Organocatalysis

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anti-Selective Asymmetric Michael Reactions of Aldehydes and Nitroolefins Catalyzed by a Primary Amine/Thiourea**

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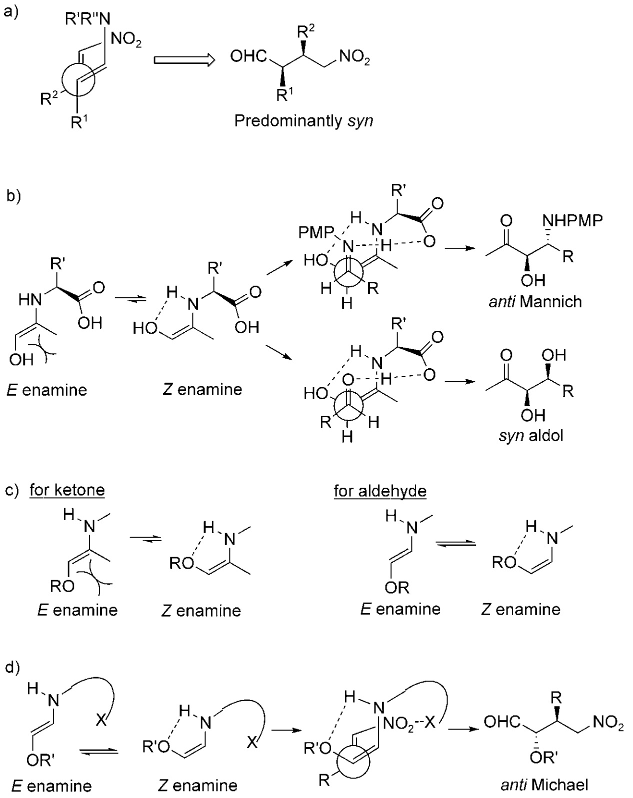
Dedicated to Professor Dieter Seebach

In the last decade, remarkable progress has been made toward direct catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically complex products under operationally simple and environmentally friendly conditions.[1] In enamine catalysis, significant effort has focused on understanding the origin of diastereo- and enantioselectivity in organocatalysis. These studies have facilitated the design of *syn*-selective aldol and *anti*-selective Mannich reactions not originally addressed by organocatalytic methods.[2–5] The organocatalytic Michael reaction is often regarded as one of the most efficient and broadly applicable carbon–carbon bond-forming reactions known because a wide variety of acceptors can be employed and high stereoselectivity has been realized.[6] Although a large number of reports on the organocatalytic Michael reaction of aldehydes have been published, to the best of our knowledge, all of these reactions are *syn* selective.[7] Several studies, however, have reported success in the *anti*-selective organocatalytic Michael reaction of ketones.[8] Herein, we report the first highly *anti*-selective asymmetric Michael reactions of aldehydes and nitroolefins using a strategy designed to control the configuration of the reacting enamine.

The predominant stereochemical outcome of the enamine-based Michael reaction was first explained in the classic studies of Seebach and co-workers.[9] Seebach deduced that high *syn* selectivity can be explained by an acyclic synclinal transition-state model (Scheme 1 a).[9a] In this transition state, the thermodynamically stable *E* enamine reacts with *E* nitroolefins in a synclinal arrangement, in which the actual donor and acceptor atoms are situated close to each other (see NO$_2$ and NR′R″ in Scheme 1 a).

We have explored two routes for control of the overall diastereoselectivity of organocatalytic enamine reactions: 1) controlling the face selectivity of the reactive enamine to affect *anti*-Mannich reactions[2] and 2) controlling the *E*/*Z* configuration of the reactive enamine to affect *anti*-Mannich and *syn*-aldol reactions (Scheme 1 b).[3] For the *anti*-Michael reactions described herein, we have taken the latter approach.



Scheme 1. a) Synclinal transition-state model, b) *anti*-Mannich and *syn*-aldol formation via *Z* enamine, c) comparison between *E* and *Z* enamines of alkoxyacetone and alkoxyaldehyde, d) strategy for *anti*-Michael reactions via *Z* enamine. PMP = *para*-methoxyphenyl.

The classic organocatalytic Michael reaction of aldehydes and ketones utilizes pyrrolidine-based catalysts which react via *E*-enamine intermediates with nitroolefins and other Michael acceptors in synclinal transition states to provide predominately *syn*-configured Michael products. The *Z*-enamine intermediate formed using secondary amine catalysts are significantly less favored. Movement from a secondary amine catalyst to a primary amine catalyst provides steric latitude which enables *Z*-enamine formation with ketones. A caveat, however, is that *Z*-enamine formation from aldehydes is likely to be more difficult than that from ketones since the *E*-configured enamine derived from an aldehyde minimizes steric conflicts between the catalyst and

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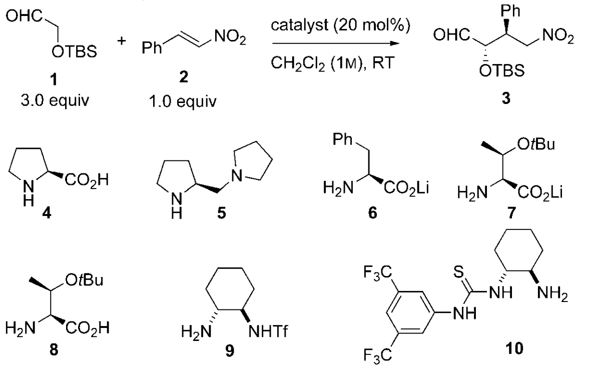
the aldehyde as compared to the *E*-configured enamine derived from a ketone (Scheme 1 c).

A second level of control of *E*/*Z*-enamine configuration can be imparted through the substrate itself. To favor *Z*-enamine formation, intramolecular hydrogen bonding through the use of α-hydroxyketone donors has been used to great effect.[3] Indeed the formation of a *Z* enamine, with the catalytic primary amine group of the active site lysine residue in aldolase antibodies, provided the first experimental evidence that this approach could be utilized to control the diastereoselectivity of the organocatalytic aldol reaction.[10] As illustrated in Scheme 1 b, with the enamine formed from α-alkoxyacetone and a primary amine catalyst, hydrogen bonding between the oxygen atom in the alkoxy group and the hydrogen atom on the enamine stabilizes the *Z* form of the enamine; the *E* enamine is somewhat destabilized by steric repulsion between alkoxy group and the methyl group of the ketone.

From these analyses, we envisioned that primary amine catalysts with an activating group (X) could catalyze *anti*-Michael reactions of alkoxyacetaldehyde and nitroolefins (Scheme 1 d). We hypothesized that the nitroolefin would approach the *Z* enamine in a synclinal overlapping fashion to provide *anti*-Michael products. In addition, the activating group (X) would control the facial selectivity to provide one enantiomer in abundance. Although catalyst/substrate systems have been designed to successfully invert the diastereoselectivity of the organocatalytic aldol and Mannich reactions involving α-hydroxyketones,[3] this approach has not been widely applied to aldehyde nucleophiles in organocatalysis.[11] A potential problem with aldehydes and primary amine catalysis, as opposed to secondary amine catalysis, is that aldehydes form a relatively stable imine that might be subject to side-reactions. Indeed, whereas there are several examples of primary amine catalyzed Michael reaction of aldehydes and nitroolefins, most of them used α,α-disubstituted aldehydes as donors.[12]

Table 1: Reaction optimization.



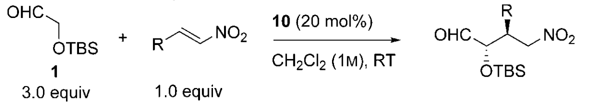
Entry	Catalyst	*t* [h]	Yield [%][a]	d.r. (*anti*/*syn*)[b]	*ee* [%][c]
1	**4**	24	20[d]	35:65	67
2	**5**	2	47[d]	48:52	72
3	**6**	24	47	97:3	−92
4	**7**	24	56	97:3	−95
5	**8**	24	5	–	–
6	**9**	24	27	98:2	97
7	**10**	4	83	98:2	98
8[e]	**10**	24	77	60:40	97
9[f]	**10**	24	50	97:3	94

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopic analysis of crude **3**. [c] Determined by chiral phase HPLC analysis of *anti*-**3**. [d] Yields after conversion into corresponding benzyloxime. [e] Used 1.5 equiv of aldehyde **1**. [f] Used 10 mol% of the catalyst **10**. Tf = trifluoromethanesulfonyl.

To explore the potential application of these principles to the *anti*-Michael reaction we chose (*tert*-butyldimethylsilyloxy)acetaldehyde (**1**) as a donor, and examined the Michael reaction using β-nitrostyrene (**2**) as a model acceptor (Table 1). Hydroxyacetaldehyde protected with *tert*-butyldimethylsilyl (TBS) was chosen based on our successful use of TBS-protected dihydroxyacetone in *anti*-Mannich and *syn*-aldol reactions. The results of catalysis with L-Pro (**4**) and 1-(2-pyrrolidinylmethyl)pyrrolidine (**5**) were determined,[7a,c] and as expected the reactions proceeded with low yield and low *syn* selectivity (Table 1, entries 1 and 2). Catalysts **6** through **10** were representative primary amine based organocatalysts. To our delight, when we used L-phenylalanine lithium salt (**6**), which was reported by Yoshida et al.[12d] to be an excellent catalyst for the Michael reaction of isobutyraldehyde and β-nitrostyrenes, we obtained *ent*-**3** in a very high, *anti*-favored diastereomeric ratio (97:3 d.r.) and in good enantiomeric excess (Table 1, entry 3).[13] We found that O-*t*Bu-L-Thr-OLi (**7**) was slightly better than **6**, whereas the free acid O-*t*Bu-L-Thr-OH (**8**) was inactive (Table 1, entries 4 and 5). Next, we performed the reaction with cyclohexanediamine-based catalysts. Surprisingly, the primary amine/sulfonamide catalyst **9**[5e,14] showed excellent enantioselectivity (97 % *ee*), though its reactivity was low. The best result was obtained with the primary amine/thiourea **10**.[15] With this catalyst, the *anti* product formed in good yield with excellent diastereo- and enantioselectivity within four hours.[16] With this catalyst and solvent system, we varied the catalyst loading and substrate ratio. Interestingly, decreasing the amount of aldehyde **1** used resulted in a significant drop in diastereoselectivity (Table 1, entry 8), whereas reduction of the amount of catalyst **10** caused the reaction to slow significantly (Table 1, entry 9).

We then investigated the substrate scope of the reaction using catalyst **10** (Table 2). Nitrostyrenes with either electron-withdrawing or electron-donating groups at the *para* position were good substrates (Table 2, entries 2–4). 3-Bromo- and 3,4-dichloro-substituted substrates also reacted well under these conditions with excellent diastereo- and enantioselectivity (Table 2, entries 5 and 6). Notably, sterically hindered *ortho*-substituted nitrostyrenes were also good substrates. When 2-trifluoromethyl-β-nitrostyrene was used as an acceptor, the reaction proceeded well with 99 % *ee* (Table 2, entry 7). With the sterically hindered 2,6-dichloro-β-nitrostyrene, a high catalyst loading was required; 50 mol % **10** was used, but the stereoselectivity of the reaction was maintained (Table 2, entry 8). Heteroaromatic (Table 2, entry 9) and, more significantly, aliphatic substrates could be also used, although 50 mol % of **10** was necessary for the reaction of *n*-C_7H_{15} nitroolefin because of its low reactivity (Table 2, entry 10).

Table 2: Substrate scope.



Entry	R	*t* [h]	Yield [%][a]	d.r. (*anti*/*syn*)[b]	*ee* [%][c]
1	Ph-	4	83	98:2	98
2	4-BrC$_6$H$_4$-	6	70	97:3	98
3	4-MeC$_6$H$_4$-	6	81	97:3	97
4	4-MeOC$_6$H$_4$-	24	67	97:3	98
5	3-BrC$_6$H$_4$-	6	66	96:4	97
6	3,4-Cl$_2$C$_6$H$_3$-	2	72	96:4	98
7	2-CF$_3$C$_6$H$_4$-	24	74	98:2	99
8[d]	2,6-Cl$_2$C$_6$H$_3$-	24	68	98:2	98
9	2-thiophenyl	6	75	97:3	97
10[d]	*n*-C$_7$H$_{15}$-	6	57	92:8	97

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopic analysis of crude product. [c] Determined by chiral phase HPLC analysis of *anti* product. [d] Used 50 mol% of the catalyst **10**.

Other donors were not effective under the reaction conditions used for catalyst **10**: Reaction with benzyloxyacetaldehyde resulted in low catalyst turnover, whereas use of aqueous chloroacetaldehyde and dimethoxyacetaldehyde did not afford the Michael product. We suspect that the bulky *tert*-butyldimethylsilyl group of **1** might prevent catalyst deactivation through an undesired side reaction such as the Mannich-type reaction with the imine generated between primary amine catalyst **10** and the aldehyde.

A proposed catalytic cycle based on catalyst **10**, which is consistent with our experimental observations, is illustrated in Scheme 2.[17] This mechanism is consistent with our previous proposals for the Michael reaction using an aldehyde,[7a,c] our *anti*-Mannich and *syn*-aldol studies,[3] and the model for the thiourea-catalyzed Michael reaction of α,α-disubstituted aldehydes and nitroolefins reported by Jacobsen and coworkers.[12a] In the first step, catalyst **10** reacts with aldehyde **1** to form imine **A**, which then tautomerizes to *Z*-enamine **B**. Our design facilitates hydrogen bonding between the oxygen atom in the alkoxy group and the hydrogen atom on the enamine making *Z*-enamine **B** thermodynamically more stable than its *E* form. The stabilizing effect in **B** is critical for facial selectivity of the enamine. Additionally, stabilization by hydrogen bonding during tautomerization from **A** to **B** may prevent side reactions. By design, this differs from the *E* enamine evoked in Jacobsen's model for his catalyst. The nitroolefin approaches the *Z*-enamine **B** as depicted in **C** and then carbon–carbon bond formation takes place to give intermediate **D**. We propose a transition state similar to that in Seebach's acyclic synclinal model which provides for hydrogen bonding of a single oxygen atom of the nitro group with the thiourea (Figure 1).[12a,18] As primary amine/sulfonamide **9** catalyzed the reaction to form the Michael adduct with excellent selectivity (Table 1, entry 6), only one hydrogen-bond donor may be necessary to afford the high selectivity.[19] Tuning of the acidity of the hydrogen-bonding group is key since the thiourea of **10** is significantly more active than **9** despite the weaker acidity of **10**. After proton transfer and hydrolysis, the Michael product is released and catalyst **10** is regenerated. The (2*S*, 3*S*) configuration determined for product **3** is consistent with this mechanism. The inactivation of catalyst **10** is possible through the direct reaction with nitroolefin to provide **E**,[20] and the reverse reaction would release **10** back into the catalytic cycle. The low reactivity of aliphatic nitroolefins might be caused by low availability of free catalyst **10** through catalyst sequestration in **E**.

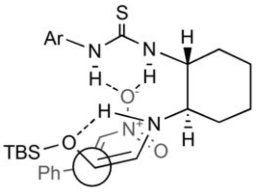
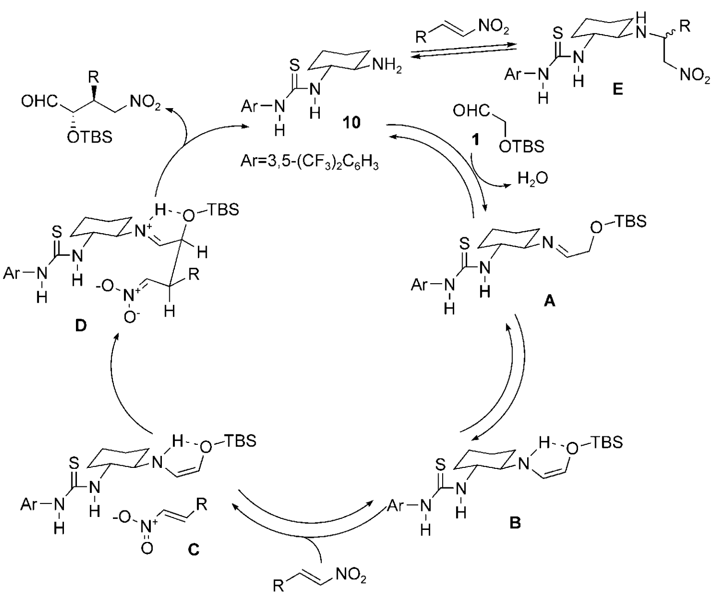


Figure 1. Proposed synclinal transition-state model.



Scheme 2. Proposed catalytic cycle for the asymmetric addition of **1** to a nitroolefin by using **10**.

In summary, we have developed the first *anti*-selective Michael reaction of aldehydes and nitroolefins with simple primary amine/thiourea catalyst **10**. The reaction was efficient with electron-deficient, electron-rich, and sterically hindered nitrostyrenes as well as alkyl-substituted nitroolefins, and provided functionalized Michael products with excellent diastereo- and enantioselectivity. The configuration of the products has been determined to be (2*S*, 3*S*), and the stereochemistry outcome strongly suggests that a *Z* enamine is the reactive species. We propose that the *Z* configuration is stabilized by intramolecular hydrogen bonding. Additional studies exploiting this approach to *Z*-enamine intermediates are currently underway and the results will be reported in due course.

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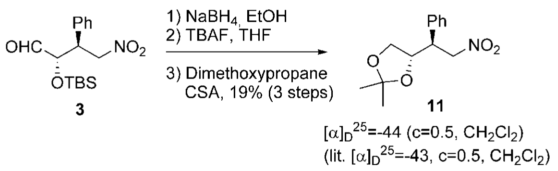

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