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Catalytic asymmetric diethylzinc addition to diphenylphosphionyl imines using chiral *tert*-butanesulfinylphosphine ligands

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ABSTRACT

A class of novel chiral *tert*-butanesulfinylphosphine ligands were designed and synthesized by a concise two-step route with high yields. High activities and enantioselectivities (up to 94% ee) were achieved when using them in catalytic asymmetric diethylzinc addition to diphenylphosphionyl imines.

α-Branched chiral amines play an important role in the synthesis of many modern active pharmaceutical ingredients and drug candidates.[1] Various methods have been developed to prepare α-branched chiral amines enantioselectively, such as asymmetric reduction of imines, resolution of racemates, and enantioselective addition of alkylmetals to imines. Remarkably, the most attractive and effective method for a convenient synthesis of α-branched chiral amines is based on enantioselective addition of diorganozinc reagents to activated amines catalyzed by chiral metal-complexes, such as Zr–peptide,[2] copper–amidophosphine,[3] thiophosphoramide,[4] Me–Duphos,[5] Me–Duphos monoxide metal complex,[6] N,O-ligand catalysis,[7] and Rh–diene complexes.[8,9] For most of these catalysis complexes, ligands are hard to obtain in a convenient way. It is still worthwhile to design and develop novel and effective ligands that can be prepared through concise routes. P,O-ligands, such as Me–Duphos monoxide,[10,11] display good coordination capacities with copper ion from one P atom and one O atom of phosphine oxide.[12] *Could the coordinating oxygen atom be replaced by other heteroatoms like sulfur atom (sulfoxides)?* Actually, chiral sulfur ligands are widely used in catalytic asymmetric reactions.[13] Particularly, chiral phosphino sulfoxides and their palladium complexes are used in catalytic asymmetric allylic nucleophilic substitution reactions.[14] Up to date, there is no literature reports about the applications of chiral phosphino sulfoxide ligands coordinated with other transition metals like copper ion in catalytic asymmetric reactions. Although both oxygen and sulfur atoms can coordinate with different transition metals,[15] in sulfoxide–Cu(II) complex,[16] it is oxygen but not sulfur atom that coordinated with copper ion very well, therefore, phosphino sulfoxide ligands might also act as a new type of P,O-ligands. Since Ellman developed an elegant catalytic asymmetric oxidation route to prepare *tert*-butyl *tert*-butanethiosulfinate with good enantioselectivity, which was then readily converted to enantiomerically pure *tert*-butanesulfinamide, it has been widely employed as chiral auxiliary in stereoselective carbon–carbon bond formation.[1c,17] Furthermore, *tert*-butanesulfinyl moiety was also utilized for the designation of C_2-symmetric sulfinyl imines,[16] P, N; N, N; P, S; N, S-ligands and widely used in catalytic asymmetric reactions.[18] In this letter, we would like to present novel phosphino sulfoxide ligands, of which both sulfoxide and chirality environment are provided by a chiral *tert*-butylsulfinyl moiety and their copper complexes are applied in catalytic asymmetric synthesis of α-branched chiral amines.

The synthesis of the novel phosphino sulfoxide ligands was accomplished through two steps using bromo-arene derivatives **1** as the starting materials. Standard bromo-lithium exchange proceeded at low temperature followed by addition of thiosulfinate **2**, which can be readily obtained in optical form according to our method[19] to give the desired product **3** in high yield (Scheme 1). Deprotonation of **3a** has been reported with *n*-BuLi, but **3b** and **3c** reacted more readily with LDA in THF at −78 °C.[20] It should be emphasized that the chiral ligands **4b** and **4c** are quite stable at ambient temperature due to electronic effect of the *meta*-OCH_3 and OCH_2OCH_3 group on *tert*-butanesulfinyl group. In fact, no phosphine oxide was detected after keeping them in desiccator for three months.

With the ligands **4** in hand, we chose diphenylphosphionyl imines as amine precursors, in which *N*-phosphinionyl-protecting group can be easily cleaved under mild acidic conditions to provide α-branched chiral amines. As showed in Table 1, the model reaction is carried out at a 0.5 mmol scale of diphenylphosphionyl imine **5a** with 4.0 equiv diethylzinc, 3 mol % ligands **4b**, and 6 mol % copper salt in anhydrous toluene. The desired product **6a** was obtained within 15 h. Except CuI (25% yield, 53% ee, Table 1,

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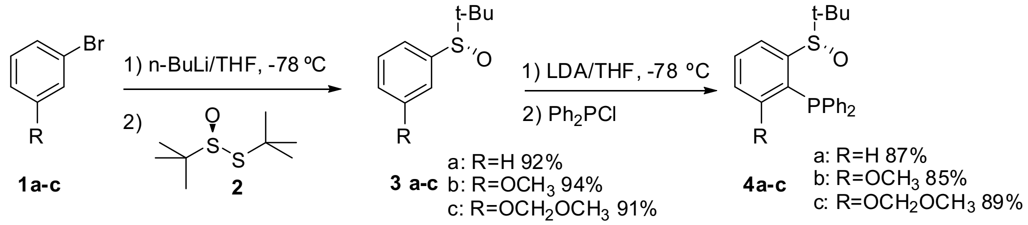
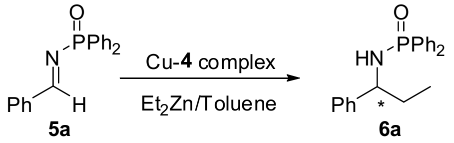


Scheme 1. Synthesis of chiral phoshino sulfoxide ligands **4a**–**c**.

Table 1

Enantioselective addition of Et_2Zn to diphenylphosphionyl imine **5a** catalyzed by copper salts and ligands **4a**–**c**[a]



Entry	L	Cu salts	T (°C)	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**4b**	CuI	0	15	25	53
2	**4b**	CuTC[e]	0	15	82	80
3	**4b**	CuOTf	0	15	81	85
4	**4b**	$Cu(OTf)_2$	0	15	87	85
5	**4b**	$Cu(II)\cdot xH_2O$	0	15	89	92
6	**4a**	$Cu(II)\cdot xH_2O$	0	15	52	47
7	**4c**	$Cu(II)\cdot xH_2O$	0	15	86	89
8	**4b**	$Cu(II)\cdot xH_2O$	−20	24	Trace	nd[f]
9	**4b**	$Cu(II)\cdot xH_2O$	rt	15	81	89
10[g]	**4b**	$Cu(II)\cdot xH_2O$	rt	6	85	86
11[h]	**4b**	$Cu(II)\cdot xH_2O$	rt	15	81	88
12[i]	**4b**	$Cu(II)\cdot xH_2O$	rt	15	80	87

[a] Reactions performed at a 0.5 mmol scale of **5a** with 4.0 equiv Et_2Zn, 3 mol % ligand and 6 mol % copper salt in 5.0 mL toluene.

[b] Isolated yield.

[c] Determined by HPLC with Daicel Chiralcel OD column.

[d] The absolute configuration is *R*-form which was assigned by comparison of the optical rotation with literature 19.

[e] CuTC = copper thiophene-2-carboxylate.

[f] nd = not determined.

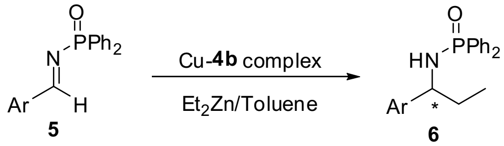
[g] 6 mol % **4b** and 12 mol % = $Cu(O_2CCF_3)_2\cdot xH_2O$ was used.

[h] 3 mol % **4b** and 3 mol % = $Cu(O_2CCF_3)_2\cdot xH_2O$ was used.

[i] 6 mol % **4b** and 3 mol % = $Cu(O_2CCF_3)_2\cdot xH_2O$ was used.

Table 2

Enantioselective addition of Et_2Zn to diphenylphosphionyl imines **5** catalyzed by $Cu(O_2CCF_3)_2\cdot xH_2O$ and ligand **4b**[a]



Entry	Imines	Ar	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	**5a**	Ph	89	92	*R*
2	**5b**	$4\text{-}MeC_6H_4$	87	93	*R*
3	**5c**	$4\text{-}ClC_6H_4$	83	89	*R*
4	**5d**	$4\text{-}BrC_6H_4$	84	89	*R*
5	**5e**	$4\text{-}MeOC_6H_4$	80	94	*R*
6	**5f**	$2\text{-}FC_6H_4$	84	80	*R*
7	**5g**	$3\text{-}ClC_6H_4$	80	83	*R*
8	**5h**	2-Furyl	81	73	*R*
9	**5i**	2-Thienyl	84	80	(−)

[a] Reactions performed at a 0.5 mmol scale of 5 with 4.0 equiv Et2Zn, 3 mol % **4b** and 6 mol % $Cu(O_2CCF_3)_2\cdot xH_2O$ ($x = 0.56$) in 5.0 mL toluene for 15 h.

[b] Isolated yield.

[c] Determined by HPLC with chiral columns (see: Supplementary data for details).

[d] The absolute configuration except **6i** was assigned by comparison of the optical rotation with literature.[22]

entry 1), other copper salts CuTC, CuOTf, and $Cu(OTf)_2$ showed similar catalytic activities and good enantioselectivities (Table 1, entries 2–4). It is interesting that copper(II) trifluoro-acetate hydrate, $Cu(O_2CCF_3)_2\cdot xH_2O$ ($x = 0.56$),[21] gave the best result (89% yield and 92% ee, Table 1, entry 5). We next examined the effect of ligands, catalyst loading, and temperature on the reactivities and enantioselectivities. Ligand **4c** manifested similar catalytic activity and high enantioselectivity (86% yield and 89% ee, Table 1, entry 7). However, ligand **4a** gave the product in a low yield and enantioselectivity (52% yield and 47% ee, Table 1, entry 6). The *meta*-substituted groups might exert electronic effect and steric hindrance. We found that the reaction was inert when the temperature was decreased to −20 °C even after 24 h (Table 1, entry 8). No obvious variation on activity and slight decrease on enantioselectivity were observed when the temperature was increased to room temperature (81% yield and 89% ee, Table 1, entry 9). Furthermore, the reaction went faster (6 h) without affecting the enantioselectivity or on yield when the catalyst loading was doubled (6 mol % **4b** and 12 mol % $Cu(O_2CCF_3)_2\cdot xH_2O$, Table 1, entry 10). In addition, there was also no effect on enantioselectivity or yield when the mole ratio of ligand **4b** and $Cu(O_2CCF_3)_2\cdot xH_2O$ was changed from 3:6 to 3:3 or 6:3 (Table 1, entries 11 and 12). Thus, the best reaction condition was to use ligand **4b** (3 mol %) and $Cu(O_2CCF_3)_2\cdot xH_2O$ (6 mol %) in toluene at 0 °C.

Under the optimized conditions, we investigated the scope of imines derived from aryl-, furyl- and thienyl aldehydes, and the results are summarized in Table 2. Most reactions demonstrated high activities and high enantioselectivities (Table 2, entries 1–5). *Ortho*-F, *meta*-Cl substituent on phenyl ring, 2-furyl- and 2-thienyl gave similar yields and moderate enantioselectivities (Table 2, entries 6–9).

In conclusion, we have designed and synthesized a class of novel *tert*-butanesulfinylphosphine ligands, of which both sulfoxide and chirality environment are provided by a chiral *tert*-butylsulfinyl moiety. The ligands can be conveniently prepared in high yields through two steps. And using the chiral ligand **4b** in the copper-catalyzed addition of diethylzinc to diphenylphosphionyl imines demonstrated high activities and up to 94% enantioselectivities. Further studies on mechanism and on other catalytic asymmetric reactions of these ligands are currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.111.

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20. *Characterization data of* **4a–c**: *Compound* **4a**: Colorless oil. $[\alpha]_D^{25}$ −13.2 (*c* 0.4, EtOH). ^{1}H NMR ($CDCl_3$): δ 7.92–7.95 (br, 1H), 7.45 (t, J = 7.3 Hz, 1H), 6.99–7.31 (m, 12H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 161.7, 151.1, 150.7, 137.1, 134.4, 134.3, 132.7, 132.5, 132.4, 132.1, 131.8, 131.3, 128.1, 127.9, 127.8, 127.7 119.4, 119.2, 114.1, 58.3, 55.1, 24.0. ^{31}P NMR ($CDCl_3$): δ −14.6; IR (liquid film) (cm^{-1}) 3051, 2960, 2921, 1582, 1432, 1432, 1047, 741,694. HRMS: calcd for $C_{22}H_{23}OPS$+Na: 389.1099, found: 389.1111.
    Compound **4b**: White solid. $[\alpha]_D^{25}$ −165.1 (*c* 0.1, EtOH), mp: 114–115 °C. ^{1}H NMR ($CDCl_3$): 7.21–7.61 (m, 12H), 6.93 (d, J = 8.0 Hz 1H), 3.32 (s, 3H),1.22 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 161.6, 161.5, 150.9, 150.5, 137.2, 134.3, 132.6, 132.4, 132.3, 132.2, 132.1, 130.4, 130.3, 130.2, 128.0, 127.9, 127.8, 127.7, 127.6, 119.2, 119.1, 114.0, 55.0, 23.9. ^{31}P NMR ($CDCl_3$): δ −18.7; IR (KBr) (cm^{-1}): 3058, 2978, 1570, 1453, 1451, 1264, 1176, 1039, 1025, 789, 743, 693. HRMS: calcd for $C_{23}H_{25}O_2PS$+Na: 419.1205, found: 419.1210.
    Compound **4c**: White solid. $[\alpha]_D^{25}$ −195.2 (*c* 0.1, EtOH), mp: 117–118 °C. ^{1}H NMR ($CDCl_3$): δ 7.21–7.72 (m, 13H), 4.61 (m, 2H), 2.95 (s, 3H), 1.23(s, 9H). ^{13}C NMR ($CDCl_3$): δ 59.6, 151.0, 150.6, 137.1, 136.9, 134.0, 133.9, 132.4, 132.3, 132.2, 132.1, 130.6, 130.4, 130.2, 128.0, 127.9, 127.8, 127.7, 120.4, 120.1, 116.5, 94.0, 58.3, 55.7, 23.8. ^{31}P NMR ($CDCl_3$): δ −18.5. IR (KBr) (cm^{-1}): 3056, 2970, 2896, 1571, 1435, 1252, 1152, 1137, 1079, 1031, 998, 789, 750, 693. HRMS: calcd for $C_{24}H_{28}O_3PS$+H: 427.1491, found: 427.1496.
21. Copper(II) trifluoroacetate hydrate($Cu(O_2CCF_3)_2 \cdot xH_2O$) was purchased from Alfa Aesar, $x = 0.56$. For literatures about improving enantioselectivities of dialkylzinc addition by adding trace water or by using metal complex hydrate, see: (a) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409; (b) Delapierre, G.; Constantieux, T.; Brunel, J. M.; Buono, G. *Eur. J. Org. Chem.* **2000**, 2507; (c) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.
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