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Palladium(II)-Catalyzed 1,4-Addition of Arylboronic Acids to β-Arylenones for Enantioselective Synthesis of 4-Aryl-4*H*-chromenes

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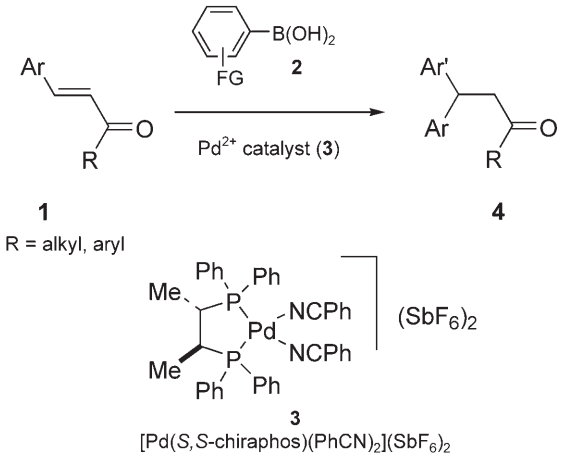
Abstract: The enantioselective 1,4-addition of arylboronic acids to β-arylenones to give β-diaryl ketones was carried out at 0–25 °C in the presence of a dicationic palladium(II) catalyst, [Pd(*S,S*-chiraphos)(PhCN)$_2$](SbF$_6$)$_2$. Addition of a silver salt such as silver tetrafluoroborate [AgBF$_4$] or silver hexafluoroantimonate [AgSbF$_6$] (5–10 mol%) was effective to achieve high enantioselectivities at low temperatures (92–99% *ee*) and to reduce the catalyst loading to 0.05 mol%. The protocol provided a simple access to 4-aryl-4*H*-chromenes. Optically active chromenes were synthesized with up to 99% *ee via* dehydration of the 1,4-adducts between arylboronic acids and β-(2-hydroxyaryl)-α,β-unsaturated ketones.

Keywords: asymmetric catalysts; asymmetric synthesis; boron; chromenes; conjugate addition; palladium

Introduction

β-Diaryl carbonyl compounds are synthetically useful as intermediates in the syntheses of natural products and drug candidates such as a muscarinic receptor antagonist (tolterodine),[1] a selective inhibitor of phosphodiesterase[2] and endothelin receptor antagonists.[3,4] For the preparation of such diarylmethine stereogenic centers at the β-carbon of carbonyl compounds, a flexible approach for introducing two different aryl fragments is the 1,4-addition of arylmetal reagents to α,β-unsaturated carbonyl compounds.[5–8] For example, Cacchi reported the palladium(II)-catalyzed 1,4-addition of (2-hydroxyaryl)mercury chlorides to β-arylenones to give 4-aryl-4*H*-chromenes,[9] which were recently identified as potent apoptosis inducers.[10,11] An enantioselective version for the synthesis of β-diaryl ketones was recently accomplished utilizing rhodium(I) complexes of chiral dienes[12] or chiraphos[4,13] for the 1,4-addition of arylboronic acids.[7] We have also shown that a dicationic palladium(II)-chiraphos complex is efficient for the analogous asymmetric 1,4-addition of [ArBF$_3$]K, ArSiF$_3$ and Ar$_3$Bi to β-arylenones at a temperature lower than 0 °C.[14,15] Although arylboronic acids are better reagents than [ArBF$_3$]K and ArSiF$_3$ because of the availability of a number of functionalized derivatives, a simple extension of the protocol to boronic acids suffered from lower yields than those obtained with [ArBF$_3$]K.[16,17] In this paper, we report the efficiency of silver salts for the palladium(II)-catalyzed 1,4-addition of arylboronic acids (**2**) to β-arylenones (**1**) to give β-diaryl carbonyl compounds (**4**) (Scheme 1). Addition of a silver salt such as AgBF$_4$ or AgSbF$_6$ (5–10 mol%) was found to be effective to achieve high



Scheme 1. Palladium-catalyzed 1,4-addition to β-arylenones.

yields and high enantioselectivities (in the range of 95–99% *ee*) and to reduce the catalyst loading to less than 0.05 mol%. The protocol provides the first catalytic method for enantioselective synthesis of 4-aryl-4*H*-chromenes[18] *via* dehydration of the 1,4-adducts between arylboronic acids and β-(2-hydroxyaryl)-enones.

Results and Discussion

Effects of Arylmetal Reagents and Silver Salts on Turnover Number of Catalysts

In a previous study on the palladium-catalyzed 1,4-addition of arylboron compounds to enones at 0°C, the use of arylboronic acids suffered from low yields due to slow transmetalation to the palladium catalyst.[16] Since it has been shown that silver salts exert a remarkable accelerating effect on transmetalation between organoboronic acids and RPd(II)X in palladium-catalyzed cross-coupling reactions,[19,20] and on the insertion step of Heck coupling,[21,22] the effects of arylmetal reagents (Ar-[*m*]) and $AgBF_4$ on yields, enantioselectivities and turnover number of the catalyst were investigated in the presence of [Pd(*S,S*-chiraphos)$(PhCN)_2$]$(SbF_6)_2$ (**3**) for acyclic enones (entries 1–8) and [Pd(*S,S*-dipamp)$(PhCN)_2$]$(SbF_6)_2$ for 2-cyclohexenone (entries 9–11). The yields, enantioselectivities and turnover numbers of the catalyst (TON) at 20°C are shown in Table 1. Among the three 3-methoxyphenyl derivatives of silicon, bismuth, potassium trifluoroborate and boronic acid, the use of the trifluoroborate salt resulted in the best yield (62%) with 0.05 mol% catalyst loading under conditions optimized for these arylmetal reagents[14] (entries 1–4). The corresponding reaction of boronic acid was not at a practical level (16%, entry 4), but the turnover number exceeded 1,800 when 10 mol% of $AgBF_4$ was added (entries 5 and 6). Although this effect is not significant for *p*-tolylboronic acids, the reactions resulted in a TON of 1,376 in the absence of $AgBF_4$ and of 1,460 in the presence of $AgBF_4$ (entries 7 and 8). The performance of $AgBF_4$ for cyclic enones was also investigated by using 2-cyclohexenone as a substrate (entries 9–11). [Pd(*S,S*-dipamp)$(PhCN)_2$]$(SbF_6)_2$ was used in place of **3** since it resulted in higher enantioselectivities (93–95% *ee*) than did **3** (<10% *ee*) for the 1,4-addition of $[ArBF_3]K$, $ArSiF_3$ and Ar_3Bi (Ar = 3-methoxyphenyl) to 2-cyclohexenone (entries 9–11).[14] In the presence of $AgBF_4$, catalyst loading can be reduced to 0.01 mol% to result in a TON of 9,900 for phenylboronic acid and of 9,800 for 3-methoxyphenylboronic acid (entries 9–11). It was interesting that these high turnover numbers of the catalyst were easily achieved using only a 20% excess of arylboronic acids toward the enones, whereas more than a 50% excess of arylboronic acids was required to achieve a TON of less than 100 with the corresponding rhodium-chiraphos catalyst[7] and a five-fold excess of arylboronic acids to achieve a TON of 13,200 with the Rh-Digm-BINAP catalyst.[23] Such an effect of silver salts can be attributed to a role in the generation of a nitrile-free palladium(II) species such as $[Pd(chiraphos)(solvent)_2]^{2+}$ active for transmetalation *via* ligand exchange between **3** and

Table 1. Effects of electrophiles and $AgBF_4$ on turnover number of the catalyst (TON)[a]

Entry		**1**	Electrophile Ar-[*m*]	Catalyst [mol%]	Additive (equivs.)	Acetone/H_2O [mL]	Time [h]	Yield [%][b]	*ee* [%][c]	TON
	Ar =	R =								
1	Ph	Me	3-$MeOC_6H_4SiF_3$	0.05	ZnF_2 (1.0)	MeOH/H_2O[d]	21	10	-	200
2	Ph	Me	$(3\text{-}MeOC_6H_4)_3Bi$	0.05	$Cu(BF_4)_2$ (0.75)	MeOH/H_2O[d]	21	30	-	600
3	Ph	Me	[3-$MeOC_6H_4BF_3$]K	0.05	none	MeOH/H_2O[d]	21	62	-	1,240
4	Ph	Me	3-$MeOC_6H_4B(OH)_2$	0.05	none	acetone/H_2O[d]	21	16	94	320
5	Ph	Me	3-$MeOC_6H_4B(OH)_2$	0.05	$AgBF_4$ (0.1)	acetone/H_2O[d]	21	90	94	1,806
6	Ph	Me	3-$MeOC_6H_4B(OH)_2$	0.01	$AgBF_4$ (0.1)	acetone/H_2O[d]	96	55	94	5,500
7	Ph	Ph	4-$MeC_6H_4B(OH)_2$	0.05	none	acetone/H_2O[e]	21	69	95	1,376
8	Ph	Ph	4-$MeC_6H_4B(OH)_2$	0.05	$AgBF_4$ (0.1)	acetone/H_2O[e]	21	73	95	1,460
9[f]	2-cyclohexenone		$C_6H_5B(OH)_2$	0.01	none	acetone/H_2O[e]	48	66	89	6,620
10[f]	2-cyclohexenone		$C_6H_5B(OH)_2$	0.01	$AgBF_4$ (0.05)	acetone/H_2O[e]	48	99	89	9,900
11[f]	2-cyclohexenone		3-$MeOC_6H_4B(OH)_2$	0.01	$AgBF_4$ (0.05)	acetone/H_2O[e]	48	98	91	9,804

[a] A mixture of enone (**1**, 5 mmol) and Ar-[*m*] (6 mmol) in aqueous solvent was stirred at 20°C in the presence of [Pd(*S,S*-chiraphos)$(PhCN)_2$]$(SbF_6)_2$ (**3**) and an additive (if used), unless otherwise noted.
[b] Isolated yields by chromatography.
[c] Enantiomer excess determined by HPLC on chiral stationary columns.
[d] In MeOH/H_2O (10 mL/1 mL) or acetone/H_2O (10 mL/1 mL).
[e] In acetone/H_2O (2.5 mL/0.25 mL).
[f] [Pd(*S,S*-dipamp)$(PhCN)_2$]$(SbF_6)_2$ was used in place of **3**.

AgX,[14c] recycle of the catalyst *via* oxidation of palladium(0) species generated by double transmetalation and reductive elimination of two aryl groups of the boronic acids,[14c,24] or activation of enones for insertion into the C–Pd bond by chelation with the double bond or carbonyl group of the enones,[25] although no mechanistic information is currently available.

Asymmetric 1,4-Addition of Arylboronic acids to β-Aryl Ketones

The results of the asymmetric 1,4-addition of arylboronic acids to the representative β-arylenones in the presence of **3** (1 mol%) and a silver salt (if used, 5–20 mol% of $AgBF_4$ or $AgSbF_6$) are shown in Table 2. Although most reactions were completed at 0 °C in the presence of 5–10 mol% of $AgBF_4$ or $AgSbF_6$, two arylboronic acids, the 3-chloro (entry 1) and the 4-acetyl derivatives (entry 6), were used at 25 °C since the reactions were very slow at 0 °C even in the presence of a silver salt. Such an effect of the substituents might be due to the coordination ability of these substituents to the cationic palladium(II) catalyst. Indeed, a thiomethoxy group in the boronic acid (entry 5) and a nitro group in the substrate (entry 13) strongly retarded the reaction. Most of the reactions were completed within 21 h at room temperature with enantioselectivities in a range of 92–99% *ee* which are comparable to those previously achieved by $[ArBF_3]K$ at −5 to +5 °C and 6–12% higher than those provided by arylboronic acids and a rhodium(I)-chiraphos catalyst at 20 °C (entries 2, 4 and 10). The absolute configurations of most products are not known, but the formation of an *S*-product from the (*S,S*)-chiraphos complex was established by the specific rotation reported for (*S*)-3-(3-methoxyphenyl)-1,3-diphenylpropan-1-one $\{[\alpha]_D$: +7.1° (*c* 0.71, $CHCl_3)\}$[14] (entry 10). Coordination of an enone to the $[Rh(Ph)(S,S\text{-chiraphos})]^+$ or $[Pd(Ph)(S,S\text{-chiraphos})]^+$ intermediate and the conformation of the chiraphos ligand at this stereodetermining insertion stage were calculated by DFT computations.[14] In both the rhodium(I) and palladium(II) intermediates, a phenyl group on the metal and one of the axial phenyl groups on the phosphine atom constitute a planar free space for coordination of an enone to the metal center, and an up-right quadrant is blocked by one of the equatorial phenyl groups of the (*S,S*)-chiraphos ligand, suggestive of *si*-coordination of enones giving *S* products and high performance of chiraphos in recognition of planar enones such as β-aryl ketones.

Synthesis of 4-Aryl-4*H*-chromenes

In a previous study on the synthesis of 4-aryl-4*H*-chromenes, Cacchi and co-workers used a combina-

Table 2. Asymmetric addition of arylboronic acids (**2**) to β-aryl enones (**1**).[a]

Entry		**1**	**2**	Additive (equivs.)	Product	Temp. [°C]	Yield [%][b]	*ee* [%][c]	Ref.[4] *ee* [%][d]
	Ar =	R =	FG =						
1	Ph	Me	3-Cl	none	**4a**	25	90	93	
2	Ph	Me	3-MeO	$AgBF_4$ (0.1)	**4b**	0	96	95	83
3	Ph	Me	4-MeO	$AgBF_4$ (0.1)	**4c**	0	75	94	
4	Ph	Me	3,4-O_2CH_2[e,f]	none	**4d**	0	77	95	89
5	Ph	Me	4-MeS	$AgBF_4$ (0.1)	**4e**	25	<10	-	
6	Ph	Me	4-COMe	none	**4f**	25	95	93	
7	Ph	*n*-C_4H_9	3-MeO	$AgBF_4$ (0.1)	**4g**	0	66	99	
8	Ph	2-C_3H_7	3-MeO	$AgBF_4$ (0.1)	**4h**	0	80	95	
9	Ph	*cyclo*-C_6H_{11}	3-MeO	$AgSbF_6$ (0.05)	**4i**	0	93	95	
10	Ph	Ph	3-MeO	$AgBF_4$ (0.1)	**4j**	0	86	97 (*S*)	86 (*S*)
11	Ph	Ph	4-Me	none	**4k**	0	91	95	
12	Ph	4-$MeOC_6H_4$	3-MeO	$AgSbF_6$ (0.1)	**4l**	0	73	95	
13	Ph	4-$NO_2C_6H_4$	3-MeO	$AgSbF_6$ (0.2)	**4m**	0	44	92	
14	4-$MeOC_6H_4$	Ph	3-MeO	$AgBF_4$ (0.1)	**4n**	0	75	99	
15	2-naphthyl	Me	3-MeO	$AgBF_4$ (0.05)	**4o**	0	99	96	

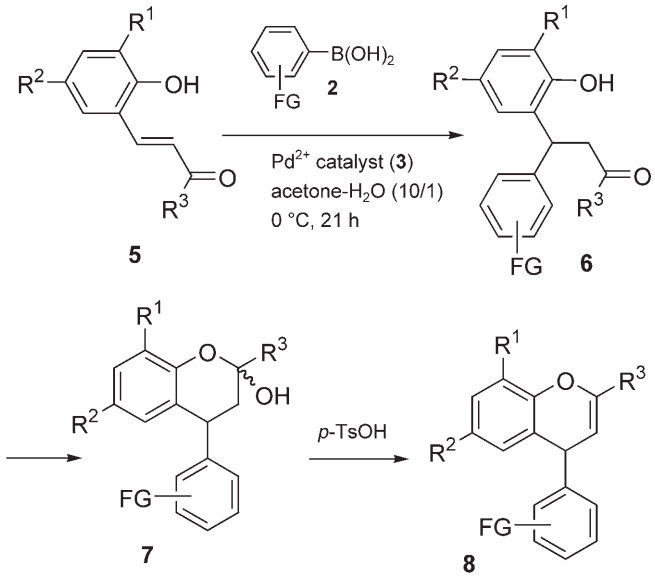
[a] A mixture of enone (**1**, 5 mmol), $ArB(OH)_2$ (6 mmol) in acetone-H_2O (10 mL/1 mL) was stirred for 21 h in the presence of a palladium catalyst (**3**, 1 mol%) and an additive (if used).
[b] Isolated yields by chromatography.
[c] Enantiomer excess determined by HPLC on a chiral stationary column.
[d] A mixture of **1** (1 mmol), $ArB(OH)_2$ (1.5 mmol) and base (1 mmol) in dioxane-H_2O (6/1) was stirred at 20 °C for 6 h in the presence of $[Rh(nbd)_2]BF_4$ (3 mol%) and (*S,S*)-chiraphos (3.3 mol%).
[e] A methylenedioxy group.
[f] The boronic acid (2 equivs.) was used.

tion of (2-hydroxyaryl)mercury chlorides and β-arylenones due to the easy availability of these nucleophiles *via* mercuration of phenols.[9] However, the presence of such an *ortho* functionality in the arylboronic acids significantly slows down the reaction rates and reduces the enantioselectivities for the present asymmetric 1,4-addition. Thus, β-(2-hydroxyaryl)-enones (**5**) were chosen as substrates for arylboronic acids (**2**). The reaction provided chromanols (**7**) as a mixture of *cis* and *trans* isomers, which then transformed to single isomers, chromenes (**8**), according to the procedures reported by Cacchi (Scheme 2).

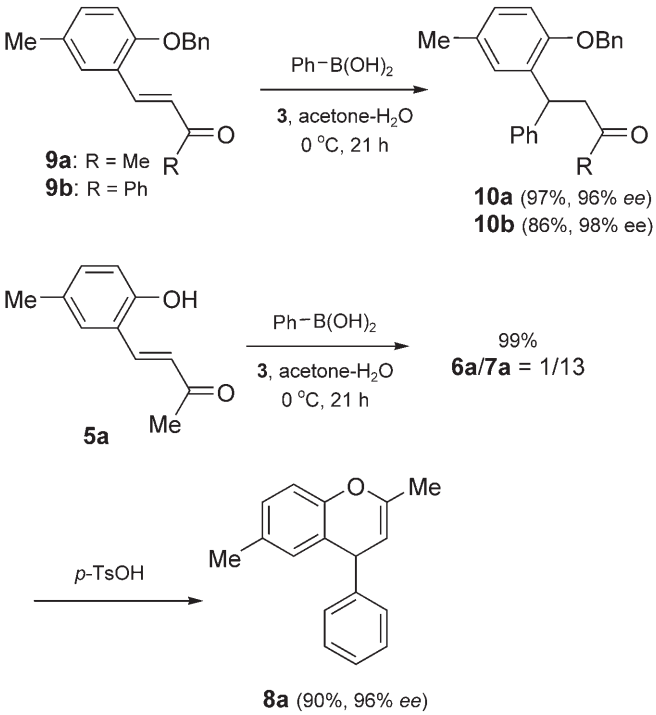
The effect of an *ortho* functionality on yields and enantioselectivities is shown in Scheme 3. Additions of phenylboronic acid to the 2-benzyloxy derivatives **9a** and **9b** smoothly took place at 0 °C in the presence of 1 mol% of a palladium(II)-chiraphos catalyst (**3**) with 96% *ee* and 98% *ee*, respectively. On the other hand, unprotected **5a** provided a 1:13 mixture of **6a** and chromanol (**7a**), which was then converted into the single 4-phenyl-4*H*-chromene (**8a**) *via* acid-catalyzed dehydration. The enantioselectivity of **10a** (96% *ee*) was the same as that of **8a** (96% *ee*). Thus, the presence of a free hydroxy group did not have an affect on the selectivity by its chelation with the cationic palladium metal center.

The mode of face selection was the same as that previously reported for the 1,4-addition of arylboronic acids to enones catalyzed by **3**.[14] Addition of phenylboronic acid to enone **5b** provided a 2:1 mixture of **6g** and **7g** (Scheme 4), which was then subjected to Baeyer–Villiger oxidation to give phenylchromanone (**11**) with 93% yield and 93% *ee*. Recrystalization from hexane/ether afforded pure **11** {99.6% *ee*, $[\alpha]_D$: −41.9°} in 70% yield (Scheme 4). Thus, the formation of the *R*-product from the (*S,S*)-chiraphos complex was well established by the specific rotation reported for (*R*)-4-phenylchroman-2-one {$[\alpha]_D$: −45.1° (*c* 0.98, $CHCl_3$)}.[26]

The 1,4-addition of the representative arylboronic acids to β-(2-hydroxyaryl)enones (**5**) catalyzed by the palladium(II)-(*S,S*)-chiraphos complex (**3**) is shown in Table 3. Phenyl- and 4-tolylboronic acids were smoothly added to enones at 0 °C without any difficulty (entries 1, 5 and 7–9), but reactions of arylboronic acids possessing oxygen functionalities such as alkoxy, methylenedioxy and acetyl groups were carried out in the presence of 10 mol% of $AgBF_4$ since these reactions were very slow in the absence of a silver salt (entries 2–4 and 6). The chromanols (**7**) thus obtained as a mixture of **6** and **7** were converted to 4-aryl-4*H*-chromenes (**8**) in high yields by acid-catalyzed dehydration. The enantioselectivities were in a range of 95–99% *ee*. Among them, phenyl ketone (**5b**) resulted in a higher selectivity (99% *ee*) than did the methyl ketones (**5a** and **5c**, 95–98% *ee*).



Scheme 2. Synthesis of optically active 2-methyl-4-aryl-4*H*-chromenes **8** (for substituents R^1, R^2, R^3 and FG, see Table 3).



Scheme 3. 1,4-Addition to protected and unprotected β-(2-hydroxyaryl)enones.

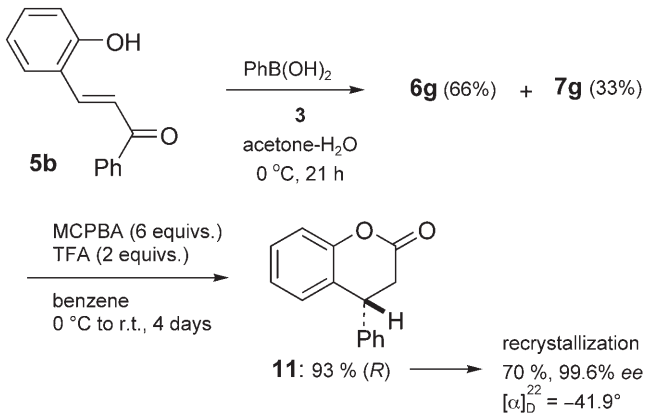
Conclusions

Our strategy based on an asymmetric 1,4-addition of arylboronic acids to enones represents a novel method for the enantiocontrolled installation of a stereogenic center in 4-arylchromanols and 4-aryl-4*H*-chromenes. The successful incorporation of an aryl

Table 3. Synthesis of 4-aryl-*4H*-chromenes *via* asymmetrical 1,4-addition of arylboronic acids.[a]

Entry	**5**				$ArB(OH)_2$ **2**	Additive [mol%]	**6** and **7**		**8**		$[\alpha]_D$
	R^1	R^2	R^3		FG =		Yield [%] of **6**/**7**[b]		Yield [%] (*ee* %[b,c]		
1	H	Me	Me	**5a**	H	none	99 (1/13)	**6a**/**7a**	90 (96)	**8a**	184 (*c* 0.25)
2	H	Me	Me	**5a**	4-OMe	$AgBF_4$ (10)	96 (1/13)	**6b**/**7b**	90 (97)	**8b**	145 (*c* 0.70)
3	H	Me	Me	**5a**	3-MeO	$AgBF_4$ (10)	96 (1/13)	**6c**/**7c**	94 (97)	**8c**	182 (*c* 0.67)
4[d]	H	Me	Me	**5a**	3,4-O_2CH_2[e]	$AgBF_4$ (10)	99 (1/16)	**6d**/**7d**	89 (98)	**8d**	185 (*c* 0.72)
5	H	Me	Me	**5a**	4-Me	none	99 (1/13)	**6e**/**7e**	94 (97)	**8e**	120 (c 0.74)
6	H	Me	Me	**5a**	4-COMe	$AgBF_4$ (10)	99 (1/16)	**6f**/**7f**	90 (96)	**8f**	263 (*c* 0.72)
7	H	H	Ph	**5b**	H	none	99 (2/1)	**6g**/**7g**	92 (99)	**8g**	31 (*c* 0.62)
8	H	OMe	Me	**5c**	H	none	99 (1/16)	**6h**/**7h**	94 (95)	**8h**	172 (*c* 0.53)
9	*t*-Bu	*t*-Bu	Me	**5d**	H	none	94 (1/99)	**6i**/**7i**	90 (nd)[f]	**8i**	156 (*c* 0.76)

[a] A mixture of enone (1 mmol), arylboronic acid (1.2 mmol), palladium catalyst **3** (1 mol%) and additive (if used) in acetone-H_2O (10/1, 2.2 mL) was stirred for 21 h at 0 °C.
[b] Isolated yields by chromatography.
[c] Enantiomer excess determined by HPLC on a chiral stationary column.
[d] $ArB(OH)_2$ (2 equivs.).
[e] A methylenedioxy group.
[f] An inseparable mixture by chiral columns.



Scheme 4. Conversion to 4-phenylchroman-2-one.

substituent at C-4 would make the method suitable for generating a library of optically pure 4-arylchromene analogues.

Experimental Section

General Remarks

All experiments were carried out under a nitrogen atmosphere. HPLC analysis was directly performed with a chiral stationary phase column, Chiralcel OD-H, AD, AD-H, OJ-H, and OB-H purchased from Dicel Co., Ltd.

General Procedure for Asymmetric 1,4-Addition

$ArB(OH)_2$ (1.2 mmol), acetone (2 mL), $AgBF_4$ (0.1 mmol, if used), enone (1 mmol) and water (0.2 mL) were added to a flask under nitrogen. [Pd(*S,S*-chiraphos)$(PhCN)_2$]$(SbF_6)_2$[14c] (0.001 mmol) was then added at 0 °C. After being stirred for 21 h at 0 °C or 25 °C, chromatography on silica gel gave the corresponding 1,4-adducts **4**. The enantiomer excess was determined by chiral HPLC analysis.

General Procedure for Synthesis of Chromenes 8

A chromanol (**7**, 0.5 mmol), 4 Å molecular sieves (1 g), *p*-toluenesulfonic acid (0.05 mmol) and toluene (4 mL) were added to a flask under nitrogen. The mixture was then heated to reflux. After being stirred for 3 h, chromatography on silica gel gave a corresponding chromene **8**.

Characterization

Compounds **4b**,[14] **4c**,[27] **4g**,[14c] **4j**,[14c] **4k**,[27] and **4o**[14c] were previously known. Characterization data for the new compounds **4a**, **4d**, **4f**, **4h**, **4i**, **4l**, **4m**, **4n**, **7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g** (as mixture with **6g**), **7h**, **7i**, **8a**, **8b**, **8c**, **8d**, **8e**, **8f**, **8g**, **8h**, **8i**, **10a** and **10b** are given in the Supporting Information.

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