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Bifunctional ferrocene-based squaramide-phosphine as an organocatalyst for highly enantioselective intramolecular Morita–Baylis–Hillman reaction†

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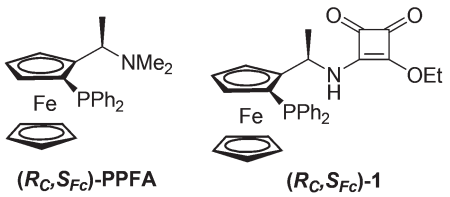
This work demonstrates that, in accord with metal catalysis, ferrocene could be an excellent scaffold for organocatalysts. The simple and easily accessible bifunctional ferrocene-based squaramide-phosphine shows high enantioselectivity in the intramolecular Morita–Baylis–Hillman reaction of 7-aryl-7-oxo-5-heptenals, 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 has developed into three important areas 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** (Fig. 1) for enantioselective intramolecular Morita–Baylis–Hillman (MBH) reaction.[17] To the best of our knowledge, this is the first example of a ferrocene-based bifunctional phosphine for highly enantioselective organocatalysis.

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.

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 ESI†), 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



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

Fig. 1 (R_C,S_{Fc})-PPFA and ferrocene-based squaramide-phosphine (R_C,S_{Fc})-**1**.

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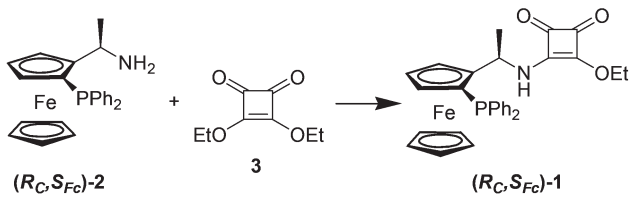
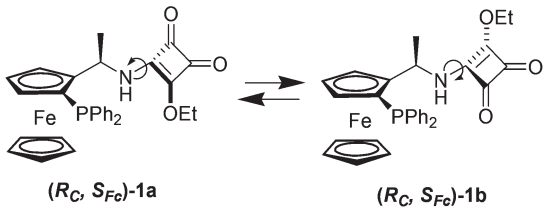


Scheme 1 Synthesis of (R_C,S_{Fc})-**1**.



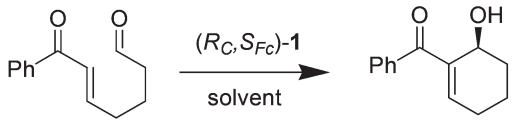
Scheme 2 Plausible conformers of (R_C,S_{Fc})-**1**.

group. The ratio of the 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).

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**, the 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 and 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, a lower reaction temperature did not improve the enantioselectivity (entries 14 and 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 the squaramide moiety of (R_C,S_{Fc})-**1** with a 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 as a racemic mixture (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 in the *para*- and *meta*-position of the phenyl ring, and 2-naphthyl

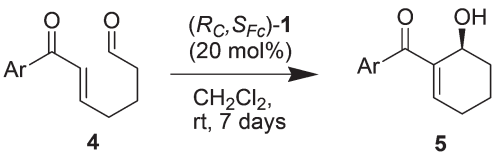
Table 1 The enantioselective intramolecular MBH reaction of 7-phenyl-7-oxo-5-heptenal catalyzed by (R_C,S_{Fc})-**1**[a]



Entry	(R_C,S_{Fc})-**1** (mol%)	Solvent	Temp. (°C)	Yield[b] (%)	ee[c] (%)
1	20	EtOH	25	68	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.

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



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.

derivative **4i**, to give the desired products in excellent enantioselectivities (91–96% ee) (Table 2, entries 1–5 and 8–9) except for the 4-CF_3 and 3-Br substituted derivatives (entries 6 and 7). Unsurprisingly, the reaction was slower for the substrates with electron-donating groups on the phenyl ring (entries 10 and 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 enantioselectivities (entries 12 and 13).

The absolute configuration of the intramolecular MBH products was assigned as (*S*) by comparing the optical rotation values with those reported in the literature.[17] A plausible transition state **A** for the (R_C,S_{Fc})-**1** catalyzed intramolecular MBH reaction is presented in Fig. 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,e,g] 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 a 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 and 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.

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 computational work by Aggarwal and co-workers.[20b] The excellent performance of this intramolecular MBH reaction in protic solvents agrees well with Aggarwal's proposal.

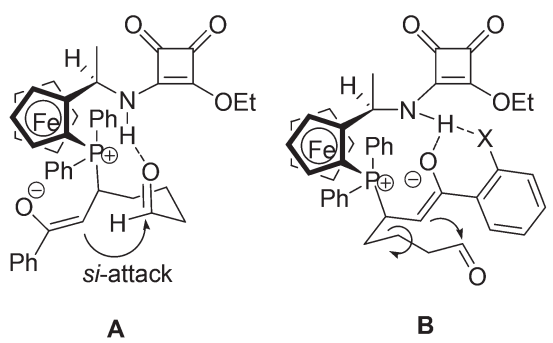


Fig. 2 Possible transition states.

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 types of organocatalysts based on a ferrocene backbone.

Acknowledgements

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