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Highly Efficient Cascade Reaction for Selective Formation of Spirocyclobutenes from Dienallenes via Palladium-Catalyzed Oxidative Double Carbocyclization−Carbonylation−Alkynylation

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Supporting Information

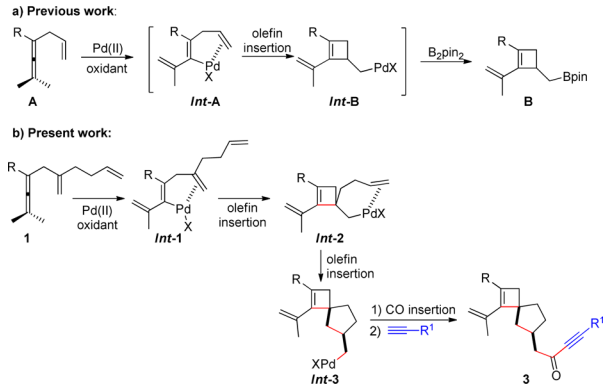
ABSTRACT: A highly selective cascade reaction that allows the direct transformation of dienallenes to spirocyclobutenes (spiro[3.4]octenes) as single diastereoisomers has been developed. The reaction involves formation of overall four C−C bonds and proceeds via a palladium-catalyzed oxidative transformation with insertion of olefin, olefin, and carbon monoxide. Under slightly different reaction conditions, an additional CO insertion takes place to give spiro[4.4]nonenes with formation of overall five C−C bonds.

Spirocarbocyclic scaffolds bearing a quaternary carbon center, have received increasing interests from organic chemists.[1,2] These structural elements occur in a wide range of natural products, pharmaceutical ingredients, and chiral ligands.[3,4] Therefore, chemists have devoted themselves to developing new strategies for addressing the challenges involving spirocarbocycles.[1] To date, different methods have been developed to construct this core motif, such as *N*-heterocyclic carbene-based organocatalysis,[5] metal-catalyzed dearomatization reaction,[6] and alkene metathesis with Grubbs catalysts.[7] However, development of methodologies for the fast and efficient construction of spirocarbocycles are still highly desirable and challenging.

Our research group has been previously involved in the development of Pd-catalyzed oxidative carbocyclization reactions of allenes to carbocyclic skeletons.[8−10] An extension of these carbocyclizations to formation of spirocarbocycles would be highly interesting because spirocarbocycles bearing a fully carbon-substituted quaternary carbon center are challenging synthetic targets.[11] One class of compounds that we considered were spirocarbocycles bearing a cyclobutene ring.[12,13] Recently, we have developed a palladium-catalyzed oxidative carbocyclization−borylation of enallenes **A** to cyclobutene derivatives (Scheme 1a).[13] Initial coordination of the olefin unit to Pd(II) and subsequent allene attack on the metal result in the formation of intermediate ***Int*-A**, which undergoes olefin insertion to form cyclobutene intermediate ***Int*-B**. The latter intermediate is trapped by the B_2pin_2 present in the reaction mixture to give **B**.

On the basis of these observations, we envisioned that with starting material **1**, having an extra olefin chain, the cyclobutene palladium intermediate (***Int*-2**) generated may be able to undergo an insertion reaction to form a spirocarbocyclic intermediate (***Int*-3**) (Scheme 1b). Subsequent carbon monoxide (CO) insertion may provide the spirocyclobutene products **3**. Spirocyclobutene derivatives of this type are unique

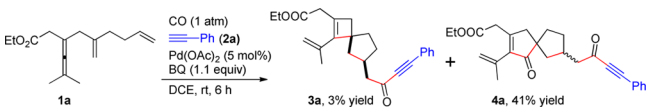
Scheme 1. Previous Work and Present Work



structures and are difficult to prepare with other methods. In this communication, we report on a palladium-catalyzed carbocyclization cascade reaction according to Scheme 1b that provides spirocyclobutene compounds.

Our study began with the palladium-catalyzed reaction of allene **1a** with alkyne **2a** (1.5 equiv) using BQ (*p*-benzoquinone, 1.1 equiv) as oxidant under 1 atm of CO (balloon) at room temperature for 6 h (Scheme 2). Interestingly, the spiro[3.4]-

Scheme 2. Initial Attempt



octene derivative **3a** was formed as envisioned, although the yield was only 3%. Meanwhile, the spiro[4.4]nonene derivative **4a** was obtained in 41% yield. To the best our knowledge, there have been no reports to date on efficient synthesis of spirocarbocycles involving a cyclobutene ring via palladium-catalyzed olefin insertion.

With these inspiring results in hand, we began to optimize the reaction conditions for the formation the spiro[3.4]octene derivative **3a** and spiro[4.4]nonene derivative **4a** (For details, see Supporting Information, Table S1). Catalyst screening showed that $Pd(TFA)_2$ produced the corresponding **4a** in a much higher yield (90%) compared to $Pd(OAc)_2$ or 1,2-bis(phenylsulfinyl)-

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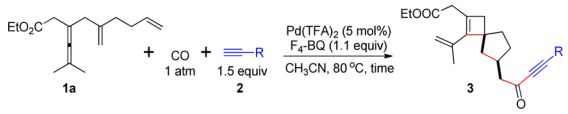
ethane palladium(II), whereas $Pd(PPh_3)_2Cl_2$ failed to realize such a transformation (Table S1, entries 1−4). Solvent screening revealed that DCE was still the best solvent for the formation of product **4a** (Table S1, entries 5−9). Interestingly, the yield of **3a** increased to 12% with CH_3CN as solvent but conversion was low with starting material **1a** being recovered in 45% (Table S1, entry 9). The yield of **3a** increased with an increased temperature (Table S1, entries 10−12) and at 80 °C the yield of **3a** was 56% (Table S1, entry 12). The favored formation of **3a** at higher temperature is probably due to a decrease in the concentration of CO in the solvent, which suppresses CO coordination and hence insertion to form **4a**. The yield of **3a** was further improved to 65% on dilution (Table S1, entry 13). Finally, the best yield (75%) and selectivity for the formation of **3a** was observed when F_4-BQ was used as the oxidant (Table S1, entry 15).

Under the optimized reaction conditions for formation of **3**, we investigated the scope of terminal alkynes **2** with the substrate dienallene **1a** (Table 1). Arylalkynes **2b**−**2g** with both electron-

Table 1. Scope of Terminal Alkynes[a]



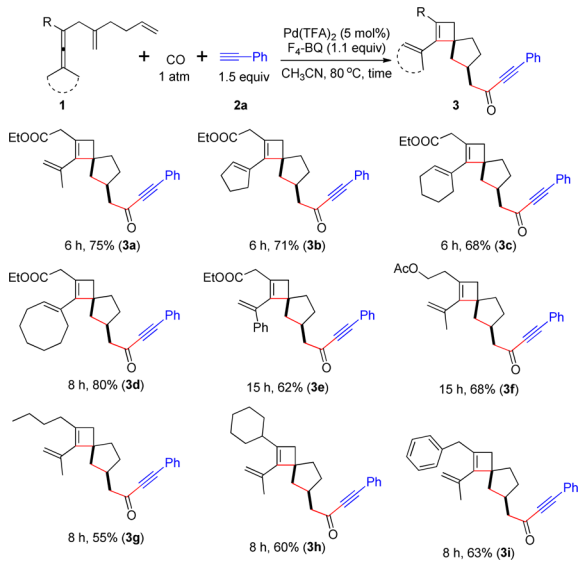
entry	R	time (h)	yield of **3** (%)[b]
1	Ph	6	75 (**3a**)
2	2-$MeOC_6H_4$	6	72 (**3ab**)
3	3-$MeOC_6H_4$	6	74 (**3ac**)
4	4-MeC_6H_4	6	79 (**3ad**)
5	4-FC_6H_4	6	64 (**3ae**)
6	4-BrC_6H_4	6	66 (**3af**)
7	4-$CF_3C_6H_4$	6	77 (**3ag**)
8	2-thiophenyl	6	83 (**3ah**)
9	3-thiophenyl	6	71 (**3ai**)
10	Cy	10	66 (**3aj**)
11	cinnamyl	10	70 (**3ak**)
12[c]	TMS	15	79 (**3al**)

[a]The reaction was conducted in MeCN at 80 °C using **1a** (0.2 mmol), **2** (1.5 equiv), F_4-BQ (1.1 equiv) in the presence of $Pd(TFA)_2$ (5 mol %). [b]Isolated yield. [c]TMS-acetylene (3.0 equiv) was used.

donating and electron-withdrawing groups on the aryl group reacted smoothly and afforded the corresponding spirocyclobutenes **3ab**−**3ag** in good yields (Table 1, entries 2−7). Moreover, selective formation of spirocyclobutenes worked well using heteroaryl acetylenes (Table 1, entries 8 and 9). Aliphatic terminal alkynes also reacted smoothly in the reaction to generate the corresponding products in good yields (Table 1, entries 10 and 11). Gratifyingly, the reaction can be extended to trimethylsilylacetylene to give product **3al** in 79% yield (Table 1, entry 12), which after desilylation could be used for further functionalization.

We next investigated the scope of the dienallenes for the reaction using phenylacetylene **2a** as the terminal alkyne (Scheme 3). In addition to two methyl substituents on the dienallene moiety, cyclopentylidene, cyclohexylidene, and cyclooctylidene dienallenes (**1b**, **1c**, and **1d**) also afforded the corresponding products (**3b**, **3c**, and **3d**) in good yields. The reaction of the unsymmetric allene **1e**, which bears methyl and phenyl groups, afforded **3e** in 62% yield. Acetate derivative **1f** also worked well under the standard conditions. Furthermore, the reaction tolerated different alkyl groups as R in the oxidative

Scheme 3. Scope for Formation of 3[a,b]

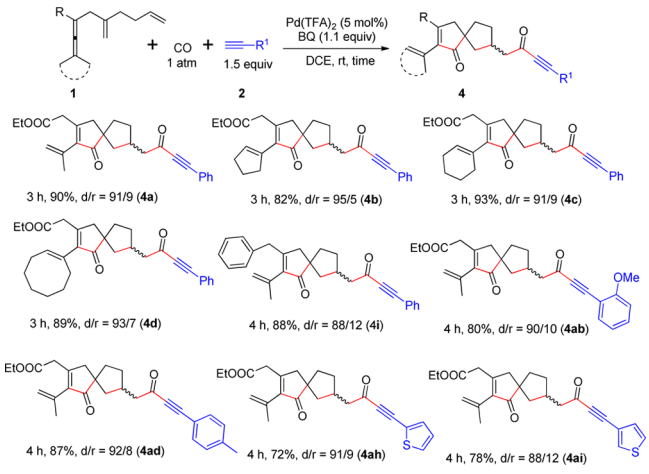


[a]The reaction was conducted in MeCN at 80 °C using **1** (0.2 mmol), **2a** (1.5 equiv), F_4-BQ (1.1 equiv) in the presence of $Pd(TFA)_2$ (5 mol %). [b]For stereochemical assignment of products by NOE, see Supporting Information (p. S31).

carbocyclization to spirocarbocyclic products **3**. For example, R = *n*-butyl (**1g**), cyclohexyl (**1h**), and benzyl (**1i**),[14] afforded the corresponding spirocyclobutene derivatives **3g**−**i**. It is noteworthy that all the spiro[3.4]octene derivatives **3** were obtained as single diastereoisomers with high selectivity.[15]

We next explored the substrate scope under the optimal reaction conditions for the formation of spirocarbocycles **4** (Scheme 4). Notably, the reaction of substrates with two methyl

Scheme 4. Scope for Formation of 4[a]



[a]The reaction was conducted in DCE at room temperature using **1** (0.2 mmol), **2** (1.5 equiv), and BQ (1.1 equiv) in the presence of $Pd(TFA)_2$ (5 mol %).

groups, cyclopentylidene, cyclohexylidene, or cyclooctylidene on the dienallene moiety all worked well, affording the corresponding products **4a**−**4d** in good yields with dr values from 91/9 to 95/5. A benzyl group on the allene unit (R) was also tolerated. Arylacetylenes substituted with *o*-MeO and *p*-Me groups reacted smoothly and afforded **4ab** and **4ad**. It is noteworthy that the

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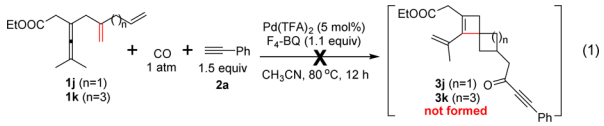
reaction with heteroaryl acetylenes proceeded well and produced the corresponding spirocarbocycles **4ah** and **4ai** in good yields.

We then explored the effect of the length of the carbon chain. Substrate **1j** with one carbon less, and substrate **1k** with one carbon more, compared to the standard substrate **1a**, failed to give spirocyclic products **3j** and **3k**, respectively (eq 1).

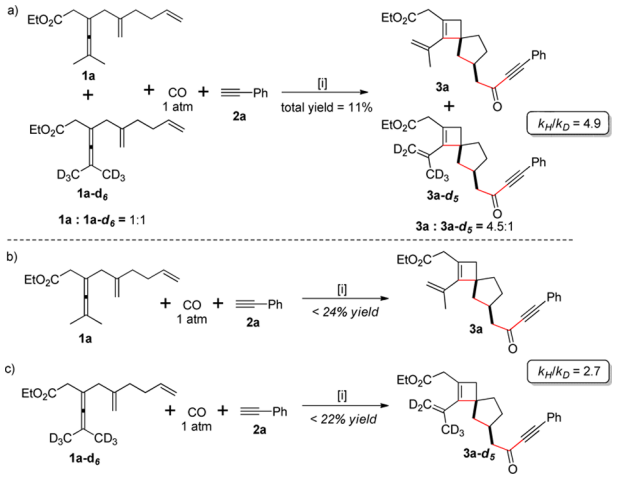


(1)

These experiments show that the second cyclization to give the spirocyclobutene derivatives is only favored for formation of a five-membered ring.

To gain further insight into the mechanism for the formation of spirocyclobutenes **3**, the deuterium kinetic isotope effects were studied (Scheme 5).[16] An intermolecular competition experiment was conducted at 80 °C using a 1:1 mixture of **1a** and **1a-d_6** (Scheme 5a). The total yield of **3a**/**3a-d_5** was 11%, and the product ratio **3a**/**3a-d_5** (ca. 11.3% conv.) measured was 4.5:1. From these results, the competitive KIE was determined to k_H/k_D = 4.9. Furthermore, parallel kinetic experiments afforded a KIE (k_H/k_D from initial rate) value of 2.7 (Scheme 5b,c). These results indicate that the initial allenylic C−H bond cleavage is partially rate-limiting. The large competitive isotope effect in the C−H bond cleavage (k_H/k_D = 4.9) requires that this step is the first irreversible step.

Scheme 5. Kinetic Isotope Effect Studies[i]

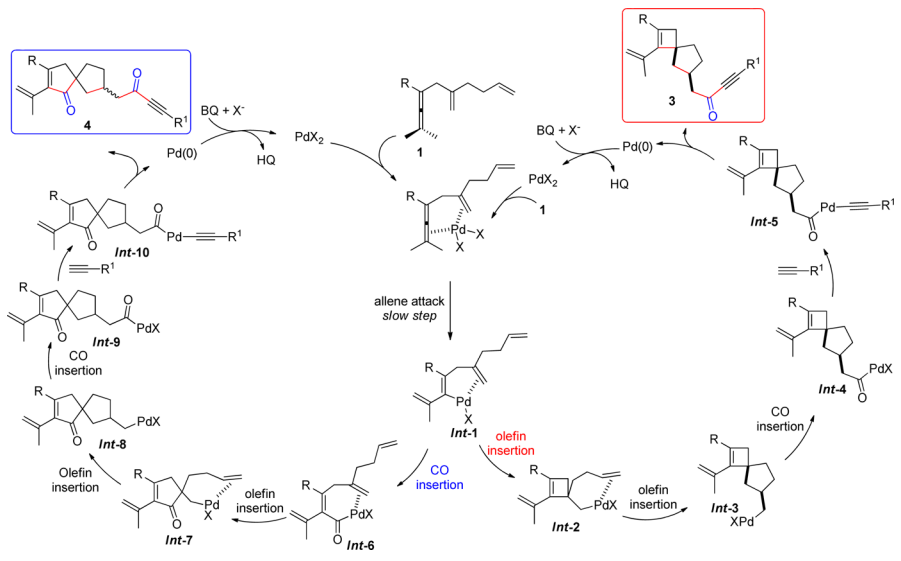


[i]Reaction conditions: allene **1a** (or **1a-d_6**) (0.2 mmol), $Pd(TFA)_2$ (5 mol %), F_4-BQ (1.1 equiv), and phenylactylene **2a** (1.5 equiv) in CD_3CN under CO (1 atm) at 80 °C.

Based on the KIE studies and the reaction outcome, a possible mechanism for the palladium-catalyzed oxidative carbocyclization of dienallene is given in Scheme 6. The reaction of $Pd(TFA)_2$ with **1** could give vinylpalladium intermediate ***Int*-1** through allene attack involving allenic C−H bond cleavage,[17,18] which is promoted by the coordination of allene and olefin to Pd(II).[19] Intermediate ***Int*-1** could then undergo an olefin insertion to afford cyclobutene intermediate ***Int*-2**. Subsequent cascade olefin and CO insertions would produce the intermediate ***Int*-4** via ***Int*-3**. Finally, reaction of ***Int*-4** with terminal alkyne **2** would produce ***Int*-5**, which on subsequent reductive elimination leads to spiro[3.4]octene derivatives **3**.[20] On the other hand, ***Int*-1** may undergo a carbonylation to give ***Int*-6**, which on olefin−olefin−CO insertion would produce ***Int*-9** via intermediates ***Int*-7** and ***Int*-8**. Intermediate ***Int*-9** would then react with terminal alkyne **2** to afford the final spiro[4.4]-nonene derivatives **4** via ***Int*-10**. The solvent effect by CH_3CN to favor ***Int*-2** over ***Int*-6** from ***Int*-1** is most likely due to coordination of CH_3CN, which suppresses CO coordination and hence insertion.

In conclusion, we have developed an efficient palladium-catalyzed oxidative carbocyclization−carbocyclization−carbonylation−alkynylation that selectively gives spirocyclobutene derivatives **3** (spiro[3.4]octenes) as single diastereoisomers with formation of overall four C−C bonds. By changing the reaction conditions, spiro[4.4]nonene derivatives **4** were selectively obtained via cascade CO−olefin−olefin−CO insertion reactions involving formation of overall five C−C bonds. Mechanistic studies showed that the allenylic C−H bond cleavage is partially rate-limiting and also the first irreversible step. The cascade reactions developed here should be useful in

Scheme 6. Proposed Mechanisms



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synthetic and materials chemistry. Further studies on the scope, synthetic application, and asymmetric variants of these reactions are currently carried out in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09240.

Experimental procedures and compound characterization data, including the $^{1}H/^{13}C$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(20) We have tried this cascade reaction with the use of B_2pin_2 as the quenching reagent; however, no borylated product was obtained. We also tried the reaction without the CO and alkyne, but no product from β-hydride elimination was formed.

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