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Chloroprene as a Source of Fine Chemicals: Palladium-Catalyzed Synthesis of Terminal Allenes

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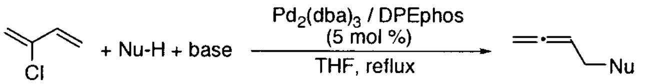
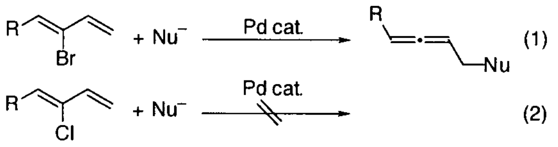
ABSTRACT



Several functionalized terminal allenes were prepared in moderate to excellent yield by a palladium-catalyzed reaction of chloroprene (2-chloro-1,3-butadiene) with soft nucleophiles.

Chloroprene (2-chloro-1,3-butadiene) is one of the few conjugate dienes that are mass-produced and utilized on an industrial scale. Although it is an economically very attractive resource, most of its use is for polymerization, producing chloroprene rubber. Its application to organic synthesis as a source of a C_4-unit is limited to Diels−Alder reactions[1] and reactions of its Grignard reagent.[2] Utilization of chloroprene for synthesis of fine chemicals, accordingly, is an interesting subject in synthetic organic chemistry.

We have recently established a novel synthetic method for preparing a variety of functionalized allenes (eq 1).[3] The substrates used for the reaction are (*Z*)-1-substituted-2-bromo-1,3-butadienes, and the corresponding chlorodienes are nearly inert to the reaction (eq 2; vide infra). However, the parent chlorodiene (chloroprene, **1**) was found to be reactive toward the palladium-catalyzed reaction, giving a terminal allene as a product (Figure 1).



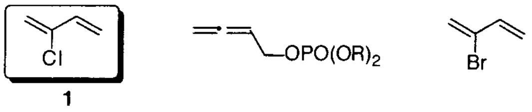


Figure 1. Substrates for functionalized terminal allenes.

Alternatively, analogous terminal allenes were prepared by the Pd-catalyzed reaction of allenylmethyl esters[4] which were prepared by multistep reactions.[5] The nonsubstituted 2-bromo-1,3-diene is another candidate for a substrate to prepare the terminal allenes, but it polymerizes easily and is relatively difficult to handle.[6] Chloroprene has advantages over these compounds because of its easy access, low-cost availability, and easier handling.

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(1) For recent examples, see: (a) Davis, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326. (b) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1741.

(2) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 2, pp 812−813, and references therein.

(3) (a) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1042. (b) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089.

(4) (a) Djahanbini, D.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1984**, *25*, 203. (b) Djahanbini, D.; Cazes, B.; Goré, J. *Tetrahedron* **1987**, *43*, 3441. (c) Cazes, B.; Djahanbini, D.; Goré, J.; Genét, J.-P.; Gaudin, J.-M. *Synthesis* **1988**, 983.

(5) (a) Djahanbini, D.; Cazes, B.; Goré, J. *Tetrahedron* **1984**, *40*, 3645. (b) Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 720.

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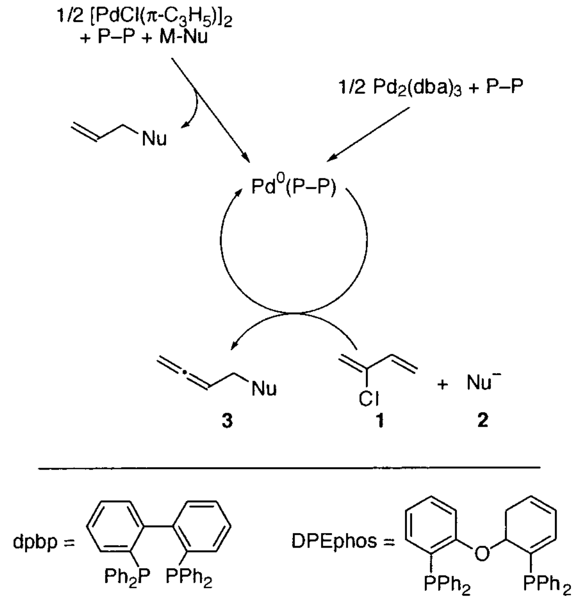
Among a numerous reports on the reactions of allenes,[7] those of *terminal* allenes have a unique position in organic synthesis.[8] In the terminal allenes, the two cumulated double bonds are effectively discriminated from each other by the steric factors, which brings about high regioselectivity. The reaction described in this report provides a simple and single-step route to these useful synthons starting from inexpensive and readily available materials.

Our initial studies were focused on the development of reaction conditions including reaction temperature, palladium precursor, and phosphine ligand for the reaction of **1** and sodium salt of $MeCH(COOMe)_2$ (**2a**) producing a terminal allene $CH_2{=}C{=}CHCH_2CMe(COOMe)_2$ (**3a**). It was found that the reaction is efficiently catalyzed by 5 mol % of a palladium complex generated in situ by mixing $Pd_2(dba)_3{\cdot}CHCl_3$ with DPEphos[9] (1.1 equiv to Pd) in the presence of a large excess of chloroprene (ca. 5 equiv to **2a**). Thus, a mixture of **1** (ca. 3.0 g, ca. 30 mmol),[10] **2a** (850 mg, 5.82 mmol), NaOMe (345 mg, 6.39 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (161 mg, 156 μmol), and DPEphos (170 mg, 316 μmol) in THF (10 mL) was heated at 70 °C (bath temperature). The reaction was complete within 3 h, and 1.08 g (94% yield based on **2a**) of **3a** was isolated as a colorless liquid by vacuum distillation. A catalyst generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and dpbp,[11] which is a bisphosphine ligand used for allene preparation from the bromodiene,[3b] showed the lower catalytic acitivity and gave only 78% of **3a** under similar reaction conditions.

As a palladium catalyst precursor, $[PdCl(\pi\text{-allyl})]_2$ can be used as well, although the allene product **3a** is contaminated with the allylated nucleophile ($CH_2{=}CHCH_2CMe(COOMe)_2$), which is formed by the catalyst during nucleophilic attack of malonate on the π-allylpalladium, generating a palladium(0) species (Scheme 1).

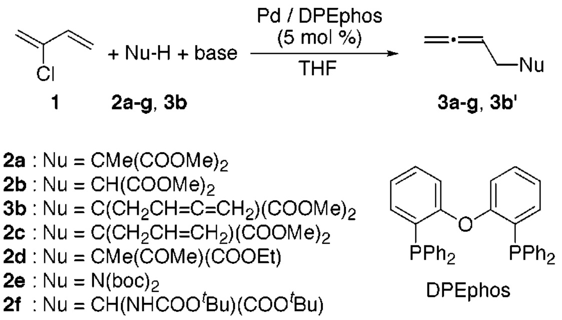
Scheme 1



The use of a large excess of chloroprene (**1**/**2a** = ca. 5/1 mol/mol) is essential for a high yield of the allene preparation. With 2 equiv of **1**, conversion of **2a** into **3a** was incomplete in 24 h (GC analysis). The necessity of excess chloroprene **1** is ascribed to competing polymerization of **1**. After removal of the generated NaCl (by filtration) and **3a** (by vacuum distillation), a nonvolatile gummy material was left in the vessel. Although the material was not characterized, it is likely to be a mixture of the residual catalyst and the chloroprene polymer/oligomer.

A variety of functionalized terminal allenes are prepared in this way. Table 1 shows the results obtained with several types of “soft” nucleophiles such as 2-substituted or unsubstituted malonates (entries 1−6), acetoacetate (entry 7), and

Table 1. Palladium-Catalyzed Synthesis of Terminal Allenes[a]



2a : Nu = $CMe(COOMe)_2$
2b : Nu = $CH(COOMe)_2$
3b : Nu = $C(CH_2CH{=}C{=}CH_2)(COOMe)_2$
2c : Nu = $C(CH_2CH{=}CH_2)(COOMe)_2$
2d : Nu = CMe(COMe)(COOEt)
2e : Nu = $N(boc)_2$
2f : Nu = $CH(NHCOO^tBu)(COO^tBu)$

entry	NuH	base[b]	temp/°C[c]	time/h	yield/%[d]
1	**2a**	NaOMe (1.1)	70	3	94 (**3a**)
2[e]	**2a**	NaOMe (1.1)	70	18	78 (**3a**)
3	**2b**	NaOMe (1.0)	70	24	57[f] (**3b**)
4[g]	**2b**	NaOMe (2.5)	100	3	67 (**3b′**)
5	**3b**	NaOMe (1.1)	70	20	91 (**3b′**)
6	**2c**	NaH (1.1)	70	12	89 (**3c**)
7	**2d**	NaH (1.1)	70	18	76 (**3d**)
8[g]	**2e**	KH (1.1)	100	20	50 (**3e**)
9	**2f**	LHMDS (2.0) + $ZnCl_2$ (1.0)	50	5	35 (**3f**)[h]

[a] With 5 mol % of the palladium catalyst generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and DPEphos (1.1 equiv) in the presence of 5 equiv of **1** unless otherwise noted. [b] Equivalence to NuH **2** in parentheses. [c] Bath temperature. [d] Yield relative to the amount of used NuH **2** after isolation by distillation or silica gel chromatography. [e] With dpbp instead of DPEphos. [f] Doubly reacted product **3b′** was isolated in 13% yield (based on **2b**). [g] In a pressure-resistant reactor. [h] 50% of **2f** was recovered.

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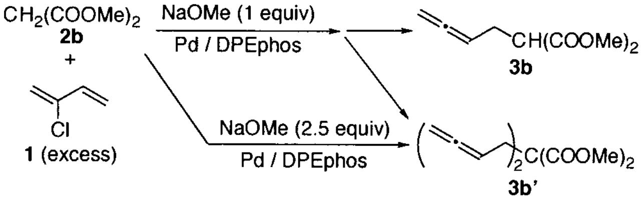
(8) For selected recent examples, see: (a) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761. (b) Ma, S.; Zhao, S. *Org. Lett.* **2000**, *2*, 2495. (c) Rutjes, F. P. J. T.; Tjen, K. C. M.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 717. (d) Sudo, T.; Asao, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2494. (e) Meguro, M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 694. (f) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 10842. (g) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4068. (h) Hideura, D.; Urabe, H.; Sato, F. *Chem. Commun.* **1998**, 271. (i) Xiao, W.-J.; Yasapollo, G.; Alper, H. *J. Org. Chem.* **1998**, *63*, 2609. (j) Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. M. *J. Org. Chem.* **1998**, *63*, 2154.

(9) DPEphos = bis[2-(diphenylphosphino)phenyl]ether. See: Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.

Scheme 2



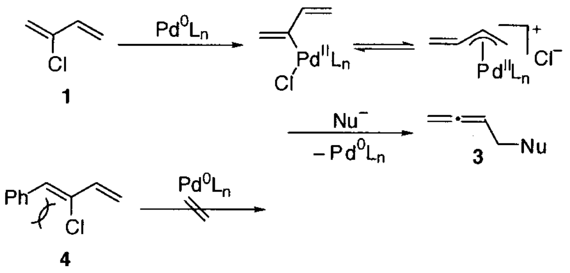
amide (entry 8). Generally, reactions proceeded very cleanly and the products were easily isolated in pure form in good to excellent yields by vacuum distillation or column chromatography after usual workup.

As shown in Scheme 2, when a mixture of unsubstituted malonate **2b** and a stoichiometric amount (to **2b**) of base (NaOMe) as nucleophile was used, the product was obtained as a mixture of mono-allene **3b** (57%) and bis-allene **3b′** (13% based on **2b**), which were separated by silica gel chromatography (Table 1, entry 4). The same result was obtained with a prepurified isolated sodium salt $Na[CH(COOMe)_2]$. Because the sodium salt of initially formed **3b** is more reactive than that of **2b**, the mono-allene **3b** could not be prepared selectively under the conditions employed for this study. Interestingly, the bis-allene **3b′** was obtained as a sole allenic product in 67% yield using more than 2 equiv (to **2b**) of NaOMe, although the higher temperature (100 °C in a pressure-resistant reactor) was required to complete the reaction (entry 4).

The present method can be applied to synthesis of an unusual α-amino acid. The reaction of **1** with a chelated zinc enolate of **2f**[12] in the presence of the Pd/DPEphos catalyst gave the allene $CH_2{=}C{=}CHCH_2CH(NHBoc)(COO^tBu)$ (**3f**) in 35% yield (Table 1, entry 9). Deprotection will afford a naturally occurring amino acid allenylalanine,[13] which is one of the simplest routes to this amino acid.[4c,14]

Chloroprene **1** and 1-substituted-2-bromo-1,3-dienes are reactive substrates for the palladium-catalyzed allene synthesis, while 1-substituted-chloroprenes, such as (*Z*)-2-chloro-1-phenyl-1,3-butadiene (**4**), were found to be nearly inert to the reaction (eq 2 and Scheme 3). The low reactivity of **4** can be ascribed to slow oxidative addition of **4** to the palladium(0) species. It was reported that the palladium-catalyzed cross-coupling reaction of 1,1-dichloro-2-substituted-ethylenes with Grignard reagents proceeded highly selectively at the position *trans* to the 2-substituents.[15] The remarkable *trans*-selectivity in the cross-coupling reaction was explained as a steric effect of the 2-substituent which inhibits the reaction at the vicinal *cis*-chloride. The two palladium-catalyzed reactions, the allene synthesis and the regioselective cross-coupling, proceed through the catalytic cycles involving oxidative addition of the olefinic C−Cl bond to a Pd(0). The low reactivity of **4** to the allene synthesis should be ascribed to steric effects of the phenyl substituent at 1-position. The phenyl group in **4** interferes with oxidative addition at the vicinal *cis*-chloride. Because there is no substituent at the vicinal *cis* position to the chloride in **1**, it exhibits high reactivity toward the palladium-catalyzed allene synthesis reaction (Scheme 3).

Scheme 3



In conclusion, we have demonstrated that chloroprene **1** is an excellent source of a variety of functionalized terminal allenes. The allene synthesis is effectively catalyzed by the palladium species generated in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ and DPEphos. The nature of chloroprene, especially its low cost, and the usefulness of the products will make the present reaction attractive for further applications.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Chloroprene, which we have used, contained ca. 10 mol % of toluene and was used for the present studies without further purification.

(11) dpbp = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl. See: Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000**, *19*, 1567, and references therein.

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