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Regioselective *anti*-addition of phenols to propargylic oxiranes by palladium(0) catalyst

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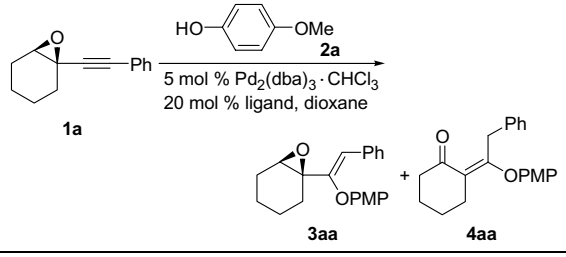
Abstract—(*Z*)-Phenol-substituted alkenes were produced by the palladium(0)-catalyzed reaction of propargylic oxiranes with phenols. The regio- and stereoselective addition of phenols to alkynes occurs via the formation of π-propargyl- and π-allylpalladium complexes. The phenoxy-substituted enones were produced simultaneously depending on the reaction conditions.

The reactions of propargylic compounds with transition metal catalysts have received considerable attention due to their versatile and specific reactivity, and extensive studies of these have now been undertaken.[1] The palladium-catalyzed reaction of propargylic compounds with soft nucleophiles is one of the most successful chemical processes that has been developed.[2,3] In the course of the reactions, various propargylic leaving groups, such as carbonates, esters or halides, can be cleaved by a palladium catalyst to generate the π-propargyl/allenylpalladium complexes, which further react with soft nucleophiles to lead the substituted products. It is also known that propargylic oxiranes exhibit a similar reactivity against a palladium catalyst,[4] but only a few examples of the reactions with soft nucleophiles were reported.[4b] During the course of our studies about the reaction of propargylic carbonates with soft nucleophiles,[5] we focused on the reactivity of oxiranes as a propargylic leaving group. Herein, we describe a palladium-catalyzed reaction of propargylic oxiranes with phenols. The regio- and stereoselective addition of phenols to alkynes occurs via the π-propargyl- and π-allylpalladium intermediate affording the (*Z*)-phenol-substituted alkenes.

The initial reactions were carried out using phenyl-substituted propargylic oxirane **1a** and *p*-methoxyphenol (**2a**) as a nucleophile.[6] When **1a** and **2a** were subjected to the reaction in the presence of 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 20 mol% dppe in dioxane at 60 °C for 2 h, the phenol-substituted alkene **3aa** and enone **4aa** were obtained in 12% and 52% yields (Table 1, entry 1). The structure of **3aa** including the stereochemistry was determined unambiguously using spectroscopic methods, and the stereochemistry of **4aa** was determined

Table 1. Palladium-catalyzed reaction of propargylic oxirane **1a** with *p*-methoxyphenol (**2a**)[a]



Entry	Ligand	Temp (°C)	Time (h)	Yield (%)	
				3aa	**4aa**
1	dppe	60	2	12	52
2	dppp	60	2	27	39
3	dppb	30	2	83	—
4	dppf	30	16	82	—
5	PPh_3[b]	30	40	63	—
6	dppb	30	20	56	18
7	dppb	80	16	—	54

[a] PMP = *p*-methoxyphenyl.
[b] 10 mol% $Pd(PPh_3)_4$ was used as a palladium catalyst.

Keywords: Palladium; Addition; Oxiranes; Phenols; Propargylic compounds.
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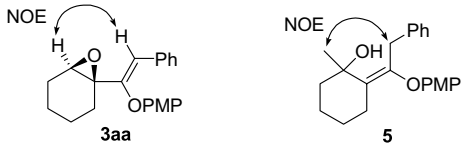
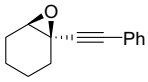
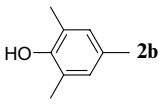
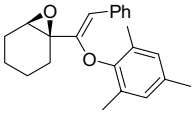
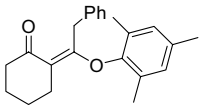
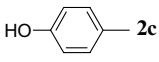
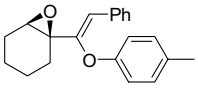
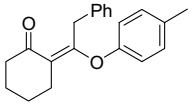
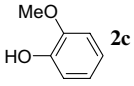
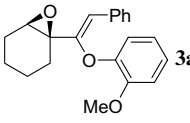
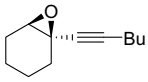
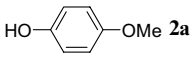
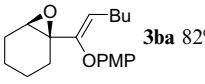
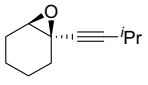
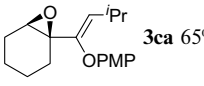
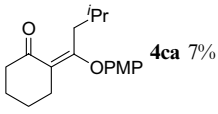
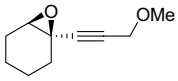
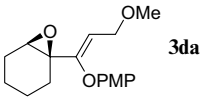
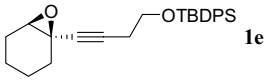
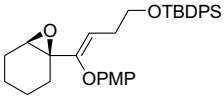
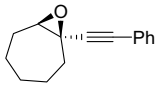
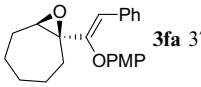
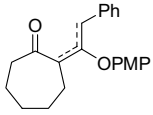
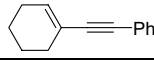


Figure 1. NOESY correlation of phenol adduct **3aa** and methylated compound **5**.

by NOESY correlation of **5**, which was produced from the reaction of **4aa** with MeLi (Fig. 1). The yield of **3aa** was improved in the presence of other phosphine ligands (entries 2–5), and **3aa** was exclusively obtained in 83% yield when the reaction was performed with dppb at rt for 2 h (entry 3). It was found that ratios of the resulting phenol adduct **3aa** and enone **4aa** can be controlled by the reaction conditions. Thus, a fair amount of **4aa** was yielded by carrying out the reaction for 20 h (entry 6), and raising the reaction temperature at 80 °C resulted in the exclusive production of **4aa** (entry 7). Since the obtained phenol adduct **3aa** had *Z* geometry in any conditions, it was ascertained that this addition reaction proceeds in a high *anti*-selective manner.

To examine the scope of the reaction, various phenols and propargylic oxiranes were next examined. The palladium-catalyzed reaction of the substrate **1a** with 2,4,6-trimethylphenol (**2b**) successfully proceeded to give the phenol-substituted alkene **3ab** (70%) and enone **4ab** (27%) (Table 2, entry 1). However, the enone **4ac** was mainly obtained in 55% yield when *p*-cresol (**2c**) was subjected to the reaction with **1a** (entry 2). After several attempts, we found that phenol adduct **3ac** was predominantly yielded in 77% by employing the reaction in the

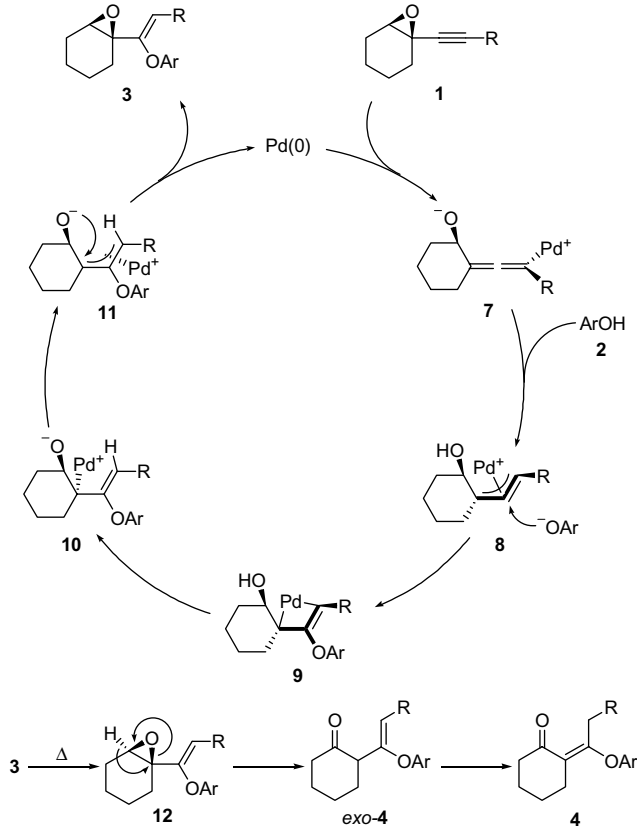
Table 2. Reaction of various propargylic oxirane **1a–f**, enyne **6** and phenols **2b–d**[a]

Entry	Propargylic oxirane **1**	Phenol **2**	Product's yield	
			3[f]	**4**[f]
1[b]	 **1a**	 **2b**	 **3ab** 70%	 **4ab** 27%
2[b]	**1a**	 **2c**	 **3ac** Trace **3ac** 77%	 **4ac** 55% **4ac** 7%
3[c,d] 4[c,d]	**1a** **1a**	 **2c**	 **3ad** 80%	—
5[c]	 **1b**	 **2a**	 **3ba** 82%	—
6[c]	 **1c**	**2a**	 **3ca** 65%	 **4ca** 7%
7[c]	 **1d**	**2a**	 **3da** 73%	—
8[e]	 **1e**	**2a**	 **3ea** 81%	—
9[e]	 **1f**	**2a**	 **3fa** 37%	 **4fa** 37% (*endo*:*exo* = 1.5:1)
10[b]	 **6**	**2a**	—	—

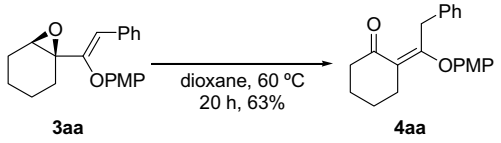
[a] All reactions were carried out in the presence of 5 mol% $pd_2(dba)_3{\cdot}CHCl_3$, 20 mol% dppb in dioxane for 2–12 h.
[b] Reactions were carried out at 60 °C.
[c] Reactions were carried out at 30 °C.
[d] 2.0 equiv of K_2CO_3 was added.
[e] Reactions were carried out at 50 °C.
[f] The stereochemistries of the products were tentatively assigned by comparisons with the NMR spectra of **3aa** and **4aa**.

presence of K_2CO_3 at 30 °C (entry 3).[7] 2-Methoxyphenol (**2d**) also successfully reacted with **1a** under the conditions producing alkene **3ad** as a sole product (entry 4). The reactions of propargylic oxirane **1b** and **1c**, having a butyl and an isopropyl group at the terminal alkynyl position, with *p*-methoxyphenol (**2a**) gave the corresponding products **3ba** (82%) and **3ca** (65%), respectively (entries 5 and 6). The substrate **1d** and **1e** containing a methoxy and a siloxy group on the inside of the alkyl side chain were uneventfully transformed to **3da** and **3ea** in 73% and 81% yields (entries 7 and 8). When the seven-membered compound **1f** was subjected to the reaction, the corresponding phenol adduct **3fa** was obtained in 37% yield with a fair amount of enone **4fa** (37%, isomeric mixture) (entry 9). On the other hand, no reaction occurred on the enyne **6**, which has no oxirane ring (entry 10). From this result, it has been made clear that the oxirane moiety is necessary for the reaction.

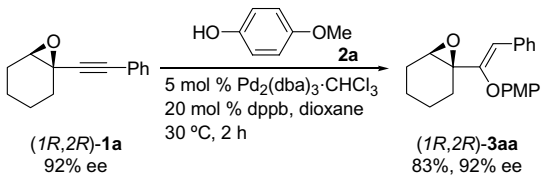
Plausible mechanisms for the formation of phenol-substituted alkene **3** and enone **4** were shown in Scheme 1. In the first step, regio- and stereoselective *anti* S_N2' attack of palladium catalyst[8] on the propargylic oxirane **1** takes place to yield the allenylpalladium complex **7**. Transformation of **7** to π-propargylpalladium complex **8** (an equilibrium process)[9] is followed by selective addition of phenol to the central carbon of π-propargyl moiety to form the palladacyclobutene **9**. Complex **9** is then converted to the allylpalladium complex **10** by proton



Scheme 1. Proposed reaction mechanism.



Scheme 2. Conversion of dihydrofuran **3aa** to enone **4aa**.



Scheme 3. Reaction of chiral propargylic oxirane (1*R*,2*R*)-**1a**.

transfer.[9b] The complex **10** is delocalized to afford π-allylpalladium complexes **11** stereoselectively,[5d] which is subjected to the intramolecular nucleophilic attack in 3-*exo* mode to produce the (*Z*)-phenol-substituted alkene **3**. The results in Table 1 imply that enone **4** would be produced from **3**, not directly from the propargylic oxirane **1**. Thus, 1,2-hydrogen rearrangement[10] (**12**) is caused under thermal conditions to yield 1,4-enone *exo*-**4**, which further isomerizes to thermodynamically stable 1,3-enone **4**.

To confirm the reaction mechanism for the formation of enone **4**, we tried the conversion of **3aa** to **4aa** (Scheme 2). When **3aa** was heated in dioxane at 60 °C for 20 h, the expected reaction proceeded to give **4aa** in 63% yield. The result clearly proved that enone **4** was produced from **3**.

We further attempted the reaction of enantiomerically enriched, chiral propargylic oxirane (1*R*,2*R*)-**1a** (Scheme 3). When (1*R*,2*R*)-**1a**[11] (92% ee) was subjected to the reaction with *p*-methoxyphenol (**2a**), the corresponding chiral adduct (1*R*,2*R*)-**3aa**[12] was provided. The enantiomeric excess of (1*R*,2*R*)-**3aa** was determined as 92%, and the result showed that the addition reaction did not affect the chirality of the oxirane ring.

In conclusion, the effort described above had led to the discovery of the palladium-catalyzed addition of phenols to propargylic oxiranes. The process yields phenol-substituted alkene in highly regio- and stereoselective manner.[13] It is known that the substituted oxiranes having oxygen functional groups on the side chain exhibit various biological activities.[14] Our methodology would provide a new and meaningful protocol for the synthesis of various alkenyl-substituted oxiranes in high efficiency.

Acknowledgements

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6. General procedure for palladium-catalyzed reactions of propargylic oxiranes with phenols. To a stirred solution of **1a** (41 mg, 207 μmol) in dioxane (2.1 mL) were added *p*-methoxyphenol (**2a**) (28 mg, 227 μmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (11 mg, 10.9 μmol) and dppb (18 mg, 41.4 μmol) in sealed tube at rt under argon atmosphere. The reaction mixture was allowed to warm to 30 °C, and stirred for 2 h. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane–NEt_3 (6:93:1 v/v) as eluent to give the alkene **3aa** (55 mg, 172 μmol, 83%) as colourless needles; $R_f = 0.55$ (AcOEt–hexane = 2:8 v/v); mp 63–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95–1.10 (m, 2H), 1.28–1.40 (m, 2H), 1.57–1.64 (m, 1H), 1.82–1.92 (m, 2H), 2.20 (dt, $J = 15.2$ and 6.3 Hz, 1H), 3.13 (d, $J = 2.9$ Hz, 1H), 3.77 (s, 3H), 6.24 (s, 1H), 6.80–6.84 (m, 2H), 6.93–6.97 (m, 2H), 7.14–7.18 (m, 1H), 7.22–7.26 (m, 2H), 7.54–7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 19.8, 24.6, 26.2, 55.6, 58.4, 62.1, 112.7, 114.5, 118.3, 127.0, 128.3, 128.6, 134.3, 149.3, 152.3, 155.0; IR (KBr) 2937, 1670, 1661, 1504, 1464, 1246, 1207, 1036 cm^{-1}; MS (EI) *m/z* (relative intensity) 322 [M^+, 100], 225 (6), 199 (28), 175 (5), 161 (3), 147 (5), 135 (6), 133 (3), 123 (27), 109 (23), 105 (15), 92 (7), 77 (15), 57(3), 43 (4); Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.23; H, 6.90.
7. The role of K_2CO_3 in the reaction is not clear, but it is presumed that the phenolic acid also causes the 1,2-rearrangement, which can be suppressed by adding K_2CO_3 as a base.
8. It is known that chiral allenes can be synthesized from the palladium-catalyzed reaction of chiral propargylic compounds via stereoselective S_N2' attack of palladium catalyst: (a) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103; (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 367; (c) Dixneuf, P.; Guyot, T.; Ness, M. D.; Roberts, S. M. *Chem. Commun.* **1997**, 2083; (d) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 1360.
9. (a) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687; (b) Ogoshi, S.; Kurosawa, H. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 14.
10. Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, p 733, Chapter 3.3.
11. Chiral substrate (1*R*,2*R*)-**1a** was prepared by the asymmetric epoxidation of **5** using Shi's fructose-derived chiral ketone with Oxone: Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.
12. Enantiomeric excess of the obtained (1*R*,2*R*)-**3aa** was determined by HPLC analysis (DAICEL CHIRALCEL OF).
13. Similar type of the reaction about *anti*-addition of oxygen nucleophile to alkynes by palladium(0) catalysts has been previously reported. Camacho, D. H.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 1085.
14. For example: Zhang, H.; Gates, K. S. *Biochemistry* **2000**, *39*, 14968.