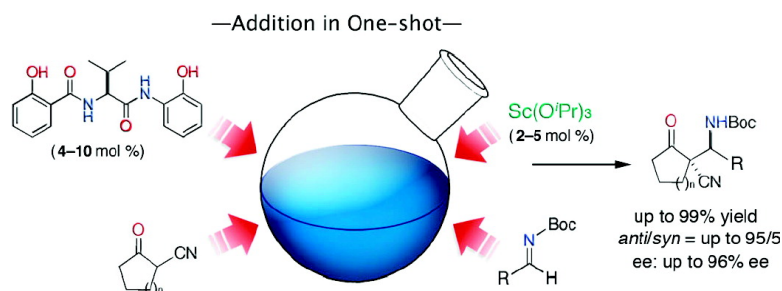


Asymmetric Catalysis via Dynamic Substrate/Ligand/Rare Earth Metal Conglomerate

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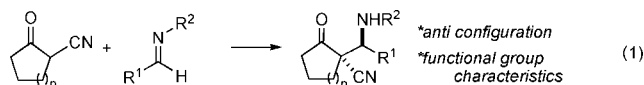
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Metalloenzymes constitute a particularly intriguing class of functional biomolecules because of their plethora of vital roles in living systems.¹ Multiple cooperative noncovalent interactions are harnessed to exhibit a highly integrated transition state architecture in an elegant spatial arrangement, arising from a diverse set of peptide chains and associated metal cations. We hypothesized that a simple amide ligand associated with a rare earth metal (RE) would mimic a unitary metalloenzyme to reproduce a highly ordered transition state.^{2,3} The high coordination number ($6 \leq \text{CN} \leq 12$) and unpredictable coordination mode may compensate for the simplicity of the ligand² and allow for a variety of assembled structures to be obtained depending on the ligand and reaction conditions. Our recent efforts in this field identified a simple amide ligand that can construct a suitable asymmetric environment upon complexation with an RE.⁴ Herein, we expanded our strategy to construct a chiral quaternary stereocenter and revealed a dynamic association of the substrate/ligand/metal mixture to produce a defined transition state assembly, furnishing the desired product in a highly stereoselective manner.

Catalytic asymmetric construction of a quaternary carbon center has attracted increasing attention due to limited methodologies to address the synthetic challenges.⁵ α -Cyanocarbanion, with its minimal steric bias and its inherent nucleophilicity, is a suitable carbon nucleophile for the formation of a chiral quaternary carbon center.⁶ We applied an amide ligand/RE catalytic system to an enantioselective addition of α -cyanoketones to imines, a Mannich-type reaction,^{7,8} affording the densely functionalized product with a contiguous quaternary carbon and trisubstituted stereocenter (eq 1). There are several recent examples of the catalytic asymmetric Mannich-type reaction of 1,3-dicarbonyl compounds producing *syn*-configured β -amino ketones with an α -quaternary carbon center.^{8a-d} None of these examples, however, exhibits high *anti* diastereo- and enantioselectivity.



We began our study by evaluating an amide ligand/RE catalyst prepared from ligand **1a** and RE(OⁱPr)₃ in a 2:1 ratio in a reaction of 2-cyanocyclopentanone (**2a**) and *N*-Boc imine **3a** (Table 1). **1a** and RE(OⁱPr)₃ were mixed and stirred for 1 h at room temperature prior to addition of the substrates. Among the initially screened combinations of **1a** with an RE, the **1a**/Sc(OⁱPr)₃ complex quickly emerged as a nearly ideal catalyst, allowing for a smooth reaction with 5 mol % of catalyst loading at 0 °C to give the Mannich product **4aa** in 91% yield with *anti/syn* = 92/8 and 80% ee (entry 1). Except for the Er(OⁱPr)₃/**1a** complex, which displayed *syn* diastereoselectivity (entry 6), the present catalytic system preferentially provided *anti*-**4aa**. Higher enantioselectivity was observed when the reaction was run in the nonpolar solvents toluene (entry 8) or CH₂Cl₂ (entry 10), presumably because of the enhanced hydrogen bond network between **1a** and the substrates, leading to

Table 1. Catalytic Asymmetric Mannich-Type Reaction Promoted by **1a**/RE(OⁱPr)₃ Complex^a

entry	RE(O ⁱ Pr) ₃	solvent	temp (°C)	time (h)	yield ^b (%)	<i>anti/syn</i> ^c	ee (<i>anti</i>) (%)
1	Sc	THF	0	12	91	92/8	80
2	La	THF	0	12	86	90/10	3
3	Nd	THF	0	12	93	96/4	–1
4	Eu	THF	0	12	76	84/16	1
5	Dy	THF	0	12	88	87/13	2
6	Er	THF	0	12	90	15/85	5
7	Yb	THF	0	12	83	59/41	6
8	Sc	toluene	0	12	92	88/12	85
9	Sc	CH ₂ Cl ₂	–20	12	78	94/6	92
10	Sc	CH ₂ Cl ₂	0	12	92	91/9	94
11	Sc	CH ₂ Cl ₂	21	6	92	93/7	93
12	Sc	CH ₂ Cl ₂	40	0.33	85	91/9	92
13	Sc	CH ₂ Cl ₂ -DMF ^d	0	12	61	55/45	14

^a **1a** and RE(OⁱPr)₃ were mixed, and the resulting mixture was stirred for 1 h at room temperature before addition of substrates. **2a**: 0.2 mmol, **3a**: 0.24 mmol, 0.2 M in **2a**. ^b Determined by ¹H NMR with DMF as internal standard. ^c Determined by ¹H NMR of crude mixture. ^d CH₂Cl₂/DMF = 1/1.

a highly ordered transition state architecture.⁹ The present reaction afforded uniformly high ee within a broad range of reaction temperatures (entries 9–12).¹⁰ The substantial decrease in both reactivity and stereoselectivity with a CH₂Cl₂/DMF mixed solvent system supports the involvement of hydrogen bonding (entry 13).¹¹

The optimized conditions were applicable to various Boc imines **3** (Table 2).^{12,13} The reaction was completed with 2 mol % of catalyst loading (entry 2). Six- and seven-membered cyclic cyanoketones also served as promising nucleophiles, providing the products in a highly stereoselective manner (entries 3 and 4). Nonpolar or noncoordinative substituents on the aromatic ring of the imines only marginally impacted stereoselectivity, giving the *anti* product with high diastereo- and enantioselectivity (entries 4–10). Stereoselectivity diminished in the reaction with imines bearing coordinative substituents (MeO, furyl, thienyl), suggesting that hydrogen bonding between the ligand and substrates is manifested in the transition state (entries 11–14). The reaction also proceeded using an aliphatic imine, albeit with lower stereoselectivity (entry 15).

Having developed a highly stereoselective Mannich-type reaction, we aimed to better understand the precise nature of the present catalysis. ¹H NMR spectroscopy of the **1a**/Sc solution produced highly complicated spectra, suggesting that an oligo- or polymeric **1a**/Sc conglomerate was formed without any order or regularity.¹⁴ No change in spectral complexity was observed after the addition of **2a** to the catalyst solution.¹⁴ We hypothesized that the reaction components would be free to associate/dissociate in the reaction mixture, and each reaction component orchestrates to form an ordered transition state through Sc–O coordination and hydrogen bonding during the reaction.¹⁵ The strong dependency of the

Table 2. Catalytic Asymmetric Mannich-Type Reaction by **1a**/Sc Catalyst^a

entry	x	n	cyanoketone		imine		product	yield ^b (%)	anti/syn ^c	ee (anti) (%)
			2	3	R	4				
1 ^d	5	1	2a	Ph	3a	4aa	90	94/6	94	
2	2	1	2a	Ph	3a	4aa	93	93/7	91	
3	5	2	2b	Ph	3a	4ba	92	95/5	91	
4 ^e	5	3	2c	Ph	3a	4ca	80	89/11	95	
5	5	1	2a	2-MeC ₆ H ₄	3b	4ab	90	91/9	93	
6	5	1	2a	4-MeC ₆ H ₄	3c	4ac	93	91/9	91	
7	5	1	2a	2-naphthyl	3d	4ad	97	90/10	94	
8	5	1	2a	2-ClC ₆ H ₄	3e	4ae	97	88/12	95	
9	5	1	2a	4-ClC ₆ H ₄	3f	4af	99	91/9	89	
10	5	1	2a	2-FC ₆ H ₄	3g	4ag	88	90/10	96	
11	5	1	2a	2-MeOC ₆ H ₄	3h	4ah	86	80/20	81	
12	5	1	2a	4-MeOC ₆ H ₄	3i	4ai	97	85/15	77	
13	5	1	2a	2-furyl	3j	4aj	94	75/25	82	
14	5	1	2a	3-thienyl	3k	4ak	98	93/7	83	
15	5	1	2a	Ph(CH ₂) ₂	3l	4al	89	64/36	50	

^a **1a** and RE(OⁱPr)₃ were mixed, and the resulting mixture was stirred for 1 h at room temperature before addition of substrates. **2a**: 0.3 mmol, **3a**: 0.36 mmol, 0.2 M in **2a**. ^b Isolated yield. ^c Determined by ¹H NMR of crude mixture. ^d 1.0 mmol scale. Average of two runs. ^e Reaction time was 48 h.

Table 3. Mannich-Type Reaction with One-Shot Addition^a

entry	substrates	product	phenolic additive	mol %	yield ^b (%)	anti/syn ^c	ee (anti) (%)
1	2a, 3a	4aa	-	-	87	94/6	93
2	2a, 3a	4aa	<i>p</i> - ^t Bu phenol	10	92	96/4	96
3	2a, 3a	4aa	Methyl salicylate	10	93	97/3	94
4	2a, 3a	4aa	Methyl salicylate	40	95	96/4	94
5 ^d	2c, 3a	4ca	-	-	96	87/13	95
6	2a, 3f	4af	-	-	94	91/9	89

^a Sc(OⁱPr)₃ was added to the CH₂Cl₂ solution of **1a**, **2**, **3**, and phenolic additive. ^b Determined by ¹H NMR with DMF as internal standard. ^c Determined by ¹H NMR of crude mixture. ^d Reaction time was 48 h.

stereoselectivity on the nature of the solvent (Table 1) and the imine substituent (Table 2) is consistent with this assumption. Furthermore, the use of **2a** in concentrations higher than 0.2 M diminished stereoselectivity,¹⁶ suggesting that concentration affects the organization process of the reaction components. If the spontaneous assembly to attain an ordered transition state is operative, precomplexation of **1a**/Sc is not required and the reaction can be run with one-shot addition of all reaction components. On the basis of this assumption, the Mannich-type reaction of **2a** and **3a** was conducted with Sc(OⁱPr)₃ added at the end of the procedure (Table 3). The reaction proceeded smoothly to afford **4aa** in 87% yield with *anti*/*syn* = 94/6 and 93% ee, which was comparable to the result obtained with the premixed **1a**/Sc catalyst (Table 2, entry 1, Table 3, entry 1). *More importantly, even in the presence of 10–40 mol % of *p*-^tBu phenol or methyl salicylate, which has a pK_a similar to that of **1a** and can disturb the preferential association of Sc and **1a**, high stereoselectivity was attained (entries 2–4). Because of the complicated NMR spectra of the **1a**/Sc mixture and the simple linear structure of **1a**, the formation of a distinct **1a**/Sc complex upon the addition of Sc(OⁱPr)₃ is less likely. In the reaction of **2a** and **3a**, a salicyl ester analogue of **1a** performed similarly, whereas a catechol analogue resulted in poor stereoselectivity, likely due to the lack of hydrogen bonding through aminophenol amide.¹⁷ Evaluation of the ee at several temperatures (Table 1) using a differential Eyring equation indicated that the entropy term mainly*

contributes to the high ee,^{14,18} suggesting that the well-organized structural integration of the reaction components occurs in the transition state.

In conclusion, we developed a catalytic asymmetric Mannich-type reaction of α -cyanoketones and Boc imines with a **1a**/Sc catalyst, generating consecutive all-carbon quaternary and trisubstituted stereocenters in a highly stereoselective manner. Particularly noteworthy is that the present catalysis proceeds through an ordered association of substrates/**1a**/Sc from a conglomerate mixture, eliminating the need for precomplexation of **1a**/Sc. More detailed mechanistic investigations are in progress.

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

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- (12) Relative and absolute configuration were determined by single crystal X-ray crystallographic analysis. See Supporting Information for details.
- (13) The reaction with an acyclic α -cyanoketone, 2-cyanopropiophenone (**2d**), was performed (imine **3a**, cat. 5 mol %, 0 °C, 18 h), giving the Mannich product (**4da**) in 95% yield, *anti*/*syn* = 8/92, 89% ee (*syn*).
- (14) See Supporting Information for details.
- (15) QFT-ESI MS analysis revealed the formation of **1a**/Sc/**2a** ternary complex upon addition of **2a** to the **1a**/Sc solution. See Supporting Information.
- (16) Reaction of **2a** and **3a** with 2 mol % of catalyst at 0.8 M in **2a** afforded **4aa** in 91% yield with *anti*/*syn* = 92/8 and 83% ee (*anti*).
- (17) Salicyl ester analogue: 93% yield, *anti*/*syn* = 89/11, 93% ee. Catechol analogue: 78% yield, *anti*/*syn* = 84/16, -24% ee. See Supporting Information for details.
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