Asymmetric Catalysis

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Highly Enantioselective Rhodium-Catalyzed Addition of Arylboroxines to Simple Aryl Ketones: Efficient Synthesis of Escitalopram

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Abstract: *Highly enantioselective additions of arylboroxines to simple aryl ketones have been achieved for the first time with a Rh/(R,R,R,R)-WingPhos catalyst, thus providing a range of chiral diaryl alkyl carbinols with excellent ee values and yields. (R,R,R,R)-WingPhos has been proven to be crucial for the high reactivity and enantioselectivity. The method has enabled a new, concise, and enantioselective synthesis of the antidepressant drug escitalopram.*

Chiral diaryl alkyl carbinol moieties exist in a number of therapeutic agents and natural products,[1] such as the antidepressant escitalopram,[2a] antihistamine clemastine,[2b] cough suppressant chlophedianol,[2c] multi-AGC kinase inhibitor AT13148,[2d] fungicide flutriafol,[2e] and lignan hydroxyotobain[2f] (Figure 1). The efficient synthesis of these chiral tertiary alcohols have thus gained a great deal of attention. Among the various methods,[3] the catalytic asymmetric arylations of ketones stand out to be most attractive.[4,5] In particular, asymmetric addition of nontoxic, stable, and operationally simple aryl boron reagents to simple unactivated ketones is highly desirable yet remains challenging. Despite the recent advances in asymmetric additions of arylboron reagents to aldehydes,[6] activated ketones,[7] or ketones in an intramolecular fashion,[8] few successful results were reported on asymmetric intermolecular addition of aryl boron reagents to simple ketones.[9] Low enantioseletivities were reported for either chiral nickel or rhodium catalysts (a Ni/chiral N-heterocyclic carbene ligand: 36% *ee*,[9a] a Rh/chiral bisphosphine: 38% *ee*,[9b] a Rh/chiral diene: 68% *ee*).[9c] A low yield was also observed in our previous study, albeit with an improved enantioselectivity (25% yield, 95% *ee*).[7l] To our knowledge, both excellent enantioselectivities and yields are yet to be achieved for intermolecular asymmetric additions of aryl boron reagents to simple ketones. Herein we report a highly enantioselective rhodium-catalyzed addition of arylboroxines to simple aryl ketones in excellent yields and with up to 99% *ee* by using Rh/(*R*,*R*,*R*,*R*)-WingPhos as the catalyst. This method has enabled an efficient and concise synthesis of the blockbuster antidepressant escitalopram.

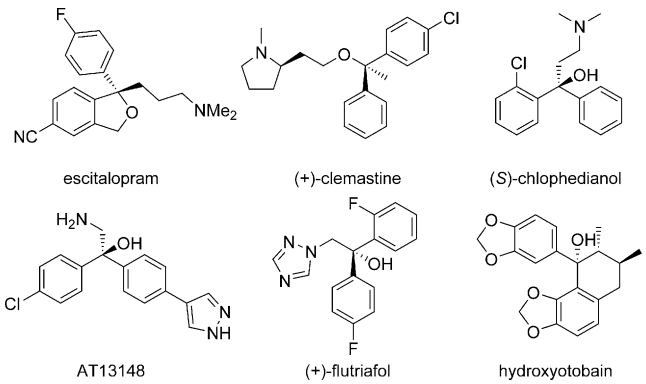

Figure 1. Therapeutic agents or natural products containing chiral diaryl alkyl carbinol moieties.

Ligand design has played a central role in the development of efficient metal-catalyzed reactions.[10] The design of chiral phosphorus ligands capable of long-range stereocontrol remain a significant challenge with limited success. Because of the less reactive nature and low coordinative ability of simple ketones, in comparison with aldehydes or imines, the intermolecular addition of arylboron reagents to simple ketones relies upon the metal catalyst to bring the two reaction partners into close proximity, as well as provide good stereocontrol at a greater distance from the metal center (Figure 2). A metal catalyst equipped with a diphosphine ligand having a shallow chiral pocket (Figure 2a) will be inefficient for such a reaction in terms of both enantioselectivity and reactivity, whereas a catalyst equipped with a ligand having a deep chiral pocket (Figure 2b) might offer improved reactivity as well as good long-range stereocontrol. In this sense, (*R*,*R*,*R*,*R*)-WingPhos,[11] having two anthryl groups in its structure, could not only offer the required stereocontrol, but also help bring two reaction partners into close proximity and lead to high reactivity. Herein we describe the applications of the Rh/(*R*,*R*,*R*,*R*)-WingPhos catalyst in enantioselective addition of arylboroxines to simple aryl ketones.

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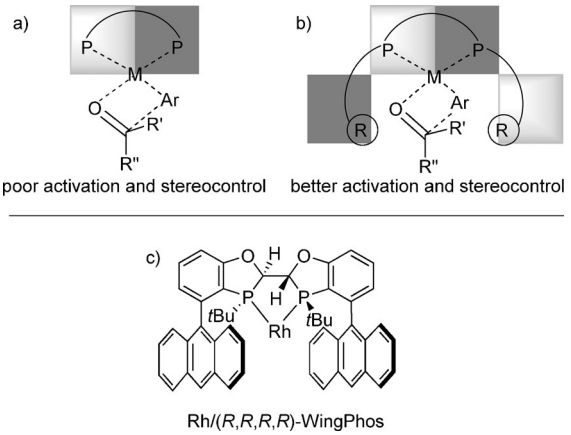
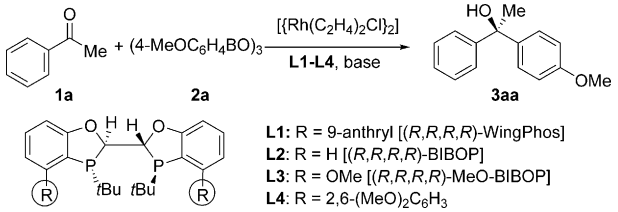


Figure 2. (*R*,*R*,*R*,*R*)-WingPhos is capable of long-range stereocontrol for enantioselective rhodium-catalyzed aryl addition to simple ketones.

We chose 4-methoxyphenylboroxine **2a** as the aryl boron reagent for the rhodium-catalyzed nueclophilic addition to acetophenone. The reaction was performed in *tert*-butyl methyl ether (MTBE) under nitrogen for 18 hours with acetophenone (0.10 mmol), 4-methoxyphenylboroxine (0.20 mmol), and K_2CO_3 as the base in the presence of $[\{Rh(C_2H_4)_2Cl\}_2]$ (1.5 mol%) and (*R*,*R*,*R*,*R*)-WingPhos (3.6 mol%; Table 1, entry 1). We were pleased that the desired tertiary alcohol **3aa** was obtained in 25% yield and 97% *ee*. Screening of various inorganic bases (entries 1–8) showed CsF provided a best yield (85%) and an almost perfect *ee* value (>99% *ee*). A solvent study (entries 8–12) proved that MTBE is among the best for this transformation. A slightly better yield was achieved when the reaction was performed at 100°C (entry 13). To further improve the yield, employment of various inorganic salts as additives was studied (entries 14–18). Gratifyingly, an excellent yield (98%) and *ee* value (>99%) were achieved when magnesium bromide was added (entry 18). The magensium salt is believed to help activate the ketone and hence lead to an enhanced yield. The boroxine **2a,** as low as 0.4 equivalents, could also be employed, albeit with a diminished yield (65%; entry 19). Use of boroxine as the aryl boron reagent was important since the corresponding boronic acid and pinacol boronate provided slightly diminished conversions (entries 20 and 21). To further demonstrate the importance of (*R*,*R*,*R*,*R*)-WingPhos for both yield and enantioselectivity of this addition, **L2** and **L3**[12] were also employed for this reaction under otherwise identical reaction conditions and both provided inferior yields and *ee* values (entries 22 and 23). A low conversion was also observed with **L4** as the ligand,[7l] thus further demonstrating the superior reactivity of (*R*,*R*,*R*,*R*)-WingPhos as the ligand (entry 24).

Next, the substrate scope of this asymmetric transformation was studied. As depicted in Table 2, a range of diaryl alkyl cabinols were prepared with excellent *ee* values (95->99%) and yields regardless the electronic properties and substitution patterns of the aryl ketones (entries 1–15). Various functional groups such as halide, nitro, sulfone, and ester were compatible. Importantly, *ortho*-substituted aryl ketones were also tolerable and provided tertiary alcohols with excellent *ee* values, albeit with diminished yields (entries 10–13). A 2-naphthyl ketone and a 2-furyl ketone were also applicable (entries 14 and 15). Besides methyl ketones, this method offered remarkably good yields and excellent enantioselectivities for ethyl, *n*-propyl, and trifluoromethyl ketones (entries 16–19). Various arylboroxines were also employed to provide the corresponding tertiary alcohols in almost perfect *ee* values and yields (entries 20–26). The reaction of 4′-methoxy acetophenone (**1j**) and phenylboroxine (**2c**) provided (*S*)-**3aa** in 99% *ee*, thus demonstrating the capability of this methodology to produce both antipodes of chiral tertiary alcohols with a single chiral Rh/(*R*,*R*,*R*,*R*)-WingPhos catalyst (entry 27). The Rh/(*R*,*R*,*R*,*R*)-WingPhos catalyst was also efficient for addition to benzofused five-membered cyclic ketones. As shown in Figure 3, the com-

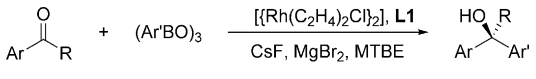
Table 1: Rhodium-catalyzed addition of 4-methoxyphenylboroxine (**2a**) to acetophenone (**1a**).



No.[a]	L*	base	T [°C]	Additive	Solvent	Yield [%][b]	*ee* [%][c]
1	**L1**	K_2CO_3	60	–	MTBE	25	97
2	**L1**	Na_2CO_3	60	–	MTBE	15	87
3	**L1**	KF	60	–	MTBE	18	99
4	**L1**	K_3PO_4	60	–	MTBE	22	95
5	**L1**	Cs_2CO_3	60	–	MTBE	47	96
6	**L1**	KO*t*Bu	60	–	MTBE	58	99
7	**L1**	KOH	60	–	MTBE	61	99
8	**L1**	CsF	60	–	MTBE	85	>99
9	**L1**	CsF	60	–	toluene	66	>99
10	**L1**	CsF	60	–	PhF	37	>99
11	**L1**	CsF	60	–	DME	45	>99
12	**L1**	CsF	60	–	CPME	52	>99
13	**L1**	CsF	100	–	MTBE	87	>99
14	**L1**	CsF	100	LiCl	MTBE	82	>99
15	**L1**	CsF	100	$MgCl_2$	MTBE	85	>99
16	**L1**	CsF	100	$AlCl_3$	MTBE	69	>99
17	**L1**	CsF	100	NH_4Cl	MTBE	88	>99
18	**L1**	CsF	100	$MgBr_2$	MTBE	98(96)	>99
19[d]	**L1**	CsF	100	$MgBr_2$	MTBE	65	>99
20[e]	**L1**	CsF	100	$MgBr_2$	MTBE	88	>99
21[f]	**L1**	CsF	100	$MgBr_2$	MTBE	86	>99
22	**L2**	CsF	100	$MgBr_2$	MTBE	56	41
23	**L3**	CsF	100	$MgBr_2$	MTBE	66	31
24	**L4**	CsF	100	$MgBr_2$	MTBE	28	96

[a] Unless otherwise specified, the reactions were performed under nitrogen for 18 h with acetophenone (**1a**, 0.10 mmol), 4-methoxyphenylboroxine (**2a**, 0.20 mmol, 0.60 mmol boron), base (0.40 mmol), and solvent (1.5 mL) in the presence of $[\{Rh(C_2H_4)_2Cl\}_2]$ (1.5 mol %), **L** (3.6 mol %), and an additive (35 mol %). The *R* absolute configuration of **3aa** was determined by comparing its optical rotation with reported data.[3d] [b] Determined by HPLC assay. Yield of isolated product given within parentheses. [c] Determined by chiral-phase HPLC using a Lux-Amylose-2 column. [d] 4-Methoxyphenylboroxine (0.04 mmol, 0.12 mmol boron) was employed. [e] 4-Methoxyphenylboronic acid was employed. [f] Pinacol 4-methoxyphenylboronic ester was employed.

Table 2: Enantioselective rhodium-catalyzed addition of arylboroxines to aryl ketones.



1a-t **2a-e** **3**

No.[a]	Ar	R	Ar′	Yield [%][b]	*ee* [%][c]
1	4-FC_6H_4 (**1b**)	Me	4-$MeOC_6H_4$ (**2a**)	95 (**3ba**)	>99
2	4-ClC_6H_4 (**1c**)	Me	4-$MeOC_6H_4$ (**2a**)	96 (**3ca**)	>99
3	4-BrC_6H_4 (**1d**)	Me	4-$MeOC_6H_4$ (**2a**)	96 (**3da**)	>99
4	4-$NO_2C_6H_4$ (**1e**)	Me	4-$MeOC_6H_4$ (**2a**)	95 (**3ea**)	>99
5	4-$CF_3C_6H_4$ (**1f**)	Me	4-$MeOC_6H_4$ (**2a**)	95 (**3fa**)	>99
6	4-MsC_6H_4 (**1g**)	Me	4-$MeOC_6H_4$ (**2a**)	93 (**3ga**)	>99
7	4-$MeO_2CC_6H_4$ (**1h**)	Me	4-$MeOC_6H_4$ (**2a**)	96 (**3ha**)	>99
8	4-MeC_6H_4 (**1i**)	Me	4-$MeOC_6H_4$ (**2a**)	90 (**3ia**)	97
9	3-$MeOC_6H_4$ (**1j**)	Me	4-$MeOC_6H_4$ (**2a**)	96 (**3ja**)	>99
10	2-FC_6H_4 (**1k**)	Me	4-$MeOC_6H_4$ (**2a**)	93 (**3ka**)	>99
11	2-ClC_6H_4 (**1l**)	Me	4-$MeOC_6H_4$ (**2a**)	45 (**3la**)	98
12	2-$MeOC_6H_4$ (**1m**)	Me	4-$MeOC_6H_4$ (**2a**)	23 (**3ma**)	>99
13	2,4-$(MeO)_2C_6H_3$ (**1n**)	Me	4-FC_6H_4 (**2e**)	30 (**3ne**)	95
14	2-Np (**1o**)	Me	4-$MeOC_6H_4$ (**2a**)	96 (**3oa**)	>99
15	2-furyl (**1p**)	Me	4-$MeOC_6H_4$ (**2a**)	80 (**3pa**)	95
16	Ph (**1q**)	Et	4-$MeOC_6H_4$ (**2a**)	91 (**3qa**)	>99
17	4-FC_6H_4 (**1r**)	Et	4-$MeOC_6H_4$ (**2a**)	71 (**3ra**)	>99
18	Ph (**1s**)	Pr	4-$MeOC_6H_4$ (**2a**)	77 (**3sa**)	99
19	Ph (**1t**)	CF_3	4-$MeOC_6H_4$ (**2a**)	90 (**3ta**)	99
20	4-ClC_6H_4 (**1c**)	Me	4-MeC_6H_4 (**2b**)	86 (**3cb**)	99
21	4-BrC_6H_4 (**1d**)	Me	4-MeC_6H_4 (**2b**)	95 (**3db**)	>99
22	4-$NO_2C_6H_4$ (**1e**)	Me	Ph (**2c**)	97 (**3ec**)	99
23	4-$CF_3C_6H_4$ (**1f**)	Me	Ph (**2c**)	93 (**3fc**)	>99
24	4-$MeO_2CC_6H_4$ (**1i**)	Me	3-$MeOC_6H_4$ (**2d**)	96 (**3id**)	99
25	Ph (**1a**)	Me	3-$MeOC_6H_4$ (**2d**)	63 (**3ad**)	99
26	4-$MeO_2CC_6H_4$ (**1i**)	Me	4-FC_6H_4 (**2e**)	95 (**3ie**)	>99
27	4-$MeOC_6H_4$ (**1j**)	Me	Ph (**2c**)	88 [(*S*)-**3aa**]	99

[a] Unless otherwise specified, the reactions were carried out at 100 °C in MTBE (1.5 mL) for 18 h with ketone (0.10 mmol), arylboroxine (0.20 mmol), $MgBr_2$ (0.35 equiv), and CsF (0.40 mmol) in the presence of $[\{Rh(C_2H_4)_2Cl\}_2]$ (1.5 mol %) and (*R*,*R*,*R*,*R*)-WingPhos (**L1**; 3.6 mol %). The absolute configurations of tertiary alcohols **3** were assigned by analogy to the absolute configuration of **3aa**, and the stereochemical model. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC.

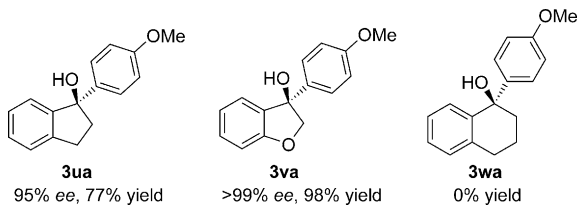


Figure 3. Chiral cyclic tertiary alcohols

pounds **3ua** and **3va** were efficiently synthesized in excellent yields and enantioselectivities. In contrast, the addition to α-tetralone was conformationally more challenging and no conversion was observed under similar reaction conditions.

A simplified mechanism for this rhodium-catalyzed asymmetric addition of arylboroxines to simple aryl ketones is proposed in Figure 4. Transmetallation of the aryl boron

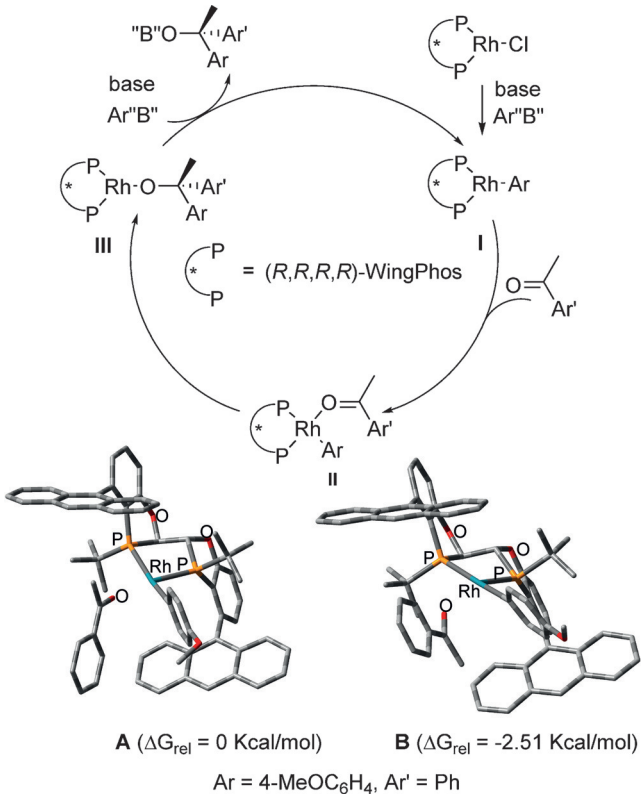
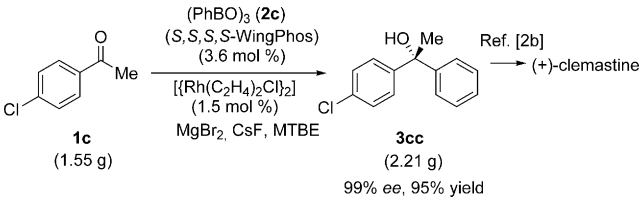


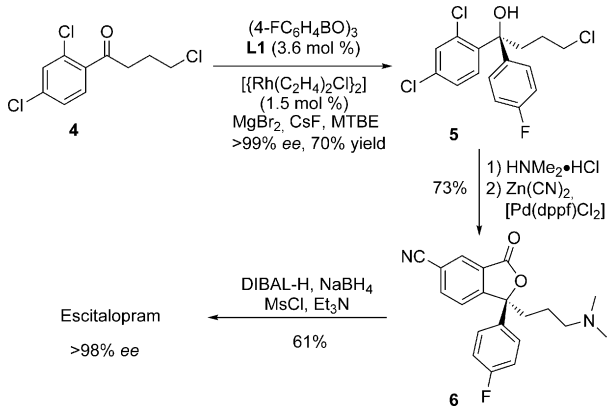
Figure 4. A proposed catalytic cycle and stereochemical model.

reagent with the [Rh(Cl){(*R*,*R*,*R*,*R*)-WingPhos}] species provides the aryl–Rh species **I**. This step is followed by coordination of an aryl ketone to form the species **II**. Migratory insertion of the aryl ketone into the aryl–Rh bond could adopt two possible conformations, **A** and **B**. DFT calculations[13] have shown that the energy of **A** is 2.51 kcal mol^{-1} higher than that of **B**, possibly because of the more severe interaction between the aryl group of the ketone and one anthryl moiety of the (*R*,*R*,*R*,*R*)-WingPhos ligand in **A**. The favorable conformer **B** undergoes insertion and transmetallation with another aryl boron reagent to provide the chiral tertiary alcohol product with the observed stereochemistry and regenerates **I**. The chiral pocket formed by the two anthryl moieties of (*R*,*R*,*R*,*R*)-WingPhos has not only helped bring the aryl group and the ketone substrate closer for high reactivity, but also differentiate effectively between **A** and **B** to provide excellent enantioselectivity.

To demonstrate the synthetic utility of this asymmetric transformation, the chiral tertiary alcohol **3cc**, a key chiral intermediate of (+)-clemastine,[2b] was prepared from commercially available starting materials in a single step (Scheme 1). Thus, a gram-scale reaction between 4′-chloroacetophenone (**1c**) and phenylboroxine (**2c**) proceeded smoothly in the presence of 1.5 mol % $[\{Rh(C_2H_4)_2Cl\}_2]$ and 3.6 mol % (*S*,*S*,*S*,*S*)-WingPhos to form **3cc** in 99 % *ee* and 95 % yield. Furthermore, an enantioselective synthesis of escitalopram was studied by using this methodology (Scheme 2). It should be noted that most reported syntheses of escitalopram rely on chemical or enzymatic resolution[14] of



Scheme 1. Synthesis of the (+)-clemastine intermediate **3cc**.



Scheme 2. Synthesis of escitalopram. DIBAL-H = diisobutylaluminum hydride, dppf = 1,1′-bis(diphenylphosphino)ferrocene, Ms = methanesulfonyl.

racemic mixtures, and their overall yields and efficiency were low. An efficient asymmetric synthesis of escitalopram[15] remains a significant challenge. We studied the asymmetric addition of 4-fluorophenylboroxine to 4-chloro-1-(2,4-dichlorophenyl)butan-1-one (**4**) with the Rh/(*R*,*R*,*R*,*R*)-WingPhos catalyst. Gratifyingly, the desired tertiary alcohol **5** was successfully obtained on a gram scale in 70% yield and with greater than 99% *ee*, thus further demonstrating the great functional-group compatibility and practicality of this rhodium-catalyzed addition. S_N2 displacement of the chloride in **5** with dimethylamine and subsequent palladium-catalyzed dicyanation-lactonization afforded the lactone **6** in 73% overall yield. Reduction of **6** using DIBAL-H/$NaBH_4$ and subsequent ring-closure by treatement of MsCl provided escitalopram in 61% overall yield and greater than 98% *ee*. Thus, a new, concise, and highly enantioselective synthesis of escitalopram was successfully developed with this methodology.

In summary, we have developed, for the first time, highly efficient rhodium-catalyzed additions of arylboroxines to aryl ketones to access a range of chiral diaryl carbinols in excellent yields and enantioselectivities with a broad substrate scope and great functional-group compatibility. (*R*,*R*,*R*,*R*)-WingPhos has been proven to be crucial for the high reactivity and enantioselectivity. The method has also enabled a new, concise, and enantioselective synthesis of the antidepressant drug escitalopram. Further applications of this methodology for chiral natural products and drug synthesis are currently ongoing and progress will be reported in due course.

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Keywords: asymmetric catalysis · enantioselectivity · ligand design · rhodium · total synthesis

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