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Palladium-catalyzed cascade ring expansion reaction of 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols with phenols

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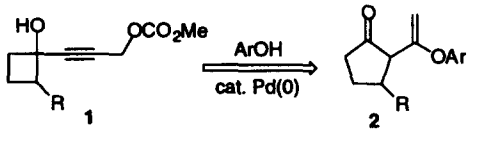
Abstract

A palladium-catalyzed transformation of 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols to cyclopentanones on treatment with phenol derivatives is described. This process can be visualized to proceed via nucleophilic attack to allenyl palladium species by phenol, followed by ring expansion reaction of π-allylpalladium complex to form the corresponding cyclopentanone.

Keywords: cyclopentanones; palladium; palladium compounds; rearrangements; ring transformations.

Palladium-promoted ring expansion reactions of 1-alkenyl or 1-alkynyl cyclobutanols is a well-investigated reaction that is triggered by release in the strain of the four-membered ring systems.[1,2] This useful methodology for the construction of five-membered ring systems has been successfully applied to the synthesis of natural products.[3] Recently, we have developed a cascade insertion–ring expansion reaction of allenylcyclobutanols with aryl iodides.[4] The reaction enables the formation of a carbon–carbon bond along with expansion of the four-membered ring system in a one-pot process. Propargyl carbonates undergo a variety of palladium-catalyzed transformations with nucleophiles, which constitute an important class of palladium-catalyzed reactions.[5,6] Here, we report a novel type of palladium-catalyzed cascade ring expansion reaction of 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols **1** with phenols. The reaction can generate a carbon–oxygen bond to afford cyclopentanones **2** in a one-pot process (Scheme 1).



Scheme 1.

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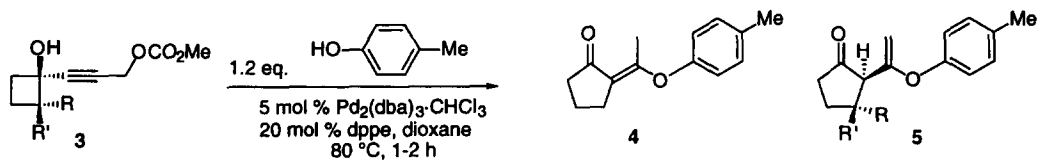
Table 1
Cascade reactions of cyclobutanols with *p*-cresol

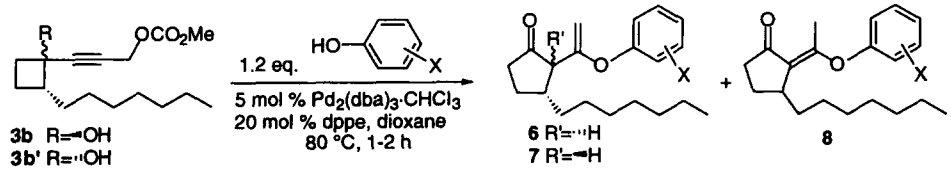


entry	substrate	product	yield(%)
1	**3a** R = R' = H	**4**	81
2	**3b** R = Heptyl R' = H	**5b**	80
3	**3c** R = Ph R' = H	**5c**	83
4	**3d** R + R' = Cyclohexyl	**5d**	99

Cascade reactions were first studied using 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols **3a–d**[7] and *p*-cresol (Table 1). Treatment of **3a** and *p*-cresol with 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol% dppe in dioxane at 80°C for 1 h provided the isomerized cyclopentanone **4** in 81% yield (entry 1). When 2-alkyl- or 2-aryl-substituted substrate **3b** or **3c** were subjected to the reaction, the *trans*-cyclopentanone **5b** or **5c** was obtained as the sole product (entries 2 and 3).[8] Similarly, the 2,2-disubstituted substrate **3d** was transformed into **5d** in quantitative yield (entry 4). Thus, it was evident that the reactions proceeded in regio- and diastereoselective manners at the more substituted carbon.

We then examined the reactions of **3b** and its diastereomer **3b′** with a variety of substituted phenols (Table 2). When **3b** was treated with the electron donating group-substituted phenols, *trans*-cyclopentanones **6** were selectively produced in high yields (entries 1–4). Since the isomers **8** were also provided in accordance with increase in the acidity of the phenols, it is expected that acid-catalyzed isomerization occcured (entries 5–7). In contrast with the case of **3b**, the isomers **8** were mainly obtained from **3b′**, and *cis*-cyclopentanones **7** were obtained as minor products when electron enriched phenols

Table 2
Cascade reactions with various substituted phenols

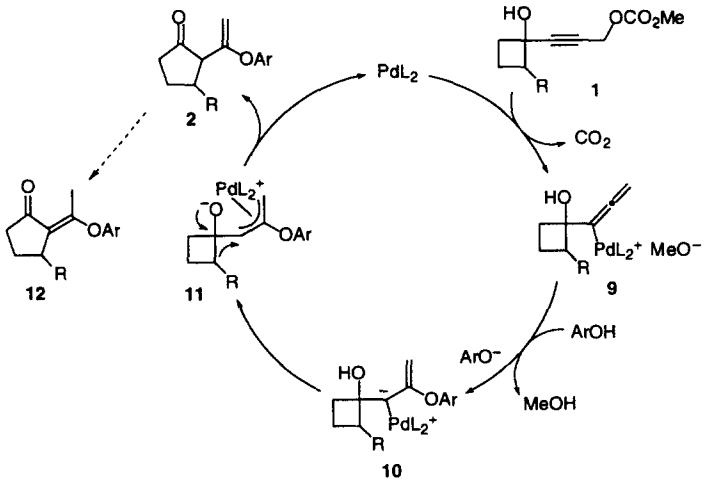


entry	substrate	X	product	yield (%)
1	**3b**	4-OMe	**6**	98
2	**3b**	2,4,6-Trimethyl	**6**	90
3	**3b**	4-Me	**6**	80
4	**3b**	2-OMe	**6**	93
5	**3b**	H	**6**:**8** = 65:35*	94
6	**3b**	4-Cl	**6**:**8** = 68:32*	67
7	**3b**	4-NO_2	**8**	23
8	**3b'**	4-OMe	**7**:**8** = 36:64*	98
9	**3b'**	2,4,6-Trimethyl	**7**:**8** = 23:77*	98
10	**3b'**	4-Me	**8**	92
11	**3b'**	2-OMe	**8**	93
12	**3b'**	H	**8**	97
13	**3b'**	4-Cl	**8**	96
14	**3b'**	4-NO_2	**8**	70

* The product ratio was determined by ^{1}H-NMR.

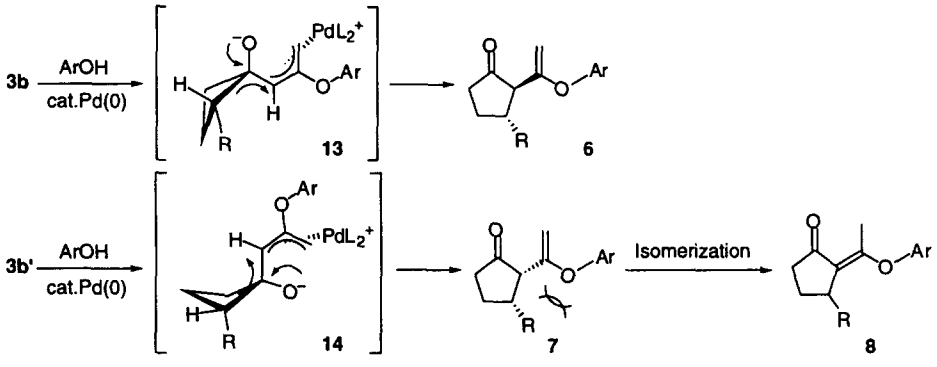
were used (entries 8 and 9). These reactions generally proceeded in high yields except in the case of nitrophenol (entries 7 and 14).

A plausible mechanism for the reacion is shown in Scheme 2. The propargylic carbonate **1** would be converted into the allenylpalladium methoxide **9** by reaction with palladium(0). The complex **9** would be subjected to the nucleophilic attack by phenols to lead to the π-allylpalladium complex **11** via the intermediate **10**. Finally, ring expansion reaction of **11** would give the phenoxy-substituted cyclopentanone **2**, which further isomerizes to **12** under the same reaction conditions.



Scheme 2.

Scheme 3 provides a possible explanation for the diastereoselectivity of the reactions. It can be presumed that the stereochemistry of the reaction is controlled by the conformation of the π-allylpalladium complex during the ring expansion step. Thus, in the case of **3b**, the ring expansion process would proceed via **13**, the most stable conformer, to give **6**. Similarly, when diastereomer **3b′** is employed, **7** would be produced via **14**. But **7** is very unstable due to the steric interaction, and can easily isomerize to **8**.



Scheme 3.

In conclusion, we have developed a novel type of cascade ring expansion reaction of 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols with phenols. Efforts to extend the scope of this reaction are currently in progress.

Acknowledgements

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7. Compounds **3a–d** were prepared from the corresponding cyclobutanones as follows: Cyclobutanone was treated with 3-(2*H*-tetrahydropyran-2-yloxy)-1-propynyl lithium at −78°C to give the acetylenylcyclobutanol. The THP group of the product was then deprotected with TsOH in MeOH to give the propargylalcohol, which was converted to 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanol using methyl chloroformate in pyridine at 0°C. Selected spectral data for 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols: **3b**: IR (neat) 3400, 2230, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=6.9 Hz), 1.18–1.46 (12H, m), 1.53–1.66 (1H, m), 1.77–1.88 (1H, m), 2.05 (1H, dt, *J*=9.6 and 10.5 Hz), 2.23–2.36 (2H, m), 2.56 (1H, s), 3.82 (3H, s), 4.82 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.0, 22.6, 26.9, 29.2, 29.6, 31.7, 31.8, 35.5, 49.0, 55.1, 55.8, 71.7, 79.4, 88.7, 155.4; MS *m/z* 254 (M^+−28); HRMS calcd for $C_{14}H_{22}O_4$: 254.1518 (M^+−28), found: 254.1563.
8. Typical experimental procedure for the cascade reaction (entry 2 in Table 1 and entry 3 in Table 2): A slurry of the cyclobutanol **3b** (35.8 mg, 0.127 mmol), *p*-cresol (16.4 mg, 0.152 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (6.6 mg, 6.4 μmol), dppe (10.1 mg, 25.4 μmol) in dioxane (3 mL) was stirred for 1 h at 80°C. After evaporation of the solvent, flash chromatography (silica gel, 98:2 v/v hexane:ethyl acetate) afforded the cyclopentanone **5b** (32.1 mg, 80%) as a colorless oil. **5b**: IR (neat) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, *J*=6.9 Hz), 1.20–1.53 (12H, m), 1.70–1.82 (1H, m), 2.20–2.35 (2H, m), 2.32 (3H, s), 2.36–2.56 (2H, m), 2.57 (1H, d, *J*=10.8 Hz), 4.03 (1H, d, *J*=2.1 Hz), 4.17 (1H, d, *J*=2.1 Hz), 6.91–6.96 (2H, m), 7.10–7.16 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.7, 22.5, 26.9, 27.3, 29.1, 29.6, 31.7, 34.6, 38.5, 40.5, 61.8, 91.3, 120.2, 121.3, 130.1, 130.2, 134.0, 152.8, 159.9, 216.7; MS *m/z* 314 (M^+); HRMS calcd for $C_{21}H_{30}O_2$: 314.2246 (M^+), found: 314.2232.