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Synthesis of Epoxides by Palladium-Catalyzed Reactions of Tertiary Allyl Alcohols with Aryl or Alkenyl Halides

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Epoxides are among the most synthetically useful intermediates and are found in many natural products and biologically active compounds.[1] Numerous methods for the preparation of epoxides have been reported so far, such as epoxidation of olefins, reaction of carbonyl compounds with sulfur ylides, and ring closure of *vic*-halohydrins.[2] However, novel synthetic methods for the construction of epoxides have been still required because of their synthetic importance in organic chemistry.

Recently, palladium-catalyzed carboetherification/arylation reactions of alkenes with aryl bromides have provided a very efficient way to construct multisubstituted five-membered heterocycles.[3,4] We serendipitously found that Wolfe's carboetherification is applicable to more rigid three-membered ring construction, which is a new synthetic strategy for the preparation of epoxides. Here we report palladium-catalyzed reactions of readily accessible tertiary allyl alcohols with aryl or alkenyl halides.

Treatment of tertiary allyl alcohol **1a** with 1-bromonaphthalene in the presence of sodium *tert*-butoxide under palladium catalysis provided epoxide **2a** in 88% yield (Table 1, entry 1). It is noteworthy that the reaction constructs both C−C and C−O bonds in a single operation. In the reaction, the choice of ligand is quite important: Only Buchwald's biaryl phosphines **P1**−**P4** and Xantphos **P5** (Figure 1) served as suitable ligands for the epoxidation reaction. The Mizoroki−Heck reaction of tertiary allyl alcohols with 1-bromonaphthalene predominated or exclusively proceeded when other phosphine ligands were used.[5] The reaction with not only aryl bromide but also aryl chloride gave the corresponding epoxide **2a** in good yield (entry 2). However, the use of naphthyl triflate as a starting material failed to afford the product (entry 3). Sterically demanding aryl bromides also participated in the epoxidation reaction (entries 4−7 and 9) except for bulkier 2-bromobiphenyl (entry 8). Aryl bromides bearing electron-donating groups as well as electron-deficient ones were converted to the corresponding epoxides in moderate yields (entries 10−12). Notably, alkenyl halides were also applicable to the epoxidation reaction (entries 13−15). Products **2k**−**2m** would be difficult to synthesize in one step from simple starting materials using traditional methods. In the reactions with alkenyl halides, the combination of $Pd_2(dba)_3$ and **P3** showed the highest catalytic activity.

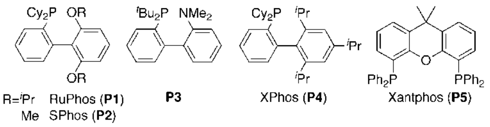
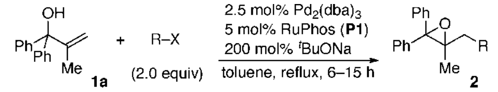
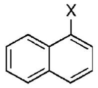
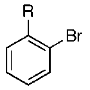
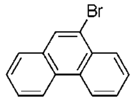
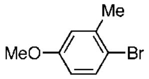
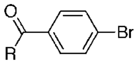
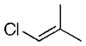
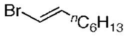


Figure 1. Ligands used in the reactions.

Reactions of a variety of tertiary allyl alcohols with 1-bromonaphthalene were then examined (Table 2). The methyl group of **1a** is not essential, and alcohol **1b** having hydrogen at the internal vinylic carbon underwent the epoxidation smoothly to yield trisubstituted epoxide **3b** (entry 1). With **1b**, the use of Xantphos improved the yield slightly (entry 2). The reactions of alcohol having an electron-rich aryl group at the tertiary carbon center furnished the corresponding product in 75% yield (entry 3).

Table 1. Scope of Aryl and Alkenyl Halides in Palladium-Catalyzed Epoxidation/Arylation or /Alkenylation[a]



entry	R–X	**2**, yield[b](%)
1	 X = Br	**2a**, 88
2	Cl	72
3	OTf	0[c]
4	 R = Me	**2b**, 82
5	Et	**2c**, 90
6	^{i}Pr	**2d**, 56
7	CH=CH$_2$	**2e**, 49
8	Ph	**2f**, 0[c]
9		**2g**, 91
10		**2h**, 67
11	 R = Ph	**2i**, 47
12	^{t}Bu	**2j**, 50
13[d]		**2k**, 77
14[d,e]		**2l**, 74
15[d]		**2m**, 62

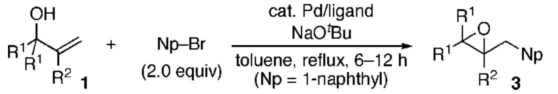
[a] A mixture of $Pd_2(dba)_3$ (0.0075 mmol), **P1** (0.015 mmol), ^{t}BuONa (0.60 mmol), **1a** (0.30 mmol), and R−X (0.60 mmol) was boiled in toluene (3.0 mL) for 6−15 h. [b] Isolated yields. [c] No reaction. [d] **P3** as a ligand. [e] The *E/Z* ratio of both 1-bromopropene and the product was 76/24.

On the other hand, an electron-withdrawing group on the benzene rings interfered with the formation of the epoxide due to the predominance of a competitive Heck reaction (entry 4). Alcohols with small alkyl substituents such as an *n*-butyl group showed lower reactivity than those with aryl substituents (entry 5). The reactions of allyl alcohols bearing ethyl and phenyl substituents at the internal olefin moiety also proceeded to give the corresponding tetrasubstituted epoxides in moderate yields (entries 6 and 7).

Subsequently, the reactions of tertiary alcohols that possess a stereogenic center at the oxygenated carbon were conducted

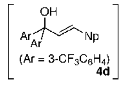
10.1021/ja8084065 CCC: $40.75

Table 2. Reactions with Tertiary Allyl Alcohols with 1-Bromonaphthalene[a]

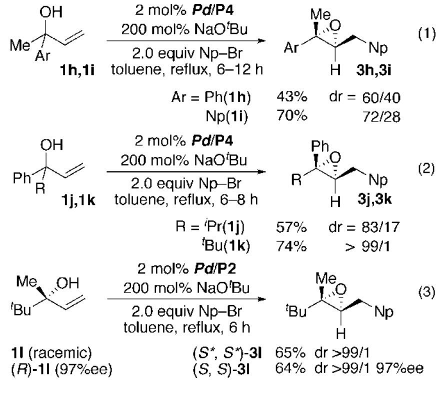


entry	R^1	R^2	ligand	**3**, yield[b](%)
1	Ph	H (**1b**)	**P1**	**3b**, 69
2[c]	Ph	H (**1b**)	**P5**	**3b**, 75
3	4-MeOC$_6$H$_4$	H (**1c**)	**P1**	**3c**, 60(75[d])
4	3-CF$_3$C$_6$H$_4$	H (**1d**)	**P1**	**3d**, 23[e]
5[f]	^{n}Bu	H (**1e**)	**P4**	**3e**, 35
6	Ph	Et (**1f**)	**P1**	**3f**, 62
7	Ph	Ph (**1g**)	**P1**	**3g**, 44

[a] Conditions: Pd$_2$(dba)$_3$ (2.5 mol%), ligand (5 mol% with **P1**, **P4** or 10 mol% with **P5**), ^{t}BuONa (200 mol%), toluene (0.1 M). [b] Isolated yields. [c] Cs$_2$CO$_3$ as a base. [d] ^{1}H NMR yield. [e] Product **4d** was obtained in 24% yield. [f] 2 mol% of [Pd] and **P4** were used.



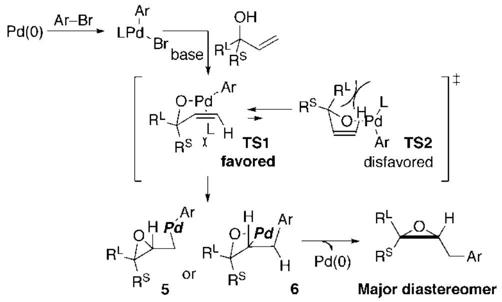
Scheme 1



(Scheme 1). Both yield and diastereoselectivity became better as the substituents at the oxygenated carbon of alcohols **1h**–**1k** became larger.[6] As depicted in eq 1, 2-naphthyl-3-buten-2-ol (**1i**) gave a better result than 2-phenyl-3-buten-2-ol (**1h**). The reactions with alcohols **1j** and **1k** afforded the corresponding epoxides **3j** and **3k**, respectively, with good diastereoselectivity, bearing phenyl and naphthylmethyl substituents in a *cis* configuration (eq 2). As expected, bulkier *tert*-butyl-substituted alcohol **1l** underwent a smooth reaction to afford the corresponding epoxide **3l** in good yield as a single diastereomer (eq 3). Finally, the reaction was applied to the synthesis of an optically active epoxide. Starting from enantiomerically enriched tertiary alcohol **1l**, which was prepared in three steps from 2,3,3-trimethyl-1-butene,[7] we obtained (*S*,*S*)-**3l** as a sole product without a loss of enantiomeric excess (eq 3).

Based on our results and Wolfe's report,[3,4] we are tempted to assume the reaction mechanism as follows (Scheme 2). Initial oxidative addition of aryl halide to zerovalent palladium occurs to afford arylpalladium halide. Subsequent ligand exchange between the palladium intermediate and allyl alcohol in the presence of the base provides palladium alkoxide. Intramolecular oxypalladation then takes place to generate alkylpalladium intermediate **5**. Another possibility is a carbopalladation pathway, en route to oxapalladacyclobutane **6**. Finally, reductive elimination from these intermediates gives the desired product and regenerates Pd(0). The diastereoselectivity would be determined in the oxypalladation or carbopalladation step. **TS1** is the more favorable transition state than **TS2** because the larger substituent R^L is located at the pseudoequatorial position, thus minimizing the steric repulsion from the vinylic proton or the ligand L which coordinates to the palladium center.[8,9]

Scheme 2. Reaction Mechanism



In conclusion, we have developed a new method for the synthesis of epoxides by palladium-catalyzed reactions of tertiary allyl alcohols with aryl halides. The details of the reaction mechanism and the synthesis of other three-membered carbo- and heterocycles are under investigation.

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Supporting Information Available: Experimental details, characterization data for new compounds, and stereochemical assignments of epoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) See Supporting Information for reaction optimization.

(6) The relative configuration was assigned by NOE experiments. For details, see Supporting Information.

(7) See Supporting Information for the preparation of (*R*)-**1l**.

(8) It is possible that other undesired reactions might proceed under the reaction conditions such as β-vinyl elimination from palladium alkoxide. These reactions would be suppressed by the proper choice of the ligand. Reviews for palladium-catalyzed reactions with tertiary alcohols:(a) Muzart, J. *Tetrahedron* **2005**, *61*, 423–9463. (b) Satoh, T.; Miura, M. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1199–1207.

(9) We cannot exclude the possibility that the insertion reaction proceeds through an *anti*-oxypalladation pathway at this stage.

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