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Enantioselective Organocatalytic Michael Additions of Aldehydes to Enones with Imidazolidinones: Cocatalyst Effects and Evidence for an Enamine Intermediate

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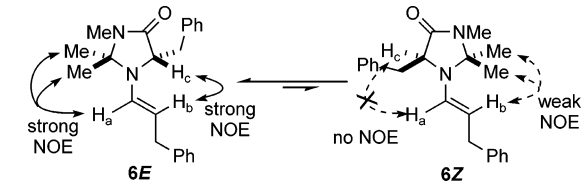
The development of conjugate addition (Michael) reactions for stereoselective generation of C−C bonds remains an important challenge in organic synthesis.[1] Lewis acid-based[2] and organocatalytic strategies have provided many successes.[3] Most organocatalyzed Michael additions of stabilized carbon nucleophiles have used either nucleophiles or electrophiles that are highly activated. For example, Michael additions of highly activated nucleophiles, such as malonates[4] or nitroalkanes[5] to simple enones, have been reported; alternatively, relatively unactivated ketones or aldehydes have been used with highly activated Michael acceptors, such as nitroalkenes.[6] Relatively few examples of organocatalyzed Michael additions have involved simple aldehyde donors with enone acceptors. Jørgensen has reported the direct Michael addition of aldehydes to enones using a chiral pyrrolidine catalyst.[7] List has reported catalysis of intramolecular aldehyde−enone Michael reactions with a MacMillan imidazolidinone catalyst.[8]

Here, we report that intermolecular aldehyde−enone Michael addition reactions can be catalyzed with a MacMillan imidazolidinone, provided that an appropriate hydrogen-bond-donating cocatalyst is employed. Cocatalyst identity is critical in terms of chemoselectivity (Michael addition vs aldol condensation) and also affects yield and stereoselectivity. Simple modification of the imidazolidinone leads to enhanced stereoselectivity. Furthermore, we have isolated an imidazolidinone-derived enamine and shown it to be a competent nucleophile. Most prior reports of imidazolidinone-catalyzed Michael additions have involved electrophilic activation of α,β-unsaturated aldehydes via iminium ion formation.[9]

We began by asking whether Michael additions of aldehydes to enones could be simultaneously catalyzed by a pyrrolidine (nucleophilic activation of the aldehyde via enamine formation) and imidazolidinone **1a** (electrophilic activation of the enone via iminium formation). Control experiments revealed that **1a**−HCl alone could catalyze the Michael addition, and that the imidazolidinone reacts with the aldehyde to form an enamine, which suggests nucleophilic activation rather than electrophilic activation. These observations meshed with recent reports from MacMillan et al., on organocatalytic α-chlorination of aldehydes catalyzed by **1a**−HCl,[10] and from List et al., on intramolecular aldehyde/enone Michael additions catalyzed by **1a**−HCl,[8] both of which speculated on the intermediacy of enamines. In contrast to the observations by List et al. with intramolecular Michael reactions, however, we found that intermolecular Michael additions catalyzed by **1a**−HCl were plagued by competition from aldol condensation of the aldehyde component (Table 1, entry 2). Use of **1a** without HCl led to enhanced chemoselectivity for the Michael reaction and substantially improved enantioselectivity but low overall yield (Table 1, entry 1).

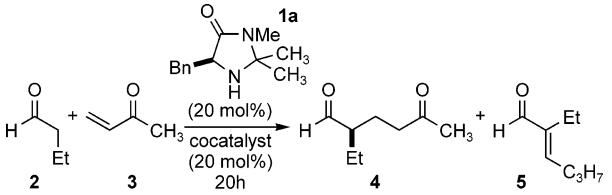
The enamine derived from hydrocinnamaldehyde and **1a** could be generated slowly but quantitatively by mixing the aldehyde and **1a** in DMSO-d_6 in the presence of 4 Å molecular sieves. NOE analysis of enamine **6** revealed a preference for the *E* configuration about the N−C(sp^2) bond as indicated below.[11]



We surveyed a range of acidic cocatalysts in an effort to improve Michael adduct yield without loss of the favorable selectivities (Table 1). The poor qualities of HCl as cocatalyst were observed also with other strong acids, but weakly acidic additives proved to be quite favorable in terms of aldol suppression and Michael adduct stereochemistry. We speculate that these additives activate the enone via hydrogen bond donation.[12] Two features seem to be important for the cocatalyst. First, additives containing two adjacent hydrogen bond donors (catechols in entries 6 and 8) are superior to single hydrogen bond donors of similar acidity (phenols in entries 5 and 7).[13] Second, increasing the acidity of the catechol additives improves the yield of the Michael addition (entries 8 and 9 vs entry 6).

Exploration of imidazolidinone derivatives showed a surprising dependence on this component (Table 2). Catalyst **1c**, derived from cyclopentanone, afforded the Michael addition product with the highest yield and enantioselectivity. The Michael addition of a variety of aldehyde/enone pairs was explored with the catalyst pair **1c** + 4-EtO_2C−catechol (Table 3); excellent enantioselectivities were obtained.

Table 1. Effect of Additives on the Catalyzed Michael Addition of Butyraldehyde to Methyl Vinyl Ketone



entry	cocatalyst	yield **4**[a] (%)	conv **5**[b] (%)	ee[c] (%)
1	none	41	<5	77
2	HCl	37	38	29
3	TFA	24	40	55
4	AcOH	48	<5	75
5	phenol	37	<5	82
6	catechol	56	<5	81
7	4-NO_2−phenol	52	<5	82
8	4-NO_2−catechol	62	<5	82
9	4-EtO_2C−catechol	85	<5	81

[a] Yield of isolated product after column chromatography on silica gel. [b] From ^{1}H NMR analysis of crude reaction mixture. [c] From chiral-phase GC of the carboxylic acid derived from **4**.

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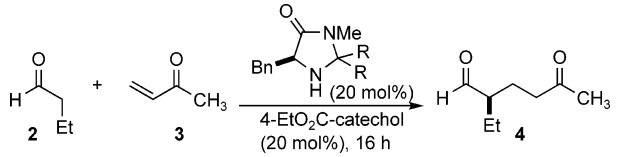
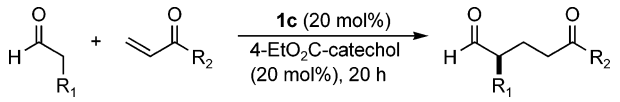
Table 2. Effect of Imidazolidinone Structure on the Catalyzed Michael Addition of Butyraldehyde to Methyl Vinyl Ketone



entry	catalyst	R	conv **4**[a] (%)	ee[b] (%)
1	**1a**	Me	78	81
2	**1b**	Bu	19	22
3	**1c**	$-(CH_2)_4-$	86	90
4	**1d**	$-(CH_2)_5-$	<5	*c*

[a] From ^{1}H NMR analysis of crude reaction mixture. [b] From chiral-phase GC of the corresponding carboxylic acid. [c] Not determined.

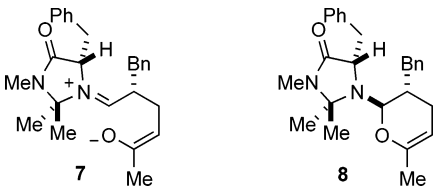
Table 3. Imidazolidinone-Catalyzed Michael Addition of Aldehydes to Vinyl Ketones



entry	R_1	R_2	yield[a] (%)	ee[b] (%)
1	Me	Me	84	90
2	Me	Et	79	92
3	Et	Et	68	92
4	*i*Pr	Me	55	82
5	Bn	Me	62	89
6	Bn	Et	54	92

[a] Yield of isolated product after column chromatography on silica gel. [b] From chiral-phase GC or HPLC of an appropriate derivative.

Having identified an optimal cocatalyst for the aldehyde/enone Michael reaction promoted by imidazolidinones, we conducted additional NMR studies to probe the reactivity of enamine **6**. The preformed enamine (neat) was allowed to react with methyl vinyl ketone in the presence of catalytic 4-EtO_2C-catechol. The enamine was consumed over 4 h, initially forming dihydropyran **8** as a single diastereomer.[14] The dihydropyran slowly hydrolyzed to generate the keto aldehyde product. No hydrolysis of the enamine to hydrocinnamaldehyde was detected.



The NMR experiments suggest that the aldehyde−enone Michael addition involves reaction of enamine **6** with a hydrogen-bond-activated enone to generate zwitterion intermediate **7**. Intermediate **7** exists in equilibrium with observed dihydropyran **8**, and **7** is hydrolyzed to the observed keto aldehyde product, regenerating the imidazolidinone catalyst.[15] The detection of only one dihydropyran diastereomer, despite the moderate product enantioselectivities, led us to wonder whether epimerization competes with the hydrolysis of **7**. Reaction of butyraldehyde and methyl vinyl ketone with the catalyst pair **1a** + 4-EtO_2C-catechol using strictly anhydrous reagents affords product with only 77% ee, while adding 20 mol % of water increases the enantioselectivity to 83% ee.[16] These experiments suggest that facilitating hydrolysis of the zwitterionic intermediate may suppress racemization, which has previously been proposed by MacMillan.[9a]

Our results support recent suggestions that imidazolidinones can serve as organocatalysts by nucleophilic activation of carbonyl compounds,[8,10] in addition to their well-precedented role as electrophilic activators (via iminium formation).[9] We have provided the first clear evidence for an imidazolidinone-derived enamine, and we have shown that such an enamine displays the requisite nucleophilicity. Our observation of coordinated action by an imidazolidinone and a hydrogen-bond-donating additive raises the intriguing prospect that juxtaposing such groups on molecular scaffolds with defined folding preferences could generate new families of selective and efficient multifunctional catalysts.[17]

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Note Added after ASAP Publication: In the version published on the Internet July 21, 2005, there was an error in ref 6. The final version, published July 27, 2005, and the print version are correct.

Supporting Information Available: Experimental procedures, spectral data, characterization of **6** and **8**, and reactivity studies of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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