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Ytterbium Triflate Catalyzed Synthesis of Alkoxy-Substituted Donor−Acceptor Cyclobutanes and Their Formal [4 + 2] Cycloaddition with Imines: Stereoselective Synthesis of Piperidines

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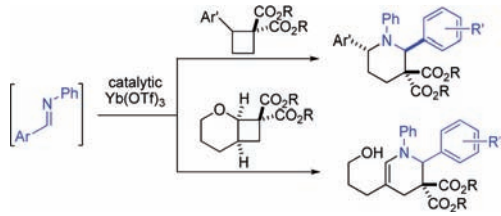
ABSTRACT



A new synthesis of 2-alkoxy-1,1-cyclobutane diesters and their first use in dipolar cycloadditions is reported. Both the formation of the donor−acceptor cyclobutanes and their subsequent annulation with in situ formed imines are catalyzed by $Yb(OTf)_3$. Cyclobutanes with carbon donor groups give piperidines with high *trans* stereoselectivity.

Because of their unique reactivity profiles and inherent strain energy, cyclopropanes and cyclobutanes have emerged as important pharmacophores and versatile building blocks in modern organic synthesis.[1,2] Lewis acid catalyzed dipolar cycloadditions involving donor−acceptor (DA) cyclopropanes are well documented and have been employed extensively for the preparation of different heterocycles,[3] including those leading to the synthesis of natural products.[4] The ring fission can occur via an S_N2-type mechanism, by ring opening and subsequent electrophilic trapping, rearrangement, and ring contraction or expansion.[5] In contrast, reports that extend similar synthetic transformations to DA cyclobutanes are comparatively rare (Scheme 1). In this regard, aldehydes have been found to undergo [4 + 2] cycloadditions with DA cyclobutanes, which was first demonstrated by Saigo in 1991.[6] More recently, Matsuo has extended this work to cyclobutanones,[7] and Christie and Pritchard[8] and Johnson[9] have demonstrated the effective use

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(3) For DA cyclopropane reviews, see: (a) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31. (b) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73–135. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (d) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (e) De Simone, F.; Waser, J. *Synthesis* **2009**, *20*, 3353–3374. For selected examples, see: (f) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312–6316. (g) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023–3026. (h) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631–9634. (i) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689–692. (j) Moustafa, M. M. A. R.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 3168–3171.

(4) For a review, see: (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev* **2009**, *38*, 3051–3060. For selected examples: (b) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469. (c) Bajtos, B.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, 1072–1077. (d) Jung, M. E.; Chang, J. J. *Org. Lett.* **2010**, *12*, 2962–2965.

(5) (a) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251–10253. (b) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597–8599. (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650.

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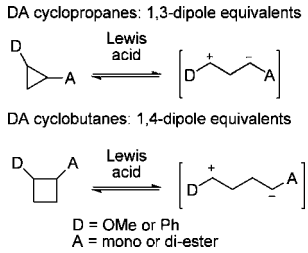
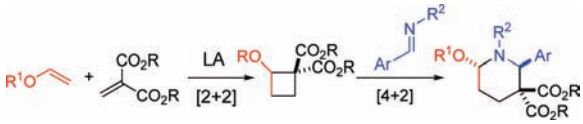
Scheme 1. Cyclopropanes and Cyclobutanes as Dipolar Equivalents



of carbon-based activating groups. Although Saigo obtained a mixture of stereoisomers with his amine-activated cyclobutanes, subsequent reports have disclosed that ring opening and cycloaddition occurred smoothly to afford tetrahydropyrans in moderate to excellent diastereoselectivity.[7−9]

Imines have been utilized by us[3d] and others[10] as dipolarophiles in Lewis acid catalyzed [3 + 2] cycloadditions with DA cyclopropanes to furnish pyrrolidine derivatives in a stereoselective manner. At the onset of this project there were no reports that extend this to DA cyclobutanes,[11] and thus we sought to access the piperidine nucleus through a Lewis acid catalyzed formal [4 + 2] cycloaddition of appropriately substituted DA cyclobutanes and imines (Scheme 2). Given our ongoing interest in alkoxy-substituted DA

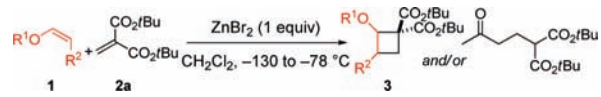
Scheme 2. Formal [4 + 2] Cycloaddition of DA Cyclobutanes and Imines



cyclopropanes,[3h,j,12] the analogous cyclobutanes were chosen as substrates for the exploration of this chemistry. Herein we report a modified procedure for the synthesis of DA cyclobutanes that are activated by an alkoxy donor group and geminal diester withdrawing groups. Furthermore, the subsequent application of these cyclobutanes for the first time in imine dipolar cycloadditions to afford highly substituted piperidine and piperideine derivatives is also reported.

The 2-alkoxy-1,1-cyclobutane diesters are interesting latent 1,4-dipole equivalents that can be prepared from enol ethers and methylidene malonates. The preparation of this class of cyclobutanes was reported by Roberts in 1986 (Scheme 3),[13]

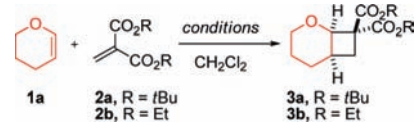
Scheme 3. $ZnBr_2$-Mediated Synthesis of DA Cyclobutanes



yet it was somewhat surprising that the use of these cyclobutanes in dipolar cycloadditions had not been realized prior to this work.

Duplication of the conditions reported by Roberts for the reaction of dihydropyran with di-*tert*-butyl methylidene malonate in our hands gave a poor yield (39% Table 1, entry

Table 1. Optimizing Cyclobutane Formation



entry	R	catalyst	temp (°C)	yield (%)[a]
1	*t*Bu	1 equiv of $ZnBr_2$	−130 to −78	39[b]
2	Et	1 equiv of $ZnBr_2$	−130 to −78	17[b]
3	Et	1 equiv of $ZnCl_2$	−130 to −78	0[c]
4	Et	1 equiv of TMSOTf	−78	0[c]
5	Et	10 mol % $Sc(OTf)_3$	−78	78
6	Et	10 mol % $Yb(OTf)_3$	−78	84

[a] Isolated yield. [b] Product contaminated by ring-opened and polymeric substance. [c] Polymeric substances observed.

1), and isolation of the cyclobutane was complicated by both considerable byproducts and the stoichiometric $ZnBr_2$. More problematic, however, was our inability to extend this methodology to the more readily available and reactive diethyl methylidene malonate, and only trace amounts of the desired cyclobutane were observed along with a complex mixture of polymerization and ring-opened byproducts (entry 2). A variety of other Lewis acids were then screened, and $Sc(OTf)_3$ and $Yb(OTf)_3$ quickly emerged as competent catalysts, with $Yb(OTf)_3$ being the catalyst of choice as a

(6) Shimada, S.; Saigo, K.; Nakamura, H.; Hasegawa, M. *Chem. Lett.* **1991**, *20*, 1149–1152.

(7) (a) Matsuo, J.-I.; Sasaki, S.; Tanaka, H.; Ishibashi, H. J. *J. Am. Chem. Soc.* **2008**, *130*, 11600–11601. (b) Matsuo, J.-I.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822–3825. (c) Matsuo, J.-I.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 5831–5833.

(8) Allart, E. A.; Christie, S. D. R.; Pritchard, G. J.; Elsegood, M. R. *Chem. Commun.* **2009**, 7339–7341.

(9) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202–14203.

(10) (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186–3189. (b) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028–4029. (c) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147–3150. (d) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242–8244. (e) Xing, S.; Pan, W.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3215–3218.

(11) While this manuscript was in preparation, Matsuo reported a [4 + 2] cycloaddition between cyclobutanones and imines. See: Matsuo, J.-I.; Okado, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3266–3268.

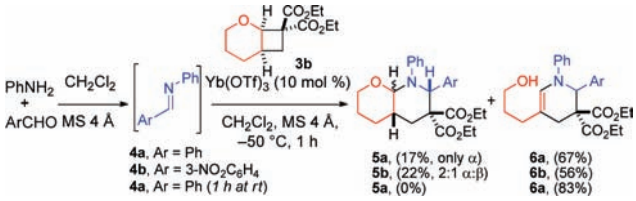
(12) (a) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099–5101. (b) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157–159. (c) Bajtos, B.; Pagenkopf, B. L. *Org. Lett.* **2009**, *11*, 2780–2783.

(13) (a) Baar, M. R.; Ballesteros, P.; Roberts, B. W. *Tetrahedron Lett.* **1986**, *27*, 2083–2086. (b) Mangelinckx, S.; Vermaut, B.; Roland, V.; De Kimpe, N. *Synlett* **2008**, *17*, 2697–2701. (c) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686–12687.

result of slightly higher yields and lower catalyst cost (entries 5 and 6). The use of catalytic $Yb(OTf)_3$ rather than stoichiometric $ZnBr_2$ made the reactions operationally much simpler to perform (up to 12 g scale), requiring only a simple filtration to provide the cyclobutane in high purity and yield.

Having identified $Yb(OTf)_3$ as a superior catalyst for the synthesis of alkoxy-substituted DA cyclobutanes, the feasibility of using it to catalyze the [4 + 2] cycloaddition of these cyclobutanes with imines was explored.[14] To our delight, upon exposure of cyclobutane **3b** and imine **4a** (prepared *in situ*) to catalytic $Yb(OTf)_3$ at −50 °C, the bicyclic piperidine **5a** as a single diastereomer and piperideine **6a** were observed (Scheme 4). On the other hand,

Scheme 4. Formal [4 + 2] Cycloaddition of Alkoxy-Substituted DA Cyclobutanes and Imines



reaction of imine **4b** gave cycloadduct **5b** as a 2:1 mixture of diastereomers as well as piperideine **6b**. The relative stereochemistry of *trans*-**5b** and *cis*-**5b** was assigned on the basis of NOE interactions and ultimately confirmed by single-crystal X-ray analysis (Figure 1). In order to isolate only

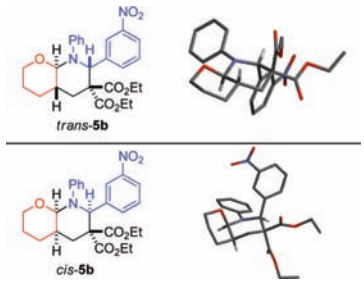


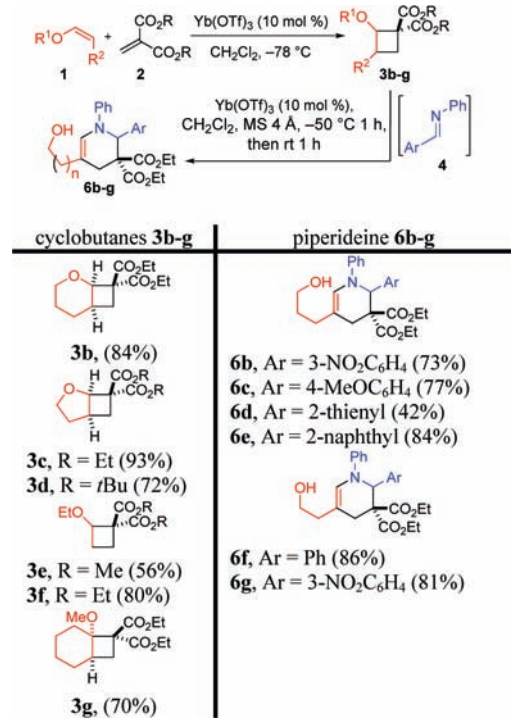
Figure 1. Single crystal X-ray structures of *trans*-**5b** and *cis*-**5b**.

the piperideine product, the reaction was warmed to room temperature for 1 h after consumption of the cyclobutane, to drive the product from the piperidine **5a** to the piperideine **6a**.

Having demonstrated that both the cyclobutane and piperideine syntheses were successful, the scope of both reactions was explored, and the results are summarized in Scheme 5. In regard to the cyclobutane formation, the range

(14) (a) Marshman, R. W. *Aldrichimica Acta* **1995**, *28*, 77–84. (b) Shibasaki, M.; Matsunaga, S.; Kumagai, N. *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, 2008; Vol. 2, pp 635−710.

Scheme 5. $Yb(OTf)_3$-Catalyzed Synthesis of DA Cyclobutanes and Piperideines

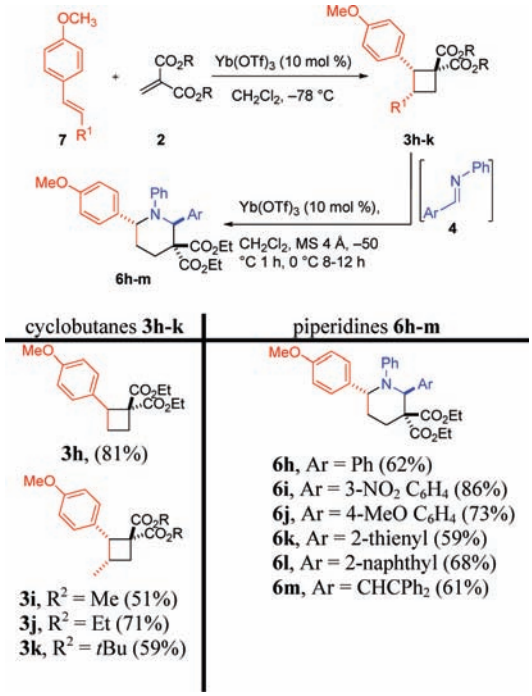


of compatible methylidene malonates has been expanded beyond di-*tert*-butyl methylidene malonate to now encompass the more reactive diethyl and dimethyl methylidene malonates. The range of enol ethers that participated in the cycloaddition was quite broad with cyclic, acyclic, and higher-substitution patterns being tolerated (**3b**−**g**). Regarding the [4 + 2] reaction, electron-rich or electron-deficient aromatic and heteroaromatic imines were found to participate in the cycloaddition to form piperideines **6b**−**g** in moderate to excellent yield. Unfortunately, the more reactive cyclobutanes **3e**−**g** gave complex mixtures when subjected to the same reaction conditions.

Next, the ability of $Yb(OTf)_3$ to catalyze the synthesis of cyclobutanes with carbon-donating groups was explored (Scheme 6). The [2 + 2] reaction of methylidene malonates with *p*-vinyl anisole and anethole gave cyclobutanes **3h**−**k** as single diastereomers. Unfortunately, no reaction was observed with styrene, and only polymerization products were observed. In contrast to the cyclobutanes activated by alkyl ethers, the cycloaddition of imines with cyclobutane **3h** required higher temperatures and longer reaction times (0 °C for 10 h vs −50 °C for 1 h). Nonetheless, the cycloaddition provided pentasubstituted piperidines with electron-deficient or -rich aromatic, cinnamyl, and heteroaromatic imines. All of the cycloadducts **6h**−**m** were obtained in moderate to good yields and exclusively as the *trans*-diastereomer. The cyclobutanes **3i**−**k** failed to react productively with imines, and only decomposition was observed.

Finally, the possibility of carrying out the cyclobutane formation/imine cycloaddition reaction sequence in one

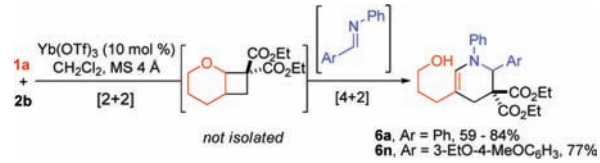
Scheme 6. Synthesis of Cyclobutanes and Pentasubstituted Piperidines



reaction vessel was examined (Scheme 7). When a CH_2Cl_2 solution of imine was added to a concentrated solution of the in situ formed cyclobutane, the cycloadduct was obtained in yields ranging from 59% to 84%. While isolating the cyclobutane is advantageous for building chemical libraries, obviating cyclobutane isolation with a one-vessel three-step reaction sequence can be a practical option for large scale target-specific synthesis.[15]

(15) For a one-pot procedure, methylidene malonate should be freshly prepared.

Scheme 7. One-Pot, Multistep Synthesis of Piperideines



In summary, a new and reliable procedure for the preparation of alkoxy-substituted DA cyclobutanes has been developed, and these cyclobutanes have been shown for the first time to undergo dipolar cycloadditions. They undergo a formal [4 + 2] cycloaddition with imines to afford highly substituted piperidines and piperideines. Additionally, a one-pot procedure for cyclobutane synthesis and subsequent imine cycloaddition has been demonstrated. Efforts are currently underway to develop new cycloaddition reactions utilizing these cyclobutanes.

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Supporting Information Available: General experimental procedures and characterization of all new compounds and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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