CHEMISTRY
A European Journal

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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201700282

Link to VoR: http://dx.doi.org/10.1002/chem.201700282

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How to Tame a Vinyl Cation with a Simple Al(OTf)$_3$ Catalyst - so that it Promotes a C-C Bond Cleavage

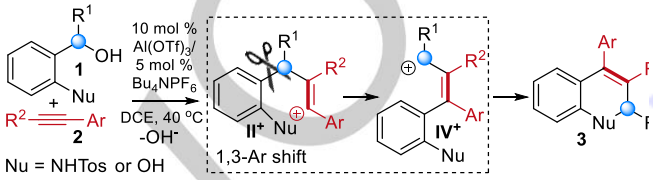
Meike Niggemann*[a], Liang Fu,[a] and Helena Damsen [a]

Abstract: Detailed mechanistic investigation identified the stepwise nature of the 1,3-aryl shift, which enables our recently disclosed Al^{3+}-catalyzed insertion of unactivated alkynes into the sp^2-sp^3 C-C bond of benzyl alcohols. The selectivity for the rearranged product was found to be induced by the continued coordination of the aluminum catalyst to the rearranging species, which is encouraged by a reversible background reaction. This participation of the catalyst beyond the ionization step is unique in the realm of carbocation driven reactions and opens up the possibility of catalyst induced chiral induction in the future. Furthermore, the study represents a rare example of detailed mechanistic analysis of a reaction with a product selectivity that changes with increasing conversion.

Vinyl cations are among the most special reactive intermediates known to propel organic reactions[1] and therefore, undoubtedly, bear great potential for the discovery of new reaction pathways. Their high reactivity, nevertheless, comes along with several, as yet mostly unsolved challenges, despite the fact that vinyl cations have been proposed as reactive intermediates,[2] quite a long time ago. These challenges start with the formation of vinyl cations. Traditionally, chemists had to rely upon the protonation of alkynes with super-acids,[3] fragmentation of elaborate precursors such as iodonium salts[4] or the often incomplete solvolysis of triflates in the presence of large excesses of the nucleophilic reaction partner under harsh conditions.[5] The challenge then continues, as once formed, vinyl cations react, not unlike radical species, rather indiscriminate with any organic molecule, also solvents, at an almost diffusion controlled reaction speed. So that, powerful driving forces are needed for a predictable reaction outcome, selective product formation and the prevention of undesired side reactions.

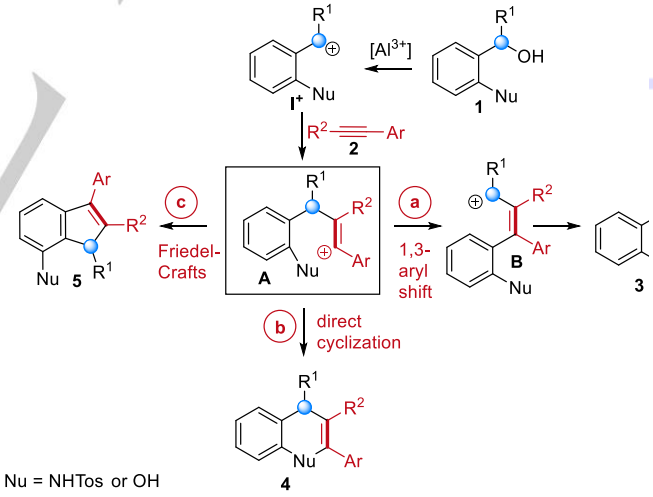
These challenges overcome, the application of vinyl cation reactivity provides highly attractive perspectives for the realization of unprecedented and complex transformations within the rapidly growing field of transition metal free reactions. Of particular interest in this context are carbocation cascade reactions, often encompassing multiple elementary mechanistic steps. Hence, a deeper understanding of the nature of vinyl cation driven reactions – first and foremost with regard to the factors controlling reaction selectivity - sets the stage for future reaction design in the field.

As a new reaction cascade for a vinyl cation intermediate we recently discovered a vinyl cation to allyl cation rearrangement (**A** → **B**, Schemes 1/2) as a driving force for an unprecedented 1,3-aryl carbon shift reaction.[6] This was used for the development of a new type of transition-metal free C-C bond cleavage reaction.[7] The transformation allows for a net insertion of internal, unactivated alkynes **2** into the sp^2-sp^3 C-C bond of *o*-amino as well as *o*-hydroxy benzylic alcohols **1** (Scheme 1) - in the absence of any transition metal and/or stoichiometric oxidant, enabled by nothing more than a simple aluminum based Lewis acidic catalyst.



Scheme 1. Vinyl cation reactivity based C-C bond cleavage.

To contribute to a better understanding of vinyl cation driven reactions, this unprecedented skeletal rearrangement intrigued us also from a mechanistic point of view, and we herewith present our efforts towards the elucidation of the mechanism of this unusual transformation.



Scheme 2. Formation and reactivity of vinyl cation intermediate **A**.

A general outline of the main reaction pathways to and from the vinyl cation key intermediate is shown in Scheme 2. In analogy to our previous work,[8] a classical Lewis acid catalyzed dehydration of benzyl alcohol **1** yields the benzylic cation $\mathbf{I}^+$. This is attacked by the alkyne moiety in **2** to form the vinyl cation key intermediate **A**. For the following, on behalf of its high reactivity certainly intramolecular reaction step, **A** is presented with 3 alternatives. Apart from the observed 1,3-aryl shift to **B** and its subsequent cyclization with the nucleophilic substituent in the arene (pathway a), **A** could also directly cyclize with the same nucleophile (pathway b).[9] In addition, a Friedel-Crafts reaction at

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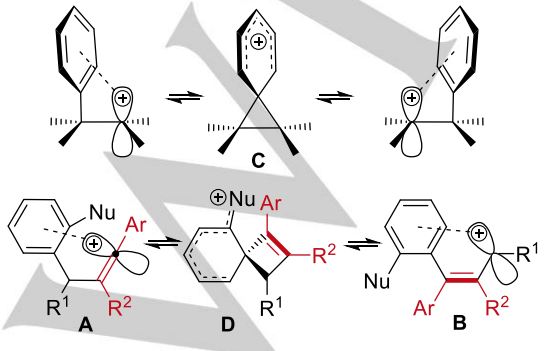
the nucleophilic substituents *m*-position could yield indene **5** (pathway c).[10,11]

Ultimately, the studies presented herein shall provide answers to the following key questions, regarding the fate of the vinyl cation:

1.) *Why is the rearranged reaction product* **3** *formed selectively - at the expanse of the direct cyclization product* **4** *and the indene* ***5****?*
2.) *What is the exact nature of the 1,3-aryl shift - and is it really cation driven?*
3.) *Why is Al(OTf)$_3$ the best catalyst for a selective formation of product* ***C****? Does it play a role beyond the ionization of the benzyl alcohol* ***1****?*

The initiating ionization process can theoretically be accomplished by a range of Lewis / Bronstedt acid catalysts[12] as the dehydration of a benzylic alcohol is comparatively easy. During the optimization studies a combination of 10 mol % Al(OTf)$_3$ with an additive of an ammonium salt of a weekly coordinating anion, such as Bu_4NPF_6, were most effective at providing selectivity towards the desired rearranged cyclization product **3**, preventing oligomerization and elimination of benzyl alcohol **1** and ensuring its complete conversion. Albeit being able to ionize the benzylic alcohol, other Lewis/Bronsted acids, e.g. In(OTf)$_3$, Ca(NTf$_2$)$_2$ or HOTf gave diminished selectivities for the rearranged product **3** and poor yields.

The products of pathways a and b were both regularly encountered, in different ratios, during the optimization studies, whereas indene **5** resulting from a direct F-C type ring closure (pathway c) was never isolated. This preference is easily rationalized. Both substituents, the NHTos as well as the OH,[13] have pronounced *o*,*p*-directing properties due to the possibility to accommodate a positive charge at the heteroatom of the substituent in the initial Wheland intermediate. Therefore, when electron density is transferred from the aromatic core to the empty p-orbital of the vinyl cation, a bond will establish in the *ipso* position rather than the *meta*, if the penalty for the formation of the four membered ring in **D** is not too high (see Scheme 3).[14] In other words, the process of "attacking" the vinyl cation is the same leading to **7** or the 4-membered ring containing **D**, it simply diverges at some point to form the more stable product, which is the 4-membered ring containing **D** in this case, due to the destabilizing effect of the NHTos/OH in the Wheyland intermediate on the way to **7**.This process, in fact, is highly analogous to the first step in an arene 1,2-shift in a classical Wagner-Meerwein reaction, which proceeds via the 3-membered phenonium ion **C**.[15]



Scheme 3. Comparison of cationic 1,2- and 1,3-aryl shift.

This rationalizes why a F-C reaction, if occurring, is selective for pathway a over c, but why is it favored over a direct cyclization of the initially formed vinyl cation with the nitrogen nucleophile (pathway b)? An answer to this question was sought for by DFT-based computational analysis. These studies were performed with a focus on the *o*-NHTos benzyl alcohols, with a model system of **1a** (Nu = NHTos; R^1 = Me) and alkyne **2a** (Ar = Ph; R^2 = Me), as the selectivity for the rearrangement was generally more pronounced for the insertion into *o*-NHTos than *o*-hydroxyl benzyl alcohols. In this inaugural study, catalyst participation beyond the ionization step was not considered, as in most carbocation driven mechanisms and all our previous mechanistic analyses the catalyst plays no further role beyond the formation of the initial carbocation species, the benzyl cation **I$^+$**. In addition, insight into the behaviour/electronic nature of the carbocationic reactive intermediates themselves is thereby provided. DFT calculations confirm that the 1,3-aryl shift occurs via the stepwise pathway proposed in Scheme 3 (Figure 1). Surprisingly in a comparative analysis of the alternative reaction pathway b - the direct nucleophilic addition of the nitrogen atom to the vinyl cation - energies were found to lay within the same range. For a more detailed analysis, depictions of selected structures, full size energy profiles and an evaluation of the computational methods we refer to the supporting information.

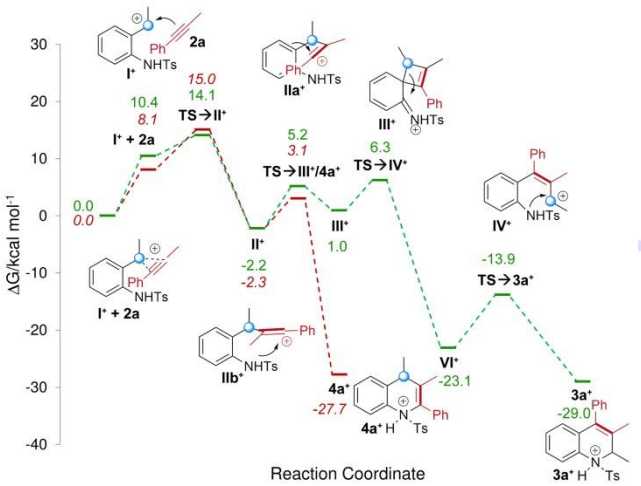


Figure 1. Computed energies (mPW1PW91/6-31+G(d,p)) for the selectivity determining key steps without catalyst participation (green - major product, red - minor product).

Hence, both the cation driven stepwise 1,3-aryl shift (pathway a) as well as the direct cyclization (pathway b) clearly are energetically accessible, but selectivity for one or the other is unexpected and a mixture of products would be consistent with the computational results. Consequently, the origin of the observed selectivity is not to be found solely in the electronic structure of the vinyl cation key intermediate.

Furthermore, determination of the product selectivity over time reveals, that selectivity improves with increasing conversion of the starting materials. From a meagre 2:1 selectivity at ~ 5 % conversion, that more or less matches the outcome of the computational analysis, a selectivity of 95:5 is reached at the end of the reaction (Figure 2). Isolation of both products **3a**, and **4a** and re-subjection to the reaction conditions shows no interconversion between the two. Nor is one of them decomposed selectively upon extended reaction times. This

finding further supports the fact that the origin of the selectivity cannot be found in the electronic structure of the vinyl cation intermediate, as it should be the same at the beginning and the end of the reaction.

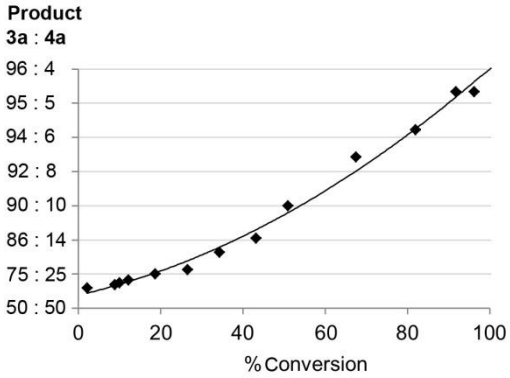
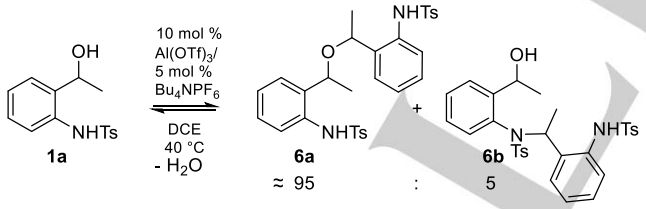


Figure 2. Product selectivity with increasing conversion.

Alcohol **1a** (0.3 mmol), alkyne **2a** (0.36 mmol) and 5 mol% Bu_4NPF_6 were added at rt to 10 mol% $Al(OTf)_3$ in 1.5 mL of DCE and stirred at 40 °C. At intervals samples were withdrawn and subjected to NMR-spectroscopic analysis after work-up.

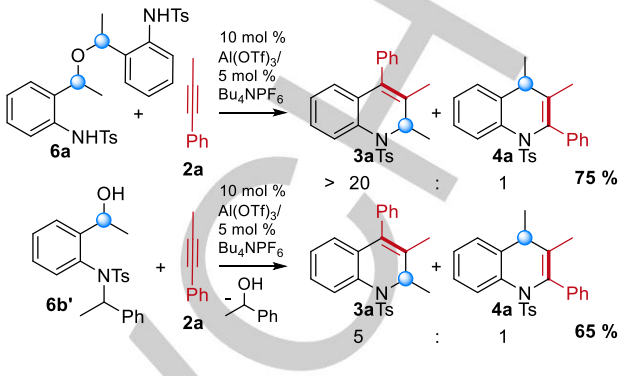
Also, the analysis of the reaction mixture at various times prior to completion indicates for a complex equilibrium between various species that are formed in reversible background reactions. In these, the initially formed cation $\mathbf{I}^+$ reacts with a further benzyl alcohol molecule **1a**, yielding ether **6a** when attacked by the hydroxyl moiety, or amine **6b** upon reaction with the benzyl alcohols nitrogen atom (Scheme 4). The ether **6a** was found to largely predominate throughout the reaction,[16] which might be assigned to both, the electron withdrawing properties of the tosyl group in **1a**, lowering the nucleophilicity of the nitrogen and steric crowding around it.



Scheme 4. Reversible Background Reaction

Deduced by HPLC/ NMR analysis of reaction mixture after 2 h, 4 h and 6 h, corresponding to 18 %, 35 % and 55 % conversion.

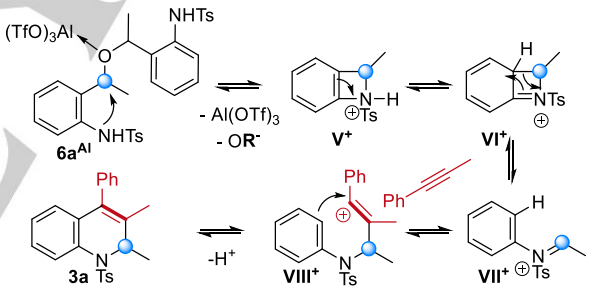
For an analysis of their influence on the product selectivity, ether **6a** was isolated, and amine **6b'** was synthesized (isolation of amine **6b** in the required amounts proved impossible). The two were subjected to the reaction conditions in the presence of the alkyne **2a** (Scheme 5). Much to our surprise, it is the ether, that yields the rearranged 1,2-dihydroquinoline **3a** with excellent selectivity without further detouring to any of the equilibrium species, albeit in a much longer reaction time. To reinforce this finding the corresponding methyl ether (OMe instead of OH in **1a**) was synthesized and subjected to the reaction conditions with an analogous result (not shown). The amine **6b'** was found to simply break down into the equilibrating species and reiterate into the original reaction. Overall, this indicates, that selectivity for product **3a** over **4a** is achieved over time, as more and more of the ether **6a** is formed and directly converted into product **3a**.



Scheme 5. Control experiments I.

Ether **6a** /Amine **6b'** (0.3 mmol), alkyne **2a** (0.36 mmol) and 5 mol% Bu_4NPF_6 were added at rt to 10 mol % $Al(OTf)_3$ in 1.5 mL DCE and stirred for 12 h at 40 °C; Ratio **3a**:**4a** determined by NMR spectroscopic analysis of the crude mixture; Isolated yields.

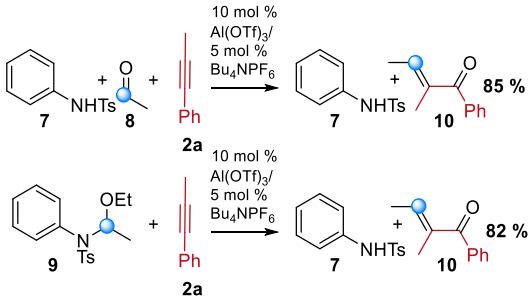
A potential explanation for the selectivity inducing effect of the ether **6a** might be found in an entirely different reaction mechanism.



Scheme 6. Retro-Friedel-Crafts / Povarov pathway.

Ionization of the benzyl alcohol **1a** is much easier for the catalyst than (re-)ionization of the ether **6a**. Therefore, it is conceivable that the ionization of this species needs further assistance by the merging of the ionization with a second, energetically more favorable process such as the nucleophilic attack of the adjacent nitrogen atom, leading to the dihydroazetium cation in $\mathbf{V}^+$ (Scheme 6). This might rearrange to the iminium ion $\mathbf{VI}^+$ via a 1,3-hydride shift followed by a retro F-C type process. Thus generated iminium $\mathbf{VII}^+$ might yield vinyl cation $\mathbf{VIII}^+$ upon nucleophilic addition of the alkyne moiety followed by ring closure to 1,2-dihydroquinoline **3a** in analogy to a Povarov reaction.[17] To probe this alternative reaction mechanism two simple control experiments were performed (Scheme 7). In these, the iminium ion $\mathbf{VII}^+$ - key intermediate in the alternative reaction pathway in Scheme 6 - is synthesized either by the in-situ condensation of aniline **7** with aldehyde **8** or the ionization of aminal **9** under otherwise identical reaction conditions. Both reactions yielded none of the previously obtained products **3a** and **4a**, but gave clean conversion to the α,β-unsaturated ketone **10** in a carbonyl alkyne metathesis process.[18] Hence, it is very

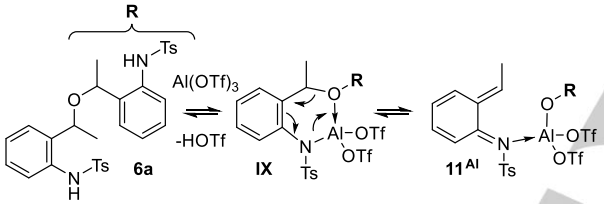
unlikely that a retro-F-C / Povarov mechanism is involved in our C-C bond cleavage.



Scheme 7. Control experiments II.

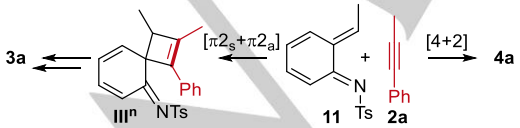
Aniline **7** (0.3 mmol), aldehyde **8** (0.36 mmol) / aminal **9** (0.3 mmol), alkyne **2a** (0.36 mmol) and 5 mol% Bu_4NPF_6 were added at rt to 10 mol% $Al(OTf)_3$ in 1.5 mL DCE and stirred for 12 h at 40 °C; Isolated yields.

Next, a potential difference in reaction initiation was examined, comparing the ionizations of ether **6a** and alcohol **1a**.



Scheme 8. Aluminum catalyzed ionization of ether **6a**.

The aluminum catalyst coordinates to alcohol **1a** at the hydroxyl moiety and thereby induces dehydration to yield the corresponding benzyl cation $\mathbf{I}^+$. In ether **6a** coordination to the nitrogen atom, leading to the chelated aluminum in **IX** (Scheme 8), followed by ether cleavage in a 6-membered transition state, yielding the uncharged *o*-azaquinone methide $\mathbf{11}^{Al}$ is more likely.[19] Alternatively, a disproportionation of the $Al(OTf)_3$ catalyst into $Al(OTf)^{2+}$ and $Al(OTf)^{4-}$ followed by chelate formation and deprotonation, thus also yielding **IX** and subsequently $\mathbf{11}^{Al}$ in analogy to Yu's work is also conceivable.[20] This is backed up by computational analysis (see s. i. for further discussion). The prevailing formation of $\mathbf{11}^{Al}$ represents a potential diversion into cycloaddition pathways (Scheme 9).[21]



Scheme 9. Pericyclic reactions of *o*-azaquinone methide **11**.

Hence, with or without prior decoordination of the aluminum catalyst, the *o*-azaquinone methide **11** can react in a hetero Diels-Alder type [4+2] reaction[22] yielding again 1,4-dihydro-quinoline **4a**. Alternatively, a geometrically forbidden yet thermally allowed [$\pi 2_s+\pi 2_a$] cycloaddition directly accesses the neutral cyclobutenone $\mathbf{III}^n$,[23] thus providing a reaction pathway that parallels the ionic dearomatization-rearomatization cascade towards **3a** in Scheme 3. Transition states for these potential reaction pathways were located computationally, clearly demonstrating that the activation barriers for these pericyclic reactions are energetically higher (by ~ 10 kcal/mol) than for the cationic pathways described above. This confirms a carbocation driven mechanism (see s.i. for further discussion). In addition, no selectivity for the [2+2] over the [4+2] would be expected from the results.

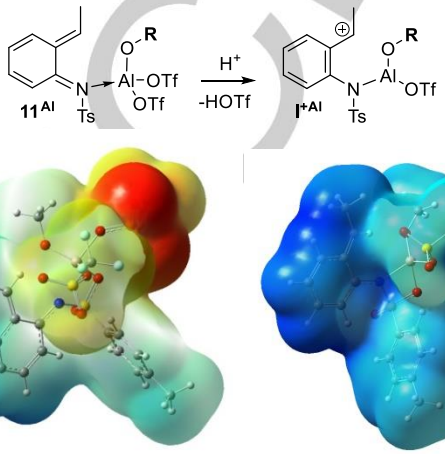


Figure 3. Electrostatic potential surfaces of $\mathbf{11}^{Al}$ and $\mathbf{I}^{+Al}$.

Blue - electropositive, green - neutral, red - electronegative.

Finally, an analysis of the electrostatic potential surface of $\mathbf{11}^{Al}$ (Figure 3) reveals a charge separation in the molecule – negative charge on two oxygens in one of the triflate anions and positive charge in the arene system - as a result of the Lewis acidity of the aluminum catalyst. This is also reflected in the slightly elongated bond between aluminum and the triflate anion in the trans-position to the nitrogen atom in $\mathbf{11}^{Al}$. The negative charge in this triflate anion makes it highly prone to protonation, which in turn induces its departure from the complex with an activation barrier of only 6.3 kcal/mol.

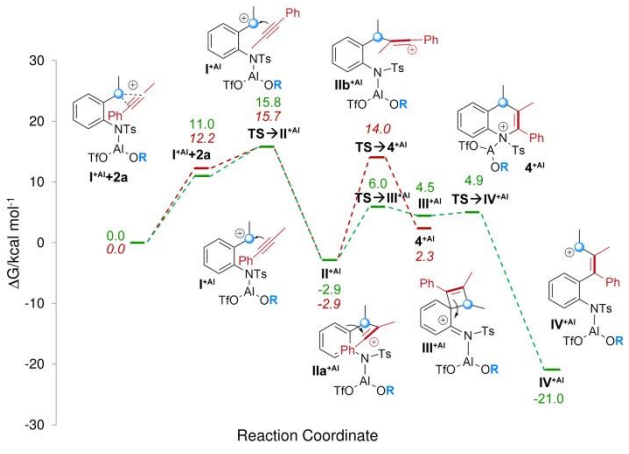


Figure 4. Computed energies (mPW1PW91/ 6-31+G(d,p)) for the selectivity determining key steps with catalyst participation (green - major product, red - minor product).

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The overall process transforms the catalyst bound *o*-azaquinone methide **11**^{Al} to the benzyl cation **I**$^{+Al}$, still coordinated to the aluminum catalyst. The energetic penalties for both, a catalyst decoordination and catalyst enhanced cycloaddition reactions were found to be higher (see s. i. for further details). Bearing a highly pronounced positive charge at the benzylic position, this species is now ideally suited for a nucleophilic addition of the poorly nucleophilic alkyne **2a** (Figure 3).

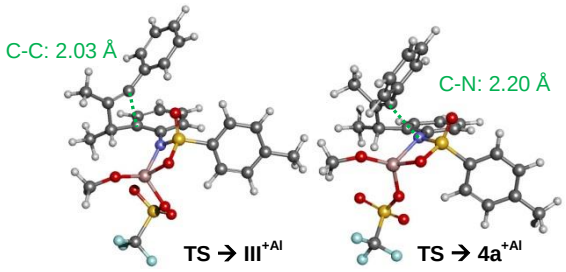
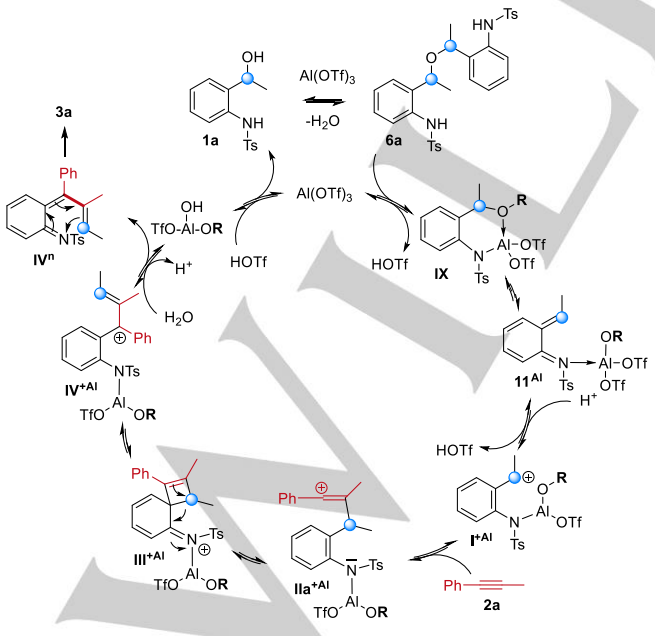


Figure 5. Structures of the transition states to **III**$^{+Al}$ and **4a**$^{+Al}$.

In the thus induced ionic pathway with catalyst participation the continued Al-coordination at the nitrogen atom provokes steric clash (Figure 5) and drastically lowers its nucleophilicity. Thereby, the energy gap between the *ipso*-F-C process and the direct nucleophilic addition of the nitrogen to the vinyl cation is increased in favour of the ring closure to the 4-membered ring in **III**$^{+Al}$ (Figure 4). In addition, the ring closure - ring opening sequence is merged into a quasi-concerted process by the catalyst's presence, so that the reaction proceeds all the way to the allyl cation **IV**$^{+Al}$ once the ring closure to the 4-membered ring in **III**$^{+Al}$ has occurred.

Bundling up all experimental and computational results we came to the following conclusions leading to the final proposed mechanism in Scheme 10:



Scheme 10. Proposed catalytic cycle.

Selectivity for the rearranged product **3a** is poor at low conversion rates and increases to ~20:1 towards the end of the reaction. Both, cation reactivity based (starting from **I**$^+$, Schemes 2+3) and cycloaddition pathways (starting from **11,** Scheme 9) are energetically accessible with and without further catalyst participation. The activation barrier for the addition of the alkyne, the first and rate determining step in all reaction pathways, is generally lower by ~ 10 kcal/mol in the ionic pathways. For reactions uncatalyzed beyond the ionization step, no clear preference for either the direct cyclization (pathway b) or the rearrangement-cyclization (pathway a) was determined. This changes dramatically when catalyst participation beyond the initial ionization step is taken into account, as the direct cyclization pathway is blocked (or strongly discouraged) by the catalysts coordination to the nucleophilic nitrogen atom. The preference for a mechanism with catalyst participation beyond the ionization step, and hence selectivity, is ultimately achieved indirectly by a background reaction leading to the formation of ether **6a**. Ionization of this ether predominantly leads to the formation of the aluminum coordinated *o*-azaquinone methide **11**^{Al}, HOTf departure from which results in the generation of the aluminum catalyst bound benzyl cation **I**$^{+Al}$. Addition of the alkyne **2a** generates vinyl cation **IIa**$^{+Al}$, that is rearranged to the allyl cation **IV**$^{+Al}$ in a stepwise process. This species, uncharged after hydrolysis induced decoordination of the catalyst, is subjected to electrocyclic ring closure to the final product **3a** (see s.i. for further details). This mechanistic picture also nicely accommodates the superior selectivity found for the Al^{3+} catalyst compared to other Lewis acids such as Ca^{2+}, Li^+ or Mg^{2+}, as these form much weaker and more fluctional coordinative bonds with nitrogen atoms. Thereby continued catalyst participation would be easily interrupted with these catalysts.

Acknowledgements

We thank the China Scholarship Council (CSC) for financial support of Liang Fu.

Keywords: carbon shift • transition metal free • cation rearrangement • aluminum catalysis • vinyl cation

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10.1002/chem.201700282

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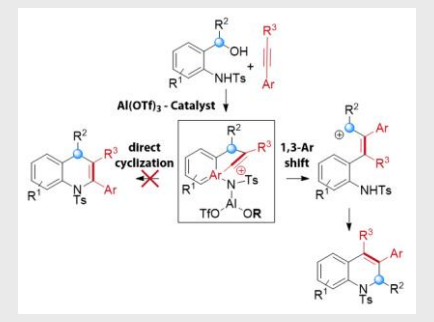
Hold on aluminum! Continued participation of the catalyst in a carbocation driven reaction proved responsible for the selective induction of a highly unusual 1,3-carbon shift. Detailed mechanistic analysis explains why a vinyl cation undergoes an unexpected rearrangement, resulting in the net insertion of unactivated alkynes into a C-C bond in benzylic alcohols.



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