Assembling Complex Structures through Cascade and Cycloaddition Processes via Non-Acceptor Gold or Rhodium Carbenes

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1 Introduction

While the upsurge of research activity on gold chemistry focused on heterogeneous catalysis, starting with the contributions of Hutchings and Haruta on the activation of acetylene and carbon monoxide, respectively, 1 the group of Teles at BASF in Ludwigshafen discovered the use of triphenylphosphine gold(I) complexes as homogeneous catalysts for the activation of alkynes. 2 After the development of a gold(III)-catalyzed synthesis of phenols by Hashmi, 3 the groups of Fürstner, Toste and ours discovered that cationic gold(I) complexes were powerful catalysts for the electrophilic activation of π-bonds in the cycloisomerization of enynes. 4 Thereafter, homogeneous gold catalysis experienced an almost exponential growth leading to the development of a plethora of synthetic transformations for the construction of complex carbon skeletons. 5

Gold(I) complexes selectively activate alkynes in the presence of other functional groups, including alkenes. The alkynophilicity of gold(I) 6-7 is directly related to the higher reactivity of the resulting (η2-alkyne) gold(I) species towards nucleophilic attack. In general, the attack of nucleophiles takes place in an outer-sphere anti fashion, giving rise to trans-alkenyl gold complexes. 8

Cycloisomerizations and cycloadditions have attracted significant attention for the assembly of complex polycyclic structures present in diverse natural products.9 These reactions typically proceed by multistep pathways that involve the formation of non-acceptor gold(I) carbene intermediates. We define non-acceptor metal carbenes as those that do not have any highly electron-withdrawing group (e.g., an ester or ketone) attached directly to the carbene carbon, but rather present electron-neutral or electron-donating functionalities. Based on this mechanistic understanding, efficient intramolecular processes that involve skeletal rearrangements, cascade processes or nucleophilic trapping have led to the discovery and development of many new gold(I)-catalyzed reactions, such as the [2+2] cycloaddition of alkynes and alkenes to afford cyclobutenes.10

Key words gold, rhodium, cascade reactions, cycloadditions, metal carbenes
2 Generation of Au(I)-Vinylcarbenes via a Cycloisomerization/1,5-Alkoxy Migration Cascade

Gold(I) vinylcarbenes are versatile intermediate species that have been mostly generated from propargylic carboxylates\(^1\) by 1,2-acyl migration, or from cyclopropenes\(^2\) via gold(I)-catalyzed ring opening. Our group developed an alternative approach for the generation of Au(I)-vinylcarbenes by cycloisomerization/1,5-alkoxy migration of 1,6-enynes.\(^1\) bearing an ether moiety on the propargylic position (Scheme 1). After activation of the alkyne by coordination to a gold(I) Lewis acid, intermediate I undergoes a 5-exo-dig cyclization to form cyclopropyl gold(I)-carbene II. The propargylic ether group can then migrate to the most electrophilic position of the cyclopropane ring, giving rise to gold(I)-vinylcarbene III. These species can be intercepted intra- and intermolecularly by different nucleophiles, releasing products 2 after ligand exchange and closing of the catalytic cycle. In this section, we will discuss the different methodologies and the applications of the reactivity of this type of gold(I) vinylcarbenes after their catalytic generation by cascade cycloisomerization/1,5-alkoxy migration.

2.1 Intramolecular Trapping of Au(I) Vinylcarbenes

The first example of the generation of this type of gold(I) vinylcarbene was reported by our group in 2009 via tandem cyclization/1,5-OR migration/intramolecular cyclopropanation of dienynes such as 3a (Scheme 2) [only the (Z)-isomer is depicted in the scheme].\(^3\) The reaction proceeds through intermediate V, which evolves through intramolecular attack of the ether moiety attached to the propargylic position on the electrophilic site of the cyclopropane to form VIa. Next, the \(\alpha,\beta\)-unsaturated gold–carbene...
intermediate VIIa forms upon cleavage of the oxonium bridge and undergoes an intramolecular cyclopropanation with the distal alkene on the side chain to form 4a. In the presence of an external nucleophile such as CD$_3$OD, intermediate V can be trapped intermolecularly prior to the aforementioned intramolecular cyclopropanation, giving rise to the corresponding deuterated epimer 4b in moderate yield.

Similarly, 1,7-enynes 5 were found to undergo an analogous 1,6-shift of the methoxy group giving rise to dehydro-5H-benzo[c]fluorenes 6a–c through a gold(I)-catalyzed cascade reaction (Scheme 3). This process proceeds via benzylic vinyl gold(I) carbene X followed by a Nazarov-type cyclization. Thereby, vinylogous nucleophilic addition of the aryl group to the conjugated carbene affords products 6a–c through intermediate XI. The methoxy migration is faster than the opening of cyclopropyl gold(I) carbene intermediate VIII, which would have delivered the corresponding tetracene derivatives by way of a formal [4+2] cycloaddition reaction.$^{14}$

2.1.1 Applications in Total Synthesis

As shown in Scheme 2, analogous dienyne (E)-3b can also engage in similar processes (Scheme 4). By way of a cyclization cascade process that involves a formal 1,5-migration of an OR group, tricyclic compounds 4c–d were obtained, bearing the skeleton present in the sesquiterpenes globulol and epiglobulol. Hence, this method was applied in the concise total syntheses of (-)-epiglobulol (7), (-)-4β,7α-aromadendranediol (8), and 4α,7α-aromadendranediol (9), proceeding via a stereodivergent gold(I)-catalyzed reaction which establishes four stereogenic centers in a single reaction step from (E,E)-farnesol derivative 3 (Scheme 4).$^{15}$ Remarkably, polycyclizations of enynes can also involve intramolecular cyclopropanation reactions leading to complex ring systems with cis-fused cyclopropanes. The corresponding trans-fused cyclopropanes were only obtained as minor products in these cascade processes.
Our group also discovered the cyclization of 1,6-enynes 10 possessing a carbonyl group, giving oxatricyclic compounds 11 by a formal [2+2+2] alkene/alkene/carbonyl cycloaddition cascade (Scheme 5).16–18 These reactions take place via intramolecular nucleophilic attack of the ketone in cyclopropyl gold(I) carbene XII to deliver oxonium cations XIII stereospecifically. Next, intermediate XIII undergoes a Prins-type cyclization forming tertiary carbocations XIV. Demetallation from XIV delivers products 11. Moreover, external nucleophiles such as ketones or aldehydes have been used to trap cyclopropyl gold(I) carbenes generated from 1,6-enynes.19,20

![Scheme 5 Intramolecular gold(I)-catalyzed [2+2+2] alkene/alkene/carbonyl cycloaddition of oxo-1,6-enynes. [Au] = AuCl.](image)

This cascade cycloaddition was also applied to build the core of several oxygen-bridged sesquiterpenoids such as (+)-orientalol F (14)21 and the antitumor compound (−)-englerin A (15)22 (Scheme 6). In this scenario, propargyl ether substituted enynes 12 do not undergo 1,5-migration (despite the similarity of the substrates to those in Schemes 2 and 4) due to the faster attack of the carbonyl moiety present in the alkyl chain. Interestingly, another total synthesis of 15 was disclosed by Ma and co-workers using this gold(I)-catalyzed cascade as the key step.23

Following our retrosynthetic plan for the total synthesis of jatropha lactone (16),24 a naturally occurring diterpenoid isolated from the roots of Jatropha curcas, we developed a new gold(I)-catalyzed cyclization cascade of substituted dienyenes that led to the selective formation of unexpected trans-fused cyclopropanes within a trans-bicyclo[5.1.0]octane framework, depending on the substrate geometry (Scheme 7).25 At first, in order to explore the feasibility of applying this transformation in total synthesis, the simpler model substrate 18 was designed with a phenyl ring instead of a less stable furan, expecting the formation of the cis-fused cyclopropane present in jatropha lactone. However, the actual product obtained (19) had a trans-fused cyclopropane, a rather unusual stereochemical feature. This rare trans-bicyclo[5.1.0]octane motif is also present in some natural products such as cneorubin B (20), emmottene (21) and hemerocallal A (22) (Scheme 7).26–28

![Scheme 7 Proposed retrosynthesis of jatropha lactone and examples of natural products bearing trans-fused cyclopropanes.](image)

Dienynes (E)- and (Z)-23 react in the presence gold(I) complexes almost instantaneously at room temperature. (E)-Configured enyne (E)-23, containing a free hydroxy group, affords trans-fused cyclopropane 24a as a single diastereomer, whereas the analogous (Z)-configured enyne reacts to give an inseparable mixture of isomers 24b and 24c in moderate yield (Scheme 8).
Intrigued by both the selective formation of trans-fused cyclopropanes and the different selectivity found with (E)-/ (Z)-dienynes in these new gold(I)-catalyzed cyclization cascade reactions, we further studied these transformations by means of DFT calculations. For both substrates, direct formation of intermediates XVa and XVb was postulated, via intermediates XVIa and XVIb, by elimination of the methoxy group (Scheme 9). These computed pathways provide a rationale for the role played by the fused tetrahydrofuran ring in the final cyclopropanation step.

To better understand the selective formation of the trans-fused ring in 24a, the final cyclopropanation step was computed starting from XVa,b (Scheme 10). Under gold(I) catalysis, diyne (E)-23 affords trans-fused cyclopropane 24a as a single diastereomer upon cyclopropanation of intermediate XVa via TSXVa–XVIIa, which is favored by at least 7.4 kcal/mol compared to the cis-cyclopropanation pathway. The analogous diastereomeric mixture of (Z)-configured 23 led to a 1:1.4 mixture of cis/trans-cyclopropane products 24b and 24c, while by calculations, competing pathways from intermediate XVb via TSXVb–XVIIb and TSXVb–XVIIc differ by 3.4 kcal/mol (indicating that only 24c should be formed). Although the calculated energy barriers are not in agreement with the experimental results for (Z)-23, the cis-cyclopropanation was found to be more favorable, as observed in the major isomer obtained experimentally (24c). Therefore, DFT calculations showed that the specific selectivity was directed by the rigidity of the system in the final cyclopropanation step.
2.2 Intermolecular Trapping of Au(I) Vinylcarbenes

The first intermolecular trappings of this class of Au(I) vinylcarbenes were published in 2009, in the same report as the first intramolecular version (Scheme 2). Upon 5-exo-dig cycloisomerization and 1,5-OR migration, the resulting gold(I) carbene was intercepted by a molecule of indole, giving product 25 in good yield (Scheme 11). Similarly, norbornene (26) could act as a nucleophile to deliver cyclopropane 27 in 75% yield and a 3:2:1 diastereomeric ratio. The use of 2,3-dimethyl-1,3-butadiene (28) as the trapping agent delivered 29 as the main product, together with smaller amounts of 30, corresponding to the (4+3)-cycloaddition adduct.

2.1.1 Total Synthesis of Schisanwilsonene A

Our group demonstrated the synthetic utility of the cascade cycloisomerization/1,5-OR migration/intermolecular trapping reaction in the total synthesis of schisanwilsonene A (36). Thus, enyne 1a with a propargylic acetate was subjected to the gold(I)-catalyzed cycloisomerization/1,5-migration/intermolecular cyclopropanation cascade with alkene 31 to deliver cyclopropane 32 in moderate yield (Scheme 12). TBS deprotection, followed by monoacetylation and DMP oxidation provided aldehyde 33 in good yield. Aldehyde 33 was then submitted to Wittig olefination to form divinylcyclopropane 34, which underwent a [3,3]-Cope rearrangement in situ, forging the fused bicyclic skeleton of 35. From this point, the first enantioselective total synthesis of schisanwilsonene A was accomplished in 8 steps. Very recently, an alternative two-stage microbial/chemical approach to this natural product was reported by the group of Xiang.

2.2.2 Trapping with Furans, 1,3-Dicarbonyl Compounds and Cyclic Alkenes

In 2014, our group reported the use of furans as trapping agents for gold(I) carbenes generated by different pathways. Gold(I) carbenes arising from the retro-Buchner reaction of cycloheptatrienes or the 1,2-acyl migration of propargylic esters reacted with furans to deliver conjugated ketones as products. Enynes 1 engage in this transformation providing products 38 in moderate to good yields (Scheme 13). Different substitution patterns on the furan ring were well tolerated, including methoxy-substituted furan 37b, which delivered the corresponding ester 38b in moderate yield. An analogous furan with a TMSO group instead of MeO delivered the free carboxylic acid.

The proposed mechanism for this intermolecular trapping starts with gold(I) carbene III, which reacts with furan 37 at its more nucleophilic and sterically accessible position.
(explaining the excellent regioselectivity). Finally, deauration promotes the opening of the furan ring in XVIII to deliver trienone 38 as a single isomer (Scheme 14).

Scheme 14 Proposed mechanism for the intermolecular trapping of III with furans.

In a later report, 1,3-dicarbonyl compounds 39 were found to react selectively as carbon nucleophiles, delivering cyclopentenes 40 in moderate to good yields and with low to moderate diastereoselectivities (Scheme 15).32 The intermolecular cyclopropanation with cyclic alkenes 41 yielded cyclopropanes 42 (Scheme 16). Adduct 42a was obtained with a low 56:44 d.r., while benzene-fused alkenes delivered good to excellent diastereoselectivities (products 42b-d). The relative configurations of the three newly formed stereocenters were confirmed by X-ray diffraction of crystalline 42d.

2.2.3 Mechanism of the Cycloisomerization/1,5-Migration Sequence and the Role of the OR Migrating Group

The OR migrating group was found to have a key role in the reactivity and selectivity of this transformation. para-Nitrophenyl ether was found to be optimal as the migrating group for the gold(I)-catalyzed cascade, giving the highest yields in all the previous examples.32 Additionally, in contrast to acetate-enzyme 1a, the enantiomeric ratio of PNP-enzyme 1b was fully transferred to product 43 after the gold(I)-catalyzed reaction with alkene 31 and TBAF deprotection (Scheme 17). On the other hand, for acetoxy 1,6-enzyme 1a, a 10% drop in enantiomeric excess was observed, attributed to the partial racemization by reversible 1,2-acyl migration.33 This improvement in yield and specificity allowed for an improved synthesis of schisanwilsonene A.

Scheme 15 Gold(I)-catalyzed cycloisomerization/1,5-OR migration/intermolecular nucleophilic trapping of enyne 1b with 1,3-dicarbonyl compounds. PNP = p-nitrophenyl. 1 [Au] = ([IPr]Au(PhCN))BAr4. 2 [Au] = [(JohnPhos)Au(MeCN)]SbF6.

Scheme 16 Gold(I)-catalyzed cycloisomerization/1,5-OR migration/intermolecular nucleophilic trapping of enyne 1b with cyclic alkenes. PNP = p-nitrophenyl. 1 [Au] = [(JohnPhos)Au(MeCN)]SbF6.

Scheme 17 Effect of the OR group on the stereospecificity. PNP = p-nitrophenyl. 1 [Au] = [(JohnPhos)Au(MeCN)]SbF6.
could evolve towards XXIa-c via single cleavage rearrangement, although the energy barriers of this pathway were found to be considerably higher.

We found that the reaction of enyne 1b with 1,2,3,4-tetramethylcyclopentadiene delivered 45a in good yield and moderate diastereoselectivity under gold(I) catalysis. Anthracene was also found to be a good reaction partner for this (4+3) cycloaddition, delivering 45b in 67% yield. Contrarily, 1,3-cyclohexadiene delivered simple cyclopropanation product 46c in good yield and moderate diastereoselectivity, with only traces of the corresponding (4+3) adduct. An acyclic 2-oxy-1,3-diene was found to deliver the desired bicyclic core in good yield (45d), whereas isoprene delivered a 1:2:1 mixture of (4+3) product 45e versus cyclopropane 46e (Scheme 19).

Experimental mechanistic investigations revealed that a Cope rearrangement of products 46 to give products 45 was not taking place under the reaction conditions, neither thermally nor catalyzed by gold(I). DFT calculations of the full system provided reasoning for the different product selectivity depending on the diene. For instance, experimentally, the reaction of 1b with cyclopentadiene delivered a 2:1 ratio of cyclopropane/(4+3) adduct, in perfect agreement with the theoretically predicted ratio. In this model, intermediate IIIb is trapped by cyclopentadiene, forming carbocation XXII. This intermediate can then undergo ring closing towards the three- or the seven-membered rings via TSXXII–XXIII and TSXXII–XXIV, respectively. Under kinetic control, the energy difference between these two transition states determines the ratio of the final products (Scheme 20).

The versatility of gold(I) vinylcarbenes III has been further demonstrated recently by our group, when we showed that this type of intermediate can be trapped by a 1,3-diene in a formal (4+3) cycloaddition reaction.24

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semble traditional cycloadditions but are not concerted pericyclic reactions. Instead, a series of charged intermediates are involved in a sequence that takes place through two or more mechanistic steps. Although these processes have been widely studied with acceptor carbenes, there are fewer reports describing formal cycloadditions of simple non-acceptor metal carbenes. This is mostly due to the prevalence of methods that lead to the generation of acceptor or donor–acceptor metal carbenes. The decomposition of stabilized diazo compounds is the most illustrative example, since non-acceptor diazo compounds are often toxic, difficult to prepare, handle or store, and can be explosive in pure form. Together with enynes (described in the first part of this account), propargyl esters, and cyclopropanes, 7-substituted cycloheptatrienes have recently emerged as versatile and safe alternatives to generate non-acceptor metal carbenes through an aromative decarbena-
tion by retro-Buchner reaction. These gold(I) and rhodi- um(II) carbenes generated in situ can engage in a variety of formal cycloadditions.

### 3.1 The Metal-Catalyzed Retro-Buchner Reaction

In 2010, while exploring the gold(I)-catalyzed cycloisomerization of 1,6-enynes, our group discovered the possibility of generating aryl carbenes through a process driven by the downhill release of an aromatic fragment. This concept led us to the discovery of the gold(I)-catalyzed retro-Buchner reaction of 7-substituted cycloheptatrienes, an aromative decarbena-
tion process in which a carbene fragment is generated upon release of a molecule of benzene. This resulted in the development of a safe and practical method for the arylcyclopropanation of alkenes (Scheme 21). The same concept could then be extended to develop a diastereoselective arylcyclopropanation of alkenes. The generation and fate of these non-acceptor carbenes was studied in detail, and it was also found to be possible to trap these intermediates intramolecularly through Friedel–Crafts-type mechanisms.

![Scheme 21](image)

Through the design and development of a new generation of more reactive cycloheptatrienes, these carbene-transfer processes could not only be carried out under much milder conditions, but also under zinc(II) or rhodi-

### 3.2 Formal Cycloadditions with Non-Acceptor Car- benes via Metal-Catalyzed Aromative Decarbena-
tions

Among the different types of reactivities in which non-
acceptor metal carbenes generated by retro-Buchner reac-
tions can engage, formal cycloadditions stand out for their potential to rapidly build up molecular complexity.

#### 3.2.1 (4+1) Cycloadditions of Au(I) Carbenes

In 2014, we found that the reaction of 7-aryl-1,3,5-cy-
loheptatrienes with methylenecyclopropanes under gold(I) catalysis led to cyclopentenes (Scheme 22). These would be the products of formal (4+1) cycloaddition between the four carbon atoms of the methylenecyclopropane and the corresponding aryl gold(I) carbene generated by aromative decarbena-
tion of cycloheptatrienes. In this manner, a range of 1,5-disubstituted cyclopentenes could be assembled in moderate to excellent yields.

![Scheme 22](image)

Based on experimental observations, a mechanistic pro-
posal involving three different gold(I)-catalyzed processes was drawn up. The first step is the gold(I)-catalyzed ring-expansion isomerization of methylenecyclopropanes to afford cyclobutenes (Scheme 23, left cycle). Next, the retro-Buchner reaction of 7-arylcyloheptatrienes would give rise to aryl gold(I) carbenes, which would cyclopo-
propanate the cyclobutene to afford bicyclic intermediates (as evidenced by its isolation in some particular cases). Finally, a ring opening followed by a 1,2-H shift affords cyclopentenes, in a process also catalyzed by gold (Scheme 23, right cycle).
The fact that cyclobutenes 51 are indeed intermediates in this transformation could be exploited to develop an analogous methodology in which these substrates are used directly instead of methylenecyclopropanes. This allowed access to other cyclopentenes 50 with a broader range of substitution patterns (Scheme 24).

In 2017, we reported that the same type of aryl gold(I) carbenes react with allenes to give indenes through a formal (3+2) cycloaddition reaction. 52 In this manner, we synthesized a variety of highly substituted indenes by reactions of 7-arylcycloheptatrienes 47 and 1,2-disubstituted allenes 52 by using a cationic gold(I) complex as the catalyst (Scheme 25, top). This strategy allowed the preparation of indene intermediate 53e, which after elaboration through 5–6 more steps led to the construction of the carbon skeletons of both the cycloaureonones and the dysiherbols,53 two families of natural products featuring a cis- or trans-decalin core, respectively (Scheme 25, bottom).

In addition, we found that if 7-styrylcycloheptatrienes 54 were used as carbene precursors, the same allenes reacted to give cyclopentadienes 55 (Scheme 26). 52 Thus, we prepared different arylcyclopentadiene derivatives with dense substitution patterns, which are significantly challenging to construct by other means. We illustrated the power of this transformation by performing the shortest total synthesis of laurokamurene B (56) reported thus far. A simple and selective hydrogenation of cyclopentadiene 55d using Wilkinson’s catalyst afforded the natural product in 39% overall yield over three total steps.

The mechanistic proposal for this transformation is depicted in Scheme 27. First, styryl gold(I) carbene XXXII is generated by aromative decarbenation of 54a. This is followed by a nucleophilic attack by the central carbon of the allene on the highly electrophilic carbene carbon, affording cationic intermediate XXXIII which evolves via a vinylogous Friedel–Crafts-type cyclization to afford exocyclic-alkene intermediate 57. Both diastereoisomers of this product could be observed and characterized by NMR. The final step of the reaction involves a downhill isomerization to afford fully conjugated cyclopentadiene 55e.

The very same mechanistic picture can be extended to the (3+2) cycloaddition between allenes and aryl carbenes (Scheme 25), considering a classical Friedel–Crafts-type cyclization instead of a vinylogous one.
More recently, we found that alkenyl carbene precursors 58 reacted smoothly with 1,3-dienes under rhodium(II) catalysis to afford 1,4-cycloheptadienes as the products of formal (4+3) cycloaddition.35 The discovery of this reaction was made possible by the development of 7-alkenyl-1,3,5-trimethyl-1,3,5-cycloheptatrienes 58 as more reactive carbene precursors, which can undergo decarbena- tions or retro-Buchner reactions under mild conditions in the presence of either gold(I) or rhodium(II) catalysis.48 In this manner, we were able to prepare a very wide variety of mono- and bicyclic 1,4-cycloheptadienes 59 in good to excellent yields, and as single diastereoisomers (Scheme 28).

This strategy was employed for the straightforward total synthesis of the pheromone dictyopterene C′ (59i). The reaction of vinyl carbene precursor 58a with 1,3-butadiene (44a) in the presence of [Rh2(TFA)4] as the catalyst at 40 °C afforded directly the natural product (Scheme 29).35 The mechanism of this transformation takes place analogously to that described in Scheme 20 for the cascade cycloaddition of gold carbenes with 1,3-dienes. DFT calculations revealed two different possible fates for adduct XXXIV, formed upon reaction of styryl rhodium(II) carbene with 1,3-cyclohexadiene (Scheme 30). First, this intermediate can close up directly to form the product of formal (4+3) cycloaddition XXXVI through TSXXXIV–XXXVI (ΔG = 2.4 kcal/mol). Alternatively, XXXIV can close to give a three-membered ring through the slightly-lower-in-energy TSXXXIV–XXXV, giving rise to 1,2-divinylcyclopropane 59a′, which can then evolve through Cope rearrangement. This rearrangement was calculated to have similar barriers either in the presence or in the absence of the rhodium(II) catalyst. Following the overall process by 1H NMR allowed the observation of a significant accumulation of divinylcyclopropane intermediate 59a′, confirming the existence of the cyclopropanation/Cope rearrangement pathway in which the latter process can be considered the rate-limiting step. Furthermore, we observed that for some 1,3-dienes the product of vinylcyclopropanation (such as 59h′) was the only product obtained under the optimized reaction conditions. Thus, we developed a simple theoretical model using DFT that could be used to predict if certain reaction partners will afford...
the product of (4+3) cycloaddition (Scheme 28, barriers <25 kcal/mol for the free Cope rearrangement) or the product of vinylcyclopropanation (Scheme 28, barriers >25 kcal/mol for the free Cope rearrangement). To further support this mechanism, some of the obtained divinylcyclopropanes were transformed into the corresponding 1,4-cycloheptadienes by heating them above 140 °C, either in the presence or in the absence of the rhodium(II) catalyst.35

Conflict of Interest

The authors declare no conflict of interest.

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