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Rh/chiral sulfinylphosphine catalyzed asymmetric 1,4-addition of arylboronic acids to chalcones

Guihua Chen [a,b,c], Junwei Xing [a,b,c], Peng Cao [b], Jian Liao [a,b,*]

[a] Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China
[b] Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China
[c] Graduate School of Chinese Academy of Sciences, Beijing 100049, China

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ABSTRACT

A general method to obtain enantioenriched 1,3,3-triarylpropan-1-ones bearing a diarylmethine stereocenter was developed using Rh/chiral sulfinylphosphine catalyzed 1,4-addition of arylboronic acids to chalcones. The catalysis progressed smoothly in the presence of 2 mol % catalyst formed in situ from $[Rh(C_2H_4)_2Cl]_2$ and chiral *tert*-butanesulfinylphosphine and gave the adducts with up to 99% yield and 98% ee.

1. Introduction

Diarylmethine-containing stereocenters are very important substructure as they exist in many pharmaceuticals (such as tolterodine and sertraline) and natural products (such as cherylline and podophyllotoxin) (Fig. 1). However, methods for the stereoselective synthesis of this structure motif are limited, due to the little discrimination of two aryl groups. The most efficient approach to the optically active 3,3-diarylalkanes is the addition of aryl nucleophiles to β-aryl-α, β-unsaturated alkenes. Since the pioneering work of Miyaura and Hayashi, the rhodium-catalyzed asymmetric 1,4-addition of organometallic reagents to α, β-unsaturated carbonyl compounds is considered as one of the most useful strategies for the enantioselective construction of C–C bond.[1] The significance of the diarylmethine motif inspired many groups to explore numerous arylnucleophilic reagents for the 1,4-addition based on the linear unsaturated carbonyl compounds.[2] The variant of asymmetric addition mostly utilized arylboronic acid as reagents for the arylation.

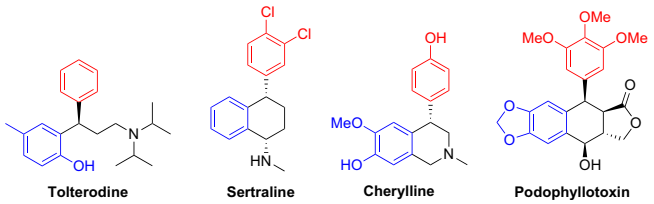

Fig. 1. Selected bioactive compounds bearing diarylmethine stereocenters.

In 2005, Carreira employed Rh(I)-diene complexes to provide access to valuable, optically enriched 3,3-diarylpropanals in 63–90% yields and 89–93% ees from readily available arylboronic acids and substituted cinnamaldehydes. This was also effective for *tert*-butyl cinnamates.[3] Meantime, similar method to chiral 3,3-diarylpropanals was developed by Hayashi and this system was used in the synthesis of chiral methyl 3,3-diaryl-2-cyanopropanoates, which was further converted to (*R*)-tolterodine.[4] For the enantioselective synthesis of 3,3-diaryl ketones, Miyaura found that the dicationic palladium (II)/chiral phosphine complex was the efficient catalyst for the addition of arylboronic acids to *β*-arylenones even at low temperature and catalyst loadings.[5] Recently, the chiral binaphthols was also found to catalyze the asymmetric 1,4-addition of arylboronates to chalcones at 120 °C with good yields and ees.[6] Given our long-standing research in the development of chiral sulfoxide-containing ligands for transition-metal-catalyzed asymmetric reactions,[7] many challenging olefins, such as chromenones[7d,7h] and β-nitrostyrenes,[7i,7k] underwent conjugate addition with arylboronic acids to give the adducts with excellent yields and ees. We envisioned that chalcone might be a good Michael acceptor for Rh-catalyzed asymmetric 1,4-addition of arylboronic acids. Herein, we described our efforts toward the construction of chiral 1,3,3-triarylpropan-1-ones using Rh/chiral

* Corresponding author. E-mail address: jliao@cib.ac.cn (J. Liao).

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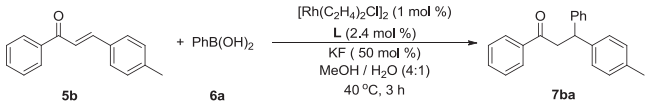
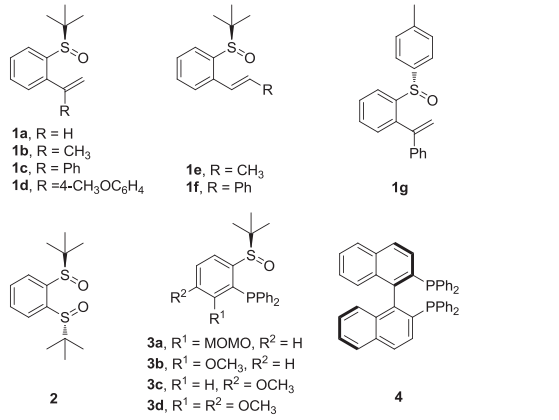
tert-butanesulfinylphosphine catalyzed 1,4-addition of boronic acids to chalcones.

2. Results and discussion

In our previous work, we found that sulfoxide–olefins can give modest enantioselectivity in rhodium-catalyzed conjugate addition of phenylboronic acid to chalcone,[7j] bis-sulfoxide is good for linear aliphatic enones,[7d] and SO-Ps are efficient ligands for electronic deficient aryl-olefins (β-nitrostyrenes).[7i] Hence, all above three classes of ligands were evaluated in this work. Using the optimal reaction conditions developed in our previous work,[7j] 1.0 mol % of $[Rh(C_2H_4)_2Cl]_2$, 2.4 mol % of ligand, 50 mol % aqueous KF in methanol at 40 °C for 3 h, various ligands including chiral sulfoxide-enes **1**, chiral disulfoxide **2**, chiral sulfinylphosphines **3** and (*R*)-BINAP **4** were tested in the addition of pheylboronic acid **6a** to (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one **5b**. As shown in Table 1, chiral sulfoxide-enes with branched olefin (**1a**, **1b**, **1c**, **1d**, **1g**) afforded the adducts in good yields but poor ees (entries 1–5), the linear olefin **1e**, **1f** and disulfoxide **2** gave very poor results (entries 6–8). Pleasingly, chiral *tert*-butanesulfinylphosphines **3a**–**3d** showed both good reactivities and enantioselectivities. With **3d** incorporating two electron-donating CH_3O group, the ee value of the product gave rise to 92% (entries 9–12). In the same conditions, the reaction failed with classical BINAP as the ligand, while the quantitative product could be obtained under the optimized condition[8] but with moderate ee (entries 13–14).

Table 1
Rh-catalyzed asymmetric 1,4-addition of phenylboronic acid to chalcone[a]



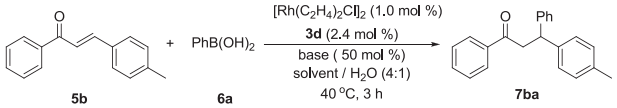


Entry	L	Yield (%)[b]	ee (%)[c]
1	**1a**	94	14
2	**1b**	95	58
3	**1c**	98	−52
4	**1d**	97	−44
5	**1g**	94	−22
6	**1e**	17	−23
7	**1f**	15	−15
8	**2**	8	−7
9	**3a**	96	91
10	**3b**	96	89
11	**3c**	97	82
12	**3d**	98	92
13	**4**	Trace	nd
14[d]	**4**	98	−75

[a] Reactions were performed with **5b** (0.3 mmol), **6a** (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.2 mg, 0.003 mmol), **L** (0.0072 mmol), KF (0.15 mL, 1.0 mol/L in H_2O, 0.15 mmol), MeOH (0.6 mL) at 40 °C for 3 h.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] 3 Mol % Rh/**4**, KOH (30 mol %), dioxane/H_2O (10:1), 40 °C, 9 h.

In the examination of the effect of solvents and bases to the reaction, we found the enantioselectivity was more consistent than the reactivity and good to excellent ees could be kept in various solvents and bases, as shown in Table 2. With the combination of 2-propanol and aqueous KF was the best choice.

Table 2
Reaction condition optimization[a]



Entry	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	Dioxane	KF	93	93
2	THF	KF	Trace	nd
3	MTBE	KF	68	93
4	DCM	KF	61	86
5	Acetone	KF	89	88
6	Toluene	KF	93	94
7	Hexane	KF	69	92
8	Acetonitrile	KF	nr	nd
9	MeOH	KF	98	92
10	EtOH	KF	96	94
11	*i*-PrOH	KF	98	95
12	*i*-PrOH	K_2CO_3	92	95
13	*i*-PrOH	K_3PO_4	94	95
14	*i*-PrOH	KOH	95	95
15[d]	*i*-PrOH	TEA	82	88

[a] Reactions were performed with **5b** (0.3 mmol), **6a** (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.2 mg, 0.003 mmol), **3d** (0.0072 mmol), base (0.15 mL, 1.0 mol/L in H_2O, 0.15 mmol), solvent (0.6 mL) at 40 °C for 3 h.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] TEA was used as neat.

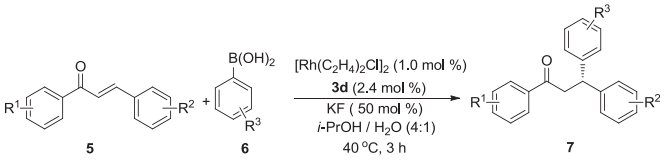
Under the optimal reaction conditions, the scope of the substrates was examined (Table 3). A number of arylboronic acids **6**, with electron-donating groups in the *para*-, *meta*-positions, reacted with (*E*)-chalcone **5a** to give adducts in excellent yields and ees (entries 1–4), while *o*-methoxylphenylboronic acid showed trace product. The lower ees were obtained when the rather electron-deficient arylboronic acids were used (entry 8). For chalcones, electron-donating substituents on 1- or 3-phenyl groups are benefit for the reaction (entries 10–13 and 16), while electron-withdrawing groups decreased the yield or ee of the product, even inhibit the reaction, and the substrates were recovered unchanged. Finally, the 3-heteroaryl groups of chalcones were also found to interfere to the catalytic reaction with moderate reactivities and stereoselectivities (entries 18–20). The aliphatic chalcone **5n** also gave very good results (entry 21).

This methodology could also provide an approach to the access to the reversal enantiomer through the exchange of 3-aryl group of the chalcone and aryl moiety of the boronic acid (Table 2, entry 11 vs Table 3, entry 1; Table 3, entry 3 vs entry 10; entry 4 vs entry 11). This is especially practical as there are various arylboronic acids available as well as chalcones can be synthesized easily while in some cases the isomers of catalysts are difficult to obtain.

3. Conclusion

In conclusion, an efficient route to the synthesis of 1,3,3-triarylpropan-1-ones bearing a chiral diarylmethine stereocenter was developed through the asymmetric addition of arylboronic acids to chalcones catalyzed by Rh(I)-chiral *tert*-butanesulfinylphosphine

Table 3
Addition of arylboronic acids to chalcones[a]



Entry	R^1	R^2	R^3	Yield (%)[b]	ee (%)[c]
1	H	H (**5a**)	4-Me (**6b**)	92	−97
2	H	H (**5a**)	3-Me (**6c**)	97	95
3	H	H (**5a**)	4-MeO (**6d**)	98	98
4	H	H (**5a**)	3-MeO (**6e**)	97	89 (*S*)[d]
5	H	H (**5a**)	2-MeO (**6f**)	Trace	nd
6	H	H (**5a**)	3, 5-Me (**6g**)	99	97
7	H	H (**5a**)	4-Cl (**6 h**)	96	81
8	H	H (**5a**)	4-F_3C (**6i**)	95	25
9	H	H (**5a**)	2-Naph (**6j**)	99	94
10	H	4-MeO (**5c**)	H (**6a**)	93	−97
11	H	3-MeO (**5d**)	H (**6a**)	99	−93 (*R*)[d]
12	H	3, 5-MeO (**5e**)	H (**6a**)	99	92
13	H	3-OH (**5f**)	H (**6a**)	99	97
14	H	4-Br (**5g**)	H (**6a**)	nr	nd
15	4-Br	4-MeO (**5h**)	H (**6a**)	nr	nd
16[e]	4-MeO	4-MeO (**5i**)	H (**6a**)	98	95
17	4-NO_2	4-MeO (**5j**)	H (**6a**)	31	97
18[e]	H	2-Th (**5k**)	H (**6a**)	83	81
19[e]	H	2-Furyl (**5l**)	H (**6a**)	94	66
20[e]	H	2-Pyr (**5m**)	H (**6a**)	34	48
21	(*E*)-$CH_3COCH{=}CHC_6H_4$-*p*-OCH_3 (**5n**)		H (**6a**)	98	90 (*R*)[f]

[a] Reactions were performed with **5** (0.3 mmol), **6** (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.2 mg, 0.003 mmol), **3d** (0.0072 mmol), KF (0.15 mL, 1.0 mol/L in H_2O, 0.15 mmol), 2-propanol (0.6 mL) at 40 °C for 3 h.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] Determined by comparison of the specific optical rotation with literature[5a] and the others were assigned by analogy.
[e] For 10 h.
[f] Determined by comparison of the specific optical rotation with literature.[9]

complex. The adducts were readily obtained in up to 99% yield and 98% ee. The application of this methodology to other linear unsaturated carbonyl compounds is underway in our laboratory.

4. Experimental section

4.1. General method

Unless otherwise noted, all commercially available reagents were used as received without further purification. Solvents used in catalysis were distilled from appropriate drying agents and bubbled with argon for 30 min prior to use. Solutions used in the catalysis were made by dissolving the salt in distilled water then bubbled with argon for 30 min prior to use. Flash column chromatography was performed on silica gel H (HG/T2354-92, Qingdao Haiyang Chemical Co. Ltd.); analytical TLC was performed on HSGF 254 glass plates precoated with 0.15–0.20 mm thickness of silica gel (Yantai Jiangyou Silica Gel Development Co. Ltd). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) in $CDCl_3$. Chemical shifts were recorded in parts per million (δ) relative to $CHCl_3$ at 7.26 for ^{1}H NMR and 77.0 for ^{13}C NMR. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were recorded on a Bruke P-SIMS-Gly FT-ICR mass spectrometer. Optical rotation was recorded on PE Model 341 polarimeter. Enantiomeric excess was determined by HPLC analysis on Chiralcel OJ-H, Chiralpak AD-H, IA column (Daicel Chemical Industries, LTD) using UV detector.

4.2. General procedure for the catalytic asymmetric 1,4-additions

Under argon atmosphere, to a 10-mL Schlenk tube was added $[Rh(C_2H_4)_2Cl]_2$ (1.2 mg, 0.003 mmol), *tert*-butanesulfinylphosphine ligand (0.0072 mmol), followed by 0.5 mL dichloromethane, the mixture was stirred at rt for 30 min, then solvent was removed and chalcone (0.3 mmol) and arylboronic acid (0.6 mmol) were added, after purging with argon, 2-propanol (0.6 mL) and KF (0.15 mL, 1.0 M in H_2O, 0.15 mmol) were added sequentially. The mixture was stirred at 40 °C for 3 h, then the solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate 20/1 as eluent to afford the adducts.

*4.2.1. 1,3-Diphenyl-3-(p-tolyl)propan-1-one (**7ba**).*[2,5a,6] Yield 98%, white solid, mp 77–78 °C, $[\alpha]_D^{20}$ −11 (c 0.110, $CHCl_3$) for 95% ee.

^{1}H NMR (300 MHz, $CDCl_3$): δ=2.34 (s, 3H), 3.78 (d, *J*=7.32 Hz, 2H), 4.86 (t, *J*=7.31 Hz, 1H), 7.14 (d, *J*=7.94 Hz, 2H), 7.23 (d, *J*=7.96 Hz, 3H), 7.32–7.33 (m, 4H), 7.45–7.50 (m, 2H), 7.56–7.61 (m, 1H), 7.98–8.00 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.9, 44.7, 45.5, 126.2, 127.6, 127.7, 128.0, 128.46, 128.50, 129.2, 133.0, 135.8, 137.0, 141.1, 144.3, 198.0.

HPLC: Daicel Chiralcel OJ-H, *n*-hexane/2-propanol=70/30, 1.0 mL/min, 254 nm, retention time: 13.5 min (minor), 16.2 min (major).

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Supplementary data

Full experimental details for all compounds, as well spectral data can be founded in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.04.096.

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