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ARTICLE TYPE

Bifunctional Ferrocene-Based Squaramide-Phosphine as an Organocatalyst for Highly Enantioselective Intramolecular Morita–Baylis–Hillman Reaction

Xiaorui Zhang[‡a,b], Pengfei Ma[‡a], Dongxu Zhang[a], Yang Lei[a], Shengyong Zhang[a], Ru Jiang*[a], Weiping Chen*[a]

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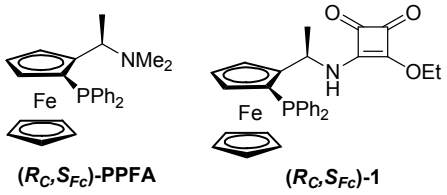
This work demonstrates that, in accord with metal catalysis, ferrocene could be an excellent scaffold for organocatalysts. The simple and easily accessible bifunctional ferrocene-based squaramide-phosphine shows high enantioselectivity in the intramolecular Morita-Baylis-Hillman reaction of 7-aryl-7-oxo-5-heptenals, giving a variety of 2-aroyl-2-cyclohexenols in up to 96% *ee*.

Asymmetric organocatalysis has emerged in the past decade as a powerful tool in contemporary organic synthesis and grown into three pillars of asymmetric catalysis together with biocatalysis and metal catalysis.[1] So far, numerous organocatalysts, developed in the past decade, have been rooted in several core structures, such as amino acids,[2] β-amino alcohols,[3] 1,2-diamines,[4] binaphthyl,[5] *cinchona* alkaloids,[6] *etc*. Ferrocene is a "privileged framework" for the construction of effective chiral ligands in metal catalysis due to its easy accessibility and derivatization, and special electronic and steric properties.[7] Surprisingly, ferrocene has not been exploited as a backbone of organocatalysts[8] excepting for the use of the planar chiral DMAP[9] and PIP[10] as acyl transfer catalysts for the kinetic resolution of racemic alcohols and amines, as well as simple chiral ferrocene-based phosphines as nucleophilic organocatalysts for the enantioselective boration of olefins,[11] dimerizations of ketenes,[12] [3+2] cyclizations[13] and (aza)-Morita–Baylis–Hillman reaction.[14] As part of a project developing ferrocene-based chiral ligands and catalysts,[15] we are interested in exploring the potential of ferrocene as a scaffold for effective organocatalysts.

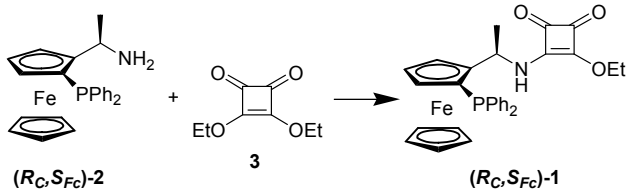
Multifunctional chiral phosphines have proven to be powerful organocatalysts.[16] The combination of a hydrogen bonding motif with a highly nucleophilic phosphorus center within one molecule bearing a chiral framework can synergistically activate the substrates in a stereocontrolled manner, leading to high enantioselectivities in asymmetric transformations. More importantly, the catalytic activities and enantioselectivities of these multifunctional/bifunctional chiral phosphine organocatalysts can be finely tuned by simply varying the chiral scaffold, the phosphorus nucleophilicity and the hydrogen bond donors. Herein, we design bifunctional ferrocene-based squaramide-phosphine (R_C,S_{Fc})-**1** (Figure 1) for enantioselective intramolecular Morita-Baylis-Hillman (MBH) reaction.[17] To the best of our knowledge, this is the first example of ferrocene-based bifunctional phosphine for highly enantioselective organocatalysis.



(R_C,S_{Fc})-PPFA (R_C,S_{Fc})-**1**

Figure 1. Ferrocene-based squaramide-phosphine (R_C,S_{Fc})-**1**.

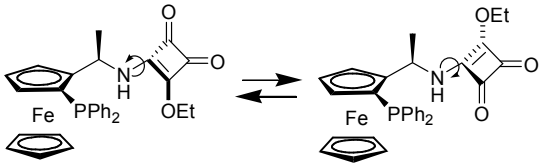
Ferrocene-based squaramide-phosphine (R_C,S_{Fc})-**1** was easily prepared by the condensation of (R_C,S_{Fc})-1-(1-aminoethyl)-2-diphenylphosphinoferrocene (R_C,S_{Fc})-**2**[18] with diethyl squarate **3** (Scheme 1). Thus, a solution of (R_C,S_{Fc})-**2** and diethyl squarate **3** (1.2 equivalent) in CH_2Cl_2 was refluxed for 24 h to give (R_C,S_{Fc})-**1** in 94% yield.



(R_C,S_{Fc})-**2** **3** (R_C,S_{Fc})-**1**

Scheme 1. Synthesis of (R_C,S_{Fc})-**1**.

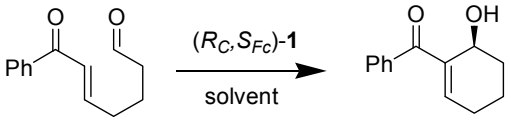
Interestingly, the NMR spectra of (R_C,S_{Fc})-**1** show that (R_C,S_{Fc})-**1** exists as a mixture of two conformational isomers (see *Supporting Information*), plausibly (R_C,S_{Fc})-**1a** and (R_C,S_{Fc})-**1b** (Scheme 2), in which the rotation of four-membered squarate ring around C-N bond is blocked by the hindered diphenylphosphino group. The ratio of two conformers is about 2:1 in $CDCl_3$ (assignment by ^{1}H NMR and ^{31}P NMR) while the ratio changes to about 1:1 in MeOH-d_4 and DMSO-d_6 (assignment by ^{31}P NMR).



(R_C, S_{Fc})-1a (R_C, S_{Fc})-1b

Scheme 2. Plausible conformers of (R_C,S_{Fc})-**1**.

Table 1. The enantioselective intramolecular MBH reaction of 7-phenyl-7-oxo-5-heptenal catalyzed by (R_C,S_{Fc})-**1**[a]



4a **5a**

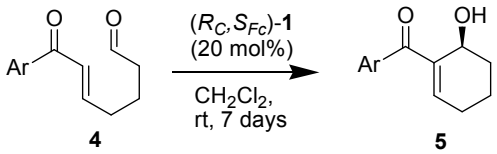
Entry	(R_C,S_{Fc})-**1** (mol%)	Solvent	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	20	EtOH	25	70	83
2	20	*n*-Hexane	25	trace	ND
3	20	Toluene	25	trace	ND
4	20	Et_2O	25	trace	ND
5	20	CH_3CN	25	trace	ND
6	20	THF	25	trace	ND
7	20	Dioxane	25	trace	ND
8	20	MeOH	25	67	81
9	20	*i*-PrOH	25	62	60
10	20	$CHCl_3$	25	68	73
11	20	CH_2Cl_2	25	70	91
12	5	CH_2Cl_2	25	20	75
13	10	CH_2Cl_2	25	35	83
14	20	CH_2Cl_2	0	45	91
15	20	CH_2Cl_2	-10	22	91
16[d]	20	CH_2Cl_2	40	68	83
17[e]		CH_2Cl_2	25	76	~0

[a] Unless otherwise specified, the reactions were performed with 0.2 mmol of **4a** in 1.0 mL of solvent for 7 days. [b] Isolated yield. [c] Determined by HPLC using a Chiralpak OD-H column. [d] Reacted for 4 days.[e] 20 mol% of (R_C,S_{Fc})-PPFA was used as catalyst.

The efficiency of (R_C,S_{Fc})-**1** was first investigated in the enantioselective intramolecular MBH reaction of 7-phenyl-7-oxo-5-heptenal **4a** (Table 1). To our delight, (R_C,S_{Fc})-**1** exhibited high enantioselectivity in the reaction *albeit* the activity was somewhat low. Thus, in the presence of 20 mol% of (R_C,S_{Fc})-**1**, reaction in EtOH at room temperature for 7 days gave the desired product **5a** in 83% *ee* and 68% yield (Table 1, entry 1). To optimize the reaction efficiency, various solvents were then examined. The reaction hardly took place with nonpolar solvents such as *n*-hexane and toluene (entries 2-3) and polar aprotic solvents such as Et_2O, acetonitrile, THF and dioxane (entries 4-7). The reactions performed in polar protic solvents MeOH and *i*-PrOH as well as chlorinated solvents $CHCl_3$ and CH_2Cl_2 proceeded smoothly (entries 8-11). CH_2Cl_2 proved to be the best solvent in terms of catalytic reactivity and enantioselectivity (entry 11). Lowering of the catalyst loading to 5 mol % and 10 mol% led to a significant decrease in both yield and enantioselectivity (entries 12-13). Interestingly, lower reaction temperature did not improve the enantioselectivity (entries 14-15). As expected, reaction at elevated temperature increased the catalytic activity but deteriorated the enantioselectivity (entry 16). The squaramide moiety of (R_C,S_{Fc})-**1** plays a crucial role in the enantioselective induction. When (R_C,S_{Fc})-PPFA, replacing squaramide moiety of (R_C,S_{Fc})-**1** with dimethylamino group, was used as a catalyst, the intramolecular MBH reaction of 7-phenyl-7-oxo-5-heptenal **4a** gave the product **5a** in 76% yield but in racemic (entry 17).

Following initial establishment of appropriate solvent, amount of catalyst, reaction time and temperature, the substrate scope was explored in the (R_C,S_{Fc})-**1** catalyzed enantioselective intramolecular MBH reaction. As shown in Table 2, the reactions worked well with 7-aryl-7-oxo-5-heptenals **4a–h**, bearing hydrogen or electron-withdrawing substituents on the *para*- and *meta*-position of the phenyl ring, and 2-naphthyl derivative **4i**, to give the desired products in excellent enantioselectivity (91–96% ee) (Table 2, entries 1–5 and 8-9) excepting for 4-CF_3 and 3-Br substituted dervatives (entries 6-7). Unsurprisingly, the reaction was slower for the substrates with electron-donating groups on the phenyl ring (entries 10-11). It is worth noting that, like the enantioselective intramolecular MBH reaction catalyzed by the amino acids derivatived thiourea-phosphines[17d] and the cyclohexane-based thiourea-phosphines[17e], the substrates bearing 2-Br and 2-Cl on the phenyl ring gave very poor enantioselectivity (entries 12-13).

Table 2. The enantioselective intramolecular MBH reaction of 7-aryl-7-oxo-5-heptenals catalyzed by (R_C,S_{Fc})-**1**[a]



4 **5**

Entry	Ar	Product	Yield (%)	*ee* (%)[b]
1	C_6H_5 (**4a**)	**5a**	70	91
2	4-$NO_2C_6H_4$(**4b**)	**5b**	85	94
3	4-FC_6H_4(**4c**)	**5c**	82	96
4	4-BrC_6H_4(**4d**)	**5d**	81	92
5	4-ClC_6H_4(**4e**)	**5e**	82	92
6	4-$CF_3C_6H_4$(**4f**)	**5f**	83	83
7	3-BrC_6H_4(**4g**)	**5g**	72	87
8	3-ClC_6H_4(**4h**)	**5h**	73	92
9	2-Naphthyl(**4i**)	**5i**	72	93
10	4-MeC_6H_4(**4j**)	**5j**	68	88
11	4-$MeOC_6H_4$(**4k**)	**5k**	41	87
12	2-BrC_6H_4(**4l**)	**5l**	74	10
13	2-ClC_6H_4(**4m**)	**5m**	73	11

[a] The reaction conditions were the same with those in Table 1, entry 11. [b] Determined by HPLC using Daicel Chiralcel OD-H, Chiralpak AS-H or Chiralpak AD-H column.

The absolute configuration of the intramolecular MBH products was assigned as (*S*) by comparing the optical rotation value with those reported in the literature.[17] A plausible transition state **A** for the (R_C,S_{Fc})-**1** catalyzed intramolecular MBH reaction was presented in Figure 2. A hydrogen-bonding interaction between the electrophilic squaramide and the oxygen atom of aldehyde

forms, and the nucleophilic phosphine attacks the α,β-unsaturated ketone to generate the transition state **A**,[17d,17e,17g] which is stabilized by the hydrogen-bonding interaction and is rigid. The planar and carbon-centered chiral ferrocenyl scaffold forces the enolate to attack the activated carbonyl of the aldehyde from the *si*-face in highly enantioselective way to afford the product with an (*S*)-configuration. The extremely poor enantioselectivity of 2-Br and 2-Cl derivatives (Table 2, entries 12-13) in the reaction can be explained utilizing a possible transition state **B**. The electrophilic squaramide might prefer forming a hydrogen-bonding interaction with the oxygen atom of ketone and 2-Br or 2-Cl *via* a six-membered ring, and the nucleophilic phosphine attacks the activated α,β-unsaturated ketone to generate the transition state **B** , which is flexible with respect to aldehyde moiety, leading to very low enantioselectivity in the addition of the enolate to the unactivated aldehyde.

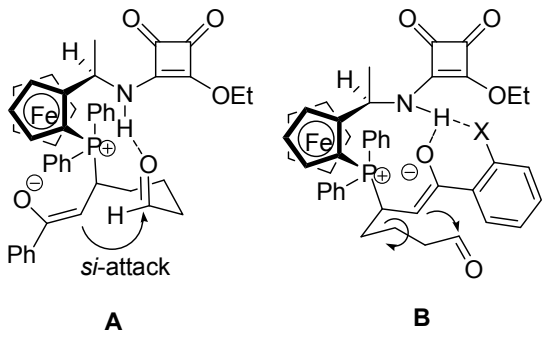


Figure 2. *Possible transition states*

Catalyst–substrate hydrogen-bonding interactions in non-enzymatic catalysis usually occur in aprotic solvents.[19] However, the (R_C,S_{Fc})-**1** catalyzed intramolecular MBH reaction gave excellent results in polar protic solvents EtOH, MeOH and *i*-PrOH. The influence of hydrogen-bond donors, *e.g.* protic solvents, products or additives, on the acceleration of the rates of the MBH reactions has been well documented. The participation of a catalytic quantity of alcohol in the proton transfer step in the MBH reactions has been proposed,[20a] and later was supported by the computational work by Aggarwal and co-workers.[20b] The excellent performance of this intramolecular MBH reaction in protic solvents well agrees with Aggarwal's proposal.

Conclusions

In summary, the easily accessible bifunctional ferrocene-based squaramide-phosphine (R_C,S_{Fc})-**1** shows high enantioselectivity in the intramolecular Morita-Baylis-Hillman reaction of 7-aryl-7-oxo-5-heptenals, giving a variety of 2-aroyl-2-cyclohexenols in up to 96% *ee*. This work demonstrates that, in accord with metal catalysis, ferrocene could be an excellent scaffold for organocatalysts. Work is actively under way in our lab to optimize bifunctional ferrocene-based phosphine, expand its application to other valuable transformations and develop other type of organocatalysts based on ferrocene backbone.

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Notes and references

[a] *X. Zhang, P. Ma, D. Zhang, Y. Lei, S. Zhang, R. Jiang, W. Chen; School of Pharmacy, Fourth Military Medical University, 169 Changle West Road, Xi'an, 710032, P. R. China; E-mail: wpchen@fmmu.edu.cn*
[b] *Department of Pharmacy, the 323th Hospital of PLA, 6 Jianshe West Road, Xi'an, 710054, P. R. China*

‡ These authors contributed equally to this work.

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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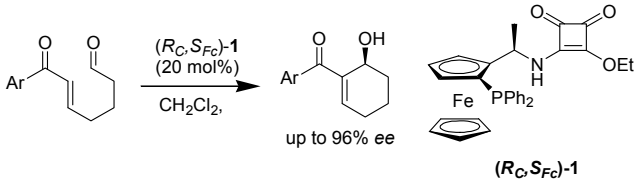

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