Palladium(0)-Catalyzed Coupling Cyclization of Functionalized Allenes with Hypervalent Iodonium Salts

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Abstract: The palladium(0)-catalyzed coupling reaction of allenic alcohols, amines, acids with hypervalent iodonium salts afforded the cyclized heterocyclic tetrahydrofurans, tetrahydropyrans, pyrrolidines, piperidines, or lactones under mild conditions.

Key words: allenes, coupling reaction, hypervalent elements, palladium compounds

The palladium-catalyzed cyclization reaction received much attention as an efficient method for the preparation of oxygen- and nitrogen-containing heterocycles. Recent reports by Walkup et al.¹ have demonstrated that γ - hydroxyallenes or 4,5-hexadienoic acid reacted with arylpalladium(II) halides generated in situ from palladium(0) and aryl halides to form cyclized tetrahydrofurans or butyrolactones via sequential cyclization-coupling reaction. It is also known by Gallagher et al.² that γ - allenic amines undergo heteroatom cyclization with aryl halides in the presence of Pd(0) to give the substituted pyrrolidinone.^{3, 4} However, these methods are limited to the formation of five-membered heterocycles and the drawbacks of the cyclization reactions are the use of excess (5 equiv) aryl halides and longer times at high temperature. In our effort to broaden the synthetic utility of this type of cyclization reactions, we focused our attention on hypervalent iodonium salts as the substitutes for aryl halides.⁵ Here we wish to report the coupling and cyclization of allenic alcohols, allenic acids, and allenic amines leading to 4, 5, and 6membered heterocycles with hypervalent iodonium salts (1.2 equiv) in the presence of a palladium catalyst, which is shown in Scheme 1.





The results of Pd(0)-catalyzed coupling cyclization of functionalized allenes with hypervalent iodonium salts are summarized in Table 1.

To determine optimum conditions, initially allenic alcohol **1a** was reacted with diphenyliodonium tetrafluoroborate (**2a**) to get the cyclized product **3a**. After a series of experiments, we found that $Pd(PPh_3)_4$ was suitable as cat-

alyst. The catalyst Pd(OAc)₂/Ph₃P or Pd₂(dba)₃/Ph₃P gave the coupled product 3a in lower yields. Of the solvent tested, DMF ad preferably CH₃CN were effective even if THF and NMP were not satisfactory. As base K₂CO₃ and Cs₂CO₃ were more suitable than Et₃N and NaOMe. The yields were improved when the reaction was run at 60 °C for 3 h rather than run at 80 °C for 1.5 h or at room temperature for 18 h. The allenic alcohol 1a reacted with diphenyliodonium tetrafluoroborate (2a) in the presence of Pd(PPh₃)₄ (5 mol %) at 60 °C in CH₃CN for 3 h to afford the alkenyl-substituted tetrahydrofuran $3a^6$ in 76% yield (entry 1 in Table 1).⁷ Under the same conditions treatment of **1a** with *p*-methoxyphenyl(phenyl)iodonium tetrafluoroborate (2b) gave a mixture of two easily separable tetrahydrofurans 3b (44%) and 3a (35%) in 79% yield (entry 2). When α -methyl-substituted allenic alcohols 1b were coupled with 2a, a mixture of *cis*- and *trans*tetrahydrofurans $3c^6$ was afforded in the ratio of 2 : 3 in 72% yield (entry 3). This method can be applied to 5,6-octadienol 1c to get tetrahydropyran derivatives. When the allenol 1c was treated with the iodonium salt 2a under the same conditions, the substituted tetrahydropyran $3d^6$ was afforded in 74% yield (entry 4). Similarly, the reaction of 1c with *p*-methoxyphenyl(phenyl)iodonium salt 2b gave a separable mixture of 3d and 3e in 73% yield (entry 5). Alternatively, when 3,4-dienylamine 1d was subjected to cyclize with 2a under the same conditions, a mixture of the four-membered ring $3f^6$ and the six membered ring $3g^6$ were obtained (entry 6).

In considering the plausible mechanism for the formation of the four membered ring **3f** and the six membered ring **3g** simultaneously, it is presumed that the phenylpalladium(II) tetrafluoroborate (PhPd⁺ BF₄⁻) formed from 2a and Pd(0) species adds to allene to form π -allylpalladium complex A, which undergoes intramolecular nucleophile addition to give **3f** and **3g** (path a in Scheme 2).⁸ The four memebered ring **3f** can be converted to **3g** by oxidative addition with Pd(0) species to form -allylpalladium complex under the reaction conditions, which eventually is converted into six membered compound 3g. However, the alternative mechanism^{1, 2} (path b) which involves the formation of the phenylpalladium tetrafluoroborate **B** via activating the allene by Ph $Pd^+BF_4^-$ for nucleopalladation followed by reductive elimination cannot be ruled out, which is shown in Scheme 2.

For allenic amine derivatives **1e**, the substituted pyrrolidine $3h^6$ was obtained in 95% yield (entry 7). Using **2b** as the iodonium source, a separable mixture of two pyrro-







lidines **3i** and **3h** was provided in 95% combined yield (entry 8). When α -methyl allenic amine **1f** was utilized as starting material, pyrrolidine **3j** (*cis* : *trans* = 2 : 3.2) was formed (entry 9). The substituted piperidines **3l** and **3k** were readily obtained from 5,6-octadienyl amine *N*-tosylate **1g** (entries 10 and 11). These results are in contrast with the results that the cyclization of **1g** with iodobenzene could not provide piperidine derivatives.² The allenic acid **1i** was also utilized to form the substituted furanone **3m** in 61% yield (entry 12). To broaden the synthetic utility of this coupling-cyclization, 5,6-heptadienoic acid **1j** was cyclized to give the six membered heterocyclic lactones **3o**⁶ and **3p** (entries 14 and 15).

Acknowledgement

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Reference and Notes

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- (6) Satisfactory physical and spectral data were obtained in accord with the structure. Selected physical and spectral data are as follows. **3a**: TLC, SiO₂, EtOAc/hexanes 1 : 3, $R_f = 0.70$. ¹H NMR (CDCl₃, 400 MHz) δ 1.67-2.10 (m,4H), 3.90 (m, 1H), 4.03 (m, 1H), 4.86 (t, 1H, *J* = 6.9 Hz), 5.30 (dd, 1H, *J* = 0.9, 1.6 Hz), 5.37 (dd, 1H, *J* = 1.6, 1.6 Hz), 7.21-7.40 (m, 5H). IR (neat) 2959, 2927, 1654, 1560, 377 cm⁻¹. MS (m/e) 174(M⁺), 173, 131, 103, 77, 71 (base peak).

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3c: TLC, SiO₂, EtOAc/hexanes 1 : 3, $R_f = 0.66$, ¹H NMR (CDCl₃, 400 MHz) *cis*: δ 1.33 (d, 3H, *J* = 6.0 Hz), 1.53-1.56 (m, 2H), 2.15-2.18 (m, 2H), 4.11 (m, 1H), 4.84 (m, 1H), 5.27 (dd, 1H, J = 0.9, 1.6Hz), 5.39 (dd, 1H, J = 1.6, 1.6Hz), 7.27-7.34 (m, 5H). *trans*: δ 1.30 (d, 3H, J = 6.0 Hz), 1.64-1.69 (m, 2H), 2.06-2.11 (m, 2H), 4.27 (m, 1H), 5.00 (m, 1H), 5.32(dd, 1H, J = 0.9, 1.6 Hz), 5.39 (d, 1H, J = 1.6, 1.6 Hz), 7.27-7.32 (m, 5H). IR (neat) 2959, 2925, 1653, 1558, 1377, 1100 cm⁻¹ MS (m/e) 188 (M⁺), 131, 118, 113, 71(base peak), 51. **3d**: TLC, SiO₂, EtOAc/hexanes 1 : 3, $R_f = 0.68$. ¹H NMR $(CDCl_{3}, 400MHz)\,\delta\,1.42\,(m,1H),\,1.51\text{-}1.70\,(m,3H),\,1.72\,(m,$ 1H), 1.85 (m, 1H), 3.60 (ddd, 1H, J = 2.3, 11.5, 11.6 Hz), 4.13 (ddd, 1H, J = 2.2, 2.3, 11.6 Hz), 4.25 (dd, 1H, J = 2.8, 10.9 Hz), 5.31 (dd, 1H, J = 0.9, 1.6 Hz), 5.38 (dd, 1H, J = 1.6, 1.6 Hz), 7.26-7.46 (m, 5H). IR (neat) 2986, 2943, 1448, 1206, 1047 cm⁻¹ MS (m/e) 188(M⁺), 144, 104, 85(base peak), 77. **3f**: TLC, SiO₂, EtOAc/hexanes 1 : 3, $R_f = 0.66$. ¹H NMR (CDCl₃, 300 MHz) δ 2.04 (m, 1H), 2.34 (m, 1H), 2.46 (s, 3H), 3.72-3.80 (m, 2H), 4.80 (t, 1H, J = 8.7 Hz), 5.49 (dd, 1H, J = 0.9, 1.6 Hz), 5.68 (dd, 1H, J = 1.6, 1.6 Hz), 7.29-7.38 (m, 7H), 7.75 (m, 2H). IR (neat) 2950, 2927, 1500, 1309, 1105 cm⁻¹ MS (m/e) 313(M⁺), 209, 155, 130(base peak), 128, 91. **3g**: TLC, SiO₂, EtOAc/hexanes 1 : 3, $R_f = 0.58$. ¹H NMR (CDCl₃, 300 MHz) δ 2.43 (s, 3H), 2.45 (m, 2H), 2.86 (m, 1H), 3.24 (m, 1H), 3.67 (m, 1H), 3.94 (m, 1H), 7.13(m, 1H), 7.26-7.38 (m, 7H), 7.73 (m, 2H). IR (neat) 2950, 2932, 1510, 1280,

7.38 (m, 7H), 7.73 (m, 2H). IR (neat) 2950, 2932, 1510, 1280, 1090 cm⁻¹ MS (m/e) 313 (M⁺), 312, 239, 158, 130(base peak), 128, 91.

3k: TLC, SiO₂, EtOAc/hexanes 1 : 3, R_f = 0.58. ¹H NMR (CDCl₃, 400 MHz) δ 1.26-1.37 (m, 3H), 1.38-1.41 (m, 2H), 1.72 (m, 1H), 2.40 (s, 3H), 3.18 (ddd, 1H, J = 3.6, 11.4, 14.6 Hz), 3.68 (ddd, 1H, J = 3.5, 3.6, 14.6 Hz), 5.20 (d, 1H, J = 1.36 Hz), 5.27 (s, 2H), 7.23-7.32 (m, 7H), 7.66 (m, 2H). IR (neat) 2950, 2932, 1608, 1511, 1300, 1120 cm⁻¹ MS (m/e) 341(M⁺), 238(base peak), 154, 91. **30**: TLC, SiO₂, EtOAc/hexanes 1 : 3, R_f = 0.48. ¹H NMR (CDCl₃, 400 MHz) δ 1.62 (m, 1H), 1.82-1.90 (m, 2H), 1.97 (m, 1H), 2.55 (m, 1H), 2.66 (m, 1H), 5.30 (dd, 1H, J = 3.2, 9.3 Hz), 5.39 (s, 1H), 5.43 (s, 1H), 7.32-7.37 (m, 5H). IR (neat) 2950, 2932, 1736, 1511, 1461, 1243, 1035 cm⁻¹ MS (m/e) 202(M⁺), 174, 146, 134, 104, 103(base peak), 99, 83.

- (7) The typical procedure is as follows. To a stirred solution of $Ph_2I^+ BF_4^-(2a)$ (302 mg, 0.82 mmol) and K_2CO_3 (237 mg, 1.71 mmol) in CH_3CN (1 mL) was added Pd(PPh₃)₄ (47 mg, 5 mol %) followed by allenic alcohol **1a** (67 mg, 0.68 mmol) in CH_3CN (1 mL). The reaction mixture was stirred at 60 °C for 3 h, cooled to room temperature, and quenched with saturated NH_4Cl solution. The mixture was extracted with ether and the organic layer was dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was separated by SiO₂ column chromatography (EtOAc/hexanes 1 : 3, $R_f = 0.70$) to afford the cyclized ether **3a** (90 mg, 76%).
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