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

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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.

Spirocyclobutylc 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 Therefore, chemists have devoted themselves to developing new strategies for addressing the challenges involving spirocarbocycles.3 To date, different methods have been developed to construct this core motif, such as N-heterocyclic carbene-based organocatalysis,4 metal-catalyzed dearomatization reaction,5 and alkene metathesis with Grubbs catalysts.6 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.6−10 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 $\text{B}_2\text{pin}_2$ 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 spirocyclobutene intermediate (Int−3) (Scheme 1b). Subsequent carbon monoxide (CO) insertion may provide the spirocyclobutene products 3. Spirocyclobutene derivatives of this type are unique 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 $\text{BQ}$ ($p$-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]-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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Supporting Information
ethane palladium(II), whereas Pd(PPh₃)₂Cl₂ 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 CH₃CN 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 F₄-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-donating and electron-withdrawing groups on the aryl group reacted smoothly and afforded the corresponding products in good yields (Table 1, entries 1–7). Moreover, selective formation of 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 dienallenenes for the reaction of phenylacetylene 2a as the terminal alkyne (Scheme 3). In addition to two methyl substituents on the dienallenene moiety, cyclopentylidene, cyclohexylidene, and cyclooctylidene dienallenenes (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 carbocyclization to spirocarbocycyclic products 3. For example, R = n-buty1 (1g), cyclohexyl (1h), and benzyl (1i), 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 groups, cyclopentylidene, cyclohexylidene, or cyclooctylidene on the dienallenene moiety all worked well, affording the corresponding diastereoisomers with high selectivity.15

Table 1. Scope of Terminal Alkynes

| entry | R       | time (h) | yield of 3 (%) |
|-------|---------|----------|---------------|
| 1     | Ph      | 6        | 75 (3a)       |
| 2     | 2-MeOC₆H₄ | 6       | 72 (3ab)      |
| 3     | 3-MeOC₆H₄ | 6       | 74 (3ac)      |
| 4     | 4-MeC₆H₄  | 6       | 79 (3ad)      |
| 5     | 4-FC₆H₄  | 6       | 64 (3ae)      |
| 6     | 4-BrC₆H₄ | 6       | 66 (3af)      |
| 7     | 4-ClC₆H₄ | 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    | TMS     | 15       | 79 (3al)      |

*The reaction was conducted in MeCN at 80 °C using 1a (0.2 mmol), 2 (1.5 equiv), and BQ (1.1 equiv) in the presence of Pd(TFA)₂ (5 mol %). bIsolated yield. cTMS-acetylene (3.0 equiv) was used.

deleted

deleated

Scheme 3. Scope for Formation of 3a,b

Scheme 4. Scope for Formation of 4a

"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 %). bFor stereochemical assignment of products by NOE, see Supporting Information (p. S31)."
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).

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 kinetic isotope experiment was conducted at 80 °C using a 1:1 mixture of 1a and 1a-d₆ (Scheme 5a). The total yield of 3a/3a-d₆ was 11%, and the product ratio 3a/3a-d₆ (ca. 11.3% conv.) measured was 4.5:1. From these results, the competitive KIE was determined to k₄H/k₄D = 4.9. Furthermore, parallel kinetic experiments afforded a KIE (k₄H/k₄D from initial rate) value of 2.7 (Scheme 5b,c). These results indicate that the initial allenyl C–H bond cleavage is partially rate-limiting. The large competitive isotope effect in the C–H bond cleavage (k₄H/k₄D = 4.9) requires that this step is the first irreversible step.

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 allkyne 2 to afford the final spiro[4.4]nonene derivatives 4 via Int-10. The solvent effect by CH₃CN to favor Int-2 over Int-6 from Int-1 is most likely due to coordination of CH₃CN, which suppresses CO coordination and hence insertion.

In conclusion, we have developed an efficient palladium-catalyzed oxidative carbocyclization–carbocyclization–carbonation–alkenylation 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 allenyl C–H bond cleavage is partially rate-limiting and also the first irreversible step. The cascade reactions developed here should be useful in...
synthetic and materials chemistry. Further studies on the scope, synthetic application, and asymmetric variants of these reactions are currently carried out in our laboratory.

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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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