Tetrahedron Letters 49 (2008) 5389–5392

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective direct vinylogous Michael addition reaction catalyzed by organic molecules

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ARTICLE INFO

Article history:
Received 22 May 2008
Revised 14 June 2008
Accepted 1 July 2008
Available online 4 July 2008

Keywords:
Dicyanoolefin
Unsaturated aldehyde
Organocatalysis
Chiral azabicyclo catalyst
Michael addition

ABSTRACT

Chiral 2-azanorbornyl-3-methanol is used as an organocatalyst for the highly enantioselective direct vinylogous Michael addition reaction of vinyl malononitriles to α,β-unsaturated aldehydes. In many cases, the products can be obtained in almost optically pure form (>95% ee) after a single recrystallization.

Interest in the total synthesis of steroids has been widespread ever since the extensive research by Windaus and Wieland on the earliest known steroids. The cholesterol and cholic acid groups have received added impetus as the recognition of the great importance of steroids in medicine has grown.[1] Steroids play vital roles in a broad range of physiological processes across both plant and animal kingdoms.

In 1963, Torgov and Ananchenko disclosed a facile access to racemic estrone,[2,3] however, its modification to a simple enantioselective version has been problematic. This has encouraged chemists to explore new methodologies for the stereoselective construction of the steroidal scaffold.[4]

In conjunction with our interest in the synthesis of steroids as well as organocatalysts, we have been interested in the development of a new asymmetric Michael addition for the synthesis of estrone methyl ether. Very recently, it was reported that α,α-dicyanoolefin compounds can behave as acceptors or vinylogous donors selectively in Michael reactions under easily controllable conditions, which simultaneously give multi-functional products with two vicinal chiral tertiary carbon centers.[5] Among these, it was found that asymmetric direct vinylogous Michael addition reactions of electron-deficient α,α-dicyanoolefins with α,β-unsaturated carbonyl compounds could be carried out smoothly, catalyzed by (*S*)-α,α-diphenylprolinol, showing excellent regio-, chemo-, diastereo-, and enantioselectivities.[5a] Therefore, we tried to apply this strategy in the asymmetric synthesis of estrone methyl ether. The key step was the asymmetric Michael reaction of 2-(6-methoxy-2,3-dihydronaphthalen-4(1*H*)-ylidene) malononitrile to 2-methyl-cyclopent-2-enone (Scheme 1). However, using (*S*)-α,α-diphenylprolinol as catalyst gave only the racemic product in low yield. Thus, chiral azabicyclo catalysts, which match the structural requirements for some highly efficient catalytic systems,[6] were synthesized and applied in this Michael reaction (Fig. 1). Unfortunately, similar results were obtained. However, we were pleased to find that good reactivity and enantioselectivity were observed, when the chiral azabicyclo catalysts were applied in the vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes.

In this Letter, we report the application of (1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane-3-*exo*-bis(phenyl)methanol as an efficient organocatalyst for the enantioselective vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes. In many cases, the products were obtained in almost enantiomerically pure form (>95% ee) after a single recrystallization.

Our initial studies began with reaction of vinyl malononitrile **6a** (Fig. 2) and crotonaldehyde **7a** in the presence of a catalytic amount of chiral 2-azanorbornyl derivative **1**. In the presence of 20 mol % of **1** in THF at room temperature, the reaction of **6a** with **7a** gave the desired product **8aa** in good yield (89%), while the ee was quite poor (Table 1, entry 1). No reaction occurred when derivative **2** was used as the chiral catalyst, even though *para*-nitrobenzoic acid (PNBA **II**) was included as an additive (Table 1, entries 2 and 3). Thus, tertiary amine catalysts were completely inert in the vinylogous Michael addition of a vinyl malononitrile and an α,β-unsaturated aldehyde. We were delighted to find that a high

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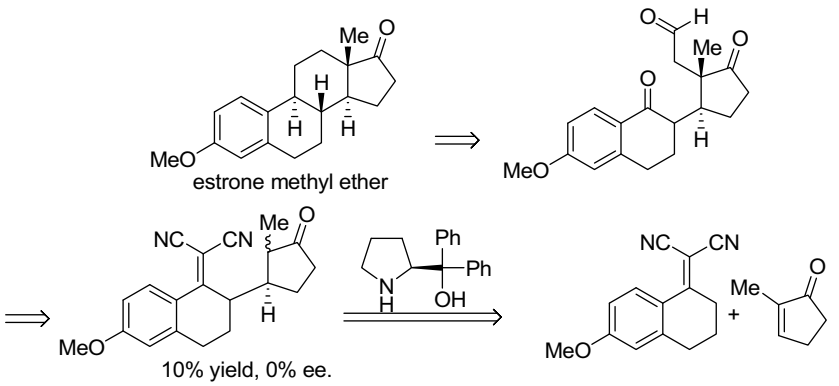
doi:10.1016/j.tetlet.2008.07.016



Scheme 1.

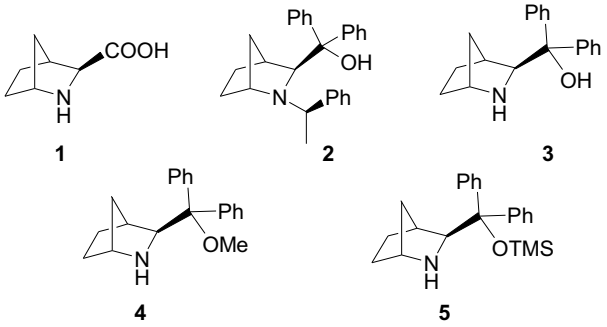


Figure 1. Chiral 2-azanorbornyl derivatives used.

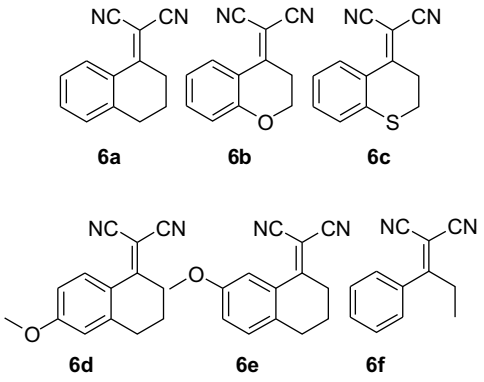


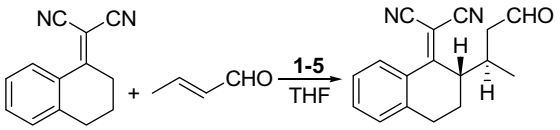
Figure 2. Structures of the starting vinyl malononitriles.

enantioselectivity of 87% could be obtained using (1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane-3-*exo*-bis(phenyl)methanol **3** as the catalyst (Table 1, entry 5). However, the product could only be obtained in low yield with moderate ee in the absence of PNBA. OH-etherified catalysts, which have been used successfully in many asymmetric reactions, were also tested in the vinylogous Michael addition. Under these reaction conditions, moderate enantioselectivities of 60% and 51% ee were observed using catalysts **4** and **5**, respectively.

Next, we investigated the effect of the reaction temperature, acid additives and solvents on the addition reaction using catalyst **3**. The results are summarized in Table 2.

Several acid additives were tested first (Fig. 3). From the results, additive **II** was superior to the other additives (Table 2, entries 1–4). Next, several solvents were screened for the reaction at room temperature. A drop in both reaction rate and enantiomeric excess was observed for solvents such as DCM, Et_2O, toluene, and CH_3CN

Table 1
Screening of chiral 2-azanorbornyl derivatives as catalysts for the vinylogous Michael addition reaction[a]

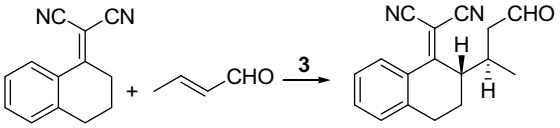


6a **7a** **8aa**

Entry	Catalyst	Additive	Yield[b] (%)	ee[c] (%)
1	**1**	—	89	24
2	**2**	—	0	—
3	**2**	**II**	0	—
4	**3**	—	41	81
5	**3**	**II**	84	87 (97)[d]
6	**4**	**II**	40	60
7	**5**	**II**	42	51

[a] Reactions performed with 0.1 mmol of **6a**, 0.4 mmol of **7a** and 20 mol % of catalyst in 1 mL of THF at rt for 20 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralcel AS)
[d] After recrystallization from *i*-PrOH.

Table 2
Investigation of the reaction temperature, acid additives, and solvents using catalyst **3**[a]



6a **7a** **8aa**

Entry	Additive	Solvent	Time	*T* (h) (°C)	Yield (%)[b]	ee[c] (%)
1	**I**	THF	40	rt	64	82
2	**II**	THF	20	rt	84	87
3	**III**	THF	20	rt	76	84
4	**IV**	THF	20	rt	74	82
5	**II**	DCM	20	rt	58	74
6	**II**	Et_2O	20	rt	62	76
7	**II**	Toluene	20	rt	67	82
8	**II**	MeCN	20	rt	79	83
9	**II**	MeOH	20	rt	0	—
10	**II**	THF	40	0	42	88
11	**II**	THF	24	−30	0	—
12[d]	**II**	THF	36	rt	74	81

[a] Reactions performed with 0.1 mmol of **6a**, 0.4 mmol of **7a**, 20 mol % of catalyst **3** and 20 mol % of additive.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralcel AS)
[d] Water (2 μL) was added.

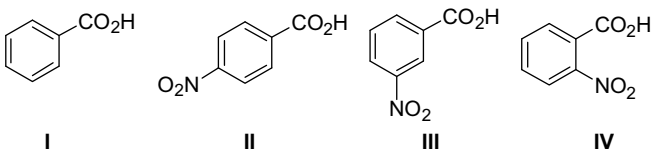


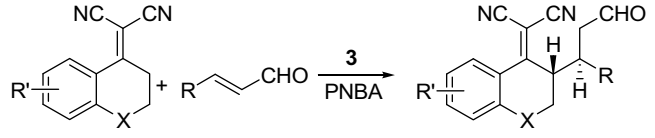
Figure 3. Structures of the additives.

(Table 2, entries 5–8). When the polar solvent methyl alcohol was tested, no product was obtained (Table 2, entry 9). In general, lowering the temperature resulted in a decrease of the reaction rate but an increase of the enantioselectivity. In the presence of 20 mol % of catalyst, an 88% ee of **8aa** was obtained at 0 °C, but the yield was only 42% after a long reaction time. Further decreasing the temperature to −30 °C resulted in no product even after 24 h (Table 2, entry 11). When a small amount of water was introduced to the reaction system, the desired product was formed in a slightly lower yield and enantioselectivity (Table 2, entry 12). From the results obtained, it can be seen that the combination of catalyst **3** (20 mol %) and PNBA **II** (20 mol %) exhibited the best catalytic activity in THF at room temperature.

Having established the optimal reaction conditions, we next examined a range of α,α-disubstituted vinyl malononitriles (Fig. 2) and α,β-unsaturated aldehydes in order to explore the generality of this catalytic system. The results are summarized in Table 3.

Several α,α-disubstituted vinyl malononitriles were tested in the reaction with crotonaldehyde. In all cases, high enantioselectivities were obtained (Table 3, entries 1–5). However, by introducing an electron-donating group into the vinyl malononitrile, we observed a decrease in the yields (Table 3, entries 4 and 5). Good ee values could also be obtained in the reaction of other alkyl α,β-unsaturated aldehydes (Table 3, entries 7–11). Unfortunately, when an aryl α,β-unsaturated aldehyde was tested, only moderate enantioselectivity was obtained (Table 3, entry 12). In all the reactions of cyclic substrates, only the *anti*-products were formed. When the acyclic substrate **6f** was tested, a major product was obtained in 71% ee, while the diastereomer was formed in 8% yield and 32% ee. When the unsaturated ketone, *trans*-4-phenyl-3-buten-2-one was tested under the same reaction conditions, no product was observed even after a long reaction time.

Table 3
Asymmetric vinylogous Michael addition of dicyanoolefins **6** to α,β-unsaturated aldehydes **7**[a]



Entry	6	R	Product	Yield[b] (%)	ee[c] (%)
1	**6a**	Me (**7a**)	**8aa**	78	87 (97)[d]
2	**6b**	Me (**7a**)	**8ba**	81	91
3	**6c**	Me (**7a**)	**8ca**	86	90 (>99)[d]
4	**6d**	Me (**7a**)	**8da**	56	86 (97)[d]
5	**6e**	Me (**7a**)	**8ea**	41	87 (96)[d]
6	**6f**	Me (**7a**)	**8fa**	42/8	71/32
7	**6b**	Et (**7b**)	**8bb**	75	88
8	**6c**	Et (**7b**)	**8cb**	83	88 (>99)[d]
9	**6d**	Et (**7b**)	**8db**	40	81
10	**6a**	*n*-Pr (**7c**)	**8ac**	60	80
11	**6c**	*n*-Pr (**7c**)	**8cc**	74	81
12	**6b**	Ph (**7d**)	**8bd**	80	57

[a] Reactions performed with 0.1 mmol of **6**, 0.4 mmol of **7**, 20 mol % of catalyst and 20 mol % of PNBA in 1 mL of THF at rt for 20 h.
[b] Isolated yield.
[c] Determined by HPLC analysis on a Chiral phase, the absolute configuration of the products was assigned by comparison with optical rotation and/or retention time on chiral HPLC in Ref. 5a.
[d] After recrystallization from *i*-PrOH.

In summary, this Letter has described an efficient method for the organocatalytic and asymmetric direct vinylogous Michael addition that employs electron deficient vinyl malononitriles as the nucleophilic species in the presence of a catalytic amount of chiral 2-azanorbornyl derivatives. The organocatalyst **3** exhibited high stereoselectivity and catalytic activity in the vinylogous Michael addition. The reaction features a metal-free approach, high efficiency of the catalyst, mild reaction conditions, high yields, and good enantioselectivities, providing a practical method to synthesize highly enantiopure multi-functional compounds. Many of these products can be obtained in almost optically pure form after a single crystallization from isopropanol. These results open a new avenue for the design of chiral azabicyclo[2.2.1] heptane analogues as organocatalysts. Further work on redesigning high affinity chiral 2-azanorbornyl derivatives applicable to the asymmetric synthesis of estrone methyl ether is in progress.

Typical procedure: (Table 3, entry 1): A mixture of **6a** (19.4 mg, 0.1 mmol), **7a** (32 μL, 0.4 mmol), catalyst **3** (5.6 mg, 0.02 mmol) and PNBA (3.4 mg, 0.02 mmol) in THF (1 mL) was stirred for 20 h at rt. Then the reaction mixture was quenched by adding 0.5 mL of 1 M HCl. The mixture was extracted with EtOAc and dried with anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel to give the desired product **8aa** in 78% yield and 87% ee; $[\alpha]_D^{22}$ −324 (*c* 0.81, DCM), R_f = 0.32 (hexane/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.28–7.26 (m, 1H), 3.04–3.02 (m, 1H), 3.00–2.96 (m, 1H), 2.91–2.84 (m, 1H), 2.45–2.41 (m, 2H), 2.38–2.19 (m, 2H), 2.12–2.04 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 177.4, 140.2, 133.8, 129.5, 129.2, 128.3, 127.0, 113.5, 113.3, 81.1, 48.7, 47.1, 28.8, 24.9, 24.5, 17.3; IR (KBr): ν 2226, 1762 cm^{-1}; MS: $C_{17}H_{16}N_2O$ 264.12 $[M]^+$. The enantiomeric ratio was determined by HPLC on a Chiralpak AS column (20% 2-propanol/hexane, 1 mL/min), *t* minor = 18.756 min, *t* major = 26.674 min.

Acknowledgments

We gratefully acknowledge the Nanyang Technological University, Ministry of Education and Biomedical Research Council (A*STAR Grant M47110003) for funding of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.016.

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