Organocatalytic and direct asymmetric vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes†

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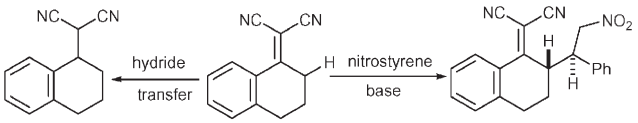
The first highly regio-, chemo-, diastereo- and enantioselective direct vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes is described, employing readily available chiral α,α-diarylprolinol salts as iminium organocatalysts.

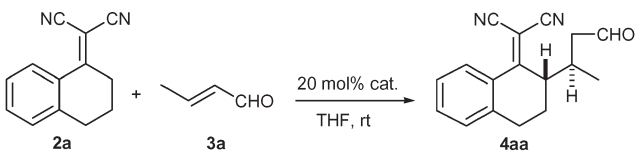
The Michael addition reaction is widely recognized as one of the most versatile carbon–carbon bond forming reactions in organic synthesis. Therefore, the development of enantioselective, catalytic protocols for this reaction have been the subject of intensive research.[1] Over the past few decades, significant advances have been made in the asymmetric Michael reactions of α,β-unsaturated ketones, esters, amides (imides) and nitroolefins.[2] However, the development of catalytic methods to promote the enantioselective Michael addition to α,β-unsaturated aldehydes,[3] especially for the construction of sp^3–sp^3 C–C bonds,[4] has proved to be more challenging. Furthermore, the nucleophiles employed in asymmetric Michael addition reactions generally have been limited to α-enolizable carbonyl compounds, nitroalkanes and organometallic reagents.[1] Expanding the scope of asymmetric Michael reactions with respect to both the electrophile and the nucleophile would be highly desirable. Recently, we have established that α,α-dicyanoolefin compounds can selectively behave as acceptors[5] or vinylogous donors[6,7] in Michael reactions under easily controllable conditions (eqn. (1)). In this paper, we describe the first asymmetric direct vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes using readily available chiral α,α-diarylprolinol[8] salts as iminium organocatalysts.[9] Notably the reactions are highly regio-, chemo-, diastereo- and enantioselective, which simultaneously give the multi-functional products with two vicinal chiral tertiary carbon centers.



(1)

While a simple tertiary amine can smoothly catalyze the Michael addition of an α,α-dicyanoolefin substrate to nitrostyrene by deprotonating the acidic γ-allylic C–H to generate the nucleophilic carbanion,[6a,c] we wondered if other activated α,β-unsaturated compounds could be successfully employed as Michael acceptors using the same strategy. It was found that no reaction occurred between α,α-dicyanoolefin **2a** and crotonaldehyde (**3a**) in the presence of catalytic NEt_3 or quinine (Table 1, entry 1). We then activated the Michael acceptor to promote this transformation. Gratifyingly, L-proline (**1a**) (Fig. 1, 20 mol%) was found to be a highly active catalyst at ambient temperature, apparently through an enal-activated intermediate.[3,4] A clean product **4aa** was obtained quantitatively with *anti*-selectivity (see ESI†),‡ while the ee was only moderate (Table 1, entry 2). Very poor results were observed when proline analogues **1b** and **1c** were applied (Table 1, entries 3 and 4). MacMillan's catalyst (**1d**) was inert in this reaction (Table 1, entry 5). On the other hand, a better ee (70%) was observed in the presence of OH-etherified (*S*)-α,α-diphenylprolinol (**1e**) and *para*-nitrobenzoic acid (PNBA) (Table 1, entry 6).[8] To our surprise, the OH-free prolinol **1f** also exhibited excellent catalytic activity in

Table 1 Screening studies of the organocatalytic vinylogous Michael addition of α,α-dicyanoolefin **2a** to crotonaldehyde **3a**[a]



2a **3a** **4aa**

Entry	Catalyst	Time/h	Yield[b] (%)	ee[c] (%)
1	NEt_3	24	0	—
2	**1a**	2	99	50
3	**1b**	2	99	0
4	**1c**	27	99	10
5	**1d**	24	0	—
6[d]	**1e**	20	83	70
7[d]	**1f**	**20**	**89**	**85**
8[d]	**1g**	20	76	83
9[d]	**1h**	20	63	78
10[d]	**1i**	20	72	79
11[d]	**1j**	20	87	79
12[d]	**1k**	20	81	81
13[d,e]	**1f**	**96**	**61**	**95**

[a] Reactions performed with 0.1 mmol **2a**. Method: 2.0 equiv. **3a**, 20 mol% catalyst in 1 mL THF at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 20 mol% PNBA was added. [e] At −50 °C.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and structural proofs for enantiopure **4aa**, **4ca** and racemic **5a**, NMR spectra and HPLC spectra. See DOI: 10.1039/b600647g

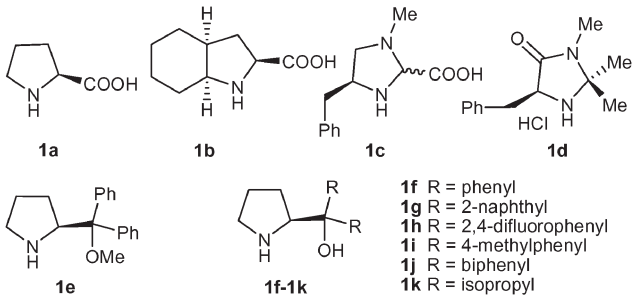


Fig. 1 Structures of the chiral secondary amine catalysts.

combination with PNBA, and an even higher enantioselectivity (85% ee) was obtained (Table 1, entry 7).§ In contrast, probably due to the formation of unreactive hemiaminal species, the results catalyzed by the free prolinols in the literature were generally poorer than those obtained using their etherified analogues.[10] Subsequently, various α,α-disubstituted prolinols **1g–1k** were screened and similar results achieved (Table 1, entries 8–12). By lowering the temperature to −50 °C, we obtained excellent enantioselectivity (95% ee) and good yield (61%) in the presence of **1f** and PNBA, while the reaction time was extended (Table 1, entry 13).

With the optimal reaction conditions in hand, we then examined a variety of α,α-dicyanoolefins (Fig. 2) and α,β-unsaturated aldehydes to establish the general utility of this novel asymmetric transformation (Table 2). The reaction's scope proved to be quite broad with respect to both the α,α-dicyanoolefins and β-substitution on the electrophiles. Only the *anti*-products were detected for all the reactions tested, except for acyclic substrate **2e** (Table 2, entry 19). High ee values were obtained in the reactions of linear or branched alkyl and aryl, or heteroaryl-substituted α,β-unsaturated aldehydes with cyclic and aromatic α,α-dicyanoolefins **2a–2d** (Table 2, entries 1–18). Up to 98% ee was found from the combination of β-isopropylacrolein **3e** and **2b** (Table 2, entry 8). In addition, an electron-donating substituent on the aryl ring of α,α-dicyanoolefin substrates tended to decrease their reactivity without affecting the excellent enantioselectivity (Table 2, entry 18). Moreover, a high ee was obtained in the case of acyclic aromatic substrate **2e** with a moderate yield, while a small amount of diastereomer (2% yield) was isolated with 48% ee (Table 2, entry 19). Simple aliphatic olefin **2f** also gave a good ee in this reaction (Table 2, entry 20). Notably, the desymmetrization of cyclic substrate **2g** was also found to be successful, and addition product **4ga**, with three chiral carbon centers, was generated with excellent diastereoselectivity (>99%), while the ee was moderate (Table 2, entry 21). However, it should be noted that α,β-unsaturated ketones show no reactivity in this catalytic system, and their reactions with the vinylogous donors remain unexplored.

To determine the absolute configuration of the vinylogous Michael addition products, a single crystal suitable for X-ray

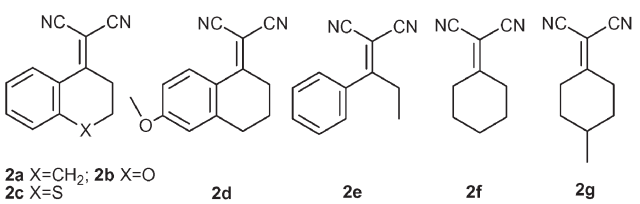
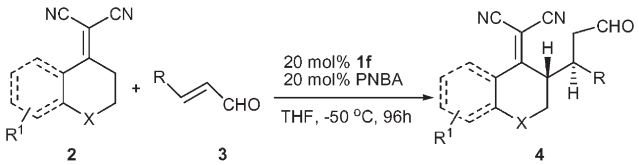


Fig. 2 Structures of the α,α-dicyanoolefins.

Table 2 Asymmetric vinylogous Michael addition of α,α-dicyanoolefins **2** to α,β-unsaturated aldehydes **3**[a]



Entry	Substrate **2**	R	Product **4**	Yield[b] (%)	ee[c] (%)
1	**2a**	Me (**3a**)	**4aa**	61	95
2	**2a**	*n*-Pr (**3b**)	**4ab**	58	94
3	**2a**	*n*-Bu (**3c**)	**4ac**	51	93
4	**2a**	Ph (**3d**)	**4ad**	80	89
5	**2b**	Me (**3a**)	**4ba**	83	95
6	**2b**	*n*-Pr (**3b**)	**4bb**	78	95
7	**2b**	*n*-Bu (**3c**)	**4bc**	80	94
8	**2b**	*i*-Pr (**3e**)	**4be**	69	98
9	**2b**	Ph (**3d**)	**4bd**	83	92
10	**2b**	*p*-Cl-Ph (**3f**)	**4bf**	60	90
11	**2b**	*p*-MeO-Ph (**3g**)	**4bg**	63	92[d]
12	**2b**	2-Furanyl (**3h**)	**4bh**	71	95[d]
13	**2c**	Me (**3a**)	**4ca**	91	92[d,e]
14	**2c**	*n*-Pr (**3b**)	**4cb**	75	93
15	**2c**	*n*-Bu (**3c**)	**4cc**	71	92
16	**2c**	*i*-Pr (**3e**)	**4ce**	55	94
17	**2c**	Ph (**3d**)	**4cd**	90	86
18	**2d**	Me (**3a**)	**4da**	48	95
19[f]	**2e**	Me (**3a**)	**4ea**	40	88
20	**2f**	Me (**3a**)	**4fa**	57	82[d]
21	**2g**	Me (**3a**)	**4ga**	49	68[d]

[a] Reactions performed with 0.1 mmol **2**. Method: 2.0 equiv. **3**, 20 mol% catalyst, in 1 mL THF at −50 °C for 96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis after conversion to the corresponding alcohol. [e] The absolute configuration was determined to be (C8*S*, C13*R*). [f] The minor diastereomer was isolated in about 2% yield with 48% ee.

crystallographic analysis was fortunately obtained from enantiopure **4ca**, bearing a sulfur atom. As shown in Fig. 3, it comprises a (C8*S*, C13*R*) configuration with an *anti*-structure.‡

Scheme 1 illustrates the synthetic versatility of the multifunctional products of this new methodology. A selective intramolecular vinylogous aldol reaction could easily be conducted with **4ad** under mild basic conditions, giving separable annulated diastereomeric products **5a** and **5b** without there being any effect on the ee. On the other hand, the carbonyl functionality could be selectively reduced to give **6** without affecting the C=C bond by using $NaBH(OAc)_3$ as the reductant. Compound **7**, with three contiguous chiral centers, was produced using the Hantzsch ester as the hydrogen source.[6a]

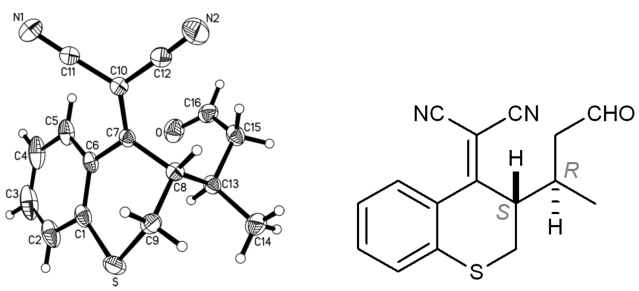
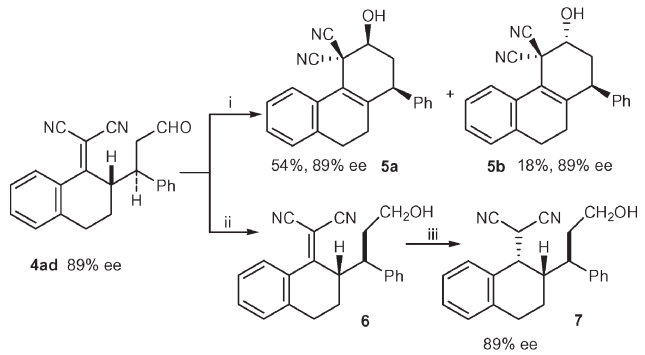


Fig. 3 Molecular structure of enantiopure **4ca** (ellipsoids of 30% probability).



Scheme 1 Selective transformation of Michael addition products.

In conclusion, we have successfully demonstrated the first asymmetric direct vinylogous Michael addition reactions of electron-deficient α,α-dicyanoolefins with α,β-unsaturated aldehydes, showing excellent regio-, chemo-, diastereo- and enantioselectivities. They employ readily available α,α-diarylprolinols as the iminium organocatalysts, which have been shown to be more effective than their etherified analogues. This novel methodology provides facile access to various enantioenriched multi-functional compounds that, to date, have not been reported in the literature. Current studies are well under way to expand the synthetic utility of this new reaction, as well as of this catalytic system in other asymmetric transformations.

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Notes and references

‡ Crystal data for **4aa**: $C_{17}H_{16}N_2O$, M = 264.32, orthorhombic, space group $P2_12_12_1$, a = 6.076(1), b = 13.777(3), c = 17.439(3) Å, U = 1459.74 (51) Å^3, Z = 4, crystal size 0.52 × 0.32 × 0.18 mm, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.076 mm^{-1}, reflections collected 2014, independent reflections 1903 (R_{int} = 0.0093), refinement by full-matrix least-squares on F^2, data/restraints/parameters 1903/0/183, goodness-of-fit on F^2 = 0.905, final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0377, $wR2$ = 0.0722, R indices (all data): $R1$ = 0.0663, $wR2$ = 0.0791, largest differential peak and hole 0.112 and −0.116 e Å^{-3}. CCDC 295476. Crystal data for **4ca**: $C_{16}H_{14}N_2OS$, M = 282.35, monoclinic, space group $P2_1$, a = 7.534(1), b = 7.610(1), c = 12.685(1) Å, β = 97.25(1)°, U = 721.52 (14) Å^3, Z = 2, crystal size 0.58 × 0.48 × 0.16 mm, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.221 mm^{-1}, reflections collected 3788, independent reflections 3158 (R_{int} = 0.0126), refinement by full-matrix least-squares on F^2, data/restraints/parameters 3158/1/183, goodness-of-fit on F^2 = 1.007, final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0362, $wR2$ = 0.0885, R indices (all data): $R1$ = 0.0472, $wR2$ = 0.0924, largest differential peak and hole 0.174 and −0.210 e Å^{-3}. CCDC 295477. Crystal data for **5a**: $C_{22}H_{18}N_2O$, M = 326.38, monoclinic, space group $P2_1/n$, a = 15.603(4), b = 6.159(1), c = 18.040(4) Å, β = 97.72(2)°, U = 1717.96 (73) Å^{-3}, Z = 4, crystal size 0.60 × 0.42 × 0.24 mm, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.078 mm^{-1}, reflections collected 3776, independent reflections 3203 (R_{int} = 0.0250), refinement by full-matrix least-squares on F^2, data/restraints/parameters 3203/0/228, goodness-of-fit on F^2 = 0.966, final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0448, $wR2$ = 0.0936, R indices (all data): $R1$ = 0.0815, $wR2$ = 0.1033, largest differential peak and hole 0.174 and −0.143 e Å^{-3}. CCDC 295478. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b600647g

§ Much less satisfactory results were obtained in the presence of **1f** without adding PNBA (48 h, 56% yield, 79% ee). For the screening of acid additives, see ESI.†

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