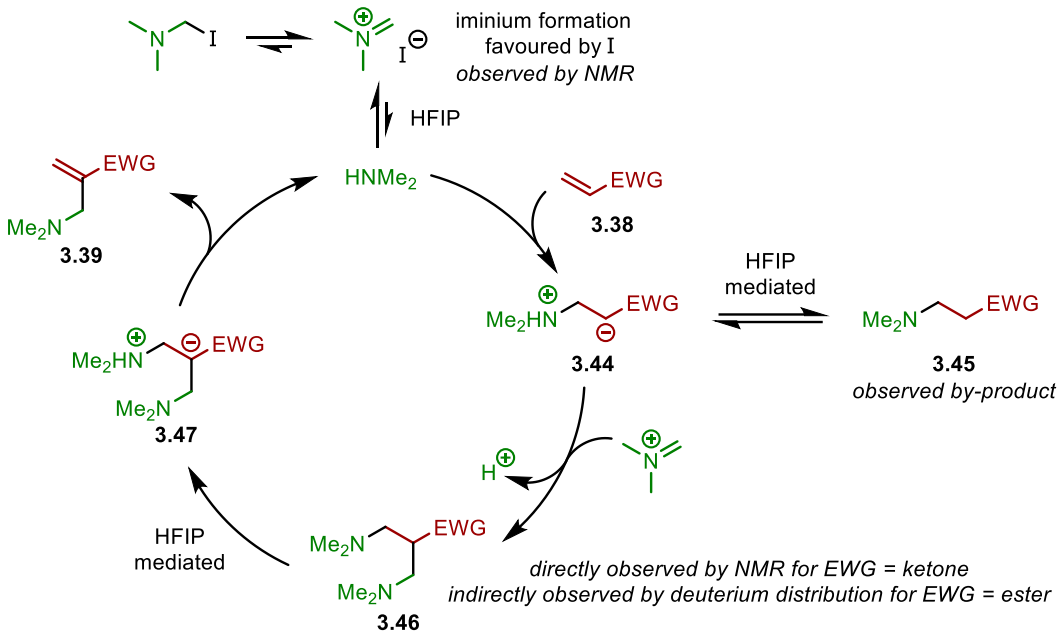
At this point, a growing body of evidence suggested that *in situ* released dimethylamine might be the hidden catalyst which allows for the transformation to be additive-free. To confirm this also for acrylic esters, for which we have not observed the pivotal dimethylamine intermediate **B** (Scheme 56), we conducted the reaction using deuterium labelled acrylate **3.38a-d$_2$** (Scheme 58). The two possible isotopomers **3.39a-βd$_2$** and **3.39a-β'd$_2$** were formed in a statistical mixture of 1:1 indicating the transient formation of diamine **3.43** also for the case of esters. The two possibilities of elimination on this pseudo-symmetric intermediate also explain the formation of amine migrated product **3.41** (Scheme 55c) which presumably forms

after dimethylamine elimination in an analogous diamine delivering the conjugated product. The ability of dimethylamine to engage in such a cycle was furthermore confirmed by the addition of 10 mol% dimethylamine to the reaction mixture using Böhme's salt finally delivering the expected product **3.39a** in 77% yield (0% without additive, see Table 5).



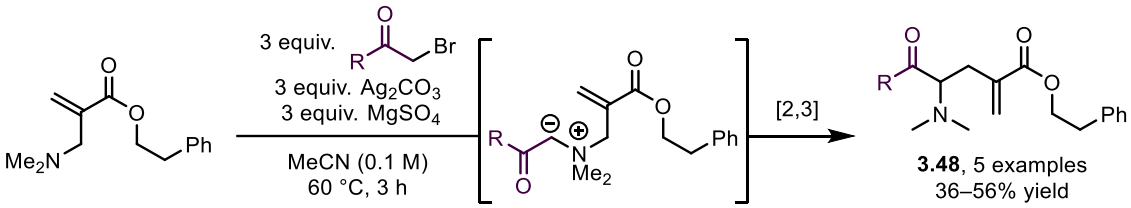
*Scheme 58: Deuterium labelled acrylate **3.38-d$_2$** forms a mixture of isotopomers indicating a diamine intermediate.*

Now confident about the nature of the hidden Lewis base catalyst we could propose the following mechanism (Scheme 59). Eschenmoser's salt is predominantly ionised in HFIP and partially solvolysed to release minor amounts of dimethylamine. This is the active catalyst in an *aza*-MBH process via zwitterion **3.44** which can tautomerise to 1,4-aminated by-product **3.45**. This step was found to be mediated by HFIP through quantum chemical calculations. The difference in activation energy for HFIP versus a hypothetical ^{i}PrOH promoted process was found to be 4.1 and 6.2 kcal/mol for ester **3.38a** and ketone **3.38r** respectively, highlighting the significant proton shuttling ability of HFIP over a sterically similar alcohol. Zwitterion **3.44** can also react with an iminium ion producing diamine **3.47** after deprotonation of **3.46**. This intermediate was observed in NMR for ketone **3.38r** (Scheme 56) and indicated by the statistical formation of isotopomers for acrylate **3.38a** (Scheme 58). The next step is a proton transfer, again mediated by HFIP. The activation energy difference for HFIP versus ^{i}PrOH was even more pronounced as in the step described before, with 6.2 an 8.0 kcal/mol for ester and ketone substrates. Dimethylamine elimination delivers the product and closes the catalytic cycle.



Scheme 59: Proposed mechanism for the C-C coupling of alkenes with Eschenmoser's salt via an in situ generated catalyst.

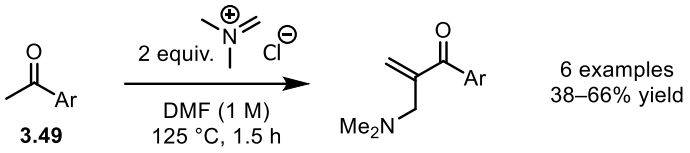
To study the reactivity of the produced allylamines we envisioned their *N*-alkylation with α-bromo carbonyls followed by a base induced [2,3]-Stevens-type rearrangement (Scheme 60). Through such a process, five different α-amino carbonyls have been produced in 36–56% yield (**3.48**).[64]



Scheme 60: Derivatisation of the produced allyl amines through a 2,3-Stevens rearrangement. Reactions performed by M. Riomet.

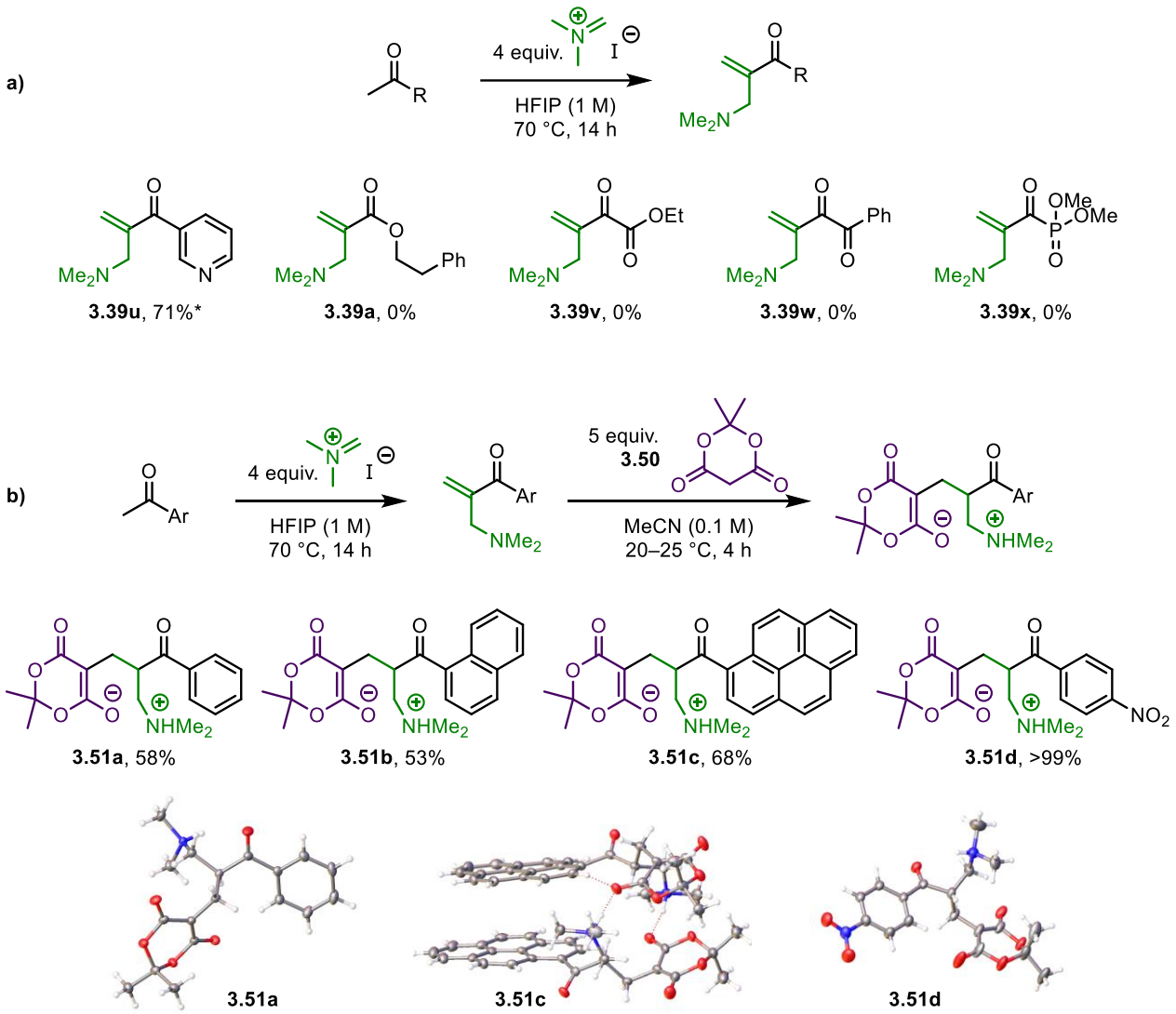
Additionally, we wished to study the replacement of electron deficient-alkenes **3.38** with simple methyl groups bearing an electron withdrawing group. In 1998 Girreser *et al.* reported the direct synthesis of *aza*-MBH type aryl ketones starting from methyl aryl ketones **3.49** rather than the ususal vinyl ketones (Scheme 61).[95] The reaction was performed in DMF and required 125 °C to achieve high yields. Inspired by this method, we envisioned a similar

process using our Eschenmoser's salt-HFIP system. This approach would be particular interesting for cases in which the vinyl ketones are highly prone to undergo polymerisation.[96]



Scheme 61: A one-pot Mannich/aza-MBH sequence as reported by Girreser et al.[95]

Indeed, the reaction proceeded smoothly using our conditions with one extra equivalent of Eschenmoser's salt, which allows for the synthesis of reactive vinyl ketone **3.39u** (Scheme 62a). Other methyl carbonyls did not engage in the reaction as desired and the amines **3.39a**–**3.39x** were not observed using this method, suggesting that such a transformation is limited to methyl ketones (likely due to a necessary balance of enol-ketone tautomers). Furthermore, we employed this method for the *in situ* synthesis of allylic amines, which were used as crude materials and treated with Meldrum's acid **3.50** to form complex zwitterions **3.51a**–**3.51d** in high yields without the need for column chromatography (Scheme 62b). These compounds readily crystallise, and their x-ray single crystal structures could be determined.



*Scheme 62: a) Investigations of a one pot Mannich/aza-MBH sequence (*Reaction performed by M. Riomet) and b) its application in the synthesis of zwitterions. (CCDC: **3.51a**:2079100; **3.51c**:2079101; **3.51d**:2079099)*

3.3 Conclusion and Perspectives

In conclusion, we have discovered a remarkable reactivity of the Eschenmoser's salt-HFIP reagent pair. It allows for a direct C–C coupling resembling an *aza*-MBH reaction, without the need for any additional Lewis base. An array of allyl amines was synthesised and the mechanism of this process was studied in an interdisciplinary effort using NMR analysis, carefully designed reactions, and quantum chemical calculations, allowing us to confidently assign the *in situ* formed catalyst. Finally, the reaction was also studied in the context of a direct Mannich/*aza*-MBH sequence starting from methyl carbonyls and the synthesised amines were further transformed via [2,3]-Stevens type rearrangements and Michael additions.

The distinct properties of HFIP have been heavily studied over the last decades by the chemistry community and further contributed to the understanding of this unique solvent. Its interaction with ionic species and the ability to transfer protons with a minimal amount of activation energy will almost certainly lead to the development of new synthetic methods in the near future.

3.4 Experimental Data

3.4.1 General information

Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. Hexafluoro isopropanol (HFIP) was purchased from Fluorochem and used without any particular precaution. All reagents were used as received from commercial suppliers unless otherwise stated. Eschenmoser's salt was purchased from TCI, stored in smaller containers when received (ca. 5 g each) and used as such. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed on an Isolera 4 or Select medium pressure chromatography system (Biotage) using silica gel 60 (230-400 mesh, Merck and co.) or aluminium oxide 90 active neutral (70-230 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 using a Bruker maXis UHR-TOF (Qq-TOF) spectrometer, using electrospray ionization (ESI). All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400, AV-500, AV-600 or AV-700 spectrometer at 300K. 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 (^{13}C-NMR), or DMSO-d_6, defined at δ = 2.50 ppm (^{1}H-NMR) and δ = 39.52 (^{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) 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).

3.4.2 Starting material synthesis

General procedure A: Esterification

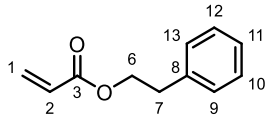
A mixture of alcohol (1.0 equiv.) and Et_3N (1.5 equiv.) in dry CH_2Cl_2 (0.5 M) was cooled to 0 °C in an ice-water bath and acryloyl chloride (1.2 equiv.) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with Et_2O, transferred to a separation funnel, washed with a saturated aqueous solution of NH_4Cl and then with a saturated aqueous solution of $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica, Heptane/EtOAc).

General Procedure B: Mannich reaction with methyl ketones

Mannich reactions were performed according to a modified literature procedure.[97] To a mixture of a carbonyl compound (1.0 equiv.) and paraformaldehyde (2.0 equiv.) in dry THF (1 M) was added diisopropylammonium 2,2,2-trifluoroacetate (1.0 equiv.) and trifluoroacetic acid (0.1 equiv.). The reaction mixture was stirred open to the atmosphere at reflux for 2 h. A second addition of paraformaldehyde (2.0 equiv.) was performed, and the reaction mixture was stirred at reflux for an additional 16 h open to the atmosphere. The reaction mixture was allowed to cool to room temperature and volatilities were removed under reduced pressure. The crude residue was dissolved in Et_2O and washed with HCl_{aq} (1 M), $NaOH_{aq}$ (1 M), and brine. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, Heptane/EtOAc) afforded the arylvinylketone.

Experimental Data

3.38a: Phenethyl acrylate

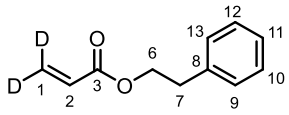


The compound was prepared using general procedure **A** from acryloyl chloride (1.95 mL, 24 mmol), homobenzyl alcohol (2.44 g, 20 mmol), Et_3N (4.18 mL, 30 mmol). Purification by flash column chromatography on silica gel (0% to 10% EtOAc in heptane) afforded compound **3.38a** in 81% (2.85 g) yield as a colourless oil.

The spectroscopic data was in accordance with those reported.[98]

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H^{Ar}), 7.26 – 7.20 (m, 3H^{Ar}), 6.39 (dd, *J* = 17.3, 1.4 Hz, 1H^1), 6.11 (dd, *J* = 17.3, 10.4 Hz, 1H^2), 5.82 (dd, *J* = 10.4, 1.4 Hz, 1H^1), 4.38 (t, *J* = 7.1 Hz, 2H^6), 2.99 (t, *J* = 7.1 Hz, 2H^7) ppm.

3.38a-*d_2*: Phenethyl acrylate-3,3-*d_2*



Phenethyl 2-(triphenyl-λ^5-phosphaneylidene)acetate (637 mg, 1.5 mmol, 1 equiv.) and paraformaldehyde-*d_2* (96 mg, 3.0 mmol, 2 equiv.) were mixed in a flame-dried Schlenk tube under argon upon which 1 mL (0.66 M) toluene was added. The mixture was stirred at 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature, hexane was added, and the resulting slurry was filtered over celite. The solvents were removed under reduced pressure and the product was purified by flash column chromatography. Purification by flash column chromatography on silica gel (0% to 10% EtOAc in heptane) afforded compound **3.38a-*d_2*** in 91% (255 mg) yield as a colourless oil.

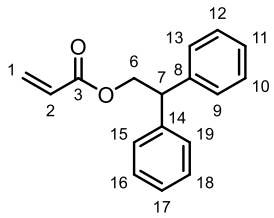
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H^{Ar}), 7.26–7.20 (m, 3H^{Ar}), 6.09 (bs, 1H^2), 4.36 (t, *J* = 7.1 Hz, 2H^6), 2.97 (t, *J* = 7.1 Hz, 2H^7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 (C^3), 137.9 (C^8), 129.1 (2CH^{Ar}), 128.7 (2CH^{Ar}), 128.4 (C^{11}), 126.7 (CH^2), 65.2 (CH_2^{6}), 35.3 (CH_2^{7}) ppm. *CD_2 carbon not observable*

IR (neat) ν_{max}: 3030, 2953, 1719, 1298, 1267, 1173, 1025, 922, 748, 697 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{10}D_2O_2Na^+$) requires 201.0855, found 201.0860.

3.38b: 2,2-Diphenylethyl acrylate



The compound was prepared using general procedure **A** from acryloyl chloride (292 µL, 3.6 mmol), 2,2-diphenylethanol (595 mg, 3.0 mmol), Et_3N (627 µL, 4.5 mmol). Purification by flash column chromatography on silica gel (5% to 20% EtOAc in heptane) afforded compound **3.38b** in 90% (683 mg) yield as a colourless oil.

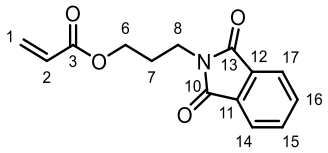
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, $10H^{Ar}$), 6.33 (dd, *J* = 17.3, 1.4 Hz, $1H^1$), 6.06 (dd, *J* = 17.3, 10.4 Hz, $1H^2$), 5.79 (dd, *J* = 10.4, 1.4 Hz, $1H^1$), 4.74 (d, *J* = 7.6 Hz, $2H^6$), 4.44 (t, *J* = 7.6 Hz, $1H^7$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C^3), 141.2 ($2C^{8,14}$), 131.0 (CH_2^1), 128.7 ($4CH^{Ar}$), 128.5 (CH^2), 128.4 ($4CH^{Ar}$), 127.0 ($2CH^{11,17}$), 66.9 (CH_2^6), 50.0 (CH_2^7) ppm.

IR (neat) ν_{max}: 3028, 1720, 1493, 1451, 1405, 1267, 1175, 1063, 982, 696 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{16}O_2Na^+$) requires 275.1043, found 275.1052.

3.38c: 3-(1,3-Dioxoisoindolin-2-yl)propyl acrylate



To acrylic acid (432 mg, 6.0 mmol, 2 equiv.) in 3 mL DMF (1 M) in a flame dried Schlenk under argon were added K_2CO_3 (829 mg, 6.0 mmol, 2 equiv.), *N*-(3-bromopropyl)phthalimide (804 mg, 3.0 mmol, 1 equiv.) and potassium iodide (49.8 mg, 0.30 mmol, 0.1 equiv.). The mixture was heated to 50 °C for 14 h. Then, after cooling to room temperature, EtOAc was added and the solution was washed first with a saturated aqueous solution of NH_4Cl and then with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (0–40% EtOAc in heptane), afforded compound **3.38c** in 84% (656 mg) yield as a colourless solid.

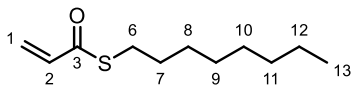
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.80 (m, 2H^{14,17}), 7.76 – 7.67 (m, 2H^{15,16}), 6.42 – 6.33 (m, 1H^{1cis}), 6.05 (app.ddd, *J* = 17.3, 10.4, 1.3 Hz, 1H^2), 5.78 (dd, J = 10.4, 1.3 Hz, 1H^1), 4.25 – 4.18 (m, 2H^{Al}), 3.87 – 3.78 (m, 2H^{Al}), 2.13 – 2.04 (m, 2H^{Al}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (2C^{10,13}), 166.2 (C^3), 134.1 (2CH^{Ar}), 132.2 (CH_2^1), 131.0 (2C^{11,12}), 128.3 (CH^2), 123.4 (2CH^{Ar}), 62.1 (CH_2^{Al}), 35.3 (CH_2^{Al}), 27.7 (CH_2^{Al}) ppm.

IR (neat) ν_{max}: 2957, 1772, 1706, 1396, 1272, 1190, 720 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{13}NNaO_4^+$) requires 282.0737, found 282.0744.

3.38j: *S*-Octyl prop-2-enethioate



The compound was prepared using general procedure **A** from acryloyl chloride (292 µL, 3.6 mmol), 1-octanethiol (521 µL, 3.0 mmol), Et_3N (502 µL, 3.6 mmol). Purification by flash

column chromatography on silica gel (0–5% EtOAc in heptane), afforded the desired compound in 16% (95.3 mg) as a colourless oil.

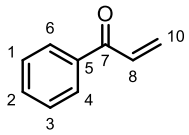
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 – 6.24 (m, 2H^{1,2}), 5.65 (d, *J* = 9.9 Hz, 1H^{1}), 2.96 (t, *J* = 7.3 Hz, 2H^{6}), 1.65 – 1.56 (m, 2H^{7}), 1.43 – 1.20 (m, 10H$^{8–12}$), 0.88 (t, *J* = 7.0 Hz, 3H^{13}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7 (C^{3}), 135.3 (CH^{2}), 126.1 (CH_2^{3}), 31.9 (CH_2^{Al}), 29.6 (CH_2^{Al}), 29.3 (CH_2^{Al}), 29.2 (CH_2^{Al}), 29.0 (CH_2^{Al}), 28.9 (CH_2^{Al}), 22.8 (CH_2^{Al}), 14.2 (CH_3^{13}) ppm.

IR (neat) ν_{max}: 2923, 2853, 1672, 1614, 1463, 1394, 1168, 1007, 975, 947, 727 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{20}NaOS^+$) requires 223.1127, found 223.1120.

3.38q: 1-(4-Methoxyphenyl)prop-2-en-1-one

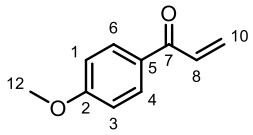


The compound was prepared using general procedure **B** from acetophenone (360 mg, 3.0 mmol), diisopropylammonium 2,2,2-trifluoroacetate (646 mg, 3.0 mmol), TFA (22 µL, 0.3 mmol), paraformaldehyde (2 × 180 mg, 2 × 6.0 mmol). Purification by flash column chromatography on silica gel (0–3% EtOAc in heptane), afforded compound **3.38q** in 22% (88 mg) yield as a colourless oil.

The spectroscopic data was in accordance with those reported.[99]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, J = 7.5 Hz, 2H^{4,6}), 7.58 (t, J = 7.3 Hz, 1H^{2}), 7.48 (app.t, J = 7.7 Hz, 2H^{1,3}), 7.16 (dd, J = 17.1, 10.6 Hz, 1H^{8}), 6.44 (dd, J = 17.1, 1.1 Hz, 1H^{10}), 5.94 (dd, J = 10.6, 1.1 Hz, 1H^{10}) ppm.

3.38r: 1-(4-Methoxyphenyl)prop-2-en-1-one



The compound was prepared using general procedure **B** from 4'-methoxyacetophenone (451 mg, 3.0 mmol), diisopropylammonium 2,2,2-trifluoroacetate (646 mg, 3.0 mmol), TFA (22 µL, 0.3 mmol), paraformaldehyde (2 × 180 mg, 2 × 6.0 mmol). Purification by flash column chromatography on silica gel (0–5% EtOAc in heptane), afforded compound **3.38r** in 40% (192 mg) yield as a colourless oil.

The spectroscopic data was in accordance with those reported.[99]

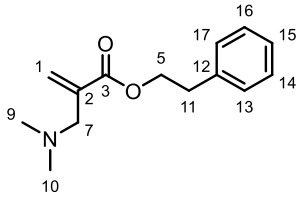
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00–7.94 (m, 2H^{4,6}), 7.17 (dd, *J* = 17.0, 10.5 Hz, 1H^{8}), 7.00–6.92 (m, 2H^{1,3}), 6.42 (dd, *J* = 17.0, 1.7 Hz, 1H^{10}), 5.87 (dd, *J* = 10.5, 1.7 Hz, 1H^{10}), 3.88 (s, 3H^{12}) ppm.

3.4.3 Product synthesis

General procedure C: *aza*-MBH reaction

Michael acceptor (0.20 mmol, 1.0 equiv.) was placed in an oven-dried vial charged with a magnetic stir bar. Then, 0.2 mL HFIP (1 M) and Eschenmoser's salt (0.60 mmol, 111 mg, 3.0 equiv.) were added. The vial was capped and placed in an oil bath at 70 °C. The mixture was stirred for 14 h upon which it was allowed to cool to room temperature. CH_2Cl_2 was added and the excess of Eschenmoser's salt was quenched with 5 mL 1 M NaOH (aq.) solution. The phases were separated and the aqueous layer was extracted three times with 10 mL CH_2Cl_2. The combined organic phases were dried over K_2CO_3, filtered and the solvent was removed under reduced pressure. The product was purified via LPLC on silica gel (for esters) or neutral alox (for ketones) using CH_2Cl_2 and DMA (DMA = CH_2Cl_2:MeOH:NH_4OH (aq.25%) 90:10:0.5; typical gradient: from 95/5 to 50/50 CH_2Cl_2/DMA).

3.39a: Phenethyl 2-((dimethylamino)methyl)acrylate



The compound was prepared using general procedure **C** from **3.38a** (35.2 mg, 0.20 mmol) and Eschenmoser's salt (111 mg, 0.60 mmol). Purification by flash column chromatography on silica gel (5% DMA-MIX to 50% DMA-MIX in DCM) afforded compound **3.39a** in 72% (33.6 mg) yield as a colourless oil.

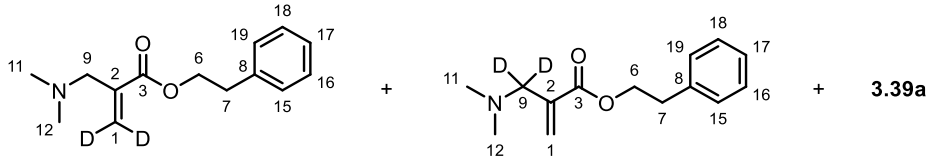
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H$^{13–17}$), 6.26 – 6.24 (m, 1H^{1cis}), 5.73 – 5.71 (m, 1H^{1trans}), 4.39 (t, *J* = 7.0 Hz, 2H^5), 3.12 (s, 2H^7), 3.00 (t, *J* = 7.0 Hz, 2H^{11}), 2.24 (s, 6H^{9,10}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9 (C^3), 138.1 (C^{12}), 137.9 (C^2), 129.1 ($2CH^{14,16}$), 128.6 ($2CH^{13,17}$), 127.1 (CH_2^1), 126.7 (CH^{15}), 65.4 (CH_2^5), 60.1 (CH_2^7), 45.5 ($2CH_3^{9,10}$), 35.26 (CH_2^{11}) ppm.

IR (neat) ν_{max}: 2818, 2768, 1714, 1454, 1269, 1178, 1160, 1134, 1032, 699 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}NO_2^+$) requires 234.1489, found 234.1489.

3.39a-d_2: Phenethyl 2-((dimethylamino)methyl)acrylate-d_2



3.39a-βd_2 **3.39a-β'd_2**

The compounds were prepared using general procedure **C** from **3.38a-d_2** (35.6 mg, 0.20 mmol) and Eschenmoser's salt (111 mg, 0.60 mmol). Purification by flash column chromatography on silica gel (5% DMA-MIX to 50% DMA-MIX in DCM) afforded compound **3.39a-d_2** (isotopomeric mixture was obtained in a ratio of 1:1:0.3 (**3.39a-βd_2**:**3.39a-β'd_2**:**3.39a**)) in 70% (33.0 mg) combined yield as a colourless oil.

Experimental Data

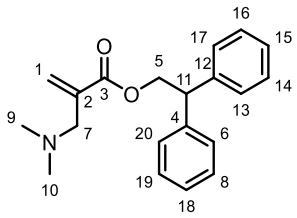
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.15k (m, 5H^{Ar}), 6.25 (s, 0.7H^{1}, 2a-β'd_2 + 2a), 5.72 (s, 0.7H^{1}, 2a-β'd_2 + 2a), 4.39 (t, *J* = 7.0 Hz, 2H^{6}), 3.11 (s, 1.3H^{9} 2a-βd_2 + 2a), 3.00 (t, *J* = 7.0 Hz, 2H^{7}), 2.23 (s, 6H^{11,12}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9 (C^{3}), 138.1 (C^{8}), 137.8 (C^{2}, isotopomers), 129.1 (2CH^{Ar}), 128.6 (2CH^{Ar}), 127.3 (CD_2^{1}), 127.2 (CH_2^{1}), 126.7 (CH^{17}), 65.4 (CH_2^{6}), 60.1 (CH_2^{9}), 60.0 (CD_2^{9}), 45.5 (2CH_3^{11,12}), 45.4 (2CH_3^{11,12}, isotopomer), 35.2 (CH_2^{7}) ppm.

IR (neat) ν_{max}: 2943, 2818, 2769, 1714, 1454, 1267, 1177, 1031, 748, 698 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+H]^+$ ($C_{14}H_{18}D_2NO_2^+$) requires 236.1614 found 236.1613.

3.39b: 2,2-Diphenylethyl 2-((dimethylamino)methyl)acrylate



The compound was prepared using general procedure **C** from **3.38b** (50.5 mg, 0.20 mmol) and Eschenmoser's salt (111 mg, 0.60 mmol). Purification by flash column chromatography on silica gel (10% DMA-MIX to 40% DMA-MIX in DCM) afforded compound **3.39b** in 63% (39.2 mg) yield as a white solid.

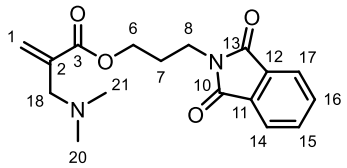
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 10H^{Ar}), 6.10 – 6.06 (m, 1H^{1cis}), 5.65 – 5.61 (m, 1H^{1trans}), 4.71 (d, *J* = 7.6 Hz, 2H^{5}), 4.42 (t, *J* = 7.6 Hz, 1H^{11}), 3.01 (s, 2H^{7}), 2.17 (s, 6H^{9,10}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8 (C^{3}), 141.3 (2C^{4,12}), 137.7 (C^{2}), 128.7 (4CH^{Ar}), 128.4 (4CH^{Ar}), 127.4 (2CH^{15,18}), 127.0 (CH_2^{1}), 67.1 (CH_2^{5}), 60.0 (CH_2^{7}), 50.0 (CH^{11}), 45.4 (2CH_3^{9,10}) ppm.

IR (neat) ν_{max}: 2818, 2769, 1716, 1494, 1452, 1304, 1269, 1177, 1160, 1135, 1033, 698 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}NO_2^+$) requires 310.1802, found 310.1807.

3.39c: 3-(1,3-Dioxoisoindolin-2-yl)propyl 2-((dimethylamino)methyl)acrylate



The compound was prepared using general procedure **C** from **3.38c** (51.9 mg, 0.20 mmol) and Eschenmoser's salt (111 mg, 0.60 mmol). Purification by flash column chromatography on silica gel (5% DMA-MIX to 40% DMA-MIX in DCM) afforded compound **3.39c** in 66% (42.0 mg) yield as a yellow oil.

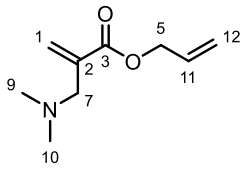
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.82 (m, $2H^{Ar}$), 7.74 – 7.69 (m, $2H^{Ar}$), 6.29 (s, $1H^{1}$), 5.77 (s, $1H^{1}$), 4.26 – 4.19 (m, $2H^{6}$), 3.87 – 3.80 (m, $2H^{8}$), 3.16 (s, $2H^{18}$), 2.27 (s, $2H^{20,21}$), 2.14 – 2.05 (m, $2H^{Al}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 ($2C^{10,13}$), 166.6 (C^{3}), 136.9 (C^{2}), 134.0 ($2CH^{Ar}$), 132.1 ($2C^{11,12}$), 128.0 ($CH_2{}^{1}$), 123.3 ($2CH^{Ar}$), 62.2 ($CH_2{}^{Al}$), 59.6 ($CH_2{}^{Al}$), 45.1 ($2CH_3{}^{20,21}$), 35.1 ($CH_2{}^{Al}$), 27.6 ($CH_2{}^{Al}$) ppm.

IR (neat) ν_{max}: 2944, 2819, 2769, 1771, 1704, 1395, 1373, 1178, 1135, 1041, 718 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{21}N_2O_4^+$) requires 317.1496, found 317.1507.

3.39d: Allyl 2-((dimethylamino)methyl)acrylate



The compound was prepared using general procedure **C** from **3.38d** (22.4 mg, 0.20 mmol) and Eschenmoser's salt (148 mg, 0.80 mmol). Purification by flash column chromatography on silica gel (10% DMA-MIX to 50% DMA-MIX in DCM) afforded compound **3.39d** in 38% (12.7 mg) yield as a colourless oil.

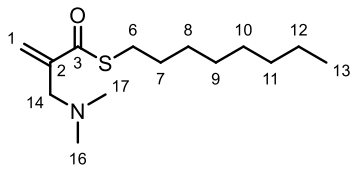
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 – 6.28 (m, 1H^{1cis}), 6.01 – 5.89 (m, 1H^{11}), 5.77 – 5.73 (m, 1H^{1trans}), 5.39 – 5.31 (m, 1H^{12}), 5.27 – 5.21 (m, 1H^{12}), 3.14 (s, 2H^{7}), 2.25 (s, 6H^{9,10}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6 (C^3), 137.8 (C^2), 132.4 (CH_2^{12}), 127.3 (CH_2^1), 118.2 (CH^{11}), 65.5 (CH_2^5), 60.1 (CH_2^7), 45.51 ($2CH_3^{9,10}$) ppm.

IR (neat) ν_{max}: 2946, 2820, 2770, 1720, 1456, 1270, 1179, 1136, 1037, 988 cm^{-1}.

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_9H_{16}NO_2^+$) requires 170.1176 *m/z*, found 170.1180 *m/z*.

3.39j: *S*-Octyl 2-((dimethylamino)methyl)prop-2-enethioate



The compound was prepared using general procedure **C** from **3.38j** (40.1 mg, 0.20 mmol) and Eschenmoser's salt (111 mg, 0.60 mmol). Purification by flash column chromatography on alox (0%–15% EtOAc in heptane) afforded compound **3.39j** in 49% (25.2 mg) yield as a yellow oil.

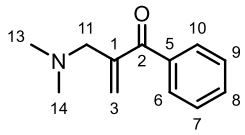
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (app.s, 1H^1), 5.69 (app.s, 1H^1), 3.17 (s, 2H^{14}), 2.92 (t, *J* = 7.4 Hz, 2H^6), 2.23 (s, 6H^{16,17}), 1.73 – 1.54 (m, 2H^7), 1.42 – 1.20 (m, 10H$^{8–12}$), 0.92 – 0.82 (m, 3H^{13}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6 (C^3), 145.5 (C^2), 124.5 (CH_2^1), 60.3 (CH_2^{14}), 45.5 ($2CH_3^{16,17}$), 31.9 (CH_2^{Al}), 29.5 (CH_2^{Al}), 29.30 (CH_2^{Al}), 29.25 (CH_2^{Al}), 29.1 ($2CH_2^{Al}$), 22.8 (CH_2^{Al}), 14.2 (CH_3^{13}) ppm.

IR (neat) ν_{max}: 2924, 2853, 1718, 1662, 1629, 1455, 1265, 971 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{28}NOS^+$) requires 258.1886, found 258.1887.

3.39q: 2-((Dimethylamino)methyl)-1-(4-methoxyphenyl)prop-2-en-1-one



The compound was prepared using general procedure **C** from **3.38q** (26.4 mg, 0.20 mmol) and Eschenmoser's salt (111 mg, 0.60 mmol). Purification by flash column chromatography on alox (0% DMA-MIX to 30% DMA-MIX in DCM) afforded compound **3.39q** in 95% (35.9 mg) yield as a yellow oil.

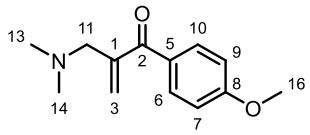
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.3 Hz, 2H^{6,10}), 7.54 (t, *J* = 7.4 Hz, 1H^{8}), 7.44 (app.t, *J* = 7.6 Hz, 2H^{7,9}), 6.02 (s, 1H^{3}), 5.75 (s, 1H^{3}), 3.35 (s, 2H^{11}), 2.31 (s, 6H^{13,14}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5 (C^2), 145.1 (C^1), 137.5 (C^5), 132.6 (CH^8), 129.8 ($2CH^{Ar}$), 128.4 ($2CH^{Ar}$), 127.3 ($CH_2{}^3$), 60.8 ($CH_2{}^{11}$), 45.6 ($2CH_3{}^{13,14}$) ppm.

IR (neat) ν_{max}: 2943, 2817, 2767, 1653, 1596, 1446, 1320, 1202, 1175, 1029, 855, 751, 694 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{16}NO^+$) requires 190,1226, found 190.1225.

3.39r: 2-((Dimethylamino)methyl)-1-(4-methoxyphenyl)prop-2-en-1-one



The compound was prepared using general procedure **C** from **3.38r** (32.4 mg, 0.20 mmol) and Eschenmoser's salt (111 mg, 0.60 mmol). Extraction afforded pure compound **3.39r** in 98% (43.0 mg) yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.7 Hz, 2H^{6,10}), 6.93 (d, *J* = 8.7 Hz, 2H^{7,9}), 5.89 (s, 1H^{3}), 5.64 (s, 1H^{3}), 3.87 (s, 3H^{16}), 3.31 (s, 2H^{11}), 2.28 (s, 6H^{13,14}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3 (C^2), 163.4 (C^8), 145.7 (C^1), 132.2 ($2CH^{7,9}$), 130.1 (C^5), 125.0 ($CH_2{}^3$), 113.6 ($2CH^{6,10}$), 61.5 ($CH_2{}^{11}$), 55.6 ($CH_3{}^{16}$), 45.7 ($2CH_3{}^{13,14}$) ppm.

IR (neat) ν_{max}: 2939, 2817, 2768, 1650, 1596, 1507, 1307, 1253, 1162, 1028, 842, 789, 568 cm^{-1}.

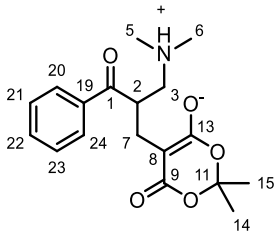
HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{18}NO_2^+$) requires 220.1332, found 220.1332.

3.4.4 Zwiterion synthesis

General procedure D: Mannich/*aza*-MBH/Michael sequence

In an oven-dried vial were mixed methyl ketone (1 equiv.) and Eschenmoser's salt (4 equiv.). HFIP (1 M) was added, and the mixture was stirred at 70 °C for 14 h upon which it was allowed to cool to room temperature. CH_2Cl_2 was added and the excess of Eschenmoser's salt was quenched with 5 mL $NaOH_{aq}$ (1 M) solution. The phases were separated, and the aqueous layer was extracted three times with 10 mL CH_2Cl_2. The combined organic phases were dried over K_2CO_3, filtered and the solvent was removed under reduced pressure. The crude material was dissolved in MeCN (0.1 M) and Meldrum's acid (5 equiv.) was added. The solution was stirred at room temperature for 4 h upon which it was diluted with CH_2Cl_2, H_2O and $NaOH_{aq}$ (0.1 M) until a pH of 7 was reached. The phases were separated, and the aq. phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude material was triturated with Et_2O to yield the analytically pure product.

3.51a: 5-(2-((Dimethylammonio)methyl)-3-oxo-3-phenylpropyl)-2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-olate



The compound was prepared using general procedure **D** from acetophenone (58.3 µL, 0.5 mmol). Trituration afforded pure compound **3.51a** in 58% (96.0 mg) yield as an orange solid.

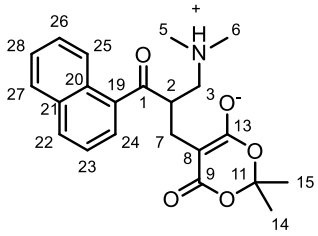
^{1}H NMR (600 MHz, OS(CD$_3$)): δ 10.45 (bs, 1H^{NH}), 8.15 – 8.11 (m, 2H^{20,24}), 7.63 (app.t, *J* = 7.4 Hz, 1H^{22}), 7.53 (app.t, *J* = 7.9 Hz, 2H^{21,23}), 4.15 – 4.08 (m, 1H^{2}), 3.28 – 3.16 (m, 2H^{Al}), 2.79 (s, 6H^{5,6}), 1.65 (s, 6H^{14,15}) ppm. *2 H not reported due to overlap with the residual solvent peak at 2.50*

^{13}C NMR (150 MHz, OS(CD$_3$)): δ 199.5 (C^{1}), 166.3 (2C^{9,13}), 135.8 (C^{19}), 133.0 (CH^{22}), 128.7 (2CH^{Ar}), 128.4 (2CH^{Ar}), 100.0 (C^{8}), 68.0 (C^{11}), 56.2 (CH$_2$^{3}), 42.7 (2CH$_3$^{5,6}), 30.7 (CH^{2}), 25.7 (2CH$_3$^{14,15}), 25.3 (CH$_2$^{7}) ppm.

IR (neat) ν_{max}: 1678, 1560, 1351, 1253, 1179, 1122, 946, 783, 703 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for [M+H]$^+$ ($C_{18}H_{24}NO_5^+$) requires 334.1649, found 334.1656.

3.51b: 5-(2-((Dimethylammonio)methyl)-3-(naphthalen-1-yl)-3-oxopropyl)-2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-olate



The compound was prepared using general procedure **D** from 1-acetonaphthone (85.1 µL, 0.5 mmol). Trituration afforded pure compound **3.51b** in 53% (102 mg) yield as an orange solid.

Experimental Data

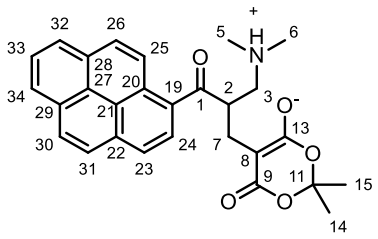
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.60 (bs, 1H^{NH}), 8.52–8.45 (m, 1H^{Ar}), 8.43 (d, J = 7.2 Hz, 1H^{Ar}), 8.15 (d, J = 7.2 Hz, 1H^{Ar}), 8.02–7.96 (m, 1H^{Ar}), 7.65–7.54 (m, 3H^{Ar}), 4.23–4.13 (m, 1H^{2}), 2.82 (s, 6H^{5,6}), 1.49 (s, 6H^{14,15}) ppm. 2 H not reported due to overlap with the residual water peak at 3.34 and 2 H not reported due to overlap with the residual solvent peak at 2.50 ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 203.2 (C^{1}), 166.3 (2C^{9,13}), 134.2 (C^{Ar}), 133.6 (C^{Ar}), 132.8 (CH^{Ar}), 130.3 (C^{Ar}), 128.9 (CH^{Ar}), 128.2 (CH^{Ar}), 127.4 (CH^{Ar}), 126.4 (CH^{Ar}), 126.2 (CH^{Ar}), 124.6 (CH^{Ar}), 100.0 (C^{8}), 68.3 (C^{11}), 56.6 (CH$_2$^{3}), 45.4 (2CH$_3$^{5,6}), 33.4 (CH^{2}), 25.6 (2CH$_3$^{14,15}), 25.0 (CH$_2$^{7}) ppm.

IR (neat) ν_{max}: 1685, 1559, 1482, 1191, 1114, 924, 766, 745 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for [M+H]$^{+}$ ($C_{22}H_{26}NO_5^{+}$) requires 384.1805, found 384.1808.

3.51c: 5-(2-((Dimethylammonio)methyl)-3-oxo-3-(pyren-1-yl)propyl)-2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-olate



The compound was prepared using general procedure **D** from 1-acetopyrene (89 mg, 0.36 mmol). Trituration afforded pure compound **3.51c** in 68% (114 mg) yield as a yellow solid.

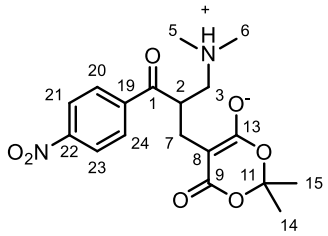
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.66 (bs, 1H^{NH}), 8.89 (d, *J* = 8.2 Hz, 1H^{Ar}), 8.79 (d, *J* = 9.3 Hz, 1H^{Ar}), 8.43–8.36 (m, 3H^{Ar}), 8.35–8.24 (m, 3H^{Ar}), 8.17–8.12 (m, 1H^{Ar}), 4.40 (bs, 1H^{2}), 3.52–3.40 (m, 2H^{3}), 2.89 (s, 6H^{5,6}), 2.69–2.56 (m, 2H^{7}), 1.50 (s, 6H^{14,15}) ppm.

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 203.6 (C^{1}), 166.4 (2C^{9,13}), 133.4 (C^{Ar}), 131.1 (C^{Ar}), 130.6 (C^{Ar}), 130.0 (C^{Ar}), 129.7 (C^{Ar}), 129.5 (CH^{Ar}), 128.8 (CH^{Ar}), 127.5 (CH^{Ar}), 127.2 (CH^{Ar}), 126.7 (CH^{Ar}), 126.4 (CH^{Ar}), 126.0 (CH^{Ar}), 125.6 (CH^{Ar}), 124.2 (C^{Ar}), 124.1 (CH^{Ar}), 123.4 (C^{Ar}), 100.0 (C^{8}), 68.3 (C^{11}), 56.7 (CH$_2$^{3}), 45.8 (2CH$_3$^{5,6}), 34.4 (CH^{2}), 25.6 (2CH$_3$^{14,15}), 25.0 (CH$_2$^{7}) ppm.

IR (neat) ν_{max}: 1714, 1671, 1558, 1414, 1114, 849 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{28}H_{28}NO_5^+$) requires 458.1962, found 458.1962.

3.51d: 5-(2-((dimethylammonio)methyl)-3-(4-nitrophenyl)-3-oxopropyl)-2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-olate



The compound was prepared using general procedure D from *p*-nitroacetophenone (82.6 mg, 0.5 mmol). Extraction afforded pure compound **3.51d** in >99% (191 mg) yield as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.30 (bs, 1H^{NH}), 8.54 (d, *J* = 8.9 Hz, 2H^{21,23}), 8.17 (d, *J* = 8.9 Hz, 2H^{20,24}), 4.20 – 4.11 (m, 1H^{2}), 3.62 (app.dd, *J* = 13.2, 5.4 Hz, 1H^{Al}), 3.33 (app.dd, *J* = 13.2, 6.5 Hz, 1H^{Al}), 2.87 – 2.73 (m, 1H^{Al}), 2.81 (s, 6H^{5,6}), 2.51 (app.dd, *J* = 15.0, 9.0 Hz, 1H^{Al}), 1.65 (s, 6H^{14,15}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0 (C^{1}), 168.5 (2C^{9,13}), 150.6 (C^{22}), 139.8 (C^{19}), 130.6 (2CH^{20,24}), 123.9 (2CH^{21,23}), 102.8 (C^{8}), 70.8 (C^{11}), 56.8 (CH_2^3), 45.4 (2$CH_3^{5,6}$), 44.1 (CH^{2}), 25.8 (CH_2^7), 25.7 (2$CH_3^{14,15}$) ppm.

IR (neat) ν_{max}: 1676, 1578, 1518, 1384, 1326, 1218, 1109, 973, 700 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{18}H_{23}N_2O_7^+$) requires 379.1500, found 379.1502.

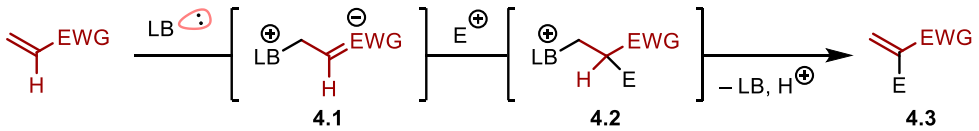
4 Intramolecular C–H Arylation Mediated by Lewis Base

4.1 Introduction

Lewis bases have long been recognised as effective additives to speed up chemical reactions by formation of complexes with electrophiles.[100,101] For example, the nucleophilicity of silanes can be enhanced by fluoride, or the electrophilicity of acid chlorides increased by amine catalysts. This chapter, however, will focus on the utility of Lewis bases in combination with electron-deficient alkenes, following up on the introduction to the Morita–Baylis–Hillman (MBH) reaction described in the previous chapter. In addition, aryl migration reactions onto electron-deficient alkenes will be introduced and, finally, these concepts will be combined in the development of a new, Lewis base-mediated aryl migration reaction for the synthesis of α-aryl acrylamides.

4.1.1 Lewis Bases as a Tool for Enolate Formation

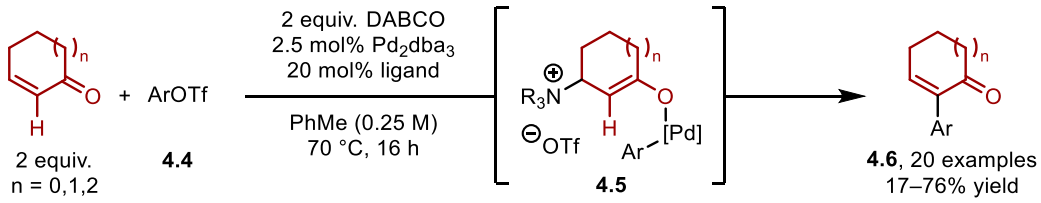
Nucleophilic catalysts, such as the ones employed in Morita–Baylis–Hillman reactions, interact with electron-deficient alkenes forming zwitterionic species **4.1** (Scheme 63). These in situ-generated, highly polar intermediates can be used for electrophilic functionalisation (**4.2**) followed by elimination, regenerating the Lewis-basic catalyst. The newly formed alkene **4.3** is the product of a formal substitution of the α-hydrogen with an electrophile.



Scheme 63: A general hydrogen-to-electrophile substitution catalysed by a Lewis base.

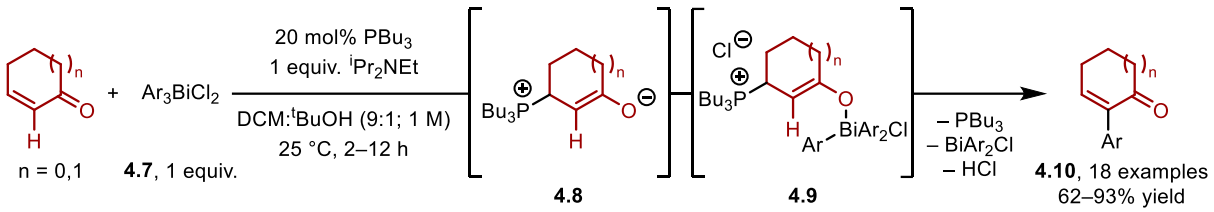
This chemistry, reminiscent of classical enolate-type reactions, can involve many different electrophiles as long as their nature is such that direct reaction with the Lewis base is

reversible (Scheme 41a). Selected examples beyond the classical MBH and Rauhut–Currier reactions involving carbon, nitrogen or halogen electrophiles have already been presented in the previous chapter (Scheme 41b). In a recent publication by Newman *et al.*, the scope was expanded to aryl triflates **4.4**, a different class of carbon-centred sp^2-hybridised electrophiles, which were coupled with DABCO-generated enolates.[102] Therein, cyclic enones were α-arylated using a transient cationic aryl palladium complex, which served two purposes: (1) it served as the cross-coupling catalyst, and (2) it also acted as a Lewis acid, rendering the ketone more electrophilic and therefore allowing for facile conjugate addition of DABCO (**4.5**, Scheme 64). The reaction scope of **4.6** indicated significant dependence of the yield on the electronic nature of the electrophile, with electron-neutral aromatic groups being coupled most effectively.



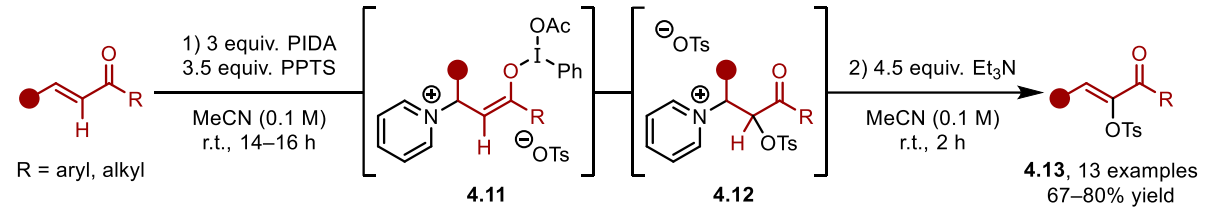
Scheme 64: The combination of DABCO and palladium catalysis allows for direct formal C–H arylation of cyclic enones. dba = dibenzylideneacetone; ligand = 2'-(Dicyclohexylphosphanyl)-N2,N2,N6,N6-tetramethyl[1,1'-biphenyl]-2,6-diamine (CPhos) or (2-Biphenyl)-di-tert.-butylphosphine (JohnPhos).

In the context of arylation of electron-deficient alkenes, similar rearrangement sequences have also been explored with other catalysts. In a 2004 publication, Krische *et al.* reported the phosphine-mediated arylation of cyclic enones with aryl bismuth reagents **4.7** (Scheme 65).[103] After Lewis base-induced enolate formation (**4.8**), ligand exchange at bismuth led to complex **4.9** which collapsed to product **4.10** with concomitant the extrusion of reduced $BiAr_2Cl$. The hydrogen chloride, generated by elimination of tributyl phosphine, was captured with $^iPr_2NEt$. While electron-deficient and -neutral aryl groups migrated efficiently, electron-donating substituents in *para*-position were not tolerated, indicating a nucleophilic attack of the enolate on the arene as the mode of aryl transfer. Besides cyclic ketones, this arylation method was also demonstrated on four examples using crotonaldehyde as the alkene reaction partner.



Scheme 65: The combination of a phosphine and an aryl-bismuth reagent allows for the α-C–H arylation of cyclic enones.

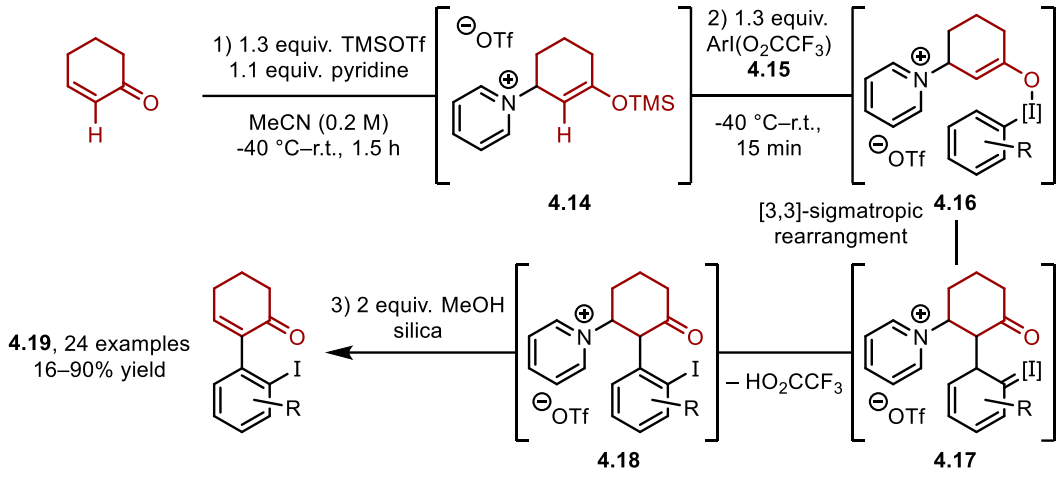
Recent developments in Lewis base-mediated α-functionalisation of electron-deficient double bonds involve further treatment of zwitterion **4.1** (Scheme 63) with additional reagents, such as hypervalent iodine compounds, to force umpolung at the α-carbon[104] or induce downstream rearrangements.[105,106] Szpilman *et al.* used a combination of pyridine and iodine(III) reagents to perform an umpolung of vinyl ketones, which allowed for a formal substitution of hydrogen with oxygen-centred nucleophiles (Scheme 66).[104] The combination of the reagents PIDA and PPTS allows for the generation of putative electrophilic enolonium intermediate **4.11**, which can be attacked by the tosylate counterion, liberating iodobenzene and acetate. The acetate ion is subsequently protonated by excess pyridinium, explaining how tosylate is the sole nucleophile. Pyridinium salt **4.12** was observed by NMR and requires deprotonation by additional triethylamine to form enone **4.13**, now oxidised in α-position.



Scheme 66: Lewis base-mediated α-umpolung of vinyl ketones.
PIDA = (diacetoxyiodo)benzene; PPTS = pyridinium p-toluenesulfonate.

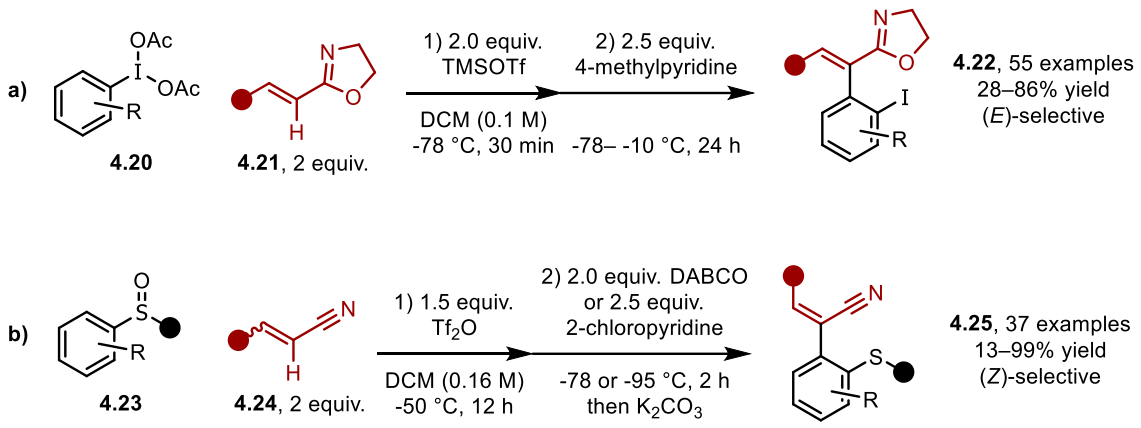
In 2020, Wengryniuk *et al.* reported aryl rearrangement/migration of an iodine complex **4.16**, similar to **4.11**, allowing for the synthesis of *ortho*-iodo-substituted α-(hetero)aryl cyclohexenones **4.19** (Scheme 67a).[105] One example each of cyclopentenone (78% yield), cycloheptenone (12%) and butenal (42%) were also reported within this study. *In situ* formation of silyl enol ether **4.14,** followed by treatment with derivatives of PIFA (**4.15**), the

trifluoroacetate analogue of PIDA, led to intermediate **4.16**, which is prone to [3,3]-sigmatropic rearrangement (**4.17**) forming the new C–C bond while simultaneously breaking the O–I bond (**4.18**).



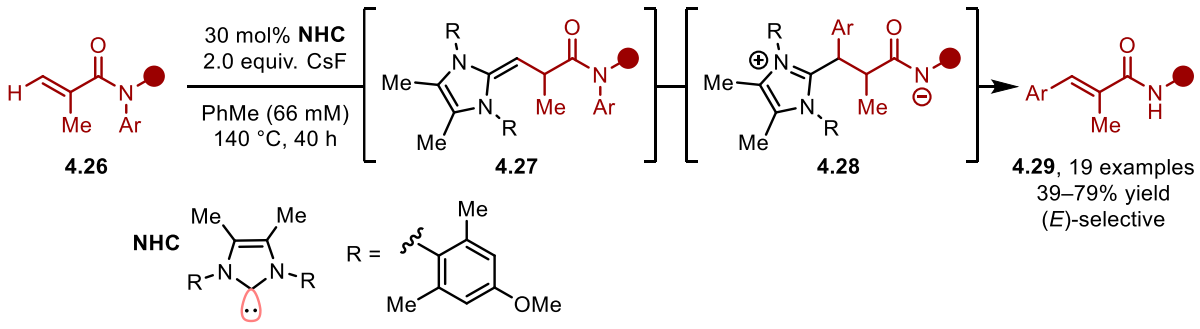
Scheme 67: a) A pyridine-mediated formal C–H arylation of enones through a conjugate addition/oxidation/[3,3]-sigmatrpic rearrangement sequence. [I] = IO_2CCF_3.

Using non-fluorinated I(III) reagents **4.20**, Peng *et al.* have demonstrated a similar process on 2-vinyl dihydrooxazoles **4.21** (Scheme 68a).[106] In this approach, use of the Lewis base 4-methylpyridine allowed for the (*E*)-selective synthesis of *ortho*-iodoaryl products **4.22** with broad functional group tolerance. However, this protocol could not be applied to other Michael acceptors like aldehydes, ketones, esters or carboxamides. The opposite stereoselectivity was observed when sulfoxides (**4.23**) were employed instead of hypervalent iodine. Here, reaction with acrylonitriles (**4.24**) resulted in α-arylation with complete (*Z*)-selectivity (**4.25**, Scheme 68b).[107] Quantum chemical calculations revealed the difference in relative transition state energy in the [3,3]-sigmatropic rearrangement to be the determining factor governing the selectivity—the diastereomer leading to the (*Z*)-product **4.25** was found to be favored by 6.1 kcal/mol.



Scheme 68: a) Arylation of dihydrooxazole derivatives with (E)-selectivity. b) Arylation of acrylonitriles with (Z)-selectivity.

While the discussed arylation methods used nitrogen- and phosphorus-centred Lewis bases, carbenes can also be employed to trigger intermolecular aryl migration on *N*-aryl acrylamides (**4.26**, Scheme 69). Tobisu *et al.,* and shortly after Zhou *et al.,* reported the synthesis of β-aryl acrylamides (cinnamides) **4.29** by *N*-heterocyclic carbene (NHC) catalysis.[108,109] Therein, the NHC catalyst reacts with the Michael acceptor to form a vinylogous Breslow intermediate (**4.27**), which subsequently undergoes a polar aryl migration through an S_NAr reaction, often referred to as a Truce–Smiles rearrangement (**4.28**).

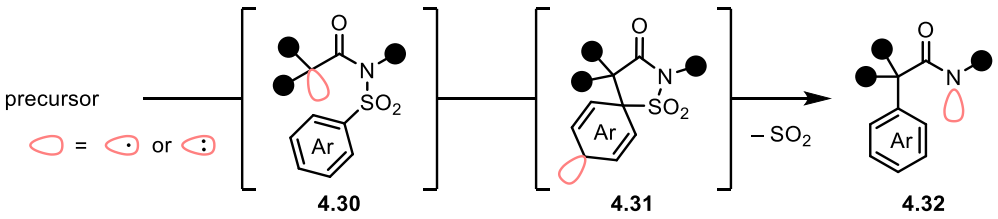


Scheme 69: NHC-catalysed aryl migration for the synthesis of cinnamides, as reported by Tobisu et al.[108]

The Truce–Smiles rearrangement is a powerful synthetic tool to migrate aromatic groups into positions of molecules which would be more difficult to functionalise using other methods. The rearrangement can process through both closed- and open-shell pathways, which will be further discussed in section 4.1.2.

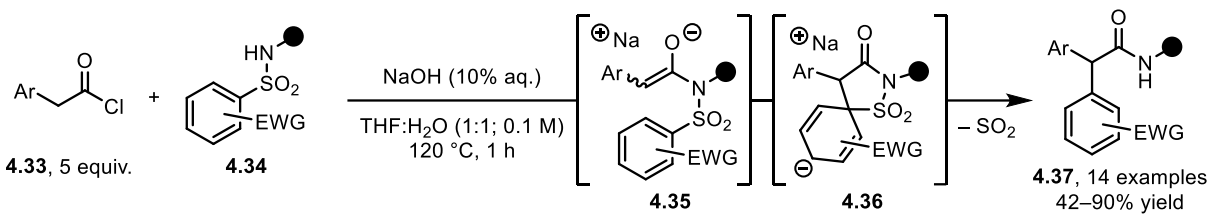
4.1.2 Aryl Migration Reactions on Sulfonyl Acrylimides

Aryl migration reactions with sulfonyl carboximides are well-established processes for the synthesis of densely functionalised α-aryl amides.[110] These methods hinge on Truce–Smiles rearrangements, which can proceed in either a closed- or an open-shell fashion[111,112] through a five-membered spirocyclic Meisenheimer intermediate or transition state (Scheme 70). Different methods allow for in situ generation of radicals[113] or anions[114] α- to the carbonyl (**4.30**), which subsequently engage the tethered aryl group, forming **4.31**—as mentioned above, **4.31** can either constitute a transition state or a discrete intermediate of this process. Ring opening and SO_2 liberation lead to the desired α-aryl carboxamide **4.32**, now bearing a reactive nitrogen (radical or anion), which can engage in further reactions.



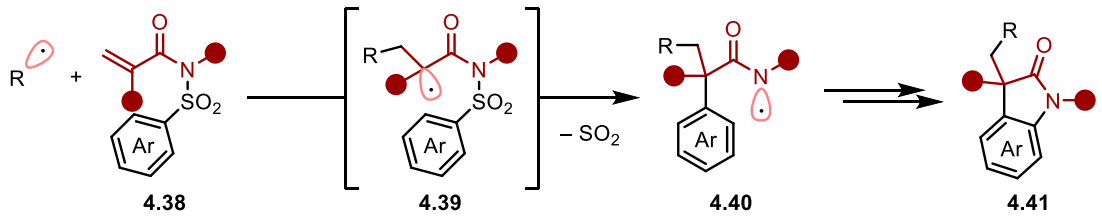
Scheme 70: A general radical or anionic Truce–Smiles sequence for aryl migration on sulfonyl carboximides.

First anionic versions of such a reaction were explored as early as 1955 by Dohmori *et al.*, who described the migration of nitrophenyl groups following deprotonation of the corresponding sulfonyl carboximide.[115] Greaney *et al.* later developed a method using carboxylic acid chlorides **4.33** together with sulfonamides **4.34**, forming enolate intermediates **4.35**, which subsequently engage in a desulfonylative aryl migration (**4.36**) (Scheme 71).[116] Owing to the anionic nature of the rearrangement, electron-deficient groups (such as nitro-substituted arenes or electron-deficient heteroarenes) were found to be required to ensure efficient reaction. Using this method, bisaryl acetamides **4.37** can be prepared in one step directly from simple carboxylic acid chlorides and sulfonamides.



Scheme 71: Anionic aryl migration allows for the direct synthesis of bisaryl acetamides, as reported by Greaney et al.[116]

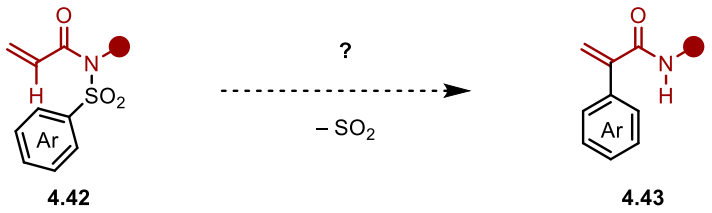
Besides anionic pathways, similar arylfunctionalisation reactions were also developed involving radical sequences. For example, (formal) α-radicals can be generated by reduction of α-bromo amides,[117–120] hydrogen atom transfer[121] or enolate oxidation.[122] In addition to saturated imides, acrylimides **4.38** are also prone to undergo such single-electron-induced migration when treated with a species capable of Giese addition to double bonds (**4.39**) (Scheme 72). The resulting densely functionalised saturated carboxamide **4.40** bears an amidyl radical which can engage in further reactions such as oxindole **4.41** formation.[110]



Scheme 72: General arylfunctionalisation of sulfonyl acrylimides initiated by radical addition to the alkene.

Over the last decade, several reports taking advantage of such reactivity have emerged. Nevado *et al.* largely contributed to initial exploration of this field, publishing a series of seminal papers using carbon-,[123–125] nitrogen-,[125,126] phosphorus-,[125,126] and sulfur-centred radical species.[125] Since then, multiple other groups have taken interest in this research field, contributing to a detailed understanding of the reaction's capabilities and boundaries.[110] Recently, Nevado *et al.* even reported a first enantiospecific version, employing enantiopure sulfinimides instead of achiral sulfonamides.[127] Remarkably, besides a handfull examples, the employed acrylimides were all α-substituted (usually methyl), presumably due to the need for radical stabilisation through hyperconjugation. Another particularly striking feature of this type of process the requirement for electron-neutral or -rich arenes, which stands in contrast to any anionic strategies, in which solely electron-deficient arenes migrate. To the best of our

knowledge, for similar sulfonyl acrylimide-based sequences, no anionic method has been reported to date. In this chapter, such a strategy will be investigated, allowing for the conversion of **4.42** into α-aryl acrylamides **4.43** which would not be accessible through a more traditional radical pathway (Scheme 73).

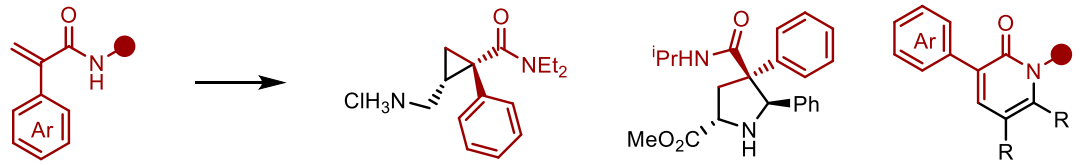


4.42 **4.43**

Scheme 73: A hypothetical formal hydrogen/aryl exchange including loss of SO_2.

4.1.3 Use and Synthesis of α-Aryl Acrylamides

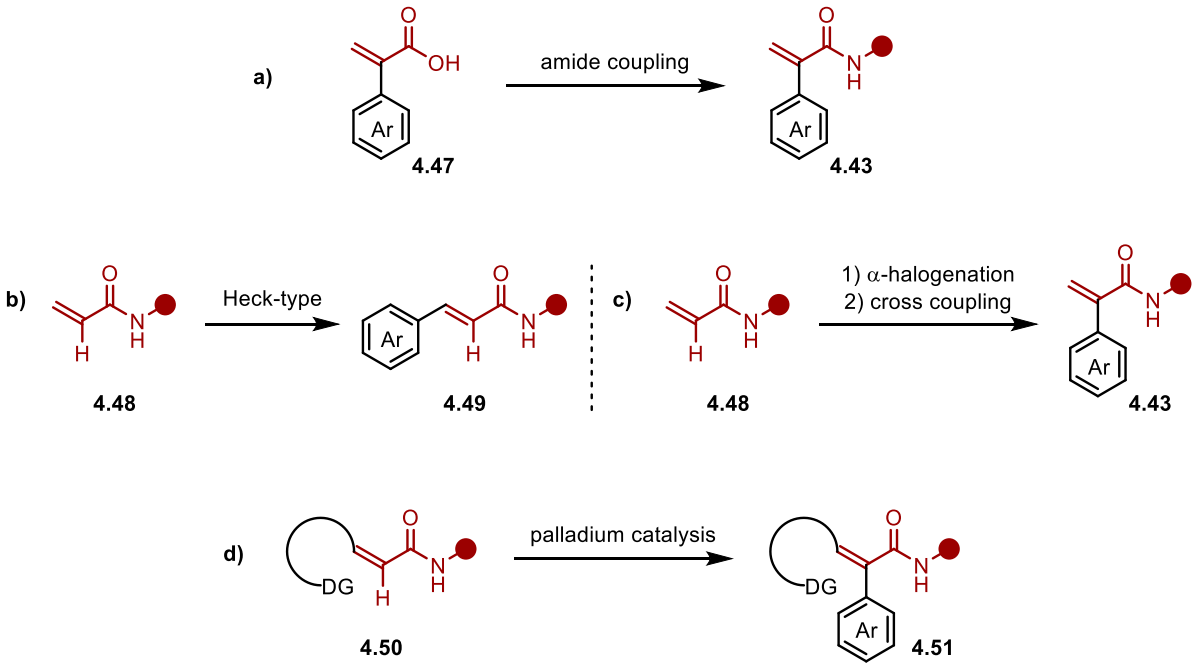
α-Aryl acrylamides are commonly used as simple building blocks for various processes. A wide range of compounds containing different-sized rings, for example, can be formed from acrylamides in cycloaddition reactions (Figure 4). Arnold *et al.,* for instance, have used these building blocks in enzymatic cyclopropanation processes for the synthesis of Levomilnacipran.[128] Wang *et al.* investigated their use in enantioselective (3+2)-dipolar cycloadditions to form densely functionalised pyrrolidines **4.44**[129] and multiple transition metal-catalysed methods for the oxidative formation of pyridinones **4.45** have also been reported.[130,131] In addition to the synthesis of cyclic compounds, the reactive wedged alkene in structures such as **4.46** allows for facile defunctionalisation, for example through electrochemical difluoromethylation,[132] or copper-catalysed carbohalogenation (not shown).[133]



4.43 *Levomilnacipran*, **4.44** **4.45** **4.46**

Figure 4: Selected examples for the use of a-aryl acrylamides in cycloaddition reactions.

The synthesis of α-aryl acrylamides is commonly performed using one of three strategies: The first one relies on an available corresponding carboxylic acid **4.47**, which is coupled to a desired amine (Scheme 74a). While this is a simple process, it cannot be used if the corresponding starting materials are not easily available, as is the case for acids bearing aryl groups other than phenyl. The second approach involves metal-catalysed cross coupling of amides **4.48**—however, as traditional Heck-type chemistry delivers the β-substituted regioisomer **4.49** (Scheme 74b),[134] a two-step strategy needs to be employed to synthesise **4.43** from **4.48** (Scheme 74c).[130] Herein, initial α-halogenation is required to set the stage for selective a cross coupling, such as a palladium-catalysed Suzuki–Miyaura reaction. The third option is substrate-dependent as it requires a directing group (**4.50**), such as a carboxylic acid, allowing for α- over β- selectivity in a C–H arylation strategy (**4.51**, Scheme 74d).[135] Since a broadly applicable and direct synthetic pathway is still elusive, inspired by the reactions discussed in sections 4.1.1 and 4.1.2, we sought to develop a process such as the one outlined in Scheme 73.



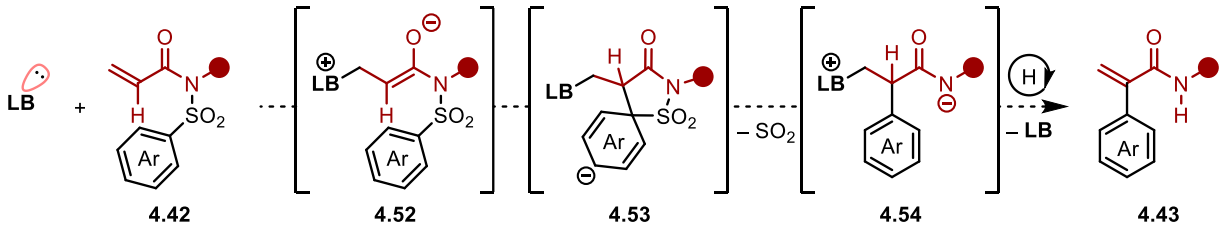
Scheme 74: Methods to synthesise secondary α-aryl carboxamides. a) Amide coupling of α-aryl carboxylic acids. b) Heck-type reactions lead to β-arylation. c) α-Arylation requires a two-step process. d) A tethered directing group allows for direct α-C-H arylation.

4.2 Results and Discussion

The results described in this chapter were obtained in collaboration with Haoqi Zhang, Tobias Fischer, Marianne Mießkes and Yi Xiao. Dr. Anthony J. Fernandes performed quantum chemical calculations which will be briefly discussed. Parts of the reactions were performed in the laboratory of Prof. Dr. Hideki Yorimitsu at Kyoto University. The results of this chapter have been reported in Angewandte Chemie International Edition.[136]

4.2.1 Synthesis of α-Aryl Acrylamides Through Lewis Based-Induced Aryl Migration

As previously described, an aryl migration on sulfonyl carboximides **4.42** can be triggered through the formation of an α-radical or an enolate (Scheme 70).[110] While the radical pathway, through addition of an exogenous radical to a sulfonyl acrylamide, followed by rearrangement and SO_2 extrusion has been extensively studied (Scheme 72), it cannot be employed for the synthesis of α-aryl acrylamides as the alkene itself is functionalised in the process. To obtain the desired products, we envisioned an anionic mechanism initiated by a Lewis base (Scheme 75). The Lewis base was thought to be able to attack the acrylimide **4.42** to form a zwitterionic intermediate **4.52**, analogously to the one formed in the Morita–Baylis–Hillman and Rauhut–Currier reactions (section 3.1.1), or the reactions outlined in section 4.1.1. Intermolecular nucleophilic attack on the aromatic group would lead to Meisenheimer stationary complex **4.53** (intermediate or transition state) which could be followed by ring opening and loss of SO_2 to form amidate **4.54**.[137] Then, proton transfer from the α-position to nitrogen would effect elimination and regeneration of the Lewis base. This mechanism would not only allow for the synthesis of products **4.43**, but also constitute a catalytic process involving a formal aryl/hydrogen exchange with the extrusion of SO_2 as one of the driving forces.



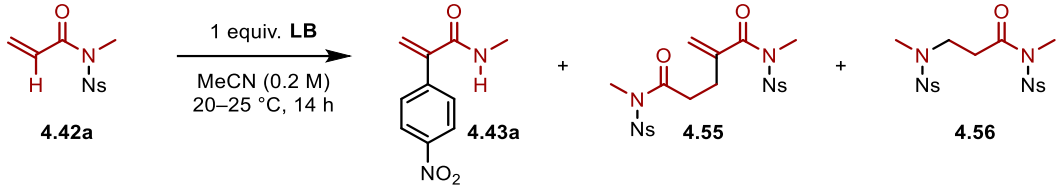
Scheme 75: A hypothetical, Lewis base-catalysed Morita–Baylis–Hillman–Smiles reaction.

In the proposed reaction sequence, several steps were initially identified as potentially problematic. For example, if the Lewis base were to add in a 1,2-fashion, as opposed to the desired 1,4-attack, unwanted C–N cleavage could become a viable pathway.[138] Moreover, Rauhut–Currier-type dimerization, instead of the formation of **4.53,** could also occur. Finally, it was also not initially clear whether a C-to-N proton transfer in **4.54** would happen under the reaction conditions, as similar processes have been known to require an additional shuttling species (see section 3.1.1).

To start our investigations, we performed a screening of different Lewis bases in the polar solvent acetonitrile, employing nosyl acrylimide **4.42a** (Table 6). We initially chose DABCO (entry 1), a common reagent for similar conjugate additions, and observed a promising 40% yield of the desired acrylamide **4.43a**. At the same time, however, we were able to detect significant amounts of by-products, predominantly those shown above Table 6. One was the result of the aforementioned Rauhut–Currier dimerization **4.55**, while the other presumably stemmed from sulfonamide liberation, triggered by Lewis base-assisted C–N cleavage, and followed by a 1,4-addition (*aza*-Michael addition) of the sulfonamide to a second molecule of **4.42a** (**4.56**). Other nitrogen nucleophiles did not improve the yield of **4.43a** (entries 2–11). Interestingly, the six-membered amine *N*-methylmorpholine (entry 6) did not deliver any **4.43a** while the five-membered *N*-methylpyrrolidine (entry 7) reacted comparably to the highly nucleophilic DABCO (entry 1). To facilitate the proton transfer in the last step of the reaction (similar to Scheme 38), amines bearing protic groups were tested; however, the yield could not be improved (entries 8–10). A sulfur-based nucleophile, such as that shown in Scheme 39, did not react with **4.42a** (entry 12). Surprisingly, phosphines did not deliver any of the previously obtained products, but rather delivered stable adducts with the alkene, presumably forming structures similar to those that have proposed as intermediates in the MBH reaction.[66,139] Trialkylphosphines induced aryl migration but did not eliminate (entries

13,14), while triphenyl phosphine seemingly formed a simple complex (entry 15). Inert conditions slightly lowered the yield and a control reaction revealed that the starting material **4.42a** is stable and does not undergo any type of reaction in absence of a Lewis base, even after two weeks (entries 16,17). From the investigated reactions, we concluded that DABCO was the most promising Lewis base.

*Table 6: Investigation of different Lewis bases for the envisioned aryl migration reaction. * Yield determined by quantitative ^{1}H-NMR. ** Not determined due to peak overlap. *** Reaction performed under argon atmosphere. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-dimethylaminopyridine.*

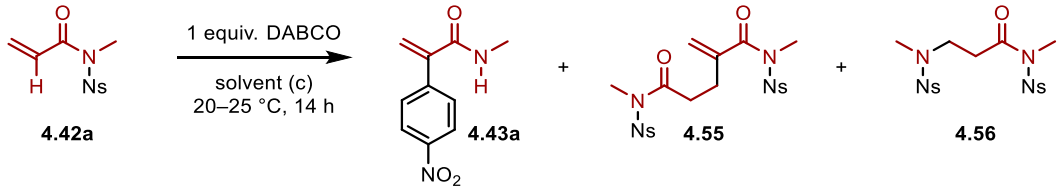


Entry	LB	Yield 4.43a*	Yield 4.55*	Yield 4.56*
1	**DABCO**	**40%**	**5%**	**4%**
2	DBU	9%	<1%	n.d.**
3	pyridine	<1%	<1%	<1%
4	DMAP	12%	<1%	n.d.**
5	quinuclidine	32%	1%	14%
6	*N*-methylmorpholine	<1%	<1%	<1%
7	*N*-methylpyrrolidine	35%	5%	6%
8	3-quinuclidinol	22%	5%	5%
9	*N*,*N*-dimethylglycine	<1%	<1%	<1%
10	*N*-benzyl-piperidine-4-ol	<1%	<1%	<1%
11	thiazole	<1%	<1%	<1%
12	tetrahydrothiophene	<1%	<1%	<1%
13	PEt_3***	<1%	<1%	<1%
14	PCy_3***	<1%	<1%	<1%
15	PPh_3***	<1%	n.d.**	n.d.**
16	DABCO***	31%	4%	4%
17	none	<1%	<1%	<1%

To further improve the yield of **4.43a**, we investigated different solvents and changed other reaction parameters (Table 7). In general, other solvents did not increase the yield of **4.43a** (entries 1–2) and, in the case of dioxane (entry 1), even led to the favoured formation of

Rauhut–Currier dimer **4.55**. It is noteworthy that acetone (entry 3) delivered almost the same results as the initially investigated solvent, acetonitrile. Protic co-solvents or additives had little to no effect on the yield of **4.43a** (entries 5–10). However, moving to more dilute conditions (50 mM, entry 11) increased the yield to 63% and moreover suppressed the formation of the two identified by-products **4.55** and **4.56**. As the dilution also resulted in a more sluggish reaction, longer reaction times (72 h) or a slight increase in temperature (to 40 °C) were required to deliver higher yields of 94% and 87%, respectively.

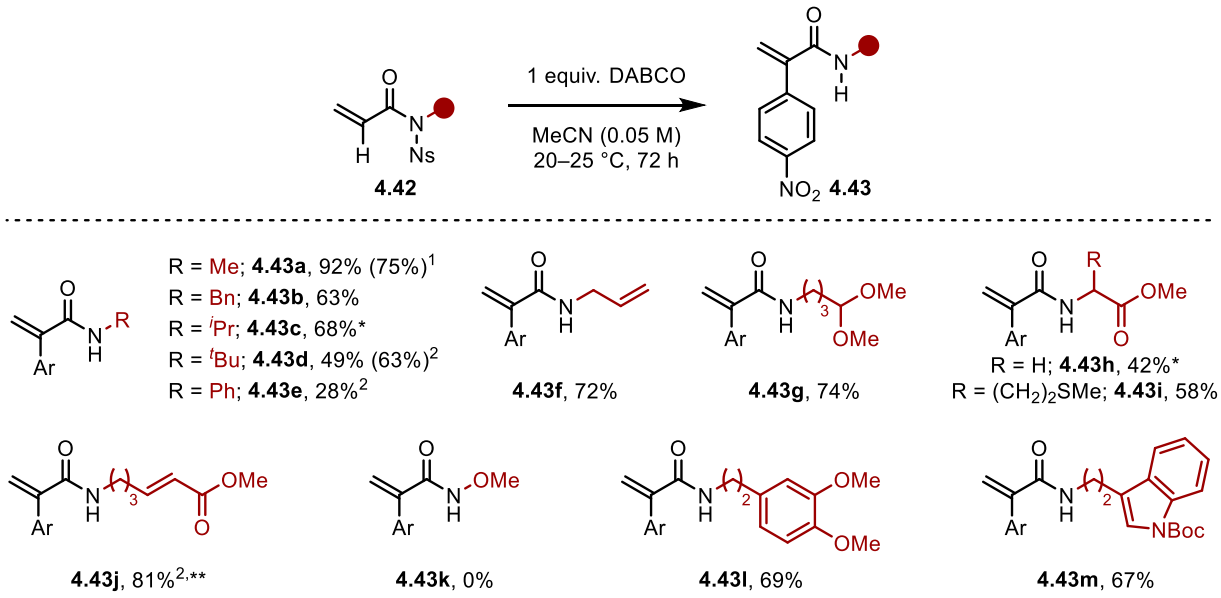
*Table 7: Investigation of solvents, additives and other parameters in the aryl migration reaction. * Yield determined by quantitative ^{1}H-NMR. ** Not determined due to peak overlap. BHT = 2,6-di-tert-butyl-4-methylphenol.*



Entry	Solvent	c [M]	Yield 4.43a*	Yield 4.55*	Yield 4.56*
1	1,4-dioxane	0.2	18%	22%	1%
2	DMF	0.2	20%	<1%	n.d.**
3	acetone	0.2	39%	6%	n.d.**
4	$MeNO_2$	0.2	<1%	<1%	<1%
5	MeCN/HFIP 4/1	0.2	<1%	n.d.**	n.d.**
6	MeCN/^{i}PrOH 3/1	0.2	26%	3%	3%
7	MeCN/^{i}PrOH 9/1	0.2	31%	6%	3%
8	MeCN/^{t}BuOH 9/1	0.2	30%	3%	2%
9	MeCN + 1 equiv. BHT	0.2	29%	4%	n.d.**
10	MeCN + 1 equiv. BnOH	0.2	30%	3%	2%
11	MeCN	0.05	63%	1%	n.d.**
12	**MeCN (72 h)**	**0.05**	**94%**	**3%**	**2%**
13	MeCN (40 °C)	0.05	87%	n.d.**	n.d.**

With high-yielding conditions in hand, we turned our attention towards the scope of the reaction (Scheme 76). To explore the influence of the nitrogen substituents, we investigated steric effects by comparing methyl (**4.43a**) to benzyl (**4.43b**), ^{i}propyl (**4.43c**), ^{t}butyl (**4.43d**) and phenyl (**4.43e**) substituents. This led to the conclusion that smaller groups afford higher yields, presumably due to a preorganisation closer to the one in the rate-determining transition state.

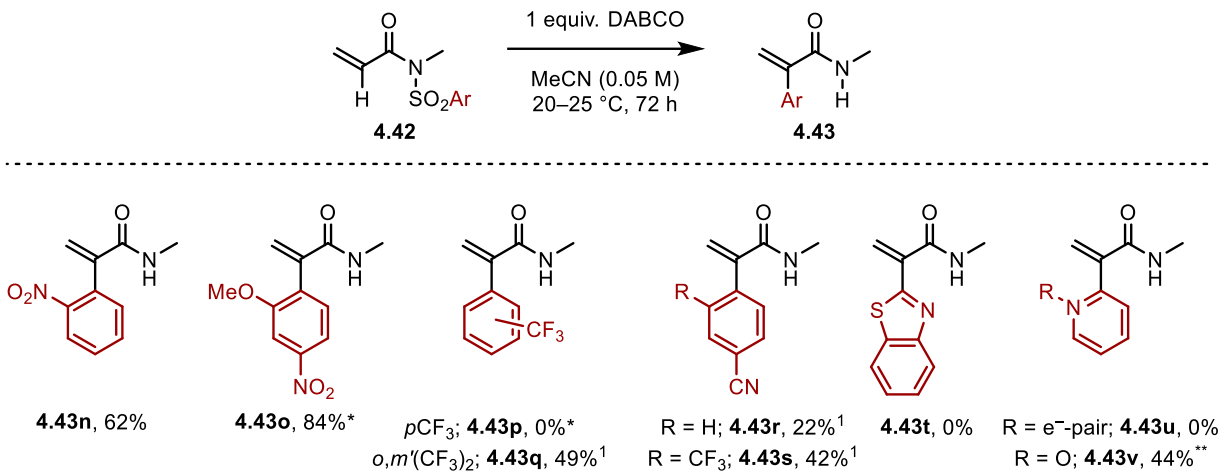
Increasing the temperature to 80 °C also increased the yield of **4.43d**. Functional group tolerance was demonstrated for tethered alkenes (**4.43f**), acetals (**4.43g**), esters (in form of the amino acid derivatives **4.43h** and **4.43i**) and even other Michael acceptors (**4.43j**). A Weinreb-type acrylamide (**4.43k**) was found to be incompatible with the reaction, as aryl migration was suppressed and carboxamide cleavage—amongst other decomposition pathways—was favoured. Finally, derivatives of dopamine (**4.43l**) and tryptamine (**4.43m**) could be synthesised in good yields, the latter also demonstrating tolerance of a carbamate protecting group.



*Scheme 76: Study on the tolerance of different nitrogen substituents. 1) Reaction performed on 1 mmol scale. 2) Reaction performed at 80 °C. *Reaction performed by M. Mießkes. **Reaction performed by T. Fischer. Ar = p-NO_2-C_6H_4.*

The anionic nature of the reaction sequence requires the aromatic group to be electron-deficient. Therefore, we sought to explore the borders of electron deficiency by varying the electron-withdrawing groups on the phenyl ring (Scheme 77). While nitro groups at different positions even allowed for the presence of an electron-donating methoxy substituent (**4.43n**, **4.43o**), a switch to simple CF_3 pinpointed first limitations of the method under the employed reaction conditions. Two trifluoromethyl groups, however, allowed for the rearrangement to proceed at elevated temperatures (**4.43p**, **4.43q**), as did a nitrile (**4.43r**) albeit with a low yield of 22%. The combination of these two moieties lead to an increased yield of 42% (**4.43s**). Aromatic heterocycles have been known to rearrange in similar reactions.[116] However, in this

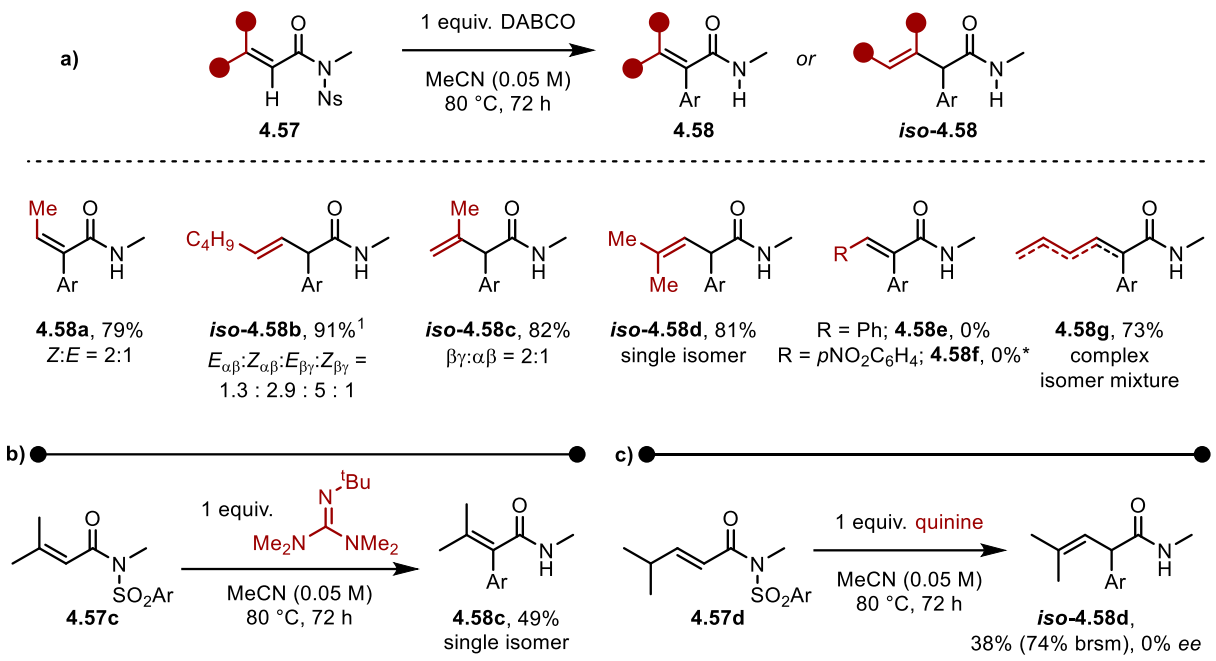
Lewis base-induced reaction, benzothiazole and pyridine (**4.43t**, **4.43u**) did not migrate, whereas pyridine *N*-oxide, which formed **4.43v**, did provide the desired product in 44% yield, even at ambient temperature.



Scheme 77: Investigation of different electron-deficient aryl groups – selected examples.
*1) Reaction performed at 80 °C. *Reaction performed by M. Mießkes. **Reaction performed by Y. Xiao.*

Finally, we turned our attention to substituents at the β-position. Interestingly, all starting materials required elevated temperature to achieve high conversion and delivered alkene isomers, the ratio of which depended on the substitution pattern (Scheme 78a). A beta-methyl-substituted starting material led to a 2:1 mixture of the *Z*- and *E*-configured α,β-unsaturated amides **4.58a**, formed as a single regioisomer in 79% yield. In contrast, the change to a longer alkyl chain resulted in a more complex mixture of alkenes (**4.58b**), including stereo- as well as regiochemical isomers, although also in high combined yield. Other substitution patterns resulted in the preferential formation of β,γ-unsaturated α-arylamides (**4.58c**, **4.58d**), presumably resulting from E2 elimination of the γ-proton instead of an E1cb mechanism abstracting the proton in α-position. Notably, this step might occur by intermolecular proton transfer onto the amidate through a six-membered transition state. Cinnimides did not form the desired products (**4.58e**, **4.58f**) and an α,β,γ,δ-unsaturated starting material delivered a complex mixture of stereo- and regioisomers (**4.58g**). The ratio of α,β- to β,γ- unsaturated product **4.58c** was further investigated by substituting DABCO with the strong Brønsted base BTMG (Scheme 78b). Surprisingly, only **4.58c** was formed (49%), while with DABCO the other isomer ***iso*-4.58c** was favoured. This switch in regioselectivity

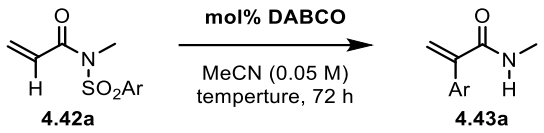
might stem from a Brønsted base-mediated isomerisation of the product mixture. Since product **4.x** bears a newly generated stereocentre in the α-position, we also tested if some enantioenrichment could be achieved using an enantiopure chiral Lewis base (Scheme 78c). When **4.57d** was treated with quinine, 38% (74% brsm) of ***iso*-4.58d** was formed, however this product was found to be racemic.



*Scheme 78: a) Different β-substitution on the employed acrylimides leads to different alkene isomers. 1) Reaction performed at for 120 h. *Reaction performed by T. Fischer. b) Comparison of reactivity to the strong Brønsted base 2-tert-butyl-1,1,3,3-tetramethylguanidine (BTMG). c) Exchange of DABCO with quinine led to no enantiomeric excess of **iso-4.58d**.*

This protocol, employing a stoichiometric amount of DABCO, delivers most acrylamides in high yields, but the efficiency of the process might be improved by lowering the Lewis base loading. The reaction, as proposed in Scheme 75, shows the possibility for catalytic turnover. We therefore investigated the rearrangement using sub-stoichiometric base loading (Table 8). Discouragingly, employing 50 mol% DABCO, the yield of **4.43a** dropped to an almost stoichiometric 53% (entry 1). While an increase in temperature to 80 °C once more effected an increase in yield (80%) (entry 2), further lowering of the catalyst loading again led to decreased yield (entry 3).

*Table 8: Investigations towards a catalytic reaction. * Yield determined by quantitative ^{1}H-NMR.*



Entry	mol%	Temperature	Yield 4.43a*
1	50	20–25 °C	53%
2	**50**	**80 °C**	**80%**
3	25	80 °C	68%

When a reaction employing 20 mol% DABCO was monitored by ^{1}H-NMR, no catalyst turnover was observed and the yield of **4.43a** plateaued at 7% (Figure 5, blue). The addition of a sterically hindered alcohol as a potential proton shuttle to facilitate elimination did not change the reaction profile (Figure 5, orange). We therefore assumed that DABCO might somehow be consumed or blocked through complex formation during the reaction sequence. Previous reports on the reaction of DABCO with SO_2 solutions suggested complex formation with the gas leading to the stable DABCO-$(SO_2)_2$ adduct DABSO.[140] We therefore investigated the reaction mixture of **4.42a** prior to aqueous work-up and indeed confirmed the presence of precipitated DABSO by ^{1}H-NMR (Figure 6, signal at 3.21 ppm marked with a green circle). As a conclusion, we attribute the need for one equivalent of DABCO at ambient temperature to the formation of a DABSO adduct which deactivates the catalyst rather than a high activation barrier elimination step as it is common in the MBH reaction. We propose that at higher temperatures, this adduct breaks, liberating the catalyst and allowing turnover (Table 8, entry 2).

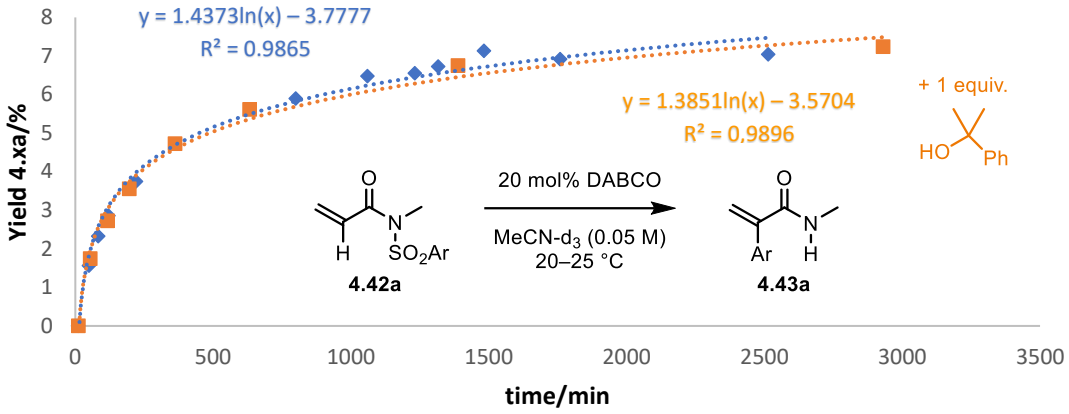


*Figure 5: Profile of the shown reaction as determined by quantitative ^{1}H-NMR (blue), and in the presence of 1 equiv. 2-phenylpropan-2-ol (orange). Trendlines of the function y(x)=a*ln(x)+b are fitted respectively.*

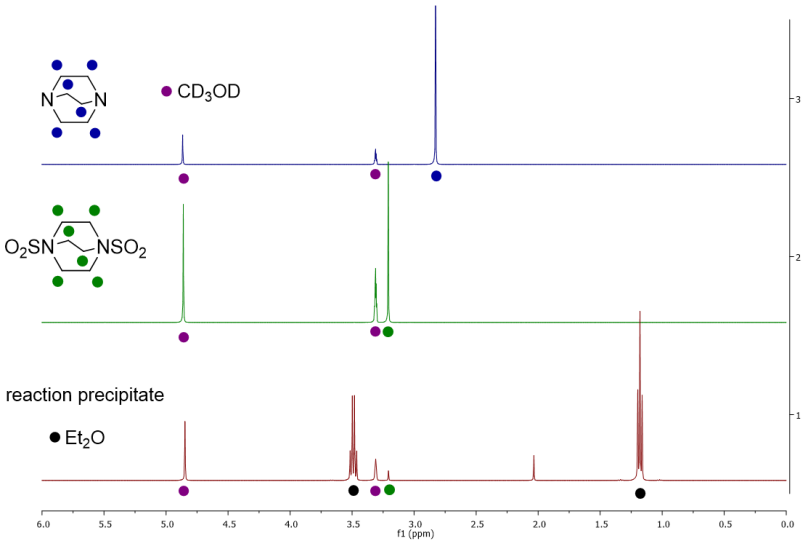
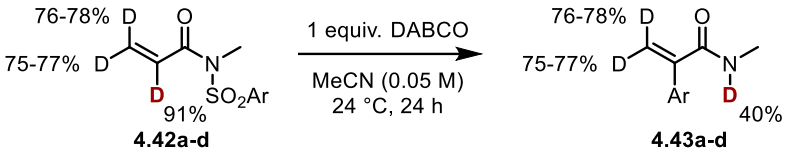


Figure 6: ^{1}H-NMR (CD_3OD) spectrum of the reaction precipitate after washing with Et_2O (bottom) in comparison to authentic samples of DABCO (top) and DABSO (middle) revealing formation of DABSO (green circle at 3.21 ppm) during the reaction.

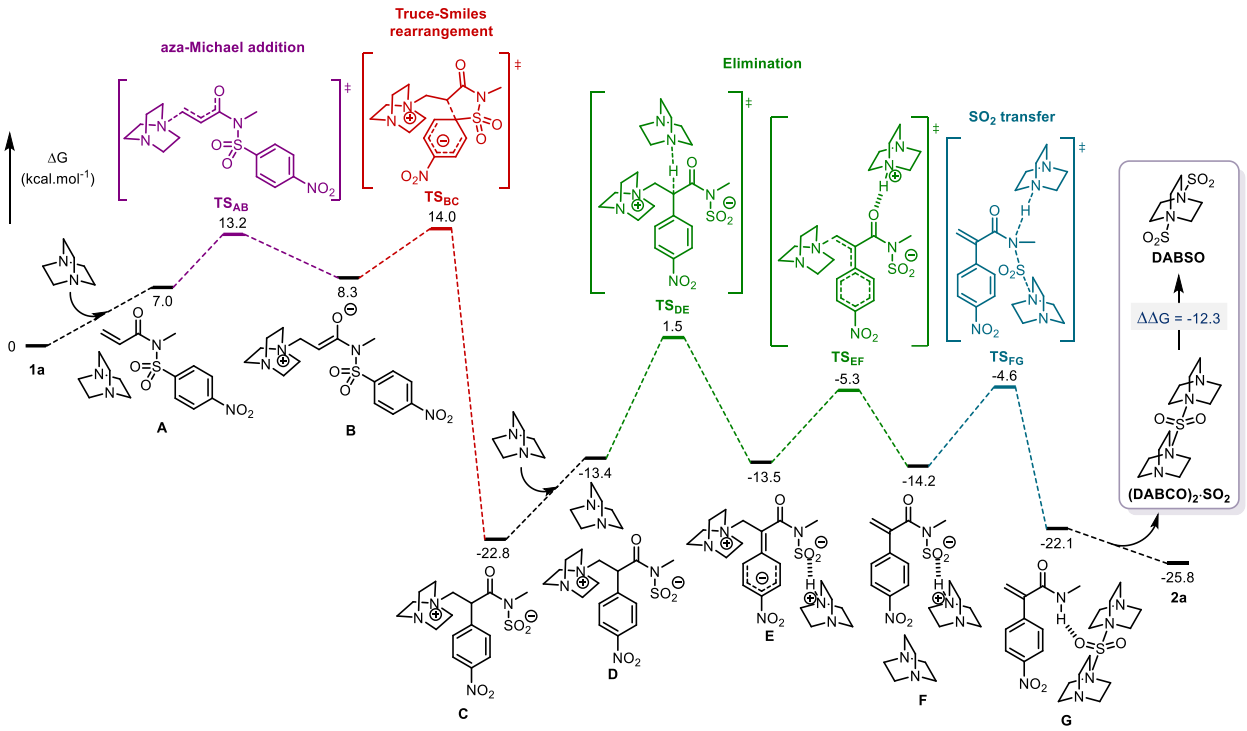
To support our proposal that the α-hydrogen of the starting material is transferred to the nitrogen of the product, we performed the rearrangement using deuterated acrylimide **4.42a-d** (Scheme 79). As measured by ^{2}H-NMR, a starting material with 91% α-deuteration led to formation of a product with a 40% D-incorporation at nitrogen (**4.43a-d**). While this suggests that proton transfer (intermolecular or intramolecular) between the α–position and at the amide nitrogen is operative, the exact mechanism of this transfer was still elusive.



Scheme 79: The rearrangement was followed by ^{2}H-NMR in MeCN by H. Zhang.

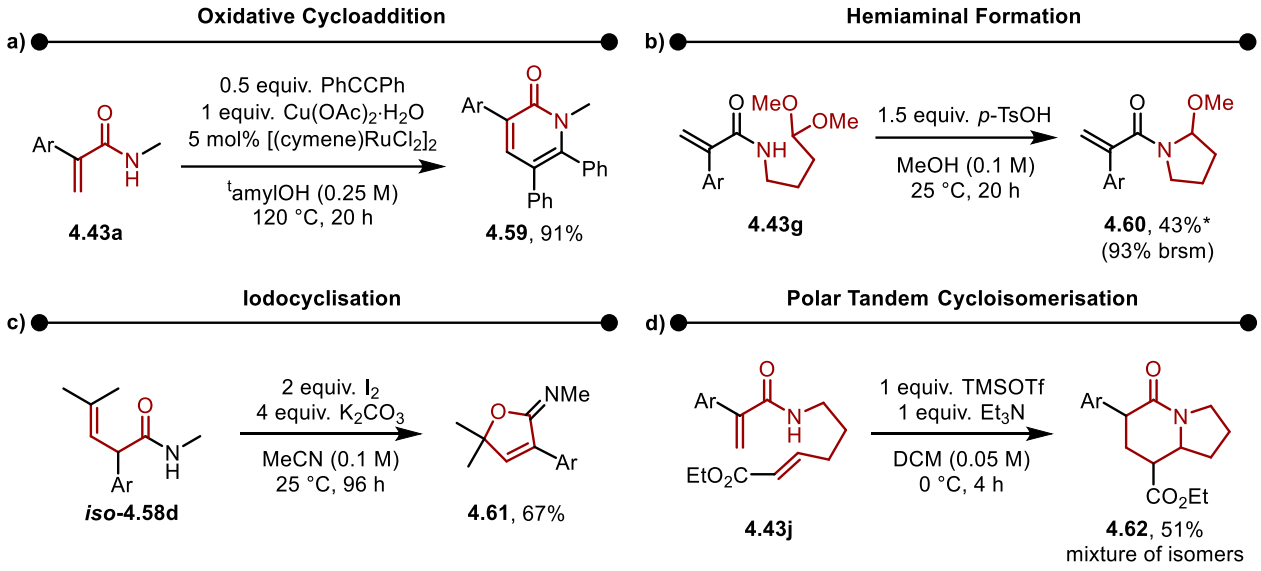
Similar evidence was provided by quantum chemical calculations conducted by A. J. Fernandes, which also revealed the complete mechanism (Scheme 80). The initial 1,4-addition/aryl migration through a Meisenheimer transition state (**TS_{BC}**) appeared to proceed as originally expected. Interestingly, the computed pathway indicated that the elusive proton transfer is initiated by deprotonation of intermediate **D** still bound to SO_2, followed by elimination (**F**) and only then simultaneous DABCO-assisted N–S cleavage and N–H bond formation. Formation of the experimentally observed DABSO was also shown to be endergonic (-12.3 kcal/mol) starting from the generated $(DABCO)_2SO_2$ adduct.

Both experimental and computational results conclude that DABCO plays multiple roles in this rearrangement sequence. For one, it serves as the intended Lewis base, generating the enolate for aryl migration. Secondly, it facilitates the proton transfer from the α-position to the amide nitrogen, and lastly, it mediates the extrusion of SO_2 by creating a thermodynamic sink through the formation of DABSO.



Scheme 80: The complete mechanism of the DABCO-mediated aryl migration reaction calculated at the PBE0-D3(BJ)/def2-TZVP,SMD(MeCN)//PBE0-D3(BJ)/def2-SVP,SMD(MeCN) level of theory by A. J. Fernandes.

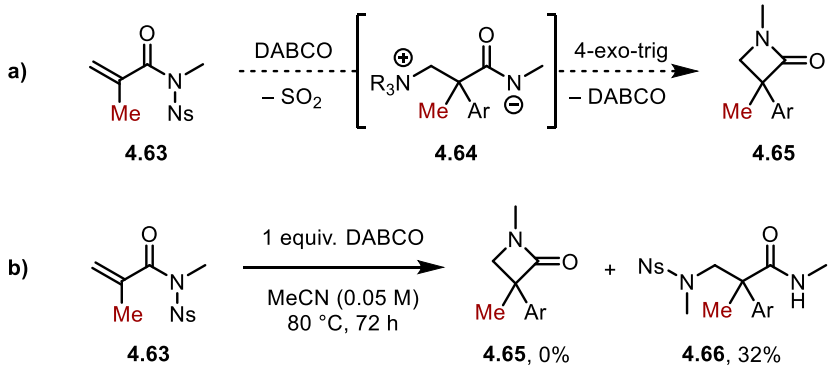
As mentioned in the introduction (4.1.3), α-aryl acrylamides constitute valuable building blocks for the synthesis of more sophisticated compounds. Four examples for such transformations are given in Scheme 81. Panel **a** shows a ruthenium-catalysed oxidative cycloaddition, following conditions published by Ackermann *et al.*, and yielding pyridone **4.59**.[131] Formation of tertiary amide **4.60** is shown in panel **b** and was performed by H. Zhang.[141] Cyclisation of ***iso*-4.58d** was achieved using iodine and K_2CO_3 to generate **4.61** (panel **c**) and finally, in panel **d**, formation of hexahydroindolizinone **4.62** from double Michael acceptor **4.43g**, as similarly reported by Fukumoto *et al.*, is illustrated.[142]



*Scheme 81: Four uses of the prepared α-aryl acrylamides in further reactions. *Reaction performed by H. Zhang.*

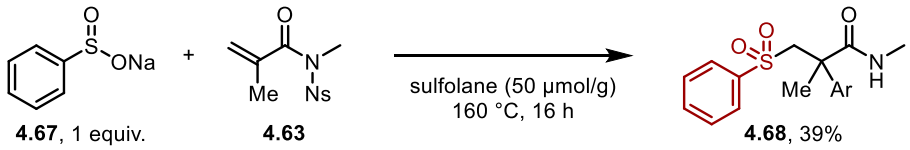
4.2.2 Exploration of Aryl Migration Reactions Initiated by Other Nucleophiles

Following the development of the Lewis base-mediated aryl migration/elimination sequence, we were interested in the possibility of steering the reaction in a different direction. For example, if no α-proton is present, such as in methacrylimide **4.63**, elimination becomes impossible. We therefore speculated whether a 4-*exo*-*trig* cyclisation of **4.64** could occur instead (**4.65**, Scheme 82a). However, when **4.63** was treated with DABCO, addition of in situ liberated sulfonamide was observed instead of the desired β-lactam (**4.66**, Scheme 82b).



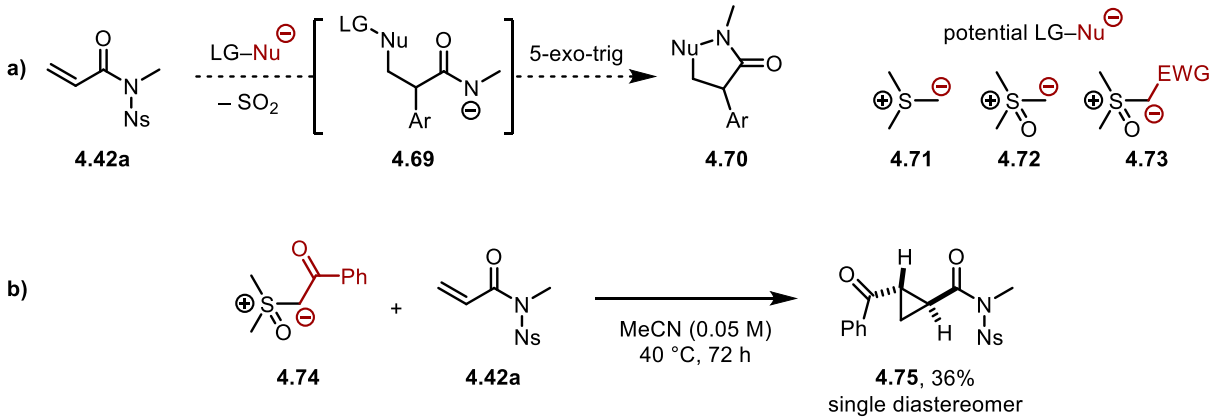
*Scheme 82: a) A hypothetic synthesis of β-lactam **4.65**.*
*b) The reaction of methacrylimide **4.63** led to formation of aminoarylated amide **4.66**.*

While the desired reaction outcome was not achieved, this example showcases how other nucleophiles can engage in such aryl migration reactions. To test a different nucleophile in absence of any Lewis base mediator, **4.63** was heated together with phenyl sulfinate (**4.67**) in sulfolane (a highly polar aprotic solvent) to 160 °C, resulting in the formation of sulfone **4.68** in 39% yield (Scheme 83). This example demonstrates the possibility of nucleophiles beyond tertiary amines to engage in such anionic aryl migration reactions, leading to saturated, doubly functionalised secondary amides bearing a quaternary centre in α-position.



Scheme 83: Aryl migration induced by phenyl sulfinate.

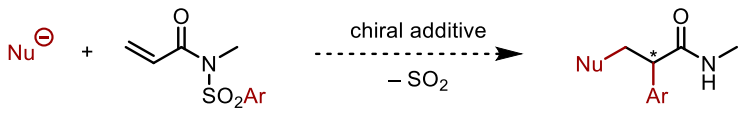
In a similar fashion to the β-lactam synthesis proposed in Scheme 82a, nucleophiles bearing a leaving group could lead to 5-exo-trig cyclisation of **4.69** and formation of γ-lactams **4.70** (Scheme 84a).[143] Sulfur-based ylides (**4.71**–**4.73**) are commonly employed nucleophiles in cases where such properties are desired. With this knowledge, both sulfonium and sulfoxonium ylides were tested under a variety of reaction conditions, using **4.42a** as the starting material. Unfortunately, however, these reactions largely returned products of unspecific decomposition. Only when **4.74** was used, could an isolable compound (cyclopropane **4.75**) be detected, albeit with no desired aryl migration having occurred (Scheme 84b). It is safe to assume that a Corey–Chaykovsky-type cyclopropanation is a much faster process than the Truce–Smiles-type aryl migration which would proceed via a five-membered cycle, and should therefore be significantly slower, rendering a reaction as envisioned in Scheme 84a difficult to achieve.



Scheme 84 Envisioned synthesis of β-lactams using sulfur-based ylides.
*b) Obseserved cyclopropanation with stabilised sulfonium ylide **4.74**.*

4.3 Conclusion and Perspectives

The development of a DABCO-mediated formal aryl/hydrogen exchange with the loss of SO_2 shows broad applicability for the synthesis of α-aryl acrylamides bearing electron-withdrawing groups. An unexpected triple role of the Lewis base, comprising enolate formation, proton-transfer mediation and SO_2 capture, was uncovered using experimental and computational methods. It paves the way for an array of new reactions utilising anionic aryl migration pathways allowing for new methods, complementary to the well-developed field of radical rearrangements of sulfonyl acrylimides.[110,112] We envision that many other nucleophiles could be used in such processes and the application of a chiral base or additive might induce enantioenrichment of the final α-chiral secondary amide, a type selectivity which has previously only been achieved in an enantiospecific process starting from enantioenriched sulfinimides (Scheme 85).[127] Such processes are currently under development in the Maulide lab and will be topic of future PhD-theses.



Scheme 85: A hypothetic double functionalization of acrylimides with enantioenrichment induced by additives.

4.4 Experimental Data

4.4.1 General Information

Unless otherwise stated, all glassware was flame dried before use and all reactions were performed under argon unless state otherwise. All reagents were used as received from commercial suppliers unless stated otherwise. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed on an Isolera 4 or Select medium pressure chromatography system (Biotage) 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 using a Bruker maXis UHR-TOF (Qq-TOF) spectrometer, using electrospray ionization (ESI). All ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Bruker AV-400, AV-500, AV-600 or AV-700 spectrometer at 300K. 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 (^{13}C-NMR), or CD_3OD, defined at δ = 3.31 ppm (^{1}H-NMR). Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) 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).

4.4.2 Starting material synthesis

General Procedure A: Sulfonamide synthesis

To sulfonyl chloride (1.00 equiv.) in THF (0.50 M) was added primary amine (1.50 equiv.) and Et_3N (1.5 equiv.) at 20–25 °C. The solution was stirred for 14 h, upon which it was diluted with EtOAc. The mixture was washed with aqueous HCl (1 M) and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the sulfonamide which was used directly without further purification.

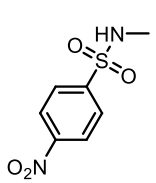
General Procedure B: Acrylimide synthesis

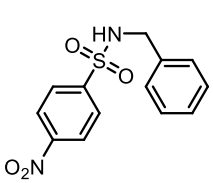
To sulfonamide (1.00 equiv.) in DCM (0.25 M) were added Et_3N (2.4 equiv.) and acryloyl chloride (2.4 equiv.) dropwise at 0 °C. The mixture was stirred at 23 °C for 14 h, upon which EtOAc was added and the mixture was transfered to a seperatory funnel. The mixture was washed with saturated, aqueous $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel eluting with EtOAc in heptane afforded the desired products.

General Procedure C: β-substituted acrylimide synthesis

To *N*-methyl-*N*-((4-nitrophenyl)sulfonyl)amide (1.00 equiv.) in THF (0.25 M) was added NaH (1.00 equiv.). The mixture was stirred at 23 °C for 15 min, upon which acyl chloride (1.2 equiv.) was added and the formed suspension was stirred for 14 h. Then, EtOAc was added and the mixture was transfered to a seperatory funnel. The mixture was washed with saturated, aqueous $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel eluting with EtOAc in heptane afforded the desired products.

The following sulfonamides have been synthesized according to the procedures in the references specified bellow.[144–150]


4.0a[144]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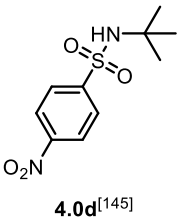
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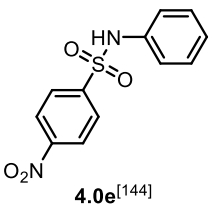
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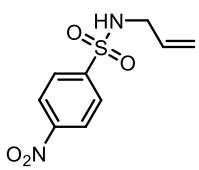
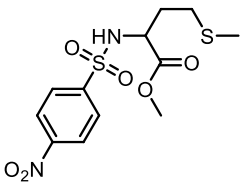
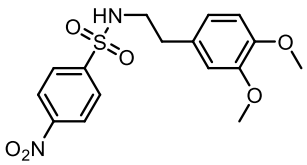
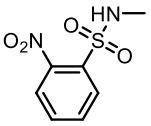

4.0f[146]


4.0i[147]


4.0l[148]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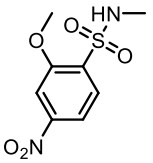
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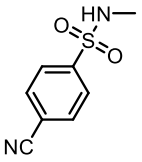
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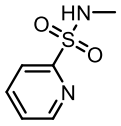
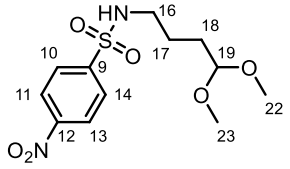

4.0u[150]

4.0g: *N*-(4,4-Dimethoxybutyl)-4-nitrobenzenesulfonamide



4.0g was prepared according to the general procedure **A** using 4,4-dimethoxybutan-1-amine (2.22 g, 10.0 mmol), the purification by flash column chromatography on silica gel (5 – 50% EtOAc in heptane) afforded compound **4.0g** in 97% (3.09 g) yield as a yellow solid.

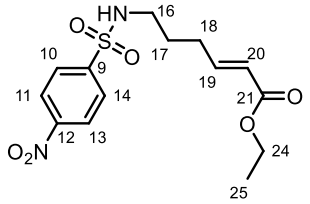
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 – 8.33 (m, 2H^{11,13}), 8.07 – 8.02 (m, 2H^{10,14}), 5.06 (t, *J* = 6.0 Hz, 1H^{NH}), 4.30 (t, *J* = 4.9 Hz, 1H^{19}), 3.31 (s, 6H^{22,23}), 3.04 (app.q, *J* = 6.4 Hz, 2H^{16}), 1.65 – 1.58 (m, 4H^{17,18}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 150.2 (C^{12}), 146.3 (C^{9}), 128.4 (2CH^{10,14}), 124.5 (2CH^{11,13}), 104.4 (CH^{19}), 53.6 (2CH$_3$^{22,23}), 43.3 (CH$_2$^{16}), 29.9 (CH$_2$$^{17 or 18}$), 24.5 (CH$_2$$^{17 or 18}$) ppm.

IR (neat) ν_{max}: 3286, 2956, 1529, 1349, 1163, 735, 611 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{12}H_{18}N_2NaO_6S^+$) requires *m*/*z* 341.0778, found *m*/*z* 341.0775.

4.0j: Ethyl (*E*)-6-((4-nitrophenyl)sulfonamido)hex-2-enoate



Following the procedure reported by Takemoto *et al.*,[151] using *N*-*p*-nitrophenylsulfonyl pyrrolidone (1.62 g, 6.00 mmol), diisobutylaluminum hydride (1.2 M in toluene, 5.00 mL, 6.00 mmol) and ethyl (triphenylphosphoranylidene)acetate (3.14 g, 9.00 mmol), the purification by flash column chromatography on silica gel (20 – 50% EtOAc in heptane) afforded compound **4.0j** in 36% (743 mg) yield as a yellow solid.

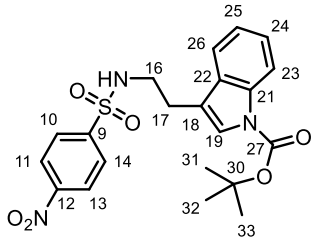
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.8 Hz, $2H^{11,13}$), 8.09 – 8.02 (m, $2H^{10,14}$), 6.84 (dt, *J* = 15.6, 6.9 Hz, $1H^{19}$), 5.77 (d, *J* = 15.7 Hz, $1H^{20}$), 4.74 (d, *J* = 5.5 Hz, $1H^{NH}$), 4.17 (q, *J* = 7.1 Hz, $2H^{24}$), 3.04 (q, *J* = 6.8 Hz, $2H^{16}$), 2.23 (td, *J* = 8.3, 1.2 Hz, $2H^{18}$), 1.69 (p, *J* = 7.2 Hz, $2H^{17}$), 1.28 (t, *J* = 7.1 Hz, $3H^{25}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C^{21}), 150.3 (C^{12}), 146.8 (CH^{19}), 146.0 (C^{9}), 128.4 ($2CH^{10,14}$), 124.6 ($2CH^{11,13}$), 122.7 (CH^{20}), 60.6 (CH_2^{24}), 42.8 (CH_2^{16}), 29.0 ($CH_2^{17 or 18}$), 28.3 ($CH_2^{17 or 18}$), 14.4 (CH_3^{25}) ppm.

IR (neat) ν_{max}: 3294, 2928, 1714, 1529, 1349, 1160, 906, 726, 609 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}N_2NaO_6S^+$) requires *m*/*z* 365.0778, found *m*/*z* 365.0769.

4.0m: *tert*-Butyl 3-(2-((4-nitrophenyl)sulfonamido)ethyl)-1*H*-indole-1-carboxylate



Following General Procedure **A** using *tert*-butyl 3-(2-aminoethyl)-1*H*-indole-1-carboxylate (1.12 g, 4.30 mmol), the purification by flash column chromatography on silica gel (5 – 80% EtOAc in heptane), afforded compound **4.0m** in 88% (1.68 g) yield as an off-white solid.

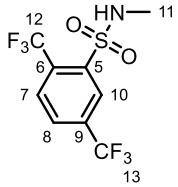
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.06 (m, $2H^{11,13}$), 8.01 (d, *J* = 7.3 Hz, $1H^{19}$), 7.84 – 7.76 (m, $2H^{10,14}$), 7.35 – 7.23 (m, $3H^{Ar}$), 7.19 – 7.12 (m, $1H^{Ar}$), 4.54 (t, *J* = 5.8 Hz, $1H^{NH}$), 3.40 (app.q, *J* = 6.2 Hz, $2H^{16}$), 2.89 (t, *J* = 6.3 Hz, $2H^{17}$), 1.69 (s, $9H^{31–33}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9 (C^{27}), 149.6 (C^{12}), 145.5 (C^{9}), 129.6 (C^{Ar}), 128.0 ($2CH^{10,14}$), 125.0 (CH^{Ar}), 124.1 ($2CH^{11,13}$), 124.0 (CH^{Ar}), 122.8 (CH^{Ar}), 118.6 (CH^{Ar}), 115.9 (C^{Ar}), 115.6 (CH^{Ar}), 84.4 (C^{30}), 42.7 ($CH_2{}^{16}$), 28.3 ($3CH_3{}^{31–33}$), 25.6 ($CH_2{}^{17}$) ppm. (1 quaternary carbons did not relax)

IR (neat) ν_{max}: 3295, 2928, 1730, 1530, 1348, 1157, 745 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{21}H_{23}N_3NaO_6S^+$) requires *m*/*z* 468.1200, found *m*/*z* 468.1197.

4.0q: *N*-Methyl-2,5-bis(trifluoromethyl)benzenesulfonamide



Following General Procedure **A** using 2,5-bis(trifluoromethyl)benzenesulfonyl chloride (375 mg, 1.20 mmol), compound **4.0q** was obtained in 91% (337 mg) yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, $1H^{10}$), 8.05 (d, *J* = 8.2 Hz, $1H^{7or8}$), 7.98 (d, *J* = 8.2 Hz, $1H^{7or8}$), 4.64 (bs, $1H^{NH}$), 2.75 (s, $3H^{11}$) ppm.

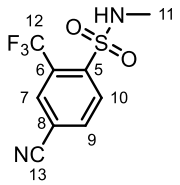
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6 (C^{5}), 134.8 (q, *J* = 34.1 Hz, C^{6or9}), 131.0 (q, *J* = 32.4 Hz, C^{6or9}), 129.9 – 129.5 (m, $2CH^{Ar}$), 129.2 – 129.0 (m, CH^{Ar}), 122.6 (q, *J* = 273.4 Hz, CF_3^{12or13}), 122.4 (q, J = 274.6 Hz, CF_3^{12or13}), 29.6 (CH_3^{11}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -58.5, -63.3 ppm.

IR (neat) ν_{max}: 3346, 1420, 1331, 1309, 1266, 1191, 1129, 1032, 585 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_9H_7F_6NNaO_2S^+$) requires *m*/*z* 329.9994, found *m*/*z* 329.9995.

4.0s: *N*4-Cyano-*N*-methyl-2-(trifluoromethyl)benzenesulfonamide



Into an oven dried 8 mL vial containing a magnetic stir bar were added 4-bromo-*N*-methyl-2-(trifluoromethyl)-benzenesulfonamide (1.27 g, 4.00 mmol) and CuCN (1.43 g, 16.0 mmol) followed by 4.0 mL anhydrous DMF (1.0 M). The vial was capped and heated to 150 °C for 24 h. After cooling to 20 – 25 °C, the mixture was diluted with 100 mL EtOAc and the mixture washed with aqueous NH_4OH solution (5%, 3 x 30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (10 – 40% EtOAc in heptane), afforded compound **4.0s** in 54% (568 mg) yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.2 Hz, $1H^{9or10}$), 8.15 (s, $1H^{7}$), 8.02 (d, *J* = 8.2 Hz, $1H^{9or10}$), 4.75 (d, *J* = 3.7 Hz, $1H^{NH}$), 2.74 (d, *J* = 5.0 Hz, $3H^{11}$) ppm.

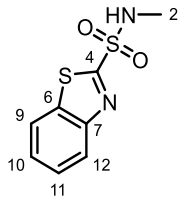
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3 (C^{Ar}), 136.0 (CH^{9or10}), 132.9 (CH^{9or10}), 132.1 (q, *J* = 6.4 Hz, CH^{7}), 129.2 (d, *J* = 34.2 Hz, C^{6}), 123.4 (q, *J* = 274.7 Hz, CF_3^{12}), 117.1 (C^{Aror13}), 116.2 (C^{Aror13}), 29.5 (CH_3^{11}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -58.6 ppm.

IR (neat) ν_{max}: 3339, 2237, 1475, 1406, 1335, 1197, 1150, 1073, 1039, 595 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_9H_7F_3N_2NaO_2S^+$) requires *m*/*z* 287.0073, found *m*/*z* 287.0063.

4.0t: *N*-Methylbenzo[d]thiazole-2-sulfonamide



Procedure adapted from the one reported by Gonçalves *et al.*[150] using 2-mercaptobenzothiazole (836 mg, 5.00 mmol, 1.00 equiv.), sodium hypochlorite (13.5% in water, 11.4 mL, 25.0 mmol 5.00 equiv.) and methylamine (2 M in THF, 6.25 mL, 12.5 mmol, 2.50 equiv.). Purification of the crude product by flash column chromatography on silica gel (10 – 30% EtOAc in heptane) afforded compound **4.0t** in 49% yield (562 mg) as a white solid.

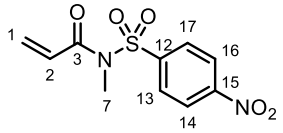
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 7.6 Hz, 1H^9), 8.02 – 7.94 (m, 1H^{12}), 7.65 – 7.53 (m, 2H^{10,11}), 5.37 (bs, 1H^{NH}), 2.93 (d, *J* = 5.2 Hz, 3H^2) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4 (C^4), 152.5 (C^7), 136.5 (C^9), 127.8 (CH^{Ar}), 127.6 (CH^{Ar}), 125.2 (CH^{Ar}), 122.3 (CH^{Ar}), 30.1 (CH_3^2) ppm.

IR (neat) ν_{max}: 3286, 2926, 1472, 1344, 1169, 761, 730, 623 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_8H_8N_2NaO_2S_2^+$) requires *m*/*z* 250.9919, found *m*/*z* 250.9922.

4.42a: *N*-Methyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide



Following General Procedure **B** using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl) amide (432 mg, 2.00 mmol), the purification by flash column chromatography on silica gel (5 – 20% EtOAc in heptane) afforded compound **4.42a** in 46% yield (250 mg) as a white solid.

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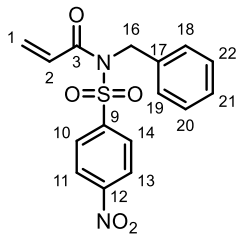
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.8 Hz, 2H^{14,16}), 8.11 (d, *J* = 8.8 Hz, 2H^{13,17}), 6.91 (dd, *J* = 17.0, 10.4 Hz, 1H^{2}), 6.43 (dd, *J* = 17.0, 1.2 Hz, 1H^{1}), 5.88 (dd, *J* = 10.4, 1.2 Hz, 1H^{1}), 3.38 (s, 3H^{7}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C^{3}), 150.8 (C^{15}), 144.6 (C^{12}), 132.9 (CH_2^{1}), 129.2 (2CH^{13,17}), 127.9 (CH^{2}), 124.6 (2CH^{14,16}), 33.5 (CH_3^{7}) ppm.

IR (neat) ν_{max}: 1698, 1528, 1348, 1178, 1079, 842, 750, 743, 710, 678, 631 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{10}N_2NaO_5S^+$) requires *m*/*z* 293.0203, found *m*/*z* 293.0201.

4.42b: *N*-Benzyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide



Following General Procedure B using *N*-benzyl-4-nitrobenzenesulfonamide (1.14 g, 3.90 mmol), the purification by flash column chromatography on silica gel (10 – 25% EtOAc in heptane) afforded compound **4.42b** in 41% yield (548 mg) as a white solid.

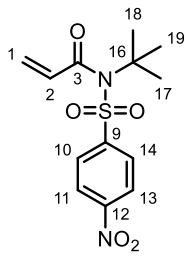
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.9 Hz, 2H^{11,13}), 7.93 (d, *J* = 8.9 Hz, 2H^{10,14}), 7.42 – 7.28 (m, 5H$^{18–22}$), 6.72 (dd, *J* = 16.6, 10.4 Hz, 1H^{2}), 6.44 (d, *J* = 16.6 Hz, 1H^{1}), 5.83 (d, *J* = 10.4 Hz, 1H^{1}), 5.16 (s, 2H^{16}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C^{3}), 150.6 (C^{12}), 145.1 (C^{9}), 135.8 (C^{17}), 133.5 (CH_2^{1}), 129.7 (2CH^{Ar}), 129.1 (2CH^{Ar}), 128.4 (CH^{Aror2}), 127.74 (CH^{Aror2}), 127.67 (2CH^{Ar}), 124.2 (2CH^{11,13}), 49.9 (CH_2^{16}) ppm.

IR (neat) ν_{max}: 1692, 1529, 1348, 1163, 1126, 974, 854, 736 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{14}N_2NaO_5S^+$) requires m/z 369.0516, found m/z 369.0518.

4.42d: *N*-(*tert*-Butyl)-*N*-((4-nitrophenyl)sulfonyl)acrylamide



Following General Procedure **B** using *N*-(*tert*-butyl)-4-nitrobenzenesulfonamide (1.29 g, 5.00 mmol), the purification by flash column chromatography on silica gel (5 – 30% EtOAc in heptane) afforded compound **4.42d** in 33% yield (515 mg) as a white solid.

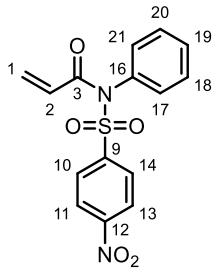
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.5 Hz, 2H^{11,13}), 8.17 (d, *J* = 8.5 Hz, 2H^{10,14}), 6.58 (dd, *J* = 16.9, 9.9 Hz, 1H^{2}), 6.48 (d, *J* = 16.8 Hz, 1H^{1}), 6.00 (d, *J* = 9.8 Hz, 1H^{1}), 1.42 (s, 9H$^{17–19}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6 (C^{3}), 150.2 (C^{12}), 148.4 (C^{9}), 134.7 (CH^{2}), 132.9 (CH_2^{1}), 129.1 (2CH^{10,14}), 124.4 (2CH^{11,13}), 62.6 (C^{16}), 30.1 (3$CH_3$$^{17–19}$) ppm.

IR (neat) ν_{max}: 1704, 1530, 1347, 1156, 1086, 979, 737, 630 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}N_2NaO_5S^+$) requires *m*/*z* 335.0672, found *m*/*z* 335.0671.

4.42e: *N*-((4-nitrophenyl)sulfonyl)-*N*-phenylacrylamide



Following General Procedure **B** using 4-nitro-*N*-phenylbenzenesulfonamide (1.39 g, 5.00 mmol), the purification by flash column chromatography (10–25% EtOAc in heptane) gave compound **4.42e** in 94% yield (1.56 g) as a yellow powder.

Experimental Data

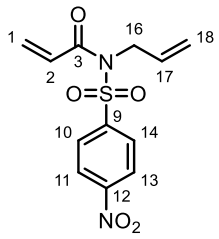
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 9.0 Hz, 2H^{11,13}), 8.25 (d, *J* = 9.0 Hz, 2H^{10,14}), 7.66 – 7.45 (m, 3H$^{18–20}$), 7.27 – 7.25 (m, 2H^{17,21}), 6.40 (dd, *J* = 16.7, 1.5 Hz, 1H^{1}), 5.78 (dd, *J* = 16.7, 10.4 Hz, 1H^{2}), 5.65 (dd, *J* = 10.4, 1.5 Hz, 1H^{1}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (C^{3}), 150.9 (C^{12}), 144.5 (C^{9}), 135.1 (C^{16}), 132.7 (CH^{1}), 130.8 (2CH^{Ar}), 130.7 (CH^{2}), 130.29 (2CH^{Ar}), 130.26 (2CH^{10,14}), 127.8 (CH^{19}), 124.1 (2CH^{11,13}) ppm.

IR (neat) ν_{max}: 1656, 1485, 1369, 1349, 1152, 1025, 742, 570 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{12}N_2NaO_5S^+$) requires m/z 355.0359, found m/z 355.0352.

4.42f: *N*-Allyl-*N*-((4-nitrophenyl)sulfonyl)acrylamide



Following General Procedure **B** using *N*-allyl-4-nitrobenzenesulfonamide (1.21 g, 5.00 mmol), the purification by flash column chromatography on silica gel (5 – 40% EtOAc in heptane) afforded compound **4.42f** in 64% yield (945 mg) as a white solid.

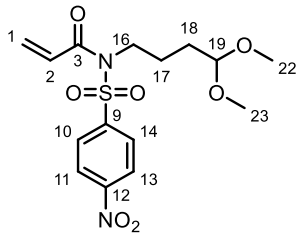
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 – 8.34 (m, 2H^{11,13}), 8.24 – 8.13 (m, 2H^{10,14}), 6.64 (dd, *J* = 16.7, 10.3 Hz, 1H^{2}), 6.43 (dd, *J* = 16.7, 1.4 Hz, 1H^{1}), 5.99 – 5.81 (m, 2H^{1,17}), 5.33 (dd, *J* = 13.7, 5.0 Hz, 2H^{18}), 4.55 (dt, *J* = 5.1, 1.5 Hz, 2H^{16}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (C^{3}), 150.7 (C^{12}), 145.1 (C^{9}), 133.4 (CH_2^{1}), 132.3 (CH^{17}), 130.0 (2CH^{10,14}), 127.4 (CH^{2}), 124.3 (2CH^{11,13}), 119.1 (CH_2^{18}), 48.9 (CH_2^{16}) ppm.

IR (neat) ν_{max}: 3108, 1688, 1527, 1346, 1166, 743, 605 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}N_2NaO_5S^+$) requires *m*/*z* 319.0359, found *m*/*z* 319.0347.

4.42g: *N*-(4,4-Dimethoxybutyl)-*N*-((4-nitrophenyl)sulfonyl)acrylamide



Following General Procedure **B** using **4.0g** (1.59 g, 5.00 mmol), the purification by flash column chromatography on silica gel (5 – 50% EtOAc in heptane) afforded compound **4.42g** in 48% yield (886 mg) as a white solid.

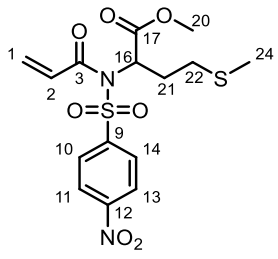
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.7 Hz, 2H^{11,13}), 8.14 (d, *J* = 8.7 Hz, 2H^{10,14}), 6.75 (dd, *J* = 16.6, 10.4 Hz, 1H^{2}), 6.43 (dd, *J* = 16.6, 1.0 Hz, 1H^{1}), 5.86 (dd, *J* = 10.4, 1.0 Hz, 1H^{1}), 4.40 (t, *J* = 5.4 Hz, 1H^{19}), 3.95 – 3.85 (m, 2H^{16}), 3.35 (s, 6H^{22,23}), 1.84 (m, 2H^{17or18}), 1.69 (m, 2H^{17or18}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5 (C^{3}), 150.7 (C^{12}), 145.2 (C^{9}), 133.2 (CH_2^{1}), 129.6 (2CH^{10,14}), 127.5 (CH^{2}), 124.4 (2CH^{11,13}), 104.3 (CH^{19}), 53.4 (2CH_3^{22,23}), 46.9 (CH_2^{16}), 29.7 (CH_2^{17or18}), 25.7 (CH_2^{17or18}) ppm.

IR (neat) ν_{max}: 2939, 1687, 1532, 1367, 1164, 742 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for [M+Na]$^{+}$ ($C_{15}H_{20}N_2NaO_7S^{+}$) requires *m*/*z* 395.0883, found *m*/*z* 395.0877.

4.42i: Methyl *N*-acryloyl-*N*-((4-nitrophenyl)sulfonyl)methioninate



Following General Procedure **B** using methyl-((4-nitrophenyl)sulfonyl)methioninate (1.05 g, 3.00 mmol), the purification by flash column chromatography on silica gel (0 – 40% EtOAc in heptane) afforded compound **4.42i** in 80% yield (964 mg) as a yellow oil.

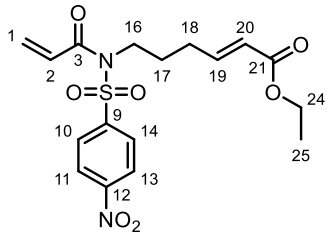
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.9 Hz, 2H^{11,13}), 8.29 (d, *J* = 8.9 Hz, 2H^{10,14}), 6.84 (dd, *J* = 16.6, 10.5 Hz, 1H^{2}), 6.36 (dd, *J* = 16.6, 1.0 Hz, 1H^{1}), 5.81 (dd, *J* = 10.5, 1.0 Hz, 1H^{1}), 5.22 (dd, *J* = 8.1, 4.8 Hz, 1H^{16}), 3.70 (s, 3H^{20}), 2.77 – 2.56 (m, 3H^{21,22}), 2.32 – 2.17 (m, 1H^{21}), 2.13 (s, 3H^{24}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (C^{17}), 165.0 (C^{3}), 150.8 (C^{12}), 144.9 (C^{9}), 133.5 (CH_2^{1}), 129.9 ($2CH^{10,14}$), 127.7 (CH^{2}), 124.4 ($2CH^{11,13}$), 59.1 (CH^{16}), 53.0 (CH_3^{20}), 31.2 (CH_2^{21or22}), 29.6 (CH_2^{21or22}), 15.4 (CH_3^{24}) ppm.

IR (neat) ν_{max}: 1741, 1687, 1531, 1347, 1157, 742, 610, 576 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2NaO_7S_2^+$) requires *m*/*z* 425.0448, found *m*/*z* 425.0449.

4.42j: Ethyl (*E*)-6-(*N*-((4-nitrophenyl)sulfonyl)acrylamido)hex-2-enoate



Following General Procedure **B** using **4.0j** (719 mg, 2.10 mmol), the purification by flash column chromatography on silica gel (10 – 30% EtOAc in heptane) afforded compound **4.42j** in 73% yield (610 mg) as a white solid.

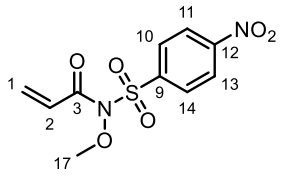
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.8 Hz, 2H^{11,13}), 8.10 (d, *J* = 8.7 Hz, 2H^{10,14}), 6.98 – 6.88 (m, 1H^{19}), 6.78 (dd, *J* = 16.6, 10.4 Hz, 1H^{2}), 6.42 (d, *J* = 16.6 Hz, 1H^{1}), 5.92 – 5.82 (m, 2H^{1,20}), 4.18 (q, *J* = 7.1 Hz, 2H^{24}), 3.88 – 3.81 (m, 2H^{16}), 2.30 (app. q, *J* = 7.2 Hz, 2H^{18}), 1.98 – 1.88 (m, 2H^{17}), 1.28 (t, *J* = 7.1 Hz, 3H^{25}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (C^{21}), 165.4 (C^{3}), 150.7 (C^{12}), 146.6 (CH^{19}), 145.0 (CH^{2}), 133.3 (CH_2^{1}), 129.3 ($2C^{10,14}$), 127.6 (CH^{2}), 124.5 ($2C^{11,13}$), 122.7 (CH^{20}), 60.5 (CH_2^{24}), 46.5 (CH_2^{16}), 29.3 (CH_2^{17or18}), 28.6 (CH_2^{17or18}), 14.4 (CH_3^{25}) ppm.

IR (neat) ν_{max}: 2924, 1713, 1686, 1530, 1348, 1157, 977, 854, 741, 576 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2NaO_7S^+$) requires *m*/*z* 419.0883, found *m*/*z* 419.0870.

4.42k: *N*-Methoxy-*N*-((4-nitrophenyl)sulfonyl)acrylamide



Following procedure **B** at r.t. using **4.0k** (929 mg, 4 mmol). Purification by flash column chromatography on silica gel (5 – 50% EtOAc in heptane), afforded compound **4.42k** in 22% (257 mg) yield as a white solid.

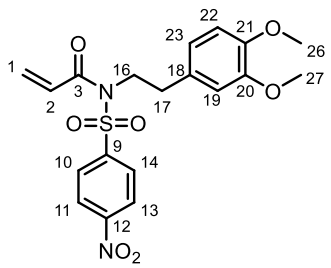
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 – 8.34 (m, 2H^{11,13}), 8.24 – 8.18 (m, 2H^{10,14}), 6.65 (dd, *J* = 17.0, 10.3 Hz, 1H^2), 6.51 (dd, *J* = 17.0, 1.5 Hz, 1H^1), 5.94 (dd, *J* = 10.3, 1.5 Hz, 1H^1), 4.11 (s, 3H^{17}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C^3), 142.2 (C^9), 134.4 (CH_2^{1}), 130.4 (2CH^{10,14}), 126.0 (CH^2), 124.4 (2CH^{11,13}), 67.7 (CH_3^{17}) ppm. (carbon 12 did not relax)

IR (neat) ν_{max}: 3108, 1704, 1533, 1349, 1181, 1088, 743 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{10}N_2NaO_6S^+$) requires *m*/*z* 309.0152, found *m*/*z* 309.0148.

4.42l: *N*-(3,4-Dimethoxyphenethyl)-*N*-((4-nitrophenyl)sulfonyl)acrylamide



Following General Procedure **B** using *N*-(3,4-dimethoxyphenethyl)-4-nitrobenzenesulfonamide (1.10 g, 3.00 mmol), the purification by flash column

chromatography on silica gel (5 – 50% EtOAc in heptane) afforded compound **4.42l** in 22% yield (283 mg) as a yellow solid.

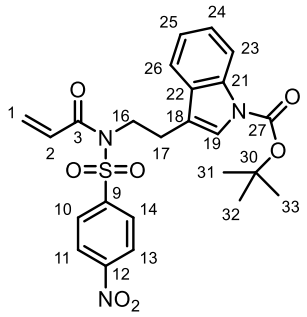
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.8 Hz, 2H^{11,13}), 8.06 (d, *J* = 8.8 Hz, 2H^{10,14}), 6.82 – 6.70 (m, 3H^{19,22,23}), 6.60 (dd, *J* = 16.6, 10.4 Hz, 1H^{2}), 6.34 (dd, *J* = 16.6, 0.8 Hz, 1H^{1}), 5.77 (dd, *J* = 10.4, 0.8 Hz, 1H^{1}), 4.10 – 4.00 (m, 2H^{16}), 3.84 (s, 3H^{26or27}), 3.84 (s, 3H^{26or27}), 3.05 – 2.93 (m, 2H^{17}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (C^{3}), 150.5 (C^{12}), 149.2 (C^{26or27}), 148.2 (C^{26or27}), 145.0 (C^{9}), 132.6 (CH_2^{1}), 129.8 (C^{18}), 129.4 (2CH^{10,14}), 127.3 (CH^{2}), 124.3 (2CH^{11,13}), 121.1 (CH^{23}), 112.3 (CH^{19or22}), 111.5 (CH^{19or22}), 56.0 ($2CH_3^{26,27}$), 48.7 (CH_2^{16}), 36.3 (CH_2^{17}) ppm.

IR (neat) ν_{max}: 1687, 1533, 1514, 1349, 1161, 1028, 742, 618 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{20}N_2NaO_7S^+$) requires *m*/*z* 443.0883, found *m*/*z* 443.0866.

4.42m: *tert*-Butyl 3-(2-(*N*-((4-nitrophenyl)sulfonyl)acrylamido)ethyl)-1*H*-indole-1-carboxylate



Following General Procedure **B** using **4.0m** (445 mg, 1.00 mmol), the purification by flash column chromatography on silica gel (5 – 80% EtOAc in heptane) afforded compound **4.42m** in 60% yield (300 mg) as a yellow solid.

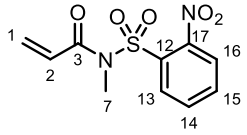
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8 Hz, 2H^{11,13}), 8.09 (d, *J* = 7.4 Hz, 1H^{Ar}), 8.04 (d, *J* = 8.8 Hz, 2H^{10,14}), 7.63 (d, *J* = 7.6 Hz, 1H^{Ar}), 7.41 (s, 1H^{19}), 7.36 – 7.22 (m, 2H^{Ar}), 6.83 (dd, *J* = 16.6, 10.4 Hz, 1H^{2}), 6.47 (d, *J* = 16.6 Hz, 1H^{1}), 5.87 (d, *J* = 10.4 Hz, 1H^{1}), 4.20 – 4.05 (m, 2H^{16}), 3.22 – 3.10 (m, 2H^{17}), 1.68 (s, 9H$^{31–33}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5 (C^{3}), 150.6 (C^{12}), 149.7 (C^{27}), 144.9 (C^{9}), 135.6 (C^{Ar}), 133.0 ($CH_2{}^{1}$), 130.1 (C^{Ar}), 129.2 ($2CH^{10,14}$), 127.8 (CH^{2}), 124.9 (CH^{Ar}), 124.3 ($2CH^{11,13}$), 123.9 (CH^{Ar}), 122.9 (CH^{Ar}), 119.0 (CH^{Ar}), 116.2 (C^{Ar}), 115.5 (CH^{Ar}), 84.0 (C^{30}), 47.2 ($CH_2{}^{16}$), 28.3 ($3CH_3{}^{31–33}$), 26.0 ($CH_2{}^{17}$) ppm.

IR (neat) ν_{max}: 2980, 1729, 1688, 1532, 1370, 1154, 742 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{24}H_{25}N_3NaO_7S^+$) requires *m/z* 522.1305, found *m/z* 522.1305.

4.42n: *N*-Methyl-*N*-((2-nitrophenyl)sulfonyl)acrylamide



Following General Procedure **B** using *N*-methyl-2-nitrobenzenesulfonamide (108 mg, 0.50 mmol). Purification by flash column chromatography on silica gel (10 – 25% EtOAc in heptane), afforded compound **4.42n** in 50% yield (66.9 mg) as a white solid.

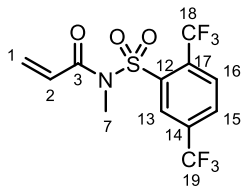
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 – 8.34 (m, $1H^{16}$), 7.78 (m, $3H^{13–15}$), 6.68 (dd, *J* = 16.7, 10.4 Hz, $1H^{2}$), 6.43 (dd, *J* = 16.7, 1.5 Hz, $1H^{1}$), 5.87 (dd, *J* = 10.4, 1.5 Hz, $1H^{1}$), 3.44 (s, $3H^{7}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C^{3}), 148.1 (C^{17}), 134.8 (CH^{Ar}), 134.4 (CH^{Ar}), 132.9 (C^{12}), 132.8 ($CH_2{}^{1}$), 132.3 (CH^{Ar}), 127.5 (CH^{2}), 124.8 (CH^{Ar}), 33.7 ($CH_3{}^{7}$) ppm.

IR (neat) ν_{max}: 1693, 1541, 1404, 1362, 1169, 1093, 715, 601 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{10}N_2NaO_5S^+$) requires m/z 293.0203, found m/z 293.0200.

4.42q: *N*-((2,5-bis(trifluoromethyl)phenyl)sulfonyl)-*N*-methylacrylamide



Following General Procedure **B** using **4.0q** (307 mg, 1.00 mmol), the purification by flash column chromatography on silica gel (5 – 20 % EtOAc in heptane) afforded compound **4.42q** in 67% yield (241 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H^{13}), 8.01 (s, 2H^{15,16}), 6.65 (dd, *J* = 16.7, 10.4 Hz, 1H^{2}), 6.42 (d, *J* = 16.7 Hz, 1H^{1}), 5.87 (d, *J* = 10.4 Hz, 1H^{1}), 3.44 (s, 3H^{7}) ppm.

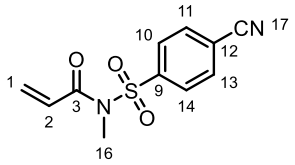
^{13}C NMR (176 MHz, $CDCl_3$): δ 165.8 (C^{3}), 139.8 (C^{12}), 134.9 (q, *J* = 33.7 Hz, 2C^{14,17}), 133.1 (CH_2^{1}), 131.2 (q, *J* = 3.7 Hz, CH^{Ar}), 130.6 (q, *J* = 3.4 Hz, CH^{Ar}), 129.3 (q, *J* = 6.3 Hz, CH^{Ar}), 127.2 (CH^{2}), 122.5 (q, *J* = 274.7 Hz, $CF_3$$^{18 or 19}$), 122.0 (q, *J* = 274.4 Hz, $CF_3$$^{18 or 19}$), 33.3 ($CH_3$^{7}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -58.8, -63.3 ppm.

IR (neat) ν_{max}: 1697, 1405, 1365, 1331, 1309, 1269, 1133, 1034, 730 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for [M+Na]$^{+}$ ($C_{12}H_9F_6NNaO_3S^{+}$) requires *m*/*z* 384.0100, found *m*/*z* 384.0103.

4.42r: *N*-((4-Cyanophenyl)sulfonyl)-*N*-methylacrylamide



Following General Procedure **B** using 4-cyano-*N*-methylbenzenesulfonamide (589 mg, 3.00 mmol), the purification by flash column chromatography on silica gel (5 – 40% EtOAc in heptane) afforded compound **4.42r** in 63% yield (470 mg) as an off-white solid.

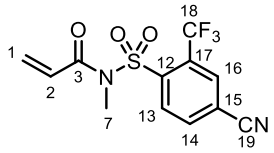
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 – 7.99 (m, 2H^{11,13}), 7.88 – 7.82 (m, 2H^{10,14}), 6.91 (dd, *J* = 16.7, 10.4 Hz, 1H^{2}), 6.41 (dd, *J* = 16.7, 1.4 Hz, 1H^{1}), 5.86 (dd, *J* = 10.4, 1.4 Hz, 1H^{1}), 3.35 (s, 3H^{16}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C^{3}), 143.0 (C^{9}), 133.1 (2CH^{10,14}), 132.7 (CH_2^{1}), 128.4 (2CH^{10,14}), 128.0 (CH^{2}), 117.7 (C$^{12 or 17}$), 117.1 (C$^{12 or 17}$), 33.5 (CH_3^{16}) ppm.

IR (neat) ν_{max}: 2234, 1684, 1400, 1352, 1157, 1081, 724, 635, 588, 567 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for [M+Na]$^{+}$ ($C_{11}H_{10}N_2NaO_3S^{+}$) requires *m*/*z* 273.0304, found *m*/*z* 273.0304.

4.42s: *N*-((4-Cyano-2-(trifluoromethyl)phenyl)sulfonyl)-*N*-methylacrylamide



Following General Procedure **B** using **4.0s** (137 mg, 0.52 mmol), the purification by flash column chromatography on silica gel (0 – 40% EtOAc in heptane) afforded compound **4.42s** in 66% yield (108 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 8.3 Hz, 1H^{13or14}), 8.15 – 8.03 (m, 2H^{16,13or14}), 6.60 (dd, *J* = 16.6, 10.3 Hz, 1H^{2}), 6.42 (d, *J* = 16.6 Hz, 1H^{1}), 5.89 (d, *J* = 10.3 Hz, 1H^{1}), 3.47 (s, 3H^{7}) ppm.

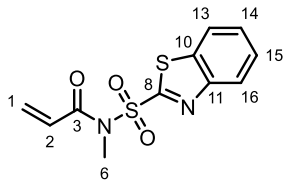
^{13}C NMR (176 MHz, $CDCl_3$): δ 165.8 (C^{3}), 142.3 (C^{Ar}), 135.8 (CH^{13or14}), 135.1 (CH^{13or14}), 133.7 (CH_2^{1}), 131.7 (q, *J* = 6.4 Hz, CH^{16}), 128.9 (q, *J* = 34.7 Hz, C^{17}), 126.8 (CH^{2}), 121.6 (q, *J* = 274.7 Hz, CF_3^{18}), 117.9 (C^{Aror19}), 116.0 (C^{Aror19}), 33.2 (app.m, CH_3^{7}) ppm.

^{19}F NMR (659 MHz, $CDCl_3$): δ -58.8 ppm.

IR (neat) ν_{max}: 2922, 2852, 2239, 1685, 1618, 1357, 1312, 1269, 1163, 1089, 742, 654, 567 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{12}H_9F_3N_2NaO_3S^+$) requires *m*/*z* 341.0178, found *m*/*z* 341.0179.

4.42t: *N*-(Benzo[d]thiazol-2-ylsulfonyl)-*N*-methylacrylamide



Following General Procedure **B** using **4.0t** (228 mg, 1.00 mmol), the purification by flash column chromatography on silica gel (5 – 20% EtOAc in heptane) afforded compound **4.42t** in 57% yield (161 mg) as a yellow oil.

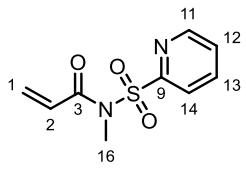
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 – 8.17 (m, 1H^{16}), 8.02 – 7.98 (m, 1H^{13}), 7.68 – 7.57 (m, 2H^{14,15}), 7.21 (dd, *J* = 16.7, 10.4 Hz, 1H^{2}), 6.45 (dd, *J* = 16.7, 1.6 Hz, 1H^{1}), 5.87 (dd, *J* = 10.4, 1.6 Hz, 1H^{1}), 3.47 (s, 3H^{6}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2 (C^{3}), 163.7 (C^{8}), 152.2 (C^{11}), 136.7 (C^{10}), 132.1 (CH_2^{1}), 128.7 (CH^{Ar}), 128.4 (CH^{Ar}), 128.0 (CH^{2}), 125.8 (CH^{Ar}), 122.3 (CH^{Ar}), 34.0 (CH_3^{6}) ppm.

IR (neat) ν_{max}: 1690, 1364, 1157, 1006, 906, 760, 724, 626, cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{10}N_2NaO_3S_2^+$) requires *m*/*z* 305.0025, found *m*/*z* 305.0028.

4.42u: *N*-methyl-*N*-(pyridin-2-ylsulfonyl)acrylamide



Following General Procedure **C** using **4.0u** (1.03 g, 6.00 mmol), the purification by flash column chromatography on silica gel (0 – 50% EtOAc in heptane) afforded compound **4.42u** in 48% yield (655 mg) as a pale yellow oil.

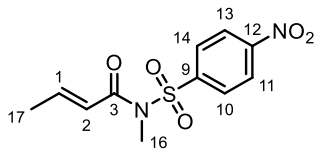
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.7 Hz, 1H^{11}), 8.08 (d, *J* = 7.8 Hz, 1H^{14}), 7.97 (app.td, *J* = 7.8, 1.5 Hz, 1H^{13}), 7.55 (dd, *J* = 7.6, 4.7 Hz, 1H^{12}), 7.11 (dd, *J* = 16.7, 10.5 Hz, 1H^{2}), 6.37 (dd, *J* = 16.7, 1.4 Hz, 1H^{1}), 5.77 (dd, *J* = 10.4, 1.4 Hz, 1H^{1}), 3.39 (s, 3H^{16}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C^{3}), 156.6 (C^{9}), 150.5 (CH^{Ar}), 138.3 (CH^{Ar}), 131.0 (CH_2^{1}), 129.0 (CH^{Ar}), 127.7 (CH^{2}), 122.9 (CH^{Ar}), 33.8 (CH_3^{16}) ppm.

IR (neat) ν_{max}:1687, 1616, 1579, 1402, 1355,1173, 1015, 909, 789,623, 575 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_9H_{10}N_2NaO_3S^+$) requires m/z 249.0305, found m/z 249.0301.

4.57a: (*E*)-*N*-Methyl-*N*-((4-nitrophenyl)sulfonyl)but-2-enamide



Following General Procedure **C** using *N*-methyl-4-nitrobenzenesulfonamide (649 mg, 3.00 mmol) and (*E*)-2-butenoyl chloride (383 µL, 3.60 mmol) the purification by flash column chromatography on silica gel (5 – 35% EtOAc in heptane) afforded compound **4.57a** in 80% yield (679 mg) as a white solid.

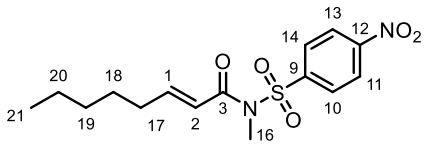
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 – 8.35 (m, 2H^{11,13}), 8.15 – 8.07 (m, 2H^{10,14}), 7.03 (dq, *J* = 13.9, 7.0 Hz, 1H^2), 6.58 (dq, *J* = 15.0, 1.6 Hz, 1H^1), 3.37 (s, 3H^{16}), 1.93 (dd, *J* = 7.0, 1.7 Hz, 3H^{17}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0 (C^3), 150.7 (C^{12}), 148.2 (CH^1), 144.9 (C^9), 129.2 (2CH^{10,14}), 124.5 (2CH^{11,13}), 122.1 (CH^2), 33.5 (CH_3^{16}), 18.8 (CH_3^{17}) ppm.

IR (neat) ν_{max}: 1684, 1634, 1527, 1347, 1158, 1081, 938, 735, 617, 582 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}N_2NaO_5S^+$) requires *m*/*z* 307.0359, found *m*/*z* 307.0353.

4.57b: (*E*)-*N*-Methyl-*N*-((4-nitrophenyl)sulfonyl)oct-2-enamide



Following General Procedure **C** using *N*-methyl-4-nitrobenzenesulfonamide (1.08 g, 5.00 mmol) and *trans*-2-octenoic acid chloride (6.00 mmol; generated according to a reported procedure[152]), the purification by flash column chromatography on silica gel (5% EtOAc in heptane) afforded compound **4.57b** in 12% yield (205 mg) as a colourless oil.

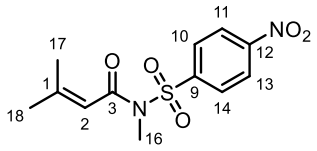
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.8 Hz, 2H^{11,13}), 8.11 (d, *J* = 8.8 Hz, 2H^{10,14}), 7.03 (dt, *J* = 15.1, 7.0 Hz, 1H^1), 6.54 (d, *J* = 15.1 Hz, 1H^2), 3.38 (s, 3H^{16}), 2.29 – 2.16 (m, 2H^{17}), 1.51 – 1.38 (m, 2H^{18}), 1.36 – 1.22 (m, 4H^{19,20}), 0.88 (t, *J* = 6.8 Hz, 3H^{21}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (C^3), 153.3 (CH^1), 150.7 (C^{12}), 144.9 (C^9), 129.2 ($2CH^{10,14}$), 124.5 ($2CH^{11,13}$), 120.5 (CH^2), 33.5 ($CH_3{}^{16}$), 32.9 ($CH_2{}^{17}$), 31.4 ($CH_2{}^{18}$), 27.7 ($CH_2{}^{19}$), 22.5 ($CH_2{}^{20}$), 14.1 ($CH_3{}^{21}$) ppm.

IR (neat) ν_{max}: 2958, 2929, 2857, 1687, 1634, 1532, 1349, 1178, 740 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}N_2NaO_5S^+$) requires *m*/*z* 363.0985, found *m*/*z* 363.0978.

4.57c: *N*,3-Dimethyl-*N*-((4-nitrophenyl)sulfonyl)but-2-enamide



Following General Procedure **C** using *N*-methyl-4-nitrobenzenesulfonamide (649 mg, 3.00 mmol) and 3-methylcrotonic acid chloride (601 mg, 6.00 mmol; generated by a reported method[153]), the purification by flash column chromatography on silica gel (0 – 30% EtOAc in heptane) afforded compound **4.57c** in 20% yield (181 mg) as a white solid.

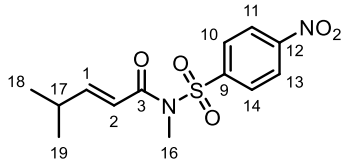
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 – 8.33 (m, *J* = 9.1, 2.1 Hz, $2H^{11,13}$), 8.15 – 8.07 (m, $2H^{10,14}$), 6.21 – 6.11 (m, $1H^2$), 3.37 (s, $3H^{16}$), 1.97 (d, *J* = 1.0 Hz, $3H^{Me}$), 1.92 (d, *J* = 1.0 Hz, $3H^{Me}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3 (C^3), 158.8 (C^1), 150.6 (C^{12}), 145.2 (C^9), 129.2 ($2CH^{10,14}$), 124.3 ($2CH^{11,13}$), 116.5 (CH^2), 33.6 ($CH_3{}^{16}$), 27.8 ($CH_3{}^{17}$), 21.1 ($CH_3{}^{18}$) ppm.

IR (neat) ν_{max}: 1688, 1531, 1349, 1158, 739, 620, 583 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}N_2NaO_5S^+$) requires *m*/*z* 321.0516, found *m*/*z* 321.0515.

4.57d: (*E*)-*N*,4-Dimethyl-*N*-((4-nitrophenyl)sulfonyl)pent-2-enamide



Following General Procedure **C** using *N*-methyl-4-nitrobenzenesulfonamide (2.16 g, 10.0 mmol) and 4-methyl-2-pentenoic acid chloride (generated by a reported method[154] from 1.31 mL, 11.0 mmol 4-methyl-2-pentenoic acid), the purification by flash column chromatography on silica gel (5 – 15% EtOAc in heptane), afforded compound **4.57d** in 94% yield (2.95 g) as an off-white solid.

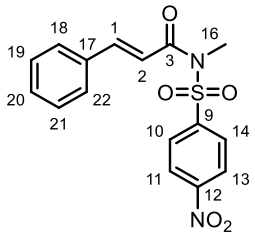
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 – 8.34 (m, 2H^{11,13}), 8.14 – 8.08 (m, 2H^{10,14}), 6.99 (dd, *J* = 15.2, 6.8 Hz, 1H^2), 6.48 (dd, *J* = 15.2, 1.3 Hz, 1H^1), 3.39 (s, 3H^{16}), 2.54 – 2.43 (m, 1H^{17}), 1.05 (d, *J* = 6.8 Hz, 6H^{18,19}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (C^3), 158.9 (CH^1), 150.7 (C^{12}), 145.0 (C^9), 129.3 (2CH^{10,14}), 124.5 (2CH^{11,13}), 118.0 (CH^2), 33.5 (CH_3^{16}), 31.7(CH^{17}), 21.3 (2CH_3^{18,19}) ppm.

IR (neat) ν_{max}: 3108, 2963, 2871, 1685, 1632, 1531, 1348, 1161, 740 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}N_2NaO_5S^+$) requires *m*/*z* 335.0672, found *m*/*z* 335.0673.

4.57e: *N*-Methyl-*N*-((4-nitrophenyl)sulfonyl)cinnamamide



To *N*-methyl-4-nitrobenzenesulfonamide (1.08 g, 5 mmol) in 20 mL DCM in a flame dried Schlenk tube under argon was added *trans*-cinnamic acid (889 mg, 6 mmol), EDCI (1.15 g, 6 mmol) and DMAP (61 mg, 0.5 mmol). The mixture was stirred at r.t. for 18 h upon which sat. aq. $NaHCO_3$ and EtOAc was added. The phases were separated, and the organic phase washed

with brine. The organic phase was dried over $MgSO_4$, and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (0 – 20% EtOAc in heptane), afforded compound **4.57e** in 28% (394 mg) yield as a white solid.

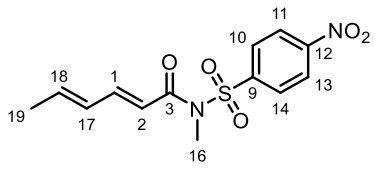
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.8 Hz, 2H^{11,13}), 8.12 (d, *J* = 8.8 Hz, 2H^{10,14}), 7.72 (d, *J* = 15.5 Hz, 1H^2), 7.59 – 7.50 (m, 2H^{18,22}), 7.47 – 7.38 (m, 3H$^{19–21}$), 7.26 (d, *J* = 15.5 Hz, 1H^1), 3.43 (s, 3H^{16}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3 (C^3), 150.7 (C^{12}), 147.5 (CH^1), 144.7 (C^9), 134.2 (C^{17}), 131.3 (CH^{20}), 129.3 (2CH^{10,14}), 129.1 (2CH^{18,22}), 128.6 (2CH^{19,21}), 124.6 (2CH^{11,13}), 117.2 (CH^2), 33.6 (CH_3^{16}) ppm.

IR (neat) ν_{max}: 1678, 1617, 1529, 1367, 1349, 1176, 1081, 855 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{14}N_2NaO_5S^+$) requires *m*/*z* 369.0516, found *m*/*z* 369.0516.

4.57g: (2*E*,4*E*)-*N*-Methyl-*N*-((4-nitrophenyl)sulfonyl)hexa-2,4-dienamide



Following General Procedure **C** using *N*-methyl-4-nitrobenzenesulfonamide (2.16 g, 10.0 mmol) and sorbic acid chloride (generated by a reported method[155] from 1.65 g, 11.0 mmol potassium sorbate), the purification by flash column chromatography on silica gel (10% EtOAc in heptane) afforded compound **4.57g** in 56% yield (1.74 g) as a yellow solid.

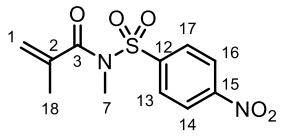
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 – 8.32 (m, 2H^{11,13}), 8.15 – 8.05 (m, 2H^{10,14}), 7.36 – 7.27 (m, 1H^{alkene}), 6.52 (d, *J* = 14.7 Hz, 1H^2), 6.31 – 6.17 (m, 2H^{alkene}), 3.38 (s, 3H^{16}), 1.92 – 1.85 (d, *J* = 5.2 Hz, 3H^{19}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C^3), 150.6 (C^{12}), 148.2 (CH^{alkene}), 144.9 (C^9), 142.7 (CH^{alkene}), 130.0 (CH^{alkene}), 129.2 (2CH^{10,14}), 124.5 (2CH^{11,13}), 117.7 (CH^2), 33.5 (CH_3^{16}), 19.0 (CH_3^{19}) ppm.

IR (neat) ν_{max}: 3107, 1678, 1634, 1602, 1529, 1348, 1169, 1072, 1000, 737 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{14}N_2NaO_5S^+$) requires *m*/*z* 333.0516, found *m*/*z* 333.0513.

4.63: *N*-Methyl-*N*-((4-nitrophenyl)sulfonyl)methacrylamide



Following General Procedure B using *N*-methyl-*N*-((4-nitrophenyl)sulfonyl) amide (2.16 g, 10.0 mmol, 1.00 equiv.), and methacryloyl chloride (1.25 g, 12.0 mmol, 1.20 equiv.) the purification by flash column chromatography on silica gel (10 – 40% EtOAc in heptane) afforded compound **4.63** in 43% yield (1.22 g) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 – 8.36 (m, $2H^{14,16}$), 8.22 – 8.17 (m, $2H^{13,17}$), 5.47 (app.d, *J* = 1.5 Hz, $1H^1$), 5.30 (s, $1H^1$), 3.34 (s, $3H^7$), 1.95 (s, $3H^{18}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (C^3), 150.8 (C^{15}), 144.3 (C^{12}), 139.76 ($CH_2{}^1$), 129.9 ($2CH^{13,17}$), 124.3 ($2CH^{14,16}$), 121.5 (C^2), 35.3 ($CH_3{}^7$), 19.4 ($CH_3{}^{18}$) ppm.

IR (neat) ν_{max}: 1692, 1528, 1348, 1305, 1172, 1064, 854, 739, 683, 606, 566 cm^{-1}.

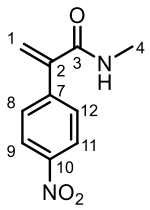
HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{12}N_2NaO_5S^+$) requires *m*/*z* 307.0359, found *m*/*z* 307.0368.

4.4.3 Characterisation of aryl migrated products

General Procedure D: Truce-Smiles rearrangement

To an oven-dried 4 or 8 mL vial containing a magnetic stir bar was added sulfonyl carboxamide (1.00 equiv.). The compound was dissolved in dry MeCN (0.05 M) and DABCO (1.00 equiv.) was added. The vial was capped and the mixture stirred at 20 – 25 °C or 80 °C in an oil bath for 72 h, upon which it was diluted with DCM (20 mL) and the solution transfered to a separatory funnel. The vial was washed with saturated, aqueous $NaHCO_3$ solution (10 mL) and transfered to the same separatory funnel. The phases were separated and the aqueous phase was extracted with DCM (2 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The mixture was purified via flash column chromatography on silica gel to afford the pure product.

4.43a: *N*-Methyl-2-(4-nitrophenyl)acrylamide



Following General procedure **D** at 20 – 25 °C using **4.42a** (54.1 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (20 – 80% EtOAc in heptane) afforded compound **4.43a** in 92% yield (37.9 mg) as a white solid.

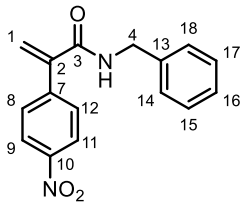
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.7 Hz, 2H^{9,11}), 7.60 (d, *J* = 7.7 Hz, 2H^{8,12}), 6.11 (s, 1H^1), 5.78 (s, 1H^1), 5.72 (bs, 1H^{NH}), 2.93, (s, 3H^4) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (C^3), 147.9 (C^{10}), 143.8 (C^{2or8}), 143.3 (C^{2or8}), 129.0 (2CH^{8,12}), 124.0 (2CH^{9,11}), 123.1 (CH_2^{1}), 26.9 (CH_3^{4}) ppm.

IR (neat) ν_{max}: 3299, 1649, 1609, 1596, 1407, 1344, 857.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{10}H_{11}N_2O_3^+$) requires *m/z* 207.0764, found *m/z* 207.0766.

4.43b: *N*-Benzyl-2-(4-nitrophenyl)acrylamide



Following General Procedure 20 – 25 °C using **4.42b** (69.3 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (5 – 40% EtOAc in heptane) afforded compound **4.43b** in 63% yield (35.3 mg) as a white solid.

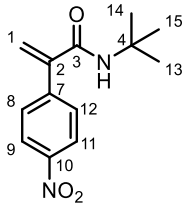
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.7 Hz, 2H^{9,11}), 7.61 (d, *J* = 8.7 Hz, 2H^{8,12}), 7.40–7.27 (m, 5H$^{14–18}$), 6.13 (s, 1H^{1}), 6.00 (bs, 1H^{NH}), 5.82 (s, 1H^{1}), 4.57 (d, *J* = 5.7 Hz, 2H^{4}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C^{3}), 148.0 (C^{10}), 143.7 (C^{2or8}), 143.2 (C^{2or8}), 137.8 (C^{13}), 129.1 (2CH^{Ar}), 128.9 (2CH^{Ar}), 128.0 (3CH^{Ar}), 124.0 (2CH^{Ar}), 123.3 (CH_2^{1}), 44.2 (CH_2^{4}) ppm.

IR (neat) ν_{max}: 3284, 1662, 1513, 1345, 858, 700 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{14}N_2NaO_3^+$) requires *m*/*z* 305.0902, found *m*/*z* 305.0901.

4.43d: *N*-(*tert*-Butyl)-2-(4-nitrophenyl)acrylamide



Following General Procedure **D** at 80 °C using **4.42d** (31.2 mg, 0.10 mmol), the purification by flash column chromatography on silica gel (0 – 50% EtOAc in heptane) afforded compound **4.43d** in 63% yield (15.8 mg) as a white solid.

[At 20 – 25 °C using **1c** (62.5 mg, 0.20 mmol) in 49% yield (24.2 mg).]

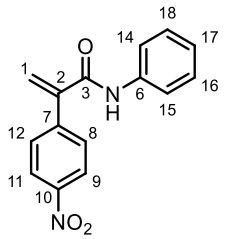
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.8 Hz, 2H^{9,11}), 7.60 (d, *J* = 8.8 Hz, 2H^{8,12}), 5.98 (s, 1H^{1}), 5.74 (s, 1H^{1}), 5.55 (bs, 1H^{NH}), 1.41 (s, 9H$^{13–15}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C^{3}), 147.8 (C^{10}), 145.0 (C^{2or7}), 143.5 (C^{2or7}), 128.7 ($2CH^{8,12}$), 124.0 ($2CH^{9,11}$), 121.8 ($CH_2{}^{1}$), 52.1 ($CH_3{}^{4}$), 28.9 ($3CH_3{}^{13–15}$) ppm.

IR (neat) ν_{max}: 3259, 3068, 2977, 1644, 1593, 1545, 1514, 1364, 860 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}N_2NaO_3^+$) requires *m/z* 271.1053, found *m/z* 271.1054.

4.43e: 2-(4-Nitrophenyl)-*N*-phenylacrylamide



Following General Procedure **D** at 80 °C using **4.42e** (66.5 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (50 – 80% EtOAc in heptane) afforded compound **4.43e** in 28% yield (14.9 mg) as a white solid.

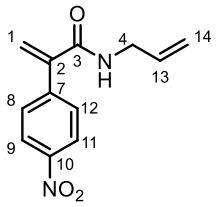
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.8 Hz, $2H^{9,11}$), 7.68 (d, *J* = 8.8 Hz, $2H^{8,12}$), 7.55 (d, *J* = 7.6 Hz, $2H^{16,18}$), 7.44 – 7.31 (m, $3H^{14,15,NH}$), 7.17 (t, *J* = 7.4 Hz, $1H^{17}$), 6.24 (s, $1H^{1}$), 5.93 (s, $1H^{1}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (C^{3}), 148.1 (C^{10}), 144.3 (C^{sp2}), 142.8 (C^{sp2}), 137.4 (C^{sp2}), 129.3 ($2CH^{8,12}$), 129.0 ($2CH^{16,18}$), 125.3 (CH^{17}), 124.2 ($2CH^{8,12}$), 123.7 ($CH_2{}^{1}$), 120.2 ($2CH^{14,15}$) ppm.

IR (neat) ν_{max}: 3286, 1651, 1595, 1514, 1340, 1247, 760, 690 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{12}N_2NaO_3^+$) requires m/z 291.0740, found m/z 291.0739.

4.43f: *N*-allyl-2-(4-nitrophenyl)acrylamide



Following General Procedure **D** at 20 – 25 °C using **4.42f** (59.3 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (15 – 50% EtOAc in heptane) afforded compound **4.43f** in 72% (33.2 mg) yield as a white solid.

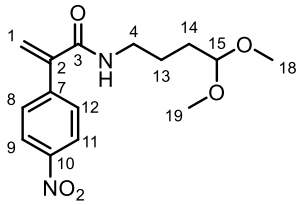
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.8 Hz, 2H^{9,11}), 7.61 (d, *J* = 8.8 Hz, 2H^{8,12}), 6.11 (s, 1H^{1}), 5.93–5.76 (m, 2H^{13,NH}), 5.80 (s, 1H^{1}), 5.24–5.13 (m, 2H^{14}), 4.04–3.95 (m, 2H^{4}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C^{3}), 147.9 (C^{10}), 143.7 (C^{2or8}), 143.2 (C^{2or8}), 133.7 (CH^{13}), 128.9 (2CH^{8,12}), 124.0 (2CH^{9,11}), 123.2 (CH_2^{1}), 117.2 (CH_2^{14}), 42.5 (CH_2^{4}) ppm.

IR (neat) ν_{max}: 3271, 1642, 1595, 1515, 1344, 856 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+Na]^{+}$ ($C_{12}H_{12}N_2NaO_3^{+}$) requires *m*/*z* 255.0740, found *m*/*z* 255.0736.

4.43g: *N*-(4,4-Dimethoxybutyl)-2-(4-nitrophenyl)acrylamide



Following General Procedure **D** at 20 – 25 °C using **4.42g** (74.5 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (15 – 80% EtOAc in heptane) afforded compound **4.43g** in 74% yield (45.8 mg) as a white solid.

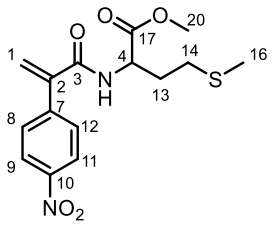
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.2 Hz, 2H^{9,11}), 7.59 (d, *J* = 8.2 Hz, 2H^{8,12}), 6.06 (bs, 2H^{1,NH}), 5.77 (s, 1H^{1}), 4.37–4.31 (m, 1H^{15}), 3.38 (app.q, *J* = 6.4 Hz, 2H^{4}), 3.29 (s, 6H^{18,19}), 1.68–1.59 (m, 4H^{13,14}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (C^{3}), 147.8 (C^{10}), 144.0 (C^{2or7}), 143.4 (C^{2or7}), 128.9 ($2CH^{8,12}$), 123.9 ($2CH^{9,11}$), 122.7 (CH_2^{1}), 104.4 (CH^{15}), 53.4 ($2CH_3^{18,19}$), 39.8 (CH_2^{4}), 30.1 (CH_2^{13or14}), 24.3 (CH_2^{13or14}) ppm.

IR (neat) ν_{max}: 1520, 1345, 903, 859, 726, 648 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}N_2NaO_5^+$) requires *m*/*z* 331.1264, found *m*/*z* 331.1256.

4.43i: Methyl (2-(4-nitrophenyl)acryloyl)methioninate



Following General Procedure **D** at 20 – 25 °C using **4.42i** (80.5 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (0 – 40% EtOAc in heptane) afforded compound **4.43i** in 58% yield (39.5 mg) as a white solid.

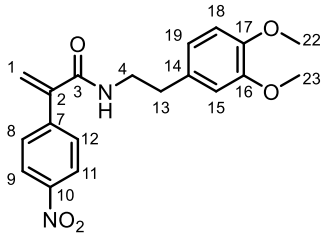
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.8 Hz, $2H^{9,11}$), 7.62 (d, *J* = 8.8 Hz, $2H^{8,12}$), 6.56 (d, *J* = 7.5 Hz, $1H^{NH}$), 6.17 (s, $1H^{1}$), 5.85 (s, $1H^{1}$), 4.89–4.79 (m, $1H^{4}$), 3.79 (s, $3H^{20}$), 2.53 (t, *J* = 7.3 Hz, $2H^{14}$), 2.27–2.18 (m, $1H^{13}$), 2.10–2.02 (m, $1H^{13}$), 2.08 (s, $3H^{16}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (C^{17}), 166.7 (C^{3}), 148.0 (C^{10}), 143.2 (C^{2or7}), 142.9 (C^{2or7}), 129.0 ($2CH^{8,12}$), 124.0 ($2CH^{9,11}$), 123.9 (CH_2^{1}), 52.9 (CH_3^{20} *or* CH^{4}), 52.2 (CH_3^{20} *or* CH^{4}), 31.2 (CH_2^{13or14}), 30.3 (CH_2^{13or14}), 15.7 (CH_3^{16}) ppm.

IR (neat) ν_{max}: 3284, 1744, 1669, 1516, 1344, 1208, 859 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2NaO_5S^+$) requires *m*/*z* 361.0829, found *m*/*z* 361.0823.

4.43l: *N*-(3,4-Dimethoxyphenethyl)-2-(4-nitrophenyl)acrylamide



Following General Procedure **D** at 20 – 25 °C using **4.42l** (84.1 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (10 – 50% EtOAc in heptane) afforded compound **4.43l** in 69% yield (49.0 mg) as a white solid.

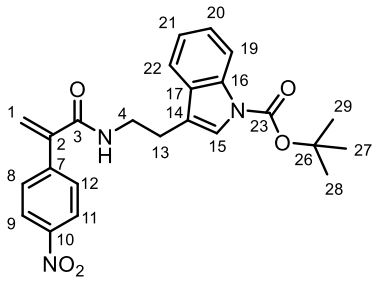
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.7 Hz, 2H^{9,11}), 7.47 (d, *J* = 8.7 Hz, 2H^{8,12}), 6.77 (d, *J* = 8.0 Hz, 1H^{19}), 6.73–6.64 (m, 2H^{15,18}), 6.04 (s, 1H^{1}), 5.73 (s, 1H^{1}), 5.67 (bs, 1H^{NH}), 3.86 (s, 3H$^{22 or 23}$), 3.84 (s, 3H$^{22 or 23}$), 3.66–3.59 (m, 2H^{4}), 2.82 (t, *J* = 6.8 Hz, 2H^{13}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C^{3}), 149.3 (C^{Ar}), 148.1 (C^{Ar}), 147.9 (C^{Ar}), 143.8 (C$^{2 or 7}$), 143.2 (C$^{2 or 7}$), 130.9 (C^{14}), 128.9 (2CH^{8,12}), 123.9 (2CH^{9,11}), 123.1 (CH_2^{1}), 120.8 (CH^{Ar}), 112.0 (CH^{Ar}), 111.4 (CH^{Ar}), 56.07 ($CH_3$$^{22 or 23}$), 56.03 ($CH_3$$^{22 or 23}$), 41.0 ($CH_2$^{4}), 35.0 ($CH_2$^{13}) ppm.

IR (neat) ν_{max}: 3345, 2935, 1663, 1513, 1343, 1261, 1234, 1027, 858 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+Na]^{+}$ ($C_{19}H_{20}N_2NaO_5^{+}$) requires *m/z* 379.1264, found *m/z* 379.1257.

4.43m: *tert*-Butyl 3-(2-(2-(4-nitrophenyl)acrylamido)ethyl)-1H-indole-1-carboxylate



Following General Procedure **D** at 20 – 25 °C using **4.42m** (99.9 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (5 – 50% EtOAc in heptane) afforded compound **4.43m** in 67% yield (58.2 mg) as a yellow oil.

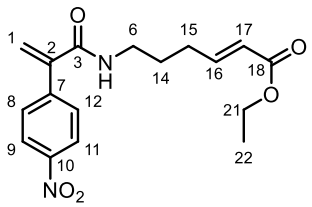
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19–8.06 (m, 3H^{9,11,15}), 7.55–7.38 (m, 4H^{8,12,19,22}), 7.33 (app.t, *J* = 6.6 Hz, 1H^{20}), 7.22 (app.t, *J* = 6.6 Hz, 1H^{21}), 6.08 (s, 1H^{1}), 5.75 (bs, 1H^{NH}), 5.72 (s, 1H^{1}), 3.71 (app.q, *J* = 6.4 Hz, 2H^{4}), 2.99 (t, *J* = 6.4 Hz, 2H^{13}), 1.67 (s, 9H$^{27–29}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C^{3}), 149.8 (C^{23}), 147.9 (C^{10}), 143.7 (C^{2or7}), 143.2 (C^{2or7}), 135.6 (C^{16}), 130.4 (C^{17}), 128.9 (2CH^{8,12}), 124.8 (CH^{Ar}), 123.9 (2CH^{9,11}), 123.49 (CH_2^{1}), 123.47 (CH^{Ar}), 122.8 (CH^{Ar}), 118.9 (CH^{Ar}), 117.4 (C^{14}), 115.6 (CH^{Ar}), 84.1 (C^{26}), 39.9 (CH_2^{4}), 28.3 (3$CH_3$$^{27–29}$), 24.9 ($CH_2$^{13}) ppm.

IR (neat) ν_{max}: 3297, 2979, 1728, 1664, 1516, 1372, 1342, 1154, 833, 746 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{24}H_{25}N_3NaO_5^+$) requires *m*/*z* 458.1686, found *m*/*z* 458.1681.

4.43j: Ethyl (*E*)-6-(2-(4-nitrophenyl)acrylamido)hex-2-enoate



Following General Procedure **D** at 80 °C using **4.42j** (39.6 mg, 0.10 mmol), the purification by flash column chromatography on silica gel (10 – 50% EtOAc in heptane) afforded compound **4.43j** in 78% yield (26.0 mg) as a white solid.

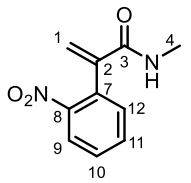
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.24 – 8.20 (m, 2H^{9,11}), 7.61 – 7.56 (m, 2H^{8,12}), 6.92 (dt, *J* = 15.6, 6.9 Hz, 1H^{16}), 6.08 (s, 1H^{1}), 5.87 – 5.80 (m, 2H^{17}), 5.78 (s, 1H^{1}), 4.17 (q, *J* = 7.1 Hz, 2H^{21}), 3.39 (app.q, *J* = 6.7 Hz, 2H^{6}), 2.29 – 2.23 (m, 2H^{15}), 1.77 – 1.71 (m, 2H^{14}), 1.27 (t, *J* = 7.1 Hz, 3H^{22}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.9 (C^{3or18}), 166.5 (C^{3or18}), 147.9 (CH^{2}), 147.5 (CH^{17}), 143.8 (C^{7or10}), 143.2 (C^{7or10}), 128.9 (2CH^{8,12}), 124.0 (2CH^{9,11}), 123.1 (CH_2^{1}), 122.3 (CH^{16}), 60.4 (CH_2^{21}), 39.6 (CH_2^{6}), 29.7 (CH_2^{14or15}), 28.1 (CH_2^{14or15}), 14.4 (CH_3^{22})ppm.

IR (neat) ν_{max}: 3301, 2924, 2853, 1716, 1649, 1518, 1345, 859, 733 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2NaO_5^+$) requires *m/z* 355.1264, found *m/z* 355.1263.

4.43n: *N*-Methyl-2-(2-nitrophenyl)acrylamide



Following General Procedure **D** at 20 – 25 °C using **4.42n** (54.1 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (5 – 60% EtOAc in heptane) afforded compound **4.43n** in 62% yield (25.4 mg) as a white solid.

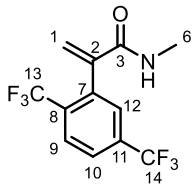
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.1 Hz, 1H^9), 7.66 (app.t, *J* = 8.1 Hz, 2H^{10}), 7.58–7.51 (m, 1H^{11}), 7.44 (d, *J* = 7.6 Hz, 1H^{12}), 6.10 (s, 1H^1), 5.75 (bs, 1H^{NH}), 5.58 (s, 1H^1), 2.87 (d, *J* = 4.9 Hz, 3H^4) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C^3), 148.1 (C^8), 143.3 (C^{2or7}), 133.7 (CH^{Ar}), 133.3 (C^{2or7}), 132.7 (CH^{Ar}), 129.7 (CH^{Ar}), 124.8 (CH^{Ar}), 121.8 ($CH_2{}^1$), 26.84 ($CH_3{}^4$) ppm.

IR (neat) ν_{max}: 3319, 1651, 1618, 1522, 1347 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{10}N_2NaO_3^+$) requires *m/z* 229.0584, found *m/z* 229.0586.

4.43q: 2-(2,5-Bis(trifluoromethyl)phenyl)-*N*-methylacrylamide



Following General Procedure **D** at 80 °C using **4.42q** (72.3 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (5 – 20% EtOAc in heptane) afforded compound

4.43q in 49% yield (29.5 mg) as an off-white solid (containing trace amounts of inseparable sulfonamide 1,4-adduct).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.3 Hz, 1H^{9or10}), 7.77 (d, *J* = 8.3 Hz, 1H^{9or10}), 7.64 (s, 1H^{12}), 6.45 (s, 1H^{1}), 5.58 (s, 1H^{1}), 5.37 (bs, 1H^{NH}), 2.86 (d, *J* = 4.9 Hz, 3H^{6}) ppm.

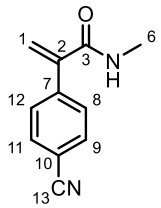
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C^{3}), 140.7 (C^{2or7}), 137.4 (C^{2or7}), 134.2 (q, *J* = 33.6 Hz, C^{8or11}), 132.6 (q, *J* = 30.4 Hz, C^{8or11}), 129.0 (q, *J* = 3.6 Hz, CH^{Ar}), 127.4 (q, *J* = 5.0 Hz, CH^{Ar}), 126.4 (CH_2^{1}), 125.8 (q, *J* = 3.6 Hz, CH^{Ar}), 123.24 (q, *J* = 274.4 Hz, CF_3^{13or14}), 123.15 (q, *J* = 273.1 Hz, CF_3^{13or14}), 27.0 (CH_3^{6}) ppm

^{19}F NMR (377 MHz, $CDCl_3$): δ -59.0, -63.2 ppm.

IR (neat) ν_{max}: 3317, 1661, 1614, 1536, 1314, 1178, 1129, 1084, 1040, 909, 842, 736 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{12}H_9F_6NNaO^+$) requires *m*/*z* 320.0481, found *m*/*z* 320.0478.

4.43r: 2-(4-Cyanophenyl)-*N*-methylacrylamide



Following General Procedure **D** at 80 °C using **4.42r** (50.1 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (20 – 80% EtOAc in heptane) afforded compound **4.43r** in 22% yield (8.1 mg) as a white solid.

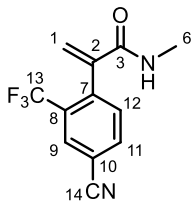
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.5 Hz, 2H^{9,11}), 7.53 (d, *J* = 7.5 Hz, 2H^{8,12}), 6.08 (s, 1H^{1}), 5.73 (s, 1H^{1}), 5.70 (bs, 1H^{NH}), 2.93 (d, *J* = 4.8 Hz, 3H^{6}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (C^{3}), 144.0 (C^{2}), 141.5 (C^{7}), 132.6 (2CH^{9,11}), 128.8 (2CH^{9,11}), 122.8 (CH_2^{1}), 118.6 (C^{13}), 112.4 (C^{10}), 26.9 (CH_3^{6}) ppm.

IR (neat) ν_{max}: 3293, 2227, 1642, 1601, 1551, 1406, 845, 744, 545 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{11}H_{10}N_2NaO^+$) requires *m*/*z* 209.0685, found *m*/*z* 209.0680.

4.43s: 2-(4-Cyano-2-(trifluoromethyl)phenyl)-*N*-methylacrylamide



Following General Procedure **D** at 80 °C using **4.42s** (33.5 mg, 105 µmol), the purification by flash column chromatography on silica gel (20 – 100% EtOAc in heptane) afforded compound **4.43s** in 42% yield (11.2 mg) as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.01 (s, 1H^9), 7.87 (dd, *J* = 7.9, 1.2 Hz, 1H^{11}), 7.54 (d, *J* = 7.9 Hz, 1H^{12}), 6.39 (s, 1H^1), 5.57 (s, 1H^1), 5.41 (bs, 1H^{NH}), 2.86 (d, *J* = 4.9 Hz, 3H^6) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C^3), 141.1 (C^{2or7}), 140.8 (C^{2or7}), 135.2 (CH^{11or12}), 133.2 (CH^{11or12}), 130.7 (q, *J* = 31.4 Hz, C^8), 130.3 (q, *J* = 5.3 Hz, CH^9), 125.9 (CH_2^{1}), 124.2 (q, *J* = 274.7 Hz, CF_3^{13}), 117.2 (C^{10or14}), 113.2 (C^{10or14}), 27.0 (CH_3^{6}) ppm

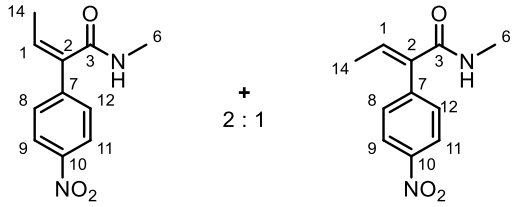
^{19}F NMR (659 MHz, $CDCl_3$): δ -59.0 ppm.

IR (neat) ν_{max}: 3081, 2942, 2236, 1664, 1610, 1537, 1315, 1173, 1132 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ ($C_{12}H_9F_3N_2NaO^+$) requires *m*/*z* 277.0559, found *m*/*z* 277.0559.

Experimental Data

4.58a: (*Z*)- and (*E*)-*N*-Methyl-2-(4-nitrophenyl)but-2-enamide



Following General Procedure **D** at 80 °C using **4.57a** (56.9 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (5 – 60% EtOAc in heptane) afforded compound **(*Z*)- 4.58a** and **(*E*)- 4.58a** as a mixture of 2:1 in 79% combined yield (34.6 mg) as a white solid.

(*Z*): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.8 Hz, 2H^{9,11}), 7.52 (d, *J* = 8.8 Hz, 2H^{8,12}), 6.30 (q, *J* = 7.1 Hz, 1H^{1}), 5.63 (bs, 1H^{NH}), 2.97 (d, *J* = 4.9 Hz, 3H^{6}), 2.01 (d, *J* = 7.1 Hz, 3H^{14}) ppm.

(*E*): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.6 Hz, 2H^{9,11}), 7.40 (d, *J* = 8.6 Hz, 2H^{8,12}), 7.12 (q, *J* = 7.3 Hz, 1H^{1}), 5.19 (bs, 1H^{NH}), 2.83 (d, *J* = 4.9 Hz, 3H^{6}), 1.66 (d, *J* = 7.3 Hz, 3H^{14}) ppm.

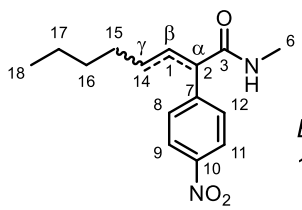
(*Z*): ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C^{3}), 147.2 (C^{10}), 143.8 (C^{7}), 137.9 (C^{2}), 131.8 (CH^{1}), 127.1 (2CH^{8,12}), 124.1 (2CH^{9,11}), 26.5 (CH_3^{6}), 16.1 (CH_3^{14}) ppm.

(*E*): ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (C^{3}), 147.8 (C^{10}), 142.9 (C^{7}), 137.4 (CH^{1}), 135.5 (C^{2}), 131.8 (2CH^{8,12}), 124.2 (2CH^{9,11}), 27.0 (CH_3^{6}), 15.2 (CH_3^{14}) ppm.

IR (neat) ν_{max} [mixture of isomers]: 3283, 1661, 1649, 1514, 1344, 854, 735 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+Na]^{+}$ ($C_{11}H_{12}N_2NaO_3^{+}$) requires *m/z* 243.0740, found *m/z* 243.0742.

4.58b: (*E*)-N-Methyl-2-(4-nitrophenyl)oct-3-enamide



$E_{\alpha\beta}$:$Z_{\alpha\beta}$:$E_{\beta\gamma}$:$Z_{\beta\gamma}$ =
1.3 : 2.9 : 5 : 1

Following General Procedure **D** at 80 °C using **4.57b** (68.1 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (20 – 40% EtOAc in heptane) afforded compound

4.58b as a mixture of isomers in 91% combined yield (50.4 mg) as a colourless oil. The major isomer ((*E*)-*N*-methyl-2-(4-nitrophenyl)oct-3-enamide) is reported herein.

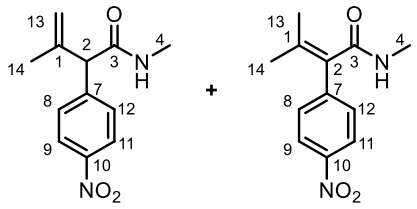
^{1}H NMR (600 MHz, $CDCl_3$) [major isomer]: δ 8.19 – 8.14 (m, 2H^{9,11}), 7.47 – 7.42 (m, 2H^{8,12}), 5.90 – 5.59 (m, 3H^{1,14,NH}), 4.20 (d, *J* = 8.2 Hz, 1H^{2}), 2.83 (d, *J* = 4.8 Hz, 3H^{6}), 2.13 – 2.03 (m, *J* = 14.3, 7.1 Hz, 1H^{15}), 1.39 – 1.24 (m, 4H^{16,17}), 0.88 (t, *J* = 7.2 Hz, 3H^{18}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) [major isomer]: δ 171.6 (C^{3}), 147.2 (C^{7or10}), 147.1 (C^{7or10}), 136.4 (CH^{1}), 129.3 (2CH^{8,12}), 126.9 (CH^{1}), 124.0 (2CH^{9,11}), 56.4 (CH^{2}), 32.3 (CH_3^{6}), 31.2 (CH_2^{Al}), 26.8 (CH_2^{Al}), 22.4 (CH_2^{Al}), 14.0 (CH_3^{18}) ppm.

IR (neat) ν_{max} [isomeric mixture]: 3287, 2957, 2928, 2855, 1646, 1518, 1345, 854, 738 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{19}N_2NaO_3^+$) requires *m*/*z* 299.1366, found *m*/*z* 299.1362.

4.58c and ***iso*-4.58c**: *N*,3-Dimethyl-2-(4-nitrophenyl)but-3-enamide



2s ***iso*-2s**

Following General Procedure **D** at 80 °C using **4.57c** (59.7 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (10 – 50% EtOAc in heptane), afforded compound **4.58c** in 55% yield (25.9 mg) as a white solid and compound ***iso*-4.58c** in 27% yield (12.5 mg) as a white solid (82% overall yield).

4.58c ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.18 (dt, *J* = 8.8, 2.0 Hz, 2H^{9,11}), 7.48 (dt, *J* = 8.8, 2.0 Hz, 2H^{8,12}), 5.83 (bs, 1H^{NH}), 5.11 (s, 1H^{13}), 4.87 (s, 1H^{13}), 4.26 (s, 1H^{2}), 2.86 (d, *J* = 4.9 Hz, 3H^{4}), 1.77 (s, 3H^{14}) ppm.

***iso*-4.58c ^{1}H NMR (700 MHz, $CDCl_3$)**: δ 8.29–8.15 (m, 2H^{9,11}), 7.49–7.39 (m, 2H^{8,12}), 5.37 (s, 1H^{NH}), 2.83 (d, *J* = 4.9 Hz, 3H^{4}), 2.07 (s, 3H^{13}), 1.70 (s, 3H^{14}) ppm.

4.58c ^{13}C NMR (175 MHz, $CDCl_3$): 170.5 (C^3), 147.3 (C^{10}), 145.4 (C^7), 143.1 (C^1), 130.1 ($2CH^{8,12}$), 123.8 ($2CH^{9,11}$), 116.2 ($CH_2{}^{13}$), 60.5 (CH^2), 26.8 ($CH_3{}^4$), 22.1 ($CH_3{}^{14}$) ppm.

***iso*-4.58c ^{13}C NMR (175 MHz, $CDCl_3$):** 169.4 (C^3), 147.1 (C^{10}), 145.1 (C^7), 140.8 (C^1), 132.1 (C^2), 130.3 ($2CH^{8,12}$), 123.9 ($2CH^{9,11}$), 26.6 ($CH_3{}^4$), 22.7 ($CH_3{}^{13}$), 22.4 ($CH_3{}^{14}$) ppm.

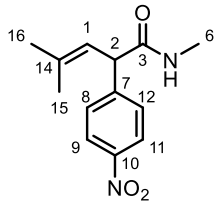
4.58c IR (neat) ν_{max}: 3311, 1681, 1518, 1375, 908, 867, 743 cm^{-1}.

***iso*-4.58c IR (neat) ν_{max}:** 3285, 1662, 1514, 1344, 1106, 851, 749, 703 cm^{-1}.

4.58c HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}N_2NaO_3^+$) requires *m*/*z* 257.0897, found *m*/*z* 257.0896.

***iso*-4.58c HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}N_2NaO_3^+$) requires *m*/*z* 257.0897, found *m*/*z* 257.0899.

***iso*-4.58d**: *N*,4-Dimethyl-2-(4-nitrophenyl)pent-3-enamide



Following General Procedure **D** at 80 °C using **4.57d** (62.5 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (0 – 40% EtOAc in heptane) afforded compound ***iso*-4.58d** in 81% yield (40.3 mg) as an off-white solid.

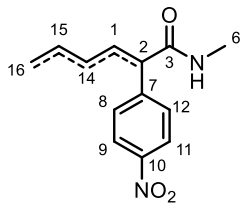
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 – 8.12 (m, $2H^{9,11}$), 7.49 – 7.40 (m, $2H^{8,12}$), 5.86 (bs, $1H^{NH}$), 5.57 – 5.50 (m, 1H), 4.44 (d, *J* = 9.3 Hz, $1H^2$), 2.83 (d, *J* = 4.9 Hz, $3H^6$), 1.80 (d, *J* = 1.0 Hz, $3H^{15 or 16}$), 1.70 (d, *J* = 1.2 Hz, $3H^{15 or 16}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (C^3), 148.0 ($C^{7 or 10}$), 147.0 ($C^{7 or 10}$), 137.8 (C^{14}), 129.1 ($2CH^{8,12}$), 124.0 ($2CH^{9,11}$), 121.7 (CH^1), 52.2 (CH^1), 26.8 ($CH_3{}^6$), 26.0 ($CH_3{}^{15 or 16}$), 18.4 ($CH_3{}^{15 or 16}$) ppm.

IR (neat) ν_{max}: 3305, 2937, 1681, 1515, 1345, 852, 741 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}N_2NaO_3^+$) requires *m/z* 271.1053, found *m/z* 271.1060.

4.58g: *N*-Methyl-2-(4-nitrophenyl)hexadienamide [isomeric mixture]



Following General Procedure **D** at 80 °C using **4.57g** (62.1 mg, 0.20 mmol), the purification by flash column chromatography on silica gel (0 – 50% EtOAc in heptane) afforded compound **4.58g** as a mixture of isomers in 73% combined yield (35.8 mg) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) [isomeric mixture]: δ 8.26 – 8.17 (m, 1.2H^{9,11}), 8.13 – 8.07 (m, 0.7H^{9,11}), 7.74 (d, *J* = 11.8 Hz, 0.1H^{9,11}), 7.56 – 7.45 (m, 0.7H^{8,12}), 7.40 – 7.31 (m, 1.8H^{8,12}), 6.99 (d, *J* = 11.8 Hz, 0.1H^{alkene}), 6.64 (d, *J* = 1.1 Hz, 0.3H^{alkene}), 6.49 – 6.30 (m, 0.4H^{alkene}), 6.22 – 6.00 (m, 0.9H^{alkene}), 5.90 – 5.67 (m, 1.1H^{alkene,NH}), 5.23 (bs, 0.6H^{NH}), 2.96 – 2.88 (m, 1.1H^6), 2.81 – 2.73 (m, 1.9H^6), 1.90 – 1.79 (m, 1.4H^6), 1.74 – 1.67 (m, 1.6H^6) ppm.

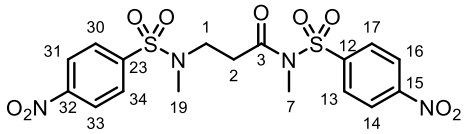
^{13}C NMR (100 MHz, $CDCl_3$) [isomeric mixture]: δ 168.5 (C^3), 166.7 (C^3), 147.7 (C^{sp2}), 147.0 (C^{sp2}), 143.7 (C^{sp2}), 143.1 (C^{sp2}), 140.6 (C^{sp2}), 138.8 (C^{sp2}), 138.6 (C^{sp2}), 136.8 (C^{sp2}), 134.3 (C^{sp2}), 133.6 (C^{sp2}), 133.0 (C^{sp2}), 132.6 (C^{sp2}), 131.5 (C^{sp2}), 130.6 (C^{sp2}), 128.1 (C^{sp2}), 127.1 (C^{sp2}), 127.1 (C^{sp2}), 127.0 (C^{sp2}), 124.7 (C^{sp2}), 124.2 (C^{sp2}), 124.1 (C^{sp2}), 124.1 (C^{sp2}), 27.1 (CH_3^6), 27.0 (CH_3^6), 26.6 (CH_3^6), 19.0 (CH_3^{Al}), 18.9 (CH_3^{Al}), 14.3 (CH_3^{16}) ppm.

IR (neat) ν_{max} [isomeric mixture]: 3419, 2937, 1655, 1628, 1513, 1343, 856, 735 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{14}N_2NaO_3^+$) requires *m/z* 269,0897, found *m/z* 269.0901.

4.4.4 Characterisation of byproducts

4.55: *N*-Methyl-3-((*N*-methyl-4-nitrophenyl)sulfonamido)-*N*-((4-nitrophenyl)sulfonyl)-propanamide



4.55 was isolated during the optimisation of the reaction conditions on standard substrate **4.42a** as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (dt, *J* = 9.3, 2.3 Hz, 2H^{Ar}), 8.38 (dt, *J* = 9.3, 2.3 Hz, 2H^{Ar}), 8.16 (dt, *J* = 9.3, 2.3 Hz, 2H^{Ar}), 7.94 (dt, *J* = 9.3, 2.3 Hz, 2H^{Ar}), 3.38 (s, 3H^{7}), 3.33 – 3.28 (m, 2H^{Al}), 3.03 (t, *J* = 6.8 Hz, 2H^{Al}), 2.81 (s, 3H^{19}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (C^{3}), 150.9 (C^{Ar}), 150.4 (C^{Ar}), 144.2 (C^{Ar}), 143.0 (C^{Ar}), 129.4 (CH^{Ar}), 128.7 (CH^{Ar}), 124.69 (CH^{Ar}), 124.66 (CH^{Ar}), 46.4 (CH_2^{Al}), 37.0 (CH_2^{Al}), 36.9 (CH_3^{19}), 33.4 (CH_2^{7}) ppm.

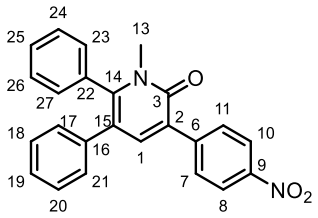
IR (neat) ν_{max} 3109, 2929, 1703, 1529, 1349, 1164, 742.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{18}N_4NaO_9S_2^+$) requires *m*/*z* 509.0407, found *m*/*z* 509.0403.

Rauhut–Currier byproduct **4.56** was isolated and charactarised by H. Zhang.

4.4.5 Characterisation of cyclisation reaction products

4.59: 1-Methyl-3-(4-nitrophenyl)-5,6-diphenylpyridin-2(1*H*)-one



Following procedure reported by Ackermann *et al.*[131] using **4.43a** (103 mg, 0.50 mmol), diphenyl acetylene (44.6 mg, 0.25 mmol), $Cu(OAc)_2{\cdot}H_2O$ (49.9 mg, 0.25 mmol) and dichloro(*p*-cymene)ruthenium(II) dimer (7.7 mg, 12.5 µmol). Purification by flash column chromatography on silica gel (10 – 40% EtOAc in heptane) afforded compound **4.59** in 91% yield (87.3 mg) as a yellow solid.

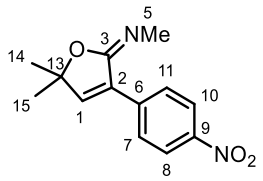
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 – 8.22 (m, 2H^{8,10}), 8.06 – 7.98 (m, 2H^{7,11}), 7.72 (s, 1H^1), 7.40 – 7.31 (m, 3H^{Ar}), 7.23 – 7.10 (m, 5H^{Ar}), 7.04 – 6.96 (m, 2H^{17,21}), 3.44 (s, 3H^{13}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 161.3 (C^3), 148.1 (C^{Ar}), 147.1 (C^{Ar}), 143.7 (C^{Ar}), 141.0 (CH^1), 138.1 (C^{Ar}), 134.1 (C^{Ar}), 129.73 (2CH^{Ar}), 129.67 (2CH^{Ar}), 129.5 (2CH^{Ar}), 129.3 (CH^{Ar}), 128.9 (2CH^{Ar}), 128.2 (2CH^{Ar}), 127.1 (C^{Ar}), 126.9 (CH^{Ar}), 123.5 (2CH^{Ar}), 120.9 (C^{Ar}), 35.6 (CH$_3$^{13})ppm.

IR (neat) ν_{max}: 1646, 1536, 1512, 1343, 910, 854, 735, 701 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{24}H_{18}N_2NaO_3^+$) requires *m*/*z* 405.1210, found *m*/*z* 405.1209.

4.61: (*Z*)-*N*,5,5-Trimethyl-3-(4-nitrophenyl)furan-2(5*H*)-imine



To an oven dried 4 mL vial containing a magnetic stir bar were added ***iso*-4.58d** (24.8 mg, 0.10 mmol), dry MeCN (1 mL), K_2CO_3 (55.3 mg, 0.40 mmol) and I_2 (50.8 mg, 0.20 mmol). The vial

was capped, and the suspension stirred rapidly at 20 –25 °C for 96 h. The mixture was diluted with DCM (10 mL) and washed with a saturated, aqueous $Na_2S_2O_3$ solution. The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (0 – 50% EtOAc in heptane) afforded compound **4.61** in 67% yield (16.6 mg) as a white solid.

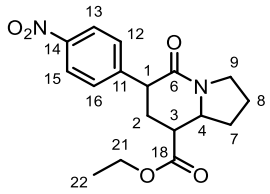
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.23 – 8.20 (m, 2H^{8,10}), 8.06 – 8.02 (m, 2H^{7,11}), 7.10 (s, 1H^1), 3.14 (s, 3H^5), 1.52 (s, 6H^{14,15}) ppm.

^{13}C NMR (175 MHz, $CDCl_3$): 161.0 (C^3), 148.2 (CH^1), 147.7 (C^{sp2}), 137.9 (C^{sp2}), 131.7 (C^{sp2}), 128.9 (2CH^{7,11}), 123.6 (2CH^{7,11}), 86.1 (C^{13}), 34.8 (CH_3^5), 26.7 ($2CH_3^{14,15}$) ppm.

IR (neat) ν_{max}: 2978, 2932, 2869, 1682, 1598, 1514, 1349, 1112, 948, 845, 759, 691 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}N_2O_3^+$) requires *m/z* 247.1077, found *m/z* 247.1077.

4.62: Ethyl 6-(4-nitrophenyl)-5-oxooctahydroindolizine-8-carboxylate



This procedure was inspired by Fukumoto *et al.*'s report.[142] To a flame-dried Schlenk flask containing a stir bar was added **4.43j** (33.2 mg, 0.10 mmol) and 2 mL dry DCM. The solution was cooled to 0 °C and Et_3N (13.9 µL, 0.10 mmol) followed by TMSOTf (18.3 µL, 0.10 mmol) were added dropwise while stirring. The now deeply red coloured solution was stirred at 0 °C for 4 h, upon which saturated, aqueous NH_4Cl solution (10 mL) was added to quench the reaction. The aqueous phase was extracted with DCM (2 x 20 mL) and the combined organic phases were dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (10 – 60% EtOAc in heptane) afforded compound **4.62** in 51% yield (17.0 mg) as a yellow oil as a mixture of isomers.

^{1}H NMR (600 MHz, $CDCl_3$) [isomeric mixture]: δ 8.21 – 8.15 (m, 2H^{13,15}), 7.46 – 7.34 (m, 2H^{12,16}), 4.22 – 4.10 (m, 2H^{21}), 3.98 – 3.50 (m, 4H^{Al}), 2.61 – 2.01 (m, 5H^{Al}), 1.94 – 1.81 (m, 1H^{Al}), 1.65 – 1.53 (m, 1H^{Al}), 1.29 – 1.21 (m, 3H^{22}) ppm.

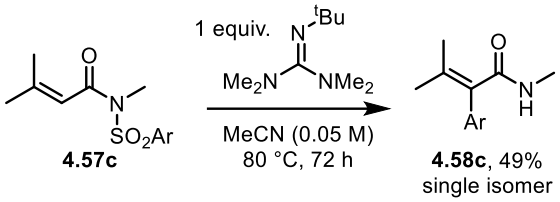
^{13}C NMR (150 MHz, $CDCl_3$) [isomeric mixture]: δ 172.6 (C^{6}), 172.3 (C^{6}), 171.9 (C^{6}), 168.9 (C^{18}), 167.7 (C^{18}), 167.6 (C^{18}), 148.6 (C^{Ar}), 148.3 (C^{Ar}), 147.13 (C^{Ar}), 147.08 (C^{Ar}), 130.3 (2CH^{12,16}), 129.5 (2CH^{12,16}), 129.4 (CH^{12,16}), 124.1 (CH^{13,15}), 124.0 (CH^{13,15}), 123.6 (CH^{13,15}), 61.4 (C^{Al}), 61.2 (C^{Al}), 60.9 (C^{Al}), 60.3 (C^{Al}), 57.5 (C^{Al}), 48.5 (C^{Al}), 46.5 (C^{Al}), 46.3 (C^{Al}), 46.1 (C^{Al}), 46.0 (C^{Al}), 45.3 (C^{Al}), 42.8 (C^{Al}), 42.0 (C^{Al}), 34.9 (C^{Al}), 33.2 (C^{Al}), 32.9 (C^{Al}), 32.8 (C^{Al}), 31.6 (C^{Al}), 29.5 (C^{Al}), 23.1 (C^{Al}), 22.4 (C^{Al}), 22.4 (C^{Al}), 14.4 (C^{Al}), 14.3 (C^{Al}), 14.3 (C^{Al}) ppm.

IR (neat) ν_{max} [isomeric mixture]: 2979, 2884, 1729, 1641, 1518, 1346, 1189, 856, 735 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+Na]^{+}$ ($C_{17}H_{20}N_2NaO_5^{+}$) requires *m/z* 355.1264, found *m/z* 355.1266.

4.4.6 Further experimental reaction investigations

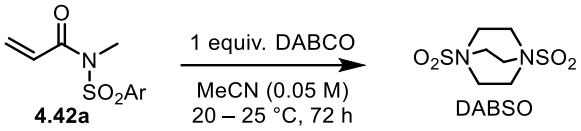
Brønsted base comparison



To an oven-dried 8 mL vial containing a magnetic stir bar was added **4.57c** (59.7 mg, 0.20 mmol). The solid was dissolved in 4 mL dry MeCN (0.05 M) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (40.3 µL, 0.20 mmol) was added. The vial was capped and the mixture was stirred at 80 °C in an oil bath for 72 h, upon which it was cooled to 20 - 25 °C, diluted with DCM (20 mL) and the solution was transfered to a separatory funnel. The vial was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and transfered to the same separatory funnel. The phases were separated and the aqueous phase was extracted with DCM (2 x 10 mL). The

combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The mixture was purified by flash column chromatography on silica gel (10 – 50% EtOAc in heptane) to afford the pure product in 49% yield (22.9 mg) as a single isomer.

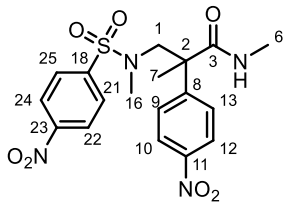
Observation of DABSO in the reaction mixture



To an oven-dried 8 mL vial containing a magnetic stir bar was added **4.42a** (54.1 mg, 0.20 mmol). The solid was dissolved in 4 mL dry MeCN (0.05 M) and DABCO (22.4 mg, 0.20 mmol) was added. The vial was capped and the mixture was stirred at 80 °C in an oil bath for 72 h, upon which it was cooled to room temperature. The solution was removed using a syringe and the solid was washed with Et_2O. The residue was dissolved in CD_3OD and the ^1H NMR spectra was compared with commercial DABSO and DABCO and revealed DABSO to be present in the reaction precipitate.

^{1}H NMR (400 MHz, CD_3OD): δ 3.21 (s, 12H) ppm.

4.66: *N*,2-Dimethyl-3-((*N*-methyl-4-nitrophenyl)sulfonamido)-2-(4-nitrophenyl)propanamide



To an oven-dried vial containing a stir bar were added acrylamide **4.63** (56.9 mg, 0.20 mmol), 1 mL dry MeCN, DABCO (22.4 mg, 0.20 mmol) and the vial was capped. It was placed in a 70 °C preheated oil bath and stirred for 4 days. The solvent was removed under reduced pressure and the product was purified by flash column chromatography on silica gel (0 – 50% EtOAc in heptane) to afford **4.66** as colourless crystals (14.0 mg, 32%).

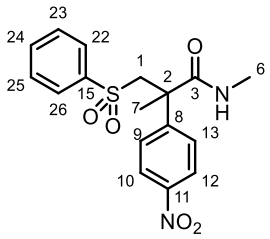
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.7 Hz, 2H^{22,24}), 8.22 (d, *J* = 8.9 Hz, 2H^{10,11}), 7.92 (d, *J* = 8.7 Hz, 2H^{21,25}), 7.59 (d, *J* = 8.9 Hz, 2H^{9,13}), 5.52 (br.s, 1H^{NH}), 3.94 (d, *J* = 14.1 Hz, 1H^{1}), 3.44 (d, *J* = 14.1 Hz, 1H^{1}), 2.81 (d, *J* = 4.8 Hz, 3H^{6}), 2.45 (s, 3H^{16}), 1.84 (s, 3H^{7}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3 (C^{3}), 150.4 (C^{23}), 149.0 (C^{18}), 147.5 (C^{11}), 143.2 (C^{8}), 128.8 (2CH^{Ar}), 128.1 (2CH^{Ar}), 124.6 (2CH^{Ar}), 124.1 (2CH^{Ar}), 58.7 (C^{1}), 51.1 (CH_2^{2}), 37.4 (CH_3^{16}), 27.1 (CH_3^{6}), 21.2 (CH_3^{7}) ppm.

IR (neat) ν_{max}: 3340, 2925, 1633, 1606, 1519, 1341, 1154, 975, 849, 600 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for [M+Na]$^{+}$ ($C_{18}H_{20}N_4NaO_7S^{+}$) requires 459.0954, found 459.0948.

4.68: *N*,2-Dimethyl-2-(4-nitrophenyl)-3-(phenylsulfonyl)propanamide



To an oven-dried vial containing a stir bar were added acrylamide **4.63** (56.9 mg, 0.20 mmol), sodium benzensulfinate (32.8 mg, 0.20 mmol), sulfolane (4 g) and the vial was capped. It was placed in a 160 °C preheated oil bath and stirred for 16 h. The solvent was removed under reduced pressure and the product was purified by flash column chromatography on silica gel (5 – 80% EtOAc in heptane) to afford **4.68** as colourless crystals (28.5 mg, 39%).

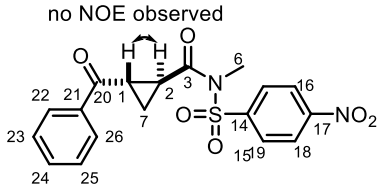
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.7 Hz, 2H^{10,11}), 7.71 (d, *J* = 7.7 Hz, 2H^{22,26}), 7.58 (t, *J* = 7.4 Hz, 1H^{24}), 7.50 (d, *J* = 8.7 Hz, 2H^{9,13}), 7.44 (app.t, *J* = 7.7 Hz, 2H^{23,25}), 5.40 (br.s, 1H^{NH}), 4.09 (d, *J* = 14.7 Hz, 1H^{1}), 3.77 (d, *J* = 14.7 Hz, 1H^{1}), 2.78 (d, *J* = 4.8 Hz, 3H^{6}), 2.08 (s, 3H^{7}) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5 (C^{3}), 147.7 (C^{11}), 147.5 (C^{15}), 141.0 (C^{8}), 133.7 (CH^{24}), 129.3 (2CH^{Ar}), 128.1 (2CH^{Ar}), 127.7 (2CH^{Ar}), 123.9 (2CH^{Ar}), 64.0 (CH_2^{1}), 49.7 (C^{2}), 27.3 (CH_3^{6}), 22.6 (CH_3^{7}) ppm.

IR (neat) ν_{max}: 3366, 2921, 1660, 1529, 1316, 1135, 844, 549 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{18}N_2NaO_5S^+$) requires 385.0829, found 385.0826.

4.75: 2-Benzoyl-*N*-methyl-*N*-((4-nitrophenyl)sulfonyl)cyclopropane-1-carboxamide



To an oven-dried vial containing a stir bar were added acrylamide **4.42a** (54.1 mg, 0.20 mmol), 4 mL dry MeCN, 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-1-phenylethan-1-one (47.1 mg, 0.24 mmol) and the vial was capped. It was placed in a 40 °C preheated oil bath and stirred for 3 days. The solvent was removed under reduced pressure and the product was purified by flash column chromatography on silica gel (5 – 40% EtOAc in heptane) to afford **4.75** as colourless crystals (27.9 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 2H^{16,18}), 8.08 (d, *J* = 8.7 Hz, 2H^{15,19}), 7.91 (d, *J* = 7.3 Hz, 2H^{22,26}), 7.60 (t, *J* = 7.3 Hz, 1H^{24}), 7.46 (app.t, *J* = 7.8 Hz, 2H^{23,25}), 3.52 (s, 3H^6), 3.16–3.07 (m, 1H^1), 3.00–2.92 (m, 1H^2), 1.69–1.60 (m, 2H^7) ppm.

^{13}C NMR (225 MHz, $CDCl_3$) δ 196.3 (C^{20}), 171.5 (C^3), 150.6 (C^{14}), 144.8 (C^{17}), 136.5 (C^{21}), 134.0 (CH^{24}), 129.2 (2CH^{15,19}), 129.0 (2CH^{23,25}), 128.4 (2CH^{22,26}), 124.5 (2CH^{16,18}), 33.8 (CH_3^6), 27.8 (CH^1), 25.3 (CH^2), 19.4 (CH_2^7) ppm.

IR (neat) ν_{max}: 3107, 2872, 1696, 1670, 1531, 1348, 1166, 744 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{16}N_2NaO_6S^+$) requires 411.0621, found 411.0621.

5 Closing remarks

To understand chemical reactions, we must look at the behavior of all components involved. A sensible first investigation starts with the reactants which provide the atoms ending up in the product. Their direct interaction is often the first step in building a conclusive model to understand the underlying process. However, frequently, other reactants are also essential; their involvement can rapidly increase the overall complexity of the process at hand and therefore makes a deep understanding more difficult. As exemplified in this thesis, counterions and specific solvents can play pivotal roles in electron- and proton-transfer processes and their interactions need to be included in detailed models of chemical reactions.

It seems, truly innocent species are quite rare and therefore, a detailed understanding of non-atom-providing reaction components such as counterions, solvents or other additives will play a central role in future developments of synthetic organic chemistry.

I learned a lot.

6 References

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