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

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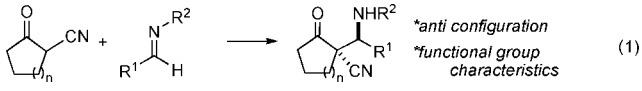
Metalloenzymes constitute a particularly intriguing class of functional biomolecules because of their plethora of vital roles in living systems.[1] Multiple cooperative noncovalent interactions are harnessed to exhibit a highly integrated transition state architecture in an elegant spatial arrangement, 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 ($6 \leq CN \leq 12$) and unpredictable coordination mode may compensate for the simplicity of the ligand[2] 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.

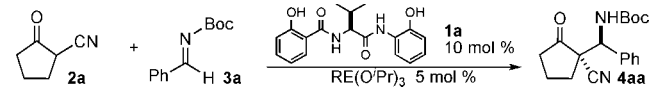
Catalytic asymmetric construction of a quaternary carbon center has attracted increasing attention due to limited methodologies to address the synthetic challenges.[5] α-Cyanocarbanion, with its minimal steric bias and its inherent nucleophilicity, is a suitable carbon nucleophile for the formation of 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.




(1)

We began our study by evaluating an amide ligand/RE catalyst prepared from ligand **1a** and $RE(O^iPr)_3$ in a 2:1 ratio in a reaction of 2-cyanocyclopentanone (**2a**) and *N*-Boc imine **3a** (Table 1). **1a** and $RE(O^iPr)_3$ 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**/$Sc(O^iPr)_3$ 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($O^iPr)_3$/**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 $CH_2Cl_2$ (entry 10), presumably because of the enhanced hydrogen bond network between **1a** and the substrates, leading to 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 $CH_2Cl_2$/DMF mixed solvent system supports the involvement of hydrogen bonding (entry 13).[11]

***Table 1.*** Catalytic Asymmetric Mannich-Type Reaction Promoted by **1a**/$RE(O^iPr)_3$ Complex[a]




| entry | $RE(O^iPr)_3$ | solvent | temp (°C) | time (h) | yield[b] (%) | *anti*/*syn*[c] | ee (*anti*) (%) |
|---|---|---|---|---|---|---|---|
| 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 | $CH_2Cl_2$ | −20 | 12 | 78 | 94/6 | 92 |
| 10 | Sc | $CH_2Cl_2$ | 0 | 12 | 92 | 91/9 | 94 |
| 11 | Sc | $CH_2Cl_2$ | 21 | 6 | 92 | 93/7 | 93 |
| 12 | Sc | $CH_2Cl_2$ | 40 | 0.33 | 85 | 91/9 | 92 |
| 13 | Sc | $CH_2Cl_2$-DMF[d] | 0 | 12 | 61 | 55/45 | 14 |

[a] **1a** and $RE(O^iPr)_3$ 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] $CH_2Cl_2$/DMF = 1/1.

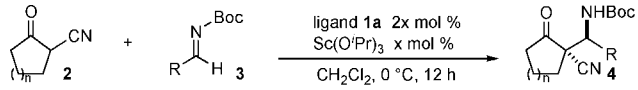
The optimized conditions were applicable to various Boc imines **3** (Table 2).[12,13] The reaction was completed with 2 mol % of catalyst loading (entry 2). Six- and seven-membered cyclic cyanoketones also served as promising nucleophiles, providing the products in a highly stereoselective manner (entries 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



10.1021/ja800326d CCC: $40.75 

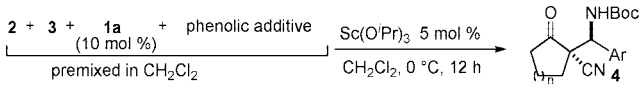
***Table 2.*** Catalytic Asymmetric Mannich-Type Reaction by **1a**/Sc Catalyst[a]




| | | cyanoketone | imine | | | | | |
|---|---|---|---|---|---|---|---|---|
| entry | *x* | *n* | R | | product | yield[b] (%) | *anti*/*syn*[c] | ee (*anti*) (%) |
| 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-Me$C_6H_4$ | **3b** | **4ab** | 90 | 91/9 | 93 |
| 6 | 5 | 1 **2a** | 4-Me$C_6H_4$ | **3c** | **4ac** | 93 | 91/9 | 91 |
| 7 | 5 | 1 **2a** | 2-naphthyl | **3d** | **4ad** | 97 | 90/10 | 94 |
| 8 | 5 | 1 **2a** | 2-Cl$C_6H_4$ | **3e** | **4ae** | 97 | 88/12 | 95 |
| 9 | 5 | 1 **2a** | 4-Cl$C_6H_4$ | **3f** | **4af** | 99 | 91/9 | 89 |
| 10 | 5 | 1 **2a** | 2-F$C_6H_4$ | **3g** | **4ag** | 88 | 90/10 | 96 |
| 11 | 5 | 1 **2a** | 2-MeO$C_6H_4$ | **3h** | **4ah** | 86 | 80/20 | 81 |
| 12 | 5 | 1 **2a** | 4-MeO$C_6H_4$ | **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$(O^iPr)_3$ 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 $^1$H 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** | *p*-$^t$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$(O^iPr)_3$ was added to the $CH_2Cl_2$ solution of **1a**, **2**, **3**, and phenolic additive. [b] Determined by $^1$H NMR with DMF as internal standard. [c] Determined by $^1$H 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$(O^iPr)_3$ 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-*$^t$*Bu phenol or methyl salicylate, which has a p*$K_a$ *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$(O^iPr)_3$ 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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(9) The catalyst prepared from different **1a**/Sc ratio gave inferior results. **1a**/Sc$(O^iPr)_3$ (5 mol %) = 1/1: 77% yield, *anti*/*syn* = 87/13, 78% ee (*anti*). **1a**/Sc$(O^iPr)_3$ (5 mol %) = 1/2: 51% yield, *anti*/*syn* = 77/23, 61% ee (*anti*).
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(11) The possibility that DMF dissociates ligand **1a** from Sc cation cannot be excluded.
(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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