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Rh(II)-Catalyzed Alkynylcyclopropanation of Alkenes by Decarbenation of Alkynylcycloheptatrienes

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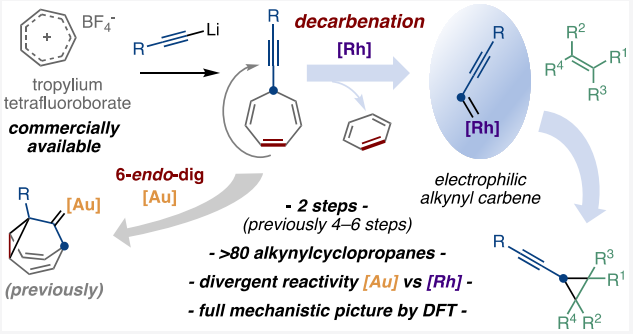
ABSTRACT: Alkynylcyclopropanes have found promising applications in both organic synthesis and medicinal chemistry but remain rather underexplored due to the challenges associated with their preparation. We describe a convenient two-step methodology for the alkynylcyclopropanation of alkenes, based on the rhodium(II)-catalyzed decarbenation of 7-alkynyl cycloheptatrienes. The catalytic system employed circumvents a fundamental problem associated with these substrates, which usually evolve via 6-*endo*-dig cyclization or ring-contraction pathways under metal catalysis. This unique performance unlocks a rapid access to a diverse library of alkynylcyclopropanes (including derivatives of complex drug-like molecules), versatile intermediates that previously required much lengthier synthetic approaches. Combining experiments and DFT calculations, the complete mechanistic picture for the divergent reactivity of alkynylcycloheptatrienes under metal catalysis has been unveiled, rationalizing the unique selectivity displayed by rhodium(II) complexes.



INTRODUCTION

Cyclopropanes are among the most studied functionalities in organic synthesis[1] and medicinal chemistry.[2] Accordingly, great efforts have been made to grant access to a wide variety of three-membered rings in a straightforward manner.[3] In particular, alkyne-substituted cyclopropanes display very diverse reactivity patterns and have been used by different research groups as starting substrates for the development of new synthetic methodologies through ring-expansion,[4] ring-opening,[5] or cycloaddition processes,[6] among others.[7] The versatility of these intermediates has been further illustrated by their application in the total synthesis of natural products.[8] Furthermore, the alkynylcyclopropane unit can be found in the structure of commercial drugs such as efavirenz, an antiretroviral medication used to treat and prevent HIV (Scheme 1A).[9] Remarkably, this structural motif was also discovered in some naturally occurring compounds, such as the callipeltoside family of highly bioactive products, which has attracted considerable interest from the synthetic community.[10]

Despite all this, the alkynylcyclopropane unit is a rather underexplored functionality, arguably due to the lack of general and short approaches for its assembly. A logical disconnection for its synthesis involves the cyclopropanation of 1,3-enynes,[11] which are not readily available substrates and can suffer from selectivity issues (Scheme 1B, right). Because of this, the most widespread method for the preparation of these compounds is the cyclopropanation of alkenes with α-diazo esters, followed by redox manipulation and subsequent homologation of the corresponding aldehydes (mainly by Corey−Fuchs or Ohira−Bestmann reactions) (Scheme 1B, left). For these reasons, several groups have recently turned their attention to the development of new methods for the synthesis of alkynylcyclopropanes, such as the hydroalkynylation of cyclopropenes[12] or methylenecyclopropanes,[13] the use of chromium Fischer carbenes,[14] and isolated examples based on the reactivity of diazo compounds and other related substrates.[15]

Considering that all these strategies require an average of 4−6 synthetic steps and often suffer from selectivity or generality issues, the development of a direct alkynylcyclopropanation of alkenes would be highly desirable (Scheme 1B, bottom). For this purpose, we hypothesized that 7-alkynyl-1,3,5-cycloheptatrienes **1** (prepared in one step from commercially available terminal alkynes and tropylium tetrafluoroborate) could be potentially used as alkynyl carbene equivalents under metal catalysis (Scheme 1C). We have previously reported that 7-substituted cycloheptatrienes can undergo retro-Buchner reactions generating metal carbenes catalytically.[16] These electrophilic intermediates can be trapped by alkenes to give cyclopropanes or engage in insertion, cycloaddition, or

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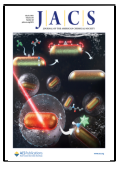

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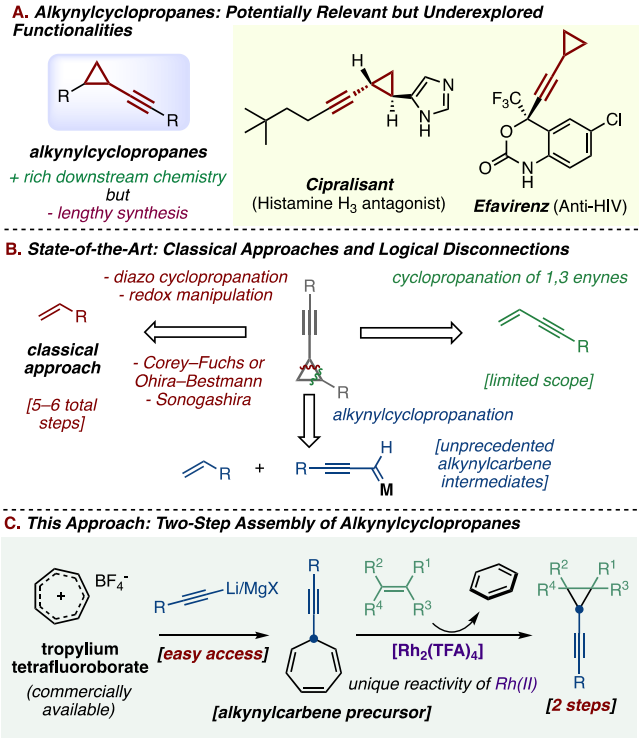
Scheme 1. Synthetic Approaches and Relevance of Alkynylcyclopropanes



Friedel–Crafts-type processes.[17] However, whereas 7-aryl[16a] or 7-alkenyl[16b] cycloheptatrienes undergo this process smoothly under Au(I) catalysis, 7-alkynyl cycloheptatrienes **1** undergo different rearrangements under metal catalysis. In the presence of gold complexes, they behave as 1,6-enynes and readily evolve through 6-*endo*-dig cycloisomerization pathways, leading to indenes **4a**/**4b**[18] or barbaralones **4d** under oxidative conditions (Scheme 2, top right).[19] Similarly, Gandon and co-workers have studied extensively the behavior of these substrates in the presence of a wide variety of catalysts, which promoted either cyclization or ring-contraction pathways to give products such as **4e** or **4f** (Scheme 2, left).[20]

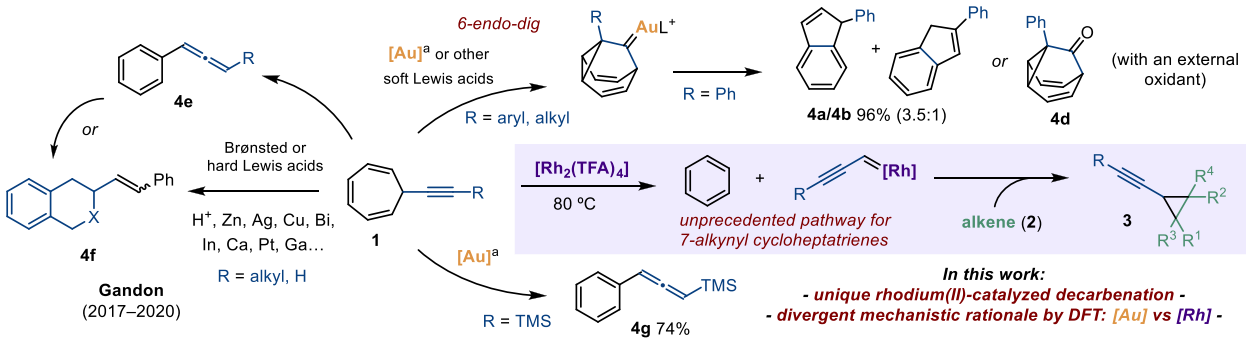
We have now found that the use of rhodium(II) catalysis allows the minimization (or even the suppression) of these undesired pathways (Scheme 2, center right). This system allowed us to promote, for the first time, a decarbenation–alkynylcyclopropanation sequence using 7-alkynyl cycloheptatrienes **1**. This resulted in the development of a convenient two-step method for the assembly of alkynyl-substituted cyclopropanes, using commercially available tropylium tetrafluoroborate, terminal alkynes, and alkenes (Scheme 1C). The relevance of this strategy is illustrated by the rapid preparation of a broad range of synthetically versatile compounds (which could be easily derivatized), as well as the late-stage derivatization of complex drug-like molecules. Experimental and theoretical studies support the formation of rhodium(II)-alkynylcarbene intermediates, which react smoothly with alkenes to deliver cyclopropanes. On the basis of DFT calculations, we have developed a full mechanistic picture that explains the divergent reactivity of 7-alkynyl cycloheptatrienes under Au(I) or Rh(II) catalysis. Furthermore, we found that the *cis*-stereoselectivity of the cyclopropanation can be rationalized in terms of attractive noncovalent interactions.

RESULTS AND DISCUSSION

At the outset of our investigation, we were aware of the rich reactivity displayed by 7-alkynyl cycloheptatrienes under metal catalysis.[18,20] The presence of a 1,6-enyne system in **1** represents a fundamental challenge for the potential development of a chemoselective metal-catalyzed retro-Buchner reaction. These decarbenation processes have mostly been studied using gold(I) complexes, which are also powerful catalysts for the cycloisomerization of these enyne systems (Scheme 2).[21]

Accordingly, when the reaction of **1a** with styrene in the presence of a cationic gold(I) complex as catalyst was attempted, the product of alkynylcyclopropanation **3a** was not detected. Rather, quantitative conversion of **1a** to indenes **4a**/**4b** (3.5:1) was observed (Table 1, entries 2, 3) through a 6-*endo*-dig cycloisomerization pathway.[18] Then, we decided to evaluate the activity of Rh(II) paddlewheel complexes, which are also active in this type of carbene-transfer processes.[17b] Gratifyingly, we found that the reaction of **1a** with styrene in the presence of 5 mol % of $[Rh_2(TFA)_4]$ using PhMe/hexane (1:1) as solvent afforded selectively the product of decarbenation–alkynylcyclopropanation (**3a**) in 70% yield and with good diastereoselectivity (10:1 *cis*/*trans* ratio), after 20 h at 80 °C (Table 1, entry 1).[22] Under these optimized conditions, only 7% and 8% yield of indenes **4b** and **4c**, respectively, were observed as side products. The use of less electrophilic Rh(II) complexes (Table 1, entries 4, 5) led to

Scheme 2. Diverse Reactivity Scenarios of 7-Alkynyl-1,3,5-cycloheptatrienes under Metal Catalysis



[a]For **4a–d** and **4g**, [Au] = [(JohnPhos)Au(MeCN)]SbF_6 (5 mol %). For more details about the known reactivity of 7-alkynyl cycloheptatrienes, see previous publications by our group (**4a–d**)[18,19] and by Gandon and co-workers (**4e**, **4f**).[20]

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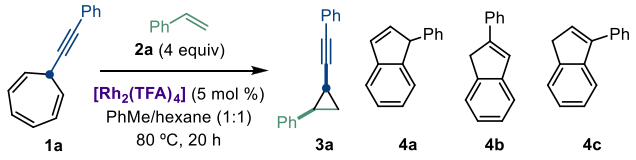
Table 1. Optimization and Control Experiments



	deviations from standard conditions [a]	3a (*cis*/*trans*)	4a	4b	4c
1	none	70% (10:1)	-	7%	8%
2	[LAuL']SbF_6 (5 mol %) at 25 °C[b,c]	-	75%	21%	-
3	[LAuL']SbF_6 (5 mol %) at 80 °C[b,c]	-	68%	17%	-
4	$[Rh_2(OAc)_4]$ (5 mol %)[b]	trace (n/d)	-	-	-
5	$[Rh_2(esp)_4]$ (5 mol %)[b]	17% (n/d)	-	-	-
6	1.7% of $[Rh_2(TFA)_4]$[d]	61% (6:1)	8%	4%	-
7	$ZnCl_2$ (10 mol %) at 80 °C[b]	-	-	2%	2%
8	PhMe as solvent	57% (9:1)	-	12%	12%
9	$CHCl_3$ as solvent	54% (8:1)	-	16%	13%
10	hexane as solvent	65% (12:1)	-	7%	8%
11	THF, MeCN, DMF, or EtOAc as solvent	-	-	-	-
12	0.05 M in hexane	64% (12:1)	12%	5%	-
13	PhMe at 40 °C (66% conversion)	36% (10:1)	9%	14%	-
14	hexane at 40 °C (17% conversion)	17% (n/d)	-	2%	3%
15	PhMe at 110 °C	27% (2.3:1)	-	9%	7%

Yields and *cis*/*trans* ratios determined by ^{1}H NMR using Ph_2CH_2 as internal standard. [a]Standard conditions: 1 equiv of **1a** with 4 equiv of **2a** using $[Rh_2(TFA)_4]$ (5 mol %) as catalyst in PhMe/hexane (1:1, 0.15 M) at 80 °C for 20 h. [b]$CHCl_3$ used as solvent. [c][(JohnPhos)-Au(MeCN)]SbF_6 used as catalyst. [d]Hexane used as solvent.

much lower yields of **3a**, and other Lewis acids such as $ZnCl_2$[23] led only to trace amounts of indenes (Table 1, entry 7). Reduced catalyst loading could be employed, leading to a small drop in yield when using 1.7 mol % of $[Rh_2(TFA)_4]$ (Table 1, entry 6). Solvent choice proved to be critical for the success of the reaction. Thus, no reaction was observed in polar or protic solvents (Table 1, entry 11). Hexane was found to behave best in terms of yield and diastereoselectivity (Table 1, entries 8–10), only outperformed by a 1:1 mixture of hexane and toluene, which was selected as a standard solvent system considering both the efficiency and solubility of more polar substrates. We found concentration to have little effect on the reaction outcome (Table 1, entry 12). Performing the reaction at 40 °C in either hexane or toluene led to lower yields and conversions (Table 1, entries 13, 14), while a significant erosion in both yield and diastereoselectivity was observed at 100 °C (Table 1, entry 15).

The scope of the alkynylcyclopropanation reaction was examined with a wide variety of 7-alkynyl cycloheptatrienes **1**, prepared in a straightforward manner by treating terminal alkynes with *n*BuLi and subsequently with tropylium tetrafluoroborate (Scheme 1C), giving exclusively the desired products **1** in high yields.

First, we examined the transfer of carbon-substituted alkynyl carbene fragments (Scheme 3). We selected styrene as model alkene to evaluate the reactivity of a wide range of (aryl)alkynyl cycloheptatrienes, obtaining disubstituted cyclopropanes **3a–j** in good to excellent yields and high selectivity for the *cis* diastereoisomer. Electronically and sterically different substituents in any position of the ring are well tolerated, including different halide groups. Interestingly, bulky aromatics such as 2-methylphenyl (**3h**) or 1-naphthyl (**3m**) give higher yields, presumably due to a more efficient minimization of the 6-*endo*-dig cyclization side pathway. Using a ferrocenyl group led to the synthesis of crystalline derivative **3p**, which allowed confirming the *cis* configuration for the major product by X-ray diffraction. A range of styrenes with a variety of substituents were also tested (**3r–aa**), providing equally good results in terms of both efficiency and stereoselectivity. The power of this methodology is illustrated by the two-step preparation of cyclopropanes such as **3b**, whose synthesis required previously six steps starting from styrene and ethyl diazoacetate.[24] Similarly, indene was cyclopropanated with excellent diastereoselectivity (**3q**). Less activated alkenes such as simple cyclohexene also react to give **3k–l**. Also, more electron-rich alkenes such as *N*-vinylphthalimide proved to be compatible with the reaction conditions, providing cyclopropylamine derivatives **3n–o** in good yield and diastereoselectivity. Then, we examined other types of carbon substituents in the alkyne terminus of **1**. 1,3-Enynyl cycloheptatrienes were prepared from terminal 1,3-enynes and were successfully employed in the carbene-transfer process. This allowed the synthesis of several 1,3-enynyl cyclopropanes, **3ab–af**, with high diastereoselectivity. The moderate yields obtained can be attributed to oligomerization pathways. Analogously, extended C(sp) systems were also tolerated, granting access to 1,3-diynyl cyclopropanes **3aw** and **3ax** (Scheme 3, bottom right). To cover the entire range of carbon substituents, we tested various cycloheptatrienes **1** with alkyl groups in the alkyne terminus (Scheme 4, top right). Tertiary C(sp^3) groups performed very well in the reaction, bearing either C- or O-substituents, giving good to excellent yields and moderate to good diastereoselectivities. Styrenes with different substitution patterns (**3ag–ak**), indene (**3al**), enamines (**3ai**), or cyclohexene (**3ao**) could be employed, and an inverse relationship between steric bulk of the R group in **1** and the diastereoselectivity could be observed (**3am** vs **3an**). Benzyloxy derivatives **3aq–av** were also prepared successfully. On the other hand, substrates with primary and secondary alkyl groups were much more prone to undergo cycloisomerization to indenes analogous to **4a–c**, giving cyclopropanes such as **3ap** in lower yield.

In order to illustrate the potential of the reaction in late-stage functionalization, we synthesized several alkynylcyclopropane derivatives of natural or drug-like molecules (Scheme 4, bottom left). Thus, new derivatives of indomethacin (anti-inflammatory, **4ba**), α-tocopherol (vitamin E, **3bb**), and estrone (steroid, **3bc**) were accessed in a diastereoselective manner. We proved the modularity of this approach by introducing the complex molecular fragment as either the alkene or the alkyne component of the reaction. For this purpose, we prepared regioisomeric derivatives **3ay** and **3az** from fenofibrate, a drug used to treat hypercholesterolemia, which has recently been suggested for the treatment of life-threatening symptoms of COVID-19.[25] These examples demonstrate the compatibility of the new method with complex molecules containing diverse functional groups such as esters, ketones, or indoles.

After observing that simple 7-ethynyl-1,3,5-cycloheptatriene did not lead to any productive reactivity, we envisioned the possibility of transferring silyl-protected alkynyl carbenes in order to access terminal alkynyl cyclopropanes. First, we explored the reactivity of different silyl-protected 7-alkynyl cycloheptatrienes (Scheme 4). To our delight, we found that in all cases these substrates afforded the product of decarbenation–cyclopropanation of styrene in excellent yields. These

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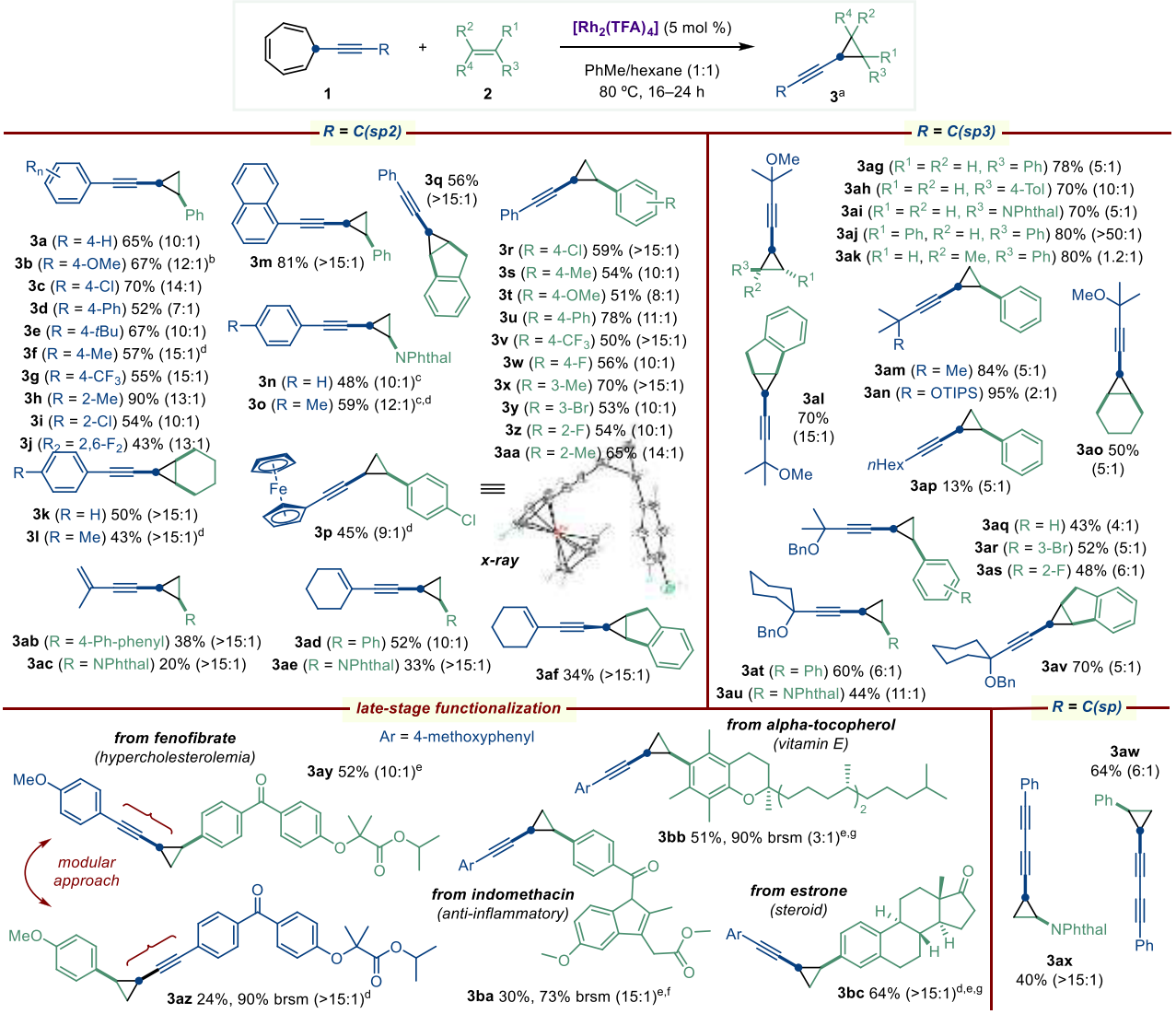
Scheme 3. Scope of the Alkynylcyclopropanation Reaction and Late-Stage Functionalization



[a]Standard conditions: 1 equiv of cycloheptatriene **1** (usually 0.3−0.5 mmol) with 4 equiv of alkene **2**, using $[Rh_2(TFA)_4]$ (5 mol %) as catalyst, in PhMe/hexane (1:1, 0.15 M) at 80 °C until full consumption of **1** (usually 16−24 h). Isolated yield. [b]60 °C instead of 80 °C. [c]$CHCl_3$ as solvent. [d]2 equiv of **2** instead of 4. [e]1 equiv of alkene **2** and 1.5 equiv of **1**. [f]PhMe/$CHCl_3$ (2:1) as solvent. [g]Obtained as a 1:1 mixture of the two possible *cis* products. NPhthal = *N*-phthalimide.

reactions proceeded smoothly, without detectable amounts of side-products, and proved to be very robust.[22] On the other hand, when this reaction was attempted under Au(I) catalysis, no cyclopropane was observed. Rather, **1b** reacts to give allene **4g** in 74% yield (Scheme 2). A clear correlation between the bulkiness of the silyl group and the *cis*/*trans* ratio of products **5a−d** was observed. We selected TMS as protecting group for the assembly of terminal alkynylcyclopropanes on the basis of giving the best diastereoselectivity, being easy to deprotect, and affordability of TMS-acetylene. A simple one-pot addition of TBAF after the cyclopropanation is completed leads cleanly to the formation of the corresponding terminal alkynylcyclopropanes **6** in good to excellent yields and diastereoselectivities. We extended the reaction to the cyclopropanation of mono-, di-, tri-, and tetrasubstituted alkenes. 1,2-Dihydronaphthalene (**6h**), indene (**6i**), and styrenes with diverse substitution patterns (**6a−g**) were employed successfully. Less activated alkenes such as cyclohexene (**5e−f**) or tetramethylethylene (**5g**) behaved similarly, as well as more electron-rich *N*-vinylphthalimide, giving almost exclusively the *cis* diastereoisomer, as evidenced by the X-ray crystal structure of **6k**. The same type of alkynylcarbene could be trapped by a dehydroalanine, giving cyclopropyl α-amino acid derivative **5i**. The alkynylcyclopropanation of a 1,3-enyne could also be carried out,[13] accessing interesting 1,2-dialkynylcyclopropanes such as **5j**/**6j**. Notably, among this library of compounds, we obtained **6g**, a gold(I)-carbene precursor recently developed by our group,[26] using only two reaction flasks, while the original preparation required four steps from ethyl diazoacetate.

We expanded the scope of this reaction to the transfer of germanylalkynyl carbenes (Scheme 5). Thus, cycloheptatriene **1z** was used to obtain cyclopropanes **5k** and **5l** in good yield and diastereoselectivity. This grants access to new types of organogermanes, reagents that have recently arisen as relevant orthogonal cross-coupling partners.[27]

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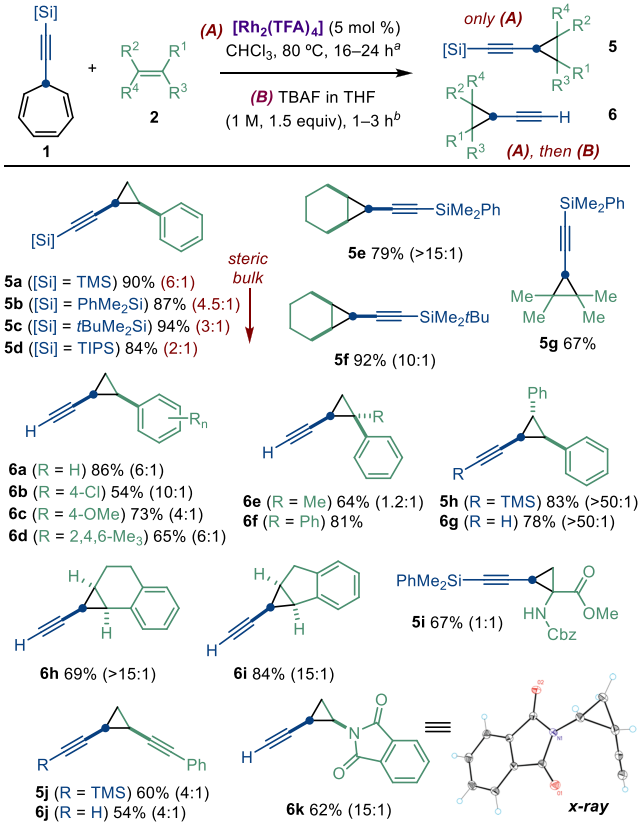
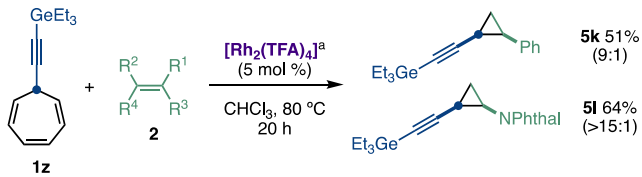
Scheme 4. Scope of the Silylalkynylcyclopropanation and One-Pot Assembly of Terminal Alkynylcyclopropanes



[a]Standard conditions: 1 equiv of **1** (usually 0.3–0.5 mmol) with 4 equiv of alkene **2**, using $[Rh_2(TFA)_4]$ (5 mol %) as catalyst, in $CHCl_3$ (0.15 M) at 80 °C until full consumption of **1** (usually 16–24 h). Isolated yield. [b]For the synthesis of terminal alkynes, [Si] = TMS was used in all cases. NPhthal = *N*-phthalimide.

Scheme 5. Transfer of a Germanylalkynylcarbene Unit



[a]1 equiv of **1z** with 4 equiv of **2**, using $[Rh_2(TFA)_4]$ (5 mol %) as catalyst, in $CHCl_3$ (0.15 M) at 80 °C for 20 h. Isolated yield. NPhthal = *N*-phthalimide.

We demonstrated the scalability of the protocol by preparing more than one gram of terminal alkynylcyclopropane **6a**, which could be obtained in excellent yield as a single diastereoisomer after flash column chromatography. This versatile intermediate could be easily diversified to access a variety of structures (Scheme 6). While exploring the general scope of the reaction, we found acceptor R groups and several heteroatoms (such as halogens) in **1** to be incompatible with the reaction conditions.[22] However, these derivatives can often be directly accessed from the corresponding terminal alkynes **6**. For example, treatment of **6a** with NBS and catalytic Ag_2CO_3 affords bromoalkynyl cyclopropane **7a** in 86% yield. Alkynylcyclopropane **6a** underwent Pd-catalyzed Sonogashira coupling to afford heterocyclic derivative **7b** quantitatively. The Au(III)-catalyzed hydration of **6a** delivers cyclopropyl ketone **7c**,[28] resulting in an overall formal transfer of an acceptor carbene, a process often carried out using diazo compounds. Conveniently, the obtained *cis* product is the opposite diastereoisomer to the one usually accessible by classical approaches that involve cyclopropanations with these classical carbene-transfer reagents. Submitting **6a** to a lithiation/borylation/oxidation sequence gave homologous carbonyl cyclopropane **7d** in 56% overall yield. In the presence of a cationic gold(I) complex, the same intermediate **6a** undergoes a smooth hydroarylation to afford bicyclic cyclopropane **7e**, in 1 h at room temperature. On the other hand, when a disubstituted alkynyl cyclopropane such as **3f** is submitted to the same gold catalysis, the product of hydroarylation is not observed. Instead, methylnaphthalene **7f** was obtained in 93% yield. This compound can be described as the product of formal (3 + 3) cycloaddition between the corresponding alkynyl carbene and styrene.

Finally, we found that benzyloxy-substituted products **3aq–av** can be transformed cleanly into allenyl cyclopropanes **8a–f**, using a modified version of a reported protocol based on a gold(I)-catalyzed retro-ene reaction, which releases benzaldehyde as byproduct.[29] This results in a two-step formal transfer of an allenyl carbene unit, a challenging transformation that has not been explored thus far (Scheme 7). A range of allenylcyclopropanes were assembled while keeping the diastereomeric ratio intact after the isomerization process. This grants easy access to another type of versatile synthetic intermediates,[30] avoiding the use of synthetically challenging 7-allenyl-1,3,5-cycloheptatrienes, which have not been described so far. All these new reactions, together with previous reports on the use of alkynylcyclopropanes in the discovery of novel methodologies,[4−7] highlight the versatility and potential of these now readily accessible compounds.

The progress of the reaction and the side-pathways leading to indenes **4a–c** can be easily followed by ^{1}H NMR (Scheme 8). When the reaction was attempted under gold(I) catalysis, quantitative cycloisomerization of **1a** to **4a** and **4b** was observed (Table 1, entry 2).[22] On the other hand, under rhodium(II) catalysis, the formation of alkynylcyclopropane **3a** was clearly observed over time (Scheme 8A). The formation of small amounts of **4a** and **4b** was also detected. Interestingly, indene **4a** slowly undergoes double-bond isomerization to more stable indene **4c** under rhodium(II) catalysis, a process that was not observed with gold(I). Furthermore, we found that, under similar reaction conditions, cycloheptatrienes **1p** and **1w** react with triisopropylsilane to afford propargyl silanes **9a** and **9b**, respectively (Scheme 8B).[31] This further supports the intermediacy of an alkynylcarbene species that can also be trapped through intermolecular Si–H insertion processes.[17b,32]

In order to rationalize the observed differences in chemoselectivity while using either rhodium(II) or gold(I) catalysis in the reaction of 7-alkynyl-1,3,5-cycloheptatrienes, we modeled both pathways theoretically: the decarbenation/cyclopropanation sequence and the cycloisomerization to give indenes. We used cycloheptatriene **1a** and styrene (**2a**) as model substrates, and $[Rh_2(TFA)_4]$ or $[(PMe_3)Au]^+$ as model catalyst, with DFT at the B3LYP-D3/6-31G(d,p)(H, C, O, F, P) + LANL2DZ(Rh, Au)//6-311G(2d,2p)(H, C, O, F, P) + LANL2TZ(Rh, Au) level of theory (Schemes 9 and 10).

For rhodium, we established $[Rh_2(TFA)_4]$ coordinated to two cycloheptatrienes **1a** (through each of the metal centers of the dimeric complex) as the resting state of the catalytic cycle,

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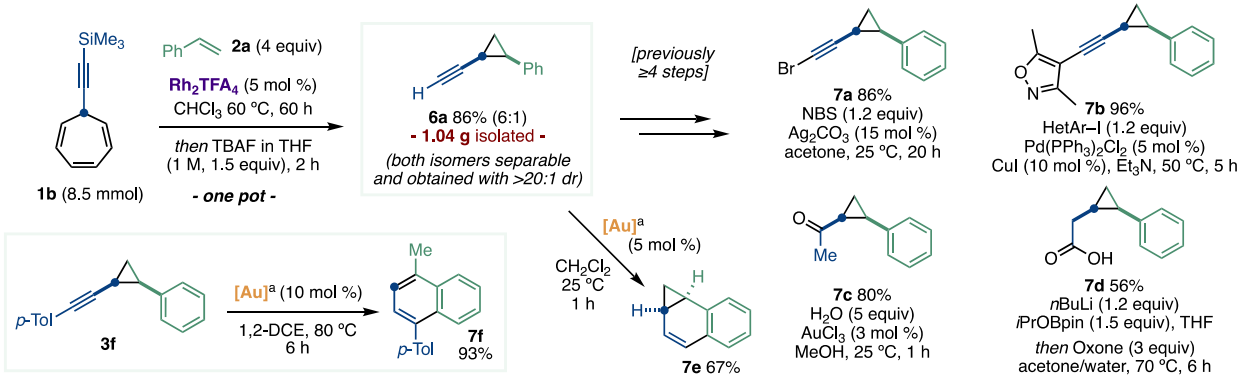
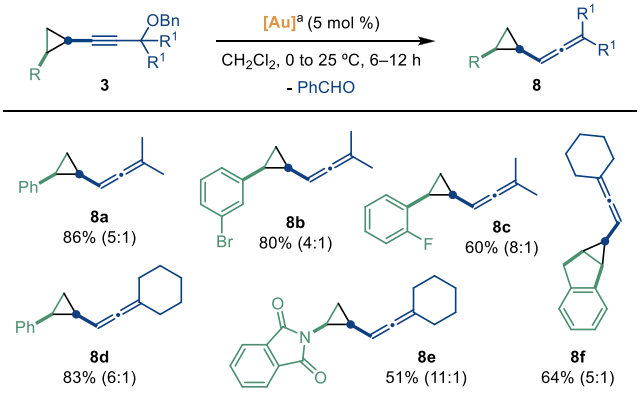
Scheme 6. Gram-Scale Alkynylcyclopropanation: Reactivity and Diversification of Versatile Intermediates



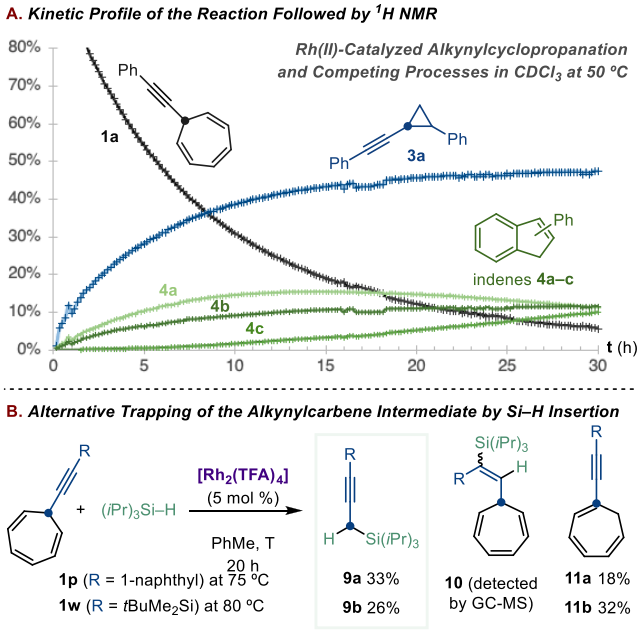
[a][Au] = [(JohnPhos)Au(MeCN)]SbF_6.

Scheme 7. Gold(I)-Catalyzed Synthesis of Allenylcyclopropanes



[a][Au] = [(JohnPhos)Au(MeCN)]SbF_6. Isolated yield.

Scheme 8. Reaction Kinetics and Mechanistic Experiments



whereas for gold, $[(PMe_3)Au]^+$ coordinated to one molecule of **1a** was identified as the most stable adduct. Alkynylcycloheptatriene–metal η^2-coordinated complexes **I** were considered to be the productive species in the cycloisomerization pathway. A 6-*endo*-dig cyclization leads to metal-stabilized barbaralyl cations **VIII**,[33] which can rearrange through rate-limiting transition states $\mathbf{TS_{VIII-IX}}$ to give indene-like intermediates **IX**. Once this point has been reached, intermediates **IX** evolve irreversibly to give indene side-products **4a–c** through a series of low-energy transition states.[20b] On the other hand, alkynyl norcaradiene intermediates **II** can undergo decarbenation or retro-Buchner reaction[34] by cleavage of the first C–C bond of the three-membered ring through rate-limiting transition states $\mathbf{TS_{II-III}}$. In accordance with our experimental observations, for gold(I), we found the transition state of the cycloisomerization reaction to be more favored than that for the retro-Buchner reaction. Contrastingly, the rhodium(II)-catalyzed cycloisomerization of **1a** is much less favorable ($\Delta G^{\ddagger}$ = 24.4 kcal·mol^{-1}), allowing the more energetically feasible decarbenation process ($\Delta G^{\ddagger}$ = 21.9 kcal·mol^{-1}) to proceed. This leads to Wheland-type carbenoid intermediate **III**-[Rh], a shallow minimum that evolves smoothly into rhodium(II) alkynylcarbene **IV** upon release of a molecule of benzene. After benzene–styrene exchange, the alkynyl carbene unit in **V** undergoes nucleophilic attack by styrene to afford carbocationic intermediate **VI**, which readily closes up to give alkynylcyclopropane complex **VII** irreversibly, in an overall stepwise cyclopropanation process (Scheme 10).[35]

In order to rationalize the diastereoselectivity observed experimentally, we compared $\mathbf{TS_{V-VI\_}}_{cis}$ and $\mathbf{TS_{V-VI\_}}_{trans}$, obtaining a significantly lower activation barrier for the *cis*-cyclopropanation ($\Delta\Delta G^{\ddagger}$ = 2.6 kcal·mol^{-1}). NCI plot analysis of these structures clearly shows the stabilizing noncovalent interactions between the two organic fragments (Scheme 10, green surfaces) present in $\mathbf{TS_{V-VI\_}}_{cis}$, but absent in $\mathbf{TS_{V-VI\_}}_{trans}$, responsible for the observed selectivity. This rationale also correlates with the fact that in some cases bulkier substituents can lower the *cis*/*trans* ratio (Scheme 4, **5a–d**), as a consequence of hampering these attractive interactions. All in all, the complete mechanistic picture for the reactivity of 7-alkynylcycloheptatrienes in the presence of metals has been fully unveiled, accounting for the unique chemoselectivity observed under rhodium(II) catalysis. All these findings are consistent with the cleanness of the diastereoselective carbene-transfer process observed experimentally.

CONCLUSIONS

In conclusion, we have developed the first general, two-step alkynylcarbene transfer reaction for the assembly of alkynylcy-

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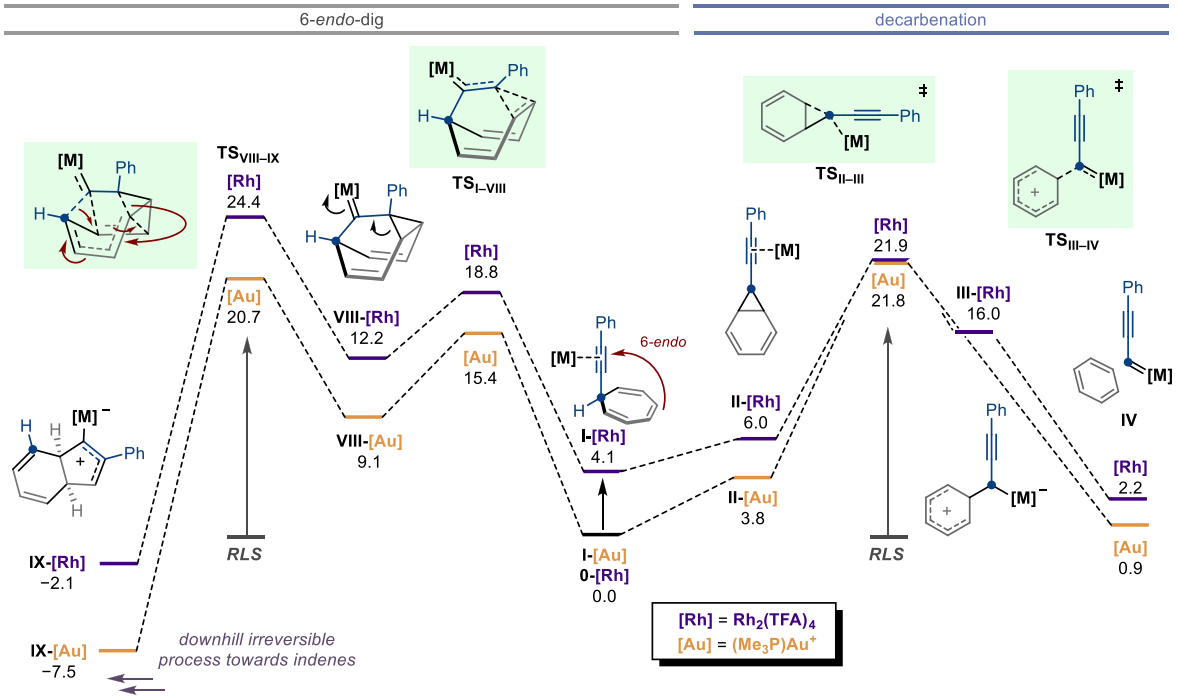
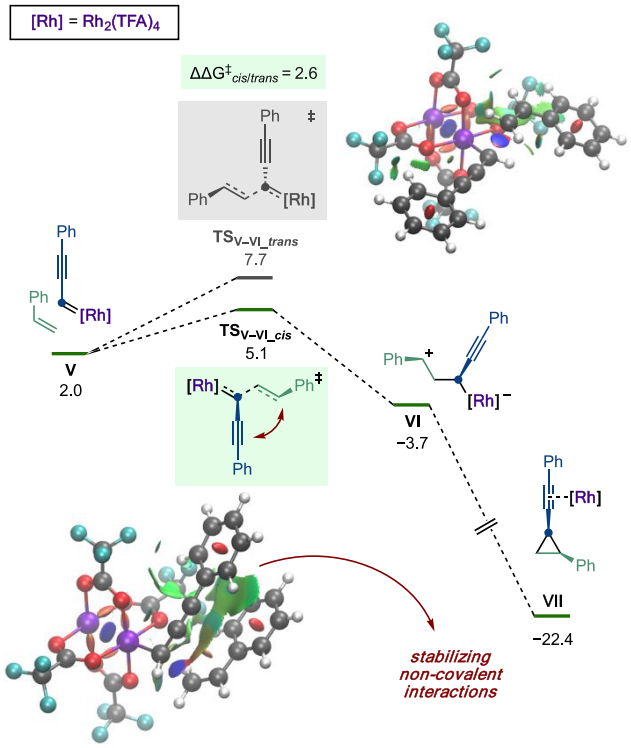
Scheme 9. Free-Energy Profile Calculated by DFT for the Divergent Reactivity of 7-Alkynylcycloheptatrienes under Metal Catalysis (kcal·mol^{-1} at 25 °C)



Scheme 10. DFT Model of the Alkynylcyclopropanation of Styrene to Rationalize the *cis*-Diastereoselectivity (kcal·mol^{-1} at 25 °C)[a]



[a]In the NCI representations, strong attractive interactions are blue (C−C bond formation), weak attractive interactions are green (noncovalent interactions), and strong repulsive interactions are red. Color code: Rh, violet; O, red; F, cyan; C, gray; H, white.

clopropanes from alkenes and terminal alkynes, through decarbenation of readily available 7-alkynyl cycloheptatrienes. The use of Rh(II) catalysis was key to this discovery, which circumvents the fundamental problem associated with the common incompatibility of these 1,6-enyne-contaning substrates with Lewis acids, due to side reactivity. This led to a straightforward synthesis of a wide library of *cis*-alkynylcyclopropanes, bearing C(sp^3)-, C(sp^2)-, C(sp)-, H-, Si-, or Ge-substituents in the alkyne terminus, streamlining the access to these synthetically complex targets. The versatility of these now readily available intermediates was illustrated by their further diversification to give not only different types of alkynylcyclopropanes but also other types of three-membered carbocycles, such as allenyl-, alkyl-, or acceptor cyclopropanes. The robustness and modularity of the new synthetic approach was demonstrated by the diastereoselective preparation of alkynylcyclopropane derivatives of several biologically relevant complex molecules. Furthermore, by means of DFT calculations, we developed a divergent mechanistic model that explains the unique chemoselectivity of Rh(II) complexes toward the retro-Buchner reaction of 7-alkynyl cyclopropanes, whereas the 6-*endo*-dig cycloisomerization pathway is favored under Au(I) catalysis. A rate-limiting Rh(II)-catalyzed decarbenation generates alkynylcyclopropane intermediates, which can be trapped efficiently by an ample variety of alkenes. The *cis*-diastereoselectivity of this cyclopropanation can be rationalized in terms of noncovalent interactions that arise between the two organic fragments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05422.

Experimental procedures and characterization data for compounds (PDF)

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Accession Codes

CCDC 2085762−2085763 contain 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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(31) The main side-products of the reaction were the ones of hydrosilylation (**10**) and isomerization (**11**, presumably by irreversible 1,5-H shift) of the starting alkynylcycloheptatrienes (**1**).

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Efficient Access to Chiral Propargylsilanes and Allenylsilanes. *J. Am. Chem. Soc.* **2021**, *143*, 6401−6406.
(33) We found different tautomeric structures connecting the intermediates of the cycloisomerization process. These species can rapidly interconvert through barriers lower than that for $\mathbf{TS}_{\mathbf{VIII-IX}}$. For details, see the Supporting Information.
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(35) A concerted pathway for the cyclopropanation of styrene could not be located.

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