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Electronically deficient (R_{ax},S,S)-F_{12}-C_3-TunePhos and its applications in asymmetric 1,4-addition reactions

Shu-Bo Hu, Zhang-Pei Chen, Ji Zhou, Yong-Gui Zhou *

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China

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ABSTRACT

A novel electronically deficient chiral diphosphine ligand (R_{ax},S,S)-F_{12}-C_3-TunePhos has been concisely synthesized. The electron-poor ligand features both chiral centers and chiral axis bearing fluoro-functional groups on each phosphorus phenyl ring based on C_3-TunePhos backbone. The catalyst composed of this ligand and rhodium showed excellent activities and enantioselectivities in asymmetric 1,4-addition reactions of arylboronic acids to diverse α,β-unsaturated ketones with up to 99% ee.

Chiral diphosphine ligands have attracted considerable attention due to their great significance in multifarious transition-metal-catalyzed reactions in recent years.[1] Subtle modifications in steric, geometric, or electronic properties of chiral ligands could dramatically affect the catalytic reactivity and stereocontrol of metal–ligand complexes in specific reactions.[2] Therefore, great efforts have been made to design and synthesize novel chiral phosphine ligands with different scaffolds or electronic characters.[3] Although studies were dominated in electron-rich diphosphine ligands in the past decades, much attention has also been focused on electron-deficient ligands recently.[3d] According to the foregoing research, following features of electron-poor ligands may alter the performance of the corresponding metal–ligand complexes in asymmetric catalytic reactions. First of all, electronically deficient phosphine ligands are good π-acceptors, which would display significant ligand *trans* influence upon coordination to a transition metal center and the transition metal with which could be more reactive.[4] What's more, the electron-poor ligands could promote reductive elimination compared with electron-rich ones.[5] In addition, the rate of transmetalation[6] and migratory insertion[7] of conjugated addition reactions could be accelerated by an electronically poor ligand-based catalyst.

Since the pioneering research on the design of C_2 symmetric fluorinated diphosphine BIFUP reported in 1991 by Achiwa's group,[8] some electron-poor chiral phosphine ligands have been synthesized and applied to a variety of asymmetric catalytic reactions. Some privileged electronically deficient chiral phosphine ligands are listed in Figure 1. Besides 6,6′-difluorinated and trifluoromethyl substituted biphenyl ligands, trifluoromethylphosphine dinaphthalene ligand has also been prepared.[2b,9] In 2003, Weissensteiner and Spindler prepared another ferrocene-based electronically deficient diphosphine ligand Walphos, which was the fluorinated analogues of JosiPhos, and successfully employed this ligand to Rh- and Ru-catalyzed asymmetric hydrogenation reactions.[10]

Afterward, the famous ligand DifluorPhos was synthesized and appropriate transition metals coordinated with this ligand could catalyze numerous types of reactions with excellent enantioselectivity.[11] In 2009, Korenaga's group developed a new fluorinated ligand MeO-F_{12}-BiPhep, which exhibited high efficiency in conjugated addition reactions of arylboronic acids to α,β-unsaturated ketones.[12] Thereafter, various other kinds of electron-poor ligands were reported gradually,[13] for example the fluorinated SynPhos analogue 3,5-diCF_3-SynPhos.[13d] Recently, our group has also prepared two kinds of electron-poor ligands TfO-BiPhep[13e] and CF_3O-BiPhep,[13f] which were applied to iridium-catalyzed asymmetric hydrogenation of quinolines with high activity and enantioselectivity. It is worth noting that the electron-poor phosphine ligands with oxazoline moiety have also been demonstrated as prepotent ligands in asymmetric allylic alkylation reactions.[14] Despite much progress has been made in this field, since there is no omnipotent ligand for every reaction, the needs for more efficient ligands are evident and the research in the exploration of versatile ligands with sterically and electronically diverse properties is of great significance. As the C_3-TunePhos backbone-based diphosphine ligands are privileged motif in the chemistry of ligand design,[15] and together with our ongoing efforts in promoting the development of asymmetric catalysis,

* Corresponding author.

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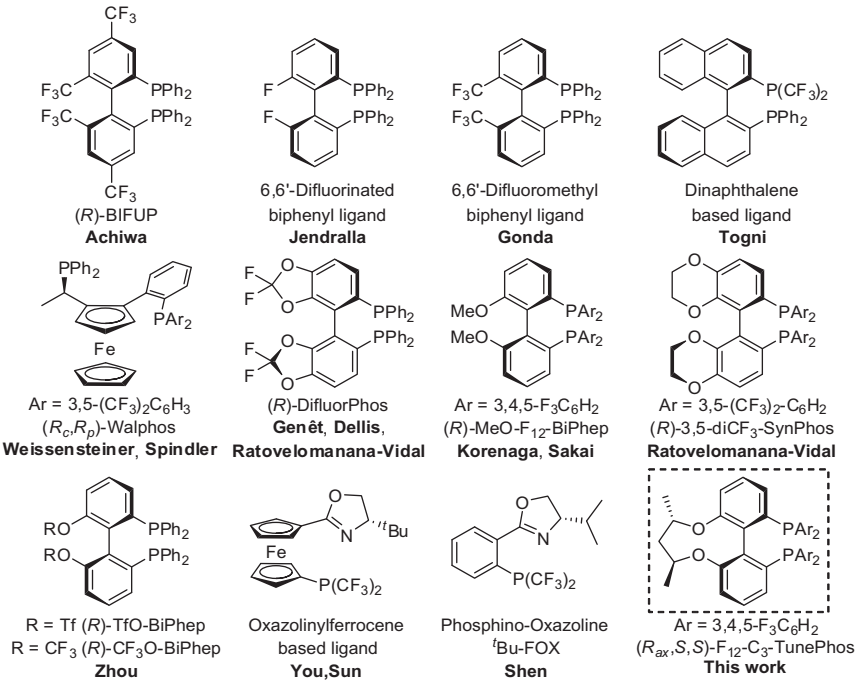
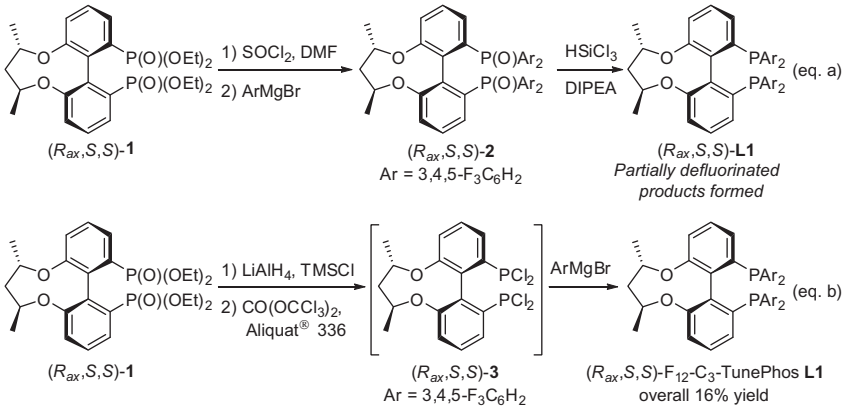


Figure 1. Some examples of electron-deficient phosphine ligands.

herein, we report the synthesis of an electronically deficient diphosphine ligand (R_{ax},*S*,*S*)-F_{12}-C_3-TunePhos, and its application in rhodium-catalyzed asymmetric 1,4-addition reactions to cyclic and acyclic enones with high reactivity and enantioselectivity.

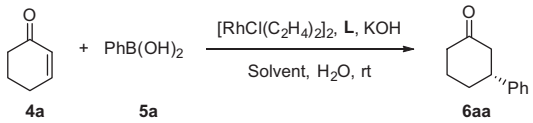
Our synthetic approach to enantiopure ligand **L1** ((R_{ax},*S*,*S*)-F_{12}-C_3-TunePhos) is depicted in Scheme 1. Initially, we tried to synthesize the ligand according to the literature report[16] (equation a): the bis(phosphonic dichlorides) was readily obtained in situ from compound **1** by the treatment with thionyl chloride, which then underwent tetrasubstitution with Grignard reagent to give the phosphine oxide **2**. However, due to some inseparable partially defluorinated side products formed in the trichlorosilane reduction of **2**, the pure compound **L1** could not be furnished. Subsequently, we turned to another way that was represented in equation b.[17] In this conversion, compound **1** was reduced with lithium aluminum hydride and chlorotrimethylsilane to give the bis(primary phosphine) intermediate, followed by treatment with triphosgene and methyltrioctylazanium chloride to offer the bis(phosphornous dichloride) **3**. Finally, substitution of **3** with Grignard reagents could be successfully performed to give the desired product ligand **L1** with 16% overall yield in three steps.

The application probability of the electronically deficient ligand **L1** prepared above was evaluated by the rhodium-catalyzed conjugated addition reaction of arylboronic acids to enones.[18] The compound 2-cyclohexenone (**4a**) was selected as the model substrate for condition optimization. Gratifyingly, the exposure of **4a** with **5a** in the presence of potassium hydroxide catalyzed by rhodium-**L1** complex at room temperature in dioxane provided 3-phenylcyclohexanone **6aa** with >99% ee and 32% yield (Table 1, entry 1). Next, a series of solvents were examined. The complete conversion was obtained in dichloromethane and toluene (Table 1, entries 1–5). Notably, the reaction could also proceed in the absence of potassium hydroxide to give **6aa** with 59% yield (Table 1, entry 6). Elevating the dosage of potassium hydroxide had an obvious promoting effect on the reactivity (Table 1, entries 4–8). Increasing the amount of **4a** to decrease the percentage of catalyst loading, the turnover frequency (TOF) reached 480 h^{-1} in dichloromethane and 760 h^{-1} in toluene (Table 1, entries 9 and 10). These

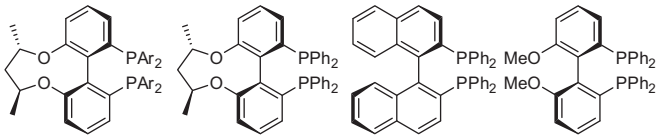


Scheme 1. Synthesis of ligand (R_{ax},*S*,*S*)-F_{12}-C_3-TunePhos.

Table 1
Optimization of asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexenone[a]



Entry	Solvent	L	Yield (%)[b]	Ee (%)[c]
1	Dioxane	**L1**	32	>99
2	THF	**L1**	42	>99
3	Et_2O	**L1**	51	>99
4	DCM	**L1**	97	>99
5	Toluene	**L1**	96	>99
6[d]	DCM	**L1**	59	>99
7[e]	DCM	**L1**	>99	>99
8[e]	Toluene	**L1**	>99	>99
9[e,f]	DCM	**L1**	48	>99
10[e,f]	Toluene	**L1**	76	>99
11[e,g]	Toluene	**L1**	99	>99
12[e]	DCM	**L2**	NR	—
13[e]	DCM	**L3**	NR	—
14[e]	DCM	**L4**	NR	—
15[h]	Toluene	**L4**	NR	—



L1 Ar = 3,4,5-F_3-C_6H_2 | **L2** (R_{ax},*S*,*S*)-C_3-TunePhos | **L3** (*R*)-BINAP | **L4** (*R*)-MeO-BiPhep

[a] **4a** (0.6 mmol), **5a** (0.72 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.5 mol %), **L** (1.05 mol %), solvent (0.8 mL), H_2O (0.3 mL), KOH (20 mol %), rt, 1 h.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Without KOH.
[e] KOH (40 mol %).
[f] **4a** (6 mmol), **5a** (7.2 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.05 mol %), **L1** (0.105 mol %), Solvent (1.5 mL), H_2O (1.0 mL).
[g] **4a** (1.2 mmol), **5a** (1.44 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.25 mol %), **L1** (0.525 mol %).
[h] The data were quoted from Ref. 12a. NR = no reaction.

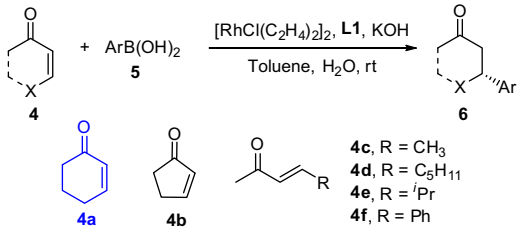
results made it clear that the catalytic system in toluene was more efficient than in dichloromethane, and thus, toluene was chosen as the optimal solvent. To our delight, with the catalyst loading of 0.25 mol %, full conversion and excellent enantioselectivity were achieved (Table 1, entry 11). In contrast, the rhodium complexes with electronic-donating ligands **L2**, **L3** or **L4** showed no catalytic activity in dichloromethane or toluene (Table 1, entries 12–15). Consequently, the optimal conditions were established as: **4a** (1.2 mmol), **5a** (1.44 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.25 mol %), **L1** (0.525 mol %), potassium hydroxide (0.48 mmol), toluene (0.8 mL) and water (0.3 mL), room temperature.

With the optimal conditions in hand, the exploration of substrate scope was carried out (Table 2). All the *meta*- and *para*-substituted aryl boronic acids reacted with cyclic enone **4a** smoothly to afford the corresponding ketones in high yields (89–97%) and excellent enantioselectivities (98–99% ee) (Table 2, entries 3–9). For *ortho*-methyl substituted phenylboronic acid, the deterioration in activity may be ascribed to the steric effect (Table 2, entry 2). Interestingly, both electron-donating and electron-withdrawing groups at the *meta*-position or *para*-position of the aryl boronic acids were well tolerated under standard conditions (Table 2, entries 3–6 and 7–9). Subsequently, the addition reactions of phenylboronic acid to the five-membered-ring 2-cyclopentenone **4b** was also studied (Table 2, entry 10), and the slightly lower enantioselectivity may be attributed to the flatness of the molecule of 2-cyclopentenone substrate resulting in less sensitive to the chiral circumstance.[19]

In order to further estimate the performance of this catalytic system, the substrate scope was expanded to more challenging acyclic unsaturated ketones[20] (Table 2, entries 11–16). Particularly, the *s*-cis and *s*-trans conformational interconversion of acyclic substrates made the enantiocontrol difficult.[19] Nevertheless, the excellent results obtained with cyclic substrates above encouraged us to investigate this enantioselective transformation. Arylboronic acid substrates bearing diverse substituents at the 4-position were reacted with a series of alkyl acyclic enones, providing the corresponding β-aryl ketones with 93–99% yields and 91–99% ees regardless of the steric effects of the alkyl group in enones (Table 2, entries 11–15). It was noteworthy that 4-phenylbut-3-en-2-one **4f** was also suitable substrate and furnish the diaryl substituted ketone **6fd** with 83% yield and 87% ee (Table 2, entry 16).

Enantiomerically pure 2-aryltetralone derivatives have owned considerable attraction due to such kind of motif played a great important role in organic synthesis and medicinal chemistry.[21] Apart from palladium- or nickel-catalyzed asymmetric α-arylation[22] and α-alkenylation[23] of carbonyl compounds, and catalytic asymmetric protonation of enolates,[24] asymmetric arylation of quinone monoketals has provided another efficient way to 2-aryltetralones. In 2007, Hayashi's group reported an elegant rhodium/chiral diene complex catalyzed asymmetric 1,4-addition of aryl- and alkenylboron reagents to quinone monoketals, and further concise derivatization of the enantiopure addition products could afford the chiral 2-aryltetralones without loss of ee values.[25] Considering the importance of the 2-aryltetralones moieties and the

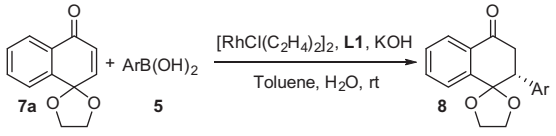
Table 2
Scope of 1,4-addition of arylboronic acids to enones[a]



Entry	*t* (h)	**4**	Ar of **5**	Yield (%)[b]	Ee (%)[c]
1	0.5	**4a**	Ph (**5a**)	99	99
2[d]	30	**4a**	2-$CH_3C_6H_4$ (**5b**)	79	95
3	0.5	**4a**	3-$CH_3C_6H_4$ (**5c**)	96	99
4	1	**4a**	4-$CH_3C_6H_4$ (**5d**)	91	99
5	1	**4a**	3-$CH_3OC_6H_4$ (**5e**)	94	99
6	3	**4a**	4-$CH_3OC_6H_4$ (**5f**)	97	99
7	0.5	**4a**	3-FC_6H_4 (**5g**)	94	99
8	0.5	**4a**	4-FC_6H_4 (**5h**)	92	99
9	2	**4a**	4-$CF_3C_6H_4$ (**5i**)	89	98
10	0.5	**4b**	Ph (**5a**)	99	90
11	4	**4c**	Ph (**5a**)	95	91
12	1	**4c**	4-ClC_6H_4 (**5j**)	90	92
13	4	**4c**	4-$CH_3C_6H_4$ (**5d**)	99	91
14	0.5	**4d**	Ph (**5a**)	99	93
15[e]	1	**4e**	Ph (**5a**)	93	99
16	13	**4f**	4-$CH_3C_6H_4$ (**5d**)	83	87

[a] **4** (1.2 mmol), **5** (1.44 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.25 mol %), **L1** (0.525 mol %), toluene (0.8 mL), H_2O (0.3 mL), rt.
[b] Isolated yield.
[c] Determined by HPLC.
[d] **4a** (0.6 mmol), **5a** (0.9 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.5 mol %), **L1** (1.05 mol %).
[e] $PhB(OH)_2$ (1.8 mmol).

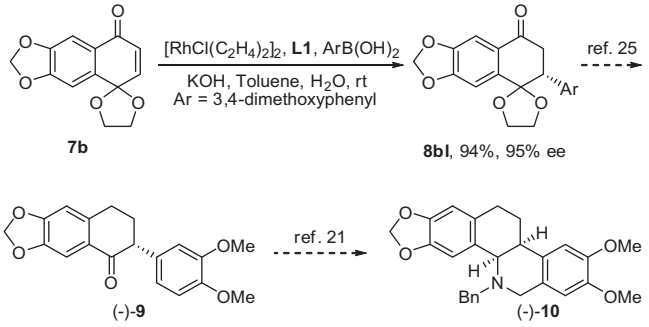
Table 3
Scope of 1,4-addition of arylboronic acids to naphthoquinone monoketal[a]



Entry	*t* (h)	Ar of **5**	Yield (%)[b]	Ee (%)[c]
1	1	Ph (**5a**)	93	99
2[d]	2	4-FC_6H_4 (**5h**)	91	97
3[d]	28	2-$CH_3C_6H_4$ (**5b**)	86	85
4	2	4-$CH_3OC_6H_4$ (**5f**)	87	97
5[e]	3	3-ClC_6H_4 (**5k**)	99	98
6[f]	12	3,4-$(CH_3O)_2C_6H_3$ (**5l**)	93	97

[a] **7a** (0.6 mmol), **5** (0.72 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.5 mol %), **L1** (1.05 mol %), toluene (0.8 mL), H_2O (0.3 mL), rt.
[b] Isolated yield.
[c] Determined by HPLC.
[d] **7a** (0.3 mmol), **5** (0.36 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.0 mol %), **L1** (2.1 mol %).
[e] **7a** (0.3 mmol), **5a** (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.0 mol %), **L1** (2.1 mol %).
[f] **7a** (0.3 mmol), **5l** (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol %), **L1** (5.25 mol %).

practicability of asymmetric 1,4-addition reactions, we tested our catalytic system in the 1,4-addition reactions of arylboronic acids to naphthoquinone monoketal compound (Table 3). To our delight, the addition of phenylboronic acid to naphthoquinone monoketal **7a** was rather efficient and gave the desired product in 93% yield and 99% ee in less than one hour (Table 3, entry 1). The sterically hindered *ortho*-methyl-substituted substrate gave the product **8ab** with slightly lower yield and moderate 85% ee (Table 3, entry 3). In general, the catalytic efficiency of our electronically deficient



Scheme 2. Synthesis of hexahydrobenzo[*c*]benzophenanthridine alkaloid **10**.

ligand/rhodium catalyst was comparable with that of Hayashi's chiral diene ligand/rhodium catalyst in this 1,4-addition reactions.

For the sake of evaluating the practicability in the synthesis of natural products, the asymmetric conjugated addition of (3,4-dimethoxyphenyl)boronic acid to naphthoquinone monoketal **7b** was also investigated. The reaction took place smoothly and produced **8bl** in 94% yield and 95% ee. Reduction of the carbonyl group and followed by deprotection of the ketal compound could give the 2-aryltetralone **9** without loss of enantioselectivity,[25] which is the key intermediate to the synthesis of hexahydrobenzo[*c*]benzophenanthridine alkaloid **10** (Scheme 2).[21]

In summary, we have prepared a new electronically deficient chiral diphosphine ligand (R_{ax},*S*,*S*)-F_{12}-C_3-TunePhos with both central and axial chiral elements, which enriched the diversity of electron-poor ligands. Moreover, the ligand was successfully employed in rhodium-catalyzed asymmetric 1,4-addition reactions of arylboronic acids to diverse α,β-unsaturated carbonyls including cyclic α,β-unsaturated ketones, acyclic α,β-unsaturated ketones, and naphthoquinone monoketals, providing versatile chiral cyclic and acyclic β-arylated ketones with up to 99% ee.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.072.

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