Palladium(0)-catalyzed direct cross-coupling reaction of allylic alcohols with aryl- and alkenylboronic acids†

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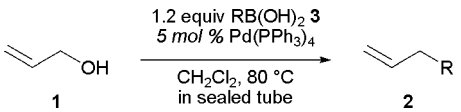
Allylic alcohols can be used directly for the palladium(0)-catalyzed allylation of aryl- and alkenylboronic acids with a wide variety of functional groups. A triphenylphosphine-ligated palladium catalyst turns out to be most effective for the cross-coupling reaction and its low loading (less than 1 mol%) leads to formation of the coupling product in high yield. The Lewis acidity of the organoboron reagents and poor leaving ability (high basicity) of the hydroxyl group are essential for the cross-coupling reaction. The reaction process is atom-economical and environmentally benign, because it needs neither preparation of allyl halides and esters nor addition of stoichiometric amounts of a base. Furthermore, allylic alcohols containing another unsaturated carbon–carbon bond undergo arylative cyclization reactions leading to cyclopentane formation.

Introduction

The palladium-catalyzed cross-coupling reaction with organometallics containing B, Mg, Zn, Sn, Si, *etc.* has been a powerful tool for carbon–carbon bond formation in organic synthesis.[1] Organoboron reagents are less nucleophilic than other organometallics, but have often been used because they are generally non-toxic, commercially available, stable and compatible with a wide variety of functional groups.[2] Compared to the significant development of the Pd-catalyzed coupling reaction with aryl- and alkenyl-halides or sulfonates,[2] that with allyl derivatives including halides,[3] carboxylates[4] and phenyl ethers[5] has received only scattered attention. These allyl derivatives are usually prepared from the corresponding allylic alcohols and, except for allyl phenyl ethers, their coupling reaction commonly requires stoichiometric amounts of a base.[5] The direct use of allyl alcohols for the cross-coupling reaction would avoid the need for the preparation of allyl derivatives and make the overall process of the coupling reaction more atom economical.[6] However, allylic alcohols themselves have been rarely used because hydroxide is a poor leaving group.[7] The Rh-[8] and Ni-[9]catalyzed coupling of allylic alcohols with arylboronic acids has been reported, but their allylating reagents were limited to only cinnamyl alcohols and 2-cyclohexen-1-ol, respectively. Recently, we developed the first palladium(0)-catalyzed cross-coupling reaction of a wider range of allylic alcohols with aryl- and alkenylboronic acids under base-free conditions (Scheme 1).[10] In spite of the less reactive substrates and reagents, this coupling process is highly active and efficient, without forming inorganic salts. Furthermore, we applied the Pd-catalyzed coupling reaction of allylic alcohols to the deprotection of allylic ethers, which was also difficult owing to their poor leaving ability.[11] Several reports on closely related coupling reactions followed us and pointed out the high catalyst loading of our own reaction.[12,13] Fortunately, our continuing studies on the coupling reaction have led to the solution of the problem and are described here.



Scheme 1 Cross-coupling of allylic alcohol with organoboronic acid.

Results and discussion

In the preliminary report, we developed reaction conditions for the cross-coupling reaction of cinnamyl alcohol (**4**) with phenylboronic acid (**3a**) as a model study. Upon heating at 80 °C in the presence of *5 mol%* of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$], **4** underwent the cross-coupling reaction to afford (*E*)-1,3-diphenylpropene (**5a**) in good yield. Although the reaction proceeded in any solvent such as toluene, 1,4-dioxane, DMF, and THF, dichloromethane turned out to be the best solvent (Table 1, entries 1, 3, 5, 7, 9). In dichloromethane, the product yield was maintained even when the catalyst loading was lowered from 5 to 2 mol% (entries 1 *vs.* 2). However, the lower catalyst loading gave higher yields of **5a** with other solvents (entries 4, 6, 8, 10)[14] and the best solvent became THF. Then, the catalyst loading effects on the product yield in THF were studied in detail. This disproportional tendency was closely preserved in the reaction with 10, 5, 2, 1, 0.5, and 0.2 mol% of the catalyst (entries 9–11, 14–16). Furthermore, the effect of the ratio of phosphine to Pd on the reaction was investigated to determine whether decreases in the amount of Pd metal or the phosphine ligand increase the product yield. Changing the ratio of phosphine to Pd from 4 : 1 to 1 : 1[15] by using Pd_2dba_3 as the Pd source instead of $Pd(PPh_3)_4$ revealed that the phosphine quantity seriously affected the product yield (entries 9 *vs.* 12, 13). Almost similar values for the sum of the phosphine quantity and product yield (entries 9–16) would indicate that an excess of phosphine competitively attacks a

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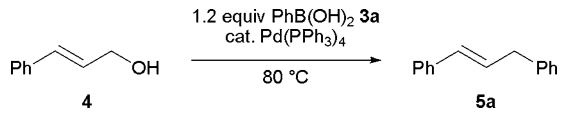
† Electronic supplementary information (ESI) available: General experimental procedures, tables of results and spectral data of the cross-coupling products. See DOI: 10.1039/b804991b

Table 1 Effects of solvent and catalyst loading on the yield of **5a**[a]



4 **5a**

Entry	Solvent	[Pd] (mol%)	[PPh_3] (mol%)	Time (h)	Yield (%)	Sum of [PPh_3] + Yield (%)
1	CH_2Cl_2	5	20	3	74	94
2	CH_2Cl_2	2	8	10	68	76
3	Toluene	5	20	3	66	86
4	Toluene	2	8	4	74	82
5	1,4-Dioxane	5	20	3	63	83
6	1,4-Dioxane	2	8	3	80	88
7	DMF	5	20	6	45	65
8	DMF	2	8	10	70	78
9	THF	5	20	3	66	86
10	THF	2	8	3	81	89
11	THF	10	40	3	47	87
12[a]	THF	5	10	3	83	93
13[a]	THF	5	5	3	83	88
14	THF	1	4	3	85	89
15	THF	0.5	2	3	87	89
16	THF	0.2	0.8	6	88	89
17	*t*AmOH	0.5	2	3	81	83

[a] Reaction with 2.5 mol% of Pd_2dba_3 and PPh_3 instead of $Pd(PPh_3)_4$.

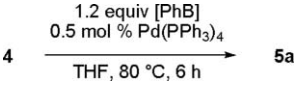
π-allylpalladium intermediate (*vide infra*). Although we could not observe the formation of the phosphonium salt or phosphorane directly, there have been several reports of attack by phosphines on π-allylpalladium complexes.[16,17] Consequently, we could not only reduce the catalyst loading from 5 mol% to 0.2 mol%, which is comparable to other cross-coupling reactions of allylic alcohols with arylboronic acids, but also increase the product yield simultaneously. Although protic polar solvents are reported to accelerate the oxidative addition to Pd^0,[18] this reaction could not be accelerated by using *tert*-amyl alcohol as the solvent (entry 17).

As with nucleophiles, boroxine as the anhydride of **3a** has the same reactivity as the boronic acid (Table 1, entry 15 *vs*. Table 2, entry 1). Boronic esters of **3a** dramatically decrease the product yield, but the more Lewis acidic catechol ester proves to be better than the pinacol ester (Table 2, entries 2, 3). Lewis acidic triphenylborane also participates in this process and provides **5a** in better yield than its borate anions (entries 4, 5). These results indicate that the Lewis acidity of the boron reagents rather than their Brønsted acidity is essential in this reaction.

As with electrophiles, the methyl ether and carbonate of **4** show comparable reactivity to the parent alcohol **4** (Table 1, entry 15 *vs*. Table 3, entries 1, 2). Reaction with the aryl ether of **4** takes a longer reaction time, but provides **5a** in high yield (Table 3, entry 3). In spite of its good leaving ability in the Tsuji–Trost reaction, the acetate of **4** leads to poor formation of **5a** (entry 4). These results indicate that the high basicity of the leaving group is essential for the cross-coupling reaction.

We also examined ligand effects on the coupling reaction (Table 4). The Pd catalysts ligated with these ligands were prepared *in situ* by mixing 0.5 mol% of Pd_2dba_3 and 1 mol% of the ligands. In contrast to Ikariya *et al*.'s report,[12a,19] triphenylphosphine turns out to be the best one, but triarylphosphines bearing methoxy and chloro groups at their *para*-positions were less effective (entries 1 *vs*. 2, 3). π-Accepting heteroarylphosphines and phosphites give much better results than σ-donating trialkylphosphines (entries 4–7 *vs*. 8, 9). Bisphosphine does not promote the reaction at all (entry 10). Triphenylarsine gives **5a** in only moderate yield (entry 11). For practical use, we decided to employ $Pd(PPh_3)_4$ as the catalyst for the following cross-coupling reactions.

Table 2 Effects of organoboron reagents

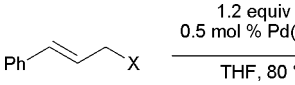


4 **5a**

Entry	[PhB]	Yield (%)
1[a]	$(PhBO)_3$	73
2	PhB(pinacolato)	nd[b]
3	PhB(catecholato)	26
4	Ph_3B	63
5	Ph_4BNa	32

[a] Reaction with 0.4 equiv. of $(PhBO)_3$. [b] Formation of **5a** was not observed by TLC.

Table 3 Effects of leaving groups



5a

Entry	X	Time (h)	Yield (%)
1	OMe	3	85
2	OCO_2Me	3	91
3	OC_6H_4-4-OMe	12	81
4	OAc	12	21

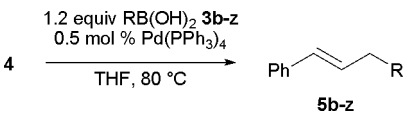
Table 4 Ligand effects

Entry	Ligand	Yield (%)
1	$P(C_6H_5)_3$	87
2	$P(C_6H_4\text{-}4\text{-}OMe)_3$	48
3	$P(C_6H_4\text{-}4\text{-}Cl)_3$	49
4	$P(2\text{-furyl})_3$	71
5	$P(2\text{-thienyl})_3$	82
6	$P(OPh)_3$	86
7	$P(OEt)_3$	83
8	PCy_3	22
9	PBu_3	nd
10	dppe[a]	nd
11	$AsPh_3$	53

[a] Reaction with 0.5 mol% of dppe. dppe = 1,2-bis(diphenylphosphino)-ethane.

Arylboronic acids with electron-donating (Table 5, entries 1–9) or -withdrawing groups (entries 10–17) serve as nucleophiles in this process, which leads to the formation of cross-coupling products **5b–r** in high yields. Whereas 2-methylphenylboronic acid (**3g**) has the same reactivity as 3- and 4-methylphenylboronic acids (**3h** and **3f**), the 2,6-dimethyl substituted version has much lower reactivity (entries 5–7 *vs.* 8). Regardless of their substitution position, naphthaleneboronic acids (**3s–t**) also participate in this process (entries 18, 19). However, the reaction with thiopheneboronic acids (**3u–v**) is dramatically affected by their substitution position (entries 20, 21).[20] Retention of stereochemistry accompanies the reactions of **4** with alkenylboronic acids **3w–z** that afford 1,3-dienes **5w–z** in good yield (entries 22–25). Generally, the newly developed reaction conditions, *i.e.* low catalyst loading and THF solvent, cause both an acceleration of the reaction rate and an improvement in the product yields.

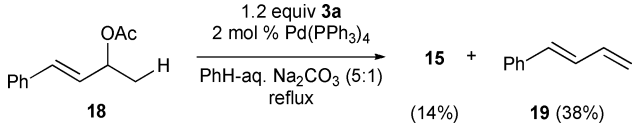
Table 5 Cross-coupling of **4** with aryl- and alkenylboronic acids



Entry	R	Product	Time (h)	Yield (%)
1	4-MeO–C_6H_4	**5b**	5	92
2	4-MeS-C_6H_4	**5c**	8	90
3	4-Me_2N-C_6H_4	**5d**	6	77
4[a]	4-AcHN-C_6H_4	**5e**	6	90
5	4-Me-C_6H_4	**5f**	3	88
6	2-Me-C_6H_4	**5g**	4	90
7	3-Me-C_6H_4	**5h**	4	88
8	2,6-diMe-C_6H_3	**5i**	3	34
9	4-H_2C=CH-C_6H_4	**5j**	3	85
10	4-F-C_6H_4	**5k**	4	87
11	4-Cl-C_6H_4	**5l**	3	83
12	4-F_3C-C_6H_4	**5m**	4	84
13	4-OHC-C_6H_4	**5n**	4	75
14	4-EtO_2C-C_6H_4	**5o**	4	85
15	4-Ac-C_6H_4	**5p**	8	83
16	4-NC-C_6H_4	**5q**	8	82
17	3-O_2N-C_6H_4	**5r**	6	73
18	1-naphthalene	**5s**	4	86
19	2-naphthalene	**5t**	3	79
20[b]	2-thiophene	**5u**	12	nd
21[b]	3-thiophene	**5v**	3	94
22	*trans*-β-styryl	**5w**	3	89
23	α – *styryl*	**5x**	3	72
24	*trans*-1-propenyl	**5y**	3	68
25	*cis*-1-propenyl	**5z**	3	76

[a] Reaction with 1 mol% of catalyst. [b] Reaction with 2 equiv. of **3**.

Phenylation of (*Z*)-cinnamyl alcohol (**6**) has a reaction time twice as long as that of the (*E*)-isomer **4**, but gives the same (*E*)-1,3-diphenylpropene (**5a**) in comparable yield (Table 6, entry 1 *vs.* Table 1, entry 15). 1-Phenyl-2-propen-1-ol (**7**), as a regioisomer of **4**, can also be coupled with **3a** leading to the formation of **5a** (entry 2). Although the reaction of 3-methyl-substituted cinnamyl alcohol **8** is much more sluggish and requires a higher reaction temperature than that of its isomeric tertiary alcohol **9**, both reactions provide tri-substituted alkene **14** as a stereoisomeric mixture in the same ratio (entries 3, 4). The coupling reactions of 1,3-disubstituted allylic alcohols **10–12** with **3a** require a long reaction time but afford phenyl-conjugated alkenes **15** and **16** in good yields (entries 5–7). Since the introduction of a methyl group at the C-2 position in cinnamyl alcohol retards the reaction remarkably, raising the reaction temperature to 110 °C and using 1,4-dioxane is necessary to improve the yield of **17** (entry 8). It is worth noting that the coupling reaction of optically active **10** results in a complete loss of chirality transfer (Table 6, entry 5)[21] and proves to be more efficient than that of the corresponding acetate **18**, which forms conjugated 1,3-diene **19** as the major product *via* Pd-H elimination from π-allylpalladium intermediates (Scheme 2).[4c,22]

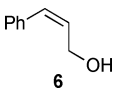
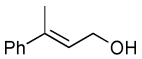
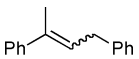
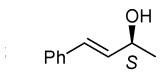
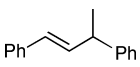
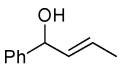
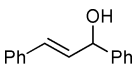
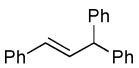
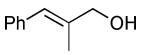


Scheme 2 Cross-coupling of allylic acetate **18** with **3a**.[4c]

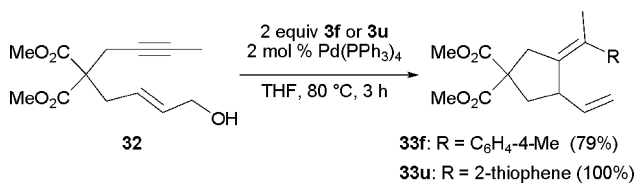
Next, unsubstituted allylic alcohol **1** and the alkyl-substituted analogs **20–25** were used for the allylation of 1-naphthylboronic acid (**3s**) (Table 7). The reaction of 2-propen-1-ol (**1**) gives **2s** in high yield (entry 1). The two regioisomers of butenols (**20** and **21**) are converted to **26-*E***, **26-*Z***, and **27** in the same regio- and stereoselectivity (entries 2, 3). Thus, alkyl substitution at the 1- or 3-position of the allylic alcohols leads to the formation of a more complex mixture than phenyl substitution (Table 6, entries 1, 2 *vs.* Table 7, entries 2, 3). Similarly, prenyl alcohol **22** and its isomer **23** are converted to the trisubstituted alkene **28** and the terminal alkene **29** in almost same ratio (entries 4, 5). The reactions of less reactive substrates such as methallyl alcohol (**24**) and 2-cyclohexen-1-ol (**25**) require a higher reaction temperature (entries 6, 7).

The Pd(0)-catalyzed reactions of alkyne-containing allylic alcohol **32** with arylboronic acids **3f** and **3u** provide 5-membered cyclic systems bearing neighboring vinyl and alkylidene groups (Scheme 3).[23] It is worth noting that 2-thiopheneboronic acid participates not in the cross-coupling process (Table 5, entry 20), but in the cyclization. These results would indicate that the poor reactivity of **3u** in the cross-coupling reaction should not result from hindrance of the oxidative addition step in the catalytic cycle.[24]

Table 6 Cross-coupling of phenyl-substituted allylic alcohols **6–13** with **3a**[a]

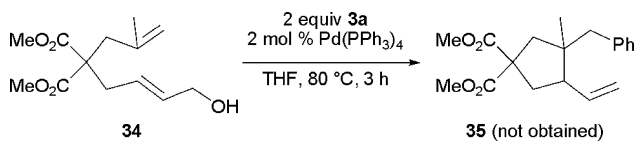
Entry	Alcohol	Product	Time (h)	Yield (%)
1	 **6**	**5a**	6	90
2	 **7**	**5a**	4	89
3[b]	 **8**	 **14**	24	69 ($E:Z = 2:1$)[c]
4	 **9**	**14**	6	80 ($E:Z = 2:1$)[c]
5	 **10** (97% ee)	 **15** (0% ee)	36	79[d]
6	 **11**	**15**	36	73
7	 **12**	 **16**	32	80
8[b]	 **13**	 **17**	24	65 ($E:Z = 2.5:1$)[d]

[a] Reaction conditions: a solution of 1 equiv. of **6–13**, 1.2 equiv. of **3a**, and 0.5 mol% of $Pd(PPh_3)_4$ in anhydrous THF is agitated at 80 °C. [b] Reaction in 1,4-dioxane at 110 °C. [c] The $E:Z$ ratio was determined by ^1H NMR analysis. [d] A small amount of (*E*)-1-phenyl-1,3-butadiene (**19**) was also formed.

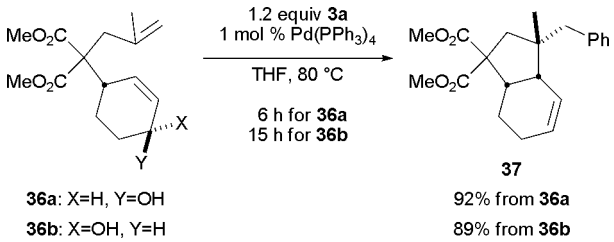


Scheme 3 Arylative cyclization of 1,6-enyne **32**.

Although replacement of the alkyne in **32** with a 1-propenyl group results in failure of the cyclization, the more conformationally restricted substrate **36a** cyclized efficiently (Scheme 4 *vs.* Scheme 5).[25] To our surprise, the cyclization of *syn*-allylic alcohol **36b** requires a longer reaction time, but provides the same bicyclic **37** in high yields.



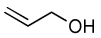
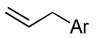
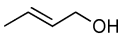
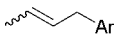
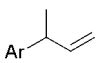
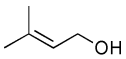
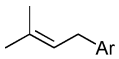
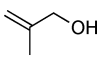
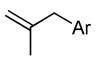
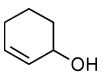
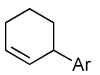
Scheme 4 Arylative cyclization of 1,6-diene **34**.



Scheme 5 Arylative cyclization of 1,6-dienes **36a–b**.

Formation of the same products in the same ratios from isomeric allylic alcohols such as **4**, **6**, and **7**, **8–9**, **10–11**, **20–21**, and **22–23** suggests that the common π-allylpalladium intermediate **40** participates in the reaction process (Scheme 6).[26] The formation of **40** through oxidative addition of the less reactive allylic alcohol **38** to the Pd(0) species would require not only the coordination of the Pd(0) to the olefin in **38** but also that of the Lewis acidic organoboron reagents **3** to the hydroxyl group in **38**.[27–29] The inefficient coupling seen with less Lewis acidic borate anions would support the importance of the latter coordination (Table 2, entries 4, 5). The following transmetalation between a cationic π-allylpalladium and an arylborate counteranion would give the

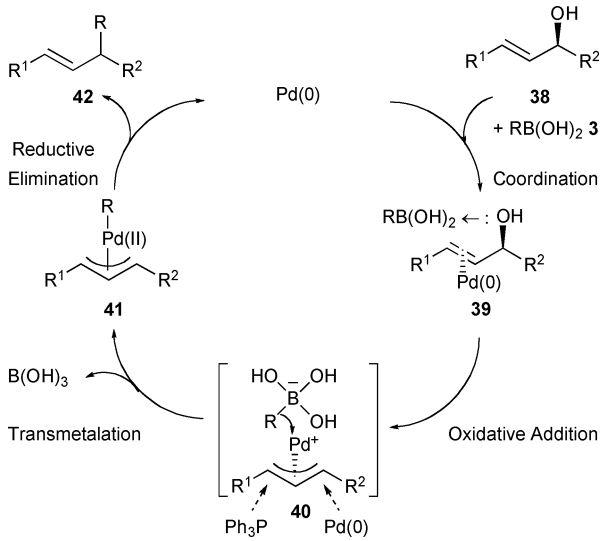
Table 7 Cross-coupling of alkyl-substituted allylic alcohols **1**, **20–25** with **3s**[a]

Entry	Alcohol	Product	Yield (%)
1	 **1**	 **2s**	80
2	 **20**	 **26** (*E*,*Z*) +  **27**	72 (**26-*E*** : **26-*Z*** : **27** = 9 : 1 : 6)[b]
3	 **21**	**26** (*E*,*Z*) + **27**	83 (**26-*E*** : **26-*Z*** : **27** = 11 : 1 : 8)[b]
4	 **22**	 **28** +  **29**	64 (**28** : **29** = 12 : 1)[b]
5	 **23**	**28** + **29**	75 (**28** : **29** = 7.4 : 1)[b]
6[c]	 **24**	 **30**	77
7[c]	 **25**	 **31**	23

[a] Reaction conditions: a solution of 1 equiv. of **1**, **20–25**, 1.2 equiv. of **3s**, and 0.5 mol% of $Pd(PPh_3)_4$ in anhydrous THF is agitated at 80 °C for 24 h. Ar = 1-naphthyl. [b] The *E* : *Z* ratio was determined by ^1H NMR analysis. [c] Reaction in 1,4-dioxane at 110 °C for 12 h.

dioorganopalladium complex **41**.[2,5,30] Reductive elimination of the coupling product **42** from **41** reproduces the Pd(0) complex.

In this catalytic cycle, the oxidative addition should be the rate-limiting step because two stereoisomers **4** and **6** and two regioisomers **8** and **9** react with **3a** at quite different rates in spite of both reactions proceeding *via* the same π-allylpalladium intermediates (Table 1, entry 15 *vs*. Table 6, entry 1 and Table 6, entries 3 *vs*. 4).[31] Due to steric and electronic reasons, it is difficult for highly substituted and cyclic allylic alcohols to coordinate and add oxidatively to the Pd(0) complex. The cationic π-allylpalladium intermediate **40** generated should be electrophilic enough to suffer competitive attack on the allylic carbon from the side opposite the Pd metal, by an excess of phosphine as well as an external Pd(0) catalyst, leading to the formation of phosphonium salts (or phosphoranes) and the epimerization of **40**, respectively. Whereas the reduction in the product yield caused by a high loading of catalyst would support attack by the phosphine (Table 1, entries 9–16), the conversion of the enantiomerically



Scheme 6 Possible mechanism for the cross-coupling reaction.

pure alcohol **10** to the completely racemic product **15** and that of *anti* and *syn* isomers **36a–b** to the same cyclized product **37** would support attack by Pd(0) (Table 6, entry 5 and Scheme 5). The epimerization of **40** in the presence of less than 1 mol% of catalyst can be explained by Bäckvall and Grandberg's report[16f] that the Pd(0) catalyst is much more nucleophilic towards the π-allyl group than the phosphine and that the less reactive allylic substrate would make the oxidative addition step rate-limiting and increase the concentration of the Pd(0), leading to the more rapid epimerization of **40**. On the other hand, the strong basicity of the hydroxyl and alkoxyl groups would promote the transmetalation step.[2,5,30] The much slower reaction with the less basic phenyl ether and acetate would be due to hindrance of the transmetalation step (Table 3, entries 1, 2 *vs*. 3, 4).

Conclusions

The present study offers an extremely facile allylation procedure for aryl- and alkenylboronic acids with a wide variety of functional groups. Low catalyst loading, poor leaving ability (high basicity) of the hydroxyl group, and Lewis acidity of the organoboron reagents are essential for the efficient cross-coupling reaction. The effectiveness is shown by suppression of conjugate diene formation through reaction of allylic alcohols, *via* β-hydrogen elimination of the π-allylpalladium intermediates. No longer are either preparation of allyl halides and esters or addition of stoichiometric amounts of a base required. Furthermore, allylic alcohols containing another unsaturated carbon–carbon bond undergo arylative cyclization reactions leading to the formation of cyclopentanes. Further studies on Pd-catalyzed organic transformations using organoboron reagents under base-free conditions are underway.[32]

Experimental section

General procedure for the cross-coupling reaction between **4** and **3a** (Table 1): to a test tube containing cinnamyl alcohol (**4**) (1 equiv., see Table 1S in the ESI†), phenylboronic acid (**3a**) (1.2 equiv.), and $Pd(PPh_3)_4$ (0.2–10 mol%) or Pd_2dba_3

(2.5 mol%)–PPh_3 (5 or 10 mol%) was added anhydrous solvent (CH_2Cl_2, toluene, 1,4-dioxane, DMF, THF, or *t*AmOH, 0.3 M) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for the time described in Table 1. The mixture was cooled down to room temperature, and then *N*,*N*-diethanolaminomethyl polystyrene[33] (PS-DEAM™, 1.63 mmol g^{-1}, 2.4 equiv., X g) and THF (10 x X mL) were added to remove any excess of **3a**. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by gel permeation chromatography (GPC) repeated four times to afford **5a** in the yield described in Table 1.

General procedure for the cross-coupling reaction between **4** and the phenylboron reagents (Table 2): to a test tube containing **4** (0.37 mmol, see Table 2S in the ESI†), phenylboron reagent[34] (0.45 mmol), and $Pd(PPh_3)_4$ (1.8 μmol) was added anhydrous THF (1 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 6 h. The mixture was cooled down to room temperature, and then partitioned between EtOAc and saturated aqueous Na_2CO_3. The organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by GPC repeated four times to afford **5a** in the yield described in Table 2.

General procedure for the cross-coupling reaction between the cinnamyl derivatives and **3a** (Table 3): to a test tube containing cinnamyl derivative[35] (0.37 mmol, see Table 3S in the ESI†), **3a** (0.45 mmol), and $Pd(PPh_3)_4$ (1.8 μmol) was added anhydrous THF (1 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for the time described in Table 3. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.63 mmol g^{-1}, 0.55 g, 0.90 mmol) and THF (5 mL) were added to remove any excess of **3a**. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by GPC repeated several times to afford **5a** in the yield described in Table 3.

General procedure for the cross-coupling reaction between **4** and **3a** (Table 4): to a test tube containing **4** (0.30 mmol, see Table 4S in the ESI†), **3a** (0.36 mmol), Pd_2dba_3 (1.5 μmol), and ligand (3 μmol) was added anhydrous THF (1 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 2 h. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.63 mmol g^{-1}, 0.44 g, 0.72 mmol) and THF (4 mL) were added to remove any excess of **3a**. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by GPC repeated four times to afford **5a** in the yield described in Table 4.

General procedure for the cross-coupling reaction between **4** and the boronic acids **3b–z**: to a test tube containing **4** (0.37 mmol, see Table 5S in ESI†), **3b-z** (0.45 mmol), and $Pd(PPh_3)_4$ (1.8 μmol) was added anhydrous THF (1 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for the time described in Table 5. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.63 mmol g^{-1}, 0.55 g, 0.90 mmol) and THF (5 mL) were added to remove any excess of **3b-z**. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by GPC repeated four times to afford **5b–z** in the yield described in Table 5.

General procedure for the cross-coupling reaction between **6–13** and **3a** (Table 6): to a test tube containing **6–13**[36] (0.37 mmol, see Table 6S in the ESI†), **3a** (0.45 mmol), and $Pd(PPh_3)_4$ (1.8 μmol) was added anhydrous THF (1 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for the time described in Table 6. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.63 mmol g^{-1}, 0.55 g, 0.90 mmol) and THF (5 mL) were added to remove any excess of **3a**. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by GPC repeated several times to afford **5a** and **14–17** in the yield described in Table 6. The optical rotation of **15** prepared from **10** was 0°.

General procedure for the cross-coupling reaction between **1** or **20–25** and **3s** (Table 7): to a test tube containing **1** or **20–25** (0.45 mmol, see Table 7S in the ESI†), **3s** (0.52 mmol), and $Pd(PPh_3)_4$ (1.8 μmol) was added anhydrous THF (1 mL for entries 1–5) or 1,4-dioxane (1 mL, for entries 6, 7) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 (for entries 1–5) or 110 °C (entries 6, 7) for the time described in Table 7. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.63 mmol g^{-1}, 0.55 g, 0.90 mmol) and THF (5 mL) were added to remove any excess of **3s**. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by GPC repeated several times to afford **2s** or **26–31** in the yield described in Table 7.

Spectral data of the cross-coupling products are described in the ESI†

(4*Z*)-3-Ethenyl-4-[1-(4-methylphenyl)ethylidene]-1,1-cyclopentanedicarboxylic acid dimethyl ester (33f)

To a test tube containing 2-butynyl-[(2*E*)-4-hydroxy-2-butenyl]propanedioic acid dimethyl ester **32**[37] (24.2 mg, 0.0952 mmol), **3f** (31.5 mg, 0.232 mmol), and $Pd(PPh_3)_4$ (1.5 mg, 1.3 μmol) was added anhydrous THF (1 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 3 h. The mixture was cooled down to room temperature, and then partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by silica gel chromatography eluting with 5% EtOAc–hexane to yield **33f** (24.8 mg, 0.0755 mmol, 79%).

Spectral data of **33f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.01 (m, 4H), 5.41 (ddd, 1H, J = 17.0, 10.4, 6.6 Hz), 4.69–4.59 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.35–3.49 (m, 1H), 3.15 (d, 1H, J = 16.8 Hz), 3.03 (d, 1H, J = 16.8 Hz), 2.51 (dd, 1H, J = 13.2, 8.0 Hz), 2.31 (s, 3H), 2.16 (dd, 1H, J = 13.1, 5.8 Hz), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 172.4, 140.7, 140.0, 135.9 × 2, 131.3, 128.6, 127.7, 114.0, 58.7, 52.8, 52.6, 45.2, 40.3, 38.8, 22.0, 21.0; IR (neat): ν_{max} (cm^{-1}) 2952, 1735, 1488, 1252, 830; EI-MS m/z (relative intensity) 328 $(M)^+$ (70), 268 (100), 209 (81), 119 (31), 107 (70); HRMS calcd for $C_{20}H_{24}O_4$ (M^+) 328.1673, found 328.1684.

(4*Z*)-3-Ethenyl-4-[1-(thiophen-2-yl)ethylidene]-1,1-cyclopentanedicarboxylic acid dimethyl ester (33u)

33u (32.6 mg, 0.102 mmol) was obtained quantitatively from **32** (25.9 mg, 0.102 mmol), **3u** (28.1 mg, 0.220 mmol), and $Pd(PPh_3)_4$ (2.4 mg, 2.1 μmol) by the same procedure as that described above.

Spectral data of **33u**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–6.91 (m, 3H), 5.63 (ddd, 1H, J = 17.3, 10.5, 5.5 Hz), 4.91–4.81 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.72–3.64 (m, 1H), 3.29 (d, 1H, J = 17.5 Hz), 3.03 (d, 1H, J = 17.5 Hz), 2.55 (dd, 1H, J = 13.2, 8.2 Hz), 2.35 (dd, 1H, J = 13.2, 4.1 Hz), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 171.9, 144.8, 138.8, 137.7, 126.4, 124.8, 123.8, 123.6, 114.8, 58.4, 53.0, 52.7, 45.9, 40.5, 39.6, 22.1; IR (neat): ν_{max} (cm^{-1}) 2952, 1731, 1434, 1254, 1173, 1065; EI-MS m/z (relative intensity) 320 $(M)^+$ (92), 260 (100), 245 (31), 289 (23), 201 (92); HRMS calcd for $C_{17}H_{20}O_4S$ (M^+) 320.1081, found 320.1083.

***trans*-[4-(Hydroxy)-2-cyclohexen-1-yl](2-methyl-2-propenyl)-propanedioic acid dimethyl ester (36a)**

To NaH (60%, 214 mg, 5.35 mmol), washed twice with anhydrous hexane, was added a solution of dimethyl (2-methylallyl)malonate[38a] (968 mg, 5.20 mmol) in anhydrous DMF (6 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, and then a solution of *cis*-1-acetoxy-4-chloro-2-cyclohexene[38b] (698 mg, 4.00 mmol) in anhydrous DMF (4 mL) was added. The whole solution was stirred at 80 °C for 2 h, cooled down to room temperature, and then partitioned between EtOAc and saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude *trans*-[4-(acetyloxy)-2-cyclohexen-1-yl](2-methyl-2-propenyl)-propanedioic acid dimethyl ester[38c] was dissolved in MeOH (20 mL) and K_2CO_3 (553 mg, 4.00 mmol) was added. The mixture was stirred at room temperature for 2 h, and then concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 40% EtOAc–hexane to yield **36a** (1.04 g, 3.68 mmol, 92%).

Spectral data of **36a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (dd, 1H, J = 10.5, 1.7 Hz), 5.70 (dd, 1H, J = 10.5, 2.4 Hz), 4.84 (s, 1H), 4.71 (s, 1H), 4.18 (m, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.00–2.96 (m, 1H), 2.75 (d, 1H, J = 14.5 Hz), 2.69 (d, 1H, J = 14.5 Hz), 2.16–2.12 (m, 1H), 1.93–1.88 (m, 1H), 1.69 (s, 3H), 1.48–1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.3, 141.1, 132.2, 129.9, 115.1, 67.2, 61.3, 52.1, 52.0, 40.7, 40.2, 32.9, 23.6, 23.1; IR (neat): ν_{max} (cm^{-1}) 3530–3330 (br), 2950, 1724, 1433, 1255, 1219, 1201, 1176, 1092, 1055, 896, 753, 737; EI-MS m/z (relative intensity) 282 $(M)^+$ (1), 265 (10), 250 (13), 223 (53), 194 (100), 155 (64), 145 (100), 122 (89), 96 (72), 79 (38); HRMS calcd for $C_{15}H_{22}O_5$ (M^+) 282.1467, found 282.1474.

***cis*-[4-(Acetyloxy)-2-cyclohexen-1-yl](2-methyl-2-propenyl)-propanedioic acid dimethyl ester**

To NaH (60%, 106 mg, 2.65 mmol), washed twice with anhydrous hexane, was added a solution of dimethyl (2-methylallyl)malonate[38a] (447 mg, 2.40 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, and then added to a mixture of *cis*-1-acetoxy-4-chloro-2-cyclohexene[38b] (350 mg, 2.00 mmol), $Pd(OAc)_2$ (11.1 mg, 0.049 mmol), and PPh_3 (54.1 mg, 0.206 mmol). The whole solution was stirred at rt for 3 h, and then partitioned between EtOAc and saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 25% EtOAc–hexane to yield *cis*-[4-(acetyloxy)-2-cyclohexen-1-yl](2-methyl-2-propenyl)-propanedioic acid dimethyl ester (637 mg, 1.96 mmol, 98%).

Spectral data of the acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (d, 1H, J = 10.3 Hz), 5.82–5.77 (m, 1H), 5.12–5.11 (m, 1H), 4.85 (s, 1H), 4.73 (s, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 2.90–2.86 (m, 1H), 2.79 (d, 1H, J = 14.4 Hz), 2.73 (d, 1H, J = 14.4 Hz), 2.01 (s, 3H), 1.91–1.87 (m, 1H), 1.76–1.66 (m, 2H), 1.70 (s, 3H), 1.55–1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.34, 170.31, 141.0, 134.5, 125.1, 115.3, 65.8, 61.0, 52.2, 51.9, 40.7, 40.1, 28.0, 23.6, 21.4, 19.4; IR (neat): ν_{max} (cm^{-1}) 2951, 1725, 1235, 1226, 1198, 1068, 1011, 991, 902; EI-MS m/z (relative intensity) 324 $(M)^+$ (0.3), 265 (32), 205 (46), 194 (34), 176 (55), 145 (100), 79 (34), 43 (34); HRMS calcd for $C_{17}H_{24}O_6$ (M^+) 324.1573, found 324.1566.

***cis*-[4-(Hydroxy)-2-cyclohexen-1-yl](2-methyl-2-propenyl)-propanedioic acid dimethyl ester (36b)**

The above acetate (309 mg, 0.953 mmol) was dissolved in MeOH (5 mL) and K_2CO_3 (146 mg, 1.06 mmol) was added. The mixture was stirred at room temperature for 2 h, and then concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 50% EtOAc–hexane to yield **36b** (272 mg, 0.953 mmol, quant.).

Spectral data of **36b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (d, 1H, J = 10.3 Hz), 5.88–5.83 (m, 1H), 4.84 (s, 1H), 4.72 (s, 1H), 4.09 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 2.87–2.82 (m, 1H), 2.80 (d, 1H, J = 14.4 Hz), 2.74 (d, 1H, J = 14.4 Hz), 1.88–1.83 (m, 1H), 1.74–1.63 (m, 2H), 1.70 (s, 3H), 1.57–1.50 (m, 1H), 1.42 (br-s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.4, 141.1, 132.3, 129.0, 115.2, 63.0, 61.0, 52.2, 52.0, 40.9, 40.5, 30.8, 23.6, 18.8; IR (neat): ν_{max} (cm^{-1}) 3534–3335 (br), 2950, 1724, 1433, 1223, 1197, 1178, 1072, 1000, 950, 898, 737; EI-MS m/z (relative intensity) 282 $(M)^+$ (0.5), 265 (2), 250 (5), 223 (30), 194 (57), 145 (100), 122 (44), 79 (23); HRMS calcd for $C_{15}H_{22}O_5$ (M^+) 282.1467, found 282.1460.

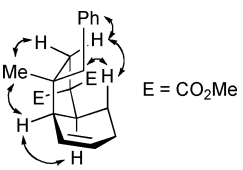
(3α,3aβ,7aβ)-2,3,3a,6,7,7a-hexahydro-3-methyl-3-(phenylmethyl)-1*H*-Indene-1,1-dicarboxylic acid dimethyl ester (37)

From **36a**: to a test tube containing **36a** (31.1 mg, 0.110 mmol), **3a** (15.6 mg, 0.128 mmol), and $Pd(PPh_3)_4$ (1.3 mg, 1.1 μmol) was added anhydrous THF (0.5 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 6 h. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.63 mmol g^{-1}, 0.16 g, 0.26 mmol) and THF (2 mL) were added to remove any excess of **3a**. The mixture was agitated at room temperature for 2 h. The mixture was filtered

and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by preparative TLC eluting with 20% EtOAc–hexane, repeating two times to yield **37** (34.6 mg, 0.101 mmol, 92%).

From **36b**: to a test tube containing **36b** (31.6 mg, 0.112 mmol), **3a** (16.3 mg, 0.134 mmol), and $Pd(PPh_3)_4$ (1.5 mg, 1.3 μmol) was added anhydrous THF (0.5 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 15 h. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.63 mmol g^{-1}, 0.16 g, 0.26 mmol) and THF (2 mL) were added to remove any excess of **3a**. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by preparative TLC eluting with 20% EtOAc–hexane, repeating two times to yield **37** (34.3 mg, 0.100 mmol, 89%).

Spectral data of **37**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.17 (m, 5H), 5.89–5.84 (m, 1H), 5.76–5.72 (m, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.02–2.95 (m, 1H), 2.90 (d, 1H, J= 14.4 Hz), 2.65–2.61 (m, 1H), 2.63 (d, 1H, J= 13.2 Hz), 2.44 (d, 1H, J= 13.2 Hz), 2.17–2.04 (m, 2H), 1.68 (d, 1H, J= 14.4 Hz), 1.44–1.37 (m, 2H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 170.5, 139.7, 130.3, 127.6, 127.2, 125.7, 125.4, 63.1, 52.6, 52.4, 49.5, 47.5, 44.2, 43.9, 43.5, 29.2, 24.6, 22.2; IR (neat): ν_{max} (cm^{-1}) 2950, 1730, 1432, 1241, 1199, 1143, 1068, 769, 705; EI-MS m/z (relative intensity) 342 $(M)^+$ (13), 310 (8), 279 (11), 251 (34), 219 (30), 191 (100), 145 (59), 131 (82), 91 (45); HRMS calcd for $C_{21}H_{26}O_4$ (M^+) 342.1831, found 342.1843.



NOESY correlation of **37**

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