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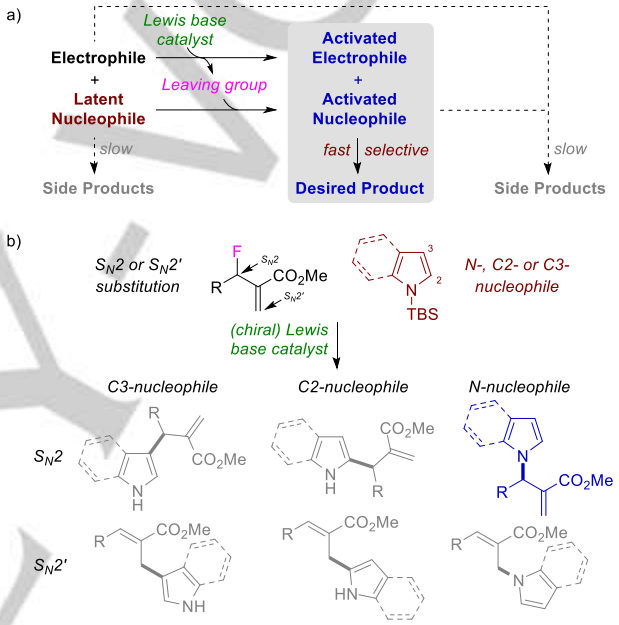
Latent Nucleophiles in Lewis Base Catalyzed Enantioselective *N*-Allylation of *N*-Heterocycles

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 of allylic fluorides catalyzed by Lewis bases. Reactions feature broad scope for both reaction partners, excellent regioselectivity and produce the enantioenriched *N*-allyl pyrroles, indoles and carbazoles when chiral cinchona catalysts are used.

Lewis base catalysts can serve to increase both 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 are observed and/or 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, derivatives of otherwise nucleophilic molecules which 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 range of reactivity/catalysts to be utilized in Lewis-base catalysis.

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 (i) the problem of activation of pyrroles, indoles and carbazoles as nucleophiles, and (ii) the problems related to the regioselectivity in their functionalization (N, C2 or C3) and substitutions of allylic fluorides (S_N2 vs. S_N2') can be addressed using latent *N*-silyl nucleophiles. Here, we report that *N*-silyl pyrroles, indoles and carbazoles serve as latent *N*-nucleophiles in substitutions of allylic fluorides and enable enantioselective allylation of *N*-heterocycles.



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

Our initial studies of different silyl groups in the latent nucleophiles revealed that the commonly used silyl protecting groups all afford the products of *N*-allylation in good yields when allylic fluoride **1a** (Scheme 2) was used in combination with the *N*-silyl pyrrole (see supporting information document for the details of optimization studies). In order to preempt interactions of 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 influence the reactions outcomes. *N*-centered Lewis base catalysts showed generally better efficacy than the corresponding *P*-centered Lewis bases. Slight excess of the latent nucleophile in combination with 5 mol% of the DABCO as 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

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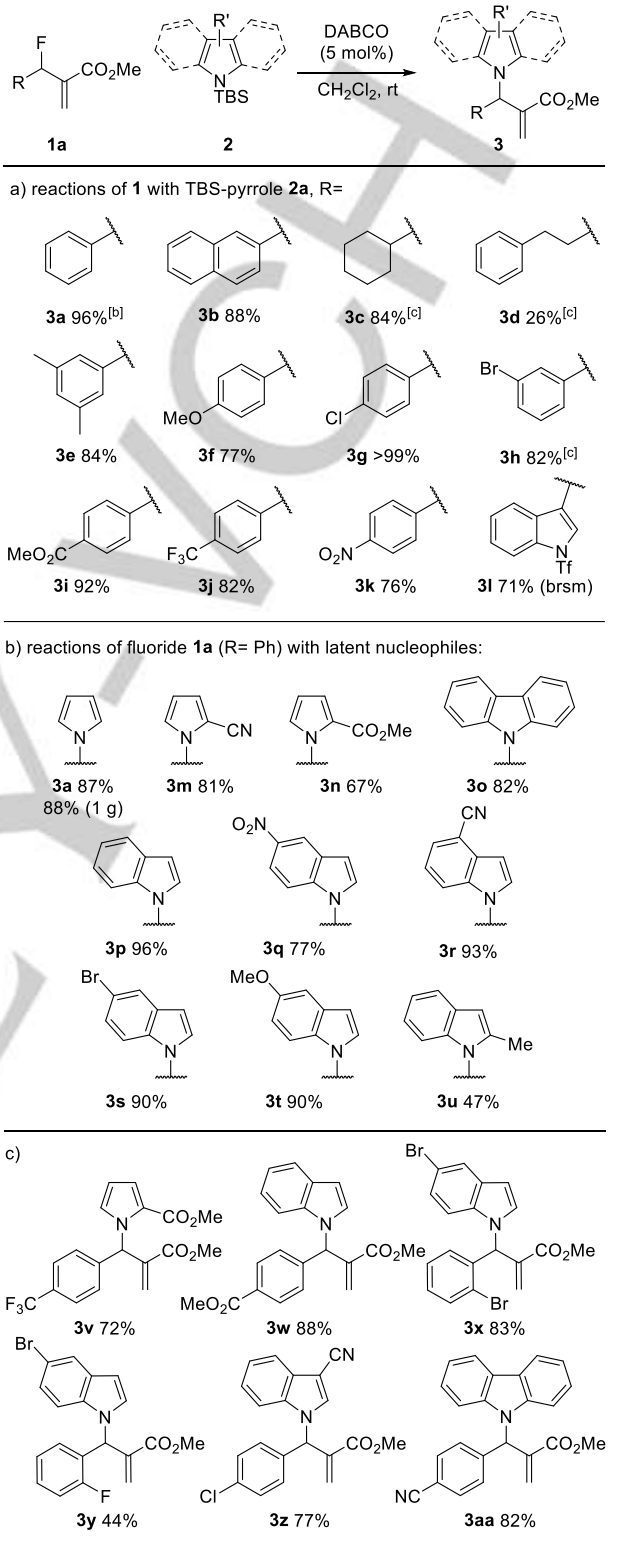
yields were observed across the board regardless of the electronic properties of the MBH fluoride (Scheme 2a). Both electron rich (**3e**-**3f**) and electron poor (**3i**-**3l**) allylic fluorides afforded the desired products in good yields with short reaction time (<5 minutes). Alkyl fluorides also proved reactive but lower yields were observed for primary alkyl substituents (**3c**, **3d**). Aryl halides, good substrates for further functionalization of the reaction products, were all well tolerated (**3g**-**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.

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, like with 2,5-dimethylpyrrole, rendered substitution reaction prohibitively slow. Further evaluation of reaction scope included indoles and carbazole. Various substituted indoles performed well in the reactions 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 the yield of 47% which could be improved by increasing catalyst loading. *N*-silyl carbazole performed even better with 82% isolated yield (**3o**). Importantly, these reactions were highly regioselective with respect to both coupling partners. Neither products of C2-/C3-allylation of pyrrole/indole nor S_N2' substitution were observed in any of these experiments.

A series of experiments where various combinations of substituted nucleophilic and substituted electrophilic partner were subjected to the optimized reaction conditions further established 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, catalyst loading could be lowered to as little as 1 mol% of DABCO without deterioration of yields, although longer reaction times were observed qualitatively in 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. Good scalability together with a plethora of methods for further functionalization of products[10] make this method attractive for applications in target oriented synthesis.

Having confirmed that the reactions using latent nucleophiles are highly regioselective and feature broad scope for both reactive partners when DABCO was used as the catalyst, investigation of the enantioselective reactions using chiral Lewis base catalysts commenced. 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, reaction temperature, concentration, solvent and the ratio of reactive partners influence the reaction outcomes (details provided in the supporting information document). The optimized conditions included $(DHQD)_2PHAL$ as a chiral Lewis base catalyst which is used in



Scheme 2. a) Scope of the allylic fluoride **1** in Lewis base catalyzed allylation of 1-(*tert*-butyldimethylsilyl)pyrrole **2a**. b) Scope of *N*-silyl pyrroles, indoles and carbazoles in *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] 1.5 equiv of **2** and 10 mol% of DABCO was used.

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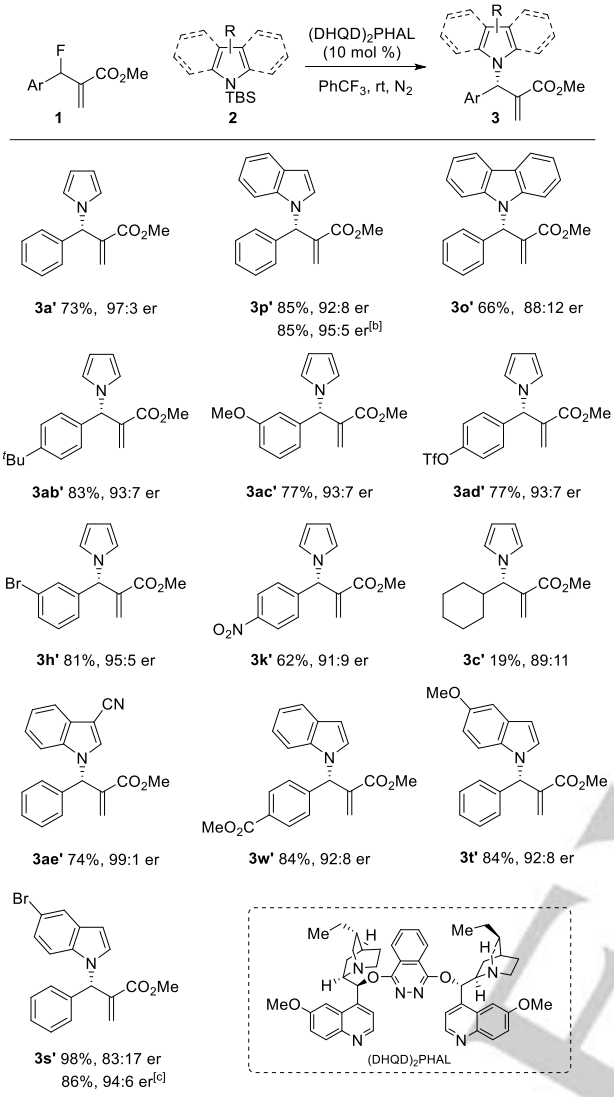
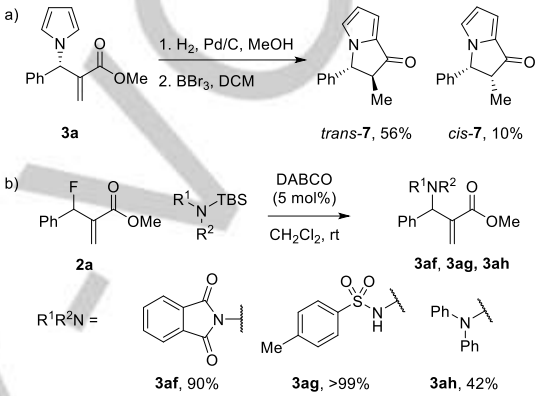


Scheme 3. Enantioselective chiral Lewis base catalyzed allylic substitutions of allylic fluorides with *N*-silyl nucleophiles. [a] The reaction of **1** (2 equiv), with **2** and $(DHQD)_2PHAL$ (10 mol%), was carried out in $PhCF_3$ at room temperature under N_2 atmosphere. [b] 1,4-dioxane was used as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

the amount of 10 mol% 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 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 higher than 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 showed moderate effects on the yields and enantioselectivity which was 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 via focused optimization for individual cases as demonstrated for **3p'** and **3s'** where enantiomeric ratios 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 the previously reported data for **3t'**[11] and the absolute configuration of other products was assigned by analogy.[12]



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

Substitution product containing pyrrole (**3a**) proved useful in the 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 latent nucleophiles in Lewis base catalysis, a broader group of silylated *N*-nucleophiles including phthalimide, tosylamide and diphenylamine was tested and shown to be competent in reactions with allylic fluorides (**3af**, **3ag**, **3ah**, Scheme 4b).

Our attention 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 formation of ammonium salt **4** was observed by NMR *in situ* (Scheme 5b).[16] In a crossover experiment where deuterium labeled indole **2af** was used in equimolar mixture with *N*-TBS-indole **2p**, both were incorporated in 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

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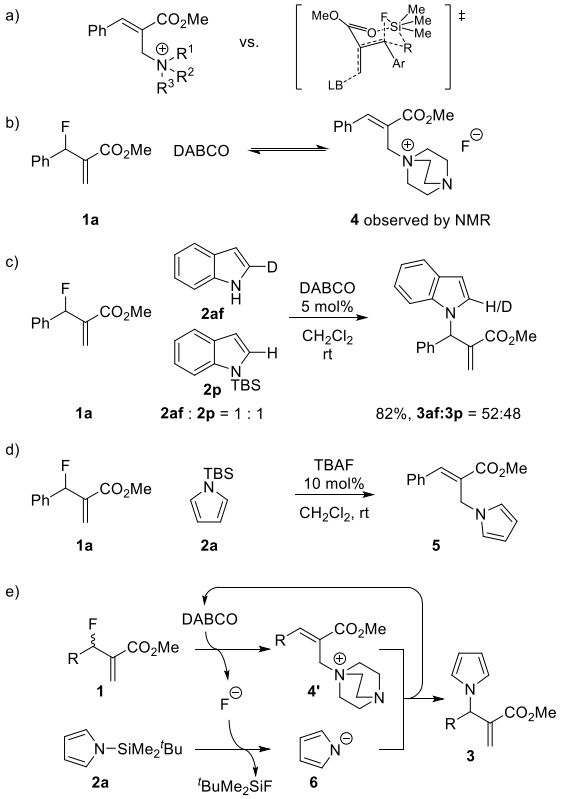

Scheme 5. Selected experiments aimed at evaluation of reaction mechanism. a) Previously proposed intermediates and transition states in related reactions, $NR^1R^2R^3$ – amine/chiral cinchona catalyst, R= CF_3, alkynyl, *N*-methyltetrazole. b) Formation of ammonium salt **1a** without silyl assistance.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

control experiments were carried out to confirm that (i) the indole itself does not react with the allylic fluoride under the reaction conditions and (ii) TBS group is not transferred between **2af** and **2p** in the presence of DABCO. Finally, when TBAF was used as a catalyst, the reaction proceeds with high rates (reaction time < 20 minutes) and only the products of S_N2' substitution were observed (Scheme 5d). Based on these experiments, we propose the mechanistic sketch 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'**. 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) and the anionic *N*-nucleophile **6**. 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 addition/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 simultaneous presence of activated electrophile/nucleophile pair in the reaction mixture and demonstrates the importance of the latent character of the nucleophile. Finally, excellent regioselectivities and good stereocontrol observed in the presence of chiral Lewis base catalysts suggests that addition of the activated nucleophile to 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 using allylic fluorides. When widely available chiral cinchona alkaloid based catalysts are used, the allylation products are 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 latent nucleophiles in Lewis base catalysis hinges on the concurrent activation of both reaction partners which allows for expanded reaction scope and improved selectivity. This concept may be generally applicable in a variety of reactions that depend on the use of heteroatom-centered nucleophiles.

Acknowledgements

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Keywords: latent nucleophile • Lewis base catalysis • nucleophilic substitution • allylation • nitrogen heterocycles

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