# Enantioselective organocatalytic conjugate addition of α-aminoketone to nitroolefins†

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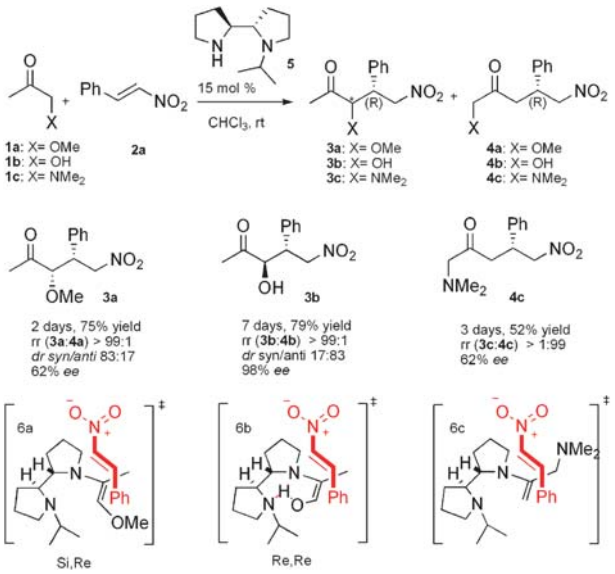
*Received (in Cambridge, UK) 26th June 2008, Accepted 29th July 2008*
*First published as an Advance Article on the web 28th August 2008*
**DOI: 10.1039/b810789k**

**The enantioselective organocatalytic conjugate addition of α-aminoketone to nitroolefins is reported.**

Thirty years after the intramolecular asymmetric aldol reaction, known as the Hajos–Parish–Wiechert reaction,[1] proline was rediscovered as an efficient enantioselective catalyst for the intermolecular aldolisation.[2] This enabled an intensive growth especially in asymmetric enamine catalysis. Many research groups subsequently developed their own organocatalyst containing a pyrrolidine moiety for various reactions.[3] Among them, asymmetric conjugate addition of carbonyl compounds to nitroolefins catalysed by pyrrolidine derivatives[4,5] appeared to be a useful method for the synthesis of γ-nitrocarbonyl compounds. Despite the high efficiency of this methodology, acyclic non-symmetrical ketones turned out to be more challenging substrates, mostly due to the problem of regioselectivity.[5d] In this context, our group published the first organocatalytic asymmetric conjugate addition of α-hydroxyacetone **1b** to nitroolefins with nearly perfect control of regioselectivity and excellent enantioselectivities (Scheme 1).[6] The favourable formation of the corresponding intermediate could be explained by the difference of acidity between the α and α′ protons of the carbonyl compounds. We also developed the first conjugate addition of α-methoxyacetone **1a** and α-dimethylaminoacetone **1c** to β-nitrostyrene **2a**.[5f] Replacing the oxygen by the nitrogen of the dimethylamino group afforded linear adduct **4c**.[5f] In the last case, the balance between steric effects and acidity presumably favours the terminal enamine formation which gives the linear adduct **4c** (Scheme 1). Actually, it should be noticed that the expected *syn*-isomer **3a** was obtained using α-methoxyacetone **1a** whereas the α-hydroxyacetone **2a** gave the *anti*-isomer **3b**. Indeed, this was explained by an internal hydrogen bond between the OH group and the tertiary nitrogen of the catalyst which leads to the formation of the rigid *cis* enamine intermediate which accounts for the inversion of the expected diastereoselectivity and the very high ee's of the adduct **3b**.[6]

To our knowledge the α-dimethylaminoacetone **1c** is the only example of α-aminoketone used in organocatalysed asymmetric conjugate addition. However, Barbas and co-workers reported Mannich reactions of other protected aminoketones with various aldehydes and *p*-anisidine in the presence of pyrrolidine-based tetrazole catalyst. These reactions enable access to chiral 1,2-diamines from azido ketones and 1,4-diamines from phthalimido ketones in excellent regioselectivities and enantioselectivities.[7] Recently, Barbas and co-workers also developed an amine-catalysed Michael reaction of an aminoaldehyde derivative to nitroolefins in the presence of a thiourea as co-additive, but erosion in the enantiomeric purity of the adducts was observed after purification.[8]




**Scheme 1** Previous work: asymmetric Michael addition of α-heterosubstituted ketones to nitroolefins.[5f]

In view of the selective synthesis of branched adducts derived from α-amino-substituted ketones, namely the control of the regioselectivity, we thought about decreasing the p$K_a$ of the α-hydrogens by introducing an electron-withdrawing group on the nitrogen atom. Herein, we report the enantioselective organocatalytic conjugate addition of α-aminoketones to nitroolefins, proceeding highly selectively towards the branched adduct. The optically active α-amino-γ-nitrocarbonyl adducts thus obtained, were further derivatised and showed to be valuable intermediates for more elaborate synthons. Firstly, we compared the organocatalysed Michael addition of three α-aminoketones, bearing different protecting groups on the nitrogen atom, to β-nitrostyrene **2a** in the presence of pyrrolidine **6** (Table 1, entries 1–3). Knowing that α-dimethylaminoacetone **1c** led exclusively to the linear adduct **4c** (Table 1, entry 1),[5f] we were delighted to observe that the enhancement of the acidity of the α-hydrogens favoured the formation of the branched adducts. Thus, the Michael addition of α-NHBoc-acetone **1d** to β-nitrostyrene **2a** provided the highly substituted regioisomer **3d** (75 : 25) as a mixture of *syn*/*anti* diastereoisomers (89 : 11) in good yield (Table 1, entry 2). By replacing the Boc by a tosyl group (**1e**), only the branched adduct **3e** was formed as a mixture of *syn*/*anti* diastereoisomers (69 : 31) (Table 1, entry 3). It is worth noting that the reaction rates increased by enhancing the acidity of the α-hydrogens in the following order: NHTs > NHBoc > $NMe_2$.

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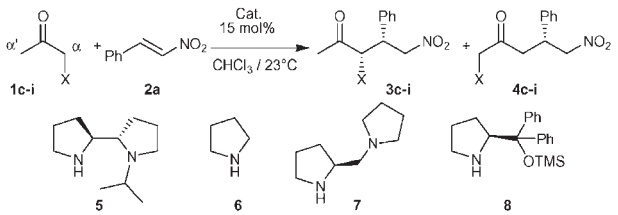
† Electronic supplementary information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/b810789k

**Table 1** Conjugate addition of α-hetero ketones **1c–i** to β-nitrostyrene **2a**




| Entry | X | Cat. | Time/days | Yield[a] (%) | rr[b] (3 : 4) | dr[c] (*syn* : *anti*) | ee[d] (%) |
|---|---|---|---|---|---|---|---|
| 1[e] | $NMe_2$ (**1c**) | **6** | 3 | 70 | >1 : 99 | — | — |
| 2 | NHBoc (**1d**) | **6** | 2 | 76 | 75 : 25 | 89 : 11 | — |
| 3 | NHTs (**1e**) | **6** | 0.5 | 73 | >99 : 1 | 61 : 39 | — |
| 4 | SPh (**1f**) | **6** | 2 | 0 | — | — | — |
| 5[f] | Cl (**1g**) | **6** | 0.5 | 0 | — | — | — |
| 6 | F (**1h**) | **6** | 2 | 0 | — | — | — |
| 7 | NHTs (**1e**) | **5** | 0.5 | 80 | >99 : 1 | 87 : 13 | 96 |
| 8 | NHTs (**1e**) | **7** | 0.5 | 79 | >99 : 1 | 85 : 15 | 90 |
| 9 | NHTs (**1e**) | **8** | 0.5 | 0 | — | — | — |
| 10 | NMeTs (**1i**) | **6** | 2 | 0 | — | — | — |

[a] Isolated yield after flash column chromatography on silica gel. [b] Regioisomeric ratio determined by $^1$H NMR or GC. [c] Determined by chiral SFC on the crude material. [d] Enantiomeric excess of the major diastereoisomer determined by chiral SFC. [e] 10 eq. of α-dimethylamino acetone **1c** (see ref. 5*f*). [f] $S_N2$ reaction occurred on the α-chloroacetone **1g**.

With a view to completing our study of α-heterosubstituted ketones, we examined α-phenylthioacetone **1f** and α-halogenoacetones **1g** and **1h** as nucleophile donors. Disappointingly, no reactivity was observed with α-phenylthioacetone **1f** with regard to the reaction conditions (Table 1, entry 4). Concerning the α-halogenoacetones, α-chloroacetone **1g** gave only the product arising from the nucleophilic attack of the pyrrolidine on the α-carbon bearing the chlorine atom (Table 1, entry 5). Finally, pyrrolidine did not catalyse the conjugate addition of α-fluoroacetone **1h** to β-nitrostyrene **2a** (Table 1, entry 6).

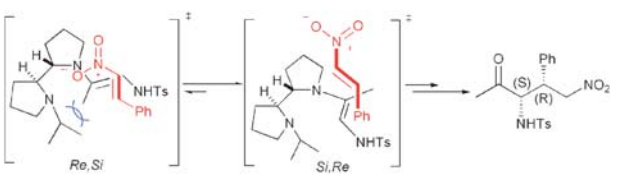
With the best α-aminoketone in hand (α-NHTs acetone **1e**), we examined the asymmetric induction with different chiral amines. The diastereoselectivities could be improved in favour of the *syn* adduct by carrying out the reaction with chiral diamines **5** and **7** (Table 1, entry 7 and 8). The highest enantioselectivity was achieved using (*S*,*S*)-*N*-*i*Pr-2,2′-bipyrrolidine **5**, with which an ee value of 96% in compound **3e** was attained (Table 1, entry 7). Comparatively, (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine **7** afforded Michael adducts with also excellent selectivity (90% ee, Table 1, entry 8). Unfortunately, no reaction occurred with diphenylprolinol silyl ether **8**, probably due to the steric hindrance of the catalyst.

In contrast to the previous procedure,[5f] the excess of ketone was pleasingly reduced from 10 to 5 equivalents without affecting the reaction outcome. Nevertheless, decreasing the amount of the amino ketone to 2 equivalents or the catalyst loading resulted in a slow reaction rate and led to many by-products. Therefore, 5 equivalents of Michael donor and 15 mol% of organocatalyst were found to be the optimal quantities and the excess of amino ketone can be easily recovered by flash column chromatography on silica gel and recycled for the next run.

In terms of stereoinduction, inversion of the diastereoselectivity to the *anti* adduct was expected because of hydrogen bonding.[6] However, in contrast to α-hydroxy acetone **1b**, steric hindrance of α-NHTs-acetone **1e** seems to prevent internal hydrogen bonding and consequently favour *trans* enamine formation. Indeed, the same major diastereoisomer was formed using either pyrrolidine **6** or chiral diamines **5** and **7** which is consistent with the absence of hydrogen bonding (Table 1, entry 3 *vs.* entries 7, 8). To confirm the relative configuration, we performed the reaction with the protected *N*,*N*-Me,Ts-aminoacetone **1i**.

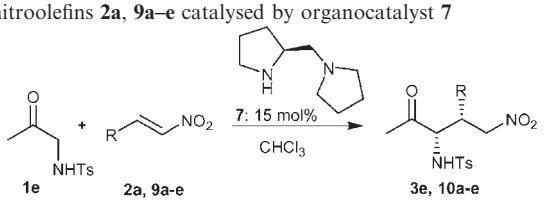
Unfortunately, no reaction occurred probably due to the steric hindrance of the α-aminoketone (Table 1, entry 10). Thus, the observed *syn* selectivity for the adduct **3e** is in accordance with Seebach's acyclic synclinal model.[9] According to steric shielding, the less hindered *Si*,*Re* transition state is well favoured in comparison with the *Re*,*Si* transition state. We assigned the absolute configuration *S*,*R* for the Michael adduct by comparison with analogous compounds resulting from (*S*,*S*)-*N*-*i*Pr-2,2′-bipyrrolidine-catalysed conjugate addition of ketones to β-nitrostyrene (Scheme 2).[5f]

To probe the scope of the reaction, we then tested the conjugate addition of α-NHTs-acetone **1e** to various nitroolefins **9a–e** catalysed by (*S*,*S*)-*N*-*i*Pr-2,2′-bipyrrolidine **5**. Unfortunately, catalyst **5** was substrate-dependent, and it was not possible to apply our previous conditions to other nitroolefins. Thus, we turned our attention towards (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **7** which seemed more broadly applicable. The enantioselectivities are within the excellent results obtained previously, ranging from 89% to 97% ee, with regard to the nature of the aromatic substituent (Table 2). Interestingly, the diastereoselectivity can be improved by decreasing the electron density of the aryl moiety following this order: 3,4-$CH_2$-dioxyPh **9d** = 4-MeOPh **9c** < 4-MePh **9a** = Ph **2a** < 4-ClPh **9b**. Seemingly, the reaction rate depends on the




**Scheme 2** Postulated transition state for the observed selectivity.

**Table 2** Asymmetric conjugate addition of α-NHTs-aminoacetone **1e** to nitroolefins **2a**, **9a–e** catalysed by organocatalyst **7**




| Entry | R | Time/ h | Yield[a] (%) | dr[b] (*syn* : *anti*) | ee[c] (%) |
|---|---|---|---|---|---|
| 1[d] | Ph (**2a**) | 14 | 80 | 85 : 15 | 90 |
| 2 | 4-MePh (**9a**) | 14 | 85 | 86 : 14 | 93 |
| 3 | 4-ClPh (**9b**) | 14 | 79 | 90 : 10 | 90 |
| 4 | 4-MeOPh (**9c**) | 36 | 85 | 83 : 17 | 89 |
| 5 | 3,4-$CH_2$-dioxyPh (**9d**) | 36 | 86 | 83 : 17 | 97 |
| 6 | 2-Thienyl (**9e**) | 14 | 83 | 88 : 12 | 90 |

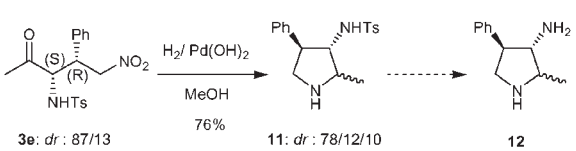
[a] Isolated yields after flash column chromatography on silica gel. [b] Determined by chiral SFC on the crude material. [c] Enantiomeric excess of the major diastereoisomer determined by chiral SFC on the purified product. [d] See typical procedure.[14]

electron density of the aromatic ring, with electron rich nitroolefins as the less reactive Michael acceptors (Table 2, entries 4, 5). This methodology is also suited to heteroaromatic nitroolefins such as 2-thienyl nitroalkene **9e** (90% ee, Table 2, entry 6). The reaction proceeds in high yields whatever the donor substrate.

The methodology presented herein provides an easy and convenient way of synthesizing optically active 2-aryl-3-amino-disubstituted γ-acetyl nitro compounds in one step with high enantioselectivity (up to 97% ee). These useful synthons can be further converted into a wide array of interesting building blocks such as 2-methyl-3-amino-4-aryl pyrrolidine **12** derivatives following the hydrogenation procedure described by List *et al.* (Scheme 3).[5a] These units are common structural motifs found in many natural and non-natural products that possess important biological properties (*i.e.* antimicrobial agents,[10] antibacterial agents,[11] dopamine $D_3$ receptor ligands,[12] glutamate receptor ligands[13]).

Hence, hydrogenation of Michael adduct **3e** with $Pd(OH)_2$ in methanol and subsequent *in situ* reductive amination afforded 3-sulfonamide pyrrolidine derivative **11** in 76% yield as a mixture of three diastereoisomers: 78 : 12 : 10. The obtained protected pyrrolidine **11** can be transformed into 3-amino pyrrolidine **12** by suitable deprotection.

In conclusion we have disclosed the enantioselective organocatalytic conjugate addition of α-NHTs-acetone to nitrostyrene derivatives in good yields and with high diastereo- and enantioselectivities. The increase of the acidity of the α′-hydrogen can be tuned by the electron-withdrawing group strength, in order to only access the branched adducts. Furthermore, diastereoselectivity of α-amino ketones was inverted in comparison to α-hydroxyacetone due to the geometry of the enamine, which is probably controlled by steric hindrance and not by hydrogen bonding. Finally, the Michael adduct can be easily converted into 3-sulfonamide pyrrolidine derivatives.




**Scheme 3** Towards the synthesis of 3-amino pyrrolidine.

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