New Chiral Ferrocenyl P,S-Ligands for Highly Diastereo-/Enantioselective Catalytic [3 + 2] Cycloaddition of Azomethine Ylides with Cyclic and Acyclic Enones
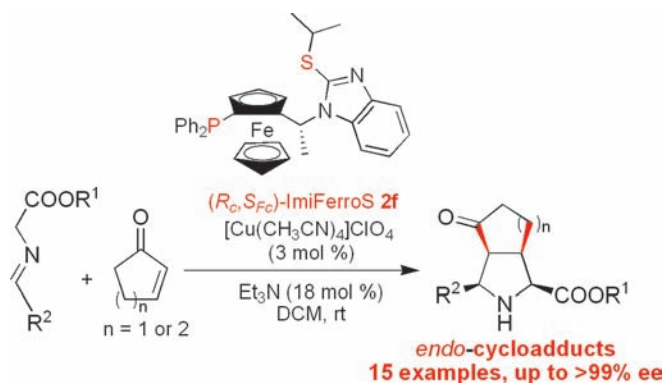
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ABSTRACT

A new family of chiral ferrocenyl P,S-ligands has been developed and successfully applied in a highly *endo*-selective catalytic asymmetric cycloaddition of azomethine ylides with various enones, including cyclic and acyclic α-enones. For cyclic α-enones, a [Cu(CH$_3$CN)$_4$]ClO$_4$/ (R_c,S_{Fc})-2f complex catalyzed the cycloaddition to give the sole *endo*-cycloadducts in perfect enantioselectivities (normally 99% ee), while an AgOAc/(R_c,S_{Fc})-2f catalytic system exhibited good *endo/exo* selectivities (*endo/exo* = 91/9 to 96/4) and high enantiocontrol (up to 98% ee) for acyclic α-enones.

The asymmetric [3 + 2] cycloaddition reaction of azomethine ylides with electron-deficient olefins is one of the most efficient methods of preparing optically active pyrrolidine derivatives, which are widely present in many natural products, pharmaceuticals, and biologically active molecules.[1] Since the first catalytic asymmetric version reported in 2002,[2] great progress has been made in this field with the development of many outstanding chiral metal catalysts and organocatalysts.[3–8] While high enantio-/diastereoselectivities

(1) (a) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670–2680. (b) Harwood, L. M.; Vickers, R. J. In *Synthetic applications of 1,3-Dipolar cycloaddition chemistry toward heterocycles and natural products*; Padwa, A., Pearson, W., Eds.; Wiley & Sons: New York, 2002.
(2) (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401. (b) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236–4238.

were observed with many dipolarophiles (i.e., α,β-unsaturated esters, maleimides, α,β-unsaturated nitriles, enals, nitroalkenes, vinyl sulfones, and fullerene), the cycloaddition of azomethine ylides with enones, in particular cyclic α-enones, is still rarely explored and remains a great challenge.[9] It was not until very recently that Carretero and co-workers[10] reported the first catalytic asymmetric cycloaddition of azomethine ylides with α,β-unsaturated ketones catalyzed by 5 mol % of Cu[I]/Fesulphos complex. In their research, *endo*-cycloadducts for 2-cyclopentenone were obtained as a major isomer in moderate to good *endo/exo* selectivities (*endo/exo* = 75/25 to 98/2) and 85−95% ee, while *exo*-selectivity (*endo/exo* = 40/60 to 98/2) with 81−96% ee for acyclic α-enones was observed. A limitation of this catalytic system lies in very low activity for a six-

membered cyclic enone such as 2-cyclohexenone. Najera et al.[5d] reported that a chiral Ag(I)/phosphoramidite complex could catalyze the cycloaddition of azomethine ylides with cyclopentenone and acyclic enones, providing *endo*-adducts in moderate to good *endo/exo* selectivities and enantioselectivities. More recently, Fukuzawa et al.[11] found that the Ag/ThioClickFerrophos complex could catalyze the highly *endo*-selective 1,3-dipolar cycloaddition reaction of azomethine ylides with acyclic α-enones, having an *endo/exo* ratio of 90/10 to 99/1 and ee values of 87−98%. However, this catalyst was less efficient for the reaction of azomethine ylides with cyclic enone such as 2-cyclopentenone since a long reaction time (24 h) and a high catalyst loading (10 mol %) were required, although the *endo*-cycloadduct was obtained as the sole isomer in 98% ee and 73% yield. The development of new, well-designed chiral ligands with high diastereo-/enantioselectivities and a broad substrate scope for the enantioselective cycloaddition of azomethine ylides with α,β-unsaturated ketones, under low catalyst loadings and mild reaction conditions, is therefore of great interest.

Recently, Chan et al. have reported a new ferrocenyl P/S ligand **1**, which showed good enantioselectivities in the Pd-catalyzed asymmetric allylic alkylation (Figure 1).[12] We

Figure 1. Structure of Chan's ligand **1** and (R_c,S_{Fc})-ImiFerroS **2**.

envision that these new ligands may also be efficient for the catalytic asymmetric cycloaddition of azomethine ylides with cycloenones because of the good performance of chiral ferrocenyl P,S-ligands in the catalytic asymmetric [3 + 2] cycloaddition. However, the results proved to be highly disappointing, and only very low enantioselectivity (26% ee for *endo*-adducts) was achieved in the Cu-catalyzed [3 + 2] cycloaddition of *N*-(4-chlorobenzylidene)glycine methyl ester (**5a**) with 2-cyclopentenone (**6a**) (entry 1, Table 1). By reversing the position of P- and S-donor atoms, herein we report a new family of chiral ferrocenyl P,S-ligands [(R_c,S_{Fc})-ImiFerroS **2**] for the highly *endo*-selective catalytic asymmetric cycloaddition of azomethine ylides with various enones, including cyclic and acyclic α-enones, in which excellent diastereo-/enantioselectivities (only *endo*-cycloadducts with normally >99% ee for cyclic α-enones) were achieved for a broad scope of azomethine ylides.

The modular synthesis of these new chiral ferrocenyl P,S-ligands is outlined in Scheme 1. In the first step, *N,N*-dimethyl

(3) Reviews on catalytic asymmetric 1,3-dipolar cycloadditon: (a) Engels, B.; Christl, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7968–7970. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902. (c) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174–3198. (d) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132–3148. (e) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285. (f) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247–12275. (g) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517. (h) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272–6276. (i) Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047–2061.

(4) For recent examples on Cu catalysts: (a) Robles-Machin, R.; González-Esguevillas, M.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2010**, *75*, 233–236. (b) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 340–343. (c) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084–10085. (d) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250–12751. (e) Llamas, T.; Ramón Gómez, A.; Carretero, J. C. *Synthesis* **2007**, 950–956. (f) Cabrera, S.; Gómez Arrayás, R.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587–6602. (g) Shi, M.; Shi, J.-W. *Tetrahedron: Asymmetry* **2007**, *18*, 645–650. (h) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979–1983. (i) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394–16395. (j) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241–4244.

(5) For recent examples on Ag Catalysts: (a) Yamashita, Y.; Guo, X.-X.; Takashita, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3262–3263. (b) Xie, Z.-Y.; Liu, T.-L.; Lu, Z.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2010**, *46*, 1727–1729. (c) Robles-Machín, R.; Alonso, I.; Adrio, J.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 5286–5291. (d) Nájera, C.; Retamosa, M. G.; Martín-Rodríguez, M.; Sansano, J. M.; Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2009**, 5622–5634. (e) Yu, S.-B.; Hu, X.-P.; Deng, J.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *Tetrahedron: Asymmetry* **2009**, *20*, 621–625. (f) Wang, C.-J.; Xue, Z.-Y.; Liang, G.; Lu, Z. *Chem. Comumm.* **2009**, 2905–2907. (g) Liang, G.; Tong, M,-C.; Wang, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 3101–3106. (h) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750–751. (i) Zeng, W.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 4619–4622. (j) Nájera, C.; Retamosa, M. D. G.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025–4028. (k) Garner, P.; Kaniskan, H. Ü.; Hu, J.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 3647–3650. (l) Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Tetrahedron* **2005**, *61*, 3745–3753. (m) Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055–5058. (n) Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569–4572.

(6) For recent examples on zinc catalysts: (a) Dogan, Ö.; Koyuncu, H.; Garner, P.; Bulut, A.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 4687–4690. (b) Dogan, Ö.; Öner, I.; Ülkü, D.; Arici, C. *Tetrahedron: Asymmetry* **2002**, *13*, 2099–2104.

(7) For recent example on nickel catalysts: Shi, J.-W.; Zhao, M.-X.; Lei, Z.-Y.; Shi, M. *J. Org. Chem.* **2008**, *73*, 305–308.

(8) For recent examples on organocatalysts: (a) Liu, Y. K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 9873–9877. (b) Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691–694. (c) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652–5654. (d) Ibrahem, I.; Ríos, R.; Vesely, J.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6252–6257. (e) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168–5170.

(9) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475–2486.

(10) Hernández-Toribio, J.; Gómez Arrayás, R.; Martín-Matute, B.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 393–396.
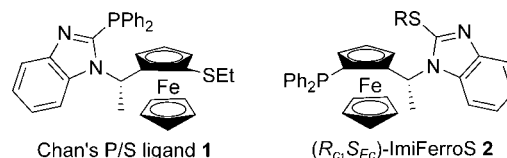
(11) Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S. *Org. Lett.* **2010**, *12*, 1752–1755.

(12) (a) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295–4298. (b) Cheung, H. Y.; Yu, W.-Y.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, A. S. C. *Adv. Synth. Catal.* **2009**, *351*, 1412–1422.

entry	ligand	M (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	**1**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (5)	3	67	26
2	**2a**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (5)	1.5	83	83
3	**2b**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (5)	1.5	78	84
4	**2c**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (5)	1.5	82	89
5	**2d**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (5)	1.5	87	97
6	**2e**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (5)	1.5	86	92
7	**2f**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (5)	1.5	84	>99
8	**2f**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (3)	2	91	>99
9	**2f**	[Cu(CH$_3$CN)$_4$]ClO$_4$ (1)	8	21	92
10	**2f**	AgOAc (3)	12	48	95

[a] The reaction was performed in DCM at room temperature using **5a** (0.3 mmol) and **6a** (0.36 mmol) in the presence of a Cu catalyst, prepared in situ from [Cu(CH$_3$CN)$_4$]ClO$_4$ and ligand, and Et$_3$N (18 mol %), unless otherwise noted. [b] Isolated yield of *endo*-**7a** after column chromatography. [c] Determined by HPLC on a chiral column.
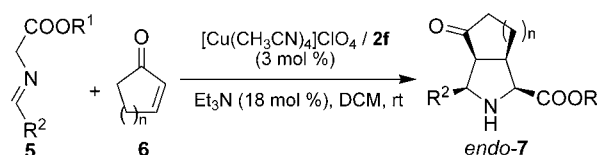
(*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(*R$_c$*,*S$_{Fc}$*)-PPFA **3**] was converted into the corresponding (*R$_c$*,*S$_{Fc}$*)-**4** in high yield by the treatment of (*R$_c$*,*S$_{Fc}$*)-**3** with benzimidazole in HOAc.[13] Subsequent lithiation of (*R$_c$*,*S$_{Fc}$*)-**4** with *n*-BuLi, followed by the treatment with various disulfides, gave the desired ferrocenyl P,S-ligands **2** [(*R$_c$*,*S$_{Fc}$*)-ImiFerroS]. These ligands are stable toward air and moisture and can be held at ambient temperature in open air for over 1 month. The structure of (*R$_c$*,*S$_{Fc}$*)-ImiFerroS **2a** was confirmed by X-ray analysis.[14]

Scheme 1. Synthesis of New Chiral Ferrocenyl P,S-Ligands, (*R$_c$*,*S$_{Fc}$*)-ImiFerroS **2**
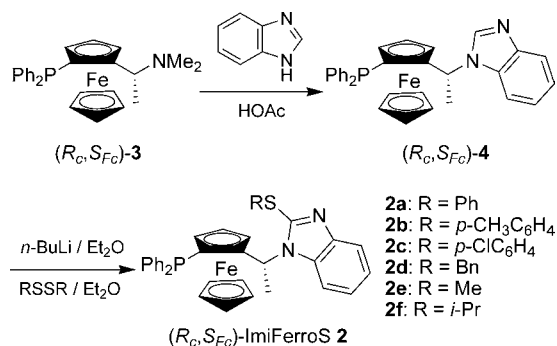
With these newly developed P,S-ligands in hand, a catalytic asymmetric 1,3-dipolar cycloaddition of *N*-(4-chlo-

(13) Wang, D.-Y.; Hu, X.-P.; Hou, C.-J.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Huang, J.-D.; Zheng, Z. *Org. Lett.* **2009**, *11*, 3226–3229.

(14) See Supporting Information.

robenzylidene)glycine methyl ester (**5a**) with 2-cyclopentenone (**6a**) was examined using 5 mol % of [Cu(CH$_3$CN)$_4$]-ClO$_4$ and 5.5 mol % of ligand in the presence of 18 mol % of Et$_3$N as base in dichloromethane (DCM) at room temperature, and the representative results are shown in Table 1. To our delight, *endo*-**7a** was obtained as the *only cycloadduct* with these newly developed P,S-ligands **2**. The results indicated that the thio group in these (*R$_c$*,*S$_{Fc}$*)-ImiFerroS ligands has a significant influence on the enantioselectivity, and a catalyst combining [Cu(CH$_3$CN)$_4$]ClO$_4$ and (*R$_c$*,*S$_{Fc}$*)-**2f** bearing an *i*-propylthio group provided the highest enantioselectivity of >99% ee (entry 7). With (*R$_c$*,*S$_{Fc}$*)-**2f**, we next optimized the reaction conditions. Solvent screening showed that dichloromethane was the best solvent.[14] Lowering catalyst loadings to 3 mol % has less effect on the catalytic activity and enantioselectivity (>99% ee) (entry 8). This result demonstrated the high efficiency of the [Cu(CH$_3$CN)$_4$]ClO$_4$/(*R$_c$*,*S$_{Fc}$*)-**2f** catalytic system for the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with cyclic α-enones. However, a further reduction in catalyst loadings to 1 mol % resulted in a significantly decreased reactivity and enantioselectivity (entry 9). The reaction with AgOAc as Lewis acid proceeded more slowly, giving lower chemical yield and enantioselectivity (entry 10).

Under the optimal reaction conditions, the scope of the 1,3-dipolar cycloaddition with the present catalytic system was investigated. As shown in Table 2, a wide array of imino esters **5** from aromatic aldehydes reacted with 2-cyclopen-

entry	**5** (R^1, R^2)	**6** (n)	**7**	yield (%)[b]	ee (%)[c]
1	**5a**: Me, 4-ClC$_6$H$_4$	**6a** (n = 1)	**7a**	91	>99
2	**5b**: Et, 4-ClC$_6$H$_4$	**6a** (n = 1)	**7b**	88	>99
3	**5c**: *i*-Pr, 4-ClC$_6$H$_4$	**6a** (n = 1)	**7c**	88	>99
4	**5d**: Me, 2-ClC$_6$H$_4$	**6a** (n = 1)	**7d**	93	>99
5	**5e**: Me, 3-ClC$_6$H$_4$	**6a** (n = 1)	**7e**	85	99
6	**5f**: Me, Ph	**6a** (n = 1)	**7f**	88	>99
7	**5g**: Me, 4-BrC$_6$H$_4$	**6a** (n = 1)	**7g**	86	>99
8	**5h**: Me, 4-FC$_6$H$_4$	**6a** (n = 1)	**7h**	82	>99
9	**5i**: Me, 4-CF$_3$C$_6$H$_4$	**6a** (n = 1)	**7i**	85	>99
10	**5j**: Me, 4-NO$_2$C$_6$H$_4$	**6a** (n = 1)	**7j**	82	>99
11[d]	**5k**: Me, 4-MeC$_6$H$_4$	**6a** (n = 1)	**7k**	89	>99
12[d]	**5l**: Me, 4-MeOC$_6$H$_4$	**6a** (n = 1)	**7l**	86	99
13[d]	**5m**: Me, 2-thienyl	**6a** (n = 1)	**7m**	82	>99
14	**5n**: Me, 2-naphthyl	**6a** (n = 1)	**7n**	89	>99
15	**5o**: Me, Cy	**6a** (n = 1)	**7o**	-	-
16[d]	**5a**: Me, 4-ClC$_6$H$_4$	**6b** (n = 2)	**7p**	87	>99

[a] The reaction was performed in DCM at room temperature using **5** (0.3 mmol) and **6** (0.36 mmol) in the presence of a Cu catalyst, prepared in situ from [Cu(CH$_3$CN)$_4$]ClO$_4$ (3 mol %) and **2f** (3.3 mol %), and Et$_3$N (18 mol %), unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC on a chiral column. [d] Catalyst loading: 5 mol %.

tenone **6a** to give the corresponding *endo*-adducts **7a−n** in high yields and perfect enantioselectivities (normally >99% ee) (entries 1−14). The ester group on imino esters showed no influence on the yield and enantioselectivity. In all cases, excellent enantioselectivities (>99% ee) were achieved (entries 1−3). It also appears that the position and the electronic property of the substituent on the phenyl ring have a smaller effect on the enantioselectivities (entries 3−12). However, the substrates bearing an electron-withdrawing substituent tended to show higher reactivity than those with an electron-donating group. Thus, the reactions for most of the substrates finished in 2 h, but for the substrate **5l** with a methoxy group extending the reaction time to 36 h was required to complete the reaction (entry 12). Heteroaryl imino ester **5m** also proved to be a suitable substrate, exclusively undergoing the *endo* cycloaddition with excellent enantioselectivity (>99% ee), although the catalyst loading should be increased to 5 mol % (entry 13). An azomethine ylide from 2-naphthylaldehyde also worked well in this transformation, producing *endo*-cycloadduct in >99% ee (entry 14). Unfortunately, no cycloaddition was observed in the case of azomethine ylides derived from the aliphatic cyclohexanecarbaldehyde (entry 15). Remarkably, the Cu(CH$_3$CN)$_4$ClO$_4$/(R_c,S_{Fc})-**2f** complex can also effectively catalyze the cycloaddition of azomethine ylides with 2-cyclohexenone (**6b**), providing *endo*-cycloadduct **7p** as the sole isomer in >99% ee (entry 16). These results represent the best outcome in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with cyclic α-enones reported so far.

To extend this asymmetric protocol, the cycloaddition of *N*-(4-chlorobenzylidene)glycine methyl ester (**5a**) with acyclic enones was also conducted, and the results are shown in Table 3. Initially, we performed the reaction of **5a** with chalcone **8a**, under the same reaction conditions as those used with 2-cyclopentenone **6a**. The reaction proceeded very quickly and completed in 10 min even at low temperature (−30 °C) and low catalyst loadings (1 mol %), to give the *endo*-cycloadduct preferentially in the perfect enantioselectivity (99% ee) (entry 1). However, a relatively low *endo*-selectivity (*endo/exo* = 2/1) was not so satisfactory. The diastereoselectivity with the present Cu-catalytic system is different from that reported by Carretero, in which *exo*-adducts were formed preferentially with a Cu/Fesulphos complex.[10] By replacing [Cu(CH$_3$CN)$_4$]ClO$_4$/(R_c,S_{Fc})-**2f** with AgOAc/(R_c,S_{Fc})-**2f** as the catalyst, the *endo*-selectivity can be significantly increased to *endo:exo* = 93:7 (entry 2). Reactions with a series of substituted chalcones **8** were then carried out by use of this Ag catalyst. The results indicated that this Ag catalyst was efficient for these chalcone-type substrates, giving *endo*-cycloadducts in high *endo*-selectivity (*endo/exo* = 91/9 to 96/4) and high enantioselectivity (up to 98% ee) (entries 2−6).

Table 3. Catalytic Asymmetric [3 + 2] Cycloaddition Reactions of **5a** with Chalcones **8**[a]

entry	**8** (Ar^1, Ar^2)	*endo/exo*[b]	*endo*-**9** yield (%)[c]	ee (%)[d]
1[e]	**8a** (Ph, Ph)	2/1	65	99
2	**8a** (Ph, Ph)	93/7	81	97
3	**8b** (Ph, 4-ClC$_6$H$_4$)	91/9	78	91
4	**8c** (4-ClC$_6$H$_4$, Ph)	96/4	81	93
5	**8d** (4-MeOC$_6$H$_4$, Ph)	95/5	86	98
6	**8e** (4-MeC$_6$H$_4$, Ph)	96/4	83	98

[a] The reaction was performed in ClCH$_2$CH$_2$Cl at −10 °C for 2 h using 0.3 mmol of **5a** and 0.36 mmol of **8** in the presence of an Ag catalyst, prepared in situ from AgOAc (3 mol %) and (R_c,S_{Fc})-**2f** (3.3 mol %), and Et$_3$N (10 mmol), unless otherwise noted. [b] Determined by ^{1}H NMR. [c] Isolated yield of *endo*-**9** after column chromatography. [d] Determined by HPLC on a chiral column. [e] The reaction was performed in CH$_2$Cl$_2$ at −30 °C for 10 min using 0.3 mmol of **5a** and 0.36 mmol of **8a** in the presence of a Cu catalyst, prepared in situ from [Cu(CH$_3$CN)$_4$]ClO$_4$ (1 mol %) and **2f** (1.1 mol %), and Et$_3$N (10 mol %).

In conclusion, we have developed a new family of chiral ferrocenyl P,S-ligands for a highly *endo*-selective catalytic asymmetric cycloaddition of azomethine ylides with various enones, including cyclic and acyclic α-enones. For cyclic α-enones, a [Cu(CH$_3$CN)$_4$]ClO$_4$/(R_c,S_{Fc})-**2f** complex catalyzed the cycloaddition to give the sole *endo*-cycloadducts in perfect enantioselectivities (normally 99% ee). For acyclic α-enones, the [Cu(CH$_3$CN)$_4$]ClO$_4$/(R_c,S_{Fc})-**2f** complex displayed excellent enantioselectivity (99% ee) but relatively low *endo*-selectivity (*endo/exo* = 2/1), while an AgOAc/(R_c,S_{Fc})-**2f** catalytic system exhibited good *endo/exo* selectivities (*endo/exo* = 91/9 to 96/4) and high enantiocontrol (up to 98% ee). Further reaction scope and mechanistic origin of high diastereo- and enantioselectivity are underway.

Supporting Information Available: Full Experimental details, spectroscopic data, and X-ray analysis of (R_c,S_{Fc})-**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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