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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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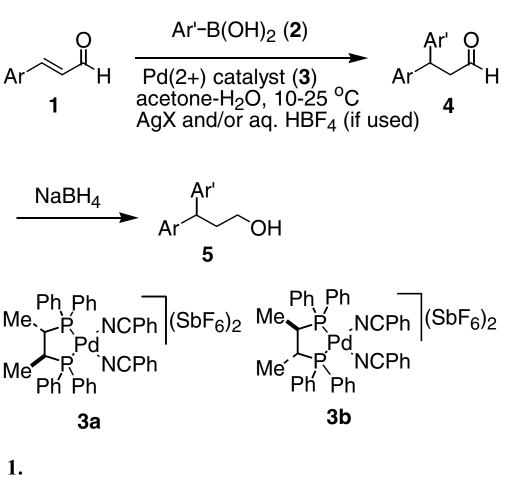
Abstract—1,4-Addition of arylboronic acid to *trans*-β-arylenals proceeded smoothly in acetone–water (10/1) at 10–25 °C in the presence of [Pd(*S*,*S*-chiraphos)(PhCN)$_2$](SbF$_6$)$_2$ (0.5 mol %), AgX (X = BF$_4$, SbF$_6$, 10 mol %) and aqueous 42% HBF$_4$ to afford optically active 3,3-diarylalkanals 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$_3$Bi,[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*-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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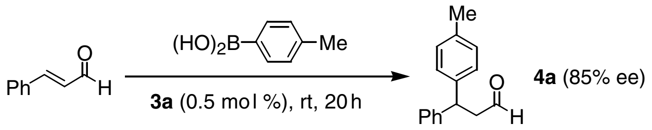
Table 1. Reaction conditions[a]



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 %).