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Palladium-Catalyzed Diastereoselective Coupling of Propargylic Oxiranes with Terminal Alkynes

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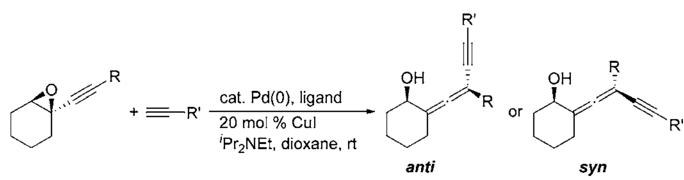
ABSTRACT



A diastereoselective coupling of propargylic oxiranes with terminal alkynes has been developed with use of a palladium catalyst. The stereochemistries of the resulting 4-alkynyl-substituted 2,3-allenols have been altered depending on the palladium catalyst. An optically active *anti*-substituted allene was synthesized from the reaction of an enantiomerically enriched propargylic oxirane without loss of chirality.

Substituted allenes are versatile building blocks for organic synthesis because of the inherent reactivity of their axially chiral backbones.[1] In addition, many natural products containing the allenic moiety have been isolated, and most of these have axial chirality.[2] As a result, the synthesis of substituted allenes has been extensively studied,[1] especially the palladium-catalyzed coupling of propargylic oxiranes, which is one of the most common methods. Organozinc,[3] stannane,[4] and -boron reagents[5] and carbon monoxide[6] were reacted with propargylic oxiranes in the presence of palladium to furnish the corresponding 4-substituted 2,3-allenols. The diastereoselectivity of the couplings was further examined,[4,5] and *anti*-substituted allenols were diastereoselectively produced via an *anti*-S_N2' attack of palladium on the propargylic oxiranes. During the course of our studies on the reaction of propargylic oxiranes in the presence of palladium catalysts,[5,7] we focused on the diastereoselective coupling with terminal alkynes.[8] Herein we describe a palladium-catalyzed coupling of propargylic oxiranes with terminal alkynes. The stereochemistries of the resulting 4-alkynyl-substituted 2,3-allenols have been altered depending on the palladium catalyst.

The initial reactions were carried out with the phenyl-substituted propargylic oxirane **1a** and trimethylsilylacetylene (**2a**). When **1a** and **2a** were subjected to the reaction with

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(2) (a) Krause, N.; Hoffmann-Röder, A. Allenic Natural Products and Pharmaceuticals. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 997. (b) Landor S. R. Naturally Occurring Allenes. In *The Chemistry of the Allenes*; Landor S. R., Ed.; Academic Press: London, UK, 1982; p 679. (c) Claesson, A. Biologically Active Allenes. In *The Chemistry of the Allenes*; Landor S. R., Ed.; Academic Press: London, UK, 1982; p 709. (d) Robinson, C. H.; Covey, D. F. Biological Formation and Reactions; In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai S., Ed.; Wiley: Chichester, UK, 1980; p 451.

(3) Kleijn, H.; Meijer, J.; Overbeek, G. C.; Vermeer, P. *Recl. Trav. Chim. Pay-Bas.* **1982**, *101*, 97.

(4) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 1787.

(5) Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705.

(6) Knight, J. G.; Ainge, S. W.; Baxter, C. A.; Eastman T. P.; Harwood, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3188.

(7) Yoshida, M.; Morishita, Y.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 3669.

(8) It has been reported that palladium-catalyzed coupling reactions of optically active propargylic carbonates with alkynylzinc reagents afford optically active allenes in an enantiospecific manner; however, the absolute configuration of the resulting allenes has not been determined: Dixneuf, P. H.; Guyot, T.; Ness, M. D.; Roberts, S. M. *Chem. Commun.* **1997**, 2083.

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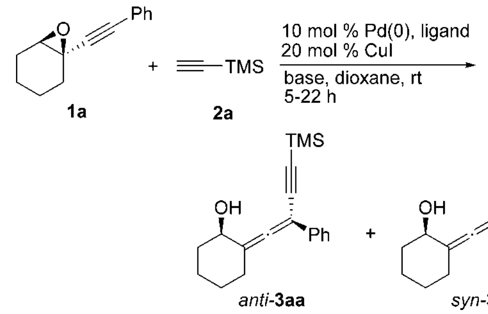
10 mol % of $Pd(PPh_3)_4$, 20 mol % of CuI, and Et_3N in dioxane at rt for 14 h, the *anti*- and *syn*-4-alkynyl-substituted 2,3-allenols *anti*-**3aa** and *syn*-**3aa** were produced in a 1:1.6 ratio and 76% yield (entry 1 in Table 1). The stereochemistry

Table 1. Reactions of Propargylic Oxirane **1a** with Alkyne **2a**

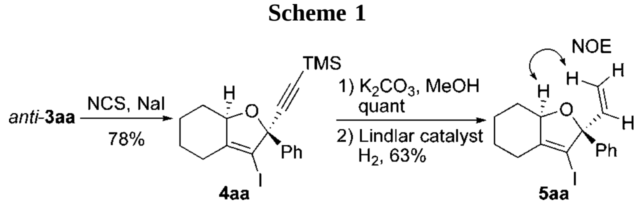


entry	ligand	base	additive	total yields (%)[a]	ratio[b] *anti*:*syn*
1[c]	PPh_3	Et_3N		76	1:1.6
2[c]	PPh_3	Et_2NH		19 (51)	1:3
3[c]	PPh_3	Bu_3N		38	1:2
4[c]	PPh_3	DABCO		45	1:1.4
5[c]	PPh_3	$^{i}Pr_2NEt$		72	1:2
6[d]	$P(4\text{-}MeOC_6H_4)_3$	$^{i}Pr_2NEt$		52	1:2
7[e]	dppf	$^{i}Pr_2NEt$		92	2.4:1
8[e]	dppm	$^{i}Pr_2NEt$		71 (88)	2.6:1
9[e]	dppe	$^{i}Pr_2NEt$		94	>20:1
10[e]	dppp	$^{i}Pr_2NEt$		87 (91)	14:1
11[e]	dppb	$^{i}Pr_2NEt$		59 (75)	4.7:1
12[e,f]	dppe	$^{i}Pr_2NEt$	DMSO	70	2.3:1
13[e,f]	dppe	$^{i}Pr_2NEt$	HMPA	83	2.6:1
14[e,f]	dppe	$^{i}Pr_2NEt$	NMP	95	3.4:1

[a] The yields in parentheses are based on recovered starting material. [b] The ratios were determined by ^1H NMR integration of the methine proton signals on the hydroxy-bearing carbon. [c] 10 mol % $Pd(PPh_3)_4$ was used. [d] 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 40 mol % ligand were used. [e] 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 20 mol % ligand were used. [f] 5 equiv of additives were used.

of **3aa** was determined unambiguously by NOESY correlation of the vinyldihydrofuran **5aa**, which was derived from *anti*-**3aa** (Scheme 1). Thus, iodine-induced cyclization[9] of

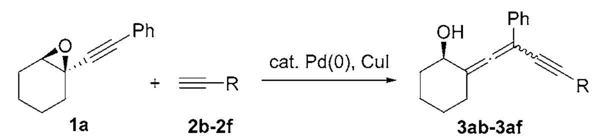
Scheme 1



anti-**3aa** stereoselectively afforded the dihydrofuran **4aa**, which was further transformed to **5aa** by desilylation and hydrogenation of the alkynyl moiety. Although the diastereoselectivity was low, it is interesting to note that the *syn*-substituted allene *syn*-**3aa** was produced predominantly under these reaction conditions. Similar results were obtained when other amines were used (entries 2−5). In the presence of $^{i}Pr_2NEt$, *anti*- and *syn*-**3aa** were produced in a 1:2 ratio and 72% yield (entry 5). Furthermore, it is now clear that the stereochemical course of the reaction is altered depending on the phosphine ligand used (entries 5−11). Contrary to the *syn*-selectivities for reactions with monodentate ligands (entries 4 and 5), *anti*-**3aa** was the predominant product in the presence of bidentate ligands (entries 6−11). High *anti*-selectivity was observed when dppe was employed as the ligand (entry 9). Further attempts to determine the effect of additives revealed that the *anti*-selectivities were lowered in the presence of polar solvents such as DMSO, HMPA, and NMP (entries 12−14).

Reactions of **1a** with various substituted terminal alkynes **2b**−**f** are summarized in Table 2. The *syn*-substituted allenes

Table 2. Reactions of **1a** with Various Alkynes **2b**−**f**



entry	R	condition[a]	product	total yields (%)	ratio[b] *anti* : *syn*[c]
1	TBS **2b**	A	**3ab**	quant	1 : 2.1
2		B	**3ab**	80	>20 : 1
3	OTBDPS **2c**	A	**3ac**	77	1 : 2.5
4		B	**3ac**	83	16 : 1
5	OTBDPS **2d**	A	**3ad**	66	1 : 2.0
6		B	**3ad**	91	>20 : 1
7	Bu **2e**	A	**3ae**	66	1 : 2.6
8		B	**3ae**	80	>20 : 1
9	Ph **2f**	A	**3af**	83	1.4 : 1
10		B	**3af**	66	>20 : 1

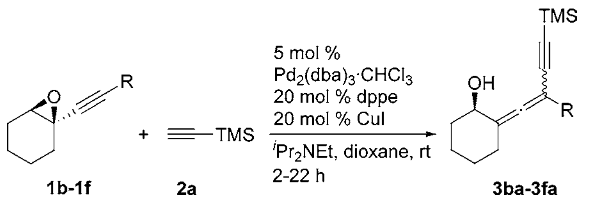
[a] Condition A: Reactions were carried out in the presence of 10 mol % $Pd(PPh_3)_4$, 20 mol % CuI and 5 equiv of $^{i}Pr_2NEt$ in dioxane at rt. Condition B: Reactions were carried out in the presence of 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol % dppe, 20 mol % CuI, and 5 equiv of $^{i}Pr_2NEt$ in dioxane at rt. [b] The ratios were determined by ^1H NMR integration of the methine proton signals on the hydroxy-bearing carbon. [c] The stereochemistries of each of the products were tentatively assigned by comparison of its NMR spectrum with **3aa**.

syn-**3ab**−**ae** were predominantly obtained from the reactions with **2b**−**e** in the presence of $Pd(PPh_3)_4$ (condition A, entries 1, 3, 5, and 7). When the styryl-substituted alkyne **2f** was used, no *syn*-predominance was observed (entry 9). On the other hand, high *anti*-selectivities were observed to give the corresponding substituted allenes *anti*-**3ab**−**af** when palladium-catalyzed reactions with **2b**−**f** were carried out in the presence of dppe (condition B, entries 2, 4, 6, 8, and 10).

Table 3 shows our attempts using the propargylic oxiranes **1b**−**f** having various R substituents at the alkynyl position

(9) Schultz-Fademrecht, C.; Zimmermann, M.; Fröhlich, R.; Hoppe. D. *Synlett* **2003**, 1969.

Table 3. Reactions with Various Propargylic Oxiranes **1a**−**f** with **2a**



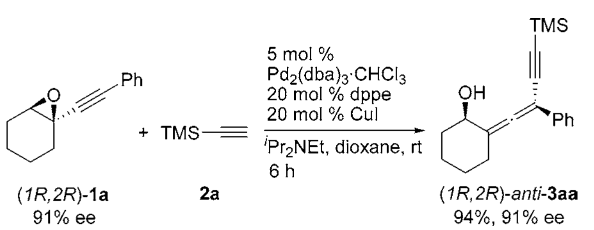
entry	R	product	total yields (%)	ratio[a] *anti*:*syn*
1	TBS (**1b**)	**3ba**	63	>20:1[b]
2	TMS (**1c**)	**3ca**	75	8.4:1[b]
3	benzyl (**1d**)	**3da**	84	3.4:1[c]
4	butyl (**1e**)	**3ea**	94	2.1:1[b]
5	H (**1f**)	**3fa**	57	1.6:1[b]

[a] The ratios were determined by ^1H NMR integration of the methine proton signals on the hydroxy-bearing carbon. [b] The stereochemistry of each product was tentatively assigned by comparison of its NMR spectrum with **3aa**. [c] The stereochemistry was determined unambiguously by NOESY correlation of dihydrofuran **5da**, which was obtained from **3da** by following the same procedure as shown in Scheme 1.

with the alkyne **2a**. When these substrates were subjected to the palladium-catalyzed reactions in the presence of dppe, the corresponding coupled allenes with *anti*-geometry were selectively produced (entries 1−5). The *anti*-coupled product *anti*-**3ba** was the sole product of the reaction with the substrate **1b**, which has a TBS group (entry 1). The diastereoselectivities were lowered when the benzyl-, butyl-, and non-substituted substrates **1d**, **1e**, and **1f** were employed (entries 3−5). These results show that the diastereoselectivity is greatly influenced by the steric bulk of the substituent R.

We attempted further reactions using the enantiomerically enriched propargylic oxirane (*1R*,*2R*)-**1a** (Scheme 2). When

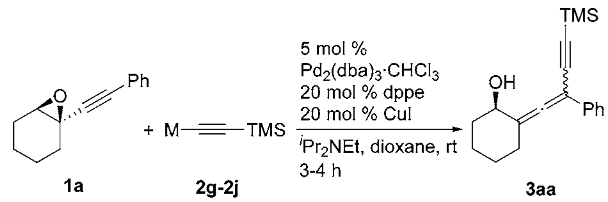
Scheme 2



(*1R*,*2R*)-**1a** (91% ee) was reacted with **2a** in the presence of dppe, the corresponding optically active coupled product (*1R*,*2R*)-*anti*-**3aa** was obtained in 94% yield. The enantiomeric excess was determined to be 91%, indicating that the chirality of the propargylic oxirane had been completely transferred to the axial chirality of allenes.

To examine the reactivity of alkynylmetal reagents for the coupling, we next attempted reactions of **1a** with the alkynylmetals **2g**−**j**. Alkynylzinc chloride **2g** reacted with **1a** in the presence of 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % of dppe, and 20 mol % of CuI[10] to provide the coupled

Table 4. Reactions of **1a** with Alkynylmetal Reagents **2g**−**j**



entry	alkynylmetal reagent		total yields (%)[a]	ratio[b] *anti* : *syn*
1	ClZn—≡—TMS	**2g**	45 (61)	3.2 : 1
2	Zn(—≡—TMS)$_2$	**2h**	quant.	8 : 1
3	ClMg—≡—TMS	**2i**	81	>20 : 1
4	Li^+ [(^{i}PrO)$_3$B—≡—TMS]$^-$	**2j**	76	>20 : 1

[a] The yields in parentheses are based on recovered starting material. [b] The ratios were determined by ^1H NMR integration of the methine proton signals on the hydroxy-bearing carbon.

anti- and *syn*-**3aa** in a 3.2:1 ratio and 45% isolated yield (entry 1 in Table 4). The successful reaction with the dialkynyl reagent **2h** gave **3aa** in quantitative yield (*anti*:*syn* = 8:1, entry 2). The alkynylmagnesium and the alkynylboronate reagents **2i** and **2j** were also coupled with **1a** to afford *anti*-**3aa** as the sole product in 81% and 76% yield, respectively (entries 3 and 4).

A plausible mechanism for the diastereoselectivities is shown in Scheme 3. Regio- and stereoselective *anti*-S_N2' attack of the palladium on the propargylic oxirane **1** takes place in the first step to yield the allenylpalladium *anti*-**6**. When a bidentate ligand is used, direct transmetallation of *anti*-**6** with the copper acetylide proceeds to produce the *anti*-substituted allene *anti*-**3** via the intermediate *anti*-**7** in a diastereoselective manner. On the other hand, isomerization of the allenylpalladium *anti*-**6** to *syn*-**6** would be caused by the presence of monodentate ligands. It has been reported that optically active allenylpalladium is racemized through the formation of the dinuclear complex.[11] We anticipated an equilibrium between the allenylpalladiums *anti*-**6** and *syn*-**6** via the dinuclear complex, in which the *syn*-**6** isomer could be preferentially formed because of the interaction between the zwitterionic palladium cation and the hydroxyl anion. As a result, the reaction furnished predominantly the *syn*-substituted product *syn*-**3** via the intermediate *syn*-**7**.

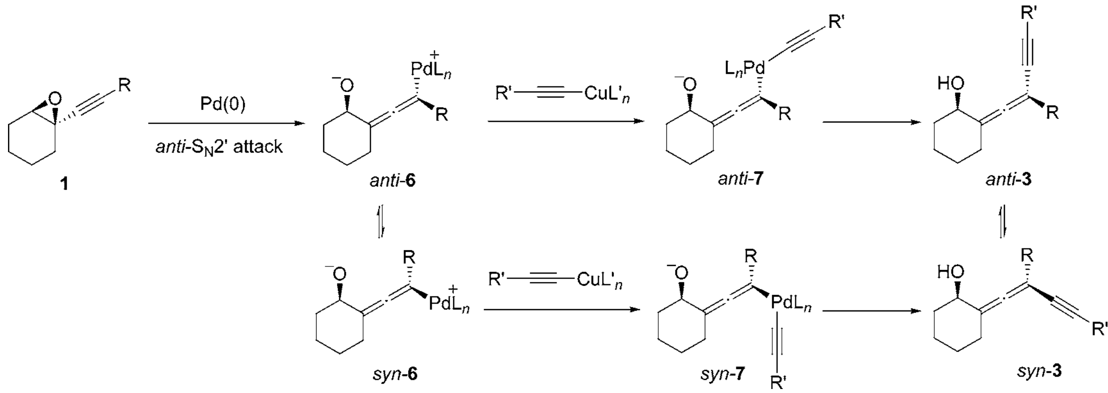
Another possible explanation for the appearance of *syn*-predominance is the isomerization of the resulting allenes *anti*-**3** to *syn*-**3**. It was recently reported that optically active allenes were racemized in the presence of palladium(II)/LiBr, in which the racemization proceeded via the *anti*-bromopalladation process.[12] To examine whether a similar process occurred in the coupling reaction, we attempted the isomer-

(10) When the reactions were carried out in the absence of CuI, the yields of **3aa** dramatically decreased (<18% yields).

(11) Ogoshi, S.; Nishida, T.; Shinagawa, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 7164.

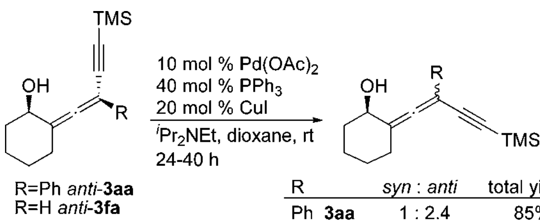
(12) Horváth, A.; Bäckvall, J. E. *Chem. Commun.* **2004**, 964.

Scheme 3



ization of *anti*-**3aa** to *syn*-**3aa** using a palladium catalyst (Scheme 4). When *anti*-**3aa** was treated with 10 mol % of

Scheme 4



R	*syn* : *anti*	total yields
Ph **3aa**	1 : 2.4	85%
H **3fa**	1 : 1.1	75%

$Pd(OAc)_2$, 40 mol % of PPh_3, 20 mol % of CuI, and $^iPr_2NEt$ in dioxane at rt, the isomerized product *syn*-**3aa** was produced as a diastereomeric mixture with *anti*-**3aa**. Although the inversion of the stereochemistry from *anti* to *syn* was not observed (*syn*:*anti* = 1:2.4), the ratio shifted to *syn*:*anti* = 1:1.1 when *anti*-**3fa** was subjected to the reaction. These results indicated that partical isomerization of *anti*-**3** to *syn*-**3** occurred during the reacion.[13,14] As the reasons for the lowered *anti*-selectivities in the presence of polar solvents (entries 12−14 in Table 1) or in the case of substrates having small R groups (entries 3−5 in Table 3), it is presumed that the isomerization of the allenylpalladium *anti*-**6** or the alkynylallene *anti*-**3** was accelerated under these reaction conditions.

In summary, the studies described above have resulted in the diastereoselective synthesis of 4-alkynyl-substituted 2,3-allenols by a palladium-catalyzed coupling between propargylic oxiranes and terminal alkynes. The stereoselectivity of the reaction can be altered by the choice of phosphine ligand. It is noteworthy that *syn*-substituted allenes were predominantly produced by the palladium-catalyzed couplings although the diastereoselectivities were low.

Acknowledgment. This study was supported in part by a Grant-in-Aid for the Encouragement for Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS) and the Takeda Science Foundation.

Supporting Information Available: Starting material preparations, spectral data, and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) When $Pd(PPh_3)_4$ was used instead of $Pd(OAc)_2$ and PPh_3 as the palladium catalyst, the production of *syn*-**3aa** was decreased (*syn*-**3aa**:*anti*-**3aa** = 1:6.5, 91% total yields). The result implies that the palladium(II) species which is partly generated in situ during the coupling process causes the isomerization of the resulting allenes.

(14) Recently, Molander et al. reported the racemization of chiral alkenylallenes in the palladium-catalyzed coupling of propargylic phosphates with alkenyl trifluoroborates: Molander, G. A.; Sommers, E. M.; Baker. S. R. *J. Org. Chem.* **2006**, *71*, 1563.