Notes

Synthesis of Chiral Bisphosphines with Tunable Bite Angles and Their Applications in Asymmetric Hydrogenation of β-Ketoesters

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Although many effective chiral bisphosphines have been developed, there is no general solution in dealing with the many challenging transition metal-catalyzed asymmetric transformations since enantioselectivities are often substrate-dependent. Subtle changes in geometric, steric, and/or electronic properties of chiral ligands can lead to dramatic variations of reactivity and enantioselectivity. Conformationally rigid and yet tunable chiral ligands offer a great advantage in optimizing the enantioselectivity of a reaction by maximizing the possibility of a low energy enantiotopic approach of substrates in the stereochemistry defining step. Recently, we have developed two conformationally rigid chiral bisphosphines[1] (BICP and PennPhos) which have been shown to be effective for several asymmetric reactions. We envision that a strategy to restrict sp2−sp2 rotation in chiral biaryl ligands such as BINAP,[2] BIPHEMP,[3] and MeO-BIPHEP[3] (Figure 1) will be useful in generating new chiral ligands with tunable bite angles. A closely related idea has been applied to generate chiral biaryl compounds with a range of dihedral angles.[4] Extensive studies by several research groups have demonstrated that changing bite angles of chelating bisphosphines have a dramatic effect on the reactivity and selectivity of reactions.[5] The correlation of bite angles of chiral chelating phosphines with the enantioselectivity of a reaction may provide significant insights for future ligand design and therefore is of fundamental importance.

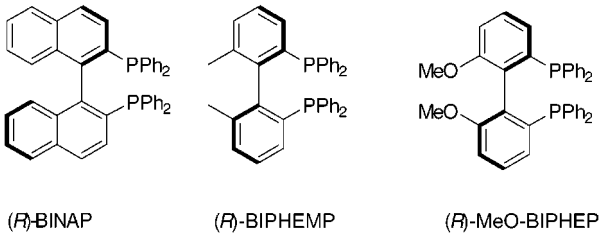

Figure 1. Chiral atropisomeric bisphosphines.

Chiral atropisomeric biaryl diphosphines such as BINAP, BIPHEMP, and MeO-BIPHEP are very effective ligands for many asymmetric reactions.[2,3] The sp2−sp2 rotation in these chiral biaryl ligands causes only a small energy change within a wide range of bite angles with transition metals. While these ligands have been proven effective, sometimes they are not efficient for certain substrates due to the lack of ligand rigidity. To overcome this drawback, we proposed to introduce a bridge with variable length to link the diaryl groups so that the new ligands are rigid with tunable bite angles.[4] Ideally, a change in the bite angle of the metal−ligand complex will allow highly enantioselective transformation with certain substrates. We chose MeO-BIPHEP as the starting compound to make these type of chiral bisphosphines, which are called TunaPhos ligands (Scheme 1). Enantiomerically pure MeO-BIPHEP was made according to a reported procedure[3] and demethylated to provide HO-BIPHEP (**7**) in high yield. Reaction of **7** with alkyl dihalides in the presence of excess anhydrous K_2CO_3 in DMF formed C1−C6TunaPhos ligands (**1**−**6**) (Scheme 1). The dihedral angles of TunaPhos, MeO-BIPHEP, and BINAP based on a CAChe MM2 calculation are listed in Table 1. The bite angle (P−metal−P) of CnTunaPhos with transition metals should increase with an increase in the dihedral angle. Furthermore, the TunaPhos ligands should be less flexible compared with BINAP and

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Scheme 1. Synthesis of CnTunaPhos Ligands

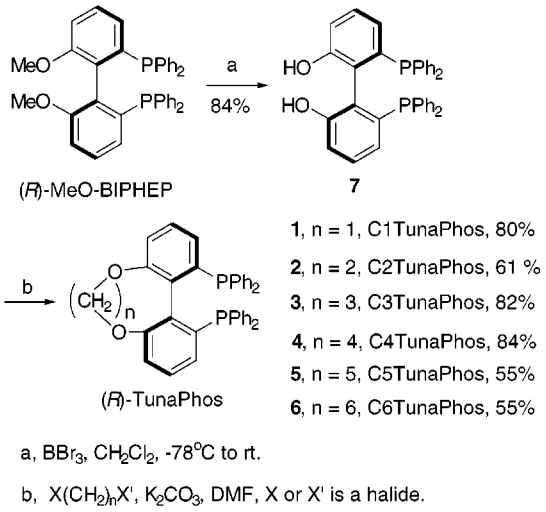

Table 1. Calculated Dihedral Angles of Chiral Bisphosphines

phosphine	**1**	**2**	**3**	**4**	**5**	**6**	MeO-BIPHEP	BINAP
dihedral angle[a] (deg)	60	74	77	88	94	106	87	87

MeO-BIPHEP because the rotation of the sp2−sp2 bond is restricted.

To establish a correlation of the dihedral angle of chelating chiral phosphines with enantioselectivity of a given reaction, a well-studied asymmetric hydrogenation of β-ketoesters was selected.[6] It is known that Ru−BINAP and Ru−MeO-BIPHEP complexes are excellent catalysts for this asymmetric transformation. We proposed that some TunaPhos ligands will offer comparable enantioselectivities as those achieved with Ru−BINAP and Ru−MeO-BIPHEP complexes because of their similar coordination environments. Although variation of the coordination environments from the BINAP and MeO-BIPHEP systems using other TunaPhos ligands may result in lower enantioselectivity for reduction of β-ketoesters, these TunaPhos ligands may provide a unique chance for achieving high enantioselectivity for other reactions.

To test this hypothesis, Ru-catalyzed asymmetric hydrogenation of β-ketoesters with six TunaPhos ligands (**1**−**6**), BINAP and MeO-BIPHEP were performed under the same reaction conditions (Table 2). These reactions were performed according to literature procedure in which the Ru-catalyst was prepared by mixing [Ru(benzene)Cl_2]$_2$ and a diphosphine ligand in situ in hot DMF.[7] The reaction was carried out under 750 psi of H_2 in MeOH at 60 °C for 20 h. While ligands C1−C6TunaPhos (**1**−**6**) showed similar reactivity, the enantioselectivity varied dramatically. For example, methyl acetoacetate (entry 1) was reduced with ca. 91% ee using both Ru−C1TunaPhos (**1**) and Ru−C2TunaPhos (**2**) catalysts. The enantioselectivity increased to 97.7%ee with Ru−C3TunaPhos (**3**) and reached a maximum of 99.1% ee with Ru−C4TunaPhos (**4**). With further increase of the dihedral angle of chiral phosphines (Table 1), enantioselectivity dropped slightly to 97.1% ee with Ru−C5TunaPhos (**5**) and 96.5% ee with Ru−C6Tunaphos (**6**). This general trend is true for all other substrates listed in Table 2 (entries 1−7) with only one exception (the result in entry 5). Overall, the Ru−C4TunaPhos (**4**) complex is a superior catalyst compared with other TunaPhos systems and the results are comparable or better than those obtained with Ru−BINAP and Ru−MeO-BIPHEP catalysts under the same conditions (entries 1−7). This observation is consistent with the fact that C4TunaPhos (**4**), MeO-BIPHEP and BINAP have similar dihedral angles (Table 1). Furthermore, the results with Ru−C3TunaPhos(**3**) and Ru−C5TunaPhos (**5**) are much higher than those obtained with Ru−C1TunaPhos(**1**) and are only slightly lower than the results achieved with Ru−C4TunaPhos (**4**). This indicates the bite angles of Ru complexes with C3, C4, and C5TunaPhos may be similar while the Ru−C1TunaPhos complex has a much smaller bite angle. Using a β-ketoester with a substituent at the α-position, syn/anti ratio about 1:1 was observed with the acyclic substrate in entry 6. However, anti product is dominant with a cyclic substrate with TunaPhos (**1**−**6**), BINAP,[7] and MeO−BIPHEP ligand systems.[8]

In conclusion, a series of chiral bisphosphines with tunable dihedral angles have been made for the first time and used for Ru-catalyzed asymmetric hydrogenation of β-ketoesters. Enantioselectivities with the Ru−C4TunaPhos(**4**) catalyst are comparable or better than those observed with Ru−BINAP and Ru−MeO-BIPHEP complexes, while enantioselectivities in asymmetric hydrogenation of β-ketoesters are low with other catalysts [e.g., Ru−C1TunaPhos(**1**) and Ru−C6TunaPhos-(**6**)]. The current study demonstrates the concept that changes in ligand dihedral angles indeed cause significant variations of enantioselectivity. Future work on applications of these TunaPhos ligands will focus on achieving new transition metal-catalyzed enantioselective reactions and extending the scope of substrates in many existing enantioselective transformations.

Experimental Section

General Procedures. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. All solvents were purified and degassed before use using the standard procedure. β-Ketoesters were redistilled and stored under N_2. NBu_3, $HSiCl_3$, BBr_3, and [Ru(benzene)Cl_2]$_2$ were purchased from Aldrich.

(*R*)-(6,6-Dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) [(*R*)-MeO-BIPHEP]. To a suspension of (*R*)-(6,6′-dimethoxybiphenyl-2,2′-diyl) bis(diphenylphosphine oxide) (46.0 g, 74.9 mmol) in *p*-xylene (490 mL) were added Bu_3N (157 mL, 660 mmol) and $HSiCl_3$ (57.1 g, 420 mmol) at room temperature under N_2. After being stirred at room temperature for 30 min, the mixture was heated at reflux for 3 h and then cooled to 0 °C followed by slow addition of 30% aqueous NaOH (350 mL, degassed). To this mixture was added CH_2Cl_2 (200 mL, degassed), and the water layer was removed with a cannula. The organic layer was treated again with degassed 30% aqueous NaOH, washed with degassed H_2O and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was heated on degassed EtOH at 80 °C for 5 min, cooled to 0 °C, and filtered. The solid product was washed with degassed EtOH and dried

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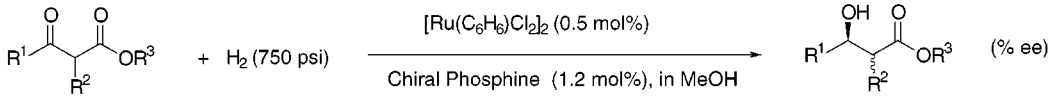
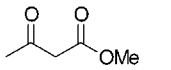
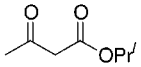
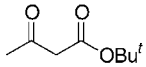
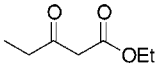
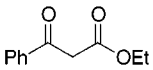
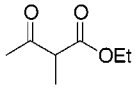
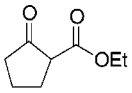
(7) (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1.

(8) (a) Genet, J. P.; Ratovelomanana-Vidal, V.; Cano de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801. (b) Genet, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Cano de Andrade, M. C.; Darses, S.; Galopin, C.;. Laffitte, J. A *Tetrahedron*: *Asymmetry* **1994**, *5*, 675.

Table 2. Ru-Catalyzed Asymmetric Hydrogenation of β-Ketoesters[a]



Entry	Substrate	1	2	3	4	5	6	MeO-BIPHEP	BINAP
1		90.9	90.8	97.7	99.1	97.1	96.5	97.9	98.4
2		90.1	90.8	97.7	99.3	96.8	96.3	98.8	98.2
3		90.0	93.9	99.0	99.2	96.8	95.9	98.5	97.6
4		89.9	93.8	99.0	99.0	96.9	95.9	98.5	97.5
5		76.8	71.4	72.0	82.3	78.5	60.5	74.8	78.4
6		79.6 (46.1% *syn*) 93.9 (53.9% *anti*)	85.6 (45.7) 95.6 (54.3)	95.5 (45.5) 98.5 (54.5)	95.8 (45.6) 98.7 (54.4)	92.5 (44.2) 98.0 (55.8)	90.7 (46.5) 97.5 (53.5)	95.2 (45.9) 98.1 (54.1)	91.3 (46.8) 95.7 (53.2)
7		87.9	89.7	95.2	96.8	94.7	91.9	97.5	93.4

[a] Hydrogenation was performed as described in the text. All reactions were complete in >99% conversion, and ee's were determined by chiral GC.

in vacuo (42.3 g, 97%): $[\alpha]^{23}_D = +42.5$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.21−7.12 (m, 18H), 7.03−6.95 (m, 4H), 6.70−6.65 (m, 4H), 3.08 (s, 6H); ^{31}P NMR ($CDCl_3$) δ −14.2; ^{13}C NMR($CDCl_3$) δ 157.5−127.8 (m, Ar−C), 110.7, 54.7.

(*R*)-(6,6′-Dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine) (7). A solution of (*R*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)-bis(diphenylphosphine) [(*R*)-MeO-BIPHEP] (23.3 g, 40 mmol) in CH_2Cl_2 (500 mL) was cooled to −78 °C and bubbled with N_2 for 15 min. To this solution was added BBr_3 (30.0 g, 120 mmol) via a syringe over a period of 10 min. The mixture was stirred at −78 °C for 1 h, and then slowly warmed to room temperature and stirred overnight. After the mixture was cooled to 0 °C, degassed water (120 mL) was added slowly and the aqueous layer was removed via cannula. The organic layer was washed subsequently with degassed H_2O and brine and dried over Na_2SO_4. The resulting organic solution was passed through a pad of neutral Al_2O_3 and evaporated to dryness to give the product, which was directly used for the next step (18.7 g, 84%): $[\alpha]^{23}_D = -10.4$ ($c = 0.5$, EtOH); ^{1}H NMR (CD_2Cl_2) δ 7.3−6.8 (m, 26H), 4.27 (s, br, 2H); ^{31}P NMR (CD_2Cl_2) δ −13.6; ^{13}C NMR(CD_2Cl_2) δ 154.9−116.7 (m, Ar−C); HRMS 555.1649, calcd [$M^+ + 1$] 555.1643.

Synthesis of [(*R*)-Cn-TunaPhos]. General Procedure. A solution of (*R*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine) (7) (1.11 g, 2 mmol) in DMF (20 mL) was bubbled with N_2 for 15 min. To this solution was added anhydrous K_2CO_3 (1.38 g, 10 mmol), and the mixture was stirred at room temperature for 15 min before bromochloromethane (2.1 mmol) was added via a syringe. The mixture was stirred at room temperature for 24 h and then heated to 60 °C until completion of the reaction (48 h). After removal of the solvent, the residue was extracted with ether, washed with water and brine, and dried over Na_2SO_4. The foamy solid obtained after evaporation of solvents was purified by a silica gel column with CH_2Cl_2−hexanes (1:3) as the eluent. C3, C4, C5, C6TunaPhos ligands were made according to this procedure. For the synthesis of C2TunaPhos, up to 3.5 equiv of 1,2-dibromoethane was used to force a complete conversion of the starting material [(*R*)-(6, 6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine)].

C1TunaPhos (1). Prepared as above from (*R*)-(6, 6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine): yield 80%; $[\alpha]^{23}_D = -396$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.8−7.0 (m, 26H), 5.41 (s, 2H); ^{31}P NMR ($CDCl_3$) δ −9.7; ^{13}C NMR ($CDCl_3$) δ 152.9−121.0 (m, Ar−C), 101.6; HRMS 567.1672, calcd [$M^+ + 1$] 567.1643.

C2TunaPhos (2). Prepared as above from (*R*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine): yield 64%; $[\alpha]^{23}_D = -294$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.8−7.0 (m, 26H), 4.30 (d, 2H, $J = 8.7$ Hz), 4.00 (d, 2H, $J = 8.7$ Hz); ^{31}P NMR ($CDCl_3$) δ −8.4; ^{13}C NMR ($CDCl_3$) δ 159.8−122.4 (m, Ar−C), 74.3; HRMS 581.1816, calcd [$M^+ + 1$] 581.1799.

C3TunaPhos (3). Prepared as above from (*R*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine): yield 82%; $[\alpha]^{23}_D = -225$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.5−6.7 (m, 26H), 4.1−4.0 (m, 4H), 1.68(t, $J = 5.7$ Hz, 2H); ^{31}P NMR ($CDCl_3$) δ −11.7; ^{13}C NMR ($CDCl_3$) δ 157.8−118.8 (m, Ar−C), 72.2, 29.6; HRMS 595.1922, calcd [$M^+ + 1$] 595.1956.

C4TunaPhos (4). Prepared as above from (*R*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine): yield 84%; $[\alpha]^{23}_D = -167$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.6−6.7 (m, 26H), 4.19 (d, $J = 11.5$ Hz, 2H), 3.77(d, $J = 10.4$ Hz, 2H), 1.68 (t, $J = 10.4$ Hz, 2H), 1.55 (d, $J = 11.5$ Hz, 2H); ^{31}P NMR ($CDCl_3$) δ −11.2; ^{13}C NMR ($CDCl_3$) 156.3−115.5 (m, Ar−C), 69.7, 25.5; HRMS 609.2100, calcd [$M^+ + 1$] 609.2112.

C5TunaPhos (5). Prepared as above from (*R*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine): yield 55%; $[\alpha]^{23}_D = -143$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.6−6.9 (m, 26H), 4.3−4.2 (m, 2H), 4.0−3.8 (m, 2H), 1.9−1.4 (m, 6H); ^{31}P NMR ($CDCl_3$) δ −11.4; ^{13}C NMR ($CDCl_3$) δ 157.0−113.5 (m, Ar−C), 67.2, 26.0, 22.3; HRMS 623.2261, calcd [$M^+ + 1$] 623.2269.

C6TunaPhos (6). Prepared as above from (*R*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine): yield 55%;

$[\alpha]^{23}_D = -122$ ($c = 0.5$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.8−6.8 (m, 26H), 4.1−4.0 (m, 2H), 3.7−3.6 (m, 2H), 1.9−1.4 (m, 8H); ^{31}P NMR ($CDCl_3$) δ −11.5; ^{13}C NMR ($CDCl_3$) δ 156.5−111.4 (m, Ar−C), 66.4, 25.9, 24.5; HRMS 637.2413, calcd for $[M^+ + 1]$ 637.2425.

P**rocedure for the Asymmetric Hydrogenation Reaction.** To a 10 mL Schlenk tube were added $[Ru(benzene)Cl_2]_2$ (10 mg, 0.02 mmol) and diphosphine (0.048 mmol of *R*-BINAP, *R*-MeO-BIPHEP, or C1−C6TunaPhos). The tube was purged with N_2 three times before addition of freshly distilled and degassed DMF (1 mL). The resulting mixture was heated at 99−101 °C for 10 min. After the mixture was cooled to 50 °C, the solvent was removed under vaccum to give the catalysts as an orange-red solid. This catalyst was taken into a glovebox, dissolved in degassed methanol (8 mL), and distributed equally to eight vials (1 mL each). The β-ketoester was added in each vial and these eight vials was transferred to a Parr bomb. The bomb was purged three times with H_2, and the pressure of H_2 was set to 750 psi. The reactor was placed in an oil bath at 60 °C and stirred for 20 h. The bomb was then cooled to room temperature and the H_2 carefully released. The methanol solution was removed and the residue dissolved in ether. The ether solution was washed with H_2O and brine and dried over Na_2SO_4. The ether solution was passed through a short silica gel column and concentrated to dryness to give products.

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