Title: Enantioselective N-heterocyclic carbene catalysis exploiting imine umpolung

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N-Heterocyclic carbene (NHC, i.e. 1) provide access to normal and reverse polarity intermediates integral to many reactions. While a wide range of reactive intermediates are accessible, they are almost invariably formed via the Breslow intermediate (2), itself derived from aldehyde substrates (i.e. 3). Alternate substrates for NHC-catalysis are known, such as esters, ketones and conjugate acceptors, however these remain less commonly examined, with a number of functional groups largely overlooked.

Imines are easily prepared electrophiles that would appear well suited to polarity inversion catalysis. Surprisingly enantioselective reactions of such substrates, under any type of catalysis, have only recently been reported, with access to 2-aza-union intermediates enabling various alkylations. NHC catalysis with imines has been known since the early 2000s, however these studies demonstrate that while they are viable as electrophilic coupling partners, they do not undergo polarity inversion. For example in 2005 Bode coupled cinnamaldehydes with sulfate-imine 4 to give pyridinone 5 (eq. 1) in a reaction that proceeds via the homoenolate intermediate, not the imine umpolung (aza-Breslow) intermediate. Independent work of Hou and Chi has demonstrated that related Ts-imines can serve as precursor to the sulfate anion, presumably through fragmentation of the azabreslow intermediate. However, it wasn’t until 2017 that Biju reported cyclosimerization of imine 6 indole 7 (eq. 2) in the first NHC catalyzed reaction involving imine umpolung. Subsequently, the azabreslow has been invoked in the oxidation of imines to amides, and a quinolone synthesis. While these reports demonstrate the viability of the azabreslow in reaction discovery key challenges remain—perhaps most notably regarding enantioselective catalysis. As part of our interest in NHC catalysis with unconventional substrates we commenced studies on this topic. In addition to providing a new enantioselective transformation, we felt that such studies could facilitate access to nitrogenous secondary intermediates analogous to those of the Breslow intermediate (Figure 1). Herein, we report the enantioselective intermolecular aza-Stetter reaction (eq. 3). The reaction proceeds with excellent enantioselectivity allowing a range of imines (i.e. 8) to couple with 3-methylene-chroman-2-ones (i.e. 9) to provide highly enantioenriched γ-imino lactones (10). While the enantioselective reaction requires 3-methylene-chroman-2-ones, achiral catalysts allow use of simple acylates.

We postulated that the imine protecting group would be most influential on aza-breslow formation, and hence reaction viability. Thus, studies commenced by screening a number of protected aldmines (8a-e) using achiral catalyst A1 (Table 1, entries 1 and 2). When heated in THF at reflux imines 8a-d gave no coupled products, with 8a, b and d isolated unchanged, while 8c gave the product of sulfinate addition. In contrast benzoyl imine 8e gave enone 12e in 82% isolated yield. The unique viability of this protecting group we believe is due to a combination of its electron-withdrawing capacity, combined with enhanced stability compared to 8c. Formation of 12e is consistent with a reaction of either the polarity inverted conjugate acceptor, or the imine, followed by isomerization of 10e to enone 12e, with subsequent mechanistic
Having achieved a highly enantioselective reaction, generality was examined through the coupling of twelve aryl and heteroaryl imines, to seven chromanones (Table 2). Aldimines bearing electron-donating, withdrawing, and heteroaromatic Ar substituents all coupled to lactone 9a to give aza-Stetter products 10c-1 with high enantiopurity (all ≥98:2 er), and highest yields using electron rich imines (Table 2, entries 1-5). Unfortunately, aliphatic imines bearing acidic α-protons, such as the benzylimine of isobutyraldehyde, underwent facile isomerization to the corresponding enamine, a common limitation in imine based catalysis. \[16\] Next, the imine protection was modified, with 4-MeOBz and 4-ClBz protected aldimines reacting to give the four products 10j-m with 59-73% yield and ≥98:2 er (Table 2, entries 6-9).

Next we examined a series of chromanone derivatives bearing alkyl (i.e. 9b, d and e), electron-releasing (i.e. 9c), or electron-withdrawing groups (i.e. 9f) at the 3-, 4-, and 5- positions. All gave the expected aza-Stetter products (10n-t) with excellent enantioselectivity (≥96:4 er). Yields suggest a sensitivity to electronics, with the electron rich and poor products 10q and t formed in modest yields of 45 and 49% (Table 2, entries 10-16). Finally naphthalene and quinoline derived chromanones (9g and 9h) coupled with various imines to give the expected products 10u-y with excellent enantioselectivity (all ≥96:4 er), although the heterocyclic products formed with modest yields (Table 2, entries 20-21).

Attempts to expand the range of conjugate acceptors met with limited success. For example, chalcone, cyclohexan-2-one, 2-aminocarboxylic acids, and methylcarboxylates all failed to couple with various imines using catalyst A5. In these cases the acceptor was often isolated while the imine dimerized to give aza-benzoin products 13 (eq. 6). In contrast to the benzoin condensation of aldehydes, which is considered to be reversible, \[15\] aza-benzoin 13 did not serve as an aza-Breslow precursor, \[17\] and hence formation of 13 impacts the generality of the aza-Stetter reaction. In contrast, when the achiral catalyst A1 was used methylcarboxylate and methylcarboxylate gave the aza-Stetter products 10z-ab (eq. 7), while acrylonitrile gave the related enamine 13g (eq. 8). These reactions suggest that alternate...
variants of the enantioselective aza-Stetter reactions may well be viable, although the current reaction shows significant sensitivity to substitution, with methylmethacrylate derived 10ab forming in low yield.

Derivatization was undertaken to examine the reactivity of the products and allow absolute configuration to be determined (Scheme 2). Exhaustive addition of PhMgBr to 10j gave triphenyl benzamide 14j, while at lower temperature chemoselective addition of PhMgBr gave diketone 15j. Some erosion of enantipurity was observed in both cases. Finally hydrolysis gave γ-keto ester 16j, from which single crystal X-ray analysis was performed to allow absolute configuration to be determined.[18]

From our optimization and scope studies it appears that the aza-Breslow is less reactive than the Breslow, and that catalysis requires highly nucleophilic NHCs. To gain more detailed mechanistic information studies commenced by examining the significance of enamine and enone formation observed during optimization. When imine 10e was resubjected to the reaction conditions a 7:7:6 mixture of 10e, 11e, and 12e (Scheme 3, eq. 9). In contrast, resubjection of enamine 11e, or enone 12e to the reaction conditions failed to produce 10e, with 11e and 12e returned, along with unidentified decomposition products. These results are consistent with imine umpolung leading to 10e, rather than homoenolate formation providing 11e or 12e, which isomerizes to imine 10e. Next experiments were performed to examine the turnover limiting step. Competition between D-8j and 8n, with associated controls.[19a] showed lack of a primary KIE (eq. 10), thus deprotonation is unlikely to be turnover limiting. When competition studies with electronically differentiated protecting groups (i.e. 8e cf. 8j) and 8e cf. 8m were undertaken it demonstrated that the reaction is enhanced by electron-withdrawing imine protection (eq. 11).[19b] This trend was also observed with competitions involving manipulation of the electronics of the imine Ar′ group (8e cf. 8f). Taken together these results are consistent with turn over limiting addition of the NHC to the imine to afford 17. Further support for this interpretation can be derived from kinetic studies into the order of the reaction.[20] Preliminary studies show the reaction to be close to 0 in chromanone (0.30), and first order in NHC (0.74) and imine (1.12). Unfortunately, while related aza-Breslow intermediates have been isolated,[7,8] this was not possible with benzoyl imine 8, with all attempts leading to formation of dimeric aza-Benzoin products 13. So turn over limiting addition to the imine is followed by BaOH mediated tautomerization to afford aza-Breslow 18, which undergoes 1,4-addition to chromanone 9 to provide enolate 19. Diastereoselective protonation provides 20[21] with elimination of the catalyst completing the cycle.

Herein, we report the first enantioselective NHC catalysed reaction involving imine umpolung. Key to its success is the use of catalysts more nucleophilic than those used in acyl anion reactions. Good generality with regard to the imine was observed, while the conjugate acceptor is more limited. Mechanistic studies implicate turn over limiting addition of the NHC to the imine.
A wealth of reactions exploit the Breslow intermediate en route to diverse secondary intermediates (Scheme 1). While our studies show the aza-Breslow to be less reactive than the Breslow, we expect related, as well as unique, enantioselective reactions designs to be possible via related secondary intermediates. Certain topics on this topic are ongoing.

Keywords: enantioselective catalysis • N-heterocyclic carbenes • imine umpolung • Stetter


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Imine umpolung is an underdeveloped area of enantioselective catalysis despite providing a new entry to nitrogenous compounds of potential utility. Herein, we report the use of NHCs, to catalyze an enantioselective aza-Stetter reaction. In contrast to the chemistry of acyl umpolung with NHCs this reaction requires highly nucleophilic catalysts. The reaction is highly enantioselective (all ≥96:4 er) with various imines and 3-methylenechroman-2-ones coupled to give γ-imino lactones.
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