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Formal [4 + 2] Cycloaddition of Donor−Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans

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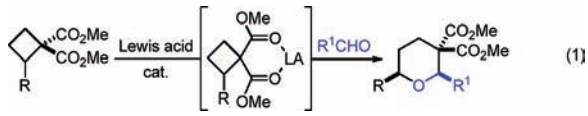
Donor−acceptor (D−A) cyclopropanes are an extensively studied class of molecules due to their unique reactivity profile.[1] Their value as synthetic building blocks has been demonstrated by the preparation of highly substituted carbo- and heterocyclic products via dipolar cycloaddition.[2] Despite the potential utility of homologous products, reports that extend this methodology to D−A cyclobutanes are rare.[3] This is particularly surprising since the strain energy of cyclobutane (26.3 kcal/mol) is similar to that of cyclopropane (27.5 kcal/mol),[4] suggesting that ring-opening reactions of cyclobutanes may be facile.

Aldehydes are competent dipolarophiles in Lewis acid-catalyzed [3 + 2] cycloadditions with D−A cyclopropanes, furnishing tetrahydrofuran derivatives in a stereoselective manner.[2d,5] Given this precedent, we sought to access tetrahydropyrans (THPs) through Lewis acid-catalyzed formal [4 + 2] cycloaddition of malonate-derived cyclobutanes and aldehydes (eq 1).[6] The resulting THP products are of interest because of their prevalence in biologically relevant and structurally interesting molecules.[7] To the best of our knowledge, there are currently no reports of 1,4-dipolar cycloadditions using D−A cyclobutanes possessing a carbon-based donor group. Herein we report the application of malonate-derived D−A cyclobutanes as synthetic equivalents for all-carbon 1,4-dipoles. Lewis acid-catalyzed formal [4 + 2] cycloaddition of these species with aldehydes provides an efficient route to *cis*-2,6-disubstituted tetrahydropyran products (eq 1).



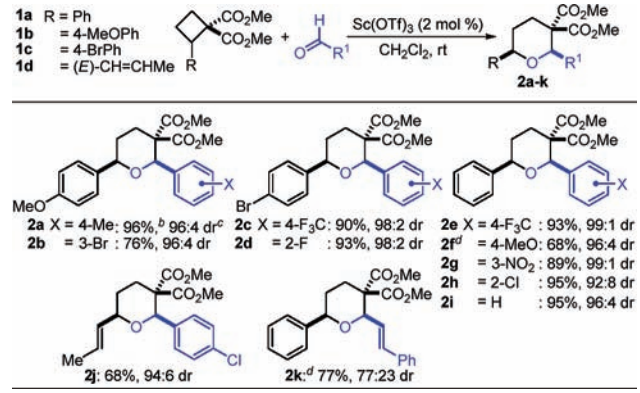
(1)

We began our studies by examining Lewis acid catalysts known to activate malonate-derived molecules via coordination to the dicarbonyl groups.[5b] Of those examined, $Hf(OTf)_4$ and $Sc(OTf)_3$ were the most effective catalysts, providing 2,6-*cis*-disubstituted THPs in high yield and diastereoselectivity. The potential for asymmetric catalysis prompted us to proceed with $Sc(OTf)_3$, as numerous enantioselective reactions have been reported using chiral Sc(III) Lewis acids.[8]

Several malonate-derived cyclobutanes underwent cycloaddition with cinnamyl and electronically diverse aryl aldehydes. $Sc(OTf)_3$ proved to be a highly active catalyst in this system, requiring only 2 mol % loading to afford the desired THP cycloadducts in high yield and stereoselectivity. In most cases, the 2,6-*cis*-diastereomer was formed in greater than 94:6 selectivity; only cinnamaldehyde and 2-chlorobenzaldehyde furnished products with a lower diastereomeric ratio (Table 1).

Attempts to extend the $Sc(OTf)_3$ system to aliphatic aldehydes were not successful. Our group recently reported that $MADNTf_2$ catalyzes dipolar cycloadditions of sensitive aldehydes while avoiding decomposition.[5d] We examined this complex as a possible alternative to $Sc(OTf)_3$ and found it to be effective in catalyzing the cycloaddition of linear, branched, and cyclic aliphatic aldehydes

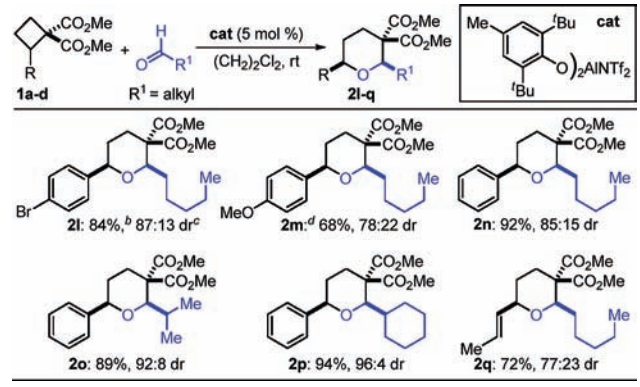
Table 1. $Sc(OTf)_3$-Catalyzed Formal [4 + 2] Cycloaddition of Cyclobutanes with Cinnamyl and Aryl Aldehydes[a]



[a] Cyclobutane (1.0 equiv), aldehyde (3.0 equiv), $Sc(OTf)_3$ (0.02 equiv), $[\mathbf{1}]_0$ = 0.25 M in CH_2Cl_2. [b] Average isolated yield of two independent trials. [c] dr was determined by ^1H NMR spectroscopy. [d] $Hf(OTf)_4$ (0.02 equiv) was used as the catalyst.

(Table 2). The diastereomeric ratio of the THP products varied, with branched and cyclic aldehydes providing the highest levels of diastereoselectivity (up to 96:4 dr).

Table 2. $MADNTf_2$-Catalyzed Formal [4 + 2] Cycloaddition of Cyclobutanes with Aliphatic Aldehydes[a]



[a] Cyclobutane (1.0 equiv), aldehyde (3.0 equiv), $MADNTf_2$ (0.05 equiv), $[\mathbf{1}]_0$ = 0.25 M in $(CH_2)_2Cl_2$. [b] Average isolated yield of two independent trials. [c] dr was determined by ^1H NMR spectroscopy. [d] Reaction temperature: 0 °C.

Since the cyclobutane starting materials can themselves arise from a Lewis acid-catalyzed cycloaddition of dimethyl 2,2-methylidene malonate (DMM) and a nucleophilic olefin,[9] we became interested in testing the notion that the title THP synthesis could be streamlined into a one-pot operation. A sequenced alkene/alkene [2 + 2] cycloaddition−cyclobutane/aldehyde [4 + 2] cycloaddition could in principle directly deliver THP products from simple linear starting materials with no processing of intermediates (eq 2).

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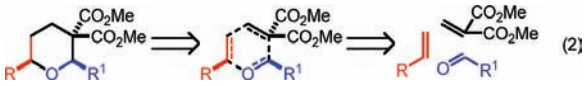
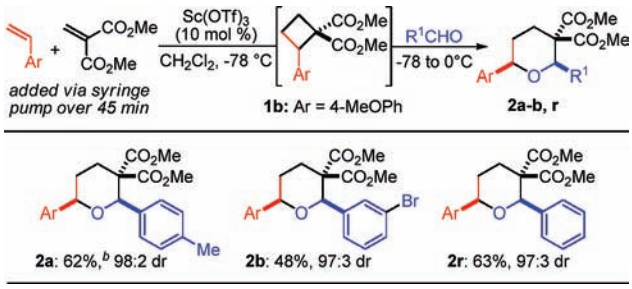


(2)

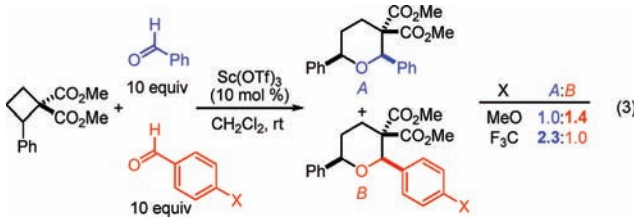
The initial [2 + 2] cycloaddition was achieved by slow addition of DMM and 4-methoxystyrene to a suspension of $Sc(OTf)_3$ in CH_2Cl_2 at −78 °C. Formation of cyclobutane **1b** was confirmed by thin-layer chromatography, and subsequent addition of the aldehyde resulted in the formation of the desired THP products (Table 3). This one-pot method furnishes THPs in greater overall yield than the two-step cyclobutane formation/[4 + 2] cycloaddition sequence. By circumventing cyclobutane isolation, we hope to expedite the exploration of these and related reagents in more complex reaction manifolds. Extension of this methodology to a diverse array of substrates is currently underway.

Table 3. Sc(OTf)$_3$-Catalyzed [[2 + 2] + 2] Cycloaddition of 4-Methoxystyrene, Dimethyl Methylidene Malonate, and Aldehydes[a]



[a] 4-methoxystyrene (1.3 equiv), DMM (1.0 equiv), aldehyde (3.0 equiv), [**1b**] = 0.15 M in CH_2Cl_2 at the time of aldehyde addition; see the Supporting Information for additional experimental details. [b] Average isolated yield of two independent trials.

In contrast to aldehyde cycloadditions with D−A cyclopropanes,[5b] electron-poor aldehydes react more rapidly with D−A cyclobutanes (e.g., formation of **2e** was complete in 4.5 h vs 6.5 h for **2i**; Table 1); however, a direct competition experiment between electronically differentiated aldehydes revealed that there is a preference for reaction with electron-rich aldehydes (eq 3). These seemingly conflicting results may indicate an increased propensity of electron-rich aldehydes to coordinate to the Sc(III) catalyst, causing a decrease in Lewis acidity [via $(RCHO)_nSc(OTf)_3$]. Thus, reaction times are not necessarily indicative of native aldehyde reactivity; the difference in reaction rates may be due to varying degrees of catalyst inhibition.



(3)

We subjected (+)-**1a** (98:2 er) to the standard reaction conditions using benzaldehyde as the dipolarophile and monitored the er's of **1a** and **2i** as functions of conversion (Figure 1). At 12% conversion, (−)-**2i** was formed with a 59.5:40.5 er while (+)-**1a** remained highly enriched (93:7 er). Moreover, while slow loss of cyclobutane enantioenrichment occurred over time, the product enantiomer ratio remained surprisingly constant. The electronic profiling (eq 3) appears to indicate that there is a nucleophilic substitution component[5] to the reaction, but Figure 1 reveals that the issue of chirality transfer is more ambiguous than for the analogous D−A cyclopropanes. Further study is necessary to elucidate the mechanism of this transformation.

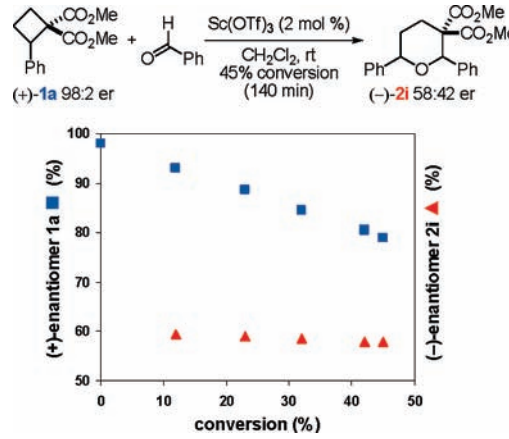


Figure 1. Stereochemical analysis of the Sc(OTf)$_3$-catalyzed formal [4 + 2] cycloaddition of (+)-**1a** and benzaldehyde.

We have developed a formal [4 + 2] cycloaddition of D−A cyclobutanes and aldehydes to furnish *cis*-2,6-disubstituted THP derivatives. We streamlined this methodology by developing a [[2 + 2] + 2] cycloaddition where in situ generation of the cyclobutane allows access to THPs directly from DMM, 4-methoxystyrene, and an aldehyde. Current work seeks to expand the scope of the [[2 + 2] + 2] and [4 + 2] cycloadditions to accommodate a range of substrates and provide access to other carbo- and heterocyclic molecules. Mechanistic studies and the development of an enantioselective variant are underway.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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