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Catalytic Enantioselective Construction of β-Quaternary Carbons via a Conjugate Addition of Cyanide to β,β-Disubstituted α,β-Unsaturated Carbonyl Compounds

Yuta Tanaka,[†] Motomu Kanai,*[,†] and Masakatsu Shibasaki*[,†,‡]

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

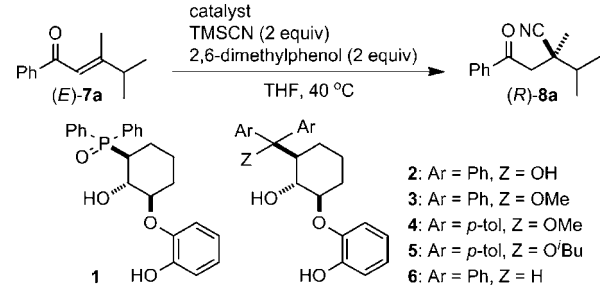
Received April 26, 2010; E-mail: kanai@mol.f.u-tokyo.ac.jp; mshibasa@bikaken.or.jp

Catalytic asymmetric construction of quaternary carbon stereocenters is an important and challenging objective in chemical synthesis.[1] Quaternary stereocenters can be constructed at the β-position of carbonyl groups by catalytic asymmetric conjugate addition of carbon-based nucleophiles to β,β-disubstituted α,β-unsaturated carbonyl compounds. Using alkyl and aryl nucleophiles, this type of reaction is successfully realized via Cu- and Rh-catalysis.[2] On the other hand, a variant using nucleophiles convertible to various functional groups is far less developed. Catalytic asymmetric conjugate addition of cyanide to α,β-unsaturated carbonyl compounds is a potential candidate for such a variant. Several reactions using β-monosubstituted substrates generating β-tertiary stereocenters have been reported.[3] Jacobsen's group recently extended their reaction to a β,β-disubstituted imide substrate by developing dinuclear {(salen)Al} catalysts, constructing a β-quaternary carbon containing a synthetically versatile cyanide group.[3c,4] The catalyst activity and substrate generality of this first isolated example, however, were not satisfactory. Here, we report a general catalytic enantioselective conjugate addition of cyanide to β,β-disubstituted enones and α,β-unsaturated *N*-acylpyrroles.

We previously developed a catalytic asymmetric conjugate addition of cyanide to β-monosubstituted α,β-unsaturated *N*-acylpyrroles and ketones using a Gd catalyst derived from ligand **1** (Gd-**1**).[3e,f] Based on this reaction, we first examined the Gd-**1** catalyst in the conjugate cyanation of (*E*)-3,4-dimethyl-1-phenyl-2-penten-1-one [(*E*)-**7a**] used as a model substrate (Table 1, entry 1). Although the desired cyanation proceeded regioselectively at the β-position, the yield of product **8a** was only 14%. Several catalytic metals were next studied in combination with ligand **1**, and the remarkable reactivity of a Sr catalyst was identified;[5,6] **8a** was obtained in 50% yield, although with only 20% ee (entry 2).

To improve the enantioselectivity, we then studied the effects of ligand structure using $Sr(O^iPr)_2$ as a metal source (entries 3−6). When Lewis basic phosphine oxide was replaced with a diphenylmethylhydroxy group, both yield and enantioselectivity were dramatically enhanced (ligand **2**, entry 3). Modifying the free alcohol to ethers further improved the enantioselectivity (ligand **3**−**5**, entry 4−6). Finally, the product was obtained with 97% ee using ligand **5**, containing a bulky di-(*para*-tolyl)methyl *iso*-butyl ether group (entry 6). Catalyst activity was also significantly improved by the use of ligand **5**. In sharp contrast, the use of control ligand **6**, lacking the ether group, resulted in poor enantioselectivity (entry 7). This result demonstrated that the Lewis basic ether functionality plays a critical role in the enantio-induction, possibly through stabilizing a defined higher-order catalyst structure (see below).[7] After further systematic optimization of the basic reaction parameters, the use of TBSCN as a cyanide source and toluene as a solvent allowed the catalyst loading to be reduced to 0.5 mol % without loss of product yield or enantioselectivety (entry 8).[8]

Table 1. Optimization of the Reaction Conditions



entry	catalyst	time (h)	yield (%)	ee (%)[b]
1	$Gd(O^iPr)_3$(10 mol %) + **1** (15 mol %)	16	14	15
2	$Sr(O^iPr)_2$ (10 mol %) + **1** (17 mol %)	16	50	20[c]
3	$Sr(O^iPr)_2$ (10 mol %) + **2** (17 mol %)	16	100	81
4	$Sr(O^iPr)_2$ (10 mol %) + **3** (17 mol %)	16	100	84
5	$Sr(O^iPr)_2$ (10 mol %) + **4** (17 mol %)	4	100	86
6	$Sr(O^iPr)_2$ (10 mol %) + **5** (17 mol %)	1	100	97
7	$Sr(O^iPr)_2$ (10 mol %) + **6** (17 mol %)	16	98	6[c]
8[a]	$Sr(O^iPr)_2$ (0.5 mol %) + **5** (0.8 mol %)	16	100	97

[a] Reaction run at room temperature using TBSCN and toluene instead of TMSCN and THF. [b] Determined by chiral HPLC. [c] (*S*)-**8a** was obtained.

The substrate scope was evaluated under the optimized reaction conditions (Table 2). Excellent enantioselectivity was realized from a wide range of β,β-disubstituted enones including aromatic- and aliphatic-substituted substrates. (*E*)- and (*Z*)-substrates produced opposing enantiomers (entries 1−10, 13 and 14). The reaction also proceeded from α,β,β-trisubstituted enone **7i** with high enantioselectivity. Although the product of asymmetric cyanation was a 1:1 mixture of diastereomers in this case, the diastereoselectivity was enriched, via epimerization of the α-stereocenter with base treatment of the crude mixture to 20:1 in high yield without effecting the excellent enantioselectivity (entry 15). In all entries, the reactions were completely 1,4-selective. The reaction was also applicable to synthetically useful ester equivalents, *N*-acylpyrroles[9] (Table 3).

To gain insight into the nature of this catalyst, the composition was investigated using ESI-MS. The Sr/ligand = 3:5 complex [MW = 2631 $(M + H)^+$] was observed as a single species under the optimized catalyst preparation conditions. This higher-order structure was stable, and the corresponding MS peak was observed as a major component, irrespective of the Sr/**5** ratio when the catalyst was prepared. This observation was consistent with the finding that consistently high enantioselectivity was obtained independent of the metal/ligand ratio.[8a]

Moreover, the complete 1,4-selectivity observed in the present conditions was partly due to the ability of the asymmetric catalyst to promote enantioselective conversion of free cyanohydrins (1,2-

[†] The University of Tokyo.
[‡] Current Address: Institute of Microbial Chemistry, Tokyo.

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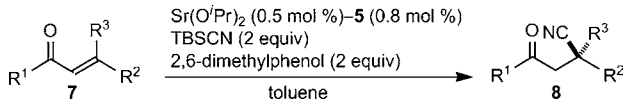
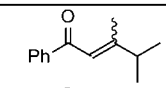
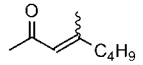
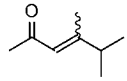
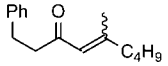
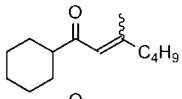
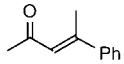
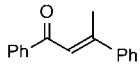
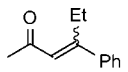
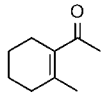
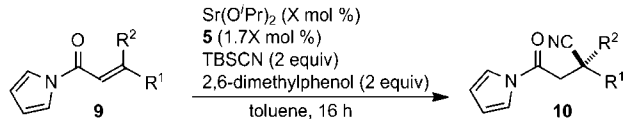
Table 2. Catalytic Enantioselective Conjugate Addition of Cyanide to β,β-Disubstituted Enones

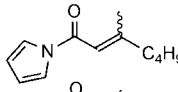
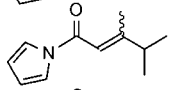
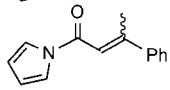


entry	substrate		temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1		(*E*)-**7a**	rt	16	100	97 (*R*)[c]
2		(*Z*)-**7a**	rt	16	100	97 (*S*)[c]
3		(*E*)-**7b**	rt	16	87	99 (+)[d]
4		(*Z*)-**7b**	rt	16	77	99 (–)[d]
5		(*E*)-**7c**	40	16	98	89 (*R*)[c]
6		(*Z*)-**7c**	40	1	100	99 (*S*)[c]
7		(*E*)-**7d**	40	2	79	99 (–)[d]
8		(*Z*)-**7d**	40	2	84	99 (+)[d]
9		(*E*)-**7e**	40	2	100	99 (+)[d]
10		(*Z*)-**7e**	40	2	100	99 (–)[d]
11		**7f**	50	16	74	99
12[e]		**7g**	50	16	100	99
13[e]		(*E*)-**7h**	50	16	70	89 (–)[d]
14[f]		(*Z*)-**7h**	50	2	80	98 (+)[d]
15[e,g]		**7i**	50	2	84[h] (dr = 20:1)[i]	99[j]

[a] Isolated yield. [b] Determined by chiral HPLC or GC. [c] The absolute configuration was determined. [d] Sign of the optical rotation of the product. [e] Reaction run using 2.5 mol % of Sr(O^{i}Pr)$_2$ and 4.2 mol % of **5**. [f] Reaction run using 10 mol % of Sr(O^{i}Pr)$_2$ and 17 mol % of **5**. [g] The crude mixture was treated with NaOMe/MeOH for 30 min at room temperature after workup. [h] Yield of *cis* (major) isomer. [i] Determined by NMR. [j] Ee of *cis* (major) isomer.

Table 3. Catalytic Enantioselective Conjugate Addition of Cyanide to β,β-Disubstituted α,β-Unsaturated *N*-Acylpyrroles

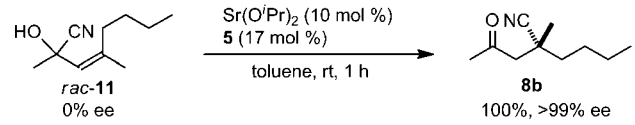


entry	substrate		X (mol %)	temp (°C)	yield (%)[a]	ee (%)[b]
1		(*E*)-**9a**	0.5	40	100	98 (–)[c]
2		(*Z*)-**9a**	2.5	40	73	95 (+)[c]
3		(*E*)-**9b**	0.5	40	100	95 (*R*)[d]
4		(*Z*)-**9b**	0.5	40	95	98 (*S*)[d]
5		(*E*)-**9c**	10	50	92	96 (+)[c]
6		(*Z*)-**9c**	2.5	50	100	99 (–)[c]

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Sign of the optical rotation of the product. [d] The absolute configuration was determined.

products) to the corresponding 1,4-products.[10] Thus, treatment of racemic cyanohydrin **11** with the catalyst (10 mol %) quantitatively produced **8b** with 99% ee (Scheme 1).[11] This result indicates that even if 1,2-addition of cyanide proceeded, the catalyst promoted retro-

Scheme 1. Catalytic Asymmetric Rearrangement of Cyanide



cyanation from the resulting cyanohydrin, and the subsequent irreversible asymmetric 1,4-cyanation produced the desired 1,4-product.

In summary, we developed the first general catalytic enantioselective conjugate addition of cyanide to β,β-disubstituted α,β-unsaturated carbonyl compounds by identifying a catalyst derived from Sr(O^{i}Pr)$_2$ and new chiral ligand **5**. Elucidation of the three-dimensional catalyst higher-order structure is currently ongoing.

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Supporting Information Available: Experimental procedures, reaction optimization, characterization of the products, and results of catalyst structural studies by ESI-MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For a catalytic enantioselective (up to 72% ee) conjugate addition of cyanide to β,β-disubstituted nitroalkenes, see: Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Synlett* **2008**, 1857.
(5) Other metals, including Ca and Ba, were less effective than Sr. Use of Sr(HMDS)$_2$ as a metal source gave comparable results to Sr(O^{i}Pr)$_2$. See SI.
(6) For the use of chiral Sr catalysts, see: (a) Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2430. (b) Kobayashi, S.; Yamaguchi, M.; Agostinho, M.; Schneider, U. *Chem. Lett.* **2009**, *38*, 296. (c) An alkaline earth metal (Ba)-**1** complex is an effective asymmetric catalyst for a Diels–Alder reaction: Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1070.
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(8) (a) For more details on optimization studies, see SI. (b) The consistent enantioselectivity (≥97% ee) was produced using TBSCN or TMSCN + 2,6-dimethylphenol, HCN, or TMSCN + MeOH as cyanating reagents in the presence of 10 mol % catalyst. Therefore, HCN should be the stoichiometric cyanide source in this reaction. (c) When the catalyst loading was 0.5 mol %, however, the use of TMSCN instead of TBSCN produced markedly lower enantioselectivity (50% ee). The concentration of HCN was much higher when using TMSCN than TBSCN in the presence of 2,6-dimethylphenol. A large excess of HCN would partially decompose the catalyst, leading to the significant difference in enantioselectivity especially when the catalyst loading was lowered.
(9) (a) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559. (b) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188. (c) For synthetically useful conversions of the products, see SI.
(10) The 1,2-adducts were not detected in any cases by TLC analysis during the reaction course. For previous examples in which 1,4-cyanation products were produced from kinetically formed 1,2-adducts via cyanide migration, see: Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255. and ref 3f.
(11) A crossover experiment revealed that this rearrangement was an intermolecular process. See SI.

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