Calcium Catalysis

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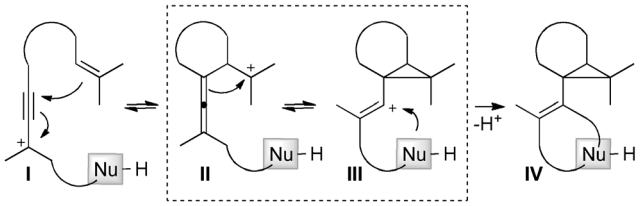
Calcium-Catalyzed Cyclopropanation

*Tobias Haven, Grzegorz Kubik, Stefan Haubenreisser, and Meike Niggemann**

Cyclopropane-containing heterocycles are essential structural units in many natural products and pharmaceuticals.[1] The stereoselective formation of highly substituted cyclopropanes has been a particularly fascinating challenge for many synthetic chemists.[2] A highly elegant way to assemble the cyclopropane ring with its substituents in one step is a cascade reaction in which multiple C–C bonds are formed. Owing to their propensity to act as π-acids for carbophilic activation, noble-metal complexes have become popular catalysts in this research field over the last decade.[3] Reactive intermediates in gold-catalyzed cycloisomerization reactions have been described either as cationic or carbenoid species.[4] In the cationic rendition, gold-stabilized homoallyl cations are in equilibrium with the corresponding, also stabilized, cyclopropyl cations. First precedent indicates the same type of equilibrium in analogous, nonstabilized homoallenyl cations **II** (Scheme 1).[5] Trapping the carbocation in its cyclopropyl



Scheme 1. Equilibrium of a homoallenyl cation and its corresponding cyclopropyl cation in the absence of a stabilizing gold species. Nu = nucleophile.

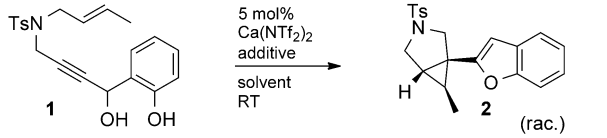
form **III** by reaction with an appropriately tethered nucleophile, which cannot reach other mesomeric forms of the cation, might thus lead to the highly substituted cyclopropane **IV**. The homoallenyl cation in turn is envisioned to be accessible through the cycloisomerization of the propagylic cation **I**, which isomerizes to an allene upon nucleophilic attack of a tethered olefin.

Over the last years we have developed a novel, biocompatible calcium catalyst as a sustainable alternative to traditionally used, expensive, rare, and oftentimes highly toxic transition-metal catalysts for organic synthesis.[6] Through the choice of appropriate counteranions, we successfully applied calcium salts as highly efficient Lewis acidic catalysts for the transformation of environmentally benign π-activated, such as benzylic, allylic, and propargylic alcohols, into reactive carbocations. The versatility of the catalyst was demonstrated by the substitution of these reactive intermediates with various nucleophiles.[7] With this excellent catalyst in hand for the generation of propargylic carbocations from the corresponding alcohols, we started investigating the above-stated hypothesis (Scheme 1), as part of our ongoing quest for stereoselective cycloisomerization reactions for the generation of complex molecules with simple non-transition-metal catalysts.

The model compound **1** was designed based on the following considerations. For the tethered nucleophile a phenol moiety was chosen, as previous investigations indicated its ability to form strong interactions with carbocations. These interactions lead to tight transition states, thus promoting stereodifferentiation.[8] To restrict the conformational freedom in favor of the ring closure by significant angle compression, a nitrogen atom was selected to connect the olefin to the propargyl portion. A disubstituted olefin is envisioned as the nucleophilic part to disfavor competitive cation formation.

We were pleased to find that model compound **1** readily reacted upon exposure to the calcium-based catalyst system to give the desired product **2** as a single diastereoisomer. Further optimization studies revealed that Bu_4NSbF_6 was the additive of choice for this cyclopropanation reaction (see Table 1). Interestingly, even subtle changes in the dielectric properties of the solvent, for example, from dichloroethane (DCE) to dichloromethane, had a huge impact on the outcome of the reaction. In dichloromethane, as in the

Table 1: Optimization of the reaction conditions.



No.[a]	$Ca(NTf_2)_2$ (mol%)	Additive (mol%)	Solv.	Yield[b] [%]
1	(10)	Bu_4NPF_6 (10)	DCE	62
2	(10)	Bu_4NBF_4 (10)	DCE	44
3	(10)	Bu_4NSbF_6 (10)	DCE	73
4	(10)	BMIM BF_4[c] (10)	DCE	63
5	(10)	$PhMe_2NH^+B(C_6F_5)_4^-$ (10)	DCE	5
6	(5)	Bu_4NPF_6 (5)	DCE	46
7	(5)	Bu_4NSbF_6 (5)	DCE	98
8	(5)	Bu_4NSbF_6 (5)	CH_2Cl_2	5
9	(5)	Bu_4NSbF_6 (5)	$MeNO_2$	–
10	(5)	Bu_4NSbF_6 (5)	Et_2O	–

[a] Additive and $Ca(NTf_2)_2$ were added at room temperature to alcohol **1** (0.25 mmol) in 1 mL of solvent and stirred for 16 h. [b] Yield of isolated **2**. [c] BMIM = 1-butyl-3-methylimidazolium.

[*] T. Haven, G. Kubik, S. Haubenreisser, Prof. Dr. M. Niggemann
Institute for Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: niggemann@oc.rwth-aachen.de
Homepage: http://www.oc.rwth-aachen.de

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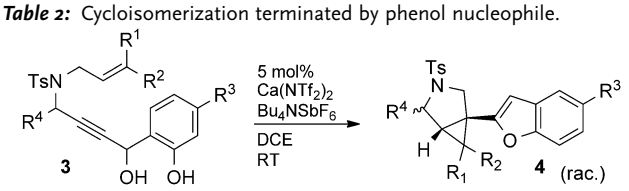
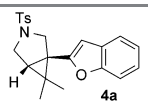
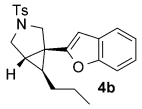
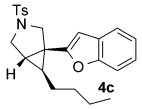
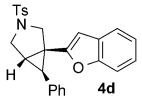
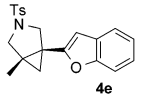
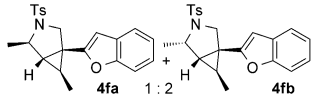
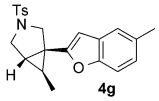
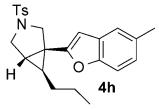
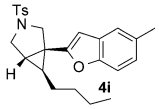
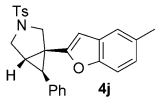
other cases where yields are low, the reaction was unselective and yields an inseparable mixture of various products including oligomers. This might be attributed to the stabilization of the carbocation in nonproductive conformers and mesomeric forms. Using these optimized reaction conditions we cycloisomerized a series of differently substituted enynols (Tables 2 and 3).

The prenyl moiety in **3a** reacted smoothly as a nucleophile and no competitive cation formation was observed (Table 2, entry 1). Substrates with aliphatic as well as aromatic olefin substituents gave the desired products, always with the same

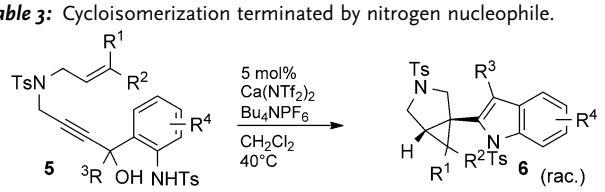
Table 2: Cycloisomerization terminated by phenol nucleophile.

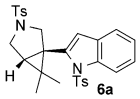
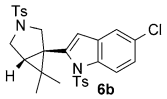
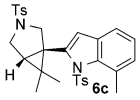
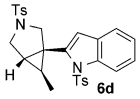
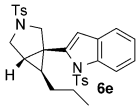
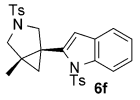
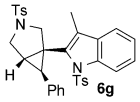
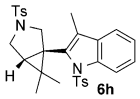
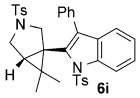


Entry[a]	Product	*t* [h]	Yield[b] [%]
1	 **4a**	16	65
2	 **4b**	2	80
3	 **4c**	16	82
4[c]	 **4d**	3	90
5	 **4e**	16	38
6[d]	 **4fa** 1 : 2 **4fb**	16	92
7	 **4g**	16	71
8	 **4h**	16	66
9	 **4i**	18	72
10	 **4j**	12	68

[a] 5 mol% $Ca(NTf_2)_2/Bu_4NSbF_6$ was added to enynol **3** (0.25 mmol) in 1 mL of DCE and the reaction mixture was stirred at RT for the time indicated. [b] Yield of isolated product. [c] 7.5 mol% $Ca(NTf_2)_2/Bu_4NPF_6$ was used. [d] Ratio determined by NMR analysis.

Table 3: Cycloisomerization terminated by nitrogen nucleophile.



Entry[a]	Product	*t* [h]	Yield[b] [%]
1	 **6a**	2	82
2	 **6b**	2	79
3	 **6c**	2	39
4	 **6d**	2	94
5	 **6e**	2	90
6	 **6f**	2	80
7	 **6g**	2	95
8	 **6h**	2	99
9	 **6i**	2	96

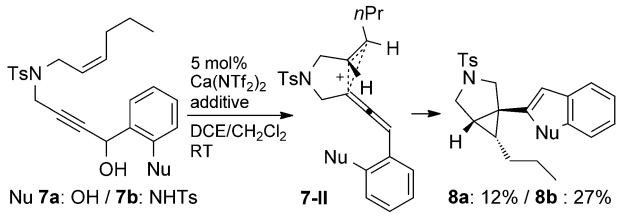
[a] 5 mol% $Ca(NTf_2)_2/Bu_4NPF_6$ was added to enynol **5** (0.25 mmol) in 1 mL of CH_2Cl_2 and the reaction mixture was stirred at 40 °C for the time indicated. [b] Yield of isolated product.

high diastereoselectivities (Table 2, entries 2–4). The 2,2-disubstituted olefin in **3e** cyclized to give the cyclopropane **4e**, albeit in moderate yield (Table 2, entry 5). The likely explanation for the modest yield is that in the carbocationic species formed the positive charge resides at a primary carbon atom (see also the mechanism below), and the high reactivity of this species encourages side reactions.

The attempt to direct the observed stereoselectivity from the pre-existing stereocenter in **3f** met only moderate success as the cyclopropane **4f** formed as a mixture of diastereomers in a ratio of 2:1 (Table 2, entry 6). The slightly decreased yield for the cyclopropanes **4g–j** formed by cycloisomerization of substrates terminated by a phenol moiety with an electron-donating methyl group can be rationalized by the lower acidity of the proton at the aryl oxygen atom, which hampers the final deprotonation step (Table 2, entries 7–10). Most

probably for the same reason, the reaction of the *N*-tosyl-substituted anilines **5** to give the cyclopropanes **6** proved more efficient, resulting in slightly higher yields in all cases (Table 3). In these cyclizations the Bu_4NPF_6 additive in dichloromethane solvent was found most effective for the cyclization of secondary and tertiary propargylic alcohols. Once again, no or electron-withdrawing substituents at the arene moiety proved to have a positive influence on the yield (Table 3, entries 1–3). The high stability of the initially formed tertiary propargylic cations **I** in the reactions leading to **6g–i** (Table 3, entries 7–9) account for an excellent reaction outcome.

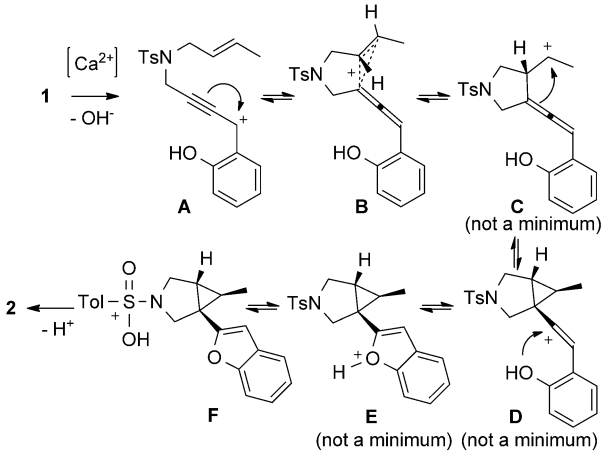
Mechanistic investigations, which were undertaken to rationalize the observed stereoselectivities, began with the analysis of the reaction of substrates **7a** and **7b**, which bear a *Z*-configured nucleophilic olefin instead of the *E*-configured one in **3h** and **6e** (Scheme 2). Both of the substrates reacted



Scheme 2. Cycloisomerization of enynols bearing *Z*-olefins.

to give the desired product, albeit in surprisingly poor yield. In both cases, the stereocenter at the tip of the cyclopropane ring was found to be reversed, indicating the transposition of the olefin geometry to the relative configuration at this position.

To gain further insight into the origin of the high diastereoselectivity and a deeper understanding of the equilibrium between the homoallenyl cation **II** and its cyclopropyl congener **III**, full mechanistic pathways for the two possible diastereoisomers of **1** were calculated by DFT-based methods (Scheme 3, Figure 1). In addition, this investigation should shed light on the origins of the difference in reaction efficiency for the two olefin geometries. The mechanism starts with a calcium-catalyzed dehydration, producing the propargylic cation **A** (Scheme 3), in which the positive charge is delocalized along the triple bond. The mechanistic pathway begins when a minimum **B**, which is stabilized by the through-space cation–π interaction of the positive charge in the



Scheme 3. Detailed mechanism based on computed structures.

allenic position with the double bond, forms in the pool of random conformers. In analogy to some enzyme-catalyzed mechanisms, which were elucidated recently for the biosynthesis of terpenes,[9] this mechanism was found to proceed in a concerted asynchronous manner. Although successive, the two C–C- and one C–O bond-forming events, which eventually lead to cyclopropane **2** after deprotonation, are merged in a concerted process with a predicted overall barrier of only 2.4 kcal mol^{-1}. A plot of the intrinsic reaction coordinate (IRC) is shown in Figure 1. The plot contains two successive, well-defined shoulders, but the reaction proceeds effectively with no further intermediates between minimum **B** and minimum **F**. Both the secondary carbocation **C** and the vinyl cation **D** appear along the reaction coordinate as indicated in Figure 1, but they are not energy minima. The absence of

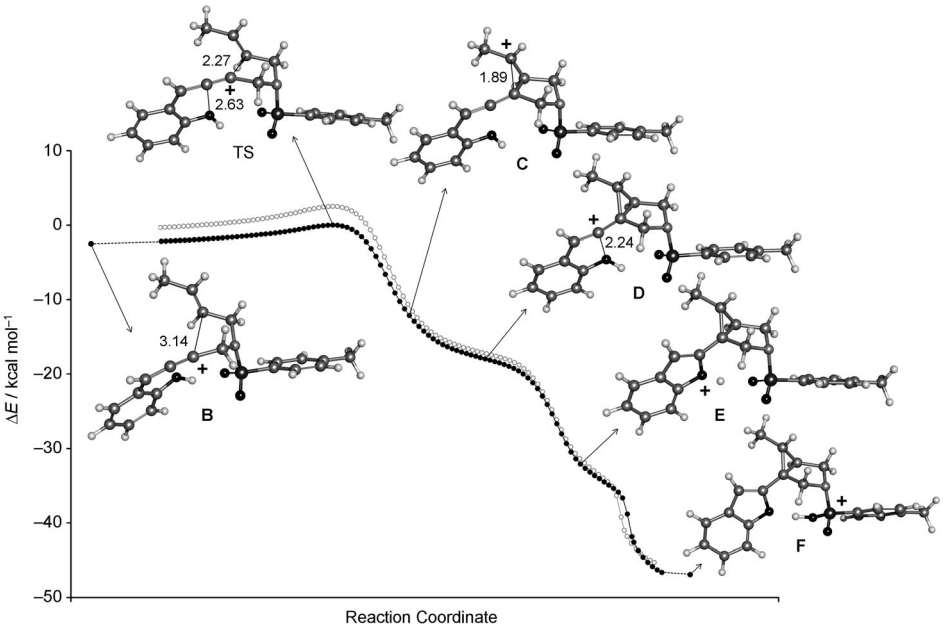


Figure 1. IRC pathways for the cyclopropanation cascade (mPW1PW91/6-31++G(d,p)). The pathway starting from (*E*)-**1** is in red, that starting from (*Z*)-**1** is in gray. Selected interatomic distances are given in Å. TS = transition state.

intermediates along the reaction pathway, which could suffer from conformational reorientation through bond rotations, explains the high stereoselectivity of the reaction. Therefore, once the minimum **B** has formed with the olefin and the phenol substituent oriented on either side of the plane of the arising five-membered ring, the stereochemical outcome of the reaction is set. Thereby, also the stereocenter at the tip of the cyclopropane ring is determined by the configuration of the olefin in the starting material. On the basis of these considerations, the moderate success of directing the stereochemical outcome of the reaction with a pre-existing stereocenter such as the methyl group in **3 f** can be explained. As it can point into open space in either orientation, a substituent in the α-position to the *N*-tosyl function has very little influence on the formation/stability of minimum **B** and the subsequent transition state.

The poor yield in the reactions starting from the *Z*-configured olefins (Scheme 2) can also be rationalized based on the results of the DFT calculations. Although the slope of this reaction is highly similar to that for the *E*-configured olefin (Figure 1), minimum (*Z*)-**B** and the transition state for the concerted process are higher in energy by 1.7 kcal mol^{-1} and 2.5 kcal mol^{-1}, respectively (see the Supporting Information) Even though the difference in energy between the two pathways is very small, the slightly higher energy of minimum **B** might impede its formation and the higher reaction barrier might prevent the reaction from following this pathway. Hence, the initially formed carbocation (*Z*)-**A** is much more prone to be entangled in undesired side reactions. The reaction mechanism of the formation of the indole cyclopropanes in Table 3 is assumed to proceed analogously.

In summary, we have developed a calcium-catalyzed cycloisomerization that yields highly substituted cyclopropane derivatives with excellent diastereoselectivity. The reaction is based on the equilibrium of a homoallenyl cation with its cyclopropane congener, an equilibrium that is well-established for gold-stabilized nonclassical carbocationic intermediates and has led to the discovery of various reactions with highly interesting skeletal rearrangements. This provides proof for the possibility to use the mechanistic features of noble-metal-bound nonclassical cations also in the absence of the metal. In addition, full analysis of the mechanistic pathway by DFT-based computational methods revealed the concerted asynchronous nature of the carbocation cascade, a reaction type that is to date a domain of enzyme catalysis. These results were also used to rationalize the observed stereoselectivity.

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