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Axially 4,4′-di-*tert*-butyl TunePhos-type chiral diphosphine ligand: synthesis and applications in asymmetric hydrogenation

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ABSTRACT

Axially 4,4′-di-*tert*-butyl TunePhos-type chiral diphosphine ligand was designed and synthesized by means of central-to-axial chirality transfer. Up to 99% and 98% ee have been achieved in Ru-catalyzed hydrogenation of β-alkyl and β-aryl-substituted β-keto esters, respectively.

Catalytic asymmetric synthesis mediated by transition metal complex is one of the most powerful methods for the construction of enantiomerically pure compounds, and the elaborate design of chiral ligands plays a crucial role in this area.[1] Since the significantly successful achievements of BINAP[2] in the asymmetric catalysis, many atropisomeric C_2-symmetric bisphosphine ligands, such as MeO–BIPHEP,[3] TunePhos,[4] P–Phos,[5] SegPhos,[6] SynPhos,[7] DifluorPhos,[8] and other important biaryl phosphine ligands,[9] have been developed in the past two decades (Fig. 1). Although a diverse array of phosphine ligands is reported, developing easily preparable and efficient ligands is still of great importance.

Recently, we and Chan have developed chiral-bridged atropisomeric diphosphine ligands by means of central-to-axial chirality transfer,[10,11] and the advantage of this method is that the tedious resolution procedure could be avoided for achieving enantiomerically pure diphosphine ligands. Herein, we report an efficient approach to a new class of substituted TunePhos-type ligands containing *tert*-butyl groups at the 4,4′-position,[12] which showed excellent enantioselectivities in Ru-catalyzed hydrogenation of β-keto esters, a reaction that has attracted considerable attention recently.[13]

The synthesis of ligand **1** is outlined in Scheme 1. Compound **3** was obtained in high yield through the efficient substitution reaction of the commercially available compound **2** with NaOMe in DMF at 80 °C in 94.5% yield. Treatment of the Grignard reagent of **3** with chlorodiphenylphosphine followed by the addition of H_2O_2 afforded the phosphine oxide **4** conveniently. The iodide compound **5** was synthesized through *ortho*-lithiation with *n*-BuLi followed by I_2 quenching. Demethylation of **5** with BBr_3 at 0 °C gave the corresponding phenol **6**. Reaction of **6** with (2*S*,4*S*)-pentanediol di-*p*-tosylate afforded the linked phosphine oxide **7**, which underwent subsequent Ullmann coupling to generate the corresponding diphosphine dioxide **8** in 69% yield with excellent enantio/diastereoselectivity (>99% ee and dr based on the ^1H and ^{31}P NMR analysis). The axial chirality was assigned as *S* according to the literature report.[10] Finally, $HSiCl_3$ reduction of enantiomerically pure **8** in the presence of tributylamine afforded the desired ligand **1**.[14]

To evaluate the effectiveness of ligand **1**, the Ru-catalyzed asymmetric hydrogenation of β-keto ester was investigated. We initiated our studies by choosing methyl acetoacetate **9** as the model substrate to examine the catalytic activity of $RuCl_2$(**1**)$(DMF)_m$ complex.[15] Hydrogenation was conducted at 50 °C and under 50 atm of hydrogen pressure with 0.5 mol % cata-

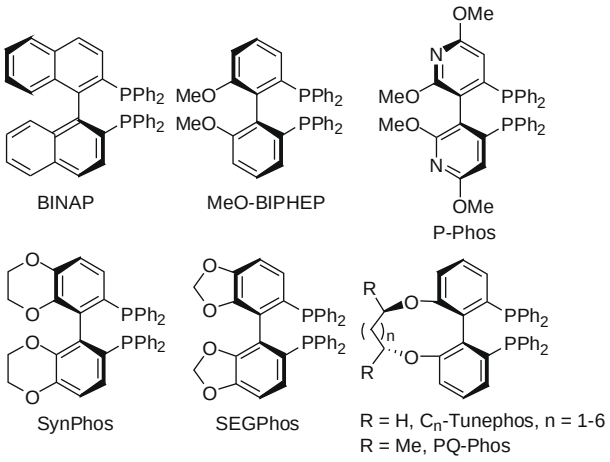

Figure 1. Examples of some atropisomeric C_2-symmetric biaryl ligands.

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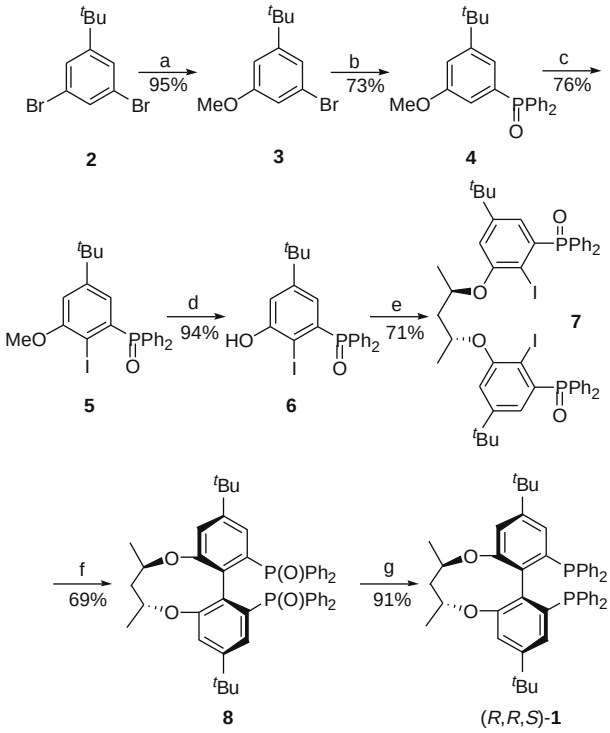
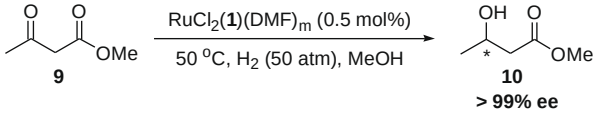


Scheme 1. Reagents and conditions: (a) MeONa, DMF, 80 °C; (b) (i) Mg, THF, reflux; (ii) $ClPPh_2$, 0 °C; (iii) H_2O_2; (c) (i) LDA, 0 °C; (ii) I_2; (d) BBr_3, CH_2Cl_2, 0 °C; (e) (2*S*,4*S*)-pentanediol di-*p*-tosylate, K_2CO_3, DMF, 80 °C; (f) Cu, DMF, 140 °C; (g) $HSiCl_3$, Bu_3N, xylene, reflux.



Scheme 2. Asymmetric hydrogenation of methyl acetoacetate **9** catalyzed by $RuCl_2$(**1**)$(DMF)_m$ complex.

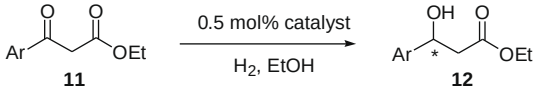
lyst. The reactions were completed in 5 h, and up to 99% ee was obtained (Scheme 2). Enhanced level of enantioselectivity in asymmetric hydrogenation of methyl acetoacetate over that of C_3-TunePhos illustrates the potential benefits of the extra substitutions.[4a] The result is comparable to those obtained with Ru–BINAP system.

Although the Ru–BINAP system has been recognized as an efficient and general catalyst for hydrogenation of β-alkyl-substituted β-keto esters, only inferior ee values were obtained for analogous β-aryl-substituted β-keto esters.[16] Asymmetric hydrogenation of β-aryl-substituted β-keto esters remains a challenging task. Only limited C_2-symmetric bisphosphine ligands have been reported to show good to excellent ee in the Ru-catalyzed hydrogenation of β-aryl-substituted β-keto esters recently.[17] For example, up to 99% ee has been reported with bisphosphinite ligands[17e] and 4,4′-substituted BINAP ligands.[17f]

To our delight, $RuCl_2$(**1**)$(DMF)_m$ complex also showed excellent enantioselectivities for β-aryl-substituted β-keto esters. The results are summarized in Table 1. Under the optimized reaction condition, a series of β-aryl-substituted β-keto esters proceeded smoothly to give the desired hydrogenation products (Table 1, entries 3–11). It appears that the steric and electric properties of the substituent on the aromatic ring have a very limited effect on the enantioselectivities. For β-aryl-substituted β-keto esters with electron-donating group on the phenyl ring, 94–98% ee were observed (Table 1, entries 1 and 4–8). The best results were obtained in the hydrogenation of 3-(4-tolyl)-3-oxo-propionic acid ethyl ester (**11b**), and up to 98% ee was achieved (Table 1, entry 4). Complete conversion and very high ee value were still observed even when the hydrogenation of **11b** was carried out with 0.1 mol % catalyst loading (Table 1, entry 5). By comparing the result for **11a** (72% ee) achieved with C_3-TunePhos,[4a] we found that the new 4,4′-di-*tert*-butyl TunePhos-type chiral diphosphine exhibited higher asymmetric induction, which could be attributed to the similar transition state proposed by Lin and coworkers using 4,4′-substituted BINAP ligands.[17f]

In summary, we have developed a new 4,4′-di-*tert*-butyl TunePhos-type chiral diphosphine ligand by means of central-to-axial chirality transfer, and we showed its utility in the asymmetric Ru-catalyzed hydrogenation of β-keto esters, and up to 99% ee has been observed for both β-alkyl-substituted and β-aryl-substi-

Table 1
Ru-TangPhos catalyzed asymmetric hydrogenation of β-alkyl-substituted β-keto ester[a]



Entry	Ar	Temperature (°C)	H_2 (atm)	ee (%)	Configuration[d]
1	Ph (**11a**)	50	30	95[b]	*R*
2	Ph (**11a**)	50	50	96[b]	*R*
3	Ph (**11a**)	80	30	95[b]	*R*
4	4-Me-Ph (**11b**)	50	30	98[c]	*R*
5[e]	4-Me-Ph (**11b**)	50	30	98[c]	*R*
6	2-Me-Ph (**11c**)	50	30	94[b]	*R*
7	3-MeO-Ph (**11d**)	50	30	94[b]	*R*
8	2-MeO-Ph (**11e**)	50	30	94[b]	*R*
9	3-Br-Ph (**11f**)	50	30	93[b]	*R*
10	4-Br -Ph (**11g**)	50	30	95[c]	*R*
11	4-Cl-Ph (**11h**)	50	30	95[c]	*R*

[a] The hydrogenations were carried out in EtOH with 0.5 mol % Ru–$RuCl_2$(**1**)$(DMF)_m$ as catalyst precursor. All reactions were completed in 100% conversion.
[b] Enantiomeric excesses were determined by chiral GC on chiral select 1000 capillary column.
[c] Enantiomeric excesses were determined by chiral HPLC on chiralpak AS-H column.
[d] The absolute configurations of the products were determined by comparing the optical rotation with the reported data.
[e] The hydrogenations were carried out in EtOH with 0.1 mol % Ru–$RuCl_2$(**1**)$(DMF)_m$ as catalyst precursor.

tuted β-keto esters. Further applications of the new ligand in other transition metal-catalyzed reactions are underway, and will be disclosed in due course.

Acknowledgments

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14. Characterization data of **3**–**8**:Compound **3**: Colorless oil. IR (KBr) ν 2963, 2869, 1599, 1567, 1453, 1421, 1277, 1054, 831, 693, 584 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.28 (s, 9H), 3.78 (s, 3H), 6.85 (s, 2H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 31.11, 34.93, 55.40, 111.26, 113.40, 121.28, 122.53, 154.58, 160.08; MS (EI) *m/z* 242 ([M]$^+$).Compound **4**: An off-white solid. Mp 106–108 °C; IR (KBr) ν: 2959, 2868, 1597, 1577, 1453, 1438, 1186, 1060, 860, 757, 695 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.24 (s, 9H), 3.77 (s, 3H), 6.99 (d, J = 13.8 Hz, 1H), 7.10 (s, 1H), 7.26 (d, J = 13.2 Hz, 1H), 7.40–7.60 (m, 6H), 7.63–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 31.35, 35.17, 55.56, 113.41, 113.56, 122.01, 122.15, 128.60, 128.76, 131.51, 131.18, 131.31, 133.44, 133.82, 153.52, 153.69, 159.46, 159.67; ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 242.86 MHz) δ 31.05; HRMS calcd for $C_{23}H_{25}O_2P$: 364.1591, found: 364.1592.Compound **5**: An off-white solid. Mp 112–115 °C; IR (KBr) ν 2962, 2905, 868, 1577, 1458, 1438, 1186, 1055, 850, 758, 698, 504 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.14 (s, 9H), 3.91 (s, 3H), 6.83 (dd, J = 14.0 and 2.3 Hz,, 1H), 6.98 (d, J = 1.2 Hz, 1H), 7.48 (m, 4H), 7.56 (m, 2H), 7.74 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 31.09, 35.11, 57.01, 88.91–159.02 (m); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 242.86 MHz) δ 35.46; HRMS calcd for $C_{23}H_{24}IO_2P$+H$^+$: 491.0637, found: 491.0631.Compound **6**: An off-white solid. Mp 207–210 °C; IR (KBr) ν 3439, 2963, 2760, 1577, 1458, 1438, 1166, 1010, 784, 751, 695, 515 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.07 (s, 9H), 6.43 (s, 1H), 6.66 (dd, J = 14.6 and 1.2 Hz, 1H), 7.21 (d, J = 1.2 Hz, 1H), 7.48 (m, 4H), 7.52 (m, 2H), 7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 29.75, 33.52, 85.68–155.98 (m); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 242.86 MHz) δ 36.25; HRMS calcd for $C_{22}H_{22}IO_2P$+H$^+$: 477.0480, found: 477.0471.Compound **7**: An off-white solid. Mp 239–240 °C; $[\alpha]_D^{25}$ −86.2 (c 0.19, $CHCl_3$); IR (KBr) ν 2961, 2902, 2869, 1589, 1554, 1478, 1196, 1012, 782, 752, 697, 507 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 0.98 (s, 18H), 1.33 (d, J = 5.7 Hz, 6H), 2.12 (m, 2H), 4.85 (m, 2H), 6.73(d, J = 14.7 Hz, 2H), 6.87 (s, 2H), 7.76 (m,10H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 20.38, 31.05, 34.93, 45.13, 73.15, 90.86–157.58 (m); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 242.86 MHz) δ 35.29; HRMS calcd for $C_{49}H_{52}I_2O_4P_2$+H$^+$: 1021.1516, found: 1021.1503Compound **8**: An off-white solid. Mp 85–87 °C; $[\alpha]_D^{25}$ +124.7 (c 0.40, $CHCl_3$); IR (KBr) ν 2964, 2905, 2869, 1591, 1558, 1479, 1438, 1187, 1026, 995, 878, 751, 695 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.13 (s, 18H), 1.25 (d, J = 3.6 Hz, 6H), 1.65 (m, 2H), 2.26 (m, 2H), 4.34 (m, 2H), 6.74 (s, 2H), 6.94 (d, J = 13.2 Hz, 2H), 7.32 (m,10H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 22.33, 31.13, 34.87, 40.918, 75.715, 118.5–157.31 (m); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 242.86 MHz) δ 24.52; HRMS calcd for $C_{49}H_{52}O_4P_2$+H$^+$: 767.3419, found: 767.3440.
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