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Axially chiral electron-rich TunePhos-type ligand: synthesis and applications in asymmetric hydrogenation

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ABSTRACT

A new electron-rich TunePhos type ligand has been synthesized; excellent enantioselectivities (up to 99% ee) have been achieved in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid methyl esters and dimethyl itaconate.

Atropisomeric biaryl ligands are among the most valuable chiral ligands for transition metal-catalyzed asymmetric hydrogenation.[1] The prototypical ligand is BINAP **1**, which was developed by Takaya and Noyori in 1980.[2] Pioneering studies on **1** by Noyori and co-workers have led to highly efficient practical asymmetric hydrogenation of a diverse set of ketones, including both functionalized and unfunctionalized (simple) ketones.[3] The success of **1** also inspired the further development of other axially chiral biaryl type bisphosphine ligands, such as MeO-BIPHEP **2**,[4] SegPhos **3**,[5] SynPhos **4**,[6] and DifluorPhos **5** (Fig. 1).[7] To investigate the effect of bite angle on enantioselectivity for biaryl ligands, we have introduced Cn-TunePhos **6** with a tunable linking bridge.[8] By systematically changing the length of the bridge, the bite angle of **6** can be optimized for the hydrogenation of different substrates. Recently, improvement of the synthesis of TunePhos type ligands was achieved by us[9a,b] as well as by Chan's group[10] in that a key step of central-to-axial chirality transfer is devised to circumvent the tedious resolution step involved in the original synthesis. Thus, a broad series of C3*-TunePhos ligands **7** bearing different aryl substituents on the phosphine donors can be prepared by a highly modular approach. Compared with **6c** ($n = 3$), **7** shows enhanced enantioselectivities toward allylphthalimides and α-keto esters.[9b] In addition, a Ru/**7** (Ar = Xylyl)/diamine catalytic system has demonstrated extremely high reactivity and enantioselectivity toward a variety of simple ketones.[9c]

While most biaryl ligands bearing triaryl phosphine donors have been developed for Ru-catalyzed hydrogenation reactions,[1e] some electron-rich dialkylaryl phosphine ligands (Fig. 2) have shown potential application in Rh-catalyzed asymmetric hydrogenation. For example, BICHEP **8** gave much better results in the hydrogenation of ethyl (*Z*)-α-(benzamido)cinnamate and dimethyl itaconate than the corresponding bis(triarylphosphine) ligand.[11] Recently, an insightful method for ligand optimization was proposed by Saito and co-workers: combined computational and experimental studies indicated that dialkyl aryl bisphosphine **9** (R = Cy or *i*Pr) is the ligand of choice for asymmetric hydrogenation of α-acetamidocinnamate.[12] Inspired by these interesting results, we further explored electron-rich biaryl ligand **10** for asymmetric hydrogenation. Herein, we report the synthesis of a new electron-rich TunePhos-type ligand and its application in highly enantioselective Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid methyl esters and dimethyl itaconate (up to 99% ee).

The synthesis of the target ligand **10** is depicted in Scheme 1.[13,14] Starting from 3-bromophenol **11**, protection of the hydroxyl group afforded the carbamate **12**. Regioselective *ortho* lithiation followed by oxidative coupling with $FeCl_3$ led to the formation of the biaryl backbone of **13** in 56% yield. The labile carbamate groups were then removed under basic condition to form the di-bromo substituted biphenol **14**, which was further subjected to Mitsunobu reaction condition (PPh_3, DIAD, sonication) in the presence of a chiral 2,4-diol. In this step, two diastereomers with opposite axial chiralities were obtained, from which the desired precursor **15** was obtained through purification by column chromatography in 22% yield. Finally, **15** was treated with *n*BuLi at low temperature for Li-Br exchange; subsequent quenching with Cy_2PCl afforded the ligand **10** in moderate yield.[13]

With the new ligand **10** in hand, Rh-catalyzed asymmetric hydrogenation was tested with the benchmark substrate methyl-2-acetamido acrylate **16a**. Solvent screening showed that the best ees were obtained in polar solvents such as THF, ethyl acetate, acetone, and methanol (Table 1, entries 3–6); in contrast, lower selectivities were observed in 2,2,2-trifluoroethanol (TFE) and weakly coordinating solvents CH_2Cl_2 and toluene (entries 1, 2, and 7). Thus, methanol was selected for the following hydrogenation reactions. As shown in Table 1, excellent enantioselectivities, up to 99% ee, have been achieved in Rh-catalyzed hydrogenation

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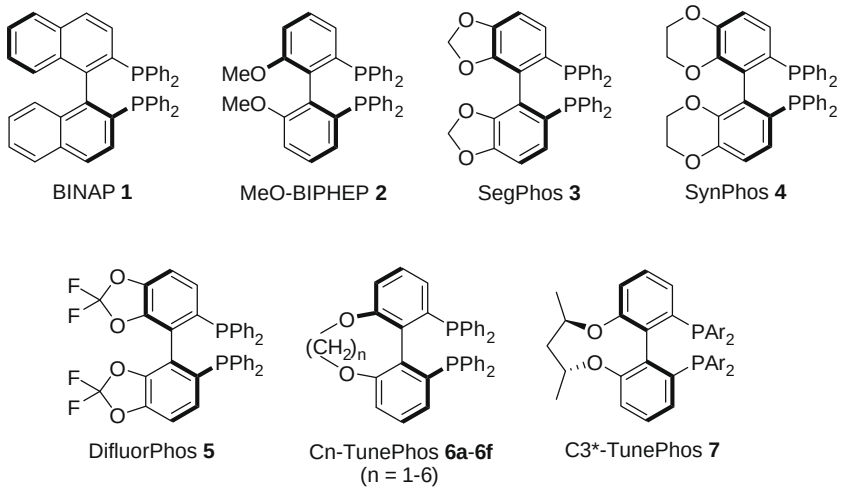


Figure 1. Typical axially chiral bisphosphine ligands for asymmetric hydrogenation.

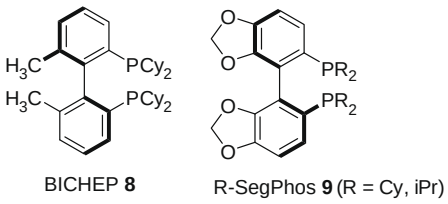
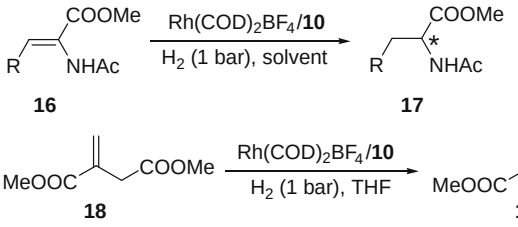


Figure 2. Electron-rich dialkylaryl bisphosphines for asymmetric hydrogenation.

of a series of α-dehydroamino acid methyl esters. Substitution on the aryl group of the substrates **16c–h** has negligible effect on enantioselectivity (entry 8 vs entries 9–14). Moreover, we found that dimethyl itaconate **18** was also hydrogenated by Rh/**10** catalyst with 90% ee in THF. These results are comparable to those obtained by the use of other bis(dialkylarylphosphine) ligands such as **8** and **9**.

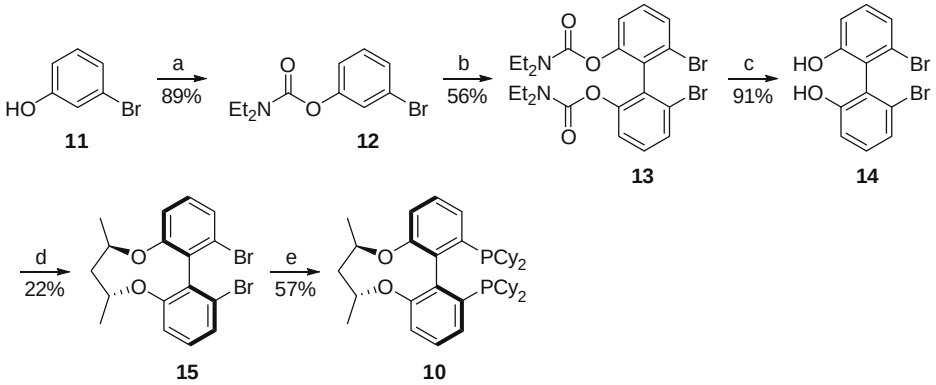
In conclusion, a new electron-rich TunePhos type ligand **10** has been synthesized and successfully applied in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid methyl esters and dimethyl itaconate. The observed enantioselectivities (up to 99% ee) are comparable to the results given by other bis(dialkylarylphosphine) ligands. Further efforts are directed toward the expansion of this synthetic strategy for the preparation of other axially chiral ligands for asymmetric hydrogenation, as well as for other asymmetric catalytic reactions.

Table 1
Asymmetric hydrogenation of methyl-2-acetamido acrylate with Rh/**10** catalyst[a]



Entry	Substrate	R	Solvent	ee (%)[b]	Configuration[c]
1	**16a**	H	CH_2Cl_2	98	*R*
2	**16a**	H	Toluene	95	*R*
3	**16a**	H	THF	99	*R*
4	**16a**	H	EtOAc	99	*R*
5	**16a**	H	Acetone	99	*R*
6	**16a**	H	MeOH	99	*R*
7	**16a**	H	TFE	93	*R*
9	**16c**	2-F–Ph	MeOH	99	*R*
10	**16d**	4-F–Ph	MeOH	99	*R*
11	**16e**	3,5-Difluoro-Ph	MeOH	99	*R*
12	**16f**	2-Br–Ph	MeOH	99	*R*
13	**16g**	4-Br–Ph	MeOH	99	*R*
14	**16h**	4-MeO–Ph	MeOH	99	*R*
15[d]	**18**	—	THF	90	*S*

[a] The hydrogenation reactions were carried out with 1% Rh/**10** catalyst at rt under 1 bar of H_2 for 18 h. In all cases, full conversion was observed.
[b] The ees were determined by chiral GC using a Chirasil-Val column.
[c] The absolute configurations were determined by comparing the optical rotations with the reported data.
[d] The ee was determined by chiral GC using a γ-dex 225 column.



Scheme 1. Reagents and conditions: (a) (i) NaH, THF, rt; (ii) $ClC(O)NEt_2$, rt; (b) (i) LDA, −78 °C; (ii) $FeCl_3$, −78 °C; (c) NaOH, EtOH, reflux; (d) (2*S*, 4*S*)-pentane-2,4-diol, PPh_3, DIAD, THF, 0 °C, sonication; (e) (i) *n*BuLi, TMEDA, THF, −78 °C; (ii) Cy_2PCl, −78 °C.

Acknowledgments

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13. Initial attempt to employ the method used for the preparation of **7** (Ref. 9b) was found to be ineffective to synthesize the desired ligand **10**.
14. *Characterization data of* **12**–**10**: Compound **12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.15 (t, J = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 3.36–3.33 (m, 4H), 1.18–1.14 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.71, 152.37, 130.44, 128.32, 125.43, 122.24, 120.87, 42.58, 42.19, 14.47, 13.56. Compound **13**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (dd, J = 8.1, 1.5 Hz, 2H), 7.65 (dd, J = 8.1, 1.5 Hz, 2H), 7.48 (t, J = 8.1 Hz, 2H), 3.40 (m, 4H), 3.18 (m, 4H), 1.26 (t, J = 7.1 Hz, 6H), 0.95 (t, J = 7.1 Hz, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 151.74, 149.21, 130.28, 128.80, 127.65, 123.38, 121.06, 42.5, 42.2, 14.5, 13.4; HRMS (M+H$^+$) calcd for $C_{22}H_{27}N_2O_4Br_2$: 541.0332, found: 541.0328. Compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 5.13 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.09, 131.97, 125.48, 125.43, 122.92, 115.50; HRMS (M+H$^+$) calcd for $C_{12}H_9O_2Br_2$: 342.8964, found: 342.8966. Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.53 (m, 2H), 1.79 (m, 2H), 1.34 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.56, 132.20, 130.16, 127.18, 125.03, 117.50, 76.68, 40.92, 22.44; HRMS (M+H$^+$) calcd for $C_{17}H_{17}O_2Br_2$: 410.9590, found: 410.9585. Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.1 Hz, 2H), 7.05 (t, J = 8.1 Hz, 2H), 6.91 (d, J = 8.1 Hz, 2H), 4.40 (m, 2H), 2.00 (m, 2H), 1.73–0.82 (m, 50H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.93, 137.99, 137.41, 126.90, 126.13, 117.13, 74.75, 40.87, 35.83, 32.51, 30.97, 30.51, 29.81, 28.91, 28.16, 28.04, 27.58, 27.52, 27.27, 26.83. ^{31}P NMR(162 MHz, $CDCl_3$): δ −10.58 (s); HRMS (M+H$^+$) calcd for $C_{41}H_{61}O_2P_2$: 647.4141, found: 647.4135.