

10-6-2010

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Moustafa, Mahmoud M Abd Rabo; Stevens, Andrew C; Machin, Ben P; and Pagenkopf, Brian L, "Formal [4 + 2] cycloaddition of alkoxy-substituted donor-acceptor cyclobutanes and aldehydes catalyzed by Yb(OTf)₃." (2010). *Chemistry Publications*. 46.
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Formal [4+2] Cycloaddition of Alkoxy-Substituted Donor-Acceptor Cyclobutanes and Aldehydes Catalyzed by Yb(OTf)₃

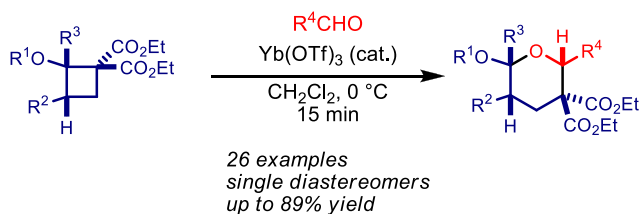
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Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



The cycloaddition between 2-alkoxy-1,1-cyclobutane diesters and aromatic, heteroaromatic or aliphatic aldehydes under Yb(OTf)₃ catalysis generates tetrahydropyrans in high yields with exclusive *cis*-stereochemistry.

Donor-acceptor (DA) cyclopropanes are now firmly established as effective partners in formal [3+2] dipolar cycloaddition reactions for the rapid assembly of highly functionalized molecules,¹ including precursors in natural product total syntheses.² In contrast, the analogous [4+2]

reactions of cyclobutanes are comparatively underdeveloped despite possessing a degree of bond strain similar to that of cyclopropanes.³ Examples of DA cyclobutane annulations date back to the early 1990's,^{4a} yet only recently did two independent reports by Johnson^{4c} and Christie and Pritchard^{4f} show that the [4+2] cycloaddition can be conducted with high

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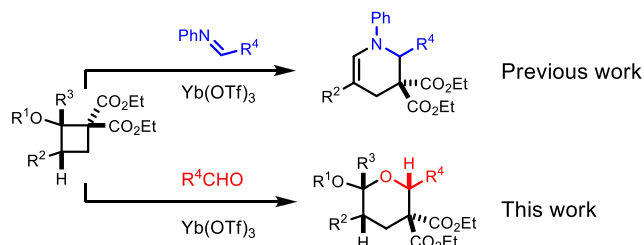
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diastereoselectivity by utilizing carbon-based activating groups.

We have been engaged in discovering reactions of alkoxy activated DA cyclopropane esters for some time, and our efforts to expand this chemistry to the related 2-alkoxy-1,1-cyclobutane diesters were rewarded with their facile conversion to functionalized piperidines by reaction with imines (Scheme 1).⁵ Herein we report a novel synthesis of fused bicyclic acetals in good yield and excellent diastereoselectivity by the formal [4 + 2] dipolar cycloaddition of alkoxy-substituted DA cyclobutanes with aromatic and aliphatic aldehydes.

Scheme 1. [4+2] Cycloadditions of alkoxy substituted DA cyclobutanes with imines and aldehydes



Our studies in this area began by examining the cycloaddition between cyclobutane **1** and benzaldehyde (Table 1). Much to our delight, upon treatment of a CH₂Cl₂ solution of cyclobutane **1** and benzaldehyde with Yb(OTf)₃ the fused acetal **2a** was obtained as a single diastereomer.⁶ Screening of reaction conditions revealed that temperature had little effect on the yield or diastereoselectivity (entries 1 – 3), and that the reaction could be effected with catalyst loadings as low as 0.5 mol % (entry 8). At 2 mol % catalyst the reactions were complete in 2 min when quickly heated in the microwave reactor and allowed to cool. For convenience, however, 10 mol % of Yb(OTf)₃ was used throughout as the reactions were complete in 15 min at 0 °C. It is important to note that only a single diastereomer was observed by NMR in this case, and in all subsequent examples.⁷

Having identified suitable reaction conditions, the scope of the transformation was explored (Table 2). Aromatic aldehydes were found to be excellent reaction partners regardless of whether they were electron rich (**2b**), halogenated (**2c**), electron poor (**2d,2e**), or conjugated (**2g–2i**). Heteroaromatic aldehydes also

underwent the cycloaddition (2-furfural, 2-thiofurfural, and indole-2-carboxaldehyde, entries **2j–2l**).

Table 1. Optimization of the [4+2] Cycloaddition between DA Cyclobutanes and Benzaldehyde

entry	conditions ^a				yield ^b (%)
	Yb(OTf) ₃ (mol %)	PhCHO (equiv)	temp (°C)	time (min)	
1	10	3.0	-40	120	70
2	10	3.0	0	15	84
3	10	3.0	20	15	78
5	10	1.1	0	15	78
6	10	0.9	0	15	68
7	2	1.1	0	45	74
8 ^c	0.5	1.1	25	18 h	79
9 ^d	2	1.1	60	2	76

^a Reactions were conducted on 0.4 mmol scale. ^b Isolated yield. ^c No reaction was observed at 0 °C. ^d Reaction was conducted in a microwave reactor.

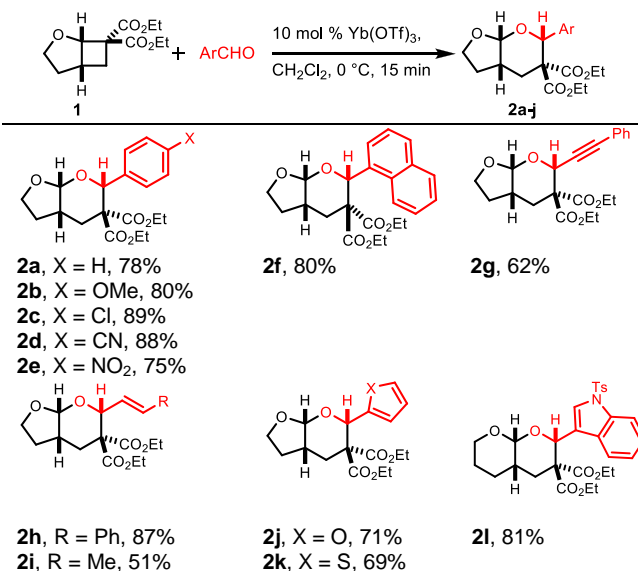


Figure 1. [4+2] Cycloaddition of DA cyclobutanes and Aromatic and Heteroaromatic Aldehydes

In Johnson's previous work stronger Lewis acids were required to coax aliphatic aldehydes to react with aryl-substituted cyclobutanes.^{4c} Gratifyingly, we discovered that the same mild Lewis acid, Yb(OTf)₃, effectively catalyzed the [4+2] cycloaddition between the alkoxy-substituted cyclobutanes and aliphatic aldehydes (Table 3). Examination of the reaction scope revealed that linear (dihydrocinnamaldehyde, **2m**, and hexanal, **2n**), branched

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(7) See the Supporting Information.

(isobutyraldehyde, **2o**), acetaldehyde (**2o**), and cyclopropyl aldehydes (**2q**) all underwent the cycloaddition to provide exclusively the *cis* bicyclic acetals.

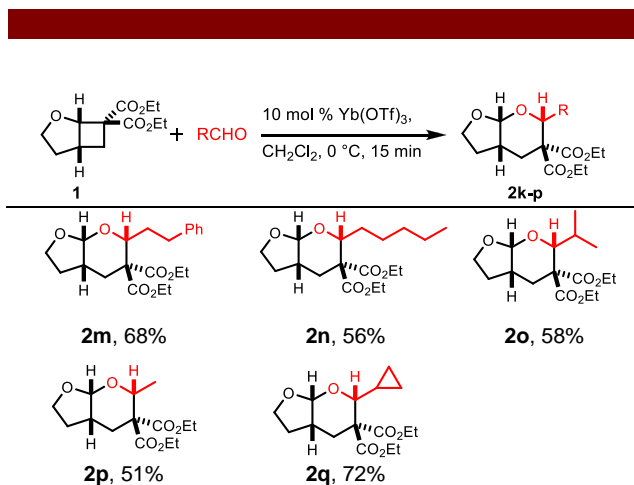
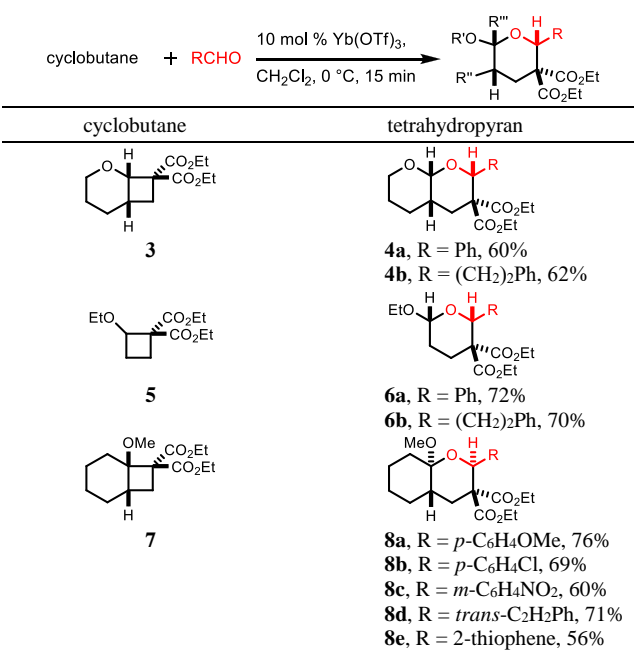


Figure 2. [4+2] Cycloaddition of DA cyclobutanes and Aliphatic Aldehydes

Lastly, several additional DA cyclobutanes were investigated (Table 4). Pyran-fused cyclobutane **3** underwent successful cycloaddition with both aromatic and aliphatic aldehydes to afford the all *cis*-products (**4a**, **4b**). The unsubstituted cyclobutane **5** also participated in the cycloaddition with aliphatic and aromatic aldehydes (**6a**, **6b**). Furthermore, the cyclohexyl-fused cyclobutane **7**

Table 4. Additional DA Cyclobutanes for the [4+2] Cycloaddition with Aldehydes



underwent cycloadditions with aromatic aldehydes to afford the fused ring systems **8a–8e**, each as a single diastereomer.

Herein, we reported an efficient $\text{Yb}(\text{OTf})_3$ catalyzed [4+2] dipolar cycloaddition between alkoxy-activated DA cyclobutanes and functionalized aldehydes to furnish fused acetals as single diastereomers. Efforts are currently underway to identify new dipolarophile partners and to develop an asymmetric variant of the current methodology.

Acknowledgement. We thank the University of Western Ontario and the National Sciences and Engineering Research Council of Canada (NSERC) for financial support. MM thanks the Egyptian Academy of Scientific Research and Technology for financial support. BPM (PGS D) thanks NSERC for a graduate fellowship.

Supporting Information Available: Detailed experimental procedures and copies of NMR spectra are included. This information is available free of charge via the Internet at <http://pubs.acs.org>.