

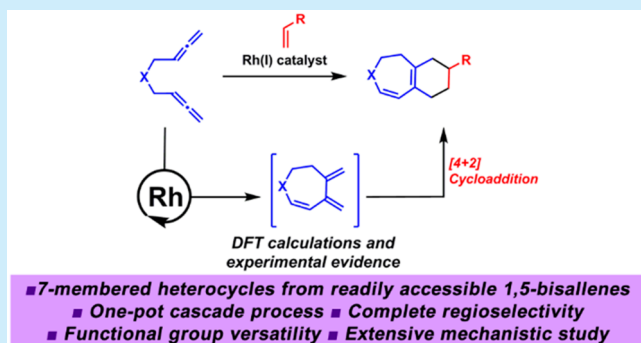
A Rh-Catalyzed Cycloisomerization/Diels–Alder Cascade Reaction of 1,5-Bisallenenes for the Synthesis of Polycyclic Heterocycles

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S Supporting Information

ABSTRACT: A novel methodology to transform bisallenenes into a variety of polycyclic derivatives employing rhodium(I) catalysis has been developed. This transformation encompasses an intramolecular Rh-catalyzed cycloisomerization of bisallenenes **1** to deliver a reactive cycloheptadiene, which concomitantly undergoes a regioselective [4 + 2] cycloaddition with alkenes. A complete mechanistic study of this transformation has been undertaken including DFT calculations. Overall, the methodology presented here constitutes a new and straightforward entry to polycyclic dihydroazepine and dihydrooxepine derivatives employing catalytic methods.



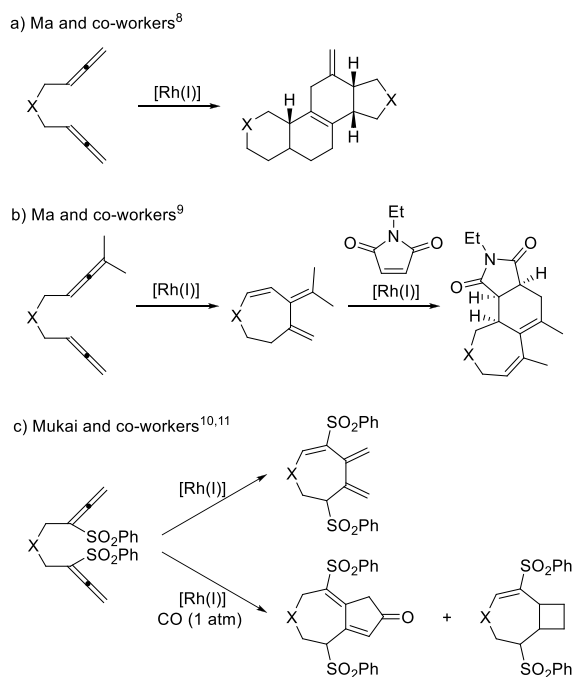
Transition-metal catalyzed cyclization reactions of unsaturated compounds have enormous synthetic potential for the preparation of a wide range of carbocyclic and heterocyclic scaffolds in a single step with perfect atom economy.¹ Among the different unsaturated substrates available, increasing attention has been focused toward the use of allenes, which have now become an established member of the synthetic arsenal for cyclization reactions and related processes.² Given that allenes are cumulated systems with two contiguous carbon–carbon double bonds, the control of the chemoselectivity—i.e., which of the two double bonds reacts—makes the construction of various products from one single substrate possible. The available chemical space is obviously increased when two allene moieties are involved.

When 1,5-bisallenenes are treated under catalysis by transition metals, products with 5-, 6-, or 7-membered rings can be obtained. Palladium, platinum, and gold favor carbocyclization processes. Under palladium catalysis, 5-membered rings have been obtained by the groups of Ma, Yu, and Kang.³ More recently, Bäckvall and co-workers described the formation of 7-membered rings.⁴ A similar trend was observed using platinum, which allowed the synthesis of products featuring 5-⁵ and 7-membered⁶ rings. An unexpected example of a rare [2 + 2] cycloaddition of bisallenenes has been described using *N*-heterocyclic carbene gold(I) catalysis to deliver 6-membered rings.⁷

On the other hand, rhodium-promoted cyclizations of 1,5-bisallenenes are postulated to proceed via oxidative cyclization. Ma and co-workers⁸ described a 2-fold cyclization of terminal bisallene under rhodium catalysis. The mechanism was postulated to be a [2 + 2 + 2] cycloaddition followed by a Diels–Alder reaction. The initial oxidative coupling can involve either the two internal double bonds or an internal

and an external double bond of the two allene moieties, affording 5-membered rhodacycles fused to either 5- or 6-membered rings, respectively (Scheme 1a). The same group⁹

Scheme 1. Previous Studies in Rh(I)-Catalyzed Cyclization Reactions of 1,5-Bisallenenes



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described the synthesis of seven-membered trienes via Rh-catalyzed cycloisomerization of 1,5-bisallenes with substituents at the terminal positions (Scheme 1b). When these dienes were treated with *N*-ethyl maleimide under rhodium catalysis, the expected [4 + 2] adduct was not obtained, but rather a product derived from an initial isomerization of the double bonds followed by Diels–Alder cycloaddition. Mukai and co-workers¹⁰ also managed to isolate an exocyclic diene when the initial bisallene was terminal although these bisallenes had the particularity of having two SO₂Ph groups at the internal carbon atom of the allene (Scheme 1c). Carbonylative [2 + 2 + 1] cycloadditions have been described by the groups of Mukai^{10,11} (Scheme 1c) and Chung,¹² although this latter group used cobalt/rhodium heterobimetallic nanoparticles. In both cases, the authors postulated that the external double bonds of both allenes were involved in the oxidative cyclization step, affording a seven-membered scaffold. In Mukai's studies, a [2 + 2] cycloadduct without CO incorporation was usually obtained as by-product.

Azepine- and oxepine-containing fused ring systems are found in some pharmacologically active compounds and in natural products,¹³ and their efficient synthesis is still highly challenging. Therefore, developing cycloaddition reactions of bisallenes with a third unsaturation being able to control the formation of a seven-membered ring is highly desirable. To the best of our knowledge, the Pauson–Khand-type reaction developed by Mukai¹¹ is the only example of such a process reported to date. Given these precedents, and based on our previous experience with Rh-catalyzed cycloaddition reactions involving allenes,¹⁴ we envisaged developing a cycloaddition reaction between 1,5-bisallenes and alkenes with the aim of controlling the reaction toward the synthesis of fused seven-six-membered bicyclic systems.

We started by studying the cycloaddition of *N*-tosyl-tethered bisallene **1a** and ethyl acrylate **2a** (see Table 1) using 10% mol of cationic rhodium complex [Rh(cod)₂]BF₄ with (*R*)-BINAP in THF/CH₂Cl₂ (4:1). Two different compounds were obtained: compound **3aa**, with a 4-aza-bicyclo[5.4.0]undeca-

1(7),2-diene skeleton, and the seven-membered cross-conjugated triene **4a**. When the bulky phosphine DTBM-Segphos was used, the yield of **3aa** was improved to 65%, and the yield of triene **4a** was reduced to 5%. However, **5a**, originating from the cycloisomerization of the bisallene, was obtained in 15% yield.¹⁵ Lowering the temperature to 40 °C avoided the formation of **4a**, resulting in our optimized set of conditions (see the Supporting Information (SI) for the complete optimization study).

Having established the optimum reaction conditions, the scope of the reaction was then evaluated, as shown in Figure 1.

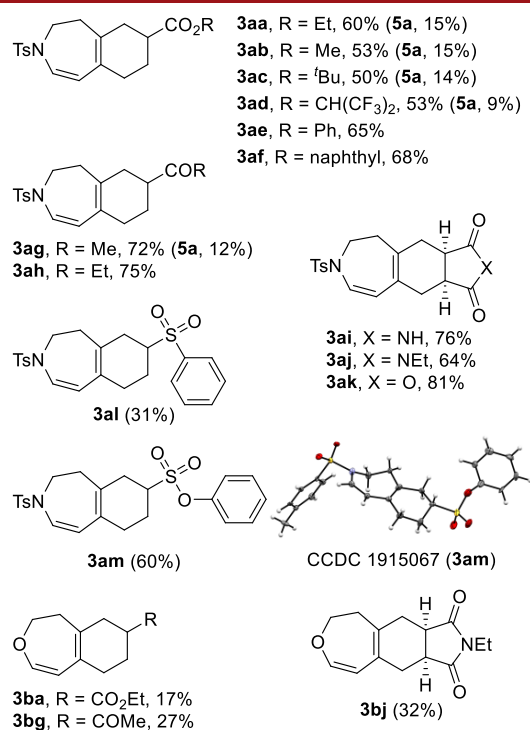


Figure 1. Scope of the cycloaddition of bisallenes **1** with alkenes **2**.

Table 1. Optimization of the Rhodium(I)-Catalyzed Cycloaddition of Bisallene **1a** with Alkene **2a**^a

Reaction scheme showing the catalytic hydrogenation of bisallene **1a** and alkene **2a** to form products **3aa**, **4a**, and **5a**.

Reagents and conditions: $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (10% mol), Ligand (10% mol), H_2 , CH_2Cl_2 , r.t., catalytic species, $\text{THF}:\text{CH}_2\text{Cl}_2$ (4:1).

Chemical structures of the products:

- 3aa**: A bicyclic compound with a TsN group and a CO_2Et group.
- 4a**: A bicyclic compound with a TsN group and a CO_2Et group.
- 5a**: A bicyclic compound with a TsN group and a CO_2Et group.

entry	ligand	temp (°C)	reaction time (h)	yield (%) 3aa / 4a / 5a
1	(<i>R</i>)-BINAP	65	4	49/45/—
2	(<i>R</i>)-DTBM-SegPhos	65	4	65/05/15
3	(<i>R</i>)-DTBM-SegPhos	40	16	60/—/15

^aReaction conditions: 0.18 mmol of **1a** ([**1a**] = 9 mM), 50 equiv of **2a**, 10% mol of Rh catalyst in 20 mL of THF/CH₂Cl₂ (4:1) at the indicated temperature and time. The 10% mol mixture of [Rh(cod)₂]BF₄ and phosphine was treated with hydrogen in dichloromethane (CH₂Cl₂) solution for catalyst activation prior to substrate addition.

Overall, the reaction proceeds in good to moderate yields with a wide range of alkenes. Reactions involving alkyl and aryl acrylates (**2a**–**2f**) deliver products in yields ranging between 50% and 68%. Vinyl alkyl ketones **2g** and **2h** also produced the corresponding cycloadducts in 72% and 75% yields, respectively. In some cases, byproduct **5a** was also formed and separated from the desired product by column chromatography.¹⁶ Disubstituted cyclic alkenes, such as maleimide (**2i**), *N*-ethyl maleimide (**2j**), and maleic anhydride (**2k**), underwent the cycloaddition reaction efficiently to produce derivatives **3ai**, **3aj**, and **3ak** in excellent yields and avoiding the formation of byproduct **5a**. The use of phenyl vinyl sulfone (**2l**) and phenyl vinyl sulfonate (**2m**) afforded derivatives **3al** and **3am** in 31% and 60% yields, respectively, and, again, no traces of **5a**. In addition, two 1 mmol scale reactions using ethyl acrylate **2a** and vinyl methyl ketone **2g** were performed, affording a 69% yield of **3aa** (15% yield of **5a**) and a 77% yield of **3ag** (14% yield of **5a**), respectively. Single crystal X-ray diffraction analysis of compound **3am** (CCDC 1915067) allowed us to unambiguously establish the structure of the cycloadduct obtained.¹⁷

To extend the methodology to other 1,5-bisallenes, oxygen-tethered bisallene **1b** was prepared and reacted with three different alkenes: ethyl acrylate **2a**, methyl vinyl ketone **2g**, and

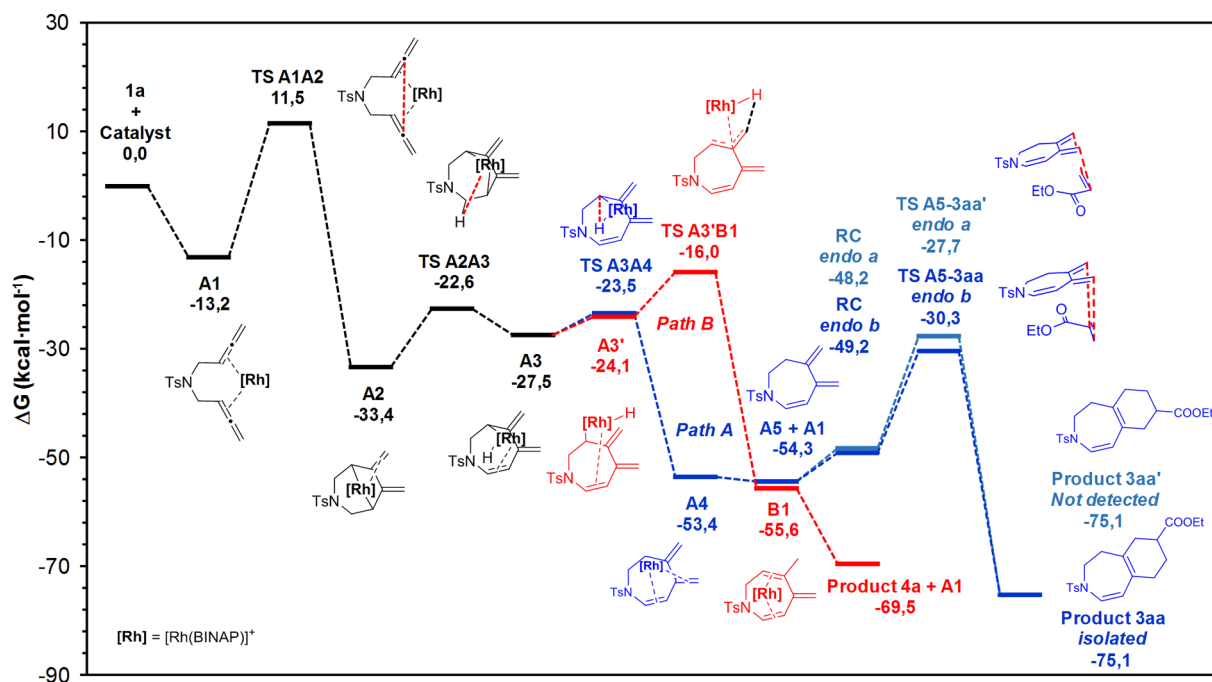


Figure 2. Gibbs energy profile for the tandem cycloisomerization/Diels–Alder cycloaddition (Path A, blue) leading to product **3aa** and cycloisomerization reaction (Path B, red) leading to product **4a**. RC = Reactant complex.

N-ethylmaleimide **2j** affording the corresponding derivatives **3ba**, **3bg**, and **3bj** in moderate yields ranging from 17% to 32%.

Since a stereogenic center was generated in derivatives **3**, the enantiomeric excess was measured in all cases, but no enantioinduction was observed regardless of the substrate or the ligand used. This result is commensurate with the mechanism proposed for this transformation (*vide infra*).

To gain further understanding of the reaction mechanism, we completed our study by evaluating computationally the process that transforms **1a** into **3aa**. The Gibbs energy profile computed at 313.15 K and 1 atm with the M06L-D3/cc-pVTZ-PP/SMD(76% THF, 24% CH₂Cl₂)¹⁸//B3LYP-D3/cc-pVDZ-PP method is depicted in Figure 2, and the catalytic cycle is shown in Figure 3 and the molecular structures of the TSs in Figure S4. To reduce the computational effort required, BINAP was chosen as the model phosphine ligand instead of the optimal ligand (*R*)-DTBM-Segphos (see SI for a complete description of the computational methods).

The reaction starts with η^4 -coordination of [Rh(BINAP)]⁺ to the two internal double bonds of 1,5-bisallene **1a** to form the square-planar 16-electron intermediate **A1**. This process is exergonic by 13.2 kcal/mol. Upon coordination, intermediate **A1** readily experiences oxidative coupling at the central carbon atoms of both allene moieties to deliver intermediate **A2**, a rhodabicyclo[3.2.1]octane complex featuring two contiguous exocyclic methylene groups. This first step has a Gibbs energy barrier of 24.7 kcal/mol through TS **A1A2** and is exergonic by 20.2 kcal/mol. Intermediate **A2** is an 18-electron species and shows a distorted octahedral geometry in which one of the O atoms of the tosyl group occupies one of the six positions ($d_{\text{Rh}-\text{O}} = 2.231$ Å) and one of the two exocyclic double bonds is η^2 -coordinated to the Rh center ($d_{\text{Rh}-\text{C}} = 2.196$ and 2.132 Å). The fact that internal bonds in allenes are more reactive than their external counterparts has already been reported in previous studies by our group.^{14a,d} An alternative mechanism

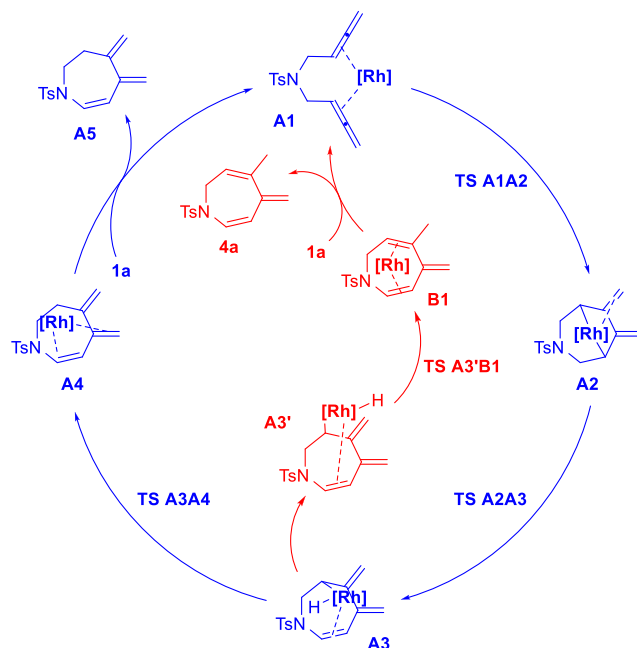


Figure 3. Catalytic cycle for the two Rh(I)-catalyzed tandem cycloisomerization reactions of 1,5-bisallene **1a** leading to intermediate **A5** (Path A, blue) and product **4a** (Path B, red).

for this transformation by which a bisallylic rhodacyclopentane intermediate resulted from the initial oxidative coupling was proposed by Ma⁹ and by Mukai,¹⁰ although no mechanistic studies were reported. Our computational calculations seem to contradict this proposal, although care should be taken when comparing these two transformations owing to the different substitution patterns of the bisallene precursors involved.

A2 is converted into intermediate **A3** through a β -hydride elimination mechanism. This process is slightly endergonic by 5.9 kcal/mol and has a Gibbs energy barrier of 10.8 kcal/mol

(TS A2A3). The Rh center in intermediate A3 is η^2 -coordinated to the newly formed C=C bond and presents a distorted tetrahedral geometry. Reductive elimination from intermediate A3 to form A4 has to surmount a barrier of 4.0 kcal/mol (TS A3A4) and releases 25.9 kcal/mol. Subsequent release of the initial Rh(I) complex leads to triene intermediate A5, completing the catalytic cycle (Path A in Figures 2 and 3). Alternatively, intermediate A3 can experience a rearrangement with a rotation through the C–Rh bond that approaches the hydride coordinated to Rh to one of the C=C exocyclic double bonds giving A3' (Path B in Figures 2 and 3). Reductive elimination through TS A3'B1 has a cost of 8.1 kcal/mol and is exergonic by 31.5 kcal/mol. This alternative mechanism provides a rational explanation for the formation of compound 4a.

On the other hand (Path A in Figure 2), the formation of intermediate A5 is followed by [4 + 2] cycloaddition with ethyl acrylate 2a to deliver compound 3aa. The formation of the desired reaction product 3aa has an overall reaction energy (ΔG_r) of -75.1 kcal/mol. Importantly, the regiochemistry of the reaction can also be explained by our computed reaction mechanism. While “endo a” approximation of the dienophile (i.e., TS A5–3aa') has a Gibbs energy barrier of 26.6 kcal/mol, the “endo b” approximation (i.e., TS A5–3aa) has a lower cost of 24.0 kcal/mol. Such a difference in energy ($\Delta\Delta G^\ddagger = 2.6$ kcal/mol) accounts for the selective formation of the actual reaction product 3aa.

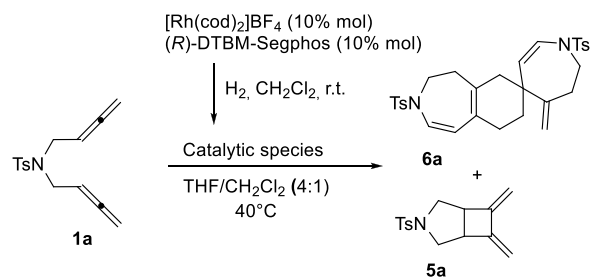
It has not escaped our attention that, in the same way that intermediate A5 does, intermediates A2, A3, and A4 are ripe to experience [4 + 2] cycloaddition with ethyl acrylate 2a before β -hydride elimination, reductive elimination or catalyst release takes place, respectively. Considering this, we computed all potential reaction paths leading to reaction product 3aa (see Figures S5, S6, and S7 in the SI). We found that all alternative reaction mechanisms analyzed have higher barriers or do not explain the observed regioselectivity.

In summary, the reaction mechanisms leading to compounds A5 and 4a (paths A and B in Figure 2) have an energetic span between the turnover frequency (TOF) determining intermediate (TDI, A1) and TOF determining transition state (TDTS, TS A1A2) of 24.7 kcal/mol.¹⁹ Once formed, intermediate A5 reacts with ethyl acrylate 2a through a regioselective catalyst-free Diels–Alder cycloaddition to provide compound 3aa.

With the aim of fully validating the proposed reaction mechanism, we completed our study by performing additional experiments. First, the involvement of reaction byproduct 5a as a reaction intermediate of the catalytic cycle was ruled out by heating a mixture of this compound and ethyl acrylate 2a in the absence and presence (Schemes S4 and S5) of the rhodium catalytic mixture. In both cases, only starting materials were recovered. Computational calculations are again in good agreement with the experiments (see Figure S8 in the SI).

Finally, in an attempt to isolate intermediate A5, we performed the reaction in the absence of a dienophile (Scheme 2). Even though A5 could not be obtained as a stable reaction product, we found indirect evidence of its formation. Homodimer 6a was isolated in 58% yield, indicating that it is a promiscuous intermediate acting as both the diene and the dienophile in Diels–Alder reactions. Remarkably, only one out of the four possible isomers of the dimer was obtained. This last finding not only gives an experimental confirmation of our computational results, but opens new avenues for the

Scheme 2. Additional Mechanistic Experiments Performed



preparation of complex spirocyclic compounds in a straightforward and selective manner starting from 1,5-bisallenes. The isolation by Ma and co-workers⁸ of another homodimer of 1a (Scheme 1a), when a different catalytic system was employed, is worth noting and highlights the importance of the coordination environment in favoring disparate mechanistic outcomes.

A related work by Breit and co-workers²⁰ was described during the preparation of this manuscript, reporting on a rhodium-catalyzed cycloisomerization of 1,6-allenes to afford six-membered ring exocyclic 1,3-dienes and further tandem Diels–Alder reaction. Our allene/allene/alkene triad of unsaturated partners offers a much complex mechanistic scenario as exemplified by our mechanistic study, and therefore a commensurate potential for developing new reactivity manifolds.

In conclusion, we have developed an efficient cascade process based on an intramolecular Rh-catalyzed cycloisomerization of 1,5-bisallenes (1) leading to a nonisolable cycloheptadiene intermediate followed by a regioselective Diels–Alder cycloaddition with alkenes (2). The new process affords a variety of polycyclic heterocycles 3 containing dihydroazepine- and dihydrooxepine-fused ring systems. DFT calculations show that the reaction leading to 3aa from 1a takes place through an oxidative coupling of the rhodium at the central carbon atoms of both allenes followed by a β -hydride elimination to form intermediate A3 and reductive elimination to give intermediate A5. An uncatalyzed and regioselective Diels–Alder cycloaddition to A5 generates the final product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02032.

Experimental procedures, optimization of the reaction, compound characterization data, crystallographic data and computational data (PDF)

Accession Codes

CCDC 1915067 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) Compound **5a** was synthesized by Ma and co-workers [see ref **3a**] through a palladium(0)-catalyzed [2 + 2] cycloaddition of bisallene **1a**.

(16) The formation or absence of product **5a** is surprising (especially comparing **3ag** and **3ah**) and points to a delicate balance of reaction rates among the multistep processes leading to products **3** and **5**.

(17) The thermal ellipsoids in the ORTEP plot of the X-ray structure of **3am** are drawn at 50% probability.

(18) (76% THF, 24% CH₂Cl₂) is equivalent to a 4:1 v/v ratio of THF/CH₂Cl₂.

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