# Novel thiourea-amine bifunctional catalysts for asymmetric conjugate addition of ketones/aldehydes to nitroalkenes: rational structural combination for high catalytic efficiency†

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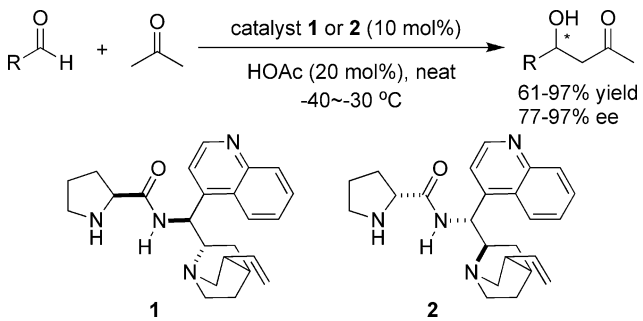
**A series of thiourea-amine bifunctional catalysts have been developed by a rational combination of prolines with cinchona alkaloids, which are connected by a thiourea motif. The catalyst 3a, prepared from L-proline and cinchonidine, was found to be a highly efficient catalyst for the conjugate addition of ketones/aldehydes to a wide range of nitroalkenes (up to 98/2 dr and 96% ee). The privileged cinchonidine backbone and the thiourea motif are essential to the reaction activity and enantioselectivity.**

Over the last decade, organocatalysis has become one of the most active and attractive research fields in modern organic chemistry.[1,2] In this context, great research efforts have been directed toward the development of efficient organocatalysts for asymmetric reactions. As a consequence, a number of chiral amines have been identified as versatile catalysts for enantioselective functionalizations of carbonyl compounds.[3–7] The asymmetric direct conjugate addition of ketones/aldehydes to nitroalkenes, which provides a straightforward approach to optically active and synthetically versatile γ-nitrocarbonyl compounds, has received extensive attention.[8–10] Inspired by the seminal works of List,[11b] and Barbas[11c,d] and co-workers, many elegant catalytic systems have been developed for the asymmetric Michael addition of carbonyl compounds to nitroalkenes.[11–14] Representative examples include Wang's pyrrolidine sulfonamides,[12h] Barbas' diamines,[12i] Tang's thiourea-secondary amines,[12j] Jacobsen's primary amine-thioureas,[13g] Takemoto's thiourea-tertiary amine,[13j] and Wang's thiourea-dehydroabietic amine.[13k] Despite remarkable advances being made, efforts to develop readily available and easily tunable organocatalysts for asymmetric Michael addition reactions continue with the goal of increasing the reaction efficiency and stereoselectivity.

Recently, our group introduced a new and powerful methodology, *combining two privileged backbones into one*, for the catalyst design, which led to two efficient chiral amines for the direct aldol reaction between aromatic aldehydes and acyclic ketones.[15,16] In the presence of 10 mol% of catalyst **1** or **2**, a broad range of aldehydes reacted efficiently with acetone, affording both enantiomers of the corresponding aldol adducts in excellent yields and enantioselectivities (Scheme 1).[15a] As a key design element, the rational coupling of two privileged chiral motifs is critical to the catalytic performance of **1** and **2**. In an effort to extend this strategy, we recently questioned whether "privileged chiral catalysts" might be combined to generate a new catalyst system for enantioselective Michael reactions. Herein, we disclose the synthesis of unprecedented thiourea-amine bifunctional catalysts **3–6** by rational incorporation of structurally privileged proline and cinchona alkaloids into one molecule (Fig. 1)[17] and the results of utilizing **3a** and **6** in the Michael addition of unmodified ketones/aldehydes to nitroalkenes.




**Scheme 1** Direct aldol reaction of aromatic aldehydes with acetone.

A detailed description of our bifunctional and tunable catalysts is presented in Scheme 2 with the synthesis of **3a** as a representative example. Treatment of (*S*)-2-aminomethyl-1-*N*-Boc-pyrrolidine (**7**)[18a] with carbon disulfide using a known procedure[18b] gave the corresponding isothiocyanate **8** in 76% isolated yield. Subsequently, the reaction of **8** with the cinchonidine-derived amine **9** in $CH_2Cl_2$ at room temperature afforded the Boc-protected thiourea-amine **10** in 88% yield,[18c] which was then deprotected directly with TFA in $CH_2Cl_2$ to give rise to the desired organocatalyst **3a** in 55% yield.[14a] Other thiourea-amine catalysts **3b–6** were synthesized according to this three-step procedure without incident. The structures of the catalysts **3–6** were fully characterized (see the Supporting Information). Notably, these catalysts could be easily prepared on gram scales. The catalytic performance of these catalysts were then evaluated in the direct asymmetric conjugate addition of cyclohexanone **11** to *trans*-β-nitrostyrene **12a** and the results are summarized in Table 1.

As shown in Table 1, catalysts **1** and **2**, which are excellent catalysts for the direct aldol reaction of acetone with aldehydes, can also efficiently promote this Michael reaction under our previous reaction conditions.[14a] High levels of reaction efficiency and diastereoselectivities were achieved (up to 96% yield and

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† Electronic supplementary information (ESI) available: Experimental details, characterization of all catalysts, NMR spectra, and HPLC spectra of Michael addition products. See DOI: 10.1039/b925962g

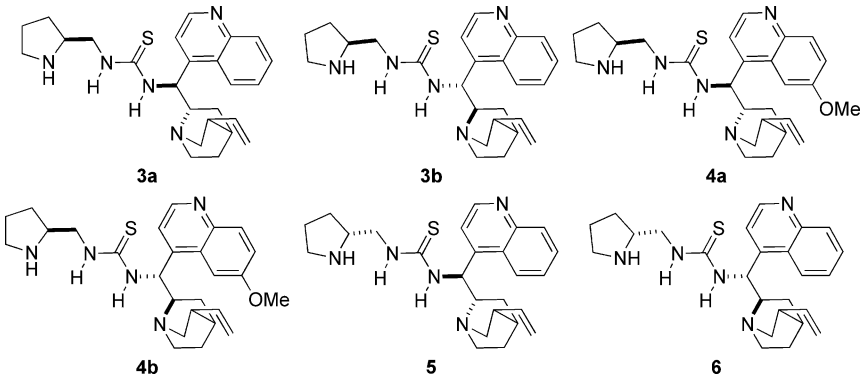
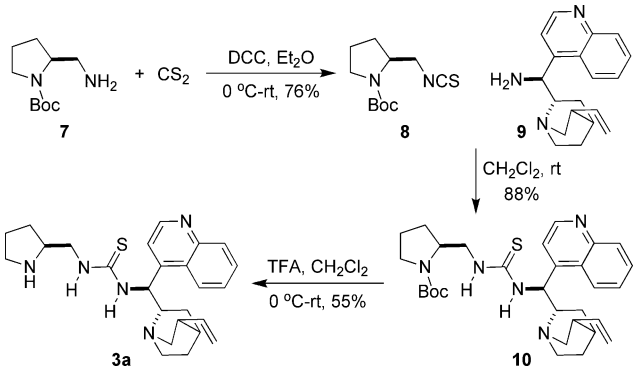



**Fig. 1** New class of thiourea-amine bifunctional catalysts.

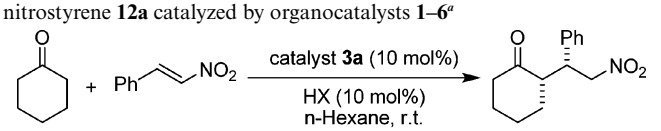



**Scheme 2** Synthesis of thiourea-amine bifunctional catalyst **3a**.

96/4 dr), but the enantiomeric excess of the corresponding Michael adduct was not satisfactory (16–34% ee). In order to overcome this limitation, we then applied the chiral thiourea-amines **3–6** to this model reaction. Indeed, the combination of the proline with cinchona alkaloid plays an important role in the stereocontrol in this Michael addition. It was found that the chiral thiourea-amines **3a** and **4a**, derived from L-proline, cinchonidine and quinine, displayed slightly higher selectivity and/or efficiency than their analogues **3b** and **4b**, respectively (Table 1, entries 3 *vs.* 4, 5 *vs.* 6). As expected, when D-proline was incorporated into the catalyst backbone (catalyst 5), the opposite enantiomer of the Michael adduct was generated in 82% yield with 95/5 dr and 86% ee (Table 1, entry 7). Furthermore, the catalyst **6**, prepared from D-proline and cinchonine, induced higher enantioselectivity than **5** did, giving the product with opposite configuration in 87% yield with 97/3 dr and 96% ee. We then simply examined the effects of other solvents on the reaction with **3a** as the catalyst. The diastereo- and enantioselectivity/solvent profile showed that the n-hexane was the ideal reaction medium (Table 1, entries 9–23).

It was documented that the addition of Brønsted acid could accelerate the formation of the enamine/iminium intermediate in the aminocatalysis, and thereby increases the reaction efficiency and selectivity. Accordingly, various Brønsted acids were then screened to further improve the diastereo- and enantioselectivity of the reaction. As can be seen from Table 2, the acid additive does indeed affect the diastereo- and enantioselectivity and reaction efficiency. For example, in the presence of formic acid, the dr and ee decreased to 90/10 and 88%, respectively (Table 2, entry 1).

**Table 1** Asymmetric Michael reaction of cyclohexanone **11** with *trans*-β-nitrostyrene **12a** catalyzed by organocatalysts **1–6**[a]




| entry | cat. | solvent | *t*/h | yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | **1** | n-Hexane | 4 | 96 | 96/4 | 34 |
| 2 | **2** | n-Hexane | 4 | 93 | 95/5 | –16 |
| 3 | **3a** | n-Hexane | 5 | 89 | 97/3 | 96 |
| 4 | **3b** | n-Hexane | 22 | 82 | 96/4 | 91 |
| 5 | **4a** | n-Hexane | 12 | 83 | 96/4 | 91 |
| 6 | **4b** | n-Hexane | 17 | 76 | 97/3 | 91 |
| 7 | **5** | n-Hexane | 13 | 82 | 95/5 | –86 |
| 8 | **6** | n-Hexane | 10 | 87 | 97/3 | –96 |
| 9 | **3a** | EtOH | 24 | <5 | — | — |
| 10 | **3a** | MeOH | 24 | <5 | — | — |
| 11 | **3a** | *i*-PrOH | 24 | <5 | — | — |
| 12 | **3a** | Toluene | 8 | 85 | 96/4 | 94 |
| 13 | **3a** | xylene | 8 | 80 | 93/7 | 90 |
| 14 | **3a** | $CHCl_3$ | 28 | 77 | 95/5 | 92 |
| 15 | **3a** | $CH_2Cl_2$ | 21 | 80 | 93/7 | 90 |
| 16 | **3a** | DCE | 8 | 88 | 95/5 | 92 |
| 17 | **3a** | $CH_3CN$ | 45 | 17 | 90/10 | 82 |
| 18 | **3a** | Dioxane | 45 | 63 | 91/9 | 86 |
| 19 | **3a** | DMSO | 24 | <5 | — | — |
| 20 | **3a** | $Et_2O$ | 21 | 82 | 95/5 | 90 |
| 21 | **3a** | THF | 45 | 62 | 93/7 | 88 |
| 22 | **3a** | TBME | 8 | 86 | 94/6 | 91 |
| 23 | **3a** | neat | 8 | 50 | 89/11 | 91 |

[a] Reactions were carried out with cyclohexanone **11** (5.0 mmol), *trans*-β-nitrostyrene **12a** (0.5 mmol) and 10 mol% catalyst and 10 mol% $PhCO_2H$ in the solvent (1.0 mL) indicated. [b] Isolated yield for both diastereomers. [c] *syn*/*anti* Ratio was determined by $^1H$ NMR. [d] ee of *syn* diastereomer, determined by chiral HPLC.

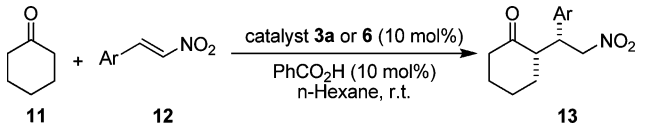
Surprisingly, in the case of *p*-TsOH, only 52% yield of the Michael adduct was obtained even after two days albeit with 94/6 dr and 90% ee (Table 2, entry 7). Among the additives examined, $PhCO_2H$ proved to benefit the reaction (Table 2, entry 14). It is worthwhile noting that the reaction proceeded much more slowly and with lower dr and ee values in the absence of $PhCO_2H$ (Table 2, entry 15 *vs.* 14).

With the optimal reaction conditions in hand, we next investigated the scope of the Michael reaction with a variety of nitroolefins and the results are shown in Table 3. In addition



**Table 2** Effect of the acid additives on the catalytic performance of catalyst **3a**[a]




**11** **12** **13**

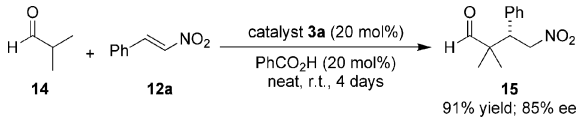
| entry | HX | *t*/h | yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | $HCO_2H$ | 14 | 90 | 90/10 | 88 |
| 2 | HOAc | 12 | 85 | 94/6 | 92 |
| 3 | $ClCH_2CO_2H$ | 12 | 91 | 95/5 | 91 |
| 4 | $NCCO_2H$ | 14 | 84 | 93/7 | 90 |
| 5 | TFA | 14 | 89 | 94/6 | 93 |
| 6 | $CH_3CH_2CO_2H$ | 12 | 81 | 93/7 | 92 |
| 7 | *p*-TsOH | 48 | 52 | 94/6 | 90 |
| 8 | *p*-MeO-$PhCO_2H$ | 12 | 89 | 93/7 | 92 |
| 9 | *p*-F-$PhCO_2H$ | 12 | 97 | 94/6 | 91 |
| 10 | 3,5-DNBA | 12 | 93 | 93/7 | 89 |
| 11 | *p*-$CF_3$-$PhCO_2H$ | 12 | 96 | 94/6 | 92 |
| 12 | $CH_3(CH_2)_{10}CO_2H$ | 12 | 87 | 91/9 | 90 |
| 13 | $CH_3(CH_2)_{14}CO_2H$ | 12 | 85 | 91/9 | 90 |
| 14 | $PhCO_2H$ | 5 | 89 | 97/3 | 96 |
| 15 | none | 72 | 17 | 91/9 | 83 |

[a] Unless otherwise noted, reactions were carried out with 0.5 mmol of *trans*-β-nitrostyrene **12a**, 5.0 mmol of cyclohexanone **11** in 1.0 mL of n-hexane in the presence of 10 mol% of catalyst **3a** and 10 mol% of co-catalyst HX. [b] Isolated yield for both diastereomers. [c] *syn*/*anti* Ratio was determined by $^1$H NMR. [d] ee of *syn* diastereomer, determined by chiral HPLC.

to *trans*-β-nitrostyrene **12a**, various electron-poor and -rich nitroolefin derivatives with different substitution patterns on the aromatic ring reacted smoothly with cyclohexanone in the presence of 10 mol% of **3a** with 10 mol% of $PhCO_2H$ as the co-catalyst, giving the corresponding Michael adducts **13a–k** in high yields with excellent diastereo- (up to 98/2 dr) and enantioselectivities (90–95% ee) (Table 3, entries 2–11). Fused aromatic nitroolefins, such as **12l**, can also be successfully employed in this transformation and high yield, dr (93/7) and ee (92%) were obtained. Heteroaromatic nitroolefins, such as **12m** and **12o**, were also viable substrates (Table 3, entries 13 and 26). As expected, the opposite enantiomeric Michael addition product can also be obtained with high dr and ee values when thiourea-amine catalyst **6**/$PhCO_2H$ was employed under the same conditions (Table 3, entries 14–26). However, aliphatic nitroolefins displayed much less reactivity in this reaction. For example, the addition of aliphatic nitroolefin **12p** proceeded very slowly and only trace amount of the product was detected even after 4 days (Table 3, entry 27).

The synthesis of quaternary stereogenic centers remains a challenging task in synthetic organic chemistry, and there have only been a few examples of the use of α,α-disubstituted aldehydes as Michael donors.[19] The Michael addition of α,α-disubstituted aldehydes to nitroolefin should provide a direct access to nitro compounds with one all-carbon quaternary center. Therefore, we primarily examined the feasibility of utilizing isobutyraldehyde **14** as Michael donor with **3a** as the catalyst. As shown in eqn (1), the Michael addition of isobutyraldehyde **14** to *trans*-β-nitrostyrene **12a** proceeded smoothly and the corresponding product was obtained in 91% yield with 85% ee. Further optimization of the reaction conditions to improve the enantioselectivity is underway in our laboratory.

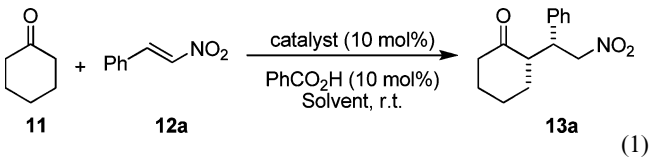
**Table 3** Asymmetric Michael addition reaction between **11** and **12** catalyzed by catalysts **3a** and **6**[a]




**14** **12a** **15**
91% yield; 85% ee

| entry | nitroolefin Ar | cat. | yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | Ph (**12a**) | **3a** | 89 | 97/3 | 96 |
| 2 | 4-$NO_2$-Ph (**12b**) | **3a** | 75 | 93/7 | 94 |
| 3 | 2-$NO_2$-Ph (**12c**) | **3a** | 76 | 98/2 | 95 |
| 4 | 4-F-Ph (**12d**) | **3a** | 92 | 97/3 | 94 |
| 5 | 4-Br-Ph (**12e**) | **3a** | 85 | 94/6 | 94 |
| 6 | 2-Br-Ph (**12f**) | **3a** | 98 | 98/2 | 90 |
| 7 | 4-Cl-Ph (**12g**) | **3a** | 89 | 93/7 | 94 |
| 8 | 2-Cl-Ph (**12h**) | **3a** | 89 | 97/3 | 94 |
| 9 | 2,4-$Cl_2$-Ph (**12i**) | **3a** | 95 | 95/5 | 95 |
| 10 | 4-Me-Ph (**12j**) | **3a** | 98 | 94/6 | 92 |
| 11 | 2-MeO-Ph (**12k**) | **3a** | 95 | 95/5 | 92 |
| 12 | 1-naphthyl (**12l**) | **3a** | 97 | 93/7 | 92 |
| 13 | 2-furyl (**12m**) | **3a** | 93 | 92/8 | 85 |
| 14 | Ph (**12a**) | **6** | 87 | 97/3 | –96 |
| 15 | 2-$NO_2$-Ph (**12c**) | **6** | 86 | 98/2 | –94 |
| 16 | 4-F-Ph (**12d**) | **6** | 92 | 91/9 | –91 |
| 17 | 4-Br-Ph (**12e**) | **6** | 80 | 94/6 | –94 |
| 18 | 2-Br-Ph (**12f**) | **6** | 97 | 98/2 | –93 |
| 19 | 4-Cl-Ph (**12g**) | **6** | 81 | 91/9 | –91 |
| 20 | 2-Cl-Ph (**12h**) | **6** | 90 | 97/3 | –94 |
| 21 | 2,4-$Cl_2$-Ph (**12i**) | **6** | 92 | 98/2 | –95 |
| 22 | 4-Me-Ph (**12j**) | **6** | 97 | 92/8 | –89 |
| 23 | 2-MeO-Ph (**12k**) | **6** | 91 | 94/6 | –91 |
| 24 | 1-naphthyl (**12l**) | **6** | 87 | 95/5 | –93 |
| 25 | 4-MeO-Ph (**12n**) | **6** | 85 | 89/11 | –85 |
| 26 | 2-thienyl (**12o**) | **6** | 87 | 85/15 | –82 |
| 27 | *t*-Bu (**12p**) | **3a** | <5 | — | — |

[a] Unless otherwise noted, the reactions were carried out with 0.5 mmol of **12**, 5.0 mmol of cyclohexanone **11** in 1.0 mL of n-hexane in the presence of 10 mol% of catalyst **3a** or **6** and 10 mol% of $PhCO_2H$ for 5–48 h. [b] Isolated yield for both diastereomers. [c] *syn*/*anti* Ratio was determined by $^1$H NMR. [d] ee of *syn* diastereomer, determined by chiral HPLC.




**11** **12a** **13a** (1)

Based on the observed stereoselectivities, we proposed a plausible catalytic mode for this asymmetric conjugate addition (Fig. 2).[20] Presumably, the *in situ* formed enamine intermediate between cyclohexanone **11** and catalyst **3a** adopts the *E*-conformation. Similar to other well-developed diamine–protonic acid-catalyzed reactions,[21] the protonated cinchonidine moiety of **3a** would act as a synergistic Brønsted acid to provide another hydrogen bond interaction with the nitro group besides the

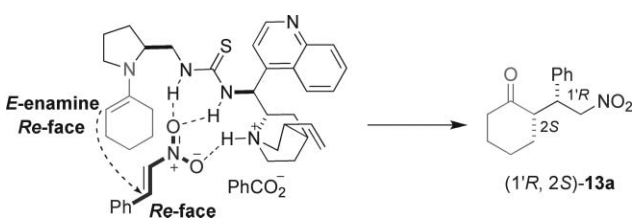



**Fig. 2** Proposed intermediate *via* concerted activation.

two NH groups of thiourea moiety. Then, the *Re* face of enamine intermediate attacks the *Re* face of *trans*-β-nitrostyrene to give the corresponding preferred *syn* Michael adduct **13a**. Nevertheless, the precise catalytic mechanism needs further investigation.

In conclusion, we have designed a new class of thiourea-amine bifunctional catalysts by a rational combination of commercially available and inexpensive proline with cinchona alkaloids. They have been successfully utilized in the asymmetric conjugate addition of ketones/aldehydes to nitroalkenes (up to 98% yield), from which both *syn*-enantiomers can be obtained in high stereoselectivity in the presence of catalyst **3a** or **6** (up to 98/2 dr and 96% ee). The present study has further demonstrated that the coupling of two chiral privileged skeletons, proline and cinchonidine is a useful strategy to reach high reaction efficiency and enantioselectivity. The development of modified catalysts with wider substrate scopes and further application of the current strategy to the design of other chiral bifunctional organocatalysts are ongoing in our laboratory.



## Acknowledgements

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