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RHODIUM-CATALYZED DIASTEREOSELECTIVE COUPLING OF PROPARGYLIC OXIRANES WITH ARYLBORONIC ACIDS IN WATER‡

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Abstract – A diastereoselective coupling of propargylic oxiranes with arylboronic acids in aqueous condition is described. 4-Aryl-substituted 2,3-allenols having *syn*-geometries were selectively synthesized by the rhodium-catalyzed reactions in water.

INTRODUCTION

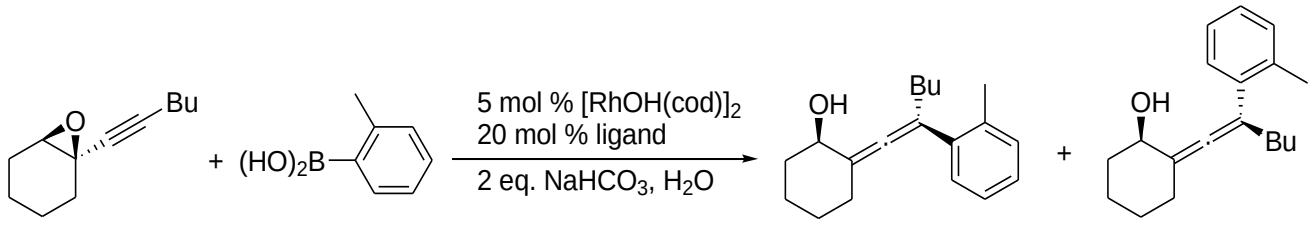
Functionalized allenes are versatile building blocks for organic synthesis because of their inherent reactivity as axially chiral backbones.[1] Furthermore, of the large number of natural products containing an allene moiety that have been isolated, most have axial chirality.[2] For these reasons, extensive studies on the synthesis of allenes have been undertaken,[1] and the S_N2'-type substitution reaction of propargylic oxiranes with organometallic reagents has emerged as one of the most successful procedures to afford 2,3-allenols.[3] For example, we have developed a palladium-catalyzed coupling reaction of propargylic oxiranes with arylboronic acids[4] that proceeds in aqueous media to give the aryl-substituted 2,3-allenols with excellent *anti*-diastereoselectivity. Murakami also recently reported a similar coupling reaction using a rhodium catalyst, in which *syn*-configured aryl-substituted 2,3-allenols were synthesized in a highly diastereoselective manner.[5] In recent years, in view of current environmental concerns, the use of organic reactions in aqueous media has increased considerably, and the development of reactions proceeding in water has become one of the most exciting research endeavors in chemistry.[7] Consequently, during the course of our studies on transition metal-catalyzed reactions in aqueous media,[4,6] we decided to investigate the use of water as a solvent in the rhodium-catalyzed coupling of propargylic oxiranes with arylboronic acids. Herein, we describe our results.

‡ This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

RESULTS AND DISCUSSION

The initial reactions were carried out using the butyl-substituted propargylic oxirane **1a**.[8] When **1a** was treated with 5 mol % of $[RhOH(cod)]_2$ and 2 equiv $NaHCO_3$ in neat water at 50 ºC for 1 h, the *syn*- and *anti*-configured 4-aryl- 2,3-allenols *syn*-**3aa** and *anti*-**3aa** were produced in a 7.5:1 ratio and 55% yield (entry 1 Table 1). The stereochemistry of **3aa** was determined unambiguously by NOESY correlation of the dihydrofuran **4**, which was stereoselectively derived from the iodine-induced cyclization[9] of *syn*-**3aa** (Scheme 1). Further attempts revealed that the presence of the water-soluble ligand TPPDS enhanced the diastereoselectivity. Thus, the reaction with TPPDS was successful and afforded the product **3aa** in a 9.5:1 ratio and 57% yield (entry 2). The ratios and yields of **3aa** were influenced by the reaction temperature and the reaction time (entries 3–5), and the best result was obtained by carrying out the reaction at 80 ºC for 0.5 h (*syn*:*anti* = 11:1, 58% yield in entry 4). The reaction also proceeded when other water soluble ligands, TPPMS and Cy-amphos, were used to produce **3aa** in a 6.3:1 ratio in 50% yield and in an 18:1 ratio in 43% yield, respectively (entries 6 and 7).

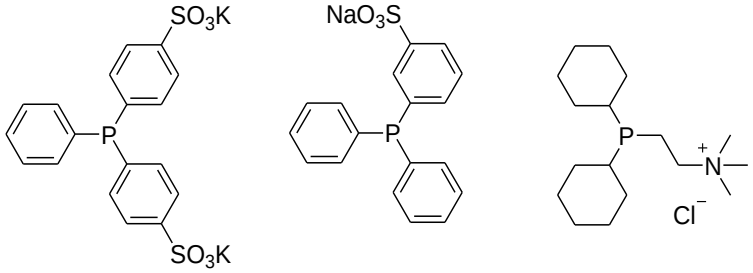
Table 1 Rhodium-Catalyzed Cyclizations of **1a** with **2a**.



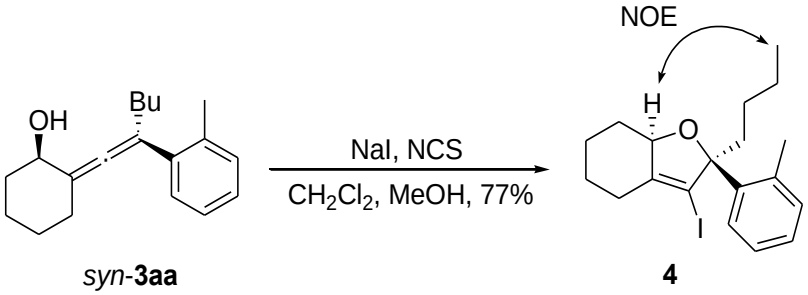
1a **2a** *syn*-**3aa** *anti*-**3aa**

Entry	Ligand	Temp (ºC)	Time (h)	Products **3aa**	
				Total yields (%)	*syn*:*anti*[a]
1	–	50	1	55	7.5:1
2	TPPDS	50	1	57	9.5:1
3	TPPDS	30	1	61	5.3:1
4	TPPDS	80	0.5	58	11:1
5	TPPDS	100	0.25	48	13:1
6	TPPMS	80	0.5	50	6.3:1
7	Cy-amphos Cl	80	0.5	43	18:1

[a]The ratios were determined by ^{1}H-NMR integration of the methine proton signals on the hydroxyl-bearing carbon.



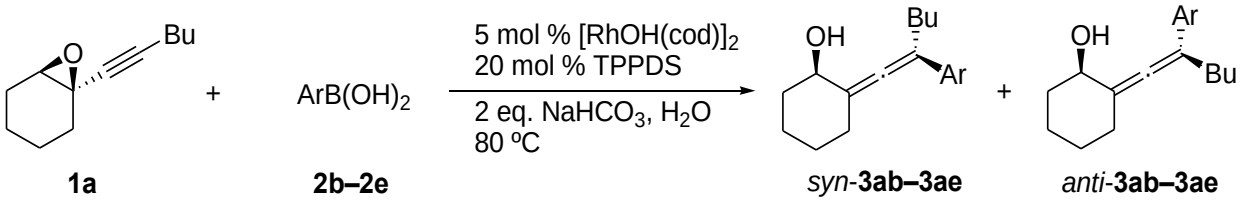
TPPDS TPPMS Cy-amphos



Scheme 1. Determination of the Stereochemistry of *syn*-**3aa**

A series of substituted arylboronic acids **2b–2e** was next subjected to the reaction (Table 2). The corresponding products **3ab** and **3ac** were obtained with high *syn*-selectivities in moderate yields when the reactions of **1a** with 2-methoxy- and 4-methylphenylboronic acids (**2b** and **2c**) were carried out (entries 1 and 2). The selectivity and yield of the product **3ad** were lower in the reaction with naphthalen-1-ylboronic acid (**2d**) (*syn*:*anti* = 9:1, 38% yield in entry 3). However, when 2-methylnaphthalen-1-ylboronic acid (**2e**) was employed, the corresponding product **3ae** was obtained with high diastereoselectivity (entry 4).

Table 2. Reactions of **1a** with arylboronic acids **2b–e**.

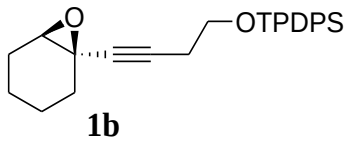
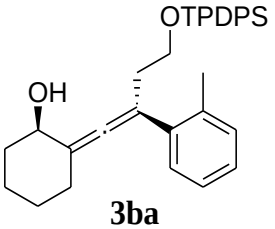
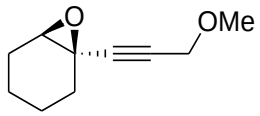
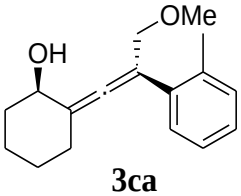
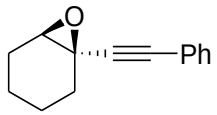
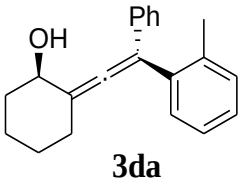


Entry	Ar	Product[a]	Total yields (%)	*syn*:*anti*[b]
1	**2b**: 2-methoxyphenyl	**3ab**	52	>20:1
2	**2c**: 4-methylphenyl	**3ac**	42	>20:1
3	**2d**: naphthalen-1-yl	**3ad**	38	9:1
4	**2e**: 2-methylnaphthalen-1-yl	**3ae**	55	>20:1

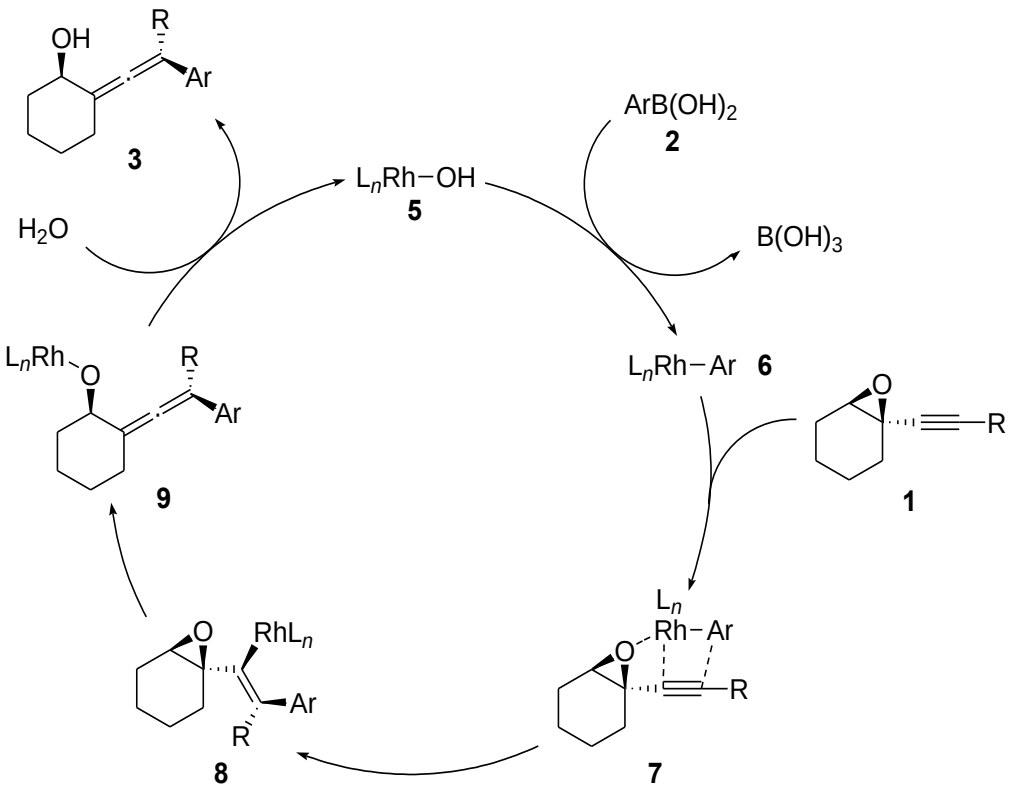
[a]The stereochemistry of each product was tentatively assigned by comparison of its ^{1}H-NMR spectra with **3aa**. [b]The ratios were determined by ^{1}H-NMR integration of the methine proton signals on the hydroxyl-bearing carbon.

Table 3 shows our attempts using the propargylic oxiranes **1b–1d** having various substituents at the alkynyl position. When the reaction of the silyloxyethyl-substituted substrate **1b** with **2a** was examined, the corresponding coupled allene **3ba** was produced in a 5:1 ratio in 48% yield (entry 1). The diastereoselectivity of the corresponding product **3ca** was lower when the propargylic oxirane **1c** having a methoxymethyl group was examined (*syn*:*anti* = 3:1, 53% yield in entry 2). In contrast, the phenyl-substituted substrate **1d** reacted with **2a** to deliver the coupled allene **3da** with high *syn*-selectivity (*syn*:*anti* = >20:1, 41% yield in entry 3).

Table 3. Reactions of various propargylic oxiranes **1b-1d** with **2a**.[a]

Entry	Substrate	Product[b]	*syn*:*anti*[c]	Total yields (%)
1	 **1b**	 **3ba**	5:1	48
2	 **1c**	 **3ca**	3:1	53
3	 **1d**	 **3da**	>20:1	41

[a]Reactions were carried out with **2a** in the presence of 5 mol % $[Rh(cod)]_2$, 20 mol % TPPDS and 2 eq $NaHCO_3$ in water at 80 °C for 0.5 h. [b]The stereochemistry of each product was tentatively assigned by comparison of its ^{1}H-NMR spectra with **3aa**. [c]The ratios were determined by ^{1}H-NMR integration of the methine proton signals on the hydroxy-bearing carbon.



Scheme 2. Proposed Reaction Mechanism

A plausible mechanism for the reaction is shown in Scheme 2. It is presumed that the (hydroxo)rhodium(I) complex **5** is the active species in this reaction, and a catalytic cycle would involve the transmetalation of the arylboronic acid to the complex **5** yielding the arylrhodium species **6** as the initial step. The coordination of the alkyne and oxiranyl oxygen of the substrate to rhodium **7**, followed by regioselective insertion into the Rh-C bond would give the alkenylrhodium complex **8**. Subsequent β-oxygen elimination occurs in a *syn* mode to open the oxirane ring. Finally, the hydrolysis of the resulting complex **9** with water affords the *syn*-4-aryl-substituted 2,3-allenol **3** along with the regenerated rhodium complex **5**. The minor *anti*-substituted products would be produced by the β-oxygen elimination in *anti* mode.[10] As the cause of the increased selectivity at the elevated temperature (entries 3–5 in Table 1), it is presumed that the isomerization of the resulting allene[11] *syn*-**3** to *anti*-**3** could be suppressed as the result of short reaction time.

In conclusion, we have developed a coupling reaction of propargylic oxiranes with arylboronic acids in aqueous media. A variety of 4-aryl-substituted 2,3-allenols having the *syn* configuration were synthesized in neat water by a rhodium catalyst in combination with the water-soluble ligand TPPDS.

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8. **General procedure for the rhodium-catalyzed coupling reaction (Entry 4, Table 1).** To a stirred solution of the propargylic oxirane **1a** (21.2 mg, 0.119 mmol) in H_2O (2 mL) were added 2-methylphenylboronic acid (**2a**) (32.3 mg, 0.238 mmol), $NaHCO_3$ (20.0 mg, 0.238 mmol), $[RhOH(cod)]_2$ (2.7 mg, 5.95 μmol) and TPPDS (10.9 mg, 23.8 μmol) at rt, and stirring was continued for 0.5 h at 80 °C. After addition of AcOEt to the reaction mixture, the mixture was stirred vigorously for 1 h at rt and then extracted with AcOEt. The combined extracts were washed with 10% NaOH aq. and brine, and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (95 : 5 v/v) as eluent to give a diastereomeric mixture of arylallenes *syn*-**3aa** and *anti*-**3aa** (18.6 mg, 58%, *syn* : *anti* = 11 : 1) as a colorless oil. *syn*-**3aa**: Colorless oil; IR (neat) 3426, 2929, 1959, 1598 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.32−1.43 (m, 7H), 1.61−1.68 (m, 1H), 1.74−1.79 (m, 1H), 1.74−1.79 (m, 1H), 1.96−1.99 (m, 1H), 2.06−2.13 (m, 1H), 2.26−2.34 (m, 2H), 2.36 (s, 3H), 2.44−2.48 (m, 1H), 4.09−4.11 (m, 1H), 7.12−7.21 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.0, 20.6, 22.3, 23.3, 26.7, 29.6, 30.1, 34.2, 35.6, 69.4, 107.6, 108.5, 125.7, 126.7, 128.1, 130.4, 135.5, 138.5, 194.2; MS (EI) *m/z* 270 [M^+]; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O$ 270.1984 (M^+), found 290.1990. *anti*-**3aa**: Colorless crystals. mp 31–32 °C; IR (neat) 3416, 2857, 1958, 1597 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.0 Hz), 1.50–1.35 (7H, m), 1.89–1.69 (3H, m), 2.13–1.98 (2H, m), 2.33 (3H, s), 2.49–2.24 (3H, m), 3.99–3.93 (1H, m), 7.19–7.09 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.0, 20.5, 22.4, 23.9, 26.9, 30.1, 34.0, 36.2, 69.1, 108.5, 109.4, 125.7, 126.7, 127.9, 130.3, 135.4, 138.4, 193.4; MS (EI) *m/z* 270 (M^+); HRMS (EI) *m/z* calcd for $C_{19}H_{26}O$ 270.1984 (M^+), found 270.1972.
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