Highly enantioselective addition of ketones to nitroolefins catalyzed by new thiourea–amine bifunctional organocatalysts†

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A new and effective organocatalytic system: primary amine derived chiral thiourea catalyst 4a and AcOH–H_2O additive, which converts different ketones to γ-nitroketones in high yields (82–99%) and enantioselectivities (90–99%) has been described.

Michael reaction of ketones with nitroolefins represent without question a convenient access to γ-nitroketones which are valuable building blocks in organic synthesis.[1] Barbas,[2] List[3] and Enders[4] with co-workers independently reported the first organocatalytic addition of acetone to *trans*-β-nitrostyrene using L-proline as the catalyst. However, only poor enantioselectivity was obtained with this natural catalyst.[2–4] As a result, considerable effort has been directed towards the development of an organocatalytic asymmetric version of the Michael addition of ketones to nitroolefins over recent years and many improvements to this reaction have been made using pyrrolidine-based catalytic systems.[5–10] Highly enantio- and diastereoselective pyrrolidine–pyridine-catalyzed nitro-Michael reactions, recently reported by Kotsuki and co-workers, have focused on the use of cyclohexanone and tetrahydrothiopyran-4-one as ketones.[10] Poor to moderate enantioselectivities still resulted when acetone (12–42% ee)[4–9] or methylethylketone (10–51% ee (*syn*))[3,6] was used as a substrate.

The use of chiral bifunctional catalysts for the synthesis of optically active compounds has become a new and exciting area of contemporary synthetic organic chemistry.[11,12]

Chiral bifunctional thiourea derivatives have recently emerged as enantioselective catalysts for different organic transformations.[13] More recently, we reported[14] on a new bifunctional organocatalyst, bearing both a thiourea moiety and an imidazole group on a chiral scaffold, as a more effective catalyst in the addition of acetone to *trans*-β-nitrostyrene. We showed that this bifunctional organocatalyst outperformed recently reported pyrrolidine-based catalytic systems,[5–10] in the context of enantioselectivity. Although a remarkable improvement in the ee value (87% ee) has been achieved, the yield was moderate (55%).

With an interest in developing an efficient chiral organocatalytic system to achieve high levels of yield and enantioselectivity in Michael additions of different ketones to nitroolefins, we have designed new chiral bifunctional organic catalysts that possess both a thiourea moiety and an amine group as a base (Fig. 1).

A transient activation of ketone donors through formation of an enamine on the primary or secondary amino group was anticipated.[15] Furthermore, the neighbouring thiourea was expected to interact, *via* hydrogen-bonding, with a nitro group of the nitroolefins and enhance their electrophilicity.[13g–j,16]

In addition, the chiral arylethyl moiety adjacent to a thiourea was expected to shield one side of the activated nitroolefin.

Here we present a successful application of the new chiral bifunctional organic catalysts **1–3** and **4a–b** (Fig. 2) to the asymmetric Michael additions of different ketones to nitroolefins.

To evaluate the catalytic efficiency of the chiral thioureas the addition of acetone to β-nitrostyrene was first performed in non-polar toluene in the presence of each of these catalysts (Table 1, entries 1, 3, 5, 7). Initial screening studies identified toluene as the optimal solvent for the reaction.

The use of proline based chiral thioureas **1** and **2** gave the product only in racemic form and in low yields (up to 36% yield, Table 1, entries 1, 3). Notably, much higher catalytic activity were displayed by catalysts **3** (74%, 82% ee, entry 5) and **4a** (75%, 87% ee, entry 7, Table 1), which contain just a primary amino group in place of proline moiety.

In the pioneering investigations of the role of acid in the formation of enamine, carried out by Hine,[17] it was shown that, in water, protonated primary amines formed imines from the corresponding carbonyl compounds at a rate that was 15 times faster than that achieved by amines alone. This fact has motivated us for the further experiments.

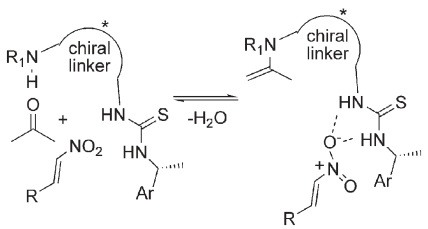

Fig. 1 Design of bifunctional organocatalysts for the Michael addition of acetone to *trans*-β-nitrostyrene.

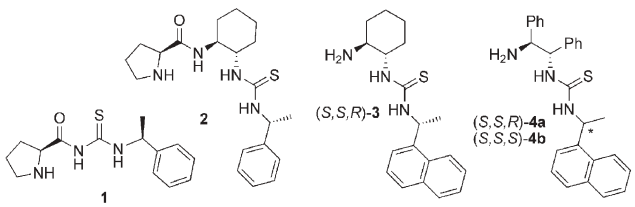

Fig. 2 Screened chiral thiourea based bifunctional organocatalysts.

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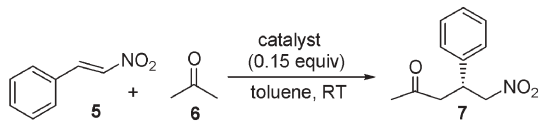
Table 1 Screening of new chiral thiourea catalysts **1–3** and **4a–b** for asymmetric addition of acetone (**6**) to *trans*-β-nitrostyrene (**5**)



Entry	Catalyst	Additive	*t*/h	Yield (%)[b]	*ee* (%)[c]
1	**1**	—	72	20	0
2	**1**	AcOH, H_2O[a]	72	50	3
3	**2**	—	72	36	0
4	**2**	AcOH, H_2O[a]	72	55	3
5	**3**	—	72	74	82
6	**3**	AcOH, H_2O[a]	48	97	84
7	**4a**	—	72	75	87
8	**4a**	AcOH, H_2O[a]	48	98	91
9	**4b**	AcOH, H_2O[a]	72	79	77

[a] 0.15 equiv. of AcOH and 2 equiv. of H_2O were used. [b] Yield of isolated product after column chromatography on SiO_2. [c] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

The Michael reaction of acetone with β-nitrostyrene was next examined with thioureas **1–3** and **4a** in the presence of AcOH and H_2O as additives.[18] Water, it is known, plays a significant role in the enamine catalytic reaction, including in regeneration of the catalyst.[15]

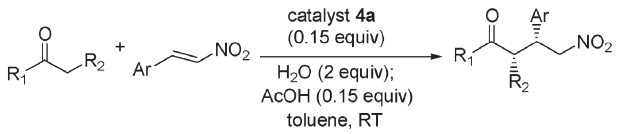
To our delight, the addition of 0.15 equiv. of AcOH and 2 equiv. of H_2O significantly improved the reaction yield as well as slightly improving the enantioselectivity relative to that with the catalysts in the absence of additives (Table 1, entries 2, 4, 6, 8 *versus* entries 1, 3, 5, 7). The acid additive, thus, functioned "cooperatively" as part of the catalysis and the catalytic system **4a**–AcOH–H_2O provided Michael product **7** in excellent yield (98%) and with 91% *ee* (Table 1, entry 8 *versus* entry 7).

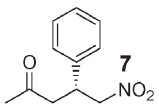
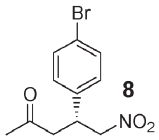
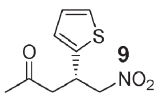
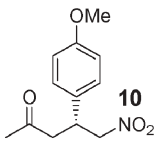
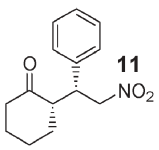
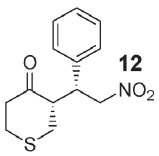
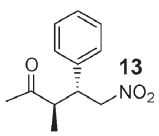
Encouraged by the excellent results obtained with bifunctional thiourea (*S,S,R*)-**4a** in the presence of AcOH–H_2O additive, we next explored the effectiveness of its stereoisomer (*S,S,S*)-**4b** for the same Michael addition. It is noteworthy that both catalysts (*S,S,R*)-**4a** and (*S,S,S*)-**4b** provide the *R* enantiomer of the adduct **7**. However, lower yield and enantioselectivity were afforded by catalyst (*S,S,S*)-**4b** *vs.* those by (*S,S,R*)-**4a** (Table 1, entry 8 *versus* entry 9). These results demonstrated that the original thiourea (*S,S,R*)-**4a** was the best choice as a chiral organocatalyst.

With optimal catalyst and reaction conditions established, a variety of aromatic nitroolefins were then evaluated as substrates and the results are summarized in Table 2. Nitroolefins underwent clean reactions with acetone as the simplest ketone affording the desired product in high yields (98–99%), with the sole exception of the slightly reduced yield (84%) achieved with aromatic nitroolefine bearing an electron-donating substituent (Table 2, entries 1–3 *versus* entry 4). At the same time, the substituents of the nitroolefin appear to have very little effect on the enantioselectivities of the reaction, which range from 90% to 91% for catalyst **4a** (Table 2, entries 1–4).

Cyclohexanone and tetrahydrothiopyran-4-one were also reacted with β-nitrostyrene in high yield and enantioselectivity (up to 89%, and 99% ee), and good diastereoselectivity (*syn* : *anti* up to 83 : 17) in the presence of catalyst **4a** (Table 2, entries 5, 6).

Table 2 Catalytic asymmetric Michael addition of ketones to nitroolefins under optimised conditions



Entry	*t*/h	Product	Yield (%)[a]	dr[b] (*syn* : *anti*)	*ee* (%)[c] (*syn*)
1	48		98	—	91
2	40		99	—	90
3	50		98	—	90
4	61		84	—	91
5	72		82	80 : 20	96
6	72		89	83 : 17	98
7	72		88	14 : 86	>99[d]

[a] Yield of isolated product after column chromatography on SiO_2. [b] Determined by ^1H NMR spectroscopy. [c] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material. [d] Ee % of *anti* diastereomer.

Surprisingly, the addition of a nonsymmetrical ketone such as methylethylketone to β-nitrostyrene under the same conditions as above, led to the opposite diastereomer (*syn* : *anti* 14 : 86) with very high enantiocontrol (>99% ee). This selectivity is the reverse of that normally found for this example in literature.[3,6] To our delight, remarkably high yields and enantioselectivities were achieved for all investigated ketones and aromatic nitroolefins with the new primary amine derived chiral thiourea catalyst **4a**.

Notably, a new interesting study by Xu and Córdova on the enantioselective nitro-Michael addition using primary amino acid derivatives as catalysts appeared during the preparation of this manuscript.[19] The authors demonstrated that amino acid derived

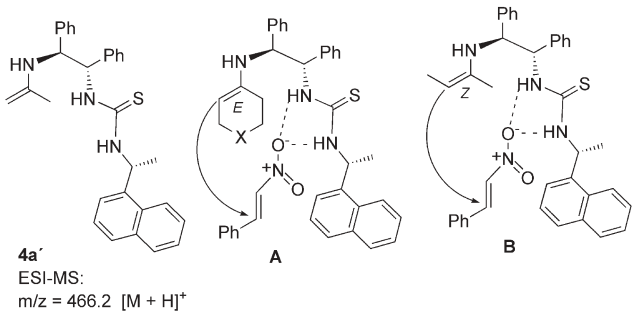


Fig. 3 ESI-MS experiment of the enamine intermediate **4a′** and proposed transition states for the Michael reaction of symmetrical (**A**) and nonsymmetrical ketones (**B**) with *trans*-β-nitrostyrene.

catalysts with a primary amine residue can successfully catalyze the asymmetric addition of ketones to nitroolefins. However, low to moderate enantioselectivities resulted when hydroxyacetone (27% ee) or methylethylketone (67% ee) were used as a substrate.[19]

To confirm the importance of the thiourea moiety of **4a** for the catalysis, (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine alone as well as with additive was next tested as catalyst. Intriguingly, whereas the combination of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine and AcOH–H_2O in toluene (72 h) gives the *R* Michael product in 26% yield and with 60% ee, the (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine alone produces the *S* product, in 10% yield and with 11% ee. These experiments show that the primary amine even in the presence of acid additive is not able to facilitate the nitro-Michael addition with good yield, and thus the prerequisite for very good yield and enantioselectivity is that the catalyst possesses both thiourea and amine functionalities, directly adjacent to the neighbouring stereogenic carbon centers of the chiral linker.

The formation of enamine intermediate **4a′** from acetone and primary amine group of catalyst **4a** was confirmed using the ESI-MS method (Fig. 3).

From these results, we propose the plausible transition-state model (**A**), which reasonably explains the relative (*syn*) and absolute configuration of the Michael adducts **11** and **12** (Fig. 3).

Finally, to explain the inversion of diastereoselectivity with methylethylketone as a substrate, we assumed the formation of the *Z* enamine intermediate **B** (Fig. 3).

In summary, we have demonstrated for the first time that primary amine derived chiral thioureas can catalyze the asymmetric nitro-Michael addition, giving high yields (82–99%), enantioselectivities (90–99% ee) and good diastereoselectivities for a wide range of ketones and aromatic nitroolefines.

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