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Cyclopropanation by Gold- or Zinc-Catalyzed Retro-Buchner Reaction at Room Temperature

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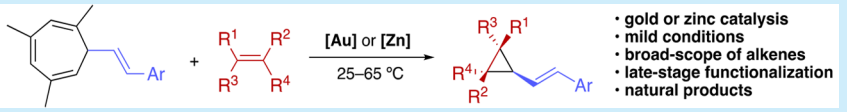
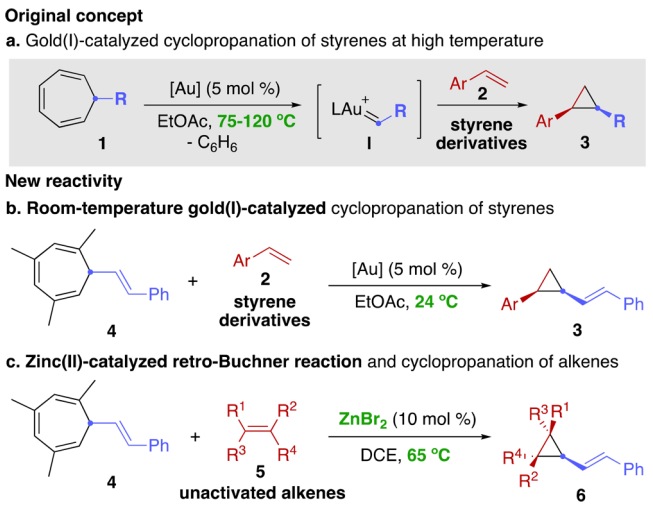
Supporting Information



ABSTRACT: Through the design of a second generation of more reactive 7-substituted 1,3,5-cycloheptatrienes, a room-temperature gold(I)-catalyzed retro-Buchner−cyclopropanation sequence and the first zinc(II)-catalyzed version of this process, which uses inexpensive $ZnBr_2$ as catalyst, have been developed. This led to a broad-scope cyclopropanation of both activated and unactivated alkenes, including late-stage derivatization of biologically relevant compounds, and to the total synthesis of (±)-lactobacillic acid.

Over the past few years, the gold(I)-catalyzed retro-Buchner reaction has emerged as a powerful tool for the generation of gold(I) carbenes (**I**) from 7-substituted 1,3,5-cycloheptatrienes such as **1** (Scheme 1a).[1] These reactive intermediates[2] can be efficiently trapped by alkenes to give aryl- or vinylcyclopropanes, undergo intramolecular Friedel−Crafts-type reactivity,[3] or engage in formal cycloadditions with different partners.[4,5]

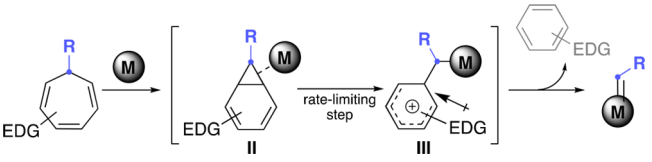
Scheme 1. New Retro-Buchner Reactivity Unlocked through a New Generation of Cycloheptatrienes



Despite the variety of reactivities that have been explored with this chemistry, the decarbenation process requires temperatures in the range of 75−120 °C. The reaction is restricted to the use of gold(I) complexes, and the resulting carbenes only react satisfactorily with aryl-substituted alkenes. We now report a room-temperature version of the gold(I)-catalyzed *cis*-vinylcyclopropanation reaction, with improved diastereoselectivity. More significantly, we have discovered the first zinc(II)-catalyzed retro-Buchner−cyclopropanation sequence.[6,7]

Based on our studies that demonstrated that the rate-limiting step for the retro-Buchner reaction is the cleavage of the first C−C bond of norcaradiene **II** to give Wheland-type cationic intermediate **III** (Scheme 2),[3] we decided to introduce electron-donating groups (EDG) in the cycloheptatriene ring to lower the activation energy of this step.

Scheme 2. Working Hypothesis for the Design of a Second Generation of Cycloheptatrienes



We found that 1,3,5-trimethyl-7-styryl-1,3,5-cycloheptatriene **4a** undergoes a retro-Buchner reaction in the presence of 5 mol % of [(JohnPhos)Au(MeCN)]SbF_6 at 24 °C to generate a gold(I) carbene that can be trapped with styrene in good yield and excellent diastereoselectivity (Table 1, entry 1), releasing one molecule of mesitylene. Trimethylcycloheptatrienes **4** were synthesized by Julia−Kocienski olefination of

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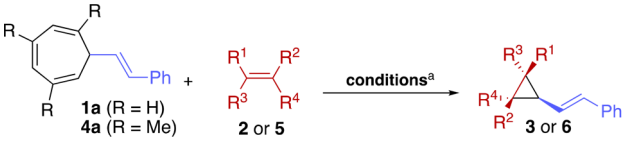
Table 1. Optimization and Comparison of the Two Reported Reaction Conditions



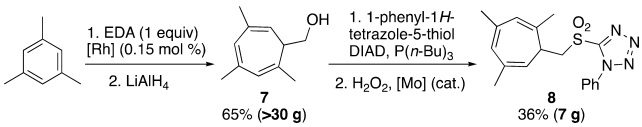
Conditions A: 1.5 equiv of olefin, 0.1 M in EtOAc, **[Au]**[b] (5 mol %), 25 °C, 24 h
Conditions B: 4.0 equiv of olefin, 0.1 M in DCE, **$ZnBr_2$** (10 mol %), 65 °C, 40 h

entry	deviation from **A** or **B**	yield/% (*dr*)[c]	olefin (**2** or **5**)
1	**A**	**80 (>20:1)**	
2	**B**	51 (>20:1)	
3	**A** with R = H (**1**)	n/d	
4	**A** in $CHCl_3$	72 (>20:1)	**styrene** (**2a**)
5	**A** in CH_2Cl_2	76 (>20:1)	
6	**B**	**55 (5:1)**	
7	**A**	12 (n/d)	
8	**B** with R = H (**1**)	traces	
9	**B** with $ZnCl_2$, 90 °C	34 (4:1)	**cyclohexene** (**5a**)
10	**B** with ZnI_2, 90 °C	15 (3:1)	

[a]R = Me for the starting cycloheptatriene unless otherwise stated. [b][Au] = [(JohnPhos)Au(MeCN)]SbF_6. [c]Yield and *dr* determined by ^{1}H NMR using diphenylmethane as internal standard. *cis*/*endo*-Cyclopropane is the major diastereoisomer.

aldehydes, using a sulfone that was prepared by a sequence starting with a Rh(II)-catalyzed ring expansion of mesitylene with ethyl diazoacetate (EDA), and the reduction of the resulting ester, giving alcohol **7**. Then a Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol and subsequent oxidation afforded Julia–Kocienski reagent **8** on a multigram scale (Scheme 3).[8]

Scheme 3. Synthesis of the Julia–Kocienski Reagent

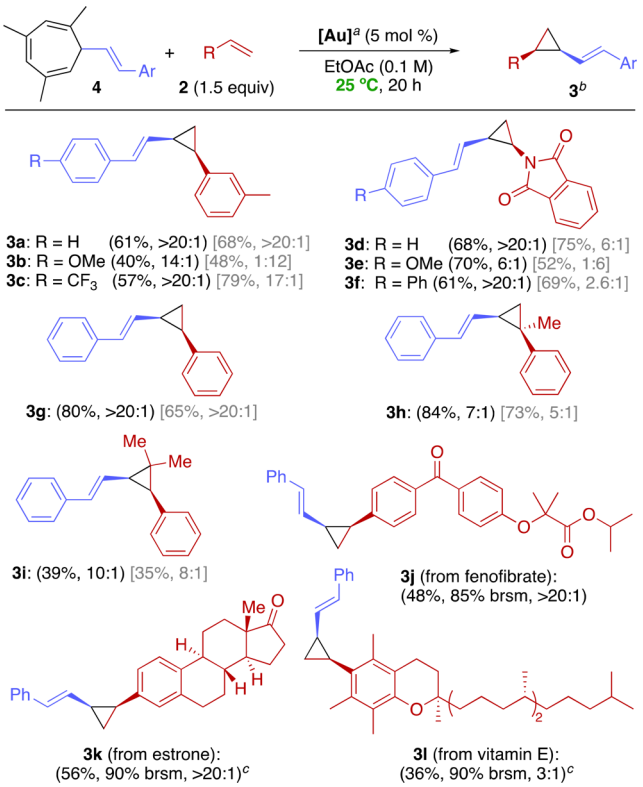


Although the use of 1,3,5-trimethyl-1,3,5-cycloheptatrienes is preferable for synthetic purposes, we also attempted to introduce more electron-donating substituents, such as methoxy, but the synthetic intermediates were found to be highly unstable. In parallel, we found that the retro-Buchner–cyclopropanation sequence could also be carried out with $ZnBr_2$ (10 mol %) at 65 °C (Table 1, entry 2). Interestingly, while the gold(I)-based conditions (**A**) gave poor yields in the cyclopropanation of unactivated alkenes such as cyclohexene, the zinc(II)-based system allowed us to obtain the corresponding cyclopropane in 55% yield. In both cases, the reaction with the corresponding first generation cycloheptatriene (**1a**) was not successful (Table 1, entries 3 and 8).

In view of those results, we adopted the two new systems as complementary methods for the diastereoselective cyclopropanation of a broad range of alkenes, selecting the gold(I)-based conditions (**A**) as the best method for the reaction with styrenes or related activated alkenes and the zinc(II)-based system (**B**) for the cyclopropanation of simple unactivated alkenes.

The results of the gold(I)-catalyzed *cis*-vinylcyclopropanation of several activated alkenes with 1,3,5-trimethyl-7-styryl-1,3,5-cycloheptatrienes **4** at room temperature were compared with those previously reported using 7-styryl-1,3,5-cycloheptatrienes at 75 °C (Scheme 4).[3c] In general, with both

Scheme 4. Room-Temperature Gold(I)-Catalyzed Cyclopropanation of Styrenes



[a][Au] = [(JohnPhos)Au(MeCN)]SbF_6. [b]Isolated yield and *cis*/*trans* ratio of diastereoisomers in parentheses. Yield and *dr* obtained with the previous generation of cycloheptatrienes (75 °C) in brackets. [c]Obtained as a 1:1 mixture of the two possible *cis*-cyclopropane products.

electron-rich and electron-poor styrylcycloheptatrienes, comparable yields and improved diastereoselectivities were obtained, especially with challenging alkenes such as vinylphtalimide (**3d–f**), which gave poor selectivities at high temperature.[3c] Remarkably, very electron-rich vinylcyclopropanes bearing a *p*-methoxy group (**3b** and **3e**), which easily undergo a gold(I)-catalyzed *cis* to *trans* isomerization at 75 °C,[3c] can be obtained at 25 °C as the *cis* products. In order to demonstrate the applicability of this transformation under mild conditions, we performed a late-stage derivatization of three biologically relevant products. We prepared *cis*-vinylcyclopropane derivatives of fenofibrate (marketed as Tricor, a treatment for hypercholesterolemia, **3j**), estrone (a steroid derived from cholesterol, **3k**), and α-tocopherol (one type of vitamin E, **3l**). In every case, the reaction proceeded cleanly, allowing almost complete recovery of all the remaining styrene derivatives.

We also prepared a (*E*,*E*)-dienyl gold(I) carbene from cycloheptatriene **4h** at 25 °C, which reacted with styrene **2f** to give diene **9** in 52% yield and a 7:1 *cis*/*trans* ratio of diastereoisomers (Scheme 5).

It has been previously shown that zinc carbenes can be generated from cyclopropenes and used to cyclopropanate

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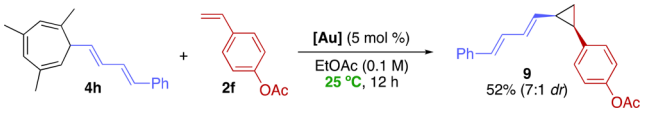
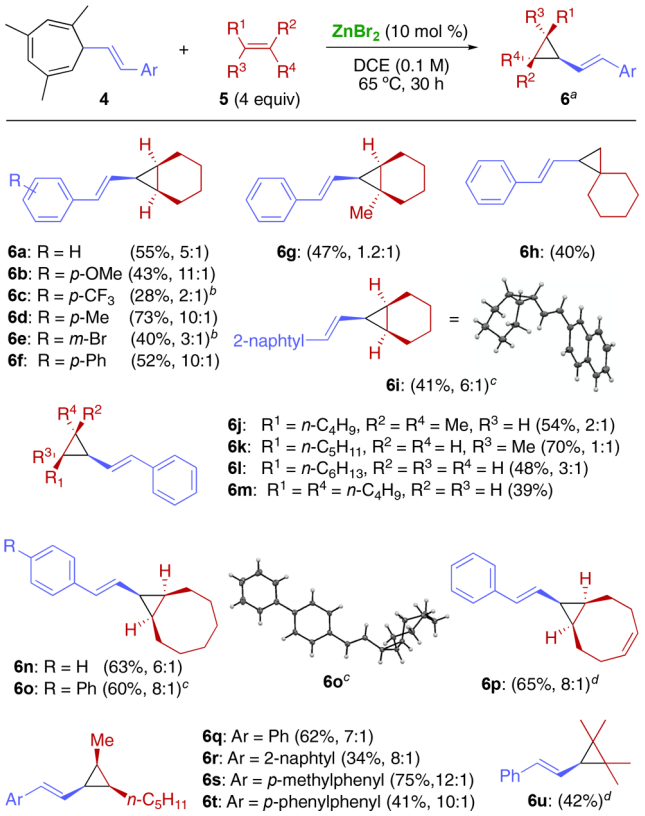
Scheme 5. Cyclopropanation with a Vinylogous Styryl Gold(I) Carbene Generated by Retro-Buchner Reaction



alkenes.[9] In our case, 1,3,5-trimethyl-7-styryl-1,3,5-cycloheptatrienes **4** reacted in the presence of 10 mol % of $ZnBr_2$ at 65 °C with alkenes to give the corresponding cyclopropanes **6** in good yields (Scheme 6). Both linear and cyclic unactivated

Scheme 6. Zinc(II)-Catalyzed Cyclopropanation of Unactivated Alkenes

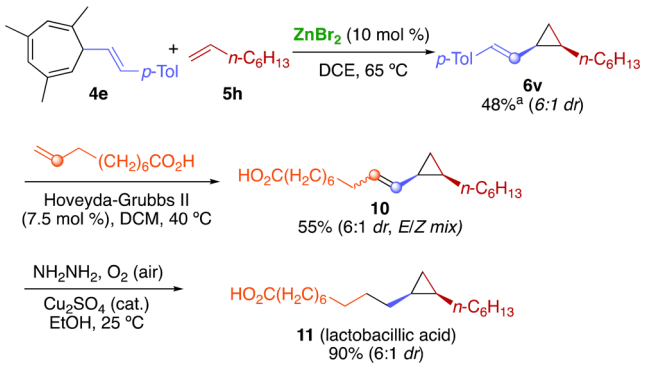


[a]Isolated yield and *cis*/*trans* ratio of diastereoisomers between parentheses. [b]At 80 °C for 60 h. [c]Structure and *cis* configuration confirmed by X-ray diffraction. [d]10 equiv of alkene employed in order to minimize volatility or selectivity issues.

alkenes with any kind of substitution pattern, from monosubstituted to tetrasubstituted, reacted satisfactorily. The *cis* or *endo* product was obtained preferably in all cases, as it was confirmed by the X-ray diffraction structures of **6i** and **6o** and by NOE experiments in all other substrates. Both electron-rich and electron-poor cycloheptatrienes can be used to give the corresponding cyclopropanes **6a**–**f**, although the reaction with electron-poor substrates was much slower and gave products **6c** and **6e** in lower yields. The best results in terms of diastereoselectivity were obtained using electron-rich substrates (**6b**) and disubstituted *Z* alkenes (**6q**–**t**).

As a part of our efforts to apply new synthetic methodologies for the total synthesis of natural products,[10] we decided to prepare lactobacillic acid (**11**), a natural fatty acid that has attracted the interest of many synthetic organic chemists since its isolation more than 50 years ago (Scheme 7).[11]

Scheme 7. Total Synthesis of (±)-Lactobacillic Acid

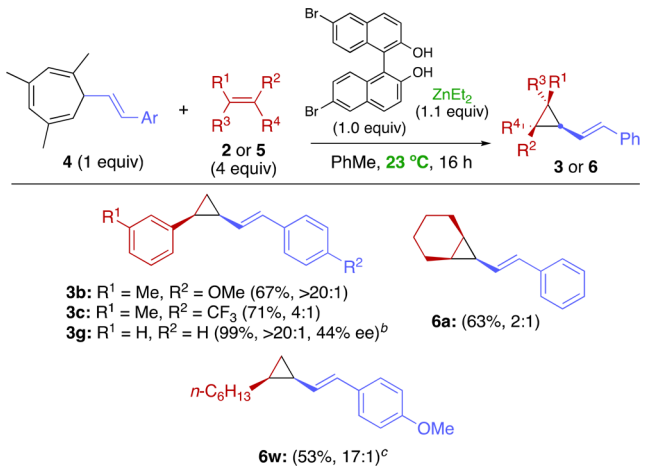


[a]NMR yield of the isolated product after flash chromatography, containing 15% w/w of mesitylene.

The reaction of cycloheptatriene **4e** with 1-octene in the presence of $ZnBr_2$ as catalyst afforded *cis*-vinylcyclopropane **6v** in a 6:1 ratio of diastereoisomers (along with 15% w/w of mesitylene that could not be removed by distillation). Then **6v** was converted into intermediate **10** as a *E*/*Z* mixture by cross-metathesis with 9-decenoic acid using the second-generation Hoveyda–Grubbs catalyst. Finally, reduction of **10** with diimide afforded lactobacillic acid (**11**). The main advantage of this straightforward route is its versatility, since it could be used to obtain a variety of natural or non-natural cyclopropane-containing fatty acids by just tuning the number of carbon atoms in the aliphatic chains of **5** and the carboxylic acid.

In our search for more reactive and selective systems, we found that the Lewis acid that is formed in situ by the combination of 1 equiv of 6,6′-Br_2-BINOL and 1.1 equiv of $ZnEt_2$[12] can also cleanly promote the retro-Buchner–cyclopropanation sequence at room temperature (Scheme 8). This

Scheme 8. Room Temperature Cyclopropanation Promoted by the BINOL–Zn System



[a]NMR yield and *cis*/*trans* ratio of diastereoisomers between parentheses. [b]Reaction performed with (*R*)-6,6′-Br_2BINOL. The absolute configuration of the major enantiomer was not determined. [c]Isolated yield at 1.5 mmol scale using BINOL.

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method gave up to quantitative yields and excellent diastereoselectivities and was tolerant to both unactivated and activated alkenes. Furthermore, an alternative intermediate for the synthesis of lactobacillic acid (**6w**), could be obtained with improved diastereoselectivity. More importantly, when employing (*R*)-6,6′-Br_2-BINOL, it was possible to obtain, for the first time in a sequence involving a retro-Buchner reaction, a product (**3g**) with 44% ee.

In conclusion, we have prepared a new generation of more reactive cycloheptatrienes, which allowed us to develop two new systems, based on gold(I) or zinc(II), that perform the retro-Buchner−cyclopropanation sequence under very mild conditions. This is the first example of a decarbenation reaction using zinc(II). Our two new catalytic systems led to a synthesis of *cis*-vinylcyclopropanes with wide scope and to the total synthesis of (±)-lactobacillic acid. Additionally, our first results with a system based on BINOL and $ZnEt_2$ demonstrate the possibility of developing an enantioselective version of this transformation. Further investigations along these lines are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01791.

Experimental procedures and characterization data for compounds (PDF)

Accession Codes

CCDC 1848066−1848067 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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