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Two Methods for Catalytic Generation of Reactive Enolates Promoted by a Chiral Poly Gd Complex: Application to Catalytic Enantioselective Protonation Reactions

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Catalytic enantioselective protonation of prochiral enolates is a synthetically versatile reaction, producing enantiomerically enriched α-tertiary substituted carbonyl compounds. This reaction is an alternative to enantioselective alkylation that affords products with a broader variety of α-substitution patterns. Due to the extremely small size of proton and possible early transition state characteristics, however, catalytic enantiocontrol of protonation reactions is a great challenge in the field of asymmetric catalysis.[1] Here, we describe two types of enantioselective protonation reactions catalyzed by a chiral polynuclear Gd complex in which the catalytic generation of chiral Gd enolates plays a key role.

Our strategy for the development of the catalytic enantioselective protonation of enol silyl ethers was based on the mechanism of asymmetric reactions catalyzed by rare earth metal complexes derived from ligands **1** and **2**, developed by our group.[2] These catalysts promote various enantioselective cyanation and azidation reactions in the presence of protic additives [2,6-dimethylphenol (DMP) or HCN]. The active catalysts are polymetallic complexes of defined higher-order structures, involving reactive nucleophiles, such as rare earth metal isocyanide (**5**) or azide (**6**) (Figure 1)

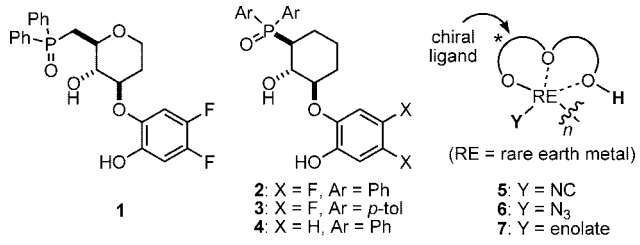


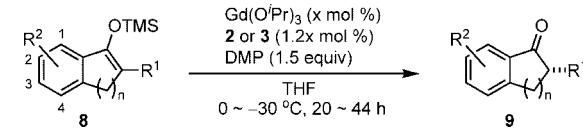
Figure 1

generated through transmetalation from TMSCN or $TMSN_3$. The protic additive incorporates an acidic proton at the catechol site in the catalyst and, thus, accelerates the turnover-limiting catalyst regeneration step.[2] We hypothesized that if an enol TMS ether could be activated by the catalyst through transmetalation, the resulting chiral rare earth metal enolate would react with the proton existing in the complex. The positions of both the activated metal enolate (Y in **7**) and the proton would be defined by the asymmetric catalyst (**7**), leading to high enantio-induction.

Systematic optimization of various reaction parameters using enol silyl ether **8a** as a model substrate led to the identification of the following characteristic features of the reaction.[3] (1) Catalysts prepared from $Gd(O^iPr)_3$ and ligand **2** or **3** in a 1:1.2 ratio, which matched the constitution of the generated polymetallic complex (5:6 complex),[2] produced the highest enantioselectivity (74% ee using **2** in the preliminary experiments).[4] (2) The reaction was a marked ligand-acceleration process and barely proceeded in the absence of the ligand, suggesting that the formation of polynuclear Gd complexes is essential for catalytic activity. (3) The enantioselectivity was constant, irrespective of the substituent on the silicon atom of enol silyl ethers, whereas the reaction rate differed. (4) DMP was the optimum proton source, but other 2,6-disubstituted phenols produced nearly comparable enantioselectivity (60−64% ee).

After thorough optimization of the reaction conditions, we examined the substrate generality (Table 1). High enantioselectivity

Table 1. Catalytic Enantioselective Protonation of Enol Silyl Ethers



entry	substrate	ligand	cat. (*x* mol %)	yield[a] (%)	ee[b] (%)
1[c]	**8a**: $n = 2$, R^1 = Me, R^2 = H	**2**	10	95	87[g]
2[c]	**8a**: $n = 2$, R^1 = Me, R^2 = H	**3**	10	>99	84[g]
3[c]	**8a**: $n = 2$, R^1 = Me, R^2 = H	**3**	5	93	83[g]
4[c]	**8b**: $n = 2$, R^1 = Et, R^2 = H	**2**	10	92	88[g]
5[d]	**8c**: $n = 2$, R^1 = allyl, R^2 = H	**2**	10	89	80[g]
6[c]	**8d**: $n = 2$, R^1 = Me, R^2 = 3-MeO	**3**	10	>99	85
7[e]	**8e**: $n = 1$, R^1 = Me, R^2 = H	**2**	10	97	86[g]
8[f]	**8e**: $n = 1$, R^1 = Me, R^2 = H	**2**	5	95	83[g]
9[f]	**8e**: $n = 1$, R^1 = Me, R^2 = H	**3**	5	94	82[g]
10[f]	**8f**: $n = 1$, R^1 = Et, R^2 = H	**2**	10	>99	86[g]
11[e]	**8g**: $n = 1$, R^1 = Me, R^2 = 3-MeO	**2**	10	88	84

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Temp = 0 °C. [d] Temp = −10 °C. [e] Temp = −30 °C. [f] Temp = −20 °C. [g] Absolute configuration was determined as shown in the scheme.[1c,d,f]

was obtained from α-aliphatic substituted tetralone- and indanone-derived substrates. The enantioselectivity was not very sensitive to the size of the α-substituent, and synthetically useful enantioselectivity was produced from α-methyl-, ethyl-, and allyl-substituted substrates. Ligands **2** and **3** afforded comparable enantioselectivity, but the reaction rate using a catalyst derived from **3** was higher than using the catalyst derived from **2**, which was particularly advantageous when catalyst loading was reduced.

To gain further insight into the reaction mechanism, we conducted kinetic studies. The initial reaction rate exhibited first, first, and zeroth order dependencies with regard to [catalyst], [enol silyl ether **8a**], and [DMP], respectively.[3] This kinetic profile, together with the tendencies observed during the optimization studies (see above), were consistent with the hypothesis that the reaction proceeds through transmetalation from an enol silyl ether to a Gd enolate and that this transmetalation is the rate-determining step.

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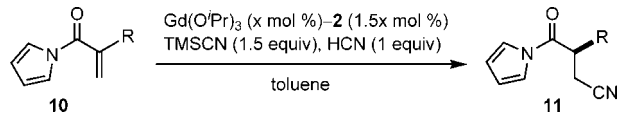
An alternative method for the catalytic generation of Gd enolates relies on the conjugate addition of a Gd-conjugated nucleophile to α,β-unsaturated carbonyl compounds.[5] Thus, we extended the utility of the Gd catalyst to the conjugate cyanation−enantioselective protonation of α-substituted α,β-unsaturated *N*-acyl pyrroles **10**.[6] An additional difficulty of this type of reaction compared to the reaction described above using cyclic enol silyl ethers is that the geometry of intervening, short-lived Gd enolates and/or the relative reactivity of the *E*-/*Z*-enolates must be strictly controlled to afford high enantioselectivity. On the other hand, the lack of a requirement for the enol silyl ether formation step is a significant synthetic advantage. In addition, due to the versatility and distinct reactivity of cyanide and *N*-acyl pyrrole,[7] the products are useful dual functional chiral building blocks.

Using the Gd catalyst derived from ligand **2**, conjugate cyanation−enantioselective protonation of **10** proceeded with high enantioselectivity in the presence of TMSCN and HCN (Table 2).[8]

Table 2. Catalytic Conjugate Cyanation−Enantioselective Protonation of *N*-Acyl Pyrroles

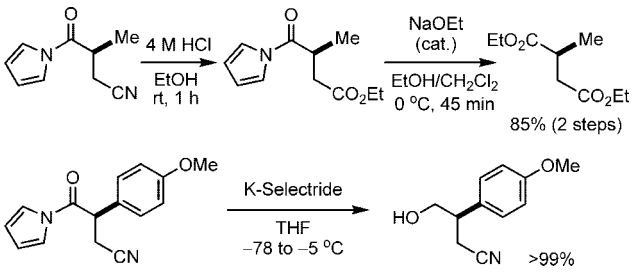


entry	R	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	Me	25	1	98	80[e]
2	Et	25	2	93	84
3	^{i}Pr	25	12	90	89
4	^{c}Hex	25	12	97	91
5[c]	^{c}Hex	25	44	90	88
6	Ph	−30	12	99 (74)[d]	85 (>99)[d]
7	4-MeO-C_6H_4	−30	40	88	83
8	4-Me-C_6H_4	−45	96	80	86
9	2-Me-C_6H_4	−45	96	83 (72)[d]	82 (97)[d]
10	3-Me-C_6H_4	−45	96	82 (59)[d]	83 (98)[d]

[a] Isolated yield. [b] Determined by chiral HPLC. [c] $x = 5$. In other entries, $x = 10$. [d] Yield and enantiomeric excess after one recrystallization. [e] Absolute configuration was assigned to be (*S*).[3]

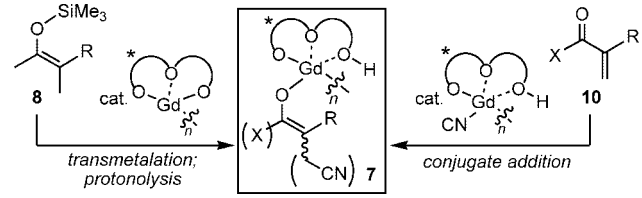
Specifically, products containing α-secondary alkyl- (entries 3−5) and α-aryl-substituted (entries 6−10) tertiary stereocenters, which are usually difficult to access via enantioselective alkylation or arylation,[9] were successfully produced. Because many of the *N*-acyl pyrrole derivatives are crystalline, the enantiomeric purity of the products was efficiently enhanced through recrystallization (entries 6, 9, and 10). Products **11** are synthetically useful chiral building blocks, and representative racemization-free transformations are shown in Scheme 1.[3]

Scheme 1. Synthetically Useful Conversion of the Products



In conclusion, we have demonstrated that the chiral polynuclear Gd complexes derived from ligands **2** and **3** are efficient enantioselective catalysts for two types of protonation reactions: that using enol silyl ethers and sequential conjugate cyanation−enantioselective protonation. Both reactions proceed through catalytic generation of chiral Gd enolates,[10] a previously unexplored function of the chiral Gd complexes (Scheme 2). Studies are ongoing to extend

Scheme 2. Two Catalytic Methods for Chiral Gd Enolate Formation



these enolate generation methods to catalytic asymmetric C−C bond-forming reactions.

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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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(2) Review: Shibasaki, M.; Kanai, M. *Org. Biomol. Chem.* **2007**, *5*, 2027.

(3) See Supporting Information for details.

(4) Ligand **1**, which provides a completely different higher-order structure (2:3 and/or 4:5 complex), and ligand **4**, which provides a 5:6 complex but contains a more electron-rich catechol (thus, containing a less acidic proton in the catalyst), produced strikingly reduced enantioselectivity (less than 42% ee).

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(6) For a catalytic enantioselective conjugate cyanation of β-substituted, α-unsubstituted *N*-acyl pyrroles catalyzed by a Gd complex derived from **2**, see: Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820.

(7) (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.

(8) The use of DMP as a proton source afforded less satisfactory enantioselectivity, and ligand **3** demonstrated no significant advantage compared to **2**. The reaction rate and enantioselectivity were much lower when using a catalytic amount of TMSCN (10 mol %) and 1 equiv of HCN (**11**: 90 h, 61% yield, 50% ee; cf. Table 2, entry 1).

(9) (a) A catalytic asymmetric cross-coupling reaction to generate carboxylic acid derivatives containing α-aryl-substituted tertiary stereocenters: Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302. (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. Organocatalyzed redox alkylation and arylation of aldehydes: (c) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (d) Nicolaou, K. C.; Reingruber, R.; Sarlah, D.; Bräse, S. *J. Am. Chem. Soc.* **2009**, *131*, 2086.

(10) Based on the absolute configuration of **11**, the geometry of the reactive intermediate enolate **7** generated via conjugate cyanation would be *E* (when the priority of R is higher than the cyanomethyl group).

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