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Alumina-Mediated Soft Propargylic C-H Activation in Unactivated Alkynes

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The discovery and development of new synthetic methods exploiting earth-abundant- element-based catalysts is an important goal in contemporary synthetic organic chemistry, which faces increasingly stringent requirements of sustainability. In this work, we disclose alumina-mediated propargylic C-H activation inducing a challenging transformation of readily available alkynes into a valuable 1,3-diene moiety under unprecedentedly mild conditions. Combining DFT-investigation and synthetic observations, we demonstrate that partial hydroxylation of alumina's surface might play essential role in this process.

1,3-Diene is an important scaffold widely used and studied in modern organic chemistry. The interest to this motif is fuelled by its presence in numerous natural[1,2] and non-natural[3] products demonstrating a broad range of functions[4,5]. Moreover, 1,3-dienes also serve as important intermediates showing diverse reactivity[6–12] and enabling synthesis of various target molecules[13] or classes of compounds[14,15].

Although there are several methods enabling synthesis of this moiety starting from different building blocks[16–20], most of the approaches require transition metal-catalysts, functional or directing groups, and multi-step procedures. Meanwhile, isomerization of alkynes into 1,3-dienes is a potentially powerful atom- and step-economic transformation that requires no functional or directing groups and enables facile access to this important structural motif.

While transition-metal catalysts based on Au[21], Ru[22], Ir, Re[23], or Pd[24] enable isomerization of ynones and ynamides into dienones and amidodienes, respectively, it remains particularly challenging to obtain 1,3-dienes from unactivated (i.e. aliphatic or aryl) alkynes[25]. This challenge arises due to weak acidity of propargylic protons (pK_a>30 for propyne in DMSO[26,27]), removal of which induces the reaction. For this reason, propargylic deprotonation generally occurs under harsh conditions exploiting either strong bases or excessive heating[28,29], where dienes become unfavorable products[30].

To enable "soft" propargylic deprotonation under mild conditions, Zhang et al. have suggested an elegant "push-pull" strategy using gold(I) complexes[31]. Here, gold species acts as a soft π-Lewis acid that interacts with a triple C-C bond and lowers pK_a of the propargyl protons (Fig. 1B). At the same time, the respective ligand acts as a base removing the propargylic proton. While being an illustrious example of rational design of the catalytic system, this approach requires multi-step synthesis of non-conventional ligands and large mass of expensive reagents.

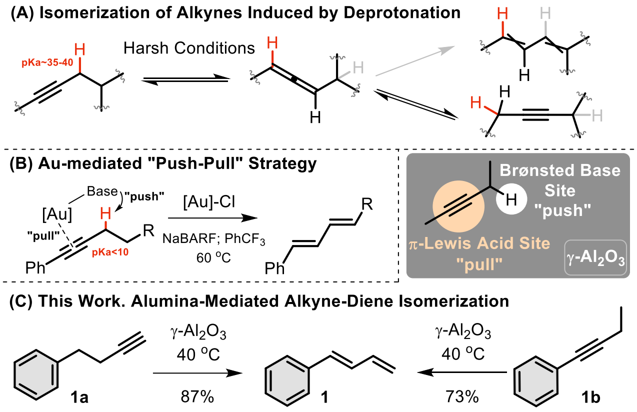

Figure 1. Isomerization of alkynes upon propargylic deprotonation. (A) Redistribution of π-bonds along an aliphatic chain. (B) Au-catalyzed alkyne-diene isomerization induced by "push-pull" activation. (C) Alumina-mediated alkyne-diene isomerization. Schematic mechanism and the key synthetic transformations.

Our recent findings demonstrate that thermally pre-treated γ-alumina acts as a soft π-Lewis acid inducing transformations of alkynes previously assigned primarily or even exclusively to Au-catalysts[32]. Provided the presence of numerous potential

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Brønsted Base O-sites located on alumina's surface, we envisioned that a similar "push-pull" activation of the propargyl-moiety may take place on γ-Al_2O_3 (Fig. 1C). In principle, soft propargylic deprotonation can induce isomerization of alkynes leading to a whole set of products, such as isomeric alkynes, allenes or 1,3-dienes (Fig. 1A). In this work, we report transition-metal-free soft propargylic deprotonation of unactivated alkynes, which transform into 1,3-dienes under ambient conditions.

Initially, we found that alkyne **1a** transforms into **1** in high yields upon exposure to activated alumina under vacuum at 40 °C. The *trans*-isomer was the only product obtained after the extraction of the reaction mixture. Noteworthy, the reaction can be scaled up to gram-quantities, whereas the used alumina can be easily recycled and reused (Table S2). While searching for the optimal **1a**-alumina ratio, we have noticed that the reduction of the alumina's quantity elongates the reaction times needed to fully convert **1a** into **1**, which demonstrates catalytic nature of the reactive centers located on alumina surface. Interestingly, internal alkyne **1b** also isomerizes into **1**, although in slightly lower yields.

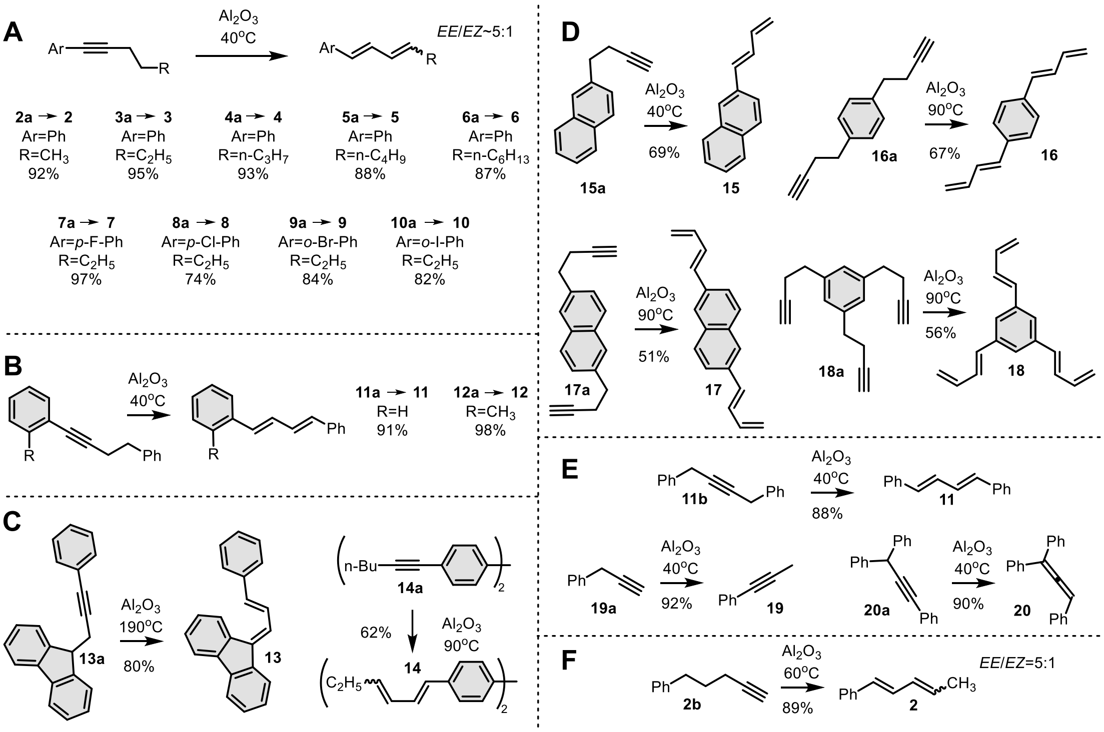

Figure 2. Reaction scope of the alumina-mediated alkyne-diene isomerization. (A) Effect of the aliphatic chain's length and tolerance to C-Hal functionalities. (B) Formation of dienes conjugated with aromatic moieties. (C) Isomerization of alkynes bearing bulky substituents. (D) Isomerization of terminal alkynes. (E) Isomerization of alkynes into 1,3-diene, alkyne, and allene. (F) Distant redistribution of π-bonds along the aliphatic chain leading to conjugated dienes. The reactions were run in the solid-state for 6h using 100 mg of the starting material and 10 g of alumina under vacuum.

We also investigated stereoselectivity of the method for the formation of the double bond distal to the phenyl moiety. To study this aspect together with the scope of the isomerization, we examined a range of internal alkynes with different substituents (Fig. 2). We found that alkynes **2a**-**6a** transform into respective mixtures of *EE*/*EZ* 1,3-dienes **2**-**6** with virtually the same ratio (5:1) in excellent yields (Fig. 2A). This experiment indicates that the length of aliphatic chain does not affect the selectivity of the method, whereas thermodynamic control is likely to dictate the distribution of the products. The transformations of **7a**-**10a** demonstrate that the reaction conditions nicely tolerate C-Hal functionalities decorating phenyl moiety. Noteworthy, if the double bond is adjacent to an aryl moiety, it isomerizes selectively into the *trans*-form. Thus, isomerization of **11a** and **12a** leads solely to *EE*-1,3-dienes **11** and **12**, respectively (Fig. 2B). Steric hindrance appears to play important role, since bulky fluorenyl-substituent did not allow conversion of **13a** at ambient temperatures (Fig. 2C). Additionally, we investigated whether more than one alkyne moiety can be isomerized. Thus, **14a** transforms into the anticipated mixture of two isomers (*EE-EE*:*EE-EZ*= 4:1) under elevated temperatures.

Then, we turned our attention to the isomerization of terminal alkynes such as **1a**, transformation of which into **1** was previously described using the explosive oxidant KO_2 [33]. The reaction conditions enable transformation of naphthalene derivative **15a** into **15** in good yields (Fig. 2D). Moreover, the transformation can be exploited to introduce two or even three 1,3-diene moieties within a single molecule as demonstrated on the examples of **16**-**18**. Moreover, the transformation of **11b** into **11** shows that the reaction works also for internal alkynes with two sp^3-substituents (Fig. 2E). To confirm that the reaction occurs via formation of allene species, we studied the isomerization of alkynes **19a**-**20a**, which cannot transform into 1,3-dienes. While **19a** readily undergoes alkyne "zipper" transformation into **19** without possibility to isolate intermediate allene species, **20a** yields the allene 20 in excellent yields. The transformation of **2b** into **2** with the same stereoselectivity as **2a** is particularly interesting because it represents quite distant redistribution of the π-bonds along the aliphatic chain, where phenyl moiety serves as an "anchor" allowing significant thermodynamic stabilization of the conjugated allene/alkyne/diene moieties (Fig. 2F). Interestingly, activation of aliphatic alkyne dec-1-yne led to a complex mixture of isomeric alkynes, allenes, and dienes, thus, once again underlining the role of the "anchoring" phenyl substituents.

The transformation of **1a** or **1b** into **1** occurs via a series of 1,3-H transfers, which induce reversible alkyne-allene rearrangements leading to **IM1**-**IM3** (Fig 3). All the mentioned intermediates were detected upon either quenching the reaction with dichloromethane prior to full conversion or monitoring in hexane. Besides IM1-IM3, we also observed cis-diene **IM4**, which together with the other intermediates completely transforms into the product **1**. While the formation of the diene moiety from allenes is expected to be irreversible, alumina is known to induce cis/trans isomerization of alkenes[34]. Therefore, **IM4** and **1** should exist in equilibrium, which is however fully shifted to the *trans*-isomer **1** due to higher thermodynamic stability of the latter. These observations evidence that the reaction occurs under thermodynamic control.

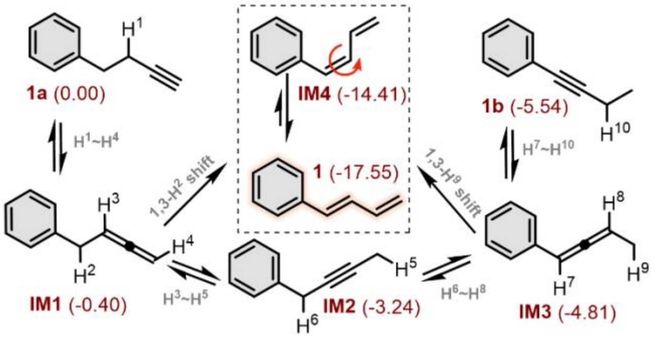

Figure 3. Isomerization of alkynes 1a and 1b into 1 via sequence of 1,3 H shifts. DLPNO-CCSD(T)/cc-pVTZ//PBE/def2-TZVP-calculated relative energies in kcal/mol are given in parentheses.

We have previously reported that activated γ-alumina allows soft π-activation of alkynes inducing their transformation similarly to transition-metal soft π-Lewis acids[32]. In that work, we have assigned such mode of reactivity to Frustrated Lewis Triads (FLTs), reactive centers consisting of one Al_{III}- and two O_{II}-sites on the (110) alumina's termination. According to the key concepts of Dewar-Chatt-Duncanson (DCD) model[35], Al_{III}-sites coordinate alkynes via σ-donation, whereas O_{II}-sites imitate the most crucial interaction in the realm of π-soft activation, namely, π-back donation. Since FLTs are surrounded with basic O-sites, the latter could remove propargylic protons, provided that FLT-centers coordinate alkyne moiety and increase acidity of the propargylic C-H bond.

Starting with this chemical concept, we investigated the interaction of but-2-yne as a model compound with (110) termination of alumina by means of DFT-calculations. Our investigation shows that the envisioned mechanism of the C-H activation may take place with the respective kinetic barrier of 23.8 kcal/mol (Fig. 4A). However, we have also observed an alternative deprotonation pathway with significantly lower barrier of 13.7 kcal/mol. In this scenario, the Al_{III}- and O_{II}-sites, belonging to the FLT moiety, act as a Lewis pair (Fig. 4B). Since there is still no conventional description of the alumina's surface; it is a challenging task to unambiguously assign the observed reactivity to a certain center. In the previous work, we based our assumption on the physical[36,37] and computational[38–41] data, indicating that the (110) facet should be considered as a predominant termination of γ-Al_2O_3, where the presence of metastable Al_{III}-centers is assumed [42,43].

However, in the recent report Khivantsev et al.[44] claims the reconstruction of the (110) facets with the formation of thermodynamically favourable (100) termination, where no Al_{III}-centers can be found. We, therefore, turned our attention to the corresponding surface, where only one AlV adsorbs the model compound but-2-yne with considerable energies (Table S3 and Fig. S69). Interestingly, the surrounding OIII-sites induce the deprotonation process with 31.5 kcal/mol barrier, which does not correspond to the experimentally observed mild conditions of the reaction (Fig. 4C) Meanwhile, it is known that certain amounts of water preserve even after the exploited thermal activation of γ-Al_2O_3. Sautet et al. have previously reported that neighbouring hydroxyl groups may play essential role in the activation of some molecules [42,43,45]. To investigate the potential role of the OH-groups, we have investigated how hydroxylation of the neighbouring Al_V-sites would affect the kinetic barriers.

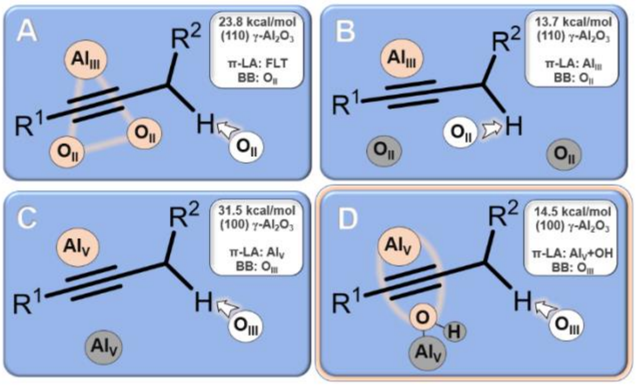

Figure 4. Schematic representation of alumina-mediated propargylic C-H activation in but-2-yne. (A and B) Deprotonation pathways observed on the (110)-alumina termination. (C and D) Deprotonation pathways observed on the (100)-alumina termination. Respective coordinates and energies can be found in the supplementary materials (Fig. S70-72). Energetic barriers for the propargylic deprotonation are given in the white section together with the considered alumina's termination. (π-LA: site serving as π-Lewis Acid; BB: Brønsted Base site).

Thus, we observed that the interaction of the introduced OH-group with the alkyne moiety drastically lowers the energy barrier for the deprotonation of but-2-yne (Fig. 4D). Therefore, the hydroxyl group appears to be a reasonable source of electron density mimicking the π-back-donation discussed in the DCD model and enabling activation of the propargylic C-H bond via soft π-activation of the triple bond. The observed mode of reactivity contributes to the current understanding of the γ-alumina's surface providing new insights into the structure-activity relation of the reactive centers. Moreover, the discovery demonstrates the potential of γ-Al_2O_3 as a sustainable catalyst inducing valuable intricate organic transformations.

Author Contributions

V.A. and M.F. carried out the synthetic part and conceived the idea. D.I.S. performed the DFT study. V.A. prepared the manuscript with the feedback from all co-authors. M.F. and D.I.S. prepared the supplementary materials.

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Conflicts of interest

There are no conflicts to declare

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