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Zinc-catalyzed Meinwald rearrangement of tetrasubstituted 1-alkynyloxiranes to tertiary α-alkynylketones[†]

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Easy access to tertiary α -alkynylketones *via* a Meinwald-type rearrangement of 1-alkynyloxiranes is reported. This transformation is selectively accomplished with an economical zinc catalyst.

Epoxides are readily available and versatile intermediates in organic synthesis as they can be easily converted into various valuable building blocks.¹ Among the broad reactivity of epoxides, one of the most useful transformations is the Meinwald rearrangement, which leads to industrially and synthetically relevant α -substituted carbonyl compounds.² It has been found that the regioselectivity observed for a particular epoxide depends largely on the substituents and the catalyst (Scheme 1(a)).³ Particularly, metal-catalyzed transformations involving 1-alkynyl epoxides have been extensively studied in the last few years, with special emphasis on the use of precious metals such as gold,⁴ platinum,⁵ silver⁶ or iridium.⁷ These compounds do not undergo a rearrangement, yet can be converted into furan derivatives when di- or trisubstituted epoxides are used (Scheme 1(b)).^{4–7} In sharp contrast, we recently found that tetrasubstituted 1-alkynyloxiranes can be transformed selectively into tertiary α-alkynylketone derivatives in the presence of gold catalysts (Scheme 1(b)).8 This study showed



Scheme 1 (a) Meinwald rearrangement. (b) Gold-catalyzed transformations of 1-alkynyl epoxides.



Scheme 2 Meinwald rearrangement of epoxide **1a**: screening (yields of isolated **2a**). ^a After 5 min at 0 °C. ^b After 24 hours at rt. ^c After 5 days using 20 mol%.

that gold likely behaves as an oxophilic Lewis acid. Accordingly, we decided to explore the ability of more economical and available Lewis acid catalysts to promote this interesting transformation. Herein we disclose the use of a cheap zinc catalyst,⁹ which promotes the completely selective and highly efficient rearrangement of tetrasubstituted 1-alkynyl epoxides into synthetically valuable tertiary α -alkynylketones.¹⁰

Our study was commenced by subjecting epoxide **1a** to various Lewis acid catalysts (5.0 mol% catalyst, CH_2Cl_2 , rt), as depicted in Scheme 2. Under these reaction conditions, we found that various catalysts were able to promote the Meinwald rearrangement to yield ketone **2a** in a selective manner. As shown in Scheme 2, $Zn(OTf)_2$ proved to be superior to other common metal triflate catalysts derived from $Cu(\pi)$, $Fe(\pi)$, $Fe(\pi)$, $Sc(\pi)$ or $Bi(\pi)$, as well as to previously studied $AuCl_3$.¹¹ Besides, the use of a strong Brønsted acid like TfOH or TsOH allowed the transformation to occur although in lower yield and reproducibility. Interestingly, phosphoric acid derived from (*R*)-BINOL (20 mol%) showed catalytic activity, however, an unpractical long reaction time was required to achieve appreciable conversion.¹²

With these results in hand, we next explored the scope of this zinc-catalyzed rearrangement using various tetrasubstituted 1-alkynyloxiranes 1. The results are shown in Scheme 3. Thus, alkynyl epoxides bearing aryl substituents ($R^1 = Ph$, MeO-C₆H₄-) gave rise to ketones 2**a**-**b** in very good yields

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Scheme 3 Zinc-catalyzed rearrangement of epoxides **1** into ketones **2** (isolated yield in parentheses, DCE = 1,2-dichloroethane).

(91 and 89%, respectively). Various alkyl substituted alkynyl epoxides were also tested, including primary, secondary and tertiary alkyl chains ($R^1 = n$ -Bu, n-C₈H₁₇, c-C₃H₇, t-Bu). Under the same reaction conditions, the corresponding alkynyl ketones 2c-f were generally obtained in good yields (66-94%). The stability of the alkynylcyclopropane moiety in ketone 2e is noteworthy, whose reactivity might be further exploited. Interestingly, a silvl group $(R^1 = TMS)$ on the alkyne was tolerated as well, providing ketone 2g in 77% yield. The use of a terminal alkyne on the epoxide also proved suitable, giving rise to ketone 2h in 83% yield. As these transformations involved a 5-to-6 ring enlargement, we subsequently proceeded with other tetrasubstituted alkynyl epoxides. Thus, epoxide 1i bearing a cyclohexane spiro core was converted into the α -alkynyl cycloheptanone 2i in a moderate yield of 66% only when the reaction was accomplished at 70 °C.¹³ Similarly, acyclic substrates were also studied as exemplified by epoxides 1j-k, which gave rise to acyclic α-alkynyl ketones 2j-k, respectively. It should be noted that the transformation involving epoxide 1j required again slightly stronger reaction conditions.¹³ Interestingly, ketone 2k was obtained under mild conditions and with complete selectivity (preference for the migration of the benzyl group).

We also studied the reactivity of the corresponding tri- or disubstituted 1-alkynyloxiranes under zinc catalysis (Scheme 4). Unfortunately, only a complex mixture of various inseparable products¹⁴ along with decomposition of the starting substrate was observed, even when the experiments were carried out at lower reaction temperatures.



Scheme 4 Unsuccessful tri- and disubstituted 1-alkynyloxiranes.





According to the commonly accepted mechanism for the Meinwald rearrangement,^{2a,3} the complete selectivity observed in these transformations can be attributed to the favoured formation of a stabilized propargylic carbocation I (Scheme 5). Further studies were directed toward finding evidence for the presence of this key intermediate. First, we accomplished the capture of the proposed intermediate using a simple nucleophile such as MeOH (Scheme 5(a)). Thus, when the reaction was conducted in MeOH as solvent, a separable mixture of the alkynol 3a and the ketone 2a was obtained in good yield after a long reaction time (72 h, 3a = 41%; 2a = 35%; 3a : 2a = 1.2:1).¹⁵ Interestingly, the formation of alkynol **3a** occurred regio- and chemoselectively, as it was the only addition product observed. On the other hand, the formation of the ketone 2a might be explained by assuming a similar reaction rate between the nucleophile addition and the Meinwald rearrangement. Nonetheless, a pinacol-type rearrangement on alkynol 3a could also account for the formation of the alkynylketone 2a. To exclude this possibility, we stirred isolated 3a in the presence of catalytic amounts of Zn(OTf)2 at room temperature in dichloromethane. The typical catalyst loading (5.0 mol%) did not give rise to the ketone 2a and most of the alkynol 3a was recovered (80%), while when using a higher catalyst loading (20 mol%) 2a was obtained in very low yield (12%) (Scheme 5(b)). Additionally, we wanted to study if the possibility that the adventitious presence of water, which would form a 1,2-diol intermediate prior to the rearrangement, could play a role in these reactions. Thus, we tried to prepare the corresponding diol analogous to alkynol 3a.

However, all attempts using various catalysts and moisture conditions led to the formation of **2a**. Conversely, we were able to prepare diol **4i** from alkynyl epoxide **1i** by treatment with TsOH-H₂O (see ESI[†] for details). When alkynol **4i** was subjected to various reaction conditions only trace amounts of ketone **2i** were observed in the crude mixture (Zn(OTf)₂, 20 mol%, 70 °C, DCE) (Scheme 5(c)). These experiments likely support a Meinwald-type rearrangement to be the operating mechanism, excluding the participation of diol species.

In summary, we have disclosed herein the preparation of synthetically valuable tertiary α -alkynylketones¹⁰ by means of a completely selective Meinwald-type rearrangement of tetra-substituted 1-alkynyloxiranes. This transformation is efficiently promoted by an inexpensive zinc catalyst. The origin of the selectivity of this rearrangement resides on the superior stability of the propargylic carbocation over other possible species.³ Further studies concerning the enantioselective version of this transformation enabling the enantiopure generation of quaternary stereogenic carbons, by using metal or Brønsted acid catalysis, are ongoing in our laboratories.

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- 12 HPLC chromatography indicated <5% ee.
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- 14 The formation of furan derivatives as described for other metal catalysts was not detected. See ref. 4–7.
- 15 When the same reaction was accomplished with 20 mol% of Zn(OTf)₂, the reaction proceeded faster (5 h) in similar yields although with reversion of the product ratio (3a = 22%, 2a = 43%, 3a : 2a = 1 : 2).