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Direct Synthesis of Stereodefined and Functionalized Dienes as Valuable Building Blocks

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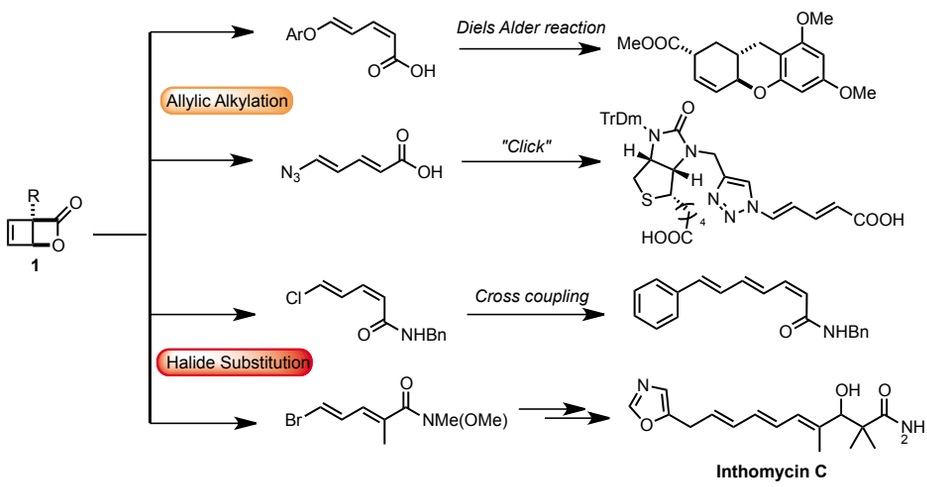
§SCS-Metrohm Foundation Award for best oral presentation

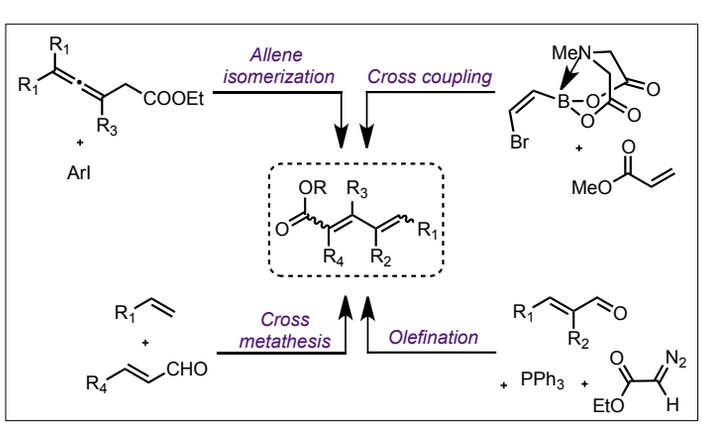
Abstract: We have reported a direct and stereoselective synthesis of functionalized dienoic carboxylates from the simple bicyclic lactone **1**. The use of *oxygen*- or *nitrogen*-based nucleophiles in a domino allylic alkylation/4π-electrocyclic ring opening affords reliable access to dienes with interesting functionalities. Alternatively, halide substitution offers synthesis of other classes of functionalized dienoic acids. Herein, we demonstrate the utility of such dienoic products as key building blocks in various transformations as well as natural product synthesis.



Keywords: Allylic alkylation · Azide · Diene · Inthomycin C · Ring opening

In the past decades, various methods have been developed for the synthesis of dienyl carboxylate and carbinol moieties. These structural subunits are present in many natural products[1] and their syntheses are typically multistep.[2] Indeed, functionalized conjugated diene carboxylates are conventionally built from simple mono-olefinic fragments through, *e.g.* olefination reactions,[3] cross-coupling,[4] cross metathesis,[2] or allene isomerization[2] (Scheme 1). The major challenge in such methodologies is usually the control of the configuration of the double bond arrays generated during the transformation.

The thermal conrotatory 4π-electrocyclic ring opening of cyclobutenes to afford 1,4-butadienes, is a well-established subset of pericyclic reactions.[5–7] In this transformation, the cyclobutene configuration is faithfully transferred into the diene geometry allowing high stereocontrol of the double bonds generated (Scheme 2). The inward or outward rotation of the C_3 and C_4 substituents of the cyclobutene can be predicted by torquoselectivity rules deduced by Houk and Niwayama.[8]



Scheme 1. Typical synthetic approaches to dienylcarboxylate building blocks.

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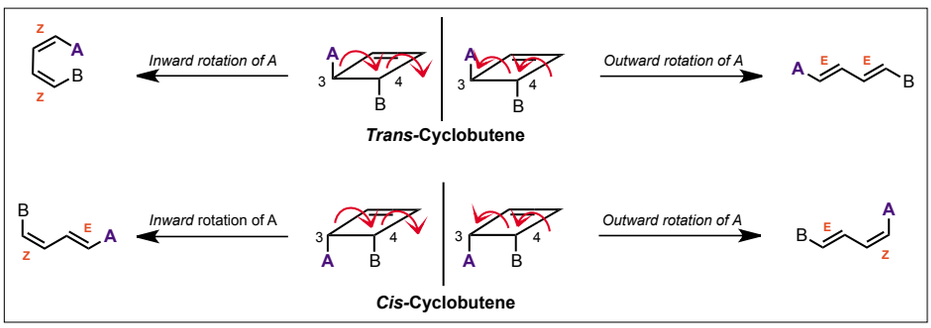
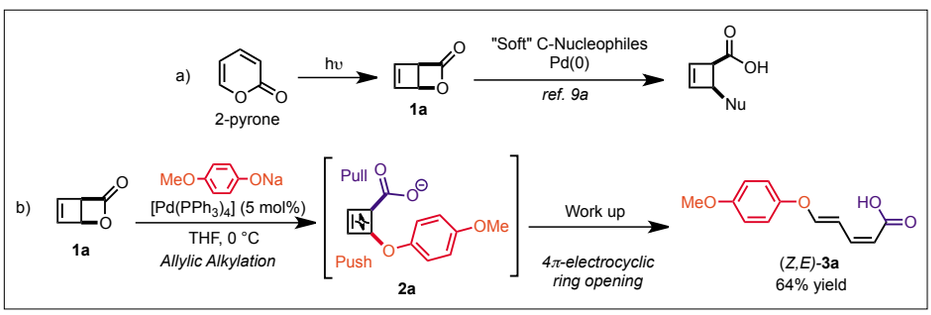


Scheme 2. Conrotatory electrocyclic ring-opening of substituted cyclobutenes.



Scheme 3. a) Prior work on the allylic alkylation of lactone **1a** and b) tandem allylic alkylation/electrocyclic ring-opening employing sodium phenolate nucleophiles.

We previously reported work on allylic alkylation of lactone **1a**[9] with stabilized *carbon*-centered nucleophiles (Scheme 3a). Considering the importance of phenols as nucleophiles in allylic alkylation, we decided to employ *oxygen*-centered nucleophiles in the reaction with lactone **1a**.[10,11]

Surprisingly, when sodium *p*-methoxyphenolate was used in conjunction with the lactone **1a**, a diene product **3a** was obtained rather than the expected cyclobutene (Scheme 3b). Moreover, the peculiar (*Z*,*E*)-diene geometry of the final product **3a** hints at its origin in a putative, unstable *cis*-disubstituted cyclobutene **2a**. It is conceivable that simultaneous presence of electron-withdrawing and electron-releasing functional groups on the cyclobutene ring creates a 'push-pull' effect on the *cis*-disubstituted intermediate **2a**, thereby triggering spontaneous ring opening.[12]

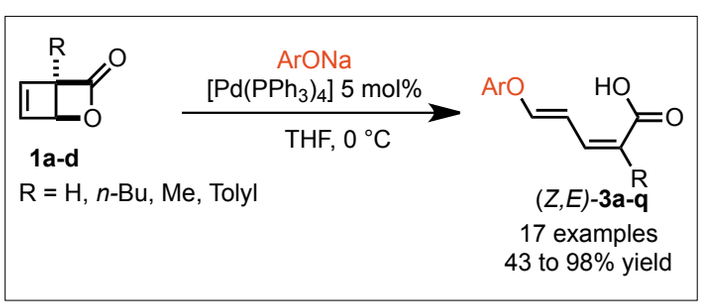
A variety of phenols can be used in this transformation, leading to the corresponding (*Z*,*E*)-5-aryloxydienyl carboxylic acids **3a–q** in moderate to excellent yields (Scheme 4).[10] The diene geometry of all products was consistent and confirmed by X-ray analysis. Additionally, substituted lactones **1b–d**, readily available by photoisomerization of 3-substituted-2-pyrones,[13] provide the corresponding (*Z*,*E*)-5-aryloxydienyl substituted carboxylic acids **3a–q** under the reported reaction conditions.

The diene products obtained by these sequences offer several reactivity manifolds. For instance, simple modification of the phenolic nucleophile with an *ortho*-disposed allylic side chain allows its use in a thermal intramolecular Diels-Alder reaction to quickly build up a densely functionalized tricyclic product **4** (Scheme 5).

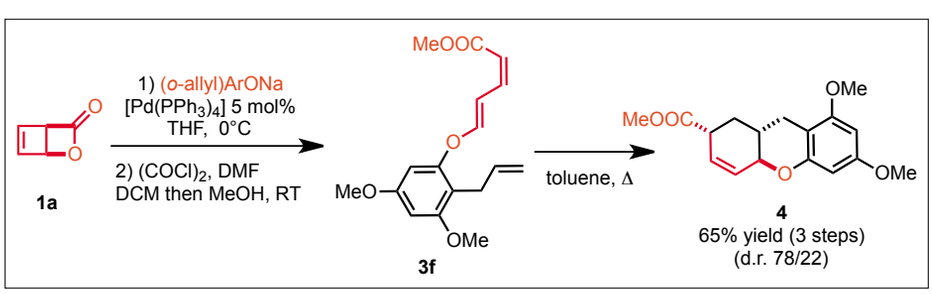
Eager to learn more about the nucleophile scope, we investigated the use of *nitrogen*-based nucleophiles. As shown, the use of trimethylsilyl azide under virtually identical conditions with lactone **1a** afforded azidodienoic acid **6a** (Scheme 6).[14] Interestingly, **6a** possesses (*E*,*E*)-diene geometry, suggesting it derives from an unstable *trans*-disubstituted cyclobutene intermediate **5**.[15]

The expeditious access to azidodienoic acids such as compound **6a** might enable useful applications in chemical biology. Indeed, the azide functionality allows a 'click' reaction with alkyne partners[16] (such as a biotin derivative, en route to **7**) whilst the carboxylic group of **6a** permits condensation to amine- or hydroxyl-groups as *e.g.* in the transformation of biologically relevant molecules like the hapten digitoxigenin to **8** (Scheme 7). The orthogonal reactivity of these functional groups adds another layer of practicality, as they can be manipulated interchangeably.

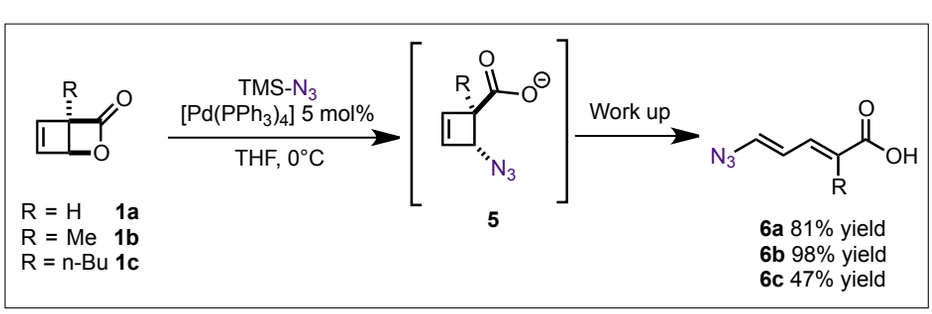
The ability to prepare dienylcarboxylates of fixed geometry in very short order and bearing useful functional groups for further elaboration could be a major asset for the streamlined total synthesis of polyene natural products. In this purpose, we turned our attention towards the synthesis



Scheme 4.



Scheme 5. Sequential (2-allyl-phenoxy)diene synthesis and Diels-Alder cycloaddition reaction.



Scheme 6. Tandem allylic alkylation/electrocyclic ring-opening employing azide as nucleophile.

of other classes of functionalized dienoic acids.

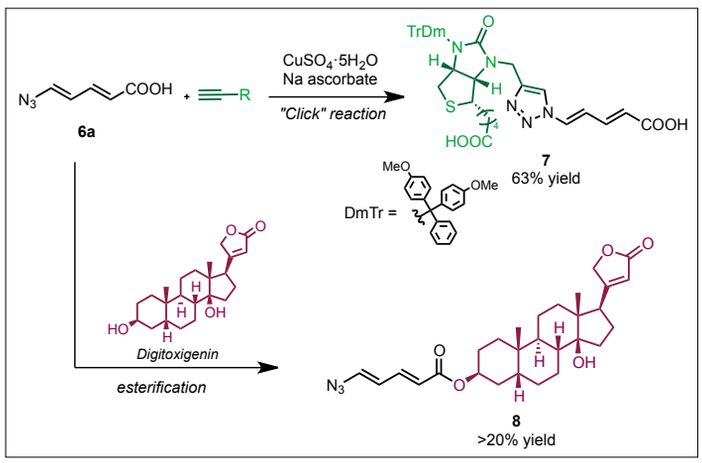
During the course of our studies on allylic alkylation of lactone **1a**, we serendipitously found that its exposure to alkali halide salts directly affords halocyclobutenes as products.[17] As shown in Scheme 8, the use of LiBr cleanly afforded *trans*-bromocyclobutene **9a** in quantitative yield. Conversely, nucleophilic chlorination mediated by HCl selectively provided the *cis*-chlorocyclobutene **9b**.

In contrast to the strong electron-donating *oxygen-* or *nitrogen*-substituents, halogen atoms enable thermal stability of the four-membered-ring products **9a**,**b**. Nevertheless, the acids **9a**,**b** (as well as their amide or ester derivatives) are prone to thermal conrotatory 4π-electrocyclic ring opening delivering halodienes. The *trans*-bromocyclobutene carboxylic acid **9a** is amenable to ester/amide coupling followed by thermal ring-opening to provide (*E*,*E*)-bromodienyl carboxylates **10a–d**. In complementary fashion, *cis*-chlorocyclobutene carboxylic acid **9b** can be readily derivatized and opened to afford the (*Z*,*E*)-chlorodienyl carboxylates **11a–d**.

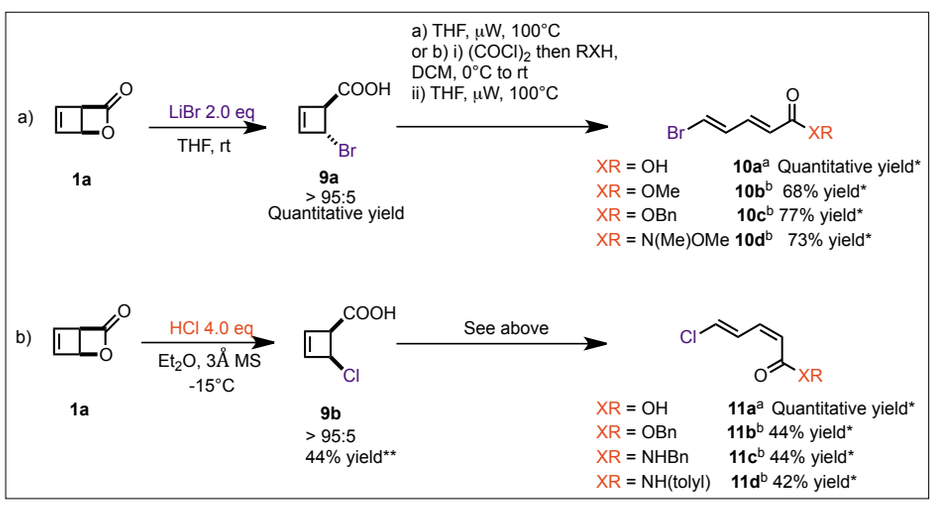
Having those halodienes in hand, we further investigated their reactivity in cross-coupling reactions. In the event, both (*E*,*E*)- and (*Z*,*E*)-halodienes (**10c**,**d** and **11c**,**d**, respectively) afforded the products of Sonogashira, Suzuki or Stille cross coupling without erosion of diene geometry (Scheme 9).

Armed with this knowledge, we then targeted the total synthesis of inthomycin C (Scheme 10), an anticancer natural product.[18] As shown, lithium bromide smoothly opened the methyl-substituted lactone **1b** (Scheme 10). A single *trans*-cyclobutenyl bromide **9d** was obtained as before. Further amide coupling and 4π-electrocyclic ring opening afforded (*E*,*E*)-2-methyl-5-bromodienoic amide **10e** as a single geometrical isomer. Stille cross-coupling with vinyl stannane **14**,[19] followed by reduction to the aldehyde **16** and organocatalytic Mukaiyama aldol reaction with silylketene acetal **17** then led to product **18** in 50% yield.[20] The conversion of **18** into Inthomycin C has been reported previously.[21]

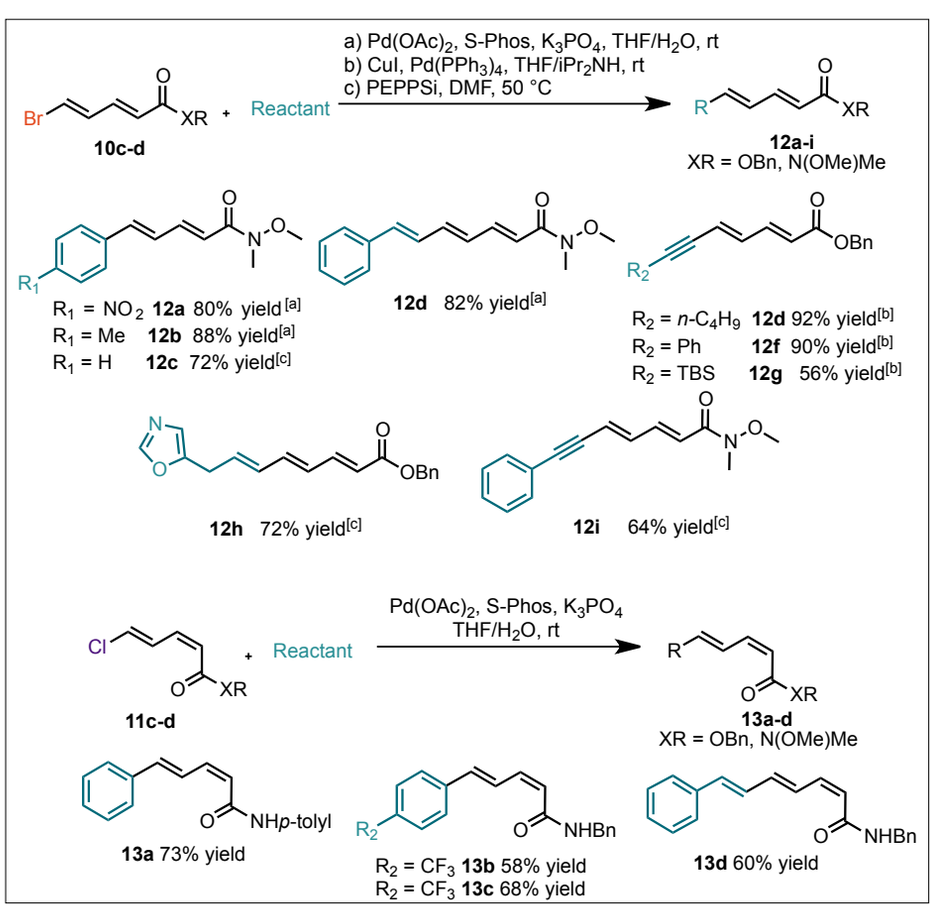
In summary, we have shown that the stereocontrolled preparation of several diene carboxylates can be achieved by taking advantage of the 4π-electrocyclic ring opening of cyclobutene derivatives. While heteroatom-substituted dienes are useful in applications ranging as far as chemical biology, halodienoic acids are prime building blocks for total synthesis. We are currently pursuing the application of this and related approaches to the total synthesis of diverse polyene natural products.



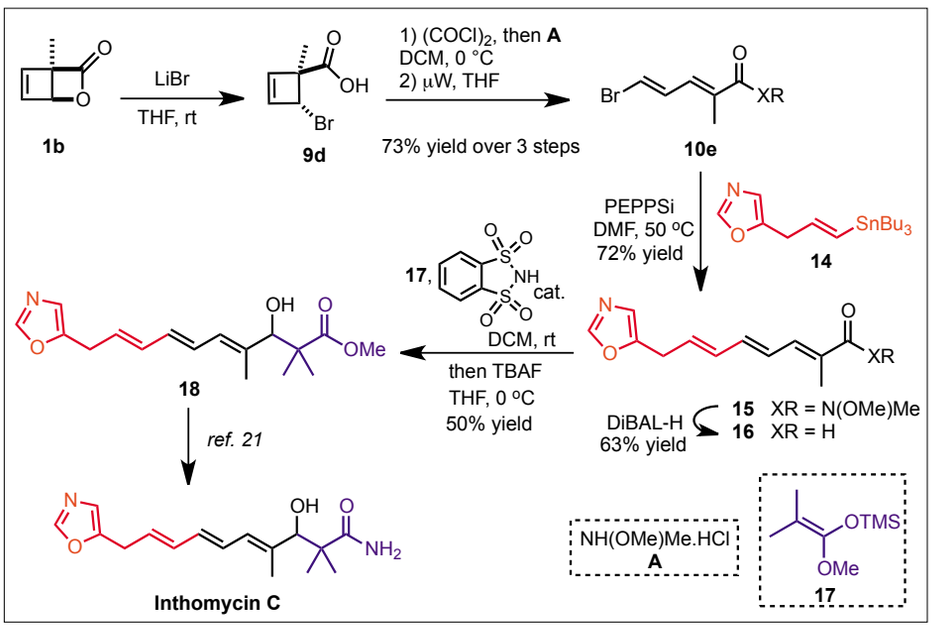
Scheme 7. Orthogonal derivatisation of azido-dienylcarboxylate **6a** through 'click' chemistry and ester coupling.



Scheme 8. *Overall isolated yield from lactone **1a**; **Isolated yield after recrystallization.



Scheme 9. Scope of catalytic cross-coupling reactions of halodienyl carboxylates.



Scheme 10. Formal synthesis of inthomycin C.

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