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π-Allylpalladium-Mediated Catalytic Synthesis of Functionalized Allenes**

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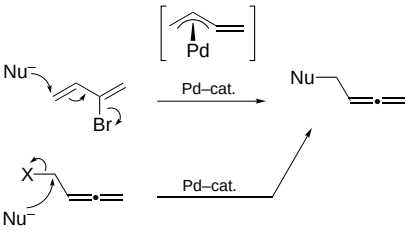
Allenes have attracted attention as useful synthons for synthetic organic chemistry.[1] The interesting reactivity of allenes originates mainly from their unique strained structure, and thus continuous efforts have been made to construct the 1,2-dienic moieties. Standard methods of allene synthesis are based on the S_N2'-type substitution of propargylic compounds [Eq. (1)].[1, 2] However, the products from these synthetic

(1)

methods are often contaminated with the corresponding propargyl compounds or 1,3-dienes, and purification steps become problematic. Recently, some highly selective synthetic methods for the formation of allenes were reported,[3] however, the yields of the allenic products were not always satisfactory. In addition, these procedures require reactive reagents, such as Grignard reagents or organolithium species, and are unable to handle substrates or products with susceptible functional groups. We describe herein a novel synthetic method for synthesizing a variety of functionalized allenes.

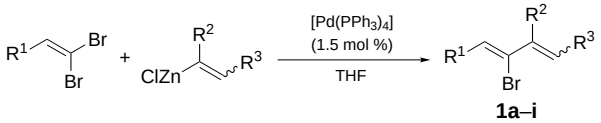
Our strategy is a formal S_N2' substitution of 2-bromo-1,3-butadienes, which is catalyzed by a palladium complex [Eq. (2), top]. The reaction proceeds under very mild conditions via a π-allylpalladium intermediate[4] and gives



(2)

the clean products in excellent yields. The reaction described here has some analogies to the Pd-catalyzed functionalization of allenyl esters with "soft" carbon nucleophiles reported by Gore and co-workers in 1984 [Eq. (2), bottom].[5] They suggested an analogous intermediate to the one established in this report. However, the substrates they employed possess 1,2-dienic moieties and thus, tedious procedures are required to construct the allenic skeletons prior to the functionalization step, which greatly reduces the synthetic usefulness of the reaction. The advantages of our approach described here are: 1) easy access to the 1,3-dienyl substrates, which enables us to introduce a wide range of substituents in the substrates and the allenic products, and 2) a variety of nucleophilic reagents, including N, O, and P nucleophiles, can be used. The reaction also represents a rare example of a transition metal catalyzed transformation to give allenes.[6]

The substrates, (*Z*)-2-bromo-1,3-butadienes (**1**), are readily available in 63–90% yield by palladium-catalyzed regio- and stereoselective cross-coupling of 1,1-dibromo-1-alkenes[7] with the corresponding vinylzinc reagents (Scheme 1).[8] The



1a–i

Scheme 1. Palladium-catalyzed selective cross-coupling of dibromoalkenes with organozinc reagents.

choice of the organometallic reagent is important for this step; while $(CH_2{=}CH)ZnCl$ gives the coupling product in satisfactory yield, the less-reactive vinyltin reagent $Bu_3Sn(CH{=}CH_2)$ gives the same product in very low yield (<20%). More basic Grignard reagents enhance the elimination of HBr from **1** to give a considerable amount of $R^1C{\equiv}C{-}CH{=}CH_2$ as a by-product. When R^1 is an alkyl substituent, a second cross-coupling proceeds to a certain extent to give a triene, $R^1CH{=}C(CH{=}CH_2)_2$, as a by-product (≈15%). The triene does not affect the allene formation, thus, a mixture of **1** and the triene can be employed in the following step without further purification.

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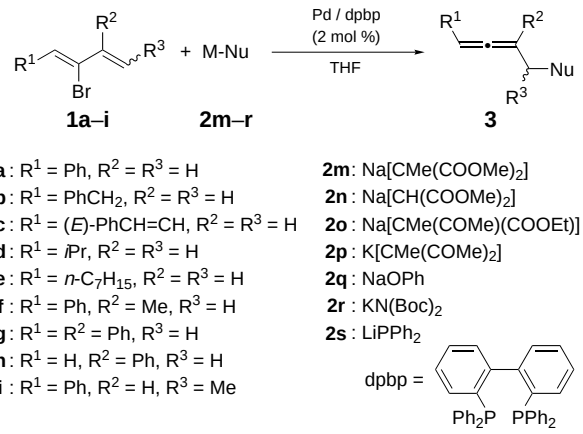
Our initial studies on the formation of the allenes focused on finding a suitable phosphane ligand for the palladium precursor, $[PdCl(\eta^3\text{-}C_3H_5)]_2$, so that the reaction of (*Z*)-2-bromo-1-phenyl-1,3-butadiene (**1a**) and Na[CMe(COOMe)$_2$] (**2m**) would occur (see Scheme 2). Although the reactions produced dimethyl 2-(4-phenyl-2,3-butadienyl)-2-methylpropane-1,3-dioate (**3am**) cleanly as we expected, the palladium–phosphane complexes initially examined did not have satisfactory catalytic activity. The catalytic efficiency of each phosphane ligand was evaluated by the conversion of **1a** to **3am** after 2 h at 20 °C in the presence of 2 mol % of the Pd catalysts: dppe gave less than 1 % conversion, dppp 4 %, dppb 12 %, dppf 11 %, and PPh_3 less than 1 %.[9] The reaction was efficiently catalyzed by a palladium–dpbp[9] complex generated in situ from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 1.1 equivalents (with respect to Pd) of dpbp. The dpbp system shows 75 % conversion in 2 h under the same conditions employed for the other Pd-phosphane catalysts. Prolonged reaction with the Pd-dpbp catalyst at room temperature gives **3am** in 91 % yield (entry 1 in Table 1). The reaction proceeds very cleanly to give the allenic compound as the sole organic product.

Table 1. Palladium-catalyzed synthesis of allenes **3** from bromodiene **1** and nucleophile **2**.[a]

Entry	Bromodiene	Nucleophile	*T* [°C]	*t* [h]	Yield [%][b]
1	**1a**	**2m**	23	12	91 (**3am**)
2	**1a**	**2n**	23	12	79 (**3an**)[c]
3	**1a**	**2o**	23	12	93 (**3ao**)[d]
4	**1a**	**2p**	23	6	96 (**3ap**)
5	**1a**	**2q**	23	24	83 (**3aq**)
6	**1a**	**2r**	23	12	89 (**3ar**)
7	**1a**	**2s**	0	3	62 (**3as**)[e]
8	**1b**	**2m**	23	12	91 (**3bm**)
9	**1c**	**2m**	23	12	92 (**3cm**)
10	**1d**	**2m**	23	6	88 (**3dm**)
11	**1e**	**2m**	23	6	93 (**3em**)
12	**1f**	**2m**	23	12	90 (**3fm**)
13	**1g**	**2m**	23	12	95 (**3gm**)
14	**1h**	**2m**	23	6	93 (**3hm**)
15	**1i**[f]	**2m**	23	60	80[g] (**3im**)[h]

[a] Reaction was carried out in THF in the presence of 2 mol % of the catalyst generated from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and dpbp. [b] Yield of isolated product after column chromatography on silica gel. [c] Doubly reacted products, *rac*- and *meso*-**3an′**, were isolated in 19 % yield (based on **1a**) as a *rac*/*meso* = 47/53 mixture. [d] Mixture of two diastereomers (50/50). [e] The product was oxidized during an aerobic work-up and isolated as a corresponding phosphane oxide. [f] Mixture of two isomers (*E*/*Z* = 5/1). [g] 18 % of **1i** was recovered (*E*/*Z* = 6/1). [h] Mixture of two diastereomers (50/50).

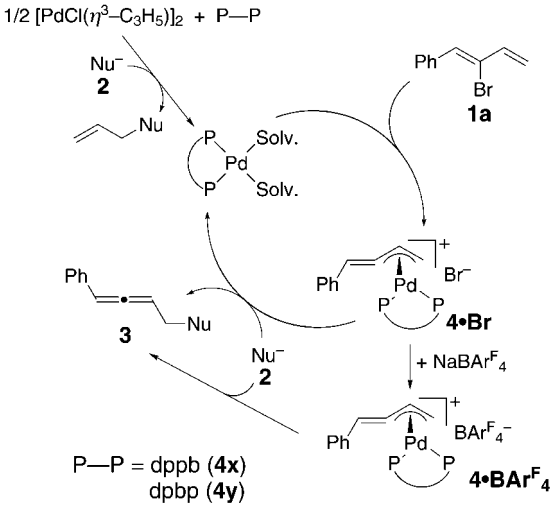
The scope of the present reaction is broad and representative examples are shown in Scheme 2 and Table 1. The reaction works well with several types of "soft" nucleophiles, including phenoxide (Table 1, entry 5), amide (entry 6), and phosphide (entry 7), while "hard" nucleophiles, such as PhMgBr and PhZnCl, produce conjugated 1,3-dienes instead of allenes.[5, 10] A wide range of substitution patterns are acceptable to the dienyl substrates. The substrates with benzyl, β-styryl, primary or secondary alkyl groups, or hydrogen as R^1 undergo the reaction (entries 8–11, 14). Substitution at the R^2 position puts the substituent at the other end of the allenic skeleton in the final product (entries 12–14). The



Scheme 2. π-Allylpalladium-mediated catalytic synthesis of functionalized allenes.

R^3 substituent, however, reduces the reactivity of the dienyl substrate. Reaction of the diene **1i**, which is a mixture of two isomers (*E*/*Z* = 5/1), with **2m** shows only 80 % conversion even after 60 h, and 18 % of **1i** is recovered (*E*/*Z* = 6/1) from the reaction mixture (entry 15). The choice of the leaving group in the dienyl substrate is critical for the success of the reaction. While bromide **1a** reacts smoothly with the nucleophiles in the presence of the Pd catalyst, the corresponding acetate, (*E*/*Z*)-PhCH=C(OAc)–CH=CH$_2$, is totally inert under the same conditions.

The reaction patterns described above indicates formation of (methylene-π-allyl)palladium[11] species **4** as a key intermediate, and we propose a catalytic cycle shown in Scheme 3. Isolation of the palladium species was achieved as follows: An



Scheme 3. Catalytic cycle of the allene synthesis reaction (Solv. = solvent).

equimolar mixture of $[Pd(\eta^3\text{-}C_3H_5)(dppb)]Cl$, generated in situ from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and dppb, and **2m** in THF was stirred at room temperature for a short period (< 1 min) to give a dark orange solution. The addition of a stoichiometric amount of **1a** to the solution changed the color to yellow on formation of **4x**·**Br** (Scheme 3). Successive anion exchange with $NaBAr^F_4$[12] in dichloromethane afforded a crude product

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as a 1:1 mixture of $\mathbf{4x}\cdot\mathbf{BAr_4^F}$ and $CH_2{=}CHCH_2CMe(COOMe)_2$ (by ^1H NMR spectroscopy). The crude mixture was purified by column chromatography over SiO_2 with $CHCl_3$ as the eluent to give $\mathbf{4x}\cdot\mathbf{BAr_4^F}$ as a yellow viscous oil. Although all attempts to obtain single crystals of $\mathbf{4x}\cdot\mathbf{BAr_4^F}$ have been unsuccessful because of its low crystallinity, the coordination of the benzylideneallyl moiety in a η^3-fashion was established by various NMR measurements (see Supporting Information). Similarly, an analogous methylene-π-allylpalladium complex with dpbp ($\mathbf{4y}\cdot\mathbf{BAr_4^F}$) was isolated and the NMR measurements of $\mathbf{4y}\cdot\mathbf{BAr_4^F}$ clarify that it exists as a mixture of two diastereomers, which originate from atropisomerism of the coordinating dpbp ligand. As expected, a stoichiometric reaction of the isolated $\mathbf{4y}\cdot\mathbf{BAr_4^F}$ with **2m** in THF gave the allene **3am** in 67% yield. Although the yield is relatively low compared to the catalytic reaction, presumably as a result of moisture in the oily complex, the nucleophilic attack on the benzylideneallyl moiety is highly selective and **3am** is the sole product from the reaction. The observations all strongly support the proposed catalytic cycle.

In summary, we have developed a general and efficient new method for the palladium-catalyzed conversion of 1,1-dibromo-1-alkenes to substituted functionalized allenes. We also established the catalytic cycle of the allene formation reaction, including the isolation and the characterization of the methylene-π-allylpalladium key intermediate. The experimental ease and the high yield of this method should enhance its attractiveness.

Experimental Section

1 (general procedure): A typical procedure is given for the preparation of **1a**. A solution of $PhCH{=}CBr_2$ (5.65 g, 21.6 mmol) and $[Pd(PPh_3)_4]$ (400 mg, 0.35 mmol) in THF (40 mL) was added at 0 °C by cannula transfer to a suspension of $(CH_2{=}CH)ZnCl$ in THF, prepared from dry $ZnCl_2$ (3.41 g, 25.0 mmol) and vinylmagnesium bromide (0.95 M in THF, 25 mL, 24 mmol). After the addition, the mixture was stirred for 1 h at room temperature. The mixture was diluted with *n*-hexane and filtered. The solvents were removed under reduced pressure and then the residue was extracted with hexane. The hexane solution was evaporated, and the residue was purified by column chromatography on silica gel with *n*-hexane as the eluent to give **1a** (3.78 g, 84% yield) as a colorless oil. All the spectral data of this material were consistent with those reported previously.[13]

3 (general procedure): The reaction conditions and results are summarized in Table 1. A typical procedure is given for the preparation of **3am** (entry 1, Table 1). $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.5 mg, 8.2 μmol/Pd), dpbp (4.7 mg, 9.0 μmol), and **1a** (89.0 mg, 426 μmol) were dissolved in THF (5 mL) and the solution was added to **2m** (80.1 mg, 476 μmol) by cannula transfer under nitrogen. The mixture was stirred at room temperature for 12 h, then filtered through a short pad of SiO_2 to remove precipitated inorganic salts. The silica gel pad was washed three times with a small amount of Et_2O and the combined solution was evaporated to dryness under reduced pressure. The yellow residue was purified by chromatography on silica gel (*n*-hexane/Et_2O = 1/1) to give the allene **3am** (106 mg, 91%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 3H), 2.70 (dd, J = 2.4, 7.7 Hz, 2H), 3.70 (s, 3H), 3.72 (s, 3H), 5.46 (dt, J = 6.3, 7.7 Hz, 1H), 6.14 (td, J = 2.4, 6.3 Hz, 1H), 7.17–7.20 (m, 1H), 7.24–7.31 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.97, 35.60, 52.60, 52.64, 53.78, 89.37, 94.62, 126.82, 126.99, 128.59, 134.14, 172.11, 172.13, 206.91. Elemental analysis calcd for for $C_{16}H_{18}O_4$: C 70.06, H 6.61; found: C 70.18, H 6.76.

$\mathbf{4}\cdot\mathbf{BAr_4^F}$ (general procedure): The complexes were isolated with dppb ($\mathbf{4x}\cdot\mathbf{BAr_4^F}$) or with dpbp ($\mathbf{4y}\cdot\mathbf{BAr_4^F}$) and a typical procedure is given for the preparation of $\mathbf{4x}\cdot\mathbf{BAr_4^F}$. A mixture of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (81.7 mg, 447 μmol/Pd), dppb (193 mg, 453 μmol), and **2m** (80.1 mg, 476 μmol) was placed in a Schlenk flask and dry THF (5 mL) added under nitrogen. The mixture was stirred at room temperature for 30 s, then **1a** (104 mg, 497 μmol) was added to the flask by means of syringe. After stirring the orange-yellow solution for 3 h at room temperature, all the volatiles were removed under reduced pressure. $NaBAr_4^F\cdot OEt_2$ (500 mg, 521 μmol) and CH_2Cl_2 (5 mL) were then added to the residue and the mixture was stirred for 30 min at room temperature. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The yellow residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give the complex $\mathbf{4x}\cdot\mathbf{BAr_4^F}$ (598 mg, 88% yield) as a yellow viscous oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.68–1.78 (m, 1H), 1.87–2.04 (m, 3H), 2.51–2.55 (m, 2H), 2.61–2.74 (m, 2H), 3.30 (dd, J = 8.3, 14.6 Hz, 1H), 4.42 (dd, J = 5.1, 8.3 Hz, 1H), 5.25 (ddd, J = 3.1, 7.8, 11.6 Hz, 1H), 5.77 (ddd, J = 3.1, 8.3, 14.6 Hz, 1H), 6.93 (m, 2H), 7.22–7.27 (m, 5H), 7.34–7.56 (m, 21H), 7.62–7.64 (m, 1H), 7.72 (br, 8H); ^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.3 (d, J = 45.3 Hz, 1P), 30.3 (d, J = 45.3 Hz, 1P).

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