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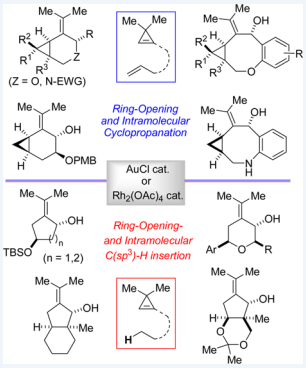
Intramolecular Cyclopropanation and C−H Insertion Reactions with Metal Carbenoids Generated from Cyclopropenes

Alexis Archambeau, Frédéric Miege, Christophe Meyer,* and Janine Cossy*

Laboratory of Organic Chemistry, Institute of Chemistry, Biology and Innovation (CBI), ESPCI ParisTech/CNRS (UMR8231)/PSL Research University 10 rue Vauquelin 75231 Cedex 05 Paris, France

CONSPECTUS: Activation of unsaturated carbon−carbon bonds by means of transition metal catalysts is an exceptionally active research field in organic synthesis. In this context, due to their high ring strain, cyclopropenes constitute an interesting class of substrates that displays a versatile reactivity in the presence of transition metal catalysts. Metal complexes of vinyl carbenes are involved as key intermediates in a wide variety of transition metal-catalyzed ring-opening reactions of cyclopropenes. Most of the reported transformations rely on intermolecular or intramolecular addition of nucleophiles to these latter reactive species. This Account focuses specifically on the reactivity of carbenoids resulting from the ring-opening of cyclopropenes in cyclopropanation and C−H insertion reactions, which are arguably two of the most representative transformations of metal complexes of carbenes.



Compared with the more conventional α-diazo carbonyl compounds, the use of cyclopropenes as precursors of metal carbenoids in intramolecular cyclopropanation or C−H insertion reactions has been largely underexploited. One of the challenges is to devise appropriately substituted and readily available cyclopropenes that would not only undergo regioselective ring-opening under mild conditions but also trigger the subsequent desired transformations with a high level of chemoselectivity and stereoselectivity. These goals were met by considering several substrates derived from the readily available 3,3-dimethylcyclopropenylcarbinols or 3,3-dimethylcyclopropenylcarbinyl amines. In the case of 1,6-cyclopropene-enes, highly efficient and diastereoselective gold(I)-catalyzed ring-opening/intramolecular cyclopropanations were developed as a route to diversely substituted heterocycles and carbocycles possessing a bicyclo[4.1.0]heptane framework.

The use of rhodium(II) catalysts enabled us to widen the scope of this transformation for the synthesis of medium-sized heterocyclic scaffolds incorporating an eight-membered ring. The reactivity of rhodium(II) carbenoids generated from 3,3-dimethylcyclopropenylcarbinols was also investigated in intramolecular C(sp^3)−H insertions. Despite their low electrophilic character, these purely donor rhodium(II) carbenoids underwent remarkably efficient diastereoselective 1,5- or 1,6-C−H insertions allowing access to a wide variety of substituted cyclopentanols, cyclohexanols, bicycloalkanols, and tetrahydropyrans with high level of diastereoselectivity and with complete tolerance of a free hydroxyl group. The products arising from the gold(I)- or rhodium(II)-catalyzed ring-opening/intramolecular cyclopropanation or C−H insertion of 3,3-dimethylcyclopropenylcarbinols or 3,3-dimethylcyclopropenylcarbinyl amines always incorporate an isopropylidene moiety, which can potentially undergo subsequent oxidative cleavage into a carbonyl group without epimerization. By virtue of this operation, the 3,3-dimethylcyclopropenyl group formally behaves as a valuable surrogate for an α-diazoketone, with obvious advantages considering the ease of access to the corresponding substrates and that no hazardous reagents are involved in their preparation.

These studies have set a useful basis for the development of other reaction pathways involving metal carbenoids generated from these readily available families of substituted cyclopropenes, including the investigation of the yet underexploited synthetic potential of purely donor rhodium(II) carbenoids.

1. INTRODUCTION

The fascinating versatile reactivity of cyclopropenes in transition metal-catalyzed reactions has captured the attention of organic chemists for more than half a century.[1] These strained carbocycles can be involved in reactions that do not break the three-membered ring to produce highly substituted cyclopropenes, cyclopropanes, or alkylidene cyclopropanes or in transformations accompanied by ring cleavage.[1] Reactions in this latter category appear diverse at first sight. However, if metathesis reactions (initiated by ring-opening with a metal carbene) are left aside,[2] most of the other transition metal-catalyzed ring-opening reactions involve metal complexes of vinyl carbenes **A** as reactive intermediates, generated from the π-complexes **B**.[1] Carbenoids **A** are also described by their second resonance form corresponding to metal-stabilized allylic carbocations **A′**, the carbon−metal bond order being modulated by the substituents as well as by the ligands of the metal.[3,4] An alternative pathway for the ring-opening of cyclopropenes relies on the oxidative addition of a low valent transition metal into a σ-bond to generate metallacyclobutenes **C**. These latter species have been suggested as intermediates in transition metal-catalyzed cycloadditions involving cyclopropenes,[5] but it is worth noting that metallacyclobutenes **C** can

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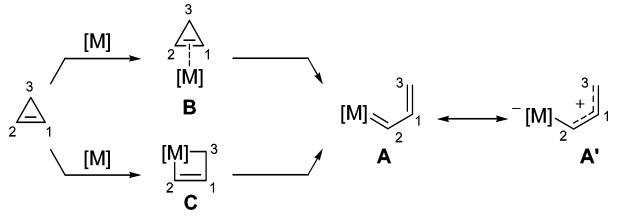
also potentially generate carbenoids **A** by cycloreversion (Scheme 1).

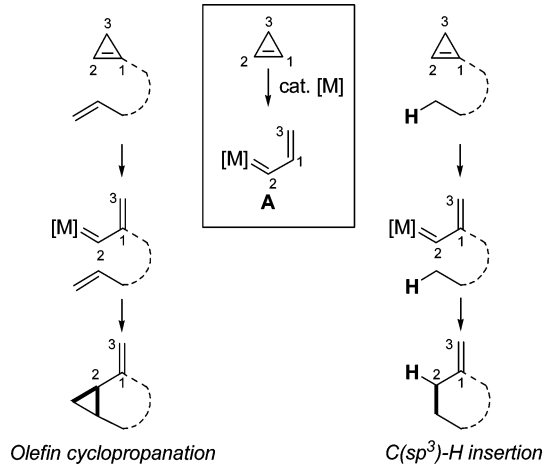
Scheme 1. Ring-Opening of Cyclopropenes with Transition Metal Catalysts[a]



[a][M] = Transition metal complex.

Cyclopropenes possessing a nucleophilic group at C3 have been widely used as substrates in transition metal-catalyzed reactions because the intermediate vinyl carbenoids **A** can be captured intramolecularly by a nucleophile. Representative transformations include the isomerization of 3-arylcyclopropenes into indenes,[6−8] 3-alkenylcyclopropenes into cyclopentadienes,[9] 3-acylcyclopropenes into furans,[10,11] and 3-(pyridin-2-yl)cyclopropenes into indolizines.[12] In recent years, intermolecular nucleophilic additions to 3,3-disubstituted cyclopropenes proceeding with concomitant ring-opening have been reported, and gold(I) complexes have emerged as useful catalysts.[11,13] In this Account, we will specifically focus on the reactivity of metal carbenoids **A** in cyclopropanation and C(sp^3)−H insertion reactions, which are undoubtedly two of the most representative reactions triggered by metal carbenoids (Scheme 2).[14−16]

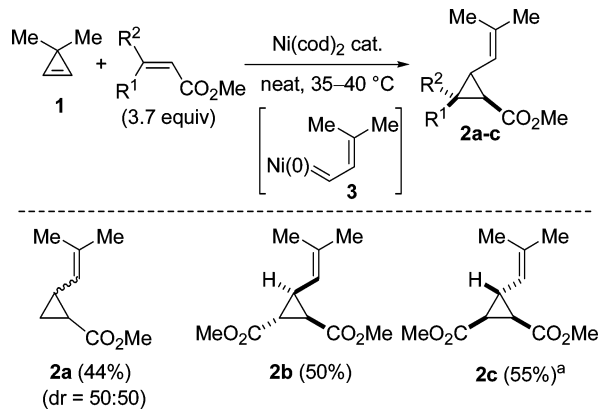
Scheme 2. Olefin Cyclopropanation and C(sp^3)−H Insertion with Metal Carbenoids Generated from Cyclopropenes



2. OLEFIN CYCLOPROPANATION WITH METAL CARBENOIDS GENERATED FROM CYCLOPROPENES

In the 1970s, the reactivity of cyclopropenes in transition metal-catalyzed homo- and co-oligomerizations was extensively investigated.[1a] Binger and McMeeking observed that codimerization of 3,3-dimethylcyclopropene **1** with methyl acrylate, dimethyl fumarate, or dimethyl maleate in the presence of a nickel(0) catalyst proceeded with ring-opening and generated vinylcyclopropanes **2a**, **2b**, and **2c**, respectively, in moderate yields (44−55%).[17] The formation of **2a−c** was explained by ring-opening of cyclopropene **1** followed by intermolecular cyclopropanation of the olefins with the organonickel carbenoid **3**. Dimethyl fumarate and maleate led to diastereomeric trisubstituted cyclopropanes **2b** and **2c**, thereby indicating a stereospecific intermolecular cyclopropanation. Observation of byproduct **2b** in the latter case was explained by partial isomerization of the olefin by the nickel catalyst prior to cyclopropanation (Scheme 3).

Scheme 3. Ni-Catalyzed Ring-Opening of 3,3-Dimethylcyclopropene and Intermolecular Cyclopropanation of Electron-Deficient Alkenes

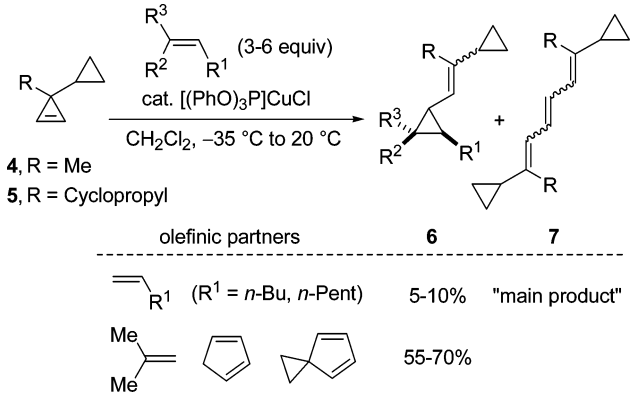


[a]Compound **2b** (6%) was detected.

The intermolecular cyclopropanation of olefins lacking an electron-withdrawing group with cyclopropenes **4** and **5** has been investigated using a Cu(I) catalyst.[18] Although the results and the stereochemical aspects of the reactions were not detailed, the authors reported that terminal olefins produced the corresponding vinylcyclopropanes **6** in low yield (5−10%) due to competitive dimerization of the copper carbenoid intermediate leading predominantly to trienes **7**. Moderate yields of the corresponding vinylcyclopropanes **6** (55−70%) were obtained with isobutene, cyclopentadiene, and spiro[2,4]-heptadiene (Scheme 4).[18]

Compared with α-diazocarbonyl compounds, the synthetic interest of cyclopropenes as precursors of metal carbenoids in catalytic intermolecular cyclopropanation of olefins appears

Scheme 4. Cu-Catalyzed Ring-Opening of Cyclopropenes and Intermolecular Cyclopropanation of Alkenes



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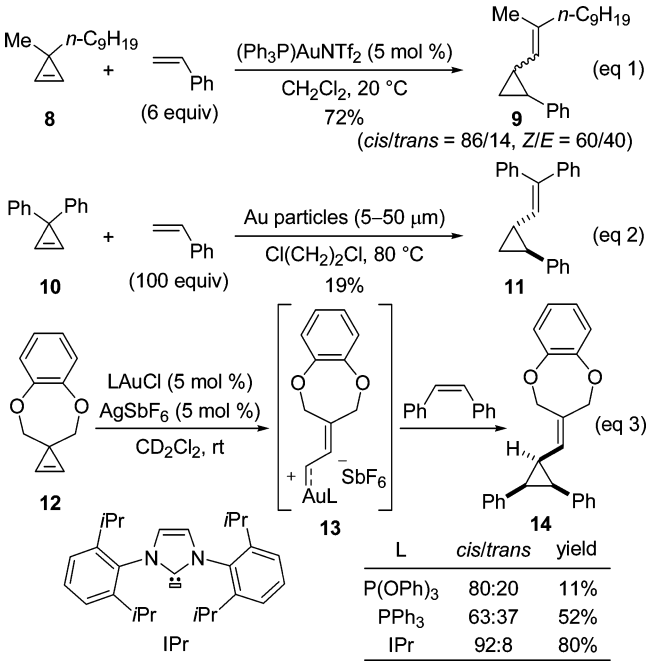
limited.[14,15] Nevertheless, cyclopropanation remains often used as a test reaction to probe the carbenic character of organometallic species generated from cyclopropenes. Thus, Lee et al. disclosed one example of intermolecular cyclopropanation of styrene with the gold carbenoid generated from cyclopropene **8** that led to vinylcyclopropane **9** as a mixture of stereoisomers (Scheme 5, eq 1).[11] Angelici, Woo et al. observed

Scheme 5. Intermolecular Cyclopropanation of Olefins with Gold Carbenoids Generated from Cyclopropenes



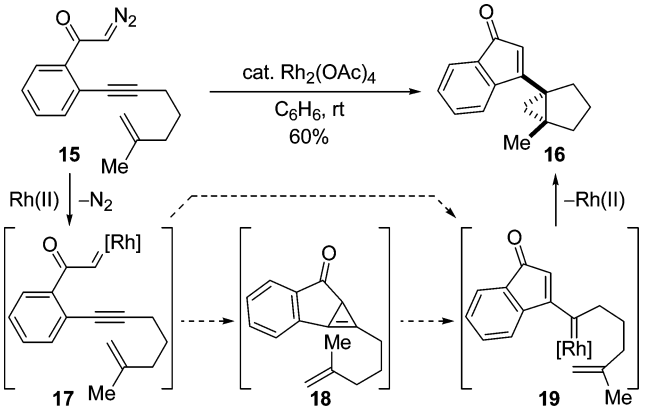
L	*cis*/*trans*	yield
$P(OPh)_3$	80:20	11%
PPh_3	63:37	52%
IPr	92:8	80%

that 3,3-diphenylcyclopropene **10** in the presence of a large excess of styrene and metallic gold particles led to the *trans*-1,2-disubstituted cyclopropane **11** albeit in low yield (Scheme 5, eq 2).[19] Toste et al. devised an experiment wherein the efficiency of the intermolecular cyclopropanation of (*Z*)-stilbene enabled the evaluation of the impact of the ligand on the structure of gold carbenoid **13** generated from cyclopropene **12**. The highest yield of cyclopropane **14** was obtained with the strong σ-donor and weak π-acceptor IPr ligand due to a high carbene character for the organogold **13**. By contrast, ligands possessing a higher π-acidic or a weaker σ-donating character led to lower yields of **14** (Scheme 5, eq 3).[4]

Examples of intramolecular cyclopropanation of olefins with metal carbenoids generated from cyclopropenes were surprisingly scarce. Padwa, Hoye, and co-workers observed the formation of bicyclo[*n*.1.0]alkanes during their exploration of the reactivity of ω-acetylenic α-diazo ketones containing 1,6- or 1,7-enynes in the presence of transition metals.[20,21] Thus, the Rh-catalyzed reaction of α-diazo acetophenone **15** afforded cyclopropane **16**, by intramolecular cyclopropanation of the remote alkene with the rhodium carbenoid **19**. If the latter species arose from a metathesis reaction of the initially generated α-oxo carbenoid **17** with the alkyne or from the ring-opening of a highly strained cyclopropene intermediate **18** formed by intramolecular cyclopropenation of the alkyne was however not unambiguously addressed (Scheme 6).[20]

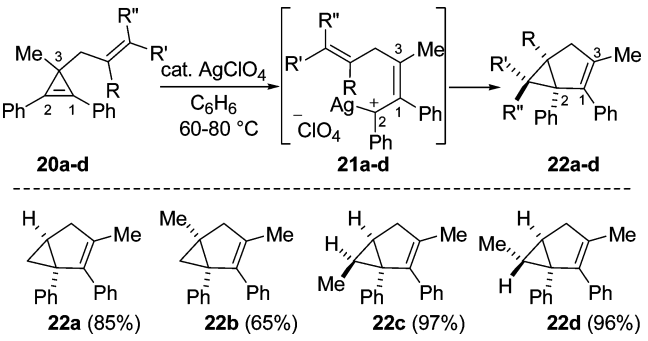
The only examples of intramolecular olefin cyclopropanation with carbenoids generated from stable isolated cyclopropenes were reported by Padwa et al.[22] Treatment of 1,2-

Scheme 6. Rh-Catalyzed Reaction of α-Diazo γ-Acetylenic Ketone 15



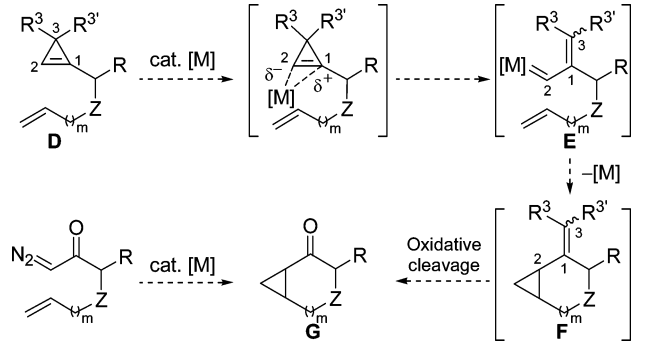
diphenylcyclopropenes **20a–d** possessing a methyl and an allyl group at C3 with $AgClO_4$ in benzene at 60–80 °C delivered the bicyclic alkenes **22a–d** by intramolecular olefin cyclopropanation via silver carbenoids **21a–d** (Scheme 7).

Scheme 7. Ag-Catalyzed Rearrangement of Cyclopropenes 20a–d



To expand the synthetic interest of the intramolecular cyclopropanation of olefins with metal carbenoids generated from cyclopropenes, we became interested in the reactivity of cyclopropene-enes **D** (Scheme 8). For these latter substrates, we hypothesized that coordination of an electrophilic transition metal complex should result in the development of a partial positive charge at the more substituted carbon (C1) thereby resulting in regioselective ring-opening to vinyl carbenoids **E**. After intramolecular cyclopropanation of the remote alkene,

Scheme 8. Transition Metal-Catalyzed Rearrangement of Cyclopropene-Enes D



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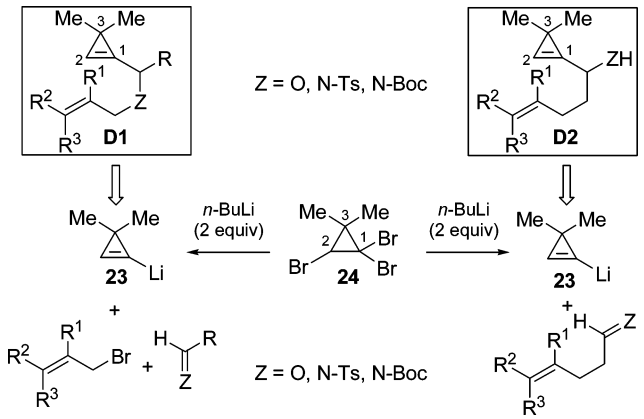
bicyclo[*n*.1.0]alkanes **F** should be obtained. As oxidative cleavage of the exocyclic alkene in compounds **F** could generate bicyclic ketones **G**, the cyclopropene in substrates **D** would behave as a surrogate for an α-diazo ketone (Scheme 8).

The single substituent on the double bond at C1 entailed that at least one substituent at C3 should be present to handle stable cyclopropenes **D**. To avoid mixtures of geometric isomers, two identical groups should be present at C3. Because the exocyclic olefin in bicyclic compounds **F** would eventually undergo oxidative cleavage, a simple *gem*-dimethyl substitution was selected at C3 and two families of readily available substrates were considered. The first one involves 1,6-cyclopropene-enes **D1**, prepared by addition of organolithium **23** (generated *in situ* from 1,1,2-tribromocyclopropane **24** by treatment with *n*-butyllithium) to aldehydes (Z = O)[23] or to activated imines (Z = NTs, NBoc),[2e] followed by alkylation of the heteroatom with allylic bromides. The second class of 1,6-cyclopropene-enes **D2**, having the heteroatom located outside of the tether, would be prepared by addition of organolithium **23** to γ,δ-unsaturated aldehydes (or imines derived thereof) (Scheme 9).

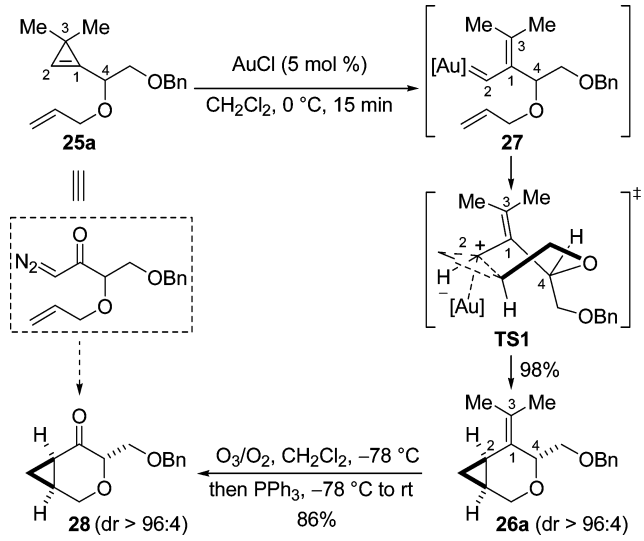
Scheme 9. Preparation of Cyclopropene-Enes D1 and D2



The transition-metal catalyzed rearrangement of 1,6-cyclopropene-enes **D1** was first investigated. A screening of catalysts revealed the remarkable activity of AuCl for the rearrangement of cyclopropene-ene **25a** into the 3-oxabicyclo[4.1.0]heptane **26a**, obtained as a single diastereomer in high yield under mild conditions.[24] As anticipated, cyclopropene **25a** underwent a regioselective ring-opening leading to the gold carbenoid **27** at the less substituted carbon (C2). Theoretical calculations later reported by Lee, McGregor et al.[25] and by Hyland, Ariafard et al.[26] supported the observed regioselectivity. Indeed, the gold-induced polarization of the cyclopropene C1−C2 bond is governed by the electronic properties of the substituents and notably by their relative π-donating abilities. The high diastereoselectivity observed in the intramolecular cyclopropanation was explained by a twist-boat transition state model **TS1**, in which the isopropylidene moiety forces the substituents at C2 and C4 to adopt pseudoaxial orientations to minimize $A^{1,3}$-strain. Ozonolysis of the isopropylidene moiety in **26a** delivered the 3-oxabicyclo[4.1.0]heptan-5-one **28** without epimerization (Scheme 10).

Related intramolecular cyclopropanation of α-allyloxy diazoketones has been reported. With Rh(II) catalysts, intramolecular 1,5-C−H insertion competed with cyclopropanation,[27,28] but the latter reaction took place in the presence of

Scheme 10. Au-Catalyzed Rearrangement of Cyclopropene-Ene 25a



a Pd(II) catalyst or a stoichiometric quantity of a Cu(II) promoter.[27] The scope of the gold-catalyzed rearrangement was explored with a variety of cyclopropenylcarbinyl ethers **25b−l**. The reaction accommodates linear or branched substituents at the α-position of the oxygen atom, as illustrated with the preparation of compounds **25b−c**. A decrease of the diastereoselectivity was observed in the rearrangement of a methallyl ether leading to **26d** but allylic ethers incorporating α,β- or β,β-disubstituted or α,β,β-trisubstituted olefins, afforded oxabicyclic compounds **26e,f**, **26g,h**, and **26i,l**, respectively, as single diastereomers in high yields. It is worth noting that the intramolecular cyclopropanation involves a stereospecific process (Scheme 11).

The reaction was extended to *N*-allyl cyclopropenylcarbinyl amine derivatives **29a−f**, which also underwent gold-catalyzed rearrangements into the corresponding 3-azabicyclo[4.1.0]-heptanes **30a−f**. The reaction is compatible with various electron-withdrawing groups on the nitrogen atom (Ts, Boc) and substituents at the α position. Interestingly, in the case of **29c**, the Boc group was cleaved *in situ* by addition of trifluoroacetic acid (TFA) to deliver the 3,4-methanopiperidine **30c** in good overall yield and excellent diastereoselectivity. A slight erosion of the diastereoselectivity was observed for the formation of **30d** (dr = 95:5), derived from a *N*-methallyl sulfonamide, as well as for **30e** arising from the cyclopropanation of an (*E*)-α,β-disubstituted alkene (dr = 90:10), but the corresponding geometric *Z*-isomer afforded **30f** as a single diastereomer (Scheme 12).[29]

The gold-catalyzed rearrangement of 1,6-cyclopropene-enes **D2** (Scheme 9) was then investigated to access substituted bicyclo[4.1.0]heptanols. For these substrates, AuCl was generally an inefficient catalyst in the presence of a free alcohol. In the case of **31**, the rearrangement took place using an *in situ* generated cationic gold(I) complex but was accompanied by transposition of the allylic alcohol to produce **32** (Scheme 13, eq 1). Protection of the alcohol as a TBS ether allowed the use of AuCl as a catalyst, as illustrated by the rearrangement of cyclopropene-ene **33** into the bicyclic compound **34** (Scheme 13, eq 2). The level of diastereoselectivity was not as high as in the gold-catalyzed rearrangement of cyclopropene-enes **D1** due to the lower steric hindrance of

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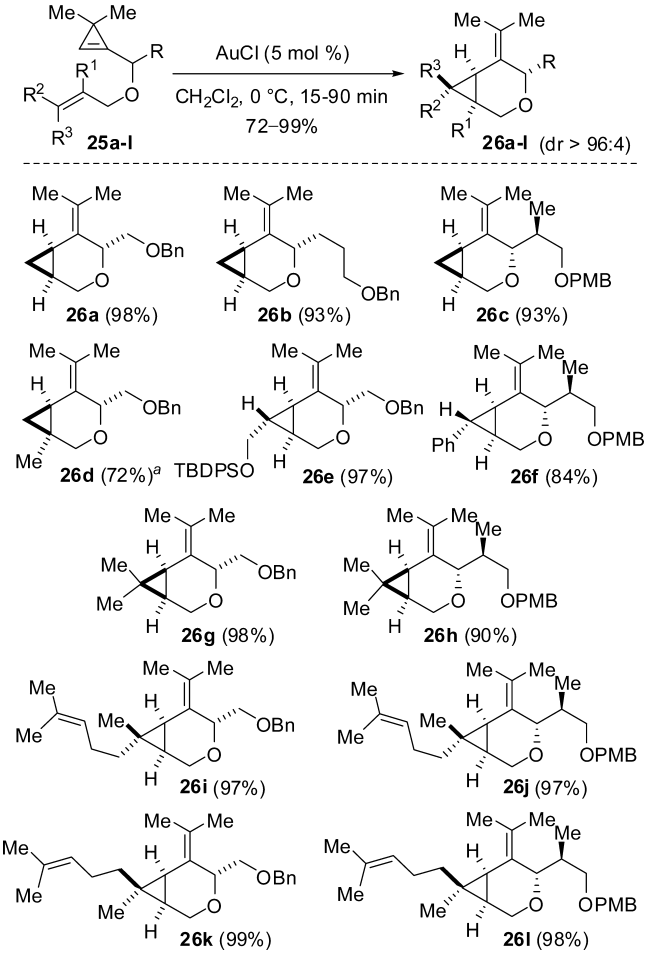
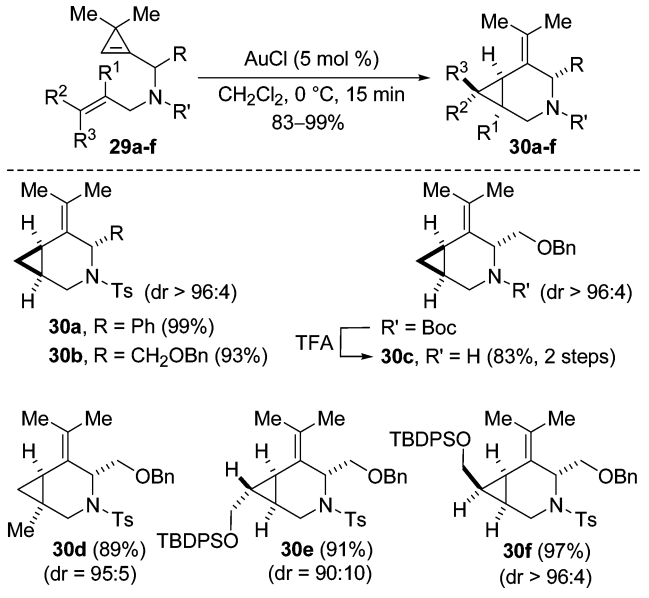
Scheme 11. Au-Catalyzed Rearrangement of 1,6-Cyclopropene-enes 25a–l



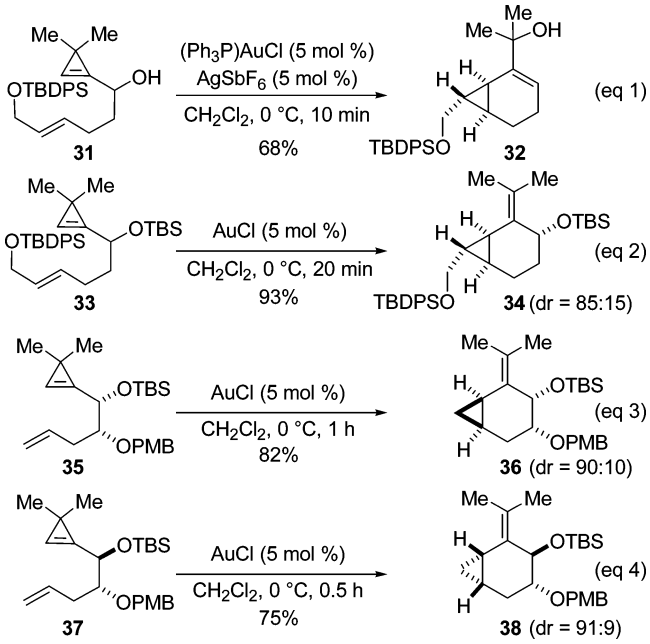
[a]Formed as an 87:13 mixture of diastereomers.

Scheme 12. Au-Catalyzed Rearrangement of 1,6-Cyclopropene-enes 29a–f



the silyloxy group compared with an alkyl or an aryl group. Nevertheless, good levels of diastereoselectivity were attained in

Scheme 13. Au-Catalyzed Rearrangement of 1,6-Cyclopropene-enes D2



the gold-catalyzed rearrangement of the epimeric 1,6-cyclopropene-enes **35** and **37**, which provided the orthogonally protected bicyclo[4.1.0]heptan-3,4-diols **36** and **38**, respectively (Scheme 13, eqs 3 and 4).[29]

As a logical extension, the construction of medium-sized rings was investigated. Initial results for the challenging formation of eight-membered rings were discouraging. Examples of formation of eight-membered rings by intramolecular cyclopropanation of alkenes with platinum or gold vinyl carbenoids, generated by rearrangement of propargylic esters, have been reported, but these cyclizations were facilitated either by a *gem*-dimethyl effect or a pre-existing ring.[30−32] Therefore, we investigated the reactivity of 1,8-cyclopropene-ene **39a** possessing an aromatic linker, prepared from salicylaldehyde. No gold complexes could be identified as suitable catalysts for the rearrangement of **39a** but in the presence $Rh_2(OAc)_4$, the tricyclic compound **40a** was obtained in quantitative yield with high diastereoselectivity.[33] Ozonolysis of **40a** produced the α-hydroxy ketone **41** without epimerization (Scheme 14).

The Rh-catalyzed rearrangement of 1,8-cyclopropene-enes **39b–l**, derived from substituted salicylaldehydes, accommodates a wide variety of substituents on the aromatic ring and on the allylic ether. The corresponding oxatricyclic compounds **40b–l** were obtained in excellent yields with high diastereoselectivity (Scheme 15).[33]

Neither the phenolic allylic ether nor the free alcohol were mandatory for the success of the reaction as illustrated with the successful formation of tricyclic compounds **42** and **43**, and only a slight decrease of the diastereoselectivity was observed for the latter compound. Replacement of the hydroxyl group by an *N*-Boc amino substituent is possible, although a longer reaction time was required, and subsequent cleavage of the Boc group *in situ* with TFA provided benzoxocane **44** possessing a free amine. The method was applied to the synthesis of benzazocane **45**, which was isolated after cleavage of the allyloxycarbonyl protecting group on the nitrogen by a Pd-

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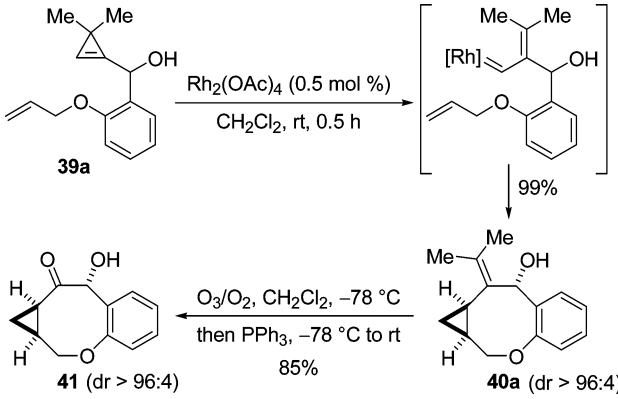
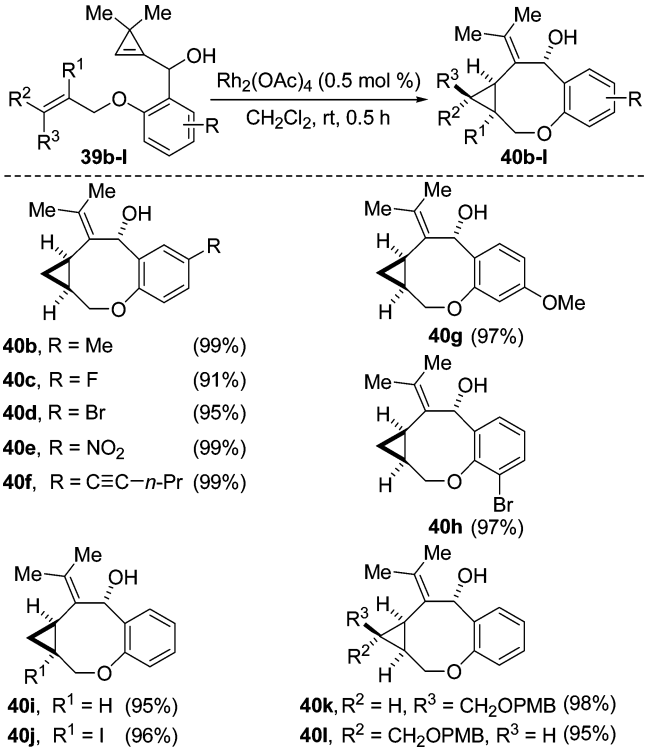
Scheme 14. Rh-Catalyzed Rearrangement of 1,8-Cyclopropene-ene 39a



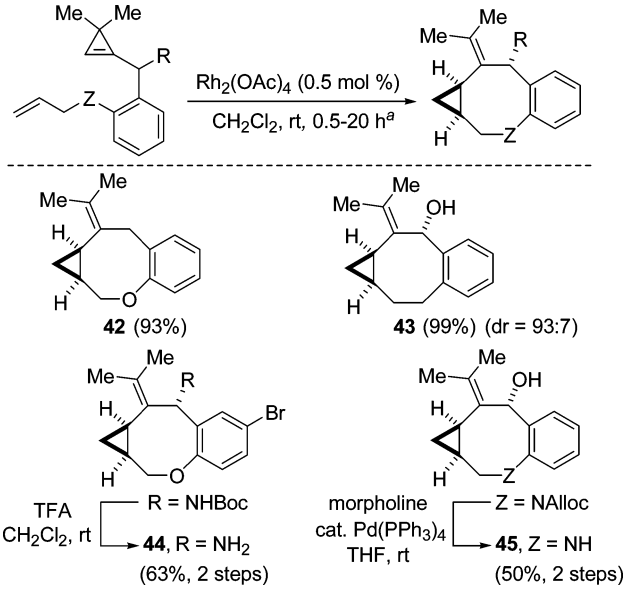
Scheme 15. Rh-Catalyzed Rearrangement of 1,8-Cyclopropene-enes 39b–l



catalyzed reaction. Although the Boc group was compatible with the Rh-catalyzed rearrangement, the nitrogen atom could not be deprotected under acidic conditions due to the sensitive alcohol at the benzylic and allylic position (Scheme 16).[33]

It is interesting to see that both gold and rhodium carbenoids generated by ring-opening of cyclopropenes can be involved in intramolecular olefin cyclopropanations. Recently, the first structures of reactive electrophilic carbenoids derived from both metals have been established.[34] However, the reason for the superiority of $Rh_2(OAc)_4$ as a catalyst for the rearrangement of 1,8-cyclopropene-enes derived from salicylaldehydes is unknown. Dirhodium(II) carbenoids are excellent reagents for olefin cyclopropanation and are usually generated from α-diazo carbonyl compounds.[14,15] The electronic properties of the substituents (π-acceptor/donor) have a marked impact on their reactivity in cyclopropanation and C–H insertion. In recent years, Davies et al. have highlighted the unique reactivity and

Scheme 16. Scope of the Rh-Catalyzed Rearrangement of 1,8-Cyclopropene-enes[a]



[a]Reaction times: 0.5–1 h for **42**, **43**, and **45** and 20 h for **44**.

synthetic utility of donor–acceptor rhodium carbenoids.[16c–f] Our results demonstrated that rhodium(II) carbenoids generated from 3,3-dimethylcyclopropenylcarbinols exhibit a high reactivity in intramolecular olefin cyclopropanation. These "donor" rhodium carbenoids, which have a lower electrophilic character compared with those substituted by an acceptor group, tolerate the presence of the free hydroxyl group and their reactivity in intramolecular C(sp^3)–H insertions appeared to be worth investigating.

3. CATALYTIC C(sp^3)–H INSERTION REACTIONS WITH RHODIUM CARBENOIDS GENERATED FROM CYCLOPROPENES

Products arising from the insertion of rhodium carbenoids, resulting from the ring-opening of isolated cyclopropenes, into C(sp^3)–H bonds have already been observed by Müller et al.[7] Substituted cycloprop-2-ene-1-carboxylates were synthesized by intermolecular cyclopropenation of alkynes with ethyl diazoacetate in the presence of $Rh_2(OAc)_4$ but did not undergo ring-opening under the conditions used for their preparation (CH_2Cl_2, rt). However, slow addition of cyclopropenyl esters **46**–**48** to a refluxing benzene solution of the electrophilic rhodium perfluorobutyrate [$Rh_2(pfb)_4$] catalyst led to mixtures of compounds containing products **49**–**51**, arising from ring-opening and intramolecular 1,5-C(sp^3)–H insertions. The yields were low due to the formation of unidentified nonvolatile byproducts and competitive 1,6-C–H insertion in the case of **46**, as well as Büchner reaction leading to cycloheptatrienes (either with benzene or with the remote phenyl group for **47**).[7] A good yield of the five-membered ring **51** (53%) was obtained from cyclopropene **48** because insertion took place at the α position of an oxygen atom, able to stabilize the developing adjacent positive charge in the transition state (Scheme 17).[16]

Having observed that 3,3-dimethylcyclopropenylcarbinols can participate in rhodium-catalyzed ring-opening/intramolecular cyclopropanation reactions, the possibility to achieve intramolecular C(sp^3)–H insertions was investigated with substrates **52a**–**d**. For compound **52a** bearing an *n*-hexyl

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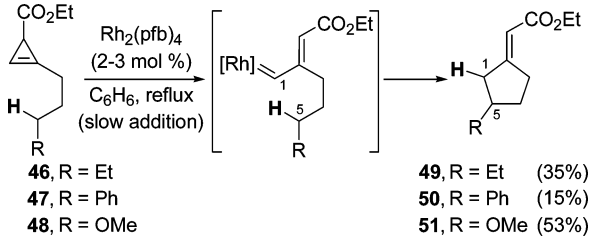
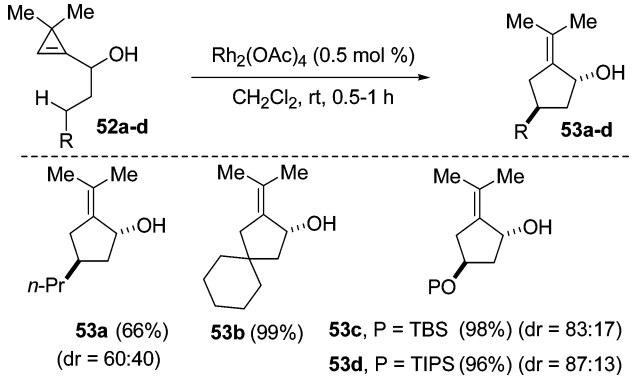
Acc. Chem. Res. 2015, 48, 1021–1031

Scheme 17. Rh-Catalyzed Reaction of Cycloprop-2-enyl Carboxylates 46-48



chain, cyclopentanol **53a** arising from ring-opening/intramolecular 1,5-C−H insertion was obtained in moderate yield and with low diastereoselectivity. The Rh-catalyzed rearrangement of cyclopropene **52b** possessing a cyclohexylmethyl group afforded spirocyclic compound **53b** in quantitative yield. The 1,5-C−H insertion occurs more favorably at a methine than at a methylene group. Insertion at the adjacent position of a silyloxy group also improved the efficiency of the reaction, as illustrated by the formation of the monoprotected cyclopentane-1,3-diols **53c** and **53d**, with diastereoselectivities reflecting the relative steric hindrance of the silyloxy groups (Scheme 18).[35]

Scheme 18. 1,5-C−H Insertion with Donor Rhodium Carbenoids

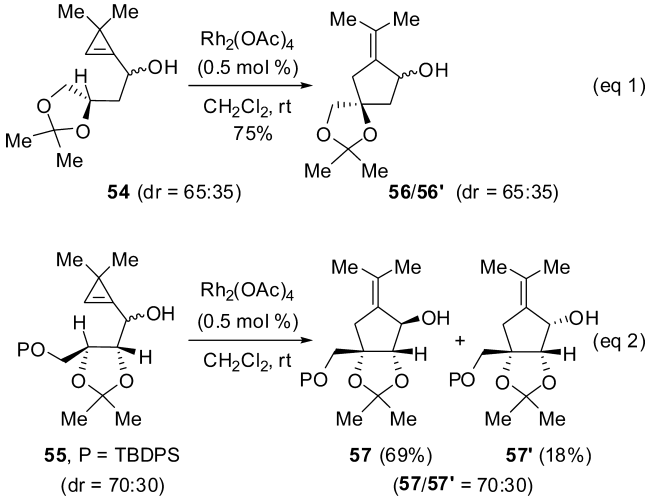


The excellent results observed for the insertion of donor rhodium carbenoids into tertiary C−H bonds or at an adjacent position of an oxygen atom led us to investigate the reactivity of substrates where both effects would act synergistically (Scheme 19).

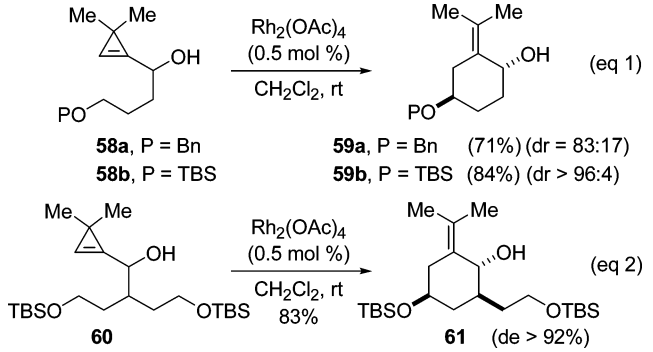
Cyclopropenylcarbinols **54** and **55** were synthesized as diastereomeric mixtures by addition of 3,3-dimethylcyclopropenyllithium to the corresponding aldehydes. The rhodium-catalyzed rearrangement of these substrates delivered the separable diastereomeric spirocycles **56**/**56′** (Scheme 19, eq 1) and the fused bicyclic compounds **57**/**57′** (Scheme 19, eq 2), respectively, in ratios reflecting the diastereomeric purity of the substrates. The intramolecular 1,5-C−H insertions occur with retention of configuration at the reacting carbon.[36]

Interestingly, Rh-catalyzed intramolecular 1,6-C−H insertion at the adjacent position of an oxygen atom can be triggered by rhodium carbenoids generated from 3,3-dimethylcyclopropenylcarbinols. The reactions proceeded efficiently for **58a** and **58b** and delivered the monoprotected 2-isopropylidenecyclohexane-1,4-diols **59a** and **59b** with moderate to high diastereocontrol, depending on the remote ether (Scheme 20, eq 1). The Rh-catalyzed rearrangement of cyclopropenylcarbi-

Scheme 19. 1,5-Insertion of Rhodium Carbenoids into Tertiary C−H Bonds Adjacent to an Oxygen Atom



Scheme 20. 1,6-C−H Insertion with Donor Rhodium Carbenoids



nol **60**, which led to cyclohexanol **61** possessing three stereocenters as a single diastereomer, constitutes an interesting example wherein a new stereogenic center is formed during the 1,6-C−H process, which discriminates two diastereotopic methylene groups (Scheme 20, eq 2). Formation of a single diastereomer among the four possible was observed by ^{1}H NMR spectroscopy (de > 92%).[35]

Capitalizing on the possibility to achieve a stereoselective C−H insertion at diastereotopic methylene groups, new access to bicyclic cycloalkanols was devised using cyclopropenylcarbinols derived from cycloalkanecarboxaldehydes. The Rh-catalyzed rearrangement of cyclopropene **62** led to bicyclo[3.3.0]octan-2-ol **63** having a *cis* ring junction (Scheme 21, eq 1). By contrast, the higher homologue **64** afforded a 65:35 mixture of *trans*- and *cis*-hydrindanes **65** and **65′** (Scheme 21, eq 2). Interestingly, when a methyl group was present on the six-membered ring, the rhodium-catalyzed reaction of **66** selectively led to *cis*-hydrindane **67** (Scheme 21, eq 3).[35] Davies et al. have shown that reactions involving donor−acceptor rhodium carbenoids lead to a relatively late transition state due to their higher stabilities compared with acceptor−acceptor or acceptor carbenoids.[37] It is thus likely that 1,5-C−H insertions triggered by the even more stable donor rhodium carbenoids generated from 3,3-dimethylcyclopropenylcarbinols involve a late product-like transition state. This is illustrated by the fact that the stereochemical outcome of the reaction of cyclopropenylcarbinols **64** and **66** parallels the known relative stabilities of *cis*- and

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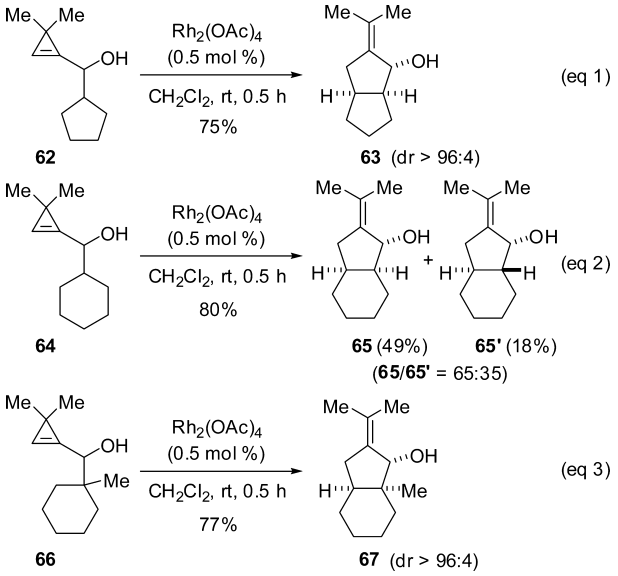
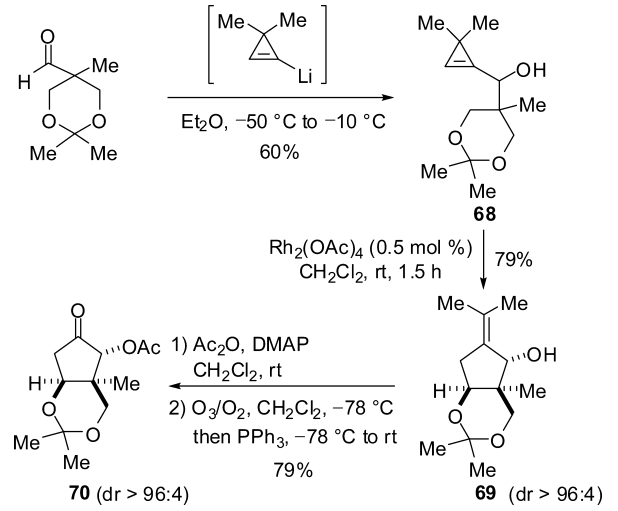
Scheme 21. Bicyclic Compounds from Cyclopropenylcarbinols by 1,5-C−H insertion



trans-hydrindanes, depending on whether a methyl group is present at the ring junction.[38]

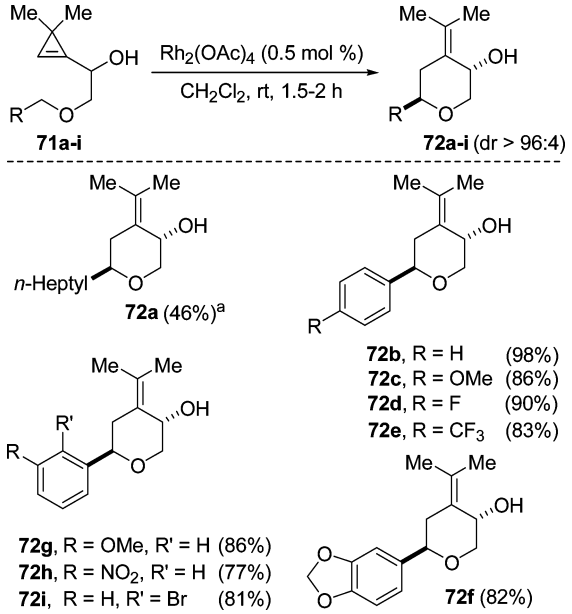
A high diastereoselectivity was observed in the rhodium-catalyzed rearrangement of cyclopropenylcarbinol **68** in which the six-membered ring is a cyclic ketal. The resulting bicyclic compound **69** was subjected to ozonolysis, after acetylation of the alcohol, to obtain the highly substituted cyclopentanone **70** possessing a quaternary stereocenter (Scheme 22).[35]

Scheme 22. Synthesis of the Cyclopentanone 70 from Cyclopropenylcarbinol 68



C−H insertion reactions triggered by donor rhodium carbenoids generated from cyclopropenes also offer the possibility to access heterocyclic compounds. In particular, cyclopropenylcarbinols **71a−i** synthesized from α-alkoxy aldehydes appeared to be suitable substrates for the synthesis of tetrahydropyrans. The location of the oxygen atom prevents the 1,5-C−H insertion process and also favors the 1,6-C−H insertion at the adjacent position. A sluggish reaction was observed in the case of the alkyl ether **71a** leading to tetrahydropyran **72a** in modest yield. Better results were obtained with cyclopropenes **71b−i** for which the 1,6-C−H insertion occurs at a benzylic position. Regardless of the substituents on the aromatic ring, aryl tetrahydropyranols **72b−i** were obtained in high yields and as single diastereomers (Scheme 23).

Scheme 23. Tetrahydropyrans by Intramolecular 1,6-C−H Insertions



[a]With $Rh_2(OAc)_4$ (1.5 mol %, CH_2Cl_2, rt, 8 h).

Because the isopropylidene group can be converted into a carbonyl, the sequence devised for the preparation of tetrahydropyrans **72b−i** could represent an interesting entry to aryl-C-glycosides.[39] These compounds are generally substituted at both adjacent positions of the cyclic oxygen atom and the reactivity of epimeric cyclopropenylcarbinols **73a** and **73b** was therefore investigated. Whereas the rhodium-catalyzed rearrangement of **73a** into tetrahydropyran **74a** could not be achieved, the rearrangement of epimer **73b** proceeded readily and afforded the trisubstituted tetrahydropyran **74b** (83%) having a 2,6-*cis* relative configuration. Subsequent ozonolysis led to tetrahydropyranone **75** and the overall sequence therefore constitutes an entry to aryl-C-glycosides derived from D-olivose, which are found in bioactive compounds such as the cytotoxic natural product aciculatinone (Scheme 24).[40]

4. CONCLUSION

Gold- or rhodium-catalyzed reactions of substituted 3,3-dimethylcyclopropenes in which the vinyl metal carbenoids, generated by regioselective ring-opening, trigger an intramolecular cyclopropanation and C−H insertion constitute interesting synthetic tools to access a wide variety of carbocycles and heterocycles. The preparation of the substrates is accomplished in a straightforward manner by addition of *in situ* generated 3,3-dimethylcyclopropenyllithium to aldehydes or activated imines. Most of the transition metal-catalyzed reactions investigated so far with these substrates occur with high levels of stereocontrol. Because the isopropylidene group, invariably encountered in products arising from intramolecular cyclopropanation and C−H insertion reactions, can be

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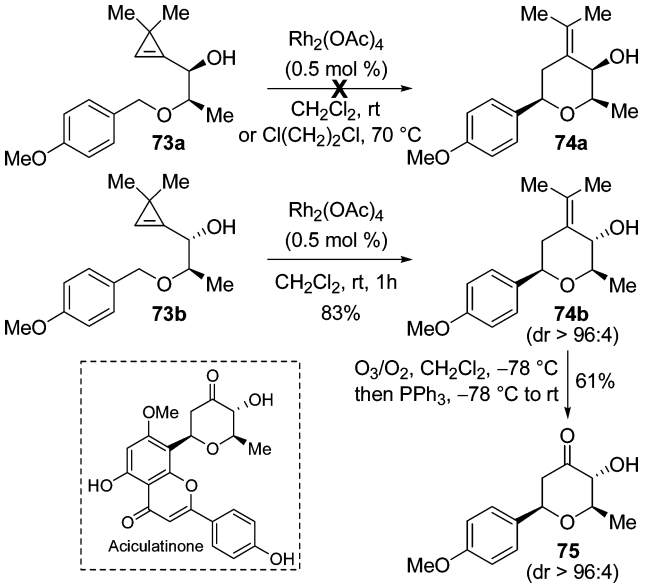
Scheme 24. Synthesis of Trisubstituted Tetrahydropyrans



eventually converted into a ketone without epimerization, the 3,3-dimethylcyclopropene moiety emerges as a useful synthetic equivalent of an α-diazoketone. Besides the expansion of the scope of the reported transformations for the synthesis of other classes of carbocycles and heterocycles, further research efforts will focus on the development of new reaction pathways in which metal carbenoids generated from readily available cyclopropenes can be involved.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: christophe.meyer@espci.fr.
*E-mail: janine.cossy@espci.fr.

Notes

The authors declare no competing financial interest.

Biographies

Alexis Archambeau graduated from the ESPCI ParisTech in 2010 and obtained his Ph.D. from University Pierre et Marie Curie (UMPC, Paris, France) in 2013 working on transition metal-catalyzed reactions involving cyclopropenes under the supervision of Dr. Christophe Meyer and Prof. Janine Cossy. He is currently a postdoctoral fellow in the group of Prof. Tomislav Rovis (Colorado State University, USA).

Frédéric Miege graduated from ESPCI ParisTech in 2008 and obtained his Ph.D. from UPMC in 2011, working on transition metal-catalyzed reactions of cyclopropenes under the supervision of Dr. Christophe Meyer and Prof. Janine Cossy (ESPCI ParisTech). After a two year postdoctoral stay in the group of Prof. Barry M. Trost (Stanford University, USA), he is currently working at Edelris (Lyon, France).

Christophe Meyer graduated from the Ecole Nationale Supérieure de Chimie de Paris in 1991 and received his Ph.D. from UPMC in 1994 under the supervision of Prof. Jean-François Normant and Dr. Ilan Marek. After a postdoctoral stay in the group of Prof. Mark Lautens (University of Toronto, Canada), he obtained a CNRS researcher position in 1996 in the group of Prof. Janine Cossy and was promoted to Director of Research in 2008. His research focuses on the development of synthetic methods and their application to natural products synthesis.

Janine Cossy's early career was spent in Reims (France), where she did her graduate studies at the University of Champagne-Ardennes, working on photochemistry under the supervision of Prof. Jean-Pierre Pète. After a postdoctoral stay with Prof. Barry M. Trost, for two years at the University of Wisconsin (USA), she returned to Reims where she became CNRS Director of Research in 1990. In the same year, she moved to Paris, and since 1990, she has been Professor of Organic Chemistry at ESPCI ParisTech. Since 2005, she has been Associate Editor of *Organic Letters*. Janine Cossy's research interests focus on the synthesis of natural products and biologically active molecules. The synthetic methods that she develops include radical reactions, photochemistry, thermal reactions, organometallic reactions, catalysis, ring expansions, opening of strained rings, methods for the synthesis of heterocyclic compounds, and stereoselective reactions. Her research efforts have resulted in more than 425 publications and 15 patents. She has received awards, among them the CNRS Bronze Medal (1987) and Silver Medal (1996), the UK Royal Society Rosalind Franklin International Lecturership awarded to internationally recognized women scientists (UK) (2005), and the Le Bel Award from the French Chemical Society (France) (2009), and she was nominated Chevalier de la Légion d'Honneur in 2013.

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