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Stereoselective Aldol-Type Cyclization Reaction Mediated by Dibutylboron Triflate/Diisopropylethylamine

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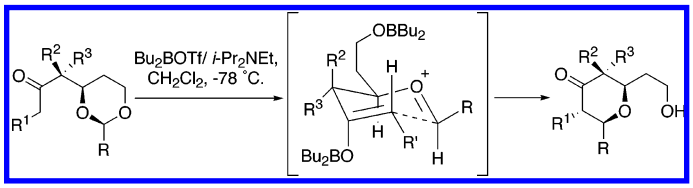
ABSTRACT



Dibutylboron triflate/diisopropylethylamine mediated aldol-type cyclization provides an expedient route for the stereoselective synthesis of cyclic ethers in a single step. The method is highly efficient for the stereoselective synthesis of 4-*cis*-tetrahydropyranones. The reaction is proposed to proceed via an S_N1-type mechanism through a chair-like transition state, in which both substituents occupy equatorial positions.

The aldol addition reaction is undoubtedly among the most powerful methods for the formation of carbon−carbon bonds.[1] A number of new methods, including enantioselective and catalytic processes, have been developed.[1a,b] Despite these developments, however, the aldol-type reaction between a carbonyl compound and an acetal has remained less explored. In 1974, Mukaiyama discovered the Ti(IV)-catalyzed reaction of silyl enol ethers with acetals to produce β-alkoxy carbonyl compounds (eq 1).[2] The process,[3,4] which requires preformation of the silyl enol ethers, can also be accomplished in a single step by in situ generation of corresponding enol ethers (eq 2).[5,6] Nonetheless, the im-

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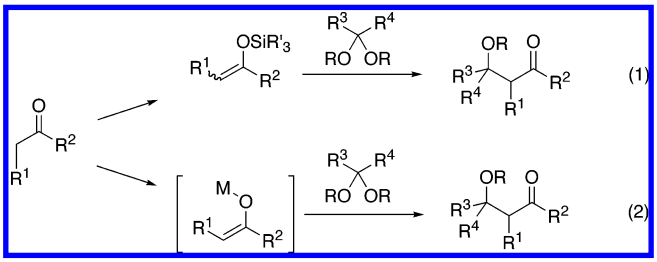
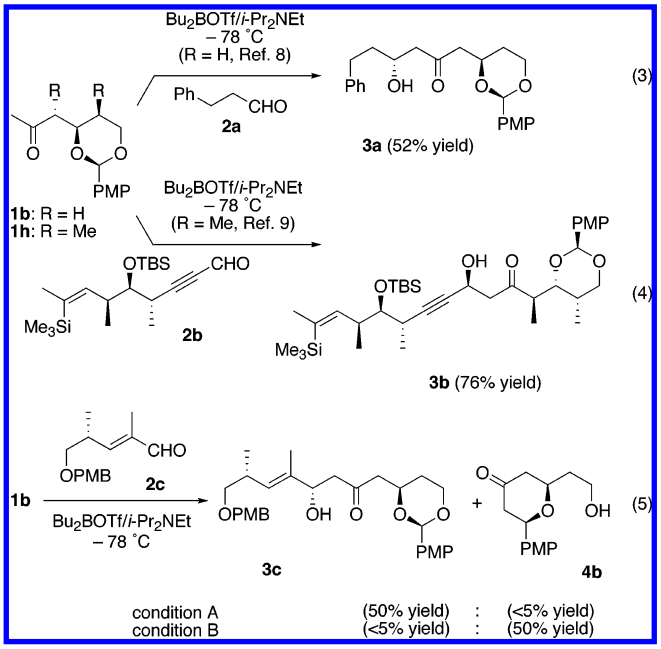
proved processes are still limited in scope, particularly for the intramolecular aldol-type reactions. Here, we report that an intramolecular aldol-type reaction of carbonyl compounds with a resident acetal or ketal can be accomplished in a single step using dibutylboron triflate and diisopropylethylamine ($Bu_2BOTf/i\text{-}Pr_2NEt$).[7] The usefulness of this approach is demonstrated by the stereoselective syntheses of five- to seven-membered 4-keto-cyclic ethers, in general, and 4-*cis*-tetrahydropyranone derivatives, in particular.



Under the conditions developed by Evans,[8] the aldol reaction of compound **1b** (PMP = *p*-methoxyphenyl) with aldehyde **2a** is mediated by $Bu_2BOTf/i\text{-}Pr_2NEt$ to afford the corresponding aldol product **3a** in moderate yield (eq 3). The keto-acetal compounds, such as **1b** or **1h,** have often been used as donors in aldol reactions, because the acetal can coordinate electron-deficient elements to increase the stereoselectivity of the process. For example, using Evans' conditions, Panek et al. reported the aldol reaction of **1h** with aldehyde **2b** to afford the aldol product, **3b**, (eq 4) in 76% yield.[9] We also prepared the aldol product **3c** in 50% yield from a $Bu_2BOTf/i\text{-}Pr_2NEt$-mediated aldol reaction of **1b** with aldehyde **2c** (eq 5) enroute to the synthesis of a natural product.[10]



On the other hand, compounds **1b**, **1h**, and analogous molecules are also poised to form cyclic ethers by $Bu_2BOTf/i\text{-}Pr_2NEt$-mediated intramolecular aldol-type reaction. Formation of the cyclic ethers as byproducts could explain why the aldol products were obtained in reduced yields. The observation by Panek et al. that the yield of product **3b** is lower on a larger scale also supports this assumption.[9] Moreover, syntheses of cyclic ethers using silyl enol ether derivatives of carbonyl compounds possessing a resident acetal group as in **1b** or **1h** have been previously reported.[3d] These facts encouraged us to reinvestigate the $Bu_2BOTf/i\text{-}Pr_2NEt$-mediated aldol-type reaction of **1b**.

We found that under Evans' conditions, the reaction constantly produced a minor byproduct (<5% yield), which was identified as a 4-*cis*-tetrahydropyrone derivative, **4b** (eq 5). A slight modification in Evans' procedure, however, completely changed the course of reaction, and compound **4b** was formed as the major product. Thus, for the aldol reaction of **1b** and **2c**, the boron enolate of **1b** was produced by slow addition of Bu_2BOTf (condition A) to a mixture of **1b** and $i\text{-}Pr_2NEt$ in CH_2Cl_2 at −78 °C,[11] whereas for the production of **4b**, Bu_2BOTf was added at a considerably faster rate (condition B).[11] Addition of aldehyde **2c** to the latter reaction mixture barely gave any aldol product (<5%), and the major product **4b** was obtained in >50% yield. These findings guided us to further explore the $Bu_2BOTf/i\text{-}Pr_2NEt$-mediated intramolecular reaction of various keto-acetals (**1a**−**l**). The results are summarized in Tables 1 and 2.

Under the optimized conditions, Bu_2BOTf (1.2 equiv) was added rapidly to the mixture of a substrate (1 equiv) and $i\text{-}Pr_2NEt$ (1.2 equiv) in CH_2Cl_2 at −78 °C (Method C).[12] In general, a higher molar ratio of Bu_2BOTf (1.5 equiv, Method D) was required for aliphatic acetals. As shown in Table 1, the reaction was quite efficient, and the cyclized products were obtained in up to 94% yield and high stereoselectivity (>98%) as observed by ^1H NMR spectroscopy. In fact, in all cases, only 4-*cis*-tetrahydropyranone derivatives[13] were detected. The *cis* configuration of the 4-tetrahydropyranone was not influenced by the substitution pattern. Thus, compounds **1c** and **1g**, which possess an *anti* and a *syn* stereochemistry, respectively, afforded *cis*-products **4c** and **4g** (entries 3 and 7, Table 1). Similarly, compounds **1h** and **1l** (entries 8 and 12, Table 1), which possess an alkyl group at C-5 of the dioxane ring, do not affect the *cis* configuration of the products irrespective of the relative configuration of C-4 and C-5 substituents.

The reaction was also applicable to ketal substrates, such as **5a** and **5b**, which provided the corresponding spiro-

(7) $Bu_2BOTf/i\text{-}Pr_2NEt$ also mediates intermolecular aldol-type coupling of ketones with acetals and ketals; see: Li, L.-S.; Das, S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 127−130.

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(11) Under condition A, Bu_2BOTf (1.05 mL, 1 M solution in CH_2Cl_2) was added over a period of 10 min to a solution of the ketone (1 mmol) and $i\text{-}Pr_2NEt$ (1.1 mmol) in 5 mL of CH_2Cl_2 at −78 °C. Under condition B, Bu_2BOTf was added within 1 min, which might increase the local concentration of Bu_2BOTf.

(12) Various other known reaction conditions, which mediate the intramolecular aldol-type reaction in a single step, as well as replacing Bu_2BOTf with $TiCl_4$, Et_2AlCl, and BF_3Et_2O, did not produce the desired products in our case.

Table 1. Synthesis of Cyclic Ethers by Bu_2BOTf/ *i*-Pr_2NEt-Mediated Aldol-Type Reaction[a]

entry	reactant	product	yield	method
1	**1a**: R = Ph (racemic)	**4a**	76%	C
2	**1b**: R = PMP (racemic)	**4b**	72%	C
3	**1c**: R = PMP	**4c**	82%	C
4	**1d**: R = -CH:CHPh	**4d**	55%	D
5	**1e**: R = $-CH_2CH_2Ph$	**4e**	85%	D
6	**1f**: R = $-CH_2CH_2OBn$	**4f**	78%	D
7	**1g**	**4g**	80%	C
8	**1h**	**4h**	94%	C
9	**1i**	**4i**	90%	C
10	**1j**: R = Et	**4j**	82%	D
11	**1k**: R = $-CH_2CH$:CH_2	**4k**	78%	D
12	**1l**	**4l**	94%	C

[a] Method C: substrate (1 equiv), Bu_2BOTf (1.2 equiv), and *i*-Pr_2NEt (1.2 equiv) in CH_2Cl_2 at −78 °C. Method D: substrate (1 equiv), Bu_2BOTf (1.5 equiv), and *i*-Pr_2NEt (1.2 equiv) in CH_2Cl_2 at −78 °C.

Table 2. Synthesis of Cyclic Ethers by Bu_2BOTf/ *i*-Pr_2NEt-Mediated Aldol-Type Reaction (Cont'd)

entry	reactant	product (s)	yield[a]
1	**1m** (racemic)	**4m**	40%
2	**1n** (racemic)	**4n**	35%
3	**5a**	**6a**	45%
4	**5b**	**6b**	90%
5	**7a**: (racemic, R = H)	**8a** (48%)	**9a** (32%)
6	**7b**: (racemic, R = Me)	**8b** (75%)	**9b** (0%)

[a] Method C was used; see Table 1.

pyranone derivatives, **6a** and **6b**, respectively (entries 3 and 4, Table 2). The higher homolog, **7a**, of the methyl ketone also reacted smoothly to produce a 3:2 mixture of seven- and five-membered cyclic ethers, **8a** and **9a** (entry 5, Table 2). This ratio is in agreement with the preferential deprotonation of the methyl hydrogen in comparison to the internal methylene hydrogens.[14] Similar regioselectivity was also obtained when the intermolecular aldol-type reaction was carried out using butanone and an acetal.[7] The regioselectivity of the reaction could be controlled when a substituent was installed at the α′-position of the carbonyl function. Thus, the substrate **7b** produced exclusively the seven-membered cyclic ether, **8b** (entry 6, Table 2).

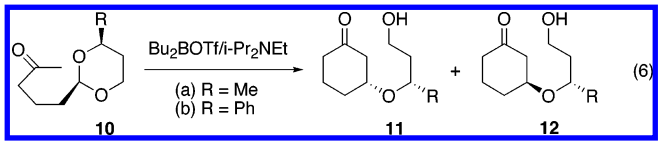
Interestingly, the reaction is highly selective for the methyl ketones. In our preliminary investigation, we found that the corresponding ethyl ketones (**1m, n**) also undergo the intramolecular coupling reaction, albeit less efficiently in comparison to the analogous methyl ketones. Nevertheless, the only isolatable products (**4m, n**) were proven to be highly substituted stereochemically pure 4-*cis*-tetrahydropyranone derivatives (entries 1 and 2, Table 2).

Analogous to the Ti(IV)-catalyzed reaction,[3d,15] both S_N1 and S_N2 mechanisms can be considered for the Bu_2BOTf-

(13) The relative configurations of all compounds were determined by the analysis of their $^1H-^1H$ COSY, NOE, or NOESY spectra.

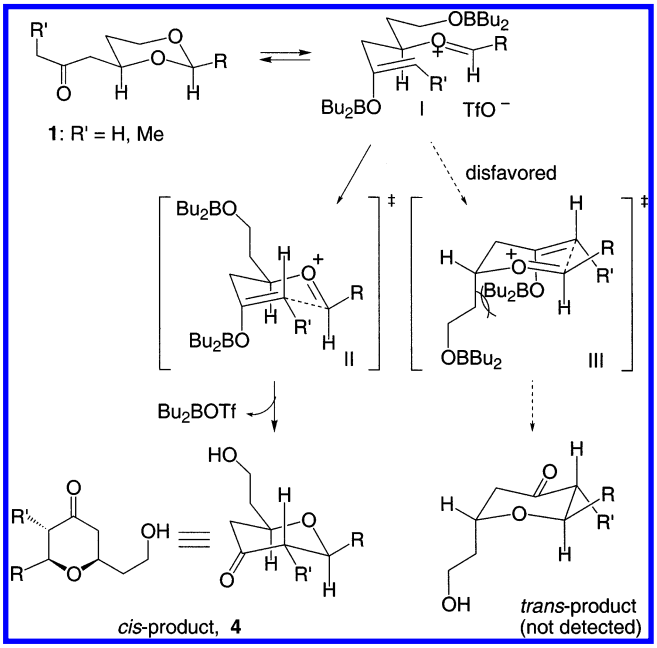
(14) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174−178.

mediated cyclization reaction. However, the intramolecular S_N2 mechanism, which could account for the exclusive formation of *cis* product, is ruled out on the following grounds. First, it would require a sterically very congested conformer in that the two substituents would occupy the 1,3-diaxial positions. Second, the Bu_2BOTf-mediated reaction of the enantiomerically pure substrates **10** provided two diastereomeric products, **11** and **12**, which is only possible by an S_N1 pathway (eq 6).



The high selectivity in the formation of the *cis* product by an S_N1 mechanism, on the other hand, can be explained as shown in Scheme 1. Presumably, the reaction proceeds via the chair-like transition structure **II**, which is derived from intermediate **I**. It should be noted that the Bu_2BOTf/*i*-Pr_2NEt-mediated reaction involves the same array of reacting sp^2-hybridized centers as in the enolate Claisen rearrangement. Thus, the structure **II** is analogous to the proposed transition states for this reaction.[16] A selective production of compounds **4m** and **4n** from the corresponding substrates also provide evidence for the chairlike transition state **II**, assuming that the Z-enolate is formed in the enolization step. The transition state **II** then collapses to afford the *cis* product. Formation of the corresponding *trans* product, in contrast, would require a high-energy transition state **III** possessing the hydroxyethyl substituent and dibutylboryloxy group in 1,3-diaxial positions.

Scheme 1



In conclusion, the Bu_2BOTf/*i*-Pr_2NEt-mediated aldol-type cyclization provides a novel process for the syntheses of cyclic ethers in a single step. The process is particularly useful for the stereoselective formation of 4-*cis*-tetrahydropyranones. Evidently, the reaction involves an S_N1-type mechanism via a chairlike transition state, in that both substituents occupy equatorial positions. Investigations of the scope and limitations of the new reaction are currently underway.

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Supporting Information Available: Typical experimental procedure and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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