

Catalytic Asymmetric Conjugate Addition of α -Cyanoketones for the Construction of a Quaternary Stereogenic Center

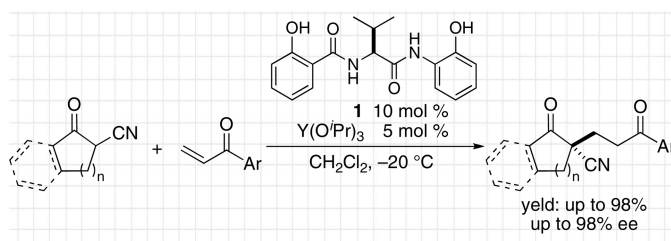
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ABSTRACT

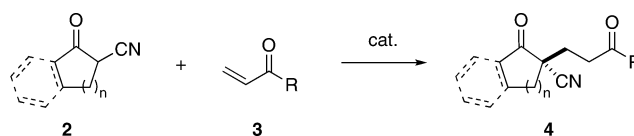


The catalytic asymmetric conjugate addition of α -cyanoketone pronucleophiles to vinyl ketones promoted by a Y/1 catalyst is described. High enantioselectivity was observed for a range of aromatic vinyl ketones, providing 1,5-dicarbonyl compounds bearing an all-carbon quaternary stereogenic center. The product was successfully converted to a spiro-piperidine entity and a bicyclo[3.3.0]octane framework through either the reduction of nitrile or intramolecular pinacol coupling.

The construction of highly functionalized organic molecules containing an all-carbon quaternary chiral center by asymmetric catalysis remains a formidable task in modern organic synthesis.¹ Recent advances in this field revealed that the catalytic asymmetric conjugate addition of active methine pronucleophiles to electron-deficient alkenes is a highly versatile strategy for producing this class of compounds bearing functional groups that are amenable to subsequent manipulation.² Extensive studies have been devoted to the development of asymmetric conjugate addition using α -substituted β -dicarbonyl compounds as pronucleophiles for the construction of an all-carbon quaternary stereogenic center;³ however, related transformations using α -cyanocarbonyl compounds have been less explored.^{4,5} The rich chemistry of functional group interconversion of nitriles allows for the

elaboration of the conjugate addition products. Previously, we reported that a rare earth metal (RE)/amide-based ligand **1** catalytic system is quite effective for a catalytic asymmetric Mannich-type reaction of α -cyanoketones **2** with switchable diastereoselection depending on the choice of RE.⁶ In our continuing efforts to expand the utility of the RE/**1** catalytic system,^{7–9} we applied the RE/**1** catalyst to the asymmetric conjugate addition of α -cyanoketones **2** to vinyl ketones **3**, affording 1,5-dicarbonyl compounds bearing an all-carbon

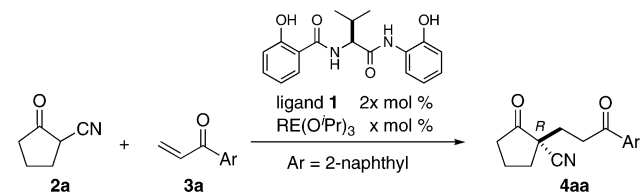
Scheme 1. Catalytic Asymmetric Conjugate Addition of α -Cyanoketones



(1) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, 37, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, 40, 4591. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5363. (d) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.

quaternary stereogenic center (Scheme 1). Facile transformation allowed for access to enantioenriched spiro-piperidine and bicyclo[3.3.0]octane entities.

Table 1. Catalytic Asymmetric Conjugate Addition of α -Cyanoketones Promoted by a RE/1 catalyst^a



entry	RE	x	solvent	time (h)	yield ^b (%)	ee ^c (%)	config
1	Sc	10	AcOEt	24	18	2	R
2	Y	10	AcOEt	24	81	77	R
3	La	10	AcOEt	24	90	28	S
4	Pr	10	AcOEt	24	96	24	S
5	Sm	10	AcOEt	24	80	4	S
6	Gd	10	AcOEt	24	86	26	R
7	Er	10	AcOEt	24	86	9	R
8	Yb	10	AcOEt	24	37	14	S
9	Y	10	THF	24	88	12	R
10	Y	10	DMF	24	81	1	R
11	Y	10	toluene	24	83	95	R
12	Y	10	CH ₂ Cl ₂	24	88	99	R
13	Y	5	CH ₂ Cl ₂	24	89	97	R

^a **2a**, 0.3 mmol; **3a**, 0.2 mmol. ^b Determined by ¹H NMR with Bn₂O as an internal standard. ^c Determined by HPLC analysis.

Initial attempts were devoted to identifying a suitable RE in combination with the amide-based ligand **1** in the reaction of 2-cyanocyclopentanone (**2a**) and naphthyl vinyl ketone (**3a**).¹⁰ The catalyst was prepared by mixing RE(OⁱPr)₃ and **1** in a 1:2 ratio, and the reactions were run with 10 mol % of catalyst (based on RE) in AcOEt solvent at −20 °C. As summarized in Table 1, Y(OⁱPr)₃ afforded the best enanti-

(2) For general reviews for catalytic asymmetric conjugate addition, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, 56, 8033. (c) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; p 569. (d) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, Germany, 2003; Suppl. 1, p 151. (e) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (f) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, 42, 1688. (g) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(3) For selected examples of catalytic asymmetric conjugate addition of α -substituted β -ketoesters for the construction of quaternary stereogenic centers, see: (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 16, 4057. (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, 124, 11240. (c) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, 45, 947. (d) Rigby, C. L.; Dixon, D. J. *Chem. Commun.* **2008**, 3798. (e) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraiishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, 42, 3796. (f) Ogawa, C.; Kizu, K.; Shimizu, H.; Takeuchi, M.; Kobayashi, S. *Chem. Asian J.* **2006**, 1–2, 121. (g) Alemán, J.; Reyes, E.; Richter, B.; Overgaard, J.; Jørgensen, K. A. *Chem. Commun.* **2007**, 3921. (h) Capuzzi, M.; Perdicchia, D.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, 14, 128. (i) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, 44, 105. (j) Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2006**, 45, 4966.

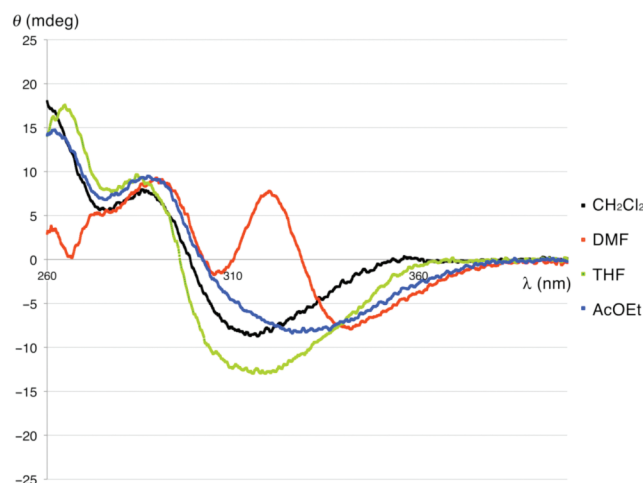


Figure 1. CD spectra of Y/1 catalyst in various solvents.

oselectivity among the RE examined (entry 2). The absolute configuration of the major enantiomer was not uniform in RE screening (entries 1–8), presumably because the structural flexibility of **1** would lead to the construction of RE/1 complexes with different structural motifs depending on slight differences in the ionic radii of the REs.¹¹ The highly coordinative nature of **1** through metal coordination and hydrogen bonding led us to investigate the solvent effect of the reaction (entries 9–13), revealing that CH₂Cl₂ was a suitable solvent in the present reaction to give the desired product **4aa** in 88% yield and 99% ee, likely due to the enhanced hydrogen bonding control for Y/1 complexation and/or the approaching direction of vinyl ketone **3** (entry 12). Indeed, CD spectra of the Y/1 solution in various

(4) For selected examples of catalytic asymmetric conjugate addition of α -substituted α -cyanocarbonyl pronucleophiles for the construction of quaternary stereogenic centers, see: (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, 114, 8295. (b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, 125, 11204. (c) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, 127, 1313. (d) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, 127, 8948. (e) Takenaka, K.; Minakawa, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2005**, 127, 12273. (f) Liu, T.-Y.; Li, R.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem.—Eur. J.* **2007**, 13, 319. (g) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, 129, 768. (h) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, 129, 1038. (i) Bell, M.; Poulsen, T. B.; Jørgensen, K. A. *J. Org. Chem.* **2007**, 72, 3053. (j) Marini, F.; Sternativo, S.; Del Verme, F.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2009**, 351, 1801. (k) Li, H.; Song, J.; Deng, L. *Tetrahedron* **2009**, 65, 3139. For a review, see: (l) Jautze, S.; Peters, R. *Synthesis* **2010**, 365.

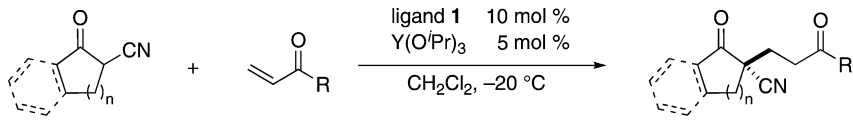
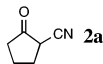
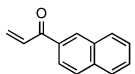
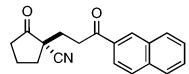
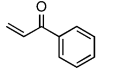
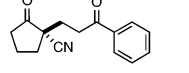
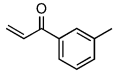
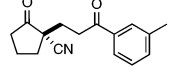
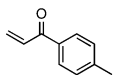
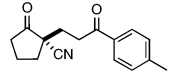
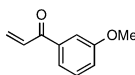
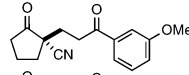
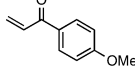
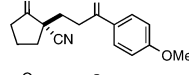
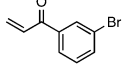
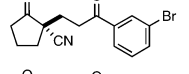
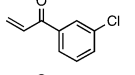
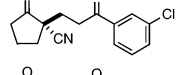
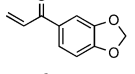
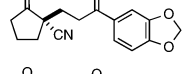
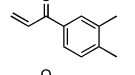
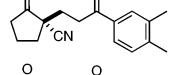
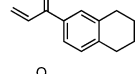
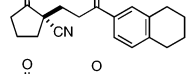
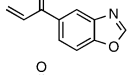
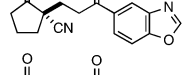
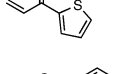
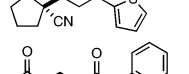
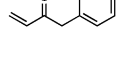
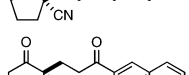
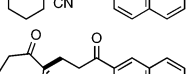
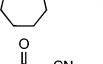
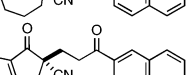
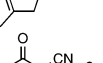
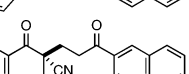
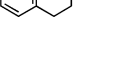
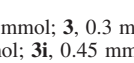
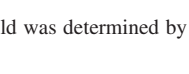
(5) For reviews on α -cyanocarboanions, see: (a) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, 31, 1. (b) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, 58, 1. (c) Fleming, F. F.; Iyer, P. S. *Synthesis* **2006**, 893.

(6) (a) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, 130, 5630. (b) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, 131, 3779.

(7) (a) Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett.* **1999**, 40, 1555. (b) Stodulski, M.; Jazwinski, J.; Mlynarski, J. *Eur. J. Org. Chem.* **2008**, 5553. (c) Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* **2008**, 130, 12588.

(8) For the utility of RE/1 catalysts and their related catalysts, see: (a) Nitabar, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, 49, 272. (b) Nitabar, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, 131, 13860. (c) Mashiko, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, 131, 14990.

Table 2. Catalytic Asymmetric Conjugate Addition of α -Cyanoketones **2** and Vinyl Ketones **3** Promoted by a Y/I Catalyst^a

						
entry	cyanoketone	enone	product	time (h)	yield ^b (%)	ee (%)
1	 2a	 3a	 4aa	24	82	97
2	2a	 3b	 4ab	24	80	81
3	2a	 3c	 4ac	24	93	98
4 ^c	2a	 3c	 4ac	24	83	97
5	2a	 3d	 4ad	24	82	87
6	2a	 3e	 4ae	24	80	93
7	2a	 3f	 4af	24	84	91
8	2a	 3g	 4ag	36	80	95
9 ^d	2a	 3h	 4ah	24	75	90
10 ^e	2a	 3i	 4ai	24	79	94
11	2a	 3j	 4aj	24	89	97
12	2a	 3k	 4ak	24	60	95
13	2a	 3l	 4al	24	88	86
14	2a	 3m	 4am	24	98	84
15	2a	 3n	 4an	48	54	69
16	 2b	3a	 4ba	48	64	86
17	 2c	3a	 4ca	48	73	95
18	 2d	3a	 4da	24	82	70
19	 2e	3a	 4ea	48	48	88

^a **2**, 0.45 mmol; **3**, 0.3 mmol. ^b Isolated yield. ^c With 1.1 g of **3c** used. ^d Yield was determined by ¹H NMR analysis with Bn₂O as an internal standard. ^e **2a**, 0.3 mmol; **3i**, 0.45 mmol.

solvents showed different patterns, suggesting that chirally different complexes would be formed depending on the properties of the solvent (Figure 1). The reaction with the catalyst prepared from different ligand/metal ratios indicated that ligand **Y**/**1** = 1:2 gave the best results.¹² Catalyst loading can be reduced to 5 mol % to complete the reaction with marginal loss of enantioselectivity (entry 13).

Having developed a suitable catalytic system for the asymmetric conjugate addition of α -cyanoketone and vinyl ketone, we then examined the substrate scope of the catalytic asymmetric conjugate addition (Table 2).^{13,14} Whereas a loss in enantioselectivity was detected in the reaction with a vinyl ketone bearing no substituents on the aromatic ring (**3b**) (entry 2), vinyl ketones with substituents at the *meta* or *para* position of the aromatic ring provided the corresponding products with high enantioselectivity regardless of their electronic nature (entries 3–12). The reaction can be run on a gram scale without any problem (entry 4). Vinyl ketones bearing a coordinative benzoxazole group or a thiophene were also applicable, albeit with lower enantioselectivity (entries 13 and 14). A significant decrease in enantioselectivity was observed with vinyl ketone **3n**, likely because the preferred flat conformation of vinyl ketones is privileged in the asymmetric environment of the catalyst (entry 15).¹⁵ The reaction using 2-cyanocyclohexanone (**2b**) or 2-cyanocycloheptanone (**2c**) proceeded sluggishly to give the corresponding products (entries 16 and 17). Phenyl-fused cyanoketones **2d** and **2e** afforded lower enantioselectivity in the present catalytic system (entries 18 and 19).

(9) For selected examples of small peptide-based asymmetric catalysis, see: (a) Oku, J.; Inoue, S. *Makromol. Chem.* **1979**, *180*, 1089. (b) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (c) Colonna, S.; Molinari, H.; Banfi, S.; Juliá, S.; Masana, J.; Alvarez, A. *Tetrahedron* **1983**, *39*, 1635. (d) Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047. (e) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. J. *Am. Chem. Soc.* **1996**, *118*, 4910. (f) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. C. *Nature* **2006**, *443*, 67. (g) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454. For reviews, see: (h) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779. (i) Blank, J. T.; Miller, S. J. *Biopolymers (Pept. Sci.)* **2006**, *84*, 38. (j) Kelly, D. R.; Roberts, S. M. *Biopolymers (Pept. Sci.)* **2006**, *84*, 74. (k) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759, and references cited therein.

(10) Ligand **1** was prepared from L-Val following the procedure described in the literature. Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342.

(11) More clear tendency between ionic radii of REs and stereoselectivity is observed for more structurally rigid catalysts: (a) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2567. (b) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165. (c) Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989.

(12) The catalyst prepared in a ratio of $Y(O^iPr)_3$ /**1** = 1:1 gave the product in 91% yield and 24% ee under otherwise identical conditions.

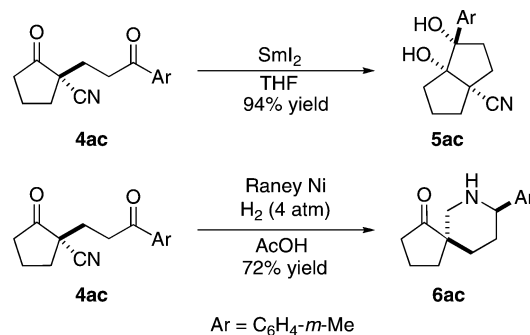
(13) The absolute configuration of **4aa** and **4ac** was determined by X-ray crystallographic analysis. See Supporting Information for details.

(14) The reaction using an acyclic α -cyanoketone or a β -substituted enone gave no desired products. Experimental details are summarized in Supporting Information.

(15) The reaction with enone **3n** using another RE/**1** catalyst did not improve the enantioselectivity. The results are summarized in Supporting Information.

The conjugate addition product bearing a quaternary stereogenic center and suitably installed functional groups was converted to enantioenriched bicyclic compounds by intramolecular cyclization (Scheme 2). Pinacol coupling of **4ac** mediated by SmI_2 exclusively afforded a diol with bicyclo[3.3.0]octane core **5ac** in 94% yield.^{16,17} Treatment of **4ac** with Raney nickel in glacial acetic acid under 4 atm H_2 atmosphere gave spiro-piperidine **6ac** in 72% yield.^{4f,18}

Scheme 2. Transformation of the Conjugate Addition Products



In summary, we documented a catalytic asymmetric conjugate addition of α -cyanoketones **2** and vinyl ketones **3** with RE/amide-based ligand **1** catalytic system, affording 1,5-dicarbonyl compounds bearing a quaternary stereogenic center. The product was transformed into enantioenriched bicyclic compounds bearing functional groups.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL100183S

(16) (a) Namy, J. L.; Girard, P.; Kagan, H. B. *New J. Chem.* **1977**, *1*, 5. (b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. For general reviews, see: (c) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (d) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (e) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607.

(17) Relative configuration was determined after converting to the corresponding cyclic carbonate. See Supporting Information for details.

(18) Relative configuration was determined by X-ray crystallographic analysis of the corresponding *p*-bromobenzoate. See Supporting Information for details.