Synthesis of (2-Arylethylidene)cyclobutanes by Palladium-Catalyzed Reactions of Aryl Halides with Homoallyl Alcohols Bearing a Trimethylene Group at the Allylic Position

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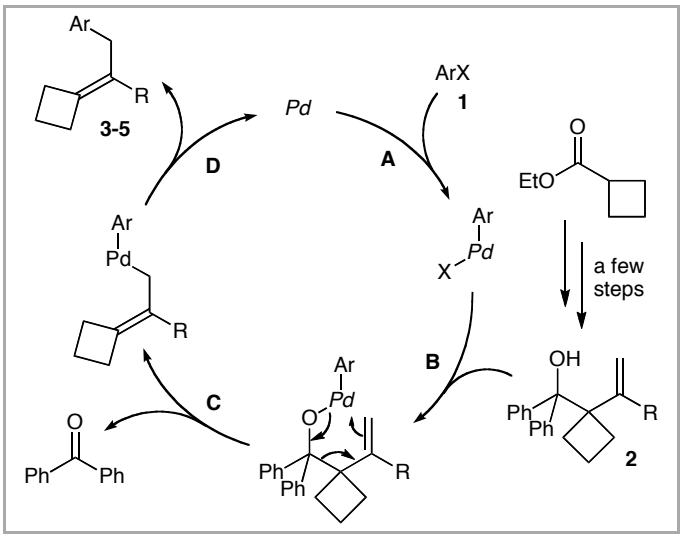
Abstract: Treatment of aryl bromides with homoallyl alcohols bearing a trimethylene group at the allylic position in the presence of cesium carbonate under palladium catalysis affords (2-arylethylidene)-cyclobutanes selectively. The selective formation of the alkylidenecyclobutane skeleton results from regiospecific retro-allylation of the homoallyl alcohols, which accompanies the transposition of the double bonds.

Key words: Palladium, Methylenecyclobutanes, Homoallyl Alcohols, Cleavage reactions, Allylation

Alkylidenecyclobutanes are interesting due to their strained skeleton and reactive double bonds and are hence useful compounds in organic synthesis.[1] Uncatalyzed[2] and catalyzed[3] cycloaddition reactions of allenes with activated alkenes represent the most useful conventional method for the synthesis of alkylidenecyclobutanes. However, the use of activated alkenes, such as acrylonitrile and styrene, limits the scope of the reactions. The Wittig alkylidenation reactions of cyclobutanone are usually effective, unfortunately suffering from moderate yields.[4] Titanium reagents have been used in the preparation of alkylidenecyclobutanes although the strong oxophilicity of the reagents leads to limited functional group compatibility.[1b,5] For those reasons, A new efficient method for constructing this intriguing strained skeleton has been awaited.

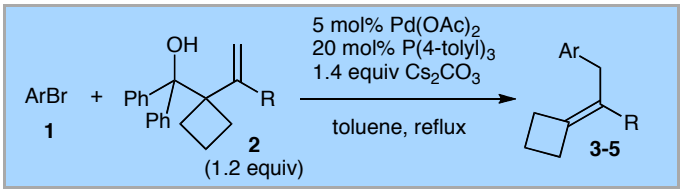
We have been interested in palladium-catalyzed reactions of aryl halides with homoallyl alcohols that result in highly regiospecific synthesis of allylarenes.[6,7] We envisioned that the allylation reaction of aryl halides would be applicable to the synthesis of alkylidenecyclobutanes by using homoallyl alcohol **2** bearing a trimethylene group at the allylic position (Scheme 1 and Table 1). After oxidative addition (Step **A**), alkoxide-halide exchange between arylpalladium halide and **2** would occur to yield aryl(alkoxy)palladium (Step **B**). The subsequent retro-allylation of the palladium alkoxide would afford aryl(3-trimethylene-2-propenyl)palladium regioselectively, whilst releasing benzophenone (Step **C**). Finally, immediate reductive elimination would lead to the regioselective synthesis of alkylidenecyclobutanes without forming the regioisomer, (1-trimethylene-2-propenyl)arene (Step **D**). Advantageously, alcohols **2** were readily prepared in a few steps from commercially available ethyl cyclobutanecarboxylate.[8]



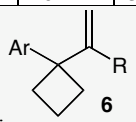
Scheme 1 Idea for Constructing Alkylidenecyclobutanes

Treatment of 2-bromonaphthalene (**1a**) with alcohol **2a** in the presence of cesium carbonate and catalytic amounts of palladium acetate and tri-4-tolylphosphine in toluene at reflux provided alkylidenecyclobutane **3a** in 94% yield (Table 1, entry 1). Sterically demanding compounds **1b** and **1c** also participated in the reaction (entries 2 and 3), as did electron-deficient aryl bromides **1f** and **1g**, which reacted smoothly to afford the corresponding products in excellent yields (entries 6 and 7). The reaction of aryl bromide **1h**, bearing an electron-donating 4-methoxy group provided **3h** in 66% yield (entry 8). Carbon–carbon bond formation took place predominantly at the brominated carbon of **1i**, leaving the chloro moiety intact (entry 9). The reaction of ethyl 2-bromobenzoate (**1j**) gave rise to a modest yield of product **3j** (entry 10). The reactions of 3,5-dimethylbromobenzene (**1d**) and 2-bromoanisole (**1k**) yielded the corresponding alkylidenecyclobutanes **3d** and **3k**, respectively, although the products were contaminated with 5% yields of regioisomers **6** (entries 4 and 11). Vinyl bromide **1l** also underwent the reaction to yield the corresponding 1,4-diene (entry 12). The methyl group of **2a** was not essential, since phenyl-substituted **2b** as well as **2c** bearing no substituents on the vinyl group also underwent the reaction (entries 13–17).

Table 1 Synthesis of (2-Arylethylidene)cyclobutanes



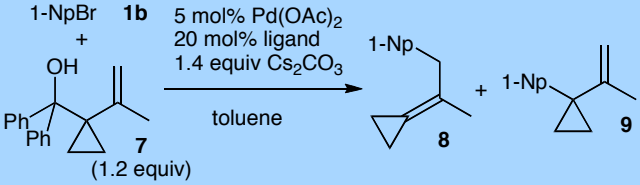
entry	Ar	1	R	2	time /h	3–5	yield /%
1	2-naphthyl	**1a**	Me	**2a**	13	**3a**	94
2	1-naphthyl	**1b**	Me	**2a**	13	**3b**	94
3	2-PhC_6H_4	**1c**	Me	**2a**	9	**3c**	67
4	3,5-$Me_2C_6H_3$	**1d**	Me	**2a**	9	**3d**	61[a]
5	4-PhC_6H_4	**1e**	Me	**2a**	9	**3e**	70
6	4-$CF_3C_6H_4$	**1f**	Me	**2a**	10	**3f**	87
7	4-$EtO_2CC_6H_4$	**1g**	Me	**2a**	13	**3g**	97
8	4-$MeOC_6H_4$	**1h**	Me	**2a**	13	**3h**	66
9	4-ClC_6H_4	**1i**	Me	**2a**	10	**3i**	66
10	2-$EtO_2CC_6H_4$	**1j**	Me	**2a**	12	**3j**	53
11	2-$MeOC_6H_4$	**1k**	Me	**2a**	12	**3k**	71[a]
12	(CH_2=CBrPh)	**1l**	Me	**2a**	10	**3l**	60
13	2-naphthyl	**1a**	Ph	**2b**	11	**4a**	75
14	4-$EtO_2CC_6H_4$	**1g**	Ph	**2b**	16	**4g**	82
15	4-$MeOC_6H_4$	**1h**	Ph	**2b**	16	**4h**	78
16	2-naphthyl	**1a**	H	**2c**	18	**5a**	62
17	4-$EtO_2CC_6H_4$	**1g**	H	**2c**	18	**5g**	87



[a] Contaminated with regioisomer **6** (5%).

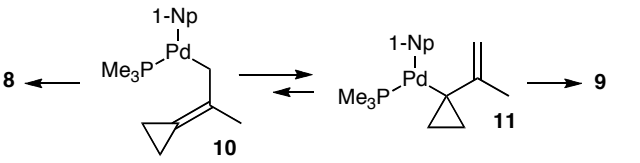
We attempted the synthesis of alkylidenecyclopropane by applying the present strategy (Table 2). However, the reaction with **7** under the standard reaction conditions was sluggish (entry 1). The rigid cyclopropane moiety of alcohol **7** would hamper the retro-allylation step probably due to the wider, fixed C(hydroxylated)–C(cyclopropyl)–C(vinylic) angle (calculated to be 114˚)[9] compared to the calculated C(hydroxylated)–C(cyclobutyl)–C(vinylic) angle of **2a** (110˚)[9] as well as the typical unstrained C–C(sp^3)–C angle (*ca.* 110˚). The high strain-energy of methylenecyclopropane skeleton is also responsible for the difficulty. According to the literature,[10] the strain energy of methylenecyclobutane (26.9 kcal/mol) is close to that of cyclobutane (26.5 kcal/mol). In contrast, the strain energy of methylenecyclopropane (40.9 kcal/mol) was calculated to be much larger than that of cyclopropane (27.5 kcal/mol). The retro-allylation of **7** would thus require a higher activation energy than that of **2**. Heating the reaction mixture at 250 ˚C under microwave irradiation afforded desired product **8** exclusively, albeit in modest yield (entry 2).

Table 2 Synthesis of (2-Arylethylidene)cyclopropanes



entry	heating	ligand	**8** /%	**9** /%
1	conventional, 110 ˚C, 11 h	$P(4\text{-tolyl})_3$	<26	0
2	microwave, 250 ˚C, 15 min	$P(4\text{-tolyl})_3$	41	0
3	microwave, 250 ˚C, 15 min	PMe_3	0	59

Interestingly, the use of trimethylphosphine instead of tri-4-tolylphosphine reversed the regioselectivity and **9** was solely obtained (entry 3). We assume that the small and electron-donating trimethylphosphine retarded the smooth reductive elimination from intermediate **10** (Scheme 2). The slow reductive elimination would lead to the isomerization of **10** to the thermodynamically more stable **11**, from which reductive elimination would occur. Unfortunately, such a drastic change in regioselectivity was not observed in the reactions of **2**.



Scheme 2 Isomerization of (3-Ethylene-2-methyl-2-propenyl)palladium

In summary, we have developed a new access to (2-arylethylidene)cyclobutanes, regarding the palladium-catalyzed retro-allylation of homoallyl alcohols **2** as a method for the transposition of the double bond.

Typical Procedure. Cesium carbonate (0.12 g, 0.36 mmol) was placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was dried in vacuo with heating with a hair dryer for 2 min. Palladium acetate (2.8 mg, 0.0125 mmol) and tri–4-tolylphosphine (15 mg, 0.050 mmol) were added to the reaction flask. The flask was then filled with argon by using the standard Schlenk techniques. Toluene (2.0 mL), homoallyl alcohol **2a** (79 mg, 0.30 mmol), and 2-bromonaphthalene (**1a**, 52 mg, 0.25 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 13 h. After the mixture was cooled to room temperature, water (20 mL) was added. The product was extracted with hexane (20 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification with hexane as an eluent gave 2–(2–cyclobutylidenepropyl)naphthalene (**3a**, 52.0 mg, 0.234 mmol) in 94% yield. **Characterization data for 3a**: IR (neat) 2826, 1600, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H), 1.95–2.01 (m, 2H), 2.68–2.72 (m, 2H), 2.80–2.82 (m, 2H), 3.35 (s, 2H), 7.30–7.32 (m, 1H), 7.40–7.47 (m, 2H), 7.60 (s, 1H), 7.75–7.81 (m, 3H); ^{13}C NMR

($CDCl_3$) δ 15.68, 15.86, 29.26, 29.43, 38.95, 124.83, 125.02, 125.78, 126.69, 127.42, 127.53, 127.58, 127.76, 132.02, 133.59, 134.38, 138.40. Found: C, 91.57; H, 8.06%. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16%.

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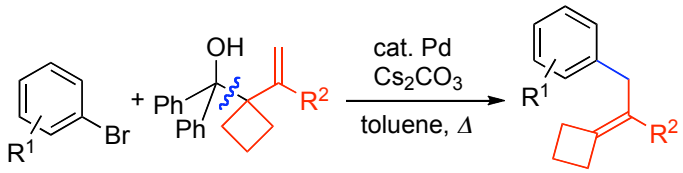

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