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An Atom-Economical and Stereoselective Domino Synthesis of Functionalised Dienes

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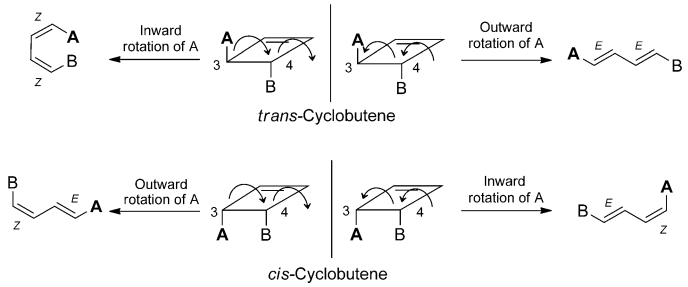
The thermal 4π-electrocyclic ring opening of cyclobutenes, a symmetry-allowed, conrotatory transformation leading to butadienes, is a well-established subset of pericyclic reactions.[1,2] This process generates either (*E*,*Z*)- or (*Z*,*E*)-diene products from a *cis*-3,4-disubstituted cyclobutene, and (*E*,*E*)- or (*Z*,*Z*)-diene products from a *trans*-3,4-disubstituted cyclobutene (Scheme 1).



Scheme 1. Conrotatory electrocyclic ring opening of substituted *cis*- and *trans*-cyclobutenes.

The inward or outward rotation of the C3 and C4 substituents of the cyclobutene starting materials, crucial in determining the geometry of the diene products, can be predicted by a set of torquoselectivity rules deduced by Houk.[3] Sterically demanding and electron-donating groups tend to rotate outward, whereas smaller and electron-withdrawing substituents prefer inward rotation. Therefore stereochemical information can be translated faithfully from 3,4-disubstituted cyclobutenes to the corresponding diene products. Nevertheless, the general preference of dienyl systems for an all-*E* geometrical configuration means that isomerisation of the initially formed products often plagues such diene syntheses, particularly in cases in which substituents A and B are an electronically antagonistic pair (see Scheme 1).

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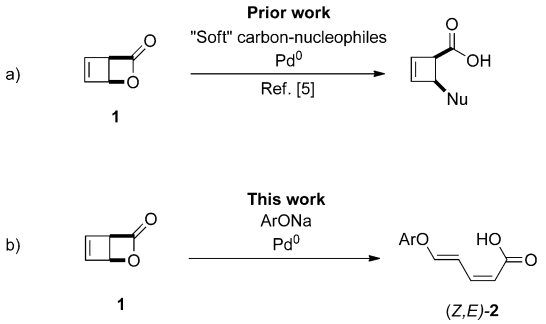
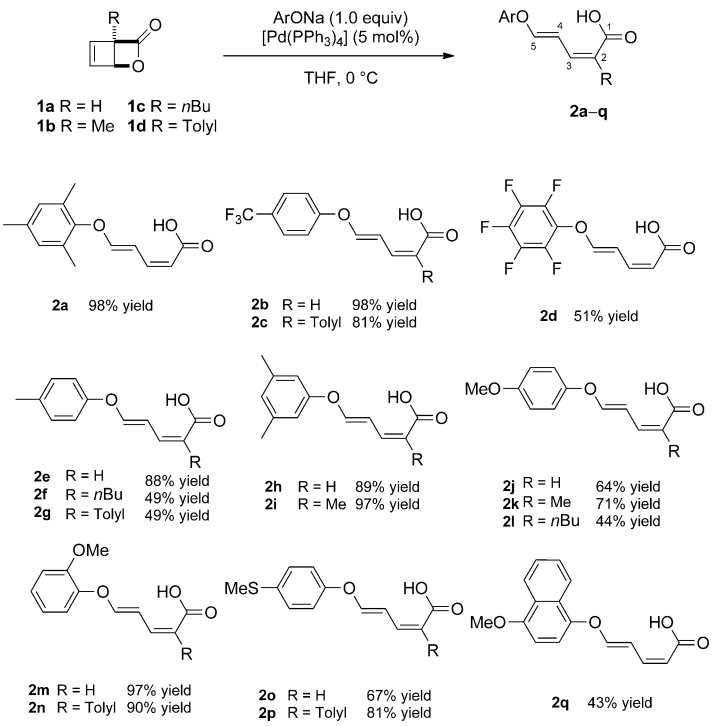
We have recently studied the allylic alkylation of lactone **1**[4] with stabilised (or "soft") carbon-centred nucleophiles (Scheme 2a).[5] Cognisant of the considerable body of work concerning the use of phenols as nucleophilic entities for allylic alkylation,[6,7] we investigated such species as a means



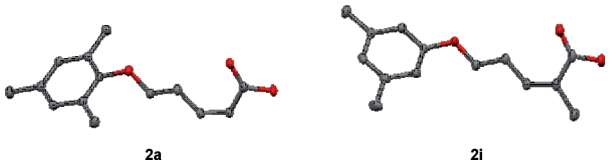
Scheme 2. Prior work and unexpected formation of dienes **2**.

to gain access to interesting heterofunctionalised *cis*-cyclobutene products. To our surprise, reaction of the sodium salt of phenols with lactone **1** under catalysis by $[Pd(PPh_3)_4]$ led cleanly to the (*Z*,*E*)-dienes **2**, formed as single reaction products (Scheme 2b). The direct formation of stereodefined, functionalised dienes under mild conditions and with complete atom economy warranted further investigation. We report herein a methodology for direct synthesis of geometrically defined dienes bearing challenging substitution patterns, and their use in atom economical domino sequences that increase structural complexity in a synthetically useful manner.

At first, we evaluated the scope of this transformation with respect to both the nucleophile and electrophile. As depicted in Scheme 3, a variety of phenols can be employed in this transformation, leading to the corresponding (*Z*,*E*)-5-aryloxydienyl carboxylic acids **2** in good to excellent yields. Noteworthy is the use of unusual nucleophiles such as pentafluorophenol, for which a much diminished nucleophilicity can be anticipated due to strong electronic deactivation.[8] Additionally, alkyl- or aryl-substituted lactones such as **1b–d**, readily available by photoisomerisation of the corresponding 3-substituted-2-pyrones,[9] also undergo a domino allylic alkylation/4π electrocyclic ring opening reaction.



Scheme 3. Scope of phenol nucleophiles and lactone electrophiles in the domino diene synthesis. Yields refer to analytically pure, isolated compounds.

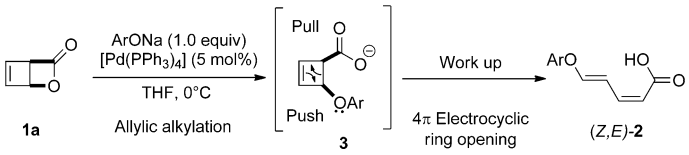


Scheme 4. Selected examples of X-ray structures of dienoic (*Z*,*E*)-5-aryloxydienyl carboxylic acids **2a** and **2i**.

Single-crystal X-ray analysis of (*Z*,*E*)-5-aryloxydienyl carboxylic acids derivatives **2** allowed unambiguous structural assignments of all products (Scheme 4).[10]

It is important to note that all diene products were obtained in geometrically pure (*Z*,*E*)-configuration (>95:5) after a simple acid–base extractive work-up, highlighting the mildness of the reaction conditions and the simplicity of this procedure.

This strictly palladium-catalysed transformation (as no product is observed when the catalyst is absent)[11] delivers doubly vinylogous esters for which known synthetic procedures are typically cumbersome, multistep, low-yielding sequences[12–14] and achieves a formal aryloxy anion addition to pyrone with extrusion of a hypothetical carboxylate leaving group.[11] Importantly, the thermodynamically more stable (*E*,*E*)-configured aryloxydienes can be obtained by a simple iodine-catalysed isomerisation.[11] It appears reasonable to infer that the simultaneous presence of the electron-releasing aryloxy moiety and the carboxylic acid residue impart "push–pull" character to the putative *cis*-disubstituted intermediate cyclobutene, thereby triggering its spontaneous ring opening (Scheme 5).[15,16]

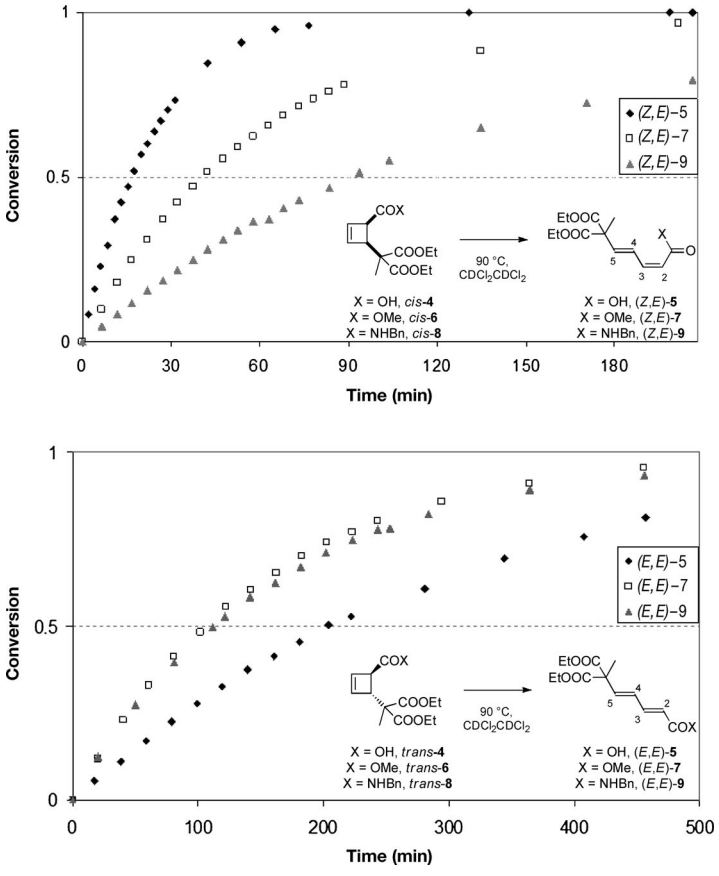


Scheme 5. Domino allylic alkylation/4π electrocyclic ring opening of lactone **1a**.

At this juncture, the direct formation of functionalised diene products decorated with synthetically useful functionality, through an atom economical allylic alkylation/4π electrocyclic ring opening sequence, appeared to hold potential as a general concept. This piqued our interest towards exploring the ring opening of cyclobutene adducts in a broader sense.

In the event, thermolysis of readily available *cis*- and *trans*-cyclobutenes **4**[5c] led to the corresponding geometrically defined dienes (*Z*,*E*)- or (*E*,*E*)-**5** (Scheme 6).[10]

Eager to obtain more information about the factors influencing ring-opening and realising that this system provides a unique opportunity to systematically study stereochemical and electronic parameters, we prepared *cis*/*trans* pairs of



Scheme 6. Thermal ring opening of *cis*- and *trans*-disubstituted cyclobutenes **4**, **6** and **8** at 90 °C in $CDCl_2CDCl_2$, as monitored by ^1H NMR spectroscopy.

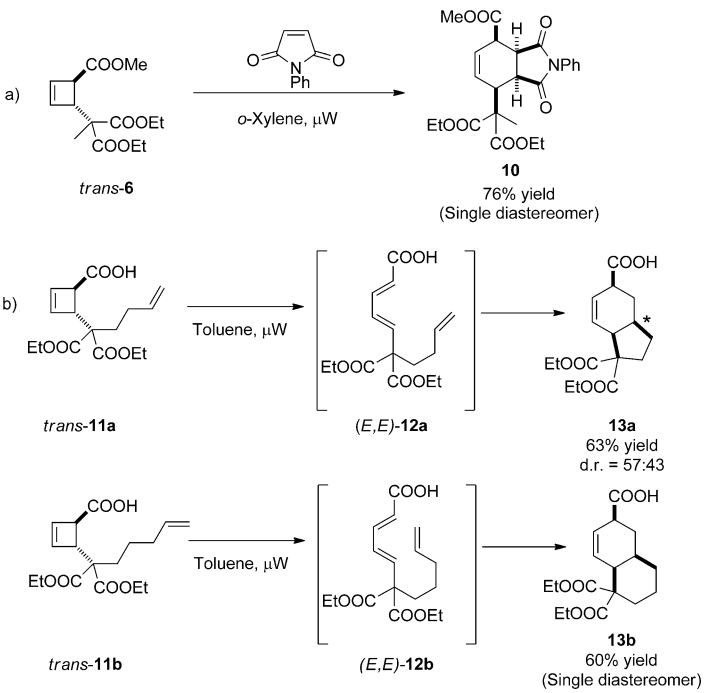
methyl esters and amides **6** and **8** from acids **4** and investigated their thermal electrocyclic transformation by means of ^{1}H NMR spectroscopy. The results are presented graphically in Scheme 6.

As a general tendency, the *cis*-cyclobutenes underwent electrocyclic ring opening faster than their *trans*-analogues, as expected based on strain release considerations.[17] The trends observed within each sub-group of either *cis*- or *trans*- cyclobutene derivatives, on the other hand, are more unusual. In the *cis* series, the free carboxylic acid *cis*-**4** underwent ring opening at the fastest rate ($t_{1/2}$ = 16.3 min) whereas the corresponding methyl ester *cis*-**6** and *N*-benzylamide *cis*-**8** were considerably slower ($t_{1/2}$ of 40.6 and 90.0 min, respectively). Surprisingly, that trend was reversed in the *trans*-cyclobutene series. In this case, the free carboxylic acid *trans*-**4** is the compound with the slowest ring opening ($t_{1/2}$ = 198.0 min) whereas the methyl ester *trans*-**6** and *N*-benzylamide *trans*-**8** show almost identical behaviour ($t_{1/2}$ of 105.0 and 113.6 min, respectively). To the best of our knowledge, the observation of such effects is unprecedented in prior studies of cyclobutene ring opening. We believe that both the notorious deceleration of the ring opening of *trans*-**4** and the acceleration of its *cis*-**4** counterpart are connected to subtle changes in the hydrogen-bonding modes of its carboxylic acid moiety.[18]

Having ascertained the stereoselectivity and the total absence of byproducts of these transformations, we sought to exploit them in the context of more complex sequences. In particular, the prospect of coupling the electrocyclic ring opening with further pericyclic reactions was appealing. To bring this idea to practice, *trans*-cyclobutene methyl ester **6** was heated in the presence of *N*-phenylmaleimide. The desired *exo*-cycloadduct **10** was isolated as a single diastereoisomer in 76% yield (Scheme 7a).[19]

We further designed *trans*-cyclobutenes **11a**,**b**, containing a tethered olefin, as substrates for sequential electrocyclic ring opening-intramolecular Diels–Alder reaction (Scheme 7b). At the onset, we were uncertain about the stereochemical outcome of this domino cycloaddition sequence, since literature precedents demonstrate that very subtle steric and electronic factors control this issue in related systems.[20] As shown, both substrates led to the desired bicyclic compounds in good yields,[10] with remarkable stereoselectivity being observed for the transformation of *trans*-cyclobutene **11b** into decalin cycloadduct **13b**.[13] It is instructive to notice how the stereochemical information initially inscribed in two stereocentres of the cyclobutene ring is ultimately translated in multiple contiguous stereocentres in cycloadducts **10** and **13**.

In spite of the numerous literature reports detailing scarce reactivity of push–pull dienes in the context of [4+2]-cycloadditions,[21] aryloxydienes **14** also proved to be competent partners for Diels–Alder cycloaddition as depicted in Scheme 8a. This prompted us to investigate the use of *o*-allylated-phenols as nucleophiles in the domino diene synthesis, hoping that the resulting pendant olefin could engage in a subsequent, thermal [4+2]-cycloaddition (Scheme 8b).



Scheme 7. Domino electrocyclic ring opening/Diels–Alder cycloaddition. Yields are for isolated, analytically pure compounds. d.r. refers to the centre marked with *. d.r. = diastereomeric ratio

As shown, thermolysis of dienes **16** in toluene led to the stereoselective formation of the desired tricyclic compounds **17**.[10] The structures of **13b** and **17a** were confirmed by X-ray crystallography (Scheme 9). Both electron-withdrawing and electron-releasing groups were well tolerated and various substitution patterns in the aromatic ring were possible in this transformation. The remarkable increases of molecular complexity depicted in Schemes 7 and 8, coupled with the near complete atom economy of the synthetic sequences portrayed render these transformations appealing. In particular, the structure of cycloadducts **17a–e** is closely related to the Euglobal natural product family as well as Isocymobarbatol (Scheme 8).[22]

In summary, we have developed an atom economical domino synthesis of functionalised and stereodefined dienes. This method hinges on an allylic alkylation/4π electrocyclic ring-opening sequence and allows direct access to doubly vinylogous esters bearing challenging substitution patterns. A systematic investigation of electrocyclic ring-opening rates along a series of substrates revealed interesting trends and an unprecedented "anomalous" carboxylic acid effect. This, in turn, enabled the design of reaction sequences that dramatically increase structural complexity from the simplest of reagents.

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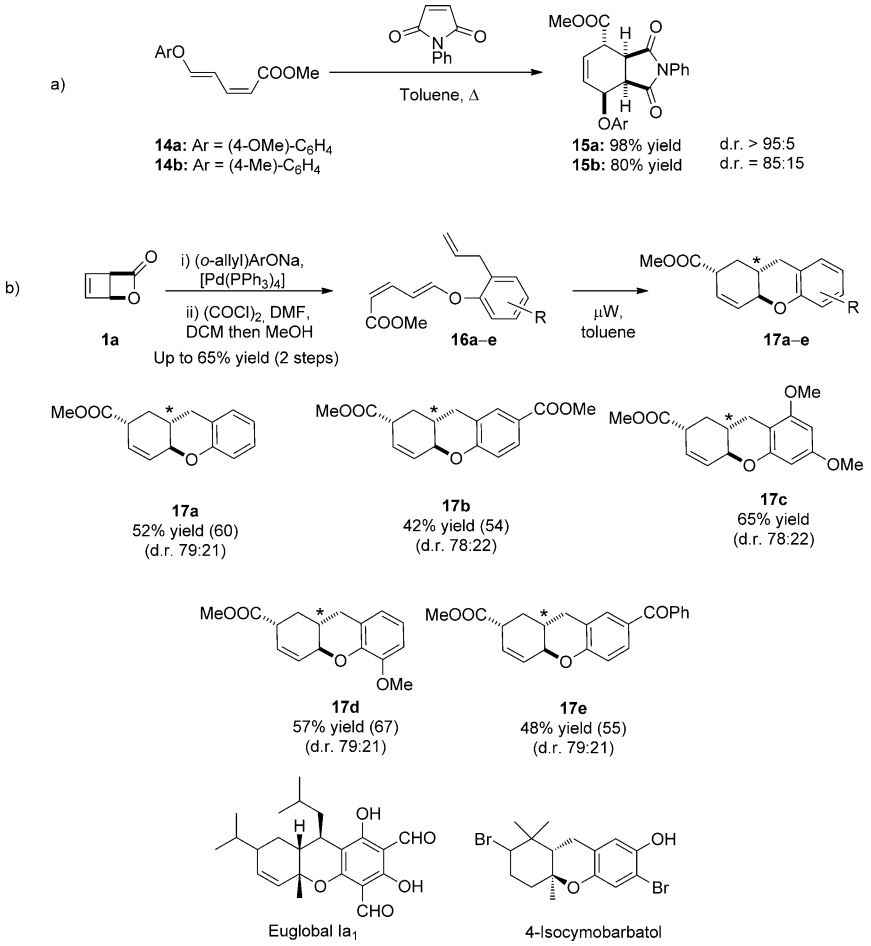
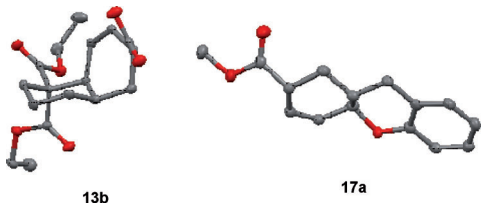


Scheme 8. Diels–Alder reactions of push–pull aryloxy-dienes. The d.r. values were determined by NMR analysis of the crude mixture and refer to the centre marked with *. Isolated yields refer to intramolecular cycloaddition reaction. Numbers in brackets refer to yields based on recovered starting material. d.r. = diastereomeric ratio



Scheme 9. Stereochemical assignment of the major diastereoisomers of **13b** and **17a** using X-ray crystallography.

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Keywords: allylic alkylation · cyclobutene · dienes · electrocyclic reactions · palladium

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[19] Interestingly, when cyclobutene methyl ester *cis*-**6** was used in this transformation under identical or harsher conditions, only unreacted (*Z*,*E*)-diene was recovered.

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Diene Synthesis

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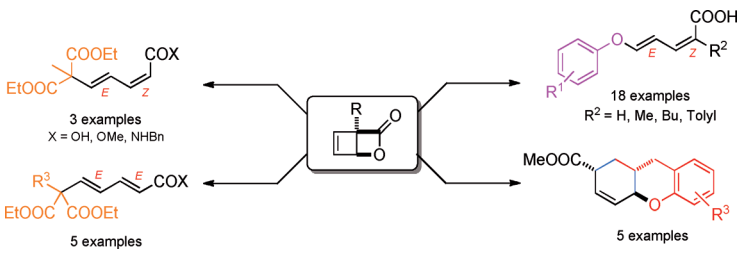
An Atom-Economical and Stereoselective Domino Synthesis of Functionalised Dienes



Open sesame: A direct synthesis of functionalised and stereodefined dienes, relying on a domino allylic alkylation/electrocyclic ring-opening sequence, is reported. This method allows concise access to doubly vinylogous esters. A further systematic study of ring-opening rates of carbon-substituted cyclobutenes allowed the design of substrates amenable to sequential pericyclic reactions (see scheme).

