ORGANIC LETTERS

2010
Vol. 12, No. 6
1280−1283

Asymmetric Cyanation of Activated Olefins with Ethyl Cyanoformate Catalyzed by a Modular Titanium Catalyst

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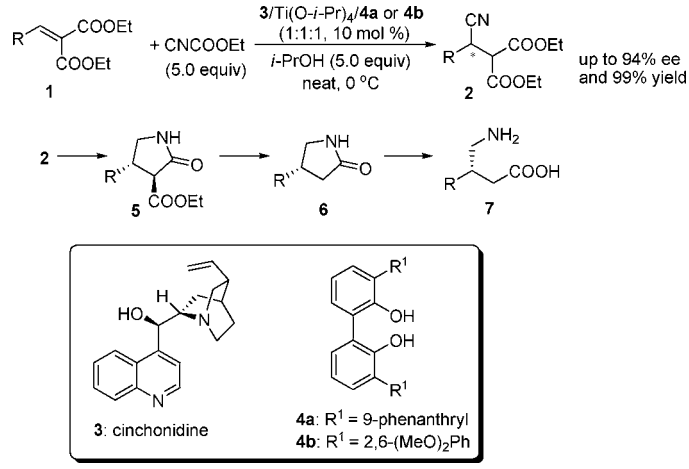
Received January 22, 2010

ABSTRACT



Asymmetric cyanation of a class of easily available olefins with a favorable cyanide source ethyl cyanoformate (CNCOOEt) was realized by an interesting modular catalyst. High yields and ee values were obtained for a range of substrates under solvent-free and mild reaction conditions. The products obtained could be easily transformed to the enantioenriched useful intermediates 5, 6, and pharmaceutically important γ-aminobutyric acid 7.

Compared with the intensively studied asymmetric catalytic cyanation of C═O and C═N double bonds,[1,2] asymmetric catalytic cyanation of the C═C double bond is less explored.[3] Until now, only two efficient catalyst systems were revealed, namely, the salen-Al(III) catalyst reported by the Jacobsen group for the cyanation of α,β-unsaturated imides[3a−d] and polymetallic Gd(III) catalysts reported by the Shibasaki group for the cyanation of α,β-unsaturated *N*-acylpyrroles[3e,f] and α,β-unsaturated ketones.[3g] Besides, Fochi, Ricci, and co-workers reported a quaternary ammonium salt catalyzed

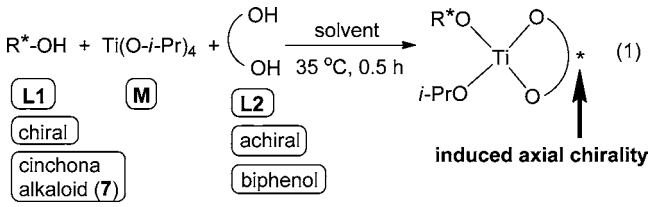
(1) For recent reviews on the asymmetric cyanation of aldehydes and ketones, see: (a) Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. *Coord. Chem. Rev.* **2008**, *252*, 593. (b) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146.

(2) For reviews on the asymmetric Strecker reaction, see: (a) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875. (b) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (c) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764. (d) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176. (e) Merino, P.; Marqués-lópez, E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219.

(3) (a) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (b) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (c) Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762. (d) Madhavana, N.; Weck, M. *Adv. Synth. Catal.* **2008**, *350*, 419. (e) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514. (f) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanaia, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820. (g) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 6072. (h) Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Synlett* **2008**, 1857.

10.1021/ol100169r
Published on Web 02/23/2010

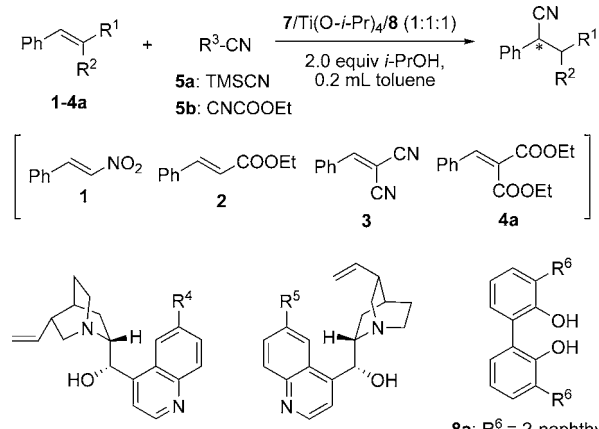
cyanation of β,β'-disubstituted nitroolefins, obtaining moderate yields and ee values.[3h] It is undoubted that more efforts are still required to contribute to this field. Significantly, the synthetic importance of this cyanide addition could be exemplified by the synthesis of various optically active γ-aminobutyric acids (GABA), which are pharmaceutically important for their anticonvulsant, antidepressant, and antineuropathic pain properties.[3a−f]



Recently, we disclosed an interesting modular catalyst generated from cinchona alkaloid, tetraisopropyl titanate (Ti(O-*i*-Pr)$_4$), and achiral 3,3′-disubstituted biphenol,[4] in which the achiral biphenol would selectively adopt a chirally matched configuration during the catalyst formation (eq 1).[5] As the catalytic property could be facilely tuned by altering either cinchona alkaloid or substituent on biphenol, this catalyst system proved generally efficient for the asymmetric cyanation of many kinds of substrates including aldehyde, ketone, aldimine, and ketimine. Encouraged by these features, we desired to extend this catalyst system to the challenging conjugate addition of cyanide to the C═C bond. After systematical screening and optimization, asymmetric catalytic cyanation of diethyl alkylidenemalonate with ethyl cyanoformate (CNCOOEt) as cyanide source was successfully achieved, affording the product in up to 99% yield and 94% ee under mild and neat reaction conditions. It should be noted the cyanide source used in the previous efficient cyanide conjugate addition was focused on trialkylsilyl cyanide (TMSCN[3a−f] and TBSCN[3g]), whereas the relatively cheap and less toxic alternative cyanide source, CNCOOEt, has never been explored before.[6,7]

Our preliminary studies showed that with TMSCN as the cyanide source and 20 mol % of quinidine **7a**/Ti(O-*i*-Pr)$_4$/biphenol **8a** (1:1:1) as the catalyst, the diethyl benzylidenemalonate **4a** exhibited the most promising enantioselectivity, although the reactivity was rather low (Table 1, entries 1−4). When the catalyst loading was decreased from 20 to 10 mol % and the temperature elevated from −20 to 0 °C, slightly improved reactivity but poor enantioselectivity was observed (Table 1, entry 4 vs 5). Screening commercially available cinchona alkaloids indicated cinchonidine **7d** was the optimal choice, giving 76% ee and moderate yield (Table 1, entries 6−8). Unexpectedly, when CNCOOEt was used instead of TMSCN as the cyanide source, the enantioselectivity was greatly enhanced to 89% ee (Table 1, entry 9).[8]

Table 1. Optimization of Reaction Conditions[a]



entry	olefin	R^3-CN	ligands	temp (°C)	time (h)	yield[c] (%)	ee[d] (%)
1	**1**	**5a**	**7a**, **8a**	−20	72	trace	
2	**2**	**5a**	**7a**, **8a**	−20	72	trace	
3	**3**	**5a**	**7a**, **8a**	−20	18	46	11
4	**4a**	**5a**	**7a**, **8a**	−20	58	27	42
5	**4a**	**5a**	**7a**, **8a**	0	19	50	20
6	**4a**	**5a**	**7b**, **8a**	0	19	67	−64
7	**4a**	**5a**	**7c**, **8a**	0	19	25	16
8	**4a**	**5a**	**7d**, **8a**	0	19	53	−76
9	**4a**	**5b**	**7d**, **8a**	0	36	50	−89
10	**4a**	**5b**	**7d**, **8b**	0	42	48	−92
11[b]	**4a**	**5b**	**7d**, **8b**	0	42	86	−93

[a] Unless otherwise noted, reactions were carried out with **7**/Ti(O-*i*-Pr)$_4$/**8** (1/1/1, 20 mol % for entries 1−4 and 10 mol % for others), olefin (0.1 mmol), cyanide reagent (0.2 mmol), and *i*-PrOH (0.2 mmol) in toluene (0.2 mL). [b] CNCOOEt (0.5 mmol), *i*-PrOH (0.5 mmol), and no solvent were used. [c] Isolated yield. [d] Determined by chiral HPLC. The minus sign signified opposite absolute configuration to others.

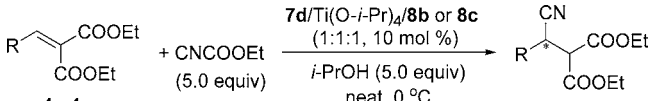
Then, some biphenols with other 3,3′-substituents were examined, and **8b** turned out to be the best, giving 92% ee (Table 1, entry 10). However, the reactivity of the reaction was still a big problem (42 h, 48% yield). Intensive studies showed that satisfying results could be obtained by increasing the stoichiometry of CNCOOEt as well as 2-propanol to 5.0 equiv under solvent-free conditions, delivering the product **6a** in 86% yield and 93% ee (Table 1, entry 11). Other parameters such as catalyst loading, temperature, and solvent were also investigated, but no better result was achieved. In addition, some other benzylidenemalonic esters were examined, and comparable ee values while inferior yields were afforded (for details, see the Supporting Information).

Under optimized conditions, a series of diethyl alkylidenemalonates were examined with results compiled in Table 2. Generally high yields and ee values were obtained regardless of the substituted position and electronic properties of the substituent on the benzene ring of the model substrate **4a** (Table 2, entries 1−12). The olefins derived from

(4) (a) Wang, J.; Hu, X. L.; Jiang, J.; Gou, S. H.; Huang, X.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8468. (b) Wang, J.; Wang, W. T.; Li, W.; Hu, X. L.; Shen, K.; Tan, C.; Liu, X. H.; Feng, X. M. *Chem.—Eur. J.* **2009**, *15*, 11642.

(5) For reviews on the asymmetric activation of racemic ligands, see: (a) Walsh, P. J.; Lurain, A. E.; Balsells, J. *Chem. Rev.* **2003**, *103*, 3297. (b) Faller, J. W.; Lavoie, A. R.; Parr, J. *Chem. Rev.* **2003**, *103*, 3345. (c) Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369. (d) Ding, K.; Du, H.; Yuan, Y.; Long, J. *Chem.—Eur. J.* **2004**, *10*, 2872.

Table 2. The Substrate Scope[a]



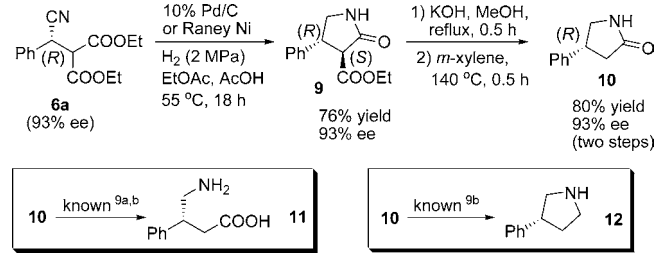
entry	R	substrate	yield (%)[d]	ee (%)[e]
1	Ph	**4a**	92	93 (*R*)
2	4-FC$_6$H$_4$	**4b**	97	92
3	4-ClC$_6$H$_4$	**4c**	87	91
4	4-BrC$_6$H$_4$	**4d**	90	89
5	4-MeC$_6$H$_4$	**4e**	91	92
6	4-MeOC$_6$H$_4$	**4f**	92	91
7	4-PhC$_6$H$_4$	**4g**	99	92
8	3-MeC$_6$H$_4$	**4h**	94	94
9	3-MeOC$_6$H$_4$	**4i**	84	92
10	3-PhOC$_6$H$_4$	**4j**	84	91
11	2-ClC$_6$H$_4$	**4k**	64	90
12		**4l**	91	90
13	2-naphthyl	**4m**	93	92
14	3-thienyl	**4n**	86	79
15[b]	c-hexyl	**4o**	53	88
16[b]	*i*-Pr	**4p**	68	86
17[b,c]		**4q**	82	80
18[b,c]	*n*-C$_5$H$_{11}$	**4r**	71	74

[a] Unless otherwise noted, reactions were carried out with **7d**/Ti(O-*i*-Pr)$_4$/**8b** (1:1:1, 10 mol %), olefin (0.1 mmol), CNCOOEt (0.5 mmol), and *i*-PrOH (0.5 mmol) at 0 °C for 72 h. [b] **8c** was used instead of **8b** for entries 15−18. [c] 0.1 mLof toluene was used as solvent. [d] Isolated yield. [e] Determined by chiral HPLC. The absolute configuration was assigned by converting **4a** to pyrrolidinone **10** and comparing its optical rotation with literature value.

2-naphthaldehyde and 3-thienyl aldehyde also showed good results (Table 2, entries 13 and 14). It is noteworthy that when it came to the aliphatic substrates, the biphenol **8c** proved superior to **8b**, giving the products with good ee values (Table 2, entries 15−18).

The synthetic utility of this methodology was then investigated. It was reported by a resolution strategy that

Scheme 1. Elaboration of Product **6a**



racemic **6a** could be elaborated to the optically active pyrrolidine **10** in seven steps,[9b] which could be further transformed to GABA and other useful compounds.[9a,b] In sharp contrast, with enantioenriched **6a** in hand herein, enantioenriched **10** could be readily prepared in three steps (Scheme 1). In addition, the optically active intermediate pyrrolidinone **9** could be facilely obtained by hydrogenation of **6a** (93% ee) with Raney nickel[9b] or Pd/C as catalyst. It should be noted when Raney nickel was used, addition of acetic acid was necessary to avoid partial racemization, which might be caused by the weak alkalinity of the catalyst prepared from Ni−Al alloy and NaOH (aq). The relative configuration of product was determined by H,H-NOESY spectroscopy, which indicated *trans*-**9** was formed selectively (for details, see the Supporting Information). Saponification of the ester **9** with alcoholic potassium hydroxide followed by acidification gave the corresponding acid, which was decarboxylated upon heating in *m*-xylene, providing 4-phenyl-2-pyrrolidinone **10** without loss of enantiopurity. The absolute configuration of **10** was determined to be *R* by comparison of optical rotation with reported value (see the Supporting Information). With **10** as material, the optically active GABA **11** and the pyrrolidine **12** could be easily prepared.[9] Similarly, 3-(aminomethyl)-5-methylhexanoic acid (pregabalin) and 3-(4-Cl-phenyl)-GABA (baclofen) could also be easily synthesized starting from enantioenriched **6c** and **6q**.

Interestingly, according to our previous studies,[4] when cinchonine **7c** or quinidine **7a** was subjected to catalyst preparation, the *S* configuration was selectively adopted by the biphenol **8a** to generate the complex **7a** (or **7c**)/Ti/(*S*)-**8a**, whereas the *R* configuration was preferred when cinchonidine **7d** was used, which was believed should also happen in the current catalyst system. As expected, when

(6) For the asymmetric cyanation of aldehydes and ketones with CNCOOEt as cyanide source, see: (a) Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636. (c) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021. (d) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505. (e) Belokon, Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433. (f) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413. (g) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592. (h) Belokon, Y. N.; Ishibashi, E.; Nomura, H.; North, M. *Chem. Commun.* **2006**, 1775. (i) Li, Q. H.; Chang, L.; Liu, X. H.; Feng, X. M. *Synlett* **2006**, 1675. (j) Gou, S. H.; Chen, X. H.; Xiong, Y.; Feng, X. M. *J. Org. Chem.* **2006**, *71*, 5732. (k) Gou, S. H.; Wang, J.; Liu, X. H.; Wang, W. T.; Chen, F. X.; Feng, X. M. *Adv. Synth. Catal.* **2007**, *349*, 343. (l) Gou, S. H.; Liu, X. H.; Zhou, X.; Feng, X. M. *Tetrahedron* **2007**, *63*, 7935. (m) Chen, S. K.; Peng, D.; Zhou, H.; Wang, L. W.; Chen, F. X.; Feng, X. M. *Eur. J. Org. Chem.* **2007**, 639. (n) Wang, W. T.; Gou, S. H.; Liu, X. H.; Feng, X. M. *Synlett* **2007**, 2875. (o) Belokon, Y. N.; Clegg, W.; Harrington, R. W.; Ishibashi, E.; Nomura, H.; North, M. *Tetrahedron* **2007**, *63*, 9724. (p) Peng, D.; Zhou, H.; Liu, X. H.; Wang, L. W.; Chen, S. K.; Feng, X. M. *Synlett* **2007**, 2448. (q) Reference 4b.

(7) For the asymmetric cyanation of aldimines and ketimines with CNCOOEt as cyanide source, see: Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 15118, and reference 4b.

(8) When TMSCN was used as cyanide source, mono- and di-TMS biphenol were detected by TLC in the reaction mixture. So as the reaction proceeded, the catalyst might be partially decomposed. In contrast, CNCOOEt was much less reactive than TMSCN to react with biphenol. In fact, no ethoxyformate protected biphenol was observed. Therefore, it might be one of the reasons for the fact that CNCOOEt gave better result. Also, it could not be ruled out the possibility that different reaction pathway might go for these two structurally total different cyanide sources.

(9) (a) Sobocinska, M.; Zobacheva, M. M.; Perekalin, V. V.; Kupryszewski, G. *Pol. J. Chem.* **1979**, *53*, 435. (b) Zelle, R. Z. *Synthesis* **1991**, 1023. (c) Martinez, C. A.; Hu, S.; Dumond, Y.; Tao, J.; Kelleher, P.; Tully, L. *Org. Process. Res. Dev.* **2008**, *12*, 392.

(*R*)- or (*S*)-3,3′-di-2-naphthyl-1,1′-bi-2-naphthol was used instead of the biphenol **8a** in the catalyst (**7d**/Ti/**8a**) for the cyanation of the olefin **4a**, the (*R*)-isomer gave a better result.[10]

In summary, asymmetric cyanation of a class of easily available α,β-unsaturated carboxylic derivatives with a favorable cyanide source (CNCOOEt) was realized by an interesting modular titanium catalyst. High yields and ee values were generally obtained for a range of substrates under solvent-free and mild reaction conditions. Moreover, the products could be easily transformed to many enantioenriched compounds of great synthetic utility and pharmaceutical importance. Compared with the previously reported methodologies, the present protocol held its own merits with regard to supplying key precursors for the GABA synthesis: (1) α,β-unsaturated diester was potentially advantageous in view of its low cost and facile availability/preparation;[11] (2) the cyanide source (CNCOOEt) employed herein was relatively cheap and less toxic, which would benefit the practical handling. Detailed mechanism studies and further application of this catalyst system to other reactions are underway.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 20732003 and 20872097), PCSIRT(No. IRT0846), and the Major State Basic Research and Development Program (No. 2010CB833300) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR analysis.

Supporting Information Available: Experimental details and analytic data (NMR, HPLC, and ESI-HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Reactions were carried out with cinchonidine **7d**/Ti(O-*i*-Pr)$_4$/(*R*)- or (*S*)-3,3′-di-2-naphthyl-1,1′-bi-2-naphthol (1/1/1, 10 mol %) as catalyst, olefin **4a** (0.1 mmol), CNCOOEt (0.2 mmol), and *i*-PrOH (0.2 mmol) in toluene (0.2 mL) for 45 h at 0 °C. Product **6a** was obtained in 33% yield with 91% ee for (*R*)-3,3′-di-2-naphthyl-1,1′-bi-2-naphthol and 23% yield with 85% ee for (*S*)-enantiomer.

(11) α,β-Unsaturated diesters could be prepared in a single step by Knoevenagel condensation of the corresponding aldehydes and diethyl malonate, both of which were very cheap and easily available. In fact, α,β-unsaturated diester has been employed as key intermediate for the large-scale synthesis of (*S*)-(+)-3-isobutyl-GABA (pregabalin). However, due to lack of efficient asymmetric method for the cyanation step, resolution procedures were generally involved in these processes (see: reference 9c and Silverman, R. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3500, and references therein).