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New chiral ferrocenyl amidophosphine ligand for remarkable improvement of enantioselectivities in copper-catalyzed addition of diethylzinc to *N*-sulfonylimines

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Abstract—(*S*)-*N*-Ferrocenoyl-2-[(diphenylphosphino)methyl]-pyrrolidine **3** was conveniently prepared from commercially available L-proline and ferrocenecarboxylic acid. In the presence of a catalytic amount of chiral ligand **3** (4 mol %) and $Cu(OTf)_2$ (3 mol %), the asymmetric addition of diethylzinc to *N*-sulfonylimines was achieved in 57–99% yield with up to 88% ee.

Much efforts have been made in the efficient asymmetric synthesis of chiral amines, which are subunits of some biologically active compounds or important resolving reagents.[1] Asymmetric addition of organometallic reagents to imines has been investigated in recent years.[2] Enantioselective addition of dialkylzinc to imines is one of the most efficient approaches to chiral amines. Many chiral β-amino alcohols have been designed to catalyze the dialkylzinc addition in the presence of stoichiometric amounts of ligands while high enantioselectivities were attained.[3] But one drawback of this system is, with catalytic amount of ligand, low reactivity and enantioselectivity were observed. This is in great contrast to the chiral amino alcohol-catalyzed asymmetric alkylation of aldehydes with dialkyzinc reagents, which becomes an effective and general method.[4] Therefore, the asymmetric addition of organometallic reagents to imines in the presence of catalytic amounts of chiral ligands is challenging. Recent studies in this field have revealed that some chiral complexes, including copper–amidophosphine,[5] rhodium–monophosphine,[6] zirconium–peptidic Schiff base,[7] allylpalladium complexes,[8] zinc complex,[9] copper–Me–DuPHOS (or Boz–PHOS),[10] copper–*N*-(binaphthyl-2-yl)thiophosphoramide, etc.[11] catalyze the addition of dialkylzinc to imines bearing different protected groups with high enantioselectivities.

In the course of our ongoing studies on the synthesis and application of novel ferrocenyl ligands containing a rigid cyclic skeleton,[12] that is considered to be the determining factor for the effectiveness of these ligands in asymmetric catalytic reactions. We found that the introduction of a ferrocenyl unit on the nitrogen atom of aziridine-based skeleton led to a remarkable improvement in the enantioselectivity when used as a catalyst in the addition of diethylzinc to benzaldehyde.[12a,b] In order to apply this idea to other chiral ligands and catalytic systems, we decided to use L-proline as a chiral source to synthesize chiral amidophosphine ligands bearing ferrocenyl group and use the ligands in asymmetric catalysis. Herein, we present our preliminary results on the asymmetric addition of diethylzinc to *N*-sulfonylimines by means of catalytic amounts of these novel chiral ligands.

The chiral ligands **3**–**5** were readily obtained from the reaction of ferrocenecarboxylic acid with L-proline. The preparation of **3**–**5** is outlined in Scheme 1. The reaction of ferrocenecarboxylic acid **1** with oxalyl chloride in CH_2Cl_2 gave ferrocenyl chloride, which was then combined with (*S*)-prolinol in the presence of Et_3N to give (*S*)-ferrocenoyl prolinol **2** in 69% yield.[13] The treatment of **2** with *p*-TsCl in the presence of pyridine afforded (*S*)-ferrocenoyl prolinol tosylate in 72% yield, which was further substituted by $NaPPh_2$ to give the ligand **3** in 84% yield[14] according to the reported procedure.[15] The treatment of **2** with $ClPPh_2$ directly in the presence of Et_3N[16] led to ligand **4** in 87% yield.[17] Ligand **3** was

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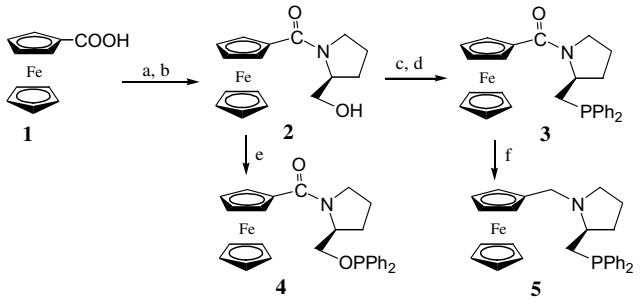


Scheme 1. Synthesis of ligands **3**–**5**. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2; (b) (*S*)-prolinol, Et_3N, CH_2Cl_2; (c) *p*-TsCl, Py, CH_2Cl_2; (d) $NaPPh_2$, THF–dioxane; (e) $ClPPh_2$, Et_3N, THF; (f) $LiAlH_4$, THF.

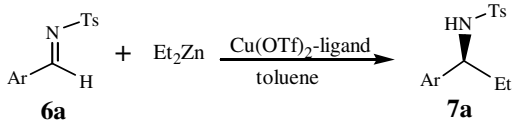
reduced by $LiAlH_4$ in THF to afford ligand **5** in 79% yield.[18]

Initially, in order to find out the best ligands and an optimal procedure, we chose the diethylzinc addition to *N*-(benzylidene)-*p*-methylbenzenesulfonamide (*N*-sulfonylimine) **6a** as a model reaction in the presence of 2 mol % of ligands **3**–**5** and $Cu(OTf)_2$ under different conditions. The enantiomeric purity of product **7a** was determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralcel OD, hexane/*i*-PrOH (10:1), 254 nm, 0.7 mL/min). The results are summarized in Table 1.

As seen from Table 1, the first important conclusion was the high yield and significant enantioselectivities (Table 1, entries 1–3). For example, when chiral ligand **3** was employed, the addition product **7a** was obtained in 84% ee (Table 1, entry 1). But under the same condition, racemic product was obtained when ligand **4** was used (Table 1, entry 2). Ligand **5** also gave poor ee (Table 1, entry 3). These results indicate that a ligand is involved in the addition reaction. Furthermore, a comparison of the enantionselectivities of ligand **3** (88% ee) with those of **4** (1% ee) and **5** (21% ee) suggests that the bite angle of ligand to transition metal is responsible for the enantioselectivity. A comparison of entries 1 and 3 in Table 1 also indicates that the presence of a conjugating carbonyl in the Cp system facilitates the formation and increases the stability of a zinc cuprate–oxygen phosphine complex, which is the reactive intermediate of 1,4-conjugate addition.[5]

Compound **3** was chosen as the best chiral ligand for further optimization (Table 1, entries 4–11). We first examined the effects of the ratio of ligand **3** to $Cu(OTf)_2$ on enantioselectivity (Table 1, entries 1, 4–9). Increasing chiral ligand loading from 1 to 4 mol % led to a significant improvement in enantioselectivity (Table 1, entry 4 vs 5) when 3 mol % of $Cu(OTf)_2$ was used. We attempted to further increase the ligand loading to 7 mol % for higher enantioselectivity, but there was no significant change in either yield or enantioselectivity. When 3 mol % of the chiral ligand **3** was employed (Table 1, entries 7–9), 5 mol % of $Cu(OTf)_2$ gave better ee (85%). So, the combination of 4 mol % of chiral ligand and 3 mol % of Cu(II) salt seemed the most suitable catalyst for the alkylation of imines. Then, we investigated the effect of reaction temperature on enantioselectivity. Increasing the reaction temperature from −5–0 °C to 15 °C led to a dramatic decrease in the enantioselectivity from 86% to 62% (Table 1, entry 5 vs 10), while lowering the reaction temperature from −5–0 °C to −15 °C resulted in an slight enhancement in the enantioselectivity from 86% to 88% (Table 1, entries 5 and 11), but with a remarkable decrease in yield from 94% to 57%.

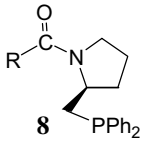
Table 1. The asymmetric diethylzinc addition to **6a** catalyzed by copper-complexes of **3**–**5**[a]



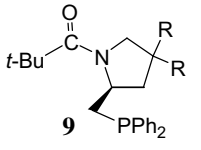
Entry	Ligand loading (%)	$Cu(OTf)_2$ (%)	Temperature (°C)	Time (h)	Yield[b]	ee[c]
1	**3** (2)	2	−5 to 0	12	88	84
2	**4** (2)	2	−5 to 0	12	86	1
3	**5** (2)	2	−5 to 0	12	92	21
4	**3** (1)	3	−5 to 0	12	84	72
5	**3** (4)	3	−5 to 0	12	94	86
6	**3** (7)	3	−5 to 0	12	95	86
7	**3** (3)	10	−5 to 0	12	86	80
8	**3** (3)	5	−5 to 0	12	93	85
9	**3** (3)	1	−5 to 0	12	70	77
10	**3** (4)	3	15	12	84	62
11	**3** (4)	3	−15	24	57	88

[a] The reactions were performed at a 0.2 mmol scale. The ratio of Et_2Zn to imine was 3:1.
[b] Isolated yield.
[c] The ee was determined by HPLC with Daicel Chiralcel OD: eluent, 10% 2-propanol in hexane. The absolute configuration of **7a** was assigned as *S* by comparing retention time of HPLC with the literature value.

Recently, Tomioka et al. reported the same type of chiral ligands **8** for the addition of diethylzinc to *N*-(benzylidene)-*p*-methylbenzenesulfonamide (*N*-sulfonylimine) **6a** with low enantioselectivities (51–65% ee).[5b] Comparison of our results (88% ee) with those of Tomioka et al. demonstrate that the introduction of a ferrocenyl group into the chiral amidophosphine ligands results in a remarkable improvement in the enantioselectivity. These results also suggest that the hindrance of rigid, bulky ferrocenyl unit plays an important role in the

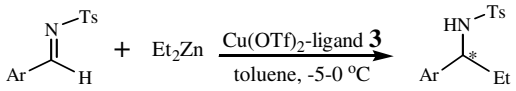


8 R = Me, Et, *n*-Bu, *n*-Oct, 1-Ad, *t*-Bu
ee: 51-65%

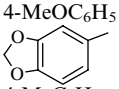


9 R = $PhCH_2$, 2,4,6-$Me_3C_6H_2CH_2$.
ee: 90-93%

Table 2. The enantioselective addition of diethylzinc to various *N*-sulfonylimines **6**[a]



6a-l **7a-l**

Entry	Ar	Imine	Yield[b] (%)	ee[c] (%)
1	C_6H_5	**7a**	94	86
2	2-$MeOC_6H_5$	**7b**	93	81
3	3-$MeOC_6H_5$	**7c**	99	85
4	4-$MeOC_6H_5$	**7d**	81	81
5		**7e**	98	84
6	4-MeC_6H_5	**7f**	79	82
7	2-ClC_6H_5	**7h**	97	79
8	3-ClC_6H_5	**7i**	97	81
9	4-ClC_6H_5	**7j**	85	82
10	3-BrC_6H_5	**7k**	94	83
11	2-Furyl	**7l**	86	80

[a] All reactions were carried out in the presence of $Cu(OTf)_2$ (3 mol %) and **6** (4 mol %) within 12 h.
[b] Isolated yield.
[c] Determined by chiral HPLC using OD column.

enantioselection of the addition of diethylzinc to *N*-sulfonylimine. In their experience, the chiral ligands **9** containing bulky substituents on the pyrrolidine ring gave excellent asymmetric induction (90–93% ee),[5] but the synthesis of the chiral amidophosphine ligands from L-glutamic acid were tedious, involving a multistep-synthesis (about a dozen steps).[15] This makes the addition of diethylzinc to imines for the preparation of chiral amines too expensive to compete with other families of chiral ligands.

The optimal procedure was then tested on a series of *N*-sulfonyl imines derived from arylaldehydes in the presence of bidentate ligand **3**, and the results are presented in Table 2. As seen in Table 2, the reaction proceeded extremely well with various *N*-sulfonylimines containing an *ortho*-, *para*-, or *meta*-substituent on the benzene ring, providing the corresponding chiral ethyl *N*-sulfonylamines in good to outstanding yields (79–99%) and high enantioselectivities (79–86% ee). The presence of electron-withdrawing or electron-donating substituents on the aromatic ring is also compatible with these conditions. Therefore, compared with other families of ligands,[11a,19] the chiral compound **3** is one of the most efficient ligand for the asymmetric addition of diethylzinc to *N*-sulfonyl imines when used in catalytic amounts.

In conclusion, we have demonstrated three new pyrrolidinyl-based chiral ferrocenoylphosphine or ferrocenylphosphine ligands which were conveniently synthesized from commercially available ferrocenecarboxylic acid and L-proline. Among them, ligand **3**–$Cu(OTf)_2$ proved to be an efficient chiral catalyst in the asymmetric addition of diethylzinc to *N*-sulfonylimines, giving the chiral amine product in good to excellent yields and high enantioselectivities with catalytic amount of catalyst and ligand. The chiral ligands **3** are competitive with other known families of chiral ligands in the asymmetric addition of diethylzinc to *N*-sulfonyl.[11a,19] Efforts are underway to extend this catalytic system to other asymmetric C–C bond forming processes, which will be reported in due time.

Acknowledgements

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14. Compound **3**: mp 114.8–116.0 °C, $[\alpha]_D^{20}$ −38.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82–1.84 (m, 1H, CH_2CHH), 1.85–2.10 (m, 3H, CH_2CHH, CH_2CH_2), 3.56–3.62 (m, 1H, NC*H*H), 3.95–3.97 (m, 1H, NCH*H*), 4.31–4.33 (m, 1H, NC*H*), 4.18–4.72 (m, 9H, Fc*H*). HRMS (ESI): *m*/*z* 481.1286 (M^+) (Calcd for $C_{28}H_{28}FeNOP^+$ 481.1258).
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17. Compound **4**: $[\alpha]_D^{20}$ −36.3 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79–1.82 (m, 1H, CH_2CHH), 1.97–2.10 (m, 3H, CH_2CHH, $CHHCH_2$), 3.45–3.47 (m, 1H, NC*H*H), 3.82–3.84 (m, 1H, NCH*H*), 4.05–4.08 (m, 1H, NC*H*), 4.13–4.73 (m, 9H, Fc*H*), 7.28–7.50 (m, 10H, Ph*H*).
18. Compound **5**: $[\alpha]_D^{20}$ −34.1 (*c* 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53–1.60 (m, 3H, $CHHCH_2$, CH_2CHH), 1.85–1.95 (m, 1H, CH_2CHH), 1.99–2.15 (m, 2H, $CHHPPh_2$, NCH*H*), 2.25–2.35 (m, 1H, NC*H*H), 2.50–2.55 (m, 1H, $CHHPPh_2$), 2.85–2.95 (m, 1H, NC*H*), 3.14, 3.68 (d, 2H, *J* = 13.2 Hz, FcC*HH*), 3.66–4.11 (m, 9H, Fc*H*), 7.24–7.46 (m, 10H, Ph*H*). HRMS (ESI): *m*/*z* 468.1543 (M^++H) (Calcd for $C_{28}H_{31}FeNP^+$ 468.1544).
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