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Palladium-catalyzed stereospecific cross-coupling of enantioenriched allylic alcohols with boronic acids†

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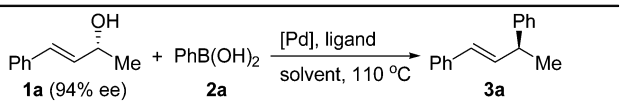
In the presence of 2.5 mol% $Pd_2(dba)_3$–TMEDA (1 : 4), a range of enantioenriched allylic alcohols smoothly coupled with boronic acids in a highly regioselective fashion with inversion of configuration to afford structurally diverse alkenes in good yields with perfect retention of ee.

Boronic acids are widely employed in cross-coupling reactions due to their ready accessibility, stability, and reactivity.[1] Particularly, the cross-coupling of boronic acids with allylic electrophiles constitutes a powerful approach for the formation of carbon–carbon bonds by introducing the allyl moiety to target compounds,[2] which permit a variety of chemical transformations such as oxidation, reduction, and addition.[3] Although allylic halides[4] and alcohol derivatives, such as allylic esters,[5] carbonates,[6] and phosphates,[7] have been identified as useful allylic electrophiles with varying reactivity and selectivity in their cross-coupling reactions with boronic acids, the use of allylic alcohols as electrophiles is more attractive with respect to atom-economy because the leaving hydroxy group has a mass of only 17 amu,[8,9] which is much smaller than common leaving groups. Moreover, the synthetic routes for allylic alcohols, including enantioenriched ones, are in general shorter than those for the corresponding halides and alcohol derivatives.[10]

Although the cross-coupling of enantioenriched allylic alcohols with boronic acids constitutes a promising atom-economic method for the synthesis of optically active alkenes, it has been reported to afford racemic products.[8e] Clearly, the poor leaving ability and compatibility of the hydroxy group impose formidable challenges to the direct substitution of enantioenriched allylic alcohols with retention of ee. To our knowledge, effective retention of ee has not yet been disclosed for the direct substitution of enantioenriched allylic alcohols with carbon nucleophiles.[11,12] Prompted by our recent exploration of substitution reactions with allylic amines,[13] we envisioned that effective retention of ee could be realized in the cross-coupling of enantioenriched allylic alcohols with boronic acids by screening palladium catalysts and reaction conditions. Here we report, for the first time, an efficient stereospecific cross-coupling reaction of enantioenriched allylic alcohols with boronic acids, which affords a range of optically active alkenes with excellent ee.[14]

A number of palladium sources and ligands were examined for the cross-coupling of enantioenriched allylic alcohol **1a** (94% ee) with boronic acid **2a** in dioxane at 110 °C (Table 1, entries 1–10). Both the yield and the stereochemistry (inverted) were significantly affected by the nature of the ligand and the palladium source, and

Table 1 Optimization of reaction conditions[a]



Entry	[Pd]	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	$Pd_2(dba)_3$	None	Dioxane	0	—
2	$Pd_2(dba)_3$	TMEDA	Dioxane	78	91
3	$Pd_2(dba)_3$	2,2′-Bipyridine	Dioxane	29	90
4	$Pd_2(dba)_3$	(±)-BINOL	Dioxane	0	—
5	$Pd_2(dba)_3$	(±)-BINAP	Dioxane	73	32
6	$Pd_2(dba)_3$	dppb	Dioxane	8	11
7	$Pd(PPh_3)_4$	TMEDA	Dioxane	32	0
8	$Pd(OAc)_2$	TMEDA	Dioxane	Trace	—
9	$PdCl_2$	TMEDA	Dioxane	Trace	—
10	$[Pd(allyl)Cl]_2$	TMEDA	Dioxane	Trace	—
11	$Pd_2(dba)_3$	TMEDA	Toluene	12	66
12	$Pd_2(dba)_3$	TMEDA	MeCN	10	11
13	$Pd_2(dba)_3$	TMEDA	DMF	Trace	—
14	$Pd_2(dba)_3$	TMEDA	DMSO	Trace	—
15	$Pd_2(dba)_3$	TMEDA	*t*-AmOH	58	93
16	$Pd_2(dba)_3$	TMEDA	Dioxane–*t*-AmOH (1 : 1)	84	94

[a] Reaction conditions: alcohol **1a** (0.30 mmol), boronic acid **2a** (0.36 mmol), [Pd] (2.5 mol%; for entries 7–9, 5 mol%), ligand (10 mol%), solvent (2.0 mL), 110 °C, 15 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

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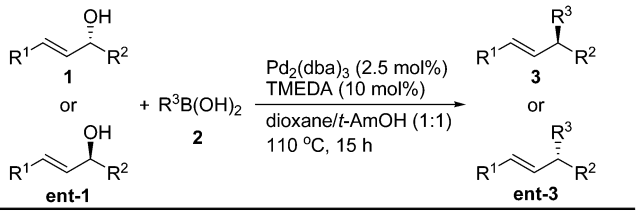
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra and HPLC traces. See DOI: 10.1039/c3cc45772a

gratifyingly, the use of $Pd_2(dba)_3$–TMEDA (1 : 4) as the catalyst system afforded alkene **3a** in 78% yield with 91% ee (Table 1, entry 2). Moreover, the reaction proceeded with exclusive α-selectivity, and no *E*/*Z* isomerization was observed for the allyl carbon–carbon double bond. To improve the efficiency of chirality transfer, we screened a number of common solvents and found that replacing dioxane with a 1 : 1 mixture of dioxane and tertiary amyl alcohol led to complete inversion of the chiral center of allylic alcohol **1a** (Table 1, entry 16).

In the presence of 2.5 mol% $Pd_2(dba)_3$–TMEDA (1 : 4), a range of unsymmetrical enantioenriched allylic alcohols (α-substituent ≠ γ-substituent) smoothly coupled with boronic acid **2a** in an α-selective fashion with inversion of configuration to afford the corresponding alkenes in good yields with perfect retention of ee and alkene geometry (Table 2, entries 1–11). The α- and γ-positions of the allylic alcohols could bear various substituents such as aryl, heteroaryl, alkyl, ester, and amide groups, but the reaction was not applicable to α-chiral allylic alcohols with β-substituents due to poor reactivity. When the γ-substituent was an alkyl group (*e.g.*, a cyclohexyl group), a considerable portion of the allylic alcohol coupled with boronic acid **2a** in a γ-selective fashion (Table 2, entry 9),[15] which could be attributed to the generation of an unsymmetrical π-allylpalladium intermediate from the palladium catalyst and the allylic alcohol (see below). The reaction worked well with a variety of aryl- and alkenylboronic acids under the standard conditions and a range of optically active alkenes were obtained in good yields with exclusive *E* selectivity and excellent ee (Table 2, entries 12–23). Nevertheless, no desired product was obtained from the corresponding reaction with alkylboronic acids such as *n*-butyl-, cyclohexyl-, and benzylboronic acids. As demonstrated by the results summarized in Table 2, the reaction tolerated a variety of functional groups such as heteroaryl, vinyl, alkoxy, chloro, fluoro, amino, ester, and amide groups.

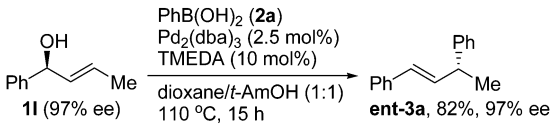
Table 2 Stereospecific cross-coupling of enantioenriched allylic alcohols with boronic acids[a]



Entry	1 (ent-1), R^1, R^2	2, R^3	3 or ent-3	Yield[b] (%)	ee[c] (%) 1	ee[c] (%) 3 or ent-3
1	**1a**, Ph, Me	**2a**, Ph	**3a**	83	99	99
2	**1b**, Ph, Et	**2a**, Ph	**3b**	73	97	97
3[d]	**1c**, Ph, $CHMe_2$	**2a**, Ph	**3c**	60	91	91
4	**1d**, 4-$MeOC_6H_4$, Me	**2a**, Ph	**3d**	77	94	94
5	**1e**, 4-ClC_6H_4, Me	**2a**, Ph	**3e**	76	96	96
6	**1f**, 2-$MeOC_6H_4$, Me	**2a**, Ph	**3f**	76	96	96
7	**1g**, 3-pyridinyl, Me	**2a**, Ph	**3g**	87	93	92
8[e]	**1h**, 2-furyl, Me	**2a**, Ph	**3h**	81	95	95
9[f]	**1i**, cyclohexyl, Me	**2a**, Ph	**3i**	70	97	97
10	**ent-1j**, CO_2Me, Me	**2a**, Ph	**ent-3j**	63	96	96
11	**ent-1k**, $CONEt_2$, Me	**2a**, Ph	**ent-3k**	72	97	97
12	**1a**, Ph, Me	**2b**, 4-MeC_6H_4	**3l**	81	99	99
13	**1a**, Ph, Me	**2c**, 4-PhC_6H_4	**3m**	70	99	99
14	**1a**, Ph, Me	**2d**, 4-FC_6H_4	**3n**	64	99	99
15	**1a**, Ph, Me	**2e**, 4-$MeO_2CC_6H_4$	**3o**	75	99	99
16	**1a**, Ph, Me	**2f**, 3-$H_2NC_6H_4$	**3p**	66	99	99
17[g]	**1a**, Ph, Me	**2g**, 3-$AcNHC_6H_4$	**3q**	61	99	99
18	**1a**, Ph, Me	**2h**, 3-$MeO_2CC_6H_4$	**3r**	61	99	99
19[h]	**1a**, Ph, Me	**2i**, 2-FC_6H_4	**3s**	63	99	99
20	**1a**, Ph, Me	**2j**, 2-naphthyl	**3t**	61	99	99
21	**1a**, Ph, Me	**2k**, 1-naphthyl	**3u**	85	99	98
22	**1a**, Ph, Me	**2l**, 9-phenanthrenyl	**3v**	80	99	99
23	**1d**, 4-$MeOC_6H_4$, Me	**2m**, (*E*)-PhCH=CH	**3w**	71	94	94

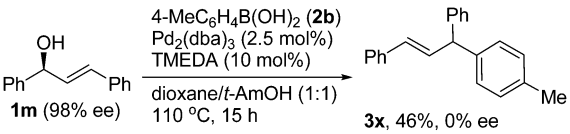
[a] Reaction conditions: alcohol **1** or **ent-1** (0.50 mmol), boronic acid **2** (0.60 mmol), $Pd_2(dba)_3$ (2.5 mol%), TMEDA (10 mol%), dioxane–*t*-AmOH (1 : 1, 3.5 mL), 110 °C, 15 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was run for 48 h. [e] 97 : 3 α/γ. [f] 88 : 12 α/γ. [g] 98 : 2 α/γ. [h] The reaction was run for 36 h.

The regioselectivity largely depends on the structure of the allylic alcohol. The cross-coupling of allylic alcohol **1l** (97% ee), a regioisomer of allylic alcohol **1a**, with boronic acid **2a** proceeded in a γ-selective fashion to afford alkene **ent-3a** in 82% yield with exclusive *E* selectivity and retention of ee (eqn (1)). The γ-selectivity probably arises from both maximizing conjugation and minimizing steric hindrance prior to the coupling of the boronic acid with the putative π-allylpalladium intermediate (see below).



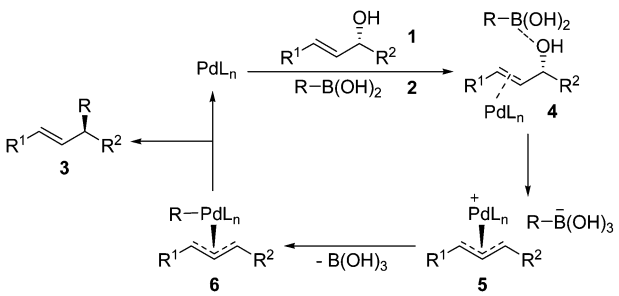
(1)

We also examined the reaction of a symmetrical allylic alcohol (α-substituent = γ-substituent). Treatment of allylic alcohol **1m** (98% ee) with boronic acid **2b** under the standard conditions led to the formation of racemic alkene **3x** (eqn (2)). The complete loss of ee should be attributed to the generation of a symmetrical π-allylpalladium intermediate during the reaction (see below).



(2)

Based on our experimental results and previous studies,[8] we propose a catalytic cycle depicted in Scheme 1 for the stereospecific cross-coupling of enantioenriched allylic alcohols with boronic acids. The hydroxy group of allylic alcohol **1** is activated by boronic acid **2** and the allylic carbon–oxygen bond is cleaved by palladium(0) (PdL_n) with inversion of configuration to give π-allylpalladium **5**, which undergoes transmetallation followed by reductive elimination to give alkene **3** and concurrently



Scheme 1 Proposed catalytic cycle.

regenerate palladium(0) to continue the catalytic cycle. The regioselectivity is determined by the steric and electronic properties of the R^1 and R^2 groups. If $R^1 = R^2$, the reaction would lose optical purity completely because of the symmetry of the π-allylpalladium intermediate. The efficiency of chirality transfer largely depends on the rate of racemization of π-allylpalladium **5** *via* Pd–Pd exchange.[2c–e] In our case, the use of TMEDA as the ligand (L) shuts down the racemization of π-allylpalladium **5** under the standard conditions and consequently the reaction proceeds with retention of ee.

In summary, we have developed an unprecedented stereospecific cross-coupling reaction of enantioenriched allylic alcohols with boronic acids. In the presence of 2.5 mol% $Pd_2(dba)_3$–TMEDA (1 : 4), a range of enantioenriched allylic alcohols smoothly coupled with boronic acids in a highly regioselective fashion with inversion of configuration to afford structurally diverse alkenes in good yields with perfect retention of ee and alkene geometry. The reaction tolerated a variety of functional groups such as heteroaryl, vinyl, alkoxy, chloro, fluoro, amino, ester, and amide groups. The current study paves the way for the direct stereospecific substitution of enantioenriched allylic alcohols with carbon nucleophiles.

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