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Stereoselective Construction of Cyclic Ethers Using a Tandem Two-Component Etherification: Elucidation of the Role of Bismuth Tribromide

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The stereodivergent construction of cyclic ethers remains an important area of synthetic interest, particularly given the ubiquity of *C*-glycoside derivatives in natural and unnatural pharmacologically important agents.[1] Bismuth(III) halides are inexpensive and environmentally benign reagents, which have been utilized as mild Lewis acid catalysts for an array of synthetic transformations.[2,3] Herein, we describe a series of stereoselective *intra*molecular etherification reactions of δ-trialkylsilyloxy aldehydes and ketones **1**, using catalytic bismuth tribromide and various trialkylsilyl nucleophiles for the construction of *cis*- and *trans*-2,6-di- and trisubstituted tetrahydropyrans **2** (eq 1).[4]

The mechanistic hypothesis, outlined in Scheme 1, describes the basis of the two-component etherification reaction. Since bismuth-(III) trihalides are known to readily undergo hydrolysis to afford bismuth oxyhalides and the requisite Brønsted acid,[2,5] we anticipated that the latter would promote the formation of **ii**, which should then undergo *in situ* desilylation to afford the lactol **iii**.[6] Acidcatalyzed dehydration of **iii** could then lead to the formation of the oxocarbenium ion **iv** and facilitate axial nucleophilic attack to furnish the cyclic ether **v**.[7] The potential advantage of this approach over that involving a Lewis acid is the unusual chemoselectivity, which will provide a powerful tool for the construction of cyclic ethers. This selectivity is presumably the result of the low reactivity of the protonated carbonyl, which requires addition of the pendant triorganosilyloxy group to afford the more reactive oxocarbenium ion.[8] Moreover, the acid concentration is modulated using the hydrolysis of the triorganosilyl halide, making it an exceedingly mild and convenient method.

Preliminary studies demonstrated that the nature of the bismuth-(III) halide was inconsequential in terms of both efficiency and selectivity (Cl ~ Br ~ I). In light of this fact we elected to utilize the less expensive $BiBr_3$. Interestingly, while the selectivity was unaffected by the nature of the triorganosilyl ether, the efficiency of the reaction was found to be directly related to the rate of protodesilylation (TMS ~ TES > TBS >> TIPS).[9] Additional studies using pendant triethylsilyl ethers then focused on providing evidence for the proposed hypothesis outlined in Scheme 1. Initial studies examined the proposal that $BiBr_3$ or triethylsilyl bromide provided a source of HBr, which then functions as the catalyst (Table 1, entries 1, 5, and 7). Consistent with this hypothesis, the addition of water to $BiBr_3$ did not prove detrimental to the reaction and further supports the notion that the BiBr3 is not acting as a Lewis acid (entry 2). Moreover, the addition of activated molecular sieves to each of these reagents, to sequester HBr and water, gave none of the desired product (entries 3, 6, and 8).[10] This idea was further supported by the addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), which neutralizes the hydrogen bromide and leads to no observable reaction (entry

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Supporting Information Available: Experimental procedures, X-ray analysis of the *p*-nitrobenzoate derivative of **5**, and spectral data for **1a**—**c**, **2a**—**h**, **4**-**5**, and **7**-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

4). The relatively poor catalytic activity of HBr and triethylsilyl bromide (entries 5 and 7) prompted additional studies to determine the potential role of bismuth in the reaction. Interestingly, the addition of an equimolar amount of BrBi=O appears to reconstitute the catalytic activity (entries 7 and 10 *vs* 9).[11] Further investigations are underway to determine the precise role of the BrBi=O.

Table 2 outlines the scope of the two-component etherification reaction in terms of various nucleophiles. This study demonstrated that δ-triethylsilyloxy-substituted aldehydes and ketones serve as substrates for the etherification reaction. Interestingly, while the two-component coupling reactions with carbon nucleophiles furnished the *trans*-diastereoisomer (entries 1-6),[12] the reductive coupling furnished the *cis*-diastereoisomer consistent with axial addition of the nucleophile (entries 7 and 8).[13,14]

We envisioned that the stereoselective construction of adjacent tertiary ethers would prove challenging and thereby highlight the synthetic utility of the *tandem* two-component etherification reaction (eq 2). Treatment of the triethylsilyl ether **4** with $BiBr_3$ and excess allyltrimethylsilane at room temperature furnished the bicyclic tetrahydropyran derivatives **5/6** in 77-81% yield, with excellent diastereoselectivity favoring **5**.[15,16] The ability to accomplish the selective formation of this *bis*-tertiary ether from the *cis*-ring fusion is particularly interesting given there are potentially two conformers of the oxocarbenium ion. Indeed, the stereochemical outcome is consistent with the Woerpel model,[14] which predicts the 4-alkoxy substituent will adopt a pseudoaxial orientation in the transition state, thereby favoring the *trans*-addition of the allylsilane.

Encouraged by the preliminary results in Table 2, we also examined the feasibility of a *sequential* two-component reaction that involved an *inter*molecular addition followed by an *intra*molecular reductive etherification as outlined in eq 3.[15,17] Treatment of the aldehyde **7** with excess trimethylsilyl enol ether **8** installs the *trans*-2,6-disubstituted tetrahydropyran, which upon addition of triethylsilane facilitates the reductive etherification to afford the *bis*-tetrahydropyran **9** in 73% yield with excellent diastereoselectivity (by GLC, eq 3). Hence, this cross-coupling reaction provides a one-step method for the installation of nonadjacent tetrahydropyran rings having complementary stereochemistry.

In conclusion, we have developed a *tandem* two-component etherification reaction for the stereoselective construction of *cis*- and *trans*-2,6-di- and trisubstituted tetrahydropyran rings in which excellent selectivity could be obtained for either stereoisomer through the judicious choice of the nucleophile and substrate. This work also provides compelling evidence for hydrogen bromide and bismuth oxybromide to be responsible for the catalysis. The synthetic utility of this protocol is highlighted in the ability to construct adjacent tertiary ethers in a highly stereoselective manner and the *sequential* two-component cross-coupling followed by reductive etherification process for the expiditious synthesis of nonadjacent tetrahydropyrans. These methods will undoubtedly be widely applicable to target-directed synthesis.

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(11). The structure of bismuth oxybromide, isolated from the hydrolysis of bismuth bromide, was confirmed *via* X-ray powder diffraction

(12). Representative Experimental Procedure for the Two-Component Allylative Etherification: 6-Phenyl-5-(triethylsilyloxy)hexanal **1a** (57.0 mg, 0.186 mmol) was dissolved in acetonitrile (2.0 mL) and stirred at room temperature. Bismuth tribromide (8.9 mg, 0.020 mmol) prepared as a solution in acetonitrile at 1 mg/10 μL was added via syringe directly followed by the rapid addition of allyltrimethylsilane (90 μL, 0.56 mmol). The reaction mixture was stirred at room temperature for ca. 16 h (tlc control). The solvent was removed in *vacuo* to afford the crude oil. Purification by flash chromatography (5% ethyl acetate/hexanes) furnished **2a** (34.6 mg, 90%) as a colorless oil (ds ≥ 99:1 by GLC)

(13). An alternative mechanistic proposal suggests that triethylsilyl bromide is formed from triethylsilane and bismuth tribromide and behaves as the Lewis acid catalyst, see:Bajwa JS, Jiang X, Slade J, Prasad K, Repic O, Blacklock TJ. Tetrahedron Lett 2002;43:6709.

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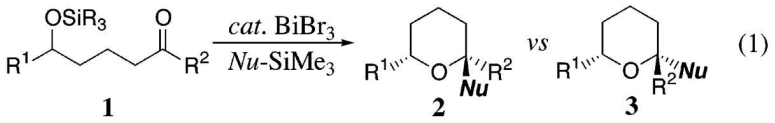
(15). In the more demanding reactions outlined in eqs 2 and 3, use of stoichiometric $BiBr_3$ improved the overall efficiency. This trend is presumably a function of the ease of desilylation of the tertiary alcohol (eq 2) and increased rate of the initial *inter*molecular reaction in the *sequential* sequence (eq 3)

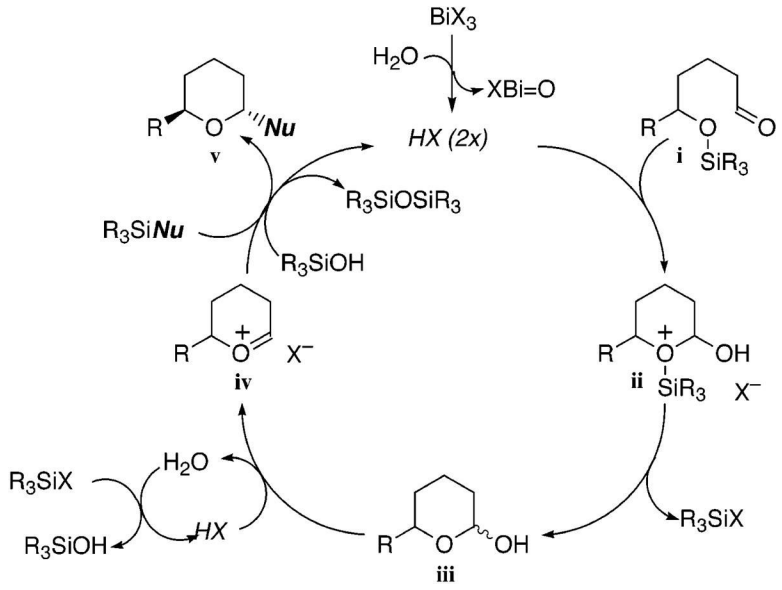
(16). The stereochemistry of **5** was established through X-ray crystallographic analysis of the *p*-nitrobenzoate derivative formed through reductive ozonolysis and esterification of the intermediary alcohol

(17). For a related *tandem* Mukaiyama aldol—Prins cyclization cascade reaction, see:Kopecky DJ, Rychnovsky SD. J. Am. Chem. Soc 2001;123:8420. [PubMed: 11516301]

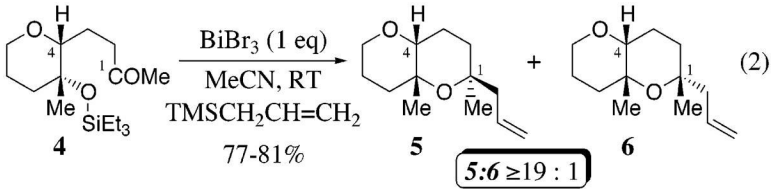


(1)

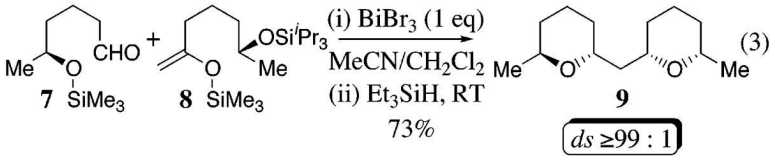
Equation 1.



Scheme 1.



Equation 2.



Equation 3.

Table 1

Elucidation of the Role of $BiBr_3$ in the Two-Component Etherification Reaction (eq 1, **1a**, R = Et; R^1 = Bn; R^2 = H; ***Nu*** = $CH_2CH{=}CH_2$)

entry	catalyst[a]	mol%	additive	ratio of 2a:3a[e,f]	(%) yield[g]
1	$BiBr_3$	10	-	≥99:1	99
2	"		H_2O[b]	≥99:1	92
3	"	"	4Å sieves[c]	NA	0
4	"	"	DTBMP[d]	NA	0
5	HBr	20	-	≥99:1	34
6	"	"	4Å sieves[c]	NA	0
7	TESBr	"	-	≥99:1	32
8	"	"	4Å sieves[c]	NA	0
9	"	"	BrBi=O[d]	≥99:1	91[h]
10	BrBi=O	"	-	NA	0

[a] All reactions were carried out on a 0.1 mmol reaction scale in CH_3CN at room temperature using 3 equiv of allyltrimethylsilane.

[b] 10 equiv based on $BiBr_3$.

[c] Molecular sieves were activated at 150 °C under high vacuum.

[d] 20 mol % based on **1a**.

[e] Ratios of diastereoisomers were determined by capillary GLC analysis.

[f] The *cis*-diastereoisomer **3a** was prepared from the ketone *via* a reductive etherification reaction.

[g] GLC yields.

[h] The addition of 4Å molecular sieves to this reaction also led to no observable reaction.

Table 2

Scope of the *Tandem* Two-Component Etherification Reactions (eq 1; **1**, R = Et; R^1 = Bn)[a]

entry	1; R^2=	R_3Si-*Nu*[b]	cyclic ether 2/3*Nu*=		ds = 2:3[c]	yield (%)[f]
1	H	A	$-CH_2CH=CH_2$	a	≥99:1[d]	90
2	Me	A	“	b	≥19:1	88
3	H	B	$-CH=C=CH_2$	c	≥19:1[e]	80
4	Me	B	“	d	≥19:1[e]	72
5	H	C	$-CH_2C(O)CH_3$	e	≥19:1	73
6	Me	C	“	f	≥19:1	80
7	^{2}H	D	-H	g	≥19:1	85
8	Me	D	“	h	≥99:1[d]	95

[a] All reactions were carried out on a 0.2-0.3 mmol reaction scale in CH_3CN at room temperature using 5-10 mol % $BiBr_3$ and 1.2-3.0 equiv. of R_3**Si-*Nu***.

[b] A = $Me_3SiCH_2CH=CH_2$; B = $Me_3SiCH_2C\equiv CH$; C = $CH_2=C(OSiMe_3)CH_3$; D = Et_3SiH.

[c] Ratios of diastereoisomers were determined by 400 MHz ^{1}H NMR on the crude reaction mixture unless otherwise indicated.

[d] Determined by capillary GLC.

[e] Contaminated with 5-10% of the propargylated derivative.

[f] Isolated yields.