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Authors: Tobias Stopka, Meike Niggemann, and Nuno Maulide

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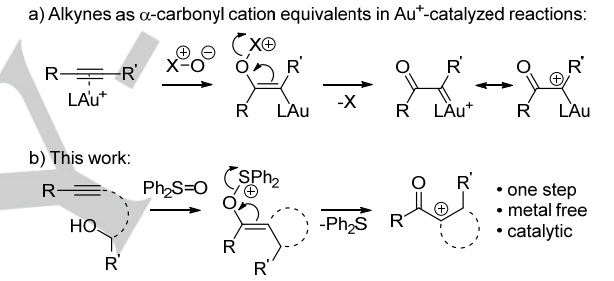
α-Carbonyl Cations in Sulfoxide-Driven, Oxidative Cyclizations

Tobias Stopka,[a] Meike Niggemann*[a] and Nuno Maulide*[b]

Abstract: A selective, metal-free generation of α-carbonyl cations from simple internal alkynes was accomplished by addition of a sulfoxide to a congested vinyl cation. The high reactivity of the thus generated α-carbonyl cations was found to efficiently induce hydrogen- and even carbon shift reactions with unusual selecivities. Thereby, complex and highly congested tertiary and quartenary, all-carbon-substituted centers are accessed in a single step from simple precursors. Mechanistic analysis strongly supports the intermediacy of the title species and provides a simple predictive scheme for the migratory aptitude of different substituents.

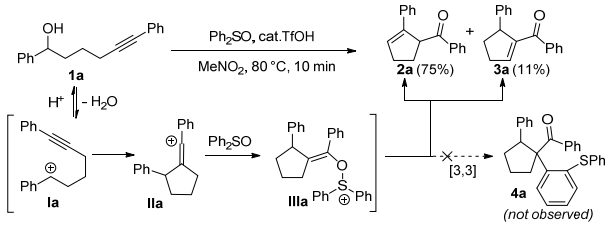
The chemistry of carbonyl compounds remains of fundamental interest for the organic chemistry community.[1] The natural polarity of these molecules - electrophilicity at the carbonyl carbon and nucleophilicity at the α-carbon - led to the development of what is arguably one of the most fundamental pillars of modern organic chemistry. Polarity reversal - or Umpolung[2] - of the α-carbonyl carbon substantially broadens the range of potential disconnections.[3] This can be achieved most prominently through the use of α-halo carbonyls,[4] but also *via* oxyallyl cations,[5] α,β-epoxy ketones,[6] enehydrazones[7] and oxygenated enamines.[8] Furthermore, oxidized enolates[9] and nitroso-type electrophiles[10] can be used for formal Umpolung processes. However, reactions that proceed via genuine polarity reversal, involving a fully developed positive charge at an α-carbonyl carbon, are still scarcely studied. This is certainly due to the high reactivity of such species – the cation being destabilized by the electron withdrawing carbonyl group – which renders them both difficult to generate and (once eventually made) difficult to control. Nevertheless, their existence as reactive intermediates was proven unequivocally in physical organic chemistry studies.[11] It should be emphasized though, that the focus of these studies lay merely on the characterization of a limited number of mechanistic probes. Until now, the generation of α-carbonyl cations heavily relies on ketones bearing a leaving group (LG) in the α-position. Cleavage of this leaving group was achieved in the presence of stoichiometric amounts of silver salts (LG= -I, -Br, -Cl),[12] an excess of strong acids (LG= -OH),[13] or Lewis acids (LG = -OH, -OTs, -$OP(O)(OMe)_2$.[14] Furthermore, mostly stabilized α-carbonyl cations (R'= Aryl) are accessible. The few scattered protocols making use of α-carbonyl cations for synthetic applications, that have been reported following the initial studies, are limited to inter- and intramolecular Friedel-Crafts,[12c,13,14b,15] or Ritter reactions[14a,16] using large excesses of the nucleophilic coupling partner.

One avenue offering synthetically useful *in-situ* formation of analogous intermediates has recently been demonstrated in the realm of Au-catalyzed reactions.[17,18] Therein, alkynes were transiently converted into α-oxo metal carbenoids – or Au-stabilized α-carbonyl cations – by treatment of the Au^+-coordinated alkyne moiety with sulfoxides[19] or *N*-oxides.[20] (Scheme 1a). Most of the reported studies focus on *N*-oxides as oxidants as they proved a reliable source of α-oxo gold carbenoids for diverse transformations; Sulfoxide-based procedures were sidelined, as the reaction mechanism of untethered sulfoxides was found to be dominated by 3,3-sigmatropic rearrangements prior to the formation of the carbenoid.[21]



Scheme 1. Alkynes as α-carbonyl cation equivalents.

In previous studies we demonstrated efficient formation of vinyl cations via π-activation of alkynes by simple carbocations[22] as well as the feasibility of the nucleophilic interception of vinyl cations by sulfoxides followed by sigmatropic rearrangement.[23] Combining our expertise we thus assumed that, as shown in Scheme 2, the addition of a sulfoxide to an *in-situ* generated vinyl cation **II** would lead to **III**, ideally poised for [3,3]-sigmatropic rearrangement leading to highly substituted arylated ketone **4**.



Scheme 2. Sulfoxide-mediated, unexpected oxidative rearrangement.

Much to our surprise, the very first experiments with benzylic alcohol **1a** and diphenylsulfoxide, under the influence of catalytic amounts of a Brønsted acid promoter, led instead to two new products assigned as the olefins **2a**/**3a** in a >7:1 ratio.

[a] Dr. T. Stopka, Prof. Dr. M. Niggemann
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: niggemann@oc.rwth-aachen.de
Homepage: http://www.oc.rwth-aachen.de
[b] Prof. Dr. N. Maulide
Institute of Organic Chemistry, University of Vienna
Währinger Straße 38, 1090 Vienna (Austria)
E-Mail: nuno.maulide@univie.ac.at
Homepage: http://maulide.univie.ac.at
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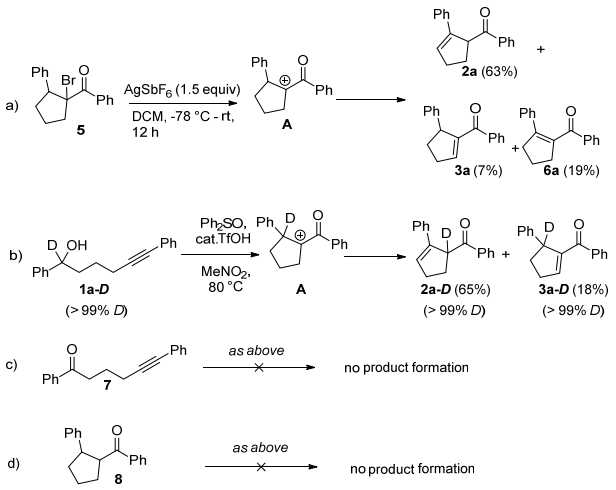
Intrigued by this unusual result, and suspecting the intermediacy of an α-carbonyl cation, we carried out a series of control experiments. Brominated compound **5** was reacted with an excess of silver salt, an experiment known to generate α-carbonyl cations[12c] (Scheme 3a). This led to a product distribution very similar to our model reaction in Scheme 2.

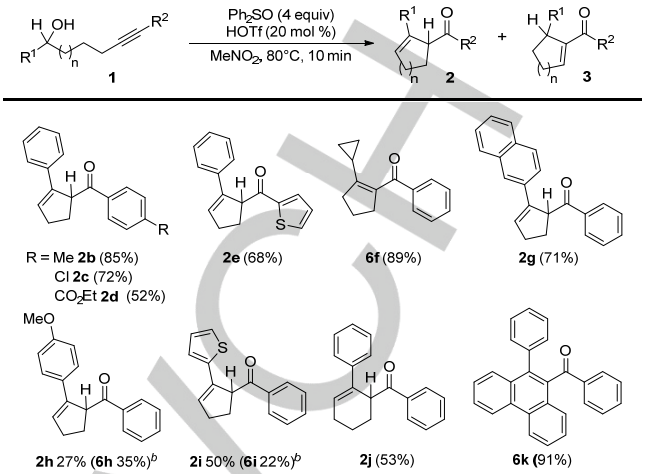


Scheme 3. Control experiments probing the intermediacy of an α-carbonyl cation **A**.

Reaction of deuterium-labeled compound **1a-*D*** lends strong support to a 1,2-hydrogen shift (Wagner-Meerwein-type rearrangement) for the formation of **2a** with **3a** being the result of the direct deprotonation of **A** (Scheme 3b). Mechanisms in which cyclization and oxidation occur independently were ruled out *via* the unproductive subjection of **7** and **8** to the reaction conditions. Hence, hypothetical oxidation of alcohol **1**, followed by hydrolysis of the alkyne to a ketone and subsequent aldol condensation (Scheme 3c), as well as hypothetical interception of vinyl cation **IIa** by H_2O and a sulfoxide-mediated oxidation (Scheme 3d) do not provide access to ketone **2a**. In addition, Ph_2S was regularly recovered from the reaction mixture.

With strong evidence for the intermediacy of a α-carbonyl cation, the influence of substitution patterns on reactivity was subsequently investigated (Table 1). A range of alkynols smoothly reacted with Ph_2SO providing access to α-oxo cations and the oxidative cyclization products in good to excellent yields. Electron-rich as well as –withdrawing substituents R^2 were well tolerated (**2b**-**d**). Also, heterocycles could be introduced (**2e**). Next, the influence of different substituents R^1 was investigated. Interestingly, even alcohol **1f** with an aliphatic cyclopropyl moiety gave **6f** in excellent 89% yield. A sterically demanding naphthyl group did not impede the reaction sequence (**2g**). With electron-rich alcohols, an isomerization of product **2** was observed, while retaining moderate to good overall yield (entries **2h-j**).[24] A starting material with an additional CH_2-unit also reacted to the desired cyclohexenyl product (entry **2j**). Here an increased yield can be explained by the more challenging 6-membered ring

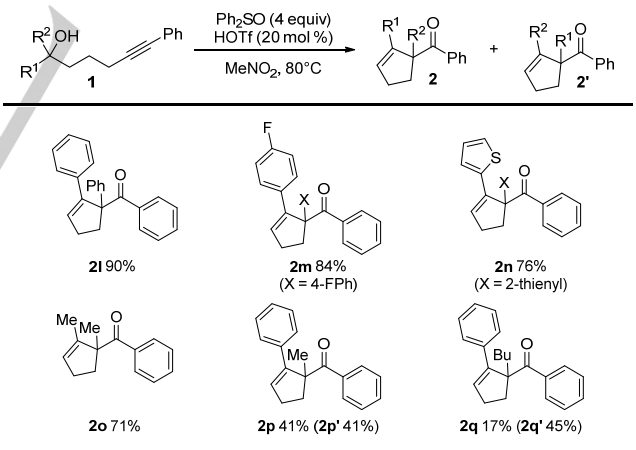
Table 1. Substrate scope: H-shift.[a]



[a] Reactions were performed at 80°C for 10 min with **1** (0.25 mmol, 1.0 equiv), Ph_2SO (1.00 mmol, 4.0 equiv) and HOTf (0.05 mmol, 20 mol %) in $MeNO_2$ (2.5 mL). Yields refer to the isolated compounds. [b] Conjugated double bond isomer (see SI for more information).

formation. However to enable these reactions, substituents inside the chain that arrange a favorable conformation might have a positive effect. For example, a phenyl-bridged substrate gave access to an interesting phenanthrene derivative in excellent yield (entry **6k**).

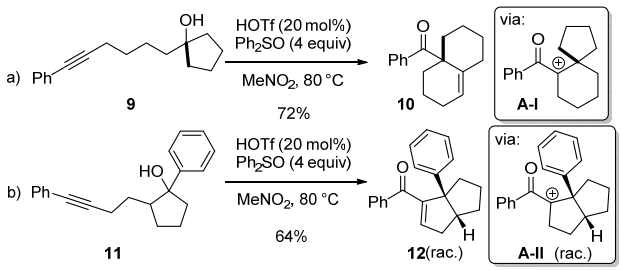
Table 2. Substrate scope: C-shift.[a]



[a] Reactions were performed at 80°C for 10 min with **1** (0.25 mmol, 1.0 equiv), Ph_2SO (1.00 mmol, 4.0 equiv) and HOTf (0.05 mmol, 20 mol %) in $MeNO_2$ (2.5 mL). Yields refer to the isolated compounds.

At this juncture we were eager to investigate the possibility of 1,2-carbon shifts by employing tertiary alcohol substrates. In the event, (Table 2) this led to an efficient synthesis of highly congested, quarternary all-carbon substituted α-carbonyl compounds. Starting from simple substrates **1l**-**q**, different aliphatic as well as aromatic groups were efficiently incorporated at the quarternary α-carbonyl position (Table 2). Electronically

different substituents such as a phenyl group, a heterocycle or a methyl group were readily shifted. Interestingly, albeit yields remained satisfactory, the carbon shift was rather indiscriminate, when it came to the differentiation between two substituents. This finding is consistent with the computational mechanistic analysis discussed below.



Scheme 4. α-Keto cation mediated synthesis of bicycles.

After this initial reactivity screen, we sought to apply this oxidative cyclization towards the synthesis of more complex structures (Scheme 3). The use of cyclopentanol **9** smoothly resulted in the ring-expanded bicyclic enone **10**. Conversely, the phenyl-substituted cyclopentanol **11** yielded selectively the diquinane **12** (Scheme 3b). Here, a carbon shift in the α-keto cation **A-II** would generate a bridged bicylic [3.3.1] system by ring-expansion, so that elimination is precluded by the Bredt rule (Ph migration is energetically unfavourable, see below). Therefore, the otherwise unfavourable direct deprotonation of **A-II** becomes predominant.

With the aim of providing a predictive model, DFT-based computational analysis was undertaken. As shown in Figure 1 ionized **1a** first stabilizes as a cyclic cation-π-complex **Ia'**. This complex is then further stabilized by interacting with the lone pairs of a sulfoxide's oxygen atom, which results in immediate cyclisation yielding sulfoxide stabilized vinyl cation **IIa**. A cyclization of **Ia'** without the assistance of $SOPh_2$ is ~ 6 kcal/mol higher in energy. From **IIa**, a quasi-concerted addition of the sulfoxide ensues. With a barrier of $\Delta G^{\ddagger}$ = 8 kcal/mol the S-O bond is easily cleaved and α-carbonyl cation **A** is formed upon departure of diphenyl sulfide. As mentioned above, the addition of sulfoxides to vinyl cations or Au^{+}-activated alkynes is dominated by a subsequent [3,3]-sigmatropic rearrangement resulting in the formation of thioethers.[21,23] The deviation from this pathway can be ascribed to the very low activation barrier for the hydride shift (**TS:Ab-B**) of only $\Delta G^{\ddagger}$ = 2.5 kcal/mol. The respective barrier for the [3,3]-sigmatropic rearrangement is ~ 10 kcal/mol higher (**TS:A'-4a-H^{+}**), with a value for $\Delta G^{\ddagger}$ = 12.4 kcal/mol.

The preference for the hydride shift over direct deprotonation of **A** was analysed next. As known from fundamental studies[11,12b] and mechanistic analyses of the gold stabilized counter-part[19b,20c,21b] the α-carbonyl cation is indeed a non-classical cation. In barrierless processes it changes conformation to allow an interaction of a free electron pair of the carbonyl oxygen with the empty p-orbital, an extreme form of this stabilization resulting in the two vinyl epoxide renditions **Aa** and **Ab**. From **Aa** an *ipso*-Friedel Crafts attack easily leads to the phenonium ion **Ac**, the energetic minimum of the non-classical cation.

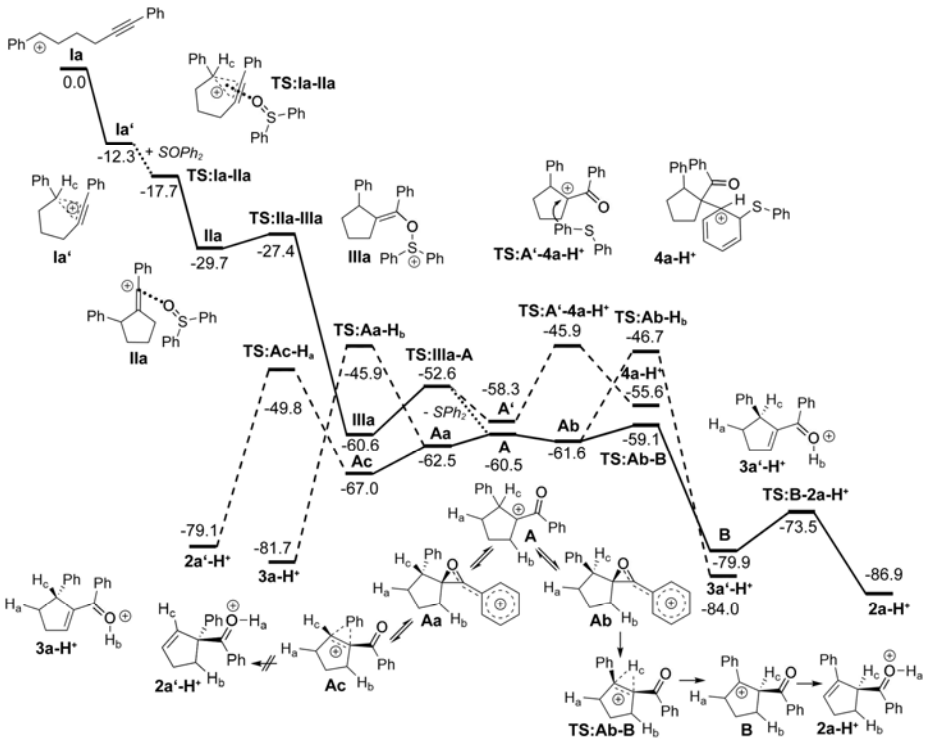


Figure 1. Profile for the formation, rearrangement and deprotonation of α-carbonyl cation **A**, calculated for the reaction of ionized **1a** with Ph_2SO. Free energy values (ΔG in kcal/mol; M06-2X/6-31+G(d,p)) relative to the separated reactants.

The high reactivity of the α-carbonyl cation strongly disfavours *inter*molecular over *intra*molecular reaction pathways. Hence, deprotonation is assisted by a carbonyl oxygen lone pair. For the cleavage of H_a a transition state was located from **Ac** (**TS**:**Ac-H$_a$**), thus completing a Ph-shift, albeit with a high activation barrier of 17.2 kcal/mol. Starting from **Aa** and **Ab**, two transition states (**TS**: **Aa-H$_b$**/**Ab-H$_b$**) were located for the deprotonation of H_b.

Both of these, however, were also much higher in energy than the transition states for the H-shift.[25] This changes dramatically for a substrate like **1p**, bearing a methyl and a phenyl group. Here, the additional stabilization provided by the methyl group lowers the activation barrier for the deprotonation of phenonium **Ac** to 5.1 kcal/mol, while the methyl shift's activation barrier rises by 3.1 kcal/mol, compared to the former H-shift, to 5.6 kcal/mol (see SI for a Figure). Thus, the migratory aptitude depends mainly on the stabilization provided by the remaining substituent.

In summary, we have reported a family of novel oxidative cyclizations driven by sulfoxide interception of a vinyl cation. This reaction involves the transient formation of a highly reactive α-carbonyl cation under moderate temperatures. DFT computations clarify the fate of the cation as a function of substitution pattern and available pathways while providing a simple predictive rationale.

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Keywords: alpha-carbonyl cation • vinyl cation • sulfoxide • oxidative cyclization • rearrangement

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[24] In these cases, resubjecting isolated **2** to the reaction conditions led to isomerization to **6**, thus suggesting isomerization as the culprit for lower selectivity. See Supporting Information for details.

[25] Please note that the products of the two deprotonation pathways, **3a-H**$^+$ and **3a-H**$^+$, have different energies, as each of the two enantiomers has a distinct preferred conformation.

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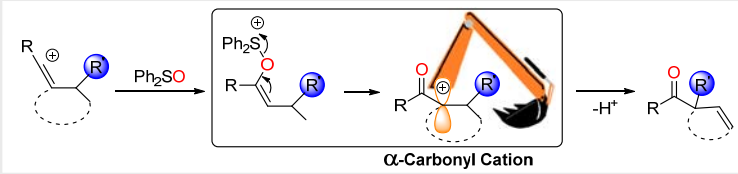

Tobias Stopka, Meike Niggemann and Nuno Maulide**

Page No. – Page No.

α-Carbonyl Cations in Sulfoxide-Driven, Oxidative Cyclizations

Combining forces to generate α-carbonyl cations from vinyl cations in an acid-catalysed procedure. Highly reactive, they induce hydrogen and carbon shift reactions with unusual selectivities. Mechanistic analysis confirmed their intermediacy and provides a prediction scheme for the migratory aptitude of different substituents.