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Letter

Diastereoselective Synthesis of 2,3,4-Trisubstituted Tetrahydrofurans via Thermally Reactive 1,5-Diene-*tert*-butyl Carbonates

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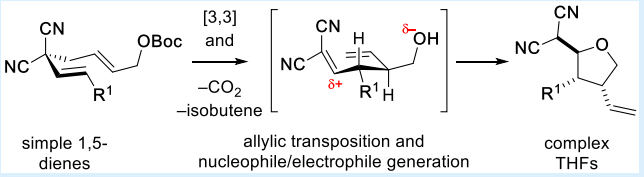
ABSTRACT: We report that 3,3-dicyano-1,5-dienes bearing *tert*-butyl carbonates can be thermally converted to 2,3,4-trisubstituted tetrahydrofurans. The transformation relies on two thermally reactive functional groups, a 1,5-diene and a *tert*-butyl carbonate, that react cooperatively to yield the furan scaffolds by thermal Cope rearrangement, Boc deprotection, and oxy-Michael addition. Described herein is background related to the discovery, optimization, and scope of the key transformation and representative functional group interconversion chemistry for the tetrahydrofuran scaffolds.



Substituted tetrahydrofurans (THFs) are a common heterocyclic core found in diverse, bioactive natural products such as terpenes (anethofuran[1] and guaioxide[2]), furanose derivatives (isosorbide[3] and xylitan[4]), lignans[5,6] (asarinin, nectandrin B, and burseran), macrolides (avermectin), fungal metabolites[7−10] (aureonitol), and pharmaceutical drug leads (LY 379268[11] and elenbecestat[12]). Considering the relevance of tetrahydrofurans to drug discovery (Figure 1), a variety of strategies have been developed to access them in efficient ways.[13] Synthetic strategies fall into one of two subcategories: (a) constructive synthesis, in which the THF scaffold is assembled,[14−22] or (b) an approach that functionalizes a preexisting THF core (e.g., C−H functionalization and cross-coupling reactions).[23−28] The former category is particularly relevant to this report. We have been advancing the classic Cope rearrangement (that of 3,3-dicyano-1,5-dienes) for application in modern chemical synthesis.[29−34] Considering that Cope rearrangement results in allylic transposition and an electrophilic alkylidenemalononitrile, we hypothesized that "trapping" with tethered nucleophiles could result in additional bond formation and structural complexity. Specifically, it was proposed that 1,5-dienes **1** derived from alkylidenemalononitrile and a *cis*-buten-1,4-diol derivative could undergo thermal transformation involving Cope rearrangement, Boc deprotection, and intramolecular oxy-Michael rearrangement (Scheme 1).[35] Reviews of the furan synthesis literature[13−28] and "domino reactions"[36,37] in general reveal that this proposal is unique and would access novel trisubstituted THFs. The most relevant prior work is summarized in Scheme 1, which demonstrates the likelihood of oxy-Michael additions to alkylidenemalonic acid derivatives.[38−40] Interestingly, our proposal and these methods for comparison result in furans in which the malonate and malononitrile functional groups are at complementary locations about the THF core.

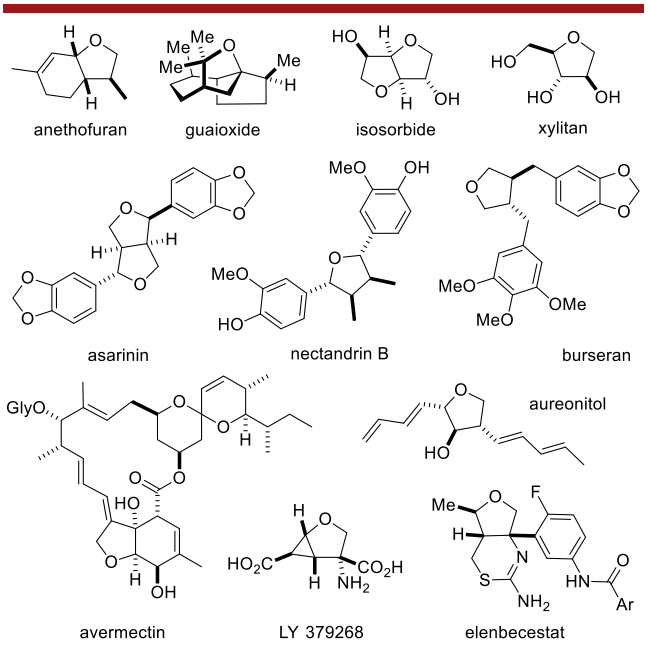


Figure 1. Representative THF-containing natural products and pharmaceuticals.

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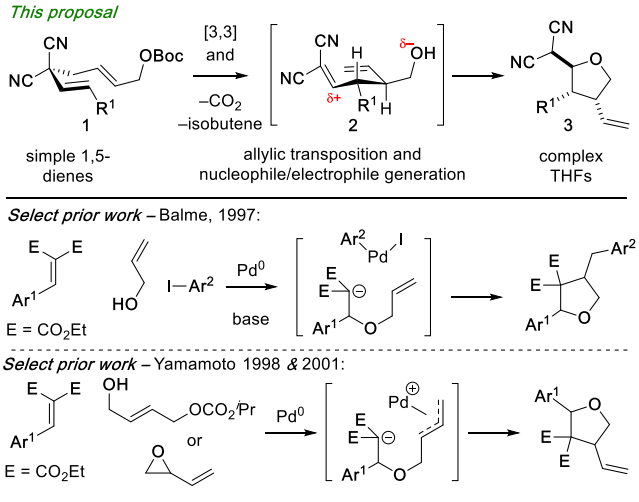
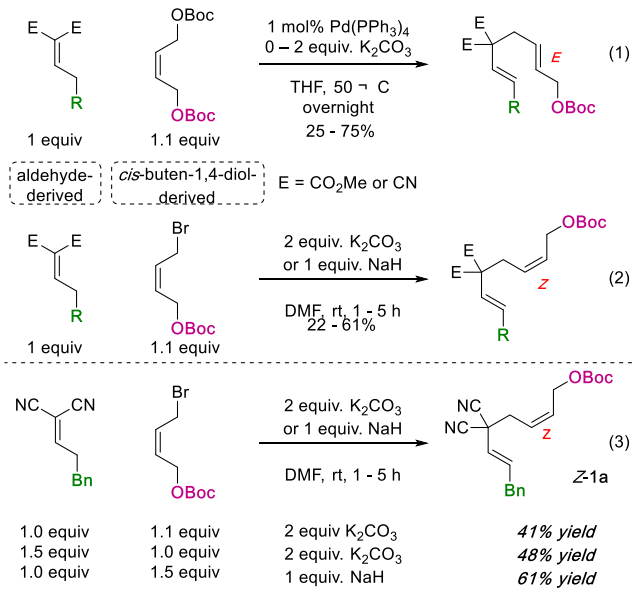
Scheme 1. Our Proposal for THF Synthesis and Representative State of the Art Protocols



We began our studies by synthesizing diastereomeric 1,5-dienes *E*-**1** and *Z*-**1** from their corresponding aldehyde-derived Knoevenagel adduct and a *cis*-buten-1,4-diol derivative (Scheme 2, eqs 1 and 2). Specifically, *E*-**1** substrates can be

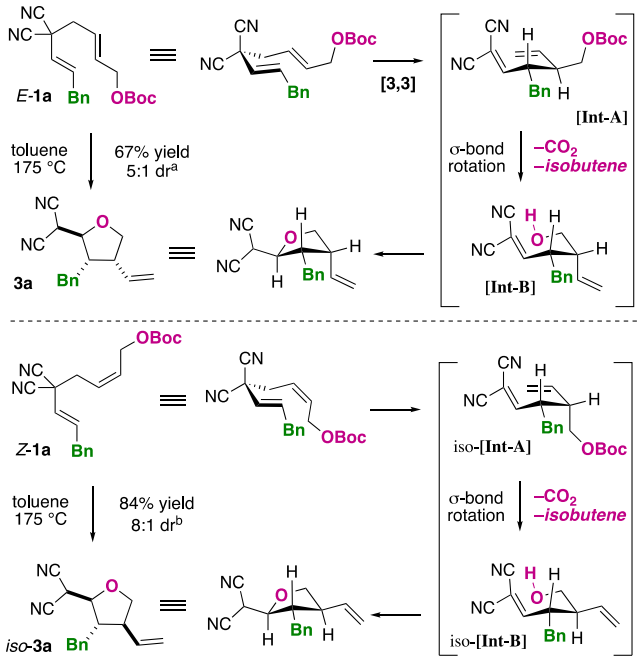
Scheme 2. Representative Synthesis of *E*- or *Z*-1,5-Dienes



prepared via Tsuji–Trost reaction between alkylidenemalononitrile and the allyl carbonate electrophile (Scheme 2, eq 1), whereas *Z*-**1** substrates are derived from the analogous allyl bromide electrophile (Scheme 2, eq 2). Notably, via Pd catalysis, the *cis*-olefin is isomerized to the *trans* isomer during the deconjugative alkylation process (Scheme 2, eq 1).[41] Finally, all 1,5-dienes in this disclosure were prepared by this method or a subtle variation thereof with modest to good yields (see the Supporting Information for details). While optimization was minimal, it was found that the yields can be increased by using an excess of the electrophile (Scheme 2, eq 3).

With *E*-**1a** and *Z*-**1a** in hand, we began by examining the substrates for the desired thermal cascade to tetrahydrofurans. The desired products **3a** and iso-**3a** could be formed when the compounds were heated at 175 °C in toluene with good yield and diastereoselectivity (Scheme 3). Interestingly, **3a** and iso-

Scheme 3. Stereospecific Furan Synthesis via a Thermal Cascade



[a]The minor diastereomer is iso-**3a**. [b]The minor diastereomer is **3a**.

3a were the only products detected in the crude mixture; none of the suspected intermediates such as [**Int-A**], [**Int-B**], or their isomers were observed. The different diastereomers *E*-**1a** and *Z*-**1a** react distinctly and diastereoselectively to yield products **3a** and iso-**3a**, respectively. In both cases, the stereochemical outcomes can be rationalized via a Zimmerman–Traxler model and an oxy-Michael addition yielding a pseudo-equatorial malononitrile functional group. Along these lines, from *E*-**1a**, the minor diastereomer is iso-**3a** (Scheme 3, footnote a). Thus, either the Cope rearrangement yields diastereomers or the Cope product is prone to epimerization at the acidic γ-C–H. This was also the case for *Z*-**1a** (Scheme 3, footnote b). Notably, the elevated temperatures in this transformation's current form are necessary. At ≤150 °C in toluene, we observed diminished conversion of the 1,5-dienes. In this case, both Cope rearrangement and Boc deprotection were sluggish over the same time period.

From our previous work on related 1,5-dienes, it was found that the classic Cope rearrangement often does not favor the product side of the equilibrium.[31,34] Rather, it was demonstrated that the Cope rearrangement could be promoted by a stoichiometric reductant that intermolecularly reacted with the product side of the equilibrium via chemoselective alkylidenemalononitrile reduction (the "reductive Cope rearrangement"). It was hypothesized that oxy-Michael addition was having a similar effect here. To examine this, we compared *E*-**1a** and *Z*-**1a** to substrates *E*-**1a-OAc** and *Z*-**1a-OAc** that have similar structures and electronics but cannot generate the nucleophilic hydroxyl group under the standard reaction conditions (Scheme 4). While *E*-**1a** transforms to the furan scaffolds with 90% conversion under standard conditions, *E*-**1a-OAc** had a lower conversion (64%). A similar trend was observed

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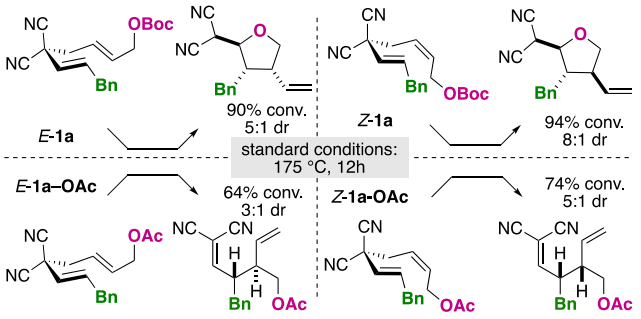
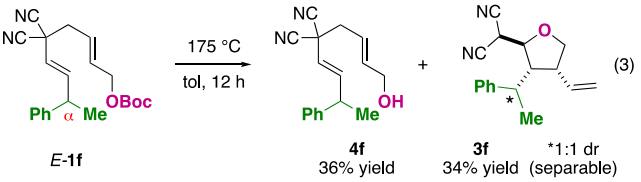
Scheme 4. Cope Rearrangement and Oxy-Michael Addition Are Cooperative Tandem Processes



for *Z*-**1a** and *Z*-**1a-OAc**, though with slightly different ratios. This suggests that the tandem transformation is cooperative. The Cope equilibrium process will not reach full conversion on its own during that period of time but is driven forward and rendered irreversible by the nucleophilic addition, the oxy-Michael reaction.

The scope of the reaction was examined next. It was found that the transformation was successful with a variety of substrates and could tolerate the incorporation of functional groups such as alkenes and TBS-protected alcohols. Furthermore, the yield and diastereoselectivity remained consistent with the previously optimized yields. It should be noted that congestion about the 1,5-diene termini has an impact on the kinetics of the transformation. For example, **1e** having an α-isopropyl group reacted under the standard conditions to produce a mixture of the desired product (50% yield, 9:1 dr) along with Boc-deprotected substrate **4e**. However, subjecting the 1,5-diene-alcohol to the same conditions again yielded additional product. As a final note, this suggests that the order of events for the tandem reaction is case-dependent. For this particular example, Boc deprotection followed by Cope rearrangement is the likely order of events (Scheme 5).

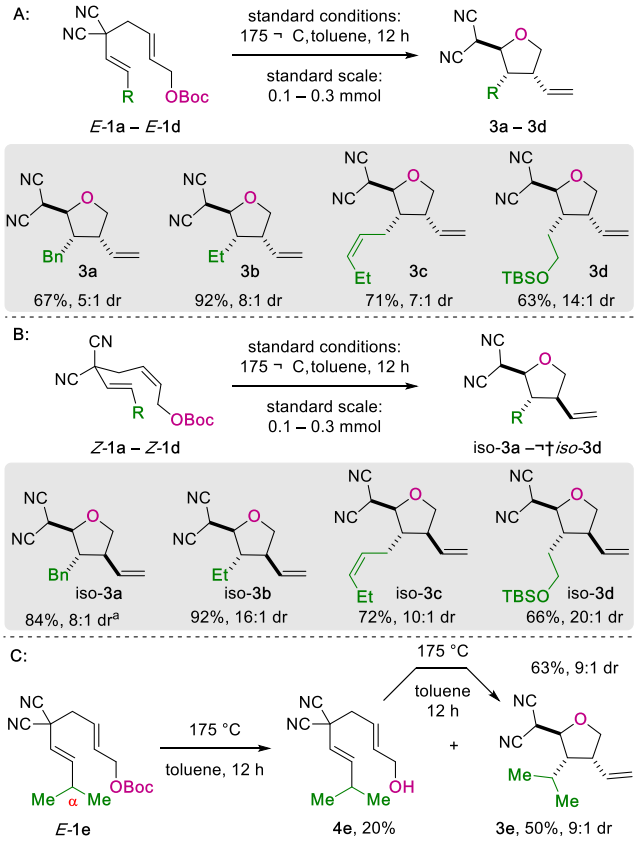
Having an understanding of the scope of the transformation, we next examined stereoinduction from an existing stereocenter on the 1,5-diene for the cascade sequence. Unfortunately, in limited studies (only the one substrate disclosed herein has currently been examined to date), the existing stereocenter on **1f** did not influence the diastereoselectivity of the Cope rearrangement (eq 3). Thus, two epimers (**3f**) were



prepared via the thermal cascade reaction. Notably, both epimers can be separated by silica gel chromatography, and each individual epimer is >20:1 dr from the tandem thermal transformation.

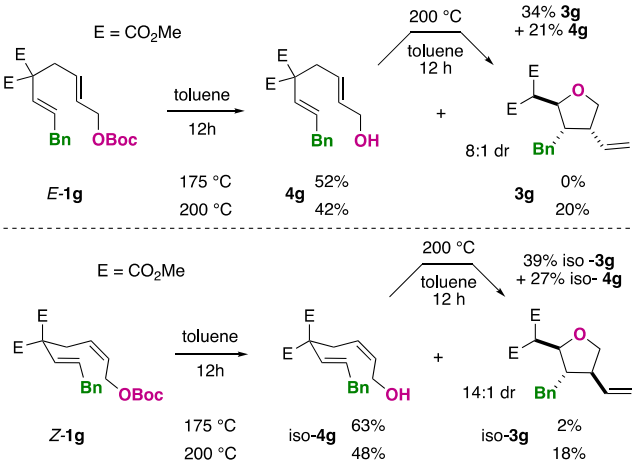
We next examined malonate-containing 1,5-dienes for tetrahydrofuran synthesis. In general terms, the malonate-1,5-dienes are less reactive to Cope rearrangement than malononitrile substrates. For example, heating *E*-**1g** at 175 °C produced only the Boc-deprotected starting material **4g** in 52% yield (Scheme 6). At 200 °C, desired product **3g** was prepared in 20% yield as an 8:1 mixture of diastereomers along

Scheme 5. Reaction Scope of (A) *E*-1,5-Dienes, (B) *Z*-1,5-Dienes, and (C) a Sterically Encumbered 1,5-Diene



[a]On a 1.87 mmol scale (395 mg of iso-**3a** isolated).

Scheme 6. Reactivities of Malonate-Containing 1,5-Dienes



with 42% of alcohol **4g**, which upon subjection again to the standard conditions produced an additional 21% of the desired furan. Similar reactivity was observed with *Z*-**1g**.

In terms of the final results related to scope, we have identified a current limitation of this furan synthesis (eq 4). While the transformation is generally successful with aldehyde- and butene-1,4-diol-derived 1,5-dienes (*E*-**1a–g** and *Z*-**1a–g**), in limited studies, a ketone-derived substrate failed (eq 4). Under the standard conditions, *E*-**1h** underwent Cope rearrangement (with significant epimerization, 2:1 dr) and Boc deprotection but no furan product was detected. The

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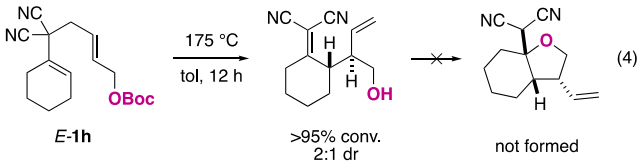
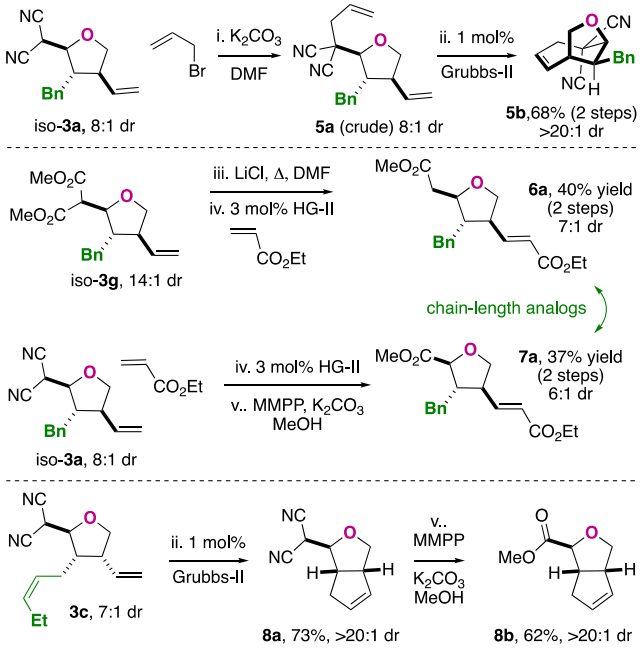


potential reasons for the lack of oxy-Michael reactivity are many. For example, there could be steric or conformational issues with the nucleophilic attack. Alternatively, the reduced electrophilicity of the tetrasubstituted alkylidene may also play a role in the undesired outcome. In any case, more studies are needed to expand the reactivity to ketones.

For our final studies, we examined functional group interconversions on the THF scaffolds (Scheme 7). As a result of the reaction design, trisubstituted THFs with complementary and orthogonal functional groups are prepared. This allows for rapid structural diversification. For example, we prepared a bicyclic THF-containing architecture **5b** via malononitrile allylation (to **5a**) followed by ring-closing metathesis[42] in 68% yield over two steps. **5b** is isolated as a single diastereomer, likely because the minor diastereomer cannot undergo ring-closing metathesis due to the *trans* orientation of the two chains. The malonate-containing THF scaffold can be converted to **6a** via Krapcho decarboxylation[43] followed by cross-metathesis[44] with ethyl acrylate in 40% over two steps. Interestingly, the analogous malononitrile scaffold iso-**3a** can be converted into a chain-length analogue (**6a** vs **7a**) via cross-metathesis and then oxidative decyanation.[45−47] Finally, **3c** was converted into bicycloalkanes **8b** via ring-closing metathesis (to **8a**) and oxidative decyanation.

Scheme 7. Representative Functional Group Interconversion Chemistry[a]



[a]Conditions: (i) 2 equiv of K_2CO_3, DMF, rt, 1 h; (ii) 1 mol % Grubbs II, toluene, 80 °C, 12 h; (ii) 1 equiv of LiCl, 1 equiv of H_2O, DMF, 150 °C, 4 h; (iv) 3 mol % Hoveyda-Grubbs II, 10 equiv of ethyl acrylate, toluene, 80 °C, 12 h; (v) 1 equiv of MMPP, 2 equiv of K_2CO_3, MeOH, rt, 1 h.

In conclusion, we have developed a new methodology for synthesizing trisubstituted and functionally dense tetrahydrofurans from readily available 1,5-dienes via a cooperative tandem process involving Cope rearrangement, OBoc deprotection, and oxy-Michael addition. The transformation occurs with good yields and diastereoselectivities within the current scope. These discoveries set the stage for numerous follow-up studies related to increasing the scope and diversity of the transformation, developing asymmetric variants, and finding unique opportunities for the transformation in complex natural product and pharmaceutical molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04306.

Supplemental information (PDF)

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Notes

The authors declare no competing financial interest.

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