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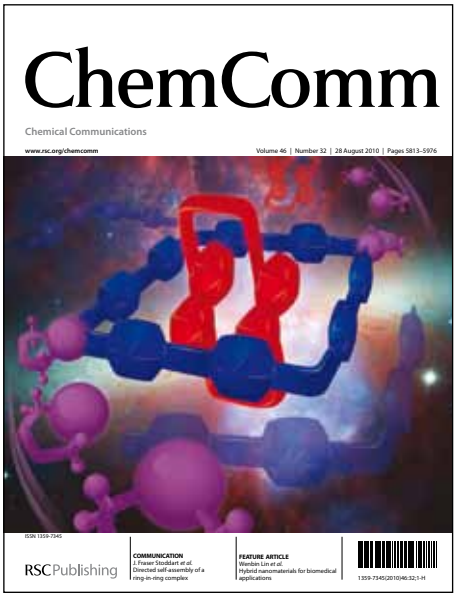

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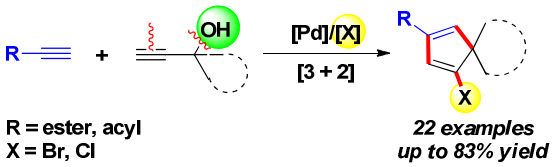

A Pd-catalyzed intermolecular [3 + 2] carbocyclization of alkynols and electron-deficient alkynes for the synthesis of halo-cyclopentadienes has been developed.

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ARTICLE TYPE

Palladium-Catalyzed Intermolecular [3 + 2] Carbocyclization of Alkynols and Propiolates: An Efficient Entry to Halo-Cyclopentadienes*

Yang Gao, Wanqing Wu*, Huawen Huang, Yubing Huang and Huanfeng Jiang*

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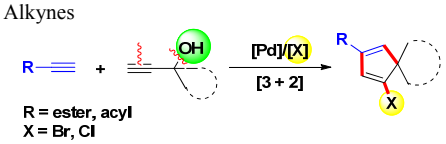
A novel and efficient Pd-catalyzed intermolecular [3 + 2] carbocyclization of alkynols and electron-deficient alkynes for the synthesis of halo-cyclopentadienes (Cps) has been developed. The present protocol employs simple propargyl alcohols as the C3 group to participate in the cyclization reaction, providing a highly convenient and atom-economical entry to the halo-cyclopentadiene framework.

Transition metal-catalyzed carbocyclization reactions of unsaturated species have provided useful methods for the preparation of a wide range of carbo- and heterocycles.[1] For examples, the elegant cycloisomerization reactions of 1,n-enynes,[2a-c] 1,n-allenynes, 1,n-allenenes[2d,e] and 1,n-diynes[2f-h] disclosed by Bäckvall and Trost *et al.* have appeared as conceptually and chemically attractive processes to construct various cyclization products. However, in the absence of the constrains imposed by the tethers in intramolecular processes, the intermolecular carbocyclization involving two or more separated alkyne entities has been less reported[3] for the difficulty in controlling the chemo- and regioselectivity. Further, the development of complementary sets of catalysts or/and conditions that provide quick access to five-membered carbocycle has been intensively pursued by the synthetic community.[4] Among them, cyclopentadienes (Cps) are useful synthetic intermediates in the field of organic and synthetic chemistry,[5] such as valuable building blocks in organic synthesis and good reaction partners for Diels−Alder reaction. Due to its importance, several methods have been developed to construct this useful framework:[6] i) nucleophilic addition of 1,4-dilithio-1,3-dienes to aldehydes or ketones; ii) [3 + 2] cycloaddition of propargyl esters with internal alkynes via Au or Rh carbene intermediates; iii) gold- or platinum-catalyzed cycloisomerizations of vinylallenes or 1,3-dien-5-ynes. Despite these substantial advances that have been achieved, further development of practical procedures which can enhance the product diversity, especially for the synthesis of polysubstituted spiro cyclopentadienes, is still fraught with challenges.[7]

On the other hand, propargylic alcohols are one of the most versatile synthetic reagents in organic chemistry.[8] Recently, several metal-catalyzed cross-coupling or/and cycloaddition reactions have been developed through propargyl carbon-oxygen bond cleavage or/and carbon-carbon bond formation.[9] In connection with our interest in the search for new synthetic methods involving alkynol reagents,[10] we envisioned that propargylic alcohols might be used as a C3 group to participate in the [3 + 2] carbocyclization reaction. Herein, we disclose the first example of Pd-catalyzed highly chemo- and regioselective intermolecular carbocyclization reaction between propargyl alcohols and electron-deficient alkynes to construct polysubstituted cyclopentadiene derivatives (Scheme 1). The present protocol directly employs simple propargyl alcohols as the three-carbon group and successfully introduces the propargylic carbon atoms to the cyclization reaction, providing convenient and atom-economical access to the halogenated cyclopentadiene framework that was difficult to be prepared by traditional methods. Various multi-substituted spiro compounds which are useful skeletons in many naturally occurring bioactive compounds[11] can be also obtained by this novel transformation.

Scheme 1. Pd-Catalyzed Intermolecular [3 + 2] Carbocyclization of Two Separated Alkynes

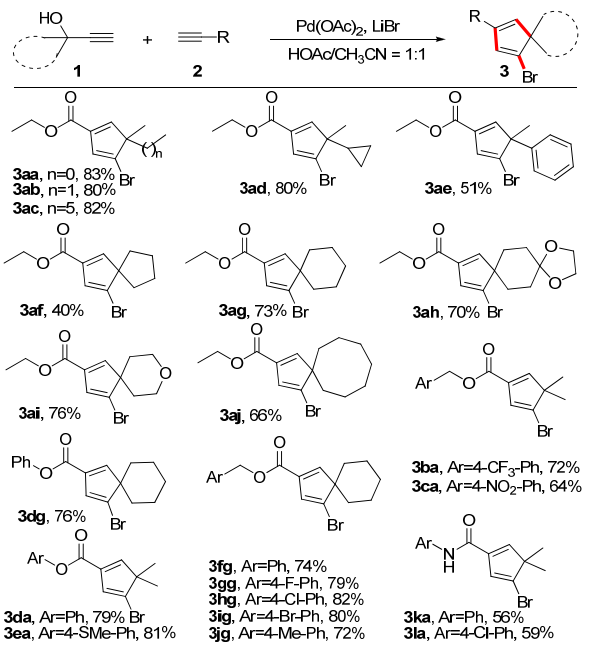


With the optimal catalytic system in hand (see ESI for details), we then examined the scope of this novel transformation. A wide variety of *tert*-propargylic alcohols were found to be successfully carbocyclized with ethyl propiolate (**2a**) to afford the corresponding bromo-cyclopentadiene derivatives (Table 1). For example, various dialkyl-substituted carbocyclization products (**3aa**–**3ad**) could be obtained with high selectivity in moderate to excellent yields (80%–83%) under the optimal reaction conditions. The phenyl substituted alkynols also underwent this cyclization reaction to provide the aryl-substituted cyclopentadiene **3ae** in 51% yield. Notably, the cycloalkane substituted alkynols (**1f**, **1j**) were found to be the suitable reaction partners for this transformation and gave the spiro cyclopentadiene compounds **3af**–**3aj** in good yields. These spiro structures may have potential applications in synthetic and medicinal chemistry.[11] In addition, the structure of **3ah** was further confirmed by X-ray crystallographic analysis (see ESI for details).[12]

Then, the scope of the reaction with respect to the propiolates was also studied (Table 1). A range of propiolates with different substituents could react smoothly with *tert*-propargylic alcohols

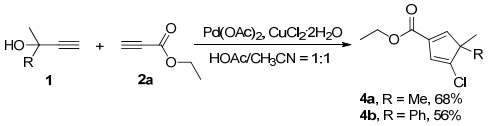
to give the bromo-cyclopentadiene products (**3ba**–**3jg**) in good yields (64%–82%). Functional groups such as (SMe, Me, F, Cl, Br, CF_3, NO_2) were well tolerated for this novel transformation. It should be noted that these functional groups could be used for further modifications to achieve more complex structures. To our delight, amide substituted cyclopentadiene products (**3ka**, **3la**) could be obtained in moderate yields by switching one of the reaction partners from propiolate to propiolamide. However, our attempts to employ internal alkyne as the substrate turned out to be unfruitful, which might be caused by the steric hindrance induced by the substitution on the alkyne moiety.

Table 1. Substrate Scope[a, b]



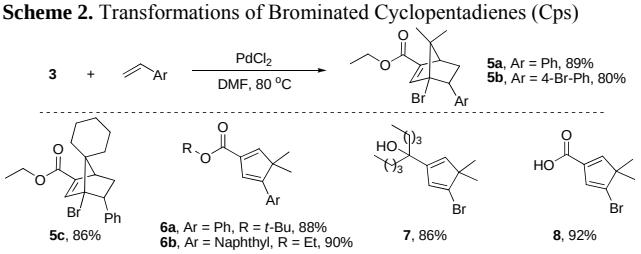
[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), LiBr (1 mmol) in CH_3CN/HOAc (2 mL, v/v = 1:1) as solvent at 60 °C for 8 h. [b] Isolated yield.

To further highlight the versatility of this strategy, we applied this method to the synthesis of chlorinated cyclopentadiene products and the result showed that the addition of 1 equiv of $CuCl_2{\cdot}2H_2O$ instead of LiBr gave the expected chlorinated cyclopentadiene products **4a** and **4b** in 56% and 68% yields.



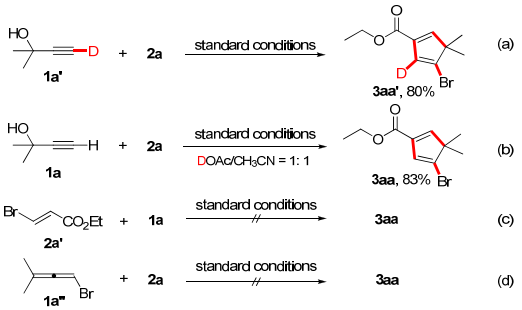
To demonstrate the synthetic utility of this protocol, the newly formed cyclopentadienes derivatives were employed for further transformations to prepare a series of functionalized products (Scheme 2). It is worth mentioning that the resulting ester-substituted cyclopentadiene derivatives could undergo Diels-Alder cycloaddition with styrene to obtain poly-substituted *endo*-norbornenes **5a-c** in 89%, 80% and 86% yields, respectively. In addition, the vinyl halide and the ester functionalities in the products enable them to be attractive and versatile synthetic building blocks in a variety of chemical transformations. The Suzuki−Miyaura cross-coupling reactions of **3** with different arylboronic acids respectively delivered arylated cyclopentadiene compounds **6a** and **6b** in excellent yields. When treated with *n*-butyl lithium reagent, **3aa** was converted to the hydroxy product **7** in 86% yields. Furthermore, **3aa** could readily undergo the hydrolysis process to provide the free carboxylic acid **8** in excellent yield.

Scheme 2. Transformations of Brominated Cyclopentadienes (Cps)

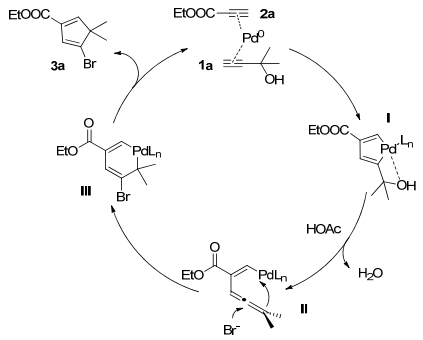


To gain insight into the mechanism of the intermolecular carbocyclization process, several control experiments were conducted (Scheme 3). First, two deuterated experiments were carried out to distinguish whether the proton transfer process existed in this carbocyclization reaction. As depicted in [eqn. (a)], deuterium product **3aa'** was obtained exclusively in 80% isolated yield and the deuterium atom (98% examined by ^1H NMR spectroscopy) was still present. However, when deuterated acetic acid was used as the solvent [eqn. (b)], there was no deuterium in the product. Furthermore, the possibility of **2a'** detected in the reaction system as an intermediate was excluded for **2a'** could not be transformed to the desire product **3aa** when treated with **1a** under the standard conditions [eqn. (c)]. Additionally, allenic bromide **1a''** could not transfer to the desired product in this reaction system, thus excluding the pathway that involved the intermolecular carbocyclization of allenic bromide and the Michael acceptor.[13]

Scheme 3. Control Experiments



Although the detailed mechanism of this intermolecular carbocyclization reaction is still under investigation, a plausible catalytic cycle is proposed (Scheme 4). The reaction might be initiated by cyclopalladation of alkyne[14] to form the palladacyclopentadiene species **I**, which would undergo the *β*-OH elimination to give the enallene intermediate **II** with the aid of HOAc.[10] Then, the nucleophilic attack of halide ion to the allene moiety formed the cyclopalladium species **III**,[15] followed by reductive elimination of the $C(sp^2)$-$C(sp^3)$ bond to afford the halo-cyclopentadiene products and regenerate the active Pd^0 species.



Scheme 4. Plausible Mechanism

In summary, we have developed a novel and efficient Pd-catalyzed method for the synthesis of halo-cyclopentadiene derivatives from intermolecular [3 + 2] carbocyclization of alkynols and propiolates. Through Pd-catalyzed propargyl carbon-oxygen bond cleavage and carbon-carbon bond formation, we successfully introduce the propargylic carbon atoms of alkynol to the cyclization reaction. This direct carbocyclization reaction of two separated alkyne entities is a conceptually and chemically attractive process that may broaden the scope of intermolecular carbocyclization reaction. Furthermore, these cyclopentadiene products can be applied to the construction of different poly-substituted norbornenes via Diels-Alder cycloaddition, thus illustrating the potential applications of this methodology in synthetic and medicinal chemistry. The detailed reaction mechanism and further synthetic applications are under investigation in our laboratory, and the results will be reported in due course.

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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