Communication

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Asymmetric Counter-Anion-Directed Aminomethylation: Synthesis of Chiral β-Amino Acids *via* Trapping of an Enol Intermediate

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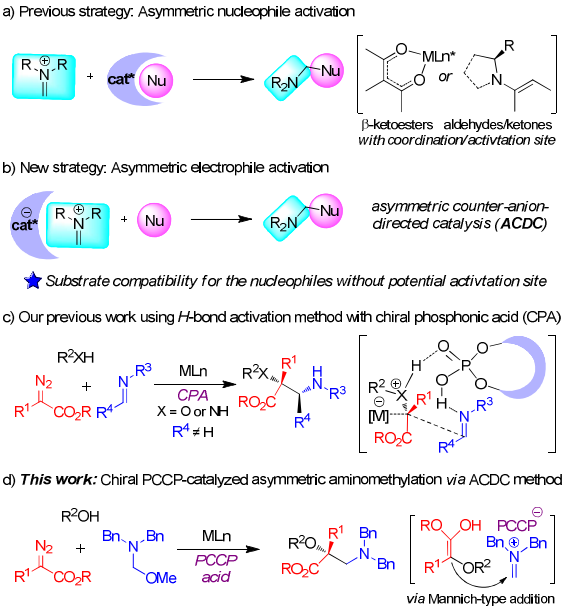
Supporting Information Placeholder

ABSTRACT: A novel enantioselective aminomethylation reaction of diazo compound, alcohol and α-aminomethyl ether enabled by asymmetric counter-anion-directed catalysis (ACDC) is disclosed that offers an efficient and convenient access to furnish optically active α-hydroxyl-β-amino acids in high yield with high to excellent enantioselectivities. Control experiments and DFT calculations indicate that the transformation proceeds through trapping the in situ generated enol intermediate with methylene iminium ion, and the asymmetric induction was enabled by chiral pentacarboxycyclopentadiene (PCCP) anion via *H*-bonding and electrostatic interaction.

The introduction of an aminomethyl group into small organic molecules has recently attracted considerable attention due to the pervasive occurrence of this moiety in a wide variety of natural products and pharmaceuticals.[1] Moreover, the resulting nitrogen-containing products are versatile synthetic building blocks for the preparation of biologically active compounds. Thus, methods for the incorporation of the aminomethyl functional group, such as nucleophilic displacement and cross-coupling reaction, have been developed.[2,3] However, most of these advances are racemic versions. To date, only a handful of catalytic asymmetric aminomethylation reactions have been reported.[3] Seminal works by Córdova and Gellman have enabled asymmetric aminomethylation of aldehydes or ketones catalyzed by a chiral secondary amine.[3a,3b] Recently, Feng and Luo reported asymmetric aminomethylation of 1,3-dicarbonyl compounds, catalyzed by chiral Lewis acid[3e] and chiral primary amine[3f] catalysts, respectively. In these advances, a precisely designed catalytic strategy of asymmetric activation of the nucleophiles was employed for the induction of the chirality. Thus, the substrate scope of these reported reactions is limited to aldehydes, ketones or β-ketoesters based on the corresponding catalytic model (Scheme 1a), and asymmetric aminomethylation at the α-position of esters, which is extremely useful for the synthesis of β-amino acid derivatives, could not be realized with these methods. In this context, development of new approaches *via* asymmetric activation of aminomethylation reagent is urgently needed (Scheme 1b); these approaches will provide a new avenue for the enantioselective aminomethylation to allow extensive exploration of the substrate generality, particularly for the nucleophiles that are reactive intermediates and for which asymmetric induction is difficult.

Scheme 1. Asymmetric Induction Models in Mannich-type Aminomethylation Reaction

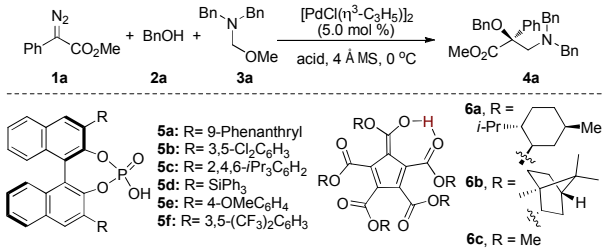


In the past decade, chiral Brønsted acid has shown versatile ability in asymmetric Mannich-type reactions. Generally, directional *H*-bonding activation of imine is the common pattern for the asymmetric induction,[4] and the Brønsted acid serves as a proton shuttle in most of these transformations.[5] Recently, we have realized enantioselective multi-component reactions by trapping ylide/zwitterionic intermediates with imines in the presence of a chiral Brønsted acid (Scheme 1c).[6-8] However, the electrophiles are still restricted to the relative stable imines in these reactions. On the other hand, asymmetric counter-anion-directed catalysis (ACDC) has been demonstrated to be an effective asymmetric induction strategy,[9,10] and the first proof-of-concept example for highly enantioselective ACDC was reported by List et al.[10a] Inspired by these works, we envisioned that by applying the ACDC concept,[10] the in situ generated tight ion pair of methylene iminium ion with corresponding chiral counter anion may enable

the trapping of the nucleophile intermediate and realize enantioselective aminomethylation *via* a novel catalytic strategy (Scheme 1b *vs* 1a). However, the asymmetric aminomethylation reaction catalyzed by a chiral Brønsted acid has never been reported, possibly due to the inherent lability and the absence of a handle for the methylene iminium ion species to interact with the catalyst.[9,11] Herein, we report the first example of an enantioselective counter-anion-directed aminomethylation reaction, and the envisioned asymmetric induction step proceeds *via* the trapping of the in situ generated enol intermediate with methylene iminium ion in the presence of pentacarboxycyclopentadiene (PCCP) acid **6** (Scheme 1d). This method not only provides a novel catalytic pattern for the asymmetric aminomethylation but also reveals an effective strategy for the interception of reactive intermediates with substrate compatibility and offers convenient access for furnishing chiral α-hydroxy-β-amino acids with an α-quaternary stereocenter.[12]

We initially test our studies by employing α-aminomethyl ether **3a** as methylene iminium ion precursor[13] to react with diazo **1a** and benzyl alcohol **2a** in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$[14] and BINOL-derived phosphoric acid **5** in dichloromethane at 0 °C. Gratifyingly, the desired product **4a** was obtained in 89%-95% yields (Table 1, entries 1-6). Further extensive evaluation of

Table 1. Condition Optimization[a]

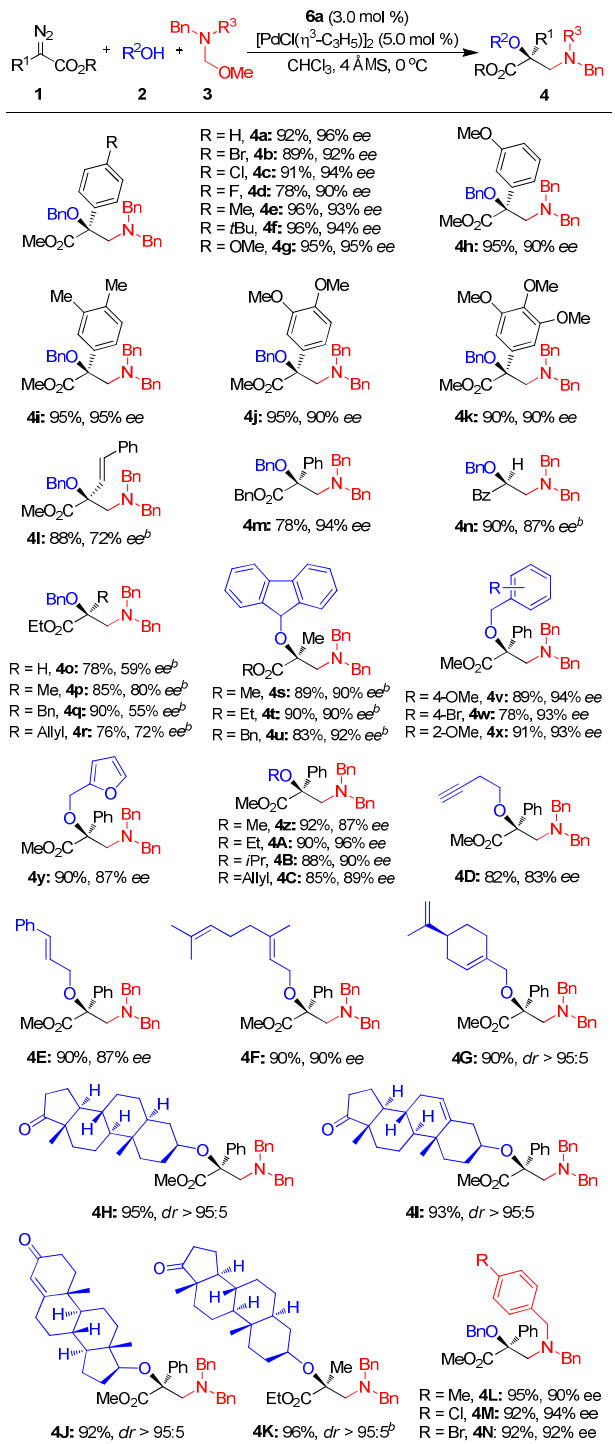


entry	solvent	acid	yield (%)[b]	*ee* (%)[c]
1	DCM	**5a**	93	<5
2	DCM	**5b**	89	5
3	DCM	**5c**	95	51
4	DCM	**5d**	92	27
5	DCM	**5e**	90	<5
6	DCM	**5f**	89	15
7	DCM	**6c**	90	-
8	DCM	**6a**	90	88
9	DCM	**6b**	88	84
10	$CHCl_3$	**6a**	92	96

[a]All reactions were conducted on a 0.2 mmol scale: **1**:**2**:**3** = 1.5:1.5:1, acid (5.0 mol % **5** or 3.0 mol % **6**). [b]Isolated yield. [c]Determined by chiral HPLC analysis.

different chiral phosphoric acids and investigation of the effects of the solvent and temperature did not provide any improved results (see Table S1). Considering the fact that the weaker and less directional nature of electrostatic ion-pairing interaction between methylene iminium ion and chiral counter anion may be the main reason for the low enantioselectivity in this reaction,[9c] a chiral counter anion with larger steric hindrance may be required to enhance the directionality of the methylene iminium ion for enantiodiscrimination. Recently, Lambert reported a novel chiral pentacarboxycyclopentadiene (PCCP) acid.[15] The acidity of this catalyst results from the aromatic nature of the cyclopentadienyl

Table 2. Substrate Scope[a]



[a]Reactions were conducted on a 0.2 mmol scale: **1**:**2**:**3** = 1.5:1.5:1. [b]$Rh_2(OAc)_4$ was used as catalyst.

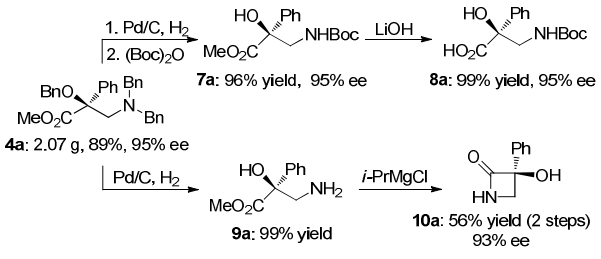
anion as the conjugate base[16] and the propeller-like steric chiral structure shows obvious advances for the enantioselectivity control with challenging substrates.[17] Significant increases in the enantioselectivity with excellent yield were observed in the presence of chiral PCCPs **6** (entries 8-9). Upon examining the solvents

and temperature with **6a** as the cocatalyst (see Table S2), **4a** was obtained in 92% yield with 96% *ee*, when chloroform was used as the solvent (entry 10).[18]

With the optimal conditions, the scope of this asymmetric aminomethylation reaction was investigated (Table 2). A series of aryl diazoesters **1** were subjected to the current conditions with **2a** and **3a** to afford the corresponding products in excellent yields with high enantioselectivities. Aryl diazoacetates bearing either electron-withdrawing or electron-donating substituents on the phenyl ring reacted smoothly, leading to the desired products **4a-4h** in high yields (78-96%) with 90%-96% *ee*.[19] Diazo compounds with di- or tri-substitutes on the aryl ring all gave the corresponding products (**4i-4k**) in good yields with comparable enantioselectivities. Various diazo compounds, including α-styryl diazoacetate **1l**, benzyl diazoacetate **1m**, and diazoketone **1n**, delivered the corresponding products **4l-4n** in high yields with 72%-94% *ee*. The α-alkyl substituted diazoacetates performed well to afford the aminomethylation products (**4o-4r**) in high yields with moderate to high enantioselectivities.[20] Further optimizations of α-alkyl diazoacetate (see Table S3 and S4) found that with the steric bulky 9-fluorenol, the reactions of diazopropanoate **1p** gave the corresponding products with 90%-92% *ee* (**4s-4u**). Then, the scope with respect to the alcohols was examined.[21] Various substituted benzyl alcohols provided the corresponding α-benzyloxy β-amino esters (**4v-4x**) with 78%-91% yields and 93%-94% *ee*. Furfuryl alcohol gave 90% yield and high enantioselectivity (**4y**). Subsequently, different alkyl alcohols also gave good results, furnishing **4z-4C** in 85%-92% yields with 87%-96% *ee*. Alcohols bearing the alkynyl and alkenyl species were also well-tolerated in this reaction and afforded **4D-4G** in 82%-90% yields with high selectivity. Notably, biomolecules, epiandrosterone, dehydroepiandrosterone, and testosterone, were tested in this reaction, and the corresponding products were formed in > 92% yields with > 95:5 *dr* (**4H-4K**). These results have shown the potential of this aminomethylation process for the selective modification of bioactive molecules that bear a hydroxyl group. In addition, the α-aminomethyl ether derivatives with substituted benzyl groups gave the comparable results with >92% yields and 90%-94% *ee* (**4L-4N**).[22]

To demonstrate the synthetic potential of this strategy, a gram-scale reaction was conducted, affording **4a** with comparative results (5.0 mmol scale, 2.07 g, 89%, 95% *ee*). Moreover, these products could be readily converted into synthetically useful building blocks (Scheme 2). The α-hydroxyl-β-amino ester **7a**

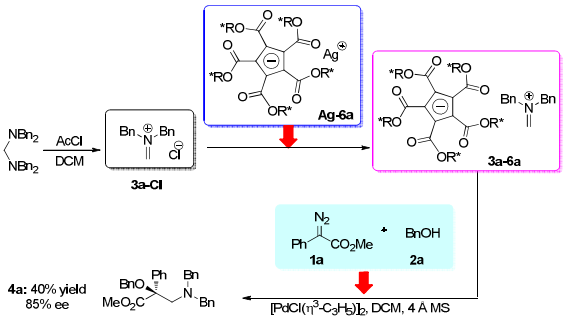
Scheme 2. Synthetic Utility



was generated in 96% yield with 95% *ee via* a one-pot operation. The β-amino acid **8a**, which is an essential secondary structure for the formation of specific β-peptide foldamers,[12] was obtained with consistent *ee* through the hydrolysis of **7a**. Furthermore, **4a** could be transformed into α-hydroxyl-β-lactam **10a** through a two-step operation, which is the core skeleton in many bioactive molecules.[23]

To gain insight into the reaction mechanism, control experiment of O-H insertion product with **3a** under the standard conditions gave no desired product **4a**, excluded the possibility that the reaction goes through a stepwise process. Moreover, control experiment by adding varying stoichiometric amounts of acid **6c** to **3a** was conducted, with monitoring by ^{1}H NMR spectroscopy. Formation of the conjugate base of **6c** and MeOH were detected simultaneously, indicating the generation of an ion pair (see Figure S2). Furthermore, the generated methylene iminium ion intermediate from **3a** in the presence of **6c** was also detected by HR-MS (see Figure S3). Methylene iminium chloride underwent anion exchange with chiral silver complex Ag-**6a** to form the chiral ion pair **3a-6a**[24] that was then employed for the reaction of **1a** with **2a** in the absence of additional **6a**, and **4a** was isolated in 40% yield with essentially the same enantioselectivity as that of the model reaction (Scheme 3). These results indicate that the

Scheme 3. Control Experiments



contact ion pair may be the key intermediate in this reaction, and the chiral counter anion is responsible for the asymmetric induction.

On the basis of the aforementioned insights and density functional theory (DFT) calculation results, the mechanistic rationale for this reaction is proposed in Figure 1. Tight chiral ion pair **V** is

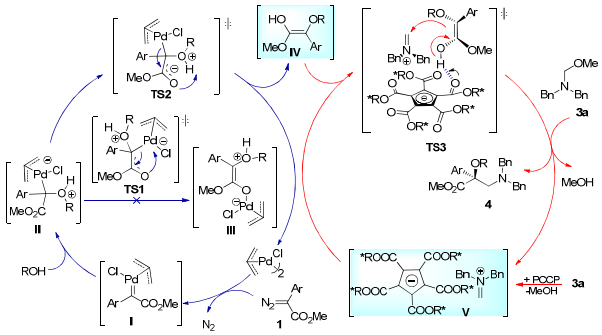


Figure 1. Proposed reaction mechanism.

generated through MeOH elimination from **3a** in the presence of chiral PCCP. In the parallel transition-metal catalysis cycle (left cycle), palladium carbenoid species **I** is generated from diazo **1** in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ that further reacts with alcohol **2** to form palladium-associated oxonium ylide **II**. This active ylide **II** may either undergoes a 1,3-Pd transfer to give an enolate species **III** through a transition state **TS1** or a 1,4-proton transfer to

afford an enol intermediate **IV** *via* the transition state **TS2**.[25] DFT calculations indicated that **TS1** is 5.3 kcal/mol higher in energy than **TS2**, and **IV** is 13.8 kcal/mol more stable than **III** (see Figure S10). Therefore, enol **IV** is more likely to be the intermediate for the next step. The subsequent convergent nucleophilic addition of **IV** with methylene iminium ion pair **V** through a transition state **TS3** led to **4**, generating the chiral ion pair **V** in the presence of **3a** simultaneously (right cycle). A control experiment with a combination of chiral **4a** (96% *ee*) and **PCCP 6a** as cocatalyst gave the identical results in comparison with model reaction under the standard conditions, further confirming the proposed catalytic cycle (see Figure S4).

According to the above mechanism, the stereo-determining step is the nucleophilic addition of the enol **IV** with the chiral ion-pair **V** *via* a three-component transition state **TS3**. To further understand the origin of the enantiocontrol of this reaction, the calculated electrostatic potential of these three components is shown in Figure 2.[26] The negative charges of the PCCP anion are mainly

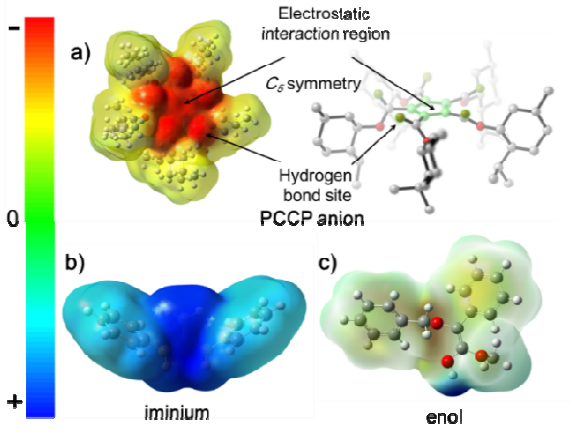


Figure 2. DFT-calculated electrostatic potential map.

located at the center of cyclopentadienyl ring and on the carbonyl groups, contributing to the electrostatic interaction and hydrogen bond formation, respectively, with the corresponding intermediates (Figure 2a). Following this way, we have located two transition states, **TS3-Re** and **TS3-Si** that directly lead to (*R*)-**4** and (*S*)-**4**, respectively (Figure 3). Due to the unique helical chirality of this propeller-like chiral PCCP cocatalyst,[15-17] in **TS3-Re**, the *Re*-prochiral face of the enol unit approaches the chiral ion pair **V** with the benzyl group residing on the one chiral alcohol group (Figure 3c). For **TS3-Si**, the *Si*-prochiral face of the enol unit reaches the chiral ion pair **V** with the benzyl group located in the cavity between the two chiral alcohol groups (Figure 3d). On the basis of this steric bias, the distance between the center of the PCCP anion and the nucleophilic site on the enol **TS3-Si** is closer than **TS3-Re** (black dash line in Figures 3c and 3d, 6.54 Å *vs* 5.53 Å). Therefore, during the Mannich-type addition, the distance between the positive iminium and the negative center of PCCP anion in **TS3-Re** is longer than that in **TS3-Si** (green line in Figures 3a and 3b, 6.06 Å *vs* 4.78 Å), so that **TS3-Si** has stronger electrostatic attraction that **TS3-Re**, resulting in the free energy preference for **TS3-Si** over **TS3-Re**. The free energy of **TS3-Re** at 273 K in $CHCl_3$ (ε = 4.71) is 2.9 kcal/mol higher than that of **TS3-Si**, predicting good enantioselectivity toward the formation of (*S*)-**4** and is comparable to the experimental value of 2.1 kcal/mol according to the Boltzmann distribution with 96% ee.[27]

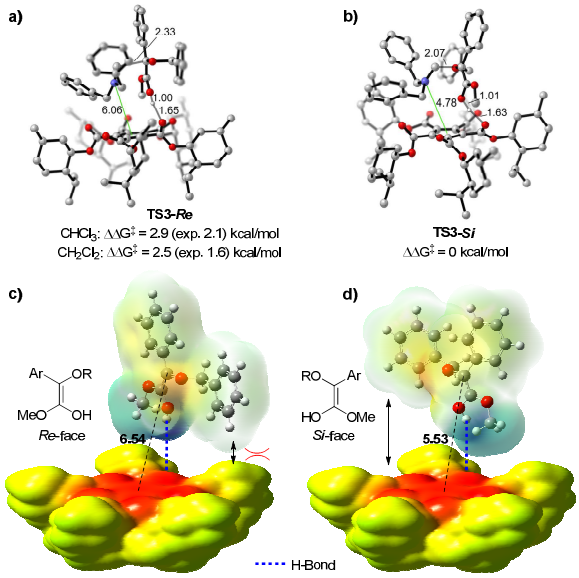


Figure 3. DFT-calculated transition states.

In conclusion, we have developed a novel enantioselective aminomethylation reaction *via* a convergent addition of two in situ generated reactive intermediates, enol intermediate and methylene iminium ion in the presence of chiral pentacarboxycyclopentadiene. The generated multi-functionalized β-amino acid derivatives are useful for further diversifications, as exemplified by the synthesis of enantiomerically pure α-hydroxyl-β-amino acid and α-hydroxyl-β-lactam. Control experiments and detailed DFT calculations indicate that the chiral cyclopentadienyl anion is responsible for the asymmetric induction due to electrostatic interaction and *H*-bonding. In addition, the present work is the only example of asymmetric aminomethylation reaction enabled by asymmetric counter-anion-directed catalysis. This asymmetric induction strategy opens a new avenue for exploring enantioselective aminomethylation reactions with challenging and structure appealing substrates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI

Experimental procedures, characterizations and analytical data of products, computational results, NMR, HPLC spectra, and crystallographic data for **4a**, **Ag-6c**, and **7a** (CIF).

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Notes

The authors declare no competing financial interests.

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(18) Comparable high selectivity was maintained when the reaction was conducted in the absence of alcohol, even though a decrease in the yields was observed (see Figure S9 in SI for details).
(19) In the case of α-aryl diazo compounds with strong electron-withdrawing groups, such as CF_3 or NO_2, the only O-H insertion product was formed mainly due to the attenuated nucleophilic reactivity of these corresponding ylide intermediates (see Figure S7 in SI for details).
(20) In the cases with alkyl diazo compounds, low yields were observed for the desired product contaminated with oxidation product and β-*H* shift product in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (see Figure S6 in SI for details).
(21) H_2O is not compatible in these conditions (see Figure S8 in SI for details).
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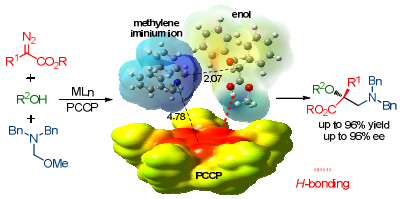
(27) The predicted free energy difference in CH_2Cl_2 (ε = 8.93) between **TS3-Si** and **TS3-Re** reduces to 2.5 kcal/mol, indicating more polar solvent disfavors for the enantioselectivity control, which is consistent with the experimental results.

TOC


methylene iminium ion
enol
2.07
4.78
MLn
PCCP
up to 96% yield
up to 96% ee
H-bonding