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Toward Efficient and Stereoselective Aromatic and Dearomative Cope Rearrangements: Experimental and Theoretical Investigations of α -Allyl- α' -Aromatic γ -Lactone Derivatives.

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Toward Efficient and Stereoselective Aromatic and Dearomative Cope Rearrangements: Experimental and Theoretical Investigations of α -Allyl- α' -Aromatic γ -Lactone Derivatives.

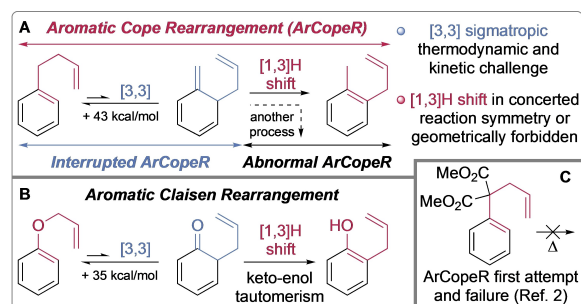
Morgane Mando,^[a] Fabienne Grellepois,^[a] Aurélien Blanc,^[b] Eric Hénon,^{*[a]} and Emmanuel Riguet^{*[a]}

The aromatic Cope rearrangement is an elusive transformation that has been the subject of a limited number of investigations compared to those seemingly close analogues, namely the Cope and aromatic Claisen rearrangement. Herein we report our investigations inspired by moderate success observed in the course of pioneering works. By careful experimental and theoretical investigations, we demonstrate that key substitu-

tions on 1,5-hexadiene scaffold allow fruitful transformations. Especially, efficient functionalisation of the heteroaromatic rings results from the aromatic Cope rearrangement, while highly stereoselective interrupted aromatic Cope rearrangements highlight the formation of chiral compounds through a dearomative process.

Introduction

Sixteen years after his discovery of “the thermal intramolecular rearrangement of allyl groups in three carbon systems” in 1940 with Elizabeth Hardy,^[1] Arthur C. Cope and co-workers described the first investigation of 1,5-hexadiene rearrangement where one of the π electron pairs is a part of an aromatic ring.^[2] The first transformation reached the standing as “named reaction”, i.e. Cope rearrangement,^[3] due to its fruitful use in the field of target oriented synthesis and by switching from the “no-mechanism reactions”^[4] status to the one of a paradigmatic class of pericyclic reactions,^[5] giving rise to fascinating intrigues and mechanistic studies.^[6] The second Cope study^[2] initiated the now so-called aromatic Cope rearrangement (ArCopeR, Scheme 1, A). The latter has been far less recognised and used than the ‘classical’ Cope rearrangement (only around 40 articles to date).^[7] Interestingly, the ArCopeR resembles to another pericyclic reaction, i.e. the aromatic Claisen rearrangement involving allyl ethers of phenols (Scheme 1, B).^[8] This analogy suggests^[2a] that a simple homoallylic substituted benzene ring



Scheme 1. Comparison of the Aromatic Cope and Claisen rearrangements. Failure of the thermal ArCopeR on α -allyl- α' -aryl malonate substrate.

could rearrange in a two steps process, affording di-substituted aromatic compound (i.e. a [3,3] sigmatropic rearrangement followed by a [1,3]H shift). Of note, the reactions involving only the first [3,3] sigmatropic rearrangement could be depicted as an interrupted ArCopeR (also called dearomative Cope rearrangement) whereas reactions involving [3,3] sigmatropic rearrangement followed by another process than rearomatisation through a [1,3]H shift should refer to abnormal ArCopeR (Scheme 1, A). In Cope’s seminal study, heating α -allyl- α' -aryl malonates at elevated temperature didn’t lead to the formation of product corresponding to “an all-carbon version of the aromatic Claisen rearrangement” product (Scheme 1, C).^[2a]

This situation obviously originates from the high thermodynamic, kinetic and geometrical requirements associated with both steps. Indeed, the rare aromatic Cope rearrangement studies^[7] highlighted the huge constraints due to [3,3] sigmatropic dearomative step (+43 kcal mol⁻¹ activation enthalpy).^[9] Only few strategies to circumvent them have been proposed such as strain-released^[9–10] or synchronized aromaticity^[11] strategies. Importantly, the most significant contrast between the

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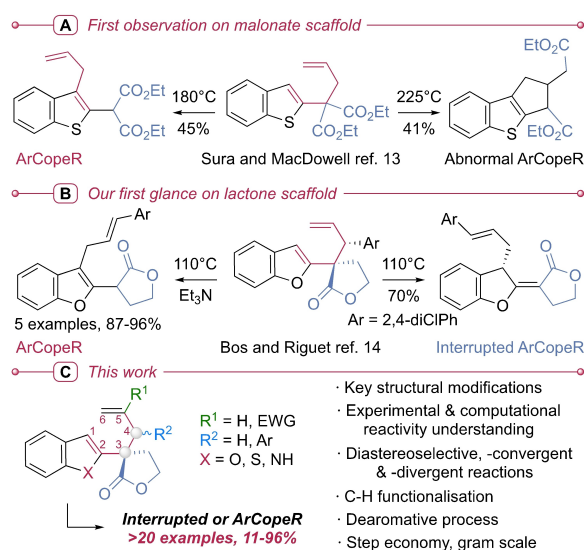
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aromatic Claisen and the aromatic Cope arises from the [1,3]H shift. Indeed, in concerted reactions, orbital symmetry rules impose that the suprafacial [1,3]H shift is forbidden while the antarafacial shift is allowed but geometrically impossible. In the aromatic Claisen rearrangement, the [1,3]H shift easily occurs through a protonation/deprotonation mechanism and thermodynamically drives the overall process (Scheme 1, B), contrasting with simple 1,5-hexadiene scaffolds where the absence of basic site upsets the [1,3]H shift and prevents a reaction otherwise exergonic. Following the failure to observe aromatic Cope product involving all carbon aromatic compounds (Scheme 1, C),^[2a] it was shown that this transformation could occur at high temperature ($\geq 180^\circ\text{C}$) using heteroaromatic thiophene^[12] and benzothiophene^[13] embedded in a α -allyl- α' -aryl malonate scaffold. These reactions afforded ArCope or abnormal ArCope products in moderate yields (Scheme 2, A). Despite the harsh reaction conditions used, the structures of the expected products suggest interesting synthetic applications notably in the field of heteroaromatic chemistry (Scheme 2, A). Indeed, the entire process allows site-specific allylation of a heteroaromatic or aromatic ring, and thus offers new route for regioselective C–H functionalisation. Furthermore, a dearomatisation reaction could lead to an innovative access to structurally diverse three-dimensional polycyclic molecules. Until now, the energetic impediments that must be overcome to use aromatic Cope rearrangement darkened its synthetic potential. However, we recently showed that α -allyl- α' -benzofuran lactones can undergo an efficient aromatic Cope rearrangement (Scheme 2, B).^[14] This study was the only modern example of ArCopeR involving heteroaromatic compound,^[7] until a very recent related work performed on functionalised *N*-triflate indole derivatives allowing to produce interrupted Cope products in excellent yields and diastereoselectivities.^[15]

In the present work, we provide deeper and fundamental knowledges on the aromatic Cope rearrangement by merging



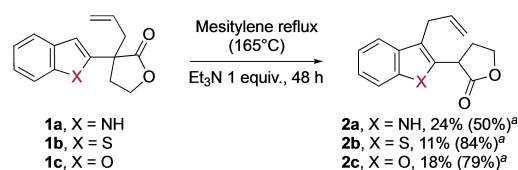
Scheme 2. Key historical account and this work towards aromatic Cope rearrangements on α -allyl- α' -aryl malonate & lactone derivatives.

experimental results, kinetic studies, and quantum mechanics calculations (Scheme 2, C). Based on the α -allyl- α' -heteroaromatic lactones scaffold, benzofuran, benzothiophene and indole ring were embedded in this study revamping, for the first time, the ArCopeR as a powerful synthetic method. Our recent efforts in the field of allylic alkylation of lactones substituted by an heteroaromatic ring leading to 1,5-hexadiene pattern,^[14,16] allow us to investigate several structural features expected to alter the potential energy surface of the overall rearrangement. Notably (i) electron withdrawing group at C5 position could entail a decrease of activation energy by polarisation of charge distribution^[17] (with respect to C2 position); (ii) Substitution at the C4 by aromatic ring embedding contrasting electronic features could impact the electronic behaviour of the C3–C4 bond that undergoes cleavage; (iii) the installation of stereogenic centers at C3 and C4 positions not only allows to explore stereoselective transformations but also provides glimpse at the transition state (TS) geometry.

Results and Discussion

Study on simple scaffolds

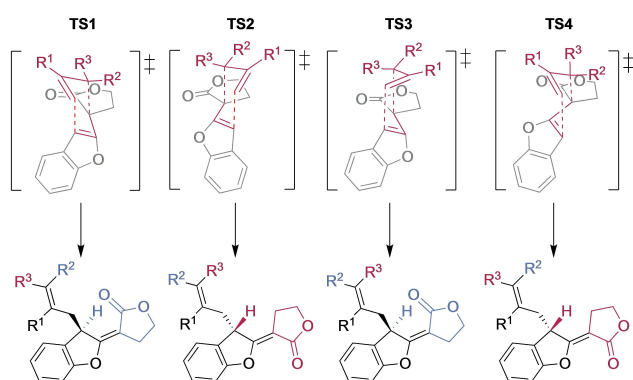
Benchmark experiments were first conducted with compounds **1a–c**, which are structurally related to the α -allyl- α' -benzothiophene malonate involved in the pioneer work.^[13] These compounds were heated at 165°C (reflux of mesitylene) in the presence of 1 equivalent of triethylamine during 48 hours (Scheme 3). The presence of a stoichiometric amount of triethylamine is used to facilitate the [1,3]H shift step by deprotonation/protonation and thus observe a transformation even in the case of endergonic [3,3] sigmatropic step. Under this reaction condition, the indolic ArCopeR product **2a** was isolated in 24% yield. The starting material **1a** was recovered in 50% yield together with a significant amount of product degradation. When the reaction was performed with benzothiophene derivative **1b**, the desired ArCope rearrangement product **2b** was isolated in only 11% yield. Noteworthy, the NMR analysis of the crude reaction mixture only revealed the presence of expected product **2b** and of starting material **1b**. The latter was recovered in 84% yield. A similar result was obtained when benzofuran ring is involved, indeed compound **2c** was isolated in 18% yield and starting material **1c** was recovered in 79% yield. As the re-aromatisation step (i.e [1,3]H shift) is assumed to be kinetically and thermodynamically favourable under these reaction conditions, the low conversion observed may reflect



Scheme 3. Thermal ArCopeR on unsubstituted α -allyl lactones derivatives **1**.
^aRecovered starting material.

the high activation energy of the [3,3] sigmatropic step when scaffolds containing the unsubstituted allyl group are involved. Moreover, the low level of side products formation can be attributed to the robustness of the lactone function.

Density functional theory calculations were performed to investigate the energetics of the [3,3] sigmatropic step through either boat or chair transition state (TS). To account for more reliable energies, geometries obtained at the PCM(toluene)-M06-2X/6-31G* level of theory were refined using the larger basis set 6-311++G(2d,2p) in conjunction with Grimme's dispersion correction (GD3)^[18] (see ESI for all computational details). Because of the presence of the stereogenic center C3 on the 1,5-hexadiene scaffold, a single reactant can follow four competing reaction channels. Thus, four TS geometries must be considered, i.e. two pseudo-chair and two pseudo-boat conformations (Scheme 4, R¹ = R² = R³ = H). The kinetic and thermodynamic properties were assessed with KiSTheIP software.^[19] The results obtained for **1c** reveal large values of the activation enthalpy ($\Delta^\ddagger H_{OK}$ in the range 33 to 40 kcal mol⁻¹, see ESI), making this reaction step unfavourable. For comparison, the barrier involved in the classical Cope rearrangement of 1,5-hexadiene is 33.2 kcal mol⁻¹.^[6c] This results in large free energy barriers at 165 °C (36 to 42 kcal mol⁻¹), in agreement with the experimental results (Scheme 3). The theoretical investigation also reveals a thermodynamically unfavourable transformation (positive free energy of reaction in the range 2 to 8 kcal mol⁻¹). Similar activation free energies are obtained for compounds **1a** and **1b** (in the range 34 to 40 kcal mol⁻¹). All these compounds are predicted to proceed through an endergonic [3,3] sigmatropic rearrangement at 383 K (1 to 8 kcal mol⁻¹, see Tables S17 to S22 in ESI). It is noteworthy that the reaction pathway involving a transient pseudo-chair conformation TS1 is always the most kinetically favourable, by 1.3 to 5.9 kcal mol⁻¹ (among the four concurrent channels). Unfortunately, at this stage, this information cannot be checked at the experimental level, which provides insight solely into the final product **2** (obtained after rearomatisation). It is also worth noting that in the benzofuran, indole and benzothiophene series, the activation energy gradually decreases from 35.9 to 34.2 kcal mol⁻¹.

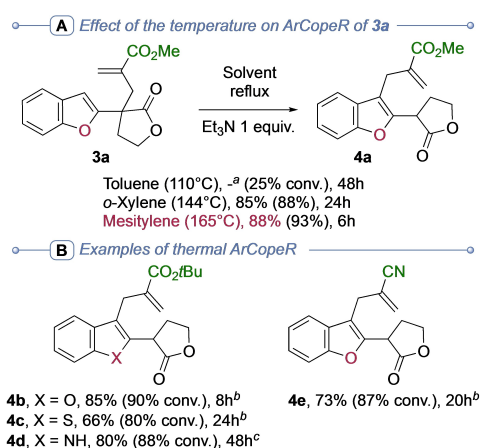


Scheme 4. Geometry of the four transition states (TS1-4) involved in the interrupted ArCopeR starting from one single stereoisomer.

Toward efficient ArCope rearrangement: Introduction of electron-withdrawing group

We next explored the impact of electron-withdrawing group at C5 using benzofuran ring as heteroaromatic model.

The aromatic Cope rearrangement appears to be facilitated by this structural modification. Indeed, the formation of ArCope product is already observed from 110 °C as a 75/25 ratio between the starting material **3a** and the expected product **4a** in the crude reaction mixture (Scheme 5, A). Notably, these two products are the only observable in the ¹H NMR of the crude mixture. At 144 °C, the conversion increased to 88% after 24 h of reaction and the ArCope product **4a** can be isolated in 85% yield. Finally, the preparative nature of the methodology was established on 2 mmol scale synthesis by the procurement of ArCope product **4a** with 88% yield in a shorter reaction time (6 h) at 165 °C. Under the latter conditions, we also established that C5-tert-butyl ester substituted compound **4b** can be isolated in high yield (85%) (Scheme 5, B). ArCopeR also occurred on compound containing a benzothiophene ring as shown by the procurement of compound **4c** in a 66% yield. Noteworthy only traces of ArCope rearrangement compounds **4b** and **4c** were observed when the reactions were carried out in absence of base (reflux in mesitylene). A significant different situation arose when indole compound was involved. Indeed, when standard conditions (i.e. refluxing mesitylene, Et₃N 1 equiv) were applied, the expected ArCope rearrangement product **4d** was observed as major compound together with a significant amount of side products. However, compound **4d** was obtained in 80% yield by using lower temperature (refluxing toluene) and base free reaction conditions. Finally, the introduction of a nitrile group on the C5 carbon had a similar effect on the ArCopeR as compound **4e** was isolated in 73% yield. Thus, the substitution of C5 position by an electron withdrawing group had a significant impact on the aromatic Cope rearrangement pathway and allowed access to valuable synthetic scaffolds.



Scheme 5. Thermal ArCopeR on C5-substituted α -allyl lactones derivatives **3**. ^aProduct **4a** not isolated. ^bReaction in refluxing mesitylene. ^cReaction in refluxing toluene without base.

Keeping in mind that the required scaffold to entail an ArCopeR is built by allylic alkylation of α -heteroaryl- γ -butyrolactone, we anticipated that a reaction sequence involving allylic alkylation followed by ArCope could constitute a valuable method to alkylate heteroaromatic ring. We highlighted this point by performing gram scale experiment starting directly from α -benzofuran- γ -butyrolactone **5** and acrylate **6**, affording compound **4a** in a 64% yield over 2 steps (Scheme 6, A). Interestingly, the overall process affords an alkylated functionalised benzofuran with an *exo*-cyclic enolisable position which can be further alkylated. Thus, di-functionalised heteroaromatic compounds **7a–h** were obtained in good yields (58–79%) by allylic alkylation of the ArCope rearrangement products (Scheme 6, B).

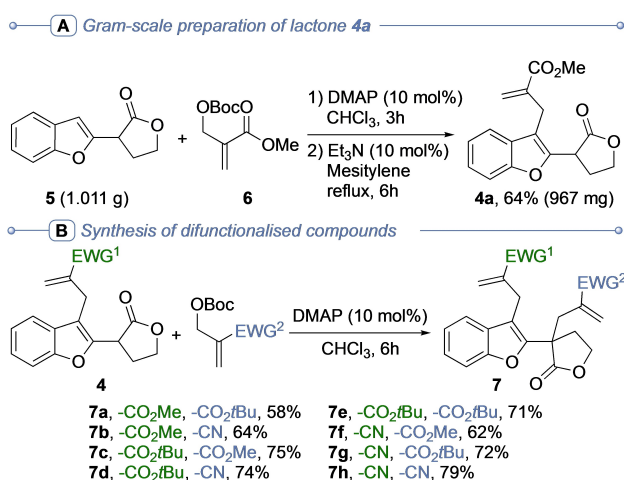
The computational investigation clearly shows the influence of the electron-withdrawing group at C5 on the [3,3] sigmatropic step. Compared to the unsubstituted compound **1c**, a substantial decrease of the energy barrier is observed for the four reaction pathways involving compound **3a**, in the range 3.2 to 4.6 kcal mol⁻¹ at 110 °C (see tables S23 and S24 in ESI). Incidentally, pathway TS1 is once more predicted to be the most favoured. But the presence of this electron-withdrawing group on C5 does not make the reaction more thermodynamically favourable. The electronic effect of the ester group on the starting material **3a** has been assessed at several levels of theory. First, the atomic partial charges (Natural Population Analysis)^[20] were calculated. Charges on C1 to C6 are barely affected by the presence of the ester (see Table S35 in ESI). Only the charges held by atoms C5 and C6 vary slightly. This last result is supplemented by the Pair Density Asymmetry (PDA) analysis^[21] showing that the electronic feature of the C5–C6 bond is particularly affected by the ester group adjunction (the PDA index increasing from 0.04 to 0.63 a.u.). Next, a dual descriptor analysis for nucleophilicity and electrophilicity was carried out.^[22] The presence of the ester at C5 substantially perturbs the electronic structure at C2 and C6 (see ESI, Figure S47). It induces a significant electrophilic character at C6

in **3a**, which is totally absent in **1c**. Therefore, the introduction of an acceptor group on C5 with the concomitant presence of a donor group on C2 (the benzofuran oxygen) assists the formation of the C1–C6 bond. Noteworthy, it was previously theoretically demonstrated that the concept of a push-pull effect of an acceptor-donor pair properly placed at C5 and C2 could be used to facilitate the Cope rearrangement through C6 activation.^[17] Going a bit deeper into the analysis using the Independent Gradient Model,^[23] (IGM) (a tool detecting and quantifying molecular interactions from electron density), we observe that the influence of the ester group at C5 on the rest of the substrate prefigures the upcoming sigmatropic rearrangement. Indeed, the bond C3–C4 destined to break displays a bond strength (measured by the IGM Intrinsic Bond Strength descriptor, IBSI) decreasing from 0.836 to 0.807 upon adding the ester group. Simultaneously, C5–C6 weakens (IBSI reducing from 1.423 to 1.385) and C4–C5 strengthens (IBSI going from 0.911 to 0.934). These changes clearly outline the forthcoming chemical reorganisation. All these computational data support the idea that the presence of the ester group activates the reactivity of the starting substrate.

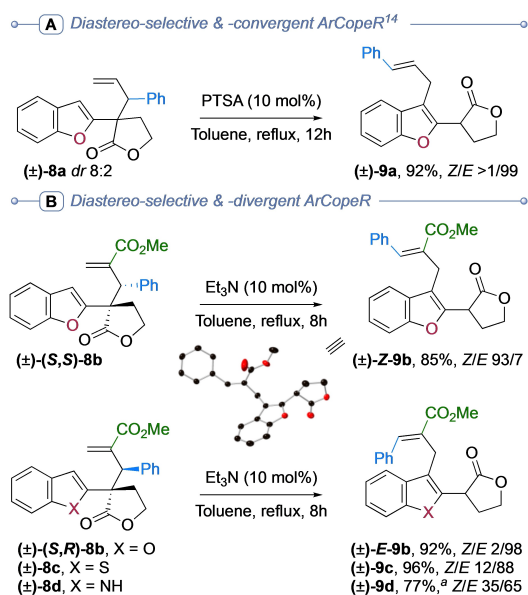
ArCope vs highly stereoselective interrupted ArCope rearrangement: the case of C4 substituted scaffolds.

Aromatic Cope reaction was then studied on scaffolds with an additional stereogenic center at C4 position. This structural modification entails the formation of aromatic Cope products with stereogenic double bond. Thus, stereoselective transformation can be performed and more importantly in regard of mechanistic investigation, this stereogenic element provides unambiguous clues about the TS geometries involved in the [3,3] sigmatropic step.

We previously described^[14] that under heating at 110 °C in the presence of a catalytic amount of strong acid (i.e. 10 mol% of PTSA) a diastereoisomeric mixture of compound **8a** (*dr* 8:2) can be converted into a single diastereoisomer **9a** through aromatic Cope rearrangement (Scheme 7, A). The diastereoconvergent feature of the ArCopeR observed for compound **8a** is not general as highlighted by experiments conducted on compounds substituted both on C4 and C5 positions (Scheme 7, B). Interestingly highly diastereoselective ArCopeR was also observed for this class of compounds. However, a diastereodivergent behaviour took place in this case. Indeed, heating of compound (\pm)-(*S,S*)-**8b** at 110 °C in the presence of 10 mol% of Et₃N, led to compound **Z-9b** in high yield (85%) and diastereoisomeric ratio (*Z/E* = 93/7). Moreover, the reaction performed on gram scale allowed the formation of diastereoisomerically pure **Z-9b** in good yield. Recrystallisation (71%) and single-crystal X-ray crystallography allowed the unambiguous determination of its chemical structure.^[24] Starting from compound (\pm)-(*S,R*)-**8b**, the ArCopeR proceeds in an excellent selectivity affording the opposite diastereomer **E-9b** in high yield 92% (*Z/E* = 2:98). The same trend was observed with benzothiophene ring, **9c** being obtained in high yield and diastereoisomeric ratio (96%, *Z/E* = 12/88) from **8c**. The behav-



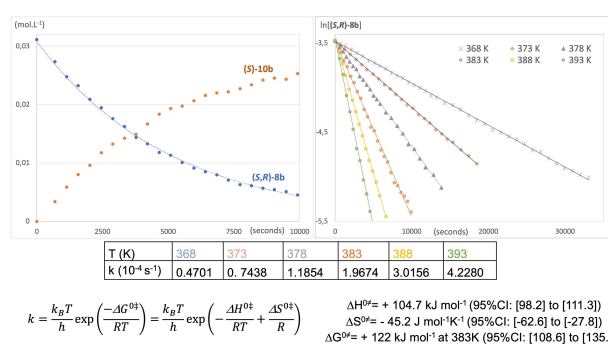
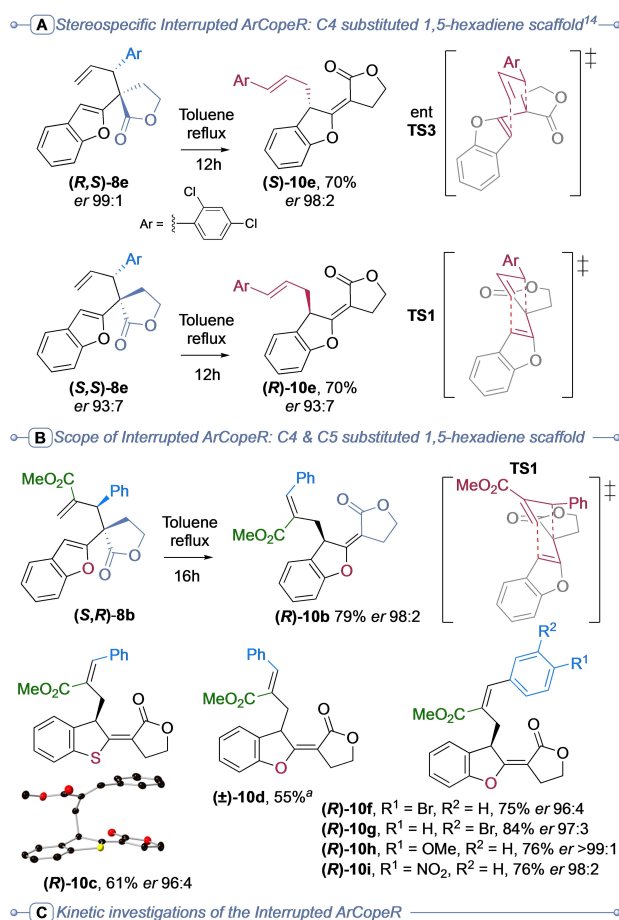
Scheme 6. Gram scale preparation of **4a** and post-functionalisation of ArCope products **4**.



Scheme 7. Thermal ArCopeR on C4-substituted α -allyl lactones derivatives **8**.
^aReaction without base.

our of indole compound **8d** contrasted in two points: as previously observed for compound **4d**, the use of basic condition was not required to perform the ArCopeR and a significant lower diastereoselectivity was found as compound **9d** was isolated (77% yield) in a Z/E ratio of 35/65.

An important feature of such compounds substituted by a phenyl ring at C4 position lies in their unique ability to be transformed through an interrupted ArCopeR (i.e. one concerted step [3,3] sigmatropic rearrangement) when the thermic process is carried out under neutral condition (Scheme 8, A). Thus, when diastereoisomerically pure and enantioenriched C4-substituted α -allyl- α' -aryl lactone derivatives **8** were used, the configuration of the three stereogenic elements of the compound resulting from the [3,3] sigmatropic rearrangement provides confident clues on the TS geometry involved. A single stereoisomer can theoretically undergo four different competing reaction pathways possibly resulting in the formation of four distinct diastereoisomers (Scheme 4). These four possibilities are distinguished by the two 'pro'-configurations (Z or E) of the C2-C3 bond at the TS and the two possible boat or chair conformations taken by the reacting backbone. We have already demonstrated that the two diastereoisomeric chiral compounds (R,S)-**8e** and (S,S)-**8e** lead to the opposite enantiomers (S)-**10e** and (R)-**10e** (Scheme 8, A).^[14] The geometries of transition state on the reaction pathway from (R,S)-**8e** to (S)-**10e** and from (S,S)-**8e** to (R)-**10e**, as far as a concerted process is involved, are attributable unequivocally to the transition states ent-TS3 and TS1 respectively (Scheme 8, A). Notably the change of favourable geometry (i.e. boat to chair) explains the diastereoconvergent feature of aromatic Cope reaction discussed previously. The two TS geometries ent-TS3 and TS1 (Scheme 8, A) involved in these transformations share, as important structural features, pseudo equatorial position of



Scheme 8. Stereospecific interrupted ArCopeR: scope, transition states and kinetic study. ^a72% conv, 15% of ArCope product **Z-9b** was also formed during the reaction. The regression analyses carried out with R software to estimate the activation enthalpy and entropy include the calculation of 95% confidence intervals (CI).

C4 aryl group and C3 lactone methylene group and an identical conformation around the C2-C3 bond (Scheme 8, A).

DFT calculations were performed to assess the energy barrier of the dearomatization process of substrates involving a phenyl group at position C4, i.e. starting from compounds (R,S)-**8e** or (S,S)-**8e**.^[25] The former shows activation free energies in the range 31 to 40 kcal mol⁻¹ and the latter in the range 29 to

37 kcal mol⁻¹ for the four competitive pathways at 110 °C. Compared to the unsubstituted reactant **1c**, like the influence of the ester group at C5 (**3a**), the presence at C4 of the phenyl group lowers the activation energy of the reaction by 1.8 to 8.2 kcal mol⁻¹, depending on the reaction pathway. Nevertheless, the reaction remains unfavourable.

DFT calculations predict TS1, TS2 and TS3 having the lowest activation energies for (*R,S*)-**8e**, very close, in the range 31 to 32 kcal mol⁻¹, i.e., within the quantum mechanical accuracy. But only TS3 (pseudo-boat approach) features an exergonic transformation (−3.3 kcal mol⁻¹) leading to (*S*)-**10e**, fully in line with the experimental findings (revealing an ent-TS3 boat approach, Scheme 8). Remarkably this theoretical result shows that the diastereoselectivity of the dearomatisation step can be driven by thermodynamics factors. This reactive pathway through the boat conformation is contrary to the expectation of a chair conformation with generally less steric strain. The equatorial position of the bulky phenyl group in ent-TS3 appears to be a decisive criterion here to rationalise this result. For the other diastereoisomer (*S,S*)-**8e**, pathway TS3 is also the one yielding the most stable product (−3.2 kcal mol⁻¹). However, in that case, the associated energy barrier is far too high (36.8 kcal mol⁻¹), compared to the barrier involved by the competitive TS1 (29.0 kcal mol⁻¹). That is the reason why (*S,S*)-**8e** is predicted to proceed through TS1 towards (*R*)-**10e**, once more, in total agreement with the experimental evidences highlighting this chair approach.

For the first time in this study (**8e** series), a significant exergonic character was predicted for the dearomatisation. Multiple factors may contribute to explain this exergonicity. First, the presence of the aryl group in **8e** involves an initial steric congestion in the reactant, mainly between vicinal C3 and C4 environments, which is released upon dearomatisation. This is demonstrated by the IGM analysis of the simple model (*S,S*)-**8e'** (model of (*R,S*)-**8e**) on Figure 1, revealing initially repulsive regions (red δg^{inter} iso-surfaces) on the reactant side that subsequently vanish during the reaction. Compound **3a** substituted only at C5 cannot leverage this advantage (non-bonding regions are still detected between fragments after rearrangement). This decongestion effect can be further amplified when the initial steric hindrance can be converted into a stabilisation through the apparition of van der Waals (vdW) interactions as exemplified through the IGM analysis of (*S,R*)-**8e'** (Figure 1). Such non-covalent stabilising features had already been identified with the NCI approach^[26] in diastereoselective indole-dearomative sigmatropic rearrangements.^[15] Finally, the inclusion of the phenyl group at C4 adds some extra π delocalisation once the new double bond C4-C5 bond is formed, which couldn't be achieved solely with the ester group at C5 in **3a**.

Driven by our recent advance in organocatalysed asymmetric allylic alkylation of α -aryl γ -lactones,^[16c] we were able to study more closely the reactivity of 1,5-hexadiene scaffold substituted at C5 position by an ester and at C4 by aromatic groups (Scheme 8, B). When compound (*S,R*)-**8b** was heated at 110 °C for 16 h hours the ¹H NMR analysis of the crude mixture showed the formation of (*R*)-**10b** as the only [3,3] sigmatropic

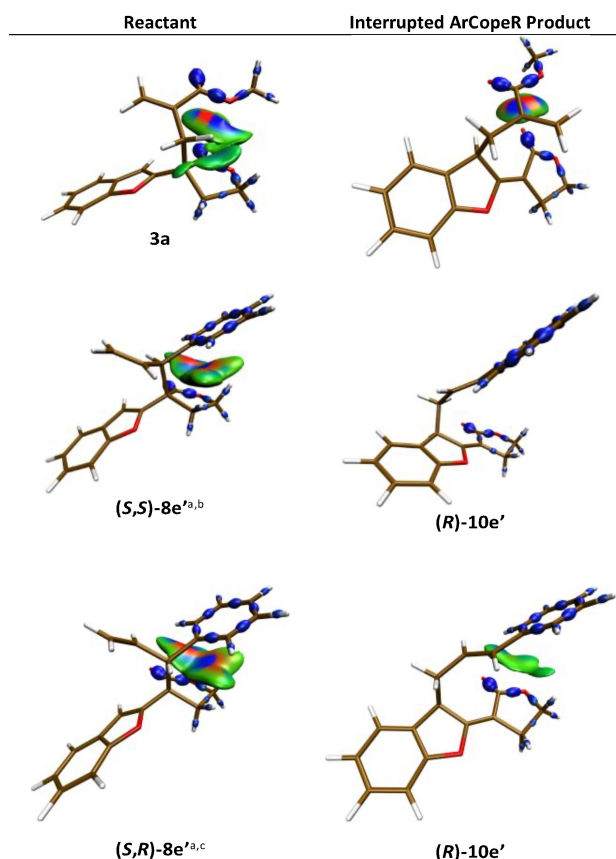


Figure 1. Non-covalent interaction IGM analysis between fragment 1 (phenyl) and fragment 2 (lactone) from DFT calculations at the PCM(toluene)-M06-2X/6-31G* level of theory; the same iso-value was used for all molecules in order to compare them on an equal footing: 0.004 a.u. δg^{inter} inter-fragment iso-surfaces colored on a BGR scheme over the range -0.02 a.u. $< \text{sign}(\lambda_2)\rho < +0.02$ a.u.; red, green and blue regions are associated with repulsive, intermediate and attractive interactions, respectively. δg^{intra} intra-fragment iso-surfaces (blue color) are also reported to visually identify involved interacting fragments. Structures are reported for the pathway involving the most favourable pathway, via 'TS1' for **3a** and (*S,R*)-**8e'**, and 'TS3' for (*S,S*)-**8e'**.^aDFT calculations were performed on model substrates with Ar=Ph instead of 2,4-diClPh. ^b(*S,S*)-**8e'** (Ar=Ph) is the pseudo-enantiomer of (*R,S*)-**8e** (2,4-diClPh). ^c(*S,R*)-**8e'** (Ar=Ph) is the model of (*S,S*)-**8e** (2,4-diClPh).

product together with residual amount of starting material (10%) and traces of ArCope product **E-9b**. The compound (*R*)-**10b** was isolated in a 79% yield albeit its sensitivity to acid and basic conditions entailing its transformation in rearomatised product. The configurations of the double bonds and the stereogenic center, as well as the absence of formation of other [3,3] sigmatropic product highlighted the strong preference for the reaction pathway involving TS1 geometry (Scheme 8, B). In the same reaction conditions, the interrupted ArCopeR proceeded with an equal strong preference for TS1 pathway with benzothiophene (*R,R*)-**8c** affording compound (*R*)-**10c** in a good 61% yield. Additionally, the isolated major interrupted Cope rearrangement product **10d** (55%) obtained from compound (\pm)-(*S,S*)-**8b** follows the TS1 pathway. Dearomatised benzofuran compounds (*R*)-**10f** and (*R*)-**10g** bearing a bromine substituted phenyl ring were obtained in good yields 75% and

85% respectively. The absolute configuration of interrupted Cope rearrangement products was unambiguously determined by single crystal X-Ray analysis of compounds (*R*)-**10c**, (*R*)-**10f** and (*R*)-**10g**. The versatility of interrupted Cope rearrangement to the electronic properties of C3 phenyl ring proved reaction efficiency on compounds bearing strong opposite electronic features. Gratefully compounds (*R*)-**10h** and (*R*)-**10i** were obtained in good yields (76%) (Scheme 8, B). A moderate impact of phenyl ring substitution on the rate constant was also highlighted by linear free energy relationships (see ESI, Table S16, Figures S44 and S45).

To gain a more accurate picture of the interrupted ArCopeR, we next performed kinetic analysis by NMR spectroscopy. The conversion of compound (*S,R*)-**8b** into the [3,3] sigmatropic product (*R*)-**10b** was monitored by ¹H NMR in deuterated *p*-xylene-d₁₀ at 383 K (Scheme 8 C see ESI for details). The data analysis at different reaction times showed the continuous evolution of compound (*S,R*)-**8b** toward product (*R*)-**10b** as a single diastereoisomer (no detectable amounts of other diastereoisomer were observed as well as no trace of aromatic Cope reaction product). By plotting the concentration of compound (*S,R*)-**8b** with respect to the time and applying first order kinetics, we determined apparent rate constants for thermal [3,3] sigmatropic rearrangement at 383 K of $1.96 \cdot 10^{-4} \text{ s}^{-1}$ (Scheme 8, C). The same procedure applied at different temperatures allowed experimental determination of activation energies, which can be compared to the calculated ones and used to refine the theoretical analysis. From the set of values of apparent rate constants at different temperatures, the Eyring equation was used to obtain these activation energies. Both the enthalpy and entropy of activation were obtained respectively from the slope of their linearised forms. For compound (*S,R*)-**8b**, the enthalpy and entropy of activation are respectively $+104.7 \text{ kJ mol}^{-1}$ and $-45.2 \text{ J mol}^{-1} \text{ K}^{-1}$, which leads to a Gibbs energy of $+122 \text{ kJ mol}^{-1}$ at 383 K (Scheme 8, C).

To determine activation and reaction energies of the different reaction paths for these transformations and to shed light on the high diastereoselectivity experimentally observed, calculations were conducted on the substrates (*S,R*)-**8b**, (*S,S*)-**8b** and (*R,R*)-**8c**. TS1 (pseudo-chair conformation) appears to be the favoured pathway for these three substrates due to a markedly low free energy barrier ($26\text{--}27 \text{ kcal mol}^{-1}$) in full agreement with experiments (Figure 2 and ESI Tables S29 to S34). These molecules combine the previously mentioned factors that favour the reaction (electronic activation by ester, C3-C4 decongestion effect and C4-C5 π -bridging). This is likely the reason why we observe the lowest barriers in these cases. Incidentally, it can be noticed that bond making (C1-C6) and breaking (C3-C4) involve very similar distances at the TS (around 2.1 Å), even for the compound (*R,R*)-**8c** having a sulfur atom. It can be also noticed that owing to several degrees of freedom in the reactant, a set of co-existing reactant conformers were identified. They lie within a few kcal mol^{-1} and are likely to interconvert at 383 K (almost free rotations are expected around these single bonds). Only one of them ultimately proceeds to the reaction and not necessarily the lowest one. Compared to the unsubstituted and monosubstituted compounds, a double

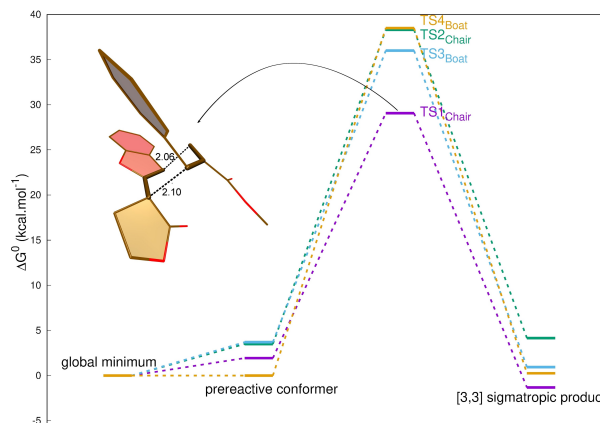


Figure 2. Free energy profiles obtained at 383 K for compound (*S,R*)-**8b** from DFT calculations at the PCM(toluene)-M06-2X-D3/6-311 + G(2d,2p)//PCM(toluene)-M06-2X/6-31 + G* level of theory; distances reported in Angstroms. For the sake of clarity, hydrogen atoms have been hidden.

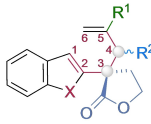
substitution at C4 and C5 results in an unusual lower free energy barrier at 110 °C: 27.1 and 26.2 kcal mol^{-1} for the benzofuran and benzothiophene derivatives, respectively. The activation enthalpies are particularly consistent with the experimental data.

Theoretical findings and experimental evidence suggest that a combination of several structural factors facilitates the dearomatization step of the Cope rearrangement on the studied compounds (see Table 1). First, an electron withdrawing group like $-\text{CO}_2\text{Me}$ positioned at C5 promotes the Cope rearrangement through C₆ activation, but it does not affect the exergonicity of the reaction. The substitution at C4 can play multiple chemical roles resulting in both decreasing the energy barrier and leading to an exergonic reaction. A bulky group offers a steric decongestion upon C3-C4 breaking. Moreover, when this voluminous group (like a phenyl) exhibits π delocalisation, the formation of the double bond C4-C5 increases the π system, offsetting to some extent the energetic penalty for dearomatization. This effect is substantially enhanced when the newly formed C4-C5 double bond bridges two separate π systems attached at C4 and C5.

Minor non-covalent interactions can also work in concert with the aforementioned effects. New strategies, including C4-C5 π -bridging, could be devised to design new molecules with the potential to lower the activation energy of the aromatic Cope rearrangement.

Conclusions

Described herein is the way to achieve efficient aromatic Cope rearrangement involving various highly functionalised benzofuran, benzothiophene and indole scaffolds. Merging experimental and theoretical investigations outline the structural requirements to jeopardise thermodynamic and kinetic impediments and to achieve interrupted and aromatic Cope rearrangements.

Table 1. Kinetics and thermodynamics parameters obtained at the DFT PCM(toluene)-M06-2X-D3/6-311++G(2d,2p)//PCM(toluene)-M06-2X/6-31+G* level of theory.


Compound	X	R ¹	R ²	TS	$\Delta^\ddagger G^\circ_{383K}$ kcal mol ⁻¹	ΔG°_{383K} kcal mol ⁻¹
1a	NH	H	H	1	34.6	5.3
1b	S	H	H	1	33.7	6.5
1c	O	H	H	1	35.5	6.0
3a	O	CO ₂ CH ₃	H	1	32.2	5.2
(S,S)-8e'	O	H	Ph	3	31.1	-3.3
(S,R)-8e'	O	H	Ph	1	29.0	0.2
(S,R)-8b	O	CO ₂ CH ₃	Ph	1	27.1	-3.2
(S,S)-8b	O	CO ₂ CH ₃	Ph	1	26.6	-2.8
(R,R)-8c	S	CO ₂ CH ₃	Ph	1	26.2	-3.4

With the simplest benzothiophene or benzofurane substituted lactones **1b,c** (containing unsubstituted allyl scaffolds) the [3,3] sigmatropic step is endergonic and aromatic Cope rearrangement (ArCopeR) can be achieved under basic conditions albeit with low yields. The introduction of an electron-withdrawing group on the exocyclic double bond (compounds **3a–c,e**) leads to a push-pull pattern entailing a decrease of activation energy and thus allowing to obtain aromatic Cope rearrangement products in good yields. Nevertheless, for this class of compounds the [3,3] sigmatropic step remains endergonic and basic conditions are still required to favour the second step of the ArCope (i.e. [1,3]-H shift). Thus, the ArCopeR affords an efficient way for the functionalisation of these heteroaromatic rings. Introduction of an additional phenyl group on the allylic position (C4, compounds **8b,c,f–m**) has a strong impact on the ArCopeR type reactivity. Significantly the first [3,3] sigmatropic step becomes exergonic. Thus interrupted ArCope products **10b–d,f–l** can be isolated in good yields when the thermal rearrangement is carried out under neutral conditions. Taking advantages of chiral scaffolds, we were able to demonstrate that a highly stereoselective dearomative process occurs through interrupted aromatic Cope rearrangement. Moreover, when basic conditions are involved, the ArCopeR products **9b,c** can still be isolated in good yields.

A significantly different reactivity is observed when indole ring is involved in such processes. Indeed, basic condition are not required to allow [1,3]-H shift to proceed and thus the ArCopeR product is always the unique product obtained whatever the substitution pattern on the [1,5] hexadiene scaffold.

The regioselectivity and high stereoselectivity of all these reactions offer new opportunities for the structural modification of heteroaromatic compounds and pave the way to further original fruitful transformations. Taking advantages of these knowledges, our next efforts will focus on inducing thermal aromatic Cope rearrangement on more challenging aromatic

compounds. To go further than strategies based only on structural modifications to decrease activation energy barrier, the alteration of the potential energy surface of the sigmatropic process by external agent is also currently under investigations in our laboratories and will be reported in due course.

Experimental section

For detailed experimental procedures, analytical data and NMR spectra, see Supporting Information.

General procedure for the Aromatic Cope rearrangement under basic conditions: A solution of lactone **1**, **3** or **8** and Et₃N (0.1 or 1 equiv) in toluene or mesitylene (0.2 M) was heated at reflux (reaction monitored by TLC analysis). The reaction mixture was cooled to rt, concentrated under reduced pressure, and purified on SiO₂ to afford the rearranged product **2**, **4** or **9**.

General procedure for the Aromatic Cope rearrangement under neutral conditions: A solution of indole lactone **3d** or **8d** in toluene (0.2 M) was heated at reflux (reaction monitored by TLC analysis). The reaction mixture was then cooled to rt, concentrated under reduced pressure, and purified on SiO₂ to afford the rearranged product **4d** or **9d**.

General procedure for the Allylic Alkylation of aromatic Cope rearrangement products: Lactone **4** (0.58 mmol) reacted with Morita-Baylis-Hillman carbonate (2.1–2.2 equiv) in the presence of DMAP (7 mg, 0.06 mmol, 10 mol %) in chloroform (2 mL). After 6 h of stirring at r.t., the reaction mixture was carefully hydrolysed with an aq. sol. of HCl (1 M) and extracted with CH₂Cl₂. The organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure, and purified on SiO₂ to afford the di-allyl-lactone **7**.

General procedure for the Interrupted Aromatic Cope rearrangement: A solution of lactone **8** (0.25 or 0.5 mmol) in dry toluene (8 or 16 mL) in a sealed tube was heated at 110 °C. After given time, the reaction was then cooled to room temperature, concentrated under reduced pressure, and purified on SiO₂ to afford the lactone **10**.

Supporting Information

Data supporting the manuscript are provided in supporting information (experimental procedures, characterisation data, details for the kinetic studies performed by ^1H NMR including the kinetic investigation of the aryl substituent effect, computational data including geometries, copies of ^1H and ^{13}C NMR spectra for all new compounds and of HPLC chromatograms). NMR FID files are available at <https://doi.org/10.57745/YGOIUH>.

The authors have cited additional references within the Supporting Information.^[27]

Author Contributions

E.R. proposed the project and contributed to the experimental study. F.G. and E.R. supervised the project. M.M. conducted the synthetic work, collected, and analyzed the corresponding data. A.B., F.G., E. H. and E. R. outlined the general strategy. E. H. conducted the theoretical study. A.B., F.G., E. H. and E. R. wrote the paper. All authors have given approval to the final version of the manuscript.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Research Data Gouv at <https://doi.org/10.57745/YGOIUH>.

Keywords: Sigmatropic Rearrangement · Diastereoselectivity · Substituent effects · Kinetics · Density Functional Calculations

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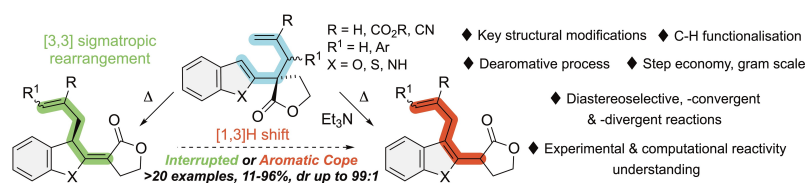
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RESEARCH ARTICLE



Fine-tuning substituents of the 1,5-hexadiene motif supported by calculations enable the stereoselective dearomative or aromatic Cope rearrange-

ments of α -allyl α' -heteroaromatic lactones, overcoming the drastic thermodynamic and kinetic requirements of such reactions.

M. Mando, Dr. F. Grellepois, Dr. A. Blanc, Prof. E. Hénon*, Dr. E. Riguet*

1 – 11

Toward Efficient and Stereoselective Aromatic and Dearomative Cope Rearrangements: Experimental and Theoretical Investigations of α -Allyl- α' -Aromatic γ -Lactone Derivatives.

