Organocatalysis

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Evidence for an Enol Mechanism in a Highly Enantioselective Mannich-Type Reaction Catalyzed by Primary Amine–Thiourea**

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Whereas impressive progress has been made in recent years in developing highly enantioselective secondary and tertiary amine–thiourea bifunctional organocatalysts for a diverse range of reactions,[1,2] little work has yet been devoted to developing primary amine–thiourea catalysis.[3] The use of chiral primary amines as organocatalysts[4] possesses particular charm because of their known occurrence in the catalytic sites of several enzymes, such as type I aldolases, dehydratases, and decarboxylases.[5] Recently, our group,[3a,c,e] as well as Jacobsen and co-workers,[3b,d] reported the first successful application of primary amine–thiourea organocatalysts to nitro-Michael addition reactions. These findings also motivated Ma and co-workers to develop a new primary amine–thiourea organocatalyst for a similar Michael addition of ketones to nitroalkenes.[3f]

The proven ability of primary amine–thioureas **1–3** (Figure 1)[3a,c,e] to catalyze the nitro-Michael reaction with high enantioselectivity and the straightforward accessibility of these thiourea–amines in a one-step synthesis from commercially available reagents, as we reported earlier,[3d,e] prompted us to also examine them for the Mannich reaction, which is among the most powerful tools for preparing β-amino carbonyl compounds.[6]

Herein we report, to the best of our knowledge, the first chiral primary amine–thiourea catalyzed simple Mannich-type addition of unmodified ketones to *N*-benzoylhydrazones, which proceeds with good yields and high enantioselectivities (up to 89% yield and >99% *ee*). Additionally, we provide some of the first computational evidence that the preferred mechanism involves enol, rather than enamine intermediates.

To evaluate the catalytic efficiency of chiral amine–thioureas **1–3**, we first investigated the known addition of acetone to *N*-PMP-protected α-imino ethyl glyoxylate (PMP = *para*-methoxyphenyl).[7] The reaction was carried out in toluene at room temperature in the presence of each of the amine–thioureas (Table 1, entries 1–3). However, amine–thioureas **1–3** gave inferior results with the selected substrate (up to 47% yield and 45% *ee* with amine–thiourea **1**, Table 1, entries 1–3). Additionally, the corresponding *N*-PMP-protected α-imino ethyl glyoxylate **4** is not very stable. We therefore sought other, readily available and more stable substrates.

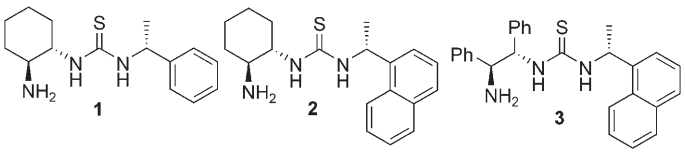
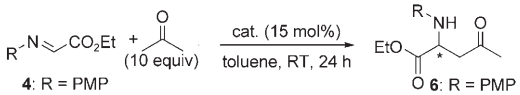


Figure 1. Bifunctional amine–thiourea catalysts.

Our efforts focused on the reaction between acetone and *N*-benzoylhydrazone **5** (Table 1, entries 4–6), which can be stored for several months at room temperature and is readily obtained from the condensation of ethyl glyoxylate and benzhydrazide.[8]

N-Benzoylhydrazones have been used as substrates for several C–C bond-forming reactions;[8] for example, the allylation[8b] and Mannich-type reactions.[8a,c–e] Kobayashi and co-workers have recently developed several metal-containing Lewis acid assisted catalytic, and stoichiometric, indirect stereoselective Mannich transformations of *N*-benzoylhydrazones that utilize preformed silyl enolate.[8a,c–e] An organocatalytic version of this reaction has not been previously reported, especially one in which unmodified ketones react with *N*-benzoylhydrazones.

Table 1: Screening of amine–thioureas **1–3** for Mannich-type reactions.



Entry	R	Catalyst	Yield [%]	*ee* [%][a]
1	PMP	**1**	47	45 (*S*)[b]
2	PMP	**2**	29	*rac*
3	PMP	**3**	45	6 (*S*)[b]
4	NBz	**1**	50	>99 (*R*)[c]
5	NBz	**2**	40	86 (*R*)[c]
6	NBz	**3**	21	58 (*R*)[c]

[a] Determined by chiral HPLC analysis and compared with authentic racemic material. [b] The stereochemistry was established by comparison with literature data.[7] [c] The absolute configuration was established by X-ray crystallographic analysis.[9] *rac* = racemic; PMP = *para*-methoxyphenyl; Bz = benzoyl.

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The use of chiral amine–thioureas **2** and **3** in the reaction of acetone with *N*-benzoylhydrazone gave the products in 86% and 58% *ee* and in 40% and 21% yields, respectively (Table 1, entries 5 and 6).

Remarkably, under the same conditions, catalyst **1** showed excellent enantioselectivity with greater than 99% *ee* and 50% yield of the isolated product (Table 1, entry 4). It is noteworthy that the less stable aromatic *N*-Boc-imines (Boc = *tert*-butoxycarbonyl) are possible substrates for this catalytic reaction.[10]

Impressed by the high enantioselectivity observed with *N*-benzoylhydrazone **5**, we focused our attention on a detailed investigation of this reaction catalyzed by amine–thiourea **1**. Additional solvent screening studies demonstrated that toluene, first chosen, was the optimal solvent under the reaction conditions used.[9] Hence, Mannich-type reactions of different ketones with several *N*-benzoylhydrazones were performed in toluene with catalyst **1** (Table 2).

When aliphatic ketones were reacted with the *N*-benzoylhydrazone, moderate to good yields (Table 2, entries 1–6) were obtained. Cyclic ketones underwent reaction with α-hydrazonoesters to give higher yields (Table 2, entries 7–11). The enantioselectivities obtained were excellent for essentially all the ketones explored, including the branched or sterically hindered ones, which gave *ee* values of up to more than 99% (Table 2).

The use of unsymmetrical ketones, such as methylethyl ketone and methylpropyl ketone, introduced the problem of regioselectivity (Table 2, entries 2 and 4). Addition of methylpropyl ketone provided products **10a** and **10b** with good regioselectivity (13:1) and excellent enantioselectivity, whereas methylethyl ketone afforded products **8a** and **8b** with modest regioselectivity (1.4:1) and high enantioselectivities (greater than 99% *ee*, Table 2, entries 2 and 4).

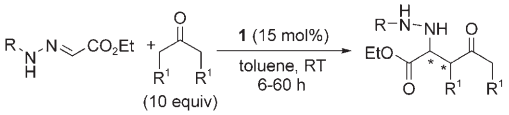
Interestingly, whereas acyclic ketones gave *anti*-Mannich products, an excess of *syn* diastereomers was observed with the cyclic ketones (Table 2, entries 2–4 versus entries 7–11). The *syn* and *anti* diastereomeric products were generated with high *ee* values (82–99%), but with low to moderate diastereoselectivities (8–72%; Table 2, entries 2–4 and 7–11).

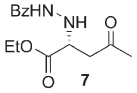
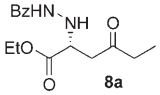
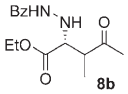
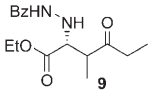
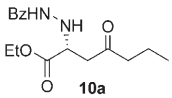
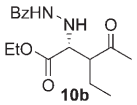
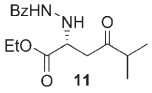
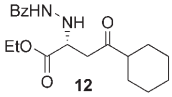
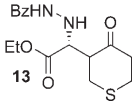
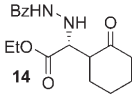
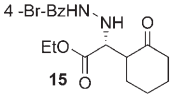
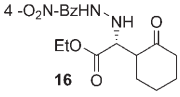
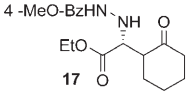
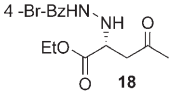
The effect of the *N*-benzoyl group on the reaction was additionally examined in the reaction of *para*-substituted *N*-benzoylhydrazones with cyclohexanone. Intriguingly, electron-withdrawing groups on the benzoyl moiety led to an increase of the reaction rate (6–7 h reaction time compared to 17 h; see Table 2, entries 8 versus 9 and 10). On the other hand, electron-donating groups decrease the rate (44 h reaction time; see Table 2, entry 8 versus 11).

Whereas the present Mannich-type reaction is simple in execution and uses readily available reagents, the elucidation of its mechanism is appealing.

Until now, most researchers have proposed[11] the involvement of the enamine mechanism in amine-catalyzed reactions that involve carbonyl group activation. In 1974, Hajos and Parrish postulated a combined carbinolamine and enol mechanism in the Robinson annulation.[12a] Nine years earlier, Spencer et al. appear to have ruled out the possibility of the enol mechanism on the basis of Bredt's rule for this

Table 2: Scope of Mannich-type reactions catalyzed by primary amine–thiourea organocatalyst **1**.



Entry	Product	Yield [%][a]	*ee* [%][b,c]	*de* [%][b]
1	 **7**	50	>99	–
2	 **8a**	86 1.4:1 rr (**8a**/**8b**)	>99	–
	 **8b**		>99 (*syn*) >99 (*anti*)	40 (*anti*)
3	 **9**	82	90 (*syn*) 99 (*anti*)	72 (*anti*)
4	 **10a**	80 13:1 rr (**10a**/**10b**)	>99	–
	 **10b**		>99 (*syn*) >99 (*anti*)	29 (*anti*)
5	 **11**	54	>99	–
6	 **12**	45	97	–
7	 **13**	88	>92 (*syn*) >82 (*anti*)	19 (*syn*)
8	 **14**	87	>96 (*syn*) >94 (*anti*)	8 (*syn*)
9	 **15**	89	>94 (*syn*) >92 (*anti*)	8 (*syn*)
10	 **16**	85	>95 (*syn*) >90 (*anti*)	8 (*syn*)
11	 **17**	83	>93 (*syn*) >92 (*anti*)	9 (*syn*)
12	 **18**	45	>99	–

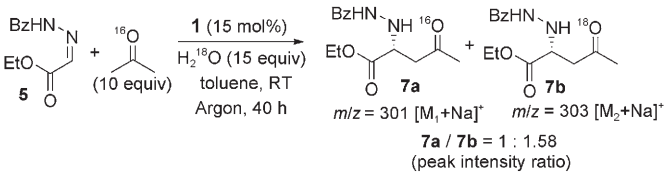
[a] Yields of isolated products. [b] Determined by chiral phase HPLC analysis. [c] The absolute configurations at the stereocenters were established by X-ray crystallography of the products, *anti*-**15** and **18**.[9] rr = regioisomer ratio.

cyclization reaction, and instead favored the enamine mechanism.[12b]

More recently, Clemente and Houk presented computational evidence that supported the enamine mechanism, partly because the transition state that leads to a carbinolamine intermediate could not be located.[13] In 2004 List et al. repeated Hajos' experiment and observed greater than 90% ^{18}O incorporation by using ^{18}O-enriched water.[14] They deduced that this resulted from the hydrolysis of an enamine intermediate in the reaction but observed only oxazalidinone intermediates in their proton NMR study. In contrast, Hajos and Parrish observed only 7.2% ^{18}O incorporation.[12a,15] Another ^{18}O-marker study of a primary amine catalyzed decarboxylation of β-keto acids by Lerner and Barbas proved that imine and enamine intermediates are formed in this type of reaction.[16]

These early results encouraged us to study the primary amine–thiourea (**1**) catalyzed addition reaction of acetone to **5** (under Argon) in the presence of a large excess (15 equiv) of ^{18}O-enriched water (97% ^{18}O, Aldrich).[9] Product **7** proved to be unstable to GC-MS analysis, therefore ESI-MS methods were used to study this reaction.

Whereas the peak at *m/z* 303 pertains to the incorporation of ^{18}O into product **7b** during hydrolysis, indicating enamine mechanism, the peak at *m/z* 301 corresponds to ^{16}O-containing product **7a** with ^{16}O from the ketone, which might be formed by the enol mechanism. From these ESI-MS experiments (Scheme 1 and the Supporting Information) we concluded that both the enol and enamine mechanisms might indeed be involved in our primary amine–thiourea catalyzed Mannich-type reaction.



Scheme 1. ^{18}O-incorporation experiment studied by ESI-MS methods.[9]

Hence, we studied the reaction of **1** with acetone computationally, considering the possibilities of both the enamine and enol mechanisms. Preoptimization of the transition-state structures for the formation of the *R* and *S* products by both the enol and enamine mechanisms were carried out at the semiempirical AM1 level. The results indicated, to our surprise, a preference for the enol over the enamine mechanism. Seeking to verify these early indications, we then employed more accurate density functional theory calculations in conjunction with single point energy minimizations at the MP2 level.[9]

Indeed, the complexation of the enol form of the ketone with catalyst **1** is preferred over the formation of the enamine at all computational levels employed, including a self-consistent reaction field (SCRF) solvation calculation.[9] The solvation effect is small and the enol adduct was confirmed to be preferred over the enamine by 9 kcal mol^{-1} at the B3PW91/6-31G* level (9.2 kcal mol^{-1} with inclusion of solvent effects). The smallest energy difference, 5.9 kcal mol^{-1}, between the two adducts was obtained at the MP2/6-311+G*//B3PW91/6-31G* level of calculations (gas phase calculation, see Scheme S1 of the Supporting Information).

It appears that the primary amine–thiourea catalyst expands the mechanistic paradigm to include enol-based chemistry together with the now-traditional enamine aminocatalysis, wherein the amine–thiourea may serve to stabilize the enol tautomer of the ketone through hydrogen bonding (see Scheme S1 of the Supporting Information). This suggestion is consistent with the emerging body of evidence by Jacobsen and co-workers that thioureas are particularly adept in anion binding.[17]

Given the wealth of possible conformations between enol/enamine and α-hydrazonoester **5**, a number of transition-state (TS) structures and the corresponding initial complexes were identified (Figure 2, only representative TS structures are shown).

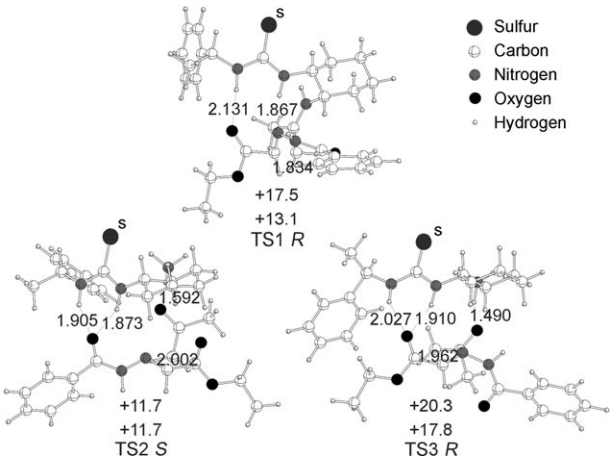


Figure 2. Transition-state structures located for the enamine (TS1, *R* product) and enol (TS2, *S* product; TS3, *R* product) mechanisms, respectively. Computed at the B3PW91/6-31G* (top number) and MP2/6-31G*//B3PW91/6-31G* (bottom number) levels of theory. Numbers within structures indicate hydrogen bond lengths.

The rate-determining step for the formation of product is the addition of the enamine or enol to the imine, respectively. For the enamine mechanism, formation of the transition state leading to the *R* product (TS1 R in Figure 2; TS4 R, TS5 R—see Figure S1 of the Supporting Information) is less unfavorable ($\Delta E + ZPE \approx 16$–$20$ kcal mol^{-1}, B3PW91/6-31G*); probably because of the absence of steric and repulsive interactions and the additional stabilization from the formation of hydrogen bonds. Despite many attempts, we were unable to locate any transition state that led to the *S* product by the enamine pathway. The strong intermolecular repulsive interactions between the two bulky phenyl rings of catalyst **1** and α-hydrazonoester **5**, and the reduced conformational flexibility in the hypothetical (AM1 calculated) transition-state structure leading to the *S* product suggest the formation of the transition state leading to the *R* product is more favorable. According to the computational results, the transition state that leads to the *S* product by the enol pathway is the lowest in

energy among the three most favorable transition states (TS1–TS3) considered for the two mechanisms (Figure 3). Solvent effects even appear to underpin this trend (see Figure 3). The transition states for the formation of both the *S*

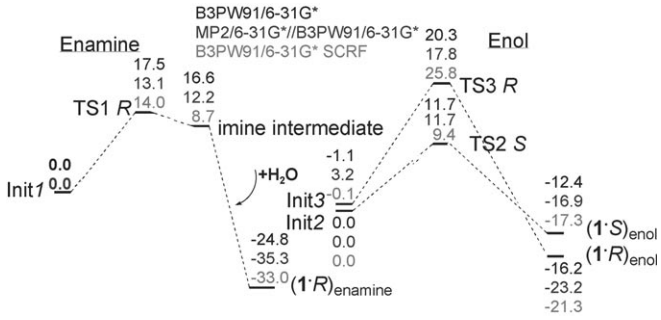


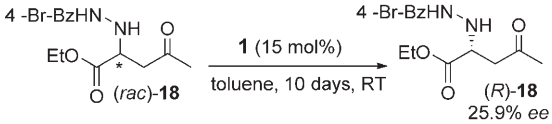
Figure 3. Reaction energy profiles for the reaction going through the enamine and enol mechanisms, $\Delta E + \mathrm{ZPE}$ in kcal mol^{-1}, at the B3PW91/6-31G* (top entry), MP2/6-31G*//B3PW91/6-31G* (middle entry), and B3PW91/6-31G* SCRF (bottom entry) level of theory. The energy profiles for the two mechanisms are compared relative to each other. Init = initial.

and *R* products by the enol pathway (TS2 S and TS3 R, Figure 2; TS6 S, TS7 R, and TS8 R—see Figure S1 of the Supporting Information) pertain to activation barriers of 11.7 and 20.3 kcal mol^{-1} (B3PW91/6-31G*), respectively (11.7 and 17.8 kcal mol^{-1} at MP2/6-31G*//B3PW91/6-31G*).

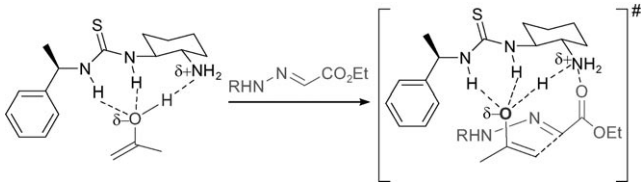
However, the formation of the final *R* product–catalyst complex $(\mathbf{1}\cdot R)_{\mathrm{enol}}$ is more favorable thermodynamically than the formation of the *S* product–catalyst complex $(\mathbf{1}\cdot S)_{\mathrm{enol}}$ by 3.8 kcal mol^{-1} (B3PW91/6-31G*); 6.3 kcal mol^{-1} at MP2/6-31G*//B3PW91/6-31G*}. The level of energy of the corresponding final complex $(\mathbf{1}\cdot R)_{\mathrm{enamine}}$ as shown in Figure 3 differs from that of $(\mathbf{1}\cdot R)_{\mathrm{enol}}$ only because of a different hydrogen-bonding pattern. Thus, the calculations suggest that, whereas the formation of the *S* product by the enol pathway is favored kinetically, the overall reaction might be thermodynamically controlled (i.e. initially faster formed $(\mathbf{1}\cdot S)_{\mathrm{enol}}$ could have been transformed gradually into more stable $(\mathbf{1}\cdot R)_{\mathrm{enol}}$).

To validate this computational finding we have stirred racemic Mannich product **18** in the presence of 15 mol% of amine–thiourea **1** (Scheme 2). The enantiomeric excess was determined after 3, 5, 7, and 10 days, respectively. Successively larger enrichment of *R* product was observed (5.8% *ee*, 9.7% *ee*, 15.7% *ee*, 25.9% *ee* after 3, 5, 7, and 10 days, respectively), confirming the presence of thermodynamic control.[9]

While we have found some evidence for an enol mechanism herein, another reaction pathway that involves a thiourea-complexed enol (Scheme 3) might also be possible



Scheme 2. Deracemization of racemic Mannich-product **18**.



Scheme 3. Alternative reaction mechanism involving an enol intermediate.

in analogy to the recent work of Jacobsen and co-workers on the cyanosilylation of a ketone assisted by a tertiary amine-thiourea catalyst.[17] However, they found computationally, that the pathway by thiourea-bound cyanide is less favorable with respect to the pathway involving a thiourea-bound ketone.[17]

In conclusion, for the first time a chiral primary amine–thiourea organocatalyst has been applied successfully to an asymmetric Mannich-type reaction of unmodified ketones with readily available and stable α-hydrazonoesters. The reaction does not require preformed enolate equivalents and provides corresponding products **7**–**18** in good to high yields (up to 89%) and excellent enantioselectivities (up to >99% *ee*). Moreover, we present the first piece of evidence for an enol mechanism in a primary amine–thiourea catalyzed C–C bond-forming transformation—the Mannich-type reaction. The use of the easily accessible bifunctional primary amine–thiourea catalysts in other valuable organic transformations, as well as additional mechanistic studies are ongoing in our laboratory.

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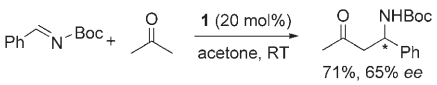

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