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Diastereomeric phosphite–pyridine ligands for enantioselective 1,4-conjugate additions

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Abstract—Diastereomeric phosphite–pyridine ligands derived from racemic biphenyl units and homochiral BINOL, achieved high enantioselectivities (up to 96.1% ee) in the Cu(I)-catalysed conjugate additions of Et_2Zn to a variety of acyclic enones.

1. Introduction

Since Mikami introduced the concept of asymmetric activation, biphenyl-based compounds have been extensively used to convey asymmetry in enantioselective catalysis without their asymmetric synthesis and resolution.[1,2] Generally, the asymmetric activation of biphenyl-based catalysts is mainly based on the catalyst enantiomers being discriminated or the chirality of the catalyst being controlled by a chiral activator. According to such a strategy, Mikami and Noroyi achieved high enantioselectivities in hydrogenation by using a BIPHEP/$RuCl_2$ complex (BIPHEP = bis(phosphanyl)-biphenyl) activated by a chiral diamine.[3] Mikami activated the catalyst of (biphenoxide)Ti(O-*i*-Pr)$_2$ with (*R*,*R*)-TADDOL and obtained almost 100% ee in the asymmetric addition of methyl group to aldehydes.[4] Other good examples of this type of asymmetric induction were also gained in Baeyer–Villiger oxidation[5] and carbon–carbon bond formation.[6] A similar methodology to the asymmetric activation of biphenyl-based catalyst has recently been highlighted, where a mixture of diasteromeric ligands derived from an achiral biphenyl subunit and a chiral moiety were successfully employed in asymmetric catalysis.[7–9] Reetz and Neugebauer demonstrated that the ligands based on the biphenol unit and a chiral diphosphite gave high enantioselectivity in the Rh-catalysed hydrogenation.[7] Gong and co-workers reported that the biphenol-based diastereomeric oxavanadium(IV) complexes provided comparable ee in the oxidative coupling of 2-naphthol in comparison with analogues 1,1′-binaphthyl ligands.[8] Similarly, Alexakis and Rosini gained success in Cu-catalysed conjugate addition reactions.[9]

We recently designed the phosphite–pyridine ligands (*S*,*S*)-**1**, derived from chiral biphenyl compound, (*S*)-2-amino-2′-hydroxy-4,4′, 6,6′-tetramethyl-1,1′-biphenyl **2** and (*S*)-BINOL (BINOL = 2,2′-dihydroxy-1,1′-binaphthyl) (Fig. 1), for high enantioselective Cu(I)-catalysed 1,4-conjugate additions of Et_2Zn to a variety of acyclic enones.[10] Encouraged by the above results, we became interested in developing the phosphite–pyridine ligands **L** from the racemic biphenyl backbone **2** and (*S*)-BINOL and testing their application in transition metal catalysed asymmetric reactions. Our more previous studies had shown that the matched phosphite–pyridine ligand (*S*,*S*)-**3a**, derived by (*S*)-NOBIN (NOBIN = 2-amino-2′-hydroxy-1,1′-binaphthyl) and (*S*)-BINOL, obtained much better result (91% ee with 92% of yield) than its diastereomer (*R*,*S*)-**3b** [derived by (*R*)-NOBIN and (*S*)-BINOL, 54% ee with 15% of yield] in the Cu(I)-catalysed asymmetric 1,4-conjugate addition of

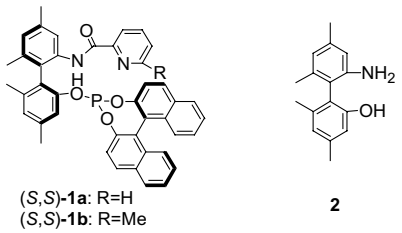

Figure 1.

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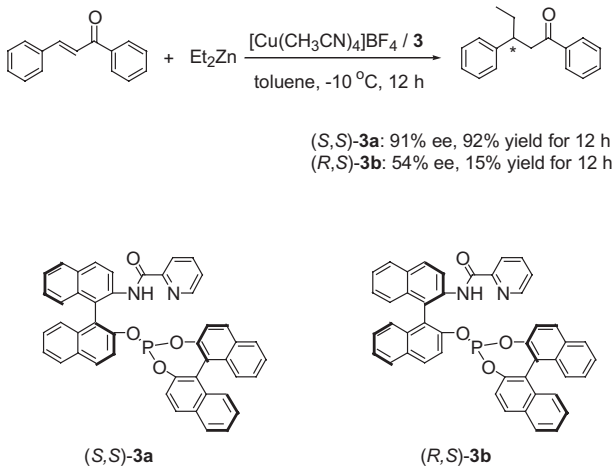


Scheme 1.

Et_2Zn to acyclic enones under the same conditions (Scheme 1). It is noteworthy that both ligands (*S*,*S*)-**3a** and (*R*,*S*)-**3b** afforded the products with the same absolute configuration.[11] Therefore, we envisioned that the strategy could obtain high stereoselectivity in Cu(I)-catalysed 1,4-conjugate addition of Et_2Zn to acyclic enones.[12,13] Moreover, the low efficient resolution of biphenyl backbones **2**[14] also drove us to develop a convenient and efficient ligands with a new strategy.

2. Results and discussion

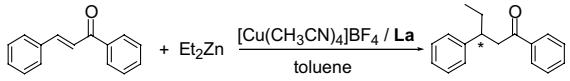
2.1. Synthesis of diastereomeric phosphite–pyridine ligands La and Lb

According to a previous report, diastereomeric P,N ligands **La** and **Lb** were conveniently synthesised in high yields, while ^1H, ^{13}C and ^{31}P NMR spectra showed two-fold parallel signals[10,11] (Scheme 2).

2.2. Enantioselective 1,4-conjugate addition of Et_2Zn to enones

Chalcone was chosen as a typical substrate to optimise the reaction conditions for the Cu(I)-catalysed 1,4-conjugate addition (Table 1). The addition of Et_2Zn to chalcone was conducted in the presence of 1 mol% of $[Cu(CH_3CN)_4]BF_4$ and 2.5 mol % of **La** in 3 mL of toluene. The results summarised in Table 1 showed that the optimal reaction conditions were −20 °C for 6 h.

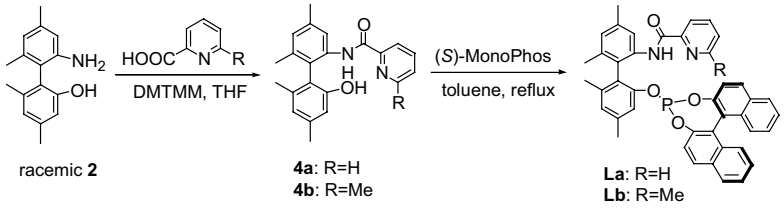
Table 1. Cu-catalysed enantioselective 1,4-conjugate addition of Et_2Zn to chalcone[a]



Entry	Temp (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]	Config[d]
1	10	6	80.5	79.4	*S*
2	0	6	77.3	87.4	*S*
3	−10	6	77.8	92.1	*S*
4	−20	6	74.2	94.5	*S*
5	−20	1	58.0	91.0	*S*
6	−20	2	67.7	91.5	*S*
7	−20	4	75.4	92.3	*S*
8	−20	12	73.1	93.8	*S*

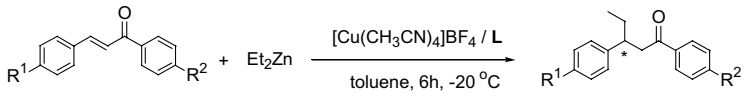
[a] The reaction was carried out in 3 mL toluene, chalcone (1.0 mmol)/$[Cu(CH_3CN)_4]BF_4$/ligand **La** = 1/0.01/0.025, Et_2Zn:substrate = 1.5:1.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD column.
[d] The absolute configuration was assigned by the comparison of the specific rotation with reported data.

To evaluate the catalytic performance of diasteromeric ligands **La** and **Lb**, two types of enones, *para*-substituted chalcones and *trans*-aryl-3-buten-2-ones were tested in Cu(I)-catalysed 1,4-conjugate additions under the optimal procedure. The results in Table 2 showed the ligands prepared from the racemic biphenyl backbone were efficient in the Cu(I)-catalysed 1,4-conjugate additions of Et_2Zn to various *para*-substituted chalcones. Ligand **La** gave comparable enantioselectivities with (*S*,*S*)-**1** for chalcone and 4-substituted chalcones. When 4-Cl-chalcone was used as the substrate, up to 96.1% ee was achieved for the addition product. For 4′-substituted chalcones, an obvious electronic effect was observed. Ligand **La** provided good enantioselectivity and catalytic activity for 4′-chloro-chalcone, whereas the results for electronic-rich substrates were much lower. Surprisingly, sterically hindered ligand **Lb** did not exhibit better stereoselectivity with low catalytic activity, while its enantiopure analogue (*S*,*S*)-**1b** showed the best results in the same reaction.[10] As there are two diastereomeric phosphite–pyridine Cu(I) complexes, which showed different reaction rates in the reaction system, there can be no doubt that these rate differences determine the product ee under this situation. To improve the reaction conversion, which resulted from the sterically hindered ligand, more catalyst was used to accelerate the reaction. The results of the conjugate additions of Et_2Zn to chalcones in the presence of 2 mol % of



Scheme 2. Synthesis of diastereomeric phosphite–pyridine ligands **L**.

Table 2. Cu-catalysed enantioselective 1,4-conjugate addition of Et_2Zn to chalcones[a]



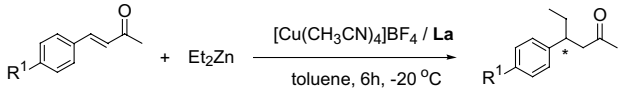
Entry	R^1	R^2	La		Lb		Config.[d]
			Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	
1	H	H	72.5	93.9	49.3 (75.7)	89.3 (91.9)	*S*
2	Cl	H	70.5	96.1	42.5 (72.5)	90.7 (91.9)	+[e]
3	Me	H	75.7	94.3	57.8 (70.6)	91.8 (93.2)	+[e]
4	MeO	H	56.0	91.2	45.0 (65.4)	93.2 (93.0)	*S*
5	H	Cl	76.3	91.7	39.5 (51.5)	81.5 (82.4)	−[e]
6	H	Me	57.4	87.2	43.3 (54.0)	87.1 (83.8)	+[e]
7	H	MeO	26.2	70.5	15.7 (32.0)	73.3 (82.0)	−[e]

[a] The reaction was carried out at −20 °C for 6 h in 3 mL of toluene, substrate (1.0 mmol)/$[Cu(CH_3CN)_4]BF_4$/**L** = 1/0.01/0.025, Et_2Zn:substrate = 1.5:1, the data in parentheses were carried out at −20 °C for 6 h in 1.5 mL of toluene, substrate (0.5 mmol)/$[Cu(CH_3CN)_4]BF_4$/**L** = 1/0.02/0.05, Et_2Zn:substrate = 1.5:1.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD column.
[d] The absolute configuration was assigned by the comparison of the specific rotation data.
[e] Sign of the specific rotation of addition product.

$[Cu(CH_3CN)_4]BF_4$ and 5 mol % of the diastereomeric ligand **Lb** were as listed in parentheses in Table 2. As expected, using more catalyst could significantly improve the chemical yields, but just provided equivalent ee's.

Under the same reaction conditions, ligands **La** were also employed in the Cu(I)-catalysed 1,4-conjugate additions of Et_2Zn to some *trans*-4-aryl-3-buten-2-ones, with moderate catalytic activity and enantioselectivity being achieved (Table 3).

Table 3. Cu-catalysed enantioselective 1,4-addition of Et_2Zn to *trans*-4-aryl-3-buten-2-ones[a]



Entry	R^1	La		Config.[d]
		Yield (%)[b]	Ee (%)[c]	
1	H	60.9	72.2	*S*
2	Cl	63.7	86.5	+[e]
3	Me	40.5	77.7	+[e]
4	MeO	31.2	75.5	+[e]

[a] The reaction was carried out at −20 °C for 6 h in 3 mL of toluene, substrate (1.0 mmol)/$[Cu(CH_3CN)_4BF_4$/**La** = 1/0.01/0.025, Et_2Zn:substrate = 1.5:1.
[b] Isolated yield.
[c] The ee value was determined by GC with a Chiral capillary gamma-225 column.
[d] The absolute configuration was assigned by the comparison of the specific rotation data.
[e] Sign of the specific rotation of addition product.

3. Conclusion

We have successfully applied Cu(I) complexes coordinated with diastereomeric ligands, derived from the racemic biphenyl backbone **2** and (*S*)-BINOL, in Cu(I)-catalysed enantioselective 1,4-conjugate additions of Et_2Zn to chalcones, and achieved up to 96.1% ee.

4. Experimental section

4.1. General

Melting points were measured on a Yazawa micromelting point apparatus (uncorrected). ^1H NMR and ^{13}C NMR spectra were recorded on a BRUKER DRX 400 system with TMS as an internal standard. ^{31}P NMR spectra were recorded with 85% phosphoric acid as the external standard. The enantiomeric excesses (ee) were determined by HPLC with a Daicel Chiral-Pak-AD column or by GC with a capillary Supelco γ-DEX 225 column. All experiments were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried before use according to standard procedures and stored under argon. (*S*)-BINOL was commercially available and directly used. The amides **4** were prepared according to the literature procedure.[10,12e]

4.2. Synthesis of diastereomeric phosphite–pyridine ligands

4.2.1. La. Racemic amide **4a** (346.0 mg, 1.0 mmol), (*S*)-MonoPhos (462.2 mg, 1.3 mmol) and 10 mL of toluene were added to a 50 mL air-free Schlenk flask with a reflux condenser under an argon atmosphere. The mixture was heated to reflux. After the reaction was complete (detected by TLC), the reaction solution was cooled to room temperature and purified by flash chromatograghy on a silica gel column [eluted with hexanes/CH_2Cl_2 (1/1)] to afford 605.0 mg (92%) of diastereomeric **La** as a white foamy solid: mp 99–120 °C; $[\alpha]_D^{13} = +164.0$ (*c* 0.520, THF), ^1H NMR (CD_2Cl_2) δ 1.84–1.90 (m, 6H), 2.33–2.35 (m, 3H), 2.43–2.45 (m, 3H), 6.60–6.80 (m, 1H), 6.91–6.98 (m, 3H), 7.11–7.31 (m, 8H), 7.65–7.70 (m,

2H), 7.78–7.80 (m, 3H), 8.00–8.20 (m, 2H), 8.33–8.35 (m, 1H), 9.62–9.68 (m, 1H); ^{13}C NMR (CD_2Cl_2) δ 22.25, 22.70, 22.86, 23.78, 24.36, 120.74, 120.85, 124.42, 124.50, 124.64, 124.78, 127.74, 127.97, 128.88, 129.11, 129.22, 129.36, 129.59, 130.35, 131.16, 132.36, 132.52, 133.11, 140.24, 142.24, 142.50, 150.66, 152.91, 164.37; ^{31}P NMR (DMSO-d_6) δ +144.70, 145.04.

4.2.2. Lb. Following a similar method for the synthesis of **La**, ligand **Lb** (607.5 mg, 90%) was prepared from amide **4b** (360.0 mg, 1.0 mmol) and (*S*)-MonoPhos (465.1 mg, 1.3 mmol) as a white foamy solid: mp 99–125 °C; $[\alpha]_D^{14} = +150.3$ (*c* 0.508, THF), ^{1}H NMR (CD_2Cl_2) δ 1.86–1.94 (m, 86H), 2.08–2.11 (m, 3H), 2..24–2.45 (m, 6H), 6.50–6.61 (m, 1H), 6.89–7.30 (m, 11H), 7.50–7.80 (m, 6H), 8.39–8.44 (m, 1H), 9.88–9.94 (m, 1H); ^{13}C NMR (CD_2Cl_2) δ 21.99, 22.40, 22.58, 23.44, 24.11, 26.01, 119.67, 121.08, 121.69, 124.52, 127.44, 124.52, 127.68, 128.16, 128.60, 128.82, 129.05, 129.13, 129.30, 130.10, 130.31, 130.87, 132.08, 132.22, 132.80, 140.04, 140.97, 142.15, 149.63, 151.75, 152.47, 159.43, 164.02; ^{31}P NMR (DMSO-d_6) δ +144.19, +145.28.

4.3. General procedure for the asymmetric 1,4-conjugate addition

4.3.1. Preparation of the catalyst. **La** (133.0 mg, 0.2 mmol), 25.2 mg of $[Cu(CH_3CN)_4]BF_4$ (0.08 mmol) and 16 mL of toluene were added to a 50 mL air-free Schlenk flask under an argon atmosphere. After 45 min of stirring at room temperature, the solvent was stripped off in vacuo, 8 mL of CH_2Cl_2 then added to the flask and the catalyst solution used for eight separate conjugate addition reactions.

4.3.2. Asymmetric 1,4-conjugate addition. Substrate (1.0 mmol) and 1.0 mL of the above prepared catalyst solution were added to a flame-dried Schlenk tube under an argon atmosphere. After stripping off the solvent, 3 mL of toluene were added. The slurry was stirred at room temperature for 10 min and then cooled to −20 °C. After the slurry was stirred for 15 min, 1.4 mL of Et_2Zn (1.1 M in toluene, 1.5 mol equiv) was added slowly. The resulting mixture was stirred at −20 °C for 6 h. HCl (5%, 4 mL) was then added to quench the reaction. The mixture was allowed to warm to room temperature, and then 15 mL of diethyl ether added. The organic layer was washed with 5 mL of saturated $NaHCO_3$ and 5 mL of brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel and eluted with EtOAc/hexane (1/40–1/20) to afford the addition product. The ee's of the addition products were determined by chiral HPLC or capillary GC, which are detailed described in the Supporting information of Refs. 10 and 12e.

Acknowledgements

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