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A Catalytic Enantioselective Conjugate Addition of Cyanide to Enones

Yuta Tanaka, Motomu Kanai,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo113-0033, Japan

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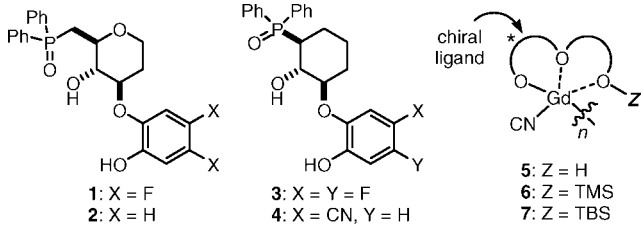
The asymmetric conjugate addition of cyanide to α,β-unsaturated carbonyl compounds is a highly versatile reaction. Significant progress was recently made in the catalytic asymmetric variant using α,β-unsaturated carboxylic acid derivatives (imides[1] and *N*-acylpyrroles[2]). Synthetically useful catalytic asymmetric conjugate addition of cyanide to enones, however, has yet to be developed.[3] This sharp contrast with respect to substrates is due to the ambident characteristics of enones. There are two possible reaction pathways from enones, 1,2-addition and 1,4-addition. Therefore, differentiation of the two pathways, in addition to enantioselection, is necessary. Catalytic control of even one of these two factors, however, is not an easy task. Here, we report the first synthetically useful catalytic enantioselective conjugate addition of cyanide to enones.

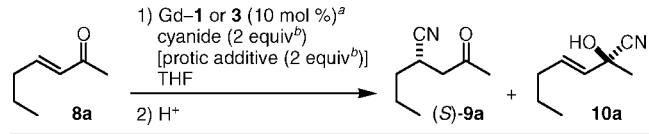
Previously, we developed an asymmetric conjugate addition of cyanide to α,β-unsaturated *N*-acylpyrroles using the Gd catalysts derived from ligands **1** and **3** in the presence of TMSCN and HCN or 2,6-dimethylphenol (DMP).[2] The active catalysts were polymetallic complexes **5** with defined higher-order structures (Gd:**1** = 2:3 and/or 4:5 + oxo, and Gd:**3** = 5:6 + oxo + OH) generated through modular self-assembly.[4] These complexes are multifunctional; gadolinium cyanide (or isocyanide) generated through transmetalation from TMSCN acting as a nucleophile, and an acidic proton (*Z* in **5**) incorporated from the protic additives acting as a turnover accelerator.[4]



We applied the Gd catalysts to an asymmetric conjugate addition of cyanide to enones. 3-Hepten-2-one (**8a**) was selected as a model substrate for initial optimization (Table 1). Preliminary ligand screening demonstrated a remarkable difference between the catalysts derived from **1** or **2** and **3**, and identified **3** as the more promising ligand in terms of regioselectivity (**9a/10a**) and enantioselectivity (entries 1 and 2). Conversely, Gd-**1/2** were completely 1,2-selective enantioselective catalysts at −60 °C; TMS-protected cyanohydrin (TMS-**10a**) was produced in 80% yield with 84% ee using 5 mol % of Gd-**2** (9 h in propionitrile, **9a/10a** = 1/>30).[5]

The effects of protic additives were then studied using Gd-**3**.[6] The addition of HCN did not change the reaction rate, however, but produced markedly lower 1,4-selectivity (entry 3). In contrast, a 1:1 ratio of TMSCN and DMP facilitated the reaction with complete 1,4-selectivity as well as improved enantioselectivity (70% yield and 84% ee; entry 4).[7] Lowering the reaction temperature, however, decreased 1,4-selectivity[8] with a gradual increase

Table 1. Optimization of the Reaction Conditions



entry	ligand	conditions	yield (%)[e]	**9a/10a**	ee (%)[g]
1	**1**	TMSCN[c] rt, 15 min	63%	19/81[f]	15[h]
2	**3**	TMSCN[c] rt, 18 h	62%	52/48[f]	40
3	**3**	TMSCN + HCN[d] rt, 18 h	67%	18/82[f]	53
4	**3**	TMSCN + DMP[b] rt, 1 h	70%	100/0	84
5	**3**	TMSCN + DMP[b] −20 °C, 24 h	40%	72/28	90
6	**3**	TMSCN + DMP[b] −40 °C, 45 h	44%	27/73	93
7	**3**	HCN[b] −20 °C, 41 h	37%	27/73	47
8	**3**	TBSCN + DMP[b] −20 °C, 24 h	77%	100/0	92

[a] $Gd(O^iPr)_3$ (10 mol %) + **1** (20 mol %) or $Gd(O^iPr)_3$ (10 mol %) + **3** (15 mol %); rt = room temperature. [b] Standard conditions. [c] Run using 1.5 equiv. [d] Reaction run using 1 equiv of TMSCN and 1 equiv of HCN. [e] Combined yield of **9a** and **10a**. [f] The 1,2-product was silylated in the reaction mixture. [g] The ee of **9a** determined by chiral GC. [h] (*R*)-**9a** was obtained.

in enantioselectivity (entries 4−6). Although TMSCN was completely converted to HCN under those conditions,[9] use of pure HCN produced much less satisfactory results (entry 7 vs 5), suggesting a key role of the silyl group for high 1,4-selectivity and enantioselectivity. Thus, the effects of the silyl group structure were studied using TBSCN in the presence of DMP (entry 8). As a result, the catalyst activity and 1,4-selectivity significantly improved, giving **9a** as the sole regioisomer in 77% yield with 92% ee.

Substrate scope was evaluated under the optimized reaction conditions (Table 2). Excellent to high enantioselectivity was produced not only from methyl ketones, but also from linear, branched, aryl, and cyclic enones. In the case of α,β-disubstituted enone **8 h** and cyclic enones **8i**, **8j**, and **8k**, the catalyst derived from electronically tuned ligand **4** afforded significantly higher enantioselectivity than **3**.[10] The catalyst loading could be reduced to 5 mol % (entries 2, 4, and 6). In all entries, the reactions were completely 1,4-selective. The products can be converted to synthetically useful keto carboxylic acid derivatives through acid hydrolysis without racemization.[10]

In addition to high enantioselectivity and wide substrate scope, it is noteworthy that the asymmetric rare earth metal catalyst selectively produced the 1,4-adducts from enones. Specifically, new reaction conditions using a 1:1 ratio of TBSCN and DMP were effective.[7] To gain insight into the origin of the pathway−selectivity, mechanistic information was collected, leading to two important findings.

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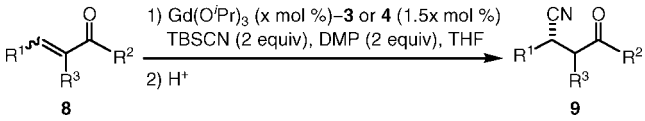
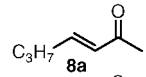
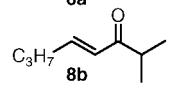
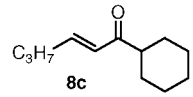
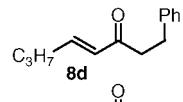
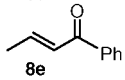
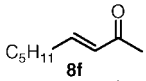
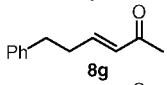
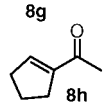
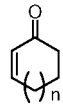
Table 2. Catalytic Enantioselective Conjugate Addition of Cyanide to Enones



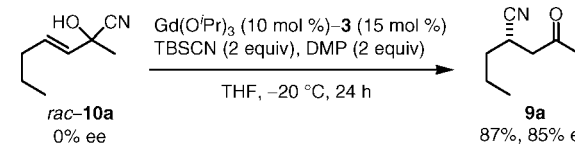
entry	substrate	temp (°C)	time (h)	yield (%)	ee (%)
1[a]	 **8a**	–20	24	77	92[f]
2[a,b]		–20	24	84	88[f]
3[a]	 **8b**	0	18	91	98
4[a,b]		0	18	80	94
5[a]	 **8c**	rt	15	94	93
6[a,b]		rt	12	87	94
7[a]	 **8d**	–20	18	100	90
8[a]	 **8e**	–20	24	100	88
9[a]	 **8f**	–20	18	77	90
10[a]	 **8g**	0	2	88	87
11[c]	 **8h**	0	24	67[d] (dr = 3.6:1)	95[d]
12[c,e]	 **8i**: n = 1	rt	4	90	81[f]
13[c]	**8j**: n = 2	rt	24	73	52
14[c]	**8k**: n = 3	rt	18	74	81

[a] Ligand **3** was used. [b] Reaction run using 5 mol % of catalyst. In other entries, 10 mol % of catalyst was used. [c] Ligand **4** was used. [d] Combined yield of cis (major) and trans isomers and enantiomeric excess of the cis isomer. [e] Reaction run using 2.5 equiv of TBSCN and 2.5 equiv of DMP. [f] The absolute configuration was determined to be (*S*).

First, whereas the Gd-**3** catalyst in the presence of TMSCN and DMP was a proton-containing poly-Gd complex (**5**: generated through protonolysis of **6**),[11] ESI-MS studies indicated that the asymmetric catalyst under the current optimized conditions was an *O*-*t*-butyldimethylsilylated complex (**7**).[10] This structural information is consistent with the experimental results; the silyl group significantly affected the reaction rate and regio- and enantioselectivities (Table 1, entries 5, 7, and 8). Together, the silylated complex might be a more efficient 1,4-selective catalyst than the proton-containing complex.[12] The complex contained a more robust silyl group when TBSCN was used (**7**) than when TMSCN was used (**6**), leading to stabilization of the silylated, 1,4-selective asymmetric catalyst.

Second, the Gd complex can enantioselectively convert free cyanohydrins to the corresponding 1,4-products.[13] Thus, treatment of racemic cyanohydrin **10a** under the reaction conditions produced 1,4-product **9a** in 87% yield with 85% ee (Scheme 1).[14] No reaction proceeded in the absence of the catalyst, indicating that the catalyst promoted retro-cyanation from the cyanohydrin (1,2-adduct) and the subsequent irreversible asymmetric 1,4-addition of cyanide. Cyanohydrin formation was detected by TLC analysis in the middle

Scheme 1. Catalytic Asymmetric Rearrangement of Cyanide



of the reaction in some entries of Table 2 (e.g., entries 4 and 6). The cyanohydrin was gradually converted to the 1,4-product according to the reaction progress. Therefore, the complete 1,4-selectivity depended on the ability of the enantioselective catalyst to promote both reversible 1,2-cyanation/retro-cyanation and irreversible 1,4-cyanation.[15]

In conclusion, we developed the first synthetically useful catalytic enantioselective conjugate addition of cyanide to enones. Combining the previous results,[5] both α-cyanohydrins (1,2-adducts) and *β*-cyano ketones (1,4-adducts) can be produced selectively from enones with high enantioselectivity. Studies are ongoing to improve catalyst turn-over and to extend these findings to quaternary carbon synthesis.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Review: Shibasaki, M.; Kanai, M. *Org. Biomol. Chem.* **2007**, *5*, 2027.
(5) For the catalytic enantioselective cyanosilylation of ketones using Gd-**2**, see: Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908.
(6) For examples of the acceleration effects of protic additives in catalytic asymmetric conjugate addition reactions: (a) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994.
(7) In the previous catalytic enantioselective conjugate addition of cyanide to α,*β*-unsaturated *N*-acylpyrroles (ref 2b), use of a slight excess of TMSCN to DMP was critical for high catalyst turnover and enantioselectivity, and the conditions of TMSCN:DMP = 1:1 were not effective. On the other hand, application of the previous conditions (2.5 equiv of TMSCN and 2 equiv of DMP) to the cyanation of enones resulted in partial formation of TMS-protected cyanohydrin (**9a**/TMS-**10a** = 75/25 in 65% combined yield at room temp). For detailed comparison between the previous and present reaction conditions (i.e., effects of the remaining TMSCN), see Supporting Information.
(8) This tendency indicates that **10a** and **9a** are kinetic and thermodynamic products, respectively: Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255.
(9) DMP was completely silylated based on TLC analysis.
(10) See Supporting Information for details.
(11) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438.
(12) Consistent with this hypothesis, preincubation of the Gd complex with a catalytic amount of TBSCN (10 mol %) produced markedly improved 1,4-selectivity (93/7) using TMSCN + DMP (1:1) as the cyanation reagent at −20 °C (cf. Table 1, entry 5). For further experimental support for this hypothesis, see Supporting Information.
(13) Analogous asymmetric rearrangement (1,2- to 1,4-adduct) of alkynyl groups was recently reported: Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14158.
(14) On the other hand, TMS cyanohydrins were intact.
(15) For a relevant pathway−selective asymmetric catalysis, see: Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439.

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