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Palladium(II)-catalyzed 1,4-addition of arylboronic acids to β-arylenals for enantioselective syntheses of 3,3-diarylalkanals: a short synthesis of (+)-(*R*)-CDP 840

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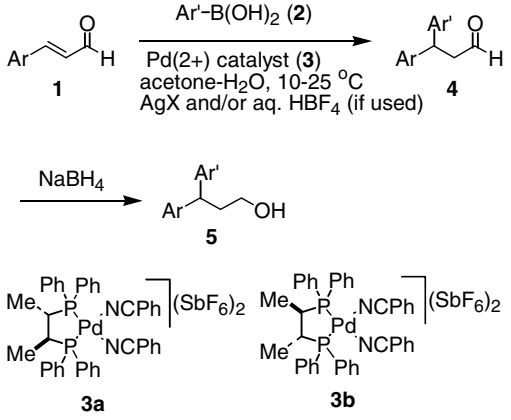
Abstract—1,4-Addition of arylboronic acid to *trans*-β-arylenals proceeded smoothly in acetone–water (10/1) at 10–25 °C in the presence of $[Pd(S,S\text{-chiraphos})(PhCN)_2](SbF_6)_2$ (0.5 mol %), AgX (X = BF_4, SbF_6, 10 mol %) and aqueous 42% HBF_4 to afford optically active 3,3-diarylalkanals with high enantioselectivities in a range of 86–97% ee. The protocol provided a method for short-step synthesis of optically active (+)-(*R*)-CDP 840.

Chiral diaryl-fragments, particularly β-diarylaldehydes, are valuable intermediates for the syntheses of natural and pharmaceutical compounds[1] since they are easily convertible into alcohol, ester, amide or alkene derivatives. A promising method for the synthesis of these optically active compounds is metal-catalyzed 1,4-addition of arylmetal reagents to β-arylenals,[2] which has been demonstrated by rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds.[3–10] Enantioselectivities exceeding 90% ee were achieved by Hayashi and Carreira by using chiral diene ligands as auxiliaries of rhodium(I) catalysts.[11,12] On the other hand, traditional chiraphos was found to be an excellent ligand for palladium(II) catalysts that achieved higher enantioselectivity than the corresponding Rh(I) complex for the 1,4-addition of arylmetal reagents to β-aryl-α,β-unsaturated ketones to give chiral β-diarylketones up to 99% ee.[13] The reaction can be used for 1,4-addition of $ArB(OH)_2$,[14] $ArSi(OMe)_3$,[15] Ar_3Bi,[16] $ArSiF_3$[17] and $[ArBF_3]K$.[17,18] Herein, we report the enantioselective preparation of β-diarylaldehydes (**4**) from arylboronic acids (**2**) and β-arylenals (**1**) with dicationic palladium(II) catalysts (0.5 mol %) in aqueous acetone (**3**). The presence of either HBF_4 or $AgSbF_6$ (10 mol %) or both of the additives was found to be effective for achieving high yields. The protocol was applied to the first catalytic synthesis of (+)-(*R*)-CDP 840. For convenience of analyses, all enantioselectivities were determined by alcohol derivatives (**5**) obtained by treatment of **4** with $NaBH_4$, since diarylaldehydes (**4**) were not easily separable by chiral stationary columns (Scheme 1).

The reaction between *p*-tolylboronic acid and *trans*-cinnamaldehyde was carried out at room temperature for 20 h in the presence of $[Pd(S,S\text{-chiraphos})(PhCN)_2](SbF_6)_2$ (**3a**, 0.5 mol %) in acetone/water (10/1) to



Scheme 1.

Keywords: Conjugate addition; Asymmetric synthesis; Asymmetric catalyst; Arylboronic acid; Chiral aldehydes.
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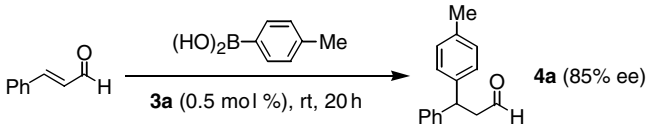
Table 1. Reaction conditions[a]



Run	AgX (mol %)	Solvent and acid	Yield (%)	Method
1	None	Acetone/H_2O (10/1)	54	
2	$AgSbF_6$ (10)	Acetone/H_2O (10/1)	75	
3	None	Acetone/H_2O/HBF_4 (20/2/1)	81	A
4	$AgSbF_6$ (10)	Acetone/H_2O/HBF_4 (20/2/1)	70	B
5	$AgBF_4$ (10)	Acetone/H_2O/HBF_4 (20/10/1)	64	C

[a] A mixture of PhCH=CHCHO (0.5 mmol), 4-MePhB$(OH)_2$ (1 mmol), Pd(*S*,*S*-chiraphos)$(PhCN)_2](SbF_6)_2$ (**3a**, 0.5 mol %), AgX (10 mol %, if used) and 42 wt % HBF_4 (0.1 mL, if used) in acetone (2 mL) and water (0.2 or 1 mL) was stirred for 20 h at room temperature.

optimize the reaction conditions (Table 1). The reaction resulted in 54% yield under the standard conditions used for previous reaction for β-arylenones (run 1), though there was no side reaction that yielded a Heck coupling product or Grignard-type addition product to the carbonyl group of aldehyde. On the other hand, the addition of $AgSbF_6$ (10 mol %) (run 2) and the addition of HBF_4 (10 mol %) (run 3, method A) had remarkable accelerating effects, giving β-diarylenal (**4a**) in 75% and 81% yield with 85% ee, respectively. Although the yields were not improved when both silver salt and HBF_4 were used in aqueous acetone (runs 4 and 5, methods B and C), the presence of both additives resulted in higher yields in other combinations of arylboronic acids and enals as shown in Table 2. Both rhodium- and palladium-catalyzed 1,4-additions of organoboronic acids to enals in aqueous solvents have suffered from slow reaction due to the formation of a stable hydrate (**7**). The acid catalyst may accelerate this equilibrium via a protonated intermediate (**6**), which would be much more activated for 1,4-addition than the parent aldehyde (**1**) (Scheme 2).

GC yields of the product were plotted against time during the reaction of *p*-tolylboronic acid with cinnamaldehyde at 20 °C under four conditions (runs 1–4) shown in Table 1 (Fig. 1). The presence of either HBF_4 (●) or $AgSbF_6$ (△) significantly accelerated the reaction, though the effect of the former additive was slightly greater than that of the latter additive. It was interesting to note that the presence of both HBF_4 and $AgSbF_6$ (10 mol %) (○) had the effect of further increasing the initial rate to complete the reaction within 2 h. The results suggest different roles of the proton and silver ion, though no mechanistic information is currently available.

Asymmetric 1,4-additions of representative arylboronic acids to β-arylenals with a palladium(II)/(*S*,*S*)-chiraphos catalyst (**3a**) in acidic aqueous acetone are shown

Table 2. Asymmetric 1,4-addition of arylboronic acids to β-arylenals

Run	**1** (Ar=)	**2** (Ar′=)	Method[a]	Temp (°C)	Yield[b] (%)	Product no.	% ee[c]
1	Ph	3-MeOPh	A	10	29	**4b**	92
2	Ph	3-MeOPh	C	10	78	**4b**	92
3	Ph	2-MeOPh	B	rt	Trace	**4c**	—
4	Ph	4-MeOPh	B	rt	59	**4d**	86
5	Ph	3-(*n*-C_4H_9O)Ph	C	rt	76	**4e**	91
6	Ph	3-($PhCH_2O$)Ph	C	10	76	**4f**	90
7	Ph	3,4-$(MeO)_2$Ph	A	10	66	**4g**	92
8	Ph	3-Me-4-MeOPh	A	10	61	**4h**	90
9	Ph	3-(*c*-C_5H_9O)-4-MeOPh[d]	A	10	72 (70)	**4i**	94 (*S*)
10	Ph	3,5-Me_2-4-MeOPh	A	10	80	**4j**	88
11	Ph	4-PhPh	A	10	79	**4k**	97
12	4-MeOPh	3-MeOPh	B[e]	10	78	**4l**	91
13	2-MeOPh	3-MeOPh	B	rt	72	**4m**	91
14	2-Naphthyl	3-MeOPh	B	rt	86 (89)	**4n**	90
15	2-Naphthyl	3-(*c*-C_5H_9O)-4-MeOPh[d]	C	rt	80 (80)	**4o**	94
16	4-MePh	3-MeOPh	C	10	78	**4p**	91
17	4-PhPh	3-MeOPh	B	rt	76 (70)	**4q**	90
18	4-PhPh	3-(*c*-C_5H_9O)-4-MeOPh[d]	C	rt	80 (75)	**4r**	93

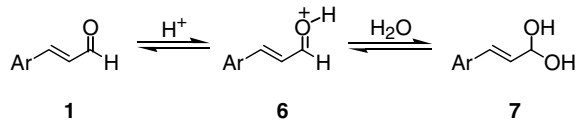
[a] See Table 1. Method A: acetone/H_2O/aq 42 wt % HBF_4 (20/2/1); method B: acetone/H_2O/aq 42 wt % HBF_4 (20/2/1) and $AgSbF_6$ (10 mol %); method C: acetone/H_2O/aq 42 wt % HBF_4 (20/10/1) and $AgBF_4$ (10 mol %).

[b] NMR yields and isolated yields are in parentheses.

[c] Enantiomeric excess of the corresponding alcohol derivatives (**5**) obtained by reduction of **4** with $NaBH_4$.

[d] 3-Cyclopentyloxy-4-methoxyphenyl group.

[e] In acetone/aq 42 wt % HBF_4 (20/1) and $AgSbF_6$ (10 mol %).



Scheme 2.

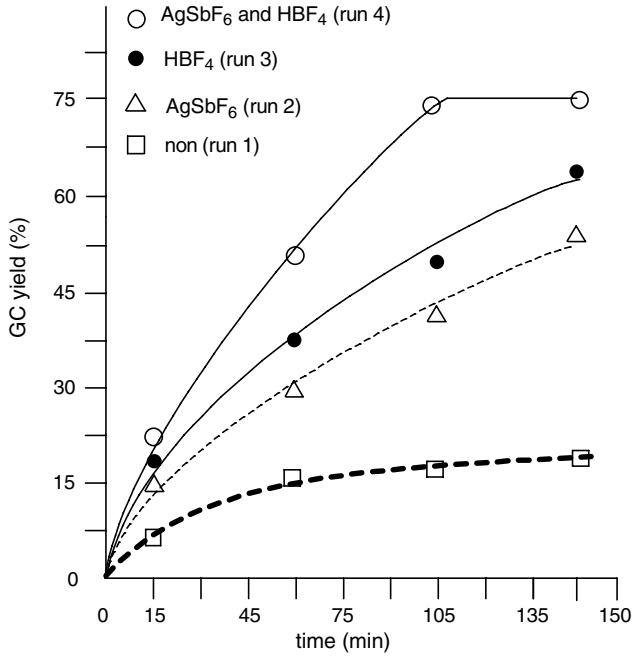
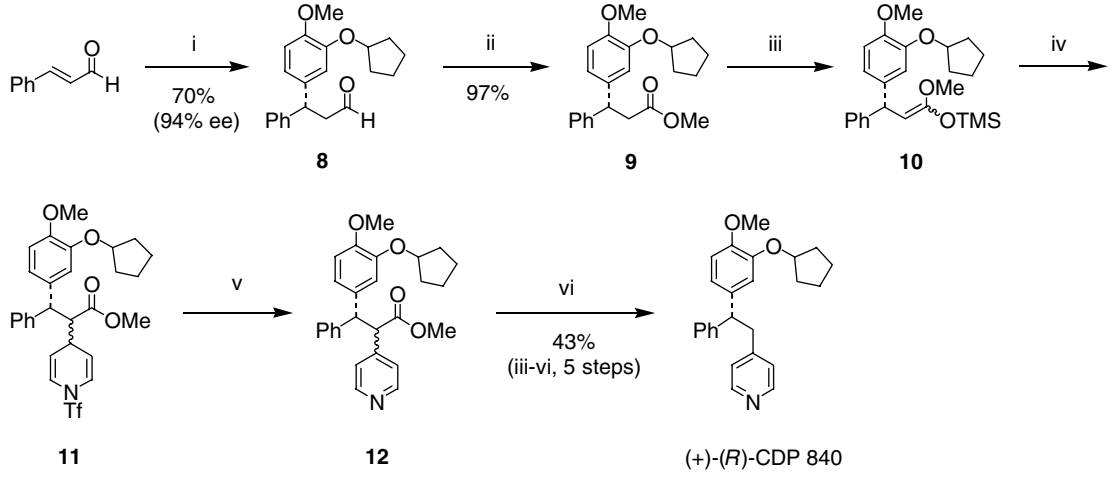


Figure 1. Effects of $AgSbF_6$ and HBF_4 on reaction rates (see, Table 1).

in Table 2. All reactions proceeded smoothly at 10–25 °C with yields and enantioselectivities in the ranges of 59–86% and 86–97% ee (runs 1–18), except for sterically hindered 2-methoxyphenylboronic acid (run 3). Yields were optimized by conducting each reaction by the three methods (methods A–C) listed in Table 1. The presence of silver salt in acidic aqueous acetone (method B or C) was particularly effective for achieving a high yield for 3-methoxyphenylboronic acid (runs 1 and 2). This system also resulted in the best yields in most combinations of boronic acids and enals (entries 4–6 and 12–18). The reaction temperature and substituents on arylboronic acids affected the enantioselectivities. The reaction at 10 °C resulted in 1–2% higher selectivities than that at room temperature. The use of arylboronic acids possessing a meta substituent always resulted in enantioselectivities higher than 90% ee (runs 2, 5–8 and 12–18), whereas 4-methyl- and 4-methoxyphenylboronic acids resulted in 85% ee and 86% ee, respectively (run 4). The absolute configurations of most products are not known, but the formation of an *S*-product from (*S*,*S*)-chiraphos complex (**3a**) was established by 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-phenylpropionaldehyde (**4i**), which was finally transformed to CDP 840 as shown in Scheme 3 (run 9). On the other hand, this catalyst was less effective for aliphatic unsaturated aldehydes. The addition of 3-methoxyphenylboronic acid to *trans*-hexenal and *trans*-crotonaldehyde resulted in 84% yield with 70% ee and 99% yield with 67% ee, respectively.

Phosphodiesterase (PDE) IV is believed to be the dominant isozyme present in inflammatory cells and in airway smooth muscle. (+)-(*R*)-CDP 840 is a potential therapeutic agent for asthma as a selective PDE IV inhibitor that leads to an increase in the concentration of cyclic AMP, resulting in the suppression of a broad range of functions in inflammatory cells.[19b] The major challenge for the synthesis of this clinically important compound was enantioselective construction of a diarylmethylene stereogenic center by using a stoichiometric chiral auxiliary for the synthesis of optically active epoxides.[19] The present reaction provided the first catalytic method for enantioselective synthesis of (+)-(*R*)-CDP 840 (Scheme 3).[19] 1,4-Addition of arylboronic acid possessing 3-cyclopentyloxy and 4-methoxy groups to *trans*-cinnamaldehyde with a Pd/(*R*,*R*)-chiraphos catalyst (**3b**) afforded (*R*)-**8** in 70% yield and with 94%



Scheme 3. Synthesis of CDP 840. Reagents and conditions: (i) 3-(*c*-C_5H_9O)-4-MeOPhB$(OH)_2$ (2 equiv), [Pd(*R*,*R*-chiraphos)$(PhCN)_2$]$(SbF_6)_2$ (**3b**, 0.5 mol %), acetone, aq HBF_4, 10 °C, 20 h; (ii) I_2 (2.5 equiv), KOH (2.5 equiv), MeOH, 0–20 °C, 20 h; (iii) LDA (1.5 equiv), TMSCl (2 equiv), THF, −78 °C to rt, 3 h; (iv) $PyTf_2O$ (3 equiv), CH_2Cl_2, 0 °C, 1 h; (v) *t*BuONa (3 equiv), DMSO, 20 °C, 20 min; (vi) (a) EtOH–water, NaOH, reflux, 0.5 h; (b) dioxane–water, concd HCl, reflux, 5 h.

ee. The oxidation of **8** with iodine and KOH in methanol led to the corresponding ester (**9**) in 97% yield.[20] Palladium- and base-catalyzed cross-coupling of **9** with 4-bromopyridine failed to introduce a pyridine ring to the α-carbon, presumably due to the bulkiness of two β-substituents. Thus, **9** was converted to the ketene silyl acetal (**10**) with LDA and TMSCl for nucleophilic substitution of a pyridinium salt of triflic anhydride to give **11**.[21] Crude **11** was treated with *t*BuONa in DMSO at 20 °C for 20 min for aromatization of pyridine ring.[22] Finally, decarboxylation of **12** gave (+)-(*R*)-CDP 840 in 43% yield (5 steps from **9**) and with 94% ee ($[\alpha]_D$ +35 (*c* 0.48, EtOH); lit. +37 (100% ee)[23]). Thus, the synthesis of CDP 840 was accomplished in seven steps with total 29% yield (84% average) starting from commercially available *trans*-cinnamaldehyde.

General procedure for asymmetric 1,4-addition: Ar-$B(OH)_2$ (2.0 mmol), acetone (4 mL), $AgBF_4$ or $AgSbF_6$ (0.1 mmol, if necessary), enal (1 mmol) and water (0.4 mL) were added to a flask under nitrogen. [Pd(*S*,*S*-chiraphos)$(PhCN)_2$]$(SbF_6)_2$ (**3**, 0.005 mmol) and HBF_4 (0.2 mL, 42 wt % aqueous solution) were then added at 10 °C. After being stirred for 20 h at 10 °C or at room temperature, chromatography on silica gel gave 1,4-adduct (**4**). The enantiomer excess was determined by chiral HPLC analysis of the corresponding alcohol (**5**) obtained by $NaBH_4$ reduction of **4**.

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