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Lewis Base Catalyzed Reactions with Latent Nucleophiles and Phosphonium Intermediates

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Y. Zi

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Documentation of authorship

This section contains a list of individual author's contributions to the publications reprinted in this thesis.

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Author		1	2	3	4	5	6
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Proposal for crediting publication equivalents		1.0					

P2	"Latent nucleophiles in Lewis base catalyzed enantioselective *N*-allylations of N-heterocycles" Y. Zi,[1] M. Lange,[2] C. Schultz,[3] I. Vilotijevic,[4] *Angew.Chem. Int.Ed.* **2019**, *58*, 10727–10731.				
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Author	1	2	3
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Synthesis and characterization of compounds	×	×	
Preparation of the manuscript	×		×
Correction of the manuscript	×	×	×
Supervision of Y. Zi			×
Proposal for crediting publication equivalents	1.0		

P6	"Lewis-base-catalysed selective reductions of ynones with a mild hydride donor" F. Schömberg,[1] Y. Zi,[2] I. Vilotijevic,[3] *Chem. Commun*. **2018**, *54*, 3266–3269.		
Author	1	2	3
Development of the concept		×	×
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Preparation of the manuscript	×		×
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P7	"*trans*-Hydroboration *vs.* 1,2-reduction: divergent reactivity of ynones and ynoates in Lewis-basecatalyzed reactions with pinacolborane" Y. Zi,[1] F. Schömberg,[2] F. Seifert,[3] H. Görls,[4] I. Vilotijevic,[5] *Org. Biomol. Chem.* **2018**, *16*, 6341–6349.					
Author		1	2	3	4	5
Development of the concept		×				×
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P8	"C-H functionalization of thiazoles via thiazol-2-yl-phosphonium intermediates" Y. Zi,[1] F. Schömberg,[2] K. Wagner,[3] I. Vilotijevic,[4] *Org. Lett.* **2020**, *22*, 3407-3411.				
Author		1	2	3	4
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P9	"Selective C-H chalcogenation of thiazoles via thiazol-2-yl-phosphonium salts" Y. Zi,[1] K. Wagner,[2] F. Schömberg,[3] I. Vilotijevic,[4] *Org. Biomol. Chem.* **2020**, accepted, *DOI: 10.1039/d0ob00684j*.				
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1 Introduction

In Lewis base catalysis, an electron pair donor (Lewis base) interacts with an acceptor (Lewis acid), forms a binding adduct that possesses an enhanced nucleophilic, electrophilic or ambiphilic character and therefore increases the rate of the catalyzed reactions.[1] As a requirement for all catalytic reactions, the Lewis base should be recovered unchanged at the end of the reaction.

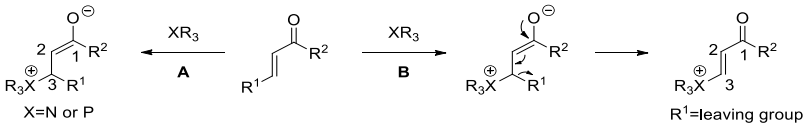
Three Lewis base-Lewis acid interactions are considered relevant for catalysis, namely n–π* interactions, n–σ* interactions and n–n* interactions.[2] The type of n– π* interactions includes the largest and most common form of Lewis base catalysis where the nonbonding electron pair of a Lewis base (n donor orbital) interacts with an unsaturated functional group of the acceptor (π* acceptor orbital), such as carbonyl[3-9], alkene[10-17] or alkyne[18-24]. Comparatively, n–σ* interactions and n–n* interactions involve the electron-pair acceptors whose coordination sphere could be expanded to a "hypervalent" state, such as organometallic reagents and boranes.[25]

Although a variety of processes can be catalyzed by Lewis bases, in comparison to Lewis acid catalysis, Lewis base catalyzed reactions are underexploited in organic synthesis.[26] This can be attributed to the limitations of valence expansion at carbon centers. Nevertheless, a variety of Lewis base catalysts were developed and evaluated in reactions of organic molecules.[1] Lewis bases containing electron-pair donor atoms from group 15, such as nitrogen and phosphorus, have attracted the most attention because of their strong nucleophilic properties and versatile character easy to modify through different substituents.[16-17, 23-24]

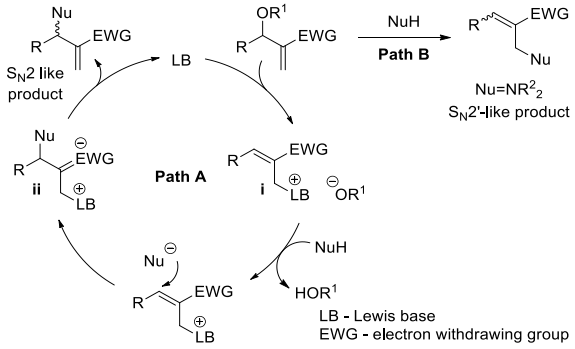
Amines and phosphines were used as Lewis base catalysts in reactions with unsaturated organic functional groups early in the development of the field.[27-30] These usually generate reactive zwitterionic intermediates via the most common n-π* interactions. The enhanced reactivity of the zwitterionic intermediates enables these species to form new bond in the presence of other reaction partners. For example, via the nucleophilic addition of a tertiary amine or phosphine to the Michael acceptor α,β-unsaturated carbonyl compounds are transformed to zwitterionic enolates that have enhanced nucleophilic character at C2 (Scheme 1-1, A).[24] With a suitable substituent at C3 position the collapse of the zwitterionic enolate produces the intermediate with enhanced electrophilic characteristics at C3 (Scheme 1-1, B). If a secondary amine is used, intramolecular proton transfer of the zwitterionic intermediate (Scheme 1-1, A) would occur and lead to the formation of a neutral tertiary amine.[31-32]

Similar process also takes place in substitutions of Morita−Baylis−Hillman (MBH) adducts in the presence of Lewis base catalysts and (pro)nucleophiles. Despite the reports of formation of C-C,[33] C-O,[34] C-N,[35] C-S[36] and C-P[37] bonds to produce the S_N2 products in substitution of MBH

adducts (Scheme 1-2, Path A), these processes are not truly general and they depend on the acidity and nucleophilicity of the pronucleophiles.[20, 38-40] Especially for *N*-centered nucleophiles, the scope is limited to substrates that are fairly N-H acidic. In addition to this limitation, their nucleophilicity can set a competition with the Lewis base catalysts, and result in the formation of S_N2' product (Path B) or a mixture of S_N2 and S_N2' products.[31-32, 41]



Scheme 1-1 Amine or phosphine catalyzed reaction of α,β-unsaturated carbonyl compounds.



Scheme 1-2 Substitutions of Morita-Baylis-Hillman (MBH) adducts.

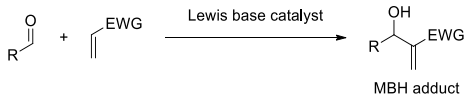
This thesis aims to address the limitations related to the requirement of N-H acidity of the *N*-centered nucleophiles and explores the Lewis base catalyzed reactions of anilines with MBH carbonates. Furthermore, this work addresses the detrimental competition of the nucleophilic reaction partner and the Lewis base catalyst by developing the concept of latent silylated nucleophiles in allylations of *N*- and *C*-centered nucleophiles (N-heterocycles and (diethoxyphosphoryl)-difluoromethyl nucleophile). The details are included in **Chapter 2**.

In contrast to substitutions of MBH adducts, a suitable substituent at C3 position enables the collapse of the zwitterionic enolate to produce the vinyl onium (phosphonium or ammonium) intermediate with enhanced electrophilic characteristics at C3 (Scheme 1-1, B). Similar vinyl phosphonium intermediates can be produced in phosphine catalyzed reactions with electron deficient alkynes in the presence of Lewis or Brønsted acids. This thesis also explores the selective transformations of such vinyl phosphonium intermediates in catalysis and in the reactions that rely on the use of stoichiometric quantities of Lewis base as a promotor or a reagent. The work on selective reductive transformations of electron deficient alkynes catalyzed by phosphines and the related C-H functionalizations via aryl phosphonium ion intermediates are described in **Chapter 3**.

2 Latent nucleophiles in Lewis base catalysis

Parts of this chapter have been published in P1) Y. Zi, M. Lange, P. Schüler, S. Krieck, M. Westerhausen, I. Vilotijevic, *Synlett* **2020**, *31*, 575–580; P2) Y. Zi, M. Lange, C. Schultz, I. Vilotijevic, *Angew. Chem. Int. Ed.* **2019***, 58,* 10727–10731; P3) M. Lange, Y. Zi, I. Vilotijevic, *J. Org. Chem.* **2020,** *85*, 1259-1269; P4) M. Lange, Y. Zi, I. Vilotijevic, *Synlett* **2020***,* accepted; P5) Y. Zi, M. Lange, I. Vilotijevic, *Chem. Commun*. **2020**, accepted, *DOI: 10.1039/D0CC01815E*.

Allylic substitution reactions are of major interest in modern organic chemistry. They have been utilized in C-C[33], C-O[34], C-N[35], C-S[36], C-P[37] bond formation. The selective formation of C-N bonds is of great interest in medicinal chemistry and, in allylic substitution reactions, is also the most challenging. The preparation of allylic amines by metal-catalyzed reactions has been studied extensively resulting in numerous protocols and methods.[42-45] Yet each of the reported methods struggles to address the selectivity issues which exist on level of regio, chemo and enantioselectivity. The regioselectivity cannot be controlled in many cases since the intrinsic reactivity of both coupling partners is determined by steric effects, normally leading to selectivity for the product with less steric clashing.[46] Chemoselectivity issues are often observed when ambident nucleophiles are employed yielding isomeric compounds or products of multiple allylation.[47] As with other stereoselective transformations, the search for the optimal chiral ligands that affords the products with high enantioselectivity is always a laborious process. Lewis base catalyzed allylic substitutions may offer alternative to the existing transition metal catalyzed processes.[1] The Morita Baylis Hillman (MBH) adducts have emerged as prime electrophiles in these reactions.[41, 48-50] Part of the appeal of MBH adducts is that they are synthesized by Lewis base induced addition of a Michael acceptor to an aldehyde or related species (Scheme 2-1) which offers high atom economy, easy reaction setup and high selectivity.[51-54]

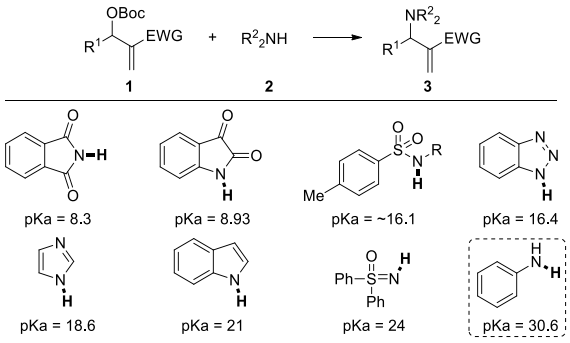


Scheme 2-1 Morita Baylis Hillman reaction.

2.1 Synthesis of β-lactams via enantioselective allylation of anilines with Morita–Baylis–Hillman carbonates

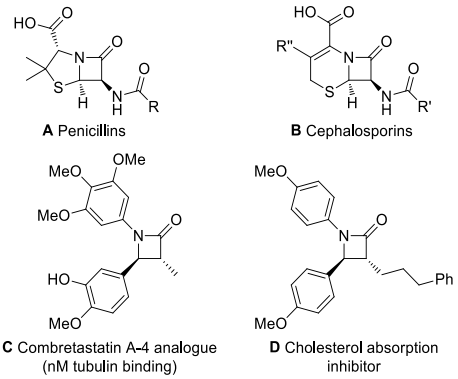
* Markus Lange has worked on this section as part of his PhD thesis.

To enhance the utility of MBH alcohols in synthesis, the hydroxyl group must be converted to a better leaving group like an ester or a carbonate. The carbonates have been the most utilized substrates in enantioselective Lewis base catalyzed substitutions. Lewis base catalyzed allylations of *N*-centered nucleophiles with MBH carbonates have been pursued by many research groups.[46, 55-59] Another approach for the same scaffold would be a direct aza-MBH reaction but this transformation comes with severe drawbacks like unstable starting materials or protecting groups which must be cleaved under rather harsh condition not allowing for a broad substrate scope or sensitive moieties.[60]



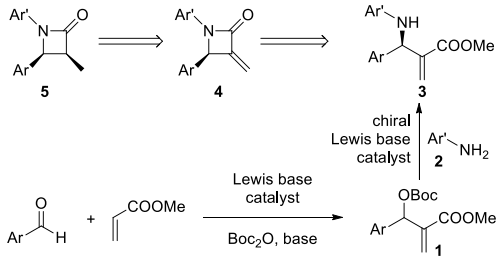
Scheme 2-2 *N*-centered nucleophiles applied with MBH carbonates.

The allylic amines produced via substitution reaction of either MBH acetates or carbonates have been used for the synthesis of N-heterocycles, such as pyridines,[61] quinolines,[62] pyrimidines,[63] pyrroles,[64] as well as complex pharmaceutical reagents or natural products[65]. The reported methods showed that the acidity of N-H plays an important role during the processes.[66] Hence, MBH carbonates are better suited due to the *in situ* release of the *tert*-butoxide anion which could deprotonate N-H with higher p*K*a (Scheme 2-2). A survey of literature indicated that the *N*-centered nucleophiles with highest p*K*a that can be utilized in Lewis base catalyzed substitutions are sulfoximines (p*K*a~24). Less acidic *N*-centered nucleophiles have not been reported and they are considered not reactive in these reactions with MBH adducts.



Scheme 2-3 Bio-active β-lactam analogues.

Our focus were the reactions of aniline (p*K*a = 30.6) and Morita-Bayliss-Hillman (MBH) adducts. The products of these reactions could be applied in synthesis of β-amino acids and their derivatives, β-lactams.



Scheme 2-4 Proposed route for asymmetric synthesis of β-lactams from aldehydes, acrylate and aniline.

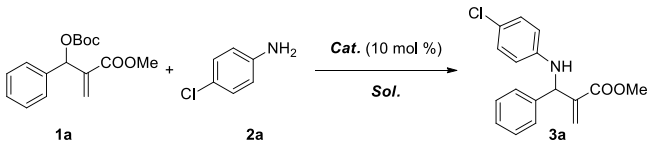
β-Lactams are a central motif in modern medicinal chemistry due to the wide presence in antibiotics like penicillins and cephalosporins (**A** and **B**, Scheme 2-3).[67] β-lactam containing are not only inhibitors of the bacterial cell wall biosynthesis, but they also exhibit a set of other biological activities such as neuroprotective, antioxidant, analgesic or immunomodulatory capabilities. Certain β-lactams (**C** and **D**, Scheme 2-3)[68-70] have been treated as potent tubulin binders and therefore potential anti-cancer agents.

A suitable route for asymmetric synthesis of β-lactams originating from aldehydes, acrylate and aniline was proposed (Scheme 2-4). In the presence of Lewis base catalyst, allylation of anilines utilizing MBH adducts would produce **3** which can be cyclized directly to form β-lactams **5**, derivatives of biologically active compounds **C** and **D**. In addition, the *exo*-methylene in the resulting lactams, **4** provided an opportunity to further modify the scaffold diastereoselectively.

Several reactions of anilines and MBH adducts have been disclosed to provide racemic *N*-allyl anilines,[71] catalyzed or promoted with DABCO. Development of an enantioselective coupling of anilines and MBH carbonates prompted us to commence our study with the chiral Lewis base catalyzed allylation of aniline **2a** with MBH carbonate **1a** (Table 2-1). The use of DABCO resulted in 52% yield for the product after 2 hours. Further optimization studies were carried out to explore how the identity of the Lewis base catalyst influences the reaction outcomes. A set of cinchona alkaloid based catalysts were utilized because of their documented performance in similar transformations.[35, 58-59, 72-77] Monomeric cinchona catalysts did initiate the reactions, albeit in lower yields and with poor enantioselectivity (Table 2-1, entries 2-3). Dimeric catalysts, such as $(DHQD)_2AQN$, $(DHQD)_2PHAL$ and $(DHQD)_2PYR$ showed distinct activities and gave high enantioselectivity (entry 4 with $(DHQD)_2AQN$, 67% yield, 92:8 er). Cyclohexane was identified as a suitable solvent (entries 7-11). By investigations on catalyst loading (entries 12-13), ratio of reaction partners (entries 14-15), concentration (entries 17-18) and temperature (entries 19-20) the optimized conditions include

cyclohexane as a solvent with 10 mol% of $(DHQD)_2AQN$ as the catalysts at room temperature, with 0.4 M concentration for the electrophile. The process can be seen as a kinetic resolution **1**, but only slight excess of aniline (**2**, 1.1 equiv.) was adequate to drive complete conversion which makes this process greener and more efficient.

Table 2-1 Optimization of conditions for asymmetric allylation of anilines.



1a 2a 3a

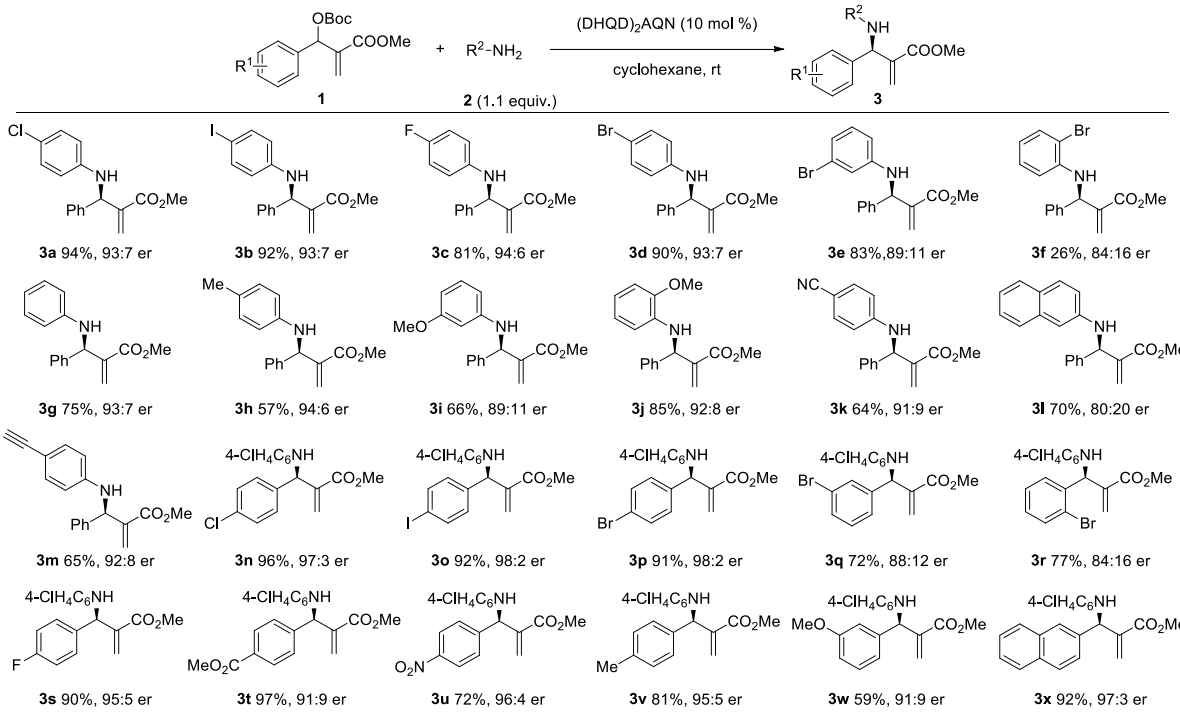
Entry	Cat. (10 mol%)	Sol.	t (h)	Yield (%)[a]	ee (%)[b]
1	**DABCO**	Toluene	2	52	/
2	**Quinine**	Toluene	56	24	-30
3	**Cinchonidine**	Toluene	56	30	25
4	**$(DHQD)_2AQN$**	Toluene	56	67	84
5	**$(DHQD)_2PHAL$**	Toluene	56	27	9
6	**$(DHQD)_2PYR$**	Toluene	56	21	-18
7	$(DHQD)_2AQN$	**THF**	56	46	79
8	$(DHQD)_2AQN$	**Dioxane**	56	46	84
9	$(DHQD)_2AQN$	**DCM**	56	86	75
10	$(DHQD)_2AQN$	**$PhCF_3$**	56	64	88
11	$(DHQD)_2AQN$	Cyclohexane	56	81	82
12	$(DHQD)_2AQN$	Cyclohexane	56	67	86[c]
13	$(DHQD)_2AQN$	Cyclohexane	56	74	86[d]
14	$(DHQD)_2AQN$	Cyclohexane	56	76	87[e]
15	$(DHQD)_2AQN$	Cyclohexane	56	79	87[f]
16	(DHQD)AQN	$C_6H_{12}/PhCF_3$	56	66	89
17	$(DHQD)_2AQN$	Cyclohexane	56	94 (94)	87[g]
18	$(DHQD)_2AQN$	Cyclohexane	56	50	88[h]
19	$(DHQD)_2AQN$	Cyclohexane	40	94	84[i]
20	$(DHQD)_2AQN$	$PhCF_3$	40	88	88[i]

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard and isolated yield in parentheses; [b] Determined by HPLC of purified product; [c] 5 mol% of catalyst was used; [d] 15 mol% catalyst was used; [e] 1.0 equiv. of 4-Cl-aniline was used; [f] 1.3 equiv. of 4-Cl-aniline was used; [g] The concentration was 0.4 M; [h] The concentration was 0.1 M; [i] The reaction was heated to 40 °C.

With the optimal conditions in hand, the following studies of the reaction scopes for anilines and MBH carbonates were carried out (Scheme 2-5). For anilines featuring halogen substitutions, the desired allylation products (**3a-3f**) were obtained in excellent yields (up to 94%) and high enantioselectivities (up to 94:6 er). Both electron rich anilines (**3h-3j**) and electron poor anilines (**3k**) gave the allylation products in good yields (57% - 85%) with high enantioselectivities (89:11 - 94:6 er). Besides halogens, ethers and nitrile, extended π-systems (**3l-3m**) within anilines were also well tolerated. Sterically hindered anilines can be utilized using this method, but the corresponding products are generated in lower yields with decreased enantioselectivity (**3f** and **3l**).

Subsequently, a set of MBH carbonates were evaluated. MBH carbonates featuring halide substituents performed well, giving good yields and enantioselectivity (**3n-3s**, up to 96% yield and 98:2 er, Scheme 2-5). Despite the generally good yields, steric bulk on the MBH carbonates resulted in lower enantioselectivity (**2r**, 77%, 84:16 er). Electron donating and electron withdrawing groups

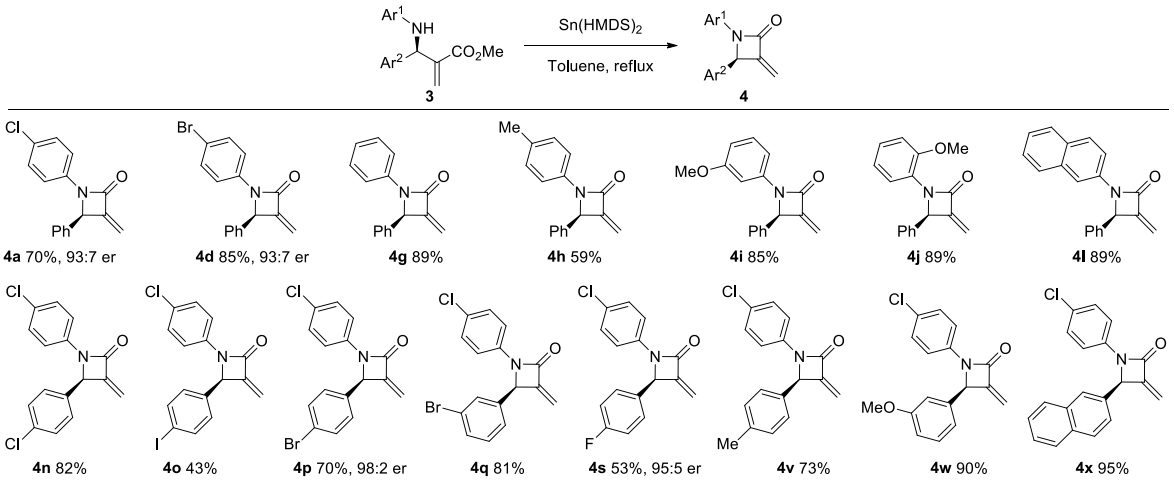
were all tolerated well, with yields of up to 97% and enantiomeric ratios up to 98:2 (**3t-3x**). To assign the absolute stereochemistry optical rotation experiments were conducted and comparison of the data for **3d**, ($[\alpha]_D^{20}$ = -115.8) with previously reported for the same compound ($[\alpha]_D^{20}$ = +115.0) confirmed the configuration of the major enantiomer in current reactions catalyzed by $(DHQD)_2AQN$.[44]



Scheme 2-5 Enantioselective Lewis base catalyzed allylation of anilines using MBH carbonates.

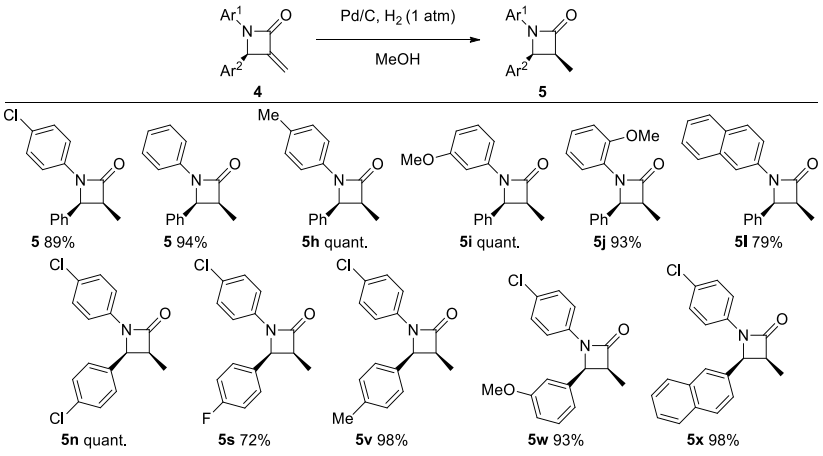
Further investigations were focused on the cyclization of the obtained allylated anilines to form the *exo*-methylene containing β-lactams. $Sn(HMDS)_2$ was chosen as suitable base to effect the cyclization and afford the desired four-membered rings. Gratifyingly, a variety of substituted β-lactams were obtained in good yields (Scheme 2-6, 43% - 95%) by treating the allylated anilines with $Sn(HMDS)_2$ and even allylation products bearing bulky substituents underwent the desired cyclization with good yields (**4j**, 89%).

With access to a range of β-lactams, we turned our attention to the enantiomeric ratios for the products. As shown in Scheme 2-6, the enantiomeric ratios remained stable and matched with those of the starting allylated anilines, demonstrating that the stereogenic center is not affected during the cyclization processes.



Scheme 2-6 Cyclization to *exo*-methylene containing β-lactams.

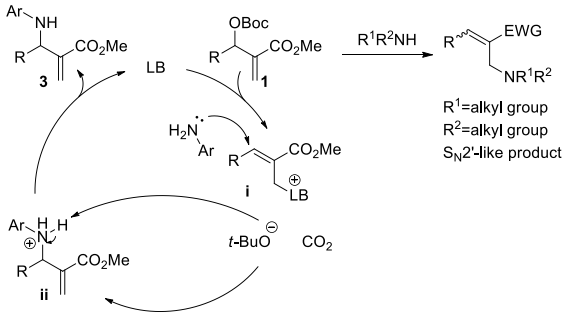
To access analogues of **5** from β-lactams **4**, 1,4-reduction is required and to simplify the operation, we opted for the general hydrogenation over a Pd/C catalyst in the presence of hydrogen. Excellent yields were achieved for the reduction of numerous β-lactams **4** (Scheme 2-7) and the major reaction product was identified as the *cis*-diastereomer being also the thermodynamically favored form which was tested by standard equilibration tests using strong base. The configuration was determined based on $^{3}J_{\text{H-H}}$ coupling constants which are consistent with the dihedral angles in the low energy conformations for these two isomers (5.9 Hz for *cis*-**5a** and 2.4 Hz for *trans*-**5a**). The enantiomeric ratios of the final β-lactams **5** matched those of the starting materials indicating that the stereogenic center adjacent to the nitrogen atom is not affected during the two-step sequence.



Scheme 2-7 Diastereoselective hydrogenation of *exo*-methylene containing β-lactams.

Due to the low acidity of aniline, the occurrence of the process with MBH adduct was attributed to its nucleophilicity which promoted the reaction with the intermediate **i** (Scheme 2-8). The formed cation **ii** has an enhanced N-H acidity which was then deprotonated by the *in situ* formed *tert*-butoxide. We hypothesized that the difference of nucleophilicity between *N*-centered

nucleophiles and the catalyst is the crucial point. The relative lower nucleophilicity of aniline compared to Lewis base catalyst resulted in the selective process with enhanced electrophile **i**. A competitive nucleophilic addition to MBH carbonate would happen between *N*-centered nucleophile and the catalyst if a higher nucleophilic amine was used. Alkyl amines were subsequently investigated and only direct S_N2' products, without a stereogenic center, were obtained. These observations are in line with previous results of the Mayr group.[78-81]



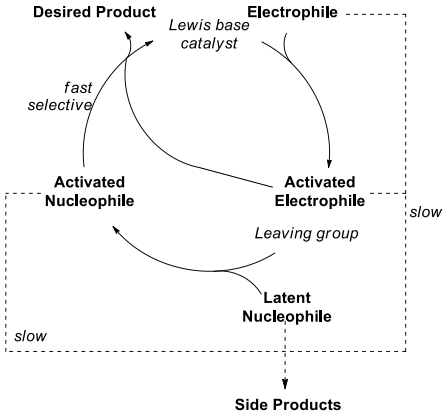
Scheme 2-8 Proposed pathway of anilines with MBH carbonates.

2.2 Enantioselective *N*-allylation of N-heterocycles

* Markus Lange has worked on this section as part of his PhD thesis and Constanze Schultz has worked on this section for her Master thesis.

Due to the possible competition between the nucleophile and the catalyst, the nucleophile must be less nucleophilic than the catalysts in Lewis base catalyzed allylic substitutions. If this requirement is not met, a mixture of S_N2 and S_N2' products is obtained and/or the reaction proceeds in the absence of catalyst which precludes the development of enantioselective catalytic reactions.[41] It was proposed that latent nucleophiles, which are derivatives of nucleophilic molecules that are not nucleophilic but can be activated to participate in the reaction, can address this problem.[82-83] The latency of the starting nucleophile would prevent its reaction with electrophilic species present in the reaction mixture and thus reduce the rates of side reactions (Scheme 2-9). Activation of the latent nucleophile can occur via a mediator that is generated as a leaving group in the process of electrophile activation. The activated nucleophile would then be produced in the reaction mixture only when the activated electrophile is already present thus enabling the reaction between the two activated species to kinetically outcompete other possible reaction pathways. This concept could be utilized to improve the substrate scope for Lewis base catalyzed reactions, control their chemo- and regioselectivity and ultimately enable enantioselective transformations to occur under mild conditions when chiral Lewis base catalysts are used.

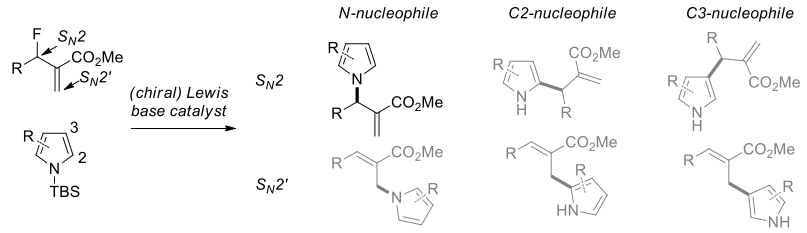
A review of the literature indicated that pyrrole derivatives have been utilized in reactions with MBH adducts but electron withdrawing groups or stoichiometric amount of Lewis base were required for efficient reactions.[35, 84-85] Nucleophilic properties of pyrrole derivatives are well documented [78-79, 81, 86] and pyrrole can act as *N*-, *C2*- and *C3*-nucleophile.[80, 84-85, 87] We hypothesized that introducing a silyl group attached to nitrogen would attenuate the nucleophilicity of pyrroles and turn them into latent nucleophiles.[78-81] In this case, a fluoride ion could be used to activate the *N*-silyl latent nucleophile indicating that the allylic fluorides derived from MBH adducts could be suitable coupling partners.



Scheme 2-9 Latent nucleophiles in Lewis base catalysis.

Shibata and co-workers have used allylic fluoride derived from MBH adducts to form C-C bond with C-silyl substituted compounds in the presence of chiral cinchona alkaloid based catalysts.[88-91] For *C*-centered nucleophiles, it is likely that only stabilized carbanions could be utilized as nucleophiles in these reactions.[88, 90] For *N*-centered nucleophiles, by virtue of all *N*-centered anions being significantly less basic than the corresponding alkyl groups from the *N*-trialkylsilyl, virtually any *N*-centered nucleophile could be accommodated in the proposed Lewis base catalyzed reactions of latent *N*-centered nucleophiles.

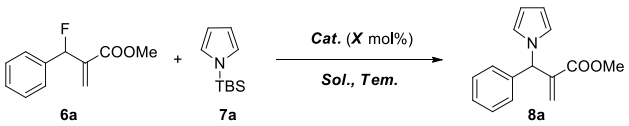
To determine the feasibility of the approach with *N*-centered latent nucleophiles, we focused on the allylic fluorides to enable a regio and enantioselective allylation of N-heterocycles (Scheme 2-10). This approach would address the problems of the activation the *N*-latent nucleophiles, the regioselectivity for the pyrrole nucleophile (*N*, *C2*, *C3*) and the regioselectivity of the substitution reaction (S_N2 and S_N2').



Scheme 2-10 Possible products in *N*-allylation of pyrrole derivatives.

N-TBS-pyrrole (**7a**) was chosen for reaction optimization whereas 1.1 equivalent of **7a** was enough for the transformation and no better results were obtained when excess **7a** was present (Table 2-2. entries 1-4). A series of catalysts were tested in which *N*-centered Lewis base catalysts performed generally with better efficacy than the corresponding *P*-centered catalysts which failed to catalyze the allylic amination with the latent *N*-nucleophile (entries 7-8). No reaction occurred in the absence of DABCO while even 1 mol% of DABCO provided good yield (79%, entry 10). Increasing the catalyst loading does not affect the yield albeit a faster reaction was observed. The examination of solvents showed that 1,2-dichloroethane and toluene could provide good yields (96% and 91%, entries 13-14). Increasing temperature showed no apparent effect other than rate acceleration (entry 17).

Table 2-2 Optimization of allylic amination.



Entry	**7a** (equiv.)	**Cat.** (**X** mol%)	**Sol.**	**Tem.** (°C)	**Yield** (%)[a]
1	**1**	DABCO (5)	DCM	25	90
2	**1.1**	DABCO (5)	DCM	25	96
3	**1.25**	DABCO (5)	DCM	25	93
4	**1.5**	DABCO (5)	DCM	25	92
5	1.1	**DBU (5)**	DCM	25	/
6	1.1	**TEA (15)**	DCM	25	73
7	1.1	**PBu_3 (5)**	DCM	25	/
8	1.1	**PPh_3 (5)**	DCM	25	/
9	1.1	DABCO (**0**)	DCM	25	/
10	1.1	DABCO (**1**)	DCM	25	79
11	1.1	DABCO (**2.5**)	DCM	25	82
12	1.1	DABCO (**10**)	DCM	25	93
13	1.1	DABCO (5)	**DCE**	25	96
14	1.1	DABCO (5)	**Toluene**	25	91
15	1.1	DABCO (5)	**THF**	25	58
16	1.1	DABCO (5)	**DMF**	25	71
17	1.1	DABCO (5)	DCE	**60**	91

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard.

With the optimal conditions in hand, the scope of the reaction was evaluated. Good to very good yields for primary (83%, **8ra**) and secondary (up to 99%) allylic fluorides were observed which demonstrates the generality of the transformation. For substituted aryl allylic fluorides featuring either electron donating groups (Scheme 2-11a, **8aa-8fa**) or electron withdrawing groups (**8ga-8la**) the

substitutions performed well to afford the desired allylation products (75% - 96%). In addition to ethers, esters, nitriles and nitro groups, halogen and alkyl substituents were also well tolerated (**8ma-8qa**, 68% - 99%). Extended conjugate systems like the substrates naphthyl (86%, **8sa**) and 3-indolyl (71%, **8ta**) substituents were also reactive under the described conditions. Aliphatic allylic fluorides were also reactive with good product yields (84% yield for **8ua** and 55% yield for **8va**). The product of S_N2' substitution was not observed in any case indicating excellent regioselectivity. Under the optimized conditions, scalability was tested with **6a** (1.00 g) and **8a** (1.03 g) which proceeded with equal efficiency (**8aa**, 88%) indicating a practical and promising prospect of this process for application in medicinal chemistry (Scheme 2-11b).

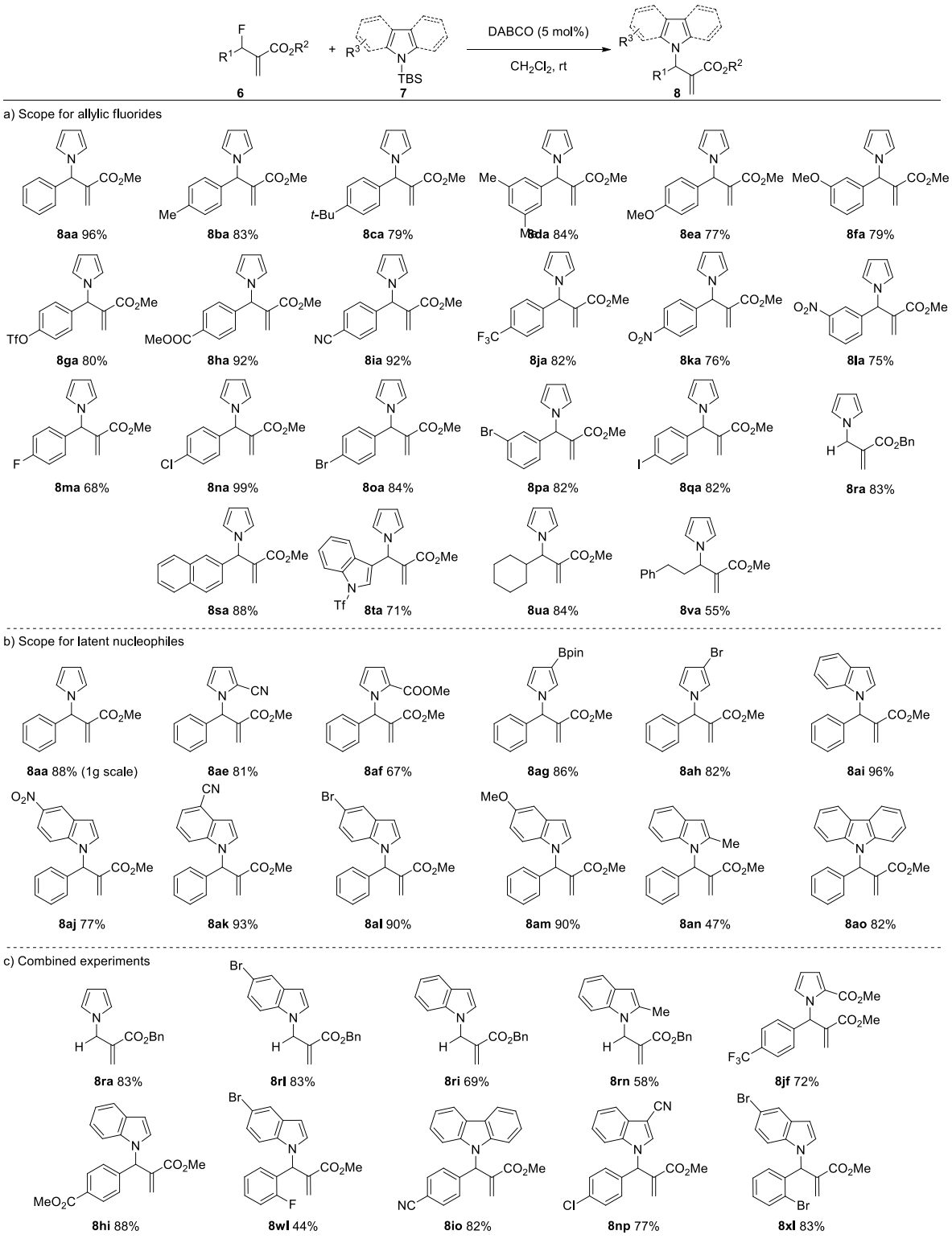
Evaluation of the scope for latent nucleophiles, *N*-TBS-pyrrole and indole derivatives, was subsequently carried out (Scheme 2-11b). Simple *N*-TBS-pyrrole as well as 2- or 3-substituted *N*-TBS-pyrroles all performed well as nucleophiles in good yields (**8ae-8ah**, 67% - 86%). Numerous substituted indoles, bearing electron donating groups and electron withdrawing groups, were then tested in the reactions which performed well and lead to the desired products in good yields (**8ai-8am**, 77% - 96%). Electron withdrawing groups (**8aj**) resulted in a slight decrease in yields. However, the reaction showed sensitivity to steric bulk resulting in lower yield for 2-methylindole (**8an**, 47%). Subsequently, *N*-silyl carbazole was also tested as a suitable substrate in the reaction (**8ao**, 82%).

To further evaluate the scope of this process, a series of experiments with electronically matching and mismatching electrophiles and substituted latent nucleophiles were carried out (Scheme 2-11c). Under the optimized conditions, pyrrole derivatives were smoothly introduced to primary and secondary allylic fluorides in good yields (44% - 88%) although some detrimental effects of steric crowding close to the reactive centers were observed (**8wl**, **8xl**).

Further investigations were carried out by treating a series of other silylated *N*-nucleophiles, including phthalimide, tosylamide and diphenylamine, with allylic fluoride under the optimized conditions and the moderate to excellent yields (up to 99%) showed the generality of the concept of Latent nucleophiles in Lewis base catalyzed allylic substitutions.

Initial attempts to achieve enantioselective allylic substitutions relied on the use of catalysts based on cinchona alkaloids, such as $(DHQD)_2PHAL$, $(DHQD)_2AQN$ and $(DHQD)_2PYR$, which are often used in similar allylic substitutions.[35, 58-59, 72-77] With $(DHQD)_2PHAL$ (5 mol%) as the Lewis base catalyst in DCM with 0.2 M concentration of the fluoride at room temperature (Table 2-3, entry 1) 91:9 er was observed after 40 hours although only 23% of the product **8aa'** was isolated. Repeated optimization of several variables followed. Switching the solvent to toluene with 10 mol% of $(DHQD)_2PHAL$ provided slightly higher yield (36%) and enantioselectivity (97:3). A set of *N*-centered catalysts were tested in this process (entries 3-9) but $(DHQD)_2PHAL$ provided the best

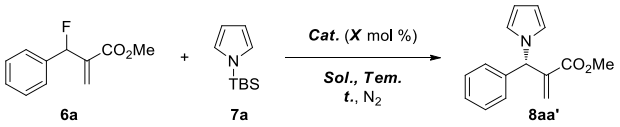
outcomes. The screening of solvent (entries 10-15) revealed $PhCF_3$ as the better choice that 60% yield and 96:4 er.



Scheme 2-11 Scope study.

Lower catalyst loading diminished the yield while and further increase from 10 mol% in catalyst loading did not improve the yields while enantioselectivity remained similar (entries 16-21). To increase the conversion, various ratios of reacting partners were considered. Due to the dynamic kinetic resolution scenario[88-91] as well as the low rate for these reactions, an excess of the allylic fluoride was required (entries 22-26). Further investigation of the influence of the reaction time, temperature and concentration led to the optimal reaction conditions: 2 equivalents of the allylic fluoride in the presence of 10 mol% of $(DHQD)_2PHAL$ in trifluorotoluene at ambient temperature.

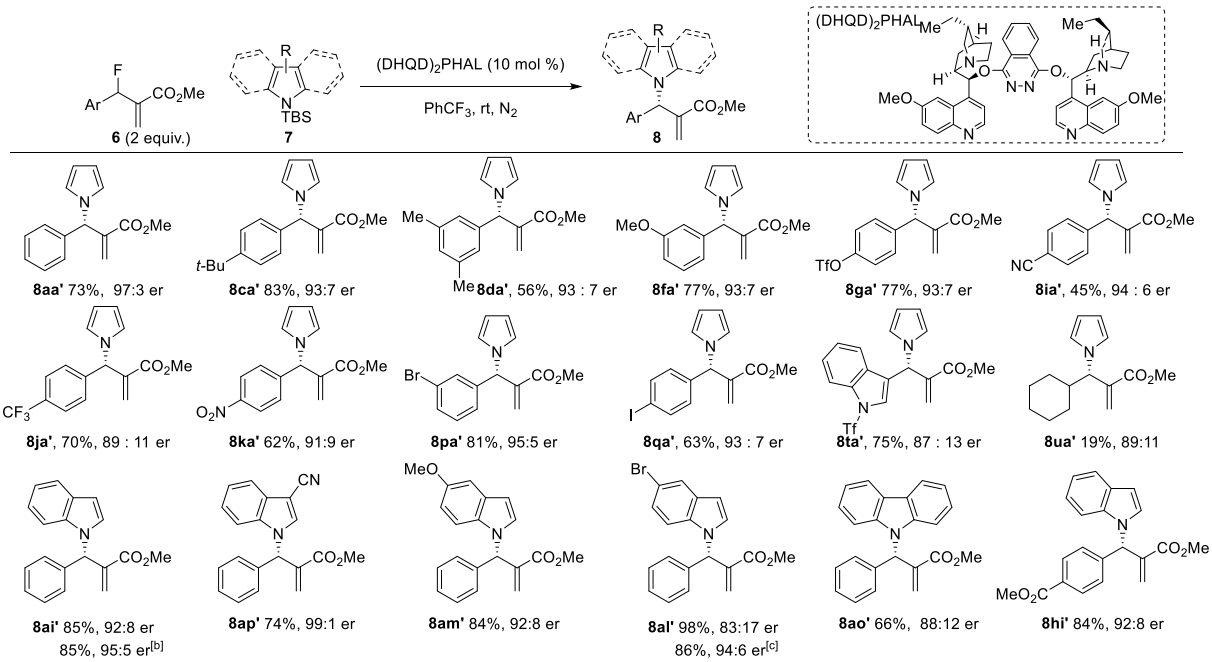
Table 2-3 Screening results of asymmetric *N*-allylic alkylation.



6a 7a 8aa'

Entry	Cat. (X mol %)	Sol.	Ratio	Concentration	Tem. (°C)	t (h)	Yield (%)[a]	er[b]
1	**$(DHQD)_2PHAL$ (5)**	DCM	1:1.3	0.2M	rt	40	23	91:9
2	**$(DHQD)_2PHAL$ (10)**	Toluene	1:1.3	0.2M	rt	40	36	97:3
3	**$(DHQD)_2AQN$ (10)**	Toluene	1:1.3	0.2M	rt	40	31	90:10
4	**$(DHQD)_2PYR$ (10)**	Toluene	1:1.3	0.2M	rt	40	11	94:6
5	**Quinine (10)**	Toluene	1:1.3	0.2M	rt	40	11	/
6	**Quinidine (10)**	Toluene	1:1.3	0.2M	rt	40	16	/
7	**Cinchonine (10)**	Toluene	1:1.3	0.2M	rt	40	12	65:35
8	**Cinchonidine (10)**	Toluene	1:1.3	0.2M	rt	40	10	/
9	**Nicotine (10)**	Toluene	1:1.3	0.2M	rt	40	/	/
10	$(DHQD)_2PHAL$ (10)	**DCE**	1:1.3	0.2M	rt	40	60	89:11
11	$(DHQD)_2PHAL$ (10)	**$PhCF_3$**	1:1.3	0.2M	rt	40	60	96:4
12	$(DHQD)_2PHAL$ (10)	**THF**	1:1.3	0.2M	rt	40	33	89:11
13	$(DHQD)_2PHAL$ (10)	**Hexane**	1:1.3	0.2M	rt	40	47	89:11
14	$(DHQD)_2PHAL$ (10)	**Mesitylene**	1:1.3	0.2M	rt	40	28	97:3
15	$(DHQD)_2PHAL$ (10)	**Dioxane**	1:1.3	0.2M	rt	40	45	97:3
16	$(DHQD)_2PHAL$ (**1**)	$PhCF_3$	1:1.3	0.2M	rt	40	20	96:4
17	$(DHQD)_2PHAL$ (**2**)	$PhCF_3$	1:1.3	0.2M	rt	40	35	96:4
18	$(DHQD)_2PHAL$ (**5**)	$PhCF_3$	1:1.3	0.2M	rt	40	44	95:5
19	$(DHQD)_2PHAL$ (**15**)	$PhCF_3$	1:1.3	0.2M	rt	40	50	95:5
20	$(DHQD)_2PHAL$ (**20**)	$PhCF_3$	1:1.3	0.2M	rt	40	52	95:5
21	$(DHQD)_2PHAL$ (**30**)	$PhCF_3$	1:1.3	0.2M	rt	40	45	95:5
22	$(DHQD)_2PHAL$ (10)	$PhCF_3$	**1:1.1**	0.2M	rt	40	51	96:4
23	$(DHQD)_2PHAL$ (10)	$PhCF_3$	**1:1.0**	0.2M	rt	40	47	95:5
24	$(DHQD)_2PHAL$ (10)	$PhCF_3$	**1.5:1**	0.2M	rt	40	65	97:3
25	$(DHQD)_2PHAL$ (10)	$PhCF_3$	**2:1**	0.2M	rt	40	77 (73[c])	97:3
26	$(DHQD)_2PHAL$ (10)	$PhCF_3$	**2.2:1**	0.2M	rt	0	70	97:3
27	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	0.2M	rt	**24**	61	96:4
28	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	0.2M	rt	**64**	50	95:5
29	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	0.2M	rt	**88**	53	97:3
30	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	**0.5M**	rt	40	77	95:5
31	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	**0.1M**	rt	40	66	95:5
32	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	**0.05M**	rt	40	50	95:5
33	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	0.2M	**0**	48	46	98:2
34	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	0.2M	**40**	40	50	97:3
35	$(DHQD)_2PHAL$ (10)	$PhCF_3$	2:1	0.2M	**60**	40	57	95:5

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard; [b] Determined by HPLC analysis using a chiral column; [c] Isolated yield.

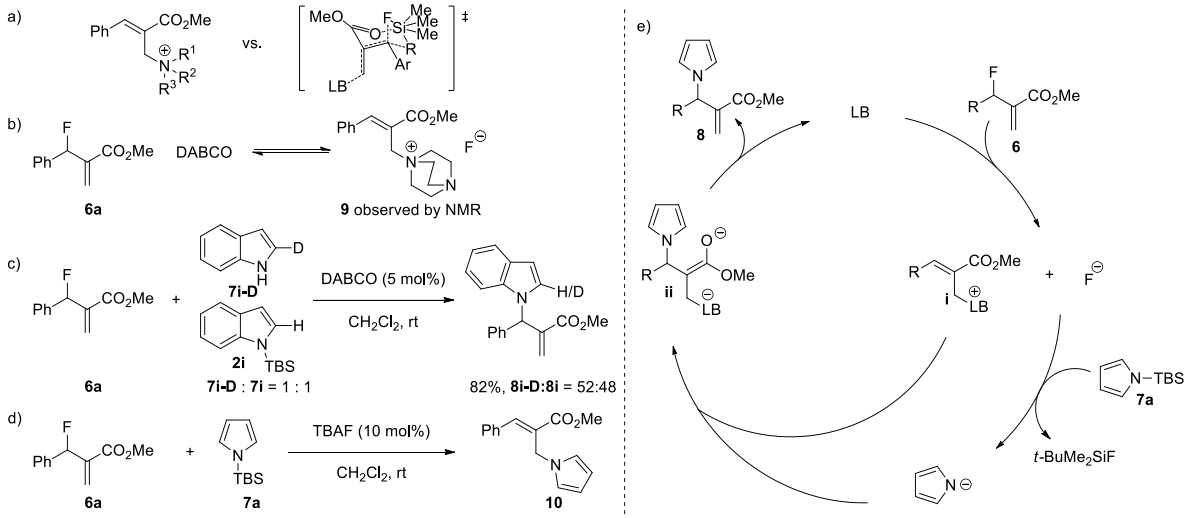


Scheme 2-12 Scope of allylic fluorides and *N*-latent nucleophiles.

The scope for the enantioselective process was examined starting with *N*-silyl pyrroles providing good yields and enantioselectivities (Scheme 2-12). Aryl fluorides featuring electron rich and poor substituents were well tolerated and produced the desired products with *N*-silyl pyrroles in good yields (45% - 83%) with enantiomeric ratios higher than 90:10. Lower reaction rates for the reactions with chiral catalysts led to competitive decomposition of aliphatic allylic fluorides, likely due to competitive elimination of HF, which led to lower yields although the enantiomeric ratios remained high (**8ua'**, 19%, 89:11 er). Indoles bearing both electron-donating and electron-withdrawing groups provided the products in yields as high as 98% and with 99:1 er demonstrating that the electronic effects had little influence on the reactions. In some cases, low stereoselectivity was observed but this could be improved by focused optimization. As shown in Scheme 2-12, a simple change of reaction solvent was sufficient to increase the enantiomeric ratios for **8ai'** and **8al'** from 92:8 to 95:5 and from 83:17 to 94:6 respectively. Carbazole nucleophiles are also competent substrates for this process affording satisfactory yield and enantioselectivity (**8ao'**, 66%, 88:12 er). The absolute configuration of the new stereogenic center in the products was assigned by comparison of optical rotation for **8am'** ($[\alpha]_D^{20}$ = +144.6) to the previously reported data for the same enantioenriched material ($[\alpha]_D^{20}$ = +135.9) which confirms the configuration to be *S*.

A set of control experiments were carried out to study the mechanistic features (Scheme 2-13). Two possible pathways, which involve either the intermolecular addition of the nucleophile to the allyl ammonium intermediate or the simultaneous intramolecular delivery of the nucleophile and the silyl assisted cleavage of C-F bond, were proposed for this process (Scheme 2-13a).[33, 35, 58, 75, 88-93]

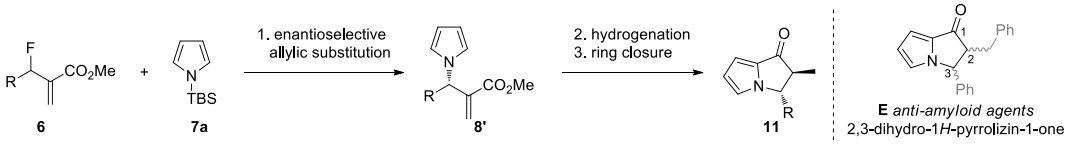
Formation of the ammonium salt **9** was observed by NMR when allylic fluoride **6a** was treated with DABCO in the absence of latent nucleophile (Scheme 2-13b)[94] suggesting that the first pathway is feasible and that the silyl assistance is not required for C-F cleavage. When deuterium labeled indole **7i-D** was used together with *N*-TBS-indole **7i** as an equimolar mixture, the reaction gave both the products with and without the deuterium label (82%, **8i-D**:**8i** = 52:48) which was attributed to the equilibrium of indolide anions (Scheme 2-13c). Additional control experiments, which showed that no reaction occurs between indole and allylic fluoride under the standard conditions and no transfer of TBS group happens between *N*-TBS-indole **7i** and deuterium labeled indole **7i-D** excluded other possible explanations for this observation. In the presence of externally added fluoride catalysts, such as TBAF, exclusive S_N2' product **10** was observed (Scheme 2-13d) indicating the high nucleophilicity of the activated latent nucleophile as well as the requirement for sequential activation of the electrophile and then the nucleophile in these reactions.



Scheme 2-13 Control experiments and proposed mechanism.

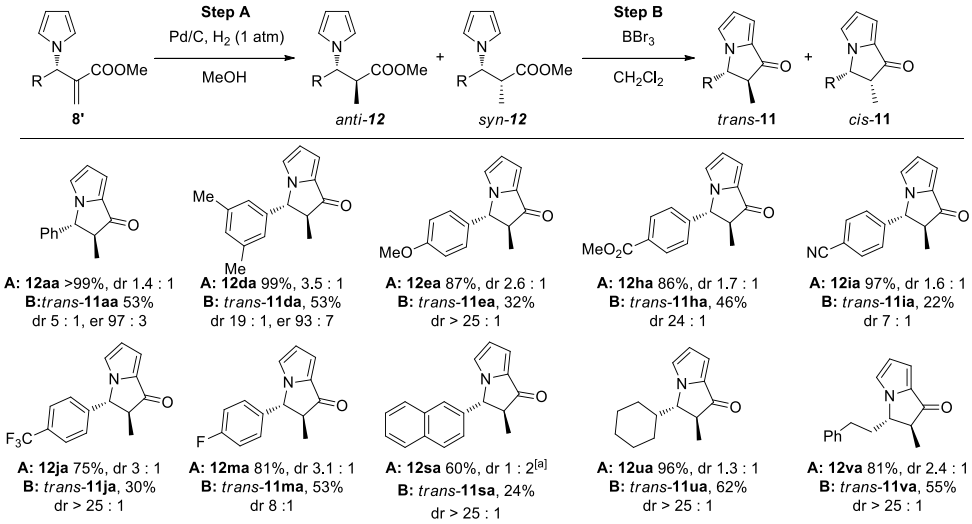
The mechanism as shown in Scheme 2-13e) can be proposed. Nucleophilic addition of the Lewis base catalyst to the allylic fluoride results in the elimination of fluoride ion, via E1cb mechanism and affords the allylic ammonium intermediate **i**. The formation of silyl fluoride facilitates the cleavage of silyl group of *N*-latent nucleophile, namely the activation of the latent nucleophile, to give the anionic *N*-nucleophile which preferred to undergo the conjugate addition to activated electrophile, ammonium intermediate **i**, to from the zwitterionic intermediate **ii**. The increased rate for the reaction between activated nucleophile and activated electrophile compared to that of the activated nucleophile and the starting fluoride is highlighted by the control experiments in the presence of DABCO and in the presence of TBAF as the catalyst (Scheme 2-13d)).[95] This demonstrates the importance of simultaneous presence of activated electrophile and nucleophile pair in the reaction mixture and the importance of the latent character of the starting silylated nucleophile.

Subsequently, the final product was obtained via the elimination of the Lewis base catalyst. Good regioselectivity and stereocontrol were observed in the presence of chiral Lewis base catalysts.



Scheme 2-14 Enantioselective approach to pyrrolizin-1-ones.

To illustrate the utility of the developed enantioselective allylation of N-heterocycles, we focused on application of this method to enantioselective synthesis of biologically active pyrrolizin-1-ones. 2,3-dihydro-1*H*-pyrrolizin-1-ones (**E**) (Scheme 2-14) exert *anti*-amyloid properties making them potential candidates for the treatment of Alzheimer disease.[96] Despite the previous synthetic work on pyrrolizin-1-one derivatives,[97-98] there are no reports of their stereoselective synthesis which prompted us to develop a new approach to these molecules starting from the enantioenriched *N*-allylpyrroles prepared in our previous study (Scheme 2-14).



Scheme 2-15 Hydrogenation and diastereoselective cyclization to pyrrolizin-1-ones; [a] Isolated yields.

Our investigation started with the reduction of the alkene in **8'** to provide inseparable mixtures of products **12** in excellent yield but with low diastereoselectivity ranging from 1.3:1 to 3.5:1 (Scheme 2-15). Friedel-Crafts-type cyclization was subsequently utilized to realize the cyclization of **12** to afford the corresponding pyrrolizin-1-ones in the presence of BBr_3.[99-100] The relative configuration of the products was assigned as *trans* based on the $^3J_{H\text{-}H}$ coupling constants for C2 and C3 protons. Independent cyclization of both *syn*-**12** and *anti*-**12** with BBr_3 afforded *trans*-**11** as the major cyclization product (Scheme 2-15). Unreacted starting material isolated when the reactions were stopped at around 50% conversion was unchanged indicating that the isomerization happened upon cyclization. Due to the three sp^2 atoms in the pyrrolidinone ring, we expected the low

energy conformations to be rather flat, causing significant *gauche* interactions between C2 and C3 substituents in the *cis*-isomer of **11** which makes the *trans*-isomer more stable than the *cis*-isomer as the substituents become larger.

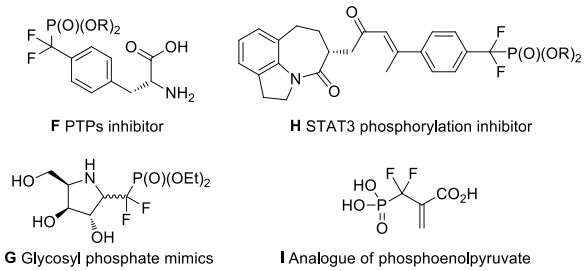
BBr_3 promoted cyclization using mixtures of diastereomers of a series of **12** was carried out. The desired pyrrolizin-1-ones (**11**) were isolated in moderate yields (the major diastereomers) with diastereoselectivity between 5:1 and >25:1 in which the *trans*-isomer was the major product in all cases. The moderated yields are supposed to be the consequence of the harsh conditions which could result in side reactions, such as the degradation of ether, ester, trifluoromethyl and nitrile substituents. Another possible reaction pathway is the intramolecular electrophilic aromatic substitution on the C3-aryl substituent, explaining the much better performance of **11ua** and **11va** which don't have an aryl substituent at C3.

The measurements for enantiomeric ratios for products *trans*-**11aa** and *trans*-**11da** showed it to be constant through the two-step sequence demonstrating that the stereogenic center set in the allylation is not changed during synthesis. This easy handling as well as the enantioselectivity provides a powerful tool for the synthesis of enantioenriched pyrrolizin-1-ones *via* the three-step sequence.

2.3 Asymmetric allylic phosphonyl difluoromethylation

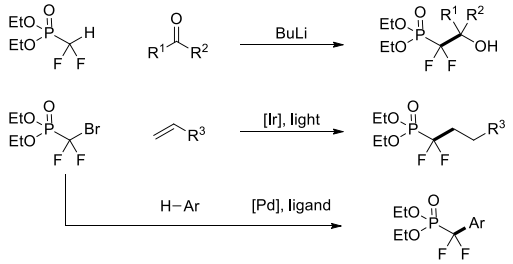
* Markus Lange has worked on this section as part of his PhD thesis.

The promising study on the enantioselective allylation of *N*-centered nucleophiles directed our attention to *C*-centered nucleophiles. Shibata has pioneered the work by using silylated C-nucleophiles in Lewis base catalyzed substitution of allylic fluorides and the results indicated that the delivered substituent should be the least basic nucleophile,[88-91] which is also in accordance for a mechanism involving an Si-ate complex.[101] To enhance the performance of silylated C-center reagent to form a less basic or a more stable C-nucleophile, stabilized anionic species were considered and due to recent relevance, phosphonates were chosen as a model system. The latency of the *C*-centered pronucleophiles could still be preserved by the introduction of silyl group as well as the sequential activation of electrophile and nucleophile which allows control of selectivity. In addition, the reaction site should also be restricted at the α position of phosphonate.



Scheme 2-16 Biologically active molecules bearing a phosphonyldifluoromethyl group.

Difluoromethylphosphonates are present in many metabolically stable and bioactive molecules,[102-105] especially nucleoside analogues.[106-109] Important examples include protein tyrosine phosphatase (PTP) inhibitors **F**[110], mimics of sugar phosphates (**G**)[111] as well as phosphorylation inhibitors **H**[105] and **I**[112] (Scheme 2-16). As an oxygen bioisostere and a lipophilic hydrogen-bond donor, difluoromethyl group is used to increase the activity of pharmaceutical molecules via replacement of hydroxyl, amino and thiol groups. Among the species featuring a difluoromethyl group, difluoromethyl phosphonates are of particular interest because they mimic the tetrahedral transition state in peptide hydrolysis and act as phosphatase inhibitors.[113]



Scheme 2-17 Approaches for the introduction of phosphonyldifluoromethyl group.

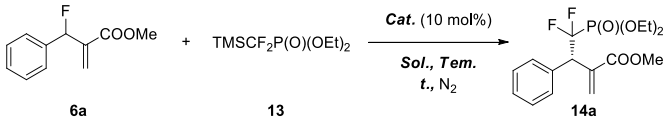
Numerous methods to introduce a phosphonyldifluoromethyl group have been recently reported and they include addition/substitution reactions with phosphonyldifluoromethyl nucleophiles, processes that involve the phosphonyldifluoromethyl radical and the transitional metal catalyzed methods (Scheme 2-17).[114-125] In spite of the apparent need for enantioenriched biologically active difluoromethyl phosphonates, there are no enantioselective methods to introduce this moiety. With the goal of developing an enantioselective reaction for allylic phosphonyldifluoromethylation, our initial work commenced with the optimization of the reaction conditions for silyl difluoromethyl phosphonate **13** with MBH derived allylic fluoride **6a** in the presence of chiral Lewis base catalyst (Table 2-4).

Focus for the optimization was initially on cinchona alkaloid derived catalysts, including $(DHQD)_2AQN$, $(DHQD)_2PHAL$ and $(DHQD)_2PYR$. In the early optimization, $(DHQD)_2PHAL$ gave the best yield of the desired product **14a** (37%, Table 2-4, entry 2) and it was chosen for focused optimization that focused on the identity of solvent, temperature, concentration and ratio of reaction

partners. DME, THF and dioxane (entries 5-6, 9) gave good yields at ambient temperature. Reactions at 0 °C resulted in slightly lower yields but higher enantiomeric ratios. Solvent mixtures of dioxane with DME or THF were subsequently tested, resulting in better enantioselectivity. Reaction with the mixture of dioxane and THF as the solvent performed the best with respect to both yield and enantioselectivity (47% yield, up to 98:2 er, entry 15) when two equivalents of **13** were used at 0 °C for 51 hours (entry 14). Further increase in the amount of the pronucleophile **13** did not improve the reaction outcomes (entries 16-18).

Despite the excellent enantioselectivity, the moderate yields were a signal that kinetic resolution of the allylic fluoride (**6a**) is taking place in the presence of chiral Lewis base catalyst (Table 2-5). The reactions conditions were therefore optimized for the kinetic resolution of **6a** and enantioenrichment and yields of both the starting material and the products were monitored by chiral-HPLC and NMR.

Table 2-4 Optimization for the reaction conditions.

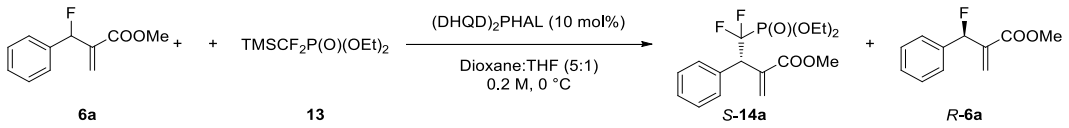


6a 13 14a

Entry	Cat. (10 mol%)	Sol.	Ratio	Concentration	Tem. (°C)	t (h)	Yield (%)[a]	er[b]
1	**$(DHQD)_2AQN$**	$PhCF_3$	1:1.3	0.2M	rt	60	18	94:6
2	**$(DHQD)_2PHAL$**	$PhCF_3$	1:1.3	0.2M	rt	60	37	94:6
3	**$(DHQD)_2PYR$**	$PhCF_3$	1:1.3	0.2M	rt	60	30	92:8
4	$(DHQD)_2PHAL$	**DCE**	1:1.3	0.2M	rt	60	12	93:7
5	$(DHQD)_2PHAL$	**DME**	1:1.3	0.2M	rt	60	42	94:6
6	$(DHQD)_2PHAL$	**THF**	1:1.3	0.2M	rt	60	41	94:6
7	$(DHQD)_2PHAL$	**CycloHexane**	1:1.3	0.2M	rt	60	31	91:9
8	$(DHQD)_2PHAL$	**Toluene**	1:1.3	0.2M	rt	60	**7**	91:9
9	$(DHQD)_2PHAL$	**Dioxane**	1:1.3	0.2M	rt	60	40	93:7
10	$(DHQD)_2PHAL$	**DME**	1:1.3	0.2M	0	40	31	96:4
16	$(DHQD)_2PHAL$	**THF**	1:1	0.2M	0	60	36	95:5
11	$(DHQD)_2PHAL$	**Dioxane:DME (5:1)**	1:1.3	0.2M	0	40	32	97:3
12	$(DHQD)_2PHAL$	**Dioxane:THF (5:1)**	1:1.3	0.2M	0	40	35	96:4
13	$(DHQD)_2PHAL$	Dioxane:THF (5:1)	1:1.3	0.5M	0	40	45	95:5
14	$(DHQD)_2PHAL$	Dioxane:THF (5:1)	1:1	0.5M	0	40	44	95:5
15	$(DHQD)_2PHAL$	Dioxane:THF (5:1)	**1:1**	0.2M	0	51	47[c]	98:2
16	$(DHQD)_2PHAL$	Dioxane:THF (5:1)	**1:2**	0.2M	0	88	45	96:4
17	$(DHQD)_2PHAL$	Dioxane:THF (5:1)	**1:3**	0.2M	0	88	43	95:5
18	$(DHQD)_2PHAL$	Dioxane:THF (5:1)	**1:4**	0.2M	0	88	38	96:4

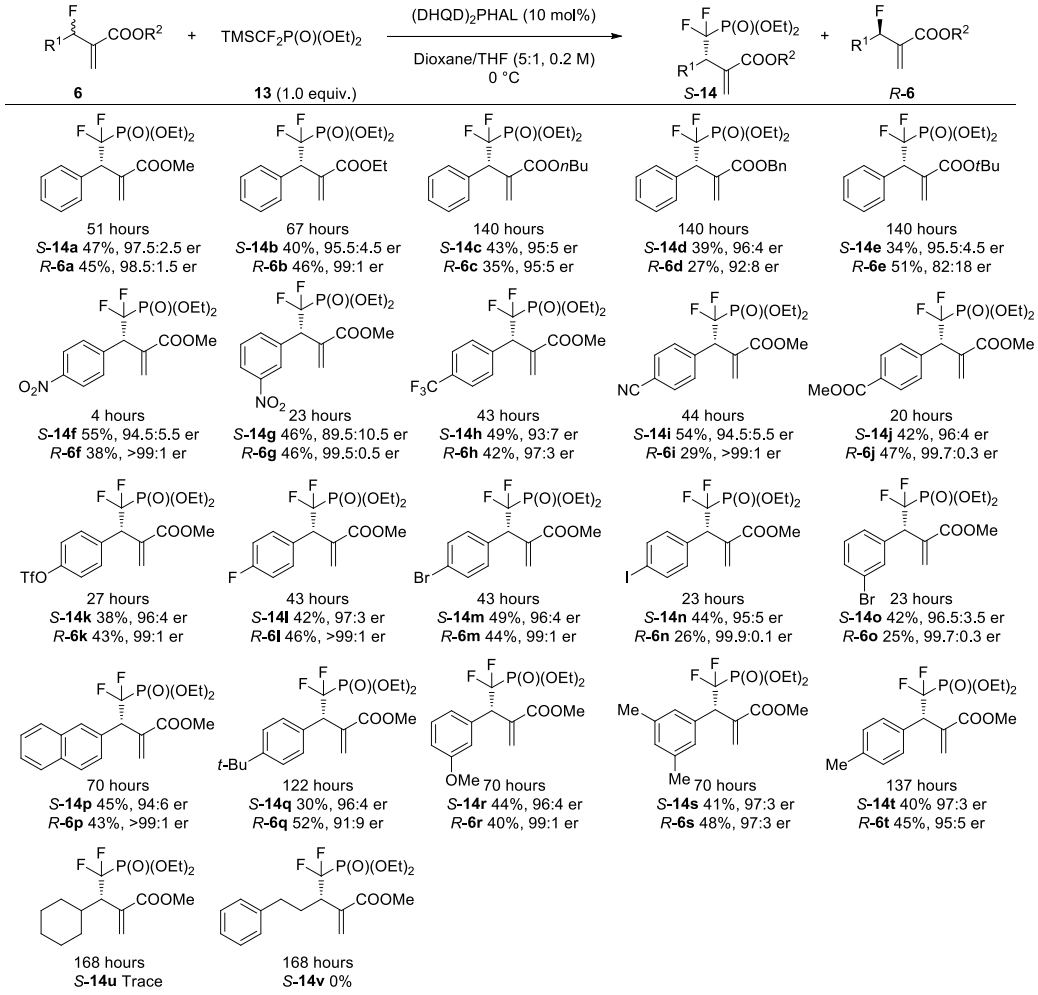
[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard; [b] Determined by HPLC analysis using a chiral column; [c] Isolated yield.

Table 2-5 Kinetic resolution of **6a** and enantioselective formation of *S*-**14**.



Entry	t (h)	Yield of *S*-14a[a]	*ee* of *S*-14a[b]	Yield of *R*-6a[a]	*ee* of *R*-6a[b]
1	3h		99%		10%
2	6h		99%		22%
3	8h		99%		29%
4	21h		98%		68%
5	24h		98%		73%
6	28h	33%	98%	60%	82%
7	31h		97%		92%
8	46h	46%	96%	45%	96%
9	51h	47%[c]	95%	45%	97%

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard; [b] Determined by HPLC analysis using a chiral column; [c] Isolated yield.

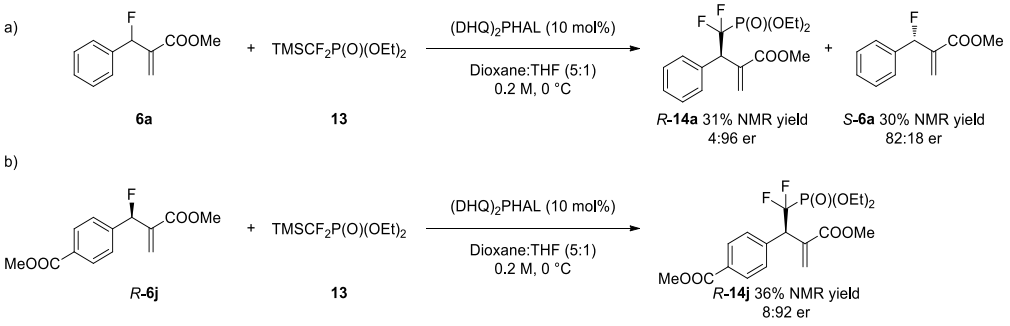


Scheme 2-18 Kinetic resolution of allylic fluorides **6** by enantioselective phosphonyldifluoromethylation.

After reacting for 3 hours, small amount of *S*-**6a** was consumed, resulting in 10% ee for the reioslated starting material (entry 1) and excellent enantioselectivity for *S*-**14a** with 99% ee. Obvious increase in ee for **6a** enantiomers were observed over time (10% - 97% ee) indicating that *S*-**6a** was continuously consumed. Only slight decrease of the enantioselectivity of the product *S*-**14a** was observed. The conversion of **6a** and the yield of *S*-**14a** were both detected based on the monitoring by ^{1}H NMR in the presence of internal standard which also demonstrated that the *S*-**6a** was smoothly converted to the corresponding *S*-**14a** and the residual amount of *R*-**6a** (45%) and the final yield of *S*-**14a** (47%) both maintained at around 50%.

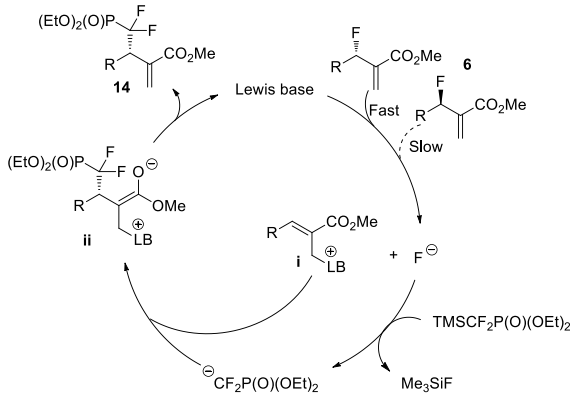
Upon optimization of the reaction conditions and the study of kinetic resolution, the scope of this reaction was evaluated for a range of allylic fluorides (**6**) in the presence of catalytic amount of chiral Lewis base $(DHQD)_2PHAL$ in dioxane/THF (5:1; 0.2M) as the solvent at 0 °C (Scheme 2-18). For each reaction, allylic fluoride **6** was consumed slowly to give the corresponding enantioenriched allylic fluoride *R*-**6** and product *S*-**14** which was detected by chiral HPLC and reactions were stopped based on the enantiomeric ratio of the residue allylic fluoride *R*-**6**. A range of esters, such as methyl, ethyl, *n*-butyl, benzyl and *t*-butyl esters (**6a-6e**), were investigated and converted to the corresponding products smoothly providing good yields with good selectivity (*S*-**14a-14e**, 34%-47%, 95:5 - 98:2 er). The allylic fluorides *R*-**6a-6e** were detected with excellent enantioselectivities (up to 99:1 er) while allylic fluoride with *t*-butyl ester group **6e** showed slightly worse enantiomeric ratio (82:18) due to the bulky group and lower reactivity.

Under the optimized conditions, a series of allylic fluorides **6f-6t** with electron poor aromatic ring were converted to the corresponding products with good yields (42% - 55%) and enantioselectivities (90:10 - 96:4 er). The electron withdrawing groups accelerated the reaction rates which shortens their reaction times. Almost every residue allylic fluoride (**6f-6k**) showed over 99:1 enantiomeric ratio. Allylic fluorides featuring halogen substituents, which were also well tolerated under the optimal conditions, gave the products in good yields (*S*-**14l-14n**, 42% - 49%) with excellent degrees of stereocontrol (95:5 - 97:3 er). The remaining unreacted allylic fluorides with over 99:1 enantiomeric ratio indicated the full conversion of the favored enantiomer of *S*-**6**. The reaction of **6p** with a sterically demanding naphthyl moiety also provided the corresponding product in good yield and selectivity. The reactions with allylic fluorides bearing electron rich aromatic ring were subsequently carried out, however, the reaction time was longer (**6q-6t**) due to the inactivation by the electron donating groups. Nevertheless, good yields and good enantiomeric ratios (96:4 - 97:3 er) were obtained. Aliphatic allylic fluorides produced only trace amount of the corresponding product *S*-**14u** and there was no conversion in the reaction of **6v** even after one week.



Scheme 2-19 Control experiments.

To further examine the kinetic resolution scenario of allyl fluorides **6a**, $(DHQ)_2PHAL$ was utilized for the reaction instead of $(DHQD)_2PHAL$ under the optimized conditions (Scheme 2-19a). The corresponding product, the opposite set of enantiomers, *R*-**14a** was obtained in 31% yield with 4:96 enantiomeric ratio while enantioenriched allylic fluoride, *S*-**6a**, was observed (82:12 er). Furthermore, enantioenriched allylic fluoride *R*-**6j** (>99:1 er) was recovered and immediately subjected to the standard reaction conditions in the presence of $(DHQ)_2PHAL$ as the catalyst (Scheme 2-19b). The corresponding product *R*-**14j** was detected in 36% yield with good enantioselectivity (8:92 er). The deterioration of the enantiomeric ratio for the residue *R*-**6j** was also observed.



Scheme 2-20 Proposed mechanism.

The proposed mechanism is shown in Scheme 2-20. Nucleophilic addition of the Lewis base catalyst to the allylic fluoride results in the formation of the corresponding allylic ammonium intermediate **i** and the free fluoride ion. The favored formation of silyl fluoride facilitates the cleavage of silyl group to give difluoromethyl phosphonate ion which undergoes the conjugate addition to the ammonium intermediate **i**. Subsequently, the final product was obtained via the elimination of the Lewis base catalyst.

3 Lewis base catalyzed or promoted reactions with phosphonium intermediates

Parts of this chapter have been published in P6) F. Schömberg, Y. Zi, I. Vilotijevic, *Chem. Commun*. **2018**, *54,* 3266–3269; P7) Y. Zi, F. Schömberg, F. Seifert, H. Görls, I. Vilotijevic, *Org. Biomol. Chem.* **2018**, *16,* 6341–6349; P8) Y. Zi, F. Schömberg, K. Wagner, I. Vilotijevic, *Org. Lett.* **2020**, *22*, 3407-3411; P9) Y. Zi, K. Wagner, F. Schömberg, I. Vilotijevic, **2020**, submitted.

3.1 Selective reduction of ynones

* Fritz Schömberg has worked on this section as part of his Master and now PhD thesis.

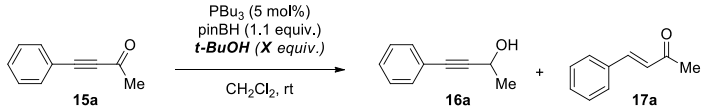
Pinacolborane (pinBH) is a mild hydride donor often used in catalytic reduction and hydroboration reactions because it's low reactivity prevents non-catalyzed background reactions to occur.[126] Metal catalysts[127-129], Brønsted or Lewis acids[130-131] and Lewis bases[132] are the common strategies for the activation of the pinBH to act as the reducing agent. We have determined that pinacolborane does not produce stable Lewis adducts with common triaryl and trialkyl phosphines which means that these compounds constitute a non-traditional frustrated Lewis pair. This could allow the combination of the two to be used in simultaneous activation of small molecules with a Lewis base and a Lewis acid which inspired us to examine the reactions of ynones as the typical substrates in Lewis base catalysis, with phosphines and pinacolborane.

We have determined that pinacolborane does not readily form Lewis adducts with phosphines.[133] Since pinacolborane itself is not a strong reducing agent[134] and it is not activated by a phosphine, we hypothesized that a nucleophilic phosphine could be used as a Lewis base catalyst that activates the other reacting partner in reactions involving pinacolborane. For our first trials we selected ynones, the quintessential substrates in Lewis base catalysis, as the starting materials. We anticipated that reduction (possible 1,2-, 1,4- and over-reduction products) and hydroboration (both alkyne and carbonyl with various regioselectivity) reactions may occur in addition to the typical dimerization, oligomerization and polymerization processes that ynones undergo in the presence of phosphines.

To initiate our study, ynone **15a** was treated with pinBH in the presence of phosphines. Dichloromethane was used as a non-coordinating solvent to avoid activation of pinBH by formation of Lewis adducts between the solvent and pinBH. With 5% PBu_3 as the catalyst, the desired product of 1,2-reduction **16a** was obtained with 62% yield while 14% of the product of 1,4-reduction **17a** was also formed (Table 3-1, entry 1). Higher catalyst loading (20%) leads to diminished yields (Table 3-1, entry 2). The major products isolated from the reaction mixture were propargylic alcohol **16a**, enone

17a and allylic alcohol together with a complex mixture of oligomers of **15a**. The screen of various additives in the reaction mixture revealed that protic additives like water and alcohols promote the 1,2-reductions and decrease the amount of overreduction and oligomerization products. *i*-PrOH and *t*-BuOH proved to be the best additives affording **16a** in yields of 94% and 90% respectively when 1.5 equiv. of the additive was used.

Table 3-1 Effects of additives on reaction selectivity and isolated yield of the 1,2-reduction product.

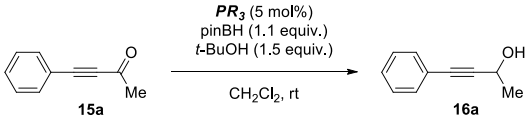


Entry	*t*-BuOH (X equiv.)	16a (%)[a]	17a (%)[a]	15a (%)[a]
1	-	62	14	24
2[b]	-	39	13	7
3	0.5	81	12	3
4	1.1	89	0	0
5	1.5	90	0	0
6	2.1	86	0	0

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard; [b] 20 mol% of Pbu_3 was used.

A set of commercially available phosphines were tested as the catalysts to reduce the ynones (Table 3-2). PPh_3 and $PMePh_2$ failed to reach full conversion even after longer reaction times (entries 1-2). Trialkyl phosphines proved more efficient with both PBu_3 and PMe_3 effecting the complete consumption of ynones within 10 minutes and affording the desired products in high yields (entries 5-6). PCy_3 and $P(t\text{-}Bu)_3$ showed decreased activity (entries 3-4). These results suggest that the nucleophilicity of the phosphine plays an important role in these reactions making the more nucleophilic, not sterically hindered trialkyl phosphines ideal for this application.

Table 3-2 Optimization of the phosphine catalyst.



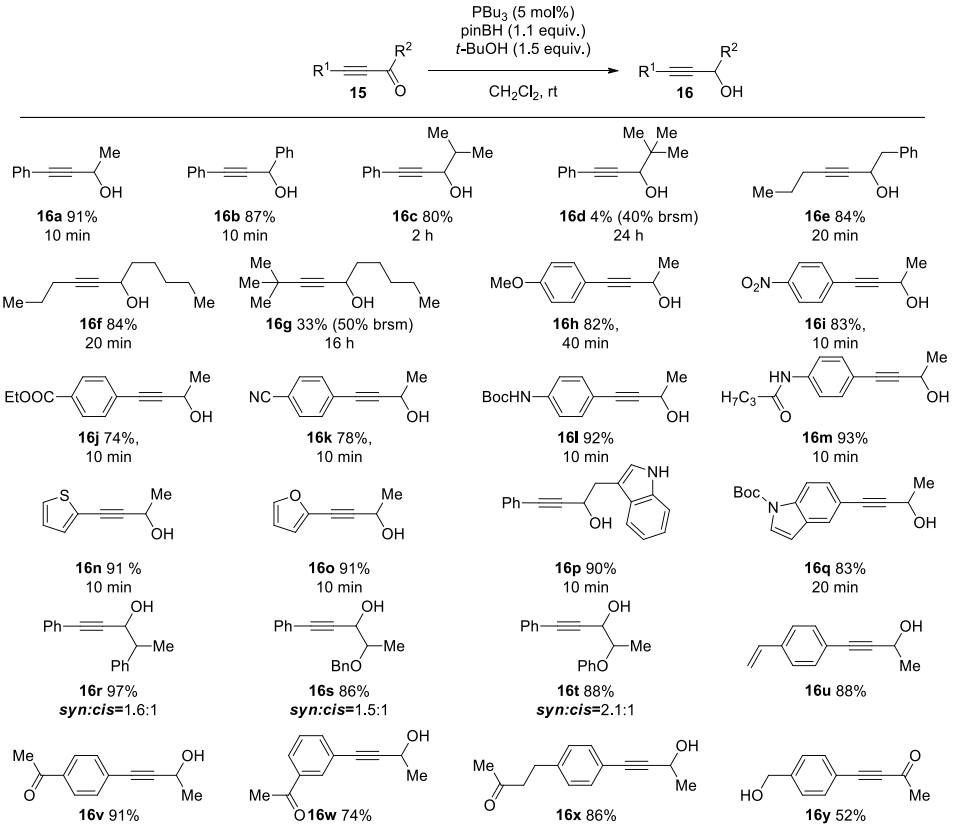
Entry	PR_3	Reaction time	Yield (%)[a]	
			16a	15a
1	PPh_3	24 h	55	28
2	$PMePh_2$	24 h	68	10
3	PCy_3	24 h	14	23
4	$P(t\text{-}Bu)_3$	24 h	3	89
5	PMe_3	10 min	89	0
6	PBu_3	10 min	89	0

[a] Yield determined by ^1H NMR spectroscopy of crude product mixtures after quenching reactions at designated time point using triphenylmethane as internal standard.

Under the optimized conditions various propargylic alcohols were obtained in good yields (Scheme 3-1). The scalability was tested with a gram-scale reduction of **15a** which proceeded efficiently with no deterioration of the yield. Both aryl and alkyl substituents in the α'-position of the ynone were well tolerated (**16a-16f**). The increasing steric bulk at the α'-carbon led to decrease in

reaction rates (**16g**). Ynones with both aryl and alkyl groups in α-position gave the propargylic alcohols in good yields. With the increase of the steric demand for the α-substituent, the reaction rates dropped. Although **16c** afforded the desired product in 80%, the reaction rate for the substrate **16d** with the *t*-butyl substituent in α-position was too low for the reaction to be synthetically useful. The diastereoselectivity of the reduction reaction was tested with ynones containing a stereogenic center in the α-position. **15r** produced the desired propargylic alcohol, a 1.6:1 mixture of diastereomers, with a combined yield of 96% while **15s** and **15t** gave a 1.5:1 mixture and 2.1:1 mixture respectively.

Electron rich (**16h**) and electron deficient ynones (**16i-16m**) provided the desired alcohol products with high rates and good yields (74% - 93%). The different in reaction rate for electron rich and electron poor ynones was noticeable and showed that the more electrophilic substrates react faster presumably due to the higher rate of the reaction with the nucleophilic phosphine. Various heterocycles, including furan, thiophene and protected indole (**16n-16q**), gave the desired products with good yields too (83% - 91%).

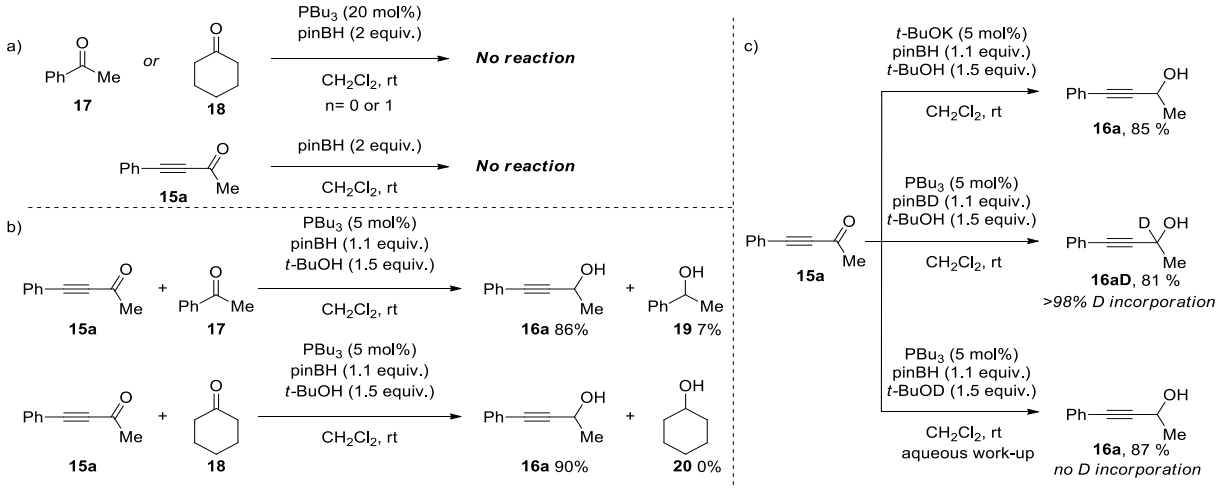


Scheme 3-1 Reaction scope for the phosphine catalyzed ynone reduction with pinacolborane.

As shown in Scheme 3-1, alkene, nitro, carbamate, amide, ester and nitrile substituents in the ynone did not undergo reduction or hydroboration. When ynones containing other ketones in the molecule were used, the ynones were selectively reduced although minor quantities of the

corresponding diol were also observed (**16v**-**16x**, 74% - 91%). When benzylic aldehydes were present in the starting ynone, chemoselective reduction of the aldehyde was observed.

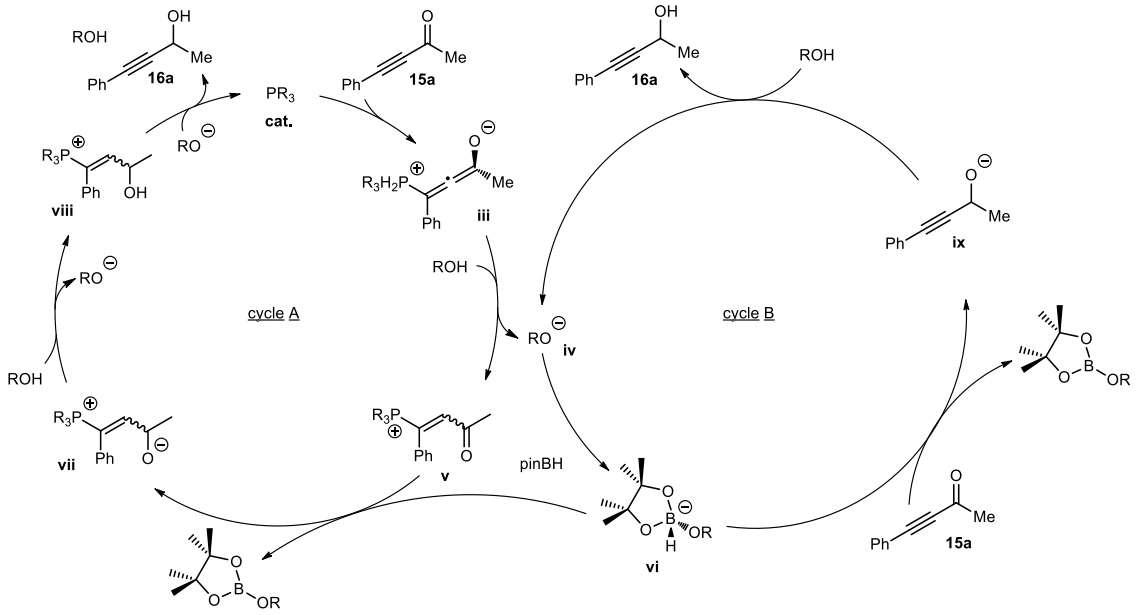
Further intermolecular competition experiments were conducted with ketones and ynones (Scheme 3-2a). Ynone **15a** undergoes 1,2-reduction in the presence of phosphine and pinacolborane. When phosphine is not present, ynone did not undergo reduction or hydroboration with pinacolborane. Simple ketones, like acetophenone and cyclohexane, also did not undergo reduction of hydroboration in the presence of phosphine and pinacolborane. In the competition experiments, when ynone and ketone are present in equimolar amounts ynones (Scheme 3-2b), however, the ynone undergoes reduction but reduction of the ketone is seen too, although in minor quantities. The deuterium labeling experiments ynones (Scheme 3-2c) demonstrated that the reducing hydride originates entirely from the pinacolborane. Together, these experiments are an indication that pinacolborane itself is not the active reducing agent in the reaction. The more likely reductant would be an activated borohydride that is only produced when the ynone is present in the reaction mixture.



Scheme 3-2 a) Evaluation of the intramolecular competition experiment; b) Evaluation of Lewis base catalyzed reduction of ketones and ynones with mild hydride donors; c) Labelling and product studies of 1,2-reduction of ynones.

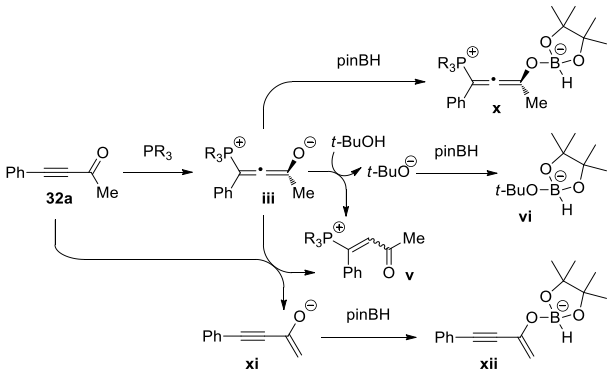
We proposed two mechanistic scenarios outlined in Scheme 3-3. Zwitterionic intermediate **iii** could be formed from ynone **15a** in the presence of phosphine.[1, 135] The nucleophilic addition of phosphine catalyst to ynone followed by protonation by the protic additive provides vinyl-phosphonium salt **v** and *tert*-butoxide anion **iv** (Scheme 3-3, cycle A). The coordination of *tert*-butoxide to pinBH could then generate the activated hydride **vi** which could reduce the carbonyl group of vinyl-phosphonium salt to produce allylic alcoholate **vii**.[132] Proton transfer could occur in the presence of protic additive subsequently to form the intermediate **viii** which could provide the desired propargylic alcohol via the liberation of the phosphine to start another catalytic cycle. Phosphonium cation results in the higher reactivity of vinyl-phosphonium salt intermediate. It makes

the vinyl-phosphonium salt more prone to accept the hydride which could explain the high selectivity for 1,2-reduction while the 1,4-reduction could be hindered by the steric phosphonium ion. Considering the activated hydride **vi** could also reduce the starting ynone directly which was confirmed by a simple experiment where *t*-BuOK was used as the catalyst instead of the phosphine, a simpler mechanism was proposed (Scheme 3-3, cycle B). The hydride source **vi** could simply reduce the ynone and produce a new alcoholate **ix** which could activate pinBH subsequently or get deprotonated by the protic additive to generate the final propargylic alcohol. Both pathways are possible and maybe operate in parallel. And the activation of pinBH via alcoholate anion is clearly required in this kind of 1,2-reduction of ynones.



Scheme 3-3 Proposed mechanisms for the phosphine catalyzed 1,2-reduction of ynones to propargyl alcohols.

The quenching of the zwitterionic intermediate **iii** plays a key role in suppressing the oligomerization and overreduction pathways that take place in the absence of an additive (Scheme 3-4). In the presence of alcohols, this intermediate is protonated and the alkoxide coordinates to pinacolborane to produce the proposed activated hydride donor **vi**. The intermediate **iii**, as an *O*-centered Lewis base, may directly interact with pinBH to provide intermediate **x**. As a base, **iii** could also deprotonate starting ynone if acidic protons are present in α-position. This generates enolate **xi** and vinyl-phosphonium ion **v** with increased electrophilicity owing to its cationic character. The different selectivity for reduction observed in reactions carried out in the presence and without protic additive may originate from the differences in reactivity of the activated hydride donor (**vi** vs. **x** or **xii**).



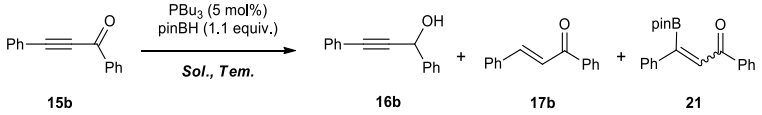
Scheme 3-4 Possible Lewis bases to activate the pinBH.

3.2 Lewis-base catalyzed *trans*-hydroboration of ynoates with pinacolborane

* Fritz Schömberg has worked on this section as part of his Master and now PhD thesis.

To understand the differences between the selectivity observed in reactions carried out with and without the protic additive, we turned our attention to the reactions without additives. In the absence of protic additive, pinBH could potentially be activated by two different enolates **iii** and **xi**. To simplify the model system, we looked into the reaction of diaryl ynone **15b** that can only produce enolate of type **iii** because it lacks acidic protons in α and α' positions.

Table 3-3 Phosphine-catalyzed reactions of ynone **15b** with pinBH.



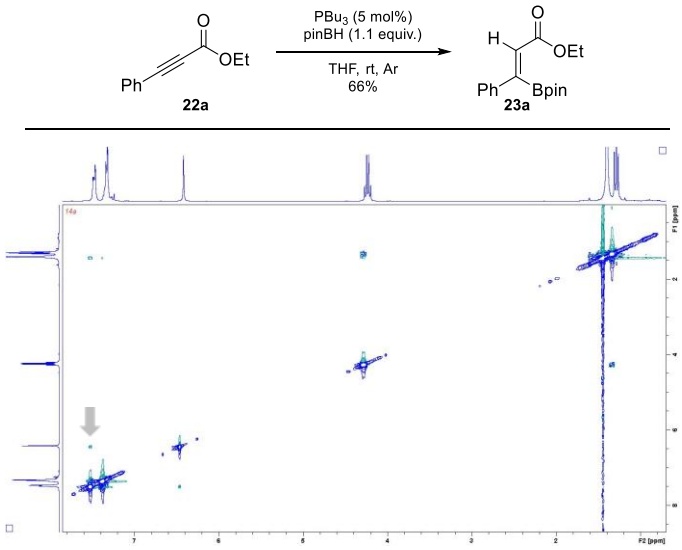
Entry	Conditions	**16b** (%)[a]	**17b** (%)[a]	**21** (%)[a]
1	DCM, rt, *t*-BuOH (1.5 euiv.)	87	-	-
2	DCM, rt	< 3	-	-
3	DCE, reflux	-	77[b]	-
4	THF, reflux	< 3	56[b]	23[b]

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard; [b] Isolated yields.

Ynone **15b** could be selectively reduced to the corresponding propargyl alcohol **16b** in 87% yield in the presence of *t*-BuOH as the protic additive (Table 3-3, entry 1). However, only trace amount of **16b** was observed in the absence of protic additive even prolonging the reaction time to 4 hours. At elevated temperature, in refluxing DCE, only enone **17b**, the product of 1,4-reduction, was obtained. When the reaction was carried out in refluxing THF, enone **17b** was isolated as the major product in 56% yield. The product of hydroboration, 2**1**, was observed in both reactions as a minor component.

Knowing that the esters are less prone to reductions with pinacolborane in the presence of phosphines, we hypothesized that ynoates may be suitable substrates for the development of

phosphine catalyzed hydroboration protocols. Ethyl phenyl propiolate **22a** underwent hydroboration with pinBH in the presence of PBu_3 as the catalyst. The characterization data for vinyl boronate **23a** did not match the presumed *Z*-configuration of the double bond that would arise via the typical *syn*-hydroboration. Instead, the NOESY spectra of **23a** (Scheme 3-5) showed a cross peak between the vinylic proton and aryl protons establishing suggesting that *E*-olefin **23a** has been produced via an unusual *trans*-hydroboration process. This assignment was later confirmed via X-ray crystallography for a heavier analog of **23a** (**23j**, Scheme 3-6).



Scheme 3-5 Initial experiments on phosphine catalyzed *trans*-hydroboration of **22a** and the NOESY spectrum of **23a**.

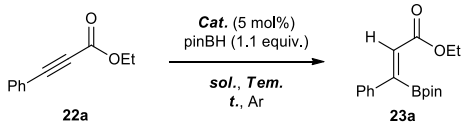
Several transition metal catalyzed approached to *trans*-selective hydroboration of terminal alkynes have been reported. [136-139] This type of transformation on internal alkynes were limited to ruthenium (II) catalyzed hydroborations[140-141] that suffer from low regioselectivity and those that are directed by a pyridyl-group or an alkene.[142-144] Since these approaches cannot be applied to electron deficient alkynes, such as ynones or ynoates, we further developed the phosphine catalyzed *trans*-hydroboration of ynoates.

Initial screening of solvents showed that the reaction performed the best in DCM and DCE (Table 3-4, entries 1-2) while the use of Et_2O, THF and toluene resulted lower yields (entries 3-5). Notably, higher temperature accelerated the reaction rate to generate the product in comparable yield as the reaction at room temperature (entry 6). Increasing the amount of pinBH did not further improve the yield.

As the catalyst is crucial (Table 3-4, entry 17), a variety of Lewis bases were investigated as the catalysts to conduct the *trans*-hydroboration of ynoates. Trialkyl phosphines proved to be the most efficient. PBu_3 and PMe_3 generated **23a** as the only product with comparable yields and excellent *E*/*Z* selectivity (>99:1, determined by ^1H NMR). Furthermore, by using PBu_3 as the catalyst, the loading

could be reduced to 2 mol% without significantly affecting the yield (entry 9). Less nucleophilic phosphines, like methyl diphenyl phosphine, provided the product in lower yield (12%) and lower selectivity (*E*/*Z* = 81:18). Bulky and significantly less nucleophilic phosphines, such as triphenylphosphine and tri-*tert*-butyl phosphine, failed to afford the desired product (Table 3-4, entries 11-12). Comparison of phosphines demonstrated the important role of catalyst's nucleophilicity in this reaction. Other types of catalysts, such as *O*- and *N*-centered Lewis bases, were also tested (entries 13-16) but no reaction was observed, presumably because of the formation of Lewis adducts between the *O*- and *N*-centered Lewis bases and pinBH.

Table 3-4 Optimization for phosphine catalyzed *trans*-hydroboration of ynoate **22a**.

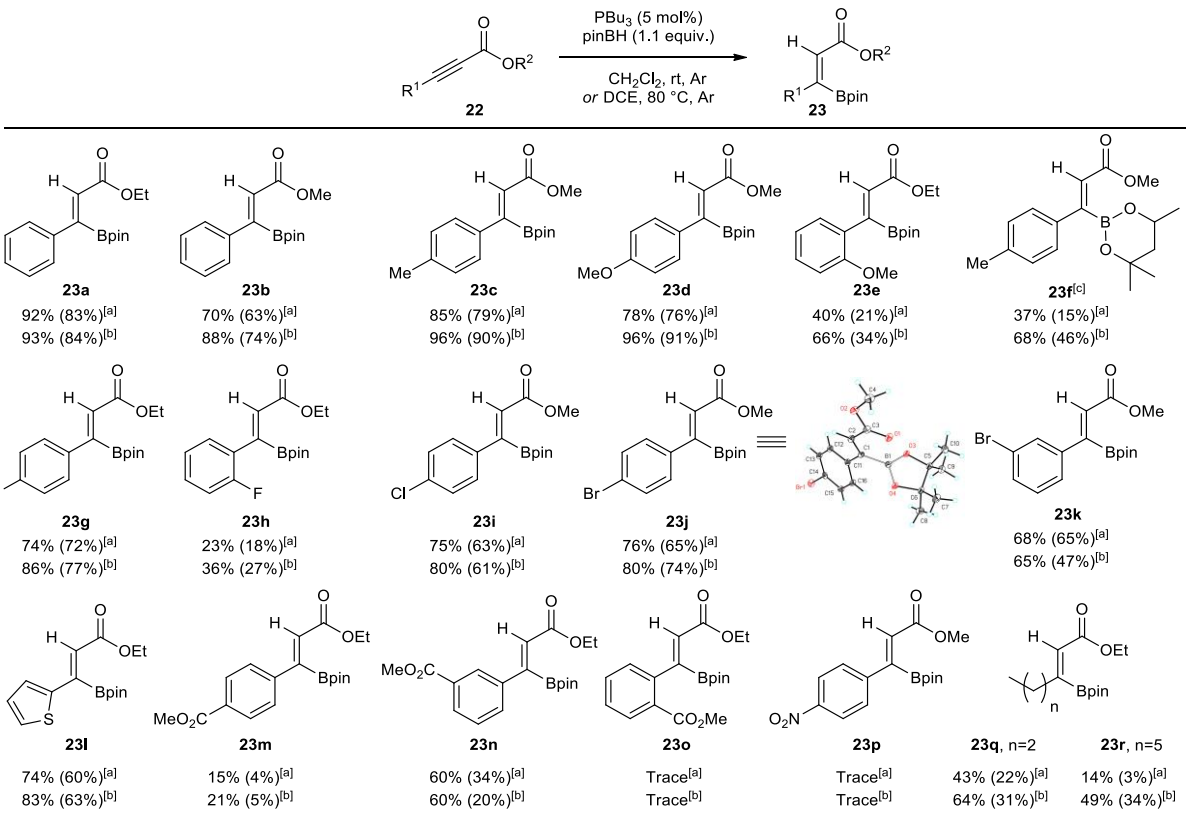


Entry	Cat. (5 mol%)	Sol.	Tem. (°C)	t (h)	Yield (%)[a]
1	PBu_3	**DCM**	rt	4	92 (83[b])
2	PBu_3	**DCE**	rt	4	93
3	PBu_3	**Et_2O**	rt	4	45
4	PBu_3	**THF**	rt	4	66
5	PBu_3	**PhMe**	rt	4	64
6	PBu_3	**DCE**	reflux	2	94
7	**PMe_3**	DCM	rt	4	90
8	**PBu_3**	DCM	rt	4	92 (83[b])
9[c]	**PBu_3**	DCM	rt	8	88
10	**$PMePh_2$**	DCM	rt	4	12 (*E*/*Z* = 82:18)
11	**PPh_3**	DCM	rt	4	NR
12	**P(*t*-Bu)$_3$**	DCM	rt	4	NR
13	**DABCO**	DCM	rt	4	NR
14	**DBU**	DCM	rt	4	NR
15	***N*-methyl pyrrolidine**	DCM	rt	4	NR
16	***t*-BuOK**	DCM	rt	4	NR
17	**none**	DCM	rt	24	NR

[a] NMR yields with triphenylmethane as the internal standard; [b] Isolated yields; [c] 2 mol% of PBu_3 was used.

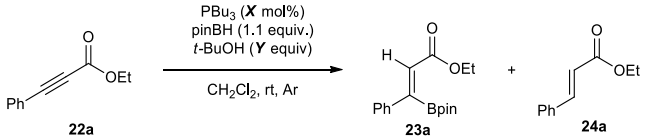
A series of aryl ynonates was used to evaluate the reaction scope (Scheme 3-6). Electron rich substrates reacted well to produce the corresponding vinyl boronates in yields between 70% and 96% (**23a-23d**). Lower yield observed for **23e** (40%) indicated that the reaction is sensitive to steric hindrance by the *ortho*-methoxy group. Aryl halides were tolerated well (**23g-23k**, up to 86% yield). Electron deficient ynoates showed lower reactivity and gave lower yields although *E*/*Z* selectivity remained high (2**2m–22n**, *E*/*Z* > 99:1). Strongly electron withdrawing substituents reduced the reactivity of the ynoates to the level where no reaction was observed. Lower reaction rates of electron deficient ynoates prompted further optimization of the conditions. The use of DCE allowed increase of the reaction temperature which increased the reaction rates and, in most cases, resulted in higher yields while maintaining high selectivity (>99:1). Disappointingly, the products **23o** and **23p** could not be observed at elevated temperatures either.

3.2 Lewis-base catalyzed *trans-hydroboration* of ynoates with pinacolborane



Scheme 3-6 *trans*-Hydroboration of ynonates. [a] NMR yields with Ph_3CH as the internal standard and isolated yields (in brackets) for reactions in DCM at rt; [b] NMR yields and isolated yields (in brackets) for reactions in DCE at reflux; [c] 4,4,6-trimethyl-1,3,2-dioxaborinane was used instead of pinacol borane.

Table 3-5 Influence of protic additive on yield and selectivity.



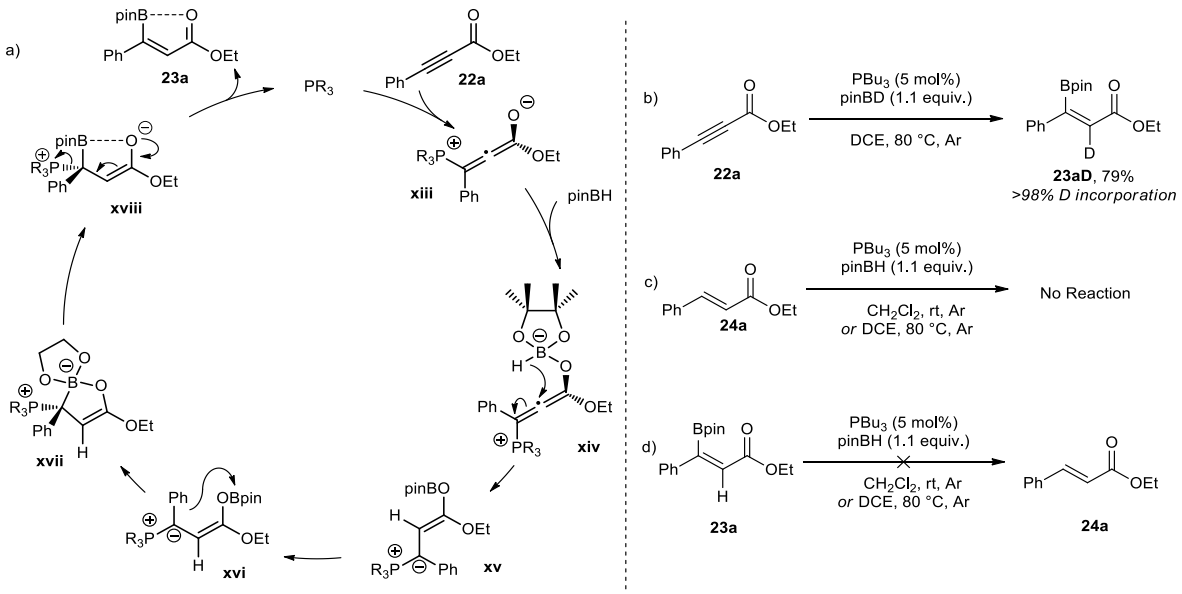
Entry	*t*-BuOH (Y equiv.)	PBu_3 (X mol%)	t (h)	Yield 23a (%)[a]	Yield 24a (%)[a]
1	0	5	4	92	-
2	1.25	5	4	68	10
3	2	5	4	<1	5
4	1.25	20	4	62	8
5	2	20	4	53	7
6	10	20	4	<1	6
7	10	100	4	<1	7

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard.

Ynoates **22q** and **22r** also underwent the hydroboration, although with lower yields (64% and 49%) and decreased *E*/*Z* selectivity, despite featuring the acidic protons in γ position. This prompted a closer inspection of the reaction sensitivity to protic additive. Control experiments demonstrated that the reaction outcome is affected by the amount of protic additive in the mixture (Table 3-5). As the

amount of *t*-BuOH in the reaction mixture increased, yields became lower. This effect could be off-set to a certain extent by increasing the amount of PBu_3 (entries 4-7). The common side product in these reactions was **24a**, the product of simple 1,4-reducton. The *trans*-hydroboration was suppressed by the protic additive presumably due to the quenching of the enolate intermediate and formation of a stable vinyl phosphonium salt.

The proposed mechanism features an intramolecular hydride transfer in intermediate **xiv** which is formed via the activation of pinBH by the zwitterionic intermediate **xiii**, generated from the nucleophilic addition of phosphine to ynoate (Scheme 3-7a). The hydride transfer is made possible by the presence of a vinyl phosphonium motif which leads to the formation of the phosphorus ylide **xv**. Allylic anion resonance allows isomerization of the double bond to form the *E*-configured intermediate **xvi**. Intramolecular boronate transfer to C3 position occurs via intermediate **xvii** followed by the E1cb elimination of phosphine to liberate the product. The strong interaction between the boronate and carbonyl oxygen in **xvii** is crucial for high selectivity and if disrupted, for example by protic additives, it leads to deterioration of selectivity.



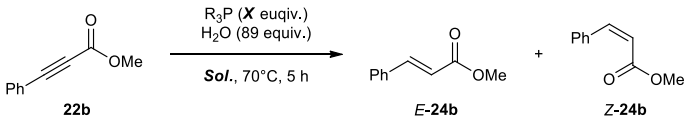
Scheme 3-7 Proposed mechanism, labeling and product studies of *trans*-hydroboration of ynoates.

This mechanistic proposal is further supported by a series of control experiments. These experiments confirmed that the hydride from pinacolborane is exclusively incorporated at the C2 of the product (Scheme 3-7b). Furthermore, enoates do not undergo hydroboration likely because of the inability of the hydride transfer within the saturated analog of the vinyl phosphonium ion **xiv** (Scheme 3-7b). The 1,4-reduction product **24a**, does not originate from proteodeborylation of the vinyl boronate product **23a** (Scheme 3-7c) and it is more likely formed via the direct 1,4-reduction of the ynoate **22a**.

3.3 *Z*-selective reduction of ynoates with phosphine and water

Knowing that 1,4-reduction occurs with ynoates in the presence of protic additives, called for a closer inspection of these reactions and suggested that this pathway may be controlled by the protic additive. We have determined that 1,4-reduction pathway depends on the amount of phosphine present in the reaction mixture and that water further promotes these reactions. We have further evaluated the reactions of ynoate **22b** in various solvents and in the presence of different phosphine and discovered that the reactions are, in fact, stoichiometric in phosphine and *Z*-selective (Table 3-6).

Table 3-6 Screening of solvents.

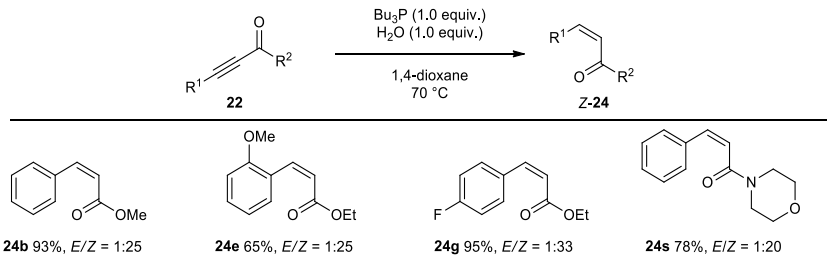


Entry	Sol.	PR_3 (X equiv.)	Yield (%)[a]	*E*/*Z*
1	**MeCN**	PBu_3 (1.1)	0	-
2	**Isopropanol**	PBu_3 (1.1)	0	-
3	**DMF**	PBu_3 (1.1)	5	1:4
4	**DMSO**	PBu_3 (1.1)	2	1:20
5	**THF**	PBu_3 (1.1)	12	1:2
6	1,4-Dioxane	PBu_3 (**1.1**)	18	1:5
7	1,4-Dioxane	PBu_3 (**2**)	8	1:0
8	1,4-Dioxane	PBu_3 (**3**)	8	1:0
9	1,4-Dioxane	PPh_3 (1.1)	55	1:2
10	1,4-Dioxane	PPh_3 (2.2)	57	1:2

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard.

Further optimization of these reactions was carried out by other group members and their work resulted in the development of highly *Z*-selective method for reduction of ynoates that use equimolar amounts of ynoate, tributyl phosphine and water.

The mechanistic proposal for the reduction reactions placed vinyl phosphonium hydroxide in the spotlight and highlighted the possibility that these reactions proceed via pentavalent phosphorus intermediates that result from nucleophilic attack of the hydroxide on the phosphonium ion. While other group members focused on the reactivity of such vinyl phosphonium ions, my attention was directed to reactivity of the aryl phosphonium ions.

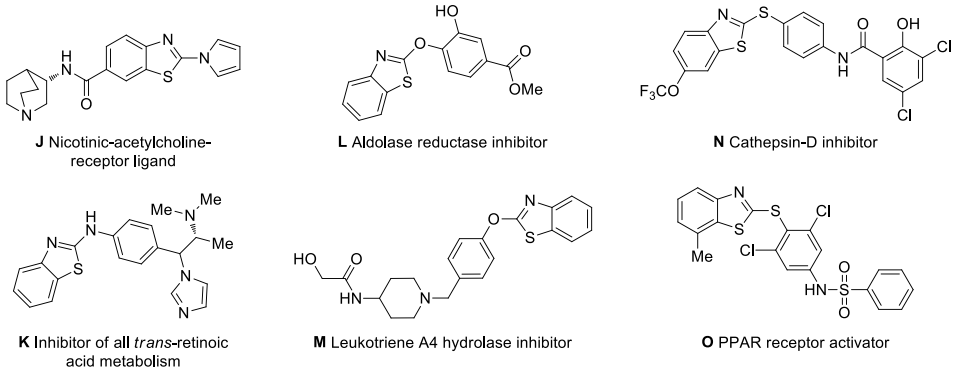


Scheme 3-8 Examples for selective reduction of activated alkynes to *Z*-olefins.

3.4 C-H functionalization of (benzo)thiazoles via aryl-phosphonium salt

*The work of this section was completed together with Konrad Wagner and Fritz Schömberg by equal contribution. Benzothiazole-2-phosphonium salts were prepared by Konrad Wagner.

The pioneering work on the synthesis and use of heteroaryl phosphonium salts has been published by Anders and revisited by the recent work of McNally and coworkers.[145-157] Their work has focused almost exclusively on azines. Our attention was, in contrast, directed towards azoles and the possibility to develop a metal free method for C-H functionalization of thiazoles, in particular.



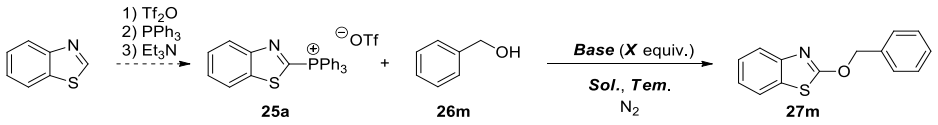
Scheme 3-9 Examples for thiazole containing molecules.

Thiazoles have attracted much attention due to the wide application in biological,[158-164] material fields[165] and organic synthesis[166-168]. As the most common 5-membered aromatic nitrogen heterocycle in FDA approved drugs,[169] thiazoles are omnipresent in mandersedicinal chemistry. For example, they are a part of Abafungin (antifungal drug), sulfathiazole (antimicrobial drug) and Tiazofurin (antineoplastic drug).[170] Their derivatives exhibit a wide range of biological activities including the nicotinic-acetylcholine-receptor ligand **J**[171], the inhibitor of all *trans*-retinoic acid metabolism **K**[172], aldolase reductase inhibitor **L**[173], the potent and selective ACC2 (acetyl-CoA - carboxylases) inhibitor **M**[174], Cathepsin-D inhibitor **N** and PPAR receptor activator **O**[175-178]. Although most of these molecules feature a heteroatom substituent at C2, the methods to perform C2-H functionalization of thiazoles and benzothiazoles remain limited mostly to those that proceed under extremely high temperature and are therefore not suitable for use in more complex settings like medicinal chemistry.

Considering the ease of synthesis of thiazolyl-phosphonium salts,[179-180] we hypothesized that, similar to what we have observed with vinyl phosphonium salts, such salts can be useful intermediates on the path for overall C-H functionalization of thiazoles and benzothiazoles. Upon preparing the benzothiazole-2-phosphonium salt **25a** following the protocol by Anders, initial optimization of the reaction conditions was carried out with focus on the reactions with benzyl alcohol (Table 3-7). Base activation of the nucleophile was required for the synthesis of the

corresponding ether. A screen of different bases used for activation of the alcohol revealed that sodium hydride performs well in THF and generates the least amount of waste. Optimization of solvent showed that the reaction in THF, Et_2O and toluene performed the best (entries 13-20). Higher yield was obtained when the amount of benzyl alcohol, as well as NaH as the base, increased to 1.5 equivalents while 2 equivalents resulted in a slightly diminished yield (entries 21-23).

Table 3-7 Simple optimization.



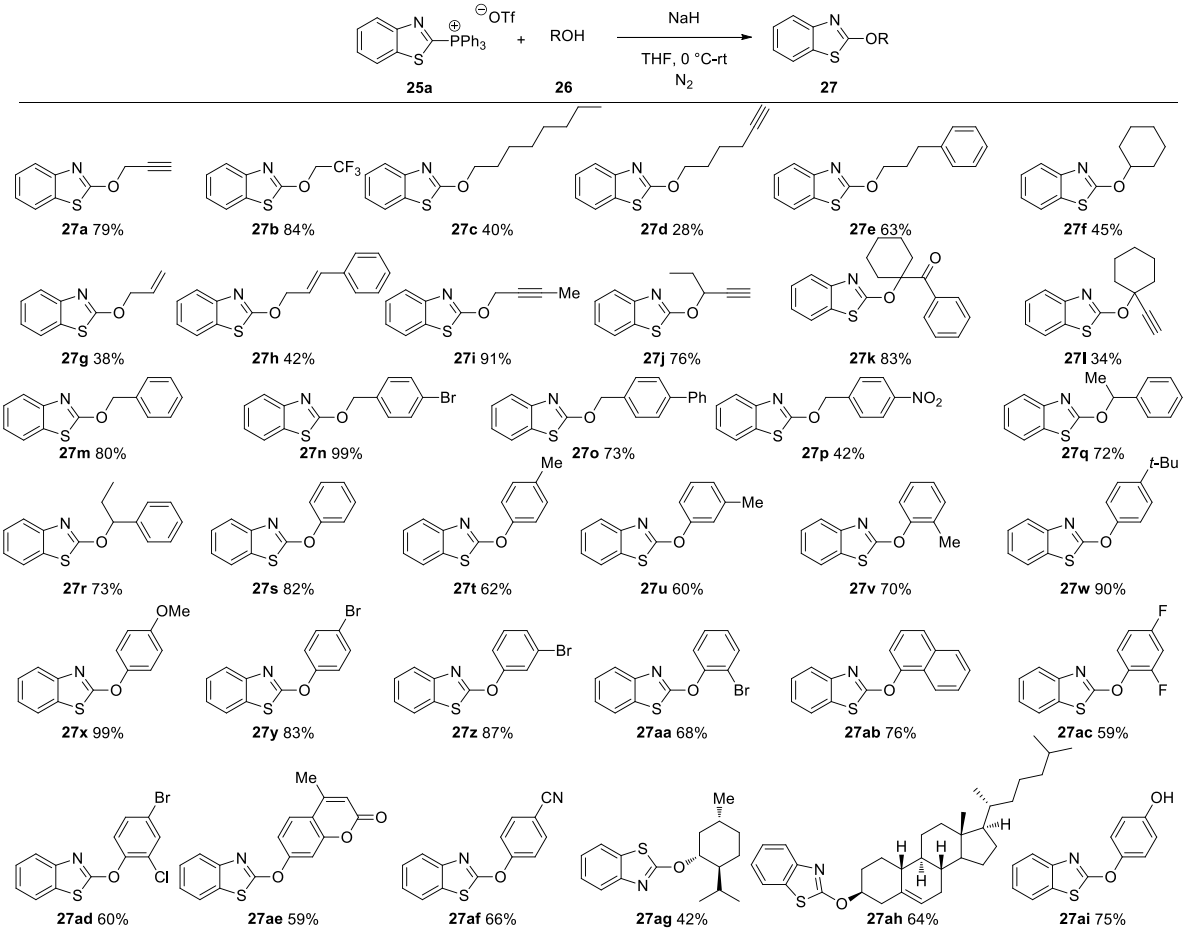
25a 26m 27m

Entry	Base (X equiv.)	26m (equiv.)	Sol.	Tem. (°C)	Yield (%)[a]
1	**NaH (1.0)**	1.0	THF	0 °C - rt	55
2	***n*-BuLi (1.0)**	1.0	THF	-78 °C - rt	44
3	**LDA (1.0)**	1.0	THF	-78 °C - rt	29
4	***i*-PrMgBr (1.0)**	1.0	THF	-78 °C - rt	Trace
5	***t*-BuOK (1.0)**	1.0	THF	-78 °C - rt	Trace
6	**Et_3N (1.0)**	1.0	THF	rt	Trace
7	**DBU (1.0)**	1.0	THF	rt	34
8	**DMAP (1.0)**	1.0	THF	rt	Trace
9	**DABCO (1.0)**	1.0	THF	rt	Trace
10	NaH (1.0)	1.0	**Et_2O**	0 °C - rt	55
11	NaH (1.0)	1.0	**Dioxane**	0 °C - rt	29
12	NaH (1.0)	1.0	***n*-Hexane**	0 °C - rt	16
13	NaH (1.0)	1.0	**Toluene**	0 °C - rt	56
14	NaH (1.0)	1.0	**DCE**	0 °C - rt	Trace
15	NaH (1.0)	1.0	**MTBE**	0 °C - rt	11
16	NaH (1.0)	1.0	**Chlorobenzene**	0 °C - rt	37
17	NaH (1.0)	1.0	**$PhCF_3$**	0 °C - rt	40
18	NaH (1.25)	**1.25**	THF	0 °C - rt	55
19	NaH (1.5)	**1.5**	THF	0 °C - rt	80[b]
20	NaH (2.0)	**2**	THF	0 °C - rt	75

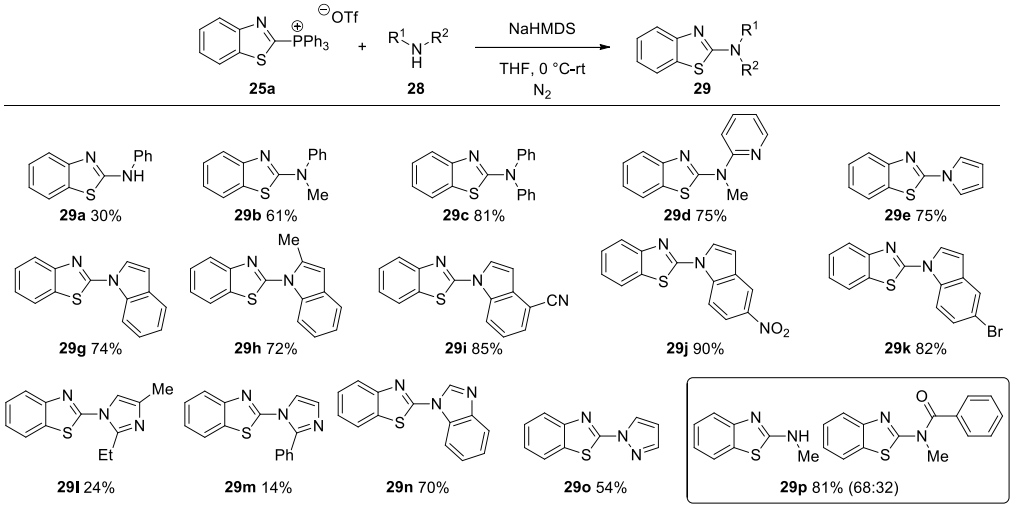
[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard; [b] Isolated yields

Under the optimal conditions, a range of alcohol nucleophiles were efficiently introduced to the benzothiazole-2-phosphonium salt (**25a**) (Scheme 3-10). Aliphatic alcohols, including primary, secondary and tertiary alcohols were investigated first under the optimal conditions producing moderate to good yields (**27a-27l**, 34% - 91%). Lower yields were seen with long alkyl chain primary alcohols and allylic alcohols. Benzyl alcohol performed well to convert to the corresponding product in 80% yield (**27m**). Halogen groups or extended conjugation system were well tolerated (**27n-27o**) and gave up to 99% yields while electron withdrawing substituents decreased the yield (**27p**, 42%) which was attributed to the lower nucleophilicity of the alcohol. Secondary benzyl alcohols showed comparable yields (**27q-27r**, 72% and 73%). Phenols bearing electron donating and electron withdrawing substituents produced the desired products under the standard conditions in good yields (59-99%) which were not affected by the steric variations (**27s-27af**). Halogens and cyano groups were tolerated well under these conditions even for multi substituted substrates (**27ac-27af,** 59% - 66%). As to demonstrate the utility of this protocol, menthol and cholesterol were also tested which

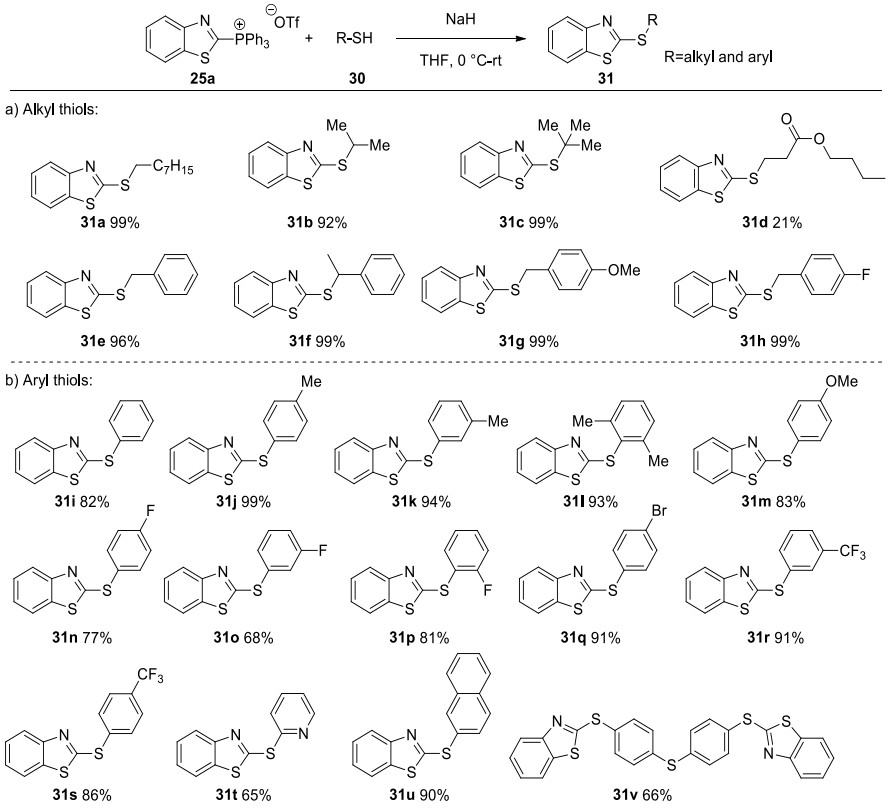
also gave the corresponding products in moderate yields (42% for **27ag** and 64% for **27ah**). When hydroquinone was used, the product of mono substitution was produced in 75% yield (**27ai**).



Scheme 3-10 Scope study of **25a** with alcohol nucleophile.

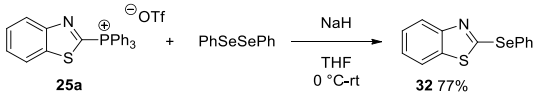


Scheme 3-11 Scope study of **25a** with *N*-centered nucleophile.



Scheme 3-12 Scope study of **25a** with *S*-centered nucleophile.

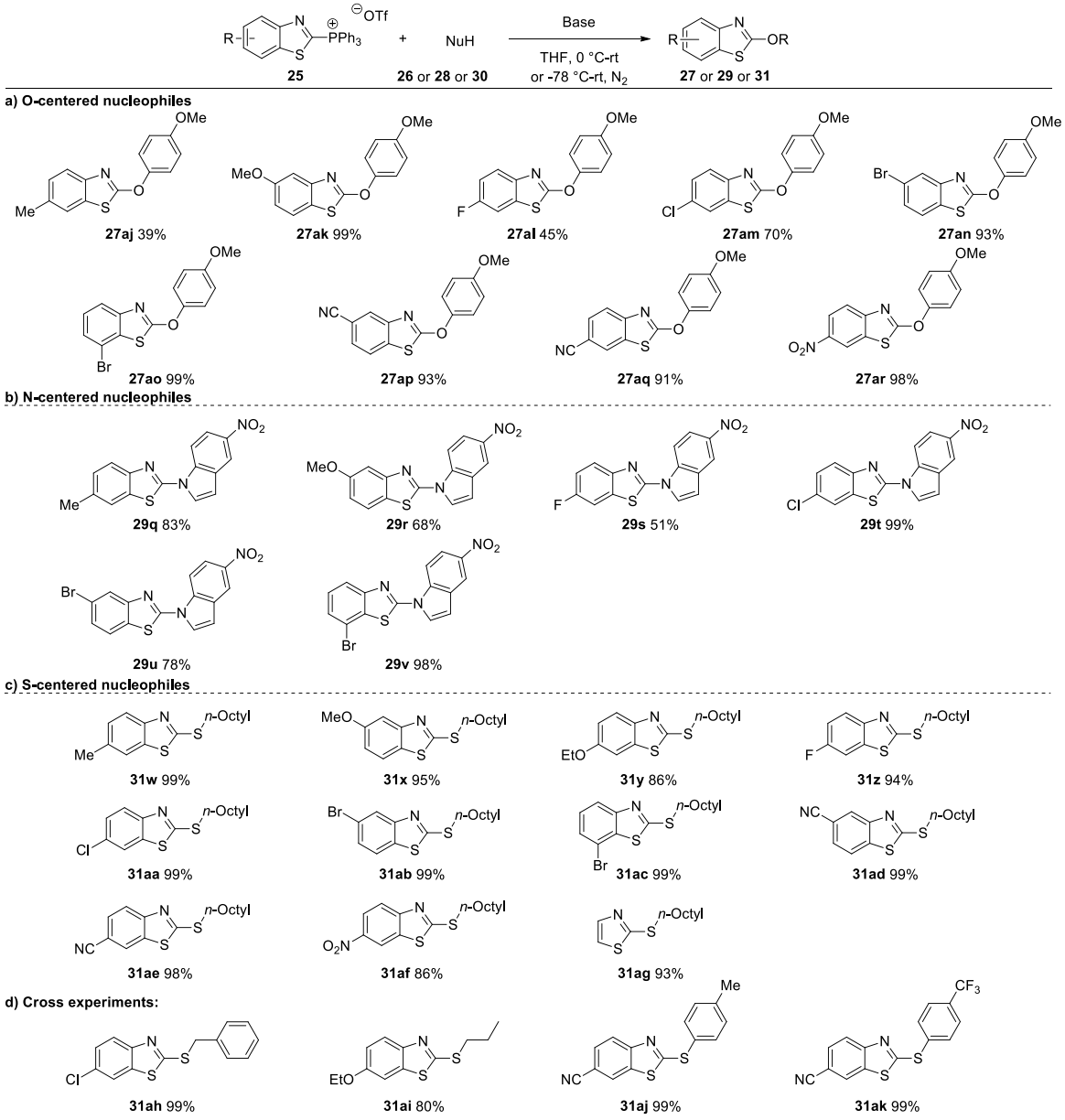
N-nucleophiles, including anilines and heterocycles, proved to be reactive under similar conditions. The products were isolated in moderated to good yields (**29b-29o**) under the optimized conditions using NaHMDS instead of NaH (Scheme 3-11). A range of reactive groups, such as cyano (**29i**, 85%), nitro (**29j**, 90%) and halogen (**29k**, 82%), were well tolerated in these processes. Deprotection happened partially to acetyl aniline and benzoyl methyl amine under the basic conditions to give the corresponding products or the deprotected ones (**29a**, **29p**). Steric effect played a role in lowering the yields when imidazole derivatives with substitution at position 2 were utilized (**29l-29m**, 24% and 14%). Phenyl group in imidazole motif diminished the yield dramatically. *1*-H-Pyrazole was also used as a competent reagent for this process and provided moderate yield (**29o**, 54%).



Scheme 3-13 Scope study of **25a** with diselenide.

Thiols were subsequently taken into consideration (Scheme 3-12). Excellent yields (up to 99%) were achieved from primary, secondary and tertiary alkyl thiols (**31a-31h**) while only 21% yield of **31d** was obtained due to its self-assembling reaction. Thiophenols featuring electron rich and electron poor groups provided the product in good to excellent yields (**31i-31u**, 65% - 99%). Halogen

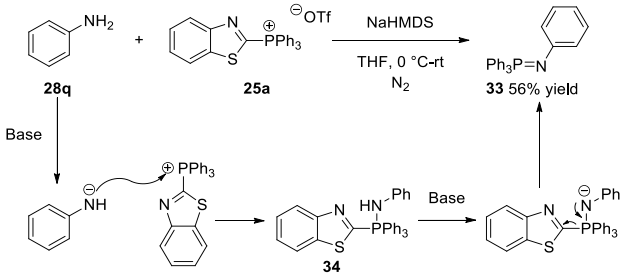
substituted thiophenols showed good performance and all para-, meta- and ortho- substitutions (**31n-31p**) resulted in comparable yields which indicated the slight influence of steric effect on this process. Despite the hindered groups of 2,6-dimethylthiphenol, 93% yield was still achieved (**31l**). Thiophenols featuring heteroaryl substitution or extended conjugation system were well tolerated (65% for **31t** and 90% for **31u**). Two benzothiazoles were introduced to **30v** generating **31v** in 66% yield. Gratifyingly, diselenide, treated with NaH, could afford the corresponding product in good yield as well (**32**, Scheme 3-13, 77%).



Scheme 3-14 Extended scope for C-hetero atom bond formation.

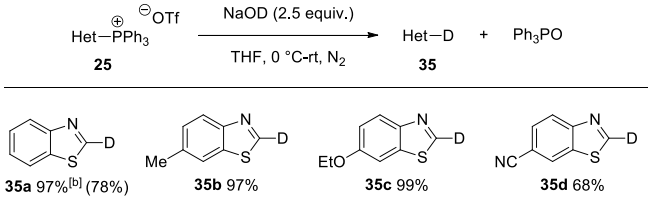
Besides the investigation of commonly used nucleophiles, a series of substituted thiazole-2-phosphonium salts were also evaluated to assess the versatility of the method (Scheme 3-14). 4-MeO-phenol, 5-NO_2-indole and octanethiol were then selected as model nucleophiles to further investigate this protocol. It was found that both thiazole-2-phosphonium salt and substituted benzothiazole-2-phosphonium salts with electron donating groups, halogen or electron withdrawing groups were suitable for this transformation in the presence of alcohols (Scheme 3-14a, 39% - 99%), amines (Scheme 3-14b, 51% - 99%) and thiols (Scheme 3-14, 80% - 99%), and the corresponding products were obtained in good to excellent yields.

Iminophosphorane (**33**) was obtained (56% yield) while aniline was treated in the presence of NaHMDS which promoted us to consider about the preliminary mechanism. As shown in Scheme 3-15, the first step of the nucleophilic attack occurred when the phosphonium salt was added to the aniline anion system to produce the phosphorane **34**. The other proton of aniline was deprotonated under the basic conditions after which, the second nucleophilic attack happened to release the iminophosphorane.



Scheme 3-15 Iminophophorane from the reaction of 99a with aniline and the proposed pathway.

Inspired by the result, we hypothesized that the use of water as the nucleophile (as hydroxide ion) would result in reduction of the thiazole and the formation of phosphine oxide. Experiments using only slight excess of sodium deuteride demonstrated that this indeed is the case. The specific C2 deuterium labeling with 97% yield and higher than 98% deuterium incorporation was observed when salt **25a** was used (Scheme 3-16). The process also appears general as benzothiazoles with both electron-donating and withdrawing substituents undergo efficient C2 labeling (**35b-35d**).

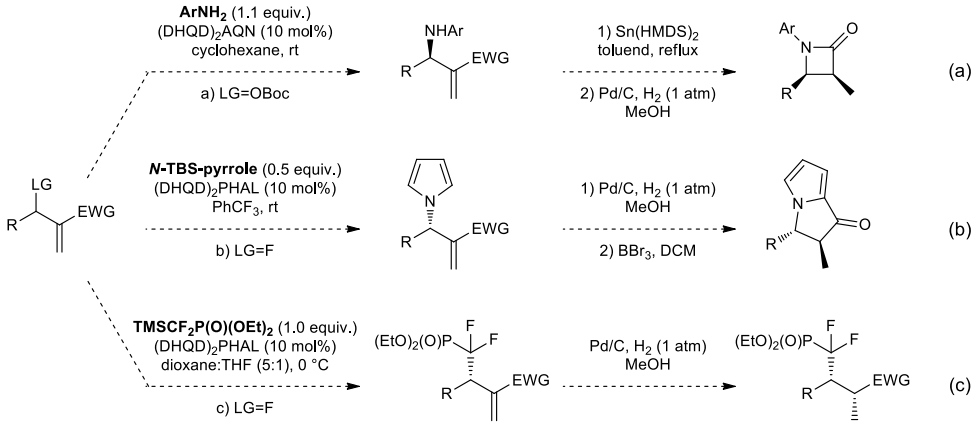


Scheme 3-16 Synthesis of deuterated heterocycles.

4 Summary and conclusion

The aim of this thesis was to develop solutions to overcome the common problem related to nucleophile scope in Lewis base catalyzed reactions and, by doing so, develop new synthetic methods and generate new knowledge and deeper understanding of these processes and reactivity of the involved molecular species.

Relying on the strategies used in previous reports of Lewis base catalyzed allylic substitutions using N-H acidic nucleophiles, we have expanded the scope for these reactions to allylation of anilines that have been considered insufficiently N-H acidic for applications in such reactions.[66] The enantioenriched products obtained in reactions that use chiral cinchona alkaloid based catalysts, have been used in enantio- and diastereoselective synthesis of β-lactams (Scheme 4-1a) structurally similar to those determined to be low nM binders of tubulin[68-70] and therefore considered potential treatment for cancer (Scheme 2-3).



Scheme 4-1 Lewis base catalyzed allylic substitutions with latent (pro)nucleophiles and examples of application of the newly developed methods in stereoselective synthesis of biologically relevant molecules.

The analogous strategy was not applicable for *N*-allylation of pyrroles which highlighted the need for a new approach to further expand the scope of Lewis base catalyzed reactions. The solution came in the form of the concept of latent nucleophiles, the molecules that are not (or not strongly) nucleophilic but can be activated to act as a nucleophile at an opportune time during the reaction. We have focused on the development of this concept for *N*-centered nucleophiles and the use of *N*-silyl compounds, where the silyl group attenuates the nucleophilicity of the parent N-H compound, as latent nucleophiles in Lewis base catalyzed reactions. The necessity for activation of such latent nucleophiles during the reaction made the molecules that feature fluoride as a leaving group their logical reaction partners in Lewis base catalyzed reactions.

The proof of principle study for the concept of latent nucleophiles was the development of enantioselective *N*-allylation of *N*-silyl pyrroles, indoles and carbazoles using allylic fluorides. These reactions proceed with excellent regioselectivity with respect to both reaction partners and expand the scope of Lewis base catalyzed allylic substitutions to otherwise problematic nucleophiles (Scheme 2-11). This new method for enantioselective synthesis of *N*-allyl pyrroles enabled the first enantio- and diastereoselective synthesis of substituted pyrrolizin-1-ones (Scheme 4-1b) that have been shown to exert *anti*-amyloid and radical scavenging effects.

Further application of the concept of latent nucleophiles in Lewis base catalysis was pursued with *C*-centered nucleophiles and in particular the diethyl (difluoro(trimethylsilyl)-methyl) phosphonate as a reagent for introduction of difluoromethyl phosphonate moiety to organic molecules (Scheme 1c). Lewis base catalyzed reactions of this reagent with allylic fluorides resulted in the first enantioselective phosphonyldifluoromethylation and synthesis of molecules that are considered bioisosteres of organic phosphates. The presence of difluoromethyl group allowed for improved diastereoselectivity in the subsequent reactions of the enantioenriched difluoromethyl phosphonate products.

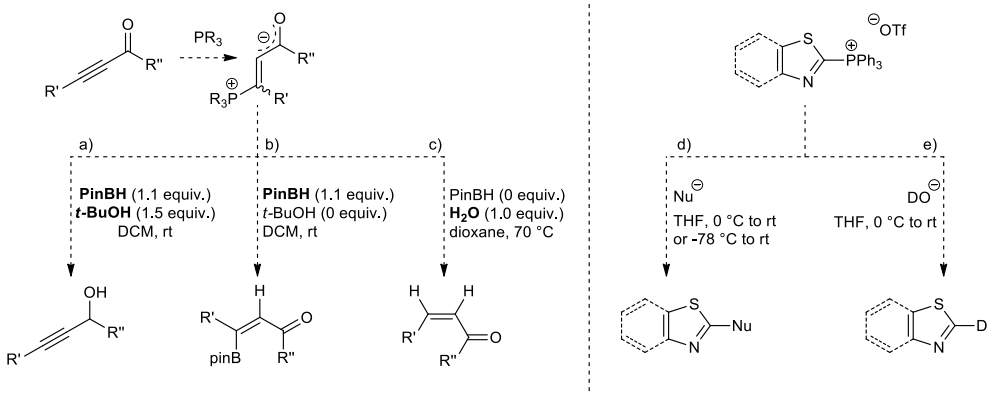
In contrast to the work with *N*-centered Lewis base catalysts, the work presented in this thesis on reactions catalyzed by *P*-centered Lewis bases was focused on the possibility of simultaneous dual activation of small organic molecules with Lewis acids and Lewis bases that do not form stable Lewis adducts and constitute non-traditional frustrated Lewis pairs.

Pinacolborane and tributyl phosphine, the two materials that do not form stable Lewis adducts, have been used in selective transformation of ynones and ynoates, the common substrates in lewis base catalyzed reactions. We have discovered that, in the presence of protic additive, ynones undergo highly selective 1,2-reduction reactions to produce the corresponding allylic alcohols (Scheme 4-2a). Mechanistic investigation of these reactions highlighted that the formation of vinyl phosphonium intermediate and the activation of pinacolborane with the *O*-centered Lewis base derived from the protic additive play important roles in control of selectivity in these reactions.

Despite the apparent similarities of ynones and ynoates, they show diverse reactivity with pinacolborane in the presence of phosphine catalysts. We have discovered and developed the atypical *trans*-hydroboration of alkynes in ynoates that is catalyzed by phosphines (Scheme 4-2b). These reactions proceed with high regio and diastereoselectivity and the mechanistic studies have shown that the vinyl phosphonium intermediates play an important role in these reactions too.

The work on the development of 1,2-reduction of ynones and *trans*-hydroboration of ynoates highlighted the versatile reactivity of vinyl phosphonium salts and inspired further studies involving these types of intermediates. The first in line were the 1,4-reductions of ynoates using stoichiometric

quantities of phosphines and water which were shown to be highly *Z*-selective (Scheme 4-2c) which contradicted the previous reports that these types of reactions produce *E*-alkenes.[181]



Scheme 4-2 Newly developed phosphine catalyzed or phosphine promoted reactions involving vinyl- or aryl phosphoniumions as catalytic or synthetic intermediates.

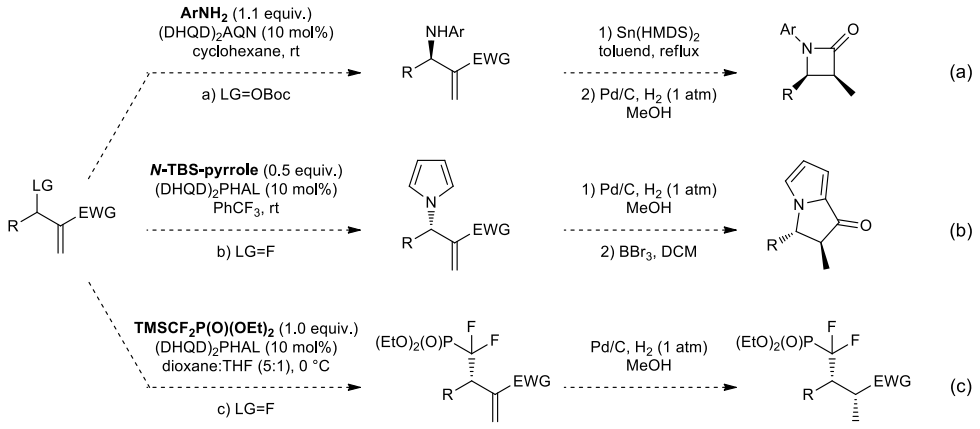
Interest in reactivity of vinyl phosphonium ions informed the interest in reactivity of aryl phosphonium ions. In this area, we have shown that thiazoles and benzothiazoles undergo regioselective C2-H functionalization with triphenylphosphine to form thiazol-2-yl-triphenylphosphonium salts and that these salts undergo efficient substitution reactions with *N*-, *O*-, *S*- and *Se*-centered nucleophiles to introduce various heteroatom substituents in the C2 position of thiazoles and benzothiazoles (Scheme 4-2d, e). The two-step sequence features a truly broad scope for various nucleophiles including secondary amines, amides, pyrroles, indoles, imidazoles, pyrazoles and related N-heterocycles, alcohols, phenols, thiols, thiophenols and selenides, and it constitutes an effective method for C-H functionalization of the parent thiazoles and benzothiazoles, the most common five membered N-heterocycles in FDA approved drugs.[169]

The newly developed synthetic methods presented in this thesis have already found application in synthesis of biologically relevant molecules, but, more importantly, they set the foundation for further applications of similar ideas and concepts in a variety of other Lewis base catalyzed or Lewis acid promoted reactions.

5 Zusammenfassung und Schlussfolgerungen

Im Rahmen dieser Arbeit sollten Lösungsansätze entworfen und etabliert werden, um Probleme bezüglich nukleophiler Reaktanden bei Lewis-Base-katalysierten Reaktionen zu umgehen. Ausgehend davon sollten neue synthetische Strategien entwickelt werden, um ein tieferes Verständnis der Prozesse zu erlangen, welche sich auf molekularer Ebene ereignen.

Basierend auf bereits etablierten Protokollen für die Allylierung von N-H-aciden Nukleophilen in der Lewis-Base-Katalyse konnten im Rahmen dieser Arbeit Nukleophile verwendet werden, welche zuvor als unreaktiv eingestuft worden sind.[66] Unter Verwendung wurden die Allylierungsprodukte in enantioselektiver Weise erhalten und anschließend diastereoselektiv in β-Lactam-Derivate überführt (Schema 5-1a). Analoge Verbindungen zeigten in bereits veröffentlichten Studien eine hohe Affinität zu Tubulin[68-70] weshalb sie potenziell zur Behandlung von Krebs eingesetzt werden könnten. (Schema 2-3).



Schema 5-1 Lewis-Base-katalysierte, allylische Substitution mit latenten (Pro)-Nukleophilen und Beispiele für die Anwendungen dieses Konzeptes für die stereoselektiven Synthesen von biologisch relevanten Molekülen.

Eine analoge Strategie ließ sich nicht in dieser Arbeit für die *N*-Allylierung von Pyrrolen entwickeln. Dies unterstreicht die Notwendigkeit einer neuen Reaktionsmethodik für die Lewis-Base-katalysierte Reaktionen, um deren Anwendbarkeit zu steigern. Als Lösungsansatz wurde hierbei das Konzept der latenten Nukleophile entwickelt und angewendet. Dies basiert auf Molekülen, die selbst nicht (oder schwach) nukleophilen Charakter zeigen, aber in Gegenwart eines geeigneten Stimulus im Verlaufe der Reaktion aktiviert werden können (sog. *Latente Nukleophile)*. Der Fokus lag hierbei auf der Entwicklung des Konzeptes bezüglich *N*-zentrierter Nukleophile, wobei die Latenz durch eine siliziumbasierte Schutzgruppe induziert werden sollte. Die Notwendigkeit einer Aktivierung prädestiniert Moleküle, welche Fluorid als Abgangsgruppe tragen, zu geeigneten Reaktionspartnern für Lewis-Base-katalysierte Reaktionen.

Zur Demonstration des Konzeptes der latenten Nukleophile wurde die enantioselektive *N*-Allylierung von Silylpyrrolen, -Indolen und -Carbazolen mit allylischen Fluoriden untersucht. Diese Reaktionen zeigten exzellente Regioselektivitäten bezüglich beider Reaktionspartner und erweitern drastisch die Anwendbarkeit allylischer Substitutionen unter Lewis-Base-Katalyse besonders für jene Nukleophile die zuvor als nicht verwendbar angesehen worden sind. (Schema 2-11). Diese neue Methode für die enantioselektive *N*-Allylierung von Pyrrolen erlaubte auch die erste enantio- und diastereoselektive Synthese von substituierten Pyrrolizin-1-onen (Schema 5-1b), einer Substratklasse die sich durch ihre *anti*-amyloide und radikalfangenden Eigenschaften auszeichnet.

Weiterhin wurden latente Nukleophile für C-zentrierte Nukleophile, in diesem Fall das Diethyl(difluoro(trimethylsilyl)methyl)phosphonate, als Reagenz benutzt, um die Difluormethylphosphonat-Gruppe mittels Lewis-Base-Katalyse einzuführen (Schema 5-1c). Die Reaktion dieses Reagenzes mit den Allylfluoriden beschreibt die erste enantioselektive Phosphonyldifluormethylierung, wobei die Produkte als Bioisostere organischer Phosphate angesehen werden können. Durch die Anwesenheit des Difluormethyl-Strukturmotivs verliefen nachfolgende Reaktionen diastereoselektiv.

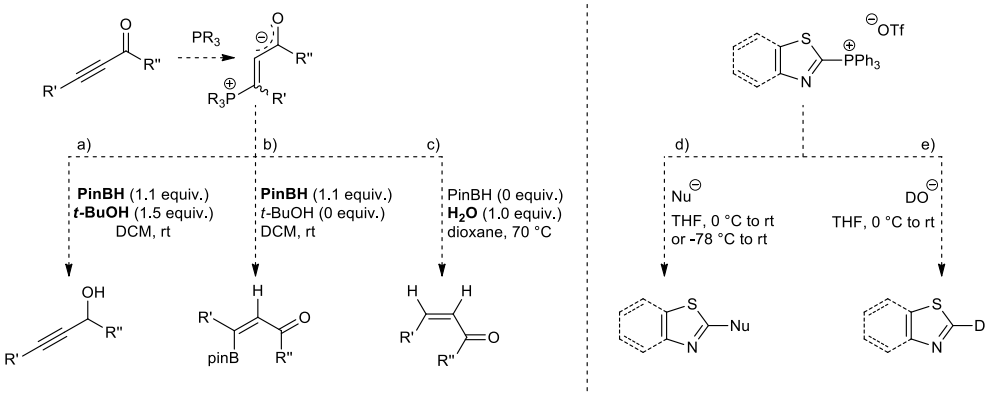
Neben den Untersuchungen von *N*-zentrierten Lewis-Base-Katalysatoren wurden im Rahmen dieser Arbeit auch Studien für P-zentrierte Katalysatoren angefertigt. Der Aspekt der dualen Aktivierung von kleinen organischen Molekülen unter Verwendung von Lewis-Säuren und -Basen stand hierbei im Vordergrund. Da diese keine stabilen Addukte ausbilden, können sie im weitesten Sinne als frustrierte Lewis-Paare angesehen werden.

Pinakolboran und Tributylphosphin, welche kein stabilen Lewis-Addukt bilden, wurden für Transformationen von Alkinonen und Alkinoaten verwendet. Es wurde gefunden, dass protische Additive Alkinone selektiv einer 1,2-Reduktion untergehen ließen, sodass Allylalkohole gebildet wurden (Schema 5-2a). Mechanistische Studien dieser Reaktion zeigten, dass die Bildung von Vinylphosphoniumsalzen als Intermediat und die Aktivierung von Pinakolboran durch eine vom Additiv gebildete *O*-zentrierte Lewis-Base essenziell für die Selektivität dieser Reaktion ist.

Obwohl Alkinone und Alkinoate chemisch sehr ähnlich sind, zeigten sie verschiedene Reaktivitäten unter Einwirkung von Pinakolboran und Tributylphosphin als Katalysator. Dies resultierte in der Entwicklung einer untypischen *trans*-Hydroborierung der Dreifachbindung von Alkinoaten unter Phosphin-Katalyse (Schema 5-2b). Die Reaktionen zeigten hohe Regio- und Diastereoselektivitäten und mechanistische Experimente offenbarten, dass auch hier das Vinylphosphonium-Salz das Schlüsselintermediat ist.

Die Untersuchungen der 1,2-Reduktion der Alkinone und die *trans*-Hydroborierung von Alkinoaten demonstrierten die mannigfaltige Reaktivität von Vinylphosphonium-Salzen und waren

somit Anstoß für weitere Untersuchungen ähnlicher Intermediate. Zunächst wurden 1,4-Reduktionen von Alkinoaten mittels stöchiometrischer Mengen von Phosphinen und Wasser untersucht, welche eine hohe *Z*-Selektivität zeigten (Schema 5-2c). Dies widerspricht den bisherigen Ergebnissen anderer Forscher, welche fast ausschließlich E-Selektivität beschrieben.[181]



Schema 5-2 Neue Phosphine-katalysierte oder -induzierte Reaktionen mit Vinyl oder Arylphosphoniumionen als katalytisches beziehungsweise isolierbares Intermediat.

Aufgrund der interessanten Reaktivität von Vinylphosphoniumionen wurden zudem auch Arylanaloga untersucht. In dieser Arbeit konnte gezeigt werden, dass Thiazole und Benzothiazole einer selektiven C2-Funktionalisierung unterworfen werden können, wenn Triphenylphosphin zur Synthese der entsprechenden Thiazol-2-yl-triphenylphosphonium-Salze verwendet wird. Diese Salze lassen sich anschließend gemäß einer Substitutionsreaktion mit diversen *N*-, *O*-, *S*-, und *Se*-zentrierten Nukleophilen umsetzen, sodass die in 2-Position-manipulierten Verbindungen erhalten werden (Schema 5-2d, e). Die aus zwei synthetischen Schritten bestehende Sequenz zeigte ein breites Anwendungsspektrum bezüglich der Nukleophile, wobei sekundäre Amine, Amide, Pyrrole, Indole, Imidazole, Pyrazole und verwandte Heterozyklen sowie Alkohole, Phenole, Thiole, Thiophenole und Selenide untersucht wurden. Somit bildet diese synthetische Strategie eine effektive Methode für die C-H-Funktionalisierung von Thiazolen und Benzothiazolen. Das Thiazolmotiv ist eines der von der FDA am häufigsten zugelassenen Medikamente.[169]

Die in dieser Arbeit neu entwickelten, synthetischen Methoden wurden dann für die Synthese von biologisch relevanten Molekülen wie β-Lactame und Pyrrolizinone verwendet. Darüber hinaus sind die hier präsentierten Ergebnisse der Grundstein für weitere Anwendungen von ähnlichen Ideen und Konzepten in Lewis-Base-katalysierten oder Lewis-Säure-induzierten Reaktionen.

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Abbreviations

Cat.	catalyst
DABCO	1,4-diazabicyclo[2.2. 2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	Enantiomeric excess
er	Enantiomeric ratio
HMDS	bis(trimethylsilyl)amine
LDA	lithium diisopropylamide
MBH	Morita-Baylis-Hillman
pinBH	Pinacolboran
Sol.	solvent
TBS	*tert*-butyldimethylsilyl
Tem.	temperature
THF	tetrahydrofuran
TMS	trimethylsilyl

Curriculum vitae

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Education

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Publication list

Peer-reviewed publications

[1] F. Schömberg, **Y. Zi**, I. Vilotijevic, "Lewis-base-catalysed selective reductions of ynones with a mild hydride donor", *Chem. Commun*. **2018**, *54,* 3266–3269.

[2] **Y. Zi**, F. Sch mberg, F. Seifert, H. G rls, I. Vilotijevic, "*trans*-Hydroboration *vs.* 1,2-reduction: divergent reactivity of ynones and ynoates in Lewis-basecatalyzed reactions with pinacolborane", *Org. Biomol. Chem.* **2018**, *16,* 6341–6349.

[3] **Y. Zi**, M. Lange, C. Schultz, I. Vilotijevic, "Latent nucleophiles in Lewis base catalyzed enantioselective *N*-allylations of N-heterocycles", *Angew. Chem. Int. Ed.* **2019**, *58,* 10727–10731.

[4] M. Lange, **Y. Zi**, I. Vilotijevic, "Enantioselective synthesis of pyrrolizin-1-ones via Lewis base catalyzed *N*-allylation of *N*-silyl pyrrole latent nucleophiles", *J. Org. Chem.* **2020**, *85,* 1259-1269.

[5] **Y. Zi**, M. Lange, P. Schüler, S. Krieck, M. Westerhausen, I. Vilotijevic, "Synthesis of β-lactams via enantioselective allylation of anilines using Morita-Baylis-Hillman carbonates", *Synlett* **2020**, *31,* 575-580.

[6] **Y. Zi**, F. Schömberg, K. Wagner, I. Vilotijevic, "C-H functionalization of thiazoles via thiazol-2-yl-phosphonium intermediates", *Org. Lett.* **2020**, *22*, 3407-3411.

[7] **Y. Zi**, M. Lange, I. Vilotijevic, "Enantioselective Lewis base catalyzed phosphonyldifluoromethylation of allylic fluorides using a C-silyl latent pronucleophile", *Chem. Commun*. **2020**, *56*, 5689-5692.

Accepted manuscripts

[1] M. Lange, **Y. Zi**, I. Vilotijevic, "Latent (pro)nucleophiles in Lewis base catalyzed allylic substitutions", *Synlett* **2020**, accepted, *DOI: 10.1055/s-0040-1707130*.

[2] **Y. Zi**, K. Wagner, F. Schömberg, I. Vilotijevic, "Selective C-H chalcogenation of thiazoles via thiazol-2-yl-phosphonium salts", **2020**, accepted, *DOI: 10.1039/d0ob00684j*.

Poster presentation

[1] ORCHEM 2018, Berlin, Germany

Y. Zi, F. Schömberg, F. Seifert, I. Vilotijević (2018)

"Phosphine-Catalyzed Anti-Selective Hydroboration of Ynoates"

[2] ORCHEM 2018, Berlin, Germany

F. Schömberg, **Y. Zi**, I. Vilotijević (2018)

"Lewis-Base-Catalyzed Selective Reductions of Ynones with Mild Hydride Donors"

[3] ORCHEM 2018, Berlin, Germany

F. Seifert, **Y. Zi**, I. Vilotijević (2018)

"Operationally Simple and Selective Phosphine-Promoted Reductions of Ynones, 2-Ynoates, 2-Ynamides and 2-Ynoic Acids"

[4] ORCHEM 2018, Berlin, Germany

M. Lange, C. Schultz, **Y. Zi**, I. Vilotijević (2018)

Lewis–Base–Catalyzed Substitution of Allylic Fluorides with Silylated Amines as Latent Nucleophiles

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Publications P1-P9

Publication P1

Synthesis of β-lactams via enantioselective allylation of anilines using Morita-Baylis-Hillman carbonates

Y. Zi, M. Lange, P. Schüler, S. Krieck, M. Westerhausen, I. Vilotijevic,

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Synlett Y. Zi et al. Cluster

Synthesis of β-Lactams via Enantioselective Allylation of Anilines with Morita–Baylis–Hillman Carbonates

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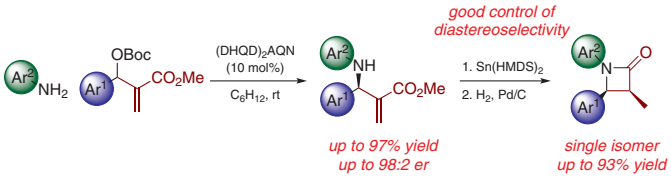
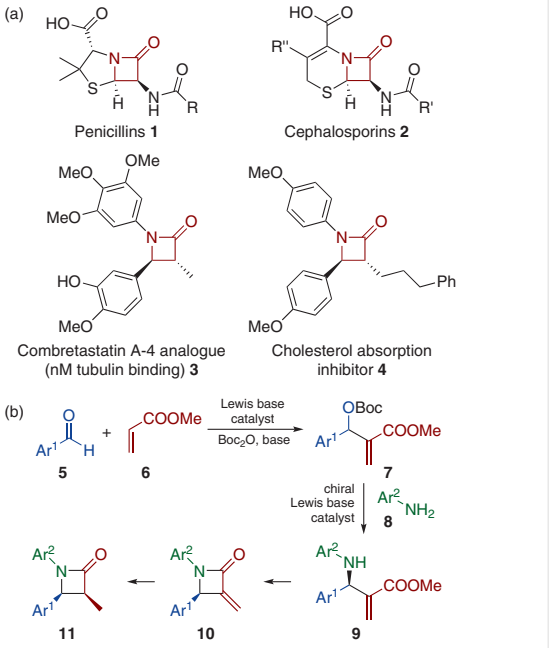
Abstract Enantioenriched β-lactams are accessed via enantioselective allylation of anilines with Morita–Baylis–Hillman carbonates followed by a base-promoted cyclization. The resulting 3-methyleneazetidin-2-ones are amenable to diastereoselective functionalization to produce analogues of biologically active β-lactams. The use of nearly equimolar quantities of the starting materials make this method efficient and straightforward.

Key words β-lactams, allylic substitution, allylation, Lewis base catalysis



β-Lactams remain a central structural motif in modern medicinal chemistry due to the widespread use of penicillins, cephalosporins, carbapenems and monobactams (**1** and **2**) (Scheme 1, a).[1] In addition to β-lactam antibiotics which inhibit bacterial cell wall biosynthesis, molecules containing this structural motif exhibit a range of other biological activities including neuroprotective, antioxidant, analgesic or immunomodulatory capabilities.[2] For example, a new class of β-lactams (**3** and **4**) (Scheme 1, a) has been identified as potent tubulin binders and therefore potential anticancer agents.[3] Although numerous synthetic approaches to β-lactams have been reported,[4] the continuing cycle of discovery of new biological activities for β-lactams creates the need for the synthesis of molecules with new substitution patterns and makes the development of new methods and the improvement of known processes a worthy endeavor.

While developing the concept of latent nucleophiles in Lewis base catalysis as a general method for enantioselective allylation of N-centered nucleophiles using cheap and widely available Morita–Baylis–Hillman (MBH) adducts **7**,[5,6] we became interested in applying such reactions to the synthesis of β-amino acids and their derivatives, β-lactams. We were particularly interested in the allylation of anilines, which would allow access to structures of type **11**, being derivatives of biologically active compounds **3** and **4**. The products of *N*-allylations using MBH adducts **9** (Scheme 1, b) appear to be perfectly equipped for this as they are a single cyclization step away from the desired β-lactams. The presence of an *exo*-methylene in the resulting lactam **10** was seen as an excellent opportunity for further modifications of the scaffold in a diastereoselective manner, which highlights the importance of efficiently constructing the



Scheme 1 (a) Bioactive β-lactam analogues. (b) Proposed route for the asymmetric synthesis of β-lactams from aldehydes, acrylate and anilines.

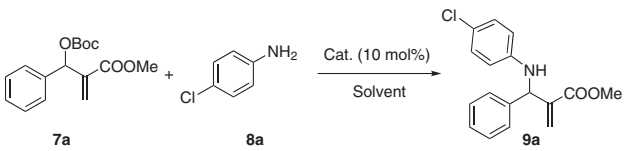
stereogenic center α to the nitrogen atom in **9**. *N*-Allyl anilines similar to **9** have been previously prepared via metal-catalyzed allylic substitutions that are often burdened with the issue of S_N2 vs S_N2' selectivity,[7] and via aza-MBH reactions where the scope for the imine is usually very limited.[8] An efficient organocatalytic method that circumvents these problems would certainly be of interest in small-scale exploratory medicinal chemistry work.

Lewis base catalyzed allylations of N-centered nucleophiles are normally limited in scope to those nucleophiles that feature an acidic N–H that can be activated by a leaving group released from a typical MBH adduct, usually a carboxylate or a carbonate/alcoholate.[7g,9] Imides/carbamates,[7g,9b,d] sulfonamides[9c,e] and sulfoximines,[9h,i] for example, perform well in allylations using MBH carbonates. The N-centered nucleophile in these reactions should also be less nucleophilic than the catalyst in order to avoid competing reactivity with the catalyst itself. With these restrictions in mind and considering their low N–H acidity (pK_a of around 30 compared to a p*K*a of around 18 for the butoxide generated upon degradation of a carbonate), predicting the reactivity of anilines in (chiral) Lewis base catalyzed allylations is not straightforward.[10]

Reactions of anilines and MBH adducts, catalyzed or promoted with DABCO, produce racemic *N*-allyl anilines.[11] These products easily undergo 3,3-sigmatropic rearrangements, which proved useful in synthesis of N-heterocycles such as quinolines and uracils.[12] With the goal of developing an enantioselective coupling of anilines and MBH carbonates, our work commenced with the optimization of the reaction conditions for the chiral Lewis base catalyzed allylation of aniline **8a** with MBH carbonate **7a** (Table 1). Focus was placed on cinchona-alkaloid-based catalysts that are often used for similar transformations.[6c,13] The chiral catalysts required significantly longer reaction times than the reactions with DABCO. In our hands, the monomeric cinchona catalysts failed to produce the desired products with high enantioselectivity. Dimeric catalysts such as $(DHQD)_2AQN$, $(DHQD)_2PHAL$ and $(DHQD)_2PYR$ were tested and surprisingly showed distinctly divergent activities and enantioselectivities. $(DHQD)_2AQN$ was identified as a suitable catalyst as it provided the desired product in good yield with an enantiomeric ratio of 92:8. Further optimization was focused on the catalyst loading and identification of the optimum reaction solvent, reaction time, concentration and temperature. The optimized conditions included reactions in cyclohexane with 10 mol% of $(DHQD)_2AQN$ as the catalyst at room temperature, with a 0.4 M concentration of the electrophile.[14]

It is apparent that these reactions fit the kinetic resolution scenario where the two enantiomers of the racemic MBH carbonate **7** react in an enantioconvergent manner to produce one enantiomer of the substitution product **9** predominantly. It is noteworthy that only a slight excess of aniline (1.1 equiv) was sufficient to drive the reactions to completion after 56 hours, allowing us to avoid the commonly seen use of superstoichiometric quantities of electrophile. The reactions reported here are thus greener and more efficient.

Table 1 Optimization of the Conditions for the Asymmetric Allylation of Anilines[a]



7a **8a** **9a**

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	DABCO	toluene	2	52	–
2	quinine	toluene	56	24	–30
3	cinchonidine	toluene	56	30	25
4	$(DHQD)_2AQN$	toluene	56	67	84
5	$(DHQD)_2PHAL$	toluene	56	27	9
6	$(DHQD)_2PYR$	toluene	56	21	–18
7	$(DHQD)_2AQN$	THF	56	46	79
8	$(DHQD)_2AQN$	dioxane	56	46	84
9	$(DHQD)_2AQN$	CH_2Cl_2	56	86	75
10	$(DHQD)_2AQN$	$PhCF_3$	56	64	88
11	$(DHQD)_2AQN$	cyclohexane	56	81	82
12[d]	$(DHQD)_2AQN$	cyclohexane	56	67	86
13[e]	$(DHQD)_2AQN$	cyclohexane	56	74	86
14[f]	$(DHQD)_2AQN$	cyclohexane	56	76	87
15[g]	$(DHQD)_2AQN$	cyclohexane	56	79	87
16	$(DHQD)_2AQN$	cyclohexane/$PhCF_3$	56	66	89
17[h]	$(DHQD)_2AQN$	cyclohexane	56	94 (94)	87
18[i]	$(DHQD)_2AQN$	cyclohexane	56	50	88
19[j]	$(DHQD)_2AQN$	cyclohexane	40	94	84
20[j]	$(DHQD)_2AQN$	$PhCF_3$	40	88	88

[a] Reaction conditions: Carbonate **7a** (1 equiv), 4-chloroaniline (**8a**) (1.1 equiv), catalyst (10 mol%), rt, 0.2 M.
[b] NMR yield based on triphenylmethane as the internal standard, yield of isolated product in parentheses.
[c] Determined by HPLC of the purified product.
[d] $(DHQD)_2AQN$ (5 mol%) was used.
[e] $(DHQD)_2AQN$ (15 mol%) was used.
[f] 4-Chloroaniline (1.0 equiv) was used.
[g] 4-Chloroaniline (1.3 equiv) was used.
[h] The concentration was 0.4 M.
[i] The concentration was 0.1 M.
[j] The reaction was heated to 40 °C.

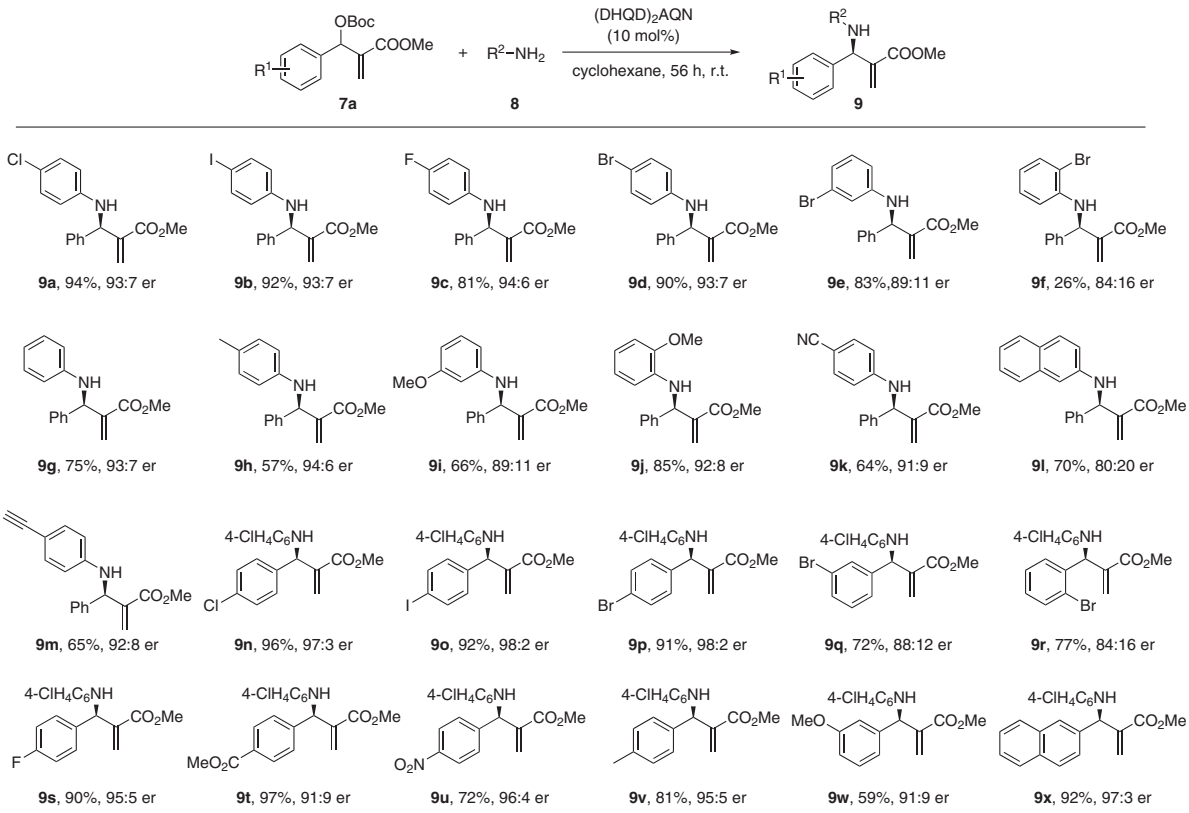
Optimization studies were followed by an investigation of the reaction scope for substituted anilines and MBH carbonates (Scheme 2). Halogen-substituted anilines gave the corresponding allylation products **9a–f** in excellent yields and high enantioselectivities. The reactions showed generally broad tolerance for substituents on the aniline. Sub-

strates with electron-donating (**9h–j**) and electron-withdrawing (**9k**) substituents gave the desired products in good yields.

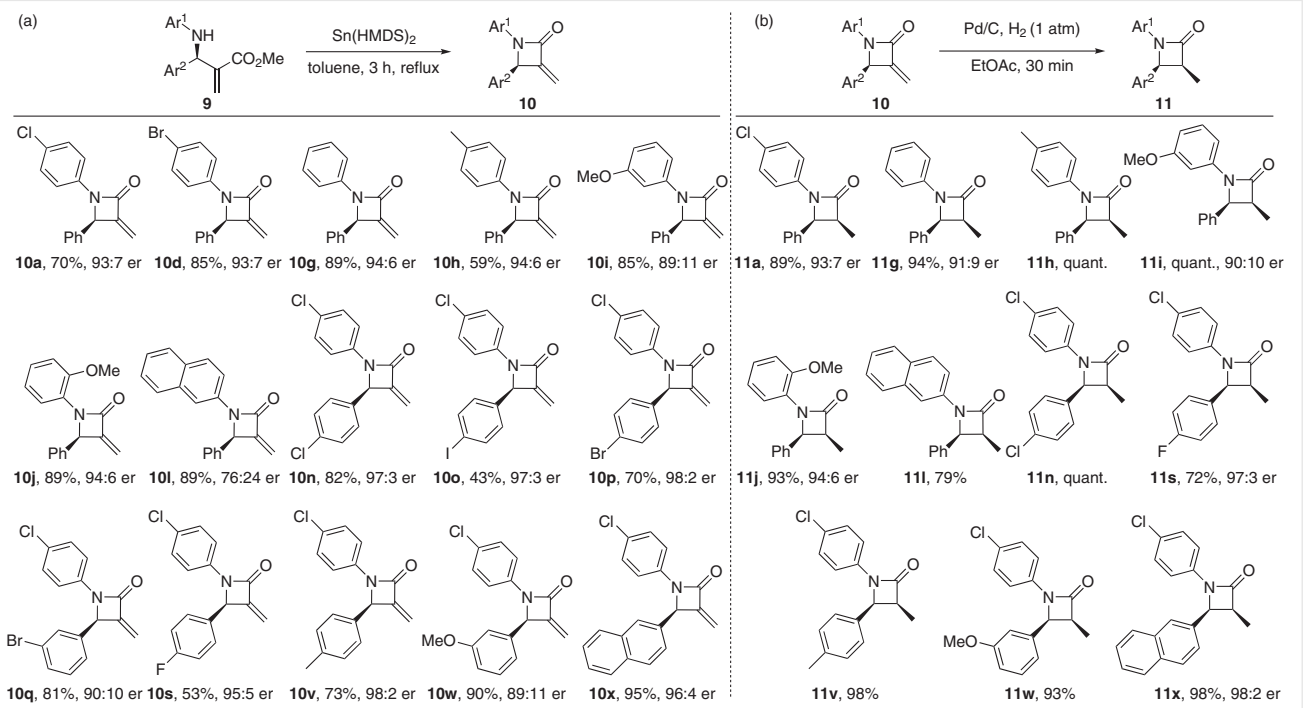
Extended π-systems within the nucleophile were also well tolerated (**9l** and **9m**). The enantiomeric ratios remained good for various combinations of reaction partners with values of up to 94:6. The enantioselectivities observed with bulkier nucleophiles like 2-naphthylamine and an *ortho*-substituted aniline were slightly lower (**9f** and **9l**). The steric bulk of the nucleophile also affected the yield when an *ortho*-substituted nucleophile was used (**9f**). A series of substituted MBH carbonates was used to assess the reaction scope for the electrophilic partner. MBH carbonates carrying halide substituents all performed well with respect to both yield and enantioselectivity (**9n–s**) (Scheme 2). Even an electrophile with an *ortho*-substituent performed well, albeit with lower enantioselectivity (**9r**, 77%, 84:16 er). Substrates with electron-donating and electron-withdrawing substituents performed equally well in these reactions, showing generally good functional group tolerance with yields of up to 97% and enantiomeric ratios of up to 98:2. The configuration of the major enantiomer in reactions catalyzed by $(DHQD)_2AQN$ was assigned by comparison of the optical rotations to those of the previously reported material.[7c] With access to a variety of allylated anilines, we turned our attention to the cyclization to form the *exo*-methylene-containing β-lactams, substituted 3-methyleneazetidin-2-ones **10**.

The focus was placed on activation of the nucleophiles with a strong base to effect cyclization. A brief optimization of the reaction conditions corroborated the previous reports that $Sn(HMDS)_2$ gives the desired four-membered rings with the highest yields. Cyclizations using $Sn(HMDS)_2$ provided a small library of compounds with various N- and C4-substituents, which included alkyl, halide and ether substituents (including methyl ethers often present in the tubulin-binding β-lactams) (Scheme 3, a). Gratifyingly, the cyclization reactions provided a variety of substituted β-lactams in good yields (43–95%) and were even able to accommodate an *ortho*-substituted substrate carrying additional steric bulk close to the reactive center (**10j**, 89%). A brief survey of the enantiomeric ratios for the products showed that they matched those of the starting materials, confirming that the stereogenic centers are not affected during the cyclization process.

The final synthetic step to access analogues **11** was 1,4-reduction. With a variety of methods to choose from,[15] we opted for simple hydrogenation over a palladium catalyst. The reactions confidently produced the reduced products in excellent yields across the set of substrates used to test the



Scheme 2 Enantioselective Lewis base catalyzed allylations of anilines using MBH carbonates



Scheme 3 (a) Cyclization to give *exo*-methylene-containing β-lactams **10**. (b) Diastereoselective hydrogenation of the *exo*-methylene group to produce β-lactams **11**.

reaction scope (Scheme 3, b). Furthermore, the hydrogenation reactions proceeded with good control of the diastereoselectivity. Attempts to isomerize the reaction product under basic conditions produced only minor quantities of the *trans*-isomers, suggesting that the *cis*-diastereomer was more stable, a fact that could be used to control otherwise less diastereoselective transformations involving the *exo*-methylene group in the resulting β-lactams. The assignment of the structures of the two diastereomers was based on $^{3}J_{H-H}$ coupling constants, which are consistent with the dihedral angles in the low energy conformations for the two isomers (5.9 Hz for *cis*-**11a** and 2.4 Hz for *trans*-**11a**). The enantiomeric ratios of the isolated β-lactams matched those of the starting materials, showing that the stereogenic center α to the nitrogen atom was not affected by the two-step sequence.

In conclusion, we have presented an efficient route for the asymmetric synthesis of biologically relevant β-lactams that relies on enantioselective Lewis base catalyzed allylation of anilines to set the stereogenic centers.[16] Considering the high atom economy in the synthesis of MBH adducts, the efficiency of the catalytic substitution reactions which require nearly equimolar quantities of starting materials and the simplicity of the cyclization/reduction sequence,[17,18] this route represents an economical and green tool for the synthesis of β-lactams. The library of prepared compounds will be evaluated for biological activity in due course.

Funding Information

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Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691570.

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(14) During the preparation of this manuscript, two independent reports describing similar reactions of anilines and MBH carbonates were published. These methods use 10 mol% of β-isocupreidine as the catalyst in toluene (1.5 equiv of carbonate) and 20 mol% of $(DHQD)_2AQN$ as the catalyst in *p*-xylene in the presence of CaF_2 (2 equiv of carbonate). In comparison, our protocol uses a lower catalyst loading and avoids the use of superstoichiometric quantities of MBH carbonate, as is the case in these two previous reports, see: (a) Formánek, B.; Šimek, M.; Kamlar, M.; Císařová, I.; Veselý, J. *Synthesis* **2019**, *51*, 907. (b) Zhao, S.; Chen, Z.-L.; Rui, X.; Gao, M.-M.; Chen, X. *Synlett* **2019**, 703.

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(16) **Enantioselective Allylation of Anilines; General Procedure**

Carbonate **7** (1 equiv), aniline **8** (1.1 equiv) and $(DHQD)_2AQN$ (10 mol%) were added to a vial containing a stir bar. The vial was evacuated and refilled with nitrogen 3 times. The reaction mixture was then stirred at room temperature after adding cyclohexane (0.4 M). After completion of the reaction, the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (eluent: 5% ethyl acetate in petroleum ether).

Methyl 2-{[(4-Chlorophenyl)amino](phenyl)methyl}acrylate (9a)

Yield: 28 mg (94%); pale yellow oil; 93:7 er (determined by HPLC analysis) [Phenomenex Lux Cellulose-1, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, λ = 253 nm, t_R (major) = 18.73 min, t_R (minor) = 14.92 min]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.27 (m, 5 H), 7.18–7.04 (m, 2 H), 6.57–6.44 (m, 2 H), 6.40 (s, 1 H), 5.92 (s, 1 H), 5.39 (s, 1 H), 4.24 (s, 1 H), 3.72 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.58, 145.23, 140.21, 139.80, 129.07, 128.88, 128.01, 127.51, 126.37, 122.60, 114.63, 59.13, 52.06.

(17) **Cyclization to β-Lactams 10; General Procedure**

To a solution of **9** (1.0 equiv) in toluene was added $Sn[HMDS]_2$ (1.5 equiv). The mixture was refluxed for 2 h and the solution then cooled and concentrated. The residue was purified by flash chromatography on silica gel (eluent: 5% ethyl acetate in petroleum ether) to afford the desired product.

(*R*)-1-(3-Methoxyphenyl)-3-methylene-4-phenylazetidin-2-one (10i)

Yield: 14 mg (85%); white solid. IR (ATR): 2927, 2360, 1743, 1597, 1492, 1454, 1369, 1249, 1114, 848, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.32 (m, 5 H), 7.17 (t, *J* = 8.1 Hz, 1 H), 7.06 (t, *J* = 2.2 Hz, 1 H), 6.84 (dd, *J* = 8.0, 1.9 Hz, 1 H), 6.63 (dd, *J* = 8.2, 2.5 Hz, 1 H), 5.86 (t, *J* = 1.9 Hz, 1 H), 5.41 (d, *J* = 1.6 Hz, 1 H), 5.19 (d, *J* = 1.6 Hz, 1 H), 3.77 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.01, 160.13, 149.77, 138.68, 136.45, 129.92, 129.10, 128.81, 126.61, 111.01, 110.11, 109.41, 103.00, 63.72, 55.28. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{15}NO_2$: 265.1103; found: 265.1094.

(18) **Reduction to β-lactams 11; General Procedure**

To a degassed ethyl acetate solution of **10** (1 equiv) was added (10 mol%) Pd/C and the reaction flask was furnished with a H_2 balloon. After stirring for 30 min, the reaction mixture was filtered over Celite and evaporated. The crude residue was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether).

(3*S*,4*S*)-1-(4-Chlorophenyl)-3-methyl-4-(naphthalen-2-yl)-azetidin-2-one (11x)

Yield: 25 mg (98%); white solid. IR (ATR): 2974, 1728, 1597, 1492, 1381, 1365, 1161, 1091, 813, 744 cm^{-1}. ^{1}H NMR (300

MHz, $CDCl_3$): δ = 7.92–7.77 (m, 3 H), 7.73–7.67 (m, 1 H), 7.53 (dt, *J* = 6.3, 3.4 Hz, 2 H), 7.37–7.28 (m, 3 H), 7.25–7.16 (m, 2 H), 5.35 (d, *J* = 6.0 Hz, 1 H), 3.80 (qd, *J* = 7.6, 5.9 Hz, 1 H), 0.93 (d, *J* = 7.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.44, 136.28, 133.18, 132.13, 129.16, 128.80, 128.72, 127.89, 127.82, 126.66, 126.45, 126.22, 124.36, 118.34, 58.74, 49.79, 9.79. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{16}ClNO$: 321.0920; found: 321.0916.

Publication P2

Latent nucleophiles in Lewis base catalyzed enantioselective *N*-allylations of N-heterocycles

Y. Zi, M. Lange, C. Schultz, I. Vilotijevic,

Angew. Chem. Int. Ed. **2019**, *58*, 10727–10731.

The paper as well as the supporting information (free of charge) are available online under: *DOI:10.1002/anie.201903392*

Nucleophilic Substitution

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German Edition: DOI: 10.1002/ange.201903392

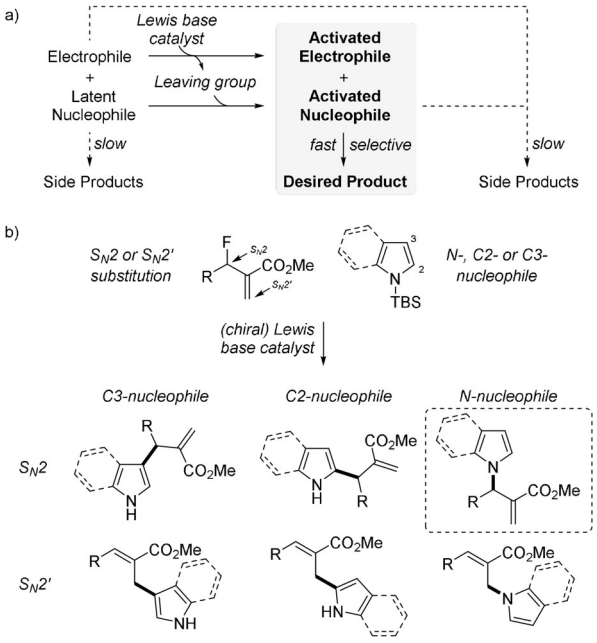
Latent Nucleophiles in Lewis Base Catalyzed Enantioselective *N*-Allylations of N-Heterocycles

*You Zi, Markus Lange, Constanze Schultz, and Ivan Vilotijevic**

Abstract: *Latent nucleophiles are compounds that are themselves not nucleophilic but can produce a strong nucleophile when activated. Such nucleophiles can expand the scope of Lewis base catalyzed reactions. As a proof of concept, we report that N-silyl pyrroles, indoles, and carbazoles serve as latent N-centered nucleophiles in substitution reactions of allylic fluorides catalyzed by Lewis bases. The reactions feature broad scopes for both reaction partners, excellent regioselectivities, and produce enantioenriched N-allyl pyrroles, indoles, and carbazoles when chiral cinchona alkaloid catalysts are used.*

Lewis base catalysts can serve to increase both the electrophilicity and nucleophilicity of reactants, which allows them to trigger a surprisingly diverse set of reactivity patterns.[1] Most Lewis base catalyzed reactions involve an interaction between a nucleophile and an electrophile. The fact that many of these reactions feature a narrow scope with respect to the nucleophilic reaction partner is often underappreciated. For example, in Lewis base catalyzed allylic substitution reactions, the nucleophilic reaction partner should be less nucleophilic than the catalyst and it should match the catalyst's Lewis base affinity.[2] If these criteria are not met, mixtures of products of S_N2 and S_N2' substitution reactions will be observed and/or the reactions may proceed without involvement of the catalyst, which precludes the development of enantioselective catalytic processes.[3] A potential solution could be provided by latent nucleophiles, which are derivatives of otherwise nucleophilic molecules that are not (or not markedly) nucleophilic but can be activated to participate in the reaction.[4] When activation of a latent nucleophile is dependent on activation of the electrophilic partner, the reaction between the activated nucleophile and the activated electrophile may outperform other competing pathways and enable selective transformations (Scheme 1a). This concept should allow us to expand the reactivity range and the type of catalysts to be utilized in Lewis base catalysis.

The nucleophilic properties of pyrroles and indoles have been studied and quantified.[5] Both pyrroles and indoles can serve as N-, C2-, and C3-nucleophiles, and the issues with regioselectivity in their functionalization are well documented.[6] We hypothesized that an *N*-silyl substituent would attenuate the nucleophilicity of pyrroles and indoles, turning them into latent nucleophiles. Activation of *N*-silyl latent nucleophiles could be mediated by fluoride ions. If activation of the nucleophile is to be dependent on activation of the electrophile, the fluoride ions should be generated during activation of the electrophilic reaction partner. For this reason, allylic fluorides were chosen as suitable coupling partners.[7] We focused on fluorides derived from Morita–Baylis–Hillman (MBH) adducts to enable a regio- and enantioselective allylation of N-heterocycles.[8] We envisioned that both 1) the problem of activating pyrroles, indoles, and carbazoles as nucleophiles and 2) the problems related to the regioselectivity in their functionalization (N, C2, or C3) and substitution of allylic fluorides (S_N2 vs. S_N2') can be addressed by using latent *N*-silyl nucleophiles (Scheme 1b). Herein, we report that *N*-silyl pyrroles, indoles, and carbazoles serve as latent *N*-nucleophiles in substitutions of allylic fluorides and enable enantioselective allylations of N-heterocycles.



Scheme 1. a) The concept of using latent nucleophiles in Lewis base catalysis. b) Latent nucleophiles in the *N*-allylation of pyrroles and indoles and the possible products.

Our initial studies of different silyl groups in the latent nucleophiles revealed that the commonly used silyl protecting groups all afforded the products of *N*-allylation in good yields when allylic fluoride **1a** (Scheme 2) was used in combination with the *N*-silyl pyrrole (see the Supporting Information for details on the optimization studies). In order to preempt

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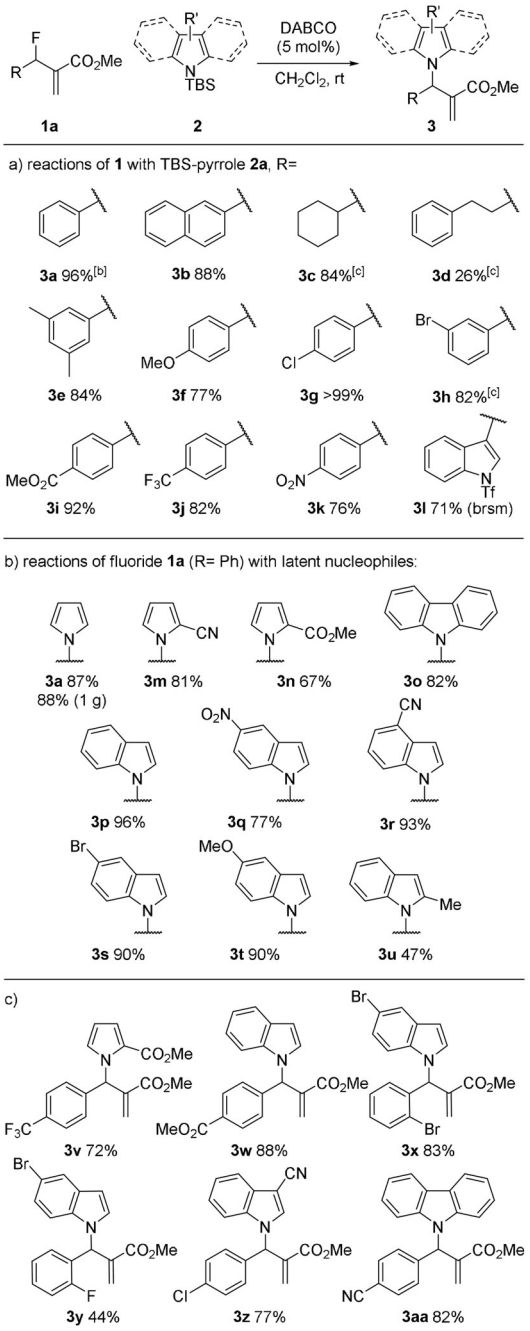


Scheme 2. a) Scope of allylic fluoride **1** in the Lewis base catalyzed allylation of 1-(*tert*-butyldimethylsilyl)pyrrole **2a**. b) Scope of *N*-silyl pyrroles, indoles, and carbazoles in the *N*-allylation with allylic fluoride **1a**. c) Various combinations of substituted *N*-silyl nucleophiles and substituted allylic fluorides. [a] The reaction of **1** with **2** (1.1 equiv) and DABCO (5 mol%) was carried out in DCM at room temperature. [b] NMR yield with Ph_3CH as the internal standard. [c] With 1.5 equiv of **2** and 10 mol% of DABCO.

interactions of the Lewis base catalyst with the silyl group of the latent nucleophile and avoid this type of nucleophile activation,[9] the bulky 1-(*tert*-butyldimethylsilyl)pyrrole was chosen for further reaction optimization, which explored how the identity of the Lewis base catalyst, solvent, catalyst loading, ratio of reaction partners, and temperature influenced the reactions outcome. N-centered Lewis base catalysts generally showed better efficacy than the corresponding P-centered Lewis bases. A slight excess of the latent nucleophile in combination with 5 mol% of DABCO as the catalyst afforded the desired products in high yields.

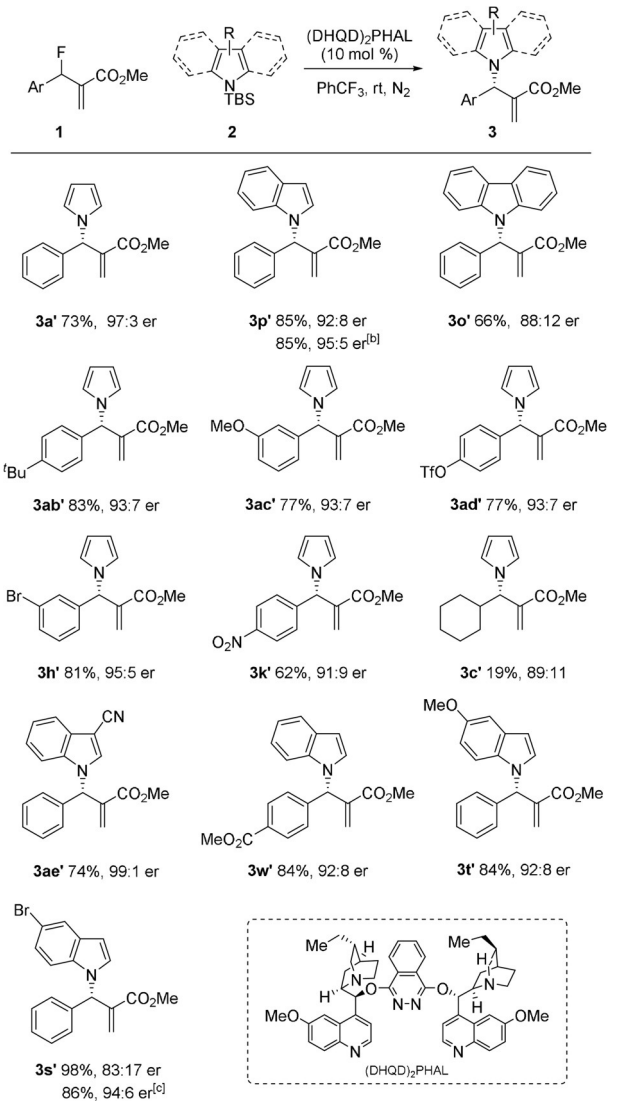
Upon optimization of the reaction conditions, the scope of the reaction was evaluated, first for the allylic fluorides and then for the *N*-silyl nucleophiles. In reactions of fluorides **1** with **2a**, good yields were observed across the board regardless of the electronic properties of the MBH fluoride (Scheme 2a). Both electron-rich (**3e–3f**) and electron-poor (**3i–3l**) allylic fluorides afforded the desired products in good yields with short reaction times (< 5 min). Alkyl fluorides also proved to be reactive but lower yields were observed for primary alkyl substituents (**3c**, **3d**). Aryl halides, good substrates for further functionalizations of the reaction products, were all well tolerated (**3g** and **3h**) as were alkyl/aryl ethers, esters, benzylic methylene groups, nitriles, and nitro compounds. Gratifyingly, no products of S_N2' substitution were observed with any of the tested substrates.

The investigation of the scope for latent nucleophiles started with a series of *N*-TBS pyrroles, which performed well and demonstrated the generality of the process (Scheme 2b). Simple *N*-silyl pyrrole and 2-substituted pyrroles all performed well as nucleophiles. Increasing the steric demands of the nucleophile, as with 2,5-dimethylpyrrole, rendered the substitution reaction prohibitively slow. Further evaluation of the reaction scope included indoles and carbazoles. Various substituted indoles performed well in the reaction, giving the desired products of substitution in good yields regardless of the electronic influences of the substituents (**3p–3u**). 2-Methylindole (**3u**) indicated the sensitivity of this reaction to steric bulk. Despite this limitation, the desired product was obtained in a yield of 47%, which could be improved by increasing catalyst loading. *N*-Silyl carbazole performed even better, with the product being isolated in 82% yield (**3o**). Importantly, these reactions were highly regioselective with respect to both coupling partners. Neither products of C2/C3 allylation of the pyrrole/indole nor of S_N2' substitution were observed in any of these experiments.

A series of experiments where various combinations of substituted nucleophilic and substituted electrophilic partners were subjected to the optimized reaction conditions further established the generality of this process (Scheme 2c) and demonstrated that even MBH fluorides with *ortho* substituents are competent substrates in these reactions (products **3x** and **3y**). With selected examples, the catalyst loading could be lowered to as little as 1 mol% of DABCO without deterioration of the yields, although the reaction times generally had to be extended for these reactions. Scalability was tested for the reaction of **1a** (1.00 g) and **2a** (1.03 g), which proceeded with equal efficiency and no changes in selectivity. Good scalability together with a plethora of methods for further product functionalization[10] make this method attractive for applications in target-oriented synthesis.

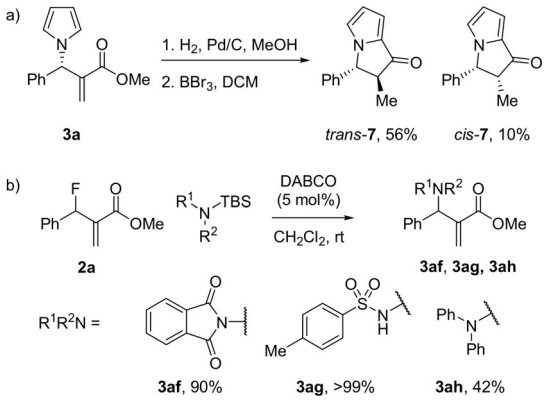
Having confirmed that the reactions with latent nucleophiles are highly regioselective and feature broad scope for both reactive partners with DABCO as the catalyst, we commenced our investigation of an enantioselective variant using chiral Lewis base catalysts. Our studies had confirmed

that N-centered Lewis base catalysts performed better in these reactions and highlighted the efficacy of DABCO, which directed our optimization efforts towards cinchona alkaloid based catalysts. We investigated how the identity of the chiral Lewis base catalyst, the reaction temperature, concentration, solvent, and the ratio of the reaction partners influenced the reaction outcome (see the Supporting Information for details). The optimized conditions included the use of 10 mol% of $(DHQD)_2PHAL$ as the chiral Lewis base catalyst in trifluorotoluene at room temperature. A clear difference in the rates of the reactions catalyzed by chiral cinchona alkaloids compared to those catalyzed by DABCO resulted in slightly lower yields (Scheme 3). *N*-Silyl pyrroles, indoles, and carbazoles all gave the products of *N*-allylation in good yields and with a good degrees of stereocontrol (**3a′**, **3p′**, **3o′**). A series of experiments showed that both electron-rich and electron-poor allylic fluorides performed well in these reactions (**3ab′**, **3ac′**, **3ad′**, **3h′**, and **3k′**), with yields of approximately 80% and enantiomeric ratios exceeding 90:10. Reactions with alkyl-substituted fluorides proved to be too slow, which allowed for competitive decomposition of the alkyl fluorides leading to lower yields, although the enantiomeric ratios for the isolated substitution products remained high. Modifying the latent nucleophiles with electron-withdrawing or -donating groups had a moderate effect on the yields and enantioselectivities, which were, in some cases, as high as 99:1 er (**3ae′**, **3w′**, **3t′**, **3s′**). Other regioisomers were not observed in any of the tested reactions. The enantioselectivities could be further improved by focused optimization for individual cases, as demonstrated for **3p′** and **3s′** where the enantiomeric ratios could be increased from 92:8 to 95:5 and from 83:17 to 94:6, respectively, simply by changing the reaction solvent. The configuration of the stereogenic center of the major enantiomer was assigned as *S* by comparison to previously reported data for **3t′**,[11] and the absolute configuration of other products was assigned by analogy.[12]



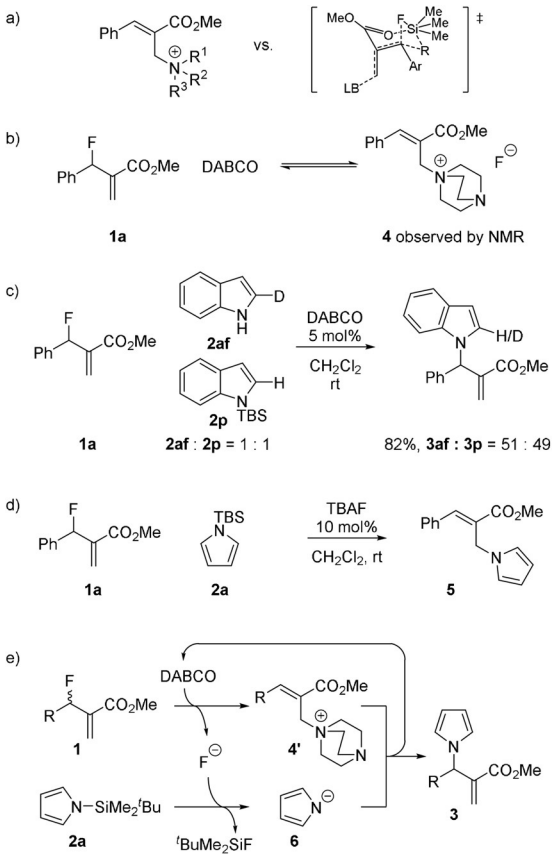
Scheme 3. Enantioselective Lewis base catalyzed allylic substitutions of allylic fluorides with *N*-silyl nucleophiles. [a] The reaction of **1** (2 equiv) with **2** and $(DHQD)_2PHAL$ (10 mol%) was carried out in $PhCF_3$ at room temperature under N_2 atmosphere. [b] 1,4-Dioxane was used as the solvent. [c] Dimethoxyethane was used as solvent.

A substitution product containing a pyrrole moiety (**3a**) proved to be useful in a short synthesis of pyrrolizinones shown to exert anti-amyloid and radical-scavenging effects (Scheme 4a).[13] Hydrogenation followed by cyclization promoted by BBr_3 afforded *trans*-**7** in 56% yield (the *cis* isomer, isolated in minor quantities, could be separated and isomerized to increase the yield of *trans*-**7**). To further demonstrate the generality and utility of the concept of using latent nucleophiles in Lewis base catalysis, a broader range of silylated *N*-nucleophiles, including phthalimide, tosylamide, and diphenylamine, were tested and shown to be competent in reactions with allylic fluorides (**3af**, **3ag**, **3ah**; Scheme 4b).



Scheme 4. a) Synthesis of pyrrolizinones that are potentially useful in the treatment of Alzheimer's disease. b) Expanded scope of *N*-nucleophiles: Phthalimide, tosylamide, and diphenylamine can also be introduced as latent nucleophile.

Our attention then turned to the mechanistic features of these processes. The reactions could proceed via allyl ammonium intermediates often evoked in substitutions of MBH acetates and carbonates (Scheme 5a).[11,14] Alternatively, a silyl-assisted cleavage of the C–F bond with simultaneous intramolecular delivery of the nucleophile (Scheme 5a) could take place.[15] When allylic fluoride **1a** was treated with DABCO in the absence of *N*-TBS pyrrole, the



Scheme 5. Selected experiments aimed at evaluating the reaction mechanism. a) Previously proposed intermediates and transition states in related reactions. $NR^1R^2R^3$ = amine/chiral cinchona catalyst; R = CF_3, alkynyl, *N*-methyltetrazole. b) Formation of ammonium salt **4** starting from **1a** without silyl assistance. c) Crossover experiment with labeled indole and a latent indole nucleophile. d) Switch in regioselectivity with TBAF as the catalyst. e) Proposed reaction mechanism.

formation of ammonium salt **4** was observed by NMR spectroscopy in situ (Scheme 5b).[16] In a crossover experiment where deuterium-labeled indole **2af** was used in an equimolar mixture with *N*-TBS indole **2p**, both indole moieties were incorporated into the reaction product (Scheme 5c), suggesting that they may equilibrate through an indolide anion. To scrutinize other reasonable pathways that would result in the same outcome, two control experiments were carried out to confirm that 1) the indole itself does not react with the allylic fluoride under the reaction conditions and 2) the TBS group is not transferred between **2af** and **2p** in the presence of DABCO. Finally, when TBAF was used as the catalyst, the reaction proceeds with high rates (reaction time < 20 min) and only the products of S_N2' substitution were observed (Scheme 5d). Based on these experiments, we propose the mechanism outlined in Scheme 5e. The allylic fluoride undergoes conjugate addition of the catalyst, which, after E1cb elimination of the fluoride ion, results in the allylic ammonium intermediate **4′**. The fluoride ion then adds to the silyl group of the *N*-silyl pyrrole/indole and after elimination forms the silyl fluoride (observed in the reaction mixture by NMR analysis) and the anionic *N*-nucleophile **6**. The activated electrophile, allyl ammonium intermediate **4′**, undergoes conjugate addition of **6** to form the product after elimination of the catalyst. The observed selectivity for the product of direct substitution of the fluoride is the consequence of two consecutive conjugate additions/eliminations. The addition rates of anion **6** to electrophile **4′** are proposed to be high because the products of S_N2' substitution were not observed in DABCO-catalyzed reactions even though competing addition of **6** to **1**, resulting in the formation of S_N2' products, occurs with high rates when TBAF is used as the catalyst.[17] This highlights the importance of the simultaneous presence of activated electrophile/nucleophile pairs in the reaction mixture and demonstrates the importance of the latent character of the nucleophile. Finally, the excellent regioselectivities and good stereocontrol observed in the presence of chiral Lewis base catalysts suggest that addition of the activated nucleophile to a non-activated electrophile does not occur.

In conclusion, the use of *N*-silyl pyrroles, indoles, and carbazoles as latent nucleophiles enables the highly regioselective *N*-allylation of these heterocycles by using allylic fluorides. When widely available chiral cinchona alkaloid based catalysts were used, the allylation products were isolated with high degrees of enantioselectivity. This is the first general enantioselective method to introduce pyrroles in Lewis base catalyzed substitution reactions. The mechanistic details of this process suggest that the concept of using latent nucleophiles in Lewis base catalysis hinges on the concurrent activation of both reaction partners, which allows for expanded reaction scope and improved selectivities. This concept may be generally applicable in a variety of reactions that depend on the use of heteroatom-centered nucleophiles.

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Conflict of interest

The authors declare no conflict of interest.

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Note

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Enantioselective Synthesis of Pyrrolizin-1-ones via Lewis Base Catalyzed N-Allylation of *N*-Silyl Pyrrole Latent Nucleophiles

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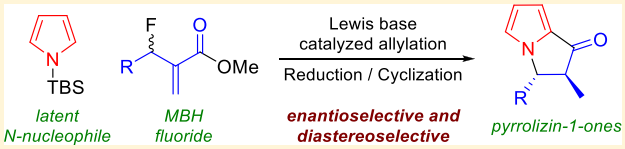
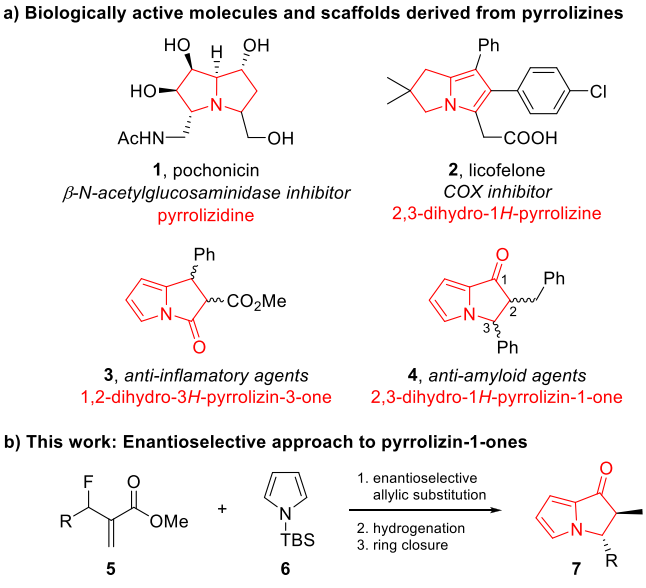
Supporting Information

ABSTRACT: Pyrrolizidine alkaloids and their derivatives often feature interesting biological activities. A class of substituted 2,3-dihydro-1*H*-pyrrolizin-1-one derivatives has been explored as a potential treatment for Alzheimer's disease, but enantioselective synthesis of these molecules is still elusive. We report that enantioselective N-allylation of *N*-silyl pyrrole latent nucleophiles with allylic fluorides followed by hydrogenation and diastereoselective Friedel−Crafts cyclization constitute an efficient synthetic route to access enantioenriched substituted 2,3-dihydro-1*H*-pyrrolizin-1-ones.



Pyrrolizidine alkaloids are a large group of plant natural products with a 1-azabicyclo[3.3.0]octane core.[1] Many of these are toxic to humans and livestock and pose a significant threat to food safety. Other members of the group exhibit medicinally relevant biological activity such as pochonicine (**1**, Scheme 1a) which has been identified as a potent *β*-*N*-acetylglucosaminidase inhibitor.[2] Among synthetic derivatives with different levels of unsaturation and oxidation of the pyrrolizidine core, the derivatives with 2,3-dihydro-1*H*-pyrrolizine, such as the dual COX/LOX inhibitor licofelone (**2**),[3] have been under intense investigation and clinical development. The ease of access to 1,2-dihydro-3*H*-pyrrolizin-3-ones (**3**) has prompted numerous SAR studies of this scaffold.[4] In contrast to this, synthetic approaches to 2,3-dihydro-1*H*-pyrrolizin-1-ones (**4**) remain scarce despite the fact that this scaffold, due to its radical scavenging and antiamyloid properties, has recently been identified as a promising platform for treatment of Alzheimer's disease.[5] The reported synthetic approaches to this scaffold lack the control of stereoselectivity; the reactions proceed with low diastereoselectivity, and the products have not been prepared in enantioenriched form.[5,6]

Scheme 1. (a) Some Biologically Active Molecules/Scaffolds Derived from Pyrrolizidine; (b) Outline of Our Approach to Enantioselective Synthesis of Substituted 2,3-Dihydro-1*H*-pyrrolizin-1-ones



Considering the possibility of easy epimerization at C2, we presumed that a successful enantioselective approach to substituted 2,3-dihydro-1*H*-pyrrolizin-1-ones would have to effectively construct the C3 stereogenic center and allow for good control of diastereoselectivity at the C2 center. We have recently reported a Lewis base catalyzed enantioselective N-allylation of pyrroles, indoles, and carbazoles which benefits from the concept of latent nucleophiles in Lewis base catalysis.[7] As these reactions construct a stereogenic center *α* to the nitrogen of the pyrrole and install the carbonyl group of the ester in an appropriate position, we saw this as an opportunity to develop a short enantioselective synthesis of substituted 2,3-dihydro-1*H*-pyrrolizin-1-ones. Here, we report the development of a short route to this scaffold that consists of enantioselective N-allylation of *N*-silyl pyrroles followed by reduction and diastereoselective cyclization (Scheme 1b).

Our work on Lewis base catalyzed N-allylation commenced as a proof of concept study for the use of latent nucleophiles in Lewis base catalysis. This concept is aimed at expanding the scope for nucleophiles and allowing for better control of chemo-, regio-, and stereoselectivity in Lewis base catalyzed reactions.[8] It is a common occurrence that heteroatom

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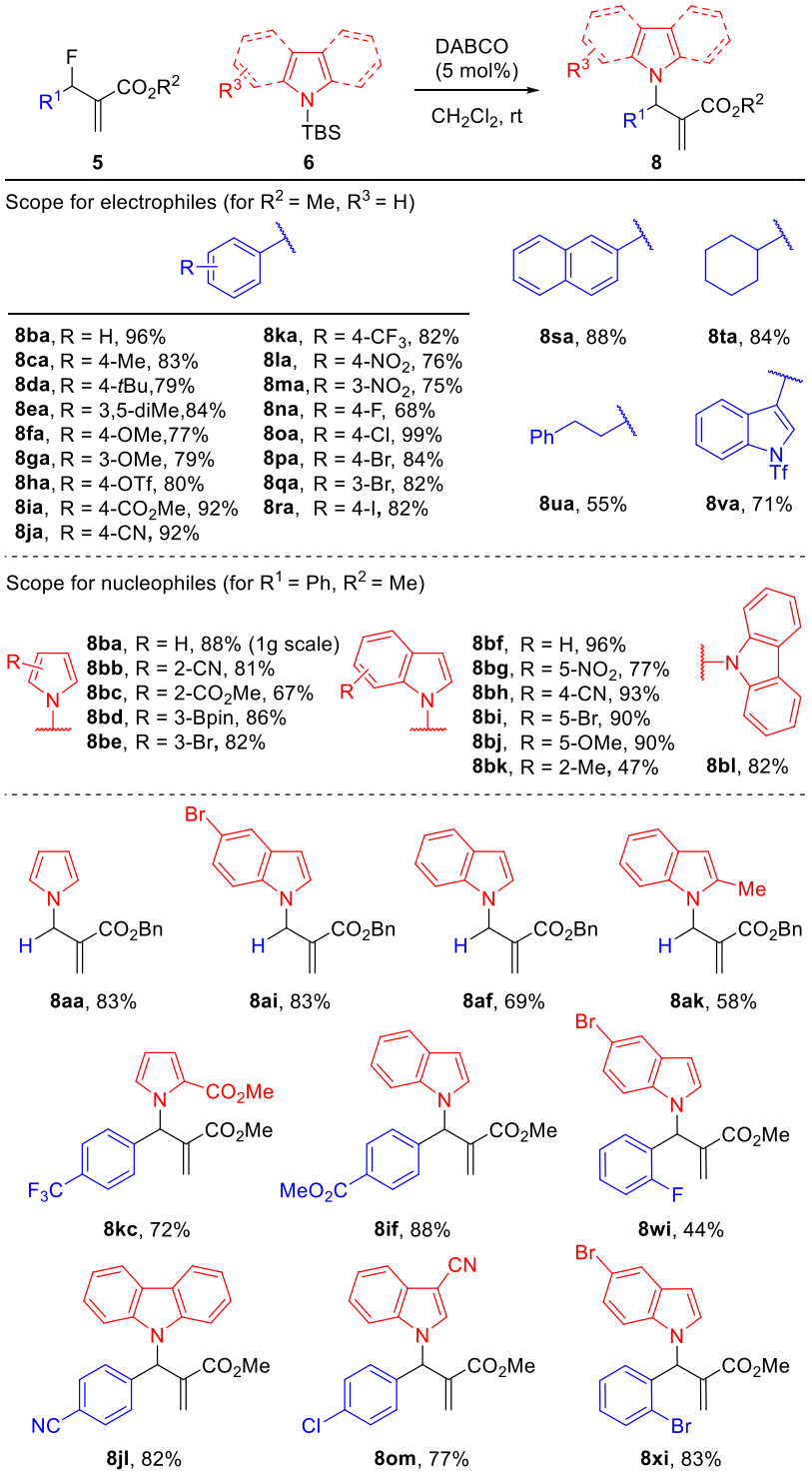
Scheme 2. N-Allylation of *N*-Silyl Latent Nucleophiles 6 with Various Allylic Fluorides 5 in the Presence of DABCO[a]



[a]Isolated yields of the *N*-allyl pyrroles, indoles, and carbazoles are shown. Conditions: 5 mol % DABCO, 1.1 equiv of **6**, CH_2Cl_2 (0.1 M). Numbering scheme follows the following formula: **5x** + **6y** gives **8xy**.

nucleophiles compete and outperform the Lewis base catalyst thus preventing the development of enantioselective Lewis base catalyzed reactions.[9] We hypothesized that lowering the nucleophilicity of the nucleophilic reaction partner would increase the reaction selectivity and allow flexibility in the choice of catalyst. For N-centered nucleophiles, introducing a silyl group at the nitrogen atom lowers the nucleophilicity of the derivative (compared to the corresponding N−H nucleophile).[10] Such latent nucleophiles require an appropriate trigger to participate in the reaction. If activation of the nucleophile depends on the activation of the electrophile, by mediacy of the leaving group from the electrophile, the activated nucleophile is produced only when the activated electrophile is already present in the reaction mixture allowing for the bimolecular reaction of the two activated reactants to outcompete other possible pathways.[7] If activation of a *N*-silyl

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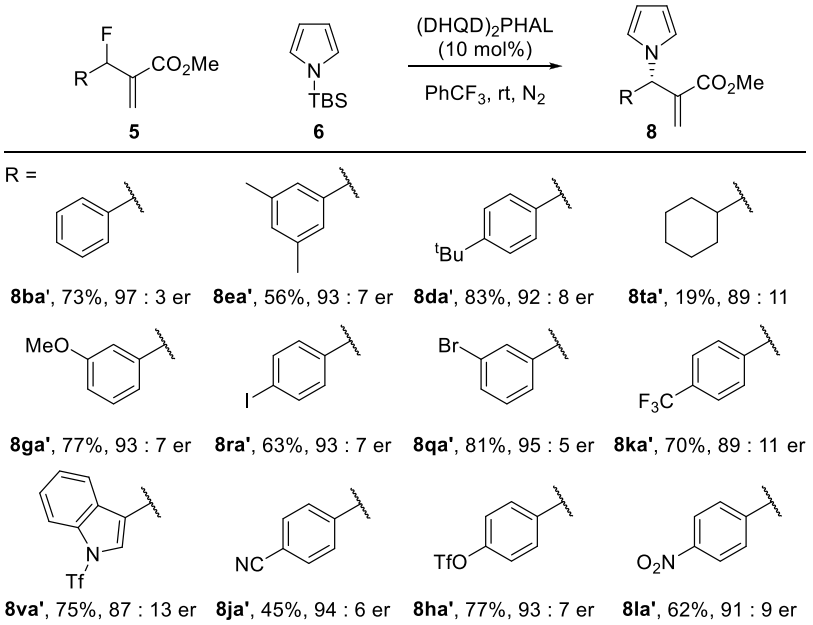
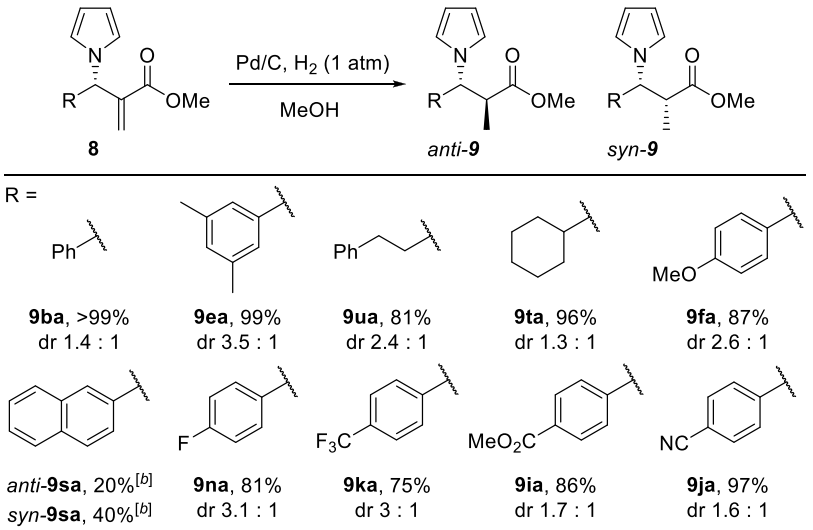
Scheme 3. Enantioselective Allylic Substitution with *N*-TBS Pyrrole 6a[a]



[a]Isolated yields and enantiomeric ratios determined by HPLC on chiral stationary phase are shown. The absolute configuration of the *N*-allyl pyrroles **8** is assigned based on analogy to previously reported material. Conditions: 10 mol % $DHQD_2(PHAL)$, 2 equiv of **5**, $PhCF_3$ (0.2 M).

Scheme 4. Hydrogenation of *N*-allyl Pyrroles 8[a]



[a]Isolated yields for the inseparable mixtures of *anti* and *syn* diastereomers and the diastereomeric ratio determined by ^{1}H NMR are shown. Relative stereochemistry is tentatively assigned based on ^{1}H NMR and the results of cyclization experiments. Reactions were performed with both racemic material and enantioenriched material (for **8ba** and **8ea**). Conditions: 10 mol % Pd/C, 1 atm. H_2, MeOH. [b]Isolated yields of *anti*-**9sa** and *syn*-**9sa** which do not account for losses of each isomer during purification.

latent nucleophile is to be dependent on activation of an electrophile, mediacy of a fluoride ion as a leaving group would be a suitable trigger which makes Morita–Baylis–Hillman derived allylic fluorides a fitting reaction partner.

The reactions of various substituted allylic fluorides with *N*-TBS pyrrole have been evaluated in the presence of catalytic amounts of DABCO (Scheme 2). This exercise demonstrated a broad electrophile scope with reactions proceeding with good yields for both primary (**8aa**) and secondary allylic fluorides regardless of their electronic properties (**8ba**–**8va**). The same is true for a variety of substituted pyrroles, indoles, and carbazoles (**8ba**–**8bl**). Electronically matched and mismatched sets of nucleophiles and electrophiles performed equally well in these reactions with generally good yields (**8kc**, **8if**, **8wi**, **8jl**, **8om**, **8xi**). Even sterically demanding nucleophiles/electrophiles, previously reported not to be reactive in related reactions, performed reasonably well with yields of around 50% (**8bk** and **8wi**).[11] The reactions proceeded with excellent regioselectivity: C2/C3 allylation of N-heterocycles and S_N2' type products were not observed in any of the reactions.

The comprehensive study of the reaction scope led to investigation of enantioselective N-allylation of pyrrole in the presence of a chiral Lewis base catalyst (Scheme 3). The cinchona alkaloid based catalysts, well-established in similar

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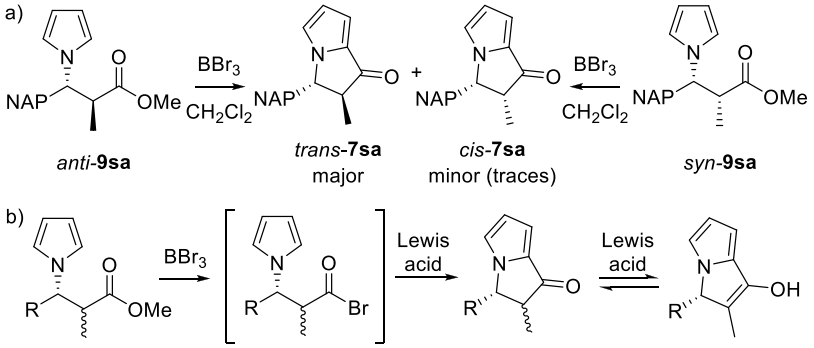
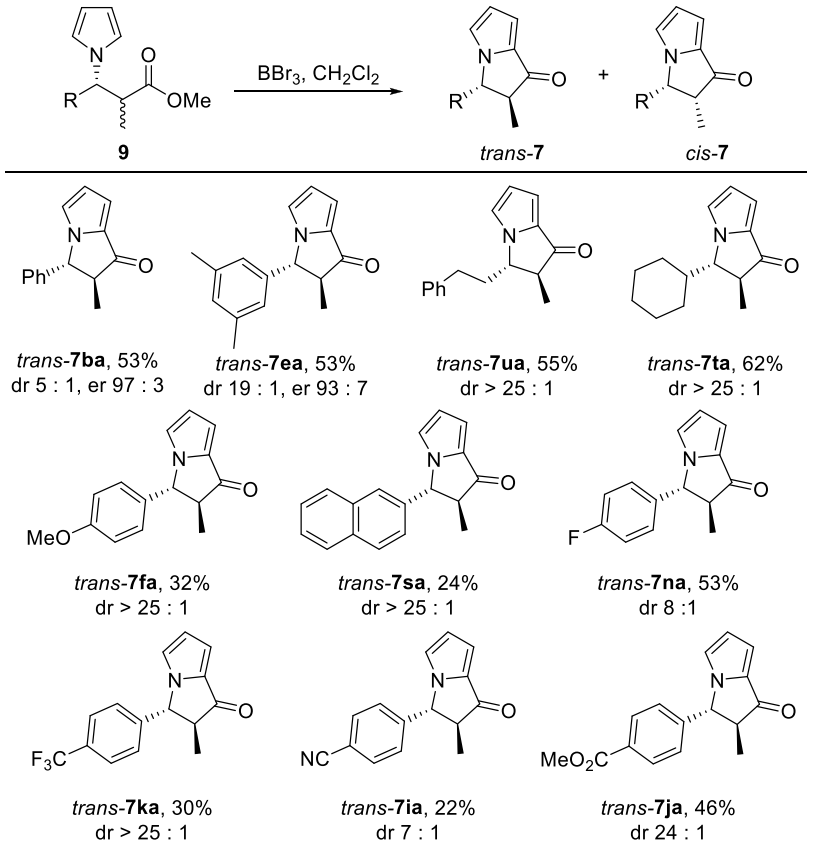
Scheme 5. (a) Evaluation of the Diastereoselectivity for Cyclizations of *anti*-9sa and *syn*-9sa and Plausible Mechanism for the Isomerization; (b) Proposed Mechanism for Cyclization and Isomerization of 9



Scheme 6. Diastereoselective Cyclization of Mixtures of *anti*-9 and *syn*-9 to Pyrrolizinones 7[a]



[a]Isolated yields for the major diastereomer and the diastereomeric ratio are shown. Conditions: 1.05 equiv of BBr_3, CH_2Cl_2 (0.1 M).

allylic substitutions,[12] performed well in these reactions too. $(DHQD)_2PHAL$, $(DHQD)_2AQN$, and $(DHQ)_2PHAL$ all gave the desired products in good yields and good enantioselectivities. The reactions proceed as kinetic resolutions of the racemic allylic fluorides,[13] which is why the optimized conditions included an excess of the allylic fluoride in the presence of 10 mol % of $(DHQD)_2PHAL$ in trifluorotoluene at ambient temperature. The excess of allylic fluoride was required to offset the low reaction rates caused by the significantly lower reactivity of the chiral catalysts and not to increase the enantioselectivities suggesting that the reactions of the two enantiomeric allylic fluorides are enantioconvergent. The enantiomeric ratios for pyrrole nucleophiles were generally higher than 90:10, and a short, focused optimization of the reaction conditions for a specific substrate can be conducted to improve enantioselectivity.[7] The yields remained good regardless of the electronic properties of the allylic fluoride (45−83%, Scheme 3). The lowered reactivity of the catalyst also allowed for competitive elimination of the fluoride from alkyl substituted allylic fluorides which led to lower yields (**8ta′**).

Further investigation was focused on the alkene reduction and the cyclization to produce the desired pyrrolizinones. The main concerns while developing the two-step procedure were the preservation of the C3 stereogenic center, the control of diastereoselectivity at C2, and the operational simplicity of the sequence. Attempts to carry out cyclization followed by reduction failed due to the lability of the Michael acceptor under acidic conditions. This prompted exploration of the reverse sequence: reduction followed by cyclization.

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With a large pool of methods for 1,4-reduction to choose from,[14] we opted for the simplest heterogeneous hydrogenation of **8** over the palladium catalyst which provided the desired reduction product in excellent yield but with low diastereoselectivity (Scheme 4). This was not seen as a setback, as it allowed access to both diastereomers of the reduced products which were of interest in subsequent cyclization attempts. The difficulties in separating the two diastereomers, however, brought about the search for a substrate that would allow the easier separation of the two isomers. All attempted reductions proceeded with good yields and low diastereoselectivities ranging from 1.3:1 to 3.5:1 without an obvious trend (Scheme 4).[4] It was only the *syn*- and *anti*-isomers of naphthyl substituted ester **9sa** that could be separated by column chromatography.

Having access to both *syn*- and *anti*-diastereomers of **9sa**, the conditions for cyclization reactions became a focal point. In the presence of a pyrrole and an aryl substituent at C3, Friedel–Crafts-type cyclization was a logical choice for cyclization, as we expected the electron-rich pyrrole to outperform the aryl substituent. On the other hand, mild reaction conditions were desired in order to minimize the epimerization at C2. To reconcile these requirements, numerous Lewis and Brønsted acids ($AlCl_3$, $Ti(O^iPr)_4$, BF_3, TMSOTf, and TfOH among others) were tested as potential promotors of the cyclization to no avail. Only the treatment with BBr_3 afforded the desired cyclization product, albeit in moderate yield.[15] This suggested the *in situ* formation of an acyl bromide which further reacts to form the pyrrolizinone (see Scheme 5). To test this, the ester was hydrolyzed, and the corresponding acid was treated with PBr_3 to form the cyclization product although in lower yields.

Independent cyclization of *syn*-**9sa** and *anti*-**9sa**, somewhat surprisingly, afforded the same isomer of **7sa** as the major cyclization product tentatively assigned as *trans*-**7sa** based on the $^3J_{H-H}$ coupling constants for C2 and C3 protons. When these reactions were stopped at ∼50% conversion, the reisolated starting material was unchanged suggesting that isomerization happens upon cyclization. With three sp^2 atoms in the pyrrolidinone ring, we expected the low energy conformations to be rather flat which would cause significant *gauche* interactions between C2 and C3 substituents in the *cis* isomer of **7** making the *trans* isomer increasingly more stable than the *cis* as the substituents become larger (as in the case of naphthyl derivative **7sa**).

Since the configuration of **9** does not appear to significantly influence the diastereoselectivity in the cyclization to form *cis*- and *trans*-**7** (although it may influence the reaction rates and overall yield), we carried out BBr_3 promoted cyclization using mixtures of diastereomers for a series of *N*-allyl pyrroles **9** (Scheme 6). The desired pyrrolizinones (Scheme 6) were isolated with good to excellent diastereoselectivity between 5:1 and >25:1. The diastereomers could be separated in each case with the *trans*-isomer being the major product in all attempted cyclizations. Assignment of the *cis* and *trans* isomers was made based on ^{1}H NMR spectra and the $^3J_{H-H}$ coupling constants for C2 and C3 protons which were consistent across the series with values of around 4.8 Hz for the *trans*-**7** and around 7.7 Hz for *cis*-**7**, the latter being indicative of the close to *syn*-periplanar arrangement of these protons in *cis*-**7**. The isolated yields for the major diastereomers range from 22% to 62% (Scheme 6). These moderate yields are likely a consequence of the rather harsh reaction conditions and the side reactions which include competitive degradation of ether, ester, trifluoromethyl, and nitrile substituents (**7fa**, **7ka**, **7ia**, and **7ja**),[16] and intramolecular electrophilic aromatic substitution on the C3-aryl substituent. The substrates with alkyl substituents, and therefore with no opportunity for the competing Friedel–Crafts involving the C3 substituent, performed much better in the cyclization reactions to produce **7ua** and **7ta**. Finally, when enantioenriched *N*-allyl pyrroles **8** were used in the two-step sequence, the yields and diastereoselectivity in both hydrogenation and cyclization reactions remained unaffected. The same is true for the configuration at C3 and therefore the enantiomeric ratios of the *trans*-**7** products. Products *trans*-**7ba** and *trans*-**7ea**, for example, were isolated with enantiomeric ratios of 97:3 and 93:7, respectively, which matches that of the of starting materials **8ba′** and **8ea′**.

In conclusion, the three-step sequence of pyrrole N-allylation followed by simple Pd-catalyzed hydrogenation and BBr_3 promoted cyclization is an effective route for the synthesis of substituted 2,3-dihydro-1*H*-pyrrolizin-1-ones. The concept of latent nucleophiles in the Lewis base catalysis is a powerful tool for the development of enantioselective allylic substitutions with a broad scope for both reaction partners. The use of *N*-TBS pyrrole as a latent nucleophile in combination with allylic fluorides and common chiral Lewis base catalysts allows for the enantioselective N-allylation of pyrrole and, for the first time, enables the synthesis of enantioenriched pyrrolizin-1-ones via the said three-step sequence. These enantioenriched materials are required for further biological evaluation of their radical scavenging and antiamyloid properties which will be reported in due course.

EXPERIMENTAL SECTION

General Remarks. All the chemicals that are not mentioned in the subsequent parts were purchased from Merck, Alfa Aesar, Acros Organics, ABCR, Fluorochem or TCI and used without further purification. The solvents if needed were dried according to standard laboratory practices. For column chromatography and TLC (SiO_2, 60M, pore size 0.04–0.063 mm), products of Machery-Nagel were used. The TLC-glass-plates DURASIL consisted of a 0.25 mm layer of silica 60 with Fluorescence indicator UV254. TLCs were checked under UV light (254 or 365 nm) and stained with an aq. $KMnO_4$ solution, PMA-stain, or DNP or PAA solution. Reaction monitoring using GC-MS was performed using HP 6890, capillary column DB5-MS, and Agilent 5973 MSD. The default method was 70 °C (2 min), ramp 20 °C/min to 270 °C, hold 10 min. Injector temperature 250 °C, Aux temperature 275 °C. All ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured with a BRUKER 250 (^{13}C), BRUKER Fourier 300 (^{1}H, ^{13}C), or a BRUKER Avance 400 spectrometer (^{1}H, ^{13}C, ^{19}F). The chemical shift of each signal was registered in ppm. For ^{1}H and ^{13}C measurements, the chemical shift refers to TMS, showing a signal at 0 ppm. As an internal standard, the remaining protons or respectively the carbons of the corresponding deuterated solvent were used ($CDCl_3$, 7.26 ppm (^{1}H NMR), 77.16 ppm (^{13}C NMR)). The chemical shift of the fluorine NMR was determined indirectly. For carbon spectra, a broad-band decoupling was performed. Enantiomeric excess was determined by HPLC analysis on Phenomenex Lux Cellulose-1 columns. High-resolution mass spectra (HRMS) were measured with EI or ESI ionization by the MS platform. A chromatographic purification was performed before each measurement. The Thermo Q-Exactive plus device for ESI-mass spectra was coupled to a binary UHPLC system using orbitrap as the mass analyzer. For EI-measurement, a GC system was coupled to the Thermo Q-Exactive (quadrupole) GC Orbitrap device. All the IR spectra were measured using the Shimadzu IR-Affinity-1 (FTIR) device.

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Synthesis of Morita–Baylis–Hillman (MBH) Fluorides **5**. DAST (1.1 or 1.2 equiv) was added to CH_2Cl_2 at −78 °C. To this, a precooled solution of MBH adduct (1 equiv) in CH_2Cl_2 was added slowly (overall concentration MBH 0.25 M in CH_2Cl_2). The mixture was stirred for 30 min and then quenched with sat. $NaHCO_3$ solution. The mixture was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography using either ethyl acetate in petroleum ether or ether in petroleum ether. The data for the known compounds **5a**,[17] **5b**, **5c**, **5g**, **5k**, **5l**, **5m**, **5n**, **5o**, **5p**, **5q**, **5s**, **5t**, **5v**[13] and **5d**, **5e**, **5f**, **5h**, **5i**, **5j**, **5u**[7] are consistent with previous reports.

*Methyl 2-((4-Iodophenyl)fluoromethyl)acrylate (**5r**).* 4-iodo-benzaldehyde (2.00 g, 8.60 mmol mmol) was treated with DABCO (0.48 g, 4.30 mmol) in methyl acrylate (1.48 g, 17.2 mmol) and stirred at ambient temperature until judged completed by TLC. The crude mixture was directly subjected to column chromatography (silica) using ethyl acetate and petroleum ether (15:85) as solvent system to give the corresponding alcohol, methyl 2-(hydroxy(4-iodo)methyl)-acrylate as a colorless solid. Yield: 1.34 g, 4.21 mmol, 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.67 (d, J = 8.8 Hz, 2H), 7.19−7.10 (d, J = 8.8 Hz, 2H), 6.36 (s, 1H), 5.85 (s, 1 H), 5.51 (d, J = 4.5 Hz, 1H), 3.75 (s, 3H), 3.16 (s. 1H). ^{13}C{1H} NMR (63 MHz, $CDCl_3$) δ 167.5, 142.4, 141.9, 138.4, 129.4, 127.4, 94.4, 73.8, 53.0. HRMS [EI]: m/z calculated for $C_{11}H_{11}IO_3$ $[M]^+$ 317.9747; found 317.9746. IR (ATR): ν = 3441 (br, w), 1709, (vs), 1420 (m), 1146 (vs), 1138 (s), 1007 (vs) cm^{-1}. The corresponding MBH fluoride was prepared by general procedure for synthesis of Morita−Baylis−Hillman fluorides. Yield: colorless solid, 434 mg, 1.36 mmol, 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 2H), 7.16 (d, $^3J_{H,H}$ = 9.4 Hz, 2H), 6.48 (d, J = 2.8 Hz, 1H), 6.24 (d, J = 45.8 Hz, 1H), 6.05 (s, 1H), 3.74 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 165.0 (d, J = 6.4 Hz), 138.9 (d, J = 22.9 Hz), 137.7, 137.1 (d, J = 20.8 Hz), 128.9 (d, i = 5.6 Hz), 126.2 (d, J = 8.8 Hz), 90.2 (d, J = 174.9 Hz), 52.1.^{19}F NMR (377 MHz, $CDCl_3$) δ −172.54 (d, J = 45.8 Hz). HRMS [EI]: m/z calculated for $C_{11}H_{10}FIO_2$ $[M]^+$ 319.9704, found 319.9702. IR (ATR): ν = 2959(w), 1713 (s), 1273 (s) 1165 (m), 964 (s), 806 (s) cm^{-1}.

Synthesis of N-Silyl-N-heterocycles **6**.[7] Under a nitrogen atmosphere, the heterocycle (1 equiv) was dissolved in THF cooled to −78 °C, and then *n*-BuLi (1.1 equiv) or NaH (1.1 equiv) was added and stirred at this temperature for 15 min. TBS-chloride (1.2 equiv) was added portionwise. The reaction mixture was allowed to warm to room temperature. The reaction was quenched with water and then extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude mixtures were either distilled or subjected to column chromatography using ethyl acetate in petroleum ether. The analytical data for known compounds **6b**, **6c**, **6h**, **6l**,[7] **6f**, **6k**,[18] and **6j**[19] matched the previously reported data. Compounds **6a**, **6d** (TIPS derivative), **6e** (TIPC derivative), **6g**, and **6i** are commercially available.

Substitution of Allylic Fluorides. The TBS protected pyrrole, indole, or carbazole **6** (for **6a**: 1.04 g, 5.67 mmol) and DABCO (28.9 mg, 0.26 mmol) were dissolved in CH_2Cl_2 (15 mL). To this, a solution of allylic fluoride (for **5b**: 1.00 g, 5.15 mmol) in CH_2Cl_2 (15 mL) was added slowly. After the completion of the reaction (monitored by TLC), the mixture was concentrated and purified by flash column chromatography using ethyl acetate in petroleum ether.

*Menzyl 2-((1H-Pyrrol-1-yl)methyl)acrylate (**8aa**).* Yield: colorless oil, 23.8 mg, 0.100 mmol, 83%. Chromatography: ethyl acetate/petroleum ether 10:90. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (s, 5H), 6.69 (t, J = 2.1 Hz, 2H), 6.36 (d, J = 1.1 Hz, 1H), 6.22 (t, J = 2.1 Hz, 2H), 5.35 (d, J = 0.9 Hz, 1H), 5.26 (s, 2H), 4.80 (s, 2H). ^{13}C{1H} NMR (63 MHz, CDCl3) δ 166.2, 138.8, 136.5, 129.5, M29.3, 129.1, 127.5, 122.1, 109.5, 67.7, 50.9. HRMS [ESI]: m/z calculated for $C_{15}H_{15}NO_2$ $[M]^+$ 241.1097, found 241.1097. IR (ATR): ν = 2924 (w), 1713 (s), 1288 (m), 1134 (m), 1088 (m), 725 (s) cm^{-1}.

*Methyl 2-(Phenyl(1H-pyrrol-1-yl)methyl)acrylate (**8ba**).*[7] Yield: colorless solid, 1.09 g, 5.15 mmol, 88%. Chromatography: ethyl acetate/petroleum ether 5:95.

*Methyl 2-((1H-Pyrrol-1-yl)(p-tolyl)methyl)acrylate (**8ca**).* Yield: colorless oil, 65.2 mg, 0.255 mmol, 83%. Chromatography: ethyl acetate/petroleum ether 5:95. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 6.51 (t, J = 2.1 Hz, 2H), 6.37 (d, J = 1.0 Hz, 1H), 6.23 (s, 1H), 6.07 (t, J = 2.2 Hz, 2H), 5.13 (dd, J = 1.6, 0.8 Hz, 1H), 3.63 (s, 3H), 2.26 (s, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 166.1, 141.2, 138.0, 135.1, 129.4, 127.9, 127.5, 120.7, 108.3, 62.6, 52.2, 21.1. HRMS [ESI]: m/z calculated for $C_{16}H_{17}NO_2$ $[M]^+$ 255.1254, found 255.1255. IR (ATR): ν = 2951 (w), 1721 (vs), 1435 (m), 1273 (s), 1138 (vs), 721 (vs) cm^{-1}.

*Methyl 2-((4-(tert-Butyl)phenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8da**).*[7] Yield: colorless oil, 63.3 mg, 0.210 mmol, 79%. Chromatography: ethyl acetate/petroleum ether 7.5:92.5.

*Methyl 2-((3,5-Dimethylphenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8ea**).*[7] Yield: colorless oil, 77.0 mg, 0.29 mmol, 84%. Chromatography: diethyl ether/petroleum ether 5:95

*Methyl 2-((4-Methoxyphenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8fa**).*[7] Yield: colorless solid, 35.7 mg, 0.130 mmol, 77%. Chromatography: ethyl acetate/petroleum ether 10:90

*Methyl 2-((3-Methoxyphenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8ga**).*[7] Yield: colorless oil, 49.0 mg, 0.18 mmol, 84%. Chromatography: ethyl acetate/petroleum ether 10:90

*Methyl 2-((1H-Pyrrol-1-yl)(4-(((trifluoromethyl)sulfonyl)oxy)-phenyl)methyl)acrylate (**8ha**).*[7] Yield: colorless oil, 65.5 mg, 0.17 mmol, 80%. Chromatography: ethyl acetate/petroleum ether 20:80

*Methyl 4-(2-(Methoxycarbonyl)-1-(1H-pyrrol-1-yl)allyl)benzoate (**8ia**).*[7] Yield: colorless solid, 88.2 mg, 0.29 mmol, 92%. Chromatography: ethyl acetate/petroleum ether 15:85.

*Methyl 2-((4-Cyanophenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8ja**).* Yield: colorless oil, 41.0 mg, 0.15 mmol, 92%. Chromatography: ethyl acetate/petroleum ether 10:90 ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73−7.60 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.61 (t, J = 2.1 Hz, 1H), 6.57 (s, 1H), 6.42 (s, 1H), 6.23 (t, J = 2.2 Hz) 5.30 (s, 1H), 3.77 (s, 3H). ^{13}C{1H} NMR (63 MHz, $CDCl_3$) δ 166.5, 144.8, 140.8, 133.5, 130.0, 129.4, 121.5, 119.3, 113.1, 110.1, 63.1, 53.4. HRMS [EI]: m/z calculated for $C_{16}H_{14}N_2O_2$ $[M]^+$ 266.1050, found 266.1052. IR (ATR): ν = 2955 (w), 2230 (w), 1721 (s), 1273 (m), 1142 (s), 725 (vs) cm^{-1}.

*Methyl 2-((4-(Trifluormethyl)-phenyl)(1H-pyrrol-1-yl)methyl)-acrylate (**8ka**).*[7] Yield: colorless solid, 60.5 mg, 0.20 mmol, 82%. %. Chromatography: ethyl acetate/petroleum ether 10:90

*Methyl 2-((4-Nitrophenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8la**).*[7] Yield: colorless oil, 30.6 mg, 0.11 mmol, 79%. Chromatography: diethyl ether: petroleum ether 30:70

*Methyl 4-((3-Nitrophenyl)(1H-pyrrol-1-yl)allyl)benzoate (**8ma**).* Yield: colorless oil, 30.0 mg, 0.10 mmol, 71%. Chromatography: ethyl acetate/petroleum ether 10:90 ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.22 (dd, J = 8.0, 1.9 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.68−7.39 (m, 2H), 6.62 (dd, J = 5.0, 2.7 Hz, 3H), 6.47 (s, 1H), 6.24 (d, J = 2.1 Hz, 2H), 5.33 (s, 1H), 3.77 (d, J = 1.6 Hz, 3H). ^{13}C{1H} NMR (63 MHz, $CDCl_3$) δ 166.4, 149.5, 141.6, 140.8, 134.8, 130.8, 123.0, 124.2, 123.7, 121.5, 110.2, 62.9, 53.4. HRMS [ESI]: m/z calculated for $C_{15}H_{14}N_2O_4$ $[M]^+$ 286.0954, found 286.0948. IR (ATR): ν = 2955 (w), 1721 (s), 1528 (vs), 1346 (vs), 1273 (s), 725 (vs) cm^{-1}.

*Methyl 2-((4-Fluorophenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8na**).* Yield: colorless solid, 62.1 mg, 0.24 mmol, 68%. Chromatography: ethyl acetate/petroleum ether 10:90. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 8.6, 5.3 Hz, 2H), 7.07 (t, J = 8.6 Hz, 2H), 6.61 (t, J = 2.1 Hz, 2H), 6.50 (s, 1H), 6.36 (s, 1H), 6.20 (t, J = 2.1 Hz, 2H), 5.25 (d, J = 2.0 Hz, 1H), 3.75 (s, 3H). ^{13}C{1H} NMR (101 MHz,) δ 165.9, 162.5 (d, J_{C-F} = 247.2 Hz), 141.0, 134.0 (d, J_{C-F} = 3.3 Hz), 129.7 (d, J_{C-F} = 8.2 Hz), 127.9, 120.6, 115.7 (d, J_{C-F} = 21.7 Hz), 108.6, 62.1, 52.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ −113.82. HRMS [ESI]: m/z calculated for $C_{15}H_{14}FNO_2$ $[M]^+$ 259.1003, found 259.1007. IR (ATR): ν = 2951 (w), 1717 (s), 1508 (s), 1265 (m), 1219 (m) 1134 (m), 733 (vs) cm^{-1}.

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*Methyl 2-((4-Chlorophenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8oa**).*[7] Yield: colorless oil, 40.0 mg, 0.14 mmol, >99%. Chromatography: ethyl acetate/petroleum ether 15:85.

*Methyl 2-((4-Bromophenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8pa**).* Yield: colorless solid, 61.7 mg, 0.19 mmol, 84%. Chromatography: ethyl acetate/petroleum ether 10:90 ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.58 (t, J = 2.2 Hz, 2H), 6.49 (s, 1H), 6.30 (s, 1H), 6.17 (t, J = 2.2 Hz, 2H), 5.23 (s, 1H), 3.72 (s, 3H). ^{13}C{1H} NMR (63 MHz, $CDCl_3$) δ 166.7, 141.5, 138.3, 132.8, 130.5, 129.1, 123.2, 121.5, 109.6, 63.1, 53.2. HRMS [EI]: m/z calculated for $C_{15}H_{14}NO_2BrNa$ $[M + Na]^+$ 342.0106, found 342.0106. IR (ATR): ν = 2951 (w), 1721 (vs), 1489 (m), 1273 (s), 1142 (s), 1072 (m), 725 (vs) cm^{-1}.

*Methyl 2-((3-Bromophenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8qa**).*[7] Yield: colorless oil, 58.0 mg, 0.18 mmol, 82%. Chromatography: ethyl acetate/petroleum ether 10:90.

*Methyl 2-((4-Iodophenyl)(1H-pyrrol-1-yl)methyl)acrylate (**8ra**).* Yield: colorless solid, 69.0 mg, 0.19 mmol, 82%. Chromatography: diethyl ether/petroleum ether 10:90 ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.50 (m, 2H), 6.96−6.80 (m, 2H), 6.57 (t, J = 2.1 Hz, 2H), 6.48 (t, J = 0.8 Hz, 1H), 6.29 (s, 1H), 6.17 (t, J = 2.2 Hz, 2H), 5.24 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 165.8, 140.6, 138.1, 137.9, 129.9, 128.3, 120.7, 108.8, 94.1, 62.3, 52.4. HRMS [ESI]: m/z calculated for $C_{15}H_{14}INO_2$ $[M]^+$ 367.0064, found 367.0066. IR (ATR): ν = 2947 (w), 1697 (vs), 1481 (m), 1439 (m), 1269 (m), 1142 (s), 1084 (s), 737 (vs) cm^{-1}.

*Methyl 2-(Naphthalen-2-yl(1H-pyrrol-1-yl)methyl)acrylate (**8sa**).*[7] Yield: yellow solid, 61.4 mg, 0.21 mmol, 88%. Chromatography: ethyl acetate/petroleum ether 10:90.

*Methyl 2-(Cyclohexyl(1H-pyrrol-1-yl)methyl)acrylate (**8ta**).*[7] Yield: colorless oil, 26.5 mg, 0.11 mmol, 84%. Chromatography: diethyl ether/petroleum ether 5:95.

*Methyl 2-Methylene-5-phenyl-3-(1H-pyrrol-1-yl)pentanoate (**8ua**).*[7] Yield: colorless oil, 45.5 mg, 0.169 mmol, 55%. Chromatography: ethyl acetate/petroleum ether 2.5:97.5.

*Methyl 2-((1H-Pyrrol-1-yl)(1-((trifluoromethyl)sulfonyl)-1H-indol-3-yl)methyl)acrylate (**8va**).*[7] Yield: colorless wax, 38.3 mg, 0.09 mmol, 71%. Chromatography: diethyl ether/petroleum ether 5:95.

*Methyl 2-((2-Cyano-1H-pyrrol-1-yl)(phenyl)methyl)acrylate (**8bb**).*[7] Yield: colorless oil, 26.6 mg, 0.100 mmol, 67%. Chromatography: ethyl acetate/petroleum ether 10:90.

*Methyl 1-(2-(Methoxycarbonyl)-1-phenylallyl)-1H-pyrrole-2-carboxylate (**8bc**).*[7] Yield: brown oil, 37.5 mg, 0.125 mmol, 67%. Chromatography: ethyl acetate/petroleum ether 10:90.

*Methyl 2-((1H-Indol-1-yl)(phenyl)methyl)acrylate (**8bf**).*[12c] Yield: colorless solid, 86.2 mg, 0.285 mmol, 96%. Chromatography: ethyl acetate/petroleum ether 10:90.

*Methyl 2-((5-Nitro-1H-indol-1-yl)(phenyl)methyl)acrylate (**8bg**).*[7] Yield: brown solid, 49.3 mg, 0.147 mmol, 77%. Chromatography: ethyl acetate/petroleum ether 15:85.

*Methyl 2-((4-Cyano-1H-indol-1-yl)(phenyl)methyl)acrylate (**8bh**).*[7] Yield: colorless oil, 7.8 mg, 0.025 mmol, 93%. Chromatography: ethyl acetate/petroleum ether 15:85.

*Methyl 2-((5-Bromo-1H-indol-1-yl)(phenyl)methyl)acrylate (**8bi**).*[12c] Yield: colorless oil, 60.7 mg, 0.163 mmol, 90%. Chromatography: ethyl acetate/petroleum ether 15:85.

*Methyl 2-((5-Methoxy-1H-indol-1-yl)(phenyl)methyl)acrylate (**8bj**).*[7] Yield: colorless solid, 74.0 mg, 0.22 mmol, 88%. Chromatography: ethyl acetate/petroleum ether 15:85.

*Methyl 2-((2-Methyl-1H-indol-1-yl)(phenyl)methyl)acrylate (**8bk**).*[7] Yield: colorless oil, 37.6 mg, 0.123 mmol, 47%. Chromatography: ethyl acetate/petroleum ether 5:95.

*Methyl 2-((9H-Carbazol-9-yl)(phenyl)methyl)acrylate (**8bl**).*[7] Yield: colorless solid, 52.4 mg, 0.15 mmol, 82%. Chromatography: ethyl acetate/petroleum ether 10:90.

*Benzyl 2-((5-Bromo-1H-indol-1-yl)methyl)acrylate (**8ai**).* Yield: colorless solid, 23.7 mg, 0.064 mmol, 89%. Chromatography: ethyl acetate/petroleum ether 10:90 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 1.8 Hz, 1H), 7.39 (dd, J = 5.0, 3.3 Hz, 5H), 7.32−7.25 (m, 1H), 7.20−7.09 (m, 2H), 6.54−6.46 (m, 1H), 6.33 (s, 1H), 5.25 (s, 2H), 5.21 (s, 1H), 5.01 (s, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 165.2, 136.1, 135.4, 134.7, 130.3, 129.5, 128.7, 128.5, 128.3, 126.7, 124.7, 123.5, 113.0, 111.1, 101.6, 67.0, 47.0. HRMS [EI]: m/z calculated for $C_{19}H_{16}NO_2Br$ $[M]^+$ 369.0365, found 369.0364. IR (ATR): ν = 2928 (w), 1721 (s), 1466 (m), 1258 (vs), 1157 (vs), 736 (vs) cm^{-1}.

*Benzyl 2-((1H-Indol-1-yl)methyl)acrylate (**8af**).* Yield: colorless oil, 24.4 mg, 0.084 mmol, 69%. Chromatography: ethyl acetate/petroleum ether 10:90 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.67 (m, 1H), 7.41 (d, J = 3.4 Hz, 5H), 7.35−7.12 (m, 4H), 6.61−6.53 (m, 1H), 6.33 (s, 1H), 5.28 (s, 2H), 5.22 (s, 1H), 5.06 (s, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 165.4, 136.4, 136.0, 135.6, 128.7, 128.6, 128.5, 128.4, 128.3, 126.6, 121.8, 121.0, 119.7, 109.6, 102.0, 66.9, 46.8. HRMS [ESI]: m/z calculated for $C_{19}H_{17}NO_2$ $[M]^+$ 291.1259, found 291.1253. IR (ATR): ν = 2951 (w), 1712 (s), 1462 (m), 1258 (vs), 1130 (s), 737 (vs) cm^{-1}.

*Benzyl 2-((2-Methyl-1H-indol-1-yl)methyl)acrylate (**8ak**).* Yield: colorless oil, 20.0 mg, 0.070 mmol, 69%. Chromatography: ethyl acetate/petroleum ether 10:90 ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.63−7.56 (m, 1H), 7.50−7.40 (m, 5H), 7.25−7.04 (m, 3H), 6.40−6.32 (m, 1H), 6.26 (s, 1H), 5.33 (s, 2H), 5.00 (t, J = 2.0 Hz, 2H), 4.87 (d, J = 2.1 Hz, 1H), 2.40 (s, 3H).). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 165.5, 136.7, 136.4, 136.1, 135.6, 128.7, 128.5, 128.3, 128.2, 125.6, 120.9, 119.8, 119.7, 109.0, 100.7, 66.9, 43.3, 12.4. HRMS [ESI]: m/z calculated for $C_{20}H_{19}NO_2$ $[M]^+$ 305.1416, found 305.1416. IR (ATR): ν = 1708 (s), 1454 (m), 1369 (m), 1292 (vs), 1130 (s), 737 (vs) cm^{-1}.

*Methyl 1-(2-(Methoxycarbonyl)-1-(4-(trifluoromethyl)phenyl)-allyl)-1H-pyrrole-2-carboxylate (**8kc**).*[7] Yield: colorless oil, 26.6 mg, 0.072 mmol, 72%. Chromatography: diethyl ether/petroleum ether 20:80.

*Methyl 4-(1-(1H-Indol-1-yl)-2-(methoxycarbonyl)allyl)benzoate (**8if**).*[7] Yield: colorless solid, 74.0 mg, 0.22 mmol, 88%. Chromatography: ethyl acetate/petroleum ether 20:80.

*Methyl 2-((5-Bromo-1H-indol-1-yl)(2-fluorophenyl)methyl)-acrylate (**8wi**).*[7] Yield: colorless oil, 30.5 mg, 0.08 mmol, 44%. Chromatography: diethyl ether/petroleum ether 10:90.

*Methyl 2-((9H-Carbazol-9-yl)(4-cyanophenyl)methyl)acrylate (**8jl**).*[7] Yield: colorless solid, 81.2 mg, 0.22 mmol, 82%. Chromatography: ethyl acetate/petroleum ether 15:85.

*Methyl 2-((4-Chlorophenyl)(3-cyano-1H-indol-1-yl)methyl)-acrylate (**8om**).*[7] Yield: wax, 65.0 mg, 0.19 mmol, 77%. Chromatography: ethyl acetate/petroleum ether 15:85

*Methyl 2-((5-Bromo-1H-indol-1-yl)(2-bromophenyl)methyl)-acrylate (**8xi**).*[7] Yield: colorless oil, 58.0 mg, 0.13 mmol, 84%. Chromatography: diethyl ether/petroleum ether 10:90

General Procedure for Enantioselective Allylation of *N*-Heterocycles. To a flask *N*-silyl heterocycle (0.1 mmol) and $(DHQD)_2PHAL$ (7.8 mg, 10 mol %) were added successively, and the flask was then evacuated and refilled with nitrogen. This procedure was repeated three times. Dry $PhCF_3$ (0.5 mL), dissolving MBH fluorides (0.2 mmol), was then added. The reaction mixture was stirred at room temperature. After stirring for 40 h or the completion of the reaction (monitored by TLC), the mixture was concentrated and purified by flash column chromatography with ethyl acetate in petroleum ether to afford the corresponding product. NMR data were compared with the racemic material. The ratio of enantiomers was determined by HPLC on chiral stationary phase.

General Procedure Hydrogenation of Substitution Products. The substrate (1 equiv) was dissolved in MeOH (1 mL) and degassed with nitrogen for 5 min. Pd/C (10 mol %) was added, and hydrogen was bubbled through the mixture until observed to be completed (by GC-MS). The reaction mixture was filtered on a plug of silica eluting with ethyl acetate if not stated differently.

*Methyl 2-Methyl-3-phenyl-3-(1H-pyrrol-1-yl)propanoate (**9ba**).* Yield: colorless solid, 166 mg, 0.68 mmol, >99%. Mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45−7.22 (m, 5H), 6.79 (m, 2H), 6.22−6.08 (m, 2H), 5.21 (m, 1H), 3.62 (s, 3H (major)), 3.62 (s, 3H (minor)) 3.55−3.40 (m, 1H), 1.16 (m, 3H).^{13}C{1H} NMR (63 MHz, $CDCl_3$) δ 175.7, 175.4, 140.3, 139.5, 129.8, 129.6, 129.1, 129.0, 128.3, 127.9, 120.6, 120.3, 109.4, 109.2, 67.2, 66.6, 53.0, 52.8, 46.0, 45.8, 16.9, 165. HRMS [ESI]: m/z

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calculated for $C_{15}H_{17}NNaO_2$ $[M + Na]^+$ 266.1157, found 266.1161. IR (ATR): $\tilde{\nu}$ = 2935 (w), 1728 (vs), 1454 (m), 1261 (m), 1092 (m), 725 (vs); 702 (vs) cm^{-1}.

*Methyl 3-(3,5-Dimethylphenyl)-2-methyl-3-(1H-pyrrol-1-yl)-propanoate (**9ea**).* Yield: colorless solid, 24.3 mg, 0.09 mmol, >99%. Mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 3H), 6.78 (m, 2H), 6.17 (m, 2H (minor)), 6.11 (m, 2H (major)), 5.12 (m, 1H), 3.59 (s, 3H, (major)), 3.52−3.40 (s, 3H (minor)), 2.31 (m, 6H), 1.13 (m, 3H).$^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.0, 174.5, 139.2, 138.38, 138.37, 138.1, 129.9, 129.8, 125.2, 124.8, 119.7, 119.4, 108.4, 108.1, 66.4, 65.6, 52.0, 51.8, 45.0, 44.9, 21.4, 16.1, 15.6, 15.5. HRMS [ESI]: m/z calculated for $C_{17}H_{21}NO_2$ $[M]^+$ 271.1567, found 271.1570. IR (ATR): $\tilde{\nu}$ = 3951 (w), 1753 (vs), 1458 (m), 1265 (m), 1165 (m), 718 (vs), 698 (s) cm^{-1}.

*Methyl 2-Methyl-5-phenyl-3-(1H-pyrrol-1-yl)pentanoate (**9ua**).* Yield: colorless oil, 22 mg, 0.08 mmol. Mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 2H), 7.27−7.18 (m, 2H), 7.17−7.06 (m, 2H), 6.70 (m, 2H), 6.23 (t, 2H (minor)), 6.19 (t, 2H (major)), 4.1 (m, 1H (major)), 4.05 (m, 1H (minor)), 3.72 (s, 1H (minor)), 3.54 (3H (major)), 2.88 (1H), 2.52−2.34 (2H), 2.30−1.98 (2H), 1.23 (3H (major)), 0.94 (3H (minor)). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.0, 174.5, 141.02, 140.97, 128.5, 128.4, 126.1, 126.0, 119.5, 119.4, 108.3, 108.0, 61.5, 61.4, 51.9, 51.8, 46.7, 46.5, 35.9, 33.8, 32.2, 32.0, 14.6, 14.4. HRMS [EI]: m/z calculated for $C_{17}H_{21}NO_2$ $[M]^+$ 271.1567, found 271.1568. IR (ATR): $\tilde{\nu}$ = 2951 (w), 1732 (s), 1265 (m), 1161 (m), 721 (vs), 698 (vs) cm^{-1}.

*Methyl 3-Cyclohexyl-2-methyl-3-(1H-pyrrol-1-yl)propanoate (**9ta**).* Yield: colorless oil, 59 mg, 0.237 mmol. Mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (m, 2H), 6.12 (m, 2H), 3.99 (dd, J = 8.6, 7.0 Hz, 1H (minor)), 3.89 (dd, J = 8.2, 6.6 Hz, 01H (major)), 3.71 (s, 3H (minor)), 3.57 (s, 3H (major)), 3.22−2.95 (m, 1H), 1.89 (dddd, J = 11.7, 8.7, 6.5, 3.3 Hz, 1H), 1.82−1.44 (m, 6H), 1.22 (d, J = 7.0 Hz, 3H), 1.18−1.07 (m, 2H (major)), 1.01 (d, J = 7.0 Hz, 2H(minor)), 0.96−0.77 (m, 1H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.3, 174.7, 120.8, 120.6, 107.5, 107.1, 67.4, 66.8, 51.9, 51.7, 42.5, 42.0, 41.2, 39.4, 30.9, 30.6, 28.7, 28.0, 26.3, 26.24, 26.21, 26.17, 26.12, 15.0, 13.49. HRMS [EI]: m/z calculated for $C_{15}H_{23}NO_2$ $[M]^+$ 249.1729, found 249.1724. IR (ATR): $\tilde{\nu}$ = 2973 (m), 2855 (m), 1735 (s), 1261 (m), 1165 (m), 721 (vs) cm^{-1}.

*Methyl 3-(4-Methoxyphenyl)-2-methyl-3-(1H-pyrrol-1-yl)-propanoate (**9fa**).* Yield: colorless oil, 20.2 mg, 0.074 mmol. Mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (m, 2H), 6.99−6.82 (m, 2H), 6.76 (m, 2H), 6.16 (m, 2H (minor)), 6.11 (m, 2H (major)), 5.16 (m, 1H), 3.80 (m, 3H), 3.60 (s, 3H (major)), 3.56 (s, 3H (minor)), 3.43 (m, 1H), 1.14 (m, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.9, 174.5, 159.4, 159.2, 131.7, 130.8, 129.9, 128.6, 128.2, 119.5, 119.3, 114.2, 114.0, 113.8, 108.5, 108.2, 65.7, 65.1, 55.3, 55.2, 52.1, 51.9, 45.3, 45.1, 29.7, 16.0, 15.6. HRMS [EI]: m/z calculated for $C_{16}H_{19}NO_3$ $[M]^+$ 273.1359, found 273.1355. IR (ATR): $\tilde{\nu}$ = 2951 (w), 1735 (s), 1512 (s), 1250 (m), 1165 (s), 723 (vs), 629 (s) cm^{-1}.

*Methyl (syn)-2-Methyl-3-(naphthalen-2-yl)-3-(1H-pyrrol-1-yl)-propanoate (syn-**9sa**).* Yield: colorless solid, 47.4 mg, 0.162 mmol, 41%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86−7.79 (m, 3H), 7.58−7.42 (m, 3H), 6.84 (t, J = 2.2 Hz, 2H), 6.20 (t, J = 2.1 Hz, 2H), 5.39 (d, J = 11.0 Hz, 1H), 3.67−3.59 (m, 1H), 3.55 (s, 3H), 1.23 (d, J = 6.9 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.5, 136.8, 133.2, 133.0, 128.7, 128.2, 127.6, 126.3, 126.3, 125.6, 125.3, 119.8, 108.7, 65.6, 52.0, 44.9, 15.7. HRMS [EI]: m/z calculated for $C_{19}H_{19}NO_2$ $[M]^+$ 293.1410, found 293.1414. IR (ATR): $\tilde{\nu}$ = 2935 (w), 1720 (vs), 1357 (m), 1269 (m), 1177 (m), 725 (vs), 383 (vs) cm^{-1}.

*Methyl (anti)-2-Methyl-3-(naphthalen-2-yl)-3-(1H-pyrrol-1-yl)-propanoate (anti-**9sa**).* Yield: colorless solid, 25.0 mg, 0.085 mmol, 21%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.78 (m, 4H), 7.55−7.49 (m, 2H), 7.44 (dd, J = 8.5, 1.8 Hz, 1H), 6.86 (t, J = 2.2 Hz, 2H), 6.14 (t, J = 2.2 Hz, 2H), 5.40 (d, J = 11.2 Hz, 1H), 3.65 (s, 3H), 3.62−3.54 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, 0$CDCl_3$) δ 174.9, 136.0, 133.2, 133.1, 129.0, 128.03, 128.02, 127.7, 126.8, 126.5, 126.4, 124.6, 119.5, 108.4, 66.4, 52.2, 44.8, 16.1. HRMS [EI]: m/z calculated for $C_{19}H_{19}NO_2$ $[M]^+$ 293.1410, found 293.1413. IR (ATR): $\tilde{\nu}$ = 2936 (w), 1728 (s), 1258 (m), 1161 (m), 725 (vs), 687 (m) cm^{-1}.

*Methyl 3-(4-Fluorophenyl)-2-methyl-3-(1H-pyrrol-1-yl)-propanoate (**9na**).* Yield: colorless oil, 18.9 mg, 0.07 mmol. Mixture of diastereomers. ^1H NMR (400 MHz,$CDCl_3$) δ 7.32 (m, 2H), 7.14−6.96 (m, 2H), 6.76 (m, 2H), 6.18 (m, 2H), 5.19 (m, 1H), 3.61 (s, 3H (major)), 3.56 (s, 3H (minor)), 3.42 (m, 1H), 1.13 (m, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.6, 174.3, 162.4 (d, J = 247.4 Hz), 134.6, 134.6, 129.0 (d, J = 8.3 Hz), 128,7 (d, J = 8.2 Hz), 119.5, 119.3, 115.8 (d, J = 21.4 Hz), 115.6 (d, J = 21.6 Hz), 108.8, 108.5, 65.5, 65.0, 52.2, 52.0, 45.2, 45.0, 16.0. 19F NMR (377 MHz, $CDCl_3$) δ −113.74, −114.01. HRMS [EI]: m/z calculated for $C_{15}H_{16}NFO_2$ $[M]^+$ 261.1160, found 261.1162. IR (ATR): $\tilde{\nu}$ = 2951 (w), 1753 (s), 1512 (s), 1265 (m), 1161 (s), 721 (vs), 623 (s) cm^{-1}.

*Methyl 3-(4-Trifluoromethyl)-2-methyl-3-(1H-pyrrol-1-yl)-propanoate (**9ka**).* Yield: colorless oil, 46.5 mg, 0.15 mmol. Mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.46 (m, 2H), 6.78 (m, 2H), 6.18 (m, 2H), 5.28 (m, 1H), 3.64 (s, 3H (major)), 3.58 (s, 3H (minor)), 3.55−3.39 (m, 1H), 1.17 (m, 3H). $^{13}C\{1H\}$ NMR (63 MHz, $CDCl_3$) δ 175.2, 175.0, 143.6, 131.4 (q, J_{C-F} = 32.4 Hz) 128.6, 128.3, 126.8 (q, J_{C-F} = 3.8 Hz), 120.5, 120.3, 110.0, 109.7, 66.6, 66.0, 53.2, 53.0, 45.7, 45.5, 16.8, 16.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.72. HRMS [EI]: m/z calculated for $C_{16}H_{16}NF_3O_2$ $[M]^+$ 311.1128, found 311.1131. IR (ATR): $\tilde{\nu}$ = 2954 (w), 1736 (s), 1250 (m), 1323 (vs), 1165 (s), 1068 (vs) cm^{-1}.

*Methyl 4-(3-Methoxy-2-methyl-3-oxo-1-(1H-pyrrol-1-yl)propyl)-benzoate (**9ia**).* Yield: colorless solid, 45 mg, 0.15 mmol, >99%. Mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02−7.86 (m, 2H), 7.38−7.26 (m, 2H), 6.66 (m, 2H), 6.07 (m, 2H (minor)), 6.02 (m, 2H (major)), 5.15 (m, 1H), 3.81 (m, 3H), 3.51 (s, 3H (major)), 3.44 (s, 3H (minor)), 3.36 (m, 1H) 1.07 (2H (minor)), 1.02 (2H (major)). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.4, 174.1, 166.5, 166.5, 144.3, 143.6, 130.2, 130.1, 130.0, 129.9, 127.4, 127.0, 119.6, 119.4, 108.9, 108.7, 65.8, 65.3, 52.2, 52.1, 52.0, 44.9, 44.6, 15.9, 15.5. HRMS [ESI]: m/z calculated for $C_{17}H_{19}NO_4$ $[M]^+$ 301.1317 found 301.1314. IR (ATR): $\tilde{\nu}$ = 2951 (w), 1720 (vs), 1435 (m), 1276 (vs), 1168 (m), 725 (m) cm^{-1}.

*Methyl 3-(4-Cyanophenyl)-2-methyl-3-(1H-pyrrol-1-yl)-propanoate (**9ja**).* Yield: colorless oil, 41.2 mg, 0.153 mmol. Mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.44 (m, 2H), 6.75 (m, 2H), 6.27−6.08 (m, 2H), 5.39−5.18 (m, 1H), 3.63 (s, 3H (major)), 3.58 (s, 3H (minor)), 3.44 (m, 1H), 1.17 (3H). $^{13}C\{1H\}$ NMR (63 MHz, $CDCl_3$) δ 175.0, 174.9, 145.5, 144.7, 133.7, 133.5, 128.9, 128.6, 120.5, 120.3, 119.2, 113.2, 113.0, 110.2, 110.0, 66.5, 66.0, 53.2, 53.1, 45.6, 45.3, 30.6, 16.8, 16.4. HRMS [EI]: m/z calculated for $C_{16}H_{16}N_2O_2$ $[M]^+$ 268.1206, found 268.1208. IR (ATR): $\tilde{\nu}$ = 2955 (w), 2230 (w), 1732 (s), 1269 (m), 1168 (m), 721 (vs) cm^{-1}.

General Procedure for Intramolecular Friedel−Craft Acylation. Under nitrogen, the substrate (1 equiv) was dissolved in CH_2Cl_2 (0.1M) and BBr_3 (1.05 equiv) was added slowly. The reaction was monitored by TLC and, when judged completed, poured into sat. $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and, after evaporation, subjected to column chromatography to yield the desired compound.

*(2S,3R)-2-Methyl-3-phenyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7ba**).* Yield: colorless oil, 74.9 mg, 0.35 mmol, 53%. Chromatography: ethyl acetate/petroleum ether 15:85. ^1H NMR (250 MHz, $CDCl_3$) δ 7.46−7.37 (m, 3H), 7.26−7.17 (m, 2H), 6.82 (d, J = 2.1 Hz, 2H), 6.56 (dd, J = 3.8, 2.5 Hz, 1H), 5.02 (d, J = 4.8 Hz, 1H), 2.98 (qd, J = 7.4, 4.8 Hz, 1H), 1.44 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (63 MHz, $CDCl_3$) δ 192.0, 140.3, 133.7, 130.2, 129.6, 127.3, 123.2, 118.1, 108.9, 67.5, 57.1, 15.1. HRMS [ESI]: m/z calculated for $C_{14}H_{13}NNaO$ $[M + Na]^+$ 234.0894, found 234.0896. IR (ATR): $\tilde{\nu}$ = 2966 (w), 1693 (vs), 1523 (m), 1454 (m), 1307 (s), 736 (vs), 798 (vs) cm^{-1}.

*(2S,3S)-2-Methyl-3-phenyl-2,3-dihydro-1H-pyrrolizin-1-one (cis-**7ba**).* Yield: colorless solid, 13.0 mg, 0.06 mmol, 10%. Chromatography: ethyl acetate/petroleum ether 15:85. ^1H NMR (400 MHz,

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$CDCl_3$) δ 7.34 (dd, J = 5.8, 1.6 Hz, 3H), 6.92 (dd, J = 2.3, 1.1 Hz, 1H), 6.85 (dd, J = 3.8, 1.2 Hz, 3H), 6.61 (dd, J = 4.0, 2.3 Hz, 1H), 5.72 (d, J = 8.0 Hz, 1H), 3.50 (p, J = 7.7 Hz, 1H), 0.86 (d, J = 7.6 Hz, 3H). $^{13}C\{1H\}$ NMR (63 MHz, CDCl3) δ 191.6, 138.3, 132.7, 128.8, 128.4, 126.9, 122.8, 117.2, 107.5, 62.6, 50.5, 12.1. IR (ATR): $\tilde{\nu}$ = 2970 (w), 2018 (w), 1693 (vs), 1524 (m), 1369 (m), 1307 (m), 741 (s), 698 (s) in cm^{-1}.

*(2S,3R)-3-(3,5-Dimethylphenyl)-2-methyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7ea**).* Yield: colorless oil, 11.3 mg, 0.047 mmol, 53%. Chromatography: ethyl acetate/petroleum ether 15:85. ^1H NMR (250 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.91−6.77 (m, 4H), 6.58 (dd, J = 3.7, 2.6 Hz, 1H), 4.94 (d, J = 4.8 Hz, 1H), 2.99 (qd, J = 7.4, 4.8 Hz, 1H), 2.34 (s, 6H), 1.44 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (63 MHz, $CDCl_3$) δ 186.9, 134.9, 134.5, 128.3, 125.9, 119.8, 117.9, 112.6, 103.5, 62.2, 51.7, 16.9, 9.8. HRMS [ESI]: m/z calculated for $C_{16}H_{18}NO$ $[M + H]^+$ 240.1383, found 240.1338. IR (ATR): $\tilde{\nu}$ = 2924 (w), 1697 (vs), 1527 (m), 1369 (m), 1307 (m), 848 (m), 741 (vs) cm^{-1}. This compound was subjected to the conventional self-disproportionation of enantiomers (SDE) test described in the literature.[20] We did not observe significant SDE for this compound, and there were no indications of significant SDE with other pyrrolizin-1-one and *N*-allyl pyrroles reported here.

*trans-2-Methyl-3-phenethyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7ua**).* Yield: colorless solid, 7.5 mg, 0.040 mmol, 55% (brsm). Chromatography: ethyl acetate/petroleum ether 10:90. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.0, 6.6 Hz, 2H), 7.30−7.20 (m, 3H), 7.05 (dd, J = 2.3, 1.0 Hz, 1H), 6.76 (dd, J = 4.0, 1.0 Hz, 1H), 6.56 (dd, J = 4.0, 2.3 Hz, 1H), 4.15 (dt, J = 8.1, 4.2 Hz, 1H), 2.87 (qd, J = 7.4, 3.9 Hz, 1H), 2.82−2.66 (m, 2H), 2.46−2.30 (m, 1H), 2.24−2.05 (m, 1H), 1.42 (d, J = 7.4 Hz, 3H).$^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 191.9, 140.4, 132.2, 128.7, 128.2, 126.4, 121.5, 116.9, 107.8, 62.1, 51.7, 37.2, 31.4, 15.9. HRMS [EI]: m/z calculated for $C_{16}H_{17}NO$ $[M]^+$ 239.1305, found 239.1303. IR (ATR): $\tilde{\nu}$ = 2928 (w), 1693 (vs), 1523 (vs), 1307 (s), 736 (vs) cm^{-1}.

*trans-3-Cyclohexyl-2-methyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7ta**).* Yield: colorless oil, 24.6 mg, 0.113 mmol, 62%. Chromatography: ethyl acetate/petroleum ether 10:90. ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.70 (d, J = 4.0 Hz, 1H), 6.52 (dd, J = 4.0, 2.3 Hz, 1H), 4.00 (t, J = 3.8 Hz, 2H), 2.85 (qd, J = 7.5, 3.3 Hz, 2H), 1.99−1.63 (m, 4H), 1.35 (d, J = 7.5 Hz, 3H), 1.31−1.14 (3H) 1.12−0.97 (m, 3H), 0.87 (m, 2H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 192.6, 132.4, 122.0, 116.61, 107.3, 67.4, 48.1, 42.4, 29.7, 28.9, 26.8, 26.3, 26.1, 25.9, 17.0. HRMS [EI]: m/z calculated for $C_{14}H_{19}NO$ $[M]^+$ 217.1467, found 217.1463. IR (ATR): $\tilde{\nu}$ = 2824 (m), 2855 (m), 1693 (vs), 1527 (m), 1369 (m), 1307 (m), 733 (vs) cm^{-1}.

*trans-3-(4-Methoxyphenyl)-2-methyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7fa**).* Yield: colorless oil, 5.0 mg, 0.023 mmol, 32%. Chromatography: ethyl acetate/petroleum ether 30:70. ^1H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.73 (dd, J = 3.9, 1.1 Hz, 1H), 6.71 (dd, J = 2.4, 1.0 Hz, 1H), 6.46 (dd, J = 3.9, 2.3 Hz, 1H), 4.87 (d, J = 5.0 Hz, 1H), 3.75 (s, 3H), 2.88 (qd, J = 7.4, 5.0 Hz, 1H), 1.33 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 191.3, 159.9, 132.7, 131.2, 127.8, 122.1, 117.1, 114.6, 107.9, 66.2, 56.2, 55.4, 14.0. HRMS [EI]: m/z calculated for $C_{15}H_{15}NO_2$ $[M]^+$ 241.1097, found 241.1095. IR (ATR): $\tilde{\nu}$ = 2931 (w), 1693 (vs), 1512 (vs), 1249 (vs), 1030 (m), 736 (s), 613 (m) cm^{-1}.

*trans-2-Methyl-3-(naphthalen-2-yl)-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7sa**).* Yield: colorless solid, 4.8 mg, 0.018 mmol, 24% (brsm). Chromatography: ethyl acetate/petroleum ether 15:85. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95−7.84 (m, 3H), 7.75 (d, J = 1.7 Hz, 1H), 7.63−7.50 (m, 2H), 7.22 (dd, J = 8.5, 1.9 Hz, 1H), 6.89 (dd, J = 3.9, 1.1 Hz, 1H), 6.84 (dd, J = 2.3, 1.1 Hz, 1H), 6.60 (dd, J = 4.0, 2.3 Hz, 1H), 5.19 (d, J = 4.9 Hz, 1H), 3.10 (qd, J = 7.4, 4.9 Hz, 1H), 1.49 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 191.1, 136.5, 133.3, 133.2, 129.6, 127.9, 127.9, 126.8, 126.8, 126.1, 123.4, 122.3, 117.3, 108.1, 66.9, 56.0, 14.2. HRMS [EI]: m/z calculated for $C_{18}H_{15}NO$ $[M]^+$ 261.1148, found 261.1152. IR (ATR): $\tilde{\nu}$ = 2928 (w), 1693 (m), 1527 (m), 1572 (m), 1366 (m), 1308 (s), 736 (vs) cm^{-1}.

*trans-3-(4-Fluorophenyl)-2-methyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7na**).* Yield: colorless solid, 9.4 mg, 0.041 mmol, 53%. Chromatography: ethyl acetate/petroleum ether 20:80. ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (m 2H), 7.11 (m2H), 6.84 (dd, J = 4.0, 1.1 Hz, 1H), 6.82−6.79 (m, 1H), 6.58 (dd, J = 4.0, 2.3 Hz, 1H), 5.01 (d, J = 4.8 Hz, 1H), 2.95 (qd, J = 7.4, 4.9 Hz, 1H), 1.44 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 190.8, 162.8 (d, J_{C-F} = 247.9 Hz), 135.2 (d, J_{C-F} = 3.1 Hz), 132.7, 128.2 (d, J_{C-F} = 8.4 Hz), 122.1, 117.3, 116.3 (d, J_{C-F} = 21.7 Hz), 108.1, 66.0, 56.2, 14.2. HRMS [EI]: m/z calculated for $C_{14}H_{12}NFO$ $[M]^+$ 229.0897, found 229.0899. IR (ATR): $\tilde{\nu}$ = 2931 (w), 1705 (s), 1512 (m), 1288 (m), 1010 (m), 829 (vs), 775 (s) cm^{-1}.

*cis-3-(4-Fluorophenyl)-2-methyl-2,3-dihydro-1H-pyrrolizin-1-one (cis-**7na**).* Yield: colorless solid, 1.2 mg, 0.005 mmol, 7%. Chromatography: ethyl acetate/petroleum ether 20:80. ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (m, 2H), 6.90 (m, 1H), 6.89−6.77 (m, 2H), 6.60 (dd, J = 4.0, 2.3 Hz, 1H), 5.71 (d, J = 8.0 Hz, 1H), 3.48 (p, J = 7.7 Hz, 1H), 0.85 (d, J = 7.6 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ −113.37. HRMS [EI]: m/z calculated for $C_{14}H_{12}NFO$ $[M]^+$ 229.0897, found 229.0900.

*trans-3-(4-Trifluormethylphenyl)-2-methyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7ka**).* Yield: colorless solid, 12.2 mg, 0.044 mmol, 30%. Chromatography: ethyl acetate/petroleum ether 15:85. ^1H NMR (250 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.89−6.86 (m, 1H), 6.83 (dd, J = 2.4, 1.0 Hz, 1H), 6.61 (dd, J = 3.9, 2.4 Hz, 1H), 5.11 (d, J = 4.8 Hz, 1H), 2.97 (qd, J = 7.4, 4.8 Hz, 1H), 1.48 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (63 MHz, CDCl3) δ 191.2, 144.4, 133.7, 132.0 (q, J_{C-F} = 32.5 Hz), 127.6, 127.2 (q, J_{C-F} = 3.76 Hz), 124.7 (q, J_{C-F} = 272 Hz), 118.5, 109.3, 67.0, 57.1, 15.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.72. HRMS [EI]: m/z calculated for $C_{15}H_{12}NF_3O$ $[M]^+$ 279.0866, found 279.0862. IR (ATR): $\tilde{\nu}$ = 2970 (w), 1697 (m), 1528 (vs), 1312 (vs), 1065 (vs), 1018 (m), 734 (m) cm^{-1}.

*trans-3-(4-Cyanophenyl)-2-methyl-2,3-dihydro-1H-pyrrolizin-1-one (trans-**7ia**).* Yield: colorless solid, 7.2 mg, 0.030 mmol, 22% (brsm). Chromatography: ethyl acetate/petroleum ether 20:80. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 6.86 (dd, J = 4.0, 1.1 Hz, 1H), 6.82 (dd, J = 2.4, 1.0 Hz, 1H), 6.61 (dd, J = 4.0, 2.4 Hz, 1H), 5.10 (d, J = 4.7 Hz, 1H), 2.92 (qd, J = 7.4, 4.7 Hz, 1H), 1.47 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 189.9, 144.8, 133.2, 132.7, 127.0, 122.1, 118.1, 117.9, 112.8, 108.5, 66.0, 56.1, 14.5. HRMS [EI]: m/z calculated for $C_{15}H_{12}N_2O$ $[M]^+$ 236.0944, found 236.0945. IR (ATR): $\tilde{\nu}$ = 2927 (w), 1701 (vs), 1458 (m), 1369 (m), 1281 (vs), 744 (m) cm^{-1}.

*trans-Methyl 4-(trans)-2-Methyl-1-oxo-2,3-dihydro-1H-pyrrolizin-3-yl)benzoate (trans-**7ja**).* Yield: colorless solid, 16.9 mg, 0.063 mmol, 46% (brsm). Chromatography: ethyl acetate/petroleum ether 20:80. ^1H NMR (600 MHz, $CDCl_3$) δ 8.07−7.96 (m, 2H), 7.17 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 4.0 Hz, 1H), 6.73 (d, J = 1.3 Hz, 1H), 6.50 (dd, J = 4.0, 2.3 Hz, 1H), 5.00 (d, J = 4.8 Hz, 1H), 3.86 (s, 3H), 2.87 (qd, J = 7.4, 4.8 Hz, 1H), 1.37 (d, J = 7.4 Hz, 3H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 190.5, 166.4, 144.4, 132.7, 130.6, 130.6, 126.3, 122.2, 117.5, 108.3, 66.2, 56.1, 52.3, 14.4. HRMS [EI]: m/z calculated for $C_{16}H_{15}NO_3$ $[M]^+$ 269.1052, found 269.1053.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b02819.

^1H, ^{13}C, and ^{19}F NMR of new compounds, ^1H NMR spectra of known compounds and HPLC chromatograms for compounds prepared in enantioenriched form (PDF)

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Notes

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Latent (pro)nucleophiles in Lewis base catalyzed allylic substitutions

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Latent (Pro)Nucleophiles in Enantioselective Lewis Base Catalyzed Allylic Substitutions

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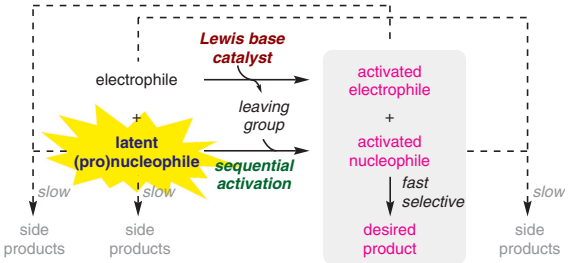

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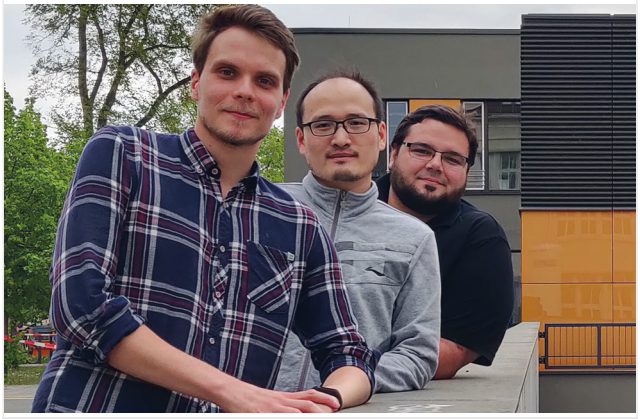
Abstract The use of latent nucleophiles, which are molecules that are not nucleophilic but can be activated to act as a nucleophile at an opportune time during the reaction, expands the scope of Lewis base catalyzed reactions. Here, we provide an overview of the concept and show examples of applications to N- and C-centered nucleophiles in allylic substitutions. N- and C-silyl compounds are superior latent (pro)nucleophiles in Lewis base catalyzed reactions with allylic fluorides in which the formation of the strong Si–F bond serves as the driving force for the reactions. The latent (pro)nucleophiles ensure high regioselectivity in these reactions and enable enantioselective transformations of Morita–Baylis–Hillman adducts by the use of common chiral Lewis base catalysts.

Key words Lewis base catalysis, enantioselective catalysis, organocatalysis, latent nucleophiles, latent pronucleophiles, allylic substitutions

1 Introduction

Enantioselective organocatalysis is still considered an emerging technology 'that will change our world' according to IUPAC.[1] The main reason for this is its potential to make synthetic organic chemistry more sustainable. Consequently, the goals in the field of enantioselective organocatalysis are grouped around the development of (i) new catalysts that maintain their efficacy with lower catalysts loading,[2] (ii) efficient heterogeneous or immobilized organocatalysts



Markus Lange (left) was born in Pritzwalk. He received his M.Sc. from Friedrich Schiller University Jena in 2018. The same year, he started his doctoral work in the Vilotijevic group as a fellow of Landesgraduiertenakademie (FSU Jena, State of Thuringia). His research interests are in organic synthesis and catalysis, and his doctoral work focuses on the development of latent nucleophiles in Lewis base catalysis and their application in organic synthesis.
You Zi (center) was born in Jiangsu province, China. He obtained his B. Sc. and M.Sc. degrees from Soochow University, Suzhou, China in 2012 and 2015. After that he joined the Vilotijevic group to start his doctoral studies. His research is focused on the concept of latent nucleophiles in Lewis base catalysis and on phosphonium ions as versatile synthetic intermediates.
Ivan Vilotijević (right) studied chemistry at the University of Belgrade, Ohio State University and the University of Illinois at Urbana-Champaign. He earned a Ph.D. in organic chemistry from Massachusetts Institute of Technology working on epoxide-opening cascade reactions in 2010. He moved to the Max Planck Institute of Colloids and Interfaces for a postdoc as a Marie Curie Fellow working on synthesis and biological studies of glycosylphosphatidylinositols. In 2015 he joined the faculty at Friedrich Schiller University Jena where his group develops novel catalytic methods for the synthesis of complex organic molecules focusing on Lewis base catalysis and organophosphorus chemistry.

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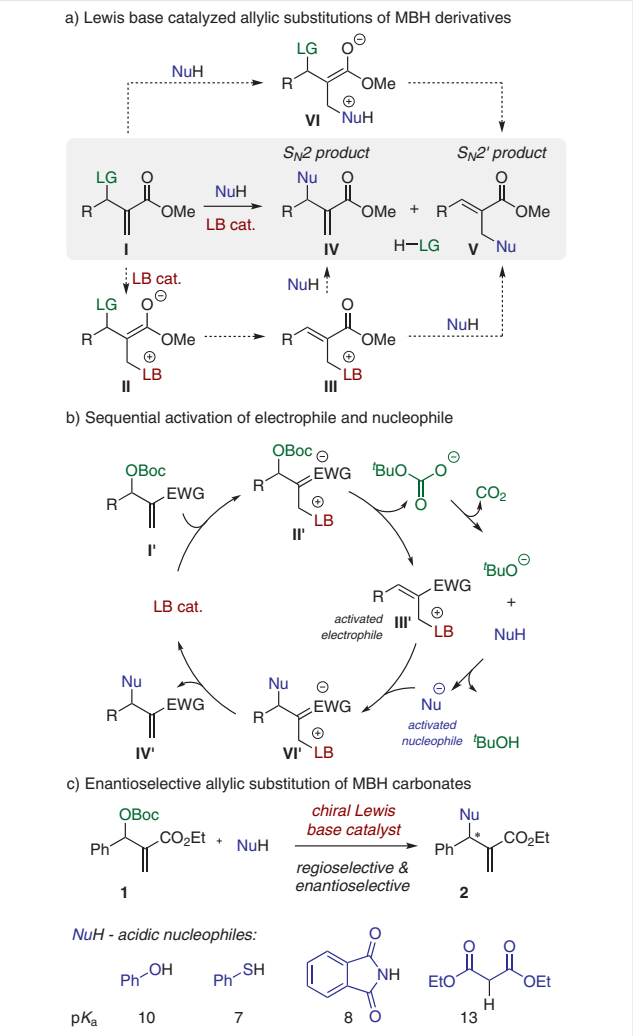
that would allow for easy catalyst recovery after the reaction,[3] and (iii) more diverse ways to utilize the green and sustainable raw materials.[4] That said, the spotlight in any discipline remains universally focused on pushing the boundaries of what is possible and, in organic synthesis specifically, discovering new types of reactivity. Lewis base catalysis offers ample opportunity for such improvements, which can be illustrated with Lewis base catalyzed allylic substitutions. These reactions have been most often studied with Morita–Baylis–Hillman (MBH) adducts, derivatives of MBH allylic alcohols.[5] MBH alcohols can be prepared via the perfectly atom economical Lewis base catalyzed reaction of a suitable Michael acceptor and an aldehyde. Their synthesis in the solid phase eliminates solvent waste and makes MBH alcohols prime examples of green synthetic products.[6]

It is not surprising that MBH alcohols became suitable substrates for allylic substitution upon transformation of the hydroxy into a better leaving group such as an ester.[7] Such substrates will undergo a substitution reaction with good nucleophiles to produce either the product of direct S_N2 substitution or the product of S_N2' substitution that proceeds with transposition of the double bond, although the underlying mechanism is unlikely to be a simple S_N2 or an S_N2' reaction (Scheme 1a). If such reactions are to be catalyzed by a Lewis base catalyst and be regioselective, the catalyst must be more nucleophilic than the nucleophilic reaction partner and must show preference for formation of a bond with one of the carbons of the allylic system. If this is not the case, the reaction may proceed without involvement of the catalyst and may lead to the formation of mixtures of S_N2 and S_N2' products (Scheme 1a).[8] It is apparent that when a chiral Lewis base catalyst is used and the reaction proceeds without involvement of the catalyst, the reactions do not result in enantioselective formation of the products.



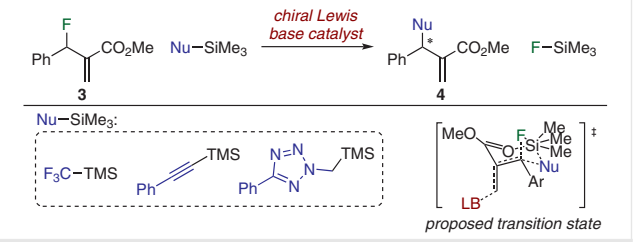
Scheme 1 An overview of (a) regioselectivity issues, (b) sequential activation mechanism, and (c) enantioselectivity, chemoselectivity and reaction scope for Lewis base catalyzed substitutions of MBH carbonates.

2 Substitution of MBH Carbonates

A common strategy to overcome the problems in Lewis base catalyzed allylic substitutions of MBH adducts emerged through a switch of the electrophiles from MBH esters to MBH carbonates.[9] Lewis base catalysts such as DABCO attack the Michael acceptor in the MBH carbonate and trigger elimination of the carbonate via the E1cB mechanism (Scheme 1b). Loss of CO_2 turns the carbonate into an alcoholate. *tert*-Butoxide, a bulky base that is not strongly nucleophilic, is formed when MBH Boc-carbonates are used. The base will readily deprotonate any sufficiently acidic X-H and generate an anionic nucleophile. This nucleophile may attack the activated electrophile **III′** and engage in a regioselective reaction that is also enantioselective when a chiral catalyst is a part of the activated electrophile **III′**.

This kind of sequential activation of the electrophile by the Lewis base catalyst and the nucleophile by the leaving group produced during activation of the electrophile ensures that the activated nucleophile is produced only when the activated electrophile is already present in the reaction mixture. If the reaction between the two activated species proceeds selectively, then the regio- and enantioselectivity observed in such reactions is high. This strategy has been utilized to introduce various types of Nu-H nucleophiles,[10] but they all have one limitation: the need for an acidic Nu-H that can be deprotonated by the *tert*-butoxide (Scheme 1c). Reactions with phthalimide, for example, proceed successfully, but other less acidic N-centered nucleophiles are not suitable for reactions with MBH carbonates. The requirement for an acidic N-H or C-H is a severely limiting factor for N- and C-centered nucleophiles.[11]

In 2013, Shibata introduced a similar method for sequential activation that is not dependent on acid/base equilibrium between the leaving group and the nucleophile but rather on a thermodynamically favorable formation of a strong Si–F bond, which also usually proceeds with high rates. This method enabled allylation of trifluoromethyl, (tetrazolyl)methyl and alkynyl nucleophiles carrying a trimethylsilyl group (Scheme 2).[12] A highly ordered ternary transition state that features silyl assistance in C–F bond cleavage and intramolecular delivery of the nucleophile has been proposed for these reactions, but the reactions could also proceed via an intermediate silicon ate complex that fragments into trimethylsilylfluoride and the anionic nucleophile. A range of other similar mechanistic scenarios can also be envisioned.



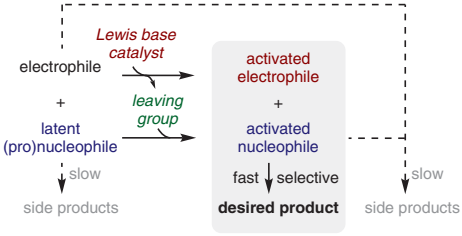
Scheme 2 Novel mode of nucleophile activation via Si–F bond formation

Since the proposed silicon ate intermediate features multiple carbon substituents, a question arises: which of these substituents will be transferred as a nucleophile? Our hypothesis was that it is the least basic group that will be transferred as the nucleophile because it should also be the best at stabilizing the negative charge. We consequently realized the potential this mode of activation has for addressing several specific limitations in the use of N-centered nucleophiles in Lewis base catalysis and allowing the development of a truly general approach to Lewis base catalyzed N-allylation. This hypothesis was a foundation of the concept of latent nucleophiles in Lewis base catalysis.

3 The Concept of Latent (Pro)Nucleophiles

Latent nucleophiles are derivatives of nucleophilic molecules that are not markedly nucleophilic but can be activated to act as a nucleophile under specific conditions or with a specific stimulus.[13] These should be distinguished from latent pronucleophiles, which are molecular species that are not nucleophilic in nature but can be transformed into a strong nucleophile by a specific stimulus or a chemical reaction.[14] As a rule, the parent molecule from which the pronucleophile is derived is not (or not markedly) nucleophilic.

Latent nucleophiles do not compete with the Lewis base catalyst. If activation of the latent nucleophile depends on the activation of the electrophile by mediacy of the leaving group, the resulting sequential activation allows for temporal control over formation of the activated nucleophile. The activated nucleophile, which could compete with the catalyst, is produced only when the activated electrophile is already present in the mixture; this allows the fast and selective reaction of the two activated intermediates to outcompete other possible pathways (Scheme 3).



Scheme 3 The concept of latent nucleophiles and the interdependent sequential activation of electrophile and nucleophile in Lewis base catalysis

Applying this concept to Lewis base catalyzed N-allylation, we envisioned *N*-trialkylsilyl compounds as latent nucleophiles. A bulky silyl group reduces the nucleophilicity of the nitrogen and makes the molecule less nucleophilic than the corresponding N-H compound.[15] A fluoride leaving group is a suitable nucleophile activator and a mediator in the sequential activation of the reaction partners, which makes allyl fluorides suitable electrophiles. Finally, the reason why this concept is best suited for N-centered nucleophiles is the fact that, by virtue of being less basic than any of the alkyl groups of the trialkylsilyl, it will always be the N-centered nucleophile that is transferred from the proposed ate intermediate derived from the *N*-trialkylsilyl compound. Through synergy of these three effects, this strategy may accommodate virtually any N-centered nucleophile.

4 Enantioselective Allylation of N-Heterocycles

The proof of principle study was the development of a general protocol for enantioselective N-allylation of pyrroles and related heterocycles with MBH fluorides using silylated heterocycles as latent nucleophiles. Pyrroles and indoles have been used in similar reactions with allylic carbonates, but these studies highlighted the need for electron-withdrawing substituents on the nucleophile that renders N-H more acidic and/or the need for stoichiometric amounts of Lewis base.[16] *N*-TBS-pyrroles, indoles and carbazoles were selected as latent nucleophiles in reactions with MBH fluorides. The reactions proceed with high rates and excellent efficiencies when DABCO is used as a catalyst with 5 mol% loading. In many cases, catalyst loading can be further reduced to 1 mol%. The reactions feature truly broad scope both for the electrophile and the latent nucleophile (Scheme 4a–c). They are not overly sensitive to steric hin-

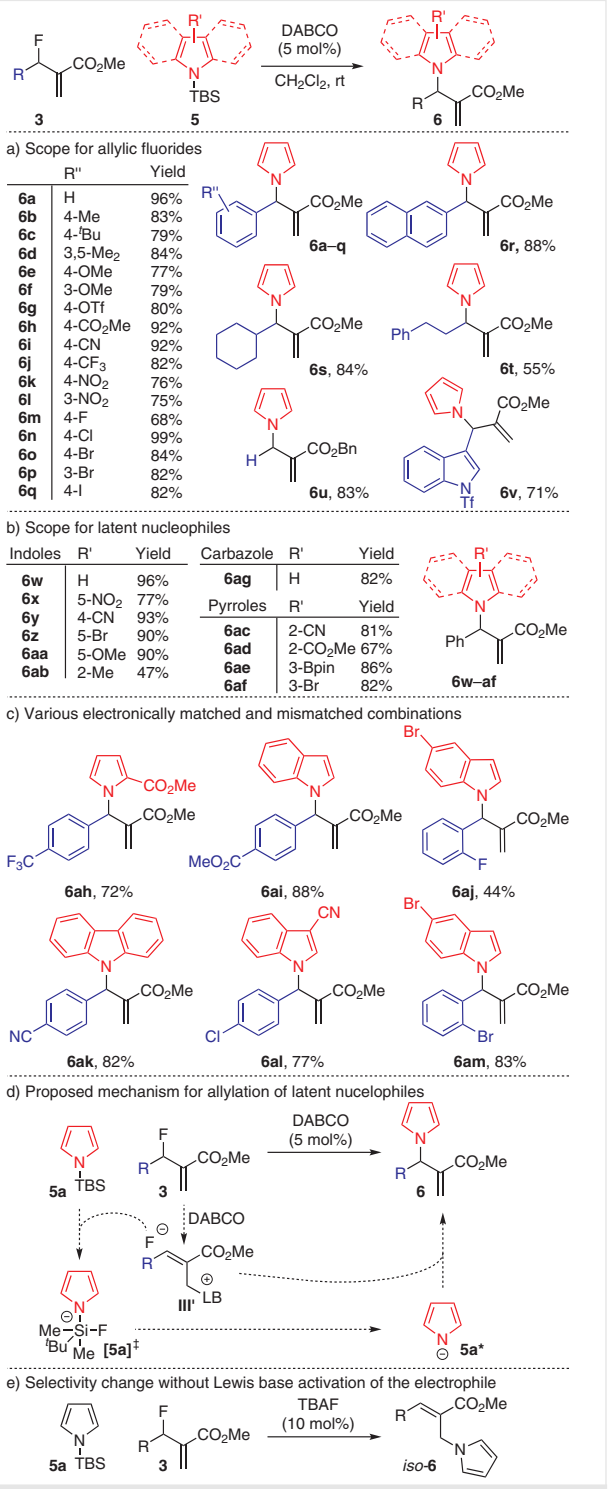
drance in the vicinity of the reactive centers nor to electronic effects of the substituents in the starting materials (electronically matched and mismatched substrates yield the desired products with similar yields). Finally, the reactions are highly regioselective, affording only S_N2 substitution products.

A series of crossover experiments revealed that the free anionic nucleophiles are likely produced in the course of the reaction (Scheme 4d). Furthermore, it was demonstrated that activation of the electrophile by the Lewis base catalysts (and further sequential activation) is instrumental for the success of these reactions. If only the nucleophile is activated[17] by a catalytic amount of exogenous fluoride ions, the reactions are autocatalytic, the regioselectivity is reversed and only the product of S_N2' substitution is observed (Scheme 4e).

Using chiral cinchona alkaloid based catalysts such as $(DHQD)_2PHAL$ in trifluorotoluene renders these reactions enantioselective. The diminished nucleophilicity of the chiral catalysts compared to DABCO results in significantly longer reactions times and highlights the need for the latent nucleophile to be truly latent. Despite the longer reaction times, the products are again isolated without regioselectivity issues (only S_N2 products observed). The products are isolated with good enantiomeric ratios (87:13 for **6v′** to 99:1 for **6ac′**; Scheme 5a and b) despite the slight drop in yields attributed to longer reaction times. Reflecting the results of the reactions with DABCO, steric and electronic properties of the reaction partners do not hinder the desired N-allylation reactions and focused optimization can be conducted to improve the efficacy of the reactions with specific pairs of reactants.[13]

The reactions with chiral Lewis bases are kinetic resolutions of the racemic allylic fluorides and the yields are highest when the fluoride is used in double the stoichiometric quantity. The allylic fluoride remaining at the end of the reactions is enantioenriched. Reactions of the two enantiomers of allylic fluoride are enantioconvergent and, based on qualitative observations, they proceed at different rates. Absolute configuration of the products is consistent with previously reported data for reactions using $(DHQD)_2PHAL$.[10,12]

The new Lewis base catalyzed enantioselective allylations of pyrrole-derived latent nucleophiles have already found application in the first enantioselective synthesis of pyrrolizin-1-ones (Scheme 5c). These compounds exhibit anti-amyloid properties, making them potentially useful for the treatment of Alzheimer's disease but have not been prepared in enantioenriched form yet.[18] Starting from the N-allylated pyrrole, a short and straightforward syntheses of pyrrolizin-1-ones includes hydrogenation of the double bond, which gives statistical mixtures of the *syn* and *anti* products in excellent yields, and the subsequent Friedel–Crafts type intramolecular acylation using BBr_3.[19] The cyclization furnishes the corresponding pyrrolizinones in a



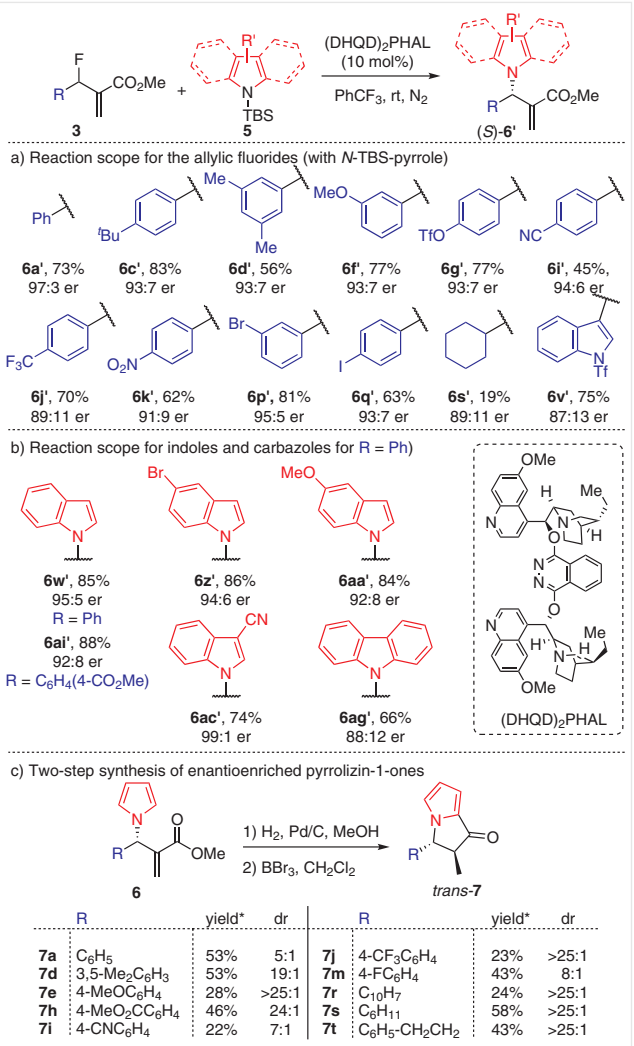
	R''	Yield
6a	H	96%
6b	4-Me	83%
6c	4-^{t}Bu	79%
6d	3,5-Me_2	84%
6e	4-OMe	77%
6f	3-OMe	79%
6g	4-OTf	80%
6h	4-CO_2Me	92%
6i	4-CN	92%
6j	4-CF_3	82%
6k	4-NO_2	76%
6l	3-NO_2	75%
6m	4-F	68%
6n	4-Cl	99%
6o	4-Br	84%
6p	3-Br	82%
6q	4-I	82%

Indoles	R'	Yield
6w	H	96%
6x	5-NO_2	77%
6y	4-CN	93%
6z	5-Br	90%
6aa	5-OMe	90%
6ab	2-Me	47%

Carbazole	R'	Yield
6ag	H	82%

Pyrroles	R'	Yield
6ac	2-CN	81%
6ad	2-CO_2Me	67%
6ae	3-Bpin	86%
6af	3-Br	82%

Scheme 4 (a–c) Reaction scope and (d, e) mechanistic studies for N-allylation



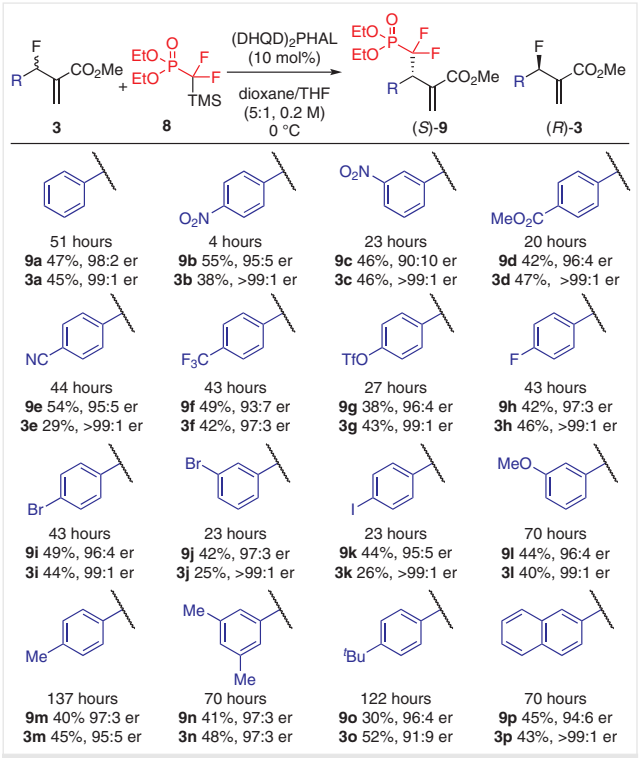
Scheme 5 (a, b) Reaction scope for the enantioselective N-allylation and (c) application for medicinal chemistry and the synthesis of pyrrolizinones. [a] Overall yield.

highly diastereoselective manner favoring the *trans* product (typically >25:1) while maintaining the enantiomeric ratios of the starting material. The origin of the diastereoselectivity in these reactions is facile epimerization at the α-carbon to the carbonyl, which is thermodynamically driven.

5 Enantioselective Phosphonyldifluoromethylation of Allylic Fluorides using a Latent Pronucleophile

The concept of latent nucleophiles applied to C-centered nucleophiles is better described as the concept of latent pronucleophiles. The latency is not necessarily imposed on the C-centered nucleophiles by a capping group like with the bulky silyl group in the case of N-centered nucleophiles.[20] Our first ventures in this direction were the attempts to carry out enantioselective allylation of the difluoromethyl anion that would arise from the difluoromethyltrimethylsilane latent pronucleophile, which met with failure. This suggested that it is only the stabilized C-centered nucleophiles that would be suitable pronucleophiles.

The difluoromethyl group is an oxygen bioisostere and a lipophilic hydrogen-bond donor commonly used by medicinal chemists as a substitute for hydroxyl groups in lead optimization.[21] Replacing the ester oxygen in a phosphate with a difluoromethyl group creates a bioisostere of phosphates that are of interest as potential inhibitor of kinases and enzymes involved in signaling through phosphorylation.[22] Intrigued by the need to introduce phosphonyldifluoromethyl group in drug-like molecules and driven by the desire to stabilize the difluoromethyl anion with additional substituents (and phosphonate fits the bill very well), we focused on diethyl (difluoro(trimethylsilyl)methyl)-phosphonate **8** as a latent pronucleophile in Lewis base catalyzed allylation (Scheme 6).[14]



Scheme 6 Scope for enantioselective allylation of difluoromethyl phosphonates.

The reactions of this unusual latent pronucleophile with allylic fluorides required an excess of the reagent to drive full conversion when DABCO was used as a catalyst. The kinetic resolution scenario discussed in the previous section usually requires an excess of the fluoride to drive full conversion of the latent nucleophile. Seemingly reconciling the

two requirements, we focused on optimization of reactions that use equimolar quantities of the two reactants. The optimized conditions involve $(DHQD)_2PHAL$ (10 mol%) as the catalyst in a mixture of dioxane and THF (5:1) at 0 °C (Scheme 6). The reactions are kinetic resolutions that, when stopped at around 50% conversion of the fluoride, give the products with enantiomeric ratios ranging from 90:10 for (*S*)-**9c** to 98:2 for (*S*)-**9a** typically with good isolated yields (30% up to 55%). Analysis of the remaining fluoride starting materials shows excellent enantiomeric ratios, often higher than 99:1. The recovered enantioenriched allylic fluoride can be easily transformed into the other enantiomer of the product by using the pseudoenantiomer of $(DHQD)_2PHAL$, $(DHQ)_2PHAL$ with similar yields and stereoselectivity. These reactions are the first examples of enantioselective phosphonyldifluoromethylation and they allowed a short investigation of the consequent transformations of the difluoromethylphosphonates. Such transformations proved to be significantly more stereoselective than related reactions with *N*-allyl-pyrroles due to the conformational preferences imposed by the difluoromethyl group.

6 Conclusion

The concept of latent nucleophiles and pronucleophiles is a powerful strategy to expand the nucleophile scope in Lewis base catalyzed reactions. The concept is based on three cornerstones: (i) the use of a capping group to impose latency and lower the nucleophilicity of the nucleophilic reaction partner, (ii) sequential activation of electrophile and the nucleophile where activation of the latter is dependent on the activation of the former and (iii) selectivity in generating the stabilized anionic nucleophiles. Although other types of latent (pro)nucleophiles are envisioned, N-silyl and C-silyl compounds have already been used as latent (pro)nucleophiles in Lewis base catalyzed allylic substitutions of allylic fluorides. In addition to expansion of the nucleophile scope in Lewis base catalyzed reactions, latent nucleophiles are instrumental in ensuring high regioselectivities and are an enabling factor in enantioselective transformations that use chiral Lewis base catalysts. The concept should not be limited to Lewis base catalysis and will likely prove to be a general strategy that is useful in other areas of organic chemistry. Numerous applications of this concept in transition-metal-catalyzed processes can be envisioned, and recent reports[23] are an indication of its broader potential.

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Publication P5

Enantioselective Lewis base catalyzed phosphonyldifluoromethylation of allylic fluorides using a C-silyl latent pronucleophile

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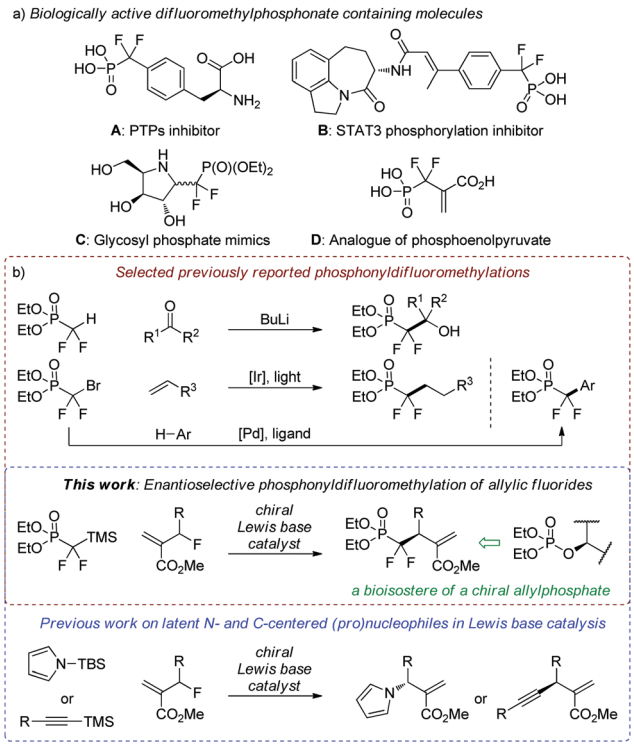
Enantioselective Lewis base catalyzed phosphonyldifluoromethylation of allylic fluorides using a *C*-silyl latent pronucleophile†

You Zi, Markus Lange and Ivan Vilotijevic *

The first enantioselective phosphonyldifluoromethylation is enabled by the use of diethyl (difluoro(trimethylsilyl)-methyl)phosphonate reagent as a latent pronucleophile in the Lewis base catalyzed substitution of allylic fluorides. The reaction proceeds as a kinetic resolution to produce both the difluoromethylphosphonate products and the remaining fluorides in good yields and with high stereoselectivity. The use of cinchona based alkaloid catalysts enables the facile synthesis of both enantiomers of the difluoromethylphosphonate products.

The difluoromethyl group, an oxygen bioisostere and a lipophilic hydrogen-bond donor, is commonly used in medicinal chemistry as a replacement for hydroxyl groups that improves the properties of biologically active molecules.[1] In a similar vein, difluoromethylphosphonate motifs ($-CF_2P(O)(OR)_2$) have emerged as metabolically stable bioisosteres of phosphates.[2] They are surprisingly resistant to hydrolysis and are therefore bioavailable unlike the typical phosphate analogues. The phosphonic acids mimic the tetrahedral transition state in the hydrolysis of peptides, which may also be the basis for the biological activity of numerous difluoromethylphosphonate containing enzyme inhibitors.[3] Pioneering examples include protein tyrosine phosphatase (PTP) inhibitors (**A**, Scheme 1),[4] STAT3 phosphorylation inhibitors (**B**),[5] mimics of sugar phosphates (**C**)[6] and analogues of phosphoenolpyruvate (**D**).[7] The resulting demand for difluoromethylphosphonates has inspired the development of strategies to introduce this structural motif into drug like molecules (Scheme 1b).[8] These include nucleophilic additions and substitutions with the difluoromethylphosphonate anion with suitable electrophiles,[9] additions of the difluoromethylphosphonate radical to π-systems,[10] and the transition metal catalyzed coupling reactions for the synthesis of aryldifluoromethylphosphonates.[11] Despite the abundance of naturally occurring chiral organophosphates, the stereoselective methods to prepare difluoromethylphosphonates featuring an adjacent stereogenic center are currently limited to substrate controlled diastereoselective reactions.[9c,9g] A catalyst controlled enantioselective method to introduce difluoromethylphosphonates while creating and controlling the configuration of an adjacent stereogenic center would be an enabling factor for further studies of this important bioisostere.[12] With this in mind, we set off to develop a method to produce such chiral bioisosteres of alkyl or allyl phosphates in an enantioselective fashion.



Scheme 1 (a) Examples of biologically active difluoromethylphosphonates. (b) Comparison of this work with the previous methods for phosphonyldifluoromethylation and the use of latent (pro)nucleophiles in Lewis base catalysis.

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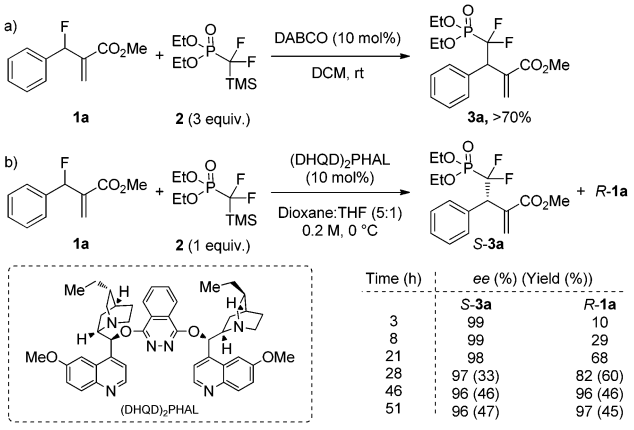
Allylic substitutions have long served as a powerful tool for stereoselective synthesis both in transition metal and Lewis base catalyzed reactions, the latter being considered an important part of the green chemistry toolbox.[13] The most common Lewis base catalyzed allylic substitutions utilize Morita–Baylis–Hillman adducts as electrophiles,[13c,d] but the scope of these reactions for *N*- and *C*-centered nucleophiles is limited.[14] To address these challenges, we introduced the concept of latent nucleophiles, molecules that are not nucleophilic themselves but can be activated to act as nucleophiles in Lewis base catalyzed reactions.[15] *C*- and *N*-trialkylsilyl latent (pro)nucleophiles[16] undergo enantioselective Lewis base catalyzed allylation with allylic fluorides (Scheme 1b).[15,17] In these reactions, the formation of the activated nucleophile depends on the decomposition of the silicate intermediate formed by nucleophilic addition of the fluoride to the silyl group of the latent pronucleophiles.[15a,17a,18] We hypothesized that this strategy could be generally applicable to a variety of stabilized *C*-nucleophiles and useful in addressing specific synthetic problems. Here, we report that (difluoro(trimethylsilyl)methyl)phosphonates serve as versatile latent pronucleophiles in Lewis base catalyzed substitutions of allylic fluorides and enable the development of the first enantioselective method to introduce the (diethoxyphosphoryl)difluoromethyl group, while controlling the configuration of the adjacent stereogenic center.

The feasibility of our approach was evaluated using commercially available diethyl (difluoro(trimethylsilyl)methyl)-phosphonate **2** in the DABCO catalyzed allylic substitution of allylic fluoride **1a**, derived from the Morita–Baylis–Hillman alcohol adduct of acrylic ester and benzaldehyde (Scheme 2a). Good yields in this reaction were achieved only if an excess of the latent pronucleophile **2** was used to increase the conversion of the fluoride to the corresponding (difluoromethyl)phosphonate **3a**. Accordingly, the initial optimization efforts using chiral Lewis base catalysts were made with superstoichiometric quantities of **2**. In the presence of $(DHQD)_2PHAL$ catalyst, most reactions proceeded with good enantioselectivity but, despite the use of an excess of the reagent, yields for the desired allylation product remained close to but below 50%. This was indicative of a kinetic resolution scenario,[17a] where one of the enantiomers of allylic fluoride readily reacts with the chiral catalyst while the other enantiomer remains unchanged.



Time (h)	*ee* (%) (Yield (%))	
	S-**3a**	*R*-**1a**
3	99	10
8	99	29
21	98	68
28	97 (33)	82 (60)
46	96 (46)	96 (46)
51	96 (47)	97 (45)

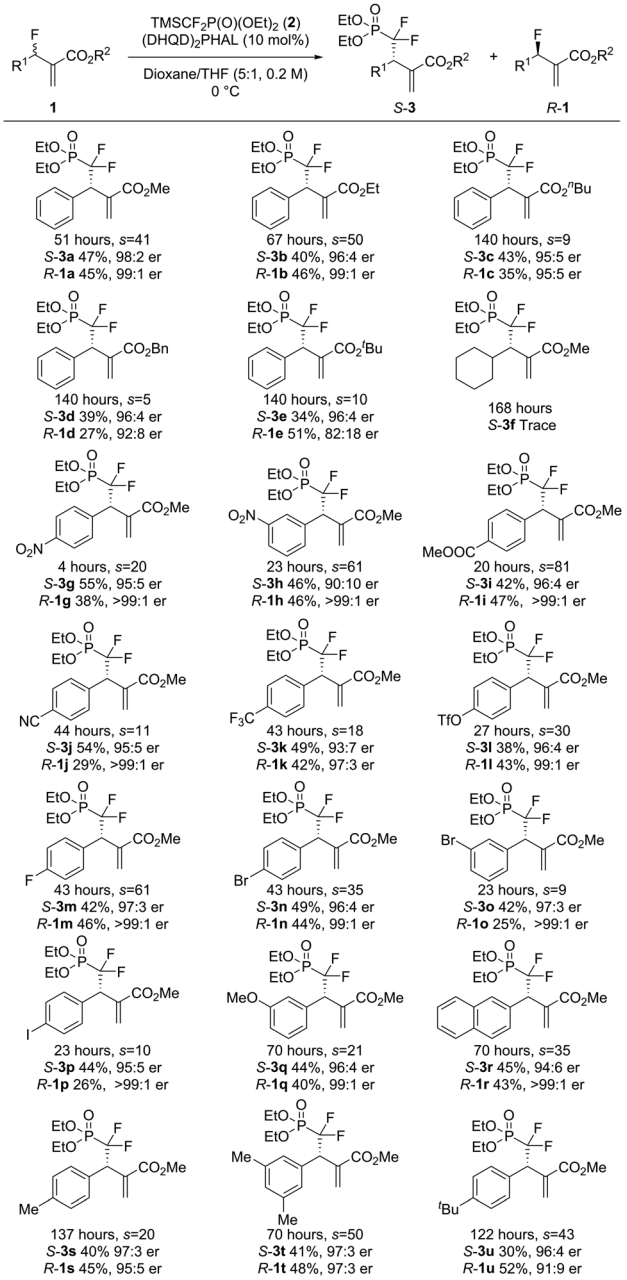
Scheme 2 Early optimization studies and the kinetic resolution of **1a**.

To reconcile the need for superstoichiometric quantities of the reagent that would increase conversion rates and the requirement for a higher concentration of the fluoride that could drive kinetic resolution to completion with respect to the reagent, further optimization studies were focused on reactions using equimolar quantities of allylic fluoride and the reagent (Scheme 2b). The variables in reaction condition screening included: the identity of the chiral catalyst, catalyst loading, reaction solvent, temperature and concentration (for details of optimization studies, please see the supporting information). In a 5 : 1 mixture of dioxane and THF at 0 °C with 10 mol% $(DHQD)_2PHAL$ catalyst, the reactions of **1a** and **2** proceeded to close to 50% conversion after 51 hours and afforded the allylation product **3a** in 47% yield and 98 : 2 ratio of enantiomers (Scheme 2b).

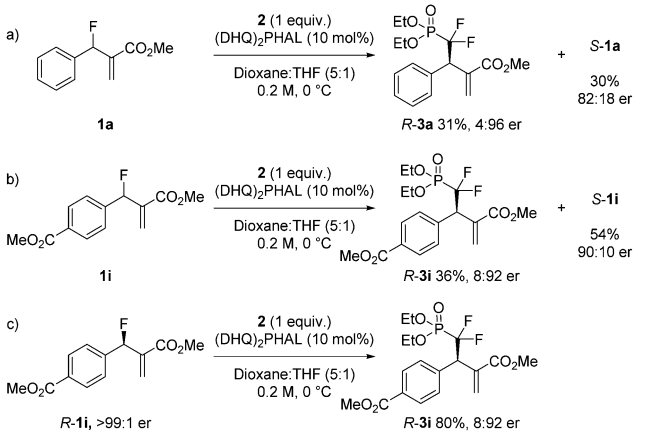
Closely monitoring the reaction progress showed that the ratio of enantiomers in the product remained nearly constant throughout the reaction, but that of the allylic fluoride steadily increased with time/conversion (Scheme 2b).

Upon optimization of the reaction conditions, the reaction scope for allylic fluorides was evaluated (Scheme 3). The low reaction rates allowed for close monitoring of the kinetic resolution reactions by NMR and/or HPLC on a chiral stationary phase. The reactions were allowed to run until there were no further changes in the er values of the remaining allylic fluoride or when it reached a level equal to or higher than 99 : 1. A range of esters, including methyl, ethyl, *n*-butyl, benzyl and *t*-butyl esters (**1a–1e**), were investigated and converted to the corresponding products *S*-**3a–3e** in good yields (34–47%) with good enantioselectivity (95 : 5 to 98 : 2 er). The presence of electron withdrawing groups in allylic fluorides **1g–1l** noticeably increased the reaction rates and the (difluoromethyl)phosphonate products *S*-**3g–3l** were isolated in both good yields (38–55%) and enantioselectivities (90 : 10 to 96 : 4 er). Allylic fluorides featuring halogen substituents, **1m–1p**, were also well tolerated under the optimal conditions, and all gave the products *S*-**3m–3p** in good yields (42–49%,) with excellent degrees of stereocontrol (95 : 5 to 97 : 3 er). The reactions with allylic fluorides bearing electron rich aromatic substituents **1q–1u** were subsequently carried out. These uniformly required a longer time to reach half-conversion but ultimately led to satisfactory outcomes with yields between 30% and 45% and enantiomeric ratios between 94 : 6 and 97 : 3. Installing alkyl instead of aryl substituents lowered the reaction rates to synthetically impractical levels (**3f**). In most reactions, the enantiomeric ratio for the remaining ally fluorides *R*-**1** was 99 : 1 er or higher. The absolute configuration of the products was assigned by analogy to similar reactions using $(DHQD)_2PHAL$.

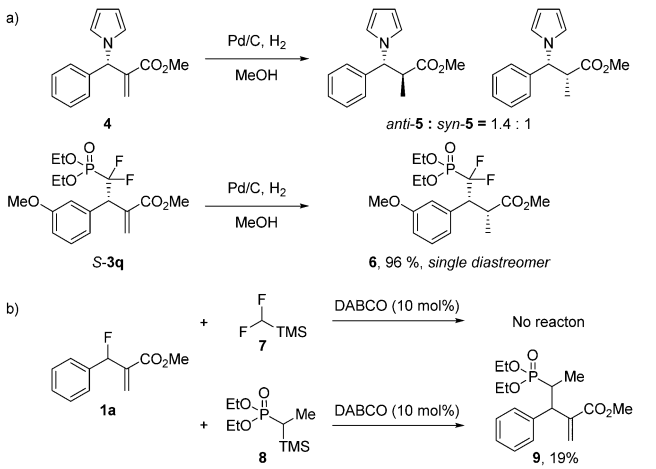
Switching the catalyst to the $(DHQD)_2PHAL$ pseudoenantiomer, $(DHQ)_2PHAL$, unsurprisingly resulted in the preferential formation of the other enantiomer although with slightly lower stereoselectivity (4 : 96 er for *R*-**3a** and 8 : 92 for *R*-**3i**, unoptimized results, Scheme 4). Furthermore, the enantioenriched allylic fluoride *R*-**1i** (> 99 : 1 er) recovered from the $(DHQD)_2PHAL$ catalyzed reactions



Scheme 3 Enantioselective $(DHQD)_2PHAL$ catalyzed allylic substitution of allylic fluorides **1** using **2** as the latent pronucleophile. The selectivity factor[19] (*s*) was based on recovered **1**.



Scheme 4 Comparative test with $(DHQ)_2PHAL$ instead of $(DHQD)_2PHAL$ and reaction with enantioenriched allylic fluoride.



Scheme 5 Diastereoselective hydrogenation of *S*-**3q** and influence of the difluoromethylphosphonate on the stereochemical outcome. Attempted reactions of **1a** with related latent pronucleophiles.

could be used as a starting material to produce *R*-**3i** with the same stereoselectivity and in 80% yield in the presence of $(DHQ)_2PHAL$.

In addition to serving as a bioisostere of phosphates, difluoromethylphosphonate strongly influences the conformational preferences of the product, which can be exploited to control stereoselectivity in the subsequent transformation. For example, simple hydrogenation of analogues containing N-heterocycles instead of the difluoromethylphosphonate proceeds with low diastereoselectivity (1.4 : 1),[15b] while the same reactions of difluoromethylphosphonate analogues afford only the *syn* diastereomer of **6** in a nearly quantitative yield of 96% (Scheme 5a).

The effects of the fluorine atoms and the phosphonate on the stability of the activated nucleophile were briefly explored by examining the DABCO-catalyzed reactions of allylic fluoride **1a** with the related latent pronucleophiles: TMS-difluoromethane **7** and the diethyl (1-(trimethylsilyl)ethyl)phosphonate **8** (Scheme 5b). **7** failed to react with the allylic fluoride while the phosphonate containing alkylsilane **8** afforded the desired product **9** although in low yields (unoptimized results). This indicates that the formation and decomposition of the silicate intermediate may be the determining factor for the outcome of the reaction.

In conclusion, the first enantioselective method to introduce a phosphate bioisostere, $-CF_2P(O)(OR)_2$, has been developed by using diethyl (difluoro(trimethylsilyl)methyl)phosphonate reagent **2** as a latent pronucleophile in the Lewis base catalyzed substitution of allylic fluorides. The reactions proceed as the kinetic resolution of the racemic fluorides, which affords both the difluoromethylphosphonate product and the recovered allylic fluoride in good yields and with high enantiomeric ratios. The reactions are operationally simple, use commercially available

reagents and catalysts and transform readily available Morita–Baylis–Hillman fluorides to the stable difluoromethylphosphonates. Both enantiomers of the product can be readily accessed and they are amenable to further stereoselective transformations owing to the conformational effects of the difluoromethylphosphonate.

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Conflicts of interest

There are no conflicts to declare.

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Publication P6

Lewis-base-catalysed selective reductions of ynones with a mild hydride donor

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Lewis-base-catalysed selective reductions of ynones with a mild hydride donor†

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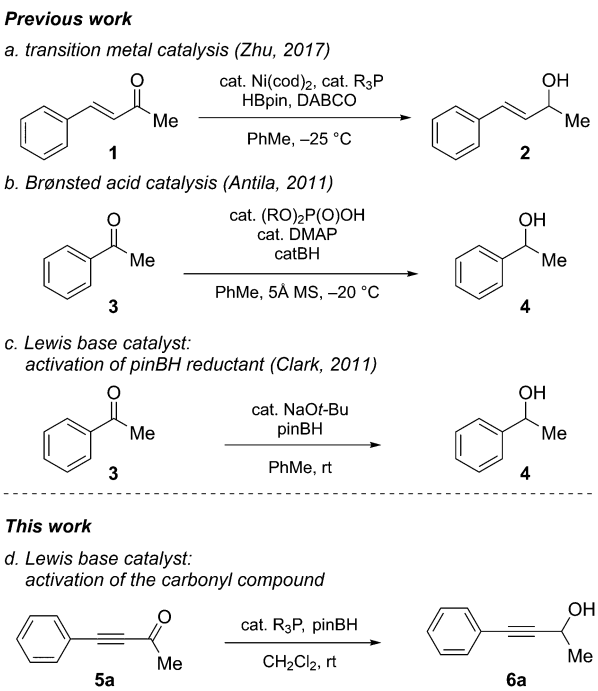
Ynones are efficiently reduced with a mild hydride donor in the presence of a catalytic amount of nucleophilic phosphines. The reactions are selective 1,2-reductions that give propargyl alcohols in yields of up to 96%. It is proposed that success in these reactions depends on the activation of ynones by a Lewis base catalyst. A protic additive plays a key role in suppressing the undesired reaction pathways and accelerating the 1,2-reductions.

Propargylic alcohols are a common moiety in natural products and biologically active molecules,[1] and they serve as versatile intermediates in organic synthesis.[2] Secondary propargylic alcohols can be prepared *via* 1,2-reduction of ynones that are easily accessible, *i.e. via* addition of alkynyl nucleophiles to various carbonyl compounds.[3] Reductions of carbonyl compounds, including ynones, and the chemoselectivity of these reactions have been the subjects of investigation for many decades.[4] Recent efforts have focused on the use of mild reducing agents, mild hydride donors, with an overall goal of developing more selective transformations.[5]

Easy to handle, mild hydride donors such as pinacolborane (pinBH) are ideal reductants for applications in the small scale preparation of compound libraries where the scope and generality are of high importance. The low reactivity of pinBH prevents its direct use as a reducing agent and enables its use in catalytic processes.[6] The common strategies to increase the reactivity of such mild hydride donors, illustrated in Scheme 1, are to rely on transition metal mediated activation,[7] Brønsted or Lewis acid activation of the substrate,[8] and/or activation of borane with a suitable Lewis base.[9] Inspired by reductions catalysed by frustrated Lewis pairs,[10] and the surge of interest in metal-free catalysts for reductions,[8,11] we speculated that (i) a suitable Lewis base may be used to activate the carbonyl substrate, instead of activating borane, and increase its reactivity towards mild hydride donors such as pinBH (Scheme 1d) and that (ii) different carbonyl compounds could be chemoselectively reduced based on their contrasting reactivities with Lewis bases.



Scheme 1 Catalytic reduction of carbonyl compounds with mild-hydride-donor boranes.

To test both of our hypotheses, we focused on reactions of pinBH with ynone **5a** and simple ketones (acetophenone and cyclohexanone) in the presence of a Lewis base catalyst. The choice of a catalyst and a reaction solvent in the initial experiments was governed with the intent to activate the carbonyl compound while avoiding activation of borane through creation of a Lewis adduct. Simple nucleophilic phosphines were chosen as catalysts because they do not form stable adducts with pinBH.[12] Dichloromethane, 1,2-dichloroethane and toluene were

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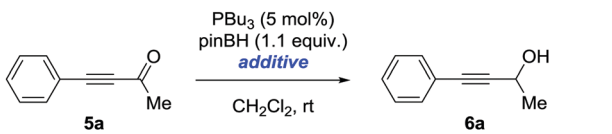
† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data for all compounds. See DOI: 10.1039/c8cc00058a

used as solvents to avoid activation of pinBH through the formation of Lewis adducts with solvent molecules. In the presence of catalytic amounts of tributylphosphine (20 mol%), ynone **5a** readily reacted with pinBH while acetophenone and cyclohexanone remained unaffected after prolonged exposure to the reaction conditions. In the absence of phosphine catalysts, pinBH does not reduce the ynone **5a**. These experiments seemingly corroborated the initial hypotheses showing (i) the effectiveness of phosphine catalysts in reductions of ynones with pinBH and (ii) that phosphines do not promote reduction of ketones which opened the door for the development of chemoselective catalytic reactions.

The product mixture isolated in the reaction of ynone **5a** highlighted the issues with reaction regioselectivity. The well-established modes of reactivity including 1,2- and 1,4-reductions with possible overreduction pathways, alkyne hydroboration, and dimerization or oligomerization of ynones could easily lead to the formation of a variety of different products. The major products in the reduction of ynone **5a**, however, were the products of 1,2- and 1,4-reductions, **6a** and **1**. The products of overreduction (allylic alcohol derived from **1**) and ynone dimerization were observed in minor quantities.

Further optimization of the reaction conditions revealed that protic additives suppress the major side reactions: 1,4-reduction and dimerization/oligomerization of ynones (Table 1). The increase in the selectivity and isolated yields of propargylic alcohol **6a** correlates with the increased amount of *tert*-butanol in the reaction milieu (Table S1, ESI† document). When 1.5 equivalents of *tert*-butanol were present in the mixture, products of 1,4-reduction and dimerization/oligomerization were not observed and the propargylic alcohol **6a** was the only product isolated upon aqueous work up. Furthermore, in the presence of the *tert*-butanol additive, catalyst loading could be reduced to as low as 1 mol% for tributylphosphine without affecting the yield. Only 1.1 equivalents of pinBH were sufficient to effect the complete consumption of the starting ynone.

Table 1 Effects of additives on reaction selectivity and isolated yield of the 1,2-reduction product



5a **6a**

Entry	Additive (1.5 equiv.)	Time	Yield of **6a**[a] (%)
1	AcOH	120 min	(Trace)
2	DABCO	16 h	0
3	NEt_3	16 h	(18)
4	*t*-BuOK	10 min	(Trace)
5	H_2O	10 min	86 (86)
6	MeOH	60 min	61
7	EtOH	60 min	64
8	i-PrOH	10 min	94
9	*t*-BuOH	10 min	87 (89)

[a] Isolated yield of **6a**. Numbers in brackets designate yields determined by ^{1}H NMR spectroscopy of crude product mixtures after quenching at a designated time point using triphenylmethane as the standard.

In the absence of phosphine, *tert*-butanol does not catalyse the 1,2-reduction reaction: reduction product **6a** was not observed after 6 hours in the presence of 2 equiv. of pinBH and 2 equiv. of alcohol.

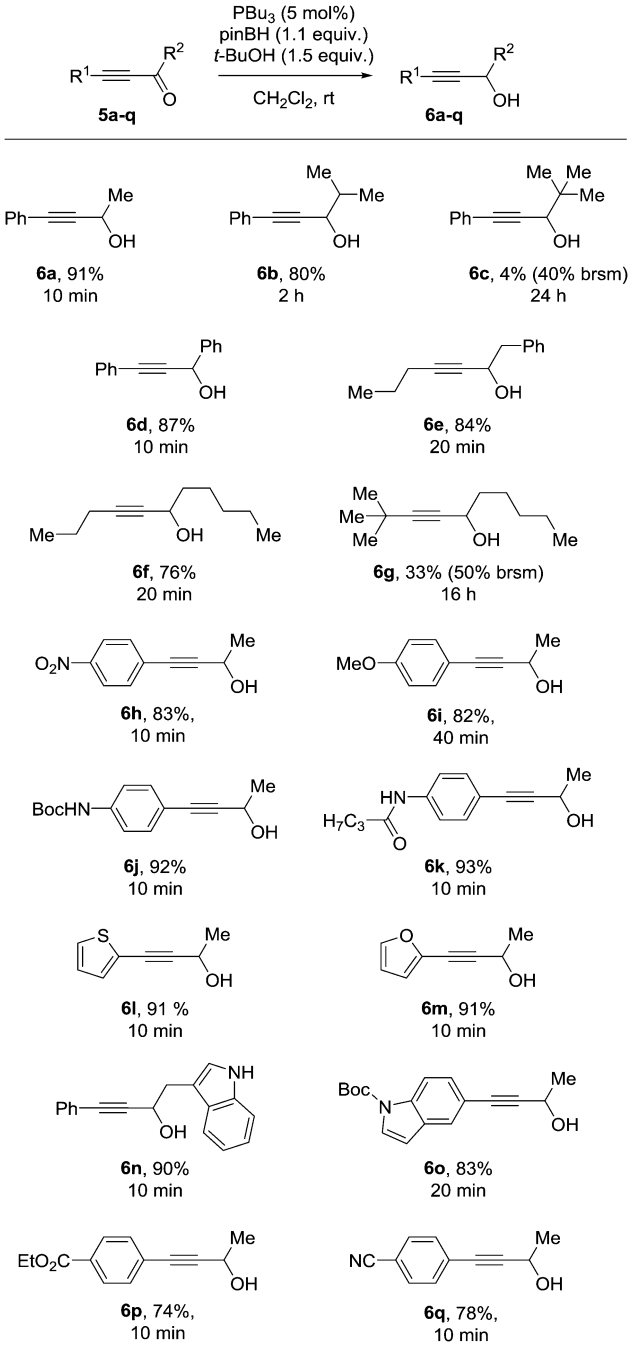
A set of commercially available and easy to handle alkyl- and arylphosphines was tested as Lewis base catalysts in the reductions of ynones (for detailed results see Table S2, ESI† document). Triphenylphosphine and diphenylmethylphosphine provided the desired products in acceptable yields but required longer reaction times and failed to drive the complete consumption of ynone after 24 hours. Trialkylphosphines proved to be more efficient catalysts with tributyl- and trimethylphosphine both effecting the full conversion of ynones within 10 minutes with desired products isolated in high yields. In contrast, bulky trialkylphosphines, tri-*t*-butylphosphine and tricyclohexylphosphine, showed decreased activity which highlighted the importance of nucleophilicity of the phosphine catalyst for a successful reaction outcome.

Upon optimizing the reaction conditions for the reduction of **5a**, the substrate scope for the 1,2-reductions of ynones was evaluated with special attention to the identity of the α' and γ substituents in the ynones. Urgency to evaluate various combinations of alkyl and aryl substituents was brought on by the previous reports which map an extremely divergent reactivity network in phosphine catalysed reaction of ynones or ynoates under similar reaction conditions.[13]

Gratifyingly, substrates with either alkyl or aryl groups in α' and γ positions were equally reactive as **5a**, all providing the products of 1,2-reductions in good yields (Scheme 2, compounds **6a**, **6b**, **6d**, **6e** and **6f**). A similar reactivity was observed even when a tertiary carbon centre was present in α' or γ positions of the ynone. However, quaternary carbon centres in these positions significantly decrease the rates of the reduction reactions making them less practical (Scheme 2, compounds **6c** and **6g**).

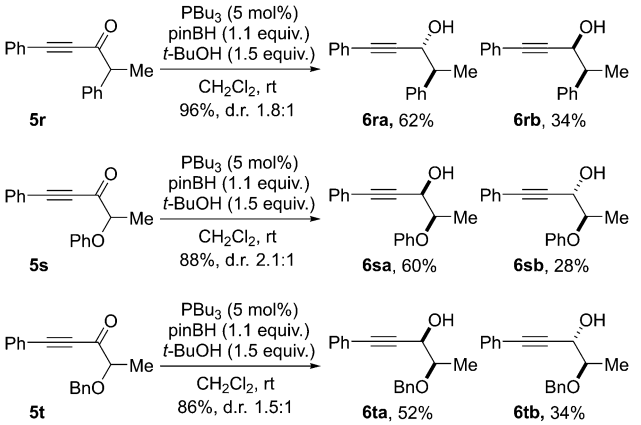
Further inspection of the substrate scope has shown that both electron rich and electron poor ynones are efficiently reduced under the optimized conditions (**6h**, **6i**, **6j** and **6k**). A selection of substrates containing various heterocycles such as furan, thiophene, both protected and non-protected indoles and protected aniline all tolerated the mild reaction conditions well and produced the corresponding propargyl alcohols in good yields (Scheme 2, compounds **6j–6o**). It is worth noting that under optimized conditions, acetophenone and cyclohexanone do not react even after longer periods of time similar to our initial experiments. Other reducible groups are also not affected under optimized conditions as illustrated by substrates **6h**, **6j**, **6k**, **6o**, **6p** and **6q** which contain nitro, carbamate, amide, ester and nitrile groups respectively.

A closer inspection of the substrate scope clearly matched the expectations arising from our initial hypothesis. The substrates with electron withdrawing substituents that should render the ynone more electrophilic were reduced significantly faster than the corresponding substrates that carry electron donor groups (*i.e.* compound **6h** *vs.* **6a** *vs.* **6i**, Scheme 2). These observations are consistent with simple hydride delivery to carbonyl substrates. Knowing that phosphine does not react



Scheme 2 Reaction scope for the phosphine catalysed ynone reduction with pinacolborane.

with *tert*-butanol or pinBH,[12] we propose that the observed rate acceleration is also a consequence of a higher rate of 1,4-addition of the phosphine catalyst to ynones. In the presence of protic additives, the resulting zwitterionic intermediate would get protonated to produce the corresponding vinylphosphonium salts.[14] Quenching of the enolate intermediate initially produced by conjugate addition of phosphine is believed to play a key role in suppressing the oligomerization of ynones which occurs rapidly in the absence of an additive or borane and in suppressing the 1,4-reduction pathways.



Scheme 3 Substrate control of diastereoselectivity in the phosphine catalysed 1,2-reductions of ynones.

After establishing that a tertiary carbon centre in the α′ position does not deter the reactivity of ynones (Scheme 2, entries **6b** and **6d**), diastereoselectivity of the reductions was briefly examined with ynones **5r**, **5s** and **5t** (Scheme 3).[15] The reactions of **5r** produced a 1.8 : 1 mixture of diastereomers **6ra** and **6rb** with a combined yield of 96%. Reductions of **5s** and **5t** which feature a phenyl and a benzyl ether substituent in α′ positions, respectively, also proceeded with moderate diastereoselectivity producing a 2.1 : 1 mixture of **6sa** and **6sb** and a 1.5 : 1 mixture of **6ta** and **6tb** (*anti* diastereomer favoured in both cases). The observed low diastereoselectivity in these reactions may be a consequence of the low selectivity in the formation of *E*- and *Z*-vinylphosphonium intermediates and suggests that the coordination of borane followed by intramolecular hydride delivery is not the dominant pathway.

Finally, the scalability of the developed transformation was tested. Reduction of **5a** on a gram-scale proceeds efficiently without deterioration of the isolated yield.

In conclusion, we have developed a phosphine catalysed chemoselective 1,2-reduction of ynones using pinBH as a mild hydride donor. The key control element in these reactions is the presence of a protic additive, *tert*-butanol, which plays a role in suppressing 1,4-reduction and ynone dimerization pathways and in increasing the reaction rates of the 1,2-reduction presumably through the activation of pinBH. The efficiency of this transformation has been demonstrated on a number of structurally diverse ynones with high yields observed for 1,2-reductions of both electron rich and electron poor ynones carrying either aryl or alkyl substituents. The reactions appear to be selective for ynones indicating that activation of the carbonyl substrate, and not the reductant, by the phosphine catalyst plays a critical role. The detailed mechanistic aspects of this process will be the subject of future investigations.

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Conflicts of interest

There are no conflicts to declare.

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Publication P7

trans-Hydroboration *vs.* 1,2-reduction: divergent reactivity of ynones and ynoates in Lewis-base catalyzed reactions with pinacolborane

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trans-Hydroboration *vs.* 1,2-reduction: divergent reactivity of ynones and ynoates in Lewis-base-catalyzed reactions with pinacolborane†

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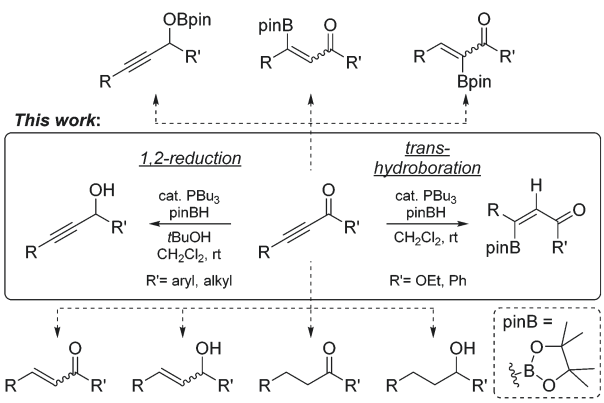
Ynones and ynoates react with pinacolborane in a divergent manner in the presence of nucleophilic phosphine catalysts. Ynones are transformed to the corresponding propargyl alcohols in good yields with high regio- and chemoselectivity. Ynoates undergo highly regio- and stereoselective *trans*-hydroboration to produce *E*-vinylboronates. Impressive divergence in reactivity of ynones and ynoates can be traced back to the mechanistic aspects of 1,2-reduction and *trans*-hydroboration. A comparative analysis of the two pathways paints a complex picture in which different reaction rates control selectivity in these seemingly unrelated processes and explains how sufficiently acidic protons in the reaction mixtures can be used to steer the selectivity in different directions.

Introduction

Neutral boron hydrides are among the most versatile reagents in organic synthesis most commonly used as stoichiometric reductants[1] and as reagents for hydroboration of unsaturated compounds.[2] Both Lewis acidic (boron atom) and nucleophilic (hydride) properties, and therefore the reactivity of boranes, can be tuned over an unusually wide range by controlling the identity of substituents on neutral boron hydrides, and the identity of the activating Lewis base in Lewis adducts that involve boranes.[3] Among neutral boron hydrides, pinacolborane has emerged as a commonly used mild reagent for reduction and hydroboration reactions.[4] Relatively low reactivity of pinacolborane towards alkenes and alkynes has made it an ideal reaction partner in catalytic reactions where catalyzed pathways easily outcompete non-catalyzed pathways and background reactions.[5] Activation of pinacolborane in these catalytic reactions has been achieved by transition metals,[2f,5d,g] Lewis bases[1i,6] and Lewis or Brønsted acids.[1e,g,h]

A large body of work in the past decade has established that small molecules can be activated by frustrated Lewis pair catalysts.[7] These Lewis pairs are often structurally complex, expensive and not easily accessible. Simple trialkyl- and triarylphosphines do not form stable Lewis adducts with pinacolborane.[6] Intrigued by the finding that these simple to handle, cheap and easily accessible reagents constitute a non-traditional frustrated Lewis pair,[8] we set off to explore the reactions of quintessential substrates in Lewis base catalysis, α,β-unsubstituted carbonyl compounds, with pinacolborane in the presence of phosphines as Lewis base catalysts.

If only the main reaction pathways, reduction and hydroboration, are considered, simple ynones could easily be transformed to upwards of twenty distinct products (Scheme 1).[4] These products would arise *via* 1,2-, 1,4- and over-reduction pathways, *syn*- and *trans*-hydroboration,[9] and various combinations of these pathways. The possibility of dimerization and



Scheme 1 Selectivity issues in reactions of ynones/ynoates with pinacolborane and outline of the selective transformations presented here: 1,2-reduction of ynones and *trans*-hydroboration of ynoates.

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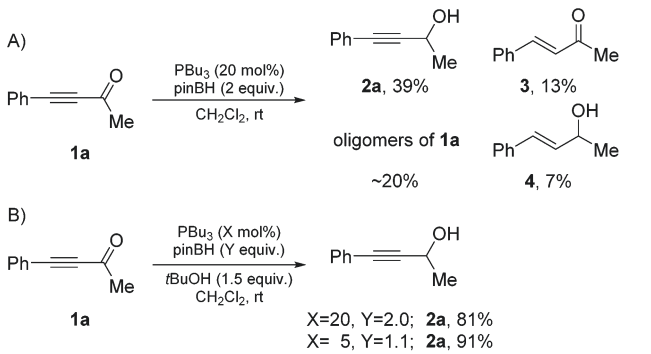
†Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data for new compounds. CCDC 1845339 for **12k** (excluding structure factors). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob01343h

oligomerization of ynone promoted by Lewis base further expands the landscape of possible products. Defying this complex network of reaction outcomes, we have recently reported that in the presence of an appropriate Lewis base catalyst and stoichiometric amount of protic additive, pinacolborane effects clean 1,2-reduction of ynones.[6] Here, we describe the chemoselectivity studies for the 1,2-reductions of ynones, present the organocatalyzed regio- and stereoselective *trans*-hydroboration reactions of ynoates, and report on the divergent reactivity of ynones and ynoates with pinacolborane in the presence of nucleophilic phosphine catalysts. A detailed analysis and comparison of the two pathways informs the means to control selectivity in related transformations.

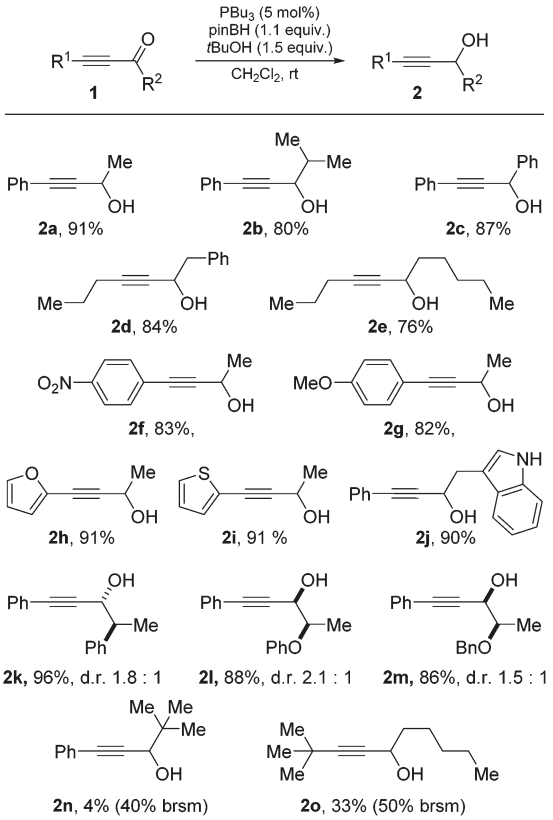
Results and discussion

When ynone **1a** in dichloromethane was treated with pinBH in the presence of catalytic amount of tributylphosphine (20 mol%), major products isolated from the reaction mixture were propargylic alcohol **2a**, enone **3** and allylic alcohol **4** together with a complex mixture of oligomers of **1a** (Scheme 2A). We have previously described that protic additives, water and simple alcohols, help steer the selectivity towards products of 1,2-reduction (Scheme 2B).[6] They accelerate the 1,2-reduction pathway and suppress 1,4-reduction and dimerization/oligomerization pathways.

Our previous studies have established that 5 mol% of PBu_3 and only 1.1 equivalents of pinBH in the presence of 1.5 equivalents of *t*BuOH in dichloromethane are sufficient to efficiently reduce a series of structurally diverse ynones to the corresponding propargyl alcohols (Scheme 3).[6] Both alkyl and aryl groups are tolerated in α′ and γ positions of the ynone (entries **2a**, **2b**, **2c**, **2d** and **2e**). Electron rich and electron poor ynones are reduced with equal efficiency (**2f** and **2g**). Various ynones containing O-, S- and N-heterocyclic motifs are also efficiently reduced to the corresponding alcohols (**2h**, **2i** and **2j**). When tertiary carbon center was present in α′ position of the ynone, yields of propargylic alcohols remained high (**2b**, **2k**, **2l** and **2m**). Low diastereoselectivity observed in reactions



Scheme 2 Lewis base catalyzed reduction of ynones with pinacolborane – the influence of protic additive on selectivity.

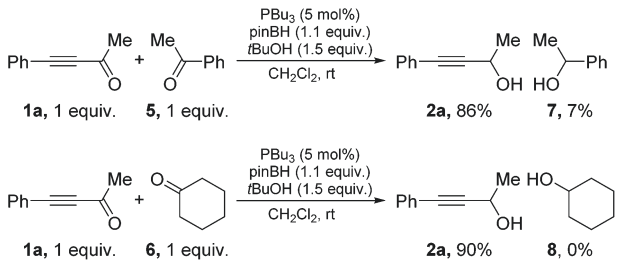


Scheme 3 Evaluation of the reaction scope for phosphine catalyzed 1,2-reduction of ynones with pinBH.[6] Isolated yields are shown.

that produce **2k**, **2l** and **2m** and apparent similarities between the substrates that feature a potential directing group in α′ position (O atom in **2l** and **2m** may coordinate to the borane and direct the delivery of the hydride) and those with non-coordinating substituents were indicative of the direct intermolecular delivery of the hydride to both π-faces of the carbonyl group. Finally, we have observed that quaternary carbon centers in α′ and γ positions reduce reaction rates significantly (**2n** and **2o**).

We have determined that simple aldehydes, ketones, esters, amides, carboxylic acids, alkenes, alkynes, aryl bromides and aryl iodides do not react with pinacolborane under the optimized reaction conditions with significant reaction rates. A study aimed at evaluating robustness of the method *via* typical competition experiments, however, led to several interesting discoveries.[10] We performed reactions using equimolar mixtures of ynone **1a** and simple substrates carrying various reducible functional groups (Scheme 4). When ketone **5** was used in the competition experiments with **1a**, partial reduction to the corresponding alcohol **7** was observed, although in low yield. In contrast, ketone **6** was not reduced under these conditions in competition experiments.

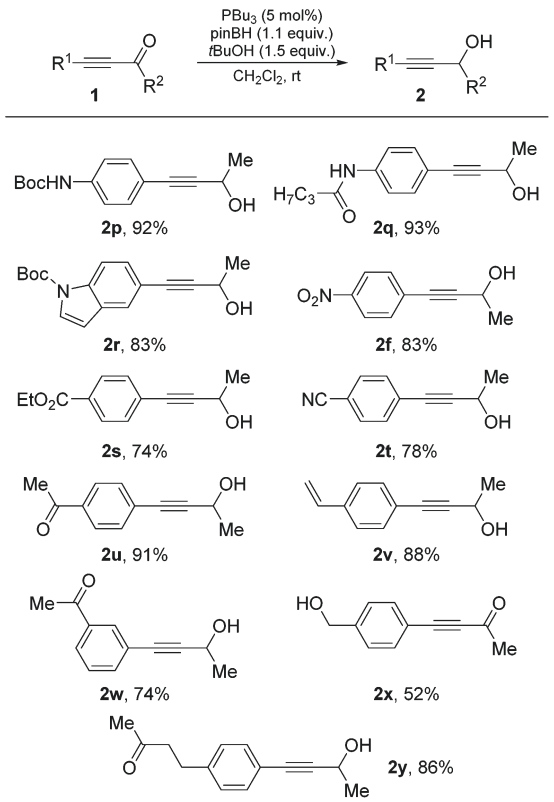
These results prompted a more detailed look into chemoselectivity of 1,2-reduction reactions. We designed and carried out a series of intramolecular competition experiments start-



Scheme 4 Competition experiments to test chemoselectivity and robustness in phosphine catalyzed 1,2-reduction of ynones with pinacolborane.

ing from compounds that feature an ynone and other groups prone to reduction (Scheme 5). These studies better mimicked the potential applications of chemoselective reductions in synthesis, and clearly demonstrated the chemoselective 1,2-reduction of ynones in the presence of carbamates (entries **2p** and **2r**), amides (**2q**), nitro compounds (**2f**), esters (**2s**), nitriles (**2t**), alkenes (**2v**) and ketones (**2u**, **2w** and **2y**). With substrates that feature both a ketone and an ynone, the corresponding diol was observed only in minor quantities. Reduction of benzylic aldehydes, regrettably, appeared to be faster than reductions of ynones under these conditions (**2x**).

Optimized conditions for 1,2-reduction of ynones do not affect reduction of simple ketones which suggested that, for



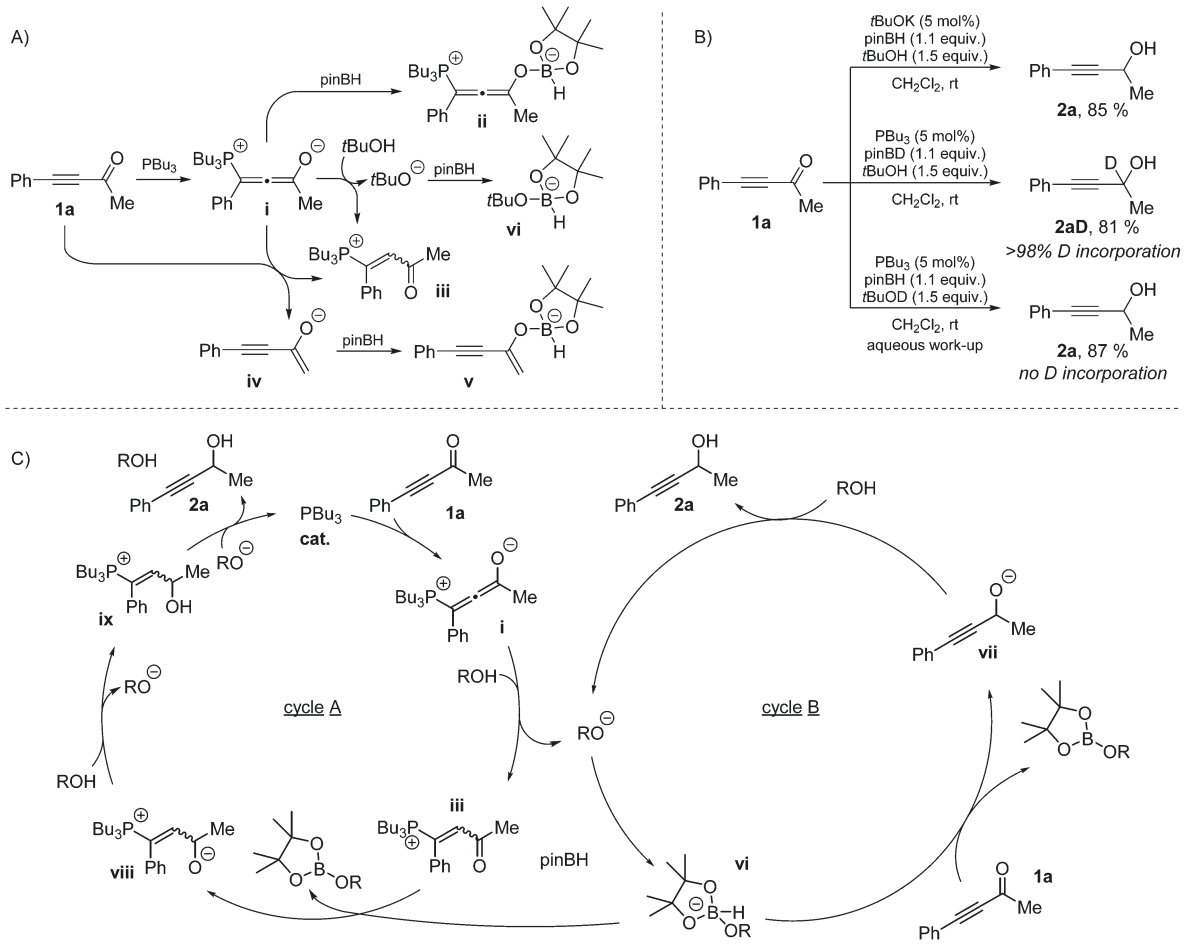
Scheme 5 Evaluation of chemoselectivity in phosphine catalyzed 1,2-reduction of ynones by pinacolborane. Isolated yields are shown.

the reaction to occur, pinacolborane must be activated by a Lewis base stronger than the carbonyl oxygen. This raised questions about the identity of the Lewis base that could coordinate to pinacolborane and increase the hydride donor ability of the resulting complex. Ynones and ynoates undergo conjugate addition of phosphines to produce enolate-type intermediates (**i**, Scheme 6A).[11] Addition of the Lewis base catalyst renders the ynone more nucleophilic and increases the Lewis basicity of oxygen atom in the intermediate. It was expected that this nucleophilic intermediate will interact with pinacolborane to produce **ii**. It was also apparent that **i** may act as a Brønsted base and deprotonate another molecule of the ynone or, if present in the mixture, a molecule of alcohol additive. The resulting enolate **iv** or *tert*-butoxide ion could interact with pinacolborane to produce adducts **v** and **vi** respectively.

Intermediate **iii** could be more prone to reduction than the starting ynone owing to its cationic character. This type of vinylphosphonium salts has been observed in the reaction mixtures by *in situ* NMR experiments.[6] Different product distribution in reactions with and without a protic additive suggested that the identity of the reductant (**ii** or **v** *vs.* **vi**) and the species that is reduced (**1** or **iii**) determine the reaction selectivity.

Initial mechanistic proposal involved addition of the phosphine catalyst to ynone followed by protonation of the resulting enolate by the protic additive to produce vinylphosphonium salt **iii** and *tert*-butoxide ion (Scheme 6C, cycle A). *tert*-Butoxide could then coordinate to pinBH to produce activated hydride **vi** which could, in turn, selectively reduce the carbonyl of vinylphosphonium salt to form allylic alcoholate **viii**.[1i] Proton transfer followed by elimination of the phosphine from intermediate **ix** could produce the propargyl alcohol and close the catalytic cycle. In this mechanistic scenario, direct reduction of vinylphosphonium salt explains the high selectivity for 1,2-reduction. The conjugate addition of the hydride on vinylphosphonium salt which would lead to 1,4-reduction is hindered by the sterically demanding phosphonium ion.

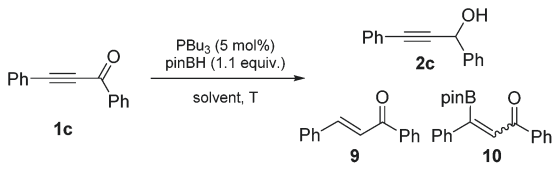
A simple experiment where potassium *tert*-butoxide was used as a catalyst instead of the phosphine, suggested that the active catalyst in the system may be the *tert*-butoxide ion (Scheme 6B). A series of labelling experiments using deuterated *tert*-butanol (*t*BuOD) and deuterated pinacolborane (pinBD) established that carbinol proton in propargyl alcohol can be traced back exclusively to the hydride of pinacolborane (Scheme 6B). Any deuterium incorporated from deuterated alcohol additive proved to be exchangeable under standard aqueous work-up conditions. These results also support a simpler mechanistic proposal where activated hydride source, intermediate **vi**, simply reduces the starting ynone directly and generates yet another alcoholate that could directly activate pinBH or deprotonate the protic additive to regenerate *tert*-butoxide ion (Scheme 6C, cycle B). While cycle A and cycle B depicted in Scheme 6C may operate in parallel, it is clear that activation of hydride source *via* alcoholate ions is required in the 1,2-reductions of ynones with pinBH.



Scheme 6 A) Possible pathways to activate pinacolborane by a Lewis base in phosphine catalysed reactions of ynones. (B) Labelling and product studies of 1,2-reduction of ynones. (C) Proposed mechanisms for the phosphine/*tert*-butoxide catalyzed 1,2-reduction of ynones to propargyl alcohols (R = *t*Bu).

With a better understanding of the role of the protic additive in the reductions of ynones, reactions without the additive were brought back to the focal point. In absence of protic additive, the role of oxygen-centered Lewis base that activates pinacolborane can be fulfilled by the enolate ions (**i** or **iv**, Scheme 6A). To prevent formation of enolate of type **iv**, we focused on the reactions of ynone **1c** which lacks acidic protons in α′ and γ position (Table 1). In the presence of protic additive, **1c** is cleanly reduced to the corresponding propargyl alcohol **2c** in 87% yield (entry 1). Without the protic additive, only trace amounts of propargyl alcohol **2c** were detected in the reaction mixture after 4 hours at room temperature (entry 2). More forcing conditions, in refluxing dichloroethane resulted only in 1,4-reduction to enone **9** (entry 3). When the reaction was performed in THF at elevated temperature, main product, isolated in 56% yield, was enone **9** along with a product of hydroboration **10** which was isolated in 23% yield (entry 4).

Table 1 Phosphine-catalyzed reactions of ynone **1c** with pinacolborane[a]



Entry	Conditions	2c	9	10
1	DCM, rt, *t*BuOH (1.5 equiv.)	87%	—	—
2	DCM, rt	<3%	—	—
3	DCE, reflux	—	77%[b]	—
4	THF, reflux	<3%	56%[b]	23%[b]

[a] NMR yields based on crude mixtures with triphenylmethane as the internal standard. [b] Isolated yields.

Knowing that the rates of hydroboration are much lower in absence of phosphine and that in absence of protic additive activation of borane by a Lewis base is unlikely,[12] we sought to test if this pathway could serve as a foundation for the development of a general method for phosphine catalyzed hydroboration of alkynes. Since ynones with acidic protons in α′ or γ

positions react predominantly *via* reductive pathways, to simplify the complex network of possible reaction outcomes, we turned our attention to aryl ynoates as surrogates of diaryl ynones.

We were pleased to discover that ethyl phenylpropiolate **11a** undergoes hydroboration in the presence of pinacolborane and catalytic amounts of tributylphosphine (Scheme 7).[13] Since ynoates are less prone to reduction, replacing the ynone with an ynoate reduced the rates of reduction reactions allowing for the vinylboronate to be isolated as the sole product. Initial assumption that the product of hydroboration **12a** is of *Z*-configuration was contradicted by the comparison to the spectral data for *Z*-vinylboronate obtained under previously reported conditions.[14] This suggested that **12a** is an *E*-olefin that could arise from a *trans*-selective hydroboration or a more common *syn*-hydroboration followed by isomerization.

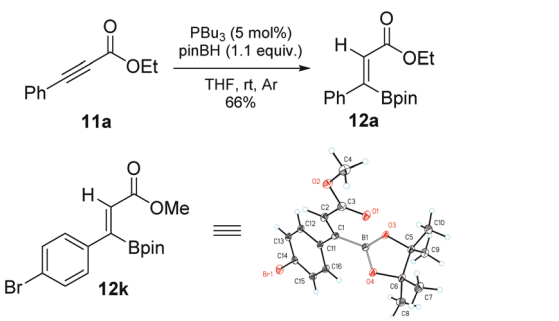
Very few examples of *trans*-selective hydroboration of alkynes have been reported to date and they uniformly rely on transition metal catalysts to confer selectivity to the system.[13,15] Pioneering work by Fürstner where cationic ruthenium(II) catalysts promote *trans*-hydroboration remains the only general method to perform this challenging transformation on internal alkynes.[16] Recent reports also describe pyridyl- and alkene-directed *trans*-hydroboration of internal conjugated alkynes.[17] These methods are, however, not suitable for electron poor alkynes and cannot be applied to *trans*-hydroboration of ynones or ynoates.

While the *anti*-difunctionalizations of ynoates reported by Ohmiya and Sawamura support the feasibility of *trans*-hydroboration,[18] the unusual outcome of this experiment called for a high scrutiny of the product structure. NOESY spectra of **12a** showed a cross peak between the vinylic and aryl hydrogens suggesting that they are on the same side of the double bond. Vinylboronate **12k** prepared from methyl 3-(4-bromophenyl) propiolate could be crystalized and crystallographic data obtained from single crystal measurement served as a proof of structure for *E*-vinylboronates (Scheme 7). No other products were observed in significant quantities in reactions of **11a**, including the *Z*-vinylboronate, the product of *syn*-hydroboration.

Optimization of solvent showed that reactions at room temperature performed best in halogenated solvents, dichloromethane and dichloroethane (Table 2, entries 1 and 4). Diethyl ether and tetrahydrofuran showed lower rates and generally lower yields for the vinylboronate **12a**. With the additional concern that ethers may activate borane for the more conventional *syn*-hydroboration and result in deterioration of stereoselectivity, the chlorinated solvents were chosen as optimal. Hydroboration of **11a** at increased temperature (Table 2, entry 5) afforded the product **12a** in comparable yields to the reactions at room temperature and the increase in reaction rates was apparent.

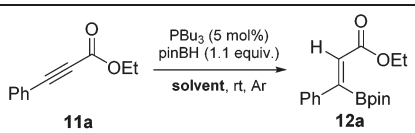
High yields of **12a** were obtained even with stoichiometric amount of pinacolborane. With slightly higher amount of borane (1.3 equiv.) there was no increase in yield and the use of 1.1 equivalents of pinacolborane was deemed optimal. While the use of methylpentanediolborane (4,4,6-trimethyl-1,3,2-dioxaborinane) resulted in diminished yields of *trans*-hydroboration product (68% NMR yield, Scheme 8A, entry **12f**), catecholborane and 9-BBN both failed to give any of the desired products.

Comparison of various Lewis base catalysts in the *trans*-hydroboration of ynoates demonstrated that identity of the Lewis base and it's nucleophilicity play crucial roles. Both O- and N-centered Lewis bases failed to catalyze the *trans*-hydroboration presumably because they form stable Lewis adducts with pinacolborane. In catalytic quantities, these also failed to sufficiently activate the borane for any other reaction pathway and no consumption of starting material was observed after 4 hours at room temperature (Table 3). Less nucleophilic phosphines, triarylphosphines and bulky trialkylphosphines failed to catalyze the reaction (Table 3, entries 5 and 6). More nucleophilic phosphines, such as methyldiphenylphosphine, afforded the reaction product in 12% yield with lower *E*/*Z* selectivity (Table 3 entry 4). Nucleophilic trialkylphosphines afforded the product of *trans*-hydroboration in high yields and excellent selectivity (>99 : 1) for the *E*-product (Table 3, entries 1 and 2). Catalyst loading with trimethyl- and tributylphosphines could be reduced to 2 mol%



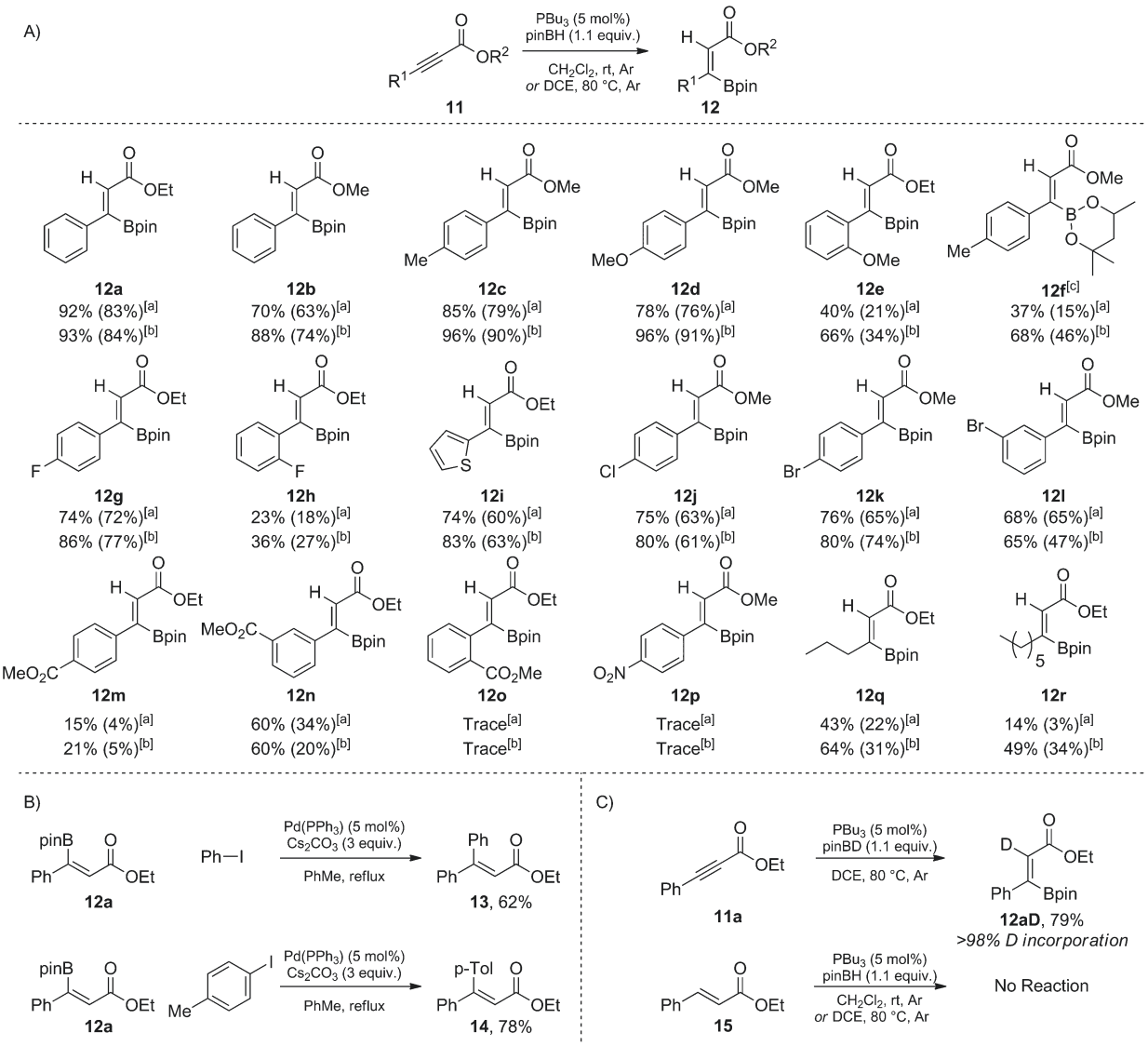
Scheme 7 Initial experiments on phosphine catalyzed *trans*-hydroboration of ynoate **11a** and the crystal structure analysis of *p*-bromo derivative **12k** as the proof of *E*-configuration of the double bond in vinylboronate products.

Table 2 Optimization of the solvent for phosphine catalyzed *trans*-hydroboration of ynoate **11a**



Entry	Cat.	Sol.	*T* (°C)	*t* (h)	NMR yield[a] (%)
1	PBu_3	DCM	rt	4	92 (83% isolated)
2	PBu_3	Et_2O	rt	4	45
3	PBu_3	THF	rt	4	66
4	PBu_3	DCE	rt	4	93
5	PBu_3	DCE	Reflux	2	94
6	PBu_3	PhMe	rt	4	64

[a] NMR yields based on triphenylmethane as the internal standard.



Scheme 8 (A) *trans*-Hydrobration of ynonates. Conditions: **11** (0.3 mmol), pinBH (0.33 mmol), PBu_3 (5 mol%), DCM, rt, or DCE, reflux. [a]NMR yields with Ph_3CH as the internal standard and isolated yields (in brackets) for reactions in DCM at rt. [b]NMR yields and isolated yields (in brackets) for reactions in DCE at reflux. [c]4,4,6-Trimethyl-1,3,2-dioxaborinane was used instead of pinacol borane. (B) *E*-Vinylboronates used in Suzuki coupling reactions. (C) Labeling and product studies of *trans*-hydroboration of ynoates.

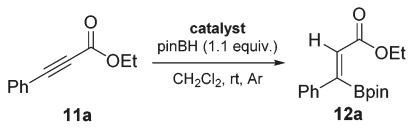
without deterioration of reaction yield in reactions of **11a** (Table 3, entry 3).

Under the optimized conditions a range of aryl ynoates are efficiently transformed to the corresponding vinylboronates (Scheme 8A). Both electron rich and electron poor substrates were processed including substrates that feature other reducible groups (**12a–12l**). Electron poor ynoates showed generally lower reaction rates which prompted further optimization of the conditions (**12m–12o**). Switching the solvent to dichloroethane allowed for the reactions to be heated to reflux temperature which significantly increased the reaction rates and, in some cases, resulted in higher yields compared to the reactions performed at room temperature. *E*/*Z* selectivity remained high across the board for ynoates **12a–12n** (>99 : 1, determined by ^{1}H NMR).

Because of low rates and low conversion of starting material, lower yields were observed with electron poor substrates (Scheme 8A, **12m**, **12n**) and substrates that feature *ortho* substituents on the aryl ring (**12e** and **12h**). Even in these cases, yields based on recovered starting material remained high. Substrates with strongly electron withdrawing substituents (**11o** and **11p**, precursors of **12o** and **12p**), however, failed to react under the optimized conditions. More forcing conditions including higher catalyst loadings and prolonged heating time in reactions of **11p** resulted in 1,4-reduction (14%) and over-reduction to the corresponding saturated ester (11%).

To demonstrate the utility of the *trans*-hydroboration in synthesis, we have tested scalability of the method and demonstrated that the reactions work with equal efficiency on a

Table 3 Optimization of the catalysts for phosphine catalyzed *trans*-hydroboration of ynoate **11a**



11a **12a**

Entry	Catalyst	Loading	*t* (h)	NMR Yield[a] (%)
1	PMe_3	5 mol%	4	90
2	PBu_3	5 mol%	4	92 (83% isolated)
3	PBu_3	2 mol%	8	88
4	$PMePh_2$	5 mol%	4	12 (*E*/*Z* = 82 : 18)
5	PPh_3	5 mol%	4	No reaction
6	P(*t*-Bu)$_3$	5 mol%	4	No reaction
7	DABCO	5 mol%	4	No reaction
8	DBU	5 mol%	4	No reaction
9	*N*-Methyl pyrrolidine	5 mol%	4	No reaction
10	*t*BuOK	5 mol%	4	No reaction
11	None	—	24	No reaction

[a] Triphenylmethane was used as the internal standard.

1.0 gram scale with **12a** isolated in 87% yield. As an illustration of versatility of *E*-vinylboronates as synthetic intermediates, Suzuki coupling was carried out with **12a** to prepare enoates **13** and **14** with a stereodefined trisubstituted double bond (Scheme 8B, the yields are not optimized). Comparison of the data for **14** to the previously reported data for same material served as additional indirect evidence of the *E*-configuration of vinylboronate **12a**.[19]

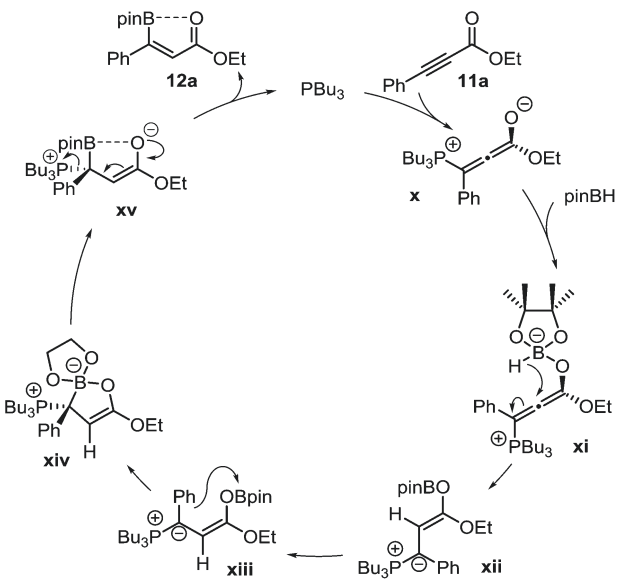
Despite the acidic protons in γ-position, alkyl ynoates **11q** and **11r** (precursors of **12q** and **12r**, Scheme 8A), surprisingly, also underwent *trans*-hydroboration. Although the yields and *E*/*Z* selectivity were lower than with the corresponding aryl ynoates (in refluxing DCE *E*/*Z* ratios for **12q** = 83 : 17 and for **12r** = 86 : 14), these results prompted a closer look at how sensitive to protic additives these reactions really are. A series of experiments demonstrated that the reaction outcome, in this case too,[6] is a function of the concentration of protic additive (Table 1, ESI†). *t*BuOH suppresses the *trans*-hydroboration in a concentration dependent manner. Enoate **15** (shown in Scheme 8C), the product of 1,4-reduction, was observed in minor quantities when protic additive was present. A separate experiment confirmed that **12a** doesn't react to produce enoate **15** under the reaction conditions suggesting that **15** is produced *via* direct 1,4-reduction of ynoate **11a** and not *via* proteodeborylation of **12a.**

To exclude the possibility that a photochemical isomerization is responsible for the stereochemical outcome of the reactions,[20] a test reaction was performed in the dark. Identical outcome of the reaction carried out in absence of light suggested that photochemical isomerization of alkene does not occur.

When pinBD was used, complete incorporation of the deuterium label in α position of the vinylboronate **12aD** was observed (Scheme 8C), suggesting that the *trans*-addition of hydrogen and boron are a consequence of unique mechanistic features of the process rather than a combination of more conventional pathways.

Based on the labeling studies, dependence of reactivity on structure of the starting material, influence of protic groups on reaction outcome and qualitative observations about effects of concentration on reaction rates, we propose that the mechanism of the reaction involves an intramolecular hydride transfer step in intermediate **xi** that results in formation of a phosphorus ylide **xii** (Scheme 9). In contrast to ynoate **11a**, enoate **15** does not react under the optimized conditions (Scheme 8C) because the enone derived intermediate analogous to **xi** cannot undergo intramolecular hydride transfer to produce a phosphorus ylide. The hydride must be delivered to the same side of the C1–C2 π-system as the boronate resulting in a *Z*-configured allylic phosphorous ylid intermediate **xii**. Allylic anion resonance enables isomerization of the double bond to the *E*-configured intermediate **xiii** which, unlike **xii**, can undergo intramolecular transfer of the boronate to C3 position *via* intermediate **xiv**. E1cb elimination of phosphine from **xv** completes the catalytic cycle, forms the product and regenerates the phosphine catalyst. *E*-Configuration of the final product is determined by the interaction between the boronate and carbonyl oxygen. If this interaction is broken, the resulting intermediate could eliminate the phosphine to produce either *E*- or *Z*-vinylboronate and deterioration of selectivity would be observed. This could be the case when elimination of phosphine is slow and other Lewis bases are present in the reaction mixture.

A comparison of the reduction reactions of ynones and ynoates under the described conditions leads to several interesting observations about the role of phosphine catalyst and the rates of the competing reduction pathways. The role of phosphine in these reactions can be to (i) generate a stronger



Scheme 9 Proposed mechanism of the phosphine catalyzed *trans*-hydroboration of ynoates.

base (O-centered Lewis base) which further modifies downstream pathways by influencing the reactivity of pinacolborane, (ii) modify the reactivity of the unsaturated carbonyl compound by making it more prone to reduction and (iii) modulate the character of the α-carbon (formal umpolung from a typically nucleophilic to an electrophilic center) and allow for hydride delivery to form a phosphorus ylide (as described in intermediate **xi**). Since ynones are more electrophilic than corresponding ynoates, the direct reduction of carbonyl compounds with Lewis-base activated pinacolborane occurs faster than the *trans*-hydroboration which is in turn faster than either 1,4-reduction, *syn*-hydroboration or direct reduction by borane. With less electrophilic ynoates, direct reduction of the carbonyl is outcompeted by the *trans*-hydroboration and 1,4-reduction. These features enable ynones to be transformed to propargyl alcohols, and ynoates to be transformed to vinylboronates in high yields and with excellent selectivities.

Conclusions

Trialkylphosphines and pinacolborane constitute a non-traditional frustrated Lewis pair which allows for dual activation of alkynyl carbonyl compounds. A careful selection of reactive partners: ynones or ynoates, and a suitable combination of the borane reductant, phosphine catalyst and protic additives can lead to selective transformation: reduction of the carbonyl and hydroboration of the alkyne as the major pathways.

Ynones are efficiently reduced with pinacolborane to produce propargyl alcohols in high yields when a nucleophilic phosphine catalyst and protic additive are present in the mixture. In absence of acidic protons, 1,2-reduction pathways for ynones are outcompeted by 1,4-reduction and hydroboration pathways.

Ynoates undergo regio- and stereoselective *trans*-hydroboration with pinacolborane in the presence of nucleophilic phosphine catalysts to produce *E*-vinylboronates in good yields. Unique mechanistic features of the process allow for unusual stereoselectivity in the reactions. An umpolung of reactivity of the α carbon in ynoates enables intramolecular delivery of the hydride which produces phosphorus ylide nucleophile that effects the transfer of pinacolboronate from the carbonyl oxygen to the β carbon of the ynoate. The reactions are to a certain extent tolerant of protic additives and allow *trans*-hydroboration of both aryl and alkyl ynoates.

Both 1,2-reductions of ynones and *trans*-hydroboration of ynoates produce versatile synthetic intermediates in high yields and with excellent selectivity. The divergent outcomes in reactions of ynones and ynoates with pinacolborane in the presence of nucleophilic phosphines provide insight into competing reaction pathways and their relative rates. With the better understanding of these pathways, selectivity in related reactions can be controlled by external factors, *i.e.* by protic additives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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8 Frustrated Lewis pairs are systems of sterically hindered Lewis donors and acceptors where steric demands preclude formation of simple Lewis acid–base adducts, allowing for the subsequent actions of both Lewis acids and bases on other molecules. They are typically seen as a combination of a bulky Lewis base and a very strong, bulky Lewis acid (a common example is $B(C_6F_5)_3$). PBu_3 and pinBH do not traditionally fit this definition, yet they do not form classical Lewis acid–base adducts which is why we refer to this system as a non-traditional frustrated Lewis pair.

9 Hydroboration reactions are typically *syn* functionalization of unsaturated compounds which proceed with suprafacial delivery of hydrogen and boron to the same π-face of the starting material. Although the opposite stereochemical outcome could be termed *anti*, the implication of the term *anti* is that the hydrogen and boron atoms are simultaneously delivered to the opposite faces of the π-system. For this reason, we prefer the term *trans*-hydroboration which carries no mechanistic implications and accurately describes stereochemical outcome of the described process. In addition to stereoisomers, hydroboration of differentially substituted alkynes can lead to different regioisomers too.

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13 During preparation of this manuscript, similar work was published by the groups of Sawamura and Ohmiya: K. Nagao, A. Yamazaki, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2018, **7**, 1861–1865. Although similar to our work on *trans*-hydroboration, this report describes hydroboration of ynoates in THF at elevated temperatures. While *trans*-hydroboration or ynoates seems to be tolerant of different solvents, 1,2-reduction of ynones specifically requires solvents that do not activate pinacolborane *via* formation of Lewis pairs (decrease of both regio- and chemoselectivity of reductions in THF, diethyl ether or dioxane have been observed in our previous study). The hydroboration reactions of ynoates in dichloromethane at room temperature and in dichloroethane at elevated temperature, presented here, enable a sound comparison of the two methods.

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Publication P8

C-H functionalization of thiazoles via thiazol-2-yl-phosphonium intermediates

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Org. Lett. **2020**, *22*, 3407-3411.

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C−H Functionalization of Benzothiazoles via Thiazol-2-yl-phosphonium Intermediates

You Zi, Fritz Schömberg, Konrad Wagner, and Ivan Vilotijevic*

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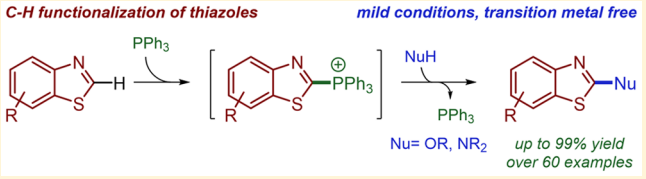
ABSTRACT: Benzothiazoles undergo regioselective C2−H functionalization with triphenylphosphine to form thiazol-2-yl-triphenylphosphonium salts, and these phosphonium salts react with a wide range of O- and N-centered nucleophiles to give the corresponding ethers, amines, and C−N biaryls. The reactions proceed under mild conditions and allow for the recovery of triphenylphosphine at the end of the sequence. In the presence of hydroxide, phosphonium salts undergo disproportionation, resulting in the reduction of the benzothiazole, which is useful for specific C2 deuteration of benzothiazoles.



Phosphonium salts are commonly used in organic synthesis as reagents in Witting-type olefinations,[1] catalysts in phase-transfer catalysis and related transformations,[2] solvents in processes that rely on the use of ionic liquids,[3] and catalytic intermediates in Lewis-base-catalyzed reactions with phosphine catalysts.[4] The breadth of their reactivity and the electrophilic character of the phosphorus atom, in particular, have driven the recent leaps in the development of synthetic methods that feature pentavalent phosphorus intermediates such as biphilic organophosphorus catalysis,[5] contractive C−C coupling via P(V) intermediates,[6] and the redox-neutral organocatalytic Mitsunobu reactions.[7] Our interest in phosphonium ions stems from reactions that use phosphines as Lewis base catalysts with typical Michael acceptors, which, in the presence of water and other protic additives, produce vinylphosphonium intermediates (Scheme 1a).[8] We hypothesized that the distinctly different outcomes these reactions have in the presence of alcohols (oxidation of C3 of the ynone)[9] and water (reduction of C3)[10] are the consequence of the differences in the reactivity of the pentavalent phosphorus intermediates generated in these processes. If this is also reflected in the reactivity of arylphosphonium salts,[11] the easily accessible heteroarylphosphonium salts would become valuable intermediates in the regioselective functionalization of heterocycles.

Thiazoles and benzothiazoles are the most common five-membered aromatic N-heterocycles among the FDA-approved pharmaceuticals,[12] and they are present in numerous biologically active molecules (Scheme 1b),[13] are important components of functional materials,[14] and are common intermediates in organic synthesis.[15] Although they almost always feature a heteroatom substituent at C2 in approved pharmaceuticals, the direct C2−H functionalization of benzothiazoles remains largely limited to metal-catalyzed processes that proceed at elevated temperatures, often as high as 130 °C (Scheme 1c).[16] A metal-free pathway for the C2−H functionalization of benzothiazoles under mild conditions would be a valuable addition to medicinal chemistry toolbox and an enabling factor for rapid access to libraries of small benzothiazole-containing molecules. In his seminal work on the synthesis of benzothiazol-2-yl-triphenylphosphonium triflate, Anders showed that the treatment of benzothiazole with triphenylphosphine in the presence of triflic anhydride and a base provides direct regioselective access to this salt.[11] Here we demonstrate the generality of this process and show that benzothiazol-2-yl-triphenylphosphonium salts react with a wide range of O- and N-nucleophiles under mild conditions and produce C2-substituted benzothiazoles (Scheme 1d). The two-step sequence constitutes an efficient method for the C2−H functionalization of benzothiazoles because the phosphine can be recovered at the end of the sequence.

Encouraged by the early observations of Anders and the later work of McNally on similar functionalization of pyridines,[6,11] our optimization studies focused on the reactions of benzo[*d*]thiazol-2-yltriphenylphosphonium triflate salt **2a** with benzyl alcohol. Activation of the nucleophile with a suitable base was required. Strong bases like sodium hydride and alkali hexamethyldisilazide (HMDS) amides performed well, providing yields of up to 82%. (For details of the optimization studies, see the SI.) The outcome depended on the quality of the base used, and some reactions benefited from increasing the amount of the nucleophile to 1.5 equiv, although a further

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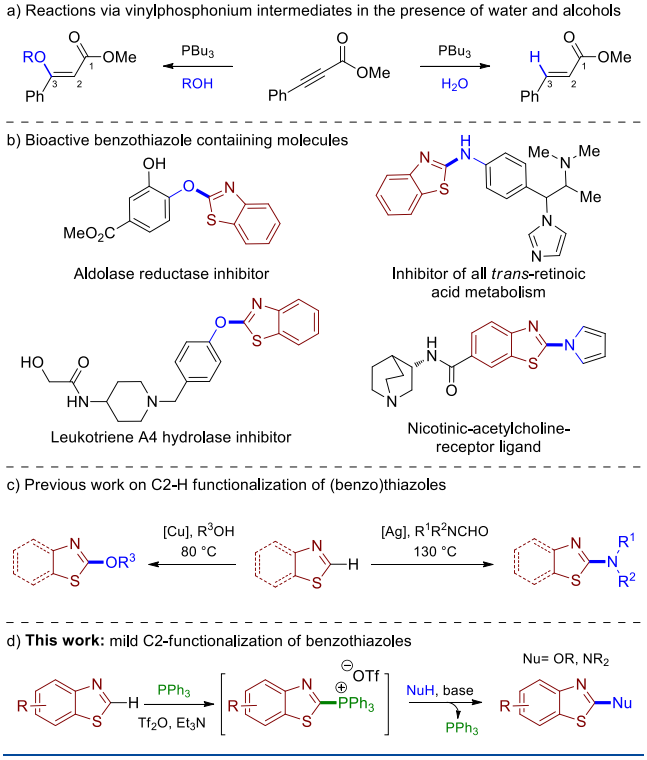
Scheme 1. Bioactive C2-Substituted Benzothiazoles, Previous Work on C2−H Functionalization of Benzothiazoles, and Our Approach Using Phosphonium Ions

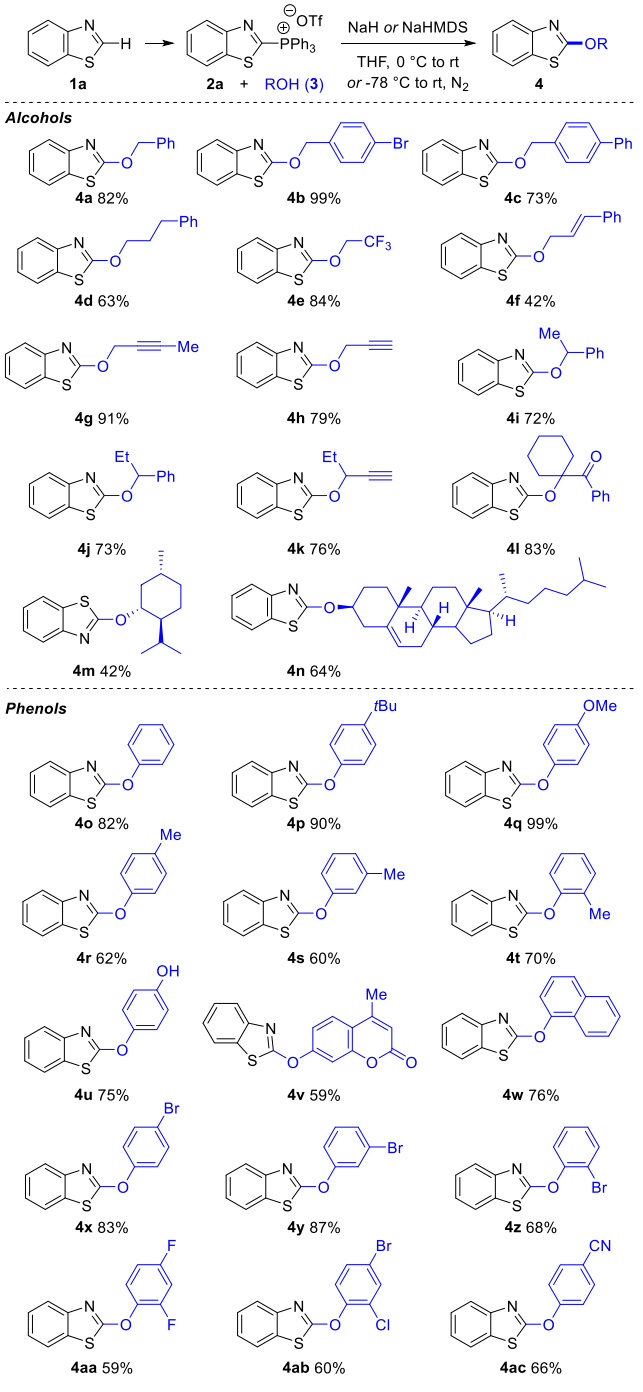


increase had the inverse effect. The reactions proceeded with high rates at room temperature in THF, with deprotonation of alcohol usually performed at a low temperature prior to the addition of the phosphonium triflate.

A range of alcohol nucleophiles were reactive with the benzothiazol-2-yl-phosphonium salt **2a** (Scheme 2). Primary alcohols, including simple alkyl, benzylic, and propargylic alcohols, all gave the desired ethers in a yield range of 42−99% (**4a**−**n**). Even electron-poor alcohol proved efficient in a yield of 84% (**4e**). Secondary (**4i**−**k**) and tertiary aliphatic alcohol (**4l**) gave the desired ethers in 72−83% yields and demonstrated that the reactions tolerate steric hindrance close to the reactive centers. The reactions performed well even in the more complex setting, when menthol and cholesterol were used as the O-nucleophiles (**4m** and **4n**). Electron-rich phenols performed well in a yield range of 60−99% (**4o**−**t**). When hydroquinone was used, the product of monosubstitution was produced in 75% yield (**4u**). Phenols with an extended conjugated system, a coumarin derivative, and naphthalen-1-ol were also suitable reaction partners (**4v** and **4w**). Halogen-substituted phenols were well tolerated in a yield range of 59−87% (**4x**−**ab**). Sterically more demanding and electron-poor substrates gave slightly lower yields between 59 and 66% (**4z**−**ac**). The main side product was triphenylphosphine, which could be recovered during purification.

Encouraged by the good reactivity observed with O-nucleophiles, the focus was shifted to N-nucleophiles (Scheme 3). NaHMDS performs significantly better than NaH with N-nucleophiles. The initial attempts with primary amines and anilines proved futile. Instead of the desired products, the corresponding iminophosphoranes were isolated. Along with

Scheme 2. Scope of the Reaction for O-Nucleophiles



this, secondary amines performed well, with **4ad**−**af** obtained in 61−81% yield. When acetanilide was used, the product of amidation could not be isolated, but the product of amide hydrolysis **4ag** was isolated in yields of 30%. Switching to *N*-methylbenzamide improved the overall yield to 81%, but a 1:2 mixture of the amide **4ah** and the hydrolysis product **4ai** was obtained. A range of N-heterocycles was shown to be reactive under the same conditions, affording good yields observed for pyrroles and indoles regardless of their electronic properties (**4aj**−**ap**, Scheme 3). Imidazoles and benzimidazoles were equally reactive (**4aq** and **4as**), but the yields were lowered by the increasing steric demand of the nucleophile (**4at** and **4au**).

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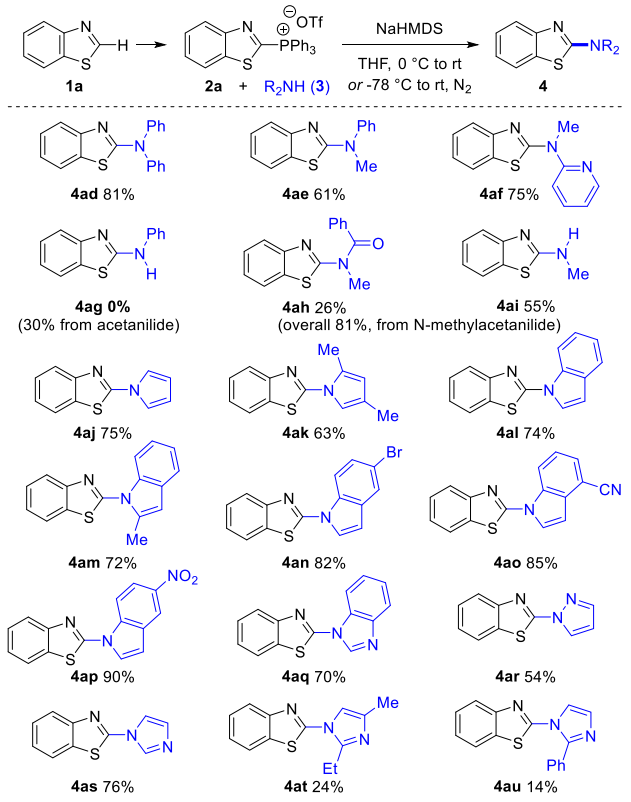
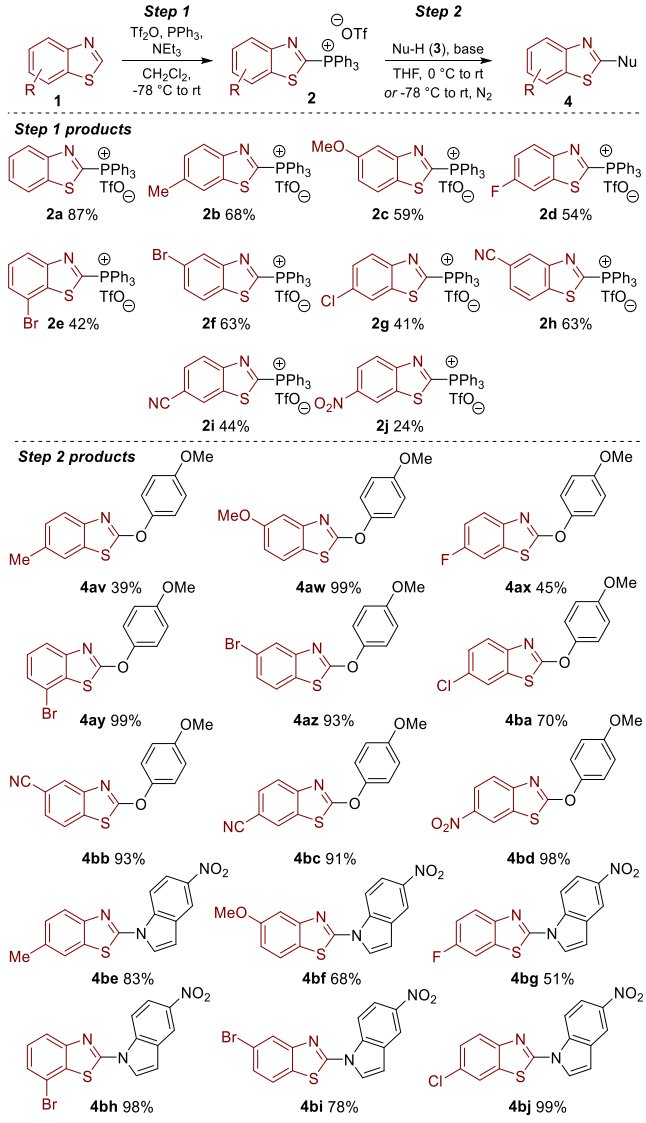
Scheme 3. Scope of the Reaction for N-Nucleophiles



Scheme 4. Reaction Scope for Substituted Benzothiazoles



Using pyrazole as the nucleophile resulted in the formation of biaryl **4ar** in a yield of 54%.

A set of benzothiazol-2-yl-phosphonium triflates carrying both electron-donating and electron-withdrawing substituents in positions five, six, and seven, **2a−j** (Scheme 4, Step 1), was prepared in a yield range of 24−87% following the method described by Anders. (The mechanistic proposal for the formation of the phosphonium salts is shown in Scheme 5a.) 4-Methoxyphenol and 5-nitroindole were used to evaluate the reactions with substituted salts. Both electron-rich and electron-poor phosphonium salts performed well, giving the products of etherification (**4av−bd**) and amination (**4be−bj**) in good yields (Scheme 4, Step 2). No obvious trends for the electronic effect of the substituents on benzothiazole could be observed, suggesting the generality of this method. The studies of scope also established the tolerance for ether, nitro, ester, nitrile, ketone, alkene, alkyne, aryl halides, and other N-heterocyclic substituents.

Aniline and other primary amines failed to produce any of the desired amination products when used in reactions with thiazol-2-yl-phosphonium salts. Instead, the reduced benzothiazole was isolated alongside the iminophosphorane **5** derived from the amine nucleophile and triphenylphosphine (Scheme 5b). It is reasonable to propose that the N−P bond is formed through direct nucleophilic attack of the anilide anion on the electrophilic phosphonium ion. This would produce the aminophosphonium intermediate ***iv*** via nucleophilic substitution or the pentavalent phosphorus intermediate ***i*** via nucleophilic addition to phosphorus. Under basic conditions, ***i*** would be deprotonated to form ***ii***, which would, in turn, fragment to produce the iminophosphorane **5** and the benzothiazolide anion ***iii***.[11b,17] Because both pathways involve the formation of benzothiazolide ***iii***, we hypothesized that the use of water as the nucleophile (as hydroxide ion) would also result in reduction of the benzothiazole and the formation of phosphine oxide. Experiments using only a slight excess of sodium deuteride demonstrated that this indeed is the case (Scheme 5c). The specific C2 deuterium labeling with 97% yield and >98% deuterium incorporation was observed for **6a**. The process appears general, as benzothiazoles with electron-donating and -withdrawing substituents both undergo efficient C2 labeling (**6b** and **6c**).

The proposed direct nucleophilic attack of the nucleophiles to the phosphorus atom in the phosphonium salt with both primary amines and water suggests that this process could also operate in the reactions that result in C2 functionalization of benzothiazole. If the pentavalent phosphorus intermediate similar to ***i*** is indeed on the reaction path, that would necessitate a contractive C−O or C−N bond formation from the same intermediate akin to reductive elimination. Another possible mechanistic scenario is the simple aromatic nucleophilic substitution reaction that would see nucleophilic attack to the C2 position of the benzothiazole. Our current studies are aiming to decipher the reaction mechanism and determine the chemical competence of the proposed

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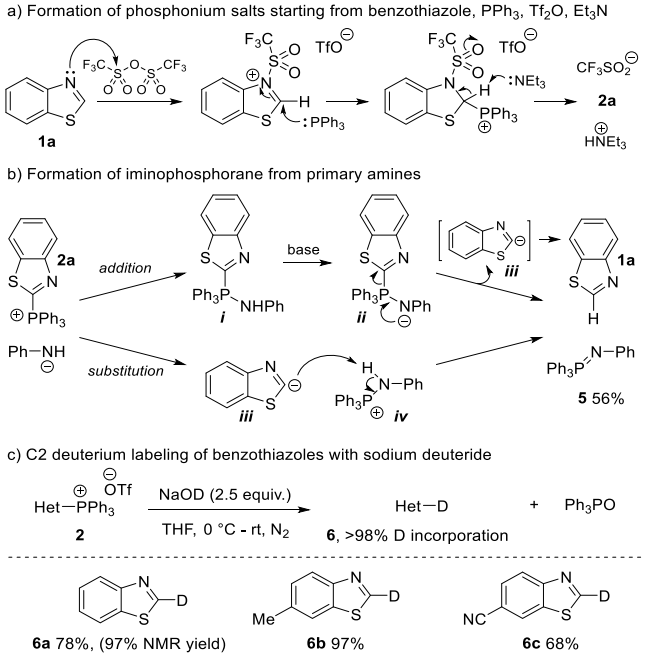
Scheme 5. Formation of Iminophosphoranes and Phosphine Oxides with Primary Amines and Water



pentavalent phosphorus intermediates that have been observed via *in situ* ^{31}P NMR.[18]

In summary, we have developed an effective method for the C2−H functionalization of benzothiazoles via thiazol-2-yl-phosphonium intermediates that readily undergo reactions with O- and N-nucleophiles under mild conditions. Reactions are productive with a range of substituted benzothiazoles and feature an unusually wide scope for nucleophiles including alcohols, phenols, amines, amides, and N-heterocycles. The resulting C2-subsituted benzothiazoles are structurally related to many biologically active molecules, making this method attractive for use in medicinal chemistry development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00882.

Detailed experimental procedures, spectral data for all new compounds, and ^{1}H, ^{13}C, ^{19}F, and ^{31}P spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Publication P9

Selective C-H chalcogenation of thiazoles via thiazol-2-yl-phosphonium salts

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Selective C–H chalcogenation of thiazoles *via* thiazol-2-yl-phosphonium salts†‡

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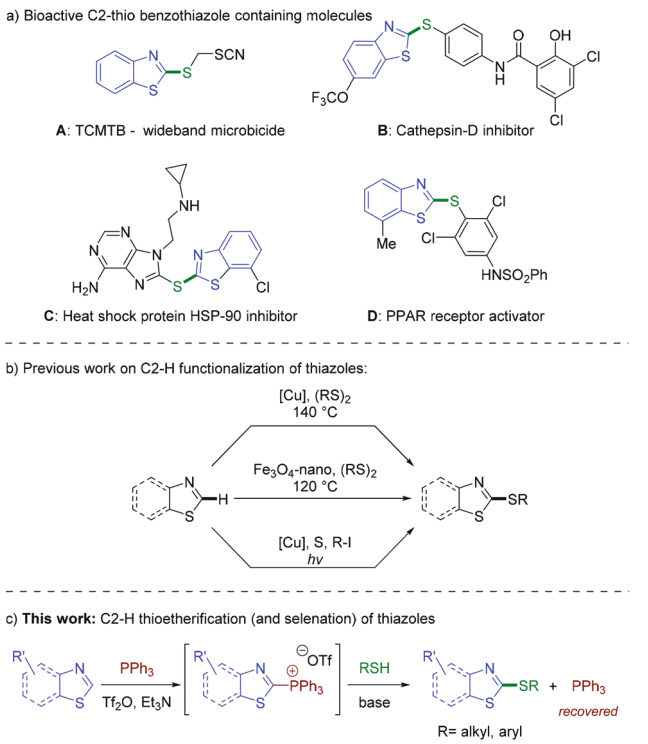
Thiazoles and benzothiazoles undergo regioselective C2–H chalcogenation *via* the sequence of thiazole C2-functionalization with phosphines to produce phosphonium salts which in turn react with S- and Se-centered nucleophiles to give products of C2–H chalcogenation and allow for recovery of the starting phosphine. The atom economical sequence proceeds under mild conditions and features broad scope for both the nucleophiles (electron-rich, electron-poor, sterically hindered thiols) and the various substituted benzothiazoles. The access to the substituted medicinally relevant C2-thio benzothiazoles also enables stereoselectivity improvements in the modified Julia olefinations.

Introduction

Thiazoles and benzothiazoles are important constituents of electronic materials,[1] common intermediates in organic synthesis,[2] and a regular occurrence in natural products[3] and biologically active molecules.[4] They are the most common aromatic 5-membered N-heterocycles among FDA approved pharmaceuticals.[5] The vast majority of these bioactive molecules feature a heteroatom substituent at C2 which highlights the need for methods to introduce such substituents and makes these methods valuable tools in medicinal chemistry.

2-Thio-substituted (benzo)thiazoles, such as the wideband microbicide TCMTB (**A**),[6] cathepsin-D inhibitor (**B**),[7] heat shock protein 90 inhibitor (**C**)[8] and PPAR receptor activator (**D**),[9] have attracted attention for their biological activities (Scheme 1a). Other 2-thio-substituted (benzo)thiazoles are common intermediates in organic synthesis where they are used to construct double bonds *via* Julia olefination[10] or as substrates for transition metal-catalysed coupling reactions.[11] While other strategies to prepare 2-thio-substituted thiazoles exist,[12] C2–H thiolation (and chalcogenation) is of particular interest as a method for their direct functionalization. Despite the apparent demand, the methods for C2–H thiolation of thiazoles have thus far been limited to transition metal mediated processes that (i) typically proceed under harsh conditions at temperatures between 120 and 140 °C with long reactions times,[13,14] (ii) use stoichiometric amounts of transition metal salts and/or (iii) require the use of strong oxidants (Scheme 1b).[14] These features greatly limit the reaction scope and prevent general application of such methods in more complex settings common in medicinal chemistry. A recent



Scheme 1 (a) Examples of biologically active C2-thio benzothiazole derivatives; (b) previous work for C2 thiolation of (benzo)thiazoles and (c) our approach.

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‡Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ob00684j

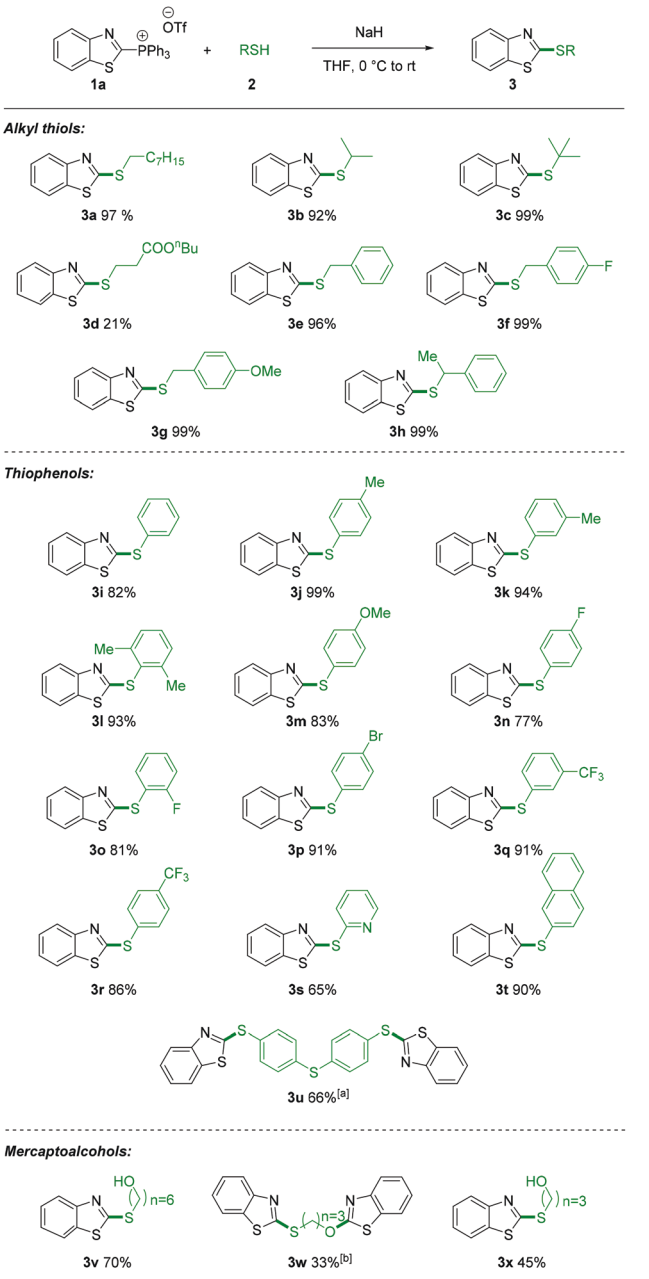
report of photochemically promoted Cu-catalyzed chalcogenation of thiazoles which proceeds at room temperature and improves the functional group tolerance is an important improvement in this field but it requires a specific photochemical setup and is limited to synthesis of diaryl sulphides (Scheme 1b).[15] A general method for C2–H thiolation of thiazoles that proceeds under mild conditions with broad substrates scope, uses readily available starting materials and avoids the use of transition metals would provide a simple way to create the C2–S bond of interest and generate libraries of medicinally relevant C2-thio substituted thiazoles.

Early work of Anders demonstrated the ease of synthesis of heteroaryl phosphonium salts by activating the corresponding heterocycle with triflic anhydride and exposing the resulting intermediate to a phosphine nucleophile.[16] In our work on phosphine promoted reactions of Michael acceptors that proceed *via* vinylphosphonium intermediates,[17] we found out that such intermediates readily undergo reactions with heteroatom-centered nucleophiles which suggested that a two-step sequence where regioselective formation of the phosphonium salt and a subsequent reaction with suitable nucleophile would constitute an efficient and selective C2–H functionalization of (benzo)thiazoles.[18] Recent work on the related reactions with pyridinylphosphonium salts also supported the feasibility of this approach.[19] Here we show that such thiazol-2-yl-phosphonium salts undergo highly efficient chalcogenation with a broad range of thiols, thiophenols and a Se-centered nucleophile and produce a variety of C2-chalcogen substituted thiazoles in excellent yields (Scheme 1c).

Results and discussion

In our initial study, benzothiazole was selected as the model system and converted to the corresponding benzo[*d*]thiazol-2-yltriphenylphosphonium triflate salt (**1a**) which was then used in reactions with 1-octanethiol. The reactions required nucleophile activation by a base. Sodium hydride proved to be a suitable and atom economical solution for this. With slight excess of the thiol, the reaction between 1-octanethiol and the benzo[*d*]thiazol-2-yltriphenylphosphonium triflate yielded the product **3a** in excellent yield. The reactions proceeded with high rates at room temperature in THF. The main side product was the triphenylphosphine which could be recovered at the end of the reaction making the entire process atom economical. The ease of preparation of benzo[*d*]thiazol-2-yltriphenylphosphonium triflate and its favourable solubility profile enabled the two-step sequence to be carried out in one pot with removal of excess ammonium salt by precipitation of the phosphonium salt and decanting between the steps. Although typical reactions used 1.5 equivalents of the thiol and sodium hydride, lower quantities (1.1 equiv.) were often sufficient to achieve good yields for the desired products.

With fast turnaround in the optimization studies, the attention was focused on exploration of the reaction scope. Primary, secondary, tertiary alkyl and benzylic thiols all produced the desired thioethers in nearly quantitative yields (**3a–3h**, Scheme 2). Thiophenols also gave the desired products in high yields (**3i–3u**) with electron rich and electron poor thiophenols showing comparable efficacy (**3j–3r**). The reactions appeared to be tolerant of steric crowding in the vicinity of the S-centered nucleophile with products **3c** and **3l** derived from *t*-BuSH and



Scheme 2 Thiolation of benzothiazole with different thiols. Conditions: Phosphonium salt (0.2 mmol), pronucleophile (0.3 mmol), NaH (0.3 mmol), THF (2 mL, 0.1 M), at 0 °C to room temperature. [a] Conditions: Phosphonium salt (0.2 mmol), pronucleophile (0.15 mmol), NaHMDS (0.3 mmol), THF (2 mL, 0.1 M), at –78 °C to room temperature. [b] Conditions: Phosphonium salt (0.2 mmol), pronucleophile (0.1 mmol), NaH (0.2 mmol), THF (2 mL, 0.1 M), at 0 °C to room temperature.

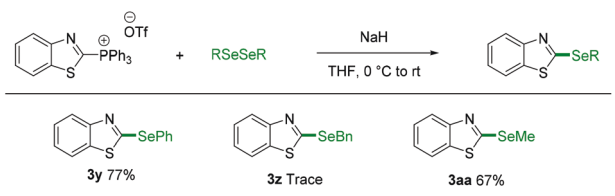
2,6-dimethylphoenylthiol produced in 99% and 93% yields respectively. The double thioetherification to produce **3u** proceeded with satisfactory yield as did the reactions with thiols with extended conjugation and those containing other heterocycles like pyridine (**3s–3t**).

To test the selectivity for S- and O-centered nucleophiles, 3-mercaptopropan-1-ol and 6-mercaptohexan-1-ol were tested under optimized conditions. 6-Mercaptohexan-1-ol provided the desired product **3v** in 70% yield, while 3-mercaptopropan-1-ol produced **3x** in 45% yield alongside the product of double functionalization of the mercaptoalcohol with two benzothiazoles in small quantities. Product **3w** could be isolated in 33% yield when 2 equiv. of phosphonium salt **1a** were used in combination with 2 equiv. of sodium hydride.

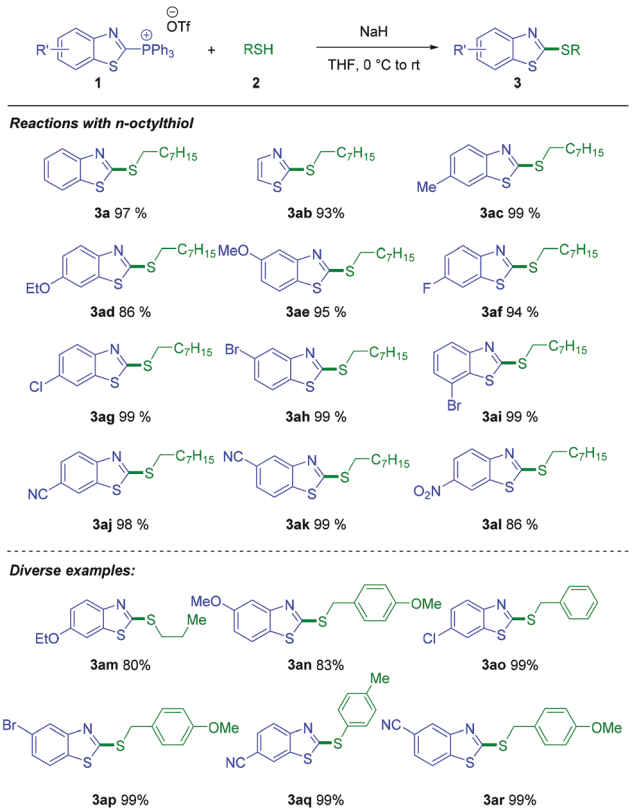
To test the feasibility of the same approach in construction of C–Se bonds, benzo[*d*]thiazol-2-yltriphenylphosphonium triflate was subjected to reaction with Se-centered nucleophile generated by reduction of diphenyl diselenide with sodium hydride to produce the 2-(phenylselanyl)thiazole **3y** in yield of 77% (Scheme 3). Dimethyl diselenide gave the corresponding methylselenide **3aa** in 67% yield. Dibenzyl diselenide failed to produce any of the desired product likely due to the high reactivity of the resulting 2-(benzylselanyl)benzo[*d*]thiazole.

The scope for the benzothiazol-2-yl-phosphonium triflates has been explored by employing various substituted salts that were available *via* the method outlined by Anders.[16] Salts derived from substituted benzothiazoles carrying both electron-donating and electron-withdrawing substituents in positions 5, 6 and 7 have been examined. 1-Octanethiol was used as a model nucleophile in these reactions to determine that they all proceed with nearly quantitative yields regardless of the electronic properties of the salt (Scheme 4). Ethers (**3ad** and **3ae**), aryl halides (**3af–3ai**), nitriles (**3aj** and **3ak**), nitro compounds (**3al**) were well tolerated in these reactions. In addition to salts derived from benzothiazoles, that derived from simple thiazole was also a competent substrate in this reaction (**3ab**). Finally, a few diverse combinations of phosphonium salts and the thiols showed the generality of the process (**3am–3ar**).

A series of control experiments was carried out to show that the formation of the phosphonium salt is indeed necessary for successful C–H functionalization. The direct use of S-nucleophiles in combination with *N*-triflyl salts of benzothiazole, similar to the previously reported methods for C4-



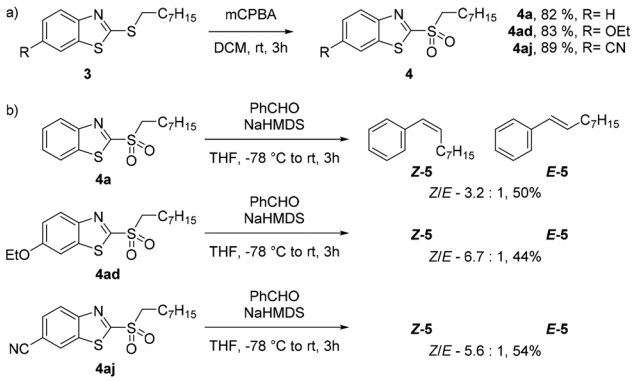
Scheme 3 Synthesis of selenides *via* reaction of phosphonium salt and Se-centered nucleophiles. Conditions: Phosphonium salt (0.2 mmol), PhSeSePh (0.3 mmol), NaH (0.6 mmol), THF (2 mL, 0.1 M), at 0 °C to room temperature.



Scheme 4 Reaction scope for substituted thiazoles. Conditions: Phosphonium salt (0.2 mmol), pronucleophile (0.3 mmol), NaH (0.3 mmol), THF (2 mL, 0.1 M), at 0 °C to room temperature.

functionalization of pyridines,[20] failed to produce any of the C2-sulfenylation products.

Having access to a variety of electronically different C2-thio substituted benzothiazoles, piqued our curiosity about the possibility of exploiting electronic effects of these substituents to address selectivity issues in modified Julia olefination reactions that otherwise proceed with lower selectivity. We hypothesized that electronic effects of the substituents may change the selectivity of the reactions by changing the nature of transition states in the selectivity determining addition of the sulfone stabilized anion to the aldehyde or by changing the kinetics of individual elementary steps during the olefination reactions that may ultimately enable different equilibria to be established.[10] With this in mind, for our model study we selected the typical modified Julia olefination substrate (**3a**) and the two substituted starting materials, one featuring an electron donating (**3ad**) and the other featuring electron withdrawing group (**3aj**) (Scheme 5). The three sulfones were easily accessed from the corresponding sulfides by *m*CPBA oxidation. Applying the typical conditions for modified Julia olefination with **4a** resulted in a 3.2 : 1 mixture of **Z-5** and **E-5** favouring the *Z* product. Under the same conditions, both **4ad** and **4aj** gave the products **5** with higher selectivity (6.7 : 1 and 5.6 : 1, respectively) while maintaining similar efficacy. Future studies will be directed towards understanding and further establishing the substituent effect in these reactions.



Scheme 5 Modified Julia olefination using differently substituted sulfones.

Conclusions

In conclusion, the regioselective C2–H functionalization of thiazoles with phosphines followed by the highly efficient base promoted reaction with S-centered nucleophiles is an effective way to produce C2-thio thiazole derivatives. The reactions proceed under mild conditions, use simple starting materials and feature broad scope that includes both alkyl thiols and thiophenols. Electronic and steric factor do not significantly change the high efficacy of reactions of phosphonium salts with S- and Se-nucleophiles. The substituted C2-thio benzothiazoles can be of use in organic synthesis to improve the selectivity of the modified Julia olefination reactions. Applications of this methodology to rapidly generate targeted libraries of compounds for medicinal chemistry are envisioned.

Experimental

General procedure for the thiolation of thiazole derivatives

NaH (0.3 mmol) was added to the pronucleophile (0.3 mmol) in dry THF (0.1 M) under inert atmosphere at 0 °C. After stirring for half an hour at room temperature, the phosphonium salt[18] (0.2 mmol) was added subsequently at 0 °C followed by three quick vacuum/nitrogen refills. The reaction mixture was warmed up to room temperature and quenched by addition of a small amount of water when it completed. The crude product was purified by column chromatography using ethyl acetate in petroleum ether.

2-(Octylthio)benzo[*d*]thiazole (3a).[21] Yield: 97%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99–7.82 (m, 1H), 7.82–7.70 (m, 1H), 7.42 (td, J = 8.2, 7.8, 1.2 Hz, 1H), 7.29 (td, J = 7.9, 1.1 Hz, 1H), 3.35 (t, J = 7.4 Hz, 2H), 1.83 (p, J = 7.3 Hz, 2H), 1.56–1.42 (m, 2H), 1.42–1.19 (m, 8H), 0.99–0.79 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.41, 153.37, 135.15, 125.97, 124.07, 121.44, 120.89, 33.64, 31.80, 29.20, 29.15, 29.07, 28.79, 22.66, 14.12.

2-(Isopropylthio)benzo[*d*]thiazole (3b).[22] Yield: 92%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 1H), 7.82–7.71 (m, 1H), 7.43 (ddd, J = 8.2, 7.3, 1.3 Hz, 1H), 7.30 (ddd, J = 8.4, 7.3, 1.2 Hz, 1H), 4.10 (hept, J = 6.8 Hz, 1H), 1.53 (s, 3H), 1.51 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.45, 153.42, 135.29, 125.97, 124.22, 121.61, 120.91, 39.47, 23.31.

2-(*tert*-Butylthio)benzo[*d*]thiazole (3c).[23] Yield: 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, J = 8.1, 1.3, 0.6 Hz, 1H), 7.81 (ddd, J = 7.9, 1.4, 0.6 Hz, 1H), 7.50–7.41 (m, 1H), 7.40–7.36 (m, 1H), 1.62 (s, 9H).

Butyl 3-(benzo[*d*]thiazol-2-ylthio)propanoate (3d). Yield: 21%. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.92–7.84 (m, 1H), 7.78–7.74 (m, 1H), 7.46–7.39 (m, 1H), 7.34–7.28 (m, 1H), 4.14 (t, J = 6.7 Hz, 2H), 3.62 (t, J = 7.0 Hz, 2H), 2.93 (t, J = 6.9 Hz, 2H), 1.69–1.57 (m, 2H), 1.48–1.31 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.64, 166.05, 153.14, 135.28, 126.03, 124.28, 121.53, 120.99, 64.81, 34.42, 30.59, 28.21, 19.12, 13.70. HRMS: [EI]: m/z calculated for $C_{14}H_{17}NO_2S_2$ $[M]^+$ 295.0701, found 295.0701. IR (ATR): 2958, 1732, 1462, 1427, 1350, 1176, 999, 756 cm^{-1}.

2-(Benzylthio)benzo[*d*]thiazole (3e).[24] Yield: 96%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, J = 8.2, 1.1 Hz, 1H), 7.76 (dd, J = 8.0, 1.2 Hz, 1H), 7.53–7.41 (m, 3H), 7.40–7.27 (m, 4H), 4.63 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.43, 153.17, 136.18, 135.34, 129.16, 128.73, 127.78, 126.08, 124.30, 121.57, 121.03, 37.72.

2-((4-Fluorobenzyl)thio)benzo[*d*]thiazole (3f).[25] Yield: 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.86 (m, 1H), 7.81–7.74 (m, 1H), 7.49–7.39 (m, 3H), 7.36–7.28 (m, 1H), 7.10–6.95 (m, 2H), 4.59 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.02, 162.27 (d, J = 246.6 Hz), 153.07, 135.34, 132.13 (d, J = 3.3 Hz), 130.82 (d, J = 8.2 Hz), 128.52 (d, J = 12.2 Hz), 126.12, 124.39, 121.31 (d, J = 39.0 Hz), 115.60 (d, J = 21.6 Hz), 36.86.

2-((4-Methoxybenzyl)thio)benzo[*d*]thiazole (3g).[26] Yield: 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.89 (m, 1H), 7.79–7.73 (m, 1H), 7.48–7.37 (m, 3H), 7.35–7.27 (m, 1H), 6.91–6.85 (m, 2H), 4.58 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.61, 159.19, 153.18, 135.30, 130.37, 127.99, 126.06, 124.26, 121.53, 121.02, 114.12, 55.28, 37.34.

2-((1-Phenylethyl)thio)benzo[*d*]thiazole (3h).[27] Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97–7.89 (m, 1H), 7.79–7.71 (m, 1H), 7.54–7.48 (m, 2H), 7.43 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.39–7.27 (m, 4H), 5.18 (q, J = 7.0 Hz, 1H), 1.87 (d, J = 7.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.87, 153.20, 141.80, 135.43, 128.69, 127.78, 127.41, 126.01, 124.33, 121.71, 120.97, 47.58, 22.67.

2-(Phenylthio)benzo[*d*]thiazole (3i).[23] Yield: 82%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (dt, J = 8.2, 0.9 Hz, 1H), 7.81–7.71 (m, 2H), 7.66 (dt, J = 7.8, 1.0 Hz, 1H), 7.57–7.45 (m, 3H), 7.42 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.33–7.23 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.72, 153.93, 135.54, 135.39, 130.50, 129.94, 126.17, 124.33, 121.96, 120.80.

2-(*p*-Tolylthio)benzo[*d*]thiazole (3j).[23] Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (dt, J = 8.2, 0.8 Hz, 1H), 7.67–7.61 (m, 3H), 7.41 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.33–7.28 (m, 2H), 7.28–7.20 (m, 1H), 2.45 (s, 3H).

2-(*m*-Tolylthio)benzo[*d*]thiazole (3k).[28] Yield: 94%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (dt, J = 8.2, 0.9 Hz, 1H), 7.66 (dt, J = 7.9, 0.9 Hz, 1H), 7.60–7.53 (m, 2H), 7.45–7.35 (m, 2H),

7.35–7.31 (m, 1H), 7.27 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 2.42 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.10, 153.94, 139.99, 135.88, 135.53, 132.39, 131.32, 129.74, 129.56, 126.13, 124.27, 121.91, 120.77, 21.31.

2-((2,6-Dimethylphenyl)thio)benzo[*d*]thiazole (3l).[29] Yield: 93%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (dt, J = 8.2, 0.8 Hz, 1H), 7.67–7.57 (m, 1H), 7.44–7.33 (m, 2H), 7.30–7.21 (m, 3H), 2.56 (s, 6H).

2-((4-Methoxyphenyl)thio)benzo[*d*]thiazole (3m).[30] Yield: 83%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87 (ddd, J = 8.2, 1.2, 0.6 Hz, 1H), 7.71–7.61 (m, 3H), 7.40 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.25 (ddd, J = 8.0, 7.3, 1.2 Hz, 1H), 7.05–6.97 (m, 2H), 3.88 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.93, 161.70, 154.18, 137.60, 135.40, 126.09, 124.06, 121.75, 120.75, 120.17, 115.51, 55.48.

2-((4-Fluorophenyl)thio)benzo[*d*]thiazole (3n).[31] Yield: 77%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (ddd, J = 8.1, 1.2, 0.6 Hz, 1H), 7.80–7.63 (m, 3H), 7.42 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.35–7.09 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.54, 164.20 (d, J = 252.2 Hz,), 153.92, 137.79 (d, J = 8.8 Hz), 135.44, 126.26, 125.09 (d, J = 3.6 Hz), 124.41, 121.97, 120.82, 117.25 (d, J = 22.2 Hz).

2-((2-Fluorophenyl)thio)benzo[*d*]thiazole (3o). Yield: 81%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (dt, J = 8.1, 0.8 Hz, 1H), 7.75 (td, J = 7.7, 7.2, 1.9 Hz, 1H), 7.71–7.65 (m, 1H), 7.60–7.50 (m, 1H), 7.42 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 7.32–7.22 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.40, 162.69 (d, J = 251.4 Hz), 153.80, 137.39, 135.62, 133.16 (d, J = 8.2 Hz), 126.23, 125.33 (d, J = 4.1 Hz), 124.51, 122.10, 120.84, 117.25, 116.85 (d, J = 22.7 Hz). ^{19}F NMR (377 MHz, $CDCl_3$) δ −104.89. HRMS: [EI]: m/z calculated for $C_{13}H_8FNS_2$ $[M]^+$ 261.0082, found 261.0082. IR (ATR): 3066, 1454, 1423, 1219, 1002, 817, 721 cm^{-1}.

2-((4-Bromophenyl)thio)benzo[*d*]thiazole (3p).[31] Yield: 91%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93–7.86 (dt, J = 8.2, 0.9 Hz, 1H), 7.73–7.65 (m, 1H), 7.61–7.55 (m, 4H), 7.43 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.30 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.07, 153.78, 136.56, 135.57, 133.13, 129.05, 126.31, 125.18, 124.59, 122.11, 120.88.

2-((3-(Trifluoromethyl)phenyl)thio)benzo[*d*]thiazole (3q).[28] Yield: 91%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05–7.99 (m, 1H), 7.97–7.89 (m, 2H), 7.79–7.69 (m, 2H), 7.61 (t, J = 7.8 Hz, 1H), 7.45 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.33 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.70, 153.66, 137.92, 135.66, 132.26 (d, J = 32.9 Hz), 131.59, 131.34 (q, J = 3.7 Hz), 130.29, 126.88 (q, J = 3.7 Hz), 126.41, 124.83, 123.40 (d, J = 294 Hz), 122.29, 120.95.

2-((4-(Trifluoromethyl)phenyl)thio)benzo[*d*]thiazole (3r).[31] Yield: 86%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (dt, J = 8.2, 0.8 Hz, 1H), 7.87–7.79 (m, 2H), 7.77–7.66 (m, 3H), 7.46 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.34 (ddd, J = 8.2, 7.3, 1.2 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.77, 153.57, 135.83, 135.28, 134.12, 131.76 (q, J = 32 Hz), 126.57 (q, J = 3.7 Hz), 126.44, 124.99, 123.66 (q, J = 266 Hz), 122.41, 120.99.

2-(Pyridin-2-ylthio)benzo[*d*]thiazole (3s).[32] Yield: 65%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.61 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 8.00 (ddd, J = 8.1, 1.3, 0.7 Hz, 1H), 7.82 (ddd, J = 7.9, 1.4, 0.6 Hz, 1H), 7.68 (ddd, J = 8.0, 7.4, 1.9 Hz, 1H), 7.55 (dt, J = 8.0, 1.0 Hz, 1H), 7.47 (ddd, J = 8.2, 7.2, 1.4 Hz, 1H), 7.37 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.24 (ddd, J = 7.4, 4.9, 1.2 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.51, 154.74, 152.72, 149.95, 137.42, 136.26, 126.23, 125.10, 125.07, 122.57, 122.48, 121.01.

2-(Naphthalen-2-ylthio)benzo[*d*]thiazole (3t).[21] Yield: 90%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 1.7 Hz, 1H), 7.98–7.85 (m, 4H), 7.74 (dd, J = 8.6, 1.8 Hz, 1H), 7.67–7.55 (m, 3H), 7.42 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.27 (ddd, J = 8.1, 7.3, 1.2 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.65, 153.94, 135.61, 135.52, 133.77, 133.74, 131.22, 129.77, 128.18, 127.91, 127.79, 127.04, 127.02, 126.20, 124.36, 121.99, 120.83.

Bis(4-(benzo[*d*]thiazol-2-ylthio)phenyl)sulfane (3u). Yield: 66%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (dt, J = 8.2, 0.8 Hz, 2H), 7.74–7.66 (m, 6H), 7.49–7.40 (m, 6H), 7.31 (ddd, J = 8.3, 7.3, 1.2 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.25, 153.77, 137.93, 135.66, 135.59, 131.97, 129.29, 126.32, 124.62, 122.12, 120.89. HRMS: [EI]: m/z calculated for $C_{26}H_{16}N_2S_5$ $[M]^+$ 515.9917, found 515.9913. IR (ATR): 3063, 2924, 1570, 1454, 1423, 1385, 1092, 1076, 1007, 818, 748, 721 cm^{-1}.

6-(Benzo[*d*]thiazol-2-ylthio)hexan-1-ol (3v). Yield: 70%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 1H), 7.68 (dd, J = 7.9, 0.6 Hz, 1H), 7.38–7.29 (m, 1H), 7.25–7.18 (m, 1H), 3.58 (t, J = 6.4 Hz, 2H), 3.28 (t, J = 6.0 Hz, 2H), 1.84–1.70 (m, 2H), 1.54–1.35 (m, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.36, 153.24, 135.09, 126.04, 124.16, 121.42, 120.93, 62.79, 33.49, 32.52, 29.14, 28.48, 25.22. HRMS: [EI]: m/z calculated for $C_{13}H_{17}NOS_2$ $[M]^+$ 267.0752, found 267.0748. IR (ATR): 3282, 2927, 1647, 1539, 1458, 1307, 995, 756 cm^{-1}.

2-((3-(Benzo[*d*]thiazol-2-yloxy)propyl)thio)benzo[*d*]thiazole (3w). Yield: 33%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.3 Hz, 1H), 7.62–7.53 (m, 2H), 7.36–7.25 (m, 2H), 7.24–7.13 (m, 2H), 4.67 (t, J = 6.0 Hz, 2H), 3.48 (t, J = 7.0 Hz, 2H), 2.42–2.29 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.63, 166.20, 153.20, 149.26, 135.24, 131.88, 126.02, 126.01, 124.27, 123.55, 121.53, 121.27, 120.96, 120.83, 69.94, 29.85, 28.76. HRMS: [EI]: m/z calculated for $C_{10}H_{12}NOS_2^+$ [M-benzothiazole + H]$^+$ 226.0355, found 226.0360. IR (ATR): 2924, 1716, 1624, 1535, 1427, 1249, 1219, 995, 756 cm^{-1}.

3-(Benzo[*d*]thiazol-2-ylthio)propan-1-ol (3x). Yield: 45%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.38–7.29 (m, 1H), 7.25–7.18 (m, 1H), 3.68 (t, J = 5.9 Hz, 2H), 3.46 (t, J = 5.9 Hz, 2H), 1.95 (td, J = 11.1, 5.9 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.91, 152.41, 135.02, 126.24, 124.49, 121.06, 121.02, 59.02, 33.11, 29.83. HRMS: [EI]: m/z calculated for $C_{10}H_{11}NOS_2$ $[M]^+$ 225.0282, found 225.0278. IR (ATR): 3294, 2927, 1535, 1458, 1423, 1238, 1049, 995, 756 cm^{-1}.

2-(Phenylselanyl)benzo[*d*]thiazole (3y).[23] Yield: 77%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (dt, J = 8.2, 0.9 Hz, 1H), 7.89–7.80 (m, 2H), 7.72–7.67 (m, 1H), 7.55–7.38 (m, 4H), 7.32–7.24 (m, 1H).

2-(Methylselanyl)benzo[*d*]thiazole (3aa).[33] Yield: 67%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89–7.81 (m, 1H), 7.72 (dd, J = 8.0, 0.6 Hz, 1H), 7.39–7.29 (m, 1H), 7.27–7.19 (m, 1H), 2.62 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.08, 153.98, 136.26, 126.04, 124.20, 121.55, 120.93, 8.06.

2-(Octylthio)thiazole (3ab). Yield: 93%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 3.4 Hz, 1H), 7.20 (d, J = 3.4 Hz, 1H), 3.28–3.12 (m, 2H), 1.76 (p, J = 7.6, 7.2 Hz, 2H), 1.55–1.37 (m, 2H), 1.37–1.20 (m, 8H), 0.97–0.80 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.32, 143.60, 119.45, 35.51, 32.68, 30.12, 30.03, 29.96, 29.66, 23.54, 15.00. HRMS [EI]: m/z calculated for $C_{11}H_{19}NS_2$ $[M]^+$ 229.0959, found 229.0959. IR (ATR): 2924, 2854, 1739, 1384, 1018, 864, 705 cm^{-1}.

6-Methyl-2-(octylthio)benzo[*d*]thiazole (3ac). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 1H), 7.58–7.53 (m, 1H), 7.22 (dd, J = 8.2, 1.7 Hz, 1H), 3.33 (t, J = 6.0 Hz, 2H), 2.46 (s, 3H), 1.88–1.76 (m, 2H), 1.54–1.43 (m, 2H), 1.37–1.25 (m, 8H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.04, 151.48, 135.31, 134.13, 127.41, 120.95, 120.76, 33.69, 31.79, 29.22, 29.13, 29.06, 28.78, 22.65, 21.40, 14.10. HRMS: [EI]: m/z calculated for $C_{16}H_{23}NS_2$ $[M]^+$ 293.1272, found 293.1265. IR (ATR): 2924, 2855, 1601, 1447, 1258, 1204, 1114, 1065, 995, 818 cm^{-1}.

6-Ethoxy-2-(octylthio)benzo[*d*]thiazole (3ad). Yield: 86%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.9 Hz, 1H), 7.22 (d, J = 2.5 Hz, 1H), 7.00 (dd, J = 8.9, 2.5 Hz, 1H), 4.07 (q, J = 7.0 Hz, 2H), 3.31 (t, J = 7.4 Hz, 2H), 1.81 (p, J = 7.3 Hz, 2H), 1.54–1.40 (m, 5H), 1.40–1.18 (m, 8H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.28, 147.84, 136.47, 121.90, 115.16, 104.79, 64.09, 33.83, 31.79, 29.27, 29.13, 29.05, 28.77, 22.65, 14.84, 14.10. HRMS: [EI]: m/z calculated for $C_{17}H_{25}NOS_2$ $[M]^+$ 323.1378, found 323.1370. IR (ATR): 2924, 2855, 1601, 1447, 1258, 1204, 1115, 1065, 1038, 995, 937, 818 cm^{-1}.

5-Methoxy-2-(octylthio)benzo[*d*]thiazole (3ae). Yield: 95%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 2.5 Hz, 1H), 6.94 (dd, J = 8.8, 2.5 Hz, 1H), 3.88 (s, 3H), 3.33 (t, J = 6.0 Hz, 2H), 1.82 (p, J = 7.2 Hz, 2H), 1.54–1.42 (m, 2H), 1.36–1.24 (m, 8H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.60, 158.88, 154.57, 126.75, 121.07, 113.78, 104.47, 55.60, 33.69, 31.79, 29.15, 29.14, 29.06, 28.78, 22.65, 14.11. HRMS: [EI]: m/z calculated for $C_{16}H_{23}NOS_2$ $[M]^+$ 309.1221, found 309.1216. IR (ATR): 2928, 2855, 1744, 1597, 1466, 1416, 1319, 1026, 810 cm^{-1}.

6-Fluoro-2-(octylthio)benzo[*d*]thiazole (3af). Yield: 94%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.9, 4.8 Hz, 1H), 7.35 (dd, J = 8.1, 2.6 Hz, 1H), 7.05 (td, J = 8.9, 2.6 Hz, 1H), 3.24 (t, J = 7.4 Hz, 2H), 1.73 (p, J = 7.3 Hz, 2H), 1.46–1.33 (m, 2H), 1.32–1.16 (m, 8H), 0.80 (t, J = 6.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.84 (d, J = 3.0 Hz), 159.75 (d, J = 244.6 Hz), 150.01 (d, J = 1.8 Hz), 136.09 (d, J = 11.1 Hz), 122.12 (d, J = 9.2 Hz), 114.26 (d, J = 24.5 Hz), 107.37 (d, J = 26.9 Hz), 33.70, 31.78, 29.18, 29.12, 29.04, 28.76, 22.64, 14.10. ^{19}F NMR (377 MHz, $CDCl_3$) δ −117.55. HRMS: [EI]: m/z calculated for $C_{15}H_{20}FNS_2$ $[M]^+$ 297.1021, found 297.1020. IR (ATR): 2924, 2855, 1601, 1566, 1447, 1308, 1254, 1192, 995, 907, 810 cm^{-1}.

6-Chloro-2-(octylthio)benzo[*d*]thiazole (3ag). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.37 (dd, J = 8.7, 2.1 Hz, 1H), 3.34 (t, J = 7.3 Hz, 2H), 1.83 (p, J = 7.3 Hz, 2H), 1.48 (p, J = 6.8 Hz, 2H), 1.37–1.25 (m, 8H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.10, 151.93, 136.31, 129.89, 126.67, 122.02, 120.54, 33.68, 31.77, 29.13, 29.12, 29.03, 28.75, 22.64, 14.10. HRMS: [EI]: m/z calculated for $C_{15}H_{20}ClNS_2$ $[M]^+$ 313.0726, found 313.0726. IR (ATR): 2920, 2855, 2191, 1431, 1300, 1261, 1196, 1103, 999, 814 cm^{-1}.

5-Bromo-2-(octylthio)benzo[*d*]thiazole (3ah). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 1.9 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.31 (dd, J = 8.5, 1.9 Hz, 1H), 3.26 (t, J = 7.4 Hz, 2H), 1.74 (p, J = 7.3 Hz, 2H), 1.48–1.34 (m, 2H), 1.27–1.16 (m, 8H), 0.81 (t, J = 6.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.49, 154.48, 133.95, 127.03, 124.31, 121.84, 119.61, 33.63, 31.78, 29.13, 29.13, 29.04, 28.77, 22.65, 14.10. HRMS: [EI]: m/z calculated for $C_{15}H_{20}BrNS_2$ $[M]^+$ 357.0221, found 357.0227. IR (ATR): 2920, 2851, 1740, 1408, 1231, 1204, 1146, 1011, 891, 868 cm^{-1}.

7-Bromo-2-(octylthio)benzo[*d*]thiazole (3ai). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.1, 1.0 Hz, 1H), 7.33 (dd, J = 7.8, 1.0 Hz, 1H), 7.23–7.17 (m, 1H), 3.26 (t, J = 7.4 Hz, 2H), 1.75 (p, J = 7.3 Hz, 2H), 1.47–1.35 (m, 2H), 1.30–1.15 (m, 8H), 0.84–0.78 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.02, 153.20, 137.91, 127.19, 126.79, 120.10, 113.15, 33.71, 31.78, 29.12, 29.08, 29.03, 28.75, 22.64, 14.10. HRMS: [EI]: m/z calculated for $C_{15}H_{20}BrNS_2$ $[M]^+$ 357.0221, found 357.0224. IR (ATR): 2924, 2855, 1740, 1450, 1377, 999, 775 cm^{-1}.

2-(Octylthio)benzo[*d*]thiazole-6-carbonitrile (3aj). Yield: 98%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 1.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 8.4, 1.6 Hz, 1H), 3.37 (t, J = 7.3 Hz, 2H), 1.83 (p, J = 7.3 Hz, 2H), 1.56–1.41 (m, 2H), 1.41–1.17 (m, 8H), 0.96–0.82 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.94, 155.70, 135.66, 129.51, 125.34, 121.82, 118.81, 107.27, 33.73, 31.76, 29.10, 29.10, 29.01, 28.74, 22.63, 14.10. HRMS: [EI]: m/z calculated for $C_{16}H_{20}N_2S_2$ $[M]^+$ 304.1068, found 304.1068. IR (ATR): 2920, 2843, 2222, 1427, 1400, 1308, 1246, 1192, 1003, 826 cm^{-1}.

2-(Octylthio)benzo[*d*]thiazole-5-carbonitrile (3ak). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 1.5 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.52 (dd, J = 8.2, 1.6 Hz, 1H), 3.37 (t, J = 7.3 Hz, 2H), 1.83 (p, J = 7.3 Hz, 2H), 1.56–1.41 (m, 2H), 1.36–1.23 (m, 8H), 0.92–0.86 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.83, 153.00, 140.20, 126.56, 125.07, 121.86, 118.85, 109.65, 33.66, 31.77, 29.12, 29.06, 29.02, 28.75, 22.64, 14.11. HRMS: [EI]: m/z calculated for $C_{16}H_{20}N_2S_2$ $[M]^+$ 304.1068, found 304.1061. IR (ATR): 2924, 2855, 1744, 1431, 1412, 1018, 826 cm^{-1}.

6-Nitro-2-(octylthio)benzo[*d*]thiazole (3al). Yield: 86%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 2.3 Hz, 1H), 8.29 (dd, J = 9.0, 2.3 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 3.40 (t, J = 7.4 Hz, 2H), 1.85 (p, J = 7.4 Hz, 2H), 1.55–1.43 (m, 2H), 1.40–1.25 (m, 8H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.64, 157.10, 143.96, 135.48, 121.84, 121.12, 117.30, 33.79, 31.76, 29.10, 29.01, 28.99, 28.75, 22.63, 14.09. HRMS: [EI]: m/z calculated for $C_{15}H_{20}N_2O_2S_2$ $[M]^+$ 324.0966, found 324.0966. IR (ATR): 2924, 2851, 1512, 1327, 1265, 1118, 1049, 1003, 829 cm^{-1}.

6-Ethoxy-2-(propylthio)benzo[*d*]thiazole (3am).[34] Yield: 80%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.9 Hz, 1H), 7.22 (d, J = 2.5 Hz, 1H), 7.00 (dd, J = 8.9, 2.5 Hz, 1H), 4.06 (q, J = 7.0

Hz, 2H), 3.29 (t, J = 7.2 Hz, 2H), 1.85 (h, J = 7.3 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.4 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.91, 156.29, 147.83, 136.47, 121.90, 115.17, 104.78, 64.09, 35.72, 22.76, 14.84, 13.38.

5-Methoxy-2-((4-methoxybenzyl)thio)benzo[*d*]thiazole (3an).[26] Yield: 83%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.41–7.34 (m, 2H), 6.96 (dd, J = 8.8, 2.5 Hz, 1H), 6.91–6.83 (m, 2H), 4.55 (s, 2H), 3.89 (s, 3H), 3.80 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.72, 159.18, 158.94, 154.40, 130.33, 127.94, 126.92, 121.18, 114.11, 113.96, 104.57, 55.62, 55.28, 37.42.

2-(Benzylthio)-6-chlorobenzo[*d*]thiazole (3ao).[35] Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 7.51–7.44 (m, 2H), 7.41–7.30 (m, 4H), 4.61 (s, 2H).

5-Bromo-2-((4-methoxybenzyl)thio)benzo[*d*]thiazole (3ap). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 1.9 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.34–7.24 (m, 3H), 6.82–6.73 (m, 2H), 4.46 (s, 2H), 3.71 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.63, 159.23, 154.27, 134.10, 130.37, 127.80, 127.20, 124.39, 121.94, 119.68, 114.13, 55.29, 37.30. HRMS: [EI]: m/z calculated for $C_{15}H_{12}BrNOS_2$ $[M]^+$ 515.9917, found 364.9544. IR (ATR): 2916, 1608, 1508, 1419, 1246, 1172, 1014, 829, 794 cm^{-1}.

2-(*p*-Tolylthio)benzo[*d*]thiazole-6-carbonitrile (3aq). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95–7.92 (m, 1H), 7.89 (dd, J = 8.5, 0.6 Hz, 1H), 7.69–7.59 (m, 3H), 7.39–7.31 (m, 2H), 2.47 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.96, 157.47, 142.93, 136.68, 132.03, 130.50, 126.12, 126.03, 123.19, 119.69, 108.25, 22.43. HRMS: [EI]: m/z calculated for $C_{15}H_{10}N_2S_2$ $[M]^+$ 282.0285, found 282.0285. IR (ATR): 3089, 2229, 2739, 1431, 1381, 1006, 794 cm^{-1}.

2-((4-Methoxybenzyl)thio)benzo[*d*]thiazole-5-carbonitrile (3ar). Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 1.5 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.45 (dd, J = 8.3, 1.6 Hz, 1H), 7.35–7.24 (m, 2H), 6.84–6.75 (m, 2H), 4.51 (s, 2H), 3.72 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.98, 159.33, 152.82, 140.32, 130.40, 127.47, 126.71, 125.19, 121.96, 118.81, 114.18, 109.75, 55.30, 37.33. HRMS: [EI]: m/z calculated for $C_{16}H_{12}N_2OS_2$ $[M]^+$ 312.0391, found 312.0391. IR (ATR): 2920, 2229, 1739, 1508, 1435, 1249, 1172, 1006, 813 cm^{-1}.

Conflicts of interest

There are no conflicts to declare.

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