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Donor Rhodium Carbenes by Retro-Buchner Reaction

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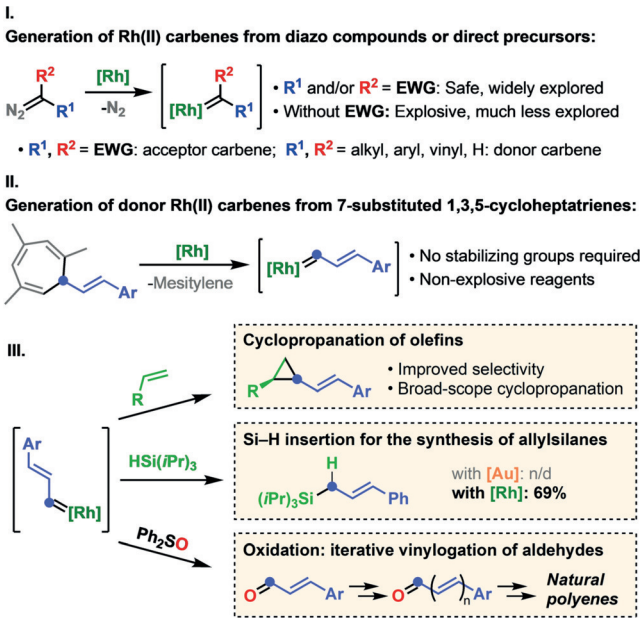
Abstract: *Rhodium carbenes are key intermediates in a range of cycloadditions and insertion reactions. Herein, we report the first generation of donor Rh^{II} carbenes by decarbenation of 7-substituted 1,3,5-cycloheptatrienes. This discovery unlocks an improved retro-Buchner-cyclopropanation sequence, a Si–H insertion reaction for a broad-scope synthesis of allylsilanes, and a new method for the vinylogation of aldehydes. The last strategy led to the development of an iterative synthesis of E-polyenes, and to the total synthesis of navenones B and C.*

Throughout the past decades, rhodium carbenes have been proposed as intermediates that can engage in an extensive range of transformations, which include cyclopropanations[1] or C–H[2] and C–X[3] insertion reactions, among others.[4] Rhodium carbenes are traditionally generated by decomposition of diazo compounds or direct precursors, such as tosylhydrazones (Scheme 1, I).[5] Some of these intermediates have been characterized recently, both spectroscopically and in solid state.[6] Diazo compounds bearing a stabilizing (electron-withdrawing) group are generally employed for the generation of carbenes, since they are safer and easier to handle, but this limits most methodologies to the use of acceptor rhodium carbenes. Although procedures are available for the synthesis of non-stabilized diazo compounds with aryl, vinyl, or even alkyl substituents (which are precursors for donor carbenes),[7] they are usually challenging to prepare, inherently unstable, explosive in pure form, cannot be stored for long periods of time,[8] and are especially prone to diazo dimerization.[9] Encouraged by the fact that alternatives to diazo compounds for the safe generation of Rh^{II} carbenes are scarce,[10] we decided to explore the use of 7-substitued 1,3,5-cycloheptatrienes to generate these intermediates through a Rh^{II}-catalyzed retro-Buchner reaction (decarbenation). The gold(I)-catalyzed decarbenation was first reported by our group in 2010,[11] and emerged as a powerful alternative for the generation of gold(I) carbenes, which can engage in cyclopropanation reactions,[12] and take part in a range of intramolecular transformations.[13] More recently, we showed that through the design of a new generation of more reactive cycloheptatrienes, a retro-Buchner-cyclopropanation sequence could be carried out at very mild conditions and using Zn^{II} salts as substitutes of Au^{I} phosphine or NHC (*N*-heterocyclic carbene) complexes.[14] These findings, backed up by an early report describing a rhodium-promoted retro-cyclopropanation of a polymethylated tricyclic structure,[15] led us to the discovery of the generation of Rh^{II} carbenes from cycloheptatrienes (Scheme 1, II). 7-Styryl-1,3,5-trimethyl-1,3,5-cyclohepatrienes undergo a retro-Buchner reaction under mild conditions in the presence of $[Rh(TFA)_2]_2$, to generate carbenes upon release of mesitylene, which can cyclopropanate a wide range of alkenes,[16] covering and improving both the complementary scopes previously developed with Au^{I} and Zn^{II} analogs.[13] While Au^{I} carbenes generated by this method do not react with silanes, the new generated donor Rh^{II} carbenes react in an intermolecular Si–H insertion process to give allyl silanes.[17] Finally, we found that the resulting carbenes can be efficiently trapped by a mild oxidant to give aldehydes. This strategy allowed to develope a method for the vinylogation of aldehydes, an iterative synthesis of conjugated *E*-polyenes, and a total synthesis of navenones B and C (Scheme 1, III).



Scheme 1. I) Traditional approach: generation of rhodium carbenes from diazo compounds or direct precursors. EWG = electron-withdrawing group (CO_2R, $CONR_2$, COR, CHO). II) This approach: safe generation of donor rhodium carbenes by decarbenation of cycloheptatrienes. III) New reactivity unlocked through this concept.

Our investigation commenced by exploring the reaction of cycloheptatriene **3a** with styrene, in the presence of $[Rh(TFA)_2]_2$. We found that at 60 °C, the generation and trapping of the Rh^{II} carbene proceeded cleanly with only

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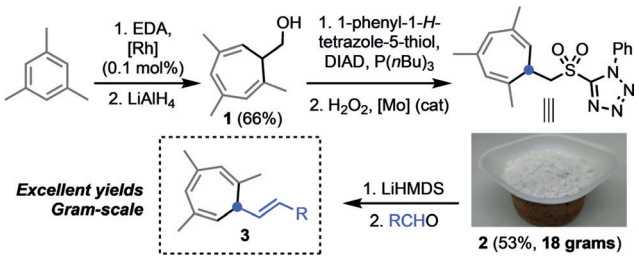
3 mol% of the catalyst, giving the corresponding *cis*-cyclopropane (**5a**) in 72% yield and 12:1 d.r. These 7-styryl-1,3,5-trimethyl-1,3,5-cycloheptatrienes were synthesized with excellent yields on a gram scale by Julia–Kocienski olefination of aldehydes using sulfone **2**, which is a stable and easy-to-handle white solid that can be prepared on a decagram scale by a sequence involving a Rh^{II}-catalyzed Buchner ring expansion of mesitylene with ethyl diazoacetate (EDA), reduction of the ester, Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol, and oxidation (Scheme 2).[12b,14] It is important to remark that very low catalyst loadings (0.1 mol%) are required for the Buchner reaction of mesitylene.

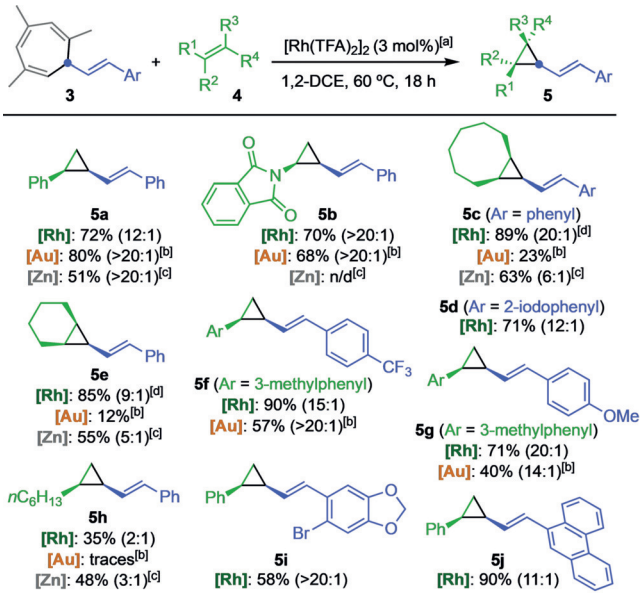


Scheme 2. Decagram-scale preparation of Julia–Kocienski reagent **2** and synthesis of starting materials. [Rh] = $[Rh(OAc)_2]_2$, DIAD = diisopropyl azodicarboxylate, [Mo] = ammonium molybdate tetrahydrate.

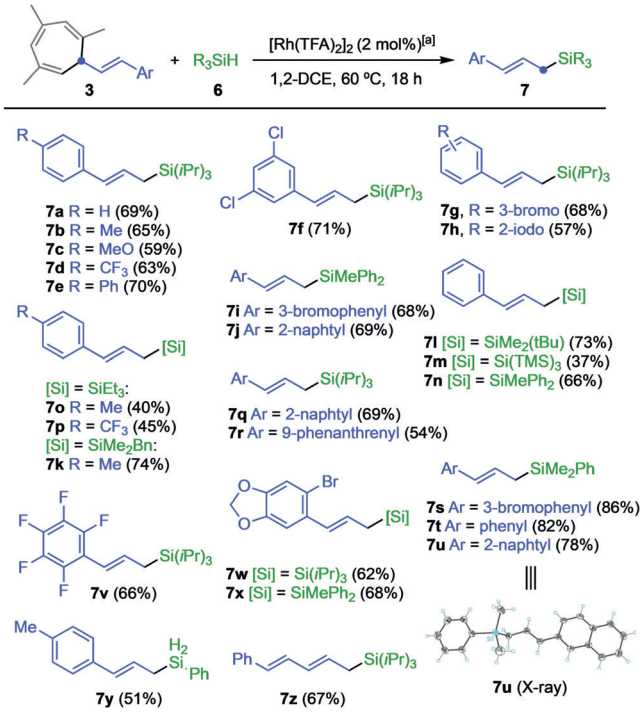
The retro-Buchner-cyclopropanation from **3a** could be carried out at 25 °C, but longer times were required, and slightly lower yields were obtained than by performing the reaction at 60 °C for 18 h in 1,2-DCE (1,2-dichloroethane), which were selected as standard conditions.[18] We compared this novel Rh^{II}-catalyzed retro-Buchner-cyclopropanation protocol to the ones previously reported based on Au^{I} or Zn^{II} catalysis (Scheme 3).[14]

The Au^{I}-based system shines on the cyclopropanation of styrenes or related activated alkenes (**5a**, **5b**), but performs poorly with unactivated alkenes (**5c–e**) (Scheme 3). The Zn^{II}-based system complemented Au^{I} by allowing an efficient cyclopropanation of these simple alkenes, but failed when substrates bearing coordinating atoms were employed (**5b**). The new Rh^{II}-based system often performed better, both in terms of yield and selectivity, across all the different types of substrates, resulting in a more general method for the *cis*-vinylcyclopropanation of alkenes. Interestingly, electron-rich carbenes (**5g**, **5i**), which are the most problematic using Au^{I},[12b] give remarkable levels of diastereoselectivity.

We found that the styryl rhodium carbenes could be efficiently trapped with silanes R_3SiH to give allylsilanes. This represents the first example of an intermolecular Si–H insertion reaction of a metal carbene generated through a retro-Buchner reaction (Scheme 4). Using only 2 mol% of $[Rh(TFA)_2]_2$, 7-styryl-1,3,5-trimethyl-1,3,5-cycloheptatriene **3a** reacted with triisopropylsilane to give **7a** in 69% yield.[17] Gold(I) complexes failed to promote this transformation, highlighting the difference in reactivity between Au^{I} and Rh^{II} carbenes. This synthetic methodology turned out to be very general (Scheme 4), affording the corresponding



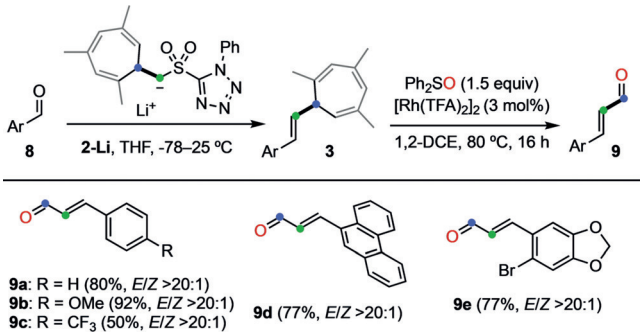
Scheme 3. Reactivity comparison of the new Rh^{II} carbenes with analogous Au^{I} and Zn^{II} intermediates and scope of the *cis*-cyclopropanation reaction. Yields are for isolated products. The *cis* or *endo* product is the major one in all cases, the obtained ratio is shown in brackets. [a] New **[Rh]** conditions: **3** (0.1 M in 1,2-DCE) with 4 equiv of **4**, 3 mol% of $[Rh(TFA)_2]_2$ at 60 °C for 16 h. [b] Previously reported **[Au]** conditions:[13] **3** (0.1 M in EtOAc) with 1.5 equiv of **4**, 5 mol% of [(JohnPhos)Au(MeCN)]SbF_6 at 25 °C for 24 h. [c] Previously reported **[Zn]** conditions:[13] **3** (0.1 M in 1,2-DCE) with 4 equiv of **4**, 10 mol% of $ZnBr_2$ at 65 °C for 40 h. [d] At 50 °C for 20 h.



Scheme 4. Synthesis of allylsilanes by Si–H insertion of donor Rh^{II} carbenes. The yields are for isolated products. [a] Reaction of **3** (0.1 M in 1,2-DCE) with 4 equiv of **6**, 2 mol% of $[Rh(TFA)_2]_2$ at 60 °C for 16 h.

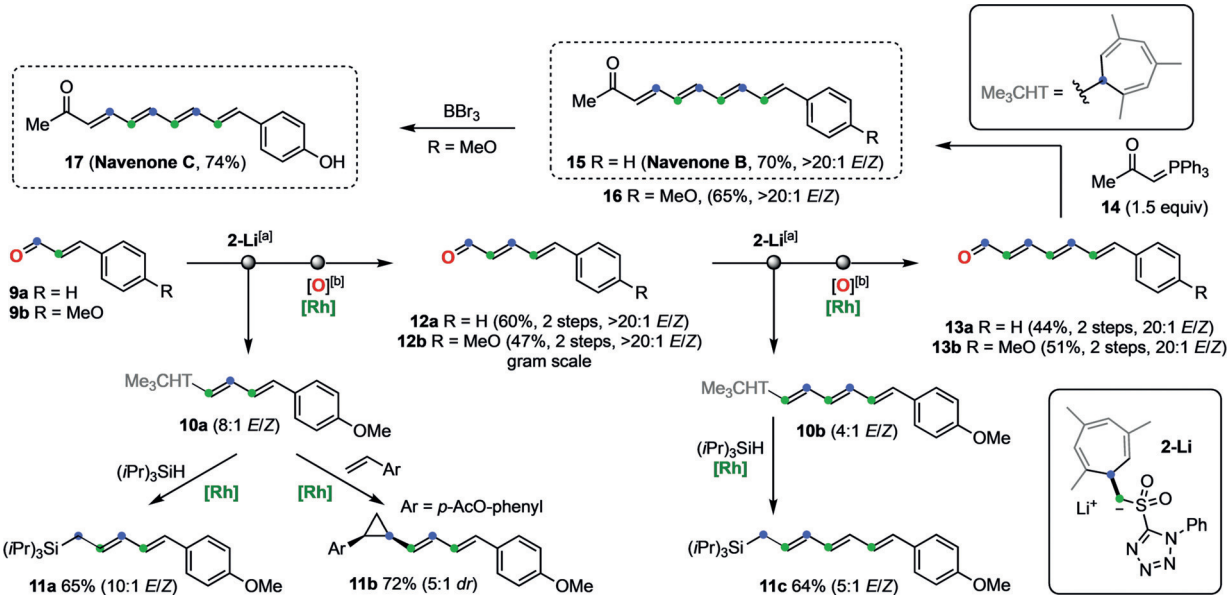
allylsilanes in good yields across a wide range of cycloheptatrienes, bearing both electron-poor and electron-rich substituents in different positions of the aromatic ring (**7a–e**). Halides, from fluoride to iodide, were tolerated (**7f–h**, **7v**), and it was possible to transfer polyarene units such as naphthalene and phenanthrene (**7q**, **7r**). Dienyl silane **7z** was also obtained in 67% yield using the same reaction conditions. The scope of the reaction is also broad in terms of the silane group, allowing to perform the Si–H insertion in substrates as bulky as $(TMS)_3SiH$ (**7m**). Selective mono-insertion could also be carried out in a primary silane, $PhSiH_3$ (**7y**).

We also discovered that the reaction of 7-styryl-1,3,5-trimethyl-1,3,5-cycloheptatriene with diphenylsulfoxide, in the presence of $[Rh(TFA)_2]_2$, led cleanly to cinnamaldehyde (**9a**). This finding allowed to develop a two-step vinylogation of aldehydes. Thus, an *E*-diastereoselective Julia–Kocienski olefination of aldehydes **8a–e** with sulfone **2** gives cycloheptatrienes **3**, which were treated with 1.5 equiv of Ph_2SO in the presence of 3 mol% of $[Rh(TFA)_2]_2$ to assemble vinylogous aldehydes **9a–e** (Scheme 5).



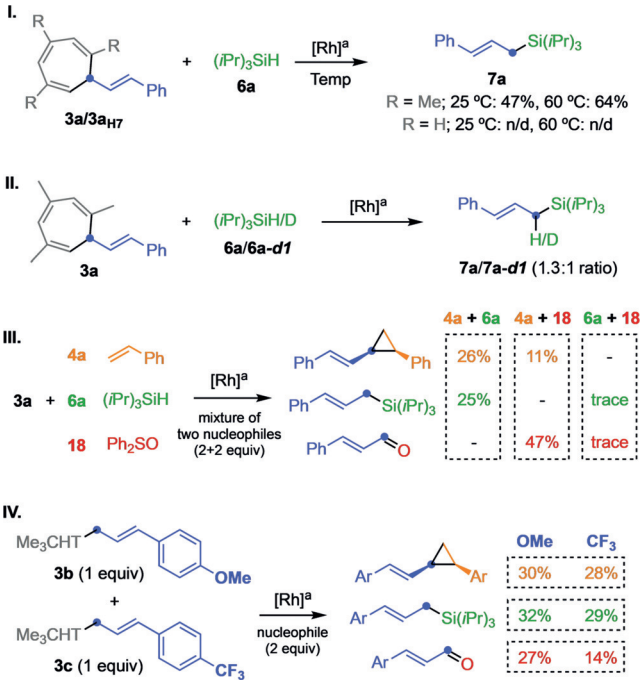
Scheme 5. Vinylogation of aldehydes via Julia–Kocienski olefination and Rh^{II}-catalyzed oxidative retro-Buchner reaction sequence. The yields are for isolated products.

Given that both the starting material and the product of this protocol are aldehydes, we envisioned that this sequence could be applied in an iterative manner. This iterative chain growth would deliver conjugated *E*-polyenes, a prevalent motif in Nature, present in hundreds of compounds which are relevant across a variety of biosynthetic pathways.[19] We decided to apply our iterative chain growth to the total synthesis of the navenones, a family of trail-breaking pheromones from the marine opisthobranch *Navanax inermis*.[20] We prepared navenone B (**15**) in 5 steps from cinnamaldehyde, after two iterations of the same Julia–Kocienski olefination and retro-Buchner-oxidation sequence (Scheme 6). This process afforded trienal **13a** in 26% overall yield (4 steps) as the all-*E* diastereoisomer. The reaction of **13a** with 1.5 equiv of stabilized ylide **14** in toluene at 100 °C gave navenone B, as an intense yellow solid, in 70% yield with excellent diastereoselectivity. Similarly, submitting 4-methoxycinnamaldehyde **9b** to two vinylogation iterations, gave trienal **13b**, which after reaction with the same ylide (**14**) gave methyl-navenone C (**16**) in 65% yield. Treatment with BBr_3 allowed demethylation of **16**, affording navenone C (**17**) in 74% yield. Finally, we decided to merge this iterative process with the other two new methodologies based on Rh^{II} carbenes: cyclopropanation (Scheme 3) and Si–H insertion (Scheme 4). Following this idea, we showed how this strategy can be used for the synthesis of *E*-polyenes bearing not only aldehyde groups, but also silanes, and cyclopropanes. Thus, 7-polyenyl-1,3,5-trimethyl-1,3,5-cycloheptatrienes **10a** and **10b** provided polyenyl *cis*-cyclopropane **11b** or polyenyl silanes **11a** and **11c** in good yield and moderate to good diastereoselectivity (Scheme 6).



Scheme 6. Iterative chain growth through Julia–Kocienski olefination and Rh-catalyzed oxidative retro-Buchner reaction for the synthesis of conjugated all-*E* polyenes, total synthesis of navenones B and C, and diversification of intermediates. The yields are for isolated products.[a] Julia–Kocienski olefination, with 1.2 equiv of **2-Li** in THF (0.1 M), from −78 °C to 25 °C over 12 h.[b] Retro-Buchner-oxidation sequence, 1.5 equiv of Ph_2SO and 3 mol% of $[Rh(TFA)_2]_2$ in 1,2-DCE (0.1 M), at 80 °C for 16 h.

In order to gain mechanistic insight on these three new transformations, we performed different control and competition experiments (Scheme 7). Although cycloheptatriene **3a** undergoes the retro-Buchner and Si–H insertion sequence



Scheme 7. Mechanistic investigations. I) Comparison between first and second generation of cycloheptatrienes. II) Deuteration experiments and kinetic isotope effect. III) Competition experiments between each pair of nucleophiles. IV) Competition experiments between **3b** and **3c**.[a] Unless otherwise stated, 1 equiv of cycloheptatriene with 4 equiv of nucleophile were stirred in 1,2-DCE (0.1 M) at 60 °C for 16 h. Yields and ratios determined by ^{1}H NMR using Ph_2CH_2 as internal standard.

even at room temperature, performing the reaction with non-methylated analog **3a$_{H7}$** did not deliver a significant amount of product in the range between 25 and 100 °C (Scheme 7-I). The reaction of **3a** with an equimolar mixture of iPr$_3$SiH and iPr$_3$SiD gave the corresponding non-deuterated and deuterated allylsilane in a in a 1.3:1 ratio, respectively (Scheme 7, II), which is consistent with previously reported values for concerted metal carbene insertions in Si–H bonds.[17d,21]

Then, we compared the reactivity of a Rh^{II} carbene with the three studied nucleophiles: an alkene, a silane, and an oxidant (Scheme 7, III). For this purpose, three reaction mixtures were prepared, each one with a combination of two nucleophiles and 1 equiv of cycloheptatriene **3a**. We observed that the affinity of the carbene towards styrene and triisopropylsilane was identical. Mixing styrene with Ph_2SO, a 4:1 distribution was obtained, favoring the product of oxidative trapping over the cyclopropane. Finally, we studied the competition between **3b** and **3c**, bearing electron-rich and an electron-poor substituents at the *para* position of the styryl group for the three reactions (Scheme 7, IV). Significant differences were only observed in the oxidative trapping (2:1 ratio favoring the electron rich carbene). These results highlight the similar reactivity of carbenes with different electronic properties, accounting for the wide scope of these transformations.

In conclusion, we have developed a new method for the rhodium(II)-catalyzed decarbenation of 7-substituted 1,3,5-cycloheptatrienes, generating intermediates which display the typical reactivity of donor Rh^{II} carbenes. It is remarkable how, by tuning the substituents on the Rh^{II} carbene (from an acetate with EDA to a vinyl group with **3**), it is possible to achieve an opposite reactivity (from a Buchner ring expansion to a retro-Buchner-cyclopropanation) using exactly the same catalytic system, $[Rh(TFA)_2]_2$. These Rh^{II} carbenes react with a broad range of alkenes, resulting in an improved retro-Buchner-cyclopropanation sequence. The same intermediates also react with silanes, which represents the first example of an intermolecular insertion reaction of a metal carbene generated by retro-Buchner. Finally, we showed that it is possible to oxidatively trap these carbenes to give aldehydes, leading to the development of an iterative protocol for the vinylogation of aldehydes. This was applied to the preparation of conjugated *E*-polyenes and to the total synthesis of navenones B and C.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbenes · retro-Buchner reaction · rhodium catalysis · silanes · total synthesis

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