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The synthesis of allenes by Cu(I)-catalyzed regio- and stereoselective reduction of propargylic carbonates with hydrosilanes†

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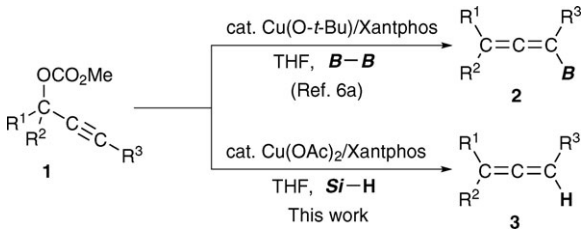
Cu(I)-catalyzed *anti*-S_N2'-type reduction of internal propargylic carbonates with hydrosilanes affords various di- and trisubstituted allenes with high regioselectivities; the reactions are compatible with functional groups and work efficiently for the synthesis of optically-active allenes.

The development of efficient synthetic methods for the production of allenes has received considerable attention because they have widespread applications in the synthesis of biologically- and pharmacologically-active compounds.[1] The highly selective reduction of propargylic alcohols or their derivatives with transition metal catalysts is an attractive method for allene synthesis. However, there are only a few examples of transition metal-catalyzed reactions that fulfil the following requirements: high S_N2'/S_N2 selectivity in the introduction of hydride, high reactivity towards substrates with bulky substituents, good functional group compatibility and high enantiomeric purity of the product in reactions of optically pure substrates.

The palladium-catalyzed reduction of formate derivatives of propargylic alcohols was first reported by Tsuji and co-workers in 1993.[2] These reactions suffer from low S_N2'/S_N2 selectivity, and their applicability to bulky trisubstituted substrates remains unresolved. The highly regioselective reduction of propargylic esters with a stoichiometric Cu(I) hydride ($[HCuPPh_3]_6$, Stryker's reagent) is known.[3] A catalytic method for this reaction was first reported by Krause and co-workers using a Cu(I)–NHC/hydrosilane (NHC: nitrogen-containing heterocyclic carbene) catalyst system. Here, propargylic oxiranes were converted to their corresponding α-hydroxyallenes in a highly regio- and stereoselective manner.[4] Lipshutz and co-workers also mentioned a Cu(I)–NHC-catalyzed reduction of propargylic esters in a review paper;[5] however, only two examples were reported. Despite these pioneering research efforts, the scope of the Cu(I)/hydrosilane catalytic system has not been fully explored in the regioselective reduction of propargylic esters.

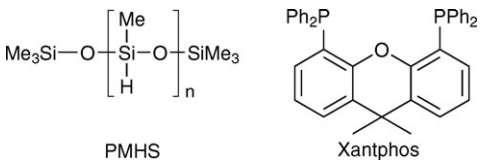
We recently reported a Cu(I)/Xantphos-catalyzed highly S_N2'-selective borylation of propargylic carbonates with diboron (Scheme 1, from **1** to **2**).[6] Here, we report that a similar reaction using a hydride compound instead of diboron



Scheme 1 Copper-catalyzed S_N2'-type reactions of propargylic carbonates.

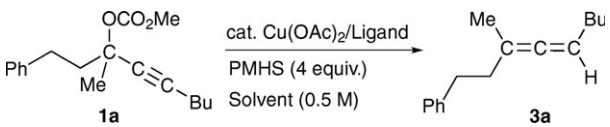
can serve as an attractive method for the synthesis of allenes through an S_N2'-type selective reduction of propargylic alcohol derivatives (Scheme 1, from **1** to **3**).

To obtain the optimal reaction conditions, we used propargylic carbonate **1a** and polymethylhydrosiloxane (PMHS) as the substrate and reducing agent, respectively (Table 1).



Initial experiments utilized the Cu(O–*t*-Bu)/Xantphos catalyst, which is quite effective for the borylation of

Table 1 The Cu(I)-catalyzed S_N2' selective reduction of propargylic carbonate **1a** with PMHS[a]



Entry	Ligand	Mol% Cu	Solvent	T/°C	t/h	Yield (%)[b]
1	Xantphos	5	THF	23	4	66
2	Xantphos	5	THF	50	1	69
3	Xantphos	2	THF	50	1.5	73
4[c,d]	Xantphos	2	THF	50	1	73 (68)
5	Xantphos	5	Toluene	23	4	62
6	Xantphos	5	DMI	23	4	20
7	dppp	5	THF	23	12	6
8	dppe	5	THF	23	12	2
9	dppf	5	THF	23	12	7
10	PPh_3	5	THF	23	12	20
11	1,10-Phenanthroline	5	THF	23	12	1

[a] Reaction conditions: carbonate **1a** (0.5 mmol), solvent (1.0 mL), PMHS (4.0 equiv., 2.0 mmol), $Cu(OAc)_2$ (0.01–0.025 mmol) and ligand (0.01–0.025 mmol). [b] Determined by GC. [c] 3 mol% of Xantphos was used. [d] Isolated yield in parentheses.

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† Electronic supplementary information (ESI) available: Detailed synthetic procedures and analytical data for all new compounds are available. See DOI: 10.1039/b910192f

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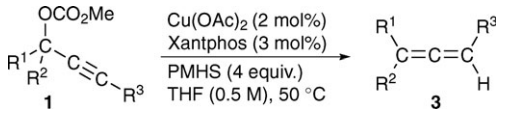
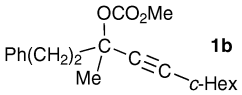
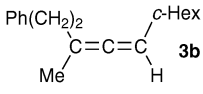
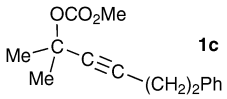
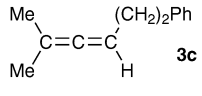
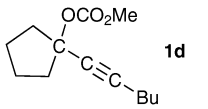
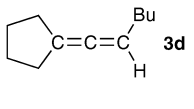
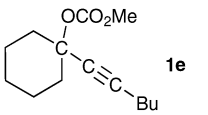
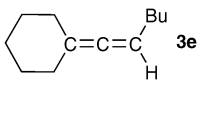
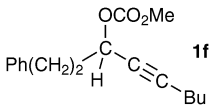
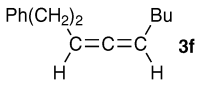
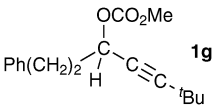
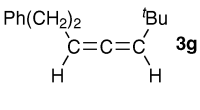
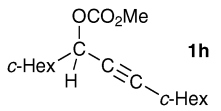
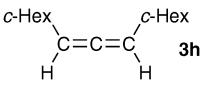
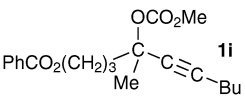
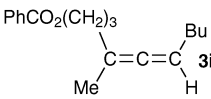
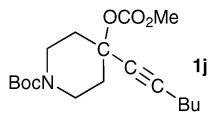
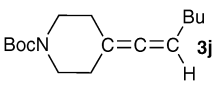
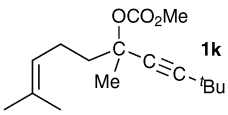
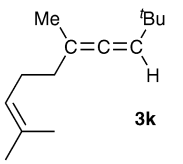
Table 2 S_N2' selective reduction of propargylic carbonates **1** with PMHS[a]



Entry	Carbonate	Allene	*t*/min	Yield (%)[b]
1	 **1b**	 **3b**	105	86
2	 **1c**	 **3c**	45	51
3	 **1d**	 **3d**	50	56
4	 **1e**	 **3e**	90	46
5	 **1f**	 **3f**	60	50
6	 **1g**	 **3g**	90	86
7	 **1h**	 **3h**	180	78
8	 **1i**	 **3i**	70	77
9	 **1j**	 **3j**	90	44
10	 **1k**	 **3k**	600	82

[a] Reaction conditions: Cu(II) acetate (2 mol%, 0.01 mmol), Xantphos (3 mol%, 0.015 mmol), THF (1.0 mL), PMHS (4.0 equiv, 2.0 mmol) and **1** (0.5 mmol). [b] Isolated yield.

propargylic carbonates,[6a] affording 60% of allene **3a** after 4 h at room temperature (data not shown). Yun *et al.* have reported that easy-to-handle $Cu(OAc)_2$ can be used instead of Cu(O–*t*-Bu) in copper-catalyzed hydrosilylation and reduction reactions.[7] The use of $Cu(OAc)_2$ rather than Cu(O–*t*-Bu) did improve the yield of the present reactions (Table 1, 66%, entry 1). Consequently, the reaction conditions were optimized using $Cu(OAc)_2$. Higher reaction temperatures led to a faster reaction rate and a slightly improved yield (69%; Table 1, entry 2). We found that the best yields were achieved with a low catalyst loading (2 mol% $Cu(OAc)_2$/Xantphos, 1.5 h, 73%; Table 1, entry 3) and when 1.5 equiv. of ligand relative to the copper salt was employed (2 mol% $Cu(OAc)_2$, 3 mol% Xantphos, 1 h, 73%; Table 1, entry 4). Toluene and the coordinating solvent DMI afforded lower yields (Table 1, entries 5 and 6). Other bidentate phosphines (dppp, dppe and dppf; Table 1, entries 7–9), monophosphines (PPh_3; Table 1, entry 10; PCy_3 and PBu_3 not shown) and 1,10-phenanthroline (Table 1, entry 11) were examined. None of these ligands provided **3a** in a yield of >20%. No S_N2 reduction product (alkyne) was detected by ^{1}H NMR in these $Cu(OAc)_2$/Xantphos-catalyzed reductions of **1a**. The best results were obtained when the reaction was terminated at an appropriate reaction time. Excessively long reaction times led to further side reactions of the allene products to form unidentified compounds.

Having identified the optimal conditions for the copper-catalyzed regioselective reduction of propargylic carbonates (Table 1, entry 4), the generality of this reduction was evaluated (Table 2).[8] Both tri- and disubstituted allenes were obtained in moderate to good yields from the corresponding tertiary and secondary propargylic carbonates (50–86%; Table 2, entries 1, 2 and 5–7). Generally, allenes from propargylic carbonates with bulky substituents at the γ-position were obtained in higher yields than those from carbonates with less bulky substituents (*cf.* **3a** (68%) *vs.* **3b** (86%) and **3f** (50%) *vs.* **3g** (86%)). The bulky substituents in the products probably prevent these compounds from reacting further and so are responsible for the observed higher yields. The carbonates involving five- and six-membered rings (**1d** and **1e**) were converted into allenes containing vinylidenecyclopentane (**3d**) and vinylidenecyclohexane (**3e**) structures, respectively (Table 2, entries 3 and 4). The reactions also showed good functional group tolerance. Benzoate ester, carbamate and C=C double bonds were compatible under the reaction conditions employed (Table 2, entries 8–10). Unfortunately, complex mixtures were obtained in reactions using substrates with a phenyl group at the α- or γ-carbon.

Our results obtained with **1l** and (*S*)-**1h** provide evidence for the *anti*-S_N2' pathway in these reactions (Scheme 2). The diastereomeric ratio of (1*R*,4*R*)-(+)-camphor-based allene **3l** was >95 : 5 (by ^{1}H NMR).[9,10] Optically-active propargylic carbonate (*S*)-**1h** (99.5% ee)[11] was converted into chiral allene (*S*)-(+)-**3h** at 0 °C with complete 1,3-chirality transfer.[12]

These regio- and stereochemical results are explained by the plausible reaction mechanism shown in Scheme 3. In the presence of Xantphos, $Cu(OAc)_2$ is reduced by the hydrosilane to Cu(I) hydride species **A**, which is then coordinated by the triple bond of the substrate. *syn*-Addition of the Cu–H bond to the triple bond produces alkenyl copper intermediate **B**. *anti*-β-Elimination of **B** gives the allene product, with the release of CO_2, forming copper alkoxide **C**. σ-Bond metathesis between **C** and the hydrosilane regenerates Cu(I) hydride **A**.

In summary, we have found a useful method for the synthesis of di- and trisubstituted allenes through a highly

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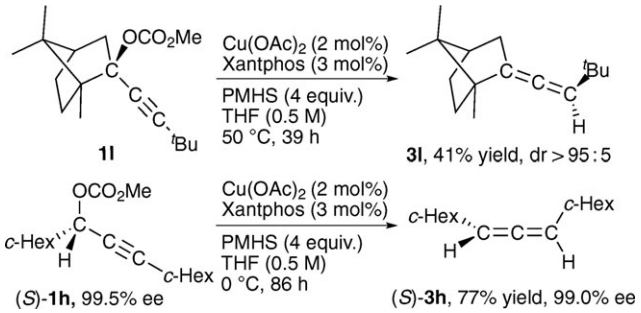
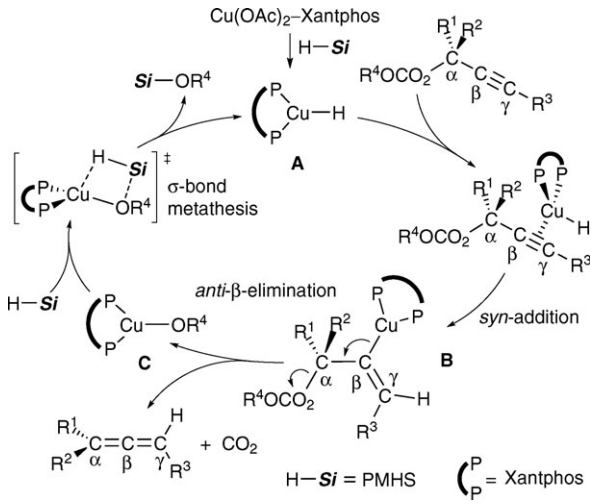


Scheme 2 The synthesis of optically-active allenes *via* the regio-selective and stereoselective reduction of propargylic carbonates with PMHS.



Scheme 3 A plausible catalytic cycle.

regio- and stereoselective copper/Xantphos-catalyzed reduction of propargylic carbonates. The catalyst system works efficiently for the synthesis of bulky substituted allenes and shows good functional group compatibility.

This work was supported by the PRESTO program (JST), Grant-in-Aid for Scientific Research (B) (JSPS). C. Z. was supported by GCOE (Catalysis as the Basis for Innovation in Materials Science, Hokkaido University). We also acknowledge Daicel Chemical Industries for chiral HPLC analysis.

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7 (*a*) D. Lee and J. Yun, *Tetrahedron Lett.*, 2004, **45**, 5415–5417; (*b*) D. Kim, B.-M. Park and J. Yun, *Chem. Commun.*, 2005, 1755–1757.
8 Experimental procedures: Cu(II) acetate (1.8 mg, 0.01 mmol) and Xantphos (8.6 mg, 0.015 mmol) were placed in a screw-capped reaction vial. The vial was connected to an argon line through a needle and was evacuated and back-filled with argon three times. After the addition of de-gassed anhydrous THF (1.0 mL), the mixture was stirred for about 20 min. PMHS (130 μL, 4.0 equiv.) was then added dropwise with a microsyringe. The solution was stirred for an additional 30 min until the mixture had assumed a characteristic yellow-orange colour. Carbonate **1** (0.5 mmol) was then added at 50 °C. The reaction mixture was stirred for a specified period of time. The reaction mixture was subsequently transferred to a 50 mL round-bottomed flask using Et_2O. Unreacted PMHS was hydrolyzed using a 1 M NaOH aqueous solution (3.0 mL). The products were purified by silica gel chromatography with hexane as the eluent.
9 **3l** was also prepared from the corresponding propargylic alcohol by reduction with stoichiometric amounts of $LiAlH_4$ and $AlCl_3$.[10] Products prepared by these two methods showed identical ^1H and ^{13}C NMR spectra.
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11 K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738–8739.
12 The enantiomeric excess (ee) of (*S*)-(+)-**3h** was determined by chiral HPLC analysis (DAICEL CHIRALCEL® OJ-RH, H_2O : MeOH = 20 : 80, 0.5 mL min^{-1}, 220 nm). The reaction with (*S*)-**1h** at a high temperature (50 °C) produced (*S*)-(+)-**3h** in a yield of 78% with a decreased enantioselectivity of 87% ee. This decrease is probably due to a side reaction of the allene product with the Cu(I) hydride species.

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