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# Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Trifluoromethyl Ketones

Renshi Luo,[a,b] Ke Li,[a] Yuling Hu,[a] and Wenjun Tang[a,*]

[a] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling Ling Road, Shanghai 200032, People's Republic of China
E-mail: tangwenjun@sioc.ac.cn
[b] School of Pharmaceutical Sciences, Gannan Medical University, Yixueyuan Road, Ganzhou, Jiangxi 341000, People's Republic of China

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**Abstract:** A new $C_2$-symmetrical, chiral bisphosphorus ligand proved to be efficient for the rhodium-catalyzed nucleophilic addition of arylboronic acids to trifluoromethyl ketones, providing a series of chiral trifluoromethyl-substituted tertiary alcohols in high yields (up to 93%) and excellent enantioselectivities (>99%).

**Keywords:** arylboronic acids; chiral phosphorus ligands; nucleophilic addition; rhodium; trifluoromethyl ketones

Syntheses of chiral tertiary alcohols have gained significant interest due to their structural relevance in biologically active natural products and pharmaceuticals.[1] Consequently, the preparations of chiral trifluoromethylated tertiary alcohols have become an important subject as an increasing number of therapeutic reagents contain such structures.[2] One major synthetic strategy is the trifluoromethylation of ketones which remains very challenging in its asymmetric versions.[3] An important alternative is the asymmetric addition of carbon nucleophiles to trifluoromethyl ketones or pyruvates[4] by alkynyl,[5] alkyl,[6] alkenyl[5d] or aryl[7] additions, as well as aldol,[8] nitroaldol,[9] carbonyl-ene,[10] Friedel–Crafts[11] or other types of reactions.[12] The addition of boronic acids to trifluoromethyl ketones to construct chiral trifluoromethylated tertiary alcohols is particularly attractive due to the ready availability, good stability, and non-toxic nature of various boronic acids as the starting materials. Since Miyaura[13] developed the first Rh-catalyzed addition of arylboronic acids to aldehydes in 1998, significant progress[1g] has been achieved on transition metal-catalyzed asymmetric additions of arylboronic acids to aldehydes,[14] α-keto esters[15] or isatins[16] with excellent enantioselectivities. In contrast, the highly enantioselective addition of arylboronic acids to ketones or trifluoromethyl ketones remains an underdeveloped area. Lu[17] and Lam[18] reported an intramolecular addition of arylboronic acids to ketones with excellent *ee*s. However, progress on its intermolecular version was scarce and, only recently, were moderate *ee*s achieved[19] To the best of our knowledge, only two reports are available on the enantioselective addition of arylboronic acids to trifluoromethyl ketones.[7] Minnaard and co-worker reported the addition of arylboronic acids to 2,2,2-trifluoroacetophenone with only moderate enantioselectivities (up to 83% *ee*).[7a] Low *ee*s (<54%) were also observed when a chiral phosphite ligand was employed.[7b] A highly enantioselective addition of arylboronic acids to trifluoromethyl ketones has yet to be developed. We herein report an efficient synthetic method for trifluoromethyl-substituted chiral tertiary alcohols by the rhodium-catalyzed addition of arylboronic acids to trifluoromethyl ketones and excellent enantioselectivities have been achieved.

The development of chiral catalysts with tunable steric and electronic properties plays a pivotol role in the realization of efficient asymmetric catalytic reactions. We have recently reported a series of tunable and operationally convenient chiral bisphosphorus ligands[20] on the basis of a 2,3-dihydrobenzo[*d*]-[1,3]oxophosphole framework (Figure 1) and their excellent applications in asymmetric hydrogenation[20a,c] and propargylation.[20b] By variation of the R groups in this structure, a series of $C_2$-symmetrical bisphosphorus ligands with various steric and electronic properties can be developed. For the rhodium(I)-catalyzed addition of arylboronic acids to trifluoromethyl ketones, a chiral bisphosphorus ligand with a deep chiral pocket is required in order to provide a well-defined chiral environment when coordinated to a rhodium center. The chiral bisphosphorus ligand **4** containing

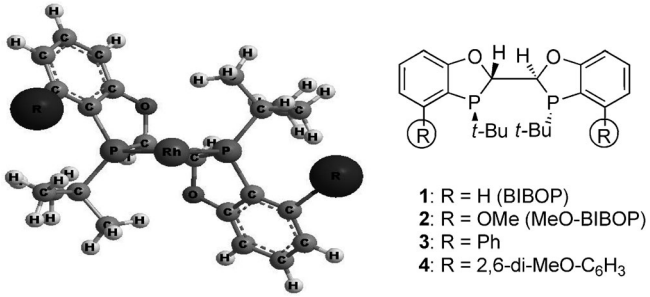


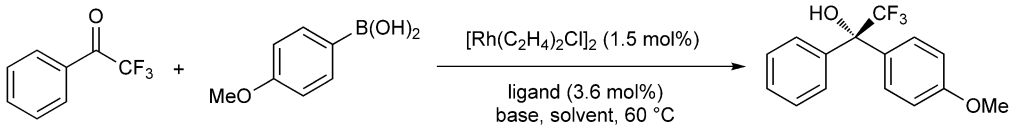

**Figure 1.** Tunable chiral bisphosphorus ligands.

2′,6′-dimethoxyphenyl substituents has proven to be an efficient ligand for this transformation (Table 1).

An initial study of various BIBOP ligands for the rhodium-catalyzed addition of 4-methoxyphenylboronic acid to 2,2,2-trifluoroacetophenone provide promising results (Table 1). With $[Rh(C_2H_4)Cl]_2$ (1.5 mol%) as the catalyst precursor and BIBOP (**1**) or MeO-BIBOP (**2**) (3.6 mol%) as the ligand, the addition proceeded at 60 °C for 20 h to provide the desired product in a moderate yield and *ee* (entries 1 and 2). With phenyl groups at the R positions, ligand **3** led to a much improved enantioselectivity (79% *ee*, entry 3). A good *ee* (85%) was achieved when ligand **4** containing 2,6-dimethoxyphenyl substituents was employed (entry 4). Optimization of the solvent further improved the yield and enantioselectivity (entries 5–8). With MTBE as the solvent, the desired tertiary alcohol was isolated in 79% yield and 96% *ee* (entry 8). Among various inorganic and organic bases screened, potassium carbonate provided a best yield (entries 8–11).

Under optimized reaction conditions, the Rh-**4** catalyst proved to be efficient for the syntheses of a wide array of trifluoromethyl-substituted chiral tertiary alcohols. As can be seen in Table 2, a variety of trifluoromethyl-substituted bis(aryl) carbinols were prepared in good yields and excellent enantioselectivities. With 2,2,2-trifluoro-1-phenylethanone as the substrate, arylboronic acids with either electron-donating or electron-withdrawing substituents at the 4-position afforded excellent yields and enantioselectivities (entries 1–4). 2-Substituted arylboronic acid was also applicable to provide a high *ee* (entry 5). Various substituted phenylboronic acids (entries 6–16) were employed in the addition with 2,2,2-trifluoro-1-(4-fluorophenyl)ethanone and high yields and *ee*s were achieved in all cases except for 2-methoxyphenylboronic acid (entry 17). Other substituted 2,2,2-trifluoro-1-phenylethanones were also applicable (entries 18–24, 27, and 28). Addition to 2′-methoxytrifluoroacetophenone also provided an excellent *ee* albeit with a low yield (entry 27). A high *ee* and good yield were also achieved with 3′-trifluoromethoxytrifluoroacetophenone (entry 28). Heteroaryl substrates such as 2-thiophenyl derivatives could also be employed to provide good to excellent *ee*s (entries 25 and 26).

**Table 1.** Optimization of reaction conditions.



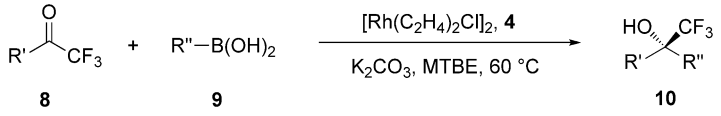

**5** **6** **7**

| Entry[a] | Ligand | Base | Solvent | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **1** | $K_2CO_3$ | toluene | 71 | 45 |
| 2 | **2** | $K_2CO_3$ | toluene | 70 | 40 |
| 3 | **3** | $K_2CO_3$ | toluene | 61 | 79 |
| 4 | **4** | $K_2CO_3$ | toluene | 68 | 85 |
| 5 | **4** | $K_2CO_3$ | dioxane | 78 | 92 |
| 6 | **4** | $K_2CO_3$ | DCM | 40 | 89 |
| 7 | **4** | $K_2CO_3$ | THF | 56 | 96 |
| 8 | **4** | $K_2CO_3$ | MTBE | 79 | 96 |
| 9 | **4** | KF | MTBE | 23 | 92 |
| 10 | **4** | $K_3PO_4$ | MTBE | 71 | 96 |
| 11 | **4** | KOH | MTBE | $<10$ | 91 |
| 12 | **4** | $Et_3N$ | MTBE | 16 | 93 |

[a] The reactions were carried out at 60 °C in solvent (1.5 mL) for 20 h with 2,2,2-trifluoroacetophenone (0.25 mmol), *para*-methoxyphenylboronic acid (0.5 mmol), and base (0.75 mmol) in the presence of $[Rh(C_2H_4)Cl]_2$ (1.5 mol%) and ligand (3.6 mol%); the absolute configurations were assigned on the basis of the absolute configuration of **10k** (table 2, entry 11) through a similar stereochemical model.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC on a Chiralcel OD-H column.

**Table 2.** Addition of arylboronic acids to trifluoromethyl aryl ketones.



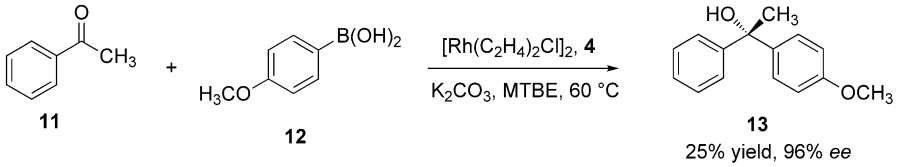

8 9 10

| Entry[a] | R′ | R“ | Yield [%] of **10**[b] | ee [%][c] |
|---|---|---|---|---|
| 1 | Ph | 4-MeO-$C_6H_4$ | 79 (**10a**) | 95 |
| 2 | Ph | 4-Me-$C_6H_4$ | 78 (**10b**) | 99 |
| 3 | Ph | 4-Cl-$C_6H_4$ | 83 (**10c**) | 97 |
| 4 | Ph | 4-Ph-$C_6H_4$ | 71 (**10d**) | 95 |
| 5 | Ph | 3-MeO-$C_6H_4$ | 83 (**10e**) | 95 |
| 6 | 4-F-$C_6H_4$ | 4-MeO-$C_6H_4$ | 81 (**10f**) | 95 |
| 7 | 4-F-$C_6H_4$ | Ph | 61 (**10g**) | 95 |
| 8 | 4-F-$C_6H_4$ | 4-Me-$C_6H_4$ | 85 (**10h**) | 97 |
| 9 | 4-F-$C_6H_4$ | 4-Cl-$C_6H_4$ | 86 (**10i**) | 97 |
| 10 | 4-F-$C_6H_4$ | 4-Ph-$C_6H_4$ | 73 (**10j**) | 97 |
| 11 | 4-F-$C_6H_4$ | 4-TMS-$C_6H_4$ | 91 (**10k**) | 98 |
| 12 | 4-F-$C_6H_4$ | 4-Bu-$C_6H_4$ | 91 (**10l**) | 96 |
| 13 | 4-F-$C_6H_4$ | 4-*i*-Pr-$C_6H_4$ | 93 (**10m**) | 97 |
| 14 | 4-F-$C_6H_4$ | 3-$CF_3O$-$C_6H_4$ | 87 (**10n**) | 99 |
| 15 | 4-F-$C_6H_4$ | 2-naphthyl | 61 (**10o**) | 95 |
| 16 | 4-F-$C_6H_4$ | 2-F-$C_6H_4$ | 73 (**10p**) | 99 |
| 17 | 4-F-$C_6H_4$ | 2-MeO-$C_6H_4$ | 37 (**10q**) | 81 |
| 18 | 4-Cl-$C_6H_4$ | 4-MeO-$C_6H_4$ | 83 (**10r**) | 93 |
| 19 | 4-Cl-$C_6H_4$ | 4-Me-$C_6H_4$ | 86 (**10s**) | 96 |
| 20 | 4-Br-$C_6H_4$ | 4-MeO-$C_6H_4$ | 81 (**10t**) | 95 |
| 21 | 4-Br-$C_6H_4$ | 4-Me-$C_6H_4$ | 81 (**10u**) | 95 |
| 22 | 4-Br-$C_6H_4$ | 4-Cl-$C_6H_4$ | 83 (**10v**) | 96 |
| 23 | 4-Me-$C_6H_4$ | 4-MeO-$C_6H_4$ | 47 (**10w**) | 93 |
| 24 | 4-Me-$C_6H_4$ | 4-*i*-Pr-$C_6H_4$ | 58 (**10x**) | 96 |
| 25 | 2-thiophenyl | 4-MeO-$C_6H_4$ | 81 (**10y**) | 81 |
| 26 | 2-thiophenyl | 4-Cl-$C_6H_4$ | 61 (**10z**) | 89 |
| 27 | 2-OMe-$C_6H_4$ | $C_6H_5$ | 31 (**10aa**) | 96 |
| 28 | 3-$OCF_3$-$C_6H_4$ | 4-MeO-$C_6H_4$ | 79 (**10ab**) | 96 |

[a] The reactions were carried out at 60 °C in MTBE (1.5 mL) for 20 h with ketone (0.25 mmol), boronic acid (0.5 mmol), and $K_2CO_3$ (0.75 mmol) in the presence of $[Rh(C_2H_4)Cl]_2$ (1.5 mol%) and ligand **4** (3.6 mol%). The absolute configuration of **10k** was determined by X-ray crystallography (Figure 3) and all the others were assigned on the basis of similar stereochemical models.

[b] Isolated yields.

[c] Determined by chiral HPLC on a Chiralcel OD-H, Chiralcel AD-H, or Lux Amylose-2 column.




11 12 13

25% yield, 96% *ee*

**Scheme 1.** Rhodium-catalyzed addition of 4-methoxyphenylboronic acid to acetophenone

Encouraged by the high enantioselectivity observed with trifluoromethyl ketones, the addition of 4-methoxyphenylboronic acid to acetophenone was also tested under similar reaction conditions. An excellent *ee* was also achieved albeit with a low conversion and yield (Scheme 1). Our further study is focusing on improving the reactivity of this catalytic system.

The X-ray structure[21] of the [Rh(**4**)(nbd)]$BF_4$ complex revealed a deep chiral pocket of the $C_2$-symmetrical Rh-**4** catalyst, providing a structural insight for the high enantioselectivities observed in this transformation. As depicted in Figure 2, the rhodium center is buried deep in the structure of ligand **4**, and the two 2′,6′-dimethoxyphenyl substituents of the ligand extend parallel towards the coordination of norborna-

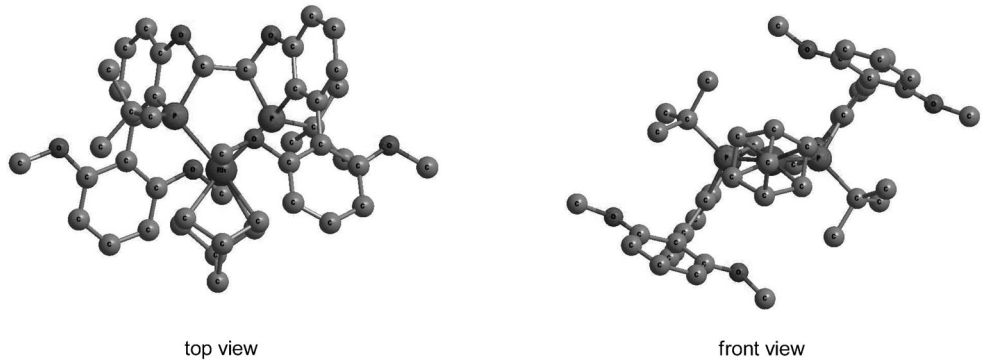



**Figure 2.** The X-ray structure of [Rh(**4**)(nbd)]$BF_4$ [hydrogen atoms, $BF_4$ anion, and inclusion solvent (dichloromethane) are omitted for clarity].

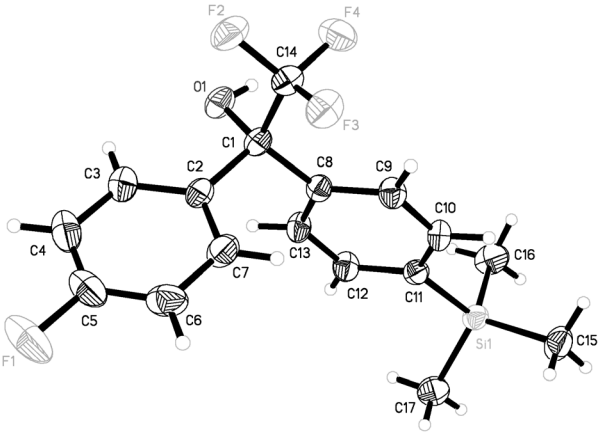



**Figure 3.** The X-ray structure of the chiral alcohol **10k** (the absolute configuration of the chiral center in **10k** is *S*).

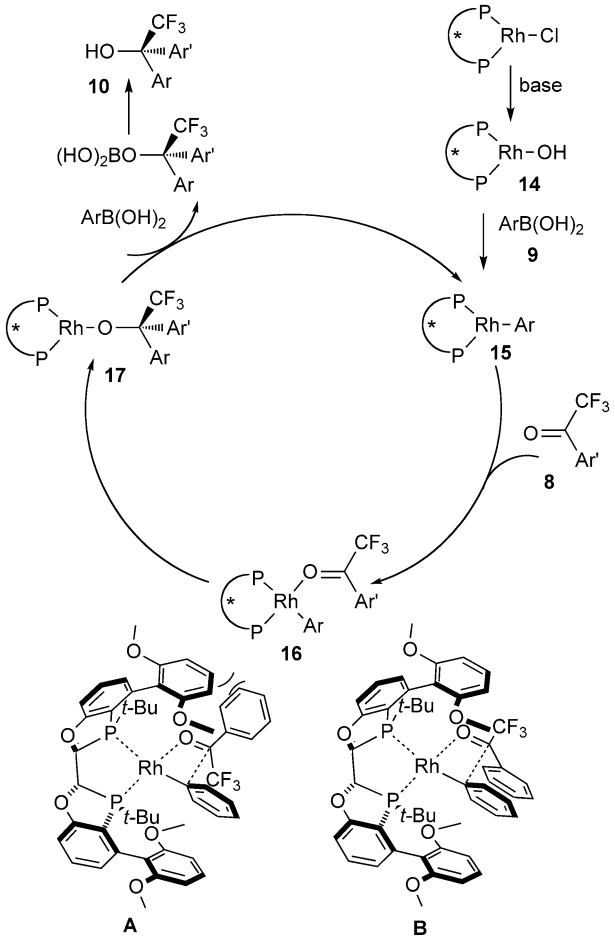



**Figure 4.** The stereochemical model of the Rh-**4** catalyst during the addition of arylboronic acids to trifluoromethyl ketones

diene, providing the major steric forces for substrate coordination. The distance between the rhodium center and the *ipso* carbon of 2′,6′-dimethoxyphenyl substituents is ~4.3 Å, well short of a length of a phenyl substituent (~5.2 Å). Thus, the orientation of an aromatic substrate could be well defined when coordinating to the Rh-**4** catalyst.

A proposed mechanism for this Rh(I)-catalyzed transformation is illustrated in Figure 4. Under basic conditions, a hydroxyrhodium(I) complex **14** is generated from the $[Rh(CH_2CH_2)_2Cl]_2$ precursor and a chiral bisphosphorus ligand. Transmetallation of **11** with arylboronic acid **9** provides an arylrhodium(I) species **15**. Substrate coordination of a trifluoromethyl aryl ketone **8** to **15** adopts two possible coordination modes A and B. A greater steric interaction is expected between the aryl group of the trifluoromethyl ketone and the ligand in mode A, whereas the more favorable mode B undergoes insertion and transmetallation to form the chiral trifluoromethyl-substituted diarylmethanol **10** and regenerate the arylrhodium(I) species **15**.[22] This stereochemical model is in accordance with the absolute configuration observed in the addition product **10k** (Figure 3).[23]

In conclusion, we have disclosed an efficient method for the rhodium-catalyzed addition of arylboronic acids to trifluoromethyl ketones, leading to the formation of a series of chiral trifluoromethyl-sub-

stituted tertiary alcohols in high yields and excellent enantioselectivities. The new chiral bisphosphorus ligand **4** with a deep chiral pocket is the key to the success of this transformation. Applications of this methodology for syntheses of biologically active molecules and further improvement of the current catalyst system are currently under investigation and progress will be reported in due course.

## Experimental Section

### General Procedure

To a mixture of trifluoromethyl ketone **5** or **8** (0.25 mmol, 1 equiv.), arylboronic acid **6** or **9** (76 mg, 0.5 mmol, 2 equiv.), $K_2CO_3$ (100 mg, 0.75 mmol, 3 equiv.), ligand **4** (5.9 mg, 0.009 mmol, 3.6 mol%) and $[Rh(C_2H_4)_2Cl]_2$ (1.5 mg, 0.00375 mmol, 1.5 mol%) was added MTBE (1.5 mL). The mixture was stirred at 60 °C for 20 h and then concentrated. The residue was directly subjected to silica gel column chromatography [dichloromethane/hexanes (7:3 v/v) as the eluent] to afford the desired alcohol product **7** or **10**. The enantioselectivity was determined by chiral HPLC on a Chiralcel OD-H, Chiralcel AD-H, or Lux Amylose-2 column.

## Acknowledgements

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[21] CCDC 901956 {[Rh(**4**)(nbd)]$BF_4$} contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk).

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