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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.

Keywords: Conjugate addition, Asymmetric synthesis, Asymmetric catalyst, Arylboronic acid, Chiral aldehydes

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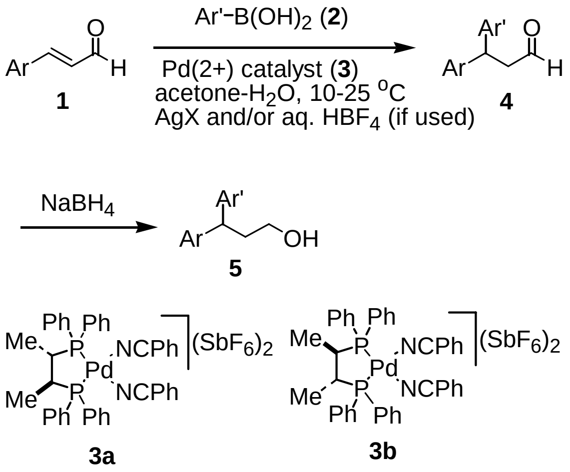
Chiral diaryl-fragments, particularly β-diarylaldehydes, are valuable intermediates for the syntheses of natural and pharmaceutical compounds[1] since they are easily convertible into alcohol, ester, amide or alkene derivatives. A promising method for synthesis of these optically active compounds is 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-diaryl ketones up to 99 %ee.[13] The reaction can be used for 1,4-addition of ArB(OH)$_2$,[14]

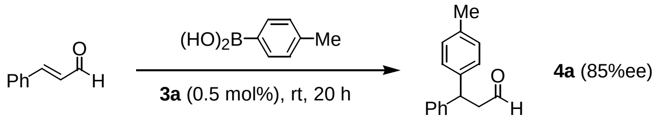
$ArSi(OMe)_3$,[15] Ar_3Bi,[16] $ArSiF_3$[17] and $[ArBF_3]K$.[17,18] Herein, we report enantioselective preparation of β-diarylaldehydes (**4**) from arylboronic acids (**2**) and β-arylenals (**1**) with dicationic palladium(II) catalysts (0.5 mol%) in aqueous acetone (**3**) (eq. 1). The presence of either HBF_4 or $AgSbF_6$ (10 mol%) or both of 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.

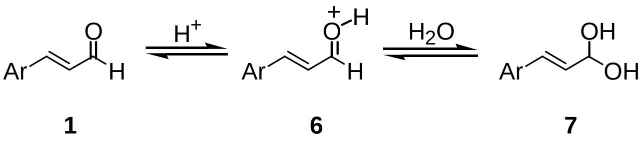
Reaction between *p*-tolylboronic acid and *trans*-cinnamaldehyde was carried out at room temperature for 20 h in the presence of $[Pd(S,S\text{-chiraphos})(PhCN)_2](SbF_6)_2$ (**3a**, 0.5 mol%) in acetone/water (10/1) to optimize the reaction conditions (Table 1). The reaction resulted in 54% yield 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**).

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)$(PhCN)_2$] $(SbF_6)_2$ (0.5 mol%), AgX (10 mol%, if used) and 42wt% HBF_4 (0.1 ml, if used) in acetone (2 ml) and water (0.2 ml) was stirred for 20 h at room temperature.



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 (Figure 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 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.

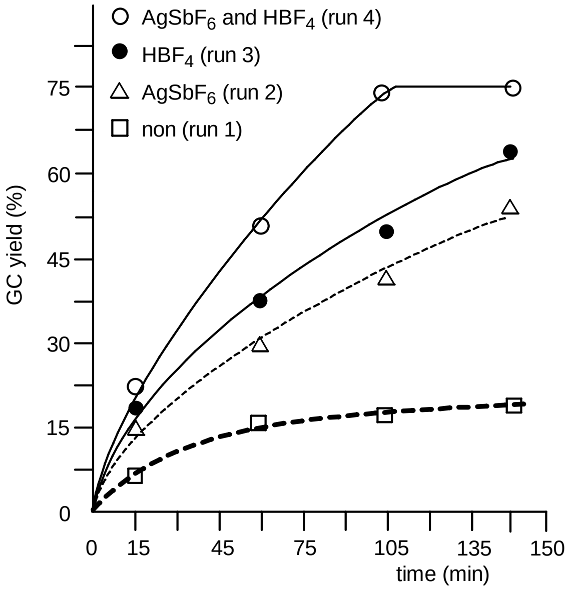


Figure 1. Effects of $AgSbF_6$ and HBF_4 on Reaction Rates (see, Table 1)

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 in Table 2. All reactions proceeded smoothly at 10-25 ˚C with yields and enantioselectivities in 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) shown 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

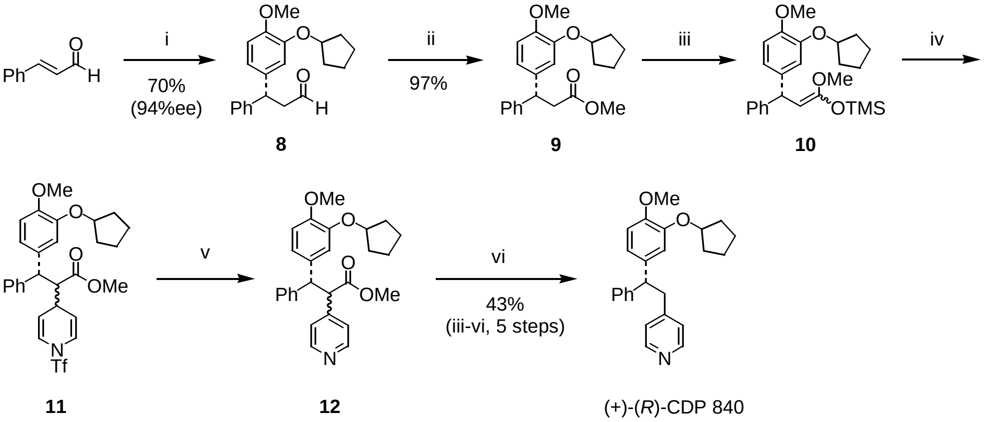
(**4i**), which was finally transformed to CDP 840 as shown in Scheme 3 (run 9). On the other hand, this catalyst was less effective for aliphatic unsaturated aldehydes. The addition of 3-methoxyphenylboronic acid to *trans*-hexenal and *trans*-crotonaldehyde resulted in 84% yield with 70%ee and 99% yield with 67 %ee, respectively.

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 42wt% HBF_4(20/2/1); method B: acetone/H_2O/aq 42wt% HBF_4 (20/2/1) and $AgSbF_6$ (10 mol%); method C: acetone/H_2O/aq 42wt% 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**) obatined by reduction **4** with $NaBH_4$.
d) 3-cyclopentyloxy-4-methoxyphenyl group. e) in acetone/aq 42wt% HBF_4(20/1) and $AgSbF_6$ (10 mol%).

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 suppression of a broad range of functions in inflammatory cells[19b]. The major challenge for the synthesis this clinically important compound was enantioselective construction of a diarylmethylene stereogenic center by using a stoichiometric chiral auxiliary for 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%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]. The 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 7 steps with total 29% yield (84% average) starting from commercially available *trans*-cinnamaldehyde.



(i) 3-(c-C_5H_9O)-4-MeOPhB$(OH)_2$ (2 eq), [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 eq), KOH (2.5 eq), MeOH, 0 to 20 °C, 20 h.
(iii) LDA (1.5 eq), TMSCl (2 eq), THF, -78°C to rt, 3 h.
(iv) $PyTf_2O$ (3 eq), CH_2Cl_2, 0 °C, 1 h.
(v) *t*BuONa (3 eq), DMSO, 20 °C, 20 min.
(vi) (a) EtOH- water, NaOH, reflux, 0.5 h. (b) dioxane-water, conc. HCl, reflux, 5 h.

Scheme 3. Synthesis of CDP 840

References and Notes

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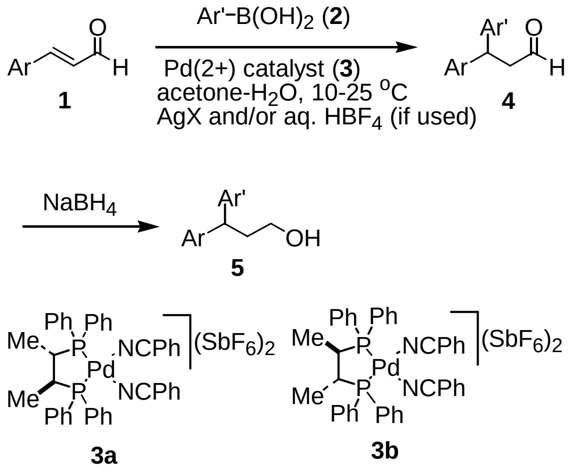
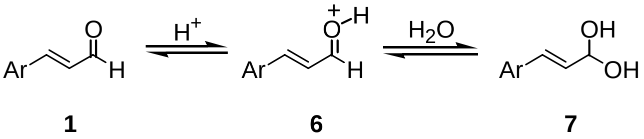
24. *General procedure for asymmetric 1,4-addition*: $ArB(OH)_2$ (2.0 mmol), acetone (4 mL), $AgBF_4$ or $AgSbF_6$ (0.1 mmol, if necessary), enal (1 mmol) and water (0.4 mL) were added to a flask under nitrogen. [Pd(*S,S*-chiraphos)$(PhCN)_2](SbF_6)_2$ (**3**, 0.005 mmol) and HBF_4 (0.2 mL, 42wt% aqueous solution) were then added at 10 °C. After being stirred for 20

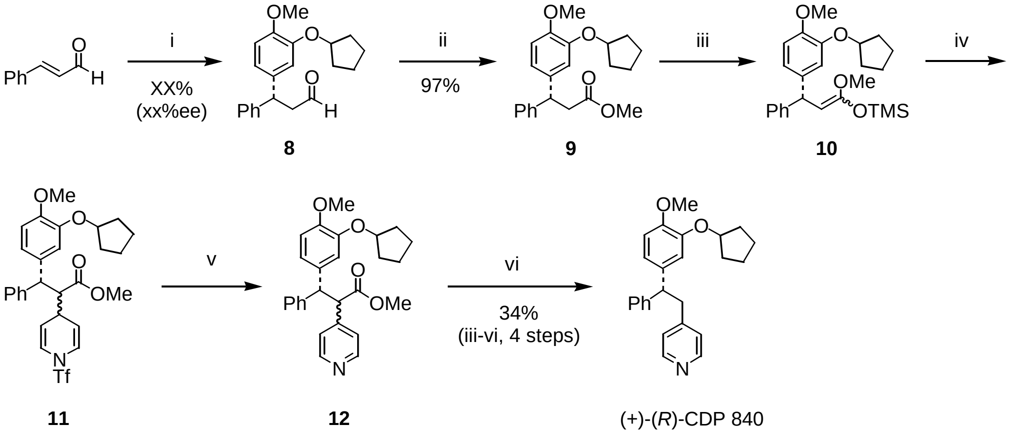
h at 10 ˚C or at room temperature, chromatography on silica gel gave 1,4-adduct (**4**). The enantiomer excess was determined by chiral HPLC analysis of the corresponding alcohol (**5**) obtained by $NaBH_4$ reduction of **4**.


Ar'-B(OH)2 (2)
Pd(2+) catalyst (3)
acetone-H2O, 10-25 oC
AgX and/or aq. HBF4 (if used)
1
4
NaBH4
5
(SbF6)2
3a
3b

Scheme 1.



Scheme 2.



(i) 3-(*c*-C_5H_9O)-4-MeOPhB$(OH)_2$ (2 eq), [Pd(*R*,*R*-chiraphos) $(PhCN)_2$]$(SbF_6)_2$ (**3b**, 0.5 mol%), acetone, aq HBF_4, 10 ^oC, 20 h.
(ii) I_2 (2.5 eq), KOH (2.5 eq), MeOH, 0 to 20 °C, 20 h.
(iii) LDA (1.5 eq), TMSCl (2 eq), THF, -78°C to rt, 3 h.
(iv) $PyTf_2O$ (3 eq), CH_2Cl_2, 0 °C, 1 h.
(v) *t*BuONa (3 eq), DMSO, 20 °C, 20 min.
(vi) (a) EtOH- water, NaOH, reflux, 0.5 h. (b) dioxane-water, conc. HCl, reflux, 5 h.

Scheme 3. Synthesis of CDP 840

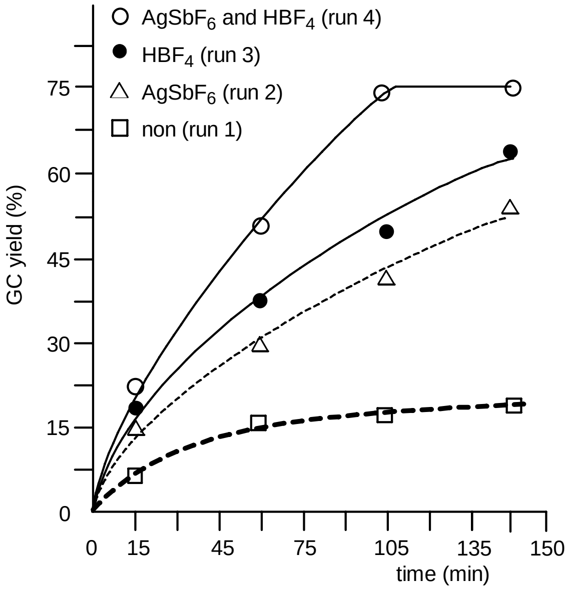
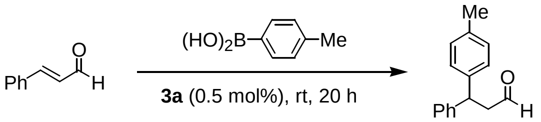


Figure 1. Effects of $AgSbF_6$ and HBF_4 on Reaction Rates (see, Table 1)

Table 1: Reaction conditions[a]


4a (85%ee)

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)		B
5	$AgBF_4$ (10)	acetone/H_2O/HBF_4 (20/2/1)		C

a) A mixture of PhCH=CHCHO (05 mmol), 4-MePhB$(OH)_2$ (1 mmol), Pd(*S*,*S*-chiraphos)$(PhCN)_2$] $(SbF_6)_2$ (0.5 mol%), AgX (10 mol%, if used) and 42wt% HBF_4 (ml, if used) in acetone (ml) and water (ml) was stirred for 20 h at room temperature.

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 42wt% HBF_4(20/2/1); method B: acetone/H_2O/aq 42wt% HBF_4 (20/2/1) and $AgSbF_6$ (10 mol%); method C: acetone/H_2O/aq 42wt% 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**) obatined by reduction **4** with $NaBH_4$.

d) 3-cyclopentyloxy-4-methoxyphenyl group. e) in acetone/aq 42wt% HBF_4(20/1) and $AgSbF_6$ (10 mol%).

Caption and Legend Pages

Scheme 1.

Scheme 2.

Scheme 3. Synthesis of CDP 840

Figure 1. Effects of $AgSbF_6$ and HBF_4 on Reaction Rates (see, Table 1)

Table 1. Reaction conditions[a]

Table 2. Asymmetric 1,4-Addition of Arylboronic Acids to β-Arylenals

For Graphical contents

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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