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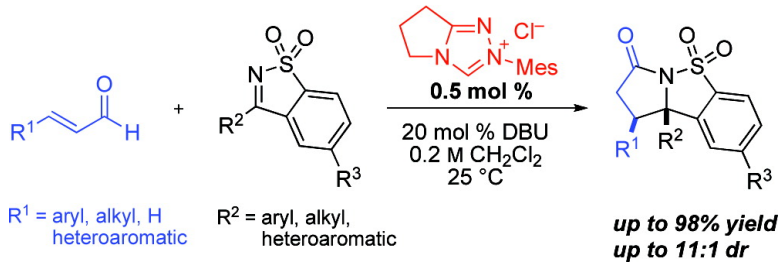

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Cyclic Ketimines as Superior Electrophiles for NHC-Catalyzed Homoenolate Additions with Broad Scope and Low Catalyst Loadings

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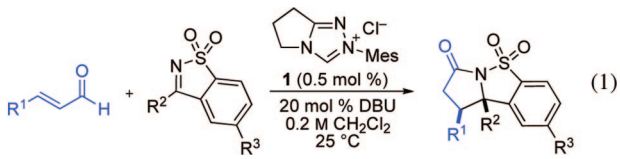
Nucleophilic additions to aldehydes and ketones provide reliable methods for the preparation of secondary and tertiary alcohols. Similar tactics can be employed for the preparation of certain amines via additions to aldimines; however, suitable ketimine derivatives are often difficult to prepare and handle due to their inherent lability.[1] We have found this to be a particular problem in the case of nucleophile-catalyzed reactions, such as those promoted by N-heterocyclic carbenes (NHCs),[2] in which the nucleophilic catalyst can promote the decomposition of imines. Thus, despite considerable effort from our group, and that of Scheidt, NHC-catalyzed additions of enals to imine electrophiles have been limited to aromatic aldehyde derived *N*-sulfonyl imines,[3] azomethine imines,[4] and *N*-phenyl nitrones.[5]

In this report, we document a simple and convenient solution to the synthesis of stereochemically defined tertiary amine derivatives via formal homoenolate additions to chemically stable, yet highly reactive, ketimines derived from saccharin.[6] In addition to providing a powerful, diastereoselective approach to γ-lactams, this is the first report of NHC-catalyzed homoenolate additions to any class of electrophiles with low catalyst loadings (0.5 mol %), for a broad range of enal and imine substrates. These findings highlight the unique and underappreciated synthetic utility of *cyclic* sulfonyl imines; they are readily prepared and stable to common transformations, including nucleophilic catalysts (eq 1).

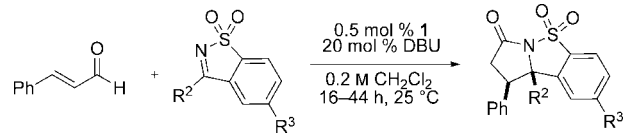


(1)

Most prior reports of NHC-catalyzed additions of enals to electrophiles including imines, aldehydes, or ketones employed *imidazolium* salts as precatalysts for homoenolate generation.[7] Our studies with saccharin derivatives therefore began with the use of IMes·HCl and DBU in protic solvents, which provided the desired product in moderate yield. In contrast to our previous experience with homoenolate additions,[8] the use of triazolium precatalyst **1**[9] proved most effective for lactam formation and completely suppressed the formation of aldehyde dimers. To our further surprise, a screen of conditions (see Supporting Information) revealed that 0.5 mol % of precatalyst **1** was sufficient for quantitative conversion at room temperature.

We applied our optimized conditions to the reaction of cinnamaldehyde with a number of different ketimines (Table 1). Electronically varied aromatic (entries 1−3) and heteroaromatic substituents (entries 4, 6, 7) were well tolerated. In most cases the *cis*-product predominated, although an electron-poor aromatic substituent (entry 5) resulted in a small preference for the *trans*-product, a trend that was amplified by installing an *ortho*-substituent (entry 6). When alkyl-substituted ketimines were employed the diastereoselectivities improved, albeit at the expense of product yield. These substrates could be coaxed toward higher yields by using more precatalyst (entries 10, 11).

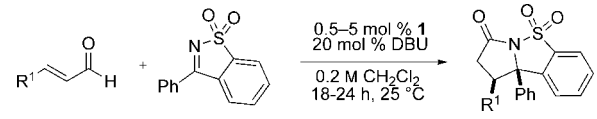
Table 1. NHC-Catalyzed Annulation of Cinnamaldehyde with Various Sulfonyl Ketimines[a]



entry	R^2 =	R^3 =	% yield[b]	cis/trans[c]
1	Ph	H	89	3[d]:1
2	*p*-MeO-C_6H_4	H	85	4:1
3	*m*-MeO-C_6H_4	H	96	3:1
4	thiophen-2-yl	H	90	4:1
5	*p*-CN-C_6H_4	H	83	1:1
6[e]	3-Br-pyridin-4-yl	H	77	1:2
7[e]	5-pyrimidinyl	H	68	>20:1
8	Ph	Me	96	4:1
9	Ph	OMe	98	4:1
10	Me	H	60(72)[e]	9[d]:1
11	*n*Bu	H	13(78)[e]	11:1

[a] See Supporting Information for reaction details. [b] Combined, isolated yields of diastereomeric lactams after chromatography. [c] Diastereomeric ratio determined by ^{1}H NMR analysis of unpurified reaction mixtures. [d] Structure determined by X-ray analysis. [e] 5 mol % **1** used.

Table 2. NHC-Catalyzed Annulation of Various Enals with Phenyl Sulfonyl Imine[a]



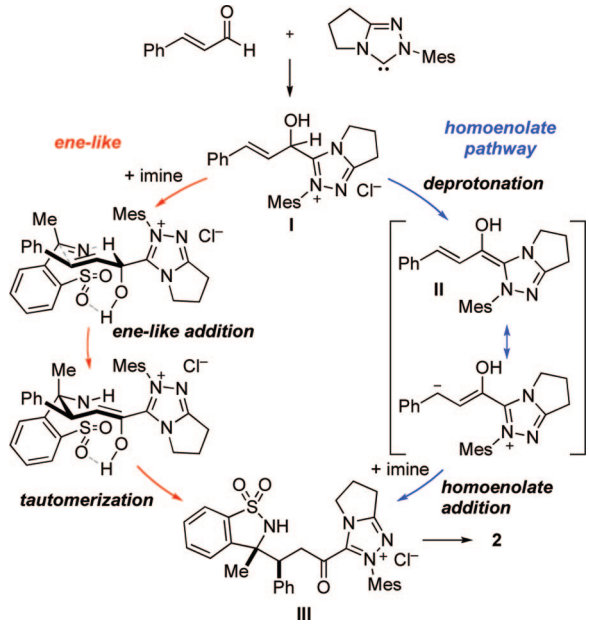
entry	R^1 =	% cat. **1**	% yield[b]	cis/trans[c]
1	*p*-MeO-C_6H_4	0.5	95	4:1
2	2-furyl	0.5	98	4:1
3	*p*-CF_3−C_6H_4	0.5	89	2:1
4	*p*-CHO-C_6H_4	0.5	55	1:1
5	1-propenyl	5.0	75	6:1
6[d]	1-propyl	5.0	96	5:1
7[d]	Me	5.0	78	3:1
8[e]	H	5.0	80	n/a

[a] See Supporting Information for reaction details. [b] Combined, isolated yields of diastereomeric lactams after chromatography. [c] Diastereomeric ratio determined by ^{1}H NMR analysis of unpurified reaction mixtures. [d] 2.0 equiv of aldehyde used. [e] 3.0 equiv of aldehyde added in two portions.

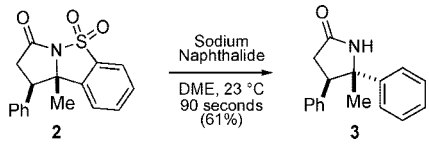
The annulation reactions with cyclic sulfonyl ketimines were not restricted to the use of cinnamaldehyde derivatives (Table 2, entries 1−4) as was the case for aldehyde or ketone electrophiles. Alkyl and alkenyl substituted enals were suitable (entries 5−7), and even acrolein was viable (entry 8). Notably, an unprotected aldehyde in the substrate survives the annulation (entry 4).

10.1021/ja807937m CCC: $40.75

Scheme 1. Possible Reaction Pathways for NHC-Catalyzed Annulations of Enals and Cyclic Sulfonyl Ketimines



Although structurally interesting in their own right, the obtained γ-lactams could be rapidly converted to the corresponding desulfonated γ-lactams **3** (eq 2).[10]

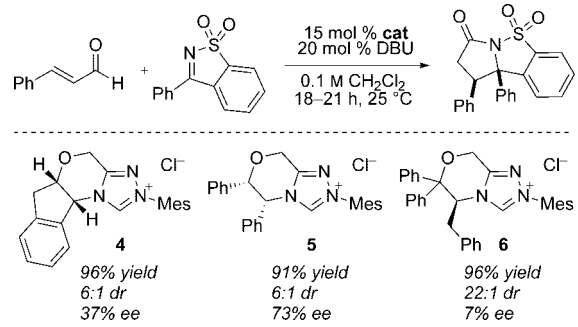


(2)

In contrast to the corresponding *N*-sulfonyl aldimines, which required an imidazolium precatalyst in a protic solvent, forcing conditions (60 °C and 15 mol % catalyst), and were limited to cinnamaldehydes or related substrates,[3] the cyclic sulfonylimines could be coupled with enals by the use of only 0.5 mol % of a triazolium precatalyst at room temperature in an aprotic solvent.[11] The great difference in reactivity, reaction conditions, and substrate scope prompted further consideration of the reaction mechanism. In one point, the acyclic and cyclic imine substrates were similar: both undergo rapid, reversible reactions with the nucleophilic N-heterocyclic carbene catalyst. Studies with molar equivalents of saccharin derivatives and triazolium precatalyst **1** revealed rapid (<1 min) and quantitative addition reactions. We therefore considered mechanisms whereby the resulting imine−catalyst adduct serves as the key reactive species. Our studies demonstrated instead that quantitative addition of the catalyst to the imine inhibits, rather than promotes, the annulation.

An alternative explanation for these discrepancies would be a different reaction pathway. Our prior studies invoked enal−catalyst adduct **I**, which is deprotonated to form Breslow intermediate **II** that serves as a homoenolate equivalent that attacks the electrophilic imine. To better rationalize the observed reactivity and stereochemical outcome, we have considered an ene-like transition state (red in Scheme 1). The presumed six-membered cyclic transition state could be stabilized by a hydrogen bond to the sulfonyl oxygen and allows for the concomitant transfer of the acyl proton to the imine nitrogen atom and formation of the new carbon−carbon bond. Our hypothesis is supported by the reactivity of the intermediate catalyst−enal adduct **I**. When **I** is generated in the absence of an imine, and the imine is subsequently added, formation of the product is not observed, suggesting that formation of Breslow intermediate **II** may be detrimental to the reaction. This pathway would rationalize both the *cis*-selectivity of the annulation reaction and the superiority of aprotic solvents. Furthermore, it could explain the high activity of the catalyst, as deprotonation of **I** is often the rate-determining step in azolium catalyzed reactions.[12]

Scheme 2. Enantioselective Annulation of Cyclic Ketimines



Preliminary efforts on the development of a catalytic, enantioselective variant are encouraging but highlight the established challenges of asymmetric additions to ketimines (Scheme 2). A number of previously reported chiral triazolium precatalysts give the desired product in excellent yield and up to 73% ee.[5,13] Importantly, the use of precatalyst **6**[5] dramatically improves the diastereoselectivity.

In summary, we have expanded the utility of NHC-catalyzed homoenolate additions by (1) identifying saccharin-derived ketimines as stable and useful electrophiles; (2) demonstrating the broad scope of both the enal and imine reaction partners; and (3) documenting, for the first time, that NHC-catalyzed reactions of enals can proceed with low (0.5 mol %) catalyst loadings.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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