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A Ferrocenyl-DHIPOH/Cu(OAc)$_2$ Complex for Diastereo- and Enantioselective Catalysis of the 1,4-Addition of Glycine Derivatives to Alkylidene Malonates

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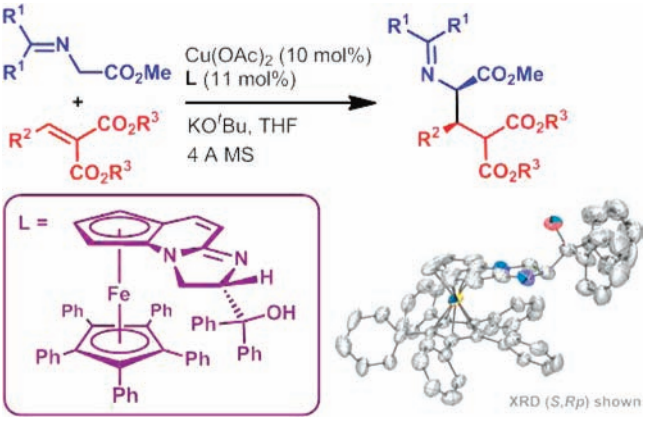
ABSTRACT



A planar chiral ferrocene derivative Fc-DHIPOH served as an excellent *N,O*- chiral ligand for asymmetric copper catalyzed 1,4-addition of glycine derivatives to alkylidene malonates. The corresponding 1,4-adducts were obtained in high yields with excellent enantioselectivities up to 95% ee.

New skeletal types and concepts in the design of novel chiral ligands have been a significantly stimulating topic in asymmetric catalysis over the past half century.[1] Yet, only a small number of ligands truly deserve the moniker of "privileged ligands".[2] Despite impressive progress in this area, discovery often relies on serendipity and systematic screening, with the design of suitable chiral ligands for particular tasks remaining challenging.

Recently we designed a planar chiral ferrocene derivative for nucleophilic catalysis,[3] through a combination of

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two inspirational catalyst systems of Fu[4] and Birman[5] (Figure 1). Our new nonenzymatic catalyst showed selectivity factors S of up to 1892 in the kinetic resolution of secondary alcohols.

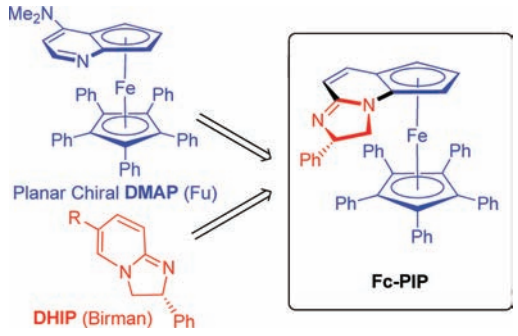

Figure 1. Design of **Fc-PIP** as the novel nucleophilic catalyst.

Additionally, we also reported that further elaboration of the **DHIP** core with a diphenylmethanol pendant group on the stereogenic position of the imidazole ring provided novel *N,O*-ligands (**DHIPOHs**).[6] Among these DHIPOHs, *N,O*-ligand **5** was found to efficiently catalyze the 1, 4-Michael addition of glycine derivative **2a** to alkylidene malonates **1** to afford the corresponding 1,4-adducts **3** in excellent yields and good enantioselectivities (79−83%) for the major *anti*-**3** adducts. The corresponding 1,4-adducts **3** were readily converted to 3-aryl glutamic acids, exemplified by the one-pot conversion of one substrate to chlorpheg, a selective L-homocysteic acid (HCA) uptake inhibitor, in 72% yield.[6b]

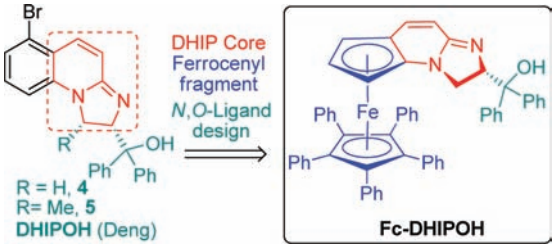

Figure 2. Design features of **Fc-DHIPOH**.

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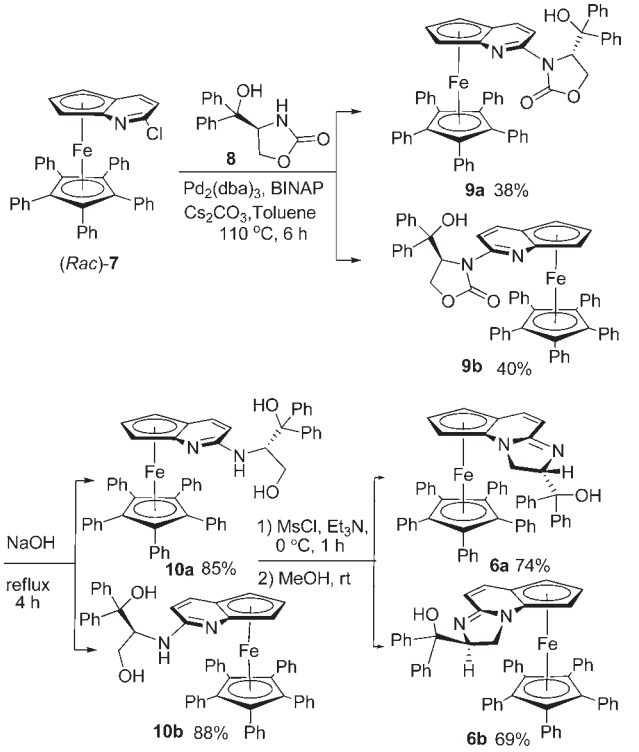
Due to their biological importance, much effort has been made toward efficient synthesis of β-alkyl substituted glutamic acid derivatives through diastereoselective[7] or catalytic[8] 1,4-additions of glycine derivatives to α,β-unsaturated esters or amides. The products serve not only as essential components of peptides and proteins but also as signal mediators.[9] In view of the biological and synthetic importance of optically active glutamic acids and their β-substituted derivatives, versatile and practical approaches to their synthesis are still required. Consequently, in order to further improve the stereoselectivity of this newly established catalytic asymmetric reaction, we set out to design novel ferrocene-based planar chiral *N,O*-ligands (**Fc-DHIPOH**) containing both planar and centrally chiral architectural features of the aforementioned **Fc-PIP** and **DHIPOH** respectively (Figure 2).

Herein we report on the newly designed and synthesized *N,O*-ligand **Fc-DHIPOH** which was found to offer improved enantioselectivities in the aforementioned ligand/$Cu(OAc)_2$ catalyzed asymmetric Michael reactions of glycine derivatives to alkylidene malonates giving 3-aryl glutamic acid derivatives with high enantioselectivities (89%−95% ee).

Scheme 1. Synthesis of *N,O*- Ligands **6a** and **6b**



The synthesis of planar chiral **Fc-DHIPOHs 6a,b** (Scheme 1) was accomplished as follows: The preparation

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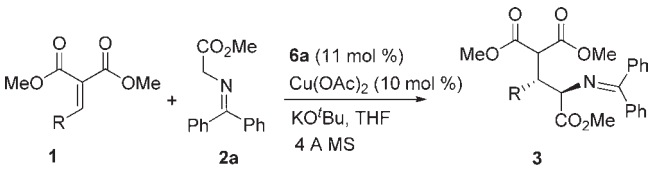
Table 1. Scope of Alkylidene Malonates **1** in Asymmetric 1,4-Michael Addition[a]



entry	R	yield (%)[b]	dr (*anti*/*syn*)	ee (*anti*/*syn*) (%)[c]	note[d]
1	4-Cl-C_6H_4 (**1a**)	94	91/9	93/57 (99)	81
2	4-Br-C_6H_4 (**1c**)	98	96/4	93/95 (98)	81
3	4-NO_2-C_6H_4 (**1d**)	94	85/15	90/55	80
4	C_6H_5 (**1e**)	85	83/17	91/81 (99)	83
5	4-CH_3-C_6H_4 (**1f**)	87	87/13	90/–[e]	82
6	4-CF_3-C_6H_4 (**1g**)	92	94/6	91/63	80
7	4-CH_3O-C_6H_4 (**1h**)	82	88/12	89/–[e]	81
8	3-Cl-C_6H_4 (**1i**)	91	87/13	89/84	79
9	2-furyl (**1j**)	95	67/33	93/91(99)	81
10	3-pyridinyl (**1k**)	91	77/23	90/84	78
11	1-naphthyl (**1l**)	71	80/20	93/90	–
12	*i*Bu (**1m**)	25	>98/2	95/–[e]	–

[a] All reactions performed in anhydrous THF at room temperature, using 11 mol % of ligand **6a**, 10 mol % of $Cu(OAc)_2$, and 10 mol % of KO^tBu. [b] Isolated yields of diastereomer mixtures. [c] All ee values were determined by HPLC, and data in parentheses were the ee of the *anti* adduct after simple crystallization. [d] The ee values given by DHIPOH **5** in previous report. [e] The ee of syn product was not determined.

of racemic **7** according to Fu's protocol,[4a] followed by a Pd-catalyzed C–N coupling of (*S*)-oxazolidinone **8** to **7**, gave two chromatographically separable diastereoisomers (S,S_p)-**9a** and (S,R_p)-**9b** in 38% and 40% yields respectively (78% overall yield).[3] Hydrolysis of the resultant isomers in the presence of methanolic sodium hydroxide afforded the corresponding alcohols **10a** and **10b**, which were then treated with $MsCl/Et_3N$ to furnish the two diastereoisomers (S,S_p)-**6a** and (S,R_p)-**6b** in 74% and 69% yields respectively. The relative configurations of the two isomers were assigned on the basis of single-crystal X-ray diffraction analysis of the isomer (S,R_p)-**6b** (see Supporting Information (SI)). With these two Fc-DHIPOHs **6a,b** in hand, our recently developed asymmetric copper-catalyzed 1,4-Michael addition of glycine derivative **2a** to alkylidene malonate **1a** was tested under the optimal reaction conditions.[6b] To our delight, *N,O*-ligand (S,S_p)-**6a** permitted the reaction to proceed smoothly affording the corresponding adducts in 94% yield, 91:9 diastereoisomer ratio, and 93% ee. Comparing this result with that obtained when a ligand **4** that does not bear a pentaphenyl ferrocene moiety revealed a 22% improvement in ee.

Significantly, the diastereoisomer (S,S_p)-**6b** was completely inactive for the same reaction. Further screening of reaction conditions confirmed the optimal reaction protocol to be in line with that we previously disclosed;[6b] details of the metal salts and solvents tried are summarized in the SI, where it can be seen that selection of the ester moiety of glycine derivative **2**, ethyl ester **2b**, gave similar diastereoselectivity but lower enantioselectivity (81% ee) and the bulkier *tert*-butyl ester **2c** gave corresponding adduct **3ac** with an excellent diastereoisomeric ratio (>99:1), but in almost racemic form (3% ee). When diisopropyl ester **1b** was used instead of dimethyl ester **1a** in a reaction with **2a**, none of the desired adduct was formed, perhaps due to the steric influence of the bulky isopropyl group. Therefore, methyl glycine derivative **2a** was used for probing the scope of methyl alkylidene malonates **1**.

A range of β-(hetero)aryl alkylidene malonates **1c**–**m** were next employed in reactions with methyl glycine derivative **2a** in the presence of (S,S_p)-**6a**/$Cu(OAc)_2$ in THF at room temperature. As shown in Table 1, all the reactions of aryl alkylidene malonate substrates containing both electron-withdrawing and -donating groups proceeded smoothly giving similar enantioselectivities (Table 1, 89–93% ee, entries 1–8). The *p*-bromophenyl alkylidene malonate gave the highest dr up to 96:4 (Table 1, entry 2).

Hetereoaryl alkylidene malonates **1i** and **1j** also reacted smoothly with **2a** to afford the corresponding Michael adducts in excellent yields and the same levels of enantioselectivity, albeit with lower diastereoselectivities (Table 1, entries 9–10). Larger naphthyl alkylidene malonate **1l** gave high enantioselectivity for both *anti* (93% ee) and *syn* isomers (90% ee), but with a slightly lower yield and

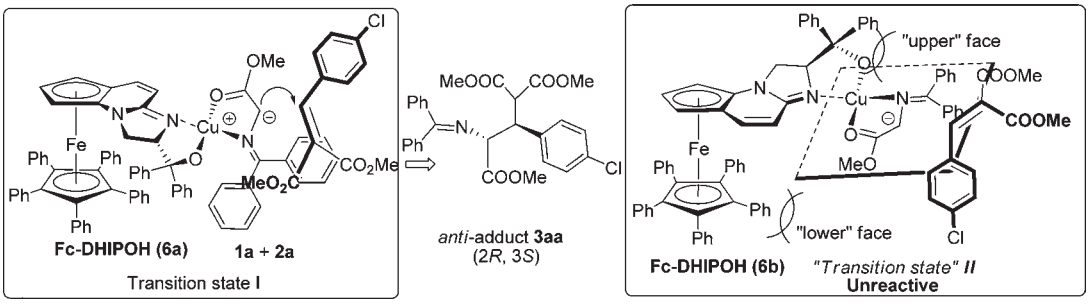


Figure 3. Proposed Transition States for Steric Control Mode of **6a** and **6b**.

diastereoselectivity (Table 1, entry 11). The aliphatic alkylidene malonate **1m** showed low reactivity to give corresponding adduct **3ma** in only 25% yield, but with excellent diastereo- and enantioselectivity (Table 1, entry 12, >98:2 dr, 95% ee). The relative and absolute configuration of major adducts of **3** were assigned as the *anti*-(2*R*,3*S*) isomer by the comparison of the retention times of *anti* enantiomers to those reported in our previous report.[6b]

Based on these results, we reasoned that the stereocontrolling modes for both **DHIPOH** and **Fc-DHIPOH** systems are similar (Figure 3, transition state **I**), and the central and planar chirality features of *N*,*O*-ligand **Fc-DHIPOH 6a** are well matched. Furthermore, the complete inactivity of diastereoisomer **6b** in the same 1,4-Michael addition implies that two chiral elements of **6b** are mismatched. A possible *transition state* **II** was proposed to account for this result (Figure 3), in which both "upper" and "lower" faces (as drawn) are blocked by the diphenylmethanol group and η^5-C_5Ph_5 moiety, respectively.

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In summary, we have developed a novel planar chiral *N*,*O*-ligand−copper catalyst construct, **Fc-DHIPOH 6a**/Cu(OAc)$_2$, which has proved to be a highly efficient catalyst for the 1,4-Michael addition of glycine derivatives to alkylidene malonates to afford 3-substituted glutamic acid derivatives in moderate to excellent yields (25−98%), with good diastereoselectivities (up to >98/2) and excellent enantioselectivities (up to 95% ee for the *anti* adducts).[10] We expect that this new DHIP-based planar chiral *N*,*O*-ligand architecture could open the door to new developments in the area of asymmetric catalysis. Further studies on the mechanism and applications of this reaction are now in progress.

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Supporting Information Available. Procedure for the synthesis of *N*,*O*-Ligand **6a,b**, table of optimization data, general procedures for 1,4-Michael addition and characterization of corresponding products, copies of 400 MHz ^{1}H and 100 MHz ^{13}C NMR of all ligands and products as well as their HPLC data. This material is available free of charge via Internet at http://pubs.acs.org.