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Aromatic Cope Rearrangements

Breanna M. Tomiczek[a], **Alexander J. Grenning**[a]

[a]Department of Chemistry, University of Florida, PO Box 117200, Gainesville, FL

Abstract

Reviewed herein is the aromatic Cope rearrangement, a Cope rearrangement where one (or both) of the alkenes of the 1,5-diene are part of a greater aromatic system. While the Cope rearrangement of 1,5-dienes has seen wide utility, variation, and application in chemical synthesis, the aromatic Cope rearrangement, comparatively, has not. This review summarizes the ~40 papers dating back to 1956 on this topic and is divided into the following sections: (1) introduction, including kinetic and thermodynamic challenges of the aromatic Cope rearrangement, and (2) key substrate features, which there are four general types (i) α-allyl-α-aryl malonates (and related substrates), (ii) 1-aryl-2-vinylcyclopropanes, and (iii) anion-accelerated aromatic oxy-Cope substrates, and (iv) the concept of *synchronized aromaticity*. Ultimately, we hope this review will draw attention to a potentially valuable transformation for arene functionalization that warrants further studies and development.

This review summarizes the ~40 papers dating back to 1956 on the aromatic Cope rearrangement, and highlights the need for further studies, development, and applications of this transformation in synthesis.

1. Introduction

The Cope rearrangement, the [3,3] sigmatropic rearrangement of a 1,5-hexadiene, is a classic transformation. Since its discovery in 1940,[1–3] this transformation has been the subject of intense research efforts ranging from physical organic and computational studies, to methods development and utilization in chemical synthesis. As testament to its value, there are historical reviews on the Cope rearrangement[4] and more focused reviews related to specific subtopics such as stereochemistry,[5–7] catalysis,[8] substrate types (*e.g.* the oxy-Cope rearrangement,[9–11] divinylcyclopropane-cycloheptadiene rearrangement,[12–15] heteroatomic Cope rearrangements[16–19]), application in complex molecule synthesis,[20] and computational studies.[21–23] One underdeveloped (and unreviewed) variant of the Cope rearrangement is the *aromatic Cope rearrangement*, where one (or both) of the alkenes in the 1,5-diene are bound within an aromatic ring. This is an attractive chemical transformation as it allows for site-specific allylation of an arene or heteroarene. Generally speaking, site-specific arene/

grenning@ufl.edu .

Conflicts of interest

There are no conflicts to declare.

heteroarene C– H functionalization is of high interest to modern synthetic chemistry.[24–26] In analogy to the aromatic Claisen rearrangement,[27] which converts allyl phenyl ethers **1** into *ortho*-allylphenols **2** by [3,3] rearrangement and keto-enol tautomerism (Scheme 1A), the aromatic Cope rearrangement would be realized in the same manner with *one notable difference*: the re-aromatization step is mechanistically a [1,3]H shift, a geometrically forbidden transformation (Scheme 1B).[28] While both transformations have significant [3,3] barriers to overcome, +35 kcal/mol[29–33] and +43 kcal/mol[34–36] for the parent aromatic Claisen and Cope rearrangement substrates **1** and **3**, respectively, this mechanistic disparity is an additional concern for developing aromatic Cope rearrangements. Therefore, successful methods centered about an aromatic Cope rearrangement must have structural features that *(a) reduce the significant kinetic barrier to the [3,3] step to <<43kcal/mol and (b) provide a non-[1,3]H shift mechanism for re-aromatization* (Scheme 1C). While there are estimated to be thousands of examples of aromatic Claisen rearrangements currently in the literature,[27] there are ~40 papers in total on the subject of the aromatic Cope rearrangement dating back to 1956. Additionally, there are reports in the literature that exploit a dearomatized ring as a driving force for "normal" Cope rearrangements.[37–39] However, these are not elaborated upon here as they are outside the scope of focus for this review. Instead, this review concentrates on [3,3] Cope rearrangements progressing through a dearomatized intermediate.

Discussed in the remainder of this review are four key structural features (or combinations thereof) that reduce kinetic barriers and provide kinetic and thermodynamic favorability to the aromatic Cope rearrangement, thus allowing the transformation to occur under practical conditions. Ultimately, we hope this review will draw attention to the aromatic Cope rearrangement, a transformation of high potential value to arene functionalization.

2. Key Substrate Features for Achieving Aromatic Cope Rearrangements

The remainder of this review on the aromatic Cope rearrangement is divided into subsections based on the structural features that allow for a controlled transformation to occur (Scheme 1C):

- Section 2.1: a-allyl-a-aryl malonates
- Section 2.2: 1-aryl-2-vinylcyclopropanes
- Section 2.3: anion-accelerated aromatic oxy-Cope substrates
- Section 2.4: synchronized aromaticity

2.1. α-allyl-α-aryl malonates and related substrates

2.1.1. Historical accounts—Cope and co-workers first reported the "rearrangement of allyl groups in three-carbon systems" in 1940–41 for a series of 1,5-dienes derived from alkylidene malonic acid derivatives and allyl bromide, a transformation that would later be named "the Cope rearrangement."[1–3] While kinetically this is a challenging transformation (150 – 200 °C), it is thermodynamically favored to proceed due to the establishment of alkylidene–malonate conjugation. As early as 1956, there were attempts to apply these principles to aromatic substrates.[40] The first example of an aromatic Cope

rearrangement was achieved on a phenanthrene-derived substrate **4** (Scheme 2).[40] This is a logical beginning to the aromatic Cope rearrangement saga considering the penalty to dearomatize phenanthrene compared to other arenes is minimal.[41] However, the barrier to achieve aromatic Cope rearrangement to **5** was high (>250 °C) and resulted in a thermal domino reaction[42–44] ultimately yielding **6** *via* a sequence involving an ene reaction, retro-Claisen condensation, and Michael addition. This entire sequence has been referred to in the literature as an "abnormal" Cope rearrangement.[45] A mechanism for this reaction was later described by MacDowell in 1986.[47]

Since the original report of the "abnormal" Cope rearrangement,[40] a few other substrates have been reported to undergo this sequence with varying degrees of success (Scheme 3). For example, Cope and co-workers also reported that naphthalene-containing substrate **7** undergoes the cascade reaction.[46] Unfortunately, the analogous benzene-based substrate **8** did not controllably react but rather decomposed under the reaction conditions. In the 1980's and 1990's, MacDowell re-examined this cascade for thiophene- and benzothiophene-based substrates **9 – 12**,[45,47] which performed similarly well to the phenanthrene/naphthalene substrates (10 – 41% yields). Interestingly, in these reports from MacDowell and co-workers, the "normal" Cope rearrangement products **17 – 20** were also observed (Scheme 4). It was found that heating thiophene- and benzothiophene-based aromatic Cope substrates **13 – 16** at temperatures ranging from 180 – 230 °C resulted in allylic transposition/rearomatization to the allylated heteroarylmalonates **17 – 20**. Thus, the "normal" vs "abnormal" aromatic Cope rearrangements can be controlled by tuning the electronics of the arene such that the "normal" aromatic Cope rearrangement occurs at a lower temperature than the downstream cascade sequence.

2.1.2. Physical organic considerations—As described in the introduction of this review, the two main challenges of aromatic Cope rearrangements are (a) dearomatization *via* [3,3] rearrangement and (b) a symmetry forbidden [1,3]H atom shift. That said, α-allyl-α-aryl malonate-type substrates are modestly successful based on the four historical reports discussed thus far in this section. While polyaromaticity is certainly significant for decreasing the barrier for the [3,3] step (*e.g.* **21** and **22**, Scheme 5A), the electron-withdrawing "E" groups are also significant (Scheme 5B). The "E" groups likely play a key role in facilitating aromatic Cope rearrangements in three-ways. First, they weaken the C3–C4 bond via an inductive effect. This is maybe best described in a concerted asynchronous mechanism where anionic charge build-up is directly stabilized by the electron-withdrawing group. Second, it provides resonance conjugation to the dearomatized cyclotriene. While electron-withdrawing group – triene conjugation does not fully compensate for arene deconjugation, the additional conjugation does provide some stability to the intermediate. Third, it provides a proton transfer-equilibration for re-aromatization, a much lower energy pathway for isomerization than a [1,3]H atom shift, which is likely a non-operative pathway in these cases. These considerations are based on results by Grenning and Houk for related Cope rearrangements of 3,3-dicyano-1,5-dienes.[48] Thus, additional validation is likely needed for the aromatic counterpart.

2.1.3. Other examples related to α-allyl-α-aryl malonates—Section 2.1.1 highlights the historic examples where α-allyl-α-aryl malonates undergo aromatic Cope rearrangements. Section 2.1.2 summarizes some of the key stereoelectronic effects at play that allow for the aromatic Cope rearrangement to proceed for this class of substrates. In this section, we will spotlight modern examples of aromatic Cope rearrangements that harness these principles. Quite surprisingly, to the best of our knowledge, we are aware of only one modern method of this type, and one serendipitous case in the context of complex molecule synthesis.

Riguet and Bos reported that 1-allyl-1-benzofuran lactones **25**, prepared *via* an Ir-catalyzed branch-selective asymmetric allylic alkylation reaction from **23** and **24**, undergo an aromatic Cope rearrangement (Scheme 6).[49] One of the interesting features of this transformation is that under neutral conditions, the aromatic Cope rearrangement occurs to the dearomatized product **26**. Thus, the formation of styrene- and acrylate-conjugation on **26** must thermodynamically compensate for dearomatization. Notably, the [3,3] step is stereospecific/diastereoselective. Using an acid or base catalyst, the "normal" aromatic Cope pathway is operative (dearomative [3,3] followed by re-aromatization by acid or base catalysis). Thus, a [1,3]H atom shift is circumvented *via* a tautomerization mechanism. This process results in stereochemical racemization.

While examining the total synthesis of welwitindolinone alkaloids, on several occasions Rawal and co-workers observed isomerizations where the aromatic Cope rearrangement was a key transformation in an unexpected cascade.[50,51] For example, they reported that **27** is converted to pentacycle **28** upon heating at 85 °C (Scheme 7). It is hypothesized that the product arises *via* an aromatic Cope rearrangement and a transannular aldol reaction. Notably, the authors come to similar conclusions as described in Scheme 5: "The ease with which the Cope rearrangement takes place is ascribed to the rigidity of the bridged skeleton as well as the presence of the two electron-withdrawing groups on the benzylic carbon, which may serve to weaken the central σ bond."[51]

2.2. 1-aryl-2-vinylcyclopropanes and related substrates

2.2.1. Historical accounts—1-Aryl-2-vinylcyclopropane derived substrates are poised to undergo [3,3] sigmatropic rearrangement due to cyclopropane strain release that can (partially) compensate for dearomatization. However, successful substrates must (a) have structural features that thermodynamically favor dearomatization or (b) have structural features that can circumvent the [1,3]H shift *en route* back to the arene (Scheme 8). Summarized in this section are such substrates.

The first example of an aromatic Cope rearrangement starting from a 1-aryl-2-vinylcyclopropane derived substrate was documented by Regitz in 1977 (Scheme 9).[52] The 1-aryl-2-vinyl cyclopropane **29**, derived from cycloheptatriene and diphenylmethane carbene, at temperatures as low as 130 °C underwent [3,3] to dearomatized intermediate **30**, which rearomatized to **31** *via* an ene reaction.

While the first example of a successful aromatic Cope rearrangement utilized an ene reaction for circumventing [1,3]H atom shift/restoring aromaticity (Scheme 9), by far the

most common strategy is by proton transfer. The first instances of this were documented by Maas and co-workers[53,54] (Scheme 10) and Marvell and co-workers (Scheme 11),[34] who concurrently demonstrated that substrates decorated with appropriately positioned functional groups could undergo aromatic Cope rearrangement. For example, the Maas group described nitrobenzene-**32**, phenylacetic acid-**33**, pyridine-**34**, pyridinium-**35**, and furan-**36** containing scaffolds could undergo aromatic Cope rearrangement to the corresponding (hetero)arenes **37 – 41**. In all cases, the C–H bond that needs to isomerize is activated for tautomerization due to the presence of an acidifying group. One interesting note from this series is the temperature range in which aromatic Cope rearrangement occurs: as low as room-temperature for the pyridinium containing substrate **35**. Similarly, the Marvell group reported that a phenolic (or phenoxide under basic conditions) component on the 1-aryl-2-vinylcyclopropane **42** could facilitate the aromatic Cope rearrangement to product **43**. Maas and co-workers also uncovered an additional unique way to rearomatize post aromatic [3,3]: an intermolecular ene reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (Scheme 12).

2.2.2. Physical organic considerations—As indicated in the previous section, the cyclopropane moiety is the key structural feature accelerating and promoting aromatic Cope rearrangements for 1-aryl-2-vinylcyclopropane substrates. Transition from the strained three-membered ring **44** to a dearomatized bicyclic system **45** is permitted, though at a significantly elevated temperature for the simplest successful examples, as the penalty for dearomatization is offset by the release of ring strain. Experimentally, it has been found that simple 1-aryl-2vinylcyclopropanes **44** have a barrier to [3,3] of 27 – 30 kcal/mol (Scheme 13A).[35] This aligns well with the calculations for effects of introducing aromaticity or a cyclopropane into a 1,5-diene structure (Scheme 13B).[34–36] While this barrier is achievable, it is clearly not the only essential feature necessary for the success of this transformation. For example, while the phenyl variant **44a → 45a** results only in decomposition (**46** is not observed), the phenol variant **44b → 45b** yields the desired product **47**. Thus, at the elevated temperatures necessary for promoting [3,3], *other* uncontrolled reaction pathways can happen in the absence of a feature that promotes rearomatization.

2.2.3. Modern examples related to 1-aryl-2-vinylcyclopropanes—Section 2.2.1 describes historical examples in which 1-aryl-2-vinylcyclopropanes were utilized as substrates for aromatic Cope rearrangements. Ene reactions (Schemes 9 and 12) and tautomerization (Schemes 10 and 11) served as alternative mechanisms for overcoming the symmetry forbidden [1,3]H shift. Section 2.2.2 clarifies the physical organic effects of this transformation. It highlights the importance of the release of ring strain upon opening of the cyclopropane to drive forward the Cope rearrangement. In this section, we will provide modern examples of aromatic Cope rearrangements pertaining to 1-aryl-2-vinylcyclopropanes, and related cyclobutane substrates, spanning from 2002 until the most current report in 2019.

Barluenga and co-workers developed an intramolecular cyclopropanation method for synthesizing 1-aryl-2-vinylcyclopropane lactones **51** that undergo aromatic Cope rearrangement to yield tricyclic ring systems **53** (Scheme 14).[55] A reaction between

tetraalkylammonium acylchromates **48** and *β,γ*-dienyl acyl chloride **49** generates the acyloxycarbene complex **50**, which upon further reaction produces cyclopropanes **51** (Scheme 14A). Heating cyclopropanes **51** at 85–110 °C results in the formation of aromatic Cope products **52** or **53** (Scheme 14B). Interestingly, when a polyaromatic or a furan derivative was utilized, the products **55 – 57** were isolated in dearomatized form. This implies that the combination of polyaromaticity, cyclopropane strain-release, and likely the formation of the vinyl ether **57** all contribute to a thermodynamically favorable dearomative Cope rearrangement. Only in the case of the monoaromatic anisole substrate did aromatic Cope rearrangement occur with tautomerization back to the arene **54**.

In working toward targeting a valuable intermediate in the synthesis of (+)-frondosin B, Davies *et al.* reported a Rh(I)-catalyzed formal [4+3] cycloaddition between benzofuranyldiazoacetates **58** and various 1,3-dienes **59** yielding the cyclohepta[b]benzofurans **60 – 64** (Scheme 15). The transformation proceeds by a metallocarbene [2+1] cycloaddition/aromatic Cope rearrangement strategy.[56] Notably, the [2+1] step is enantioselective, and the aromatic [3,3] and tautomerization steps are diastereoselective, yielding enantioenriched building blocks diastereoselectively. For products **63** and **64**, the Cope rearrangement required heating at 110 °C for the reaction to occur.

Stephenson and co-workers developed a method employing visible light photoredox catalysis to synthesize tricyclic pyrrolidinones from a radical cyclization/aromatic Cope rearrangement cascade (Scheme 16).[57] A 5-exo-dig radical cyclization followed by hydrogen atom abstraction (HAT) forms vinylcyclopropane **65**. Under the conditions for achieving photoredox catalysis (DMF, Et_3N, visible light), **65** undergoes aromatic Cope rearrangement to yield **67**. It is likely that the basic conditions promote a catalytic proton transfer from the dearomatized intermediate **66** to product **67**. This method was high-yielding and tolerant of both electron-donating- and electron-withdrawing-aryl substituents. A limitation as noted by the authors is that even diastereomerically pure substrates (with non-equivalent aryl groups, *e.g.* **68**) react without selectivity. This is likely because of epimerization during the photoredox-catalyzed steps. Similarly, the best substrates bore an *N,N*-dipropargyl moiety. Monopropargylamides resulted in lower yields likely because of the same epimerization issue: only one of the *epimeric* radicals can productively collide with the alkyne for reaction along the desired trajectory.

The biosynthesis of prenylated indole alkaloids, formulated by Arigoni and Wenkert (Scheme 17A) has provided inspiration for many synthetic developments, where dearomatized and reverse-prenylated tryptophan **69** undergoes aromatic Cope rearrangement to **70**, whereby tautomerism serves as the mechanism for rearomatization.[58,59] Initial attraction to this biosynthetic hypothesis led Tanner *et al.* in 2011 to suggest support for C4 prenylation occurring by means of reverse C3 prenylation paving the way for an aromatic Cope rearrangement.[60] Related to this hypothesis are two reports, one by Gaich and co-workers involving an aryl-vinyl cyclopropane (Scheme 17B), and another by Viswanathan *et al.* (Scheme 17C) that is closer in structure to the natural substrate. While lacking a cyclopropane, we have chosen to describe Viswanathan's work here alongside the Gaich lab's work for comparison, but the structural features are also reminiscent of those described

in Section 2.1 of this review. In 2012, Gaich and co-workers reported the aromatic Cope rearrangement of oxindole-based 1-aryl-2-vinylcyclopropanes (Scheme 17B).[61] To probe the likelihood of Tanner's biosynthetic hypothesis, Gaich *et al.* designed the bioinspired spirocyclic vinylcyclopropane substrate **71,** which reacted as hypothesized yielding **72** in 55% yield. These products are structurally related to indole alkaloid natural products such as welwitindolinones and dragmacidin E.[61,62] In 2014, Viswanathan *et al.* developed a biomimetic aromatic Cope rearrangement of an oxindole variant lacking the central cyclopropane, and thus, more closely related to the natural counterpart (Scheme 17C).[63] The reverse prenylated oxindole analogue of α- L-tryptophan **73** underwent aromatic Cope rearrangement to C4-prenylated oxindole **74**. The key aromatic Cope rearrangement proceeded under two different sets of reaction conditions; heating in dimethylacetamide or heating under microwave conditions in the presence of a phosphate buffer both led to formation of **74**. Notably, a single diastereomer of **73** underwent aromatic Cope rearrangement in ~3:1 dr. The diastereomers arise from a modestly selective oxindole protonation event.

Another report from Gaich and co-workers detailed the use of a domino-Wittig reaction / aromatic Cope rearrangement to synthesize cyclohepta[*b*]indole cores (Scheme 18).[64] Substrate **75** was prepared enantioenriched by an enantioselective Simmons-Smith reaction, as reported by Charette,[65] and underwent Wittig reaction with a stabilized ylide **76** to vinylcyclopropane **77**, which upon heating, further reacted *via* Cope rearrangement to **78**. Notably, for many Cope rearrangements from this type of substrate, the aromatic [3,3] thermodynamically favoured the *dearomatized* product. In the case shown in Scheme 18A, the Cope product was not purified and directly subjected to hydrogenation conditions, which resulted in indole-rearomatization and hydrogenation yielding **79**, a precursor to a SIRT1 inhibitor. Thirteen additional examples of this reaction sequence are described in the original report. As select results, it was shown that the aromatic Cope rearrangements were stereospecific in that *Z*-alkenes yielded epimeric products compared to analogous *E*-alkenes (Scheme 18B). Finally, 2-indolevinylcyclopropanes **80** reacted similarly to form regioisomeric products. In these cases, the rearomatization process was spontaneous.

In a report from 2013, Ávila-Zárraga and co-workers demonstrated an aromatic Cope rearrangement (**81** to **82**) that employed a 1-aryl-2-vinylcyclobutane core structure (Scheme 19A).[66] Other activating features on the substrate **81** include a *m*-phenol, which provides a tautomerization-based mechanism for rearomatization (see Scheme 11 for further discussion of this topic), and an appropriately positioned electron withdrawing group, which in addition to acidifying the dearomatized intermediate, provides resonance stability (see Section 2.1) to the scaffold. Thus, upon deprotonation of the phenol to the phenoxide, **81** undergoes aromatic Cope rearrangement to **82**, facilitated by strain release and resonance conjugation from phenoxide-to-nitrile, which by proton transfer yields the product **82**, comprised of two alkene regioisomers, in 66% combined yield. The group later went on to utilize a version of this transformation in the total synthesis of parvifoline (Scheme 19B).[67] And finally, a related report involving an aryl-vinylcyclobutane scaffold is discussed in the next section on aromatic oxy-Cope substrates (see Scheme 28).[68]

Curran and co-workers described the synthesis of tricyclic spirolactam products **84** from thermal rearrangements of 1,1-divinyl-2-phenylcyclopropanes **83** (Scheme 20).[69] The divinylcyclopropane substrates **83**, when refluxed in toluene, underwent Cope rearrangement that was terminated by an intramolecular ene reaction for rearomatization. Notably, at these temperatures, cyclopropane epimerization occurs by homolytic cleavage. Regarding the scope of this aromatic Cope rearrangement, the authors showed examples with different amide groups such as benzyl, cinnamyl, and propargyl producing the tricyclic products **85 – 87**, respectively.

Clark *et al*. published the synthesis of hexahydroazuleno[4,5-*b*]furans from 1-furanyl-2-alkenylcyclopropanes (Scheme 21).[70] The vinylcyclopropane-substituted furans **89** were prepared by a Brønsted acid catalyzed cyclization of enynedione **88**. Cope rearrangement of substrates **89** provided tricyclic products such as **90** and **91** in 36% – 50% yields. The Cope rearrangement was thermodynamically favored to progress to the dearomatized furan **90** and **91** because of the strain release and the relatively low resonance energy of furan. An interesting result from this paper emphasized that only substrates containing an *E* olefin underwent Cope rearrangement at 40 °C. Substrates containing *Z* olefins did not undergo Cope rearrangement at this temperature and computational studies confirmed the higher kinetic barrier. That said, the data also supports that in some cases, the *E/Z* isomers can equilibrate *via* homolytic cleavage of the cyclopropane prior to Cope rearrangement.

Tunge and co-workers reported their studies related to aryl vinyl cyclopropane Cope rearrangements in 2019.[71] In this work, they realize that *trans*-aryl vinylcyclopropanes **95** could be prepared by a Pd-catalyzed sequence between arylcyanoacetones **92** and butadiene epoxide **93**. Specifically, Tsuji-Trost-like allylation results in intermediate **94** and deacylative allylation mediated by triazabicyclodecene (TBD) yields the product **95** (Scheme 22A). Upon heating of the *trans*-1-aryl-2-vinylcyclopropanes **95** under *neutral* conditions, cycloheptenes **97** or **98** were isolated (Scheme 22B). Evidence supports that under the reaction conditions (150 °C, DMSO), *trans/cis* isomerization is feasible *via* homolytic cyclopropane ring-opening/closing, thus allowing for a dynamic equilibration to the reactive *cis*-isomer **96**, which is funneled down the standard aromatic Cope rearrangement / proton transfer pathway to **97** or **98**. The authors also show in Scheme 22C that aromatic Cope rearrangement with concomitant cycloheptene olefin isomerization to the styrene is possible under basic conditions (TBD as base).

2.3. Anion-accelerated aromatic oxy-Cope substrates

2.3.1. Historical accounts—The third section of this review pertains to the anion-accelerated aromatic oxy-Cope rearrangement. It was hypothesized in the literature as early as 1978 that the underlying features present in oxy-Cope substrates that renders this class of 1,5-dienes so effective in a kinetic- and thermodynamic sense (Scheme 23A),[9] could be applied to aromatic-Cope rearrangements (Scheme 23B). It can be envisaged that α-allylbenzyl alcohols **99**, under basic conditions, can undergo anion-accelerated aromatic oxy-Cope rearrangement to dearomatized intermediate **100**, in which, if kinetically and thermodynamically favorable, protonation can occur to afford the dearomatized enal **101**. As shown in the transition state, the key underlying feature to this class of substrates

is the stabilization of the dearomatized transition state with the 3-oxygroup. However, this feature alone is not effective *enough* at decreasing kinetic barriers and providing thermodynamic favorability to the transformation, as made abundantly clear by Marvell and coworkers in 1979 (Scheme 24).[72] They reported that a potential aromatic oxy-Cope substrate **102** with relatively few *other* structural features undergoes transformation to **103** and **104**. The major product is likely the result of a two-step process involving homolytic cleavage to allyl/benzyl fragments that recombine at the benzylic and least substituted allylic position, respectively. The minor product could also be derived by this mechanism where the allyl/benzyl fragments recombine on the arene or by a unimolecular aromatic oxy-Cope rearrangement.

A breakthrough for aromatic oxy-Cope rearrangements was achieved by Jung and co-workers.[73] They found that aromatic *oxy*-Cope substrates such as **105**, containing a bicyclo[2.2.1]heptane, underwent efficient anion-accelerated rearrangement with concomitant dearomatization (Scheme 25A). Notably, while Marvell's naphthalene-based substrate was unreactive, Jung's was reactive. However, the benzene-based starting material **106** was poorly reactive to formation of the dearomatized Cope product **107.** Other polyaromatic substrates with reduced penalties for dearomatization were successful, such as the benzofuran **108**, which underwent efficient rearrangement to **109** and converted to coronafacic acid in 12 additional steps (Scheme 25B).[74]

2.3.2 Physical organic considerations—It is hypothesized that the kinetic barrier for achieving aromatic Cope rearrangement can be lowered by including the *oxy*-Cope rearrangement features. Specifically, that incorporation of a benzylic alcohol/alkoxide moiety will stabilize the [3,3] transition state (*e.g.* benzyl cationic or radical stabilization). While the hypothesis is sound, the question as to *how much* stabilization this functional group alone will provide was in question at the outset of the research (*ca.* late 1970s). Through the aforementioned historical accounts, it becomes apparent that transition state stabilization from the benzylic alcohol/alkoxide alone cannot yield a practical kinetic barrier for achieving aromatic Cope rearrangement: Additional features are necessary (Scheme 26). For example, Jung and co-workers described that an aromatic oxy-Cope substrate containing a naphthalene and a rigid and strained norbornene was a functional combination for lowering the barrier to aromatic oxy-Cope rearrangement by (a) raising the ground state of the starting material (ring strain), (b) decreasing the energetic penalty for dearomatization (polyaromaticity), and (c) stabilizing the transition state (with an oxy-electron-donor group).

The next section of this review will highlight more recent examples (last ~25 years) of aromatic oxy-Cope rearrangements that either utilize the aforementioned functional combinations to reduce the barrier to aromatic Cope rearrangement to a practical level and provide thermodynamic stability, or introduce new principle driving forces for promoting aromatic Cope rearrangements centered about an *oxy*-Cope scaffold.

2.3.3 Modern examples related to aromatic oxy-Cope substrates—Recall the work from Jung and co-workers where they identified that anion-accelerated aromatic oxy-Cope rearrangements could occur efficiently when substrates were polyaromatic and bore a strained norbornene component (Scheme 25).[73,74] This reaction was poorly effective with

a benzene-derived substrate. Uyehara and co-workers reported that similar benzene-based arenes could undergo anion-accelerated aromatic oxy-Cope rearrangement.[75] Specifically, a bicyclo[2.2.2]octene-based substrate containing an integral bridge head donor group (methoxy), underwent anion-accelerated aromatic oxy-Cope rearrangement even when the arene was a simple benzene ring (**110** to **111**) (Scheme 27A). The major difference between Jung's attempt to dearomatize benzene (Scheme 25, **106** to **107**) and this successful version is the inclusion of the additional donor group: the methoxy-group likely provides additional stability to the transition state. Essentially, both the allylic component and the benzylic component of the aromatic Cope rearrangement transition state is stabilized by a donor group. Substrates that lack this donor group have a more limited scope. For example, the simple benzene-containing substrate **112** was unreactive, but the anisole derivative **113** was reactive. Karikomi, Uyehara, and co-workers later went on to use this Cope rearrangement in the synthesis of helicenes **114**,[76] including an enantioselective variant (Scheme 27B).[77]

Moore and co-workers demonstrated that anion-accelerated aromatic oxy-Cope rearrangement can be achieved with added ring-strain release (Scheme 28).[68] They found that the addition of 1-naphthyllithium **116** to the cyclobutene **115** produced an intermediate **117** that directly underwent a cascade to **118** involving Cope rearrangement and transannular aldol condensation (Scheme 28A). In this work, they outlined other arene components including furans and thiophene. They also disclose that addition of vinyl lithium **120** to the naphthalene-containing cyclobutene scaffold **119** also underwent a similar cascade reaction to **121** (Scheme 28B).

There is one example of an aromatic Cope rearrangement that involves simultaneous dearomatization of two arenes (Scheme 29). Huq and co-workers reported that the 1,2-diphenyl-1,2-diol **122** derived from acenaphthoquinone, under various basic and thermal conditions, yield products **124** and **125** that are hypothesized to arise *via* doubly dearomatized intermediates.[78] For example, **124** and **125** are thought to arise from the dearomatized intermediate **123** by an unspecified isomerization and a transannular aldol reaction, respectively, yielding **124** and **125**. Depending on the conditions, the ratios of **124** to **125** could vary. In this work, the authors also disclosed two other substrates that reacted to yield similar products.

The final examples of anion-accelerated aromatic oxy-Cope rearrangement are those recently disclosed by Matsumoto and co-workers. They found that aromatic Cope substrates **126** prepared from 1-fluoroxanthone and prenylmagnesium bromide underwent a Cope rearrangement and a subsequent fluoride-elimination reaction to yield the prenylated xanthones **127** (Scheme 30).[79] One noteworthy feature of this reaction is the use of a fluoro-group to direct the [3,3] reaction and provide a facile rearomatization process for the substrates, which likely is a significant contributor to the success of this transformation. Additionally, this transformation has been used by the group for the synthesis of xanthone natural products such as elliptoxanthone A.[80] They also recently described a variant that achieves xanthone geranylation (Scheme 31).[81] In this transformation, the initial coupling was not diastereoselective yielding **128a** and **128b**. However, each individual diastereomer reacted selectively (*via* transitions states **129** and **130**) to their respective *E*- or *Z*-geranylated xanthones **131** or **132**.

2.4 Synchronized Aromaticity

The final topic of discussion for this review is the concept of synchronized aromaticity. The phrase *synchronized aromaticity* in a sense refers to the swapping of aromaticity between a *dearomatized* ring and an aromatized ring by a [3,3] process (Scheme 32A). The term was coined by Frantz *et al* in their seminal work on the subject where it was observed that a dearomatized pyrazine **134**, prepared *via* electrocyclization and proton transfer from the diazo starting material **133**, *can dearomatize* a naphthalene ring with *synchronous* pyrazine aromatization as a driving force (Scheme 32B).[82] Interestingly, the thermodynamics are as such that the dearomatized naphthalene product **135** can be isolated in high yield or rearomatized to the fully aromatic product **136** with additional heating. Additional studies in this work outlined the scope showing that electron deficient arenes are best suited for the aromatic Cope rearrangement.

Synchronized aromaticity is a relatively new concept (*ca. 2012*) and we are only aware of one additional example that leverages this idea, though it seems like a highly promising concept for further study. The work of Yamada *et al*. from 2019 also constitutes an example of synchronized aromaticity (Scheme 33). Specifically, they developed a tandem benzyl Claisen/aromatic Cope rearrangement as a novel route to synthesize 4-benzylated oxindole products **139**.[83] 2-Benzyloxyindole **137** first undergoes benzyl Claisen rearrangement to the intermediate dearomatized toluene **138**, which *via* an aromatic Cope rearrangement yields the desired product **139** (Scheme 33). Though not described as “synchronized aromaticity” in the original work, the concept is present.

3. Conclusions

This review aims to shed light on the aromatic Cope rearrangement and the key obstacles it presents in relation to organic synthesis. This transformation is associated with, and challenged by, high kinetic barriers for [3,3] dearomatization and 1,3 H-shift re-aromatization. Thus, successful and practical aromatic Cope rearrangement substrates must include structural features that overcome, decrease the kinetic barriers to, or circumvent these challenging fundamental steps. We highlight aromatic Cope rearrangements with the following unifying features: α-allyl-α-aryl malonates (or related) (section 2.1), 1-aryl-2-vinylcyclopropanes (section 2.2), aromatic oxy-Cope substrates (section 2.3), and *synchronized aromaticity (*section 2.4). These structural classes can provide the necessary driving forces for achieving an aromatic Cope rearrangement. Physical organic considerations were discussed for each of these substrate classes. Examples of aromatic Cope rearrangements and the strategic design that enabled them to occur were showcased in reports from as early as 1956 up until recently in 2020. Hopefully this review will spark a newfound interest in aromatic Cope rearrangements as a powerful tool for the construction of aromatic C–C bonds and as a valuable tool for aromatic C–H functionalization. In particular, as this review summarizes the known driving forces for achieving aromatic Cope rearrangement, it provides key understanding for devising new and unique transformations of high modern interest to the synthesis of valuable and complex aromatic building blocks.

Acknowledgements

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Biographies

Breanna Tomiczek attended Saint Vincent College in Latrobe, Pennsylvania as a chemistry major (B.Sc., 2017, Magna Cum Laude). She participated in the NSF-Funded REU programs at Syracuse University (Summer 2015) and The University of Akron (Summer 2016) under the guidance of Dr. Daniel A. Clark and Dr. George R. Newkome, respectively. She is currently pursuing a Ph.D. at the University of Florida.

Alex Grenning was born and raised on the north suburbs of Chicago. He studied organic chemistry at Lake Forest College (B.A., 2007), University of Kansas (Ph.D., 2012), and Boston University (Postdoctoral studies, 2012 – 2014) under the mentorship of Profs. William B. Martin, Jon A. Tunge, and John A. Porco, respectively. He began his independent career at the University of Florida in Gainesville in 2014.

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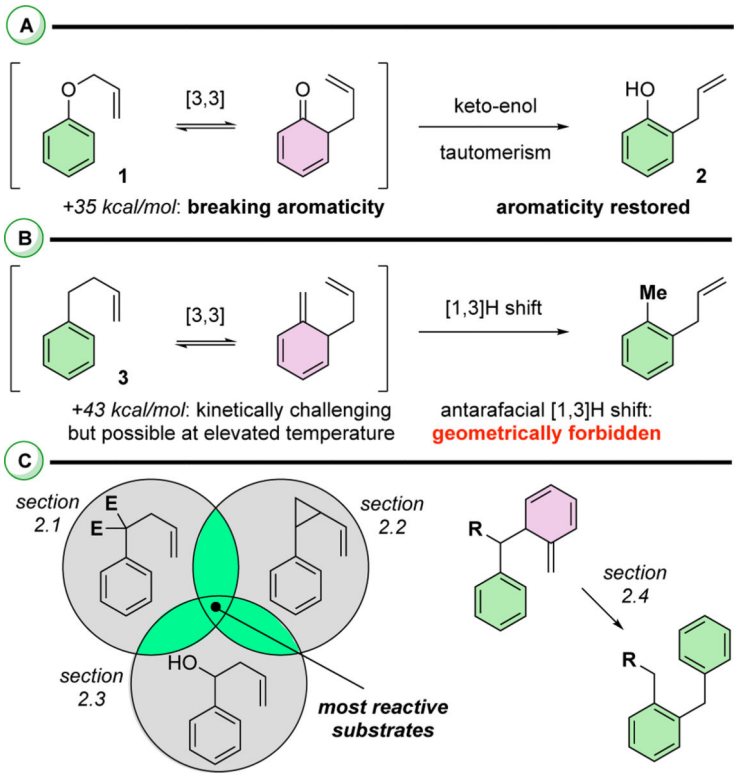
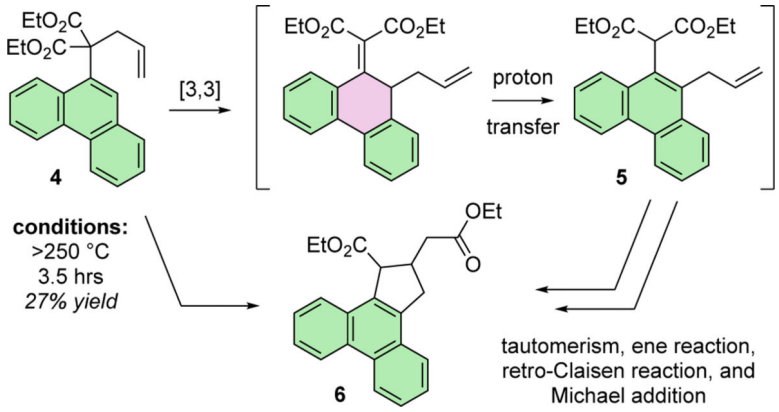


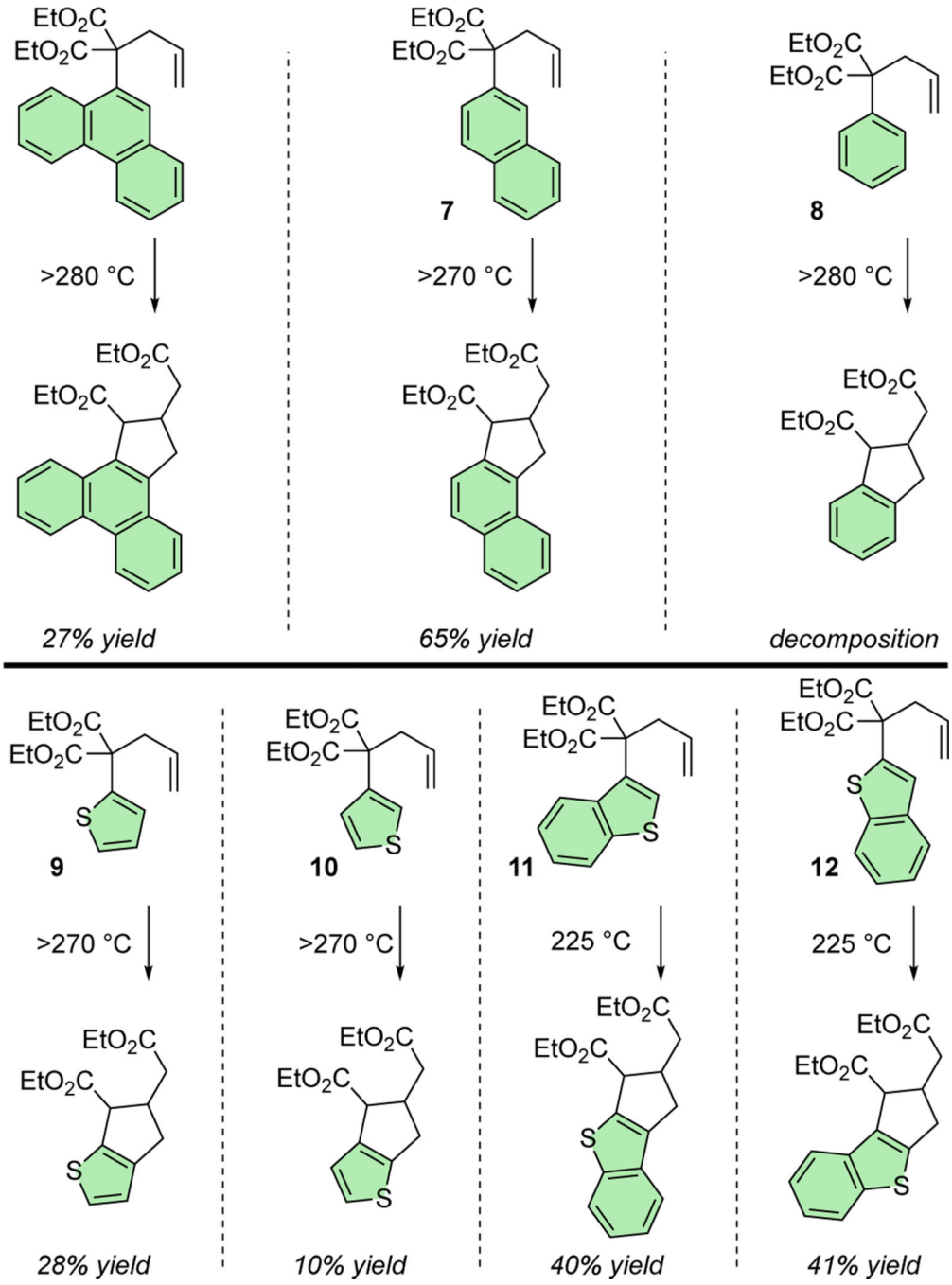
Scheme 1.

A – B: The aromatic Claisen and Cope rearrangements and kinetic challenges associated with the transformation. **C:** The focus of this review: structural features that facilitate aromatic Cope rearrangement.



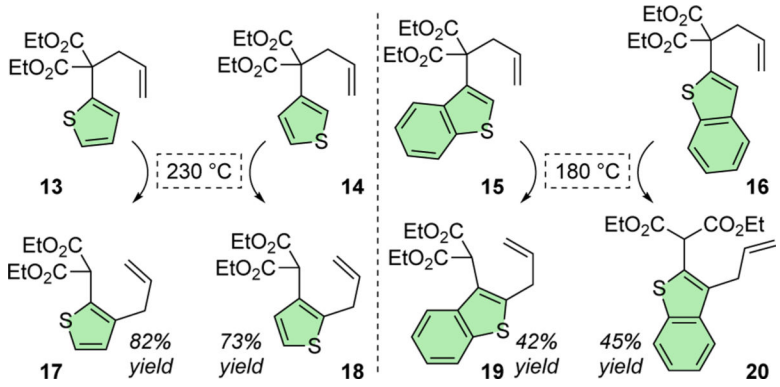
Scheme 2.

The first aromatic Cope rearrangement was part of a reaction sequence now referred to as the “abnormal” Cope rearrangement. (Cope *et al.*, 1956)



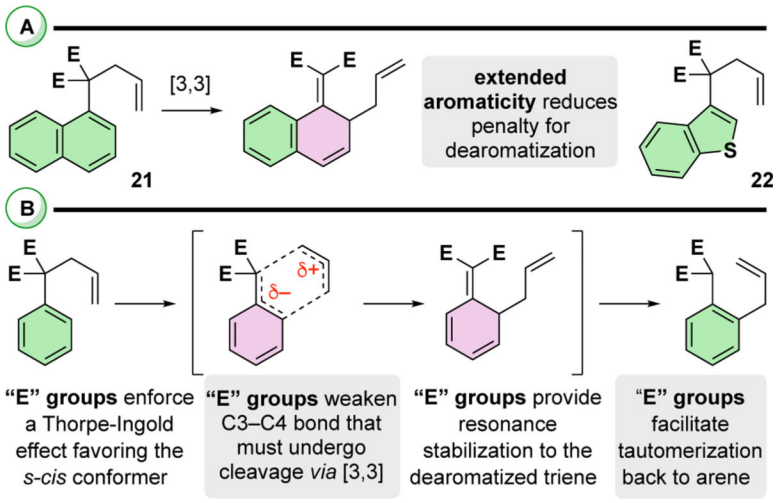
Scheme 3.

Scope of “abnormal” aromatic Cope rearrangement. (Cope *et al.*, 1956; MacDowell *et al.*, 1986 & 1993)



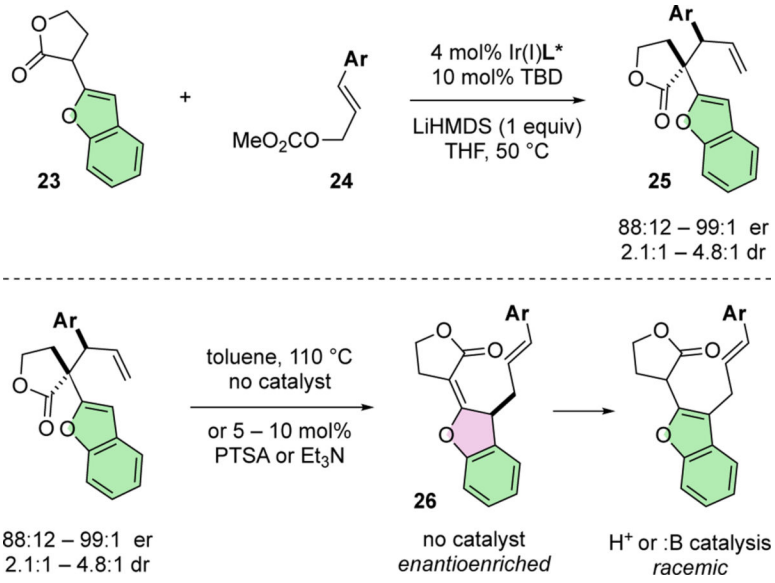
Scheme 4.

Scope of “normal” aromatic Cope rearrangement. (MacDowell *et al.*, 1986 & 1993)



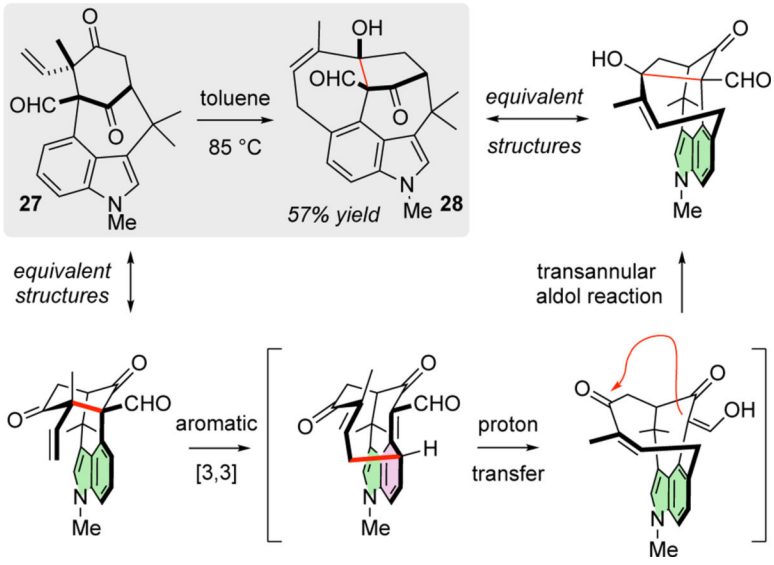
Scheme 5.

Stereoelectronic effects for the aromatic Cope rearrangements of a-allyl-a-aryl malonates. Polyaromaticity (**A**) and the "E" groups (**B**).



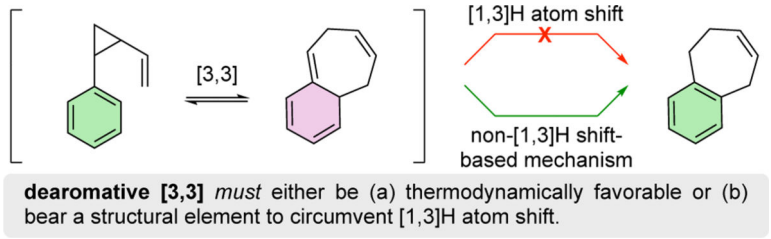
Scheme 6.

1-arylallyl-1-benzofuran lactones are efficient aromatic Cope substrates. (Riguet *et al.*, 2017)



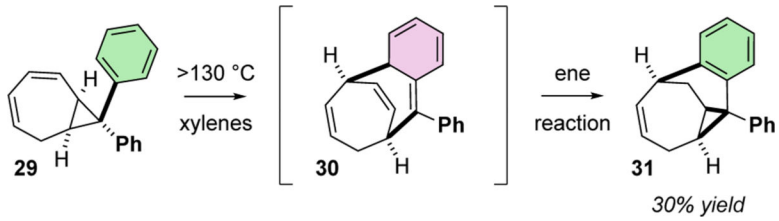
Scheme 7.

An unexpected aromatic Cope rearrangement was observed during the studies of welwitindolinone total synthesis. (Rawal *et al.*, 2011)



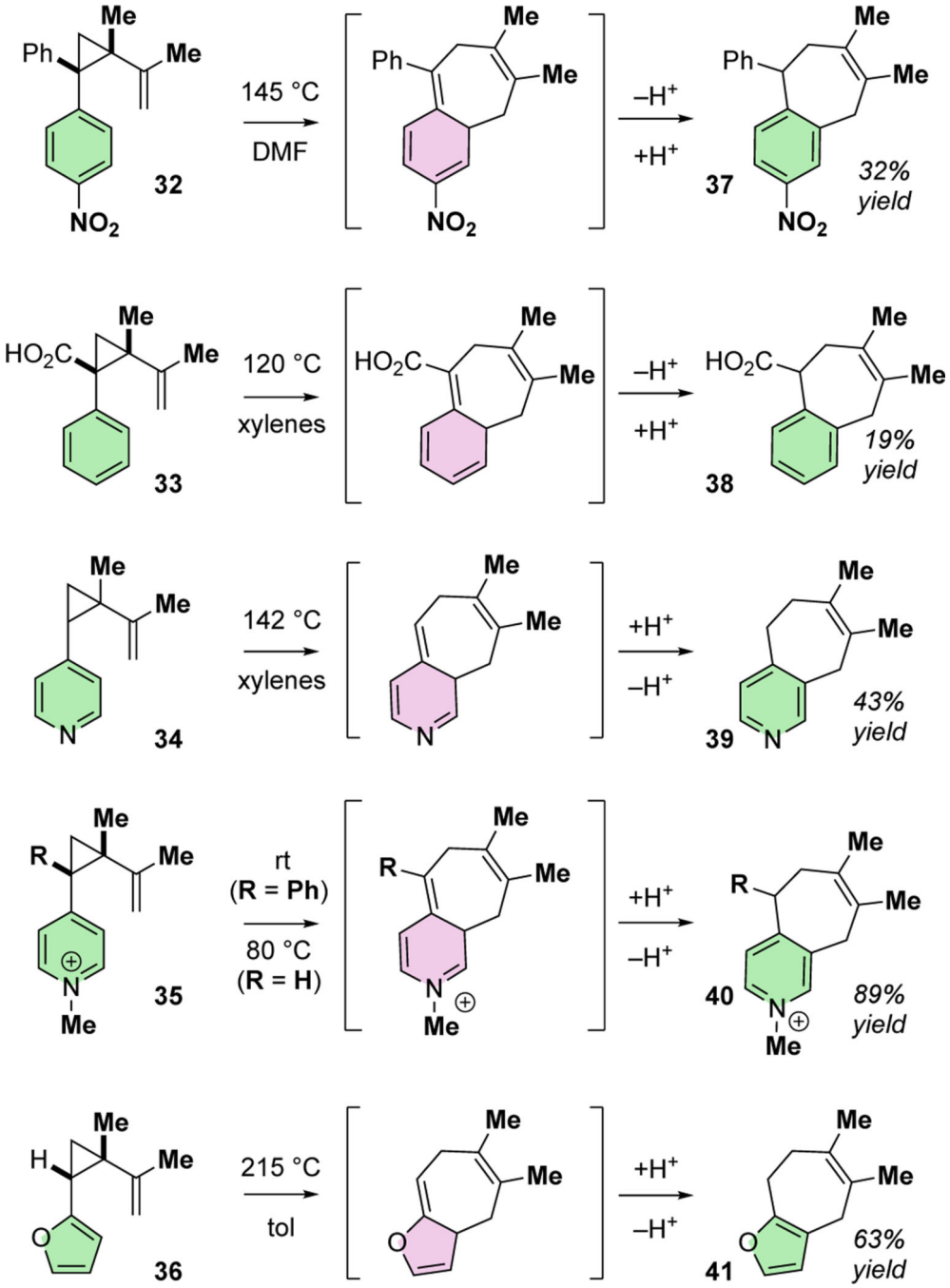
Scheme 8.

Aromatic Cope rearrangement of 1-aryl-2-vinylcyclopropane derived substrates.



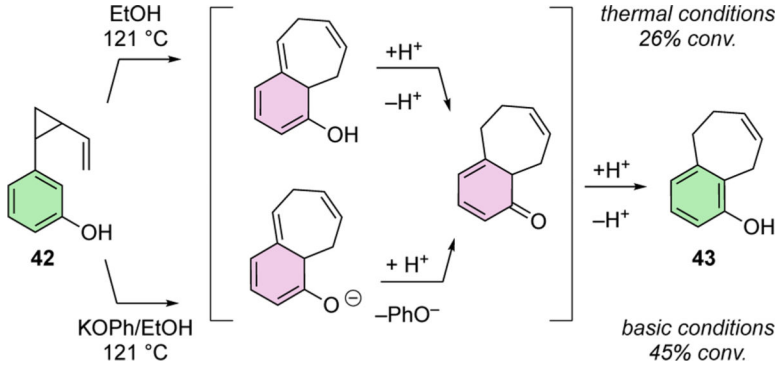
Scheme 9.

Aromatic Cope rearrangement enabled by an ene reaction to restore aromaticity. (Regitz *et al.*, 1977)



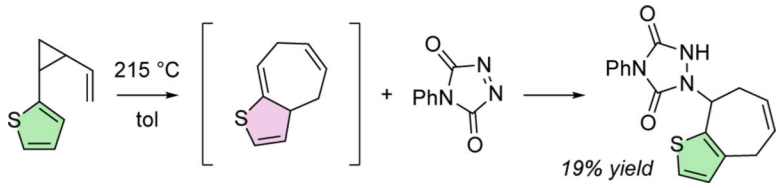
Scheme 10.

Utilization of appropriately positioned functional groups can facilitate aromatic Cope rearrangement. (Maas, 1979 & 1980)

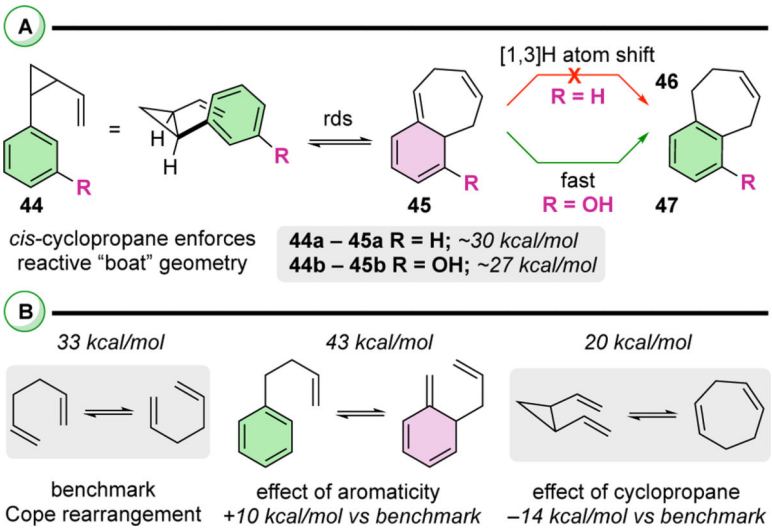


Scheme 11.

Utilization of appropriately positioned functional groups can facilitate aromatic Cope rearrangement. (Marvell *et al.*, 1978)

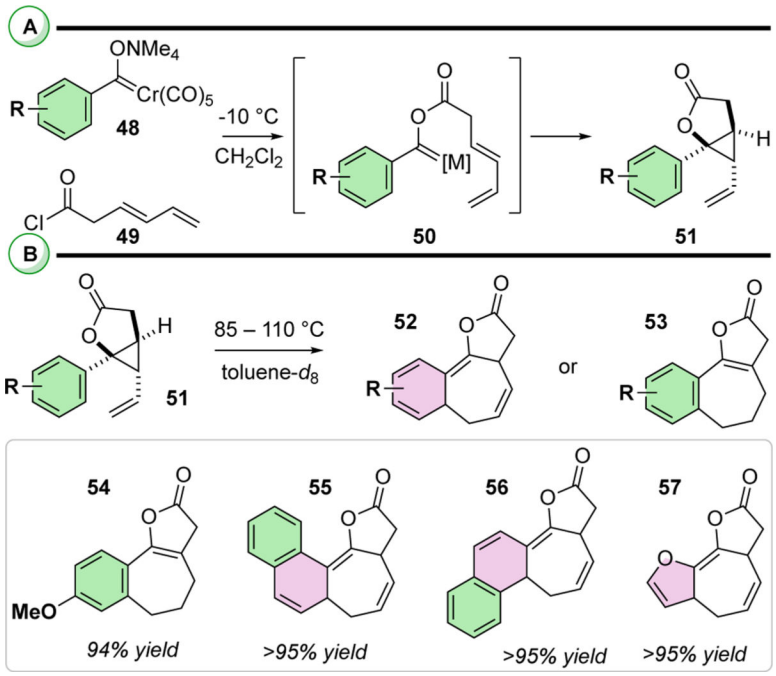


Scheme 12.
Re-aromatization by intermolecular ene reaction. (Maas *et al.*, 1980)



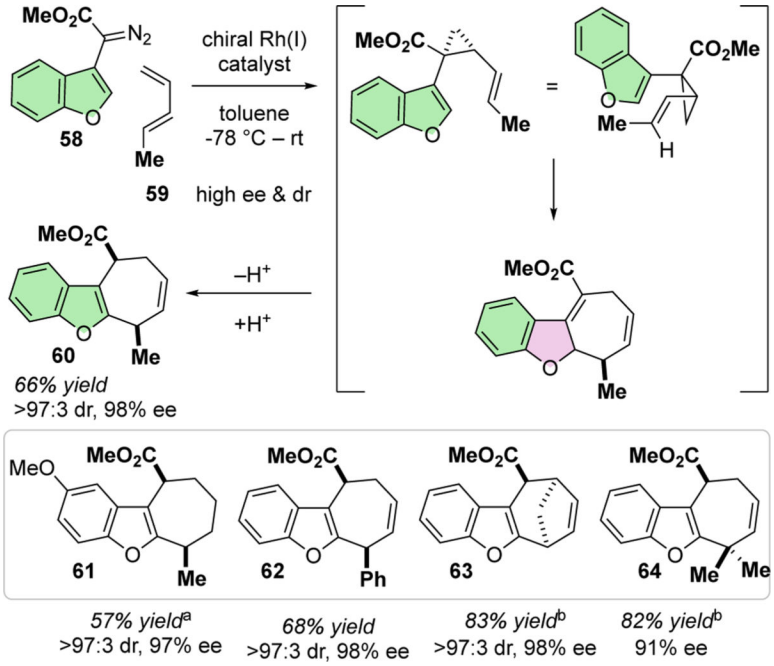
Scheme 13.

How and why are 1-aryl-2-vinylcyclopropanes successful substrates?



Scheme 14.

1-aryl-2-vinylcyclopropanes prepared by intramolecular [2+1] cycloaddition underwent an aromatic Cope rearrangement. Some substrates underwent dearomative [3,3]. (Barluenga *et al.*, 2002)

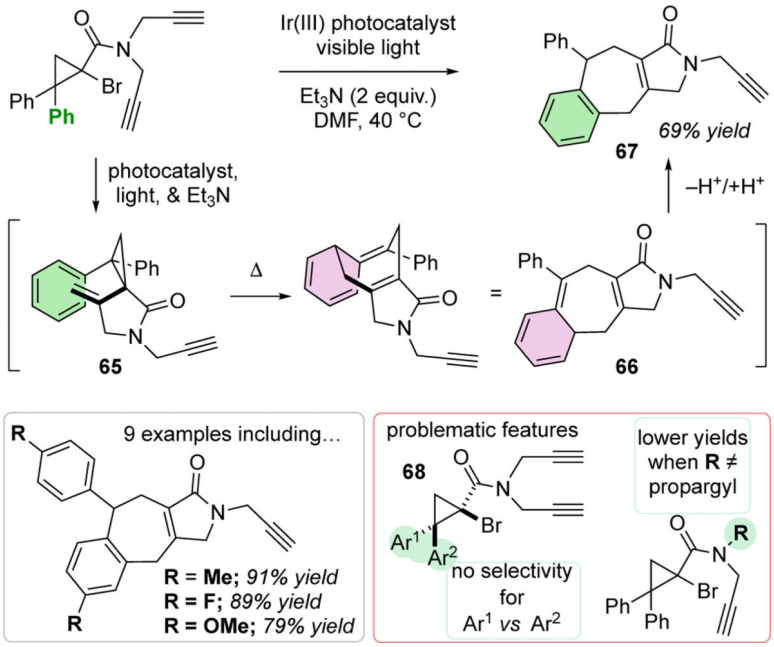


Scheme 15.

[4+3] cycloaddition provides 1-benzofuranyl-2-vinylcyclopropanes as substrates for an aromatic Cope rearrangement. (Davies *et al.*, 2008)

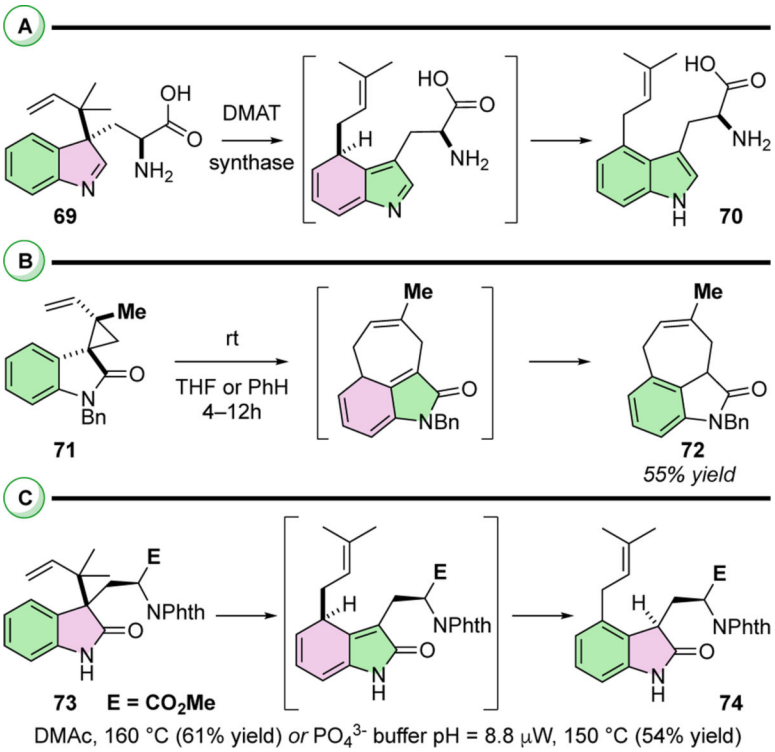
[a]Isolated after hydrogenation as the corresponding [4+3] cycloadduct is unstable.

[b]The Cope rearrangement required heating at 110 °C.



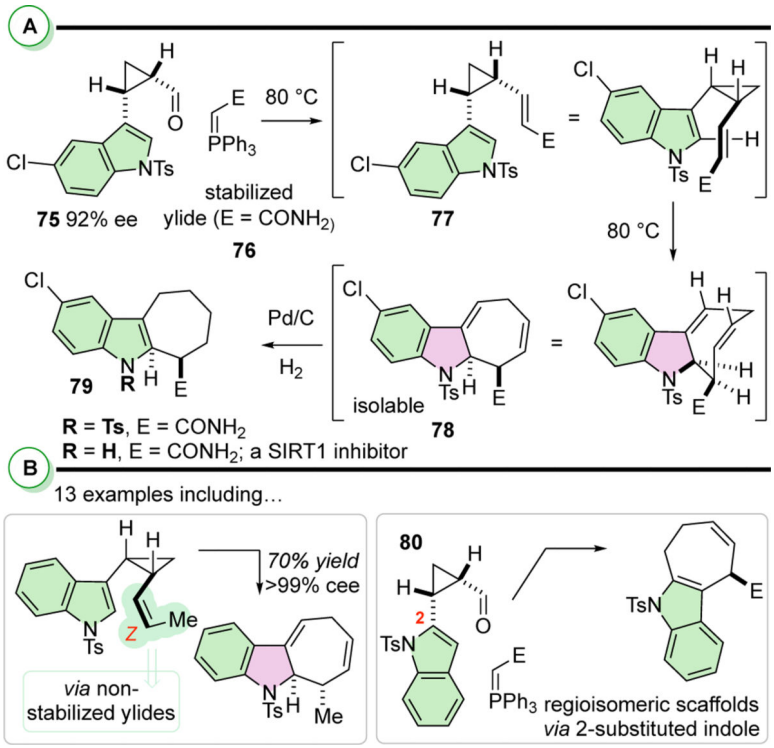
Scheme 16.

Aromatic Cope rearrangements of vinylcyclopropanes generated through photoredox catalysis. (Stephenson *et al.*, 2011)



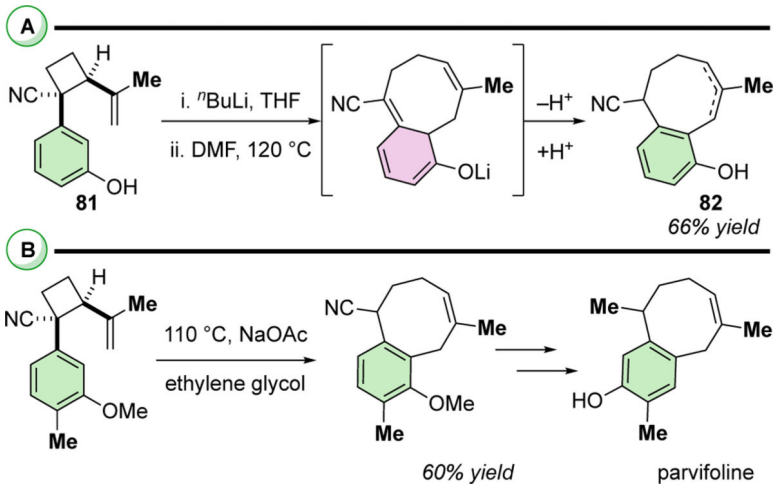
Scheme 17.

A: Biosynthesis of prenylated indole alkaloids. **B:** A bio-inspired spirocyclic vinylcyclopropane substrate underwent an aromatic Cope rearrangement to support a biosynthetic hypothesis related to C4 prenylation of indole. (Gaich *et al.*, 2012) **C:** Cope rearrangement of an oxindole resulting in C3 to C4 prenyl transfer. (Viswanathan *et al.*, 2014)



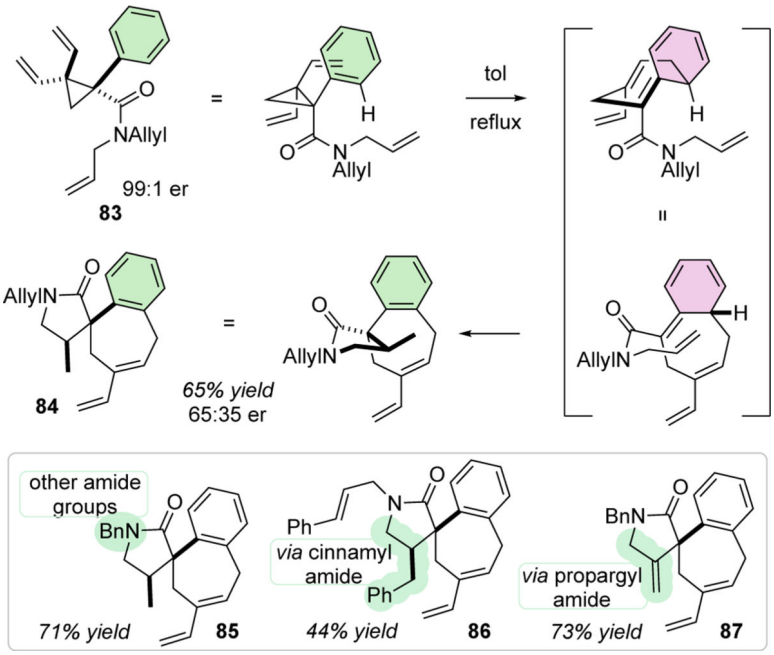
Scheme 18.

Synthesis of cyclohepta[*b*]indoles from a domino-Wittig/Cope rearrangement. (Gaich *et al.*, 2013)



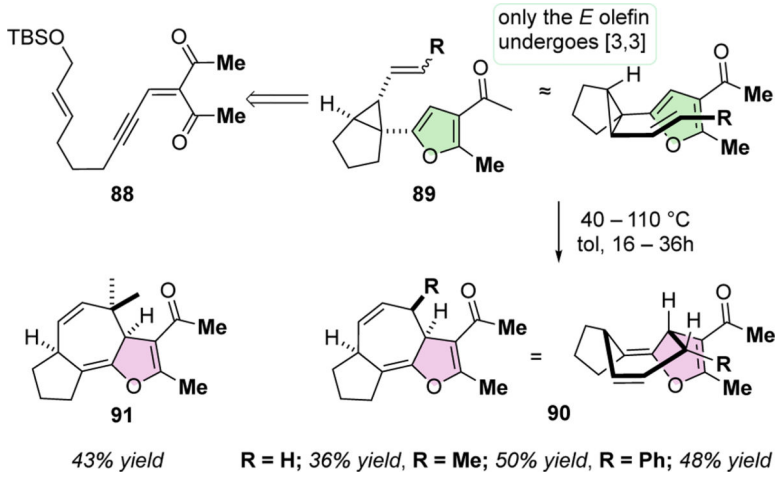
Scheme 19.

Aromatic Cope rearrangements of 1-aryl-2-ethenylcyclobutanecarbonitrile substrates. (Ávila-Zárraga *et al.*; 2013 & 2017)



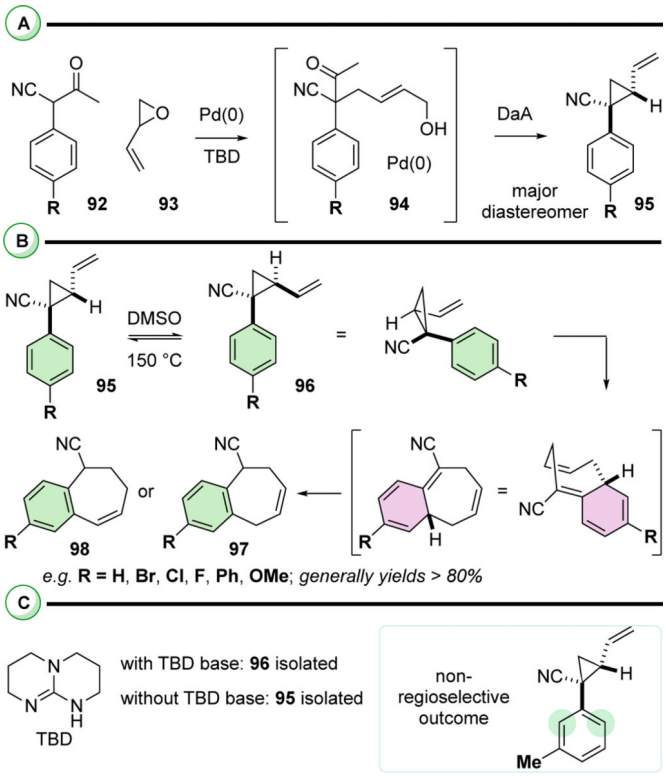
Scheme 20.

Thermal Cope rearrangement/ene reaction of 1,1-divinyl-2-arylcyclopropanes. (Curran *et al.*, 2015)



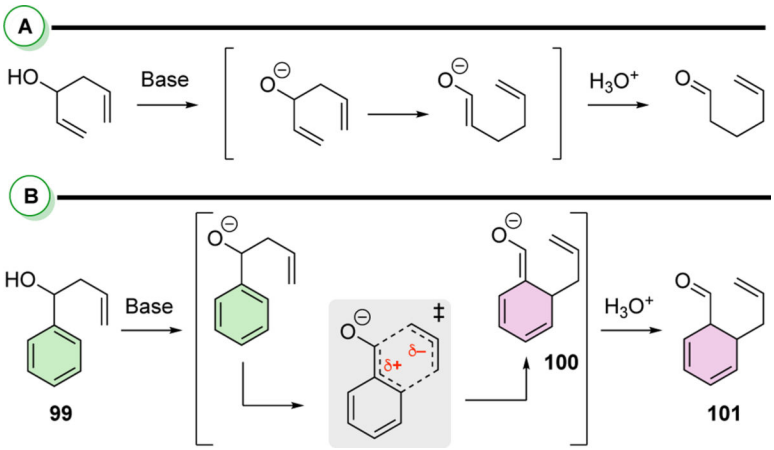
Scheme 21.

1-furanyl-2-alkenylcyclopropanes underwent Cope rearrangement to afford hexahydroazuleno[4,5-*b*]furan products. (Clark *et al.*, 2018)



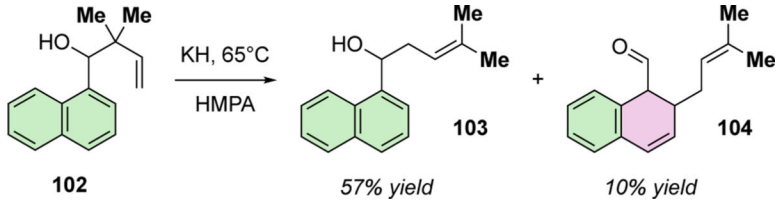
Scheme 22.

Aryl vinyl cyclopropanes undergo a dynamic equilibration to the reactive conformer followed by an aromatic Cope rearrangement to produce benzocycloheptenes. (Tunge *et al.*, 2019)



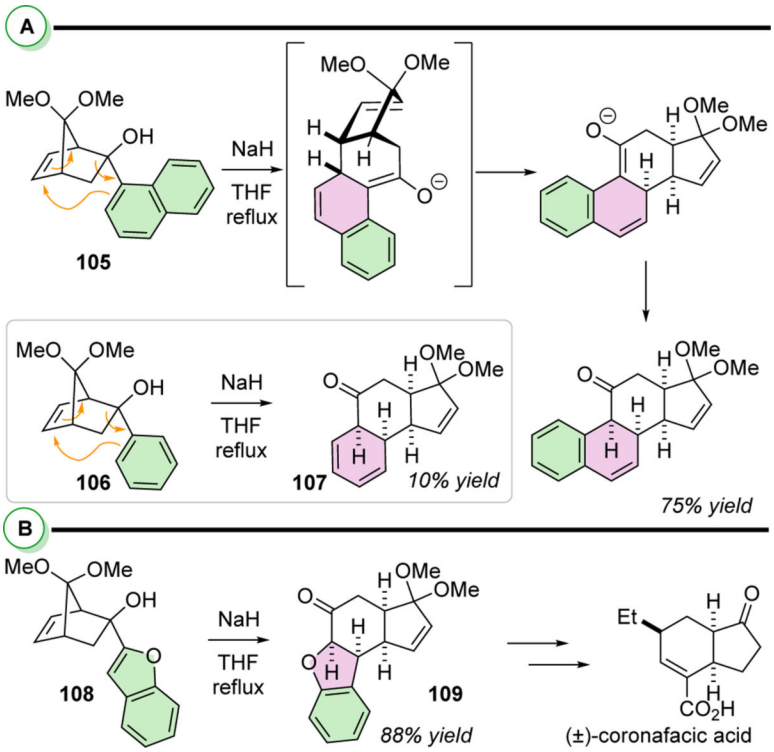
Scheme 23.

Oxy-Cope rearrangement (**A**) *vs.* aromatic oxy-Cope rearrangement (**B**).



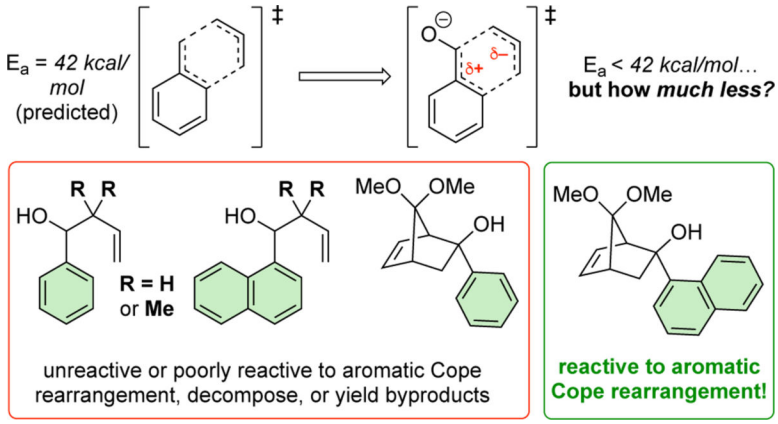
Scheme 24.

A potential aromatic oxy-Cope substrate with few *other* structural features is poorly reactive to aromatic oxy-Cope rearrangement. (Marvell *et al.*, 1979)



Scheme 25.

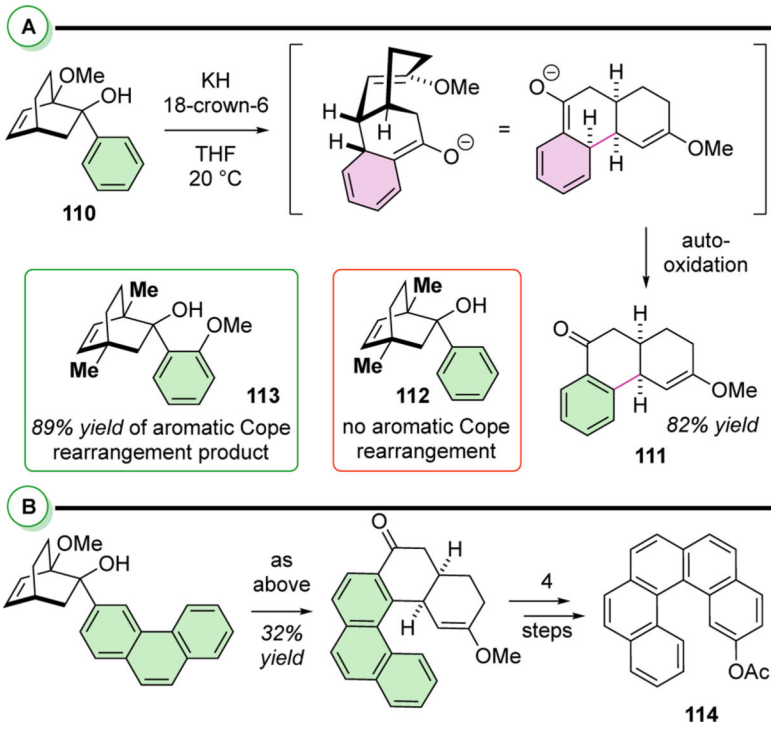
Anion-accelerated aromatic oxy-Cope rearrangement of norbornene systems (**A**), including an application in the synthesis of coronafacic acid (**B**). (Jung *et al.*, 1978 & 1980)



Scheme 26.

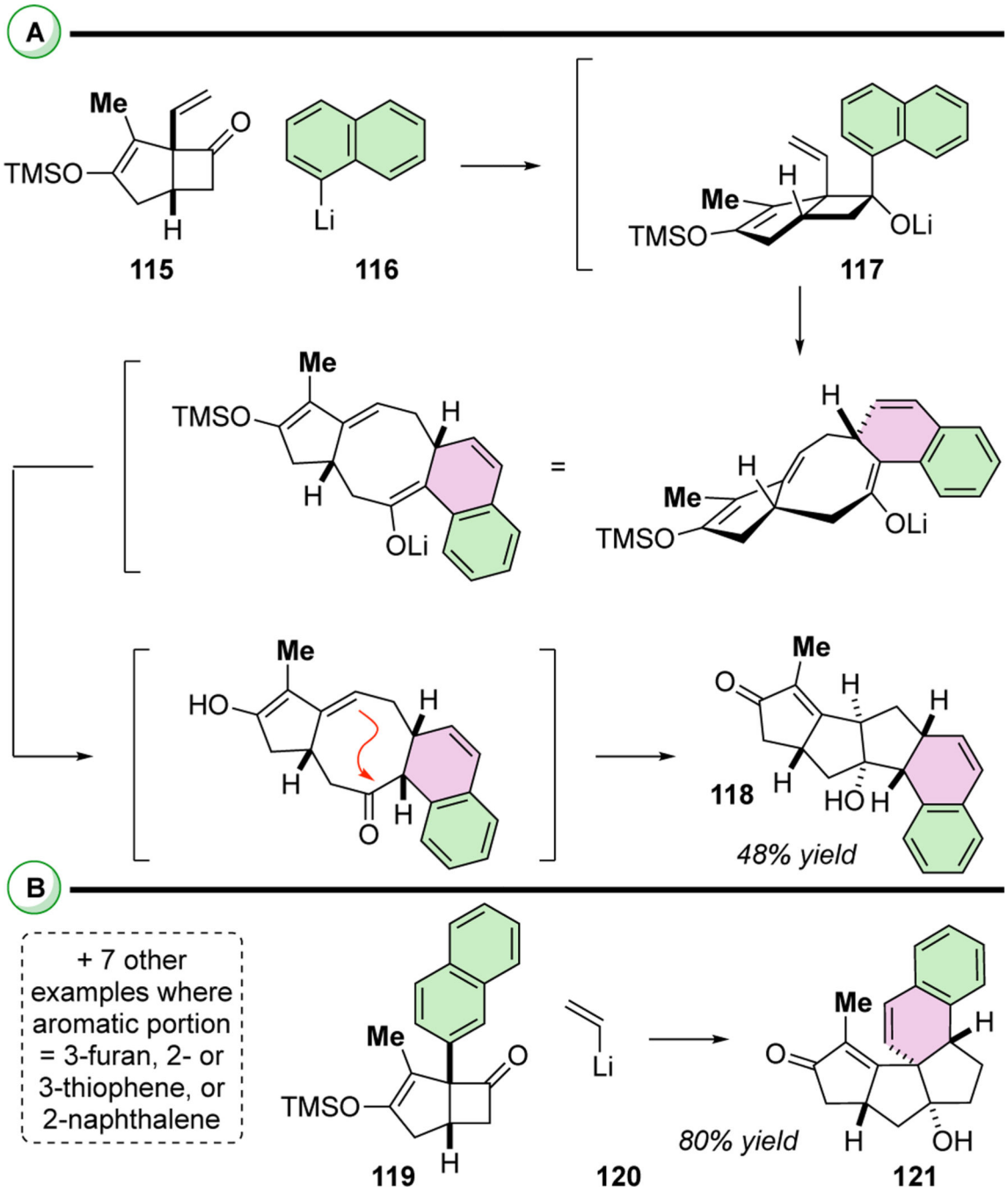
A summary of structural features that can be compounded to result in successful anion-accelerated aromatic oxy-Cope rearrangement.

Aromatic oxy-Cope substrates with additional stabilizing features (**polyaromaticity**, norbornene ring-strain release, and conformational restrictions) are reactive to [3,3].



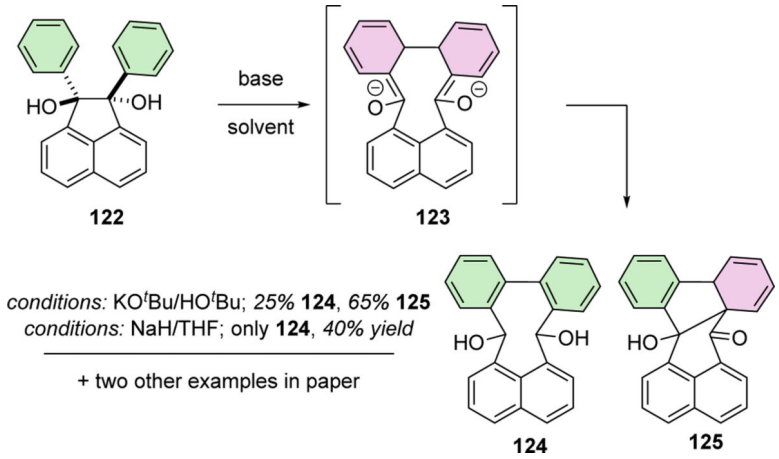
Scheme 27.

Anion-accelerated aromatic oxy-Cope rearrangement made possible by bridgehead donor substituents on the bicyclo[2.2.2]octene component of the scaffold. (Uyehara *et al.* & Karikomi *et al.*, 1998 & 2002)



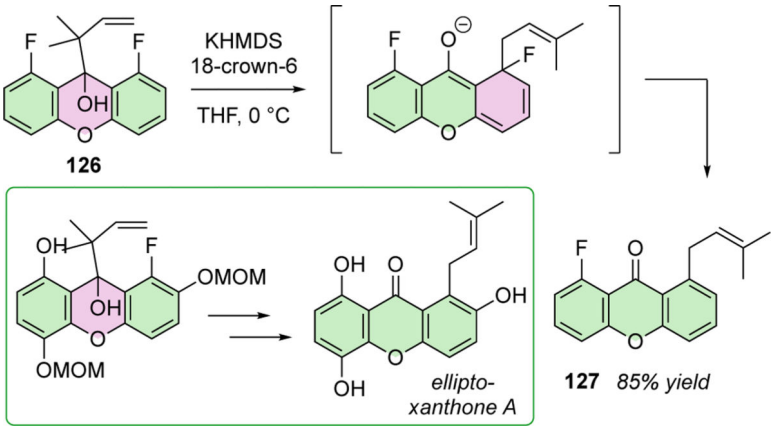
Scheme 28.

Bicycloheptenone substrates possessing aromatic substituents underwent an oxy-Cope ring expansion sequence in the process of generating fused polyquinane ring systems. (Moore *et al.*, 1996)



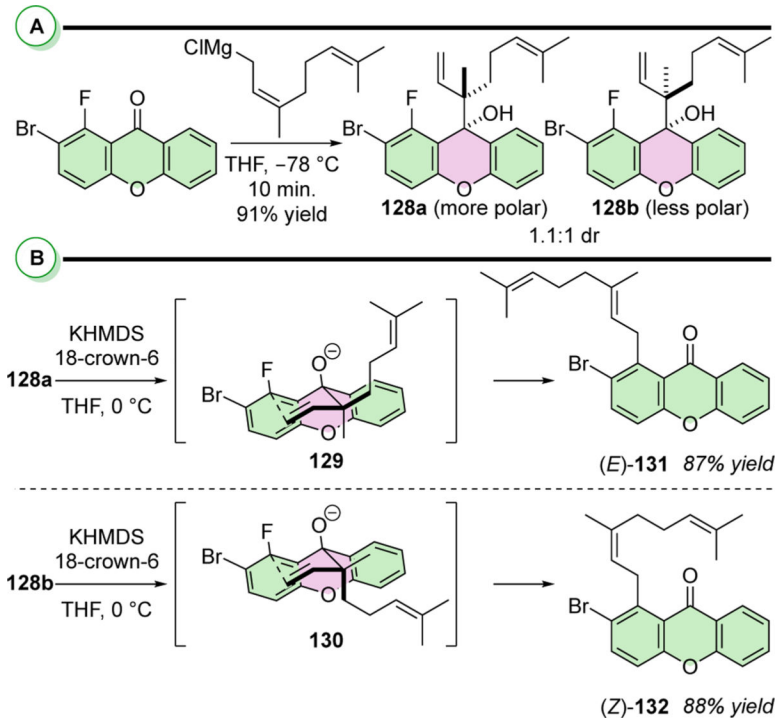
Scheme 29.

Polycyclic compounds were synthesized from diaromatic, dianionic oxy-Cope rearrangements. (Huq *et al.*, 2007)



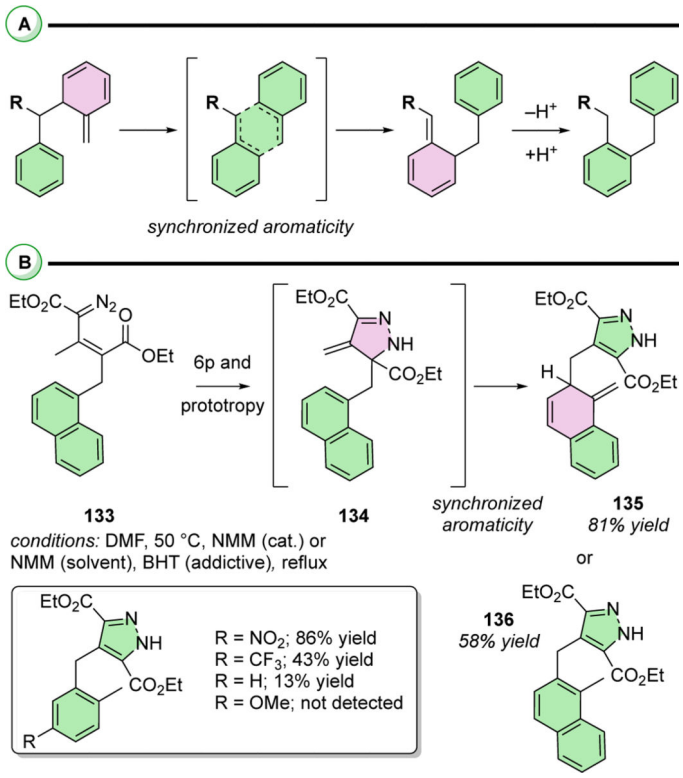
Scheme 30.

Application of an anionic, aromatic oxy-Cope rearrangement in the synthesis of xanthones such as elliptoxanthone A. (Matsumoto *et al.*, 2016)



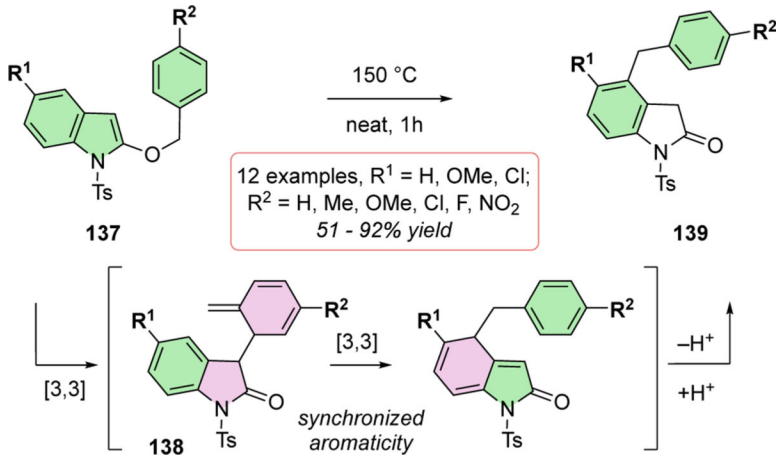
Scheme 31.

Anion-accelerated aromatic oxy-Cope rearrangements proceeded through a chair transition state to afford stereospecific xanthone products containing a geranyl or neryl side chain at the C1 position. (Matsumoto *et al.*, 2020)



Scheme 32.

A: Conceptualization of *synchronized aromaticity*. **B:** *Synchronized aromaticity* for the construction of 1-pyrazine-1-aryl methanes (Frantz *et al.*, 2012)



Scheme 33.

A tandem benzyl Claisen/aromatic Cope rearrangement provides a new method for accessing 4-substituted 2-oxindole products. (Yamada *et al.*, 2019)