

Bicyclic Carbopalladation Reaction with Two *gem*-Reaction Centers. Efficient Construction of Fused Bicyclic Skeletons

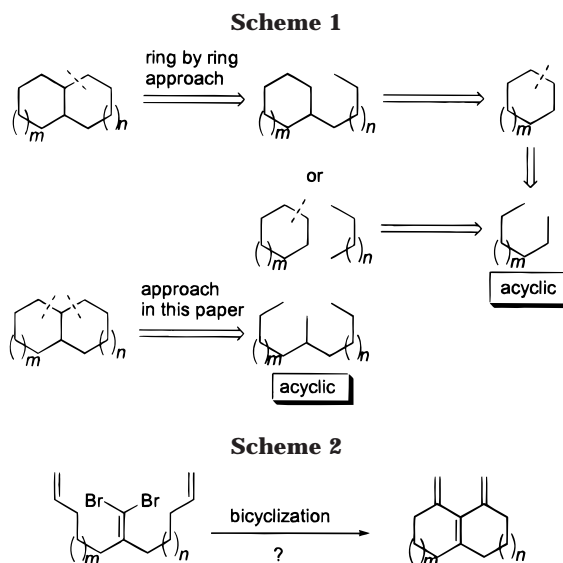
Shengming Ma* and Bin Xu

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

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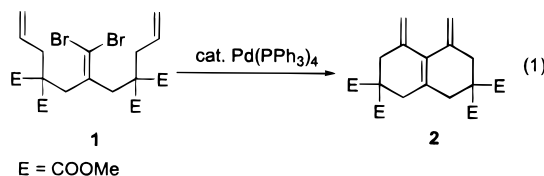
Synthetic efficiency is one of the most pursued objectives for chemists. Although bicyclic compounds are present in many important compounds, such as synthetic intermediates, target molecules of biological interests, etc.,^{1,2} among so many methodologies, one of the most commonly used approaches is a "ring by ring" strategy with low to moderate efficiency.^{3–7} We would like to propose here a new strategy for the efficient synthesis of bicyclic compounds, in which the two rings are expected to be formed *in one step* (Scheme 1). The advantage of this protocol is that *the bicyclic compounds with different ring sizes as well as the functional groups can be prepared from the corresponding precursors in just "one shot"*.

Cyclic carbopalladation reaction of unsaturated C–C bonds has become one of the most powerful tools for the synthesis of cyclic compounds via a C–C bond-formation reaction,⁸ with overwhelming emerging of both new cyclization protocols and synthetic applications to complex target molecules. We began our hypothesis with a well-designed cyclic carbopalladation, i.e., *bicyclic carbopalladation reaction* of the corresponding precursors with two carbon–bromine bonds, in which the two bromine atoms are connected to the same carbon atom (Scheme 2). One formidable



challenge in this bicyclization is α -dehalopalladation,⁹ from which the formation of an sp^2 -carbon-centered carbene intermediate would be expected. We report herein the realization of our hypothesis. To our knowledge, this represents the first transitional metal-catalyzed bicyclic carbometalation reaction of *gem*-dibromides.¹⁰

We started our study with dibromide **1**¹¹ (eq 1). After



tedious attempts, finally we found that this reaction afforded fused 6,6-bicyclic product **2** in 68% yield *in xylene* at 80–85 °C for 24 h under the catalysis of 10 mol % $Pd(PPh_3)_4$ and $n-Bu_4NCl^2$ using K_2CO_3 as the base (conditions A). The results in CH_3CN , EtOH–DMF, and toluene were poor. Using Et_3N , Ag_2CO_3 (in CH_3CN), or K_2CO_3 (without $n-Bu_4NCl$) as the base, the reactions were low-yielding and not clean. The 1H NMR data are as follows: 5.23 (s, 2 H), 5.04 (s, 2 H), 3.70 (s, 12 H), 2.82 (s, 4 H), 2.63 (s, 4 H) ppm. The simplicity of the 1H NMR data led us to doubt the structure of this cyclized product, since the six sp^2 -carbon atoms will not be on the same plane. This would, in principle, make the cyclic protons chemical environmentally unequal, thus complicating the splitting patterns. We determined the structure of the cyclization product as **2** unambiguously by X-ray study.¹³ α -Debromopalladation was not observed under the current reaction conditions.⁹

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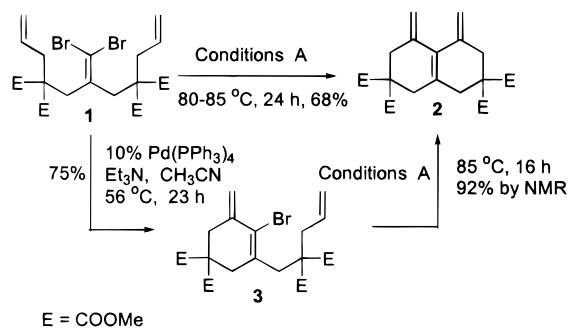
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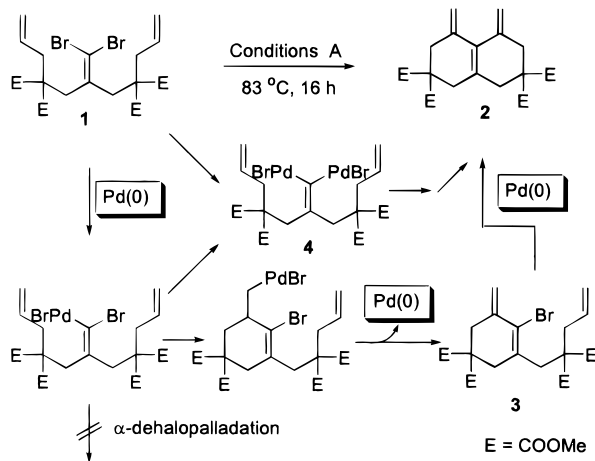
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Scheme 3



Scheme 4



Under the catalysis of $\text{Pd}(\text{PPh}_3)_4$ and using CH_3CN as the solvent/ Et_3N as the base, the monocyclization reaction of **1** to afford monocyclic product **3** was observed cleanly; even with longer reaction times the further cyclization of **3** was not observed. However, **3** cyclized to form **2** under conditions A in 92% NMR yield, indicating that **3** might be one of the reaction intermediates in the bicyclization shown in eq 1 (Scheme 3, for plausible mechanisms of this reaction, see Scheme 4).

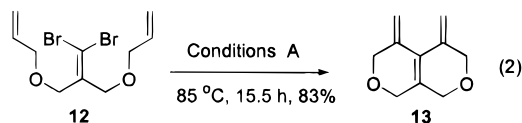
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(13) **Crystal data for 2:** $\text{C}_{20}\text{H}_{24}\text{O}_8$, $M = 392.40$, monoclinic, $C2/c$ (#15), colorless, $a = 14.448(3)$ Å, $b = 11.673(5)$ Å, $c = 12.885(4)$ Å, $111.32(2)$ Å, $Z = 4$, $\mu(\text{Mo K}\alpha) = 1.00$ cm^{-1} , $D_{\text{calc}} = 1.287$ g/cm^3 , $F(000) = 832.00$, 2439 unique reflections were measured to $2\theta_{\text{max}} = 55.0$ °C, 1491 reflections with $I > 3.00\sigma(I)$ were used in the refinement, $R = 0.056$.

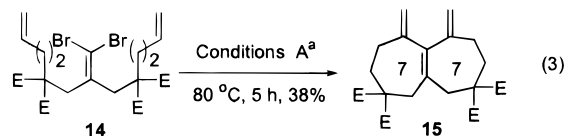
(14) For the formation of seven-membered rings via an exo-mode cyclic carbopalladation reaction of benzylic halides, see: Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, 54, 2507. (b) For the formation of seven-membered rings via an endo-mode cyclic carbopalladation of alkenyl halides, see: Negishi, E.; Ma, S.; Sugihara, T.; Noda, Y. *J. Org. Chem.* **1997**, 62, 1922.

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Under similar conditions, bicyclic ether **6** with one oxygen atom on each ring could be prepared in 83% yield (eq 2).

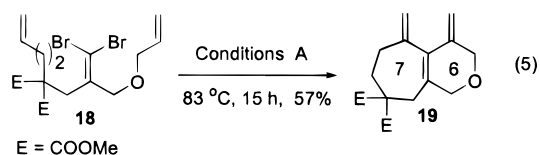
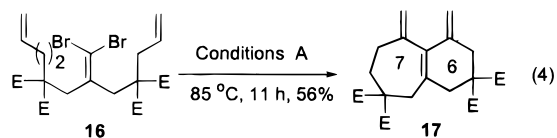


Although seven-membered ring formation via cyclic Heck reaction is not so well-documented,¹⁴ 7,7-bicyclic compound **8** was prepared in 38% yield using Ag_2CO_3 ¹⁵ instead of K_2CO_3 as the base (eq 3). The reaction under conditions A afforded **8** together with its C=C bond isomer(s).



^a Ag_2CO_3 (2.5 equiv) was used instead of K_2CO_3 .

According to the strategy described in this paper, if two C=C double bonds are fixed with different side chains, the corresponding bicyclic compounds could be synthesized in one shot. Two such examples for the formations of 6,7-bicyclic compounds **10** and **12** are listed in eqs 4 and 5.



In conclusion, we have developed the first bicyclic carbopalladation reaction, which was proven to be highly efficient for the construction of bicyclic compounds; α -dehalopalladation was not observed. The scope and cyclization patterns of these reactions are being investigated in our laboratory.

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Supporting Information Available: Experimental section, X-ray data of compound **2** and the ^1H NMR spectra of the compounds **2**, **3**, **6**, **8**, **10**, and **12** (17 pages).

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