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# Palladium-catalyzed stereospecific ring expansion reaction of allenylcyclobutanols with aryl iodides: a novel route to the α-substituted cyclopentanones with quaternary carbon stereocenters

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**Abstract**

Stereoselective synthesis of α-substituted cyclopentanones with quaternary carbon stereocenters has been achieved by the palladium-catalyzed rearrangement of allenylcyclobutanols with aryl iodides. 

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

Palladium-catalyzed ring expansion reaction of cyclobutanol derivatives is one of the useful methodologies for the construction of five-membered ring systems, which has been successfully applied to the synthesis of natural products.[1] In recent years, we have developed a novel type of ring expansion reaction of allenylcyclobutanols with aryl iodides.[2] The reaction enables the formation of a carbon–carbon bond along with expansion of the four-membered ring system in one-pot process, and thereby constitutes a potentially useful synthetic method for the efficient synthesis of natural products. However, the reaction often caused double bond isomerization to give the more stable α,β-unsaturated cyclopentenone, which restricted the utility of this method. Herein, we describe the palladium-catalyzed ring expansion reaction of allenylcyclobutanols having a substituent at the 1-position of the allenyl moiety (Scheme 1).[3] By introducing a substituent at the allenyl moiety, the isomerization of the products could be suppressed and in addition, cyclopentanones with quaternary carbon stereocenters could be constructed. Furthermore, it is expected that a stereochemical investigation would provide precise details on the mechanism of the reaction.

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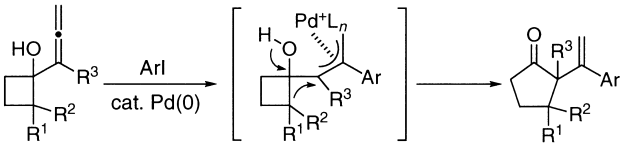
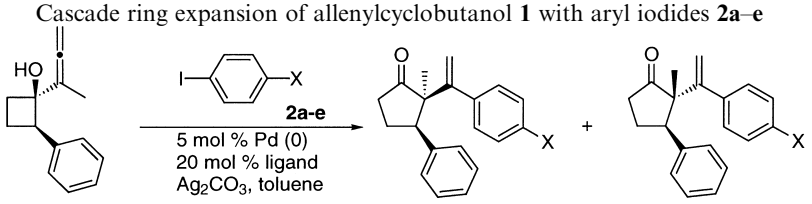



Scheme 1.

Ring expansion reactions were first studied using (1*R**,2*R**)-1-(1-methylallenyl)-2-phenylcyclobutanols **1**[4] with iodobenzene **2a** (Table 1).[5] When a mixture of **1** and **2a** was treated with 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol% dppe and $Ag_2CO_3$ in toluene at 60°C for 20 h, the reaction proceeded successfully to provide the cyclopentanone **3a** and its diastereomer **4a** as a 3:2 mixture in 80% yield (entry 1). It was interesting to observe that the formation of **3a** increased in accordance with an increase in the reaction temperature (entries 2 and 3). The reaction also proceeded uneventfully in the presence of various ligands (entries 4–8). The best result was obtained by employing 5

Table 1
Cascade ring expansion of allenylcyclobutanol **1** with aryl iodides **2a–e**




**1** **3a-e** **4a-e**

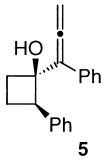
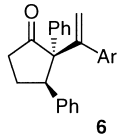
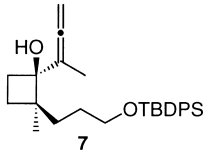
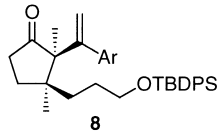
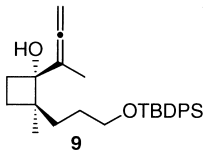
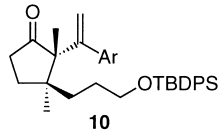
| | | | | | product | |
|---|---|---|---|---|---|---|
| entry | catalyst | temp (°C) | ArI | time (h) | **3** : **4**[a,b] | yield (%) |
| 1 | $Pd_2(dba)_3{\cdot}CHCl_3$, dppe | 60 | **2a**: X = H | 20 | 60 : 40 | 80 |
| 2 | $Pd_2(dba)_3{\cdot}CHCl_3$, dppe | 80 | **2a**: X = H | 4 | 88 : 12 | 70 |
| 3 | $Pd_2(dba)_3{\cdot}CHCl_3$, dppe | reflux | **2a**: X = H | 3 | 97 : 3 | 57 |
| 4 | $Pd_2(dba)_3{\cdot}CHCl_3$, dppp | 80 | **2a**: X = H | 2 | 89 : 11 | 31 |
| 5 | $Pd_2(dba)_3{\cdot}CHCl_3$, dppb | 80 | **2a**: X = H | 1 | **3a** only | 66 |
| 6 | $Pd_2(dba)_3{\cdot}CHCl_3$, dppf | 80 | **2a**: X = H | 24 | 72 : 28 | 55 |
| 7 | $Pd_2(dba)_3{\cdot}CHCl_3$, P(*o*-tolyl)$_3$ | 80 | **2a**: X = H | 1.5 | 89 : 11 | 78 |
| 8 | $Pd(PPh_3)_4$ | 80 | **2a**: X = H | 3 | **3a** only | 80 |
| 9 | $Pd(PPh_3)_4$ | 80 | **2b**: X = OMe | 1.5 | **3b** only | 72 |
| 10 | $Pd(PPh_3)_4$ | 80 | **2c**: X = Me | 1 | 94 : 6 | 89 |
| 11 | $Pd(PPh_3)_4$ | 80 | **2d**: X = $NO_2$ | 1.5 | **3d** only | 66 |
| 12 | $Pd(PPh_3)_4$ | 80 | **2e**: 1-iodo-naphthalene | 3 | 84 : 16 | 79 |

[a]The product ratios were determined by $^1$H-NMR integration of olefinic methylene signals ($\delta$ 4.87 and 5.01 for **3a**, $\delta$ 5.22 and 5.34 for **4a**, $\delta$ 4.82 and 5.00 for **3c**, $\delta$ 5.18 and 5.32 for **4c**, $\delta$ 5.11 and 5.27 for **3e**, $\delta$ 4.99 and 5.06 for **4e**). [b]The stereochemistry of the products **3b** and **3e** were determined by $^1$H-NOESY. The stereochemistry of the products **3a**, **3c**, **3d** were tentatively assigned by analogy of $^1$H-NMR spectrum of **3b**.

mol% of $Pd(PPh_3)_4$ at 80°C for 3 h (entry 8), and **3a** was exclusively obtained from **1** in 80% yield. Then, the reactions of **1** with various substituted aryl iodides **2b–e** were examined. In all the cases, the ring expansion could be carried out smoothly to furnish the corresponding cyclopentanones **3b–e** with satisfactory selectivities and yields (entries 9–12).

Next, we attempted the reaction using various substituted allenylcyclobutanols (Table 2). The substrate **5**, which was substituted with phenyl group at the allenyl moiety, reacted with 4-iodoanisole to give the corresponding cyclopentanone **6** in 20% yield (entry 1). The rather low yield reflects the difficulties to construct the highly strained phenyl-substituted product **6**. When the allenylcyclobutanol **7** was used, the cyclopentanone **8** was obtained as the sole product (entry 2). On the other hand, the diastereomer **9** produced **10** exclusively (entry 3). From these results, it could be ascertained that the ring expansion process proceeds in a stereospecific manner.

Table 2
Cascade reactions of various substituted allenylcyclobutanols[a]

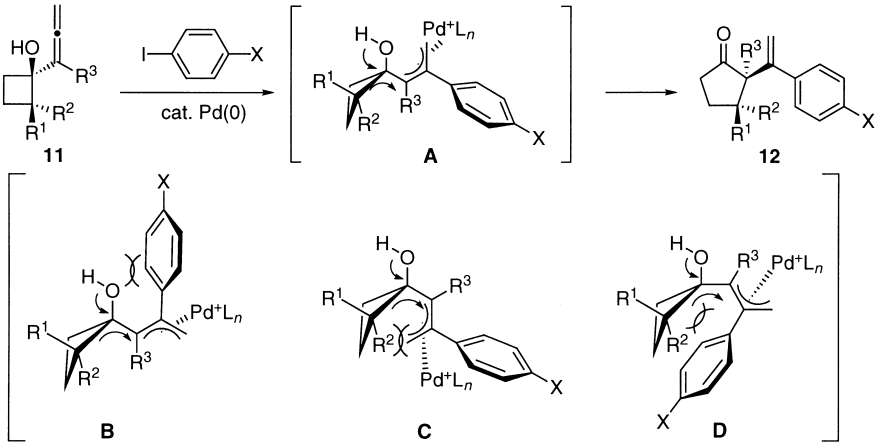
| entry | substrate[b] | time (h) | product[b] | yield (%) |
|---|---|---|---|---|
| 1 |  **5** | 3 |  **6** | 20 |
| 2 |  **7** | 23 |  **8** | 79 |
| 3 |  **9** | 18 |  **10** | 81 |

Ar = *p*-methoxyphenyl

[a]All the reactions were carried out using substrate, 4-iodoanisole, 5 mol % $Pd(PPh_3)_4$ and $Ag_2CO_3$ in toluene at 80 °C. [b]The stereochemistry of all compounds **5-10** were determined by $^1$H-NOESY.

A possible explanation for the diastereoselectivity of the reaction is described in Scheme 2. It could be presumed that the stereochemistry of the reaction is controlled by the conformation of the π-allylpalladium complex during the ring expansion step. Among four possible conformers **A**, **B**, **C** and **D** for the π-allylpalladium complex derived from **11**, the rearrangement would take place via **A**, the most stable conformer, to give the cyclopentanone **12**.[6]

In summary, we have developed a novel route to the α-substituted cyclopentanones with quaternary carbon stereocenters by the palladium-catalyzed stereospecific ring expansion reaction of allenylcyclobutanols with aryl iodides. As the stereoselective construction of molecules with quaternary carbon stereocenters represents a very challenging and dynamic area in organic synthesis, our methodology would provide a new synthetic protocol in this area.




Scheme 2.

## Acknowledgements

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1. For some recent works on the palladium-catalyzed ring expansion of cyclobutanols, see: (a) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291–296. (b) de Almeida Barbosa, L.-C.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 177. (c) Kim, S.; Uh, K. H.; Lee, S.; Park, J. H. *Tetrahedron Lett.* **1990**, *32*, 3395–3396. (d) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74–79. (e) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850–7857. (f) Nemoto, H.; Yoshida, M.; Fukumoto, K.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 907–910. (g) Nemoto, H.; Miyata, J.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1933–1936. (h) Nemoto, H.; Takahashi, E.; Ihara, M. *Org. Lett.* **1999**, *1*, 517–519. (i) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583–8586.
2. Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450–6451.
3. Recently, Nagao et al. reported the palladium-catalyzed hetero- and carbocyclic ring expansion reactions of allenic alcohols having a substituent at the 1-position of the allenyl moiety. (a) Jeong, I.-Y.; Nagao, Y. *Tetrahedron Lett.* **1998**, *39*, 8677–8680. (b) Jeong, I.-Y.; Nagao, Y. *Synlett* **1999**, 576–578.
4. Allenylcyclobutanol **1** was synthesized by the reaction of 2-phenylcyclobutanone with propargyl aluminum reagents, which was prepared from 1-bromo-2-butyne, powdered aluminum and a catalytic amount of mercuric chloride. The stereochemistry of **1** was determined by $^1$H NOESY.
5. *Typical experimental procedure for the ring expansion reaction* (entry 8 in Table 1). A slurry of the allenylcyclobutanol **1** (28.5 mg, 0.142 mmol), iodobenzene **2a** (0.024 mL, 0.213 mmol), $Pd(PPh_3)_4$ (8.1 mg, 7.0 μmol), $Ag_2CO_3$ (78.0 mg, 0.283 mmol) in toluene (5 mL) was stirred for 3 h at 80°C. The reaction mixture was filtered through Celite. The residue upon work up was chromatographed on silica gel with hexane–AcOEt (95:5 v:v) as eluant to give the cyclopentanone **3a** (31.5 mg, 80%) as a colorless oil. Compound **3a**: IR (neat) 1730, 1600 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.36 (3H, s), 2.10–2.20 (2H, m), 2.40–2.45 (2H, m), 3.22 (1H, t, $J$ = 9.0 Hz), 4.87 (1H, d, $J$ = 0.6 Hz), 5.01 (1H, d, $J$ = 0.6 Hz), 6.54 (2H, dt, $J$ = 7.8 and 1.2 Hz), 7.06–7.13 (3H, m), 7.22–7.24 (2H, m), 7.30–7.33 (3H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.2, 24.2, 37.6, 54.9, 58.8, 118.9, 126.9, 127.1, 127.5, 127.5, 128.2, 128.2, 128.6, 128.6, 128.8, 128.8, 139.9, 142.5, 149.2, 221.9; MS $m/z$ 276 ($M^+$). Anal. calcd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.53; H, 7.16.
6. As an alternative pathway, it is also possible that the chelation of the hydroxyl group to the cationic palladium species would cause the formation of conformer **A**.