Asymmetric 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Esters Catalyzed by Dicationic Palladium(II)–Chiraphos Complex for Short-Step Synthesis of SmithKline Beecham's Endothelin Receptor Antagonist

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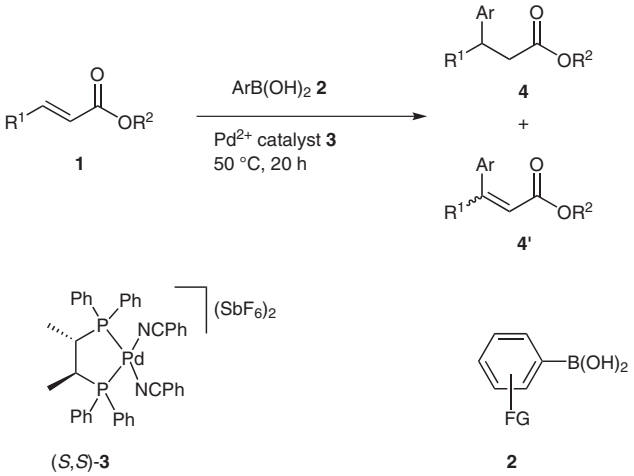
Abstract: An asymmetric 1,4-addition of arylboronic acids to $RCH{=}CHCO_2Ar$ (Ar = Ph or 4-acetylphenyl) was carried out at 50 °C in aqueous acetone in the presence of $[Pd(chiraphos)(PhCN)_2](SbF_6)_2$. The reaction gave optically active β-aryl esters in up to 98% ee. The protocol provided a simple access to an endothelin receptor antagonist reported by SmithKline Beecham.

Key words: arylboronic acids, palladium catalyst, asymmetric reaction, conjugate addition, β-arylalkanoate, bioactive compound

Metal-catalyzed 1,4-additions of organometallic compounds to α,β-unsaturated carbonyl compounds have attracted much attention as methods for constructing chiral centers via C–C bond-forming reactions. Although Rh-based complexes have been used extensively as catalysts for 1,4-additions of arylmetal compounds,[1] palladium catalysts have recently been found to be an excellent alternative.[2] Palladium(II) catalysts have higher turnover numbers than those of rhodium catalysts for cyclic and acyclic unsaturated ketones, aldehydes and *N*-acylamides with excellent enantioselectivities.[3,4] However, they have a strong tendency to undergo β-hydride elimination, giving Heck coupling products for unsaturated esters.[2e,3e,5] Formation of such alkene by-products for unsaturated esters has also been reported for rhodium,[6] iridium,[7] and ruthenium catalysts.[8] Thus, we recently reported the synthesis of chiral β-arylalkanoates, including total synthesis of (+)-(*R*)-tolterodine, via stepwise palladium-catalyzed 1,4-addition of arylboronic acids to enones and regioselective Baeyer–Villiger oxidation.[4f] In this paper, we report that aryl esters (**1**, R^2 = Ph, 4-AcC_6H_4) selectively afford 1,4-addition products **4** of arylboronic acids in the presence of the dicationic palladium catalyst $[Pd((S,S)\text{-chiraphos})(PhCN)_2](SbF_6)_2$ [(*S*,*S*)-**3**], whereas the corresponding alkyl esters such as **1** (R^2 = Me) result in Heck coupling (**4′**; Scheme 1). The protocol provides a simple access to an optically active endothelin receptor antagonist reported by SmithKline Beecham.

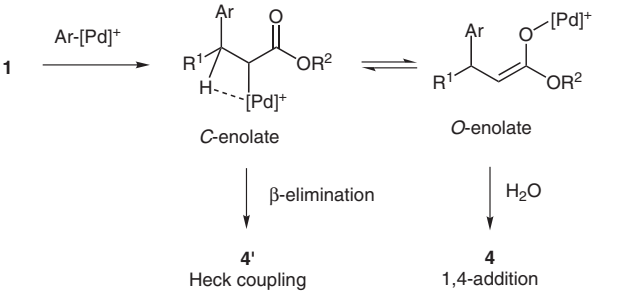
This 1,4-addition and the Heck reaction may involve a common *C*-enolate intermediate generated by insertion of an alkene into the C–Pd bond (Scheme 2). The *C*-enolate



Scheme 1 Asymmetric 1,4-addition of $ArB(OH)_2$ to α,β-unsaturated esters

which undergoes Heck coupling (**4′**) is in equilibrium with *O*-enolate susceptible to hydrolysis by water to produce 1,4-addition products **4**.[9] For smooth formation of such *O*-enolates in aqueous solvents, cationic palladium(II) complexes are better catalysts than neutral complexes, and unsaturated ketones and aldehydes are better substrates than esters and amides.

We recently succeeded in using palladium catalysts for 1,4-addition to electron-deficient amides such as RCH=CHCON(Ph)COPh.[4h] Although simple extension of this protocol for acid anhydrides $PhCH{=}CHCO_2COR^3$ (R^3 = Ph, *t*-Bu, NMe_2, O*t*-Bu) failed due to rapid hydrolysis of these substrates with water, aryl esters (**1**, R^2 = Ph, 4-AcC_6H_4) selectively provided 1,4-addition products. The effects of ester groups and stoichiometry of arylbo-



Scheme 2 1,4-Addition vs. Heck coupling

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Table 1 Reaction Conditions[a]

Entry	R^2 of **1** (R^1 = Ph)	4-$MeC_6H_4B(OH)_2$ (equiv)	Yield (%)[b]	**4**:**4′**
1	Me	1.5	7	20:80
2	Ph	1.5	48	92:8
3	4-AcC_6H_4	1.5	51	98:<2
4	4-AcC_6H_4	3.0	71	98:<2
5	4-AcC_6H_4	4.0	80	98:<2

[a] A mixture of unsaturated ester (0.5 mmol), 4-$MeC_6H_4B(OH)_2$ and Pd catalyst **3** (1 mol%) in acetone–H_2O (2 mL/0.2 mL) was stirred at 50 °C for 20 h.
[b] NMR yields.

ronic acids at 50 °C in aqueous acetone (10:1) are shown in Table 1. The Heck product was the major product for methyl ester (entry 1), but the reaction provided the 1,4-addition product with 92% selectivity for phenyl ester (entry 2) and with more than 98% selectivity for 4-acetylphenyl ester (entry 3). Other ester derivatives such as C_6F_5, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-$PhCOC_6H_4$, and 4-CNC_6H_4 esters (R^2 of **1**) were less effective. The yields were very low when 1.5 equivalents of boronic acid were used (entry 3), but they were increased to practical levels (70–80%) in the presence of 3–4 equivalents of boronic acid (entries 4 and 5).

Results of enantioselective 1,4-additions of arylboronic acids (3 equiv) to the representative α,β-unsaturated esters are shown in Table 2. All reactions selectively gave 1,4-addition products with concomitant formation of less than 2% of Heck product. Although rhodium-catalyzed reactions of electron-deficient arylboronic acids resulted in

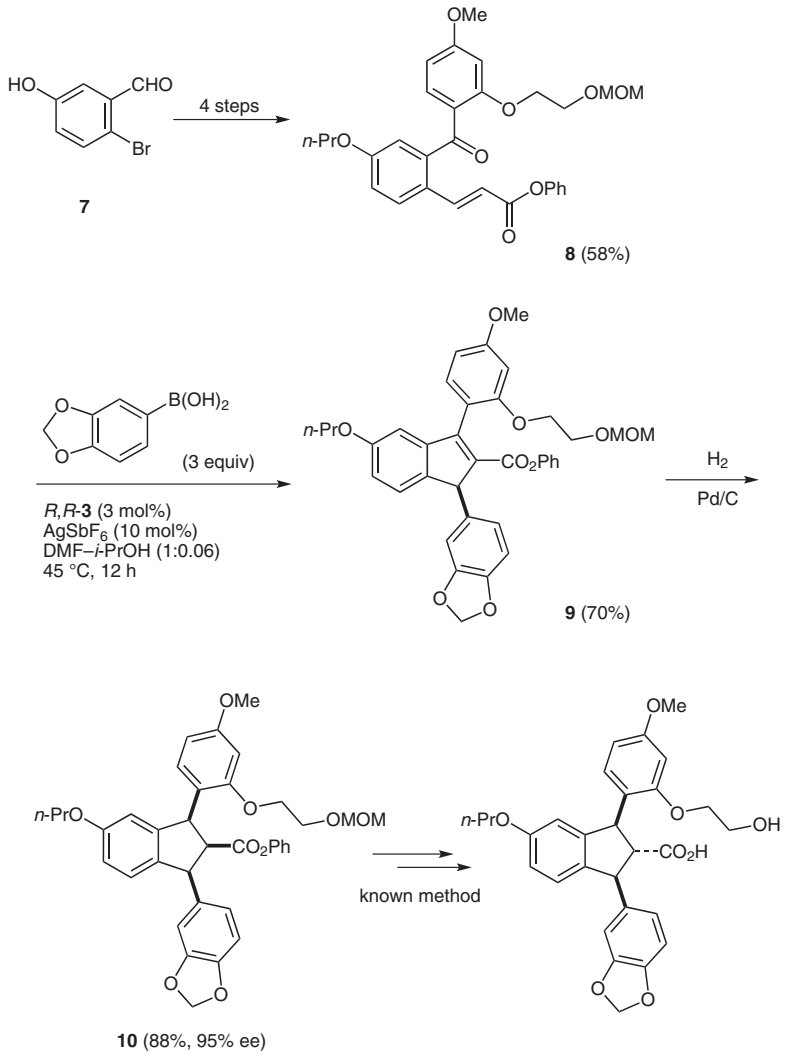
Table 2 Synthesis of Chiral β-Aryl Esters[a,13]

Entry	R^1	R^2	Ar of $ArB(OH)_2$	Product	Yield (%)[b]	ee (%)
1	Ph	4-AcC_6H_4	4-MeC_6H_4	**4a**	(71)	97 (*S*)
2	Ph	4-AcC_6H_4	3-MeC_6H_4	**4b**	(81)	95
3	Ph	4-AcC_6H_4	3-$MeOC_6H_4$	**4c**	(90)	97
4	Ph	4-AcC_6H_4	3-$MeO_2CC_6H_4$	**4d**	89	95
5	Ph	4-AcC_6H_4	4-ClC_6H_4	**4e**	(88)	97
6	Ph	4-AcC_6H_4	3-$MeCOC_6H_4$	**4f**	(99)	96
7	Ph	4-AcC_6H_4	4-$MeOC_6H_4$	**4g**	99	96[c]
8	2-$MeOC_6H_4$	4-AcC_6H_4	Ph	**4h**	(80)	97
9	3-$MeOC_6H_4$	4-AcC_6H_4	Ph	**4i**	(80)	97
10	4-$MeOC_6H_4$	4-AcC_6H_4	Ph	**4j**	(71)	95
11	4-$MeOC_6H_4$	4-AcC_6H_4	3-$MeCOC_6H_4$	**4k**	87	95
12	2,3-$(MeO)_2C_6H_3$	4-AcC_6H_4	Ph	**4l**	(86)	97
13	Me	4-AcC_6H_4	3-$MeCOC_6H_4$	**4m**	80	90
14[d,e]	Me	4-AcC_6H_4	3-$MeOC_6H_4$	**4n**	78	92
15	*n*-Pr	4-AcC_6H_4	3-$MeCOC_6H_4$	**4o**	69	84
16[d]	*n*-Pr	Ph	3-$MeCOC_6H_4$	**4p**	80	90
17	$Me(CH_2)_3CH_2$	4-AcC_6H_4	3-$MeCOC_6H_4$	**4q**	88	88
18[d,f]	$Me(CH_2)_3CH_2$	Ph	3-$MeCOC_6H_4$	**4r**	80	91
19	*i*-Pr	4-AcC_6H_4	3-$MeCOC_6H_4$	**4s**	60	88
20[d,f]	*i*-Pr	Ph	3-$MeCOC_6H_4$	**4t**	90	90

[a] A mixture of unsaturated ester (0.5 mmol), $ArB(OH)_2$ (1.5 mmol) and Pd catalyst (1 mol%) in acetone–H_2O (2 mL/0.2 mL) was stirred at 50 °C for 20 h.
[b] Isolated yields of **4**. NMR yields are in parentheses.
[c] The product was converted into ethyl ester for analysis of enantioselectivity.
[d] The reaction was carried out at 35 °C for 20 h.
[e] The reaction was carried out in THF–H_2O (10:1).
[f] A higher amount of Pd catalyst (5 mol%) was used.

low yields due to their slow insertion into Ar–Rh bond, both boronic acids possessing an electron-withdrawing group and those possessing an electron-donating group afforded good yields of products with excellent enantioselectivities in a range of 95–97% ee (entries 1–7). Substrates having alkoxy substituents in the β-aryl ring also resulted in high selectivities (95–97% ee, entries 8–12). It was interesting to note that aliphatic substrates having an alkyl substituent at the β-carbon gave selectivities higher than 90% ee (entries 13–20), which are clearly higher than those in the case of analogous reactions with aliphatic ketones, which resulted in 78–89% ee for *n*-pentyl, isopropyl and cyclohexyl β-substituents at –15 °C.[4c] For these reactions of aliphatic substrates, phenyl esters (entries 16, 18 and 20) resulted in yields and selectivities comparable to those of 4-acetylphenyl ester (entries 13, 14, 15, 17 and 19). Addition of 4-methylphenylboronic acid to 4-acetylphenyl cinnamate afforded *S* product (entry 1). The absolute configuration was determined by reported specific rotation of the corresponding methyl ester $\{[\alpha]_D$ –2.7°, ($CHCl_3$)} after conversion of **4a** into methyl ester $\{[\alpha]_D$ +2.4° ($CHCl_3$)}.[10]

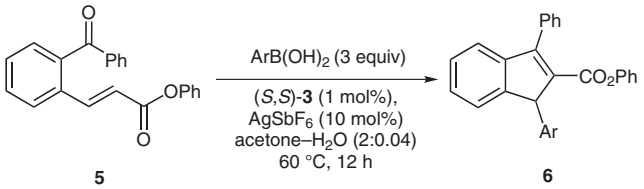
Selective antagonists of endothelin receptors are currently being evaluated as potential therapeutic agents for the treatment of hypertension, congestive heart failure and renal diseases. 1,3-Diarylindan-2-caraboxylic acid derivatives are highly potent antagonists selective for endothelin receptors. We recently reported the synthesis of two antagonists reported by SmithKline Beecham (Scheme 3)[11] and Merck–Banyu[12] by the rhodium-catalyzed 1,4-addition to build the first stereogenic center in a five-membered ring of **10**. Although a rhodium–chiraphos catalyst achieved 89% ee,[4j] this selectivity can be improved by using the corresponding palladium–chiraphos catalyst. Palladium catalysts are also advantageous for accessing an indene intermediate (**9**) in one step from **8** by a tandem 1,4-addition–aldol cyclization protocol recently developed by our group.[4i] β-(2-Benzoylphenyl) α,β-unsaturated ester **5** produced optically active indenes **6** via sequential 1,4-addition–aldol condensation (Table 3). Representative boronic acids afforded good yields of arylindenes with excellent enantioselectivities in the range of 88–98% ee. Indeed, the palladium–(*R*,*R*)-chiraphos catalyst (*R*,*R*)-**3** directly provided **9** in the absence of an acid



Scheme 3 SmithKline Beecham's endothelin receptor antagonists

co-catalyst, which was previously used for accelerating 1,4-addition and final dehydration.[4i] After hydrogenation of the double bond in **9** to yield **10**, the enantiomeric excess was determined by HPLC {88%, 95% ee; $[\alpha]_D$ –94° ($CHCl_3$)}. The total yield of **10** starting from **7** was 38% (Scheme 3). Compound **10** was led to the desired antagonist by epimerization and hydrolysis of the ester group by a known method.[4j,11]

Table 3 Synthesis of Chiral Arylindenes[a]



5 **6**

Entry	Ar of $ArB(OH)_2$	Yield (%)[b]	ee (%)
1	Ph	78	93
2	3-FC_6H_4	80	91
3	3-MeC_6H_4	87	92
4	3-$MeOC_6H_4$	73	95
5	3-HOC_6H_4	81	97
6	3,5-$Me_2C_6H_3$	68	98
7	4-ClC_6H_4	88	88
8	4-MeC_6H_4	61	96
9	4-PhC_6H_4	66	98

[a] A mixture of **5** (0.5 mmol), $ArB(OH)_2$ (1.5 mmol), Pd catalyst (1 mol%) and $AgSbF_6$ (10 mol%) in acetone–H_2O (2 mL/0.04 mL) was stirred at 60 °C for 12 h.
[b] Isolated yields of **6**.

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(13) **General Procedure**: A flask charged with [Pd((*S*,*S*)-chiraphos)$(PhCN)_2$]$(SbF_6)_2$ [(*S*,*S*)-**3**; 1 mol%], $ArB(OH)_2$ (1.5 mmol) and **1** (0.5 mmol) was flushed with nitrogen. Acetone (2 mL) and H_2O (0.2 mL) were then added. After stirring for 20 h at 50 °C, the product was isolated by chromatography on silica gel. The enantiomer excess was determined by Chiral HPLC using Daicel Chiralpak IA, IB or IC.