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Efficient One-Step Aldol-Type Reaction of Ketones with Acetals and Ketals Mediated by Dibutylboron Triflate/ Diisopropylethyl Amine

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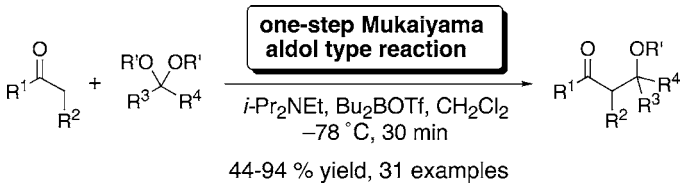
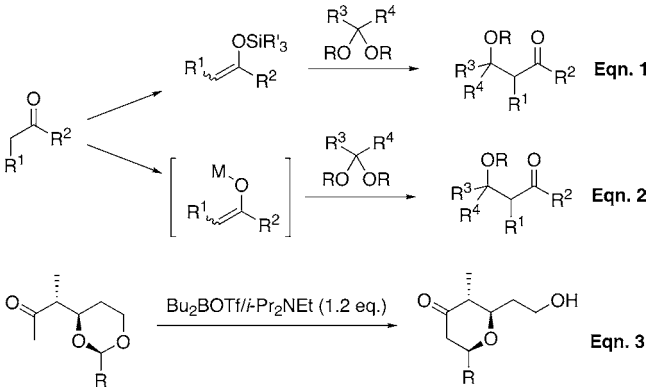
ABSTRACT



A highly efficient one-step Mukaiyama aldol-type reaction has been developed for the synthesis of *β*-alkoxy carbonyl compounds starting from ketones and acetals/ketals. The reaction is mediated by a combination of Bu_2BOTf and *i*-Pr_2NEt affording the products in high yields. Formation of the two possible diastereoisomers of the *β*-alkoxy ketones from the chiral acetals shows that the condensation takes place by an S_N1 mechanism, involving prior opening of the acetal to an oxonium ion.

Mukaiyama aldol-type reaction of a silyl enol ether with an acetal or ketal providing the corresponding *β*-alkoxy carbonyl compound[1] has been a subject of extensive investigations.[2,3] The reaction requires the preformation of silyl enol ether from corresponding carbonyl compounds, which then undergoes a Lewis acid-catalyzed coupling to the acetal or ketal in a separate step (eq 1). In a modified process, both the enol ether formation and the subsequent addition to an acetal or ketal have also been realized in a single-step (eq 2).[4] In this communication, we describe a new single-step method using dibutylboron triflate/diisopropylethylamine (Bu_2BOTf/*i*-Pr_2NEt) for the Mukaiyama aldol-type reaction between ketones and acetals (or ketals).



Recently, we have described the Bu_2BOTf/*i*-Pr_2NEt-mediated intramolecular cyclization of keto-acetal compounds to afford the cyclic ethers in a single step (eq 3).[5] In this process, the dibutylboron enolate of ketone reacted with the resident acetal, which was activated by Bu_2BOTf. To check the feasibility of this one-step process for the analogous

(1) (a) Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15−16. (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817 and references therein.

(2) (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248−3249. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899−3910. (c) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259−4275.

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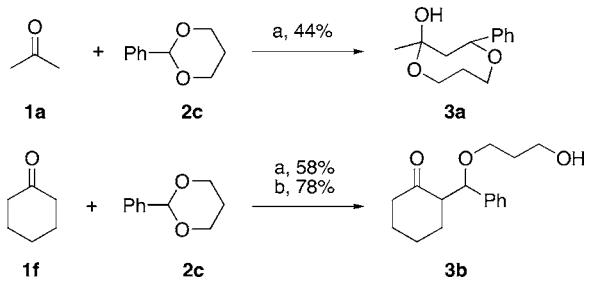
intermolecular coupling reaction (eq 2, M = BBu_2), initially, we examined the condensation of acetone (**1a**) and hexanone (**1f**) with acetal **2c**, using a procedure similar to that used in the intramolecular reaction (procedure A).[6] Fortunately, the reaction proceeded smoothly to afford the desired products, **3a**, as its semiketal form, and **3b** in 44 and 58% yields, respectively (Scheme 1). Compound **3b** was obtained as a

Scheme 1[a]



[a] Key: (a) **1a** (or **1f**), **2c**, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, then Bu_2BOTf (procedure A); (b) **1f**, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, Bu_2BOTf, 0.5 h, then **2c** (procedure B).

separable mixture of *syn* and *anti* isomers (56:44). Interestingly, when other boron-Lewis acids such as BCl_3, *c*-Hex_2BCl, or 9-BBNOTf[7] were used, none of them provided the desired product. Next, we varied the reaction conditions, including the mode of addition of the substrates. In an optimized process (procedure B),[8] we preformed the dibutyl boron-enolate of **1f** by treatment with Bu_2BOTf/*i*-Pr_2NEt at −78 °C for 30 min, to complete the enolization,[9] and then a solution of acetal **2c** was added slowly. Using a workup procedure similar to procedure A led to a cleaner reaction, affording **3b** in 78% yield.

The scope of the reaction was explored using a series of ketones, acetals, and ketals. Condensation of various ketones, including acetophenone (**1b**), propiophenone (**1c**), 2-methylbutanone (**1d**), cyclopentanone (**1e**), and cyclohexanone (**1f**), with acetals (**2a**−**g**) was examined using procedure B. In all cases, the desired β-alkoxy ketones were obtained in good yields (Table 1). The substituted cyclic acetal, **2b**, underwent highly regioselective acetal opening to produce the β-alkoxy ketone (**3d)** with a primary alcohol (entry 2, Table 1). The isomeric secondary alcohol was not detected. The reaction slightly favored the formation of *syn* isomer (entries 8−13, Table 1). The highest *syn* selectivity was obtained when propiophenone was used as the ketone counterpart (entry 9, Table 1). We next investigated reactions of ketones (**1b**,**c**) with various ketals (**4a**−**g**) using procedure B, which also gave satisfactory results (Table 2). Functionalized ketals such as **4f** and **4g** also afforded the desired products with high yields.

To check the regioselectivity of this reaction with respect to ketone, two sets of experiments were conducted. In one experiment, 2-butanone (**1g**) and acetal **2e** were used (Scheme 2A). The reaction of **1g** with **2e** (Scheme 2A) using Bu_2BOTf/*i*-Pr_2NEt in CH_2Cl_2 afforded the two regioisomeric compounds, **6** and **7**, in a nearly 1.4:1 ratio. Whereas no change in regioselectivity of the reaction was noticed when the reaction was conducted in ether, a minor improvement in the stereoselectivity of *syn*-**7** over *anti*-**7** was realized. In another experiment (Scheme 2B), condensation of **1b** with *n*-butyl THP ether was investigated, which predominantly gave the open chain product (**8a**, 73% yield) and a minor amount of tetrahydropyran derivative (**8b**, 7%). Use of 3-methyl-2-butanone, on the other hand, exclusively formed the open chain product (**9a**, 72% yield). Therefore, this method also provides an easy protocol to give 5-alkoxy-7-keto-alkan-1-ols (such as **8a** and **9a**).

To extend the scope of the reaction, we briefly studied the Bu_2BOTf/*i*-Pr_2NEt-mediated coupling of ketone and esters with trialkyl ortho esters and acetals, respectively (Scheme 3). As shown, ketone **1c** reacted with triethyl orthoformate to afford the corresponding β-keto acetal, **11a**. However, under similar conditions, the reaction did not take

(3) (a) Ishitani, H.; Iwamoto, M. *Tetrahedron Lett.* **2003**, *44*, 299−301. (b) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45−48. (c) Trehan, A.; Vij, A.; Walia, M.; Kaur, G.; Verma, R. D.; Trehan, S. *Tetrahedron Lett.* **1993**, *34*, 7335−7338. (d) Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* **1998**, 1249−1251 and references therein. (e) Ooi, T.; Tayama, E.; Takahashi, M.; Maruoka, K.; *Tetrahedron Lett.* **1997**, *38*, 7043−7046. (f) Kamata, M.; Yokoyama, Y.; Karasawa, N.; Kato, M.; Hasegawa, E. *Tetrahedron Lett.* **1996**, *37*, 3483−3486. (g) Kamata, M.; Nagai, S.; Kato, M.; Hasegawa, E. *Tetrahedron Lett.* **1996**, *37*, 7779−7782. (h) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759−1762. (i) Mukaiyama, T.; Iwakiri, H. *Chem. Lett.* **1985**, 1363−1366. (j) Murakami, M.; Minamikawa, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 1051−1052. (k) Sakurai, H.; Sasaki, K.; Hosomi, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3195−3196. (l) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1983**, 405−408. (m) Jung, M. E.; Hogan, K. T. *Tetrahedron Lett.* **1988**, *29*, 6199−6202. (n) Kawai, M.; Onaka, M.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237−1245.

(4) For direct formation of silyl enol ether, see: Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1993**, *58*, 2647−2649. For direct generation of Titanium enolates, see: (a) Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covel, J. A.; McLaw, M. D.; Krishnamurthy, D.; Cee, V. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 231−234. (b) Cosp, A.; Romea, P.; Talavera, P.; Urpi, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org.* Lett. **2001**, *3*, 615−617. (c) Cosp, A.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **2001**, *42*, 4629−4631. (d) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216. For BF_3·OEt_2-mediated reaction, see: Hashigaki, K.; Yoshioka, S.; Yamato, M. *Synthesis* **1986**, 1004−1007.

(5) For the Bu_2BOTf/*i*-Pr_2NEt-mediated intramolecular one-step aldol-type coupling of ketones with acetals and ketals, see: Das, S.; Li, L.-S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 123−126.

(6) **Procedure A.** To a solution of acetone (1 mmol) and acetal 2 (1 mmol) in 5 mL of CH_2Cl_2 at −78 °C was added *i*-Pr_2NEt (1 mmol), followed by a rapid addition of Bu_2BOTf (1.2 mmol). The resulting reaction mixture was stirred at −78 °C for 30 min, and then buffer (pH = 7.4, 1.2 mL), methanol (1.2 mL), and H_2O_2 (0.4 mL) were added. Stirring was continued for 1 h at room temperature, and then the mixture was worked up using ether. The organic layer was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Solvents were removed, and the crude product was purified by column chromatography on silica gel.

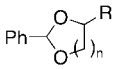
(7) It has been reported that 9-BBNOTf could catalyze the aldol-type reaction between silyl enol ether and acetals. Ishihara, K.; Yamamoto, H.; Heathcock, C. H. *Tetrahedron Lett.* **1989**, *30*, 1825−1828.

(8) **Procedure B.** Bu_2BOTf (1.0 M, 1.3 mL, 1.3 mmol) was added dropwise to a solution of ketone (1 mmol) and *i*-Pr_2NEt (0.2 mL, 1.15 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C under argon. The resulting mixture was stirred for 30 min, and then a solution of an acetal (1 mmol) in dry CH_2Cl_2 (3 mL) was added slowly. Stirring was continued for 30 min, and then the reaction was quenched by addition of PBS buffer (1.3 mL), methanol (1.3 mL) and H_2O_2 (0.5 mL). The resulting mixture was warmed to room temperature and stirred for 1 hour, extracted with ether, washed with brine and dried over $MgSO_4$. The crude product was purified by chromatography on silica gel column.

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

Table 1. $Bu_2BOTf/i\text{-}Pr_2NEt$-Mediated Aldol-Type Condensation of Ketones with Acetals

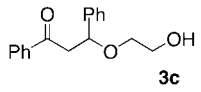
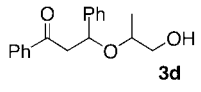
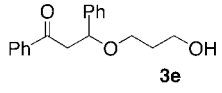
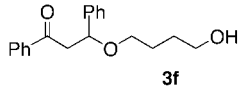
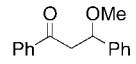
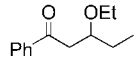
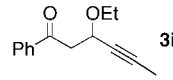
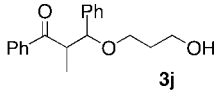
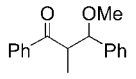
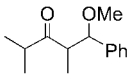
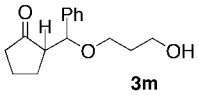
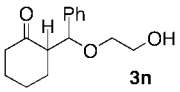
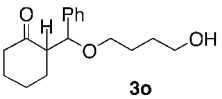
1b: R = Ph, R' = H
1c: R = Ph, R' = Me
1d: R = Me_2CH, R' = Me
1e: R,R' = $-(CH_2)_3-$



2a: n = 1, R = H
2b: n = 1, R = Me
2d: n = 3, R = H

2e

2f: R =Et, R' = H
2g: R = MeCC, R' = H

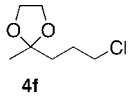
entry	ketone	acetal/ ketal	major product/ number	yield (%)[a] (*syn*:*anti*)[b]
1	**1b**	**2a**	 **3c**	72
2	**1b**	**2b**	 **3d**	78
3	**1b**	**2c**	 **3e**	83
4	**1b**	**2d**	 **3f**	82
5	**1b**	**2e**	 **3g**	88
6	**1b**	**2f**	 **3h**	90[c]
7	**1b**	**2g**	 **3i**	82
8	**1c**	**2c**	 **3j**	85 (4:1)
9	**1c**	**2e**	 **3k**	91[c] (6:1)
10	**1d**	**2e**	 **3l**	89 (3:1)
11	**1e**	**2c**	 **3m**	86 (2:1)
12	**1f**	**2a**	 **3n**	64 (14:11)
13	**1f**	**2d**	 **3o**	72 (2:1)

[a] Isolated yield. [b] Ratio of *syn* and *anti* isomers was determined by ^{1}HNMR, and the relative configuration was determined by comparing the corresponding NMR data with the literature. [c] Performed with 1.2 mol of ketone.

Table 2. $Bu_2BOTf/i\text{-}Pr_2NEt$-Mediated Aldol-Type Condensation between Ketones and Ketals

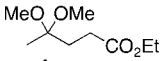
1f

4b: R = Me
4c: R = $-(CH_2)_2-$
4d: R = $-CHMeCH_2-$
4e: R = $-(CH_2)_3-$

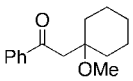
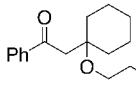
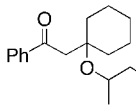
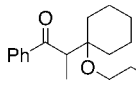
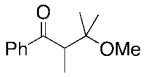
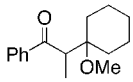
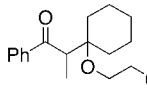
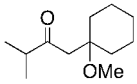
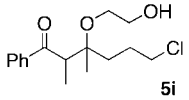
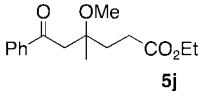
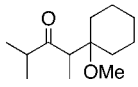


4f

4a



4g

entry	ketone	ketal	major product/ number	yield (%)[a] (*syn*:*anti*)[b]
1	**1b**	**4b**	 **5a**	94[c]
2	**1b**	**4c**	 **5b**	90
3	**1b**	**4d**	 **5c**	80
4	**1b**	**4e**	 **5d**	82
5	**1c**	**4a**	 **5e**	68
6	**1c**	**4b**	 **5f**	87
7	**1c**	**4c**	 **5g**	90
8	**1c**	**4b**	 **5h**	76
9	**1c**	**4f**	 **5i**	48 (3.3:1)
10	**1c**	**4g**	 **5j**	84
11	**1e**	**4b**	 **5k**	64

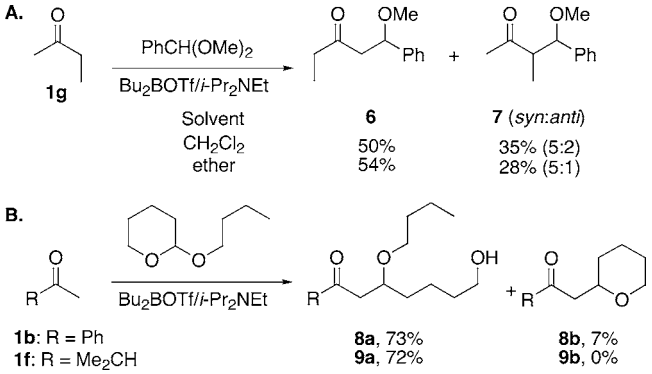
[a] Isolated yield. [b] Ratio of *syn* and *anti* isomers was determined by ^{1}HNMR, and the relative configuration was determined by comparing the corresponding NMR data with the literature. [c] Performed with 1.2 mol of ketone.

place when triethyl orthoacetate was used. Esters such as methylpropionate (**10**), on the other hand, reacted efficiently with **2c** and **4b** to afford **12a** and **12b**, respectively.[10]

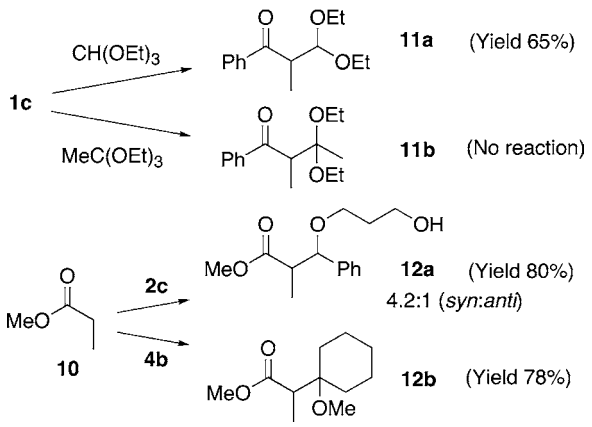
The $Bu_2BOTf/i\text{-}Pr_2NEt$-mediated intermolecular aldol-type reaction of a ketone with acetals ketals can be rationalized

(10) Enolization was carried out at −78 °C for 2 h before the acetal or ketal was added.

Scheme 2



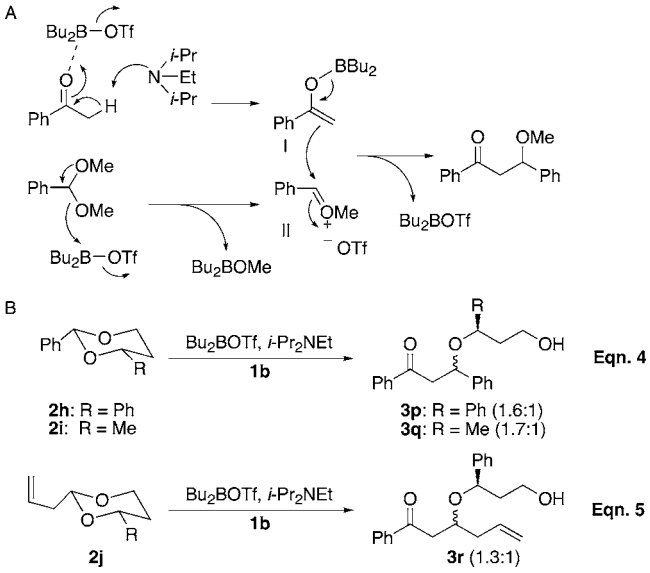
Scheme 3



as shown in Scheme 4A. Analogous to the $TiCl_4$-mediated reaction of silyl enol ether with acetal,[11] the reaction takes place via an S_N1 mechanism. Presumably, boron enolate (**I**) of a ketone reacts with the intermediate **II** that is generated by the Bu_2BOTf-catalyzed activation to afford the product. In the overall process, more than 1 equiv of Bu_2BOTf is required for both the enolization of a ketone and activation of an acetal or ketal. That the reaction takes place by the

(11) (a) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916. (b) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *11*, 9258−9260. (c) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock. C. H. *J. Org. Chem.* **1990**, *55*, 6107−6115.

Scheme 4



S_N1 mechanism, was evident from an examination of the reaction of **1b** with the chiral acetals, **2h**−**j**. The products obtained from these acetals were mixtures of both diastereomers of **3p**, **3q**, and **3r**, respectively (eqs 4 and 5). Since only primary alkoxy is the leaving group, only an S_N1 pathway could explain the formation of the diastereoisomeric mixtures of the products. The S_N2 pathway, on the other hand, would provide only one stereoisomer in each case.

In conclusion, we have developed a highly efficient one-step intermolecular aldol-type reaction of ketones and acetals or ketals using Bu_2BOTf/*i*-Pr_2NEt. Evidence has been provided to support the S_N1-type mechanism for this one-pot, operationally simpler method. Further development of this process to carry out the reaction in a highly stereoselective manner is in progress.

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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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