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Enantioselective Rhodium-Catalyzed Addition of Arylboroxines to N-Unprotected Ketimines: Efficient Synthesis of Cipargamin

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Abstract: *Highly enantioselective rhodium-catalyzed addition of arylboroxines to N-unprotected ketimines is realized for the first time by employing chiral BIBOP-type ligands with a Rh loading as low as 1 mol %. A range of chiral α-trifluoromethyl-α,α-diaryl α-tertiary amines or 3-amino-3-aryloxindoles were formed with excellent ee values and yields by employing either WingPhos or PFBO-BIBOP as the ligand. The method has enabled an efficient enantioselective synthesis of cipargamin.*

Enantioselective transition metal catalyzed addition of arylboron compounds to N-protected ketimines has become an effective method for the synthesis of chiral α-tertiary amines.[1,2] In the presence of a chiral Rh,[3] Pd,[4] or Ni[5] catalyst, a variety of chiral cyclic/noncyclic N-protected α-tertiary amines can be prepared in excellent yields and enantioselectivities (Figure 1). However, one significant drawback with current known approaches is the requirement of N-protected ketimines as the substrates. In many cases, *N*-sulphonyl or *N*-carbonyl ketimines were employed, but they are not ideally atom-economical and cost-effective. Moreover, deprotection of the *N*-sulphonyl or *N*-carbonyl amine products often required harsh reaction conditions, therefore limiting the practicality and applicability of such methods. It is attractive to develop enantioselective addition of aryl boron compounds to N-unprotected ketimines for the direct synthesis of chiral α-tertiary amines. Such an approach is not only protection/deprotection-free, but also more practical and cost-effective. Herein we report for the first time a highly enantioselective rhodium-catalyzed addition of arylboroxines to two series of N-unprotected ketimines, directly forming α-tertiary amines with excellent yields and *ee* values. The method has enabled an efficient enanatioselective synthesis of the antimalarial agent cipargamin.

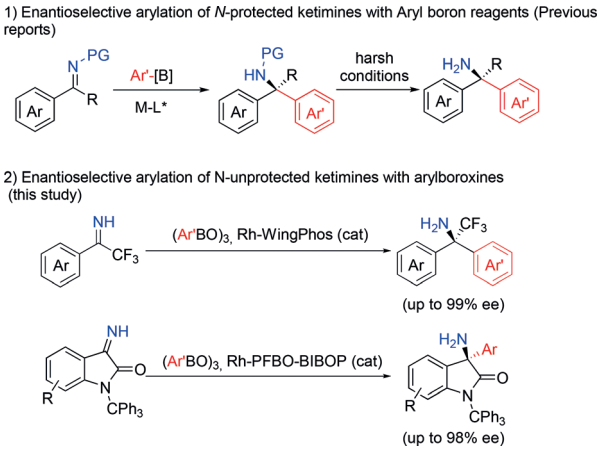
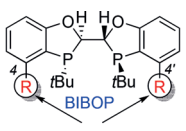


Figure 1. Enantioselective rhodium-catalyzed arylation of N-unprotected ketimines.

Only limited examples are available for the enantioselective metal-catalyzed addition to N-unprotected imines, with a few reports on either allylation or alkynylation.[6] Enantioselective arylation of N-unprotected imines is yet to be realized. The major challenge is the lack of efficient chiral catalysts/ligands that can provide high reactivities and enantioselectivities. We have recently developed a series of BIBOP-type ligands for various asymmetric catalytic reactions.[7] One salient feature of these ligands is the substitution at the 4,4′-positions, adjacent to the phosphorus atoms, providing tunability of their chiral pockets in shape, depth, and electronic properties (Figure 2). For example, WingPhos,[8] bearing two 9-anthryl groups at the 4,4′-positions, possesses deep chiral pockets and is efficient for rhodium-catalyzed enantioselective addition of arylboroxine to ketones. Herein we report the applications of WingPhos as well as a related ligand, PFBO-BIBOP, in the enantioselective rhodium-catalyzed addition of arylboroxines to N-unprotected ketimines, leading to the direct formation of chiral α-trifluoromethyl-α,α-diaryl amines and 3-amino-3-aryloxindoles in excellent enantioselectivities and yields.



L1: R = 9-anthryl ((*R*,*R*,*R*,*R*)-WingPhos)
L2: R = H ((*R*,*R*,*R*,*R*)-BIBOP)
L3: R = OMe ((*R*,*R*,*R*,*R*)-MeO-BIBOP)
L4: R = 2,6-DiMeO-C_6H_3
L5: R = OBn ((*R*,*R*,*R*,*R*)-BnO-BIBOP)
L6: R = OPFB ((*R*,*R*,*R*,*R*)-PFBO-BIBOP)

R groups allow the tunability of the chiral pockets in shape, depth, and electronic properties

Figure 2. BIBOP-type ligands.

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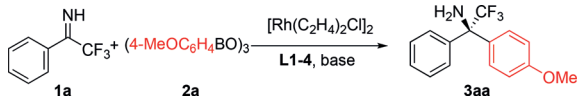
Chiral α-(trifluoromethyl)amines[9] have become increasingly important building blocks in medicinal chemistry and exist in structures of several therapeutic agents such as odanacatib[9b] and DPC-083.[9c–f] Efficient synthesis of such structures has gained a great deal of interest. However, few reports are available on enantioselective synthesis of chiral tertiary α-(trifluoromethyl)amines. The groups of Xu,[3d] Zhang,[4a] and Lu/Hayashi[4f] reported enantioselective arylation of *N*-sulphonyl and *N*-carbonyl ketimines. We proposed that an enantioselective arylation of N-unprotected ketimines would provide a more convenient method for accessing chiral tertiary α-(trifluoromethyl)amines. Thus, 4-methoxyphenylboroxine (**2a**) was chosen as the aryl boron reagent for rhodium-catalyzed nucleophilic addition to 2,2,2-trifluoro-1-phenylethan-1-imine (**1a**). The reaction was performed in toluene under nitrogen for 10 hours with **1a** (0.20 mmol), **2a** (0.10 mmol, 0.30 mmol "B"), and a base in the presence of $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol%) and WingPhos (**L1**, 3.6 mol%; Table 1, entry 1). Encouragingly, a 22% yield and 98% *ee* were observed when **L1** was applied as the ligand. Screening of various bases (entries 1–7) revealed that CsF was the best

Table 1: Rh-catalyzed addition of 4-methoxyphenylboroxine (**2a**) to 2,2,2-trifluoro-1-phenylethan-1-imine (**1a**).



1a **2a** **3aa**

Entry[a]	L*	Base	*T* (°C)	Solvent	Yield [%][b]	*ee* [%][c]
1	**L1**	K_2CO_3	110	toluene	22	98
2	**L1**	K_3PO_4	110	toluene	24	97
3	**L1**	KF	110	toluene	28	98
4	**L1**	Cs_2CO_3	110	toluene	35	95
5	**L1**	KOH	110	toluene	42	99
6	**L1**	NaO*t*Bu	110	toluene	<5	–
7	**L1**	CsF	110	toluene	66	99
8	**L1**	CsF	110	xylenes	47	99
9	**L1**	CsF	110	PhF	19	99
10	**L1**	CsF	110	MTBE	8	99
11	**L1**	CsF	110	CPME	54	99
12	**L1**	CsF	90	toluene	69	99
13	**L1**	CsF	70	toluene	75(72)	99
14	**L1**	CsF	60	toluene	48	99
15[d]	**L1**	CsF	70	toluene	51	99
16	**L2**	CsF	70	toluene	17	63
17	**L3**	CsF	70	toluene	39	26
18	**L4**	CsF	70	toluene	21	91
19	(*S*)-BINAP	CsF	70	toluene	15	41
20	(*S*,*S*)-Me-Duphos	CsF	70	toluene	41	55
21	(*R*,*S*)-Josiphos	CsF	70	toluene	19	7

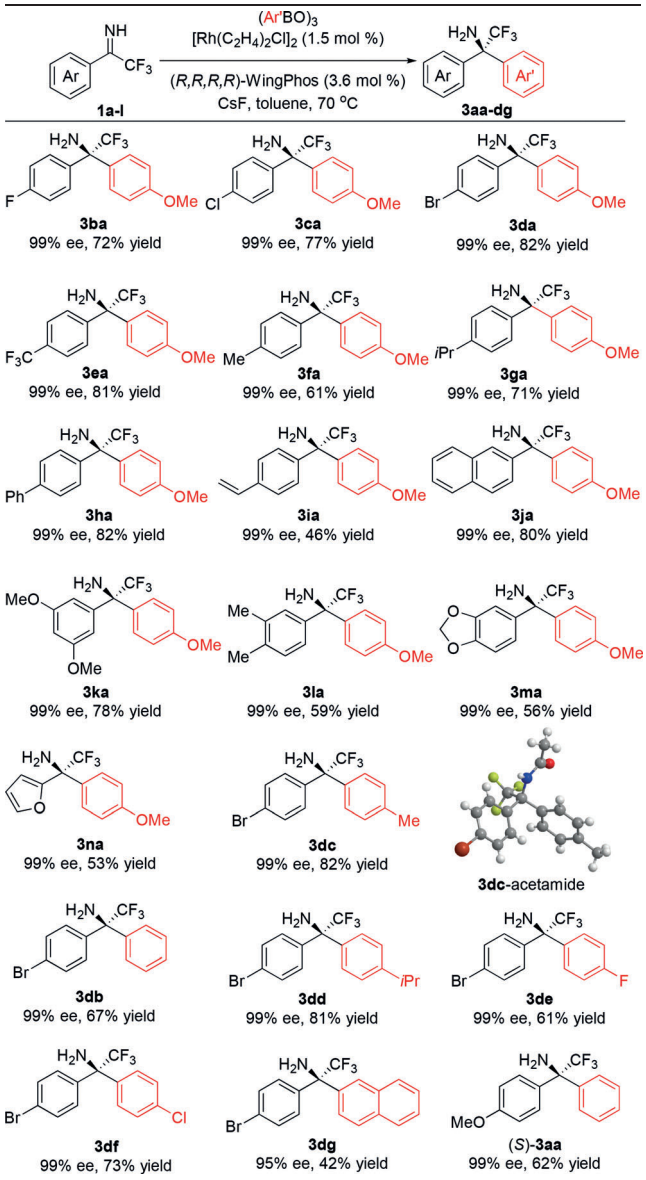
[a] Unless otherwise specified, the reactions were performed under nitrogen for 10 h with 2,2,2-trifluoro-1-phenylethan-1-imine (**1a**, 0.20 mmol), 4-methoxyphenylboroxine (**2a**, 0.10 mmol, 0.30 mmol "B"), base (0.40 mmol), and solvent (1.0 mL) in the presence of $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol%), L* (3.6 mol%). The *R* absolute configuration of **3aa** was assigned by analogy according to the X-ray structure of **3dc**-acetamide.[10] [b] Yield determined by HPLC assay. Yield of isolated product given within parentheses. [c] Determined by chiral HPLC using a chiralcel OD-H column. [d] 4-Methoxyphenylboronic acid (0.3 mmol) was employed. CPME = cyclopentyl methyl ether, MTBE = methyl *tert*-butyl ether.

in terms of yield and the product **3aa** was formed in 66% yield and 99% *ee*. Study of various solvents (entries 7–11) showed toluene was superior. We found the reaction even proceeded at 70°C, providing **3aa** in 72% yield and 99% *ee* (entry 13). The less-than-perfect yield was due to the high sensitivity of **1a** to moisture which leads to formation of a less reactive water adduct. A lower yield (48%) was observed when the reaction was operated at 60°C. Arylboronic acid could also be employed, albeit with a diminished yield (entry 15). WingPhos (**L1**) proved to be important for both high enantioselectivity and yield, since lower yields and *ee* values were observed with the related ligands **L2**–**L4** and other commercially available ligands including BINAP, Me-DuPhos, and Josiphos (entries 16–21). This preference could be due to the presence of the deep chiral pockets of WingPhos compared to those of other chiral ligands.[8b,14]

The substrate scope of the enantioselective addition was studied. As can be seen in Table 2, a series of chiral α-trifluoromethyl-α,α-diaryl α-tertiary amines were formed directly from *N*-H-α-trifluoromethyl-α-aryl ketimines with excellent *ee* values and good yields. A 2-furyl-substituted substrate was well tolerated to provide **3na** in a moderate yield and with an excellent *ee* value. Various arylboronic acids were tolerated to form the corresponding chiral α-tertiary amines (**3db–dg**). Interestingly, switching the substitution pattern of the aryl group between the ketimine and the aryl boroxine provided the product (*S*)-**3aa** in a good yield and with an excellent *ee* value, but with the opposite stereoconfiguration, demonstrating the capability of this method for preparing both enantiomers of chiral products using a single configuration of the same chiral ligand. This method provides expedited access to a series of chiral α-trifluoromethyl-α,α-diaryl amines which are difficult to prepare otherwise.

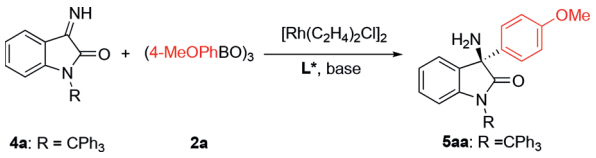
Chiral 3-amino-3-aryloxindoles are present in many biologically active natural products and pharmaceutical drugs.[11] Their efficient syntheses have become a subject of research interest.[12] While high enantioselectivities have been achieved on the enantioselective arylation of N-protected 3-ketimino-2-oxindoles,[4e] no study is available on enantioselective arylation of *N*-H 3-ketimino-2-oxindoles. We applied WingPhos as the chiral ligand in rhodium-catalyzed nucleophilic addition of **2a** to 3-imino-1-tritylindolin-2-one (**4a**; Table 3, entry 1). The product **5aa** was isolated with an excellent *ee* value (91%), albeit in low yield. Encouraged by this result, a series of BIBOP-type ligands, **L3, L5**, and **L6**, were used for this transformation. An improved yield was obtained when MeO-BIBOP (**L3**) was employed as the ligand, indicating that the reaction was better promoted by ligands with shallow chiral pockets. When a more-electron-deficient ligand, PFBO-BIBOP (**L6**), was used, the addition product was isolated in an excellent yield (93%) and *ee* (97%; entry 4). The bulky *N*-trityl substituent in **4a** was important for achieving both high enantioselectivity and good yield, as substrates containing *N*-Me and *N*-Bn substituents proved to be less enantioselective (entries 5 and 6). Screening of various parameters including base, solvent, and temperature revealed that K_3PO_4 as the base, toluene as the solvent, and 80°C as the reaction temperature were suitable in terms of both yield and enantioselectivity.[13]

Table 2: Enantioselective Rh-catalyzed addition of arylboroxines to ketimine.



[a] Unless otherwise specified, the reactions were carried out at 70 °C in toluene (1.0 mL) for 10 h with ketimine (0.20 mmol), arylboroxine (0.10 mmol, 0.30 mmol "B"), and CsF (0.40 mmol) in the presence of $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol %) and **L1** (3.6 mol %). The absolute configuration of **3dc** was determined by the X-ray structure of **3dc**-acetamide, and the others were assigned accordingly. Yields are those of the isolated products. The *ee* values were determined by chiral-phase HPLC.

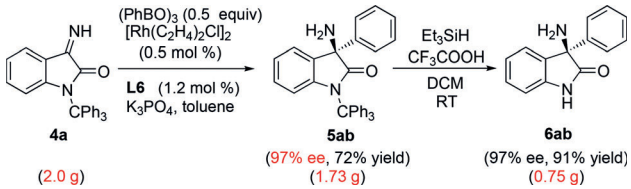
Table 3: Rh-catalyzed addition of **2a** to 3-imino-1-tritylindolin-2-one (**4a**).



Entry[a]	L*	R	Base	*T* [°C]	Solvent	Yield [%][b]	*ee* [%][c]
1	**L1**	CPh_3	K_3PO_4	80	toluene	20	91
2	**L3**	CPh_3	K_3PO_4	80	toluene	60	89
3	**L5**	CPh_3	K_3PO_4	80	toluene	85	83
4	**L6**	CPh_3	K_3PO_4	80	toluene	95 (93)	97
5	**L6**	Me (**4x**)	K_3PO_4	80	toluene	79	86
6	**L6**	Bn (**4y**)	K_3PO_4	80	toluene	85	88

[a] Unless otherwise specified, the reactions were performed under nitrogen for 14 h with isatine imine (**4a**, 0.20 mmol), 4-methoxyphenylboroxine (**2a**, 0.10 mmol, 0.30 mmol "B"), base (0.40 mmol), and solvent (3.0 mL) in the presence of $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol %), **L*** (3.6 mol %). The *R* absolute configuration of **5aa** was assigned by analogy on the basis of the absolute configuration of **6ab**.[12c] [b] Yield determined by HPLC assay. Yield of isolated product given within parentheses. [c] Determined by chiral-phase HPLC using a chiralcel AD-H column.

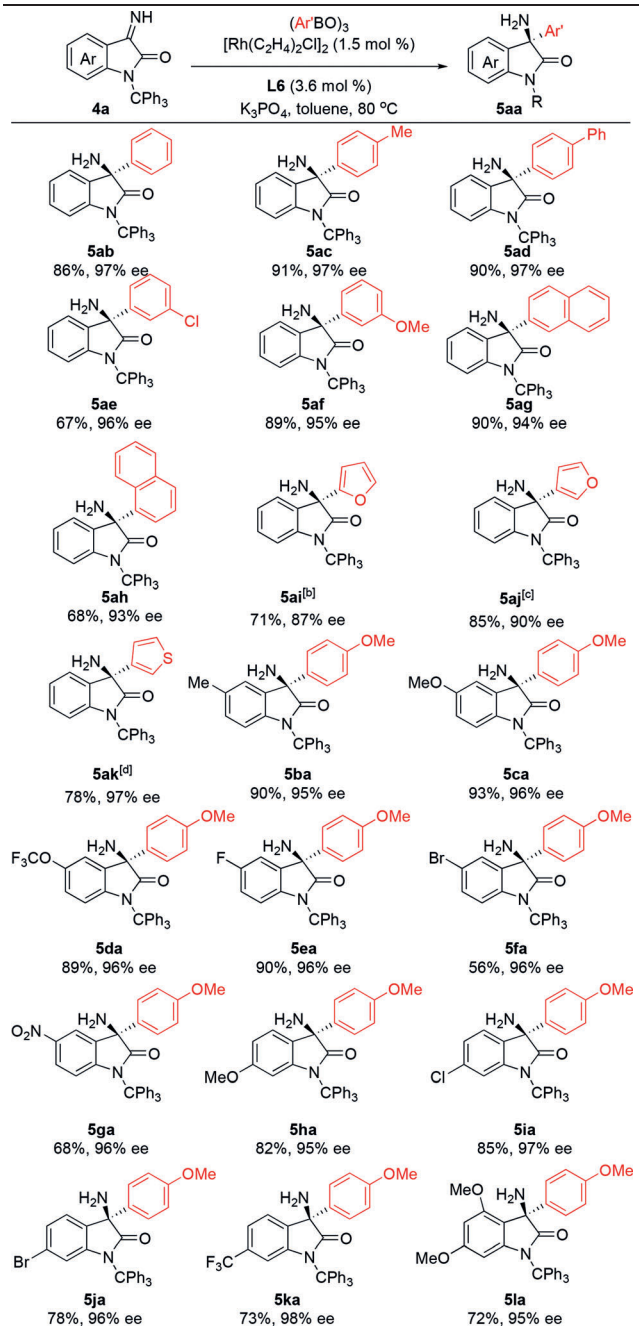
The substrate scope of the enantioselective arylation of *N*-H 3-ketimino-2-oxindoles was studied (Table 4). Thus, a wide array of chiral 3-amino-3-aryloxindoles were prepared with excellent *ee* values and yields. Various aryl and heteroarylboroxines, including substituted phenyl, naphthyl, furyl, and thiophenyl groups, were well tolerated. Oxindoles with different electronic properties and various substitution patterns on the aryl ring were all compatible. A nitro-substituted substrate was also compatible, providing the product **5ga** in 96 % *ee* and 68 % yield. Interestingly, a 4-methoxy-substituted substrate, which was considered as a difficult substrate with greater steric hindrance,[4] proceeded smoothly to form **5la** in 95 % *ee* and 72 % yield. To demonstrate the practicality of this method, a gram-scale addition of phenylboroxine to **4a** in the presence of 1 mol % of the Rh-PFBO-BIBOP catalyst provided the product **5ab** (1.73 g) in 97 % *ee* and 72 % yield (Scheme 1). Simple removal of the *N*-trityl provided (*R*)-3-amino-3-phenylindolin-2-one (**6ab**) in 97 % *ee* and 91 % yield. The protocol constitutes one of most facile and efficient synthesis of chiral 3-amino-3-aryloxindoles.[14]



Scheme 1. Preparation of (*R*)-3-amino-3-(phenyl)indolin-2-one (**6ab**). DCM = dichloromethane.

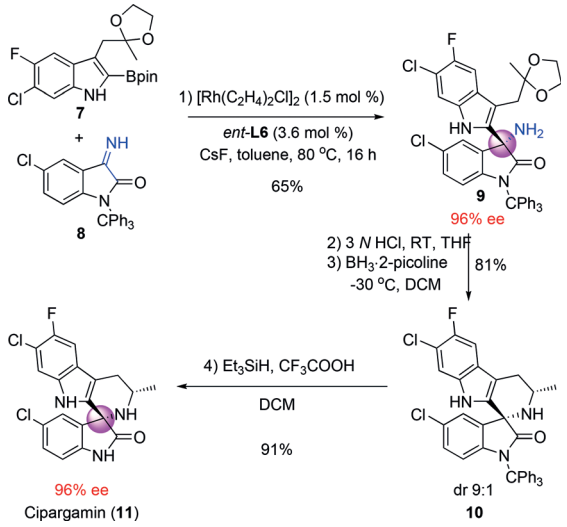
Cipargamin (**11**) is a PfATP4 inhibitor for the treatment of malaria, currently under Phase II clinical trials.[15] To date, only two enantioselective preparations are reported. Shibasaki and co-workers developed a highly enantioselective alkynylation to *N*-(diphenylthiophosphinoyl)ketimine for the establishment of the α-tertiary amine component. However, a nine-step linear sequence was required to furnish the molecule after the key addition.[16a] The group of Feng reported an elegant synthesis of **11** by employing an enantioselective aza-Diels–Alder reaction of 3-vinylindole, albeit with the requirement of a long reaction time (6 days) and a high loading of chiral Lewis acid (10 mol %).[16b] We believed that an addition of the indolylboronic ester **7** to *N*-H

Table 4: Enantioselective Rh-catalyzed addition of arylboroxines to *N*-trityl-protected isatin imines.[a]



[a] Unless otherwise specified, the reactions were carried out at 80 °C in toluene (3 mL) for 14 h with ketimine (0.20 mmol), arylboroxine (0.10, 0.30 mmol "B"), and K_3PO_4 (0.40 mmol) in the presence of [Rh-$(C_2H_4)_2Cl]_2$ (1.5 mol %) and **L6** (3.6 mol %). The absolute configurations of tertiary amines **5ab–la** were assigned by analogy on the basis of the absolute configuration of **6ab**. Yields are those of the isolated products. The *ee* values were determined by chiral-phase HPLC. [b] 2-Furanboronic acid (0.3 mmol) was employed; [c] 3-Furanboronic acid (0.3 mmol) was employed. [d] 3-Thiopheneboronic acid (0.3 mmol) was employed.

ketimine **8** would provide a more convergent and expedient synthesis of **11** (Scheme 2). Thus, addition of **7** to **8** in the presence of the Rh/*ent*-**L6** catalyst (3 mol %) with CsF as the



Scheme 2. A concise enantioselective synthesis of cipargamin (**11**). THF = tetrahydrofuran.

base and toluene as the solvent provided the chiral amine **9** in 96 % *ee* and 65 % yield. Acidic treatment followed by reduction with Shibasaki's conditions (BH_3.2-picoline) led to the ring closure product **10** in 81 % yield with a diastereomeric ratio of 9:1. Final trityl removal with Et_3SiH/TFA provided **11** in 96 % *ee* and 91 % yield, thus completing an efficient enantioselective synthesis of cipargamin.

In summary, we have demonstrated for the first time the highly enantioselective rhodium-catalyzed addition of arylboroxines to N-unprotected ketimines by employing chiral BIBOP-type ligands, providing expedient and practical access to a range of chiral α-trifluoromethyl-α,α-diaryl amines and 3-amino-3-aryloxindoles with excellent *ee* values and yields when using a Rh loading as low as 1 mol %. The unique tunability of the BIBOP-type ligands in terms of depth, shape, and electronic effects has enabled the success of the protection-free transformations that are advantageous over the addition protocols to N-protected ketimines in terms of atom economy and cost effectiveness. The Rh-PFBO-BIBOP catalyst further enabled an efficient enantioselective synthesis of antimalarial agent cipargamin.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · enantioselectivity · ketimines · P ligands · rhodium

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Communications

Asymmetric Catalysis

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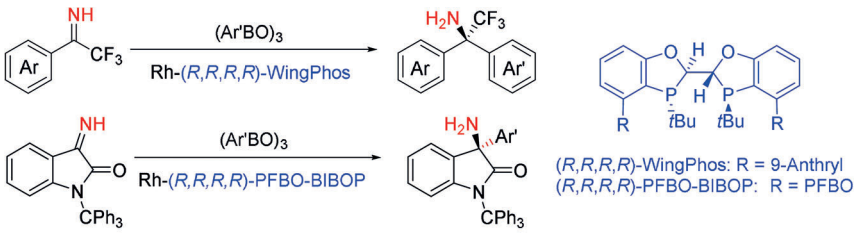
Enantioselective Rhodium-Catalyzed Addition of Arylboroxines to N-Unprotected Ketimines: Efficient Synthesis of Cipargamin



Wing it: Highly enantioselective rhodium-catalyzed addition of arylboroxines to N-unprotected ketimines is realized for the first time by employing chiral BIBOP-type ligands with a Rh loading as low as 1 mol%. A range of chiral α-trifluoromethyl-α,α-diaryl α-tertiary amines or 3-amino-3-aryloxindoles were formed in excellent yields by employing either WingPhos or PFBO-BIBOP as the ligand. The method enabled an efficient enantioselective synthesis of cipargamin.

