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Synthesis of electron-deficient (S_a,R,R)-$(CF_3)_2$-C_3-TunePhos and its applications in asymmetric hydrogenation of α-iminophosphonates

Huan-Ping Xie [a,b], Zhong Yan [a], Bo Wu [a], Shu-Bo Hu [a], Yong-Gui Zhou [a,*]

[a] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China
[b] University of Chinese Academy of Sciences, Beijing 100049, China

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ABSTRACT

A novel electron-deficient chiral diphosphine ligand bearing trifluoromethyl groups at the 6- and 6′-positions of the biphenyl backbone, (S_a,R,R)-$(CF_3)_2$-C_3-TunePhos, has been synthesized from the commercially available chiral 2,4-pentanediol. The above ligand was successfully applied to palladium-catalyzed asymmetric hydrogenation of linear and cyclic α-iminophosphonates with up to 99% ee.

Chiral diphosphine ligands occupy a prominent position in a myriad of transition-metal-catalyzed asymmetric reactions, which are powerful routes to provide enantiomerically pure bioactive molecules, pharmaceuticals and natural products [1]. Therefore, the design and synthesis of novel chiral diphosphine ligands have received extensive attention and great progress has been made on this research area over the past decades [2]. The steric and electronic properties of the chiral diphosphine ligands have a significant influence on the reactivity and stereoselectivity [3]. Although the majority of the chiral diphosphine ligands are electron-rich, electronically deficient chiral diphosphine ligands have been noticed and several studies suggested that electron-poor chiral diphosphine ligands can dramatically improve the reactivity and enantioselectivity for some transition-metal-catalyzed asymmetric reactions [2d,4]. Some representative examples of electronically deficient chiral diphosphine ligands are listed in Fig. 1. Achiwa's group designed the first electron-poor C_2 symmetric fluorinated diphosphine BIFUP and C_1 symmetric ligand FUPMOP, which was proved to be efficient in ruthenium-catalyzed asymmetric hydrogenation of methyl 3-oxobutanoate with high enantioselectivity [5]. Then, Spindler and Weissensteiner disclosed the use of electronically deficient diphosphine ligand WalPhos, a fluorinated analogue of JosiPhos, in ruthenium-catalyzed asymmetric hydrogenation of ketones [6]. Subsequently, a distinguished ligand DifluorPhos bearing a bi(difluorobenzo-dioxole) backbone [7] was developed and this electron-poor ligand exhibited higher enantioselectivity for several transition-metal-catalyzed processes in comparison with electron-rich ligands [2d,8]. Afterward, MeO-BiPhep and SynPhos analogues bearing electronically deficient motifs on the phosphorus atoms have been reported [9]. Among them, a highly electron-poor ligand MeO-F_{12}-BiPhep can successfully improve the catalytic activity for rhodium-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated ketones at room temperature [9a]. Recently, our group prepared two electron-poor atropisomeric ligands TfO-BiPhep [10a] and CF_3O-BiPhep [10b], which displayed high efficiency in iridium-catalyzed asymmetric hydrogenation of quinolines with up to 25,000 turnover number (TON).

In the chemistry of ligand design, C_3-TunePhos backbone-based diphosphine ligands are privileged framework and have proven highly efficient in a variety of asymmetric reactions [11]. As our continuing interests and efforts in asymmetric catalysis, we focused on the design of new and efficient chiral ligands. In our previous work, we prepared C_3-TunePhos backbone-based diphosphine ligand bearing electron-withdrawing groups on the phosphorus phenyl ring, (R_a,S,S)-F_{12}-C_3-TunePhos, which showed excellent activities and enantioselectivities in rhodium-catalyzed asymmetric 1,4-addition reactions of arylboronic acids and α,β-unsaturated ketones [12]. We envisioned the introduction of trifluoromethyl groups to the biphenyl framework of C_3-TunePhos ligand would decrease cloud density of coordinating atoms and affect the dihedral angle of the ligand, which could greatly enhance the enantioselectivity in certain asymmetric reactions. Herein, we reported the synthesis of a novel electronically deficient diphosphine ligand bearing trifluoromethyl groups at the 6- and 6′-posi-

* Corresponding author.
E-mail address: ygzhou@dicp.ac.cn (Y.-G. Zhou).

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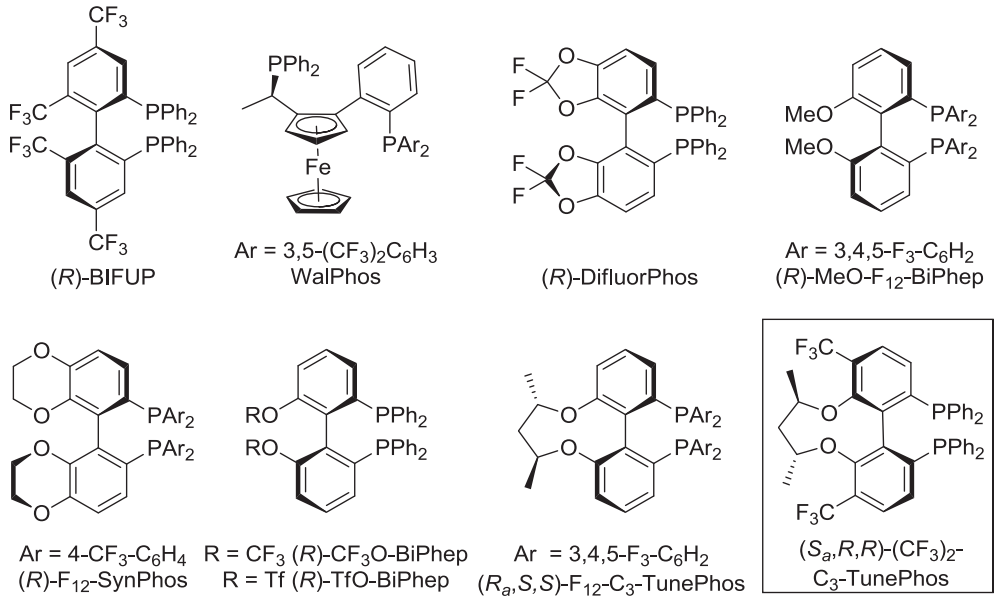
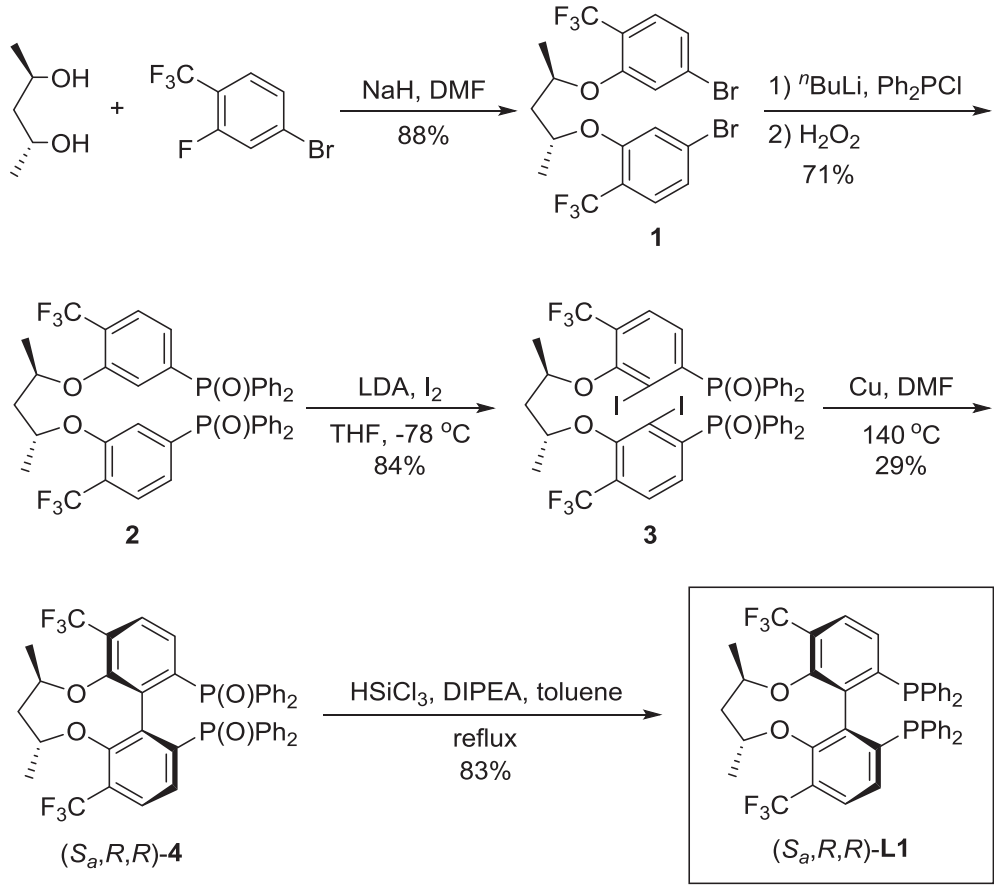


Fig. 1. Examples of electronically deficient diphosphine ligands.

tions of the biphenyl backbone, (*Sa*,*R*,*R*)-$(CF_3)_2$-C_3-TunePhos, and its application in palladium-catalyzed asymmetric hydrogenation of α-iminophos-phonates [8k] to afford optically active α-aminophosphonates with excellent enantioselectivity (Fig. 1).

Our synthetic approach to optically pure ligand (*Sa*,*R*,*R*)-$(CF_3)_2$-C_3-TunePhos was outlined in Scheme 1. Starting from commercially available (2*R*,4*R*)-pentanediol and 4-bromo-2-fluorobenzotrifluoride, the chiral bis(bromoether) **1** was obtained *via* electrophilic substitution under the basic conditions. A consecutive treatment of bromide **1** with *n*-butyllithium and chlorodiphenylphosphine followed by oxidation with hydrogen peroxide resulted in the formation of diphosphine oxide **2** in 71%



Scheme 1. Synthesis of ligand (*Sa*,*R*,*R*)-$(CF_3)_2$-C_3-TunePhos.

yield. The diiodide **3** was prepared by *ortho*-lithiation with lithium diisopropylamide (LDA) and iodination in 84% yield. Then, intramolecular Ullmann coupling could occur, giving the chiral diphosphine dioxide **4** with 29% yield. The low yield of intramolecular Ullmann coupling might ascribe to the unwanted deiodination and intermolecular reactions [11c]. Finally, reduction of **4** with trichlorosilane/*N*,*N*-diisopropylethylamine (DIPEA) delivered the desired enantiomerically pure ligand **L1** in 83% yield.

The absolute configuration of diphosphine dioxide **4**, which was recrystallized from dichloromethane and *n*-hexane as a colorless crystal, was unambiguously determined to be (S_a,*R*,*R*) by X-ray crystallographic analysis (Fig. 2) [13]. Therefore, the ligand **L1** reduced from **4** was assigned as (S_a,*R*,*R*)-$(CF_3)_2$-C_3-TunePhos.

After obtaining the enantiomerically pure electronically deficient ligand (S_a,*R*,*R*)-$(CF_3)_2$-C_3-TunePhos, we started to evaluate its performance in palladium-catalyzed asymmetric hydrogenation of α-iminophosphonates. Initially, (*E*)-diiso-propyl(phenyl(tosylimino)methyl)phosphonate **5a** was chosen as model substrate for condition optimization. To our delight, the hydrogenation of **5a** proceeded smoothly in the presence of 4 Å MS in trifluoroethanol (TFE) with chiral $Pd(OCOCF_3)_2$/**L1** as catalyst, providing the desired α-aminophosphonate **6a** with good yield and 87% of enantioselectivity (Table 1, entry 1). Further screening of solvents showed that the hydrogenation was very sensitive to the reaction medium. Toluene and THF displayed no reactivity (entries 2–3). The mixed solvent of TFE/DCM (2/1) was proved to be the most favorable solvent in view of *enantio*-selectivity and reactivity (entries 4–8). Additives scarcely affected the hydrogenation and the reaction performed very well in the absence of 4 Å MS with 95% ee (entry 9). Notably, C_3-TunePhos **L2** without electron-withdrawing group revealed lower enantioselectivity than **L1** in this transformation (entry 10). This result suggested that the introduction of trifluoromethyl groups on the biphenyl backbone may decrease cloud density of coordinating atoms and affect the dihedral angle of the ligand [14], which could dramatically enhance the enantioselectivity. Therefore, the optimal reaction conditions were established: using $Pd(OCOCF_3)_2$/**L1** as catalyst, TFE/DCM (2/1) as mixed solvent to perform the hydrogenation at 40 °C with the hydrogen pressure of 600 psi.

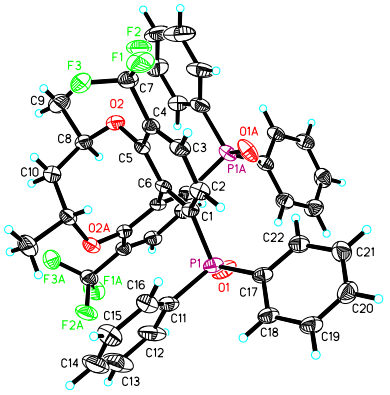
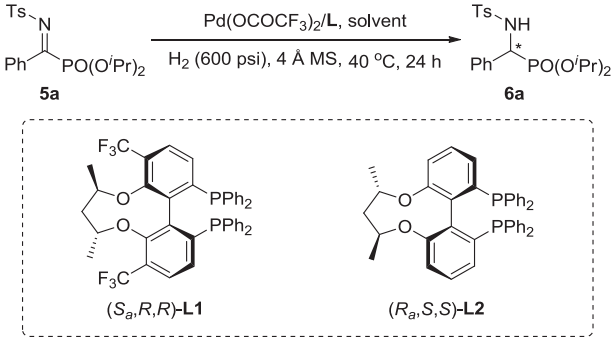


Fig. 2. X-ray crystal structure of compound **4**.

With the aforementioned optimal reaction conditions, substrate scope of the linear α-iminophosphonates was examined and the results were depicted in Table 2. In general, the asymmetric hydrogenation of various aryl-substituted α-ketiminophosphonates proceeded smoothly, providing the desired chiral α-aminophosphonates with excellent yields and enantioselectivities. For α-iminophos-phonates **5a**–**5d**, the phosphonate substituents had slight influence on the yields and enantioselectivities (entries 1–4). Regardless of the electronic properties, the substrates with

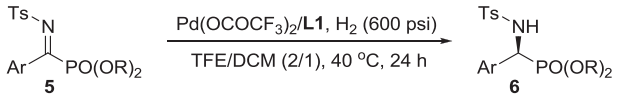
Table 1
Condition optimization[a].



Entry	Solvent	L	Yield (%)[b]	Ee (%)[c]
1	TFE	**L1**	94	87
2	Toluene	**L1**	NR	NA
3	THF	**L1**	NR	NA
4	DCM	**L1**	<5	54
5	TFE/DCM = 4:1	**L1**	>95	94
6	TFE/DCM = 2:1	**L1**	>95	95
7	TFE/DCM = 1:2	**L1**	86	95
8	TFE/DCM = 1:4	**L1**	80	96
9[d]	TFE/DCM = 2:1	**L1**	>95	95
10[d]	TFE/DCM = 2:1	**L2**	>95	62

[a] Conditions: **5a** (0.10 mmol), $Pd(OCOCF_3)_2$ (2.0 mol%), **L** (2.4 mol%), solvent (1.5 mL), 4 Å MS (50 mg), H_2 (600 psi), 40 °C, 24 h.
[b] Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard.
[c] Determined by chiral HPLC analysis.
[d] Without 4 Å MS. NR: no reaction. NA: no analysis.

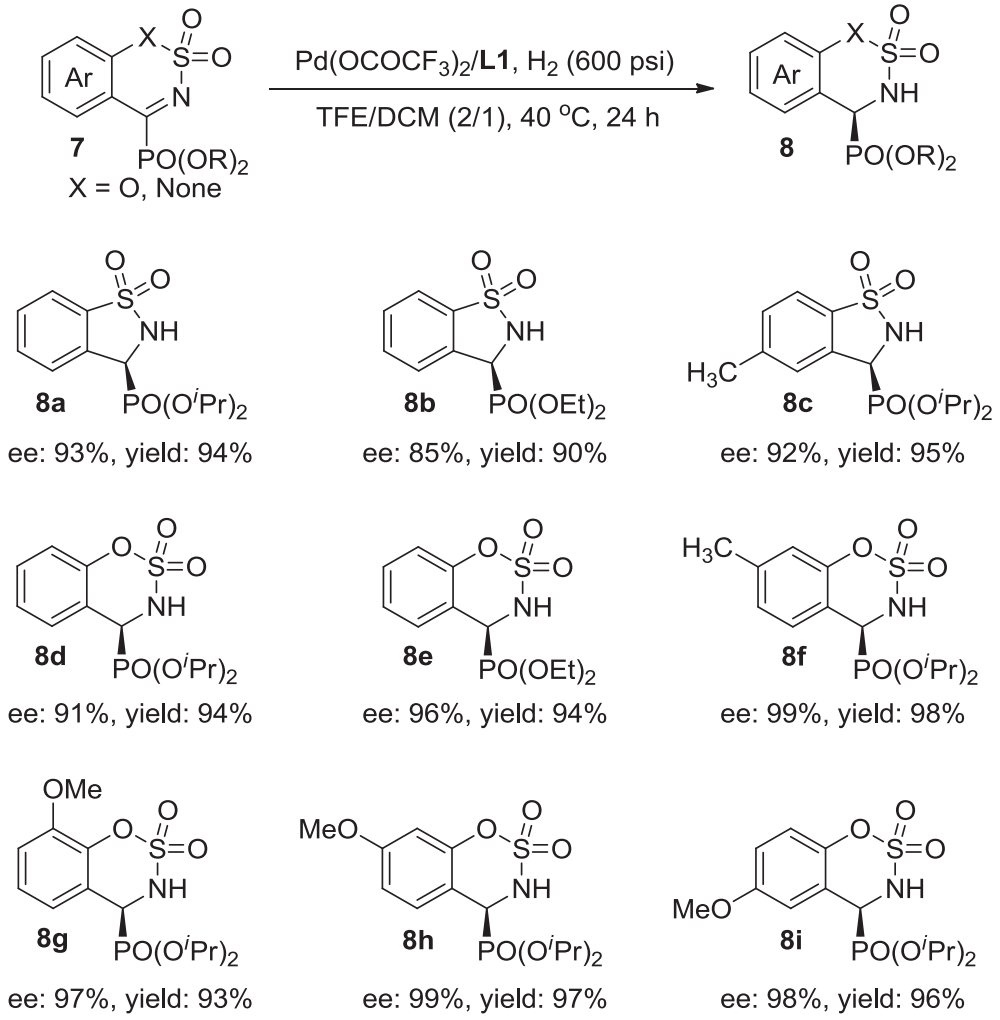
Table 2
Substrate scope: linear α-iminophosphonates **5**[a].



Entry[a]	Ar	R	Yield (%)[b]	Ee (%)[c]
1	Ph	^{i}Pr	94 (**6a**)	95
2	Ph	Me	93 (**6b**)	93
3	Ph	Et	92 (**6c**)	93
4	Ph	Bn	91 (**6d**)	93
5	4-MeC_6H_4	^{i}Pr	96 (**6e**)	96
6	4-FC_6H_4	^{i}Pr	94 (**6f**)	94
7	4-ClC_6H_4	^{i}Pr	96 (**6g**)	97
8	4-BrC_6H_4	^{i}Pr	97 (**6h**)	98

[a] Conditions: **5** (0.20 mmol), Pd(OCOCF$_3$)$_2$ (2.0 mol%), **L1** (2.4 mol%), TFE/DCM (2:1) (3.0 mL), H_2 (600 psi), 40 °C, 24 h.
[b] Isolated yields.
[c] Determined by chiral HPLC.

different substituents at the 4-position of the phenyl ring conducted the transformations successfully to give the corresponding adducts in high ee values and yields (entries 4–7). For example, the reactions furnished the desired products **6e** and **6h** in the 96% and 98% ee values, respectively. The absolute configuration of compound **6a** was determined to be *S* by comparison of the specific rotation with the reported literature data (see the Supporting Information) [8k].



Scheme 2. Substrate scope: cyclic α-iminophosphonates **7**[a]. [a]Conditions: 7 (0.20 mmol), Pd(OCOCF3)2 (2.0 mol%), L1 (2.4 mol%), TFE/DCM (2:1) (3.0 mL), H2 (600 psi), 40 °C, 24 h.

In order to further assess the performance of this electronically deficient (S_a,*R*,*R*)-$(CF_3)_2$-C_3-TunePhos, the substrate scope of cyclic α-iminophosphonates was explored (Scheme 2). Five-membered ring α-iminophosphonate **7a** conducted successfully to afford the target product in 94% yield and 93% ee. The less sterically hindered ethyl phosphonate substituent could cause the decrease in enantioselectivity to 85% ee (**8b**).

Additionally, the six-membered ring α-iminophosphonates also exhibited excellent enantioselectivities and reactivities in this asymmetric hydrogenation. Impressively, when a methyl group was introduced at the 7-position of the phenyl ring (**8f**), the high 99% ee was achieved. In spite of the steric properties, the substrates with methoxy group at the different positions of phenyl ring performed very well to deliver the corresponding adducts **8g**–**8i** in high enantioselectivities.

In summary, we have synthesized a novel electronically deficient chiral diphosphine ligand bearing trifluoromethyl groups at the 6- and 6′-positions of the biphenyl backbone, (S_a,*R*,*R*)-$(CF_3)_2$-C_3-TunePhos. This ligand was successfully employed in palladium-catalyzed asymmetric hydrogenation of α-iminophosphonates, providing optically active α-aminophos-phonates with up to 99% ee. Further exploration on the application of this ligand to various transition-metal catalyzed asymmetric reactions is ongoing in our laboratory.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.06.037.

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[13] CCDC 1835503 contains the supplementary crystallographic data for this paper. These can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk.
[14] The dihedral angle of diphosphine dioxide **4** with trifluoromethyl groups is 87.8° based on the X-ray diffraction data. The dihedral angle of diphosphine dioxide of **L2** without trifluoromethyl groups is 75.6° (please see ref. [11c]).