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Stereoselective construction of *cis*-2,6-disubstituted tetrahydropyrans via an intramolecular bismuth-mediated oxa-conjugate addition reaction

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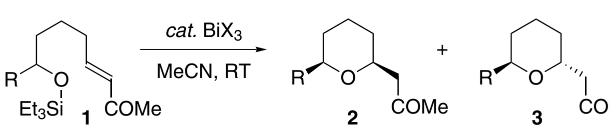
Abstract—The intramolecular oxa-conjugate addition of tethered triethylsilyloxy substituted α,β-unsaturated ketones mediated by bismuth(III) nitrate pentahydrate provides a mild and efficient method for the stereoselective construction of *cis*-2,6-disubstituted tetrahydropyrans.

Bismuth(III) salts provide a convenient, inexpensive, and environmentally benign source of the corresponding Brønsted acid.[1–3] For example, the hydrolysis of bismuth(III) bromide is known to afford two equivalents of hydrogen bromide and insoluble bismuth oxybromide, in which the former is responsible for the observed catalysis.[2a] We recently demonstrated that this reagent promotes the intramolecular reductive and two-component etherification reactions for the construction of *cis*- and *trans*-2,6-disubstituted tetrahydropyrans, respectively.[2] A striking feature of this approach is the ability to initiate the cyclization based on the nature and proximity of the triorganosilyl ether.



(1)

In a program directed toward exploring the synthetic utility of bismuth(III) salts, we envisioned using a bismuth(III) salt to accomplish an intramolecular oxa-conjugate addition for the stereoselective synthesis of cyclic ethers.[4,5] Although the intramolecular oxa-conjugate addition with alkoxides has been extensively studied, there is a surprising paucity of Brønsted acid catalyzed versions of this transformation.[6,7] Herein, we now describe the intramolecular bismuth-mediated oxa-conjugate addition of tethered trialkylsilyloxy substituted α,β-unsaturated ketones **1** for the stereoselective construction of *cis*-2,6-disubstituted tetrahydropyrans **2** (Eq. 1).

Preliminary studies focused on the development of the intramolecular bismuth-mediated oxa-conjugate addition using the triethylsilyloxy substituted α,β-unsaturated ketone **1a** (R = $PhCH_2$) as outlined in Table 1.[8] Treatment of **1a** with a catalytic amount of bismuth(III) bromide in reagent grade acetonitrile at room temperature, furnished the 2,6-disubstituted tetrahydropyrans **2a**/**3a** in 16% yield, favoring the *cis*-diastereoisomer **2a** (entry 1). Although the yield was not particularly encouraging, the high stereoselectivity and the fact that the unreacted α,β-unsaturated ketone **1a** was completely recovered stimulated further optimization studies. The low conversion was initially attributed to an inefficient protodesilylation of the secondary triethylsilyl ether by the hydrogen bromide.[11,12] This prompted the examination of related bismuth(III) salts (entries 4–7), in which the halides gave analogous results (entries 4–5), whereas the pseudo halide (entry 6) afforded **2a** with somewhat improved efficiency and diastereoselectivity. Gratifyingly, bismuth(III) nitrate, which is commercially available as the pentahydrate, gave the *cis*-2,6-disubstituted tetrahydropyran **2a** in quantitative yield and with excellent diastereoselectivity (entry 7).[13,14] This dramatic improvement was attributed to the increased water

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Keywords: Bismuth mediated; Cyclic ethers; Diastereoselective; Oxa-conjugate addition.

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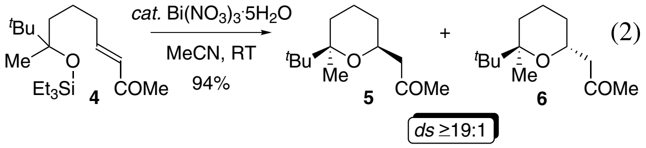
Table 1. Optimization for the intramolecular bismuth-mediated oxa-conjugate addition (Eq. 1; **1a**, R = $PhCH_2$)[a]

Entry	Bismuth(III) salts (5 mol %)	Additive	Ratio of **2a/3a**[b]	Yield (%)[c]
1	$BiBr_3$	—	17:1	16
2	$BiBr_3$	H_2O[d]	44:1	⩾99
3	$BiBr_3$	DTBMP[e]	NA	0
4	$BiCl_3$	—	23:1	16
5	BiI_3	—	23:1	11
6	$Bi(OTf)_3$	—	45:1	57
7	*$Bi(NO_3)_3{\cdot}5H_2O$*	—	*50:1*	*⩾99*
8	$Bi(NO_3)_3{\cdot}5H_2O$	DTBMP[e]	NA	0

[a] All reactions were carried out on a 0.25 mmol scale in reagent grade acetonitrile (1 M) at room temperature for ca. 12 h.
[b] Ratio of diastereoisomers determined by capillary GLC analysis on crude reaction mixtures.
[c] GLC yields relative to the internal standard *n*-pentadecane.
[d] 1 equiv added based on **1a**.
[e] 2 equiv based on BiX_3.

content rather than the acidity of the requisite Brønsted acid. Consistent with this hypothesis, the addition of water to the bismuth(III) bromide mediated reaction, provided the *cis*-2,6-disubstituted tetrahydropyran **2a** in an analogous manner to bismuth(III) nitrate pentahydrate (entry 2 vs 7). Moreover, the addition of the hindered base 2,6-di-*tert*-butyl-4-methylpyridine to neutralize the Brønsted acid, led as expected to no observable reaction (entries 3 and 8).

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 7) to various tethered triethylsilyloxy substituted α,β-unsaturated ketones.[15] The intramolecular oxa-conjugate addition is tolerant of both linear (entries 2 and 3) and branched substituents (entries 4 and 5), in which even the *tert*-butyl substituent (entry 6) affords the cyclic ether in 99% yield with excellent diastereoselectivity. The intramolecular oxa-conjugate addition was also applicable to substrates containing protected heteroatoms (entries 7–10), which is significant given that these products provide important synthons for synthetic applications.[6,7] Interestingly, the nitrogen containing substrate required an electron-withdrawing group, which presumably avoids the basic nitrogen sequestering the Brønsted acid (entry 7). Another interesting feature of this study was that the benzyl protected alcohol derivative afforded lower diastereoselectivity (entry 8), which was attributed to the formation of a hydrogen-bonded hemiacetal that alters the facial selectivity in the oxa-conjugate addition.[16] This problem was easily circumvented by either replacing the benzyl ether with an electron-withdrawing protecting group (entry 9), or a bulky trialkylsilyl ether (entry 10), which result in higher diastereoselectivity. Moreover, the latter example is particularly impressive, since it demonstrates that certain primary trialkylsilyl ethers may be tolerated, without competitive desilylation.



(2)

In an attempt to extend the scope of this reaction, tertiary triethylsilyl ethers were also examined in the context of the diastereoselective intramolecular oxa-conjugate addition (Eq. 2). Treatment of the triethylsilyloxy substituted α,β-unsaturated ketone **4** under the optimized reaction conditions, albeit with 20 mol % bismuth(III) nitrate pentahydrate, furnished the tetrahydropyrans **5/6** in 94% yield, with ⩾19:1 diastereoselectivity favoring **5**.[18] The increased loading is presumably due to the increased stability of the tertiary trialkylsilyl ethers toward protodesilylation.

Table 2. Scope of the intramolecular bismuth(III) nitrate pentahydrate mediated oxa-conjugate addition[a]

Entry	α,β-Unsaturated ketone	R =	Ratio of **2/3**[b,c]	Yield (%)[d]
1	$PhCH_2$–	**a**	⩾19:1	97
2	CH_3–	**b**	⩾19:1	90
3	$CH_3(CH_2)_2$–	**c**	⩾19:1	88
4	$(CH_3)_2CHCH_2$–	**d**	⩾19:1	96
5	$(CH_3)_2CH$–	**e**	⩾19:1	96
6	$(CH_3)_3C$–	**f**	⩾19:1	99
7	$Ts(PhCH_2)NCH_2$–	**g**	⩾19:1	90
8	$PhCH_2OCH_2$–	**h**	16:1	95
9	$PhCO_2CH_2$–	**i**	⩾19:1	87
10	$^{i}Pr_3SiOCH_2$–	**j**	⩾19:1	72

[a] All reactions were carried out on a 0.25 mmol scale with 5 mol % $Bi(NO_3)_3{\cdot}5H_2O$ in reagent grade acetonitrile (1 M) at room temperature for ca. 12 h.[17]
[b] Ratio of diastereoisomers determined by 400 MHz ^1H NMR on crude reaction mixtures.
[c] The stereochemistry was confirmed using NOE studies, see supplemental material.
[d] Isolated yields.

In conclusion, we have developed a general and highly diastereoselective intramolecular Brønsted acid catalyzed oxa-conjugate addition for the construction of *cis*-2,6-disubstituted tetrahydropyrans using bismuth(III) nitrate pentahydrate. This work demonstrates the importance of water in facilitating the hydrolysis of the bismuth(III) salt, to afford the Brønsted acid necessary to promote protodesilylation. Furthermore, we have provided compelling evidence that it is the Brønsted acid rather than the bismuth(III) salt, which is responsible for the catalysis. Finally, we extended this methodology to a tertiary alcohol nucleophile, thereby making this a mild and efficient method that will be particularly attractive for applications to target directed synthesis.

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Supplementary data

The supplementary data (^1H NMR, ^{13}C NMR, IR, and MS), including NMR spectra for **1/2a–j** and **4/5**, associated with this article is available online with ScienceDirect (doi:10.1016/j.tetlet.2005.06.071).

References and notes

1. Suzuki, H.; Matano, Y.; Ikegami, T. In *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: New York, 2001; pp 1–245.
2. (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456; (b) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883.
3. Wabnitz, T. C.; Yu, J.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484, and pertinent references cited therein.
4. For a recent review on the use of bismuth compounds in organic synthesis, see: Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373.
5. Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481.
6. Betancort, J. M.; Martin, V. S.; Padron, J. M.; Palazon, J. M.; Rammirez, M. A.; Soler, M. A. *J. Org. Chem* **1997**, *62*, 4570, and pertinent references cited therein.
7. For examples of the acid-catalyzed intramolecular addition of oxygen nucleophiles to an α,β-unsaturated ketones, see: *with CSA*: (a) Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599; *with HF*: (b) O'Brien, M.; Taylor, N. H.; Thomas, E. J. *Tetrahedron Lett.* **2002**, *43*, 5491.
8. The α,β-unsaturated ketone **1a** was prepared in 72% yield (*E*-isomer exclusively) from the cross metathesis reaction of the terminal alkene with excess methyl vinyl ketone using the Hoveyda–Grubbs catalyst.[9,10]
9. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, A. D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.
10. (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168; (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451.
11. Interestingly, the rate of protodesilylation of the triorganosilyl ether mirrors the overall efficiency of this transformation (TMS > TES > TBS > TIPS ≫ TPS).
12. Schelhass, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2056.
13. The mechanistic hypothesis that bismuth salts are a mild source of Brønsted acid was further supported by the following experiment. Treatment of **1a** with 10 mol % HNO_3 furnished the 2,6-disubstituted tetrahydropyrans **2a/3a** in quantitative yield, favoring the *cis*-diastereoisomer **2a** (*ds* = 42:1).
14. The diastereoselectivity remains constant at 50:1 over a 24 h period, indicating that there is no apparent equilibration over time, which infers a kinetic ratio. This is further supported by the fact that the equilibration of **2a/3a** (*ds* = 35:1) with catalytic 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) in benzene at room temperature for 24 h, provided **2a/3a** with an improved ratio (*ds* = 65:1) in 99% recovered yield.
15. The application of this methodology to α,β-unsaturated esters proved unsuccessful. This was attributed to the reduced electrophilicity of esters as compared to ketones.
16. Merbouth, N.; Bobbitt, J. M.; Bruckner, C. *J. Org. Chem.* **2004**, *69*, 5116.
17. *Representative experimental procedure for the intramolecular oxa-conjugate addition*: The α,β-unsaturated ketone **1a** (0.086 g, 0.25 mmol) was dissolved in reagent grade acetonitrile (250 μL) and stirred at room temperature. $Bi(NO_3)_3\cdot 5H_2O$ (6.6 mg, 0.0125 mmol) was then added via a tared vial in a single portion. The resulting white slurry was stirred at room temperature for ca. 12 h (TLC control; 20% ethyl acetate/hexane). The reaction mixture was diluted with dichloromethane (1 mL), quenched by the addition of 2,6-lutidine (5 μL, 0.04 mmol), and concentrated in vacuo to afford a white slurry. Purification via flash chromatography on silica gel (eluting with a 0–10% ether/pentane gradient) provided **2a** (0.056 g, 97%) as a colorless oil: IR (Neat) 3028 (m), 2952 (s), 2877 (s), 1699 (s), 1678 (s), 1628 (s), 1253 (s), 1092 (s), 742 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (2H, m), 7.22–7.16 (3H, m), 6.76 (1H, dt, J = 16.1, 6.9 Hz), 6.05 (1H, d, J = 15.9 Hz), 3.89 (1H, quintet, J = 6.0 Hz), 2.79 (1H, dd, A of ABX, J_{AB} = 13.4, J_{AX} = 6.2 Hz,), 2.71 (1H, dd, B of ABX, J_{AB} = 13.4, J_{BX} = 6.7 Hz,), 2.23 (3H, s), 2.23–2.17 (2H, m), 1.78–1.57 (1H, m), 1.55–1.39 (3H, m), 0.93 (9H, t, J = 8.0 Hz,), 0.53 (6H, q, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.68 (e), 148.21 (o), 139.08 (e), 131.54 (o), 129.66 (o), 128.30 (o), 126.24 (o), 73.43 (o), 44.25 (e), 36.24 (e), 32.58 (e), 26.90 (o), 23.89 (e), 7.00 (o), 5.04 (e). HRMS (CI, $M+H^+$) calcd for $C_{21}H_{35}O_2Si$ 347.2401, found 347.2403.
18. The cyclic ether **6** was isolated as an inseparable mixture with 5% of the deprotected α,β-unsaturated ketone derived from **4**. Interestingly, the resubmission of this mixture to the reaction conditions afforded no improvement in the conversion.