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RESEARCH ARTICLE

Enolate Structure Enabled Anionic Cascade Cyclization Reaction: An Easy Access to Complex Scaffolds with Contiguous Six-, Five- and Four-Membered Rings

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Supporting information for this article is given via a link at the end of the document.

Abstract: Catalyst-free addition of ketone enolate to non-activated multiple C-C bonds involves non-complementary reaction partners and typically requires super-basic conditions. On the other hand, highly aggregated or solvated enolates are not reactive enough to undergo direct addition to alkenes or alkynes. Herein, we report a new anionic cascade reaction for one-step assembly of intriguing molecular scaffolds possessing contiguous six-, five- and four-membered rings, representing a formal [2+2] enol-allene cycloaddition. Reaction proceeds under very mild conditions and with excellent diastereoselectivity. Deeper mechanistic and computational studies revealed unusually slow proton transfer phenomenon in cyclic ketone intermediate and explained peculiar stereochemical outcome.

Introduction

Cascade cyclization reactions, where several chemical steps occur one after another in a well-defined sequence, is a powerful tool to access complex polycyclic molecular scaffolds in a single synthetic operation with high overall yield and stereoselectivity.[1] The required acyclic precursors for such transformations are usually obtained using well-established synthetic methods from readily available materials. In this regard, the utilization of polyunsaturated substrates to affect multiple C-C bond formation is very attractive, and in fact, is extensively utilized by Nature as in cation-induced cyclase-catalyzed transformation of polyenes into terpenoids.[2] Recent elegant studies aiming at applying the lessons learned from biological systems in synthetic chemistry has resulted in the development of multitude efficient cyclization cascades.[3] On the other hand, anion-induced cyclizations of alkenes require the inversion of innate electron density of π-bond either by introducing the electron withdrawing groups or activation with Lewis acids or transition metals. Thus, non-catalyzed addition of nucleophiles to non-activated alkenes is rare.[4]

In this context, the enolate addition to non-activated π- bond is a highly sought-after transformation having huge potential to deliver valuable carbonyl compounds in a single step. The Conia-ene reaction, known as the intramolecular addition of enols to alkenes or alkynes, represents a versatile synthetic tool, however, it proceeds via concerted (pericyclic) rather than ionic mechanism (Figure 1a).[5] Moreover, non-catalytic version of this reaction requires very harsh conditions, not compatible with heavily functionalized substrates. Taguchi *et. al*. has shown that more reactive allene π-bond can be engaged in intramolecular addition reaction with lithium enolates of 1,3-dicarbonyl compounds

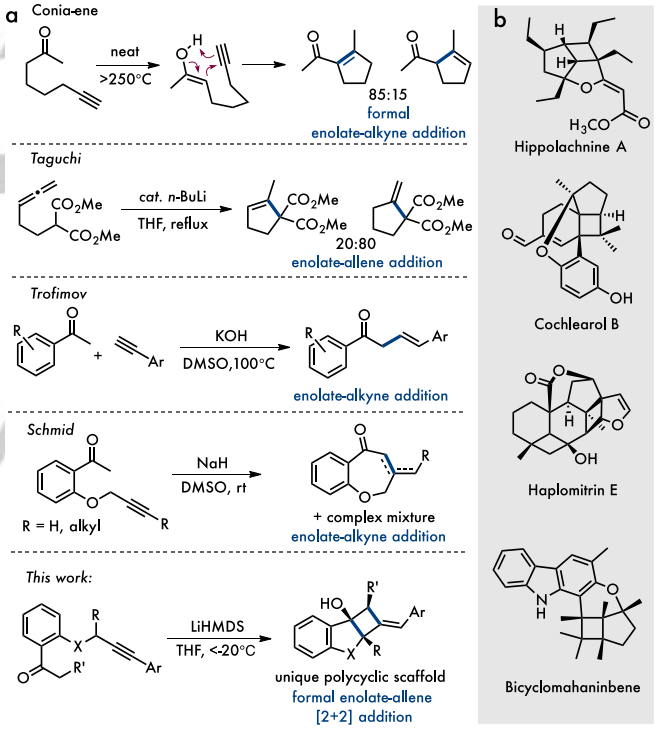

Figure 1. a) Addition of enolates (enols) to a non-activated carbon-carbon π-bonds. Currently known examples and reported development. b) Bioactive natural products featuring fused oxygenated five-membered rings and cyclobutane.

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(Figure 1a).[6] Based on high basicity of an anion produced after cyclization, the reaction can be conducted using only catalytic amount of base.

Recently, Trofimov *et al*. have developed an efficient procedure for α-vinylation of ketones based on enolate addition to terminal alkynes under super basic conditions (Figure 1a).[7] The reaction requires high temperature and highly coordinating dimethyl sulfoxide solvent pointing toward the necessity of using dissociated (i.e. "naked") and therefore very reactive enolate.

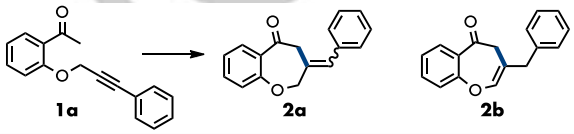
Much earlier, similar intramolecular addition of sodium enolate to tethered alkyne in 2-hydroxyacetonaphthone derivatives has been described by Schmid and co-workers[8] (Figure 1a) and later expended to other intramolecular variations by Dixon[9] and Trauner[10]. Although the isomerization of propargylic ether into the corresponding allene under basic conditions seems very plausible, the reaction is believed to proceed *via* direct addition of an enolate to a triple bond as judged from the configuration of exocyclic double bond and nearly stoichiometric amount of the base used. The seven-membered product obtained may undergo competing double bond migration and rearrangement reactions, resulting in a complex mixture. Intrigued by the possibility to employ the addition reaction of enolates to simple triple bonds based on the above report, we have set up to investigate the possible reaction mechanism and synthetic scope of this transformation. This has led to a discovery of new cascade cyclization to afford unique polycyclic scaffold consisting of fused six-, five- and four-membered rings (Figure 1a). The novel reaction documented herein features enolate addition to allene as a key step followed by intramolecular addition of a carbanion to the carbonyl group and formally represents currently unknown [2+2] enol-allene addition reaction. The reaction reported opens up the way for the synthesis of novel molecular scaffolds reminiscent of the ones found in the structure of a variety of bioactive natural products, possessing oxygenated five-membered ring fused with cyclobutane (Figure 1b).[11]

Results and Discussion

Conditions Screening In contrast to alkyl propargylic substrates reported by Schmid *et al*. (R = alkyl, Figure 1a), we have instead decided to use the arylated analogues as starting materials. Besides the novelty of substrates, we have reasoned that in this case, base induced isomerization of propargyl moiety into the respective allene would be facilitated and the weaker base could be employed. The starting materials **1** were obtained by modular approach starting from various commercially available 2-hydroxyacetophenone derivatives via propargylation followed by Sonogashira coupling (see the Supporting Information) or by alkylation with arylpropargyl bromides.

The initial optimization results with **1a** revealed that expected seven membered ketone **2** having exocyclic double bond was exclusively formed in moderate yields (24-42%) using NaH as a base in dimethylsulfoxide (DMSO) (Table 1). Only *E*-stereoisomer was obtained as confirmed by ROESY spectrum (see the Supporting Information). Dimsyl lithium ($Li^+CH_3SOCH_2^-$) proved to be less efficient (Table 1, entry 6). Switching the solvent to tetrahydrofuran (THF) required increasing the temperature to 80°C for NaH to afford 58% of the product **2a** as Z/E mixture. Using KO^{t}Bu as a base, a mixture of *E*-**2a** and *Z*-**2a** was obtained in DMSO whereas in THF **2b** was also formed in considerable amount. Control experiment in THF where *E*-**2a** was treated with KO^{t}Bu showed that *Z*-**2a** but not **2b** derived from the *E*-**2a**, initially formed during the cyclization (Page S28). In contrast to slow cyclization of alkyl derivatives,[8] all reactions with **1a**, except using NaH in THF, were complete within 5 min, in line with higher anion stabilizing effect of the phenyl group. Unexpectedly, none of the conditions provided enone product. Weaker base such as MeONa or K_2CO_3 were not effective. The above screening results indicates high reactivity of dissociated enolate towards non-activated triple bond.

Table 1. Screening of reaction conditions



entry	conditions	yield (%)[a]
1	NaH (1.1 equiv.), DMSO, rt	**2a** 42%
2	NaH (3.5 equiv.), DMSO, rt	**2a** 24%
3	NaH (3.5 equiv.), THF, 80°C	**2a** (E/Z = 5:1) 58%[b]
4	KO^{t}Bu (3.5 equiv.), THF, rt	**2a** (E/Z = 2.4:1) 26% **2b** 28%[b]
5	KO^{t}Bu (1.0 equiv.), DMSO, rt	**2a** (E/Z = 1.3:1) 66%[b]
6	*n*-BuLi (1.1 equiv.), DMSO, rt	**2a** 34%
7	K_2CO_3 (3.0 equiv.), DMF, 80°C	ND[c]
8	MeONa (2.1 equiv.), MeOH, rt or Δ	ND[c]
9	LDA (2.1 equiv.), THF, -78°C	ND[d]

[a]Isolated yields; [b]Inseparable mixture. Product ratios were determined by NMR; [c]Starting material was recovered; [d]Complex mixture; ND – not detected.

Further screening was continued with less polar solvents to deliberately reduce the enolate activity. Using 2.1 equivalents of lithium diisopropylamide (LDA) as a base in THF at low temperature, complex intractable mixture of products was obtained.

Remarkably, weaker base, lithium hexamethyldisilazane (LiHDMS), resulted in spot to spot conversion of **1a** into a new product with 86% isolated yield. Using less than 2.0 equivalents of LiHMDS (1.0 equiv. < LiHDMS < 2.0 equiv.), the formation of the product was also observed, however, the reaction rate and conversion were slightly lower. Starting material was recovered almost quantitively when stoichiometric amount of LiHMDS was used. To our surprise, the product **3a** obtained turned out to be not the expected seven-membered unsaturated ketone (Table 1), but tricyclic tertiary alcohol, comprising of fused five- and four-membered rings (Figure 2). The compound **3a** was obtained as a single diastereomer as indicated by NMR and its structure was secured by X-ray crystallography.

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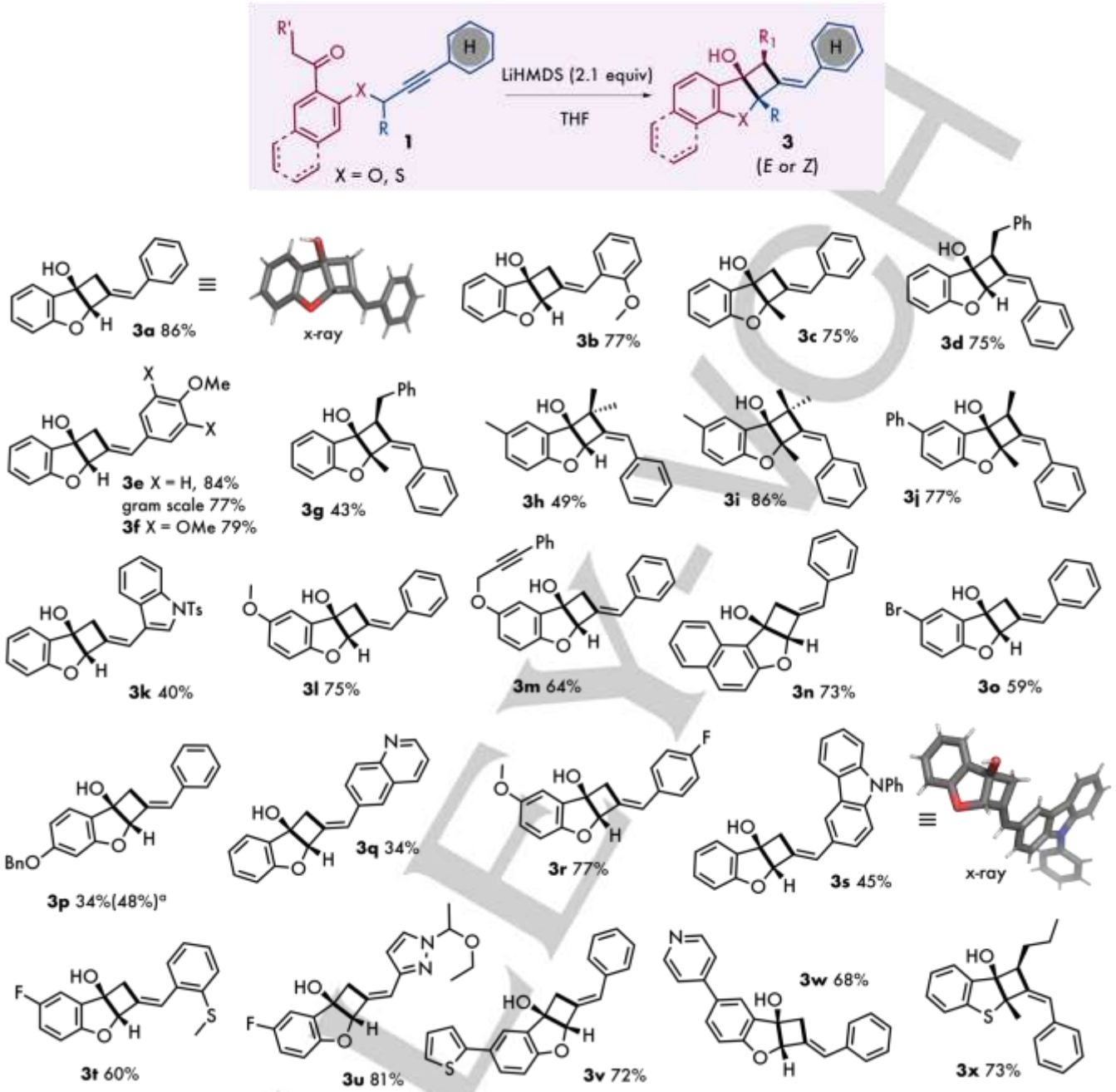

Figure 2. Exploration of substrate scope. [a]Yield based on recovered starting material. Standard reaction conditions: **1** (1.0 equiv), LiHMDS (2.1 equiv), THF (1.0 - 2.0 M), -60°C ÷ 20°C, 2-5 h.

The reaction scope was further evaluated as outlined in **Figure 2**. The reaction is compatible with various substituents on both acetophenone and aryl rings of the propargylic fragment. Heteroaromatic derivatives with indole, pyridine, thiophene and carbazole moieties were also successfully converted into respective products. The reaction was also applied for sulfur analogue to give **3x** in 73% yield. Notably, starting materials substituted at α-position of the carbonyl group as well as at the propargylic positions (**3d**, **3g**-**j**) were competent substrates, indicating high tolerance of steric hindrance in this transformation. In these cases, higher reaction temperatures were usually required to reach full conversion. Of special note is the compound **3i** possessing four consecutive quaternary carbons, obtained in 86% yield with full diastereoselectivity. The reaction was successfully reproduced on a gram scale with only slight decrease in the yield (**3e**, Figure 2). Interestingly, the stereochemistry of the double bond seems to be a function of substitution at α-position and not of the size of the aryl substituent. Namely, all unsubstituted acetophenone starting materials provided *E*-products even with large carbazole moiety (**3s**, X-ray structure), whereas substituted ones selectively afforded *Z*-products.

From a mechanistic point of view, the observed cyclization reaction can be rationalized assuming the formation of the corresponding allene as an intermediate. Regioselective addition

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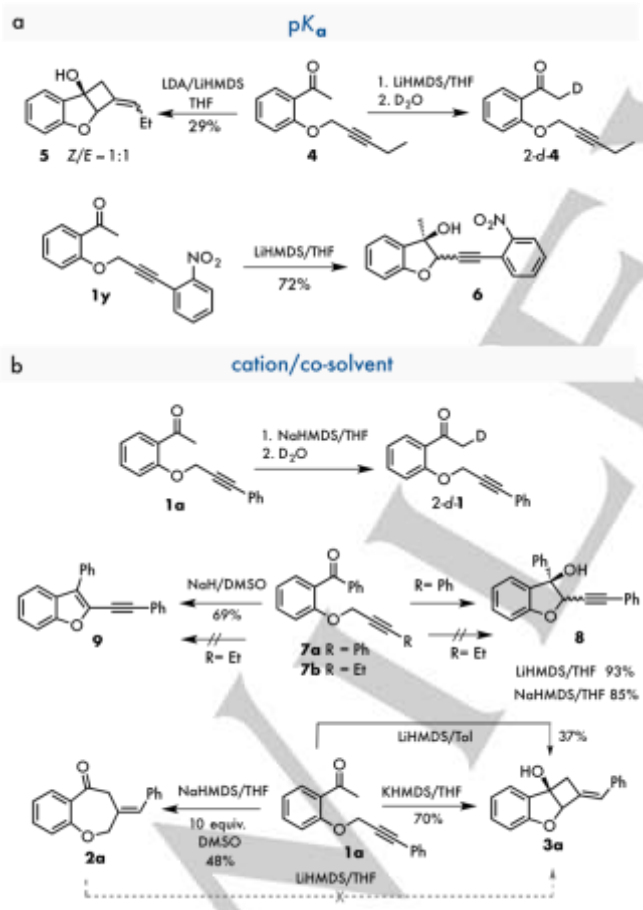
of lithium enolate to allene double bond would result in C(sp^3) carbanion of allylic ether. An ensuing intramolecular addition of the latter to the carbonyl group would afford the observed product (vide infra). Despite of apparent simplicity, this transformation is intriguing for several reasons. First, stereochemistry of the alkene double bond in *E*-products is opposite to what is expected considering an addition of a nucleophile to allene from a less hindered side. Second, the proton transfer from ketone α-position does not quench the more basic intermediate carbanion indicating either a very fast addition to the carbonyl group or unfavorable proton transfer. Finally, dramatic solvent and cation effect on the reaction outcome was noted.

Mechanistic Investigations In order to elucidate mechanistic details further, we conducted a series of control experiments. First, subjecting compound **4** having alkyl substituent on the triple bond, analogous to the ones used by Schmid et al., to LiHMDS, no reaction was observed (Scheme 1a). Quenching with D_2O gave no deuterium incorporation at propargylic carbon. This result shows that isomerization of propargylic ether to allene is a prerequisite, and the direct addition of enolate to triple bond is not taking place. On the other hand, increasing the strength of the base by switching from LiHMDS (pK_a = 24) to LDA (pK_a = 35) indeed afforded the tricyclic product **5** as a mixture of *Z/E*-stereoisomers, albeit in low yield.[12]



Scheme 1. Control experiments to probe a) role of the base strength and b) role of the counterion and solvent.

The importance of relative acidities of C-H bonds at carbonyl α-position and propargylic position was further revealed with compound **1y** possessing strongly electron withdrawing o-nitro group on the alkyne aromatic ring. In this case deprotonation of propargylic position is faster due to lower pK_a resulting in the attack of the carbonyl group by propargylic anion to afford product **6**.

Although lithium enolates dominate the field of enolate chemistry, the strong dependence of enolate structure and reactivity on counterion nature is also well documented in literature.[13] In fact, sodium and potassium enolates in most cases are more reactive than lithium enolates. Unexpectedly, NaHMDS base, even used in excess, provided neither the expected product **3a** nor seven-membered product **2a** from starting material **1a**. To find out whether the absent reactivity of sodium enolate in THF was related with too low basicity of NaHMDS for allene generation, quenching experiment with D_2O was performed. Indeed, no deuterium was incorporated at propargylic position. Interestingly, when non-enolizable ketone **7a** was used as a control, cyclization product **8** was obtained by using both LiHMDS and NaHMDS bases (Scheme 1b). This observation can be explained by higher acidity at the propargylic position in **7a** possessing electron withdrawing benzoyl group, whereas in enolate of **1a**, the electronic properties of substituent are inversed. NaH/DMSO system gave benzofuran product **9** after carbonyl group attack and subsequent loss of H_2O, however, was incapable to deprotonate less acidic alkyl propargylic substrate **7b** and therefore ruled out allene involvement in Schmid cyclization (Figure 1a). NaHMDS is a stronger base compared to LiHMDS, however the lithium ion is significantly more oxophilic than sodium and therefore, deprotonation might be facilitated by the directing effect of the oxygen atom. By changing counterion from lithium to potassium, product **3a** was also obtained in slightly lower yield as compared to LiHMDS; however, cyclization reaction proceeded at lower temperature (Scheme 1b). The intrinsic basicity of KHMDS is high enough to allow efficient isomerization of propargylic ether to the corresponding allene. Although no formation of **3a** was observed when using NaHMDS as a base, the reactivity of the sodium enolate could be restored by replacing sodium coordination shell and weakening the O-Na bond with 10 equiv. of DMSO to afford enolate-alkyne addition product **2a**, analogous to pure DMSO. Interestingly, other commonly used complexation agent N,N'-dimethylpropylene urea (DMPU) was fully ineffective, perhaps due to its weaker cation coordination ability. We have also shown that the enolate of compound **2a** is not an intermediate *en route* to **3** by a control experiment wherein starting material was recovered after treatment with LiHMDS (Scheme 1b).

Taken together, all the above results show that: a) deprotonation of propargylic methylene group is essential for cascade cyclization reaction (**1** to **3**) in THF to take place, corroborating the involvement of allene as an intermediate. b) pK_a of C-H bond in α-position to carbonyl group is lower than pK_a of C-H bond in propargylic position, c) successful deprotonation of propargylic C-H bond in **7a** suggests that at least in theory allene pathway can also be operating during the cyclization of **1** to **2** (Table 1) in DMSO, and d) naked enolate is required for the cyclization of **1** to **2**.

Based on the above insights, we proposed possible reaction mechanisms outlined in Scheme 2 to explain solvent-dependant reactivity modes of **1**.

The reactivity and selectivity of lithium enolates are greatly influenced by the structures and reaction conditions, including

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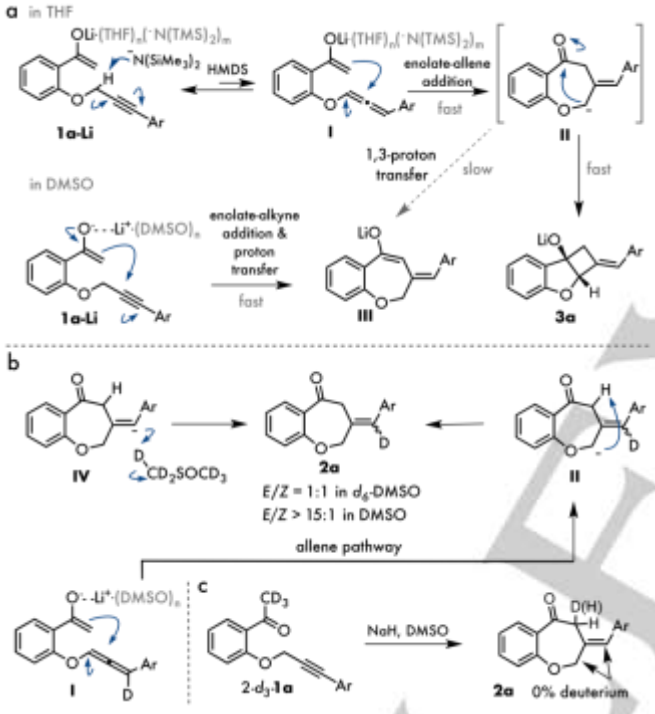
particularly the solvents and additives interacting with lithium ion as recognized by early work of Jackman,[13] Seebach,[14] Willard [15] and others.[16] According to detailed fundamental studies on lithium amide-mediated enolization of ketones reported by Arnett,[17] and later by Reich[18] and Collum[19], the lithium enolate most likely exist in a form of mixed aggregate with lithium ion coordinating to both solvent THF and lithium hexamethylsilazide, present in excess (denoted as -OLi(THF)$_n$(N(TMS)$_2$)$_m$ in Scheme 2a). Such mixed aggregate structure seems to provide an optimum reactivity of enolate for this cascade transformation; more aggregated lithium enolate of **1a** in toluene started to react only at room temperature and gave mere 37% of product **3a** (Scheme 1b). On the other hand, metal enolates in DMSO are believed to exist either as highly reactive free ions, solvent-separated ions or the mixture thereof in equilibrium with other aggregates.[20] To date, no reliable structural characterization of Li enolates in this solvent has been reported.



Scheme 2. a) Proposed reaction mechanism. b) Control deuterium labelling experiments.

In THF, complexed lithium enolate is not nucleophilic enough for direct addition to a triple bond.

In the presence of excess of LiHMDS in THF, **1a** is converted into the corresponding enolate followed by deprotonation at propargylic position based on the results of the control reaction from **7a** to **8** (Scheme 1b). The metalated propargylic ether undergoes isomerization to allene via proton transfer from HMDS, however the extent of such isomerization is very low. This assumption was confirmed by another control reaction where simple phenylpropargylic ether of phenol was subjected to identical reaction conditions; no allene product was detected in the reaction mixture. In case of **1a**, very small amount of allene intermediate **I** formed is immediately consumed in the following cyclization step to afford carboanion **II** thus shifting the isomerization reaction further. To our knowledge, addition of enolate to allenyl ethers has only been attempted once by Trofimov *et al.* in intermolecular reaction with limited success using superbase KOH (KO^{t}Bu)-DMSO conditions.[21] The yields were low, mixture of mono- and diallylated products were obtained, but most importantly, the addition never occurred to generate carboanion adjacent to oxygen atom as in II. In terms of addition regioselectivity, the reported results were analogous to our case using KO^{t}Bu in THF (Table 1, entry 4, compound **2b**). Given the well-reported utility of KO^{t}Bu as a base for propargylic ether and amine isomerization to the corresponding allenes, 7-exo-trig addition of enolate to allene seems very reasonable to account for the formation of **2b**.[22]The fact that **3a** and not **2b** is obtained using KHMDS derived potassium enolate stress the paramount importance of enolate structure (dissociated *vs* aggregated) for the reaction outcome. Intermediate II then undergoes a second cyclization reaction to afford final product **3a**. It is worth noting that 1,3-proton transfer in intermediate II must be very slow for such cyclization to occur despite the much higher acidity of C-H bond in carbonyl α-position.

In DMSO, the enolate formed is reactive enough to directly add to a triple bond to afford product **III** (**2a**-Li) after intra- or intermolecular proton transfer to vinylic carboanion intermediate. To gain more insights into proton transfer process, deuterium labelling studies were performed (Scheme 2b). Cyclization reaction in d_6-DMSO unexpectedly delivered product **2a** deuterated at vinylic position indicating that proton transfer is realized by deuterium abstraction from solvent d_6-DMSO (pK_a = 31) rather than from ketone α-position (pK_a = 25). Moreover, in contrast to fully diastereoselective process in non-deuterated DMSO, reaction in d_6-DMSO afforded mixture of *Z/E* diastereomers. Most likely, the deuteron abstraction from d_6-DMSO is much slower due to kinetic isotopic effect and as a result vinylic anion has enough time for inversion. Indeed, aryl substituted vinyl anions are known to be configurationally labile.[23] The above assumption was further confirmed with alkyl derivative **4** (for structure see Scheme 1) as starting material which afforded diastereomerically pure *Z*-product in both deuterated and non-deuterated solvents via configurationally stable alkyl vinyl anion. The very sluggish proton transfer might also account for very slow reaction of **1a** with NaH in aprotic THF (Table 1, entry 3) and the formation of *Z/E* mixture of the product under these conditions. If a direct addition of enolate to triple bond is assumed, the stereochemical outcome of the reaction is easily explained by trans-addition of nucleophile commonly observed in such reactions.[24] Although the scrambling of the alkene stereochemistry in d_6-DMSO and isotope labelling position serve as a very strong support for direct addition of enolate to alkyne triple bond, a small possibility for allene mechanism still exists. Namely, deuterated allene **I** produced from starting material via base catalysed isomerization may undergo cyclization to produce seven-membered carboanion **II** which then could give **III** after proton transfer (Scheme 2b). To unambiguously rule out such possibility, deuterated starting material **1a**-d_3 was used as a model substrate. No deuterium was introduced to neither vinylic nor allylic position corroborating enolate-alkyne addition mechanism and the absence of intra- or intermolecular proton transfer involving cyclic product. Partial D to H exchange at α-position was observed due to enolization of product during the quench.

Alternatively, one may argue that the reaction with LiHMDS in THF could also proceed by direct addition of lithium enolate to alkyne to first produce **IV** which then would isomerize to the

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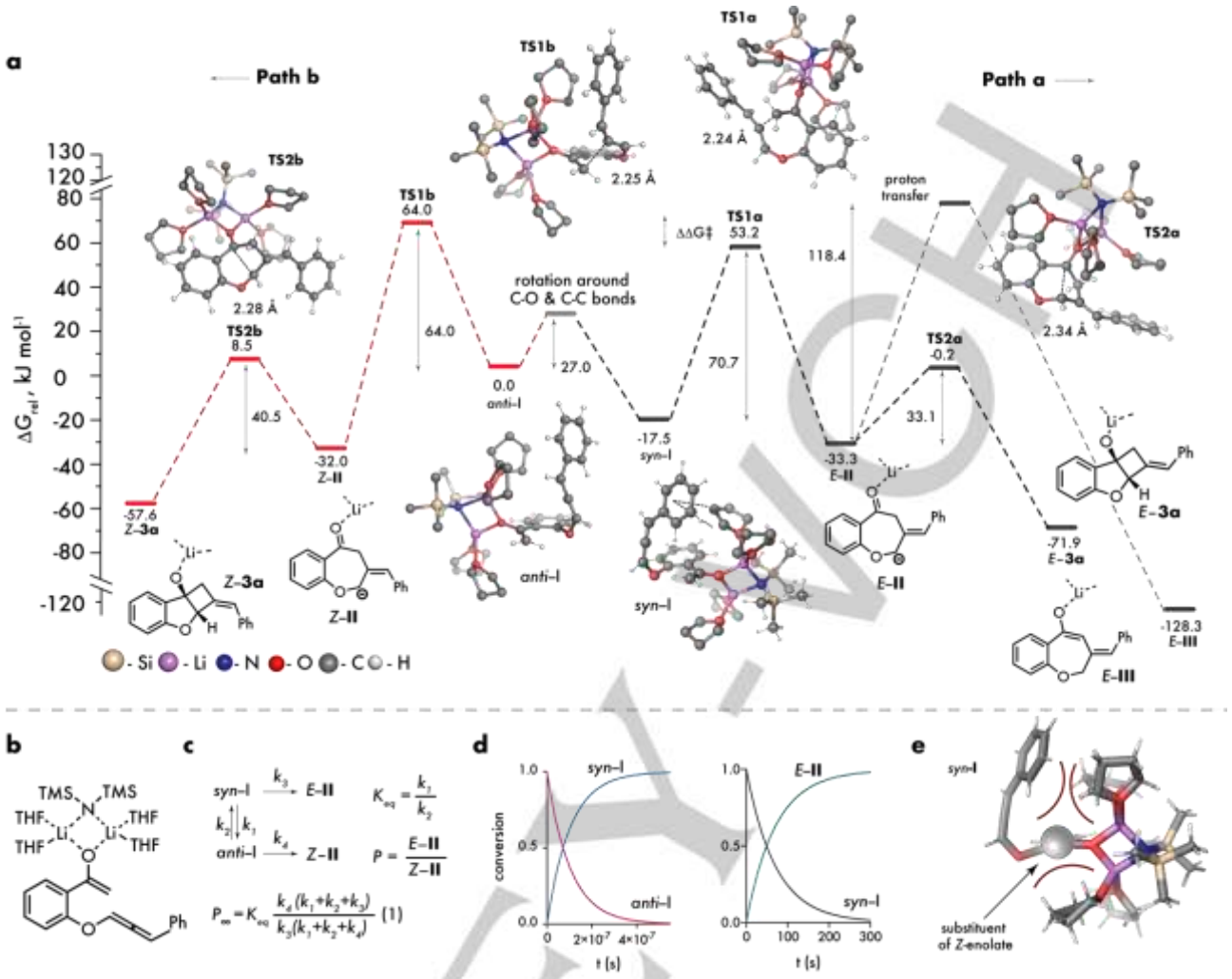

Figure 3. a) DFT-computed energy profile of the reaction starting from *anti*-**I** and *syn*-**I** lithium enolate rotamers leading to stereoisomers *E*-**3a** (path a) and *Z*-**3a** (path b). The dashed line in the transition structures indicates the forming bond together with the distance between the connecting atoms. The dashed line in *syn*-**I** indicates C-H···π-dispersive interactions. TS, transition state; ΔG_{rel}, Gibbs free energy with respect to *anti*-**I** (given in kJ mol^{-1}); $\Delta G^{\ddagger}$, Gibbs free energy of activation. Energies are computed at the SMD/IEF-PCM/B3LYP-D3/6-31G(d,p) (tetrahydrofuran) level of theory (see Supplementary Information for more details and references). b) Structure of the enolate used for calculations in a). c) Kinetic scheme for *E*-**II** and *Z*-**II** formation and general equation (1) describing their ratio P as a function of all *k* involved. d) Theoretical simulation of the reaction course (T = 253 K) using computationally derived activation energies. The fast establishment of equilibrium (left) and subsequent conversion of *syn*-**I** to *E*-**II**. The concentration of Z-**II** is negligible and coincides with the baseline. e) Stereochemical model indicating destabilizing steric interaction between α-substituent (grey ball) of *Z*-enolate and both THF and phenyl group in *syn*-**I** rotamer.

required intermediate **II**. This possibility is ruled out by the fact that cyclization reaction does not take place using one or less equivalent of LiHMDS.

Computational Studies. Regarding the cyclization mechanism in THF outlined in Scheme 2a, one issue remained to be rationalized, *i.e*. the unexpected *E*-configuration of the exocyclic double bond in products **3** derived from α-unsubstituted acetophenones. If one assumes the addition of enolate to an allene, the addition is expected to take place from the opposite side to phenyl substituent leading to *Z*-alkene. To resolve this matter, we addressed the reaction mechanism computationally using density functional theory (DFT) (Figure 3). As a starting point, we selected a variation of heterodimeric enolate structure featuring tetracoordinated lithium ions with THF and HMDS anion ligands, similar to the one first proposed by Arnett[17] for LiHMDS derived enolates (Figure 3b). Although such structure perhaps is an oversimplification of the real enolate aggregation mode, it should correctly reflect the reactivity trends from both steric and electronic perspective.

The computed free energy profile of the key steps along the reaction path is shown in Figure 3a. Calculations of two alternative reaction pathways a and b leading to *E*-**3a** and *Z*-**3a**, respectively, were carried out starting from two rotamers (*anti* and *syn*) of allenyl ether Li-enolates. As anticipated, the first cyclization step of *syn*-**1** rotamer into intermediate *E*-**II** requires 6 kJ mol^{-1} higher energy than that of *anti*-**1** rotamer forming intermediate *Z*-**II**. Both anion intermediates are essentially isoenergetic. Analysis of the whole energy profile shows that the first cyclization step plays a decisive role in establishing alkene stereochemistry in product **3a**. Indeed, the subsequent step of second cyclization of allylic anion is more favourable for *E*-**II** by 7 kJ mol^{-1} leading to experimentally observed product *E*-**3a**. Higher activation energy towards *E*-**II** from *syn*-**I** would imply the preferential formation of product *Z*-**3a**,

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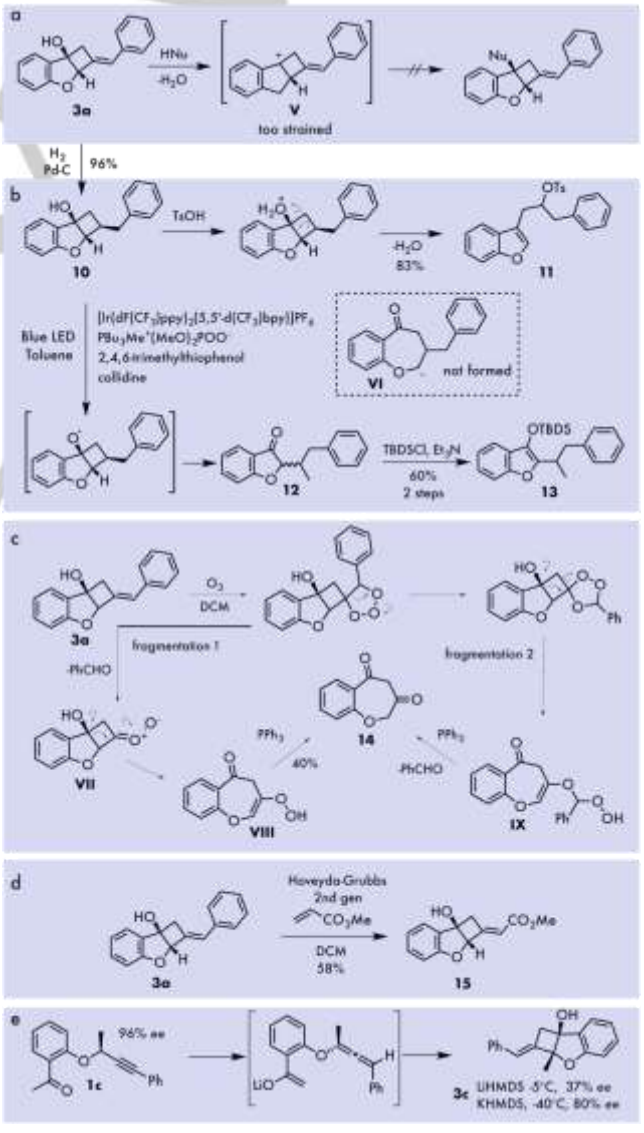
however, we noticed that *syn*-**I** rotamer is significantly stabilized in the ground state as compared to anti-congener. If one assumes a possible low-barrier channel for the interconversion of *syn*- and *anti*-rotamers that would lead to a Curtin-Hammett scenario with inversed rates for *Z*-**II** and *E*-**II** formation as compared to non-interconverting rotamers. The Curtin–Hammett principle[25] outlined in Figure 3c in the most general form (1) shows that product selectivity P in competitive pathways depend both on the relative reactivity of the two intermediates *syn*-**I** and *anti*-**I**, expressed by the ratio of their rate constants for product formation, k_3/k_4, as well as on the ratio of syn/anti isomerization constants k_1 and k_2. In special case for rapidly equilibrating reactants (k_1, k_2 >> k_3, k_4), equation (1) can be simplified to P ≈ $K_{eq}k_3/k_4$ ≈ exp(-$\Delta\Delta G^{‡}$/RT) and it can be shown that the ratio of products depends not solely on the absolute values of activation energy but rather on the difference $\Delta\Delta G^{‡}$. In our case, less active but more stable intermediate *syn*-**1** leads to the major product, the Curtin-Hammett scenario termed "monopolyzing kinetics" by Blackmond *et al*.[26] DFT calculations revealed that *syn* and *anti*-rotamers can be interconverted by a series of rotation around single C-O and C-C bonds with the highest barrier not exceeding 30 kJ mol^{-1} (see Figure S12). Simulation of time-dependent speciation of *syn*-**I**, *anti*-**I**, *E*-**II** and *Z*-**II** at -20ºC starting from pure *anti*-**I** and by solving a set of differential equations describing the kinetic scheme in Figure 3c indeed resulted in high P (*E*-**II**/*Z*-**II**) = 165 values and subsequently full selectivity for *E*-**3a** formation.[27] Higher stability of *syn* rotamer most likely stems from C-H···π dispersive interaction between THF ligands and phenyl substituent located in close proximity, stressing the importance of the role of lithium ion coordination shell beyond simple attenuation of enolate reactivity. For comparison, the free energy profile was also obtained for a hypothetical reaction based on the same mechanism and solvent but involving enolate with non-coordinated lithium ion (see Figure S13). In this case, the activation barrier for path b remains lower than for path a, but the energy of TS1a becomes higher compared to TS1b, which leads to the formation of "wrong" stereoisomer *Z*-**3a**. In addition, computational studies also predicted very high activation barrier (ΔG = 118 kJ mol^{-1}) for the intramolecular proton transfer in intermediate *E*-**II** in accord to experimental data. In fact, combined with data from Scheme 2, it seems that intramolecular 1,3-proton transfer in seven-membered ring from α-position is extremely sluggish to both vinylic and ether carboanions.

The inverse of stereochemical outcome for α- substituted substrates can also be explained based on the computed geometries. The use of LiHMDS in THF is known to selectively produce *Z*-enolate.[19] For Z-enolates, transition state similar to **TS1b** derived from *syn*-**I** and leading to *E*-products becomes impossible due to sterically crowding imparted by the alkyl substituent (Figure 3e). Therefore, reaction proceeds via path b rather than path a, where steric interaction of alkyl group with phenyl ring is avoided. Moreover, close examination of the geometry of transition states **TS1b** and **TS2b** also provided a simple model to explain the observed all-*syn* geometry of the products **3j**, **3g** and **3x** derived from more substituted substrates (Table 2).

Chemical Reactivity. With products **3** in hand, we preliminary probed some of their properties in the context of reactivity and synthetic applicability (Scheme 3a). In our initial attempts to accomplish an S_N1 type reaction with **3a** we noticed its high reluctance to form tertiary carbocation **V** even under forcing conditions such as treatment with trifluoromethane- or methanesulfonic acids. The reason for this is likely the geometric constrain of the bicyclic scaffold where C(sp^3) atom adjacent to carbocation renders planarization of the latter impossible. In addition, the presence of the double bond in the cyclobutene ring also prevents stabilization of the forming cation via ring fragmentation. On the other hand, the saturated compound **10** obtained by diastereoselective hydrogenation of **3a** undergoes fragmentation reaction to **11** upon treatment with *p*-toluenesulphonic acid. The cleavage of cyclobutane ring produces secondary carbocation which is then captured with sulfonate anion to afford benzofuran derivative **11** in good yield.
In another test reaction we explored **10** as a substrate for a photocatalytic ring-opening reaction enabled by proton-coupled electron transfer (PCET), recently developed by Knowles and co-workers.[28] In this reaction, the cyclic alcohols are isomerized into acyclic carbonyl compounds and during the process C-C bond adjacent to oxygen atom of alkoxy radical is cleaved in a direction to produce the most stable carbon radical. We speculated that



Scheme 3. Synthetic elaboration of the reaction products.

dihydrobenzofuran ring in **10** could serve the same purpose as *p*-methoxyaryl substituent in providing radical cation intermediate upon oxidation with the excited state of Ir(III) photocatalyst. We were surprised to find out that in case of **10**, the β-scission in cyclobutane ring resulted in the formation of primary radical rather than expected secondary radical **VI** enjoying an additional stabilization from adjacent oxygen atom. (Scheme 3b). Although the exact reason for such selectivity remains elusive, it represents the first example of alkoxy radical fragmentation displaying features of β-elimination[29] rather than β-scission mechanism where the choice between the two is given. The obtained mixture of diastereomers **12** was converted into a single benzofuran derivative **13**.

The facile fragmentation of the fused ring system was also demonstrated in ozonolysis reaction (Scheme 3c). Instead of expected cyclobutanone, seven-membered diketone **14** was obtained from **3a** as a major product. The formation of **14** might be explained by two alternative fragmentation pathways involving either carbonyl oxide (Criegee intermediate, fragmentation 1) or secondary ozonide (fragmentation 2). The fact that only benzaldehyde and not **14** was observed in the reaction mixture before the reductive quench with PPh_3 strongly supports the former pathway. Few examples of anomalous ozonolysis of strained allylic alcohols are reported in literature, however, to our knowledge, no such fragmentation has ever been reported for homoallylic alcohols.[30],[31]

Although the newly developed cascade reaction presented herein is limited to alkenylaryl derivatives, by performing alkene metathesis reaction of **3a** with methylacrylate we have shown that the alkenylaryl moiety can be successfully replaced with synthetically useful Michael acceptor to give **15** in 58% yield (Scheme 3d).

Finally, the possibility of chirality transfer from propargylic stereogenic center throughout cascade transformation was evaluated by using easily available enantiomerically pure propargyl ether **1c** (Scheme 3e). The postulated transformation would constitute an example of point (single)-axial-point (multiple) chirality transfer. Disappointingly, the first attempt using LiHMDS base delivered the product **3c** in 29% *ee* only. This is likely related to significant racemization of carboanion stereogenic center before isomerization to allene as the reaction proceeded at relatively high temperature. Indeed, by using more basic KHMDS, the reaction temperature could be lowered to -40 ºC and the ee of the product drastically increased to 80%; the value is within a range of *ee* suitable for potential further enrichment by crystallization. The absolute configuration of the major enantiomer of **3c** was predicted based on the computationally derived mechanism (Figure 3) and verified by single-crystal X-ray analysis of the derived 3,5-dinitrobenzoate (Page S128).

Conclusion

In summary, we have developed a novel anionic cascade transformation initiated by the addition of lithium enolate to non-activated allene, generated in situ from propargylic ethers. Intriguingly, the cascade was not interrupted by the presence of thermodynamically more acidic protons within the intermediate, resulting in simultaneous forging of fused five and four -membered rings. Mechanistic and theoretical studies corroborate the involvement of the allene intermediate, whereas low-barrier rotational interconversion of two reactive conformations of the latter is responsible for unorthodox stereochemical outcome of the reaction. Our findings confirm, and reinforce, in yet another context, the importance of enolate structure on its reactivity. As opposed to very polar solvents such as DMSO, where direct addition of enolate to triple bond is extremely fast, the attenuated reactivity of aggregated lithium enolate in THF enables the precise orchestration of enolization-isomerization-addition events in time, necessary for herein disclosed cascade transformation. Besides from providing unique molecular scaffolds in just one step from trivial starting materials, the possible extension of this cascade reaction to other substrates having different arrangement of ketone and propargylic ether functionalities is easy to spot and is pursued in ongoing studies.

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Keywords: Enolate • Allenes • Domino reactions • Cyclobutane • Rearrangements

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RESEARCH ARTICLE

All sizes in one fell swoop. Anionic cascade reaction initiated by an addition of enolate to an *in situ* generated non-activated allene has been developed. Herein presented formal [2+2] enol-allene cycloaddition cleanly provides functionalized molecular scaffolds with fused six-, five- and four-membered rings with full diastereoselectivity.