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

Yuji Kawato, Noriko Takahashi, Naoya Kumagai,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

mshibasa@mol.f.u-tokyo.ac.jp; nkumagai@mol.f.u-tokyo.ac.jp

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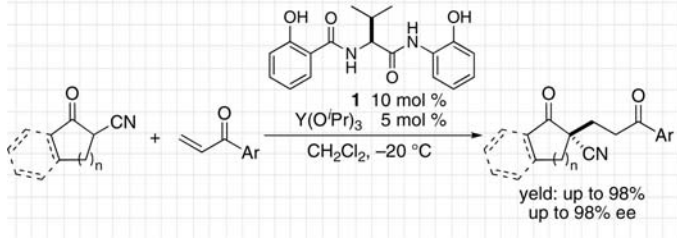
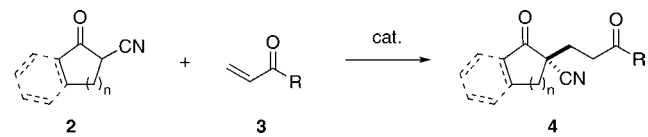
ABSTRACT



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



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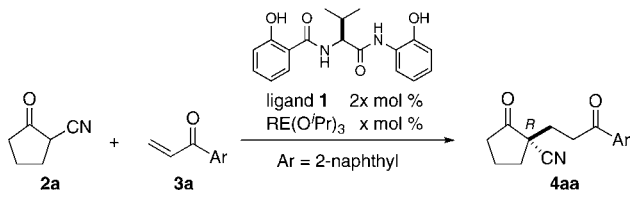
quaternary stereogenic center (Scheme 1). Facile transformation allowed for access to enantioenriched spiro-piperidine and bicyclo[3.3.0]octane entities.

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_2Cl_2	24	88	99	*R*
13	Y	5	CH_2Cl_2	24	89	97	*R*

[a] **2a**, 0.3 mmol; **3a**, 0.2 mmol. [b] Determined by ^{1}H NMR with Bn_2O 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(O^iPr)$_3$ 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(O^iPr)$_3$ afforded the best enantioselectivity 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 CH_2Cl_2 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

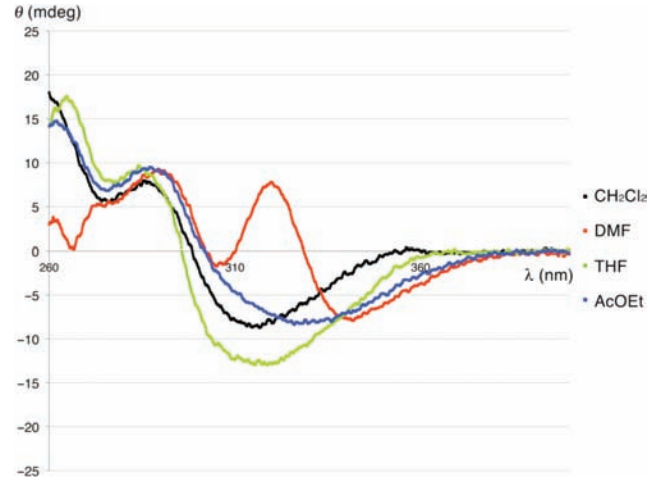


Figure 1. CD spectra of Y/**1** catalyst in various solvents.

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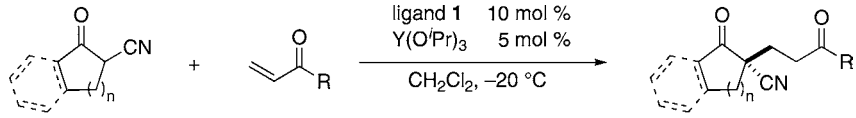
Table 2. Catalytic Asymmetric Conjugate Addition of α-Cyanoketones **2** and Vinyl Ketones **3** Promoted by a Y/**1** Catalyst[a]



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

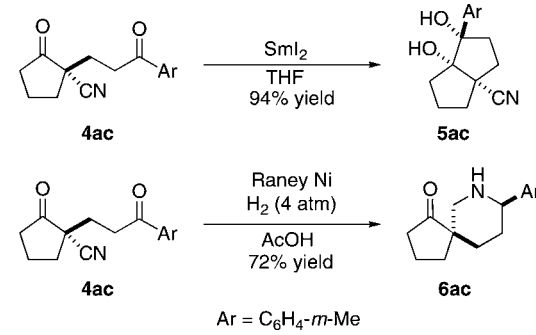
[a] **2**, 0.45 mmol; **3**, 0.3 mmol. [b] Isolated yield. [c] With 1.1 g of **3c** used. [d] Yield was determined by ^{1}H NMR analysis with Bn_2O as an internal standard. [e] **2a**, 0.3 mmol; **3i**, 0.45 mmol.

solvents showed different patterns, suggesting that chiroptically 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 thiophen 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).

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.

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(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.

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(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.