α-Allenol Synthesis

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Stereoselective Synthesis of α-Allenols by Rhodium-Catalyzed Reaction of Alkynyl Oxiranes with Arylboronic Acids**

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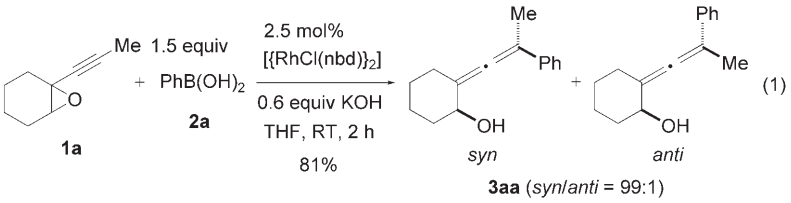
Allenes constitute an important class of building blocks possessing axial chirality as well as unique reactivities.[1] The S_N2'-type substitution of propargylic alcohol derivatives with organometallic reagents is one of the most reliable procedures for the stereoselective preparation of substituted allenes.[2] We previously described the rhodium-catalyzed substitution reaction of propargylic acetates with phenylboronic acid, wherein the resulting alkenylrhodium(I) intermediate underwent β-oxygen elimination to afford a trisubstituted allene.[3] In an extension of this work we set out to examine the use of alkynyl oxiranes as acceptors for arylboronic acids owing to the considerable interest in the resulting α-allenols as building blocks for the construction of oxygenated heterocycles of biological and pharmacological relevance.[4] We report herein on the rhodium-catalyzed reaction of alkynyl oxiranes with arylboronic acids which yields α-allenols with excellent diastereoselectivity.

Alkynyl oxirane **1a** (1.0 equiv) was treated with phenylboronic acid (**2a**, 1.5 equiv) in the presence of [{RhCl(nbd)}$_2$] (5 mol% of Rh, nbd = norborna-2,5-diene)[5] and KOH (0.6 equiv) in THF (0.1 M) at room temperature. The reaction was completed in 2 h, and an extractive workup followed by chromatographic isolation afforded the α-allenol **3aa** in 81% yield with excellent diastereoselectivity (*syn*/*anti* = 99:1)[6] [Eq. (1)].

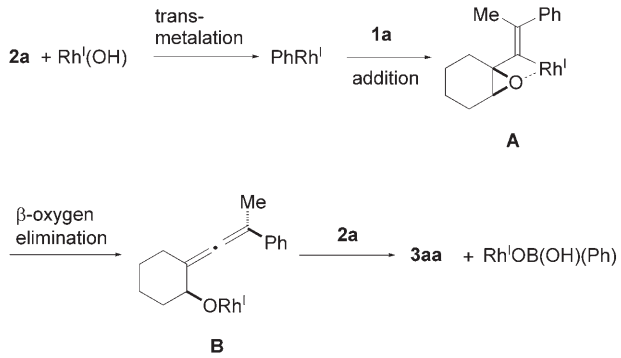


(1)

The highly stereoselective formation of the *syn*-configured α-allenol is noteworthy among other S_N2'-type reactions of alkynyl oxiranes with organometallic reagents.[7] Organocopper and organocuprate reagents preferentially afford *anti*-configured α-allenols in most cases[8] with very few exceptions.[9] Palladium-catalyzed reactions with organostannanes[10] and organoborons[11] also give the corresponding *anti*-substitution product. On the other hand, *syn*-configured α-allenols were selectively produced by the iron-catalyzed reaction of alkynyl oxiranes with Grignard reagents.[12] However, the iron-catalyzed reaction of **1a** with PhMgBr exhibited only moderate diastereoselectivity (*syn*/*anti* = 66:34).

The mechanism shown in Scheme 1 explains the stereoselective formation of **3aa**. Initially, a phenylrhodium(I) species is generated by transmetalation of hydroxorhodium(I) with **2a**.[13] Then, *cis* 1,2-addition of the phenylrhodium(I) species to **1a** takes place to afford the alkenylrhodium(I) intermediate **A**. Noteworthy was that addition of the phenylrhodium(I) species across the carbon–carbon triple bond of the epoxy-substituted alkyne, which otherwise required heating over 80 °C,[14] occurred at room temperature. We assume that precoordination of the oxygen atom of the oxirane ring to rhodium contributes to the high stereoselectivity as well as high reactivity, similar to the case of the iron-catalyzed reaction.[12] Subsequent β-oxygen elimination occurs in a *syn* mode to open the oxirane ring.[15] The resulting rhodium(I) alkoxide **B** reacts with **2a** to release the product **3aa** along with a rhodium(I) boronate.[16]

Other examples of the stereoselective synthesis of α-allenols **3** from various combinations of alkynyl oxiranes **1** and arylboronic acids **2** are listed in Table 1. The catalytic



Scheme 1. Mechanism explaining the stereoselective formation of the *syn*-configured α-allenol.

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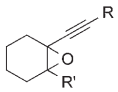
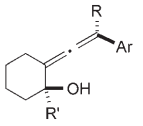
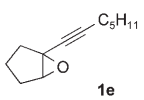
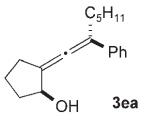
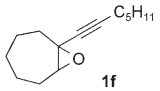
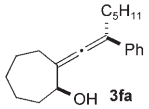
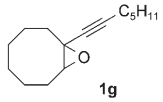
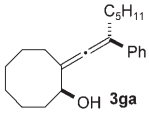
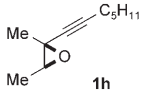
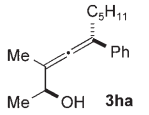
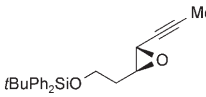
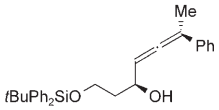
Table 1: Rhodium-catalyzed *syn*-selective synthesis of α-allenols from alkynyl oxiranes using arylboronic acids.[a]

Entry	Substrate **1**	$ArB(OH)_2$ **2**	Major product **3**	Yield [%][b]	*syn*/*anti*[c]
					
1	**1a** R = Me, R′ = H	**2b** Ar = 4-FC_6H_4	**3ab**	76	98:2
2	**1a**	**2c** Ar = 4-BrC_6H_4	**3ac**	86	99:1
3	**1a**	**2d** Ar = 4-MeC_6H_4	**3ad**	77	98:2
4	**1a**	**2e** Ar = 3-$MeOC_6H_4$	**3ae**	80	99:1
5	**1a**	**2f** Ar = 3-ClC_6H_4	**3af**	74	99:1
6	**1a**	**2g** Ar = 3-$CHOC_6H_4$	**3ag**	72	96:4
7	**1a**	**2h** Ar = 2-MeC_6H_4	**3ah**	83	83:17
8	**1a**	**2i** Ar = 2-thienyl	**3ai**	75	97:3
9	(*R*,*R*)-**1a** (82% *ee*)	**2a** Ar = Ph	(*R*,S_a)-**3aa** (82% *ee*)	84	99:1
10	**1b** R = C_5H_{11}, R′ = H	**2a** Ar = Ph	**3ba**	74	97:3
11	**1c** R = C_5H_{11}, R′ = Me	**2a** Ar = Ph	**3ca**	65	99:1
12	**1d** R = H, R′ = H	**2a** Ar = Ph	**3da**	19	83:17
13	 **1e**	**2a** Ar = Ph	 **3ea**	82	97:3
14	 **1f**	**2a** Ar = Ph	 **3fa**	83	99:1
15	 **1g**	**2a** Ar = Ph	 **3ga**	83	99:1
16	 **1h**	**2a** Ar = Ph	 **3ha**	85	99:1
17		**2a** Ph		61	94:6
	(*S*,*S*)-**1i** (80% *ee*)		(*S*,R_a)-**3ia** (80% *ee*)		

[a] All reactions were carried out using **1** (0.4 mmol), **2** (0.6 mmol), KOH (0.2–0.3 mmol), [{RhCl(nbd)}$_2$] (0.01 mmol, 5 mol% of Rh) in THF (4.0 mL) at RT for 3–16 h. [b] Yield of isolated product. [c] Relative stereochemistry assigned by comparison with an authentic *anti* isomer prepared by the literature procedure,[8g,9,11] and the ratios were determined by HPLC analysis of the isolated mixture of the α-allenols or the corresponding acetates.

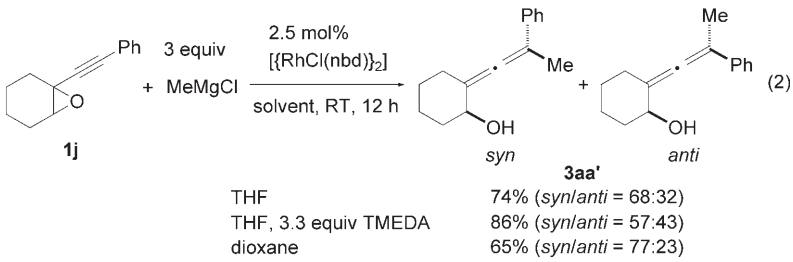
process of **1a** worked well with an array of sterically and electronically diverse arylboronic acids **2b**–**2h**, as well as heteroarylboronic acid **2i**, to give *syn*-configured α-allenols **3ab**–**3ai** with stereoselectivities higher than 96:4, except in the case of the sterically hindered *ortho*-tolylboronic acid (Table 1, entries 1–8).[17] It is worth pointing out that the reaction conditions tolerate various functional groups including a formyl group, which is incompatible with Grignard reagents. Substrate **1c**, which has a tetrasubstituted oxirane, also gave the tertiary alcohol **3ca** stereoselectively (Table 1, entry 11). The reaction of substrate **1d** having a terminal alkyne moiety afforded the product **3da** with a decreased selectivity in only 19% yield (Table 1, entry 12). Substrates **1e**–**1g** with five-, seven-, and eight-membered-ring structures gave the respective products **3ea**–**3ga** stereoselectively in high yield (Table 1, entries 13–15). In addition, the acyclic substrate **1h** also reacted with high yield and selectivity (Table 1, entry 16). When enantiomerically enriched **1a**[18] and **1i**[19] were used, the enantiomeric purity of the product **3aa** and **3ia** were exactly identical to those of the starting oxiranes (Table 1, entries 9 and 17).[20]

Next, we explored nucleophiles other than arylboronic acids, and found that MeMgCl reacted analogously.[21] For example, treatment of substrate **1j** (1.0 equiv) with MeMgCl (3.0 equiv) in the presence of [{RhCl(nbd)}$_2$] (5 mol% of Rh) for 12 h at room temperature afforded the desired methylated α-allenol **3aa′** [Eq. (2); TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine]. However, the *syn* selectivity was lower than that observed with arylboronic acids.

In summary, we have developed a rhodium-catalyzed reaction that permits the construction of *syn*-configured α-allenols from alkynyl oxiranes and arylboronic acids. Occurring with a high level of diastereoselectivity under mild conditions, the reaction will become a good supplement to the well-studied copper-catalyzed reactions.

Experimental Section

Typical procedure: An oven-dried, Ar-purged flask was charged with [{RhCl(nbd)}$_2$] (4.3 mg, 9.3 μmol), **2a** (68.0 mg, 0.56 mmol), KOH (13.0 mg, 0.23 mmol), THF (1.8 mL), and a solution of **1a** (50.0 mg, 0.37 mmol) in THF (1.8 mL). The reaction mixture was stirred at room temperature for 2 h and quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was



removed under reduced pressure and the residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate 5:1) to give **3aa** (63.6 mg, 81%, *syn*/*anti* = 99:1) as a pale yellow oil.

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[1] Reviews: a) *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; b) S. Ma, *Chem. Rev.* **2005**, *105*, 2829 – 2871.
[2] Review: M. Ogasawara, T. Hayashi in *Modern Allene Chemistry*, *Vol. 1* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, pp. 93 – 140.
[3] M. Murakami, H. Igawa, *Helv. Chim. Acta* **2002**, *85*, 4182 – 4188.
[4] Reviews on cyclization of α-allenols: a) R. W. Bates, V. Satcharoen, *Chem. Soc. Rev.* **2002**, *31*, 12 – 21; b) A. S. K. Hashmi in *Modern Allene Chemistry*, *Vol. 2* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, pp. 877 – 923. For recent examples, see: c) S. Ma, Z. Gu, *J. Am. Chem. Soc.* **2005**, *127*, 6182 – 6183; d) B. Alcaide, P. Almendros, T. Martinez del Campo, *Angew. Chem.* **2006**, *118*, 4613 – 4616; *Angew. Chem. Int. Ed.* **2006**, *45*, 4501 – 4504, and references therein.
[5] Lower yields were observed with other diene ligands such as cyclohexa-1,4-diene, cycloocta-1,5-diene, and bicyclo[2.2.2]octa-2,5-diene.
[6] The hydroxy and phenyl groups are oriented on the same face in the *syn* isomer and on opposite faces in the *anti* isomer. The relative stereochemistry (*syn*/*anti*) was assigned by comparison with NMR spectra of the known *syn*- and *anti*-configured **3aa**.[9] The ratio was determined by HPLC analysis of the isolated mixture of the α-allenols.
[7] Reviews: a) F. Chemla, F. Ferreira, *Curr. Org. Chem.* **2002**, *6*, 539 – 570; b) N. Krause, A. Hoffmann-Röder, *Tetrahedron* **2004**, *60*, 11671 – 11694.
[8] Review: a) N. Krause, A. Hoffmann-Röder in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 145 – 166. Selected examples, b) A. C. Oehlschlager, E. Czyzewska, *Tetrahedron Lett.* **1983**, *24*, 5587 – 5590; c) C. R. Johnson, D. S. Dhanoa, *J. Org. Chem.* **1987**, *52*, 1885 – 1888; d) J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180 – 7184; e) C. Deutsch, B. H. Lipshutz, N. Krause, *Angew. Chem.* **2007**, *119*, 1677 – 1681; *Angew. Chem. Int. Ed.* **2007**, *46*, 1650 – 1653; f) C. Deutsch, A. Hoffmann-Röder, A. Domke, N. Krause, *Synlett* **2007**, 737 – 740.
[9] For a CuBr-catalyzed *syn*-selective reaction of **1a** with alkyl Grignard reagents in the presence of trimethylsilyl chloride, see: a) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677 – 1696. For a $Cu(OTf)_2$-catalyzed *syn*-selective reaction of **1d** with dialkylzinc reagents in the presence of TADDOL-derived phosphorus amidites, see: b) C. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Tetrahedron Lett.* **1999**, *40*, 4893 – 4896.
[10] J. Kjellgren, H. Sundén, K. J. Szabó, *J. Am. Chem. Soc.* **2005**, *127*, 1787 – 1796.
[11] M. Yoshida, H. Ueda, M. Ihara, *Tetrahedron Lett.* **2005**, *46*, 6705 – 6708.
[12] A. Fürstner, M. Méndez, *Angew. Chem.* **2003**, *115*, 5513 – 5515; *Angew. Chem. Int. Ed.* **2003**, *42*, 5355 – 5357.
[13] T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052 – 5058.
[14] a) T. Hayashi, K. Inoue, N. Taniguchi, M. Ogasawara, *J. Am. Chem. Soc.* **2001**, *123*, 9918 – 9919; b) M. Lautens, M. Yoshida, *Org. Lett.* **2002**, *4*, 123 – 125; c) E. Genin, V. Michelet, J.-P. Genêt, *Tetrahedron Lett.* **2004**, *45*, 4157 – 4161.
[15] a) M. Lautens, C. Dockendorff, K. Fagnou, A. Malicki, *Org. Lett.* **2002**, *4*, 1311 – 1314; b) M. Murakami, H. Igawa, *Chem. Commun.* **2002**, 390 – 391.
[16] P. Zhao, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 1876 – 1877.
[17] Alkyl- and alkenylboronic acids failed to successfully participate in the reaction under the same conditions.
[18] Z.-X. Wang, G.-A. Cao, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7646 – 7650.
[19] A. Fürstner, E. Kattnig, O. Lepage, *J. Am. Chem. Soc.* **2006**, *128*, 9194 – 9204.
[20] For the synthesis of optically active α-allenols, see: a) D. Xu, Z. Li, S. Ma, *Chem. Eur. J.* **2002**, *8*, 5012 – 5018; b) M. Inoue, M. Nakada, *Angew. Chem.* **2006**, *118*, 258 – 261; *Angew. Chem. Int. Ed.* **2006**, *45*, 252 – 255; c) E. Hernandez, C. H. Burgos, E. Alicea, J. A. Soderquist, *Org. Lett.* **2006**, *8*, 4089 – 4091; d) G. Xia, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 496 – 497, and references therein.
[21] For other example of the rhodium-catalyzed addition of MeMgCl, see: a) T. Miura, M. Shimada, M. Murakami, *Chem. Asian J.* **2006**, *1*, 868 – 877. For an example of the rhodium-catalyzed addition of Me_2Zn, see: b) T. Nishimura, Y. Yasuhara, T. Hayashi, *Org. Lett.* **2006**, *8*, 979 – 981.

