NHC Catalysis

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Enantioselective, NHC-Catalyzed Annulations of Trisubstituted Enals and Cyclic *N*-Sulfonylimines via α,β-Unsaturated Acyl Azoliums**

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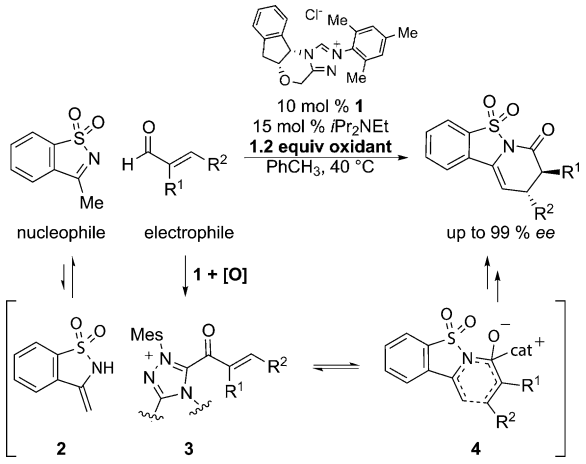
The combination of N-heterocyclic carbene (NHC) catalysts with α,β-unsaturated aldehydes has emerged as one of the most powerful methods for enantioselective C–C bond forming reactions via the catalytic generation of reactive intermediates.[1] From this single substrate class, NHC catalysis provides access to nucleophiles including acyl anion equivalents,[1e] homoenolate equivalents,[1b] and ester enolate surrogates,[1f] as well as the electrophilic acyl azoliums and α,β-unsaturated acyl azoliums.[1a] Dozens of new C–C, C–N, C–S, and C–O bond forming reactions have been reported using the unique chemistry of these catalytically generated species, most of them with good yields, outstanding enantioselectivities, and simple reaction methods.

Despite the versatility of enantioselective NHC-catalyzed reactions, they are restricted to simple enals. The α- and β,β′-substituted enals are usually unreactive, and only a few successful annulations with these substrates have been reported.[2] This limitation parallels the development of enantioselective, secondary-amine catalyzed reactions of α,β-unsaturated aldehydes and ketones, which until 2005 were restricted to α-unsubstituted substrates.[3] Herein we disclose a new NHC-catalyzed, highly enantioselective annulation that makes two significant advances in the substrate scope: 1) it permits, for the first time, highly enantio- and diastereoselective annulations of α- and β,β′-substituted enals and 2) it demonstrates the utility of cyclic sulfonylimines as nucleophiles in highly enantioselective NHC-catalyzed reactions (Scheme 1). Previously, these saccharine-derived cyclic imines had proven to be electrophiles[4] for NHC-catalyzed γ-lactam formation via homoenolates, but only with poor enantioselectivity.[5]

α,β-unsaturated acyl azoliums may be generated by internal redox reactions of ynals,[6] by nucleophilic additions to acyl fluorides or esters,[7] or from α,β-unsaturated aldehydes in conjunction with an external oxidant.[8] Studies from ourselves[9,10] and Lupton[11] have shown that these electrophilic reactive species can undergo annulation reactions by a Coates–Claisen process in which the nucleophile pre-



Scheme 1. An enantioselective annulation of trisubstituted enals and cyclic *N*-sulfonylimines.

associates with the highly electrophilic ketone of the acyl azolium followed by a sigmatropic rearrangement.[12] The ability of α,β-unsaturated acyl azoliums to also serve as acceptors in conjugate addition reactions[13] implies that they should also be outstanding partners for other nucleophiles, but catalytic reactions involving nucleophiles that cannot also give 1,2-addition products have not been successful to date; the scope of the annulations has remained limited to activated ketones[8,14] and N-unprotected enamines.[15]

The potential for cyclic sulfonylimine **5** to serve as a nucleophile through enamine generation is apparent from facile the H–D[16] exchange of the CH_3 group, but only a single report of its use as a nucleophile has appeared.[17] To test their potential for NHC-catalyzed aza-Claisen annulations, we combined imine **5** and cinnamaldehyde in the presence of an NHC precatalyst, oxidant **7**,[18] and base (Table 1). Azolium salts **10** and **11**, which have been used in NHC-catalyzed annulations with 1,3-diketones,[8a,13c] were unreactive. Achiral azolium salts bearing N-mesityl groups, in contrast, delivered the desired annulation product contaminated with a small amount of homoenolate addition product **9** (entry 4). In the absence of oxidant, only homoenolate product **9** was detected (entry 5). Chiral N-mesityl substituted triazolium salt **1**,[19] used together with Hünig's base,[2a,20] proved to be an outstanding catalyst for the annulation, affording the desired dihydropyridinone[21] product exclusively in 99% *ee*. The use of stronger bases such as DBU or other chiral azolium salts (i.e. **14**), led to diminished yield and byproducts (entries 6 and 8).

These conditions were adopted for further studies of the reaction scope. With respect to the enal partners, the reaction

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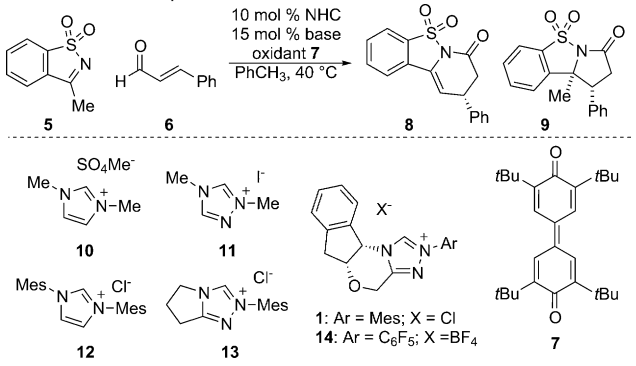
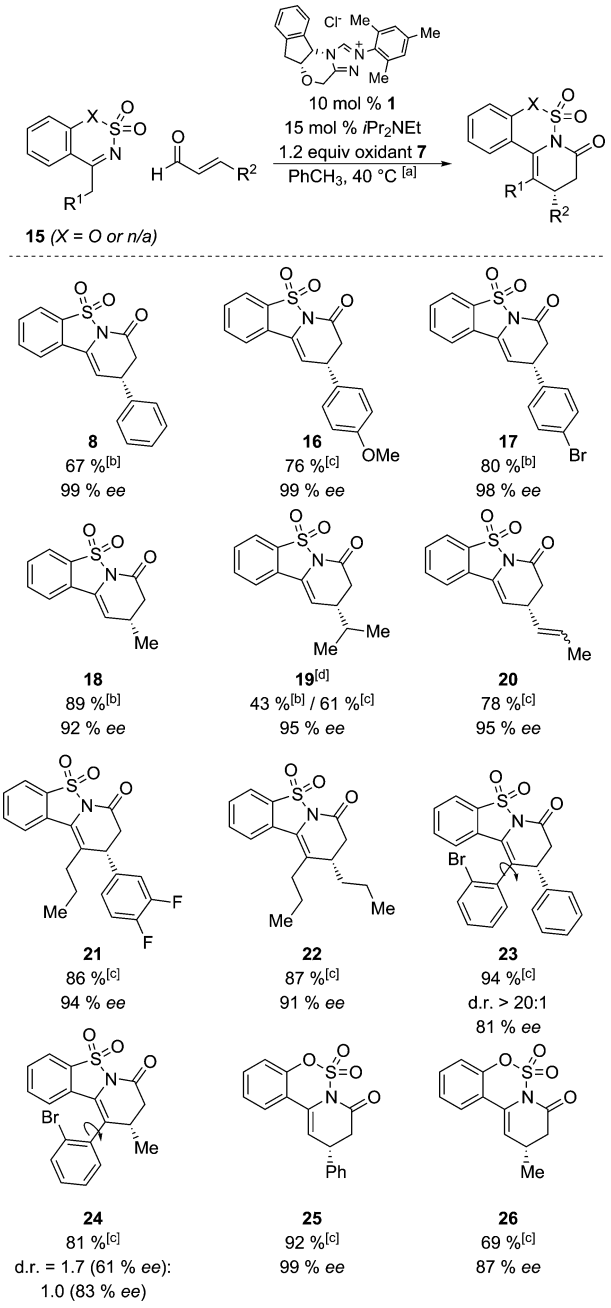
Table 1: Reaction optimization.



Entry	NHC	Base	[O]	Conversion [%]	**8/9**
1	**10**	iPr$_2$NEt	**7**	0	–
2	**11**	iPr$_2$NEt	**7**	trace	–
3	**12**	iPr$_2$NEt	**7**	27	1.0:0
4	**13**	iPr$_2$NEt	**7**	91	1.0:0.1
5	**13**	DBU	n/a	100	0:1.0
6	**1**	DBU	**7**	47	1.0:0
7	**1**	iPr$_2$NEt	**7**	100	1.0:0
8	**14**	iPr$_2$NEt	**7**	18	1.0:0.1

Table 2:



[a] Reaction conditions: 0.1 M $PhCH_3$ at 40 °C for 12–72 h. [b] Yield refers to isolated products after recrystallization. [c] Yield refers to isolated products after chromatography. [d] The absolute configuration of (*R*)-**19** was established by X-ray analysis; others were assigned by analogy.

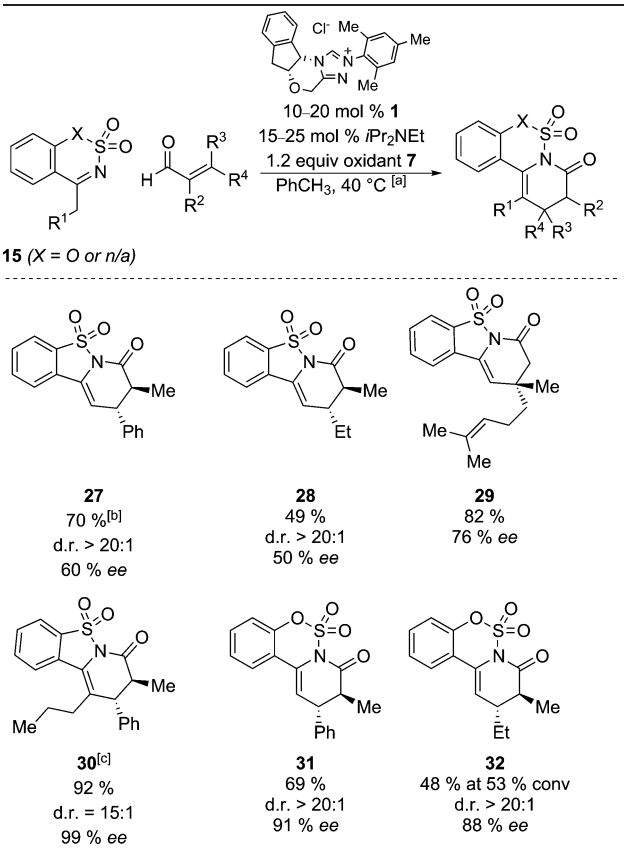
tolerated all tested *E*-enals including cinnamaldehyde, its derivatives (with electron-donating and electron-withdrawing groups), aliphatic and alkenyl side chains (**18**–**20**, Table 2). Saccharine-derived cyclic sulfonylimines bearing either aromatic or aliphatic substituents were competent reactions partners in good (**23**, **24**) to excellent (**21**, **22**) enantioselectivity. Sulfonylimine **15** (X = O, R^1 = H) was also found to be successful under these reaction conditions (**25**, **26**). In many cases, the desired product crystalized from the crude reaction mixture; purification by chromatography was not required.

The failure of trisubstituted enals to participate in NHC-catalyzed annulations is a long-standing limitation of the substrate scope. We were therefore pleased to find that (*E*)-α-methyl-cinnamaldehyde, (*E*)-α-methyl-pentenal, and geranial participated in this reaction (Table 3). Unlike disubstituted enals, highly substituted enals generally required a much longer reaction time and/or higher catalyst loading, which we attributed to a change in the rate-determining step from C–C bond formation to oxidative formation of the sterically congested α,β-unsaturated acyl azoliums.[22] Nonetheless, the coupling with cyclic saccharine-derived sulfonylimines proved to be high yielding and highly diastereoselective, albeit moderate in enantioselectivity (**27**–**29**). Sulfonylimine **15** (X = O, R^1 = H) was a better substrate, affording the desired product in good yield, d.r., and *ee* (**31**, **32**).

Mechanistically, we propose that the combination of enal and chiral *N*-mesityl triazolium salt **1** led to the formation of the Breslow intermediate (**I**, Scheme 2), which is oxidized to form the key α,β-unsaturated acyl azolium (**II**).[23] Tautomerization between the imine and the enamine occurred readily with base, and the enamine was intercepted by **II** to form hemiaminal **III**. Alternatively, N-acylation of the imine, which increased the acidity of the adjacent proton, could occur first followed by a base-mediated deprotonation directly to **III**. In either case, the hemiaminal engaged in a Stork-Hickmott-Stille-type annulation[24] via a "tight-ion-pair/aza-Claisen-type" transition state.[15] This step determined the absolute stereochemistry of the product and has the same sense of asymmetric induction as observed in all our prior annulations by this reaction mode.[12,15] The subtle details of the stereochemical induction of a related reaction has been recently outlined.[10] Lactam formation followed the protonation of enolate **IV** and effected catalyst turnover to complete the catalytic cycle.

An unresolved question was the stereochemical course of protonation of enolate **IV**.[25] NHC-mediated enantioselec-

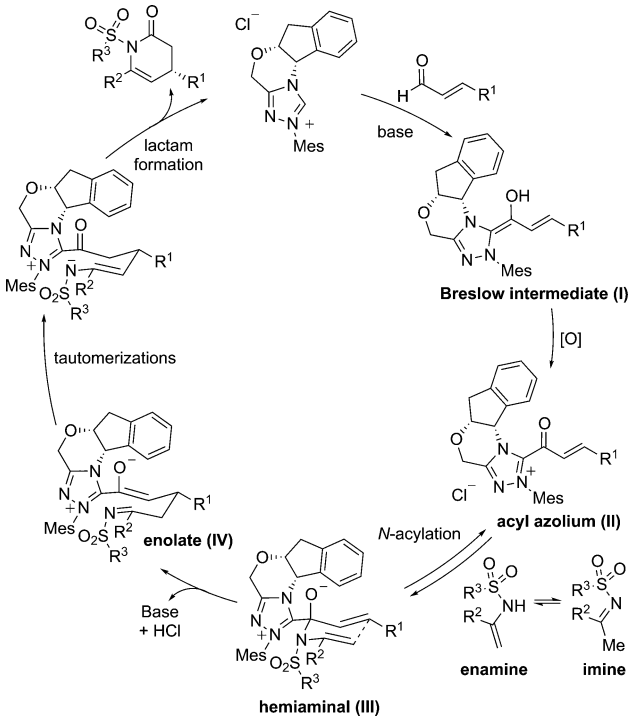
Table 3:



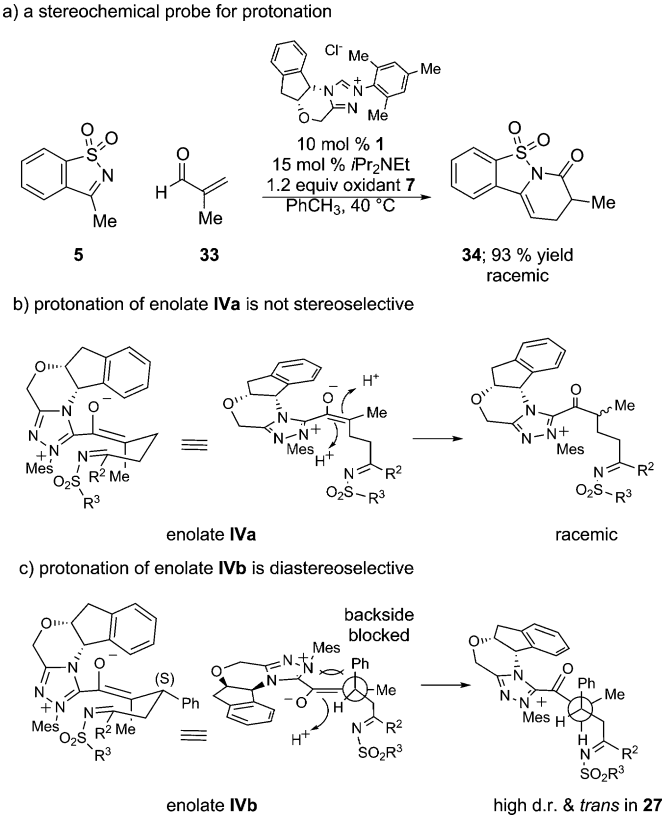
[a] Reaction conditions: 0.1 M $PhCH_3$ at 40 °C for 1–8 days; *E*-enals were used in these reactions. [b] Yield refers to isolated products after chromatography. [c] The configuration of **30** was established by X-ray analysis; others were assigned by analogy.

tive[26] and diastereoselective[27] protonation reactions have been described, and we first considered catalyst control of the stereoselectivity. To probe this issue, we subjected methacrolein (**33**) to the standard conditions of our enantioselective annulation with **5**. The reaction smoothly afforded expected product **34**, but as a racemic mixture. Based on our proposed catalytic cycle, this result indicated that protonation of enolates (such as **IVa**, Scheme 3b) is not stereoselective. The high diastereomeric ratio observed for all the products in Table 3 is, therefore, an outcome of diastereoselective protonation. Stereoinduction arose from the stereocenter formed after the rearrangement of hemiaminal **III**. For the observed *trans*-products, such as **27**, a stereochemical model shown in Scheme 3c, based on minimizing $A^{1,3}$ (1,3-allylic) strain, rationalizes the stereochemical course of protonation.[28]

In summary, we have disclosed a new class of NHC-catalyzed annulations of cyclic sulfonylimines operating through the catalytic generation of α,β-unsaturated acyl azoliums. These studies both extend the scope of highly enantioselective NHC-catalyzed reactions to cyclic imines bearing both aliphatic and aromatic substituents and offer, for the first time, the opportunity for stereoselective annulations using trisubstituted enals. By demonstrating that there is no mechanistic limitation to NHC-catalyzed annulations of more substituted substrates and that diastereocontrol can arise from substrate-directed protonation, rather than catalyst-directed protonation, these studies will provide the founda-



Scheme 2. A proposed catalytic cycle for enantioselective, NHC-catalyzed annulations of enals and cyclic *N*-sulfonylimines.



Scheme 3. A stereochemical probe and proposed stereochemical models for protonation of enolates **IVa–c**.

tion for further advances in substrate scope and reactivity in NHC-catalyzed processes.

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Communications

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A. G. Kravina, J. Mahatthananchai, J. W. Bode* ——— ■■■■–■■■■

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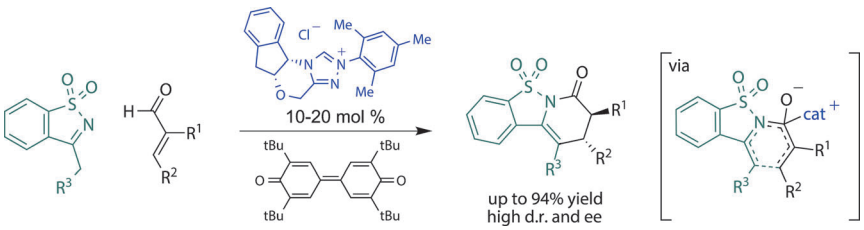

All aboard please! A new reaction of enals and cyclic sulfonylimines, as the nucleophiles(!), is the first highly enantioselective NHC-catalyzed annulation of trisubstituted enals. The catalytically generated α,β-unsaturated acyl azolium undergoes a reaction with the enamine tautomer of the imine via an aza-Claisen rearrangement as the key C—C bond-forming step. High yields and enantioselectivities were achieved using β-, α,β-, and β,β′-substituted enals.