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Base-Catalyzed [1,*n*]-Proton Shifts in Conjugated Polyenyl Alcohols and Ethers

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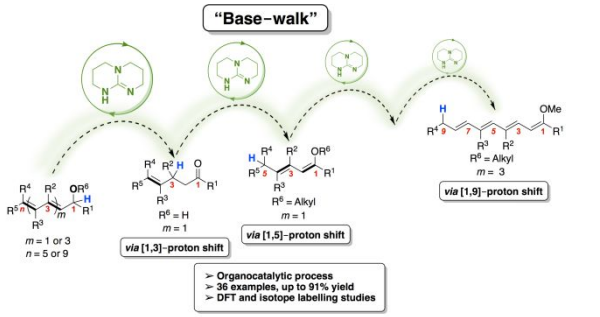
Supporting Information Place holder

ABSTRACT: The isomerization of dienyl alcohols and polyenyl alkyl ethers catalyzed by TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) under metal-free conditions is presented. Two reaction pathways have been observed. For dienyl alcohols, the reaction proceeds by a [1,3]-proton shift to give γ,δ-unsaturated ketones exclusively. On the other hand, the reaction with polyenyl alkyl ethers gives the corresponding conjugated vinyl ethers in good yields (up to 83%), with regioselectivities up to >20:1. Experimental and computational investigations suggest that the mechanism proceeds through consecutive "chain-walking" proton shifts ("base-walk") mediated by TBD.



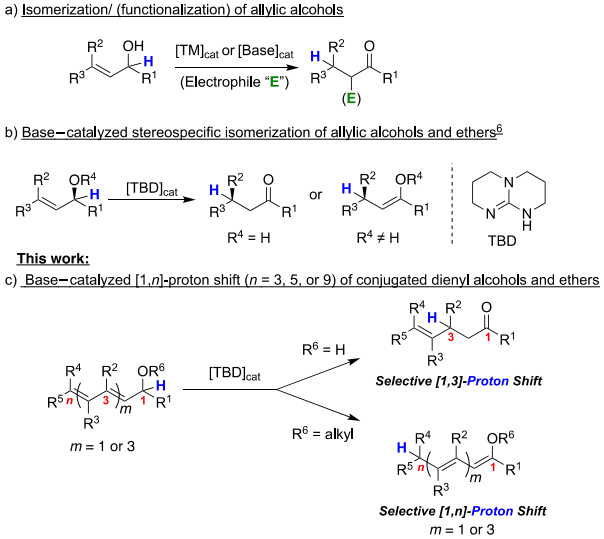
KEYWORDS: *base-catalysis, mechanism, superbase, isomerization, proton shift, base-walk*

The isomerization of allylic alcohols into carbonyl compounds is a fundamental and powerful tool in organic synthesis. The reaction results in a functional-group interconversion, thus allylic moieties may be treated as carbonyl equivalents.[1,] Since the pioneering work of Logn *et al*.,[2a] some effort has gone into the development of more efficient catalytic systems for this transformation.[3,3] Our own group has reported the use of a family of complexes with the general structure [Cp*Ir(III)X] for the isomerization of primary and secondary allylic alcohols, as well as for the synthesis of α-functionalized carbonyl compounds from allylic alcohols under very mild conditions (Scheme 1a).[4] Although the isomerization of allylic alcohols has traditionally been accomplished using metal catalysts, a few examples of transition-metal-free isomerizations are also known.[5] In 2016 we reported that the isomerization of electron-poor allylic alcohols and allylic ethers could be mediated by a simple base, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), through a stereospecific [1,3]-proton shift (Scheme 1b).[6]

Extended conjugated systems such as dienyl alcohols and dienyl ethers (Scheme 1c) are common structural motifs in biologically active natural products.[7] Compounds containing these structures are also extensively used as key intermediates in organic synthesis.[8-11] Despite the importance of these structural motifs, their isomerization into carbonyl compounds or enol ethers has proved challenging, though. A reason for this is that transition-metal-catalyzed approaches are ineffective for the isomerization of such complex conjugated systems due to the formation of stable diene–metal complexes that prevent hydride migration.[12]

In this article, we describe the first examples of the isomerization of conjugated allylic alcohols and ethers, using a base catalyst (Scheme 1c). The process is reminiscent to the recently explored metal-catalyzed "chain-walking" or "metal-

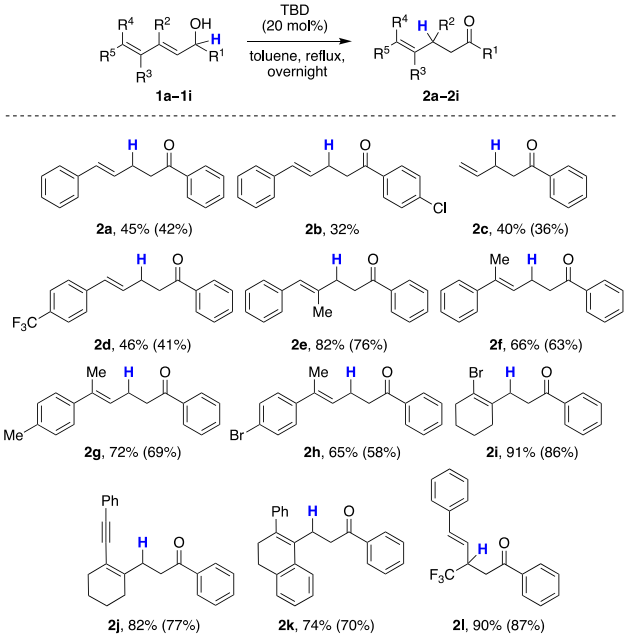
Scheme 1. Isomerization of unsaturated alcohols and ethers



walk" processes, which refer to the ability of certain metal complexes to perform a series of consecutive [1,2]- or [1,3]-hydride shifts along a hydrocarbon chain.[13] This formal alkene migration might be terminated by an enol tautomerization.[14,15] The work presented here consists, in contrast, of a formal proton migration alongside a polyenylic chain, constituting the first example of a "base-walk" process in these type of substrates.[16] The reaction is regioselective: the isomerization of conjugated allylic alcohols proceeds through a [1,3]-proton shift. On the other hand, the analogous ethers follow a formal [1,*n*]-proton shift where *n* = 3, 5 or 9. The substrate scope, experimental and computational mechanistic investigations are presented.

We started by investigating the isomerization of conjugated dienyl alcohols, and we selected dienol **1a** as a model substrate. As the catalyst, we used the base TBD, as it gave excellent results in the isomerization of allylic alcohols.[6] A first attempt conducted with 10 mol% of TBD in toluene at 60 °C overnight did not give any product, and **1a** was recovered. When 20 mol% of TBD was used in refluxing toluene (Scheme 2), dienol **1a** was converted completely and exclusively into γ,δ-unsaturated ketone **2a**, albeit in a moderate yield of 45%. The introduction of a chloride group in the *para* position of the aryl ring at R^1 was detrimental to the reaction, and a yield of only 32% of **2b** was obtained. Decomposition was also observed when a terminal dienol **1c** was tested, and **2c** was obtained in a low yield of 40%. Dienyl alcohol **2d** bearing a trifluoromethyl group in the para position of the aryl ring at R^5 was converted to the corresponding γ,δ-unsaturated ketone with a yield of 46%. In contrast, the introduction of substituents onto the terminal alkene (i.e., R^3 and R^4) prevented the decomposition of the starting dienyl alcohols, and significantly enhanced the yields of the products (**2e**–**2l**). For instance, compounds **1e** and **1f**, bearing a methyl group at either R^3 (**1e**) or R^4 (**1f**), were converted into the corresponding γ,δ-unsaturated ketones in good yields. Both electron-donating and electron-withdrawing substituents in the para position of the aryl ring at R^5 were tolerated and ketones **2g** and **2h** were obtained in good yields (72% and 65% respectively).

Scheme 2. Substrate scope of the isomerization of dienyl alcohols[a]



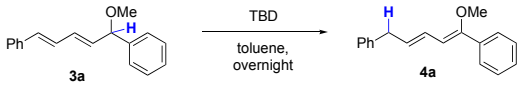
[a]**1a**–**1l** (0.1 mmol) and TBD (20 mol%) in toluene (1.0 mL). Isolated yields in parentheses.

Similarly, when the second alkene was part of a cyclic structure (**1i**–**1l**), very good yields were obtained. The presence of a bromide or an alkyne was tolerated, and compounds **2i** and **2j** were formed in 91 and 82% yields. The introduction of a trifluoromethyl group at R^2 was also found to be beneficial, and **1l** gave the product in an excellent yield of 90%. Products derived from [1,5]-proton shifts were not detected in the isomerization of dienyl alcohols **1a**–**1l**.

Next, we turned our attention to the isomerization of dienyl ethers. When ((1*E*,3*E*)-5-methoxypenta-1,3-diene-1,5-diyl)dibenzene (**3a**) was treated with TBD (20 mol%) in toluene at 60 °C overnight, interestingly, and in contrast to the reaction of conjugated dienyl alcohols, diene **4a** formed as the major product as a result of a formal [1,5]-proton shift ([1,5]:[1,3] > 20:1). Compound **4a** was obtained in 70% yield, as a mixture of stereoisomers [(1*Z*,3*E*)/(1*Z*,3*Z*) = 78:22] (Table 1, entry 1). We also tested other bases, and found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) did not catalyze the reaction under similar reaction conditions (i.e., substoichiometric amount of base, 60 °C, entries 2–4). A stoichiometric amount of DBU (1.0 equiv.), on the other hand, gave **4a** in 52% yield (entry 5).

As the best results were obtained with TBD, we carried out further optimization experiments with this base. We found that the catalyst loading could be lowered to 10 mol% when the temperature was raised to 85 °C; under these conditions, **4a** was formed in 83% yield (entry 6). Increasing the reaction time did not have any significant effect on the formation of the product (entry 7). In all instances, the stereoisomeric ratio of the product **4a**, i.e., (1*Z*,3*E*)/(1*Z*,3*Z*), remained essentially constant, at *ca.* 78:22, suggesting that a thermodynamic equilibrium was reached. A complete list of the optimization experiments can be found in the Supporting Information (Table S1). The reaction did not take place in the absence of the base catalyst (entry 8).

Table 1. Base-catalyzed isomerization of 3a[a]



Entry	TBD (mol%)	*T* [°C]	**4a** [%] / (1*Z*,3*E*)/(1*Z*,3*Z*)[b,c]
1	TBD (20)	60	70 / 78:22
2	DBU (20)	60	< 5 / -
3	DBU (40)	60	< 5 / -
4	DABCO (40)	60	< 5 / -
5	DBU (100)	80	52 / 77:23
6	TBD (10)	85	83 (80%)[d] / 78:22
7[e]	TBD (10)	85	83 / 78:22
8[f]	-	85	< 5 / -

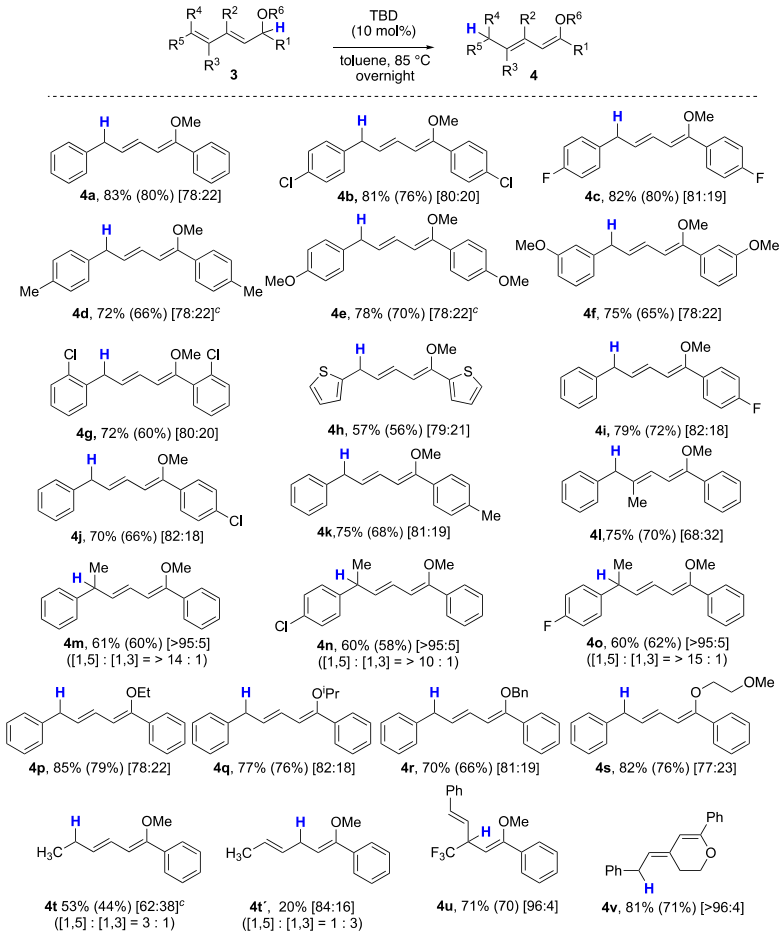
[a]Unless otherwise noted, **3a** (0.1 mmol) in toluene (1 mL). [b]Yields determined by ^{1}H NMR spectroscopy using an internal standard. [c]*E*/*Z* ratios were calculated by ^{1}H NMR spectroscopy. [d]Isolated yield in parentheses. [e]Run for 24 h. [f]Without TBD.

We went on to study the substrate scope of the reaction under these optimal reaction conditions. We tested substrates bearing electron-donating and electron-withdrawing substituents on the phenyl groups at R^1 and R^5 (Scheme 3). Dienyl ethers bearing electron-withdrawing groups in both aryl rings (**4b**–**4c**) were converted into the products in good yields. The introduction of electron-donating substituents in both aryl rings in the *para* position decreased the rate of the reaction (**3d**–**3e**), but good yields were still obtained at 110 °C. The presence of a methoxy group at the *meta* position of the phenyl ring had no effect on the rate, and **4f** was obtained in 75% yield under standard conditions. A chloride group at the *ortho* position was well tolerated, and **4g** was obtained in 72% yield. Dienyl ether **3h**, bearing two heterocyclic thiophenyl substituents at R^1 and R^5, gave **4h** in 57% yield. Fluoride, chloride, and methyl groups at the *para* position of the aryl ring at R^1 were all well tolerated, and **4i**–**4k** were obtained in good yields. Dienyl ethers with additional substitutents on the double bonds of the conjugated system, i.e., at R^3 or R^4 (**3l**–**3o**), underwent the isomerization reaction to give the products in moderate to good yields (60–75%). Interestingly, **4m**, **4n**, and **4o** were obtained with a high (1*Z*,3*E*)/(1*Z*,3*Z*) ratio of >95:5. We also tested substrates bearing different substituents at R^6. The [1,5]-proton shift worked well for ethyl (**3p**), isopropyl (**3q**), benzyl (**3r**) and 2-methoxyethyl (**3s**) ethers under the optimized conditions. Next, we investigated the introduction of an aliphatic substituent at R^5 (**3t**). Surprisingly, the reaction gave a mixture of products (3:1) in a total yield of 20%. The major product was derived from the [1,3]-proton shift pathway (**4t´**); the product of the [1,5]-shift (**4s**) was the minor product. However, when the catalyst loading was increased to 20 mol% and the temperature to reflux temperature, **4t** was formed in a better yield of 53%. Notably, compound **3u**, with a CF_3 substituent at R^2, gave only the product derived from the corresponding [1,3]-proton shift (**4u**) in 71% yield. From (*E*)-6-phenyl-4-styryl-3,6-dihydro-2*H*-pyran (**3v**), the reaction proceeded smoothly and gave **4v** in very good yield with an excellent *E*/*Z* ratio (96:4).

To test the generality of the method, more extended conjugated polyenyl ethers were tested, (Scheme 4). Tetraenyl ether **3w** afforded 46% yield of **4w** as a result of an overall [1,9]-proton shift. A tetraenyl ether with additional substituents along the conjugated chain (**3x**) reacted also in a [1,9]-proton shift yielding **4x** in an isolated 69% yield.

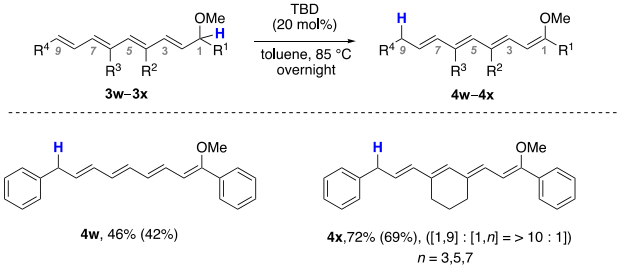
Deuterium-labeling studies were carried out with dienyl alcohol **1a**-*d*[1] and dienyl ether **3a**-*d*[1] (Scheme 5). The KIEs[17] were found to be 2.4 ± 0.5 and 3.8 ± 0.5 for the dienol and dienyl ether, respectively. These results suggest that in both cases the reaction starts with a rate-determining deprotonation at C-1. In the reaction of **1a**-*d*[1], 24% deuterium content was found at C-3 (54% of deuterium transfer) and no deuterium was found at C-5 in the product; this indicates that this substrate reacts exclusively through a [1,3]-proton-shift mechanism (Scheme 5a). The presence of deuterium (12%) at C-2 in the product is due to keto/enol tautomerization. These results are consistent with our previous work.[6] In the reaction of **3a**-*d*[1], the deuterium content at C-5 was 28% which corresponds to 61% of deuterium transfer to that position (Scheme 5b). The deuterium content at C-3 was found 20% suggesting that the mechanism follows, at least partially, a pathway involving two consecutive [1,3]-proton shifts, i.e., a [1,3]-shift followed by a [3,5]-shift. To test this idea, **3a**-*d*[3] was subjected to the reaction conditions; the product of this reaction had 20% deuterium at C-5 (41% of deuterium transfer from C-3 to C-5), which confirms that the [3,5]-proton shift does take place (Scheme 5c). Cross-over experiments performed with substrates **3a**-*d*[1] and **3s** at different concentrations suggest that the proton shift does not

Scheme 3. Substrate scope of the isomerization of dienyl ethers[a,b]



[a]**3a**–**3u** (0.1 mmol) and TBD (10 mol%) in toluene (1.0 mL). Isolated yields in parentheses. [b]Ratio of (1*Z*,3*E*)/(1*Z*,3*Z*) in brackets determined by ^{1}H NMR spectroscopy. [c]110 °C instead of 85 °C.

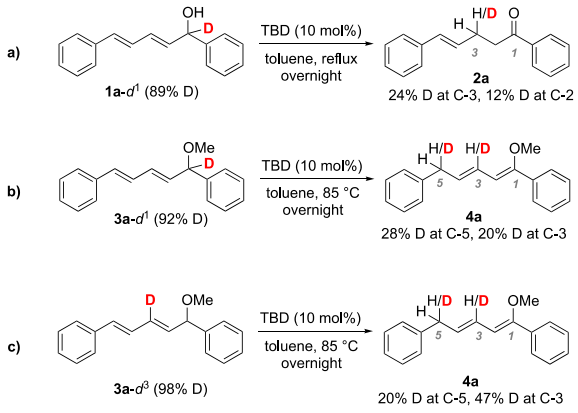
Scheme 4. Isomerization of tetraenyl ethers.[a,b]



[a]**3v**–**3w** (0.1 mmol) and TBD (10 mol%) in toluene (1.0 mL). Isolated yields in parentheses.

occur exclusively by an intramolecular pathway (See SI, Scheme S2).

Scheme 5. Deuterium-labeling studies



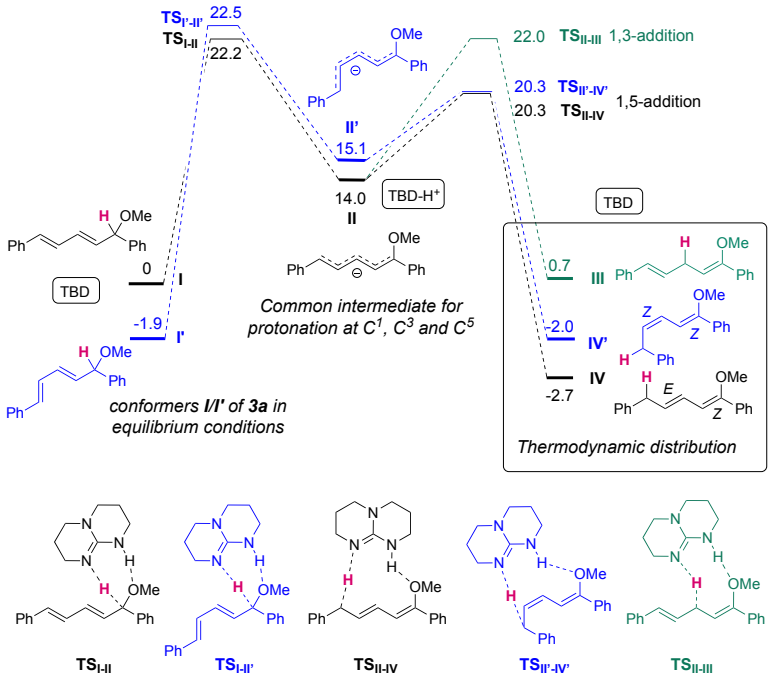


Figure 1. Calculated energy profile of the reaction. Values correspond to Gibbs free energies in kcal/mol.

To better understand the reaction, DFT calculations (Figure 1) were carried out on dienyl ethers using the Gaussian 16 software (see Supporting Information for details). Substrate **3a** was chosen as a simplest model compound for the calculations. This compound exists as an equilibrium mixture of conformers **I/I'** (Figure 1), interconverting by easy rotation around a σ-bond ($\Delta G^{\ddagger}$ = 6.4 kcal/mol). The reaction starts with the rate-limiting deprotonation of the C-1–H bond in **I** or **I'** by the TBD base with activation energies of 22.2 kcal/mol ($\mathbf{TS_{I\text{-}II}}$) and 24.4 kcal/mol ($\mathbf{TS_{I'\text{-}II'}}$), respectively. After this step, an intimate ion pair consisting of the dienylic anion and the protonated base is formed; the two intermediates **II** and **II'** cannot interconvert easily ($\Delta G^{\ddagger}$ = 16.9 kcal/mol). Each anion, for example **II**, can undergo then protonation at C-3 ($\mathbf{TS_{II\text{-}III}}$), at C-5 ($\mathbf{TS_{II\text{-}IV}}$), or at C-1 (in a reversible $\mathbf{TS_{I\text{-}II}}$) to form the three possible adducts **III**, **IV**, and **I**, respectively, with similar energies (22.0 kcal/mol for $\mathbf{TS_{II\text{-}III}}$, 20.3 kcal/mol for $\mathbf{TS_{II\text{-}IV}}$, and 22.2 kcal/mol for $\mathbf{TS_{I\text{-}II}}$). The low activation barriers seem to indicate that all possible adducts might be in equilibrium under the reaction conditions. The fact that the energies of the transition states for the transformations of **I** into the (1*Z*,3*E*) product (**IV**) and of **I'** into the (1*Z*,3*Z*) isomer (**IV'**) are very similar for both of the two steps (22.2 vs 22.5 and 20.3 vs 20.3 kcal/mol) confirms that the stereoselectivity of this reaction is not expected to be under kinetic control. Rather, the observed experimental selectivities are in good agreement with the relative stabilities of all the possible products. This indicates that thermodynamic equilibrium is reached between **I**, **I'**, **III**, **IV**, and **IV'**, with the latter two species being the most stable (–2.7 and –2.0 kcal/mol). Thus, the stereoisomeric ratio depends exclusively on the relative stabilities of the products. The (1*Z*,3*E*) stereoisomer (**IV**), which is the major isomer observed experimentally, is 0.7 kcal/mol lower in energy than the (1*Z*,3*Z*) isomer (**IV'**). The reaction kinetics was also simulated with COPASI software;[18] we calculated a ratio of stereoisomers of 71:29, which is in perfect agreement with the experimental selectivity, 78:22 (Scheme 3), and >20:1 ratio of [1,5]- *vs* [1,3]-proton shift. We were also able to explain the results obtained in the deuterium labeling experiments using DFT calculations. The calculated energies of the rate-determining transition states ($\mathbf{TS_{I\text{-}II}}$ and $\mathbf{TS_{I\text{-}II'}}$, Figure 1) increase by 0.6–0.9 kcal/mol when H is replaced with D (see Supporting Information for further details). This explains the KIE, and also the lower rates observed for the deuterated substrate **3a**.

To summarize, we have described the first method for the remote transfer of protons through extended conjugated allylic ethers. As a catalyst, the base TBD was used. The method was found to be remarkably general and the proton was successfully transferred as far as to 8 carbons away, resulting in a formal [1,9]-proton shift. In the case of extended conjugated allylic alcohols, the proton selectively transfers only to C-3 through a [1,3]-proton shift, yielding the corresponding γ, δ-unsaturated carbonyl compounds. Based on deuterium-labeling studies, it was established that the rate-determining step is the deprotonation at C-1. For polyenyl ethers, DFT studies suggest that the rate-

determining deprotonation is then followed by a consecutive number of proton shifts until the last carbon of the conjugated system. The "base-walking" stops when the most thermodynamically stable product is formed. Thus, a simple base enables the isomerization reaction, which cannot be accomplished with transition-metal catalysts due to formation of stable coordination complexes. To the best of our knowledge, this is the first example of a proton being transferred alongside a polyenylic hydrocarbon chain *via* iterative proton shifts.

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Author Contributions

⊥These authors contributed equally to this work.

NOTES

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details, spectroscopy data and computational details (PDF).

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REFERENCES

(1) (a) Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. New Pathways for Organic Synthesis—Practical Applications of Transition Metals, Plenum Press, London, **1984**, pp. 173–193. (b) Trost, B. M. Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way**.** *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281. (c) Trost, B. M. On Inventing Reactions for Atom Economy. *Acc. Chem. Res*. **2002**, *35*, 695–705.

(2) (a) Damico, R.; Logan, T. Isomerization of Unsaturated Alcohols with Iron Pentacarbonyl. Preparation of Ketones and Aldehydes. *J. Org. Chem.* **1967**, *32*, 2356–2358. (b) Uma, R.; Crevisy, C.; Grée, R. Transposition of Allylic Alcohols into Carbonyl Compounds Mediated by Transition Metal Complexes. *Chem. Rev*. **2003**, *103*, 27 −52. (c) Cadierno, V.; Crochet, P.; Gimeno, J. Ruthenium-Catalyzed Isomerizations of Allylic and Propargylic Alcohols in Aqueous and Organic Media: Applications in Synthesis. *Synlett* **2008**, 1105−1124. (d) Ahlsten, N.; Bartoszewicz, A.; Martín-Matute, B. Allylic Alcohols as Synthetic Enolate Equivalents: Isomerisation and Tandem Reactions Catalysed by Transition Metal Complexes. *Dalton Trans.* **2012**, *41*, 1660 −1670. (e) Lorenzo-Luis, P.; Romerosa, A.; Serrano-Ruiz, M. Catalytic Isomerization of Allylic Alcohols in Water. *ACS Catal*. **2012**, *2*, 1079−1086.

(3) For examples of the isomerization of allyl ethers, see: (a) Wille, A.; Tomm, S.; Frauenrath, H. A Highly *Z*-Selective Isomerization (Double-Bond Migration) Procedure for Allyl Acetals and Allyl Ethers Mediated by Nickel Complexes. *Synthesis* **1998**, 305−308. (b) Mereyala, H. B.; Gurrala, S. R.; Mohan, S. K. Study of Metal and Acid Catalysed Deprotection of Propargyl Ethers of Alcohols *via* their Allenyl Ethers**.** *Tetrahedron* **1999**, *55*, 11331−11342. (c) Taskinen, E. Thermodynamic, Spectroscopic, and Density Functional Theory Studies of Allyl Aryl and Prop-1-Enyl Aryl Ethers. Part 1. Thermodynamic Data of Isomerization**.** *J. Chem. Soc*., *Perkin Trans*. **2001**, *2*, 1824−1834. (d) Reid, J. P.; McAdam, C. A.; Johnston, A. J. S.; Grayson, M. N.; Goodman, J. M.; Cook, M. J. *J. Org. Chem.* **2015**, *80*, 1472−1498.

(4) (a) Ahlsten, N.; Martín-Matute, B. Ir-Catalysed Formation of C−F Bonds. From Allylic Alcohols to α-Fluoroketones. *Chem. Commun*. **2011**, *47*, 8331−8333. (b) Ahlsten, N.; Bermejo Gómez, A.; Martín-Matute, B. Iridium-Catalyzed 1,3-Hydrogen Shift/Chlorination of Allylic Alcohols. *Angew. Chem., Int. Ed*. **2013**, *52*, 6273−6276. (c) Gomez, A. B.; Erbing, E.; Batuecas, M.; Vázquez-Romero, A.; Martín-Matute, B. Iridium-Catalyzed Isomerization/Bromination of Allylic Alcohols: Synthesis of α-Bromocarbonyl Compounds. *Chem. - Eur. J.* **2014**, *20*, 10703−10709. (d) Vázquez-Romero, A.; Bermejo Gómez, A.; Martín-Matute, B. An Acid- and Iridium-Catalyzed Tandem 1,3-Transposition / 3,1-Hydrogen Shift / Chlorination of Allylic Alcohols. *ACS Catalysis* **2015**, *5*, 708−714. (e) Martinez-Erro, S., Bermejo Gómez, A.; Vázquez-Romero, A.; Erbing, E.; Martín-Matute, B. 2,2-Diiododimedone: a Mild Electrophilic Iodinating Agent for The Selective Synthesis of α-Iodoketones from Allylic Alcohols. *Chem. Commun.* **2017**, *53*, 9842−9845. (f) Sanz-Marco, A.; Mozina, S.; Martinez-Erro, S.; Iskra, J. Martín-Matute, B. Synthesis of α-iodoketones from Allylic Alcohols through Aerobic Oxidative Iodination. *Adv. Synth. Catal.* **2018**, *360*, 3884−3888. (g) Sanz-Marco, A.; Martinez-Erro, S.; Martín-Matute, B. Selective Synthesis of Unsymmetrical Aliphatic Acyloins through Oxidation of Iridium Enolates. *Chem. Eur. J*. **2018**, *45*, 11564−11567.

(5) (a) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. A Catalytic Enantioselective Synthesis of the Endothelin Receptor Antagonists SB-209670 and SB-217242. A Base-Catalyzed Stereospecific Formal 1,3-Hydrogen Transfer of a Chiral 3-Arylindenol. *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551. (b) Johnston, A. J. S.; McLaughlin, M. G.; Reid, J. P.; Cook, M. NaH mediated isomerisation–allylation reaction of 1,3-substituted propenols. *J. Org. Biomol. Chem.* **2013**, *11*, 7662–7666. (c) Zheng, H.-X.; Xiao, Z.-F.; Yao, C.-Z.; Li, Q.-Q.; Ning, X.-S.; Kang, Y.-B.; Tang, Y. Transition-Metal-Free Self-Hydrogen-Transferring Allylic Isomerization. *Org. Lett.* **2015**, *17*, 6102–6105. (d) Mondal, K.; Mondal, B.; Pan, S. C. Organocatalytic Redox Isomerization of Electron-Deficient Allylic Alcohols: Synthesis of 1,4-Ketoaldehydes. *J. Org. Chem.* **2016**, *81*, 4835–4848. (e) Suchand, B.; Satyanarayana, G. KOtBu-Mediated Domino Isomerization and Functionalization of Aromatic Allylic Alcohols. *Eur. J. Org. Chem.* **2017**, 3886–3895. (f) Hamada, Y.; Kawasaki-Takasuka, T.; Yamazaki, T. Base-promoted isomerization of CF3-containing allylic alcohols to the corresponding saturated ketones under metal-free conditions. *Beilstein J. Org. Chem.* **2017**, *13*, 1507–1512. (g) Zheng, H.-X.; Yao, C.-Z.; Qu, J. -P.; Kang, Y. -B. $^{n}Bu_4NOTf$-promoted radical self-hydrogen transferring isomerization under transition metal-free conditions. *Org. Chem. Front.* **2018**, *5*, 1213–1216. (h) Liu, Y.; Liu, S.; Li, D.; Zhang, N.; Peng, L.; Ao, J.; Song, C. E.; Lan, Y.; Yan, H. Kinetic Resolution of Allylic Alcohol with Chiral BINOL-Based Alkoxides: A Combination of Experimental and Theoretical Studies. *J. Am. Chem. Soc.* **2019**, *141*, 2, 1150–1159.

(6) Martinez-Erro, S.; Sanz-Marco, A.; Bermejo-Gómez, A.; Vázquez-Romero, A.; Ahlquist, M.; Martín-Matute, B. Base-Catalyzed Stereospecific Isomerization of Electron-Deficient Allylic Alcohols and Ethers through Ion-Pairing. *J. Am. Chem. Soc.* **2016**, *138*,

13408−13414.

(7) (a) Thirsk, C.; Whiting, A. Polyene Natural Products: *J. Chem. Soc., Perkin Trans*. *1*, **2002**, 999−1023. (b) Ghosh, S.; Kumar, S. U.; Shashidhar, J. Total Synthesis of (-)-Bitungolide F and Determination of Its Absolute Stereochemistry. *J. Org. Chem*. **1988**, *53*, 231−235. (c) Liu, M.; Yokomizo, T. The Role of Leukotrienes in Allergic Diseases. *Allergology International,* **2015**, *64*, 17−26. (d) Schöning, K.−W.; Hayashi, R. K.; Powell, D. R.; Kirschning, A. Synthetic Studies Toward Ansatrienines: Application of the Evans−Tishchenko Reaction to Chiral Enones. *Tetrahedron*: *Asymmetry* **1999**, *10*, 817−820. (e) Zhang, H.-P.; Kakeya, H.; Osada, H. Biosynthesis of 1-Aminocyclopropane-l-carboxylic acid Moiety on Cytotrienin A in Streptomyces sp. *Tetrahedron Lett.* **1998**, *39*, 6947−6948. (f) Birnbaum, G. I.; Hall, S. R. Structure of the Antibiotic Griseoviridin. *J. Am. Chem. Soc.*, **1976**, *98*, 1926−1931.

(8) Synthesis of furans from dienyl ethers: Zhang, M.; Jiang, H.-F.; Neumann, H.; Beller, M.; Dixneuf, P. H. Sequential Synthesis of Furans from Alkynes: Successive Ruthenium(II)- and Copper(II)-Catalyzed Processes. *Angew. Chem. Int. Ed.* **2009**, *48*, 1681−1684.

(9) Barluenga, J.; Fañanás, F. J.; Sanz, R.; García, F.; García, N. New Reduction of Divinylketones to Rearranged Polyenyl Ethers Under Luche Conditions. *Tetrahedron Lett.* **1999**, *40*, 4735−4736.

(10) For applications of dienyl ethers, see: (a) Dalko, P. I.; Moisan, L.; Cossy, J. Modular Ligands for Asymmetric Synthesis: Enantioselective Catalytic Cu^{II}-Mediated Condensation Reaction of Ethyl Pyruvate with Danishefsky's Diene. *Angew. Chem. Int. Ed*. **2002**, *41*, 625−628. (b) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. Synthesis of Tetra-ortho-substituted, Phosphorus-Containing and Carbonyl-Containing Biaryls Utilizing a Diels-Alder Approach. *J. Am. Chem. Soc.* **2007**, *129*, 9109−9116. (c) Tiefenbacher, K.; Arion, V. B.; Mulzer, J. A Diels−Alder Approach to (−)-Ovalicin. *Angew. Chem. Int. Ed*. **2007**, *46*, 2690−2693. (d) Jewett, J. C.; Rawal, V. H. Total Synthesis of Pederin. *Angew. Chem. Int. Ed*. **2007**, *46*, 6502−6504. (e) Batsanov, A. S.; Knowles, J. P.; Lightfoot, A. P.; Maw, G.; Thirsk, C. E.; Twiddle, S. J. R.; Whiting, A. A Novel, Efficient, Diastereo- and Enantioselective Mukaiyama Aldol-Based Synthesis of a Vinyl Cyclopentanone Core Derivative of Viridenomycin. *Org. Lett.* **2007**, *9*, 5565−5568. (f) Ghosh, A. K.; Xi, K. Enantioselective Synthesis of (−)-Platensimycin Oxatetracyclic Core by Using an Intramolecular Diels−Alder Reaction. *Org. Lett*. **2007**, *9*, 4013−4016. (g) Strübing, D.; Kirschner, A.; Neumann, H.; Hübner, S.; Klaus, S.; Gördes, D.; Bornscheuer, U. T.; Beller, M. Synthesis of Enantiomerically Pure Cyclohex-2-en-1-ols: Development of Novel Multicomponent Reactions. *Chem. Eur. J.* **2005**, *11*, 4210−4218. (h) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. Gold-Catalyzed Double Migration-Benzannulation Cascade toward Naphthalenes. *Org. Lett*. **2008**, *10*, 1465−1468.

(11) Eberle, M. K.; Weber, H.-P. The Regio- and Stereoselectivity of Intramolecular Diels-Alder Reactions of Fumarates: An Unusual Rearrangement-Cyclization. *J. Org. Chem*. **1988**, *53*, 231−235.

(12) Cherkaoui, H.; Soufiaoui, M.; Grée, R. From Allylic Alcohols to Saturated Carbonyls Using $Fe(CO)_5$ as Catalyst: Scope and Limitation Studies and Preparation of Two Perfume Components. *Tetrahedron* **2001**, *57*, 2379−2383.

(13) Crabtree, H. R. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons, Inc.: New Haven, CT, **2014**; p 229-231.

(14) (a) Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. Extensive Isomerization of Alkenes Using a Bifunctional Catalyst: An Alkene Zipper. *J. Am. Chem. Soc.* **2007**, *129*, 9592−9593. (b) Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. Scope and Mechanism in Palladium-Catalyzed Isomerizations of Highly Substituted Allylic, Homoallylic, and Alkenyl Alcohols. *J. Am. Chem. Soc.* **2014**, *136*, 16882−16894.

(15) Related: (a) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote Functionalization through Alkene Migration. *Nat. Chem.* **2016**, *8*, 209−219. (b) Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I. Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153−165. (c) Kapat, A.; Sperger, T.; Guven, S.; Schoenebeck, F. *E*-Olefins through intramolecular radical relocation. *Science,* **2019**, 363, 391−396. (d) Kathe, P.; Fleischer, I. Cooperative Use of Brønsted Acids and Metal Catalysts in Tandem Isomerization Reactions of Olefins. *ChemCatChem* **2019**, *11*, 3343−3354.

(16) The alkyne zipper reaction is an example of "base walk" that isomerizes internal alkynes into more thermodynamically stable terminal alkynes. For more literature about this reaction see: Avocetien, K.; Li, Y.; O´Doherty, G. A. The Alkyne Zipper Reaction in Asymmetric Synthesis. In Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations; Trost, B. M.; Li, C.-J. Ed.; Wiley-VCH, **2015**.

(17) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C—H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072.

(18) (a) Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. *Bioinformatics*, **2006**, *22*, 3067−3074. (b) COPASI version 4.24, available free of charge from http://copasi.org. See Supporting Information for further details.