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Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Coumarins: Asymmetric Synthesis of (*R*)-Tolterodine

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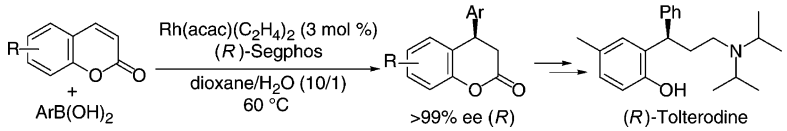
ABSTRACT



Rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to coumarins proceeded with high enantioselectivity in the presence of a rhodium catalyst (3 mol %) generated from Rh(acac)$(C_2H_4)_2$ and (*R*)-Segphos to give the corresponding (*R*)-4-arylchroman-2-ones in over 99% ee. This asymmetric reaction was applied to the synthesis of (*R*)-tolterodine.

Some of the enantiomerically enriched compounds possessing a chiral diarylmethane unit are known to be biologically active, and their preparation by asymmetric synthesis has recently attracted growing attention.[1,2] One of the straightforward methods of constructing a stereogenic carbon center connected with two different aryl groups and one alkyl group is asymmetric conjugate addition of an aryl nucleophile to electron-deficient olefins substituted with another aryl group at the β-position. Although the rhodium-catalyzed asymmetric conjugate addition[3] has been successfully applied to a variety of electron-deficient olefins, including α,β-unsaturated ketones,[4,5] esters,[6] amides,[7] alkenylphosphonates,[8] nitroalkenes,[9] and alkenyl sulfones,[10] its application to the β-aryl-substituted substrates remains to be studied.[11] Herein we report that coumarin derivatives are suitable substrates for the rhodium-catalyzed asymmetric conjugate addition to give 4-arylchroman-2-ones, in which the stereogenic carbon center at the 4 position is substituted with two aryl groups,

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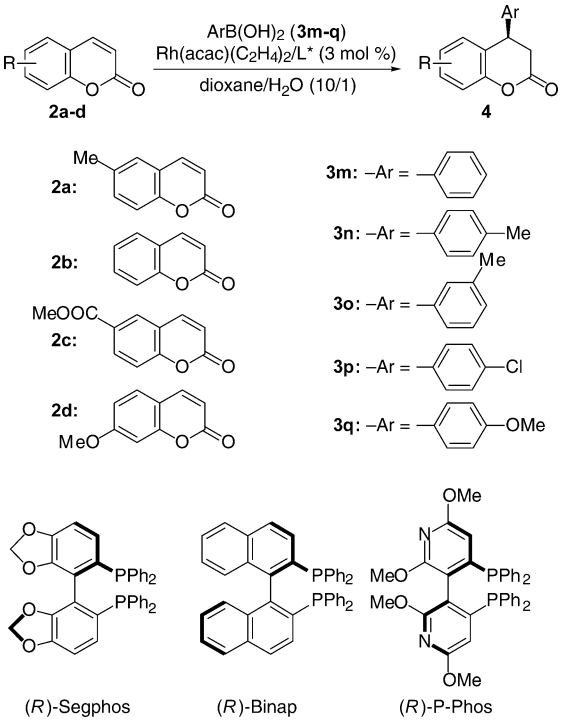
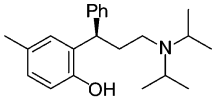
Scheme 1. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids **3** to Coumarins **2**

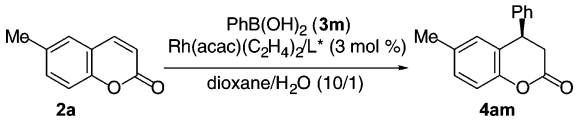


with high (>99%) enantioselectivity (Scheme 1). We also report that (*R*)-tolterodine (**1**),[12] an important urological drug, is readily obtained from one of the asymmetric conjugate addition products. To the best of our knowledge, there has been only one example in which coumarin was examined for rhodium-catalyzed asymmetric addition.[13]



The results obtained for the reaction of 6-methylcoumarin (**2a**) with phenylboronic acid (**3m**) under several reaction conditions are summarized in Table 1. It was found that coumarin **2a** is less reactive toward the rhodium-catalyzed 1,4-addition than standard α,β-unsaturated ketones such as 2-cyclohexenone.[3−5] As it has been often observed in the reaction of less reactive substrates,[3] hydrolysis of phenylboronic acid giving benzene was a main side reaction, and hence a large excess (5 or 10 equiv with respect to **2a**) of the boronic acid was used to obtain high yields of the 1,4-addition product. Of three axially chiral biarylbisphosphine ligands, (*R*)-Binap,[14] (*R*)-P-Phos,[15] and (*R*)-Segphos,[16] which have been successfully used for rhodium-catalyzed asymmetric addition to α,β-unsaturated ketones and related compounds, (*R*)-Segphos was the most enantioselective for the coumarin substrate **2a**. The best result was obtained at the reaction temperature of 60 °C (entry 3). Thus, the reaction of coumarin **2a** with phenylboronic acid (**3m**) in the presence of 3 mol % of a rhodium catalyst generated from Rh(acac)-$(C_2H_4)_2$ and (*R*)-Segphos in dioxane/H_2O (10/1) at 60 °C for 8 h gave 88% isolated yield of 6-methyl-4-phenylchroman-2-one (**4am**), whose enantiomeric purity was determined to be over 99% by HPLC analysis with a chiral stationary phase column. Its absolute configuration was assigned to be *R* by correlation with (*R*)-tolterodine (vide infra). At a higher reaction temperature (100 or 80 °C), the yield of **4am** was lower (entries 1 and 2) mainly because the hydrolysis of the

Table 1. Rhodium-Catalyzed Asymmetric Addition of Phenylboronic Acid (**3m**) to 6-Methylcoumarin (**2a**)[a]



entry	ligand	temp (°C)	time (h)	conversion (%)[b]	yield (%)[c]	% ee[d] (config)[e]
1	(*R*)-Segphos	100	8	70	60	99.1 (*R*)
2	(*R*)-Segphos	80	8	82	78	99.1 (*R*)
3	(*R*)-Segphos	60	8	93	88	99.6 (*R*)
4	(*R*)-Segphos	50	12	86	78	99.4 (*R*)
5	(*R*)-Binap	60	8	84	75	96.4 (*R*)
6	(*R*)-P-Phos	60	8	97	91	96.7 (*R*)
7	(*R*)-P-Phos	50	12	99	93	97.1 (*R*)
8[f]	(*R*)-Segphos	60	10	74	64	99.6 (*R*)

[a] Reaction was carried out in dioxane/H_2O (10/1, 1.1 mL) with 0.30 mmol of coumarin **2a** and 3.0 mmol of boronic acid **3m** in the presence of 3 mol % of a rhodium catalyst generated from Rh(acac)$(C_2H_4)_2$ (9.0 μmol) and a bisphosphine ligand (9.9 μmol). [b] Conversion of **2a** was determined by ^{1}H NMR analysis of the reaction mixture. [c] Isolated yield of **4am** by chromatography on silica gel (hexane/ethyl acetate = 5/1). [d] Determined by HPLC on a Chiralcel OD-H column with hexane/2-propanol (95/5). [e] Absolute configuration was determined by conversion into known (*R*)-tolterodine L-tartrate (see text). [f] Amount of phenylboronic acid (**3m**) was 1.5 mmol.

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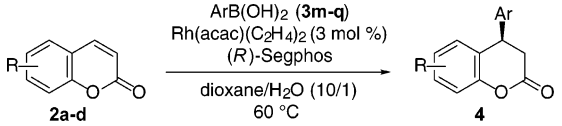
Table 2. Asymmetric Addition of Arylboronic Acids **3** to Coumarins **2** Catalyzed by Rh/(*R*)-Segphos[a]



entry	coumarin **2**	$ArB(OH)_2$ **3** (Ar)	time (h)	yield (%)[b]	% ee[c] (config)[d]
1	**2a**	**3m** (Ph)	8	88 **4am**	99.6 (*R*)
2	**2a**	**3n** (4-MeC_6H_4)	10	91 **4an**	99.8 (*R*)
3	**2a**	**3o** (3-MeC_6H_4)	8	93 **4ao**	99.7 (*R*)
4	**2a**	**3p** (4-ClC_6H_4)	10	45 **4ap**	99.1 (*R*)
5	**2a**	**3q** (4-$MeOC_6H_4$)	10	75 **4aq**	99.5[e] (*R*)
6	**2b**	**3m** (Ph)	12	86 **4bm**	99.4 (*R*)
7	**2b**	**3n** (4-MeC_6H_4)	12	89 **4bn**	99.7 (*R*)
8	**2b**	**3o** (3-MeC_6H_4)	10	90 **4bo**	99.7 (*R*)
9	**2c**	**3m** (Ph)	8	94 **4cm**	99.3[f] (*R*)
10	**2d**	**3m** (Ph)	12	28 **4dm**	nd

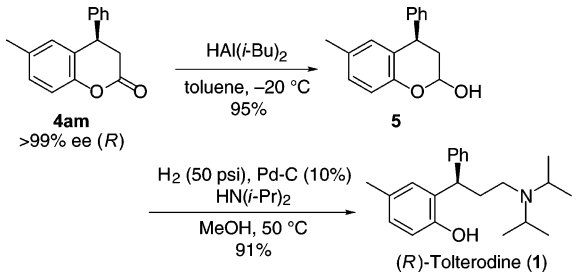
[a] Reaction was carried out at 60 °C in dioxane/H_2O (10/1, 1.1 mL) with 0.30 mmol of coumarin **2** and 3.0 mmol of boronic acid **3** in the presence of 3 mol % of a rhodium catalyst generated from $Rh(acac)(C_2H_4)_2$ (9.0 μmol) and (*R*)-Segphos (9.9 μmol). [b] Isolated yield of **4** by silica gel chromatography. [c] Determined by HPLC on a Chiralcel OD-H column with hexane/2-propanol (95/5) unless otherwise noted. [d] Absolute configuration was determined by analogy with (*R*)-**4am**. [e] Determined by HPLC on a Chiralpak AD-H column with hexane/2-propanol (90/10). [f] Chiralcel OD-H (hexane/2-propanol = 2/1).

phenylboronic acid is faster. At a lower temperature (50 °C), the conversion was lower even after a prolonged reaction time (entry 4). It should be noted that the enantioselectivity was kept high (>99% ee) with (*R*)-Segphos as a chiral ligand irrespective of the reaction temperature. (*R*)-Binap and (*R*)-P-Phos ligands were slightly less enantioselective than (*R*)-Segphos, although the enantioselectivity was still higher than 96% (entries 5−7). It is interesting that the rhodium catalyst coordinated with (*R*)-P-Phos ligand was catalytically more active than the others, with the highest yield (93%) being observed at 50 °C with (*R*)-P-Phos (entry 7).

Table 2 illustrates the scope and limitations of the present asymmetric addition to coumarin derivatives. Under the optimized conditions, 6-methylcoumarin (**2a**) underwent asymmetric addition of methyl-substituted phenylboronic acids **3n** and **3o** to give high (>90%) yields of the corresponding 1,4-addition products **4an** and **4ao** with almost perfect (>99%) enantioselectivity (entries 2 and 3). The enantioselectivity was also high for the addition of *p*-chlorophenylboronic acid (**3p**) and *p*-methoxyphenylboronic acid (**3q**), although the yields are not satisfactorily high (entries 4 and 5). Unsubstituted coumarin (**2b**) is an equally good substrate, giving high yields of the asymmetric arylation products in the reaction with phenyl- and tolylboronic acids (entries 6−8). The addition of phenylboronic acid (**3m**) to 6-methoxycarbonylcoumarin (**2c**) also proceeded smoothly to give the adduct **4cm** in a high yield (entry 9). On the other hand, the addition to 7-methoxycoumarin (**2d**) was very slow (entry 10), demonstrating that the electron-donating methoxy group impairs the reactivity of the coumarin moiety. It should be emphasized that the enantioselectivity in the asymmetric 1,4-addition to the coumarin derivatives with Segphos as a ligand is always over 99%.

The asymmetric 1,4-addition product, (*R*)-6-methyl-4-phenylchroman-2-one (**4am**), which was obtained from 6-methylcoumarin (**2a**) and phenylboronic acid (**3m**) in 99.6% ee (entry 3 in Table 1), was readily converted into (*R*)-tolterodine (**1**) according to the procedures reported for racemic **4am**[17] (Scheme 2). Thus, reduction of (*R*)-**4am** with

Scheme 2. Asymmetric Synthesis of (*R*)-Tolterodine (**1**)



diisobutylaluminum hydride at −20 °C gave a 95% yield of lactol **5**, which was then subjected to palladium-catalyzed hydrogenation in the presence of diisopropylamine to produce a 91% yield of (*R*)-tolterodine (**1**),[12,18] whose absolute configuration was confirmed by comparison of the optical rotation of its tartrate salt with that reported.[19] The present synthetic route, which consists of catalytic asymmetric arylation of coumarins and a straightforward derivatization, provides a new and efficient method of preparing enantiomerically enriched chiral diarylmethanes represented by (*R*)-tolterodine (**1**). In the literature, (*R*)-tolterodine was obtained by optical resolution of the racemate,[17] diastereoselective additions using chiral auxiliaries,[20] or asymmetric hydrogenation.[19]

A linear α,β-unsaturated ester **6**, which is substituted with a 2-methoxy-5-methylphenyl group at the β position, was also examined for rhodium-catalyzed asymmetric addition of phenylboronic acid, because the addition product **7** would be another good precursor to tolterodine if the enantioselectivity is high (Scheme 3). The asymmetric phenylation resulted in low enantioselectivity with either Segphos or Binap ligand to give **7** of around 50% ee. These results indicate that the coumarin derivatives **2** are particularly suitable for the rhodium-catalyzed asymmetric addition in terms of enantioselectivity.

In summary, we have developed a rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to coumarin derivatives that proceeds in high yields with excellent

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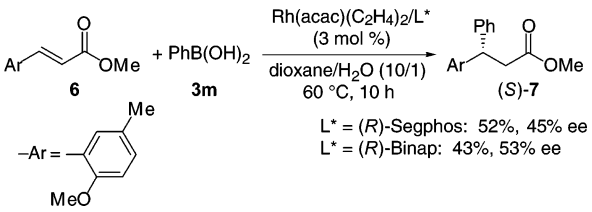
Scheme 3. Rhodium-Catalyzed Asymmetric Addition of Phenylboronic Acid (**3m**) to Cinnamate Ester **6**



(>99%) enantioselectivity. This asymmetric reaction provides an efficient route to enantiomerically enriched compounds where the stereogenic center is bonded to two different aryl groups, and its highlight is the asymmetric synthesis of (*R*)-tolterodine.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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