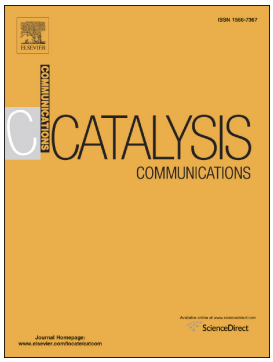

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Ferrocene-Based Bifunctional organocatalyst for Highly Enantioselective Intramolecular Rauhut–Currier Reaction

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Abstract

Three series of novel ferrocene-based bifunctional chiral phosphines have been designed and synthesized. Thethiourea-phosphine **A7** showed good performance in enantioselective intramolecular Rauhut–Currier reaction of bis(enones), giving the corresponding products in good yield with up to 98% *ee*. Moreover, with amino acid derived amide-phosphine **B3**, optically active *α*-methylene-*δ*-valerolactone was obtained in 88% yield and > 99.9% *ee* utilizing the enantioselective intramolecular Rauhut-Currier reaction of chalcone derivative.

Keywords: Ferrocene-based organocatalyst; Rauhut–Currier reaction; Bifunctional chiral phosphine; Enantioselective

1. Introduction

Chiral phosphine catalysis, especially the use of bi- and multi-functional chiral phosphines, has progressed at an astonishingly rate over last decade and it offers the efficient creation of a diverse range of structural architectures [1]. Phosphines usually show distinctive catalytic behaviors mainly because of stronger nucleophilicity and weaker basicity compared to amine catalysts[2]. In a general mode of activation, relying on the non-bonded electron pairs, a phosphine adds to activated alkenes, allenes, or alkynes to form an ylide type zwitterionic intermediate, which reacts with activated electrophilic partners, such as olefins, imines, and aldehydes, resulting in diverse transformations such as Morita−Baylis−Hillman (MBH) [3], Rauhut−Currier (RC) [4], and multiple annulation reactions [5].

Rauhut-Currier (RC) reaction [4, 6-9], also known as vinylogous MBH reaction, is one of the oldest phosphine-catalyzed reactions, first reported as early as 1963 [10], and is an efficient, atom-economic approach to densely functionalized alkenes via forming a new carbon-carbon bond. One alkene is activated by nucleophilic catalysts to serve as a latent enolate and the other is used as a Michael acceptorin RC reaction. Asymmetric RC reactions presents significant challenges due to low reactivity and poor control of chemo- and stereoselectivity of the process [4]. The first successful enantioselective RC reaction was reported by Miller utilizing a cysteine-based catalyst in 2007 [11]. The following years have witnessed different groups contributed to the catalyst development, and a significant progress was achieved by the introduction of bi- and multi-functional chiral phosphines [12-19]. Complementing the

nucleophilicity of the phosphine with a Lewis acidic functionality, the new generation of bifunctional catalysts accessed several RC products in extraordinary yields and selectivities [12,13,16,18]. However, even those catalysts have their limits, such as high catalyst loading and limited substrate scope. Hence, the development of new catalysts is still highly desirable.

Ferrocene has been recognized as a "privileged framework" for the construction of effective chiral ligands in metal catalysis [20]. Surprisingly, ferrocene had not been exploited as a chiral backbone of organocatalysts until 2014 [21], except for the use of the planar chiral DMAP [22] and PIP [23] 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 [24], dimerizations of ketenes [25], [3 + 2] cyclizations [26] and (*aza*-)Morita–Baylis–Hillman reaction [27]. In 2014, we reported ferrocene-based bifunctional amine–thiourea (R_C,S_{Fc})-**1** (Fig. 1) for highly effective Michael addition of acetylacetone to nitroolefins [28]. This work demonstrated that, in accord with metal catalysis, ferrocene could be an excellent chiral scaffold for organocatalysts for the first time. As a part of our ongoing project for the development of ferrocene-based chiral ligands and catalysts [29-35], we became interested in developing new ferrocene-based bifunctional phosphines as catalysts for enantioselective RC reaction. Previously, we reported bifunctional ferrocene-based squaramide-phosphine, FerroSquaPhos (Fig. 1), as an efficient organocatalyst for highly enantioselective intramolecular MBHreaction (up to 96% *ee*, 82% yield) [33]. Due to the mechanistic

similarity of MBH and RC, the FerroSquaPhos was first tested in the enantioselective intramolecular RC reaction of bis(enone). Unfortunately, FerroSquaPhos did not show any catalytic activity in the reaction. Then, three series of new ferrocene-based bifunctional phosphines **A-C** were then designed (Fig.1). We envisioned that replacement of diphenylphosphino moiety on ferrocene with dialkylphosphino groups might increase the nucleophilicity, and hence enhances the catalytic activity of bifunctional phosphines. Three different H-bonding donors were introduced since the H-bonding donor of bifunctional phosphines also plays important role in catalysis.

Fig.1. Structures of the designed ferrocene-based bifunctional organocatalysts.

2. Results and discussion

The new bifunctional phosphines were easily prepared *via* a simple synthetic route (Scheme 1). According to the "one-pot" synthesis that we developed previously [29,31,33], lithiation of Ugi's amine (*R*)-**2** with *tert*-BuLi in *t*-butyl methyl ether (TBME) at 0 °C, followed by reaction with PCl_3 at −78 °C, and then reaction with RMgBr to afford the PPFA derivatives (R_C,S_{Fc})-**3**. After reaction of **3** with Ac_2O at 100 °C, followed by treatment with a large excess of ammonia in a mixture of water, methanol and THF at 60 °C, the dimethylamino group of **3** was substituted by an amino group to give primary amines (R_C,S_{Fc})-**4**. Finally, (R_C,S_{Fc})-**4** was converted to catalysts **A-C**.

Scheme 1. Synthesis of ferrocene-based bifunctional phosphines **A**-**C**.

With the new ferrocene-based bifunctional phosphines in hand, the enantioselective intramolecular RC reaction using (2*E*,7*E*)-1,9-diphenylnona-2,7-diene-1,9-dione **5a** as model substrate was tested (Scheme 2). The reaction was performed using 10 mol% catalyst **A**-**C** with 0.1 mmol of **5a** in 2 mL of CH_2Cl_2 at room temperature for 24 h. As shown in Scheme 2, the introduction of dialkylphosphino groups on ferrocene indeed increased the catalytic activity. Thiourea-phosphines gave better results than other three types of catalysts. The best result was achieved using **A7** (R^1 = Et, R^2 = 3,5-$(CF_3)_2$-C_6H_3), giving **6a** in 61% yield and 98% *ee*.

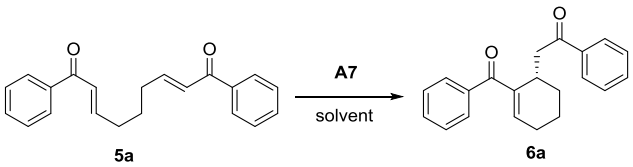
Scheme 2. Catalysts screening.

To optimize the reaction efficiency, various conditions were then examined (Table 1). Unlike FerroSquaPhos-catalyzed enantioselective intramolecular Morita–Baylis–Hillman (MBH) reaction [32], the **A7** catalyzed enantioselective intramolecular RC reaction of (2*E*,7*E*)-1,9-diphenylnona-2,7-diene-1,9-dione **5a** could take place in all solvents tested, although polar protic solvent MeOH gave very poor result (entry 1). TBME, THF and EtOAc afforded higher yield and good enantioselectivity (entry 2, 6 and 8). CH_2Cl_2 proved to be the best solvent in terms of catalytic reactivity and enantioselectivity (entry 13). Lowering or increasing the

catalyst loading slightly affected both yield and enantioselectivity (entries 14-15). Surprisingly, lower reaction temperature deteriorated significantly the enantioselectivity and catalytic reactivity (entry 16). In addition, the addition of NaI, K_2CO_3, phenol and AcOH as an additive also could not improve the performance.

Table 1.

Optimization of the reaction conditions.[a]



Entry	**A7** (mol%)	Solvent	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	10	MeOH	25	26	15
2	10	TBME	25	74	65
3	10	Toluene	25	46	65
4	10	Et_2O	25	56	75
5	10	CH_3CN	25	41	90
6	10	THF	25	73	88
7	10	Dioxane	25	53	74
8	10	EtOAc	25	77	78
9	10	Acetone	25	62	85
10	10	DMSO	25	29	77

11	10	DMF	25	28	91
12	10	$CHCl_3$	25	42	95
13	10	CH_2Cl_2	25	61	98
14	5	CH_2Cl_2	25	54	95
15	20	CH_2Cl_2	25	67	95
16	10	CH_2Cl_2	0	14	89
18[d]	10	CH_2Cl_2	25	26	98
19[e]	10	CH_2Cl_2	25	65	98

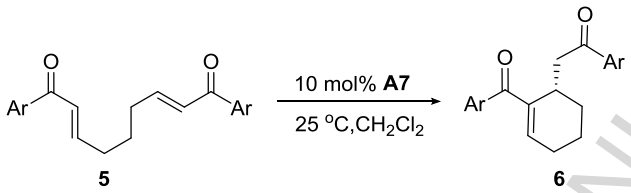
[a]Unless otherwise specified, the reactions were performed with 0.1 mmol of **5a** in 1.0 mL of solvent for 24 h. [b]Isolated yield. [c]Determined by HPLC using a Chiralpak AD-H column. Absolute configuration was assigned by comparing the optical rotation values with those reported in the literature [11,18]. [d]Reaction for 12 h. [e]Reaction for 48 h.

Following initial establishment of appropriate solvent, the substrate scope was explored in the **A7** catalyzed enantioselective intramolecular RC reaction. As shown in Table 2, the reactions worked well with (2*E*,7*E*)-1,9-diarylnona-2,7-diene-1,9-diones **5a–n**, bearing hydrogen, halo and electron-donating substituents on the *para*- and *meta*-position of the phenyl ring to give the desired products in excellent enantioselectivity (92–98% *ee*) (Table 2, entries 1–10). However, the (2*E*,7*E*)-1,9-diarylnona-2,7-diene-1,9-diones bearing strong electron-withdrawing substituents on the *para*- and *meta*-position of the phenyl ring

significantly descreased the enatioselectivity (entries 11–12). The low enantioselectivity of *meta*-nitro substituted substrate is understandable (entry 12) since nitro can interact with thiourea, and hence interferes with the catalysis. Notably, the substrates bearing *ortho*-substituents on the phenyl ring gave very poor enantioselectivity (entries 13-14), possibly due to the steric hindrance.

Table 2.

Substrate scope of asymmetric intramolecular RC reaction catalyzed by A7.[a]



Entry	Ar	Product	Yield (%)	*ee* (%)[b]
1	C_6H_5 (**5a**)	6a	61	98
2	4-$CH_3C_6H_4$ (**5b**)	6b	56	96
3	4-FC_6H_4 (**5c**)	6c	68	98
4	4-BrC_6H_4 (**5d**)	6d	75	97
5	4-ClC_6H_4 (**5e**)	6e	47	95
6	4-$CH_3OC_6H_4$ (**5f**)	6f	35	93
7	3-$CH_3OC_6H_4$ (**5g**)	6g	42	96
8	3-FC_6H_4 (**5h**)	6h	73	94
9	3-ClC_6H_4 (**5i**)	6i	41	92

10	3-BrC_6H_4 (**5j**)	6j	91	93
11	4-$CF_3C_6H_4$ (**5k**)	6k	85	82
12	3-$NO_2C_6H_4$ (**5l**)	6n	63	62
13	2-ClC_6H_4 (**5m**)	6l	88	40
14	2-CH_3O-C_6H_4 (**5n**)	6m	40	38

[a]The reaction conditions were the same with those in Table 1, entry 13.

[b]Determined by HPLC using Chiralpak AS-H or Chiralpak AD-H column.

According to the above experimental results and related reports [16,18,19], a plausible transition state for **A7** catalyzed intramolecular RC reaction is presented in Figure 3. A nucleophilic addition of the phosphine to the *β*-position of the Michael acceptor generates an enolate, while the bis(enones) are activated by the electrophilic thiourea through hydrogen-bonding interactions. The planar and carbon-centered chiral ferrocenyl scaffold forces the phosphinoyl-associated enolate to attack the activated C=C of the bis(enones) from the *si*-face in a highly enantioselective way to afford the product with an (*S*)-configuration.

Fig. 2. Proposed transition state for the **A7** catalyzed intramolecular RC reaction.

Preliminarily, catalysts A-C were also screened in the enantioselective intramolecular RC reaction of (*E*)-2-(3-oxo-3-phenylprop-1-enyl)phenyl acrylate **7**, and catalyst **B3** gave very promising results, providingα-methylene-δ-valerolactone **8**

with 88% yield and > 99.9% *ee*, which is a common structural motif in a large family of natural products with a broad range of biological activities (Fig.3) [17].

Fig.3. Enantioselective intramolecular Rauhut-Currier reaction of (*E*)-2-(3-oxo-3-phenylprop-1-enyl)phenyl acrylate **7** catalyzed by **B3**

3. Conclusion

Three series of new ferrocene-based bifunctional phosphines have been designed and synthesized. The ferrocene-based bifunctional thiourea-phosphine **A7**, with diethylphosphino group, is a highly efficient catalyst for the enantioselective intramolecular Rauhut-Currier reaction of (2*E*,7*E*)-1,9-diarylnona-2,7-diene-1,9-diones, giving the products with up to 91% yield and up to 98% *ee* enantioselectivity. In a preliminary test, in the enantioselective intramolecular Rauhut-Currier reaction of (*E*)-2-(3-oxo-3-phenylprop-1-enyl)phenyl acrylate amino acid derived bifunctional phosphine **B3** afforded product in 88% yield and > 99.9% *ee*. These results are comparable to the best results so far reported. Work is actively under way in our lab to expand its application to other substrates.

4. Experimental section

*4.1 Synthesis of catalysts **A***

Isothiocyanate (2 mmol) in dry THF (3 mL) was added dropwise into a solution of (R_C,S_{Fc})-**4** (1 mmol) in dry THF (8 mL) at room temperature under an N_2 atmosphere, and the corresponding mixture was stirred at this temperature until the reaction

completed (monitoring by TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to afford the afford the desired catalysts **A**.

*4.2 Synthesis of catalysts **B***

Boc-protected amino acid (1.0 mmol),(R_C,S_{Fc})-**4** (1.0 mmol) and EDCI (1.5 mmol) were added into dry THF (10 mL) under an N_2 atmosphere. After the mixture was cooled to 0 °C, DMAP (0.3 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise into the solution. Then the mixture was gradually warmed to room temperature and stirred until the reaction completed (monitoring by TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate 10:1) to afford the afford the catalysts **B**.

*4.3 Synthesis of catalysts **C***[33]

To a solution of (R_C,S_{Fc})-**4**(1 g, 2.4 mmol) in dry THF (5 mL) was added *n*-BuLi (1 mL, 2.4 mmol, 2.4 M) at -30 °C under an N_2 atmosphere, and the mixture was stirred for 10 min. A solution of enantiopure *tert*-butanethiosulfinate (0.47 g, 2.4 mmol) in 1 mL of dry THF was added slowly to the lithium amine solution. Then the mixture was stirred for 2 h at -30 °C, and then ice water were carefully added. The volatile material was removed, and the residue was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash chromatography (petroleum ether/ethyl acetate 4:1) to afford the catalysts **C**.

*4.4Enantioselective intramolecular RC reaction of (2E,7E)-1,9-diarylnona-2,7-diene-1,9-diones **5***

To a solution of ferrocene-based phosphine catalyst (0.01 mmol) in CH_2Cl_2 (1.0 mL) was added the bis(enones) **5** (0.1 mmol) at 25 ℃. The mixture was stirred at the same temperature for 24 h. Then the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the desired cyclic products **6**. The *ee* values were determined by HPLC analysis with Chiralpak AS-H or Chiralpak AD-H column.

*4.5Enantioselective intramolecular Rauhut-Currier reaction of (E)-2-(3-oxo-3-phenylprop-1-enyl)phenyl acrylate **7***

To a stirring solution of catalyst **B3** (0.01 mmol) in CH_2Cl_2 (1.0 mL) was added (*E*)-2-(3-oxo-3-phenylprop-1-enyl)phenyl acrylate **7** (0.1 mmol) at 25 ℃. The mixture was stirred at the same temperature for 24 h. Then the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford *α*-methylene-*δ*-valerolactone **8**. The *ee* value was determined by HPLC analysis with Chiralpak AD-H column.

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Highlights

- Chiral ferrocene-based organocatalystforintramolecular Rauhut-Currier reaction.
- H-bonding donor has a synergistic effect with nucleophilic dialkylphosphino group.
- Ferrocene could be an excellent chiral scaffold for chiral organocatalyst.