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Fast Oxy-Cope Rearrangements of Bis-alkynes: Competition with Central C−C Bond Fragmentation and Incorporation in Tunable Cascades Diverging from a Common Bis-allenic Intermediate

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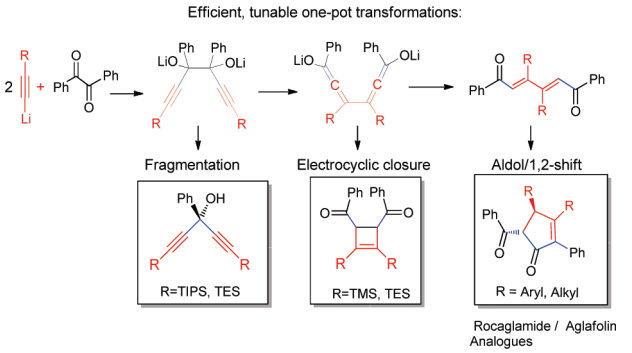
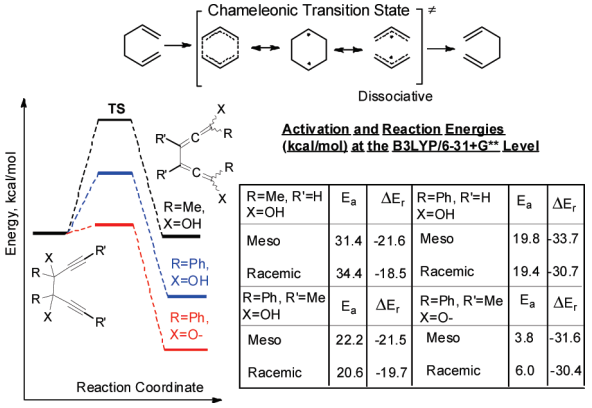


Fast anionic oxy-Cope rearrangements of 1,5-hexadiyn-3,4-olates can be incorporated into cascade transformations which rapidly assemble densely functionalized cyclobutenes or cyclopentenones via a common bis-allenic intermediate. The competition between fragmentation, 4π-electrocyclic closure, and aldol condensation can be efficiently controlled by the nature of the acetylenic substituents. The rearrangement of bis-alkynes with two hydroxyl substituents opens a conceptually interesting entry in the chemistry of ε-dicarbonyl compounds and suggests a new approach to analogues of rocaglamide/aglafolin.

Efficient control of the Cope rearrangement and related reactions[1] is important for incorporation of this useful C−C bond-forming process in subsequent reaction cascades, especially if these cascades have to be tunable.[2] Extensive experimental and computational data suggest that the rearrangement transition state is very sensitive to the nature and position of substituents.[3] For example, Evans reported a dramatic acceleration of the oxy-Cope rearrangement via introduction of anionic substituents,[4] while Doering and others controlled the electronic character of the Cope transition state with appropriately positioned Ph groups.[5]

The rich mechanistic spectrum of reactions "under the umbrella of Cope rearrangement family" was further illustrated by predictions of unusual Cope rearrangement patterns based on a comprehensive heuristic approach.[6] Previous computational evidence suggested that some anionic Cope rearrangements proceed via a dissociative mechanism initiated by a homolytic cleavage of the central C−C bond (Scheme 1).[7]

SCHEME 1. (Top) Alternative Descriptions of the Cope Rearrangement TS. (Bottom) Cumulative Accelerating Substituent Effects on the Cope Rearrangent of Bis-alkynes



R=Me, R'=H X=OH	E_a	ΔE_r	R=Ph, R'=H X=OH	E_a	ΔE_r
Meso	31.4	-21.6	Meso	19.8	-33.7
Racemic	34.4	-18.5	Racemic	19.4	-30.7
R=Ph, R'=Me X=OH	E_a	ΔE_r	R=Ph, R'=Me X=O-	E_a	ΔE_r
Meso	22.2	-21.5	Meso	3.8	-31.6
Racemic	20.6	-19.7	Racemic	6.0	-30.4

Taking into account the tunable nature of the Cope transition state and our previous explorations of alkyne reactivity,[8] we decided to investigate how this process responds to weakening of the central C−C bond in bis-alkynes by *two* pairs of accelerating substituents.[9] Our exploratory computations (Scheme 1 and Supporting Information) predicted that such accelerating effects are likely to be substantial. In this work, we report experimental observations regarding the

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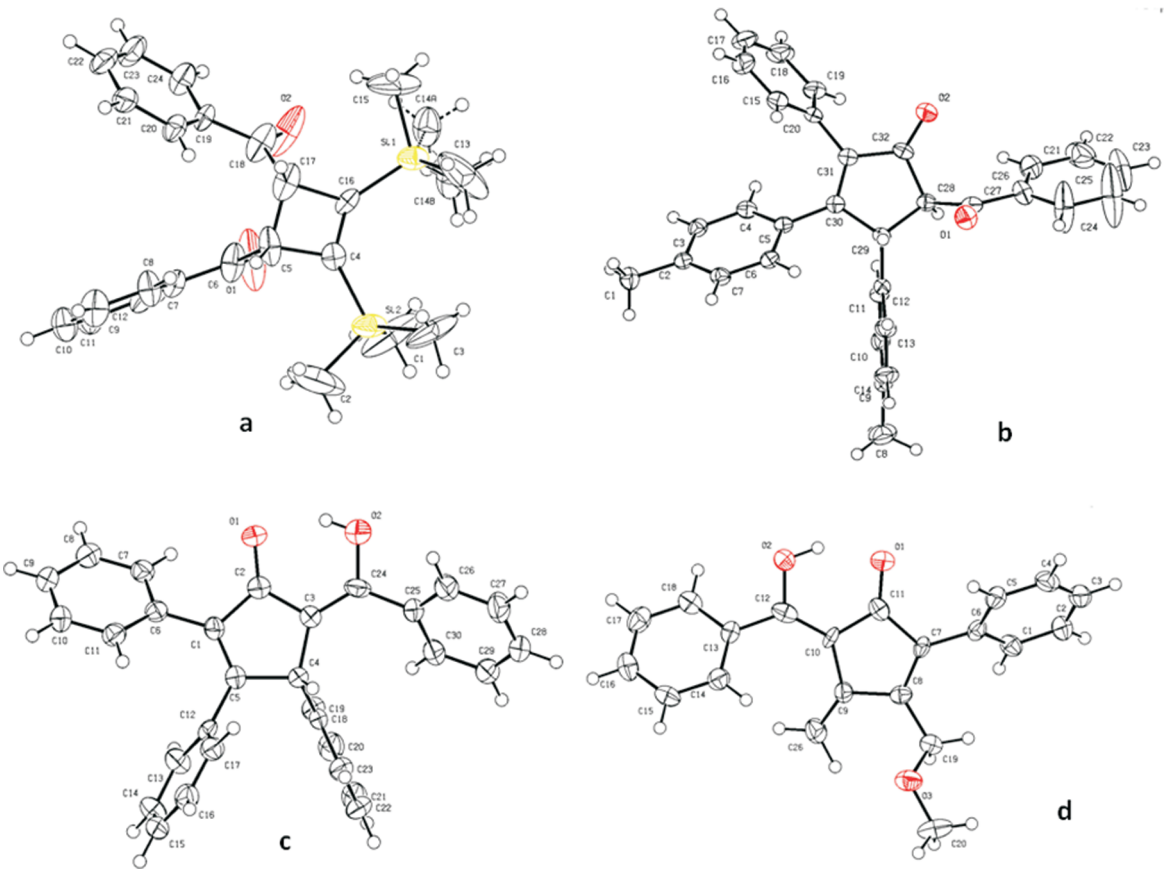

FIGURE 1. ORTEP diagram for (a) compound **3-TMS-cis**, (b) compound **7a**, (c) compound **6b**, and (d) compound **9b**.

fast anionic oxy-Cope rearrangement of 1,5-hexadiyn-3,4-olates as well as the remarkable sensitivity of subsequent cascade transformations to the nature of alkyne substituents.

The starting materials can be prepared conveniently via reaction of 1,4-diphenyl-2,3-ethanedione (benzil) with 2 equiv of metal acetylides. Remarkably, oxy-Cope rearrangement of the resulting bis-adduct occurs readily as the reaction mixture warms to room temperature. The essential role of the two Ph substituents at the central bond is illustrated by the lack of oxy-Cope rearrangement of analogous adducts formed from 2,3-butanedione[10] and 1-phenyl-1,2-propanedione. The Ph groups weaken the central C−C bond in the bis-alkyne **1** and provide additional thermodynamic stabilization to the newly formed C=C bonds in the product **2**.

Subsequent rearrangement of the bis-allene oxy-Cope products **2** can be controlled efficiently by the nature of substituents in the acetylenic nucleophiles. Depending on the alkyne, divergent anionic cascades of the bis-allenic intermediates either transform simple acyclic starting materials into densely functionalized cyclobutene and cyclopentenone products or produce fragmentation products via a dissociative pathway.

In particular, the bis-allenic Cope product **2** formed in situ in the reaction of benzil with TMS-substituted acetylide undergoes rapid 4π-electrocyclic closure to a mixture of *cis*- and *trans*-cyclobutenes **3-TMS** in ~80% overall yield.[11] Structure of the *cis*-isomer (**3-TMS-cis**) was confirmed by X-ray crystallography (Figure 1a). This isomer is initially present as the major product in the reaction mixture (~10:1 *cis*/*trans* selectivity, Scheme 2). This selectivity suggests that kinetic protonation of the keto−enol intermediate favors formation of a less stable product.[12] The *cis*-isomer can be epimerized quantitatively into the more

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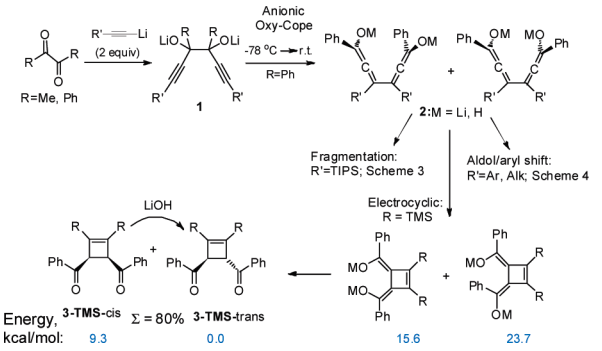
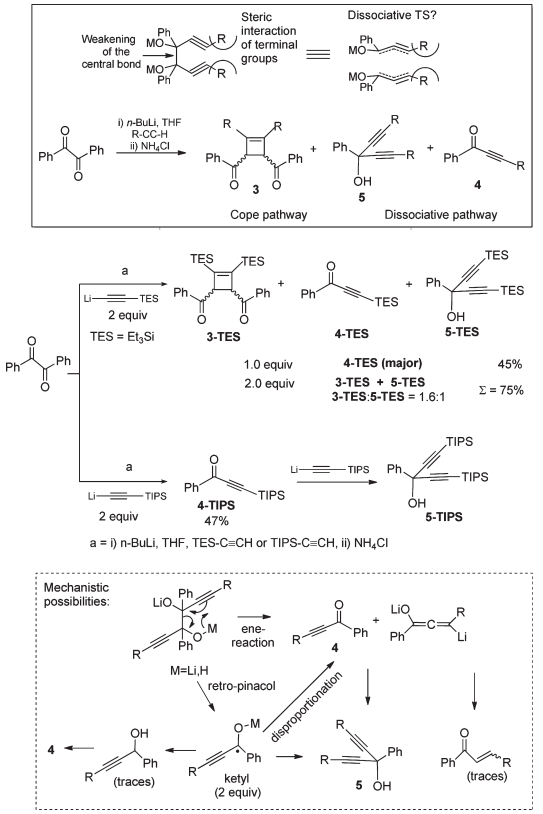
SCHEME 2. Cope Rearrangement/4π-Electrocyclic Ring-Closure Sequence for the Formation of Cyclobutenes[a]



[a]B3LYP/6-31+G** energies of the two stereoisomers of enol and keto-tautomers (R = SiH_3; M = H) are given at the bottom of the scheme.

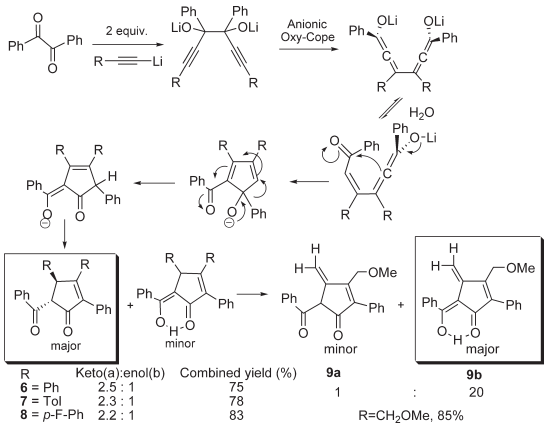
SCHEME 3. Competition between the Oxy-Cope Rearrangement and Fragmentation in the Reactions of TES- and TIPS-Substituted Acetylenes



stable *trans* **3-TMS** isomer under basic conditions (stirring with the LiOH/THF/H_2O system or keeping the reaction mixture for 6 h at pH ~9).

The Cope rearrangement step is expected to be highly asynchronous due to the accumulative weakening of the central C−C bond by *four* substituents: the two anionic oxygens and the two Ph groups (Scheme 3). Related anionic rearrangements have been suggested to proceed through a dissociative mechanism via the central bond cleavage.[7] In accord with this model, we found that an increase in the steric bulk of the alkyne substituents prevents the formation of the new C−C bond in the Cope product and diverts the reaction to the fragmentation

SCHEME 4. Yields, Selectivity, and Proposed Mechanism for the Formation of Keto and Enol Forms of the Cyclopentenone Products



of the weakened C−C bond. The ratio between the cyclobutene and fragmented product is controlled by the size of the silyl substituents. Although cyclobutenes are the major products for R = TMS, a mixture of cyclobutene and fragmented product is formed when 2 equiv of TES-acetylide are used. The fragmentation path becomes dominant for R = triisopropylsilyl (TIPS where only ketone **4-TIPS** and alcohol **5-TIPS**) were obtained in ratios dependent upon the amount of lithium acetylide. Ketone **4**[13] was formed as the major product with 2 equiv of acetylide, whereas a larger excess (4.5 equiv) of acetylide led to the formation of **5-TIPS** exclusively.

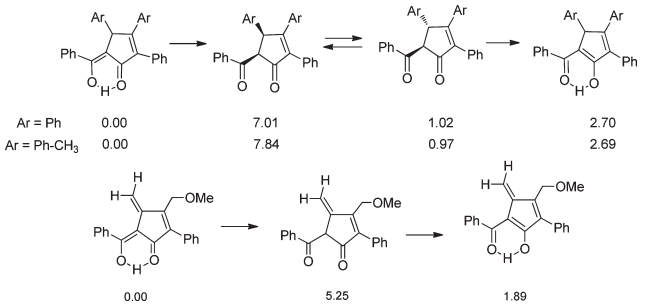
The structure of the fragmented products has been confirmed by their independent synthesis (described in the Supporting Information),[14] but the exact mechanism for their formation remains unclear. Minor products isolated from the reaction mixtures suggest that it includes either an ene reaction or a retro-pinacol fragmentation, topologically analogous to the Cope rearrangement diverted via a fully dissociative transition state (Scheme 3). Because the rate of the second TIPS-acetylide addition to the diketone is relatively slow, contribution from an additional fragmentation pathway from the monoadducts is also plausible.

Because of the presence of two hydroxyl groups at the central bond of the bis-acetylenes **1**, these compounds can be considered as a latent dicarbonyl functionality that is revealed by the oxy-Cope process in its bis-enolized state. As a result, one can couple the pericyclic step with typical carbonyl chemistry, such as intramolecular aldol condensations. In accord with this notion, reactions of benzil with aryl and alkyl substituted acetylides proceed with the formation of cyclopentenones in 75−85% yield (~2:1 mixture of keto and enol forms, Figure 1b−d). Neither *p*-CH_3 nor *p*-F substituents have a large effect on the reaction yield or the keto/enol ratio. Although the reaction with methyl propargyl ether produced the same 5-cyclopentenone framework, the cascade continued one step further toward the formation of an *exo*-cyclic double bond via methanol elimination. In the latter case, the tautomeric equilibrium is shifted toward enol (Scheme 4).

(13) Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872.

(14) The ketone was prepared via a literature procedure: Feng, L.; Kumar, D.; Kerwin, S. M. *J. Org. Chem.* **2003**, *68*, 2234. The bis-alkyne alcohol was synthesized in 89% yield via reaction of 2.2 equiv of TIPS-acetylide with ethyl benzoate (see the Supporting Information for details).

SCHEME 5. Calculation of Relative Energies (kcal/mol) for Keto-enol Tautomerizations and Energies in Parentheses Obtained from the Single-Point Calculations at the SCRF(PCM)-B3LYP/6-31+G//B3LYP/6-31+G** Level with THF Solvent**

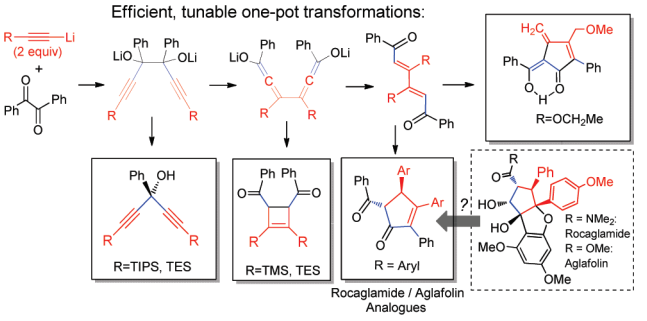


The path leading to the formation of the cyclopentenones[9] diverges from the same bis-allenic intermediate. Subsequent to the Cope step, aldol condensation closes the cycle in a favorable 5-(enolexo)-exo-trig fashion.[15] Due to the high migratory aptitude of the phenyl group in the intermediate, the cyclization is accompanied by a highly exothermic (~32.4 kcal/mol at the B3LYP/6-31+G** level) 1,2-phenyl migration and concomitant enolization as depicted in Scheme 4.

The structures of the keto and enol products were unambiguously confirmed by X-ray crystallography (Figure 1b,c). Only the trans ketone was isolated, possibly due to the equilibration into the most stable tautomer under the thermodynamic control conditions. The thermodynamic origin of the observed selectivity is supported by the calculated relative energies for the keto and enol products. Even though the enol form (**6b**−**8b**) is stabilized by a relatively strong resonance-assisted hydrogen bond (RAHB) with the β-ketone moiety, there is still ~1 kcal/mol thermodynamic preference for the keto form (**6a**−**8a**). In contrast, the computations suggest that the enol form (**9b**) is the most stable tautomer in the keto−enol equibrium in the β-diketone (**9a**) system formed in the reaction of CH_2OMe-substituted alkyne (Scheme 5). Gratifyingly, this is exactly what we observe experimentally (see Figure 1d for the crystal structure of the enol form). Neither the cis-ketone nor the endocyclic enol, both of which are calculated to be less stable, were detected experimentally.

In summary, simultaneous weaking of the central C−C bond in 1,5-hexadiyn-3,4-olates leads to fast anionic oxy-Cope rearrangements (Scheme 6). This process can be either redirected down a dissociative path or coupled with subsequent reactions in efficient cascade trasformations which provide densely substituted cyclobutenes and cyclopentenones via a common bis-allenic intermediate. Furthermore,

SCHEME 6. Summary of Cascade Transformations Initiated by Anionic Oxy-Cope Rearrangements of Activated Bis-acetylenes and Structural Resemblance between Cyclopentenones and Natural Products of the Rocaglamide/Aglafolin Family



this cascade offers a conceptually interesting entry in the ε-dicarbonyl chemistry and, if a regio- and stereoselective version of this process is developed in the future, a potentially useful shortcut to the rocaglamide and aglafolin[16] analogues.

Experimental Section

General Procedure. *n*-BuLi (4.46 mL, 1.6 M in hexanes, 5.24 mmol) was slowly added to a 10 mL THF solution of the terminal acetylene (5.24 mmol) at −78 °C. The reaction mixture was kept at this temperature for 60 min and then warmed to 0 °C for 45 min. After that time, the reaction mixture was recooled to −78 °C, and a solution of 1,4-diphenyl-2,3-ethanedione (2.60 mmol) in 5 mL of THF was added. The reaction mixture was warmed to room temperature and then quenched with 15 mL of saturated aqueous ammonium chloride after 5 h of stirring. The aqueous layer was extracted with dichloromethane, which was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated and purified by column chromatography to afford compound **3-TMS-*cis*** as white crystals NMR δ_H (300 MHz, $CDCl_3$) 7.62 (d, J = 7.2 Hz, 4H), 7.33 (t, J = 7.4 Hz, 2H), 7.19 (t, J = 7.7 Hz, 4H), 5.08 (s, 2H), 0.14 (s, 18H); NMR δ_C (75 MHz, $CDCl_3$) 197.8, 167.5, 137.0, 132.4, 128.1, 127.8, 55.1, 0.7; MS (ESI) m/z 407 $[M + H]^+$, 429 $[M + Na]^+$; HRMS (ESI) calcd for $C_{24}H_{30}O_2Si_2$ $[M]^+$ 406.1784, found 406.1790. Compound **7a** has been obtained analogously as white crystals: NMR δ_H (300 MHz, $CDCl_3$) 8.06 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.25−7.22 (m, 5H), 7.13 (d, J = 8.1 Hz, 2H), 7.03 (m, 4H), 6.92 (d, J = 8.1 Hz, 2H), 5.19 (d, J = 1.8 Hz, 1H), 4.64 (d, J = 1.8 Hz, 1H), 2.23 (s, 3H), 2.20 (s, 3H); NMR δ_C (75 MHz, $CDCl_3$) 199.9, 193.3, 170.8, 140.0, 138.3, 137.5, 136.8, 136.2, 133.4, 131.8, 131.4, 131.3, 130.0, 129.7, 129.1, 128.9, 128.4, 128.3, 127.9, 127.5, 66.4, 50.2, 21.3, 21.0; MS (ESI) m/z 465 $[M + Na]^+$; HRMS (ESI) calcd for $C_{32}H_{26}O_2$ $[M]^+$ 442.1933, found 442.1934.

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Supporting Information Available: Experimental, procedures, crystallographic data, and full characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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