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Synthesis of Homoallylic Alcohols via Palladium-Catalyzed Three-Component Coupling of an Arylboronic Acid with Allenes and Aldehydes

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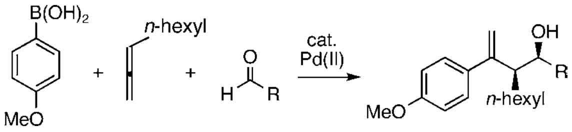
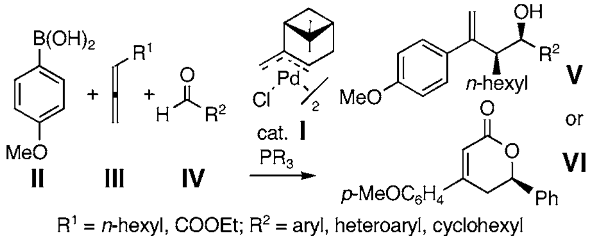
ABSTRACT



Racemic homoallylic alcohols have been synthesized by palladium-catalyzed three-component coupling of an arylboronic acid, an allene, and an aldehyde.

Homoallylic alcohols represent synthetically versatile building blocks,[1] traditionally accessed via allylmetal-aldehyde additions.[2] A one-pot protocol, in which a transition metal catalyst would mediate both the assembly of an allyl fragment and its transfer to an electrophile, would constitute an attractive approach to homoallylic alcohols. Inspired by Yamamoto's[3] and Szabó's[4] studies on allylation via bis-π-allylpalladium complexes, we set out to design a three-component coupling[5] of arylboronic acid **II**,[6] allenes **III**, and aldehydes **IV** (Scheme 1). Reactions catalyzed by π-allylpalladium(II) dimer **I** provided branched alcohols **V**. Allenyl ester **III** (R^1 = COOEt) afforded lactone **VI** via a reversal of the allylation regiochemistry.

Scheme 1. Synthetic Strategy



The new methodology complements related nickel-catalyzed multicomponent coupling reactions.[7] The described concept provides a mechanistically distinct alternative to strategies exploiting palladium-catalyzed in situ formation

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(1) (a) Liu, B.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 71−74. (b) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569−572.

(2) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793.

(3) Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641−6647.

(4) Szabó, K. J. *Chem. Eur. J.* **2000**, *6*, 4413−4420.

(5) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959−5989.

(6) For transition metal-catalyzed reactions of boronic acids with organohalides, dienes, aldehydes, and enones, see: (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Oh, C.-H.; Ahn, T.-W.; Reddy, V. R. *Chem. Commun.* **2003**, 2622−2623. (c) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450−4452. (d) Hayashi, T.; Takahashi, M.; Takayay, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052−5058.

(7) For a nickel-catalyzed coupling of allenyl aldehydes and alkylzincs, see: (a) Montgomery, J.; Song, M. *Org. Lett.* **2002**, *4*, 4009−4011. Attempted *intermolecular* three-component coupling with an arylzinc afforded benzylic alcohols via a direct addition of arylzincs to aldehydes, see: (b) Montgomery, J.; Oblinger, E. *J. Am. Chem. Soc.* **1997**, *119*, 9065−9066. An example of a nickel-catalyzed coupling of boronic acids with alkynes and imines yielding allylic amines is known; see: (c) Patel, S. J.; Jamison, T, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364−1367. For additional related nickel-catalyzed multicomponent coupling reactions, see: (d) Molinary, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076−8077. (e) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473. (f) Mori, M.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1624−1634. (g) Ikeda, S.-I. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120−5122.

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of allylmetals, either from derivatives of main-group metals and allyl electrophiles,[8] or via coupling of organohalides with allenes and metal components.[9]

Anticipating that η^1-bonded ligands in hypothetical complexes **VII** or **VIII** (Figure 1) would act as the requisite nucleophiles,[3,4] we envisioned that intermediates **VII** or **VIII** could arise from π-allylpalladium(II) dimer catalysts **1a** or **1b** and mixtures of organometals (ArM) and allenes.[10]

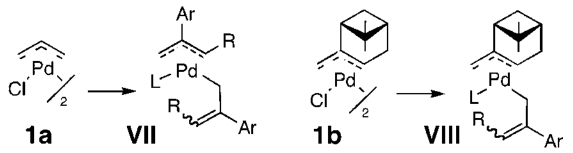
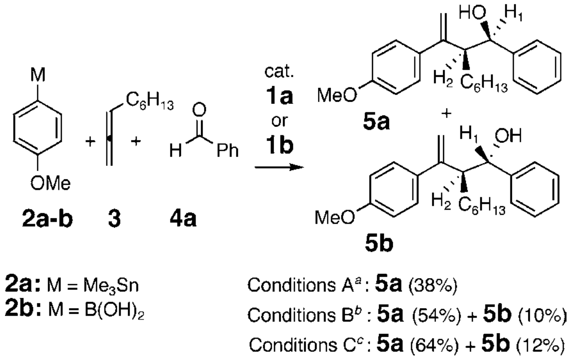


Figure 1. Hypothetical catalytic intermediates.

The reaction of arylstannane **2a** with 1,2-nonadiene **3** and benzaldehyde **4a** catalyzed by complex **1a** (10 mol % Pd)[11] in the presence of triphenylphosphine (PPh_3) provided alcohol **5a** in 38% yield as a single diastereomer (conditions A, Scheme 2).[12] Treatment of boronic acid **2b**, allene **3**, and benzaldehyde **4a** with an increased load of catalyst **1a** (20 mol % Pd), tricyclohexylphosphine (PCy_3), and CsF[13] afforded chromatographically separable diastereomers **5a** (54%) and **5b** (10%) (conditions B, Scheme 2). An omission of the PCy_3 ligand under conditions B caused only a moderate decrease in the combined yield (55%) of alcohols **5** (82% de).[14] The assignment of syn and anti stereochemistry in diastereomers **5a** and **5b**, respectively, was based on ^1H NMR spectroscopy[15] via comparison with related alcohols.[16]

Scheme 2[a]



[a]Conditions A: **4a** (1.0 equiv), **2a** (1.0 equiv), **3** (2.0 equiv), **1a** (0.05 equiv), PPh_3 (0.1 mol), 1,2-dichloroethane, 60 °C, 24 h. [b]Conditions B: **4a** (1.0 equiv), **2b** (2.0 equiv), **3** (2.0 equiv), **1a** (0.1 equiv), PCy_3 (0.4 mol), CsF, (2.0 equiv), DMF, rt, 24 h. [c]Conditions C: **4a** (1.0 equiv), **2b** (2.0 equiv), **3** (5.0 equiv), **1b** (0.05 equiv), CsF (4.0 equiv), $[HPPh(t\text{-}Bu)_2]BF_4$ (0.1 mol), THF, rt, 24 h.

Instability of catalytic species under conditions A and B (Scheme 2), manifested by precipitation of palladium(0), was deemed to be responsible for the low catalyst turnover and modest yields of alcohols **5**. Reasoning that the presence of a "nontransferable"[17] β-pinene-derived allyl ligand in the catalytic intermediates[18] might alleviate this problem, a process catalyzed by complex **1b**,[19] was investigated (Scheme 2). The best result (76% yield, **5a**:**5b** = 5.3:1) in the reaction catalyzed by complex **1b** (10 mol % Pd) was achieved upon treatment of boronic acid **2b** with benzaldehyde **4a** in the presence of excess allene **3** (5 equiv), ligand $[HPPh(t\text{-}Bu)_2]BF_4$ (Pd:P, 1:1),[20] and CsF[21] (conditions C, Scheme 2). Indeed, the precipitation of palladium(0) was eliminated under these conditions. The use of a palladium(0) complex $Pd_2dba_3/[HPPh(t\text{-}Bu)_2]BF_4$ or omission of the palladium

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[8] (a) Sebelius, S.; Walner, O. A.; Szabó, K. J. *Org. Lett.* **2003**, *5*, 3065−3068. (b) Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2003**, *68*, 2934−2943. (c) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163−3185. (d) Kimura, M.; Kiyama, I.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6795−6798. (e) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *6*, 847−849. (f) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577−2586.

[9] (a) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376−4379. (b) Cheng, C.-H.; Yang, F.-Y.; Wu, M.-Y. *Tetrahedron Lett.* **1999**, *40*, 6055−6058. Palladium-catalyzed indium-mediated intermolecular coupling of aryl iodides and aldehydes with *n*-octylallene afforded linear homoallylic alcohols, see: (c) Anwar, U.; Rasparini, M.; Savic, V.; Sridharan, V.; Grigg, R. *Chem. Commun.* **2000**, 645−646. In contrast, analogous transformation with allenes possessing heteroatom-containing substituents afforded branched alcohols; see: (d) Cleghorn, L. A. T.; Cooper, I. R.; MacLachlan, W. S.; Sridharan, V.; Grigg, R. *Tetrahedron Lett.* **2003**, *44*, 7969−7973.

[10] For a review of palladium-catalyzed reactions of allenes, see: Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067−3125.

[11] Following an "unproductive" transfer of the 2-propenyl group in the first turnover, catalyst **1a** was expected to yield the symmetrical bis-π-allylpalladium complex **VII** (Figure 1).

[12] Under conditions A, but in the absence of catalyst **1a**, addition of allyltributyltin failed to afford any homoallylic alcohol, indicating that a hypothetical in situ formation of an allylstannane, followed by its uncatalyzed addition to benzaldehyde, was not a viable pathway to alcohol **5a**. In contrast, uncatalyzed additions of allylboronic acids to aldehydes are known to be facile; see: Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1866−1874.

[13] Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

[14] Notably, PPh_3 present in reaction mixtures containing bis-π-allylpalladium complexes and aldehydes was found to promote an allyl−allyl coupling; see: Nakamura, H.; Bao, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3208−3210.

[15] Magnitudes of the *J* constants for coupling of protons H_1, H_2 (J_{H1-H2} = 4.81 Hz in major product **5a** and J_{H1-H2} = 8.50 Hz in the minor diastereomer **5b**) were consistent with dihedral angles anticipated in the most stable conformations of syn and anti diastereomers of alcohol **5**, respectively.

[16] For the syn diastereomer of 2,3-dimethyl-1-phenylbut-3-en-1-ol, coupling constant J_{H1-H2} = 4.88 Hz was reported; see: ref 8f.

[17] For the effect of substitution on the relative transfer abilities of allyl ligands in bis-π-allylpalladium complexes, see: (a) Reference 3. (b) Solin, N.; Narayan, S.; Szabó, K. J. *J. Org. Chem.* **2001**, *66*, 1686−1693.

[18] For asymmetric allylation of imines catalyzed by analogues of complex **1b**, see: (a) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133−14139. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242−4243.

[19] Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318−2323.

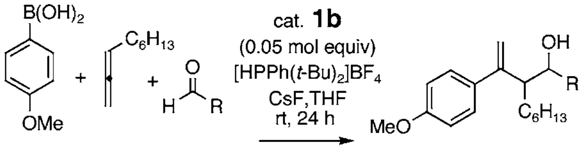
[20] Effects of the nature of solvents (THF, DMF, 1,2-dichloroethane, and toluene) and the phosphine ligand were surveyed. Under conditions C (Scheme 2) but in the absence of a phosphine ligand, alcohol **5** was isolated in 57% yield and precipitation of Pd(0) was observed. Replacement of the optimum ligand $PPh(t\text{-}Bu)_2$ (Pd:P, 1:1) with PPh_3, PPh_2Me, or PCy_3 limited the yields of alcohols **5** to 35−39%, and precipitation of Pd(0) persisted. Application of an excess of ligand $PPh(t\text{-}Bu)_2$ (Pd:P, 1:2) or the use of $P(i\text{-}Pr)_3$ (Pd:P, 1:1) limited the yields of alcohols **5** to 6% and 9%, respectively, although precipitation of Pd(0) was eliminated.

[21] Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

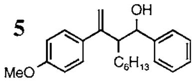
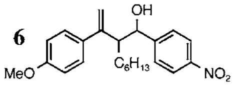
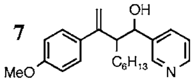
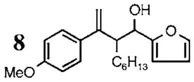
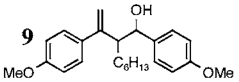
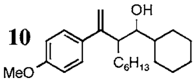
catalyst **1b** caused a failure of the coupling procedure. However, less efficient reactions providing alcohol **5a** in 39 and 20% yields occurred upon the replacement of catalyst **1b** with $Pd(OAc)_2/[HPPh(t\text{-}Bu)_2]BF_4$ or $Pd(OAc)_2$/1,2-bis(diphenylphosphino)ethane (dppe) catalysts, respectively. Disappointingly, alcohol **5a**, isolated from reactions catalyzed by complex **1b**, was produced as a racemic mixture.[22]

The optimized protocol proved to be generally applicable, allowing for an efficient coupling of boronic acid **2b** and allene **3** with aldehydes **4b−f**, including electron-rich and electron-poor aromatic, heterocyclic, and aliphatic aldehydes (Table 1).

Table 1. Homoallylic Alcohols via Palladium-Catalyzed Three-Component Coupling



2b **3** **4** **5-10**

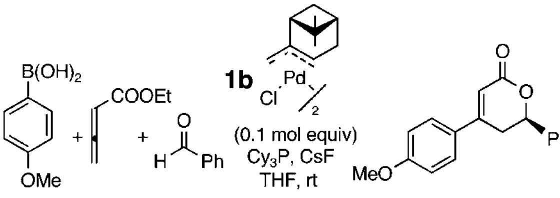
entry	aldehyde **4a-f** R	products	yld %	dr[a]
1	**4a** C_6H_5	**5** 	76[b]	5.3 : 1
2	**4b** p-$NO_2C_6H_4$	**6** 	85[b]	1.9 : 1
3	**4c** 3-pyridyl	**7** 	71[c]	8.1 : 1
4	**4d** 2-furanyl	**8** 	76[b]	4.4 : 1
5	**4e** p-$MeOC_6H_4$	**9** 	54[d]	32 : 1[e]
6	**4f** cyclohexyl	**10** 	46[c]	3.0 : 1

[a] Diastereomeric ratio; major diastereomer was syn. [b] Combined yield of pure, separated diastereomers. [c] Combined yield of chromatographically inseparable diastereomers. [d] Isolated yield of a pure syn diastereomer. [e] Traces (<3%) of the minor anti diastereomer were detected in the crude reaction mixture.

Diastereomers of alcohols **5−10** were isolated in good combined yields (46−85%) and 33−94% de. Electron-deficient p-nitrobenzaldehyde **4b** proved to be the most reactive (entry 2, Table 1). In contrast, aliphatic aldehyde **4f** provided only a modest yield of alcohol **10** (entry 6, Table 1). Diastereomers of alcohols **5**, **6**, **8**, and **9** were obtained as pure compounds after chromatography (entries 1, 2, 4, and 5, Table 1), while alcohols **7** and **10** were isolated as chromatographically inseparable mixtures (entries 3 and 6, Table 1). In all cases, major products were assigned as syn and the minor products as anti isomers.[23] Only the branched regioisomers **5−10** arising from the attack of the substituted termini of the in situ-assembled allyl ligand (Figure 1) on the carbonyl carbon were detected (Table 1).[3,4]

Surprisingly, a reaction with allenyl ester **11** proceeded via a regiochemically opposite pathway (Scheme 3). Coupling of boronic acid **2b** and benzaldehyde **4a** with allene **11** catalyzed by complex **1b** (20 mol % Pd) in the presence of PCy_3 and CsF afforded lactone **12** in 65% yield (Scheme 3) and 23% ee[24] as a single product. Formation of the expected branched homoallylic alcohol was not observed. The directing effect of the ester substituent on regioselectivity of the allylation with 1,3-disubstituted allenyl esters is being investigated.

Scheme 3



2b **11** **4a** **12** (65%)

A plausible coupling mechanism relies on the assembly of the new allyl fragment from a boronic acid and an allene via transmetalation[6] and migratory insertion,[10] yielding intermediates **IX** and **VIII**, respectively (Figure 2). The nucleophilic η^1-bonded allyl ligand is likely transferred to

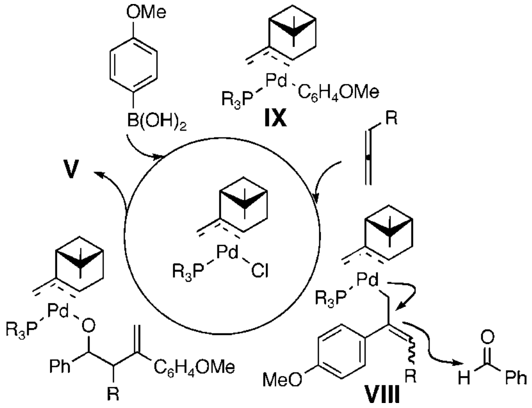


Figure 2. Proposed mechanistic rationale.

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[22] In asymmetric allylations of imines, catalyst **1b** proved to be less effective than its more substituted derivatives; see: ref 18b.

[23] In ^1H NMR spectra of alcohols **5−9**, the magnitudes of J_{H1-H2} coupling constants in major (syn) products were 4.2−5.5 Hz, and those for minor (anti) products were 7.8−8.9 Hz. Due to the complexity of ^1H NMR spectra of alcohol **10**, the syn/anti assignments for **10** remain tentative.

[24] Determined by chiral-phase HPLC.

aldehydes via an "open" transition state,[25] documented by the formation of syn diastereomers of branched alcohols **V**. Although improbable, allylation via "free" allylboron reagents was not rigorously ruled out.[26] At this time, it is unclear whether Lewis acid activation of aldehydes is involved. The low-yielding coupling in the presence of Pd$(OAc)_2$/dppe catalyst might occur via (P−P)Pd(aryl)(η^1-allyl) complex, analogues of which have been shown to react with electrophiles.[27] The reversal of regiochemistry in reactions with allenyl esters could be rationalized by a possible intervention of oxygen-bonded palladium dienolate. Further studies aiming to support this model are in progress. The inefficient asymmetry transfer from catalyst **1b** was attributed to the lack of substituents at both termini of the nontransferable allyl ligand,[22] and allylation via an "open" transition state.[25] The design of an asymmetric variant of this method is underway.

In conclusion, new avenues for allylation via bis-π-allylpalladium intermediates have been investigated. The concept of an in situ assembly of structurally complex bis-π-allylpalladium(II) complexes from arylmetals and allenes has been validated by a successful allylation of aldehydes. A new, catalytic, convergent, and regiospecific synthesis of highly substituted homoallylic alcohols and a 2-pyranone was demonstrated. The reaction proceeds under mild conditions and employs a stable, nontoxic, and functional group-tolerant boronic acid. Extension of this strategy to the synthesis of functionalized amines is being pursued.

Acknowledgment. Acknowledgment is made to the donors of The American Chemical Society Petroleum Research Fund (PRF 41232-AC1), for support of this research.

Supporting Information Available: Complete description of the synthesis and characterization of all compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) (a) In allylations catalyzed by bis-π-allylpalladium complexes, prior coordination of electrophiles to palladium was proposed to occur under "phosphine free" conditions; see references 3 and 8b. Lower diastereoselectivity for the anti product was noted in analogous allylations in the presence of phosphine; see: Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2002**, *4*, 1563−1566. (c) For allylations via "open" transition states yielding syn products, see: Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865−2868.

(26) In situ formation of allylboron reagents via a reduction of mono-π-allylpalladium complexes with Et_3B (reduction failed with Ph_3B) is known; see reference 8d.

(27) (a) Soling, N.; Kjellgren, J.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3656−3658. (b) Kurosawa, H.; Urabe, A. *Chem. Lett.* **1985**, 1839−1840.