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Microwave-assisted palladium-catalyzed allylation of aryl halides with homoallyl alcohols via retro-allylation

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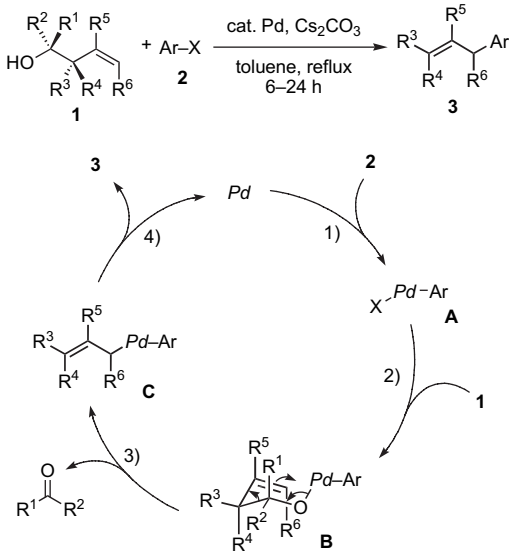
Abstract—The palladium-catalyzed allylation of aryl halides with homoallyl alcohols via retro-allylation proceeds at 200–250 °C in a toluene–DMF mixed solvent using microwave heating. Even at such high temperatures, the regio- and stereospecificity of the allyl transfer reaction is still satisfactory. The amount of the palladium catalyst can be reduced to 0.5 or 0.05 mol %.

1. Introduction

Recently we reported the use of homoallyl alcohols as the allyl sources in the palladium-catalyzed allylations of organic halides instead of allylmetal reagents (Scheme 1).[1] The allylation reaction would proceed as follows: (1) oxidative addition of aryl halide **2**, (2) ligand exchange with homoallyl alcohol **1** to afford alkoxy(aryl)palladium **B**, (3) retro-allylation reaction of **B** providing σ-allyl(aryl)palladium **C**, and (4) reductive elimination to yield **3**. Since the oxidative addition, the ligand exchange, and the reductive elimination would occur even at ambient temperature, the retro-allylation seems to be the rate-determining step of this reaction. Due to the slow retro-allylation, the allylation of aryl halides in refluxing toluene required prolonged reaction time, ca. 6–24 h. Shorter reaction time is preferable to improve the productivity of the reaction and to enable high-throughput screenings. Here we report the microwave-assisted allylation reactions of aryl halides with homoallyl alcohols, which proceed to completion within 15 min in most cases.[2,3]



Scheme 1.

2. Results and discussions

Treatment of 1-bromonaphthalene (**2a**) with homoallyl alcohol **1a** in the presence of cesium carbonate at 200 °C for 15 min under microwave irradiation and palladium catalysis provided 1-methallylnaphthalene (**3a**) in excellent yield (Table 1, entry 1). Instead of toluene alone,[1] a toluene–*N*,*N*-dimethylformamide (DMF) mixed solvent was used to improve the efficiency of microwave heating. Not only diisopropyl-substituted **1a** but also dimethyl-substituted **1b** participated in the methallyl transfer reaction (entry 2). Aryl bromides having substituents at the *ortho* positions were smoothly methallylated to yield the corresponding products in high yields (entries 3 and 4). The yields were comparable to those previously reported.[1a] When the reactions were performed at 250 °C, the amount of the palladium

Keywords: Palladium; Allylation; Microwaves; Carbon–carbon bond cleavage.
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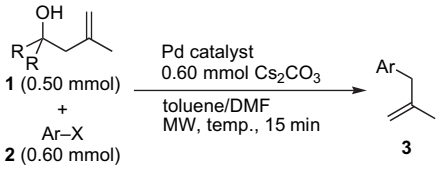
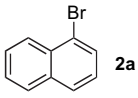
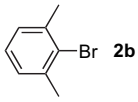
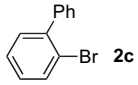
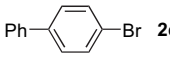
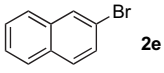
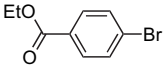
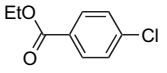
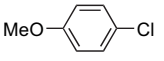
Table 1. Allylation of aryl halides with homoallyl alcohols under microwave irradiation



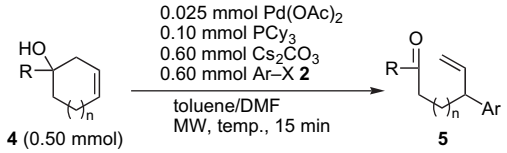
Entry	1[a]	2	$Pd(OAc)_2$/mmol	Ligand, mmol	Temp[b]/°C	3, Yield[c]/%
1	**1a**	 **2a**	0.025	P(*p*-tol)$_3$, 0.10	200	**3a**, 90 (86)
2	**1b**	**2a**	0.025	P(*p*-tol)$_3$, 0.10	200	**3a**, 94
3	**1a**	 **2b**	0.025	P(*p*-tol)$_3$, 0.10	200	**3b**, 87 (90)
4	**1a**	 **2c**	0.025	P(*p*-tol)$_3$, 0.10	200	**3c**, 100 (91)
5	**1a**	**2b**	0.0025	P(*p*-tol)$_3$, 0.010	250	**3b**, 62
6	**1a**	**2c**	0.0025	P(*p*-tol)$_3$, 0.010	250	**3c**, 95
7	**1a**	 **2d**	0.025	P(*p*-tol)$_3$, 0.10	200	**3d**, 41 (34)
8	**1a**	**2d**	0.025	PCy_3, 0.050	200	**3d**, 61 (83)
9	**1a**	 **2e**	0.025	PCy_3, 0.050	200	**3e**, 53 (86)
10	**1b**	 **2f**	0.025	PCy_3, 0.15	250	**3f**, 97[d]
11	**1a**	 **2g**	0.025	PCy_3, 0.050	220	**3f**, 72 (79)
12	**1a**	**2g**	0.0025	PCy_3, 0.015	250	**3f**, 86
13	**1a**	**2g**	0.00025	PCy_3, 0.0015	250	**3f**, 78
14	**1a**	 **2h**	0.025	PCy_3, 0.15	250	**3g**, 98 (70)

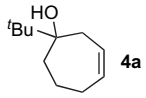
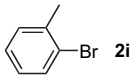
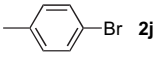
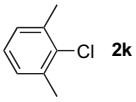
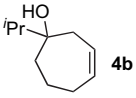
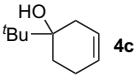
[a] Compound **1a**: R=^{i}Pr, **1b**: R=Me.
[b] The reactions at 200 °C and at 220 °C were performed in a mixed solvent of toluene (2.0 mL) and DMF (0.20 mL). The reactions at 250 °C were performed in toluene (2.0 mL) and DMF (0.40 mL) to improve the efficiency of microwave heating further.
[c] The yields reported in the literature[1] by performing the reactions in refluxing toluene for 8 h are in parentheses.
[d] Performed for 20 min.

catalyst could be reduced from 5 mol % of $Pd(OAc)_2$ and 20 mol % of P(*p*-tol)$_3$ to 0.5 mol % and 2 mol %, respectively (entries 5 and 6). The reaction of 4-bromobiphenyl (**2d**), which has no substituent at the *ortho* position, resulted in a moderate yield of the coupling product (entry 7). To improve the yield of **3d**, tricyclohexylphosphine (PCy_3) was used as ligand (entry 8).[1b] PCy_3 also allowed the use of aryl chlorides as substrates (entries 11–14). Electron-rich as well as electron-deficient aryl chlorides underwent methallylation. It is worth noting that only 0.05 mol % of $Pd(OAc)_2$ functioned to catalyze the reaction wherein the turnover number was 1.6×10^3 (entry 13). The best $Pd(OAc)_2/PCy_3$ ratio was 1:6 at 250 °C under microwave irradiation, whereas a $Pd(OAc)_2/PCy_3$ ratio of 1:2 was effective at 200 °C (entries 8 and 9) as well as in the previous report[1b] performed in refluxing toluene. When we used a 1:2 ratio at 250 °C under microwave irradiation, palladium black was likely to be generated during the heating. The palladium black would be heated extremely by microwaves, causing the reaction vial to shatter.[4]

Microwave heating was applicable to the arylative ring-opening reactions of endocyclic homoallyl alcohols (Table 2). In most cases, the yields were higher than those obtained by the conventional heating at 140 °C.[1b] The reactions of aryl halides having *ortho* substituents proceeded at 200 °C (entries 1–3 and 5). The reaction of *p*-bromotoluene (**2j**) required heating at 250 °C to attain satisfactory yield (entry 4).

Table 2. Arylative ring-opening reaction using microwave heating



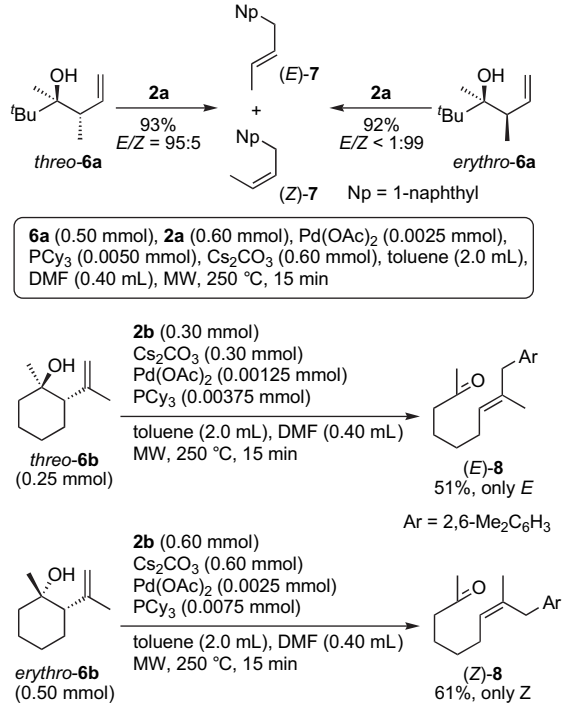
Entry	4	2	Temp[a]/°C	Yield[b]/%
1	 **4a**	**2b**	200	**5a**, 88 (80)
2	**4a**	**2c**	200	**5b**, 76 (68)
3	**4a**	 **2i**	200	**5c**, 94 (70)
4[c]	**4a**	 **2j**	250	**5d**, 75 (65)
5	**4a**	 **2k**	200	**5a**, 83
6	 **4b**	**2b**	250	**5e**, 36 (20)
7[d]	 **4c**	**2b**	250	**5f**, 47 (59)

[a] The reactions at 200 °C were performed in a mixed solvent of toluene (2.0 mL) and DMF (0.20 mL). The reactions at 250 °C were performed in toluene (2.0 mL) and DMF (0.40 mL).
[b] The yields reported in the literature[1b] by performing the reactions in refluxing xylene for 12 or 24 h are in parentheses.
[c] 0.15 mmol of PCy_3 was used.
[d] 0.050 mmol of PCy_3 was used.

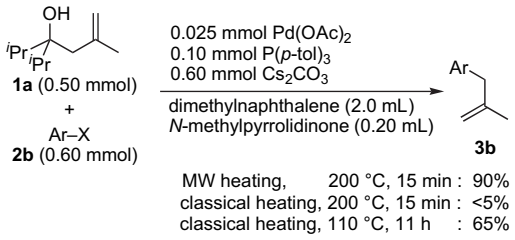
Unfortunately, the reactions of **4b** and **4c** at 250 °C were still unsatisfactory by using microwave heating.

Treatment of **2a** with *threo*-**6a** in the presence of 0.5 mol % of palladium acetate and 1.0 mol % of PCy_3 at 250 °C afforded (*E*)-1-crotylnaphthalene (*E*)-**7** stereoselectively (Scheme 2). Similar treatment with *erythro*-**6a** afforded (*Z*)-**7** exclusively. Stereospecificity was thus observed even at 250 °C. Stereospecificity was also observed in the reactions of alkenylcyclohexanol, *threo*- and *erythro*-**6b**.

It was reported that microwave heating is not only a simple heating method but also can have so-called *nonthermal microwave effects*.[2,5] This was also the case for the present reaction (Scheme 3). The reaction of **1a** with **2b** completed smoothly within 15 min in a dimethylnaphthalene (bp: ca. 260 °C)/*N*-methylpyrrolidinone (bp: 202 °C) mixed solvent by using microwave heating at 200 °C, whereas the same reaction was sluggish by classical heating for 15 min at 200 °C. We cannot explain how nonthermal microwave effects operated. Possible nonthermal microwave effects may include: (1) microwave-assisted activation of the polar transition state of the retro-allylation step, (2) preventing the formation of palladium black, and (3) intervention of localized microscopic high temperatures.



Scheme 2.



Scheme 3.

3. Conclusion

Microwave heating promotes the palladium-catalyzed allylation of aryl halides with homoallyl alcohols. The microwave heating easily allowed us to perform the reactions at 200–250 °C. Even at such high temperatures, the regio- and stereospecificity of the allyl transfer reaction are excellent. In addition, the amount of the palladium catalyst can be reduced to 0.5 or 0.05 mol %.

4. Experimental section

4.1. General

Unless otherwise noted, all the reactions were carried out using a focused microwave unit (Biotage Initiator™). The maximum irradiation power is 400 W. Each reaction was run in a 5-mL glass pressure vial, which is a commercially available vial specially for the Biotage Initiator™. It took 2 min and 6 min to reach 200 °C and 250 °C, respectively. After reaching the indicated temperatures, controlled microwave irradiation started and continued for 15 min, keeping the reaction temperature constant. The classical heating at 200 °C shown in Scheme 3 was performed in a Kugelrohr

distillation apparatus (Shibata, GTO-250RS). With the apparatus, it took 5 min to reach 200 °C and additional heating continued for 15 min. The classical heating at 110 °C shown in Scheme 3 was done in an oil bath.

^{1}H NMR (300 MHz and 500 MHz) and ^{13}C NMR (75.3 MHz and 125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.0 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene, DMF, and *N*-methylpyrrolidinone were purchased from Wako Pure Chemical Co. Dimethylnaphthalene (mixture of regioisomers) was obtained from TCI. Toluene was stored over slices of sodium. Dimethylnaphthalene, DMF, and *N*-methylpyrrolidinone were used as received. Tri(*p*-tolyl)phosphine and cesium carbonate were purchased from Wako Pure Chemical Co. Palladium acetate and tricyclohexylphosphine were obtained from TCI and Acros, respectively. The homoallyl alcohols **1**, **4**, and **6** were prepared according to the literature.[1b]

4.2. Typical procedure

The reaction of entry 1 in Table 1 is representative. Cesium carbonate (0.20 g, 0.60 mmol), palladium acetate (5.6 mg, 0.025 mmol), and tri(*p*-tolyl)phosphine (30 mg, 0.10 mmol) were placed in a 5-mL glass pressure vial. The vial was flushed with argon and sealed with a PTFE–silicon septum. Toluene (2.0 mL) and DMF (0.20 mL) were added, and the mixture was stirred for 1 min. Homoallyl alcohol **1a** (85 mg, 0.50 mmol) and 1-bromonaphthalene (**2a**, 83 μL, 0.60 mmol) were added. The suspension was heated at 200 °C with stirring for 15 min in the microwave reactor. The mixture was then cooled to room temperature. Hydrochloric acid (1 M, 3 mL) was added. The organic layer formed was then washed with brine (5 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated. Silica gel column purification with hexane as an eluent afforded 1-methallylnaphthalene (**3a**, 82 mg, 0.45 mmol) in 90% yield.

4.3. Characterization data

Spectral data for **3**, **5**, **7**, and **8** were found in the literature[1,6] except for **5f**.

4.3.1. 2,2-Dimethyl-6-(2,6-dimethylphenyl)-7-octen-3-one (5f). IR (neat) 2967, 1705, 1453, 1367, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 2.02–2.09 (m, 1H), 2.14–2.22 (m, 1H), 2.32 (s, 6H), 2.34–2.47 (m, 2H), 3.84–3.89 (m, 1H), 5.05 (dt, J=10.5, 2.0 Hz, 2H), 6.08 (ddd, J=17.5, 10.5, 5.5 Hz, 1H), 6.96–7.02 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.67, 26.54, 26.59, 34.54, 43.27, 44.25, 114.47, 126.28, 129 (br s), 136.95, 139.51, 140.29, 215.87. Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14%. Found: C, 83.66; H, 10.09%.

Acknowledgements

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References and notes

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4. *Caution*: the black precipitate resulted in extreme microwave absorption that caused reaction vial to shatter. Although the microwave reactor is explosion-proof, proper precautions should be taken.
5. (a) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136–9139; (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (c) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863–1866; (d) Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589–3590.
6. For **3c:** Thatia, T.; Jayanth, T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921–2924.