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AgOAc catalyzed asymmetric [3+2] cycloaddition of azomethine ylides with chiral ferrocene derived P,S ligands

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Abstract—Ferrocene derived P,S-heterodonor ligands were effectively used in AgOAc catalyzed asymmetric cycloaddition of azomethine ylides. The roles of planar chirality and electronic properties of the phosphorous substituents have been examined, and up to 93% ee was obtained.

The 1,3-dipolar cycloaddition reaction has become a powerful synthetic tool, providing access to highly functionalized O-, S- and N-containing heterocycles.[1] The [3+2] cycloaddition of azomethine ylide 1,3-dipoles with olefinic dipolarophiles constitutes a powerful and reliable approach to the synthesis of highly substituted pyrrolidine derivatives, which are important building units in organic synthesis and can be used as organic catalysts in many asymmetric transformations.[2] In early research, stereoselectivity in the 1,3-dipolar cycloaddition of azomethine ylides was achieved in the presence of a stoichiometric amount of chiral Lewis acid[3] or a chiral auxiliary.[4] The methodology of using a catalytic amount of chiral Lewis acid might be more desirable and has been well developed recently.[5–8] A variety of Lewis acids such as Ag(I),[5] Cu(I),[6] Cu(II)[7] and Zn(II)[8] have proved to be excellent catalytic precursors. Fesulphos ligands, P,S ligands only with planar chirality developed by Carretero's group, were successfully used in the Cu(I) catalyzed cycloaddition of azomethine ylides, and excellent results were obtained when *N*-phenylmaleimide was used as dipolarophile.[6c] However, bad *endo*/*exo* selectivity was achieved when the dipolarophile was changed to dimethyl maleate. Our group[5b] has explored bifunctional AgOAc catalyzed 1,3-dipolar cycloaddition of azomethine ylides with ferrocenyloxazoline derived chiral P,N ligands, and up to 98% ee was obtained. Intrigued by the effectiveness of P,S-heterdonor ligands in asymmetric reactions,[9] we decided to explore the application of ferrocene derived P,S ligands in AgOAc catalyzed asymmetric [3+2] cycloaddition of azomethine ylides. The roles of planar chirality and electronic properties of the phosphorous substituents were also studied.

The chiral P,S ligands (**1a**–**d** and **2**) can be easily prepared according to known methods.[9a] Ligands **1a**–**d** were previously synthesized by our group and used in the asymmetric hydrogenation of quinolines. In the asymmetric cycloaddition, our initial study showed that AgOAc/**1a** effectively catalyzed the cycloaddition of **5a** with *N*-phenylmaleimide, and **6a** was obtained within 2 h with only *endo* selectivity and good enantioselectivity (Table 1, entry 1). The ligand **2** has the same central chirality and opposite planar chirality compared to **1a**. The opposite absolute configuration and lower enantioselectivity were obtained when **2** was used (entry 2). The lower ee may be caused by the mismatched nature of (*S*) planar chirality with the (*S*) central chirality. Next, the effect of the substituent R in ligands **1b**–**d** was studied in order to obtain better enantioselectivity. When R is an electron-withdrawing group, the ee decreased to 82% (entry 3). On the other hand, the ee can be enhanced slightly when R is an electron-donating group (entry 4–5).

The cycloaddition was also studied in different solvents. Complete conversion was observed within 2 h in Et_2O, THF, CH_2Cl_2 and toluene. The highest ee was obtained in Et_2O.

Further improvements in enantioselectivity were made through the variation of the electronic properties of the phosphorous substituents in ligand **1c**.[5b,6b,10] As

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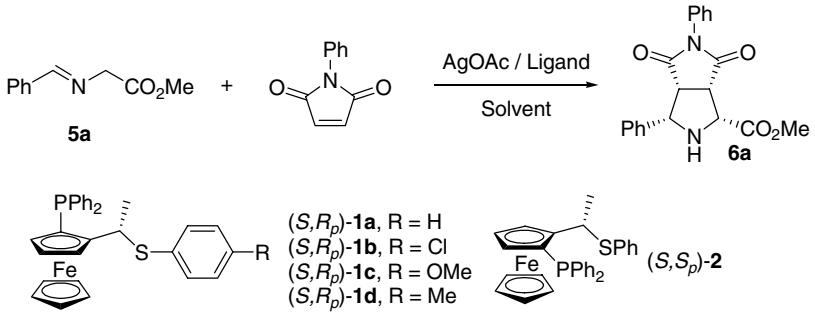
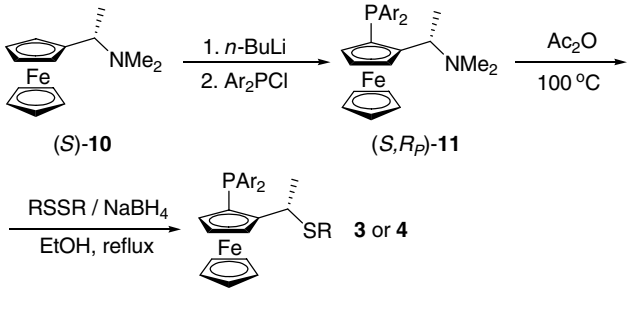
Table 1. AgOAc catalyzed asymmetric cycloaddition of **5a** with *N*-phenylmaleimide[a]



Entry	Ligand	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	Et_2O	0	2	91	86
2	**2**	Et_2O	0	2	83	−78
3	**1b**	Et_2O	0	2	88	82
4	**1c**	Et_2O	0	2	97	87
5	**1d**	Et_2O	0	2	94	87
6	**1c**	CH_2Cl_2	0	2	98	75
7	**1c**	THF	0	2	91	82
8	**1c**	Toluene	0	2	97	84
9	**3a**	Et_2O	0	2	94	83
10	**3b**	Et_2O	0	2	98	87
11	**3c**	Et_2O	0	2	98	92
12	**3d**	Et_2O	0	2	91	88
13	**3c**	Et_2O	−25	3.5	68	91

[a] Conditions: **5a** (1.0 equiv), *N*-phenylmaleimide (1.5 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration (0.12 M).
[b] Isolated yields based on **5a**.
[c] Determined by HPLC.

shown in Scheme 1, ligands **3a**–**d** were synthesized conveniently according to literature procedures from the commercially available *N*,*N*-dimethyl-(*S*)-α-ferrocenylethylamine.[11] Ligands **3a**–**d** all can catalyze the cycloaddition smoothly with high *endo* selectivity (*endo*/*exo* > 95/5). Ligands **3b** and **3d** gave similar results to ligand **1c**. The enantioselectivity slightly decreased with ligand **3a** bearing an electron-donating methoxyl group at the *para*-position of the phenyl ring. Notably, much higher ee was afforded with ligand **3c**, which has two strong electron-withdrawing groups CF_3 at the *meta* position (entry 11). However, no improvement in ee was obtained when the reaction temperature was decreased, although the reaction proceeded slowly at this temperature. Therefore, the optimal condition for the reaction is AgOAc/**3c**/Et_2O/0 °C.



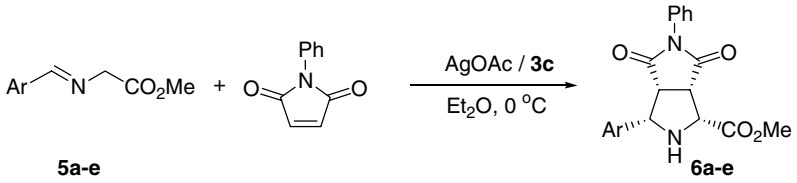
(*S*,*R*$_P$)-**3a**: Ar = 4-$MeOC_6H_4$, R = 4-$MeOC_6H_4$
(*S*,*R*$_P$)-**3b**: Ar = 3,5-$Me_2C_6H_3$, R = 4-$MeOC_6H_4$
(*S*,*R*$_P$)-**3c**: Ar = 3,5-$(CF_3)_2C_6H_3$, R = 4-$MeOC_6H_4$
(*S*,*R*$_P$)-**3d**: Ar = 4-$CF_3C_6H_4$, R = 4-$MeOC_6H_4$
(*S*,*R*$_P$)-**4a**: Ar = 4-$CF_3C_6H_4$, R = 4-ClC_6H_4
(*S*,*R*$_P$)-**4b**: Ar = 4-$CF_3C_6H_4$, R = 4-$CF_3C_6H_4$

Scheme 1. Synthesis of ferrocene derived chiral S,P-ligands.

To explore the scope of the reaction, a wide range of imines **5a**–**e** derived from aromatic aldehydes were employed in the cycloaddition. As summarized in Table 2, electronic and steric properties have a certain effect on enantioselectivity. 95–98% isolated yield and 86–93% ee were obtained with excellent *endo* selectivity. Substrate **5d** bearing an electron-donating substituent on the phenyl brought about a slight decrease in the enantioselectivity (86% ee, entry 4). On the other hand, an electron-withdrawing group on the phenyl ring of substrate **5c** had no obvious effect on enantioselectivity (entry 3).

Variation of the dipolarophile to dimethyl maleate resulted in lower ee and opposite absolute configuration were obtained when ligand **2** was used (Table 3, entries 1, 2). Among the solvents examined, Et_2O was the best solvent. A monodentate phosphine ligand **12**, which has a similar structure with ligand **1a** but without the sulfur atom, was also employed and much lower ee (45%) was achieved (entry 3). The result means the sulfur atom does coordinate to the metal. Interestingly, different effects of the substituent R were observed when ligands **1b**–**d** were used. The presence of an electron-withdrawing group at the *para*-position of phenyl ring gave rise to the positive effect on the enantioselectivity (entry 4). In the same way, the influence of the electronic property of the phosphorous substituents was also stud-

Table 2. Variation of the R-substituent on **5** for the cycloaddition with *N*-phenylmaleimide[a]

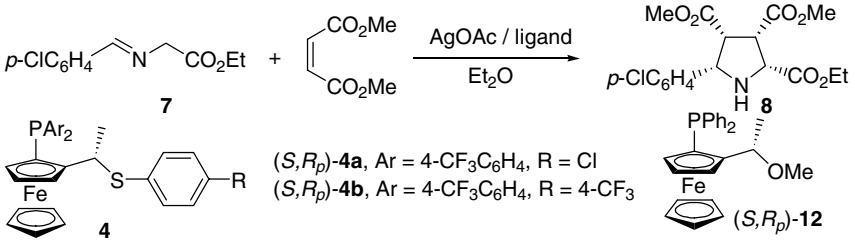


5a-e **6a-e**

Entry	Ar in **5**	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph (**5a**)	2	98	92
2	2-Naphthyl (**5b**)	4	97	93
3	4-Fluorophenyl (**5c**)	3	96	93
4	*p*-Anisole (**5d**)	2	98	86
5	*o*-Toluyl (**5e**)	2	95	90

[a] Conditions: **5** (1.0 equiv), *N*-phenylmaleimide (1.5 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration (0.12 M).
[b] Isolated yields based on **5**.
[c] Determined by HPLC.

Table 3. AgOAc catalyzed asymmetric cycloaddition of **7** with dimethyl meleate[a]



7 **8**

4

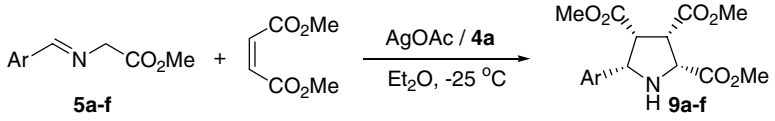
(S,R_p)-**4a**, Ar = 4-$CF_3C_6H_4$, R = Cl
(S,R_p)-**4b**, Ar = 4-$CF_3C_6H_4$, R = 4-CF_3

(S,R_p)-**12**

Entry	Ligand	*T* (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	0	2	98	75
2	**2**	0	2	94	−58
3	**12**	0	0.5	98	45
4	**1b**	0	2	92	77
5	**1c**	0	2	93	73
6	**1d**	0	2	92	75
7	**3a**	0	2	95	69
8	**3b**	0	2	93	74
9	**3c**	0	21	95	71
10	**3d**	0	2	96	80
11	**4a**	0	2	98	86
12	**4b**	0	2	96	84
13	**4a**	−25	3	95	91

[a] Conditions: **7** (1.0 equiv), dimethyl maleate (1.5 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration (0.12 M).
[b] Isolated yields based on **7**.
[c] Determined by HPLC.

Table 4. Variation of the R-substituent on **5** for the cycloaddition with dimethyl meleate[a]



5a-f **9a-f**

Entry	Ar in **5**	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	Ph (**5a**)	3	93	87
2	2-Naphthyl (**5b**)	3	86	89
3	4-Fluorophenyl (**5c**)	3	96	89
4	*p*-Anisole (**5d**)	3	86	88
5	*o*-Toluyl (**5e**)	3	96	84
6	4-Chlorophenyl (**5f**)	3	96	87

[a] Conditions: **5** (1.0 equiv), dimethyl maleate (1.5 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration (0.12 M).
[b] Isolated yields based on **5**.
[c] Determined by HPLC.
[d] Ligand **4b** was used.

ied. When ligand **3c** was used, the reaction became sluggish with a slightly lower ee (entry 9). However, we were pleased to find that the ee can be improved to 80% using ligand **3d**, a strongly electron-withdrawing group at the *para*-position of phenyl ring (entry 10). Ligands **4a** and **4b** were then synthesized according to the effect of the substituent R and the electronic property of the phosphorous substituents. Ligand **4a** gave a slightly higher enantioselectivity than **4b** at 0 °C. The ee was enhanced to 91% when the reaction was carried out at −25 °C (entry 13).

To examine the generality of the AgOAc/**4a**/Et_2O catalyzed cycloaddition with dimethyl maleate, we studied several imine substrates with a variety of electronic and steric properties (Table 4). The reactions proceeded smoothly in all cases with high *endo* selectivity, and up to 89% ee was obtained.

In conclusion, the ferrocenyl derived chiral P,S ligands are effective for AgOAc catalyzed asymmetric cycloaddition of azomethine ylides, with up to 93% ee and high *endo* selectivity obtained. The planar chirality plays an important role in the stereoselection in the cycloaddition. The electronic properties of the phosphorous substituents in ligands have an obvious effect on enantioselectivity and reactivity.

Acknowledgement

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