Asymmetric Catalysis

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Palladium/Chiral Amine Co-catalyzed Enantioselective β-Arylation of α,β-Unsaturated Aldehydes

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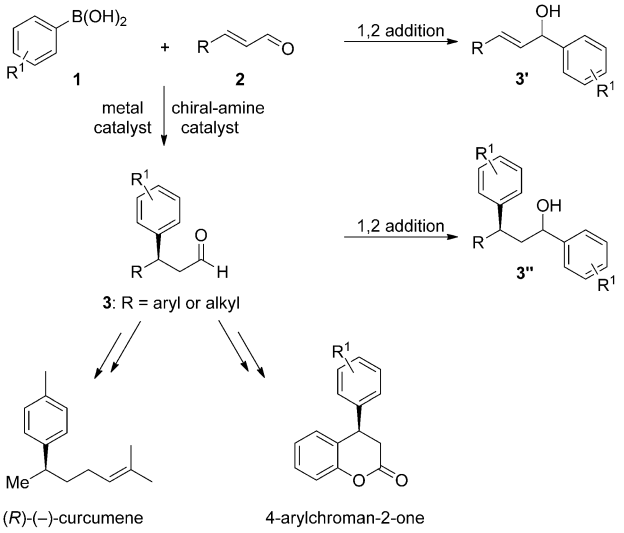
Enantioenriched chiral 3,3-diaryl-substituted aldehydes are valuable chiral building blocks for the preparation of numerous natural products and pharmaceuticals (e.g. 4-arylchroman-2-ones, sertraline, and tolterodine).[1] However, asymmetric synthesis of these aldehydes is cumbersome and challenging, because little distinguishes the two arenes sterically or electronically, in particular, when the aryl moiety is substituted at the *para* position. One catalytic way to synthesize nonracemic 3,3-diarylpropanals and 3-alkyl-3-arylpropanals is the amine-catalyzed addition of aromatic nucleophiles to enals.[2] However, this approach is restricted to electron-rich aromatic nucleophiles. In fact, the low reactivity of electron-poor aromatic nucleophiles leads to no conjugate addition products.

The enantioselective conjugate addition (ECA) of aryl boronic acids to Michael acceptors has been employed as the key step in the preparation of enantioenriched 3,3-disubstituted carbonyl compounds.[3–9] In this context, Carreira[7] and Hayashi[8] recently reported the use of chiral dienes as ligands for the rhodium-catalyzed ECA of aryl boronic acids to β-aryl-substituted acrolein derivatives.[7–10] Miyaura et al. demonstrated that chiraphos can be used as the auxiliary for Pd-catalyzed β-arylations of 3-aryl-substituted enals.[11] Despite these advances, there are very few examples of catalytic asymmetric conjugate additions of aryl boronic acids to 3-alkyl-substituted enals.[8,9a,11b] In fact, the state of the art with respect to the use of Pd catalysis is one example, giving the corresponding product in poor yield (30%) and moderate e.r. (74.5:25.5).[11c]

Based on our previous research on synergistic catalysis,[12] we envisioned a general co-catalyzed ECA of aryl boronic acids **1** to both β-aryl- and β-alkyl-substituted α,β-unsaturated aldehydes **2** by combining transition-metal and chiral amine catalysts (Scheme 1).[12–15] The corresponding products **3** would next be used in the total synthesis of natural products and biologically active substances (e.g. 4-arylchroman-2-ones or bisabolane sesquiterpenes, such as (*R*)-(−)-curcumene).



Scheme 1. Co-catalyzed β-arylation of enals **1** with possible side-reaction pathways (1,2 additions) and further synthesis.

However, α,β-unsaturated aldehydes represent an especially challenging class of substrates in metal-catalyzed conjugate additions of aryl boronic acids.[16] This is due to the high reactivity of aldehydes, which can undergo competitive 1,2 addition either to the starting enal (regioselectivity) or to the product (enal vs. product, chemoselectivity). We envisioned that the ability of a chiral amine to lower the LUMO of an enal **2** by iminium activation[17] in combination with transition-metal-catalyzed conjugate addition of aryl boronic acids **1** to this intermediate may allow the enantioselective 1,4 addition over 1,2 addition to give the corresponding chiral β-arylated products **3** (Scheme 2).[12]

Herein we report the co-catalyzed ECA of electron-rich and electron-poor aryl boronic acids **1** to β-alkyl- and β-aryl-substituted enals **2**, by combining simple palladium and chiral amine catalysts. Excellent 1,4 selectivity was achieved and the corresponding chiral 3,3-disubstituted aldehydes **3** were isolated in high yields with up to 95:5 e.r.

We began our studies by investigating the catalytic ECA of phenyl boronic acid **1a** to *trans*-2-hexenal **2a** using different metal complexes, chiral amines (**4**), and additives (key results in Table 1). The reaction that was performed without an amine catalyst was not successful (Table 1, entry 1). The same reaction with the chiral amine catalyst **4a**, but without $Pd(OAc)_2$ as co-catalyst, did also not provide the β-arylated product **3a** (Table 1, entry 2). To our delight,

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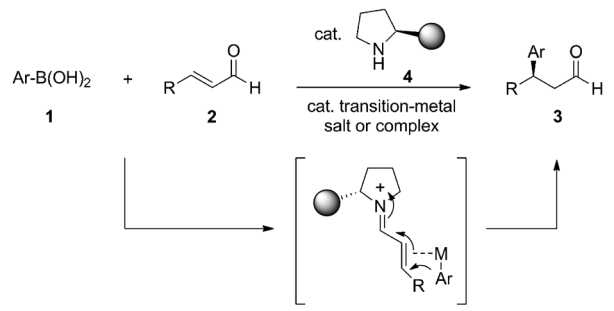
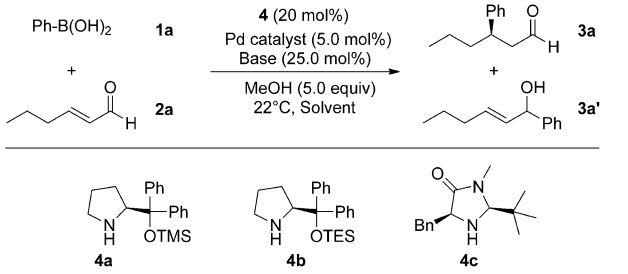


Scheme 2. Merging of iminium activation with transition-metal-catalyzed nucleophilic activation.

Table 1: Screening of the catalytic ECA of **1a** to β-alkyl-substituted enal **2a**.[a]



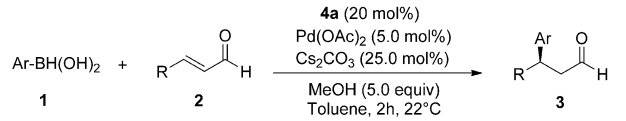
Ent.	Cat.	Metal salt	Base	Solvent	*t* [h]	Conv. [%][b]	Ratio **3a**/**3a′**[b]	e.r.[c]
1	–	$Pd(OAc)_2$	Cs_2CO_3	toluene	8	<2	n.d.	n.d.
2	**4a**	–	Cs_2CO_3	toluene	8	<2	n.d.	n.d.
3	**4a**	$Pd(OAc)_2$	Cs_2CO_3	toluene	2	98	>99:1	87:13
4	**4a**	$Pd(OAc)_2$	Cs_2CO_3	CH_2Cl_2	8	<2	n.d.	n.d.
5	**4a**	$Pd(OAc)_2$	Cs_2CO_3	THF	6	10	n.d.	n.d.
6	**4a**	$Pd(OAc)_2$	Cs_2CO_3	DMF	6	<2	n.d.	n.d.
7	**4a**	$Pd(OAc)_2$	–	toluene	8	10	n.d.	n.d.
8	**4a**	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	8	30	0:100	n.d.
9	**4a**	$Ni(PPh_3)_4$	Cs_2CO_3	toluene	8	<2	n.d.	n.d.
10	**4a**	$Cu(OTf)_2$	Cs_2CO_3	toluene	8	<2	n.d.	n.d.
11	**4a**	CuCl	Cs_2CO_3	toluene	8	<2	n.d.	n.d.
12	**4a**	$[Rh(nbd)Cl]_2$	Cs_2CO_3	toluene	8	60	80:20	47:53
13	**4a**	$PdCl_2$	Cs_2CO_3	toluene	6	15	n.d.	n.d.
14	**4a**	$Pd(CF_3CO_2)_2$	Cs_2CO_3	toluene	2	98	>99:1	85:15
15[d]	**4a**	$Pd(OAc)_2$	Cs_2CO_3	toluene	8	20	n.d.	n.d.
16	**4b**	$Pd(OAc)_2$	Cs_2CO_3	toluene	3	98	>99:1	87:13
17	**4c**	$Pd(OAc)_2$	Cs_2CO_3	toluene	8	<2	n.d.	n.d.

[a] Under N_2 atmosphere. Final concentration 0.20 M. See the Supporting Information for details. [b] Determined by ^1H NMR spectroscopy on the crude reaction mixture. [c] Determined by chiral-phase HPLC analysis. [d] No MeOH was added. Bn = benzyl, DMF = *N*,*N*-dimethylformamide, nbd = 2,5-norbornadiene, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

when the chiral amine catalyst **4a** (20 mol%) and $Pd(OAc)_2$ (5 mol%) were used as co-catalysts together with Cs_2CO_3 (25 mol%) and MeOH (5 equiv) as additives in toluene, the corresponding β-aryl-substituted aldehyde **3a** was formed with high conversion and 87:13 e.r. within 2 h (Table 1, entry 3). No 1,2 addition products **3a′** or **3a″** were observed. The use of toluene as the solvent and Cs_2CO_3 and MeOH as additives was essential in order to achieve high conversion (Table 1, entries 3–7 and 15). Of the investigated metal catalysts, $Pd(OAc)_2$ and $Pd(O_2CCF_3)_2$ were the most efficient in combination with chiral amine **4a**[18] (Table 1, entries 3, 14, and 16). The use of $[Rh(nbd)Cl]_2$ as metal co-catalyst also gave product **3a**. However, the e.r. was low and some 1,2 addition product **3a′** was also formed (Table 1, entry 12). The highest enantiomeric ratios of **3a** were achieved by combining catalysts **4a** or **4b** with the palladium co-catalyst $Pd(OAc)_2$ (Table 1, entries 3 and 16, respectively).

With these results in hand, we decided to probe the scope of the catalytic ECA of aryl boronic acids **1** to enals **2** using **4a** and $Pd(OAc)_2$ as co-catalysts together with Cs_2CO_3 and MeOH as additives in toluene (Table 2). The co-catalyzed

Table 2: ECA of aryl boronic acids **1** to enals **2** co-catalyzed by Pd^{II} and chiral amine **4a**.[a]



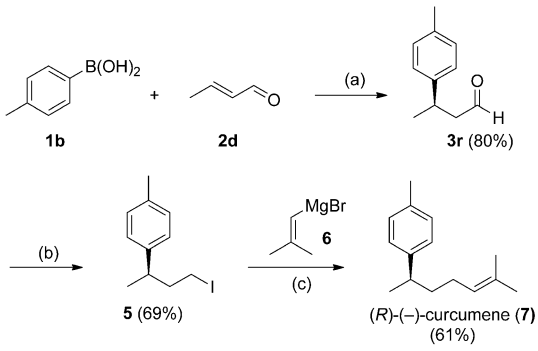
Ent.	**1**, Ar	**2**, R	Product	Yield[%][b]	e.r.[c]
1	**1a**, C_6H_5	**2a**, *n*Pr	**3a**	79	87:13
2	**1b**, 4-$CH_3C_6H_4$	**2a**, *n*Pr	**3b**	80	86:14
3	**1c**, 4-$CF_3C_6H_4$	**2a**, *n*Pr	**3c**	81	87:13
4	**1d**, 4-ClC_6H_4	**2a**, *n*Pr	**3d**	79	89:11
5	**1e**, 4-BrC_6H_4	**2a**, *n*Pr	**3e**	81	87:13
6	**1d**, 4-ClC_6H_4	**2b**, *n*Bu	**3f**	83	89:11
7	**1d**, 4-ClC_6H_4	**2c**, Et	**3g**	78	87:13
8[d]	**1d**, 4-ClC_6H_4	**2d**, Me	**3h**	80	83:17
9[e]	**1b**, 4-$CH_3C_6H_4$	**2e**, Ph	**3i**	80	94:6
10[e]	**1c**, 4-$CF_3C_6H_4$	**2e**, Ph	**3j**	79	93:7
11[e]	**1d**, 4-ClC_6H_4	**2e**, Ph	**3k**	81	93:7
12[e]	**1e**, 4-BrC_6H_4	**2e**, Ph	**3l**	79	93:7
13[f]	**1a**, C_6H_5	**2f**, 4-$MeOC_6H_4$	**3m**	75	92:8
14[f]	**1a**, C_6H_5	**2g**, 4-ClC_6H_4	**3n**	76	95:5
15[f]	**1a**, C_6H_5	**2h**, 4-BrC_6H_4	**3o**	77	94.5:5.5
16[g]	**1a**, C_6H_5	**2i**, 2-$BnOC_6H_4$	**3p**	70	90:10
17[g]	**1d**, 4-ClC_6H_4	**2i**, 2-$BnOC_6H_4$	**3q**	71	91:9

[a] Under N_2 atmosphere, **1** (1.5 equiv), $Pd(OAc)_4$ (5 mol%), **4a** (20 mol%), Cs_2CO_3 (25 mol%), MeOH (5.0 equiv), and **2** (1 equiv) in toluene at 22°C. Final concentration 0.20 M. See the Supporting Information for details. [b] Yield of purified product **3** after column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral stationary phase. [d] **1** (1.0 equiv), enal **2d** (2 equiv). [e] Reaction time was 3 h. [f] Reaction time was 6 h. [g] Reaction time was 3 h and temperature 50°C. No 1,2 addition products (**3′** or **3″**) were observed (entries 1–17).

additions of aryl boronic acids **1a**–**1e** to β-alkyl-substituted enals **2a**–**2d** proceeded with excellent 1,4 selectivities and good enantioselectivities to give the chiral aldehyde products **3a**–**3h** in high yields with good e.r. (Table 2, entries 1–8). It is noteworthy that aryl boronic acids **1** with both electron-withdrawing and electron-donating substituents could be used as donors.[19]

We next investigated the co-catalyzed ECA of aryl boronic acids **1** to a wide range of β-aryl-substituted enals (**2e**–**2i**, Table 2, entries 9–17). The reactions proceeded smoothly and gave the corresponding 3,3-diaryl-substituted aldehydes **3i**-**3q** in high yields (77–81%) with up to 95:5 e.r.

The absolute configuration of chiral β,β-disubstituted aldehydes **3** was established by total syntheses (Schemes 3 and 4). We began with the expeditious total synthesis of (*R*)-(−)-curcumene (Scheme 3).[20] Thus, the initial co-catalyzed

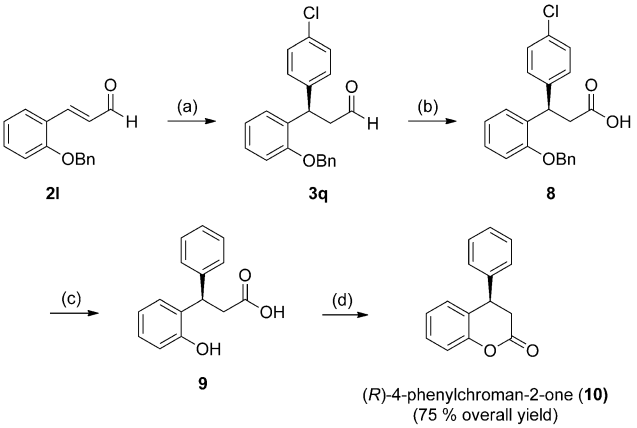


Scheme 3. Asymmetric synthesis of (*R*)-(−)-curcumene **7**. a) Cat. **4a** (20 mol%), cat. $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (25 mol%), MeOH (5 equiv), toluene, RT; b) 1) $NaBH_4$, CH_2Cl_2, MeOH, 0°C; 2) TsCl, pyridine, CH_2Cl_2, RT, 5 h; 3) NaI, acetone, reflux, 2 h; c) **6**, CuI, THF, 0°C, 9 h.

asymmetric synthesis of aldehyde **3r** (80% yield with 83:17 e.r.) was followed by subsequent reduction, tosylation, and nucleophilic displacement to give iodine **5** in 69% overall yield (3 steps). Grignard addition of **6** to **5** gave (*R*)-curcumene **7** in 61% yield with 84:16 e.r. Comparison with the literature showed that the stereochemistry of **7** was (*R*) ($[\alpha]_D^{20}=-24.0$ ($c=0.5$, $CHCl_3$); Ref. [20a]: $[\alpha]_D^{20}=-37.5$ ($c=2.9$, $CHCl_3$); Scheme 3).

After accomplishing the above total synthesis, we embarked on the total synthesis of 4-arylchroman-2-ones such as **10**.[6a,3q] Thus, the reaction of 4-chlorophenyl boronic acid **1d** with 2-OBn-substituted cinnamic aldehyde **2i** co-catalyzed by amine **4a** and $Pd(OAc)_2$ gave the corresponding 3,3-diaryl-substituted aldehyde **3q** in 71% yield. Next, oxidation gave the corresponding acid **8** (Scheme 4), and subsequent catalytic hydrogenation (H_2, Pd/C in EtOAc) afforded hydroxy acid **9**. Interestingly, HRMS analysis of **9** showed that dechlorination had occurred under these conditions. If desired, this side reaction can be circumvented by the employment of PtO_2 as the catalyst for the hydrogenation step.[21] Acid-mediated lactonization by treatment of **9** with *p*-toluenesulfonic acid in benzene gave the desired (*R*)-4-phenylchroman-2-one **10**[3q] (75% overall yield, 3 steps). Comparison with the literature showed that the stereochemistry of **10** was also (*R*) ($[\alpha]_D^{20}=-38.2$ ($c=0.2$, $CHCl_3$); Ref. [3q]: $[\alpha]_D^{20}=-45.1$ ($c=0.98$, $CHCl_3$); Scheme 4).

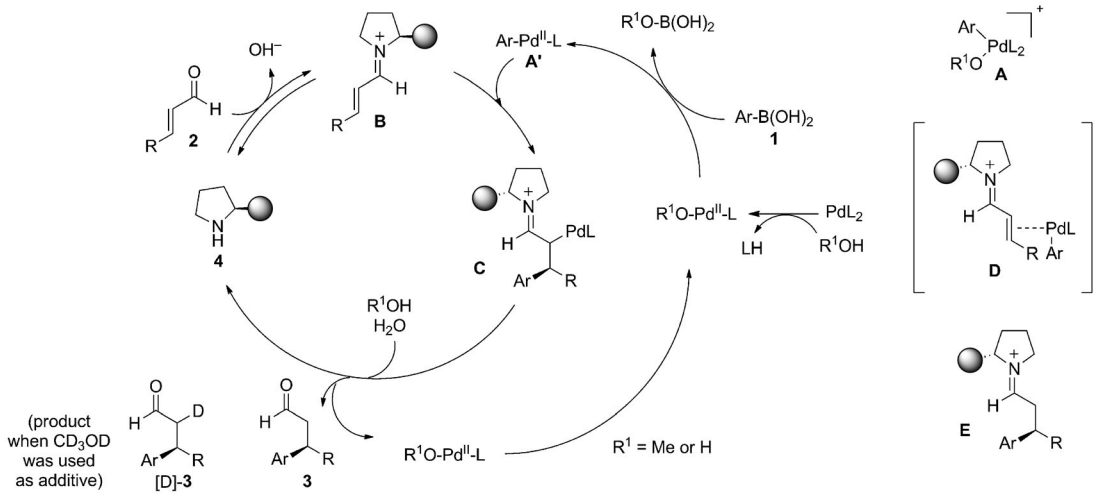
With respect to the catalytic cycles of the palladium-co-catalyzed conjugate addition, Miyaura and co-workers have previously proposed a mechanism for the cationic Pd^{II}-complex-catalyzed conjugate addition of aryl boronic acids.[10,11a] However, these types of reactions can also be catalyzed by neutral Pd^{II} complexes.[10a,22,23] The addition of MeOH significantly accelerated our co-catalyzed reaction, and the experimental results show clearly that the reaction is not catalyzed by a Pd^0 intermediate (Table 1, entry 8). In



Scheme 4. Asymmetric synthesis of (*R*)-4-phenylchroman-2-one **10**. a) **1d**, cat. **4a** (20 mol%), cat. $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (25 mol%), MeOH (5 equiv), toluene, 50°C, 3 h; b) $NaClO_2$, CH_2Cl_2, 22°C, 18 h; c) Pd/C, EtOAc, 22°C, 18 h; d) *p*-toluenesulfonic acid, benzene, 80°C.

addition, the reaction was inhibited by the addition of phosphine ligands. Based on these results, the above-cited literature,[10,11,22] the absolute configuration of products **3**, and our previous DFT calculations,[12a] we propose a mechanism involving stereoselective addition of monocationic $[ArPd^{II}(OMe)L_2]^+$ **A** or neutral $ArPd^{II}L$ **A′** to chiral iminium intermediates **B** (Scheme 5).[10,23c] Here, we show the co-catalyzed mechanism in which the neutral aryl–palladium(II) species **A′** is generated by transmetalation of the aryl boronic acid (Scheme 5).[10,23c] In parallel, iminium intermediate **B** is generated in situ by reaction of enals **2** with chiral amine catalyst **4**. Next, the catalytic cycles are merged and stereoselective addition of **A′** to iminium intermediate **B** leads to the C-bound-Pd^{II}/iminium intermediate **C**. Here, efficient shielding of the *Re* face (R = aryl) of **B** by the bulky chiral group of **4** leads to *Si*-facial nucleophilic attack at the β-carbon atom via transition state **D**.[12a] Subsequent protonolysis of the palladium–carbon bond of **C** and hydrolysis of the iminium intermediate **E** leads to release of the Pd^{II} species, the chiral amine co-catalyst, and the corresponding product **3** (Scheme 5). The presence of iminium intermediates **B** and **E** was confirmed by direct HRMS analysis of the crude reaction mixture.[24] It is noteworthy that deuterium-labeling experiments with CD_3OD instead of MeOH confirmed the presence of deuterated products [D]-**3**. Thus, a C-bound-Pd^{II}/iminium intermediate **C** was most likely present in the catalytic cycle. In addition, this experiment confirms that MeOH was a proton source for the C–Pd bond cleavage of **C**.

In summary, we have disclosed a co-catalyzed β-arylation of α,β-unsaturated aldehydes with aryl boronic acids by combining simple Pd and chiral amine catalysts. The reactions are highly 1,4-selective and the corresponding aldehyde products were obtained in high yields with good enantiomeric ratios (up to 95:5 e.r.). The co-catalyzed asymmetric β-arylation reaction allowed the use of both β-alkyl- and β-aryl-substituted aldehydes as acceptors. The reaction was employed for the short total syntheses of (*R*)-(−)-curcumene and (*R*)-4-phenylchroman-2-one. It should also serve as an



Scheme 5. Proposed catalytic cycle.

efficient entry for diversity-oriented synthesis. Results in this area and other total synthesis will be disclosed in due course.

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