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# A novel method to access chiral nonnatural 2,4-disubstituted pyrrolidines from aldehydes and nitroolefins only with an α-substituent†

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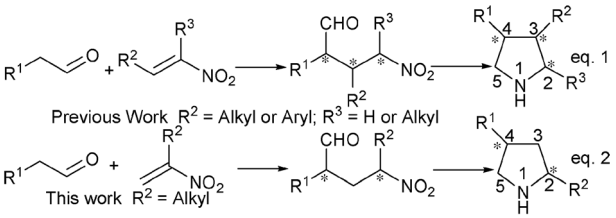
**A series of α-substituted nitroolefins were employed in organocatalytic asymmetric Michael reactions with aldehydes. γ-Nitro carbonyl products were achieved in good yields (up to 86%) with good stereoselectivities (up to 96% ee and 24 : 1 dr). Reduction of the nitro group followed by intramolecular reductive amination successfully afforded various novel optically active 2,4-disubstituted pyrrolidine compounds.**

Pyrrolidine, as one of the five-membered heterocycles, is ubiquitous as a core skeleton in many drug candidates and natural products.[1] In addition, a series of chiral organocatalysts containing a pyrrolidine ring have been developed and successfully employed in many useful asymmetric transformations.[2] Because of the importance of the chiral pyrrolidine framework, great efforts have been devoted towards the development of asymmetric methods for synthesizing novel pyrrolidine derivatives, and thus leading to the successful synthesis of chiral 2,3-,[3] 2,4-,[4] 3,4-[5] or 2,5-[6] disubstituted; 2,3,4-,[7] 2,4,5-[8] or 2,3,5-trisubstituted[9] and 2,3,4,5-tetrasubstituted pyrrolidines.[10] Despite the significant advances that have been made in the construction of various chiral substituted pyrrolidines, the methodology to synthesize chiral pyrrolidines with nonfunctional 2,4-disubstituents remains rather limited.[4a] This challenge stimulated us to develop a novel method for achieving this target.

Owing to the rich chemistry of the nitro group,[11] catalytic asymmetric Michael additions of aldehydes and ketones to nitroolefins have attracted much attention. A number of organocatalysts have been employed for these transformations.[12] However, the reactions reported to date have been mainly restricted to using β-monosubstituted nitroolefins as acceptors with aldehydes and ketones, and through this approach, optically active 3,4-disubstituted pyrrolidines could be achieved subsequently (Scheme 1, eqn (1): $R^2$ = alkyl or aryl; $R^3$ = H).[5] Although α,β-disubstituted nitroolefins have also been successfully applied in the asymmetric Michael reactions with aldehydes (Scheme 1, eqn (1): $R^2$ = aryl; $R^3$ = alkyl),[7d,e] nitroolefins only with an α-substituent have rarely been used as substrates in asymmetric catalysis;[13] therefore, we were intrigued by the possibility of developing the asymmetric addition of aldehydes to them. The resulting optically active 2,4-disubstituted γ-nitro carbonyl compounds could also be further converted into a wide array of interesting useful synthons such as 1,4-amino alcohols or amino acids, and especially significantly those could be transformed into the chiral 2,4-disubstituted pyrrolidines also (Scheme 1, eqn (2)). Herein, we wish to report our preliminary results.




**Scheme 1** Previous work and this work.

The Michael addition reaction of isovaleraldehyde **5a** to α-substituted nitroolefin **6a** was selected as the model reaction (Table 1). Catalyst **1**, (Scheme 2) which had shown excellent catalytic performance in the asymmetric reactions of aldehydes and ketones with β-substituted nitroolefins,[5c] gave only moderate yield (50%) and stereoselectivities (60% ee and 83 : 17 dr) in this reaction (Table 1, entry 1). This may be explained as illustrated by Wennemers;[7d] for β-monosubstituted nitroolefins, the stereocontrol of the reaction is mainly by the catalyst in the C–C bond formation step. On the basis of the structure of catalyst **1**, introducing sterically hindered groups –OTBS (**2a**) and –OTBDPS (**2b**) at the 4-position with *trans*-configuration relative to the existing $-CH_2NHSO_2CF_3$ at the 2-position increased the performance: **2a** led to 80% yield, 90% ee and 94 : 6 dr, and **2b** gave the best enantioselectivity (95% ee)

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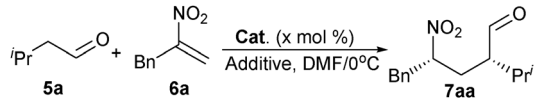
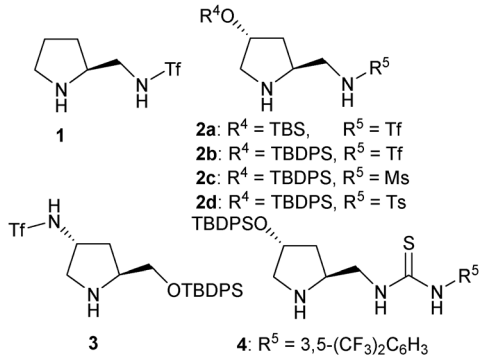
‡ These authors contributed equally to this work.

**Table 1** Catalytic asymmetric Michael reaction of isovaleraldehyde with α-substituted nitroolefin under various catalysts and conditions[a]




| Entry | Cat. (*x*) | Additive | Time (h) | Yield[b] (%) | dr[c] | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **1** (20) | — | 24 | 50 | 83 : 17 | 60 |
| 2 | **2a** (20) | — | 24 | 80 | 94 : 6 | 90 |
| 3 | **2b** (20) | — | 24 | 78 | 96 : 4 | 95 |
| 4 | **2c** (20) | — | 24 | Trace | n.d | n.d |
| 5 | **2d** (20) | — | 24 | 15 | n.d | n.d |
| 6 | **3** (20) | — | 24 | 22 | 28 : 72 | 28 |
| 7 | **4** (20) | — | 24 | 26 | 25 : 75 | 84 |
| 8 | **2b** (20) | $CH_3(CH_2)_2CO_2H$ | 4 | 80 | 96 : 4 | 95 |
| 9 | **2b** (20) | $PhCO_2H$ | 4 | 76 | 95 : 5 | 94 |
| 10 | **2b** (20) | *p*-$CH_3OC_6H_4CO_2H$ | 4 | 80 | 96 : 4 | 95 |
| 11 | **2b** (20) | *p*-$NO_2C_6H_4CO_2H$ | 4 | 86 | 95 : 5 | 94 |
| 12 | **2b** (10) | *p*-$NO_2C_6H_4CO_2H$ | 11 | 86 | 95 : 5 | 94 |
| 13 | **2b** (5) | *p*-$NO_2C_6H_4CO_2H$ | 26 | 84 | 96 : 4 | 95 |
| 14 | **2b** (2) | *p*-$NO_2C_6H_4CO_2H$ | 84 | 80 | 95 : 5 | 95 |

[a] Unless specified, reactions were conducted on a 0.2 mmol scale of nitroolefin in solvent (1 mL) with isovaleraldehyde (2.0 mmol) in the presence of catalyst and equal equivalence of acid was added at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.



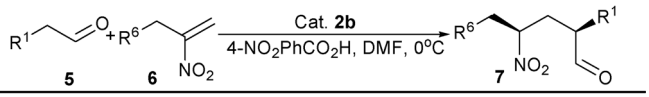

**Scheme 2** Pyrrolidine-based chiral organocatalysts.

and diastereoselectivity (96 : 4 dr) with 78% yield after 24 h. Replacement of the trifluoromethanesulfonyl (**2b**) subunit with methanesulfonyl (**2c**) and 4-methylbenzenesulfonyl (**2d**), respectively, caused the reactivity to decrease dramatically, with only trace amounts or 15% yield being obtained (Table 1, entries 4 and 5). This inferior catalytic performance can be correlated to the decrease in the hydrogen bond donating ability of the sulfonamide hydrogen, which is closely linked to acidity and governed by the electronic nature of the $R^5$ group. In catalyst **2b**, with stronger electron-withdrawing groups ($-CF_3$), both the hydrogen bond donating ability and the acidity were stronger than those in **2c** and **2d**. When the strongly hydrogen bond donating thiourea (**4**) was introduced instead of trifluoromethanesulfonyl, only 26% yield, 84% ee and 25 : 75 dr were achieved (Table 1, entry 7). When catalyst **3**, in which the functional groups of **2b** are exchanged, was employed to promote the reaction, the reactivity decreased dramatically and only gave 22% yield with 28% ee and 28 : 72 dr (Table 1, entry 6). With the best catalyst **2b** in hand, a series of solvents, including hexane, toluene, *t*-$BuOCH_3$, THF, $CH_2Cl_2$, $CHCl_3$, $CH_3CN$, DMF, i-PrOH and $CH_3OH$, were screened in the reaction, with the best result being achieved in DMF (see ESI†).

In order to improve the efficiency of the catalytic system, various acids have been investigated for expediting the reaction by accelerating the formation of the enamine intermediate between the catalyst and the substrate. The results demonstrated that the reaction time could be shortened to 4 h from 24 h in the presence of equal amounts of butyric acid and catalyst **2b**, while giving almost the same yield and stereoselectivities as those of the reaction catalyzed by **2b** alone (Table 1, entries 3 and 8). Benzoic acid and *p*-methoxylbenzoic acid gave similar good results (Table 1, entries 9 and 10). The best yield was achieved when *p*-nitrobenzoic acid was used as the additive and led to 86% yield with 95 : 5 dr and 94% ee (Table 1, entry 11). The influence of catalyst loading was also investigated (Table 1, entries 11–14). In the presence of an equal amount of *p*-nitrobenzoic acid, 5 mol% catalyst can give the same good results—84% yield, 96 : 4 dr and 95% ee—if the reaction time is extended to 26 h. Upon further reducing the catalyst load to 2 mol% a very long reaction time (84 h) was required to maintain a good yield (80%) with the same stereoselectivities (Table 1, entry 14). The other reaction conditions were also optimized and the best ratio of *p*-nitrobenzoic acid to **2b** was 1 : 1; 0 °C was selected as the best reaction temperature and a 5-fold excess of aldehyde was used (see ESI†).

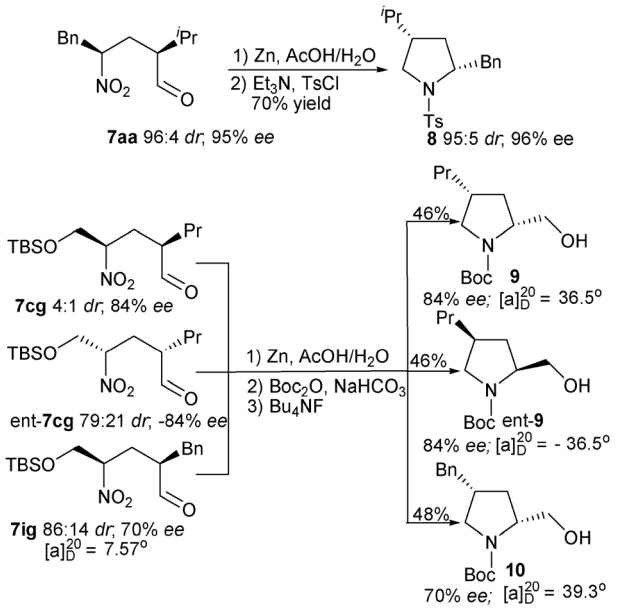
After the optimal reaction conditions had been established, we turned our attention to the reaction scope (Table 2). The results have shown that the asymmetric Michael addition of a variety of acyclic aldehydes to α-nitroolefin proceeded smoothly to give the desired products in good yields (60%–80%) with good stereoselectivities (91 : 9–96 : 4 dr and 90%–95% ee) (Table 2, entries 1–8).

**Table 2** Catalytic asymmetric Michael reaction of aldehydes with α-substituent nitroolefins[a]




| Entry | $R^1$ | $R^6$ | Time (h) | Yield[b] (%) | dr[c] | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | i-Pr | Ph | 28 | 80 (**7aa**) | 96 : 4 | 95 |
| 2[d] | *n*-$C_2H_5$ | Ph | 20 | 66 (**7ba**) | 93 : 7 | 93 |
| 3[d] | *n*-Pr | Ph | 13 | 62 (**7ca**) | 95 : 5 | 95 |
| 4[d] | *n*-$C_4H_9$ | Ph | 36 | 64 (**7da**) | 91 : 9 | 90 |
| 5[d] | *n*-$C_5H_{11}$ | Ph | 20 | 62 (**7ea**) | 92 : 8 | 90 |
| 6[d] | *n*-$C_6H_{13}$ | Ph | 36 | 60 (**7fa**) | 94 : 6 | 91 |
| 7[d] | *n*-$C_7H_{15}$ | Ph | 36 | 64 (**7ga**) | 91 : 9 | 90 |
| 8[d] | *n*-$C_8H_{17}$ | Ph | 36 | 64 (**7ha**) | 91 : 9 | 90 |
| 9 | i-Pr | 4-$CH_3OPh$ | 36 | 86 (**7ab**) | 94 : 6 | 94 |
| 10 | i-Pr | 2-ClPh | 30 | 70 (**7ac**) | 94 : 6 | 92 |
| 11 | i-Pr | 3-ClPh | 35 | 86 (**7ad**) | 99 : 1 | 93 |
| 12 | i-Pr | 2-BrPh | 29 | 82 (**7ae**) | 93 : 7 | 91 |
| 13 | i-Pr | H | 60 | 56 (**7af**) | 95 : 5 | 98 |
| 14[e] | i-Pr | OTBS | 15 | 85 (**7ag**) | 89 : 11 | 91 |
| 15[e] | *n*-Pr | OTBS | 12 | 85 (**7cg**) | 80 : 20 | 84 |
| 16[f] | *n*-Pr | OTBS | 12 | 86 (ent-**7cg**) | 79 : 21 | −84 |
| 17[e] | Bn | OTBS | 48 | 63 (**7ig**) | 86 : 14 | 70 |

[a] Unless specified, reactions were conducted on a 0.2 mmol scale nitroolefin in solvent (1 mL) with isovaleraldehyde (1.0 mmol) in the presence of catalyst **2b** (5%) and *p*-nitrobenzoic acid (5%). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] *p*-Nitrobenzoic acid (50%) was added. [e] Catalyst **2b** (10%) and *p*-nitrobenzoic acid (10%) were added. [f] ent-**2b** (10%) was used as catalyst.




**Scheme 3** Synthesis of 2,4-disubstituted pyrrolidines.

α-Nitroolefins with various electron donating and withdrawing substituents on the phenyl ring were also tested, and were suitable for the asymmetric Michael addition with isovaleraldehyde (Table 2, entries 9–12). The position of the substituent has some influence on the reactivity, since 2-ClPh gave only 70% yield but 3-ClPh gave 86% yield with almost the same level of stereoselectivities (94 : 6 dr *vs.* 99 : 1 dr and 92% ee *vs.* 93% ee) (Table 2, entries 10 and 11). 2-Nitropropene gave excellent stereoselectivities (98% ee and 95 : 5 dr), but only a moderate yield (56%) was achieved (Table 2, entry 13). The nitropropene tethered functional –OTBS at the 3-position worked well in the reactions and led to good yields (63%–85%), enantioselectivities (70%–91% ee) and diastereoselectivities (80 : 20–89 : 11 dr) (Table 2, entries 14, 15 and 17).

In order to demonstrate the synthetic utility of the resultant Michael addition products, the 2,4-disubstituted γ-nitro carbonyl compound **7aa** was treated with Zn/AcOH, and the corresponding optically active 2,4-disubstituted pyrrolidine **8** was achieved successfully by intramolecular reductive amination. Then, we protected the amine by a one-pot reaction with tosyl chloride to afford the *N*-tosyl derivative **8** in good overall yields (Scheme 3). Almost no epimerization and racemization occurred during the procedure of reductive amination. We further carried out the same reductive amination process with **7cg**, ent-**7cg** and **7ig**, followed by Boc-protection and deprotection of TBS to give **9**, ent-**9** and **10**.

The structure and relative configuration of compound ent-**9** were identified using $^{1}$H NMR and $^{13}$C NMR, its absolute configuration could be determined by comparison of the optical rotation data and was found to be in agreement with that reported in the literature.[4f] Correlating the ee values of **7cg** with those of ent-**7cg** and specific rotation data of **9** with those of ent-**9**, we concluded that the absolute configurations of **7cg** and **9** were both (2*R*, 4*R*). Other product configurations were deduced based on analogy, which were further verified by correlating the specific rotation data of **10** with those of ent-**10** reported in the literature.[4f] To account for the stereochemical outcome, a catalytic cycle and transition state model was proposed (see ESI†).

In conclusion, we have developed an asymmetric catalytic Michael reaction involving aldehydes and α-substituted nitroolefins. A variety of γ-nitro carbonyl products were afforded in good yields with good stereoselectivities. To the best of our knowledge, this is the first report of using α-substituted nitroolefins in the catalytic asymmetric Michael reaction with aldehydes for synthesizing optically active 2,4-disubstituted pyrrolidine compounds.

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