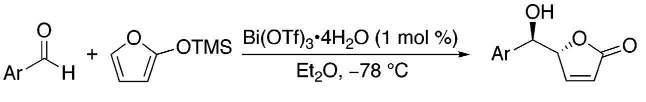
Diastereoselective Mukaiyama Aldol Reaction of 2-(Trimethylsilyloxy)furan Catalyzed by Bismuth Triflate

Thierry Ollevier,* Jean-Emmanuel Bouchard, and
Valerie Desyroy

Département de chimie, Université Laval, Québec,
Canada G1K 7P4

thierry.ollevier@chm.ulaval.ca

Received September 23, 2007



syn/anti up to 98:2

We have developed an efficient vinylogous Mukaiyama aldol reaction of 2-(trimethylsilyloxy)furan with various aromatic aldehydes mediated by bismuth triflate in low catalyst loading (1 mol %). The reaction proceeds rapidly and affords the corresponding 5-(hydroxy(aryl)methyl)furan-2(5*H*)-ones in high yields with good to very good diastereoselectivities (dr up to >98:2). Such selectivities, albeit previously reported with other Lewis acids, could this time be achieved with a much lower catalyst loading. 5-(Hydroxy(alkyl)methyl)furan-2(5*H*)-ones derived from ketones could also be obtained with good diastereoselectivities.

The aldol reaction is well recognized as one of the most powerful synthetic tools for a fast carbon−carbon bond connection. This route provides rapid access to β-hydroxy carbonyl compounds, which have attracted much synthetic efforts and enjoyed widespread use in natural products and bioactive molecules synthesis.[1] The Mukaiyama aldol reaction and its variants are probably the most notable achievements that have been made in the field by focusing on the addition of enolsilanes to aldehydes in the presence of catalytic amounts of Lewis acids.[2]

The vinylogous Mukaiyama aldol reaction rapidly provides 5-(hydroxy(aryl)methyl)furan-2(5*H*)-ones by addition of the γ carbon of a dienolate on a carbonyl framework.[3] Over past years, some elegant enantioselective versions of this reaction have been described, using catalytic amounts of various chiral mediators.[4] Recently, synthetic methods involving numerous lanthanide triflates have been reported.[5] High catalytic activity, moisture, and air tolerance make lanthanide triflates attractive catalysts. However, their cost often restricts their utilization.

To our knowledge, all racemic examples up to now of vinylogous Mukaiyama aldol with silyloxyfurans have employed Lewis acids such as $SnCl_4$, $ZnCl_2$, $TiCl_4$, $BF_3{\cdot}OEt_2$, $SiCl_4$, or silyl triflates.[6] Yet, moisture sensitivity of these catalysts and the high cost of some of them often restrain their use. In addition, all reported racemic reactions were involving the Lewis acid in large amounts or even in stoichiometric amount.[6] In view of the versatile synthetic utility of 5-(hydroxy(aryl)methyl)furan-2(5*H*)-ones and 5-(hydroxy(alkyl)methyl)furan-2(5*H*)-ones, for example, for the preparation of γ-alkylidene-butenolides,[7] there is clearly a need for practical and efficient conditions that involve a bench-stable catalyst, used in very low loading.

As a part of our ongoing interest in bismuth(III)-catalyzed aldol condensation reactions,[8] we report herein a bismuth(III)-catalyzed vinylogous Mukaiyama aldol reaction. Aldols are obtained efficiently in the presence of 1 mol % of $Bi(OTf)_3{\cdot}4H_2O$. Bismuth compounds have attracted recent attention due to their low toxicity, low cost, and high stability.[9] Bismuth salts have been reported as catalysts for opening of epoxides,[10] Mannich-type reactions,[11] formation and deprotec-

---

(1) Shiina, I. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 105−166.

(2) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011−1014. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509. For reviews of catalytic Mukaiyama aldol reactions: (c) Mukaiyama, T.; Matsuo, J.-i. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 127−160. (d) Carreira, E. M. in *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. 3, pp 997−1065.

(3) For a recent review, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972.

(4) (a) For a review on enantioselective vinylogous Mukaiyama aldol, see: Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682−4698. (b) Matsuoka, Y.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, *32*, 584−585. (c) Szlozek, M.; Figadère, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799−1801. (d) Szlozek, M.; Franck, X.; Figadère, B.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 5169−5172. (e) Palombi, L.; Acocella, M. R.; Celenta, N.; Massa, A.; Villano, R.; Scettri A. *Tetrahedron: Asymmetry* **2006**, *17*, 3300−3303. (f) For a recent organocatalytic approach, see: Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 8−9.

(5) (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227−2302. (b) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165−167. (c) Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* **1993**, 371−373. (d) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625−1628.

(6) For reviews on vinylogous aldol reaction with silyloxyfurans, see: (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333−1350. (b) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607−626. For original reports: (c) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037−4040. (d) Acocella, M. R.; De Rosa, M.; Massa, A.; Palombi, L.; Villano, R.; Scettri A. *Tetrahedron* **2005**, *61*, 4091−4097. (e) Kong, K.; Romo, D. *Org. Lett.* **2006**, *8*, 2909−2912. (f) Yoshii, E.; Koizumi, T.; Kitatsuji, E.; Kawazoe, T.; Kaneko, T. *Heterocycles* **1976**, *4*, 1663−1668. (g) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897−7900. (h) López, C. S.; Álvarez, R.; Vaz, B.; Faza, O. N.; de Lera, A. R. *J. Org. Chem.* **2005**, *70*, 3654−3659. (i) Sarma, K. D.; Zhang, J.; Curran, T. T. *J. Org. Chem.* **2007**, *72*, 3311−3318. (j) For a recent organocatalytic approach, see: De Rosa, M.; Citro, L.; Soriente, A. *Tetrahedron Lett.* **2006**, *47*, 8507−8510.

(7) (a) von der Ohe, F.; Brückner, R. *New J. Chem.* **2000**, *24*, 659−669. (b) von der Ohe, F.; Brückner, R. *Tetrahedron Lett.* **1998**, *39*, 1909−1910. (c) Görth, F. C.; Umland, A.; Brückner, R. *Eur. J. Org. Chem.* **1998**, 1055−1062. (d) Görth, F. C.; Brückner, R. *Synthesis* **1999**, 1520−1528.

(8) (a) Ollevier, T.; Desyroy, V.; Debailleul, B.; Vaur, S. *Eur. J. Org. Chem.* **2005**, 4971−4973. (b) Ollevier, T.; Desyroy, V.; Nadeau, E. *ARKIVOC* **2007**, *x*, 10−20.

(9) (a) *Organobismuth Chemistry*; Suzuki, H.; Matano, Y., Eds.; Elsevier: Amsterdam, 2001. (b) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517−2532. (c) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373−8397.

(10) (a) Ogawa, C.; Azoulay, S.; Kobayashi, S. *Heterocycles* **2005**, *66*, 201−206. (b) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49−52. (c) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2002**, *43*, 7891−7893.

10.1021/jo702085p CCC: $40.75 © 2008 American Chemical Society
Published on Web 12/11/2007

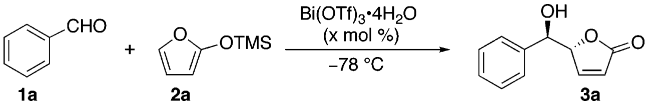
tion of acetals,[12] Friedel−Crafts reactions,[13] Fries and Claisen rearrangements,[14] and Sakurai reactions.[15] Bi(OTf)$_3$ is particularly attractive because it is commercially available or can be easily prepared from commercially available starting materials.[16]

Bismuth triflate has been reported by Dubac as an efficient catalyst for the Mukaiyama aldol reaction with silyl enol ethers[17] and was recently used with a chiral ligand as reported by Kobayashi in an elegant enantioselective method.[18] The Bi(OTf)$_3$·4H$_2$O-catalyzed vinylogous Mukaiyama aldol reaction has been studied only with dioxinone-derived silyl dienol ethers and proceeded regioselectively (γ-attack only).[19] In regard to the importance of a diastereoselective synthesis of 5-(hydroxy(aryl)methyl)furan-2(5*H*)-ones, the Bi(OTf)$_3$·4H$_2$O-catalyzed-vinylogous Mukaiyama aldol has been investigated with 2-(trimethylsilyloxy)furans and various carbonyl compounds.

Initially, various solvents were screened for the Mukaiyama aldol reaction of benzaldehyde **1a** with 2-(trimethylsilyloxy)furan **2a** in the presence of 1 mol % of Bi(OTf)$_3$·4H$_2$O. Among the various polar solvents tested, acetonitrile, dichloromethane, and tetrahydrofuran afforded good yields of the expected product although with moderate diastereoselectivity (Table 1, entries 1−3). The most suitable solvent was found to be diethyl ether. 5-(Hydroxy(phenyl)methyl)furan-2(5*H*)-one **3a** was obtained in best yield and diastereoselectivity (Table 1, entry 4). With further optimization of the reaction conditions, we found that a lower catalyst loading (0.5 mol %) did not allow the reaction to proceed (Table 1, compare entry 5 and entry 4), although a higher catalyst loading (5 mol %) afforded the product with close diastereoselectivity but decreased yield (Table 1, compare entry 6 and entry 4).

Encouraged by our results in the reaction with benzaldehyde **1a**, we studied the scope and limitations of this reaction with respect to the aldehyde employed in the process. The results are summarized in Table 2. The addition of 2-(trimethylsilyloxy)furan **2a** to various aldehydes **1** proceeded readily employing Bi(OTf)$_3$·4H$_2$O as the Lewis acid (Scheme 2, Table 2). Generally, excellent yields of 5-(hydroxy(aryl)methyl)furan-2(5*H*)-ones were obtained with 1.2 equiv of 2-(trimethylsilyloxy)furan **2a** and 1 mol % of Bi(OTf)$_3$·4H$_2$O at −78 °C in Et$_2$O. Heteromatic aldehydes as well as an α,β-unsaturated aldehyde reacted smoothly to give the corresponding substituted

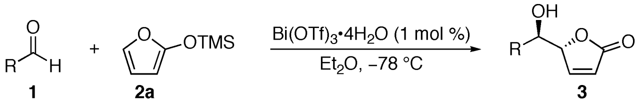
TABLE 1. Vinylogous Bi(OTf)$_3$-catalyzed Mukaiyama Aldol Reactions Involving Benzaldehyde 1a and 2-(Trimethylsilyloxy)furan 2a[a]

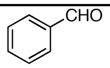
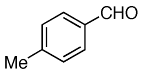
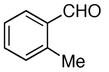
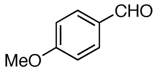
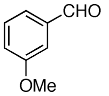
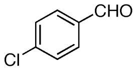
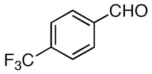
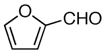
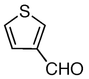
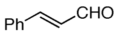


entry	solvent	x mol %	dr (*syn/anti*)[b]	yield **3a** (%)[c]
1	MeCN	1	60:40	75[d]
2	CH$_2$Cl$_2$	1	87:13	81
3	THF	1	89:11	87
4	Et$_2$O	1	94:6	91
5	Et$_2$O	0.5	nd	−
6	Et$_2$O	5	93:7	80

[a] Conditions: benzaldehyde **1a** (1.0 equiv), 2-(trimethylsilyloxy)furan **2a** (1.2 equiv), Bi(OTf)$_3$·4H$_2$O (x mol %). [b] Determined from ^{1}H NMR of the crude reaction mixture. [c] Isolated yield. [d] Reaction was run at 0 °C.

TABLE 2. Vinylogous Bi(OTf)$_3$-Catalyzed Mukaiyama Aldol Reactions Involving Various Aromatic or Unsaturated Aldehydes 1 with 2-(Trimethylsilyloxy)furan 2a[a]



entry	aldehyde **1**	time (h)	dr (*syn/anti*)[b]	product	yield **3** (%)[c]
1		0.5	94:6	**3a**	91
2		1	94:6	**3b**	90
3		0.25	94:6	**3c**	90
4		0.5	90:10	**3d**	84
5		2	93:7	**3e**	81[d]
6		0.5	93:7	**3f**	90
7		0.5	> 98:2	**3g**	65[d,e]
8		0.7	72:28	**3h**	86[d]
9		0.25	80:20	**3i**	85
10		0.15	70:30	**3j**	80

[a] Conditions: aldehyde **1** (1.0 equiv), 2-(trimethylsilyloxy)furan **2a** (1.2 equiv), Bi(OTf)$_3$·4H$_2$O (1 mol %), Et$_2$O, −78 °C. [b] Determined from ^{1}H NMR of the crude reaction mixture. [c] Isolated yield. [d] Warmed to −45 °C. [e] Using 2 mol % of Bi(OTf)$_3$·4H$_2$O.

---

(11) (a) Ollevier, T.; Nadeau, E. *Org. Biomol. Chem.* **2007**, *5*, 3126−3134. (b) Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292−9295. (c) Ollevier, T.; Nadeau, E.; Eguillon, J.-C. *Adv. Synth. Catal.* **2006**, *348*, 2080−2084. (d) Ollevier, T.; Nadeau, E. *Synlett* **2006**, 219−222. (e) Ollevier, T.; Nadeau, E.; Guay-Bégin, A.-A. *Tetrahedron Lett.* **2006**, *47*, 8351−8354.

(12) (a) Leonard, N. M.; Oswald, M. C.; Freiberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 5202−5207. (b) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027−1030.

(13) (a) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181−200. (b) Desmurs, J. R.; Labrouillère, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871−8874. (c) Répichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J. R. *Eur. J. Org. Chem.* **1998**, 2743−2746.

(14) (a) Ollevier, T.; Desyroy, V.; Asim, M.; Brochu, M.-C. *Synlett* **2004**, 2794−2796. (b) Ollevier, T.; Mwene-Mbeja, T. M. *Synthesis* **2006**, 3963−3966. (c) Ollevier, T.; Mwene-Mbeja, T. M. *Tetrahedron Lett.* **2006**, *47*, 4051−4055.

(15) (a) Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215−7218. (b) Wieland, L. C.; Zerth, H. M.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 4597−4600. (c) Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, *44*, 9003−9005. (d) Leroy, B.; Markó, I. E. *Org. Lett.* **2002**, *4*, 47−50. (e) Sreekanth, P.; Park, J. K.; Kim, J. W.; Hyeon, T.; Kim, B. M. *Catal. Lett.* **2004**, *96*, 201−204. (f) Choudary, B. M; Chidara, S.; Raja Sekhar, C. V. *Synlett* **2002**, 1694−1696. (g) Ollevier, T.; Li, Z. *Org. Biomol. Chem.* **2006**, *4*, 4440−4443.

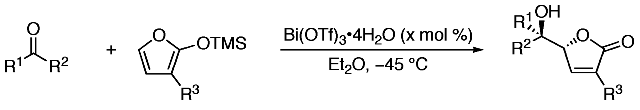
(16) (a) Répichet, S.; Zwick, A.; Vendier, L.; Le Roux, C.; Dubac, J. *Tetrahedron Lett.* **2002**, *43*, 993−995. (b) Labrouillère, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J.; Desmurs, J. R. *Tetrahedron Lett.* **1999**, *40*, 285−286. (c) Peyronneau, M.; Arrondo, C.; Vendier, L.; Roques, N.; Le Roux, C. *J. Mol. Cat. A* **2004**, *211*, 89−91. (d) Bi(OTf)$_3$·4H$_2$O has been prepared from Bi$_2$O$_3$ according to ref 16a.

(17) Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* **1998**, 1249−1251.

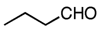
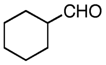
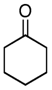
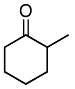
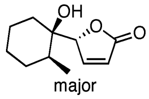
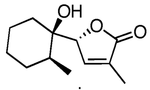
(18) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. *Org. Lett.* **2005**, *7*, 4729−4731.

(19) Ollevier, T.; Desyroy, V.; Catrinescu, C.; Wischert, R. *Tetrahedron Lett.* **2006**, *47*, 9089−9092.

TABLE 3. Vinylogous Bi(OTf)$_3$-Catalyzed Mukaiyama Aldol Reactions Involving Various Aliphatic Aldehydes and Ketones with 2-(Trimethylsilyloxy)furan 2[a]



1 **2a** (R = H) **2b** (R = Me) **3**

entry	carbonyl compound **1**	R^3	x mol %	dr[b]	yield **3** (%)
1		H	5	70:30[c]	30 (**3k**)[d]
2		H	2	75:25[c]	25 (**3l**)[d]
3		H	5	na	75 (**3m**)
4		H	5	82:7:7:4	65 (**3n**)  major diastereoisomer[e]
5		Me	5	73:10:9:8	78 (**3n'**)[f]  major diastereoisomer

[a] Conditions: carbonyl compound **1** (1.0 equiv), 2-(trimethylsilyloxy)-furan **2a** or 3-methyl-2-(trimethylsilyloxy)furan **2b** (1.5 equiv), Bi(OTf)$_3$•4H$_2$O (x mol %), Et$_2$O, −45 °C, 0.5-−3 h. [b] Determined from ^{1}H NMR of the crude reaction mixture. [c] *Syn/anti* ratio. [d] Isolated yield. [e] Relative stereochemistry of **3n** was tentatively assigned by comparison of ^{1}H NMR with **3n′** of known relative stereochemistry.[6e] [f] Reaction was stirred for an additional hour at 0 °C.

furan-2(5*H*)-one **3** in high yield (Table 2, entries 8−10). Electron-rich *p*-, or *m*-methoxybenzaldehyde led to the desired product in good yield (Table 2, entries 4 and 5). The reaction worked well with a variety of aldehydes including those bearing an electron-withdrawing group, and the expected product **3** was obtained with excellent yield (Table 2, entry 6), except *p*-trifluoromethyl derivative **1g** leading to a moderate yield of product due to low conversion even at higher temperature (Table 2, entry 7). Such high diastereoselectivity (90:10 up to >98:2) had only been previously reported with aromatic aldehydes usually requiring high catalyst loadings or even stoichiometric amounts of a Lewis acid (1 equiv of SiCl$_4$, 2-(trimethylsilyloxy)-furan, benzaldehyde, dr = 75:25;[6d] 0.5 equiv of TBSOTf, 3-benzyl-2-(*tert*-butyldimethylsilyloxy)-4-isopropylfuran, 4-(*tert*-butyldimethylsilyloxy)-3,5-dichlorobenzaldehyde, dr = 73 :27;[6g] 1 equiv of BF$_3$•OEt$_2$, 3-bromo-2-(trimethylsilyloxy)furan, benzaldehyde, 72%, dr >99:1).[6h] In addition, heteroaromatic aldehydes such as furfural or thiophene 3-carboxaldehyde can also serve as a substrate in this reaction, giving the corresponding aldol in a very good yield (Table 2, entries 8 and 9). Conjugated aldehydes were good substrates as well (Table 2, entry 10).

Our conditions were then applied to aliphatic aldehydes (Table 3). When *n*-butyraldehyde or cyclohexylcarboxaldehyde were reacted, the corresponding aldols **3k** and **3l** were obtained in moderate diastereoselectivity and poor yield due to low conversion (Table 3, entries 1 and 2).

At this point, we were curious to verify if our methodology could be extended to ketones. It was surprising to find very limited number of examples in the literature for the construction of tertiary alcohols by nucleophilic addition on unsymmetrical ketones.[6e,20] Clearly, this widely studied approach for aldehydes has not led to similar levels of success when employed with ketones. Apparently, low reactivity and low selectivity is the origin of this disparity.[6c,21] Romo's recent study does show that high diastereoselectivities could be obtained with ketones when choosing 3-methyl-2-(*tert*-butyldimethylsilyloxy)furan; however, high quantities of Lewis acids (0.4−3.0 equiv) were necessary.[6e] When our conditions using 5 mol % of Bi(OTf)$_3$•4H$_2$O were applied to ketones, such as cyclohexanone or the more hindered 2-methyl-cyclohexanone, we were delighted to isolate the aldol **3m** in good yield and **3n** with good diastereoselectivity albeit moderate yield (Table 3, entries 3 and 4). The reaction of 3-methyl-2-(trimethylsilyloxy)furan **2b**[7a] with 2-methyl-cyclohexanone afforded a very major diastereoisomer **3n′** in good yield (Table 3, entry 5).

In summary, we have found the vinylogous Mukaiyama aldol reaction proceeds smoothly with silyloxyfurans and a catalytic amount of Bi(OTf)$_3$•4H$_2$O. This method offers several advantages including mild reaction conditions, highly catalytic (1 mol %) process, no formation of byproducts, as well as air-tolerance. Yet the process does not involve strictly anhydrous conditions as, although solvents were distilled prior to use, no inert atmosphere was required for the reaction to proceed with the same yield and diastereoselectivity. High yields and good diastereoselectivities were obtained with aromatic aldehydes. Moreover, our methodology efficiently promotes the vinylogous Mukaiyama aldol reaction with ketones providing one major diastereoisomer with good diastereoselectivity. Because of its numerous benefits, the Bi(OTf)$_3$•4H$_2$O protocol should find utility in the synthesis of biologically active compounds. Development of other Bi(OTf)$_3$•4H$_2$O-catalyzed Mukaiyama aldol reactions and related mechanistic studies will be reported in due course.

Experimental Section

Typical Procedure for the Bismuth Triflate-Catalyzed Mukaiyama Aldol Reaction with Aromatic Aldehydes. To a solution of the aldehyde (0.71 mmol) in diethyl ether (0.5 mL) was added Bi(OTf)$_3$•4H$_2$O (0.007 mmol). The mixture was brought to −78 °C, stirred at this temperature for 0.25 h, and a solution of 2-(trimethylsilyloxy)furan **2a** (0.85 mmol) in 0.5 mL of diethyl ether was added dropwise. The mixture was stirred at −78 °C until the reaction was completed as indicated by TLC. The reaction was diluted in tetrahydrofuran (1.0 mL) and quenched with 10% aqueous HCl (1.0 mL). The mixture was stirred for 0.25 h at room temperature, neutralized by addition of a saturated aqueous NaHCO$_3$ solution, and extracted with ethyl acetate. The organic phases were combined, dried over Na$_2$SO$_4$, and concentrated under reduced pressure (rotary evaporator). The *syn/anti* ratio of the product was determined by ^{1}H NMR analysis of the crude reaction mixture. The relative configurations of the products were assigned according to the literature.[4b−c] The crude products were purified by silica gel chromatography (ethyl acetate/hexanes). **3a**, **3d**, **3e**, **3h**, and **3j**

---

[20] Naito, S.; Escobar, M.; Kym, P. R.; Liras, S.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4200−4208.

[21] (a) Pelter, A.; Al-Bayati, R.; Lewis, W. *Tetrahedron Lett.* **1982**, *23*, 353−356. (b) Asaoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 4269−4270.

accord exactly with those that have been previously reported in the literature.[4c,6d,22]

5-(Hydroxy(2-tolyl)methyl)furan-2(5*H*)-one (3c). Reagents: *o*-tolualdehyde (90 mg, 0.75 mmol), **2a** (140 mg, 0.89 mmol), and $Bi(OTf)_3 \cdot 4H_2O$ (5.3 mg, 0.0075 mmol). The reaction was stirred for 0.25 h at −78 °C and quenched according to the typical procedure. The *syn/anti* ratio (94:6) was determined by ^1H NMR analysis of the crude product (δ major: 4.95 ppm, δ minor: 5.12 ppm). The residue was purified by silica gel chromatography (20% ethyl acetate/hexane) to afford 138 mg (90%) of **3c** as the pure *syn* diastereoisomer (colorless oil): $R_f = 0.15$ (30% ethyl acetate/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.48-7.52$ (m, 1H), 7.26 (t, $J = 1.5$ Hz, 2H), 7.18 (m, 1H), 7.10 (dd, $J = 5.9$, 1.6 Hz, 1H), 6.13 (dd, $J = 5.9$, 2.0 Hz, 1H), 5.19−5.21 (m, 1H), 4.95 (d, $J = 7.3$ Hz, 1H), 3.20 (br s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.6$, 153.2, 136.0, 135.5, 131.1, 129.0, 126.9, 123.4, 87.5, 72.2, 19.7; IR (film): 3459, 1756 cm^{-1}; HRMS: Calcd for $C_{12}H_{12}O_3$ (M^+) 204.0786, found 204.0779.

Typical Procedure for the Bismuth-Catalyzed Mukaiyama Aldol Reaction with Aliphatic Aldehydes and Ketones. To a solution of $Bi(OTf)_3 \cdot 4H_2O$ (0.036 mmol) in diethyl ether (0.5 mL) at room temperature was added the aldehyde or the ketone (0.71 mmol). The mixture was brought to −45 °C, stirred at this temperature for 0.25 h, and a solution of 2-(trimethylsilyloxy)furan **2** (1.1 mmol) in diethyl ether (0.5 mL) was added dropwise. The mixture was stirred at −45 °C for 3 h. The mixture was diluted in tetrahydrofuran (1.0 mL) and quenched with 10% aqueous HCl (1.0 mL). The mixture was stirred for 0.25 h at room temperature, neutralized by addition of a saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure (rotary evaporator). The *syn/anti* ratio of the product was determined by ^1H NMR analysis of the crude reaction mixture. The crude product was purified by silica gel chromatography (ethyl acetate/hexanes). **3k** and **3l** accord exactly with those that have been previously reported in the literature.[4c,23]

5-(1-Hydroxycyclohexyl)furan-2(5*H*)-one (3 m). Reagents: cyclohexanone (70 mg, 0.71 mmol), **2a** (167 mg, 1.1 mmol), and $Bi(OTf)_3 \cdot 4H_2O$ (25 mg, 0.036 mmol). The mixture was stirred at −45 °C for 3 h and then quenched according to the typical procedure. The crude product was then purified on silica gel (20% ethyl acetate/hexanes) to afford 97 mg (75%) of **3m** as a white solid: mp 51 °C; $R_f = 0.18$ (20% ethyl acetate/hexanes); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$ (dq, $J = 5.9$, 0.9 Hz, 1H); 6.17 (m, 1H), 4.85 (m, 1H), 2.12 (br s, 1H), 1.40−1.65 (m, 9H), 1.16−1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.6$, 154.1, 122.9, 89.8, 72.8, 33.8, 33.5, 25.6, 21.3; IR (KBr): 3459, 1810 cm^{-1}; HRMS: Calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943, found 182.0947.

Acknowledgment. This work was financially supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT, Québec, Canada), the Canada Foundation for Innovation, and Université Laval. V. D. thanks NSERC for a postgraduate scholarship. We thank Rhodia (Lyon, France) and Sidech s.a. (Tilly, Belgium) for a generous gift of chemicals.

Supporting Information Available: Experimental details, characterization data, and NMR spectra for compounds **3a**−**n**, **3n′**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702085P

---

(22) Pohmakotr, M.; Tuchinda, P.; Premkaisorn, P.; Reutrakul, V. *Tetrahedron* **1998**, *54*, 11297−11304.

(23) Hjelmgaard, T.; Persson, T.; Rasmussen, T. B.; Givskov, M.; Nielsen, J. *Bioorg. Med. Chem.* **2003**, *11*, 3261−3271.