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Novel chiral copper complexes of *N*,*P*-ferrocenyl ligands with central and planar chirality as efficient catalyst for asymmetric addition of diethylzinc to imines

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Abstract—A new type of chiral copper complexes of *N*,*P*-ferrocenyl ligands with central and planar chirality as efficient catalyst was applied to the enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines. The (*R*)- and (*S*)-enantiomers of the addition reaction were obtained for this transformation. In the presence of 6 mol % of bidentate ligand **1** and 12 mol % of $Cu(OTf)_2$, the asymmetric addition process affords *N*-diphenylphosphinoylamides in up to 97% ee and 95% yields.

1. Introduction

The discovery and development of new efficient catalytic asymmetric methods for the preparation of chiral amines by the addition of organometallic reagents to C=N of imines is an important objective in organic synthesis.[1] While there have been numerous efforts to control the stereoselectivity of this reaction either by chiral auxiliaries[1b,c,2] or (stoichiometric) chiral ligands,[1e,3] the catalytic asymmetric addition of simple alkyl metals has only been achieved very recently.[4–10] Indeed, recent studies in this area have revealed that the catalytic generation of reactive organometal–chiral ligand complexes from the corresponding less reactive organometallic reagents in situ under mild conditions catalyzed the addition of organometallic reagents to imines bearing different protecting groups with high enantioselectivity. Among these, copper complexes of *O*,*P*-ligands,[6] rhodium complexes,[7] zirconium complexes of peptidic Schiff-base ligands,[8] copper complexes of *P*,*P*-ligands,[9] and copper complexes of *N*,*S*-ligands,[10] showed impressive success. To the best of our knowledge, the evaluation of chiral copper complexes of *N*,*P*-ligands in diethylzinc addition to imines has not been reported. Herein, we report that a new type of chiral copper complex of *N*,*P*-ferrocenyl ligands with central and planar chirality represents an efficient catalyst promoting the enantioselective addition of diethylzinc to the C=N bond of *N*-diphenylphosphinoylimines with up to 97% ee and 95% isolated yield.

Over the past few years, ferrocenyl derivatives, because of their planar chirality, rigid bulkiness, ease of derivatization, and stability,[1] have attracted growing attention as chiral ligands in asymmetric catalysis, with excellent asymmetric induction being realized in many types of asymmetric reactions.[11] Our interest in the application of chiral ferrocenyl ligands in the catalytic asymmetric reaction[12] promoted us to explore chiral ferrocenyl ligands in the use of a new catalytic asymmetric system.

2. Results and discussion

Chiral ferrocenyl ligands **1**–**4** were easily synthesized according to the literature.[13] (Fig. 1). They have the advantage of being quite stable in air and more attractively are commercially available. Our initial efforts focused on the identification of the optimal copper(II) complexes in terms of both yields and ee in the presence of 12 mol % of $Cu(OTf)_2$ and 6 mol % of chiral *N*,*P*-ferrocenyl ligands. Two pairs of enantiomers **1** and **2**, and **3** and **4**, with *N*,*P* chelating atoms were

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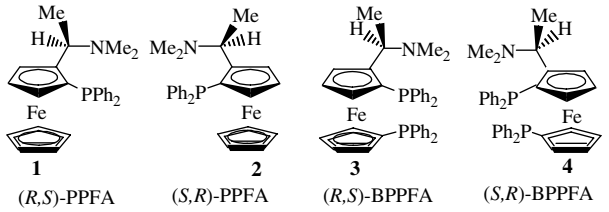
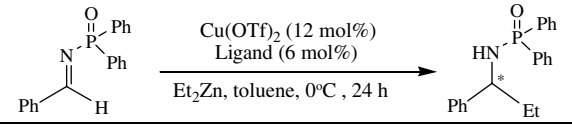


Figure 1. The chiral ferrocenyl ligands used for this study.

screened, with the results summarized in Table 1 (entries 1–4).

As can be seen from Table 1, the addition of diethylzinc to the C=N bond of *N*-diphenylphosphinoylimine led to the protected amine in 50–91% yields with 34–92% ee (entries 1–4). It was shown that both enantioselectivity and reactivity were very sensitive to the structure of the chiral ligands. When bidentate ligand **1** and its enantiomer **2** were employed, the addition of diethylzinc to the *N*-diphenylphosphinoylimine afforded outstanding ee values (92% ee) and high chemical yields (85%, 91%, Table 1, entries 1 and 2). Tridentate ligand **3** and its enantiomers **4** not only showed moderate catalytic activity (50%), but also gave the product with low ee values (42–45% ee, Table 1, entries 3 and 4). These observations suggest that *N*,*P*-bidentate coordination of the ligands to the catalytically active copper species might be crucial for obtaining high asymmetric induction and yields.

Table 1. The $Cu(OTf)_2$-ferrocenyl ligands catalyzed Et_2Zn addition to *N*-diphenylphosphinoylimines

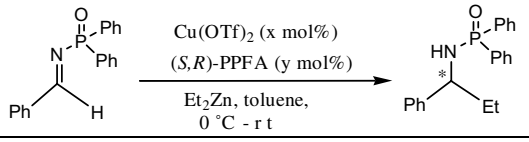


Entry	Ligand	Yield (%)[a]	ee (%)[b]	Config.[c]
1	(*R*,*S*)-PPFA **1**	85	92	*R*
2	(*S*,*R*)-PPFA **2**	91	92	*S*
3	(*R*,*S*)-BPPFA **3**	50	42	*R*
4	(*S*,*R*)-BPPFA **4**	50	45	*S*

[a] Isolated yield.
[b] Enantiomeric excesses were determined by HPLC.
[c] Absolute configuration was assigned by comparing the retention time on HPLC with the literature value.[9,15]

Bidentate ligand **2** was chosen as the best chiral ligand for further optimization, with the results shown in Table 2. We first investigated the effect of reaction temperature on enantioselectivity. Lowering the reaction temperature from room temperature (20–25 °C) to 0 °C led to a slight enhancement in the additional selectivity from 91% to 92% (Table 2, entries 1 and 2). Addition of 4 Å molecular sieves (MS) to the reaction system did not benefit the enantioselectivity or the yield of the products (Table 2, entries 3 vs 1). In contrast, Gong and other groups have reported that the use of 4 Å MS could affect their reactions very obviously both in yields and enantiomeric excesses.[14] We then examined the effects of the ratio of $Cu(OTf)_2$ to ligand **2** on either yield or enantioselectivity (Table 2, entries 2, 4–8). When 6 mol % of ligand **2** was used, lowering the amount of $Cu(OTf)_2$ from 12 to 6 or 3 mol %, even if the overall yield was increased slightly (Table 2, entries 2, 4 and 5), a decrease in product ee was observed. Doubling the amounts of $Cu(OTf)_2$ relative to chiral ligand **2** was selected for further optimization. An increase in ligand loading from 6 to 8 mol % led to a decrease in product ee and yield. Decreasing the amount of ligand from 6 to 4 or 2 mol % was detrimental to the enantioselectivity. So, the combination of 6 mol % of chiral ligand **2** and 12 mol % of Cu(II) salt seemed the most suitable catalyst for the alkylation of imines. One equivalent more of Cu salts than the amount of ligands appeared to be reasonable; this was also found in other systems.[9]

Table 2. Optimization of the reaction conditions of the stereoselective alkylation of imines

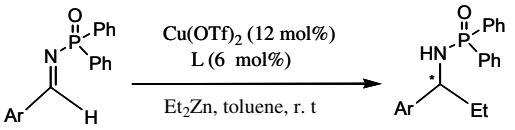


Entry	*x*	*y*	Temp (°C)	Yield (%)[a]	ee (%)[b]	Config.[c]
1	12	6	rt	92	91	*S*
2	12	6	0	91	92	*S*
3[d]	12	6	rt	90	91	*S*
4	6	6	0	92	90	*S*
5	3	6	0	94	87	*S*
6	16	8	0	88	89	*S*
7	8	4	0	90	87	*S*
8	4	2	0	90	86	*S*

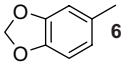
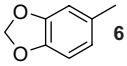
[a] Isolated yield.
[b] Enantiomeric excesses were determined by HPLC on chiral stationary phase.
[c] Absolute configuration was assigned by comparing retention time on HPLC with the literature values.[9,15]
[d] 4 Å MS were added.

These reaction conditions were then tested on other *N*-phosphinoylimines derived from different arylaldehydes in the presence of bidentate ligands **1** and **2** with the results shown in Table 3. As can be seen from Table 3, good yields and high to excellent enantioselectivities could be achieved for various aromatic *N*-phosphinoylimines containing *ortho*-, *para*- and *meta*-substituents on the benzene ring (Table 3, entries 3–12). The presence of electron-donating or electron-withdrawing substituents on the aromatic ring is also compatible with these reaction conditions. The best asymmetric induction (as high as 97% ee) was found by using an imine bearing a 2-$MeOC_6H_4$ group as the substrate in the presence of bidentate ligand **1** (Table 3, entry 5). It is advantageous that imines derived from furfural can be converted to adducts in 85% yields and 90% ees (entries 13 and 14), because the products are useful intermediates for the synthesis of biologically active compounds.[16] These results are comparable with the best literature values hith-

Table 3. Addition of Et_2Zn to *N*-diphenylphosphinoylimines



5-11 **12-18**

Entry	Ar	Ligand	Time (h)	Yield (%)[a]	ee (%)[b]	Config.[c]
1	Ph **5**	(*R*,*S*)-PPFA **1**	24	85	92 **12**	*R*
2	Ph **5**	(*S*,*R*)-PPFA **2**	24	91	92 **12**	*S*
3	 **6**	(*R*,*S*)-PPFA **1**	48	75	84 **13**	*R*
4	 **6**	(*S*,*R*)-PPFA **2**	48	76	84 **13**	*S*
5	2-$MeOC_6H_4$ **7**	(*R*,*S*)-PPFA **1**	24	95	97 **14**	*R*
6	2-$MeOC_6H_4$ **7**	(*S*,*R*)-PPFA **2**	24	95	95 **14**	*S*
7	4-$MeOC_6H_4$ **8**	(*R*,*S*)-PPFA **1**	48	73	88 **15**	*R*
8	4-$MeOC_6H_4$ **8**	(*S*,*R*)-PPFA **2**	48	76	86 **15**	*S*
9	4-MeC_6H_4 **9**	(*R*,*S*)-PPFA **1**	48	94	92 **16**	*R*
10	4-MeC_6H_4 **9**	(*S*,*R*)-PPFA **2**	48	94	91 **16**	*S*
11	4-ClC_6H_4 **10**	(*R*,*S*)-PPFA **1**	48	92	88 **17**	*R*
12	4-ClC_6H_4 **10**	(*S*,*R*)-PPFA **2**	48	92	88 **17**	*S*
13	2-Furyl **11**	(*R*,*S*)-PPFA **1**	48	85	90 **18**	*R*
14	2-Furyl **11**	(*S*,*R*)-PPFA **2**	48	85	90 **18**	*S*

[a] Isolated yield.
[b] Enantiomeric excesses were determined by HPLC on chiral stationary phase.
[c] Absolute configuration was assigned by comparing the retention time on HPLC with the literature value.[9,15]

erto reported for the asymmetric addition of diethylzinc to *N*-phosphinoylimines.[9,10]

Although the mechanistic details of the asymmetric process are currently unclear, they should be analogous to the well-studied chemistry of organocuprates.[17] The catalytically active species is the copper(I) complex, which can be formed at the initial reaction stage through the in situ reduction of the copper(II) complex by Et_2Zn, followed by a 1,4-conjugate addition-type alkylation.

Additional studies demonstrated that the total process can be extended to asymmetric amine synthesis. The acidic hydrolysis of the phosphinamides liberated the corresponding aromatic primary amines with no loss of enantiomeric purity.[3a,18] The first availability of a pair of antipodal chiral amines, compared with other catalytic asymmetric systems, is of critical importance to organic synthesis because the two enantiomers of biologically active compounds often exhibit quite different types of biological activity in pharmaceutical and agricultural application. Hence, this new synthetic method for enantiomerically pure amines might be a potential procedure used in drug synthesis and biological and related fields.

3. Conclusion

In conclusion, we have reported another new type of chiral copper complex of *N*,*P*-ferrocenyl ligands with central and planar chirality for use as efficient catalysts for the enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines. In the presence of bidentate ligands **1** and **2**, the asymmetric addition process affords *N*-diphenylphosphinoylamides in high to excellent ee and good yields in toluene under mild conditions. The availability of a pair of antipodal chiral amines suggested that his new synthetic method for enantiomerically pure amines might be a potential procedure used in the synthesis of some natural products, physiologically active substances and pharmaceutical compounds. Efforts are underway to elucidate the mechanistic details of this catalytic system and to study the role of planar chirality in the asymmetric addition of diethylzinc to *N*-diphenylphosphinoylimines.

Acknowledgements

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