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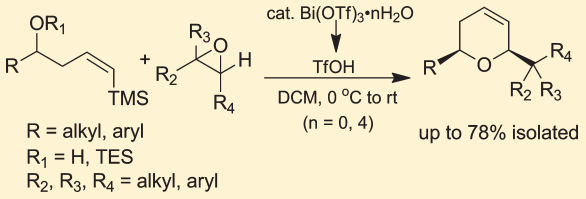
Bi(OTf)$_3$-, TfOH-, and TMSOTf-Mediated, One-Pot Epoxide Rearrangement, Addition, and Intramolecular Silyl-Modified Sakurai (ISMS) Cascade toward Dihydropyrans: Comparison of Catalysts and Role of Bi(OTf)$_3$

R. Frederick Lambert, Robert J. Hinkle,* Stephen E. Ammann, Yajing Lian, Jia Liu, Shane E. Lewis, and Robert D. Pike

Department of Chemistry, The College of William & Mary, P.O. Box 8795, Williamsburg, Virginia 23187-8795, United States

Supporting Information

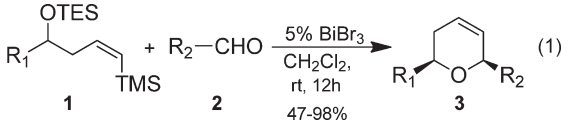
ABSTRACT: Catalytic quantities of bismuth(III) triflate efficiently initiate the rearrangement of epoxides to aldehydes, which subsequently react with (*Z*)-δ-hydroxyalkenylsilanes to afford 2,6-disubstituted 3,6-dihydro-2*H*-pyrans. Isolated yields of desired products using Bi(OTf)$_3$ were compared with yields obtained when the reactions were run with TfOH and TMSOTf in the presence and absence of several additives. These studies, as well as NMR spectroscopic analyses, indicate an initial Lewis acid/base interaction between Bi(OTf)$_3$ and substrates providing TfOH in situ.



INTRODUCTION

A variety of bismuth compounds have been used in organic reactions over the last 10−15 years because of low toxicities, a wide range of reactivities, and low cost.[1] Catalytic quantities of Bi(III) compounds are effective in promoting allylations and cyanations,[2] etherification,[3] Diels−Alder,[4] and protection/deprotection reactions. Furthermore, asymmetric total syntheses of leucascandrolide,[5] centrolobine,[6] mucocin,[7] and bistramide C[8] have included Bi(III)-mediated sequences. As part of a program to increase the uses of Bi(III) in the synthesis of cyclic ethers, we have described two- and three-component reactions toward tetrahydropyrans[9] and dihydropyrans[10,11] using catalytic quantities of bismuth bromide ($BiBr_3$) at room temperature. Extension of this work to a cascade reaction involving epoxide rearrangement[12] followed by a tandem addition/silyl-Prins reaction is reported herein along with comparisons of BiX_3 (X = Br, OTf), trimethylsilyltrifluoromethanesulfonate (TMSOTf), and trifluoromethanesulfonic acid (TfOH) as initiators/catalysts.

Although a wide variety of protocols have been used for the synthesis of dihydropyran ring systems, the Prins[13] and silyl-Prins[14] reactions remain widely used and studied. Dobbs' $InCl_3$-mediated synthesis,[15] Rychnovsky's segmented Prins reaction,[16] and Markó's intramolecular silyl-modified Sakurai reaction (ISMS)[17] are all chemically related to the $BiBr_3$-mediated reaction shown in eq 1.[11]



(1)

Despite the drastic increase of Bi(III) salts in synthesis, debate continues over their exact role in catalytic cycles. Several authors have noted that Bi(III) salts generate Brønsted acids in situ,[18] whereas Shibasaki et al.,[19] Kadam and Kim,[20] and Kobayashi and co-workers[21] propose that the bismuth is acting as a Lewis acid in amination, substitution, and asymmetric Mukaiyama aldol reactions, respectively. In addition, both Cook[22] and Donnelly[23] report that allylic halide substitution reactions occur readily in the presence of catalytic quantities of bismuth compounds and attribute the success of these reactions to the Lewis acid character of Bi(III).[24−26] The Lewis acidic nature of Bi(III) compounds is usually attributed to the tendency for expanded coordination, the availability of unoccupied orbitals (Bi−X σ* and d), and the presence of electron-withdrawing atoms or groups bonded to the metal center.[1f,27] Finally, Lambert and co-workers recently proposed a mechanism for furan synthesis in which in situ production of TMSOTf participated in a multicatalytic system along with TfOH and bismuth triflate (Bi(OTf)$_3$).[28]

In order to both expand the repertoire of reactions that Bi(III) compounds catalyze as well as investigate the role(s) of this metal ion, we chose to examine the cascade reaction shown in eq 2. Epoxides add versatility to the synthesis, since they are common, useful reagents which are easy to handle and prone to neither aldol condensations nor oxidation to the corresponding carboxylic acids during storage. Although a limited number of examples have been implied for this type of reaction with $InCl_3$,[15] to the best of our knowledge, no expanded studies or

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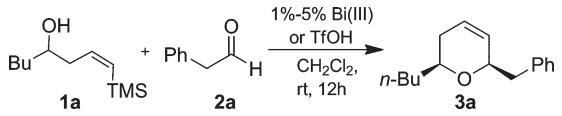
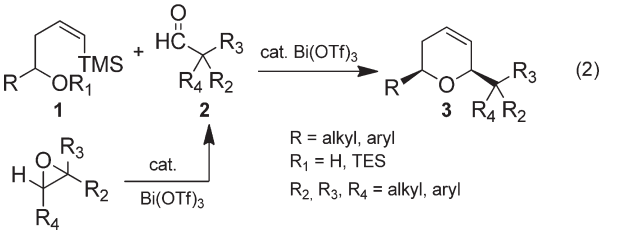
Table 1. Comparison of Catalyst Loading on Tandem Reaction of (*Z*)-δ-Hydroxyalkenylsilane 1a and Phenylacetaldehyde



cat.	amt (mol %)	yield (%)[a]
TfOH	1	87
$Bi(OTf)_3 \cdot nH_2O$	1	45
$Bi(OTf)_3$	1	50
$BiBr_3$	1	61
TfOH	5	82
$Bi(OTf)_3 \cdot nH_2O$	5	78
$Bi(OTf)_3$	5	66
$BiBr_3$	5	75

[a] Isolated yields of pure *cis*-**3a** after flash chromatography.

investigations of the catalytic species for this type of transformation have been performed.



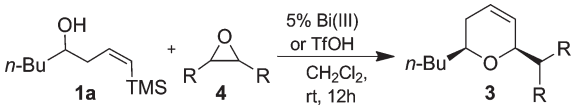
RESULTS AND DISCUSSION

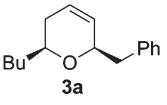
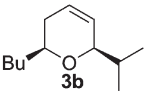
Comparison Studies. Prior to attempting the complete one-pot synthesis, we studied the effect of different catalysts with differing ratios on the tandem cyclization (Table 1). Although the triethysilyloxy analogues of (*Z*)-δ-hydroxyalkenylsilanes **1** were attempted first, the $Bi(OTf)_3$-mediated reactions afforded more complex mixtures than those conducted with $BiBr_3$. Therefore, the free alcohol version of the (*Z*)-δ-hydroxyalkenylsilane **1** was added to phenylacetaldehyde (**2a**; product which results from epoxide rearrangement of styrene oxide), giving 6-benzyl-2-butyl-3,6-dihydro-2*H*-pyran (**3a**) as the final product (Table 1). Each reaction was carried out with both 1 and 5 mol % catalyst. The following catalysts were chosen for comparison: TfOH, $Bi(OTf)_3 \cdot nH_2O$ prepared according to Dubac's method,[29] and both $Bi(OTf)_3$ and $BiBr_3$ obtained from Sigma-Aldrich, Inc. Triflic acid was chosen because of its potential production from the hydrolysis of bismuth triflate (eq 3).[30]

$$BiX_3 + H_2O \rightarrow O{=}BiX + 2\ H{-}X \qquad (3)$$

Both the $Bi(OTf)_3 \cdot 4H_2O$ synthesized in this work and the commercially available $Bi(OTf)_3$ gave moderate yields of the desired dihydropyran product **3a** at 1 mol % loading. When the catalyst loading was increased to 5 mol %, bismuth triflate afforded good yields of **3a**. The increased yield could be due to either an increased amount of $Bi(OTf)_3$ as a Lewis acid or the formation of an increased amount of triflic acid produced in situ from hydrolysis of bismuth triflate.

Table 2. Epoxide Rearrangement Followed by Addition and ISMS Using the Unprotected δ-Hydroxyalkenylsilanes



epoxide	product	catalyst	yield (%)[a]
 4a	 3a	$BiBr_3$	NR
		$Bi(OTf)_3 \cdot nH_2O$	41
		$Bi(OTf)_3$	40
		TfOH	78
 4b	 3b	$BiBr_3$	NR
		$Bi(OTf)_3 \cdot nH_2O$	59
		$Bi(OTf)_3$	44
		TfOH	52

[a] Isolated yields of pure cis isomers after flash chromatography on silica gel.

After establishing that $Bi(OTf)_3$ can be used for the tandem addition/ISMS sequence, we once again examined both triethylsilyl-protected and unprotected (*Z*)-δ-hydroxyalkenylsilanes in the cascade involving epoxide rearrangement, intermolecular addition, and an intramolecular silyl-modified Sakurai (ISMS) sequence. We again compared $BiBr_3$, $Bi(OTf)_3$, and TfOH as catalysts/initiators (Table 2).

As with the reactions in Table 1, reaction of the unprotected (*Z*)-δ-hydroxyalkenylsilane **1a** with styrene oxide (**4a**) and isobutylene oxide (**4b**) afforded fewer of the problematic silane byproducts (e.g., disiloxanes, TES-O-TES, TMS-O-TES, and TMS-O-TMS as well as unidentified silanes). Although efficient for reactions between δ-silyloxy-[11] or δ-hydroxyalkenylsilanes and aldehydes, $BiBr_3$ failed to induce initial epoxide ring opening to give the aldehyde needed for the addition/ISMS sequence. As confirmed by NMR spectroscopic analysis, the starting materials predominantly remained after 12 h for the reaction run with 5 mol % $BiBr_3$. This indicates that $BiBr_3$ (or HBr) is not a strong enough acid to facilitate the rearrangement.

In contrast, bismuth triflate promoted the epoxide rearrangement followed by the addition/ISMS cascade to afford 3,6-dihydro-2*H*-pyrans **3a**,**b** in 40−59% isolated yields. As with the reactions between δ-hydroxyalkenylsilanes and aldehydes (Table 1, vide supra), TfOH also initiated the cascade reaction sequence (Table 2) and, in the case of styrene oxide, afforded DHP **3a** in 78% isolated yield.

Since a number of authors argue that TfOH is the real catalyst in $Bi(OTf)_3$-mediated reactions, we synthesized 15 2,6-disubstituted-3,6-dihydro-2*H*-pyrans using both $Bi(OTf)_3 \cdot nH_2O$ and TfOH as catalysts/initiators (Table 3). At least 2 equiv of TfOH is possible from hydrolysis of each Bi(III) salt (eq 3); therefore, 5 mol % $Bi(OTf)_3 \cdot nH_2O$ and 10 mol % TfOH were compared directly. In most cases, the yields of isolated, pure products were similar for $Bi(OTf)_3 \cdot nH_2O$ and TfOH. Regardless of its actual role in the catalytic cycle, however, stable, easily handled $Bi(OTf)_3 \cdot nH_2O$ provides a convenient, practical alternative to corrosive and dangerous TfOH.

Reaction Scope. We evaluated the utility of the protocol by testing a variety of substrates under the developed reaction conditions (Table 3). Phenyl, halogenated aryl, and 1,1-dialkyl

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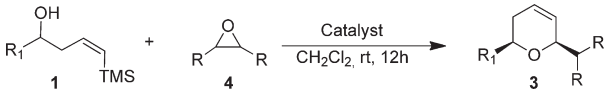
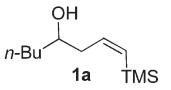
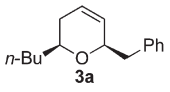
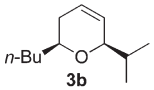
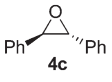
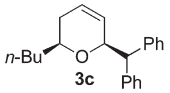
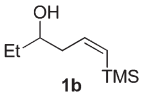
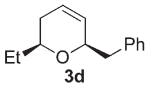
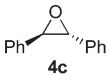
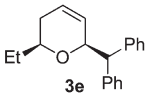
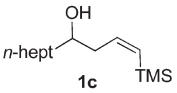
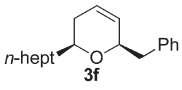
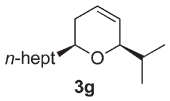
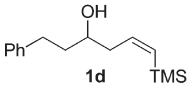
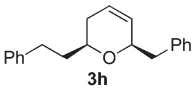
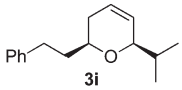
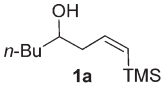
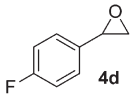
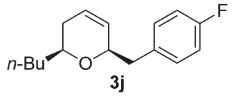
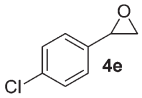
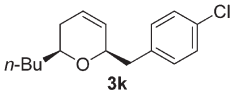
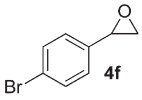
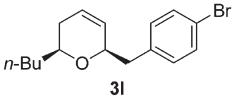
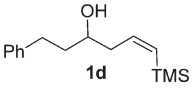
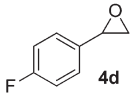
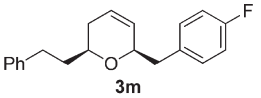
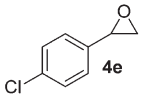
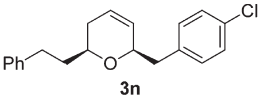
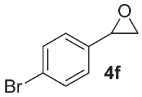
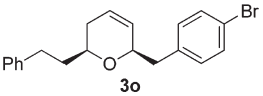
Table 3. Synthesis of 2,6-Disubstituted 3,6-Dihydropyrans



entry	vinylsilane	epoxide	product	yield(%)[a,b]	yield(%)[a,c]
1	 **1a**	 **4a**	 **3a**	56	58
2		 **4b**	 **3b**	66	70
3		 **4c**	 **3c**	31	27
4	 **1b**	 **4a**	 **3d**	53	50
5		 **4c**	 **3e**	28	29
6	 **1c**	 **4a**	 **3f**	59	74
7		 **4b**	 **3g**	57[d]	65[d]
8	 **1d**	 **4a**	 **3h**	71	62
9		 **4b**	 **3i**	42	60
10	 **1a**	 **4d**	 **3j**	47	45
11		 **4e**	 **3k**	49	50
12		 **4f**	 **3l**	41	46
13	 **1d**	 **4d**	 **3m**	45	60
14		 **4e**	 **3n**	54	56
15		 **4f**	 **3o**	59	53

[a] Isolated yield of pure cis isomers only, after flash column chromatography. Reactions were carried out on a ~0.5 mmol scale in 5.0 mL of CH_2Cl_2 at room temperature using 2.0 equiv of the corresponding epoxide. [b] 5 mol % $Bi(OTf)_3 \cdot nH_2O$. [c] 10 mol % TfOH. [d] 8/2 mixture of product and inseparable 2,6-diheptyl-3,6-dihydro-2*H*-pyran.

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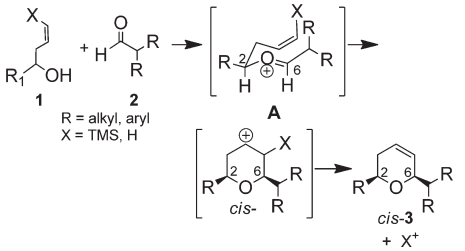
Scheme 1. Overall Mechanism for Silyl-Prins Reaction Affording *cis*-Dihydropyrans



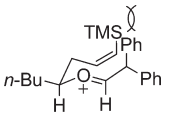


Figure 1. Proposed steric hindrance limiting the transformation of *trans*-stilbene oxide to the desired DHP product.

alkyl epoxides could be used, but each requires substituents that can stabilize an intermediate cation necessary for rearrangement to occur. Overall yields range from moderate to good, and only cis diastereomers were isolated after column chromatography, with no trans diastereomers detected by either ^{1}H NMR spectroscopy or GC-MS analyses of the crude reaction mixtures.

The cis relative stereochemistry was further confirmed by X-ray crystallographic analysis of the isolated product **3e**, shown in entry 5 of Table 3 (see the Supporting Information). The diastereoselectivity is in agreement with the stereochemistry reported by Dobbs and co-workers in their $InCl_3$-mediated study[15] and is consistent with that reported by Speckamp's group[14e] and Rychnovsky and co-workers in other Prins-type reactions.[13b,16]

The overall mechanism (Scheme 1) involves intermolecular attack of an alcohol (or silyloxy) oxygen on an activated aldehyde or ketone, formation of oxocarbenium ion **A** (2,6-substituents pseudoequatorial), and intramolecular attack of pendant π electrons to afford an intermediate carbocation which either deprotonates for X = H (Prins) or loses silane for X = $SiMe_3$ (silyl-Prins) to form a dihydropyran product.

The moderate yields as well as the formation of several unidentified byproducts prompted the examination of crude reaction mixtures to determine alternative reaction pathways which were detracting from desired products. The lowest yields invariably resulted when *trans*-stilbene oxide (**4c**) was used as an aldehyde surrogate. Despite the efficiency of the stilbene oxide rearrangement to 2,2-diphenylacetaldehyde (99%), this epoxide afforded low yields of DHP products **3** regardless of the (*Z*)-δ-hydroxyalkenylsilane **1** to which it was subjected (Table 3, entries 3 and 5). The low yields are likely due to steric hindrance within the intermediate (Figure 1) necessary to achieve the requisite silyl-Prins cyclization. We observed the same low yields when bypassing the epoxide rearrangement altogether and conducting the addition/ISMS reaction with freshly purified 2,2-diphenylacetaldehyde.[31]

The reaction shown in entry 7 of Table 3 resulted in a mixture containing **3g** and a minor amount of an inseparable second dihydropyran (Scheme 2, **G**). As reported by Rychnovsky and co-workers, immediately following the formation of oxocarbenium ion **A** there is competition between the π electrons of the olefin and other molecules with nucleophilic character (e.g., H_2O) for attack of the electrophilic carbon. Reaction of the

Scheme 2. Side-Chain Exchange Reactions of Oxocarbenium Ion Intermediates

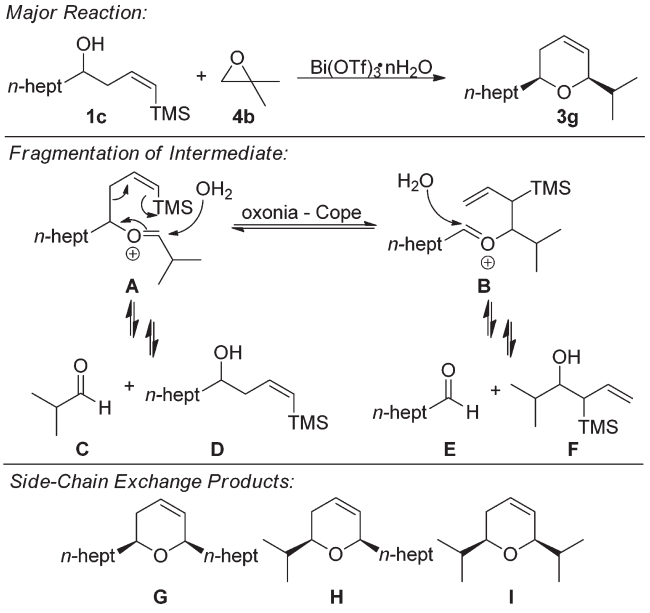
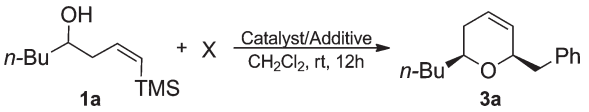
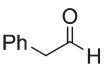
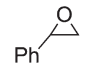


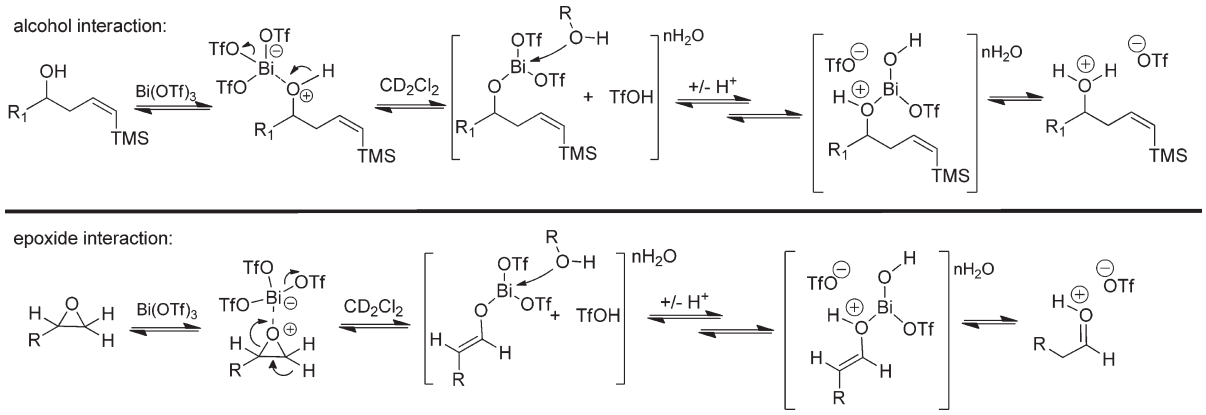
Table 4. Effects of Additives on the Addition/ISMS Reaction Sequence



entry	X	catalyst	mol%	additive	(%) yield[a]
1		$BiBr_3$	15	–	66
2		"	"	DTBMP[b]	0
3		TMSOTf	10	DTBMP[b]	0
4		$Bi(OTf)_3$•nH_2O	5	–	41
5		"	"	3Å sieves[c]	48
6		"	"	4Å sieves[c]	53
7		"	"	DTBMP[b]	0
8		$Bi(OTf)_3$•nH_2O[d]	10	–	0
9		$Bi(OTf)_3$	"	4Å sieves[c]	47
10		DTBMP•HOTf[e]	5	–	0
11		"	10	–	0
12		TfOH	"	–	58
13		TMSOTf	"	–	57
14		TMSOTf	"	DTBMP[b]	0
15		TfOH	"	DTBMP[b]	0

[a] Isolated yields of pure cis isomers only, after flash column chromatography. All the reactions were carried out on a ~0.5 mmol scale in 5.0 mL of CH_2Cl_2 at room temperature using 2.0 equiv of the corresponding epoxide. [b] 15 mol % 2,6-di-*tert*-butyl-4-methylpyridine. [c] Activated by heating with a propane torch under high vacuum. [d] $Bi(OTf)_3 \cdot nH_2O$ was stirred in dichloromethane for 30 min and filtered. Only filtrate was used in the reaction flask. [e] 2,6-Di-*tert*-butyl-4-methylpyridinium triflate.

Scheme 3. In Situ Generation of Ionic Triflates by Interaction of Substrates and $Bi(OTf)_3$



olefinic π electrons affords the desired cyclization, whereas readdition of water to the intermediate ion would result in the regeneration of the starting materials, **C** and **D**. Intramolecular oxonia-Cope rearrangement of the intermediate affords a different oxocarbenium ion, **B**, and results in the formation of new aldehyde **E** and hydroxyallylsilane **F**. The resulting mixture of aldehydes (**C** and **E**) and hydroxysilanes (**D** and **F**) can then undergo competing addition/ISMS sequences to potentially produce the three additional dihydropyran byproducts **G**−**I**. GC-MS analysis of dihydropyran **3g**, however, showed no change after exposure to catalyst, indicating that once the silyl-Prins step is complete, no further rearrangements or exchanges occur.[32]

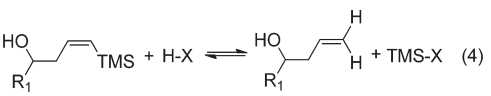
Probing the Role of $Bi(OTf)_3$. In an effort to explore the nature of $Bi(OTf)_3$ in the overall reaction scheme, experiments were run using a number of additives (Table 4). Initial studies focused on the production of HBr and TfOH in situ.[33] Consistent with the hypothesis that the purported Lewis acid acts as a source of HX, which in turn functions as the catalyst or initiator, addition of 15 mol % of the hindered, non-nucleophilic base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) completely suppressed the reaction (entries 2, 3, 7, 14, and 15).[30a] Given Ollevier and co-workers' report that DTBMP−TfOH efficiently catalyzed the three-component Mannich reaction,[34] we added 5 and 10 mol % of this salt to a solution of the epoxide and (*Z*)-δ-hydroxyalkenylsilane (entries 10 and 11). This resulted in no observable reaction. To confirm the efficacy of DTBMP as an acid scavenger, all reactivity was suppressed when the protocol was run with TfOH as the catalyst (entry 15).

Adventitious water was eliminated by running the reaction with both 3 Å and 4 Å activated molecular sieves. Neither of these had any effect on the reaction, resulting in moderate yields of product (entries 5, 6, and 9). If the Lewis acid had been producing the active catalytic species (HX) through hydrolytic interactions with adventitious H_2O, then presumably both the sieves and acid scavenger would have suppressed the reaction.

As shown in Scheme 3, a Lewis acid/Lewis base interaction between Bi(III) and the hydroxyl group on the (*Z*)-δ-hydroxyalkenylsilane could explain the inability of molecular sieves to suppress the sequence. To confirm that adventitious water alone does not contribute to the in situ production of TfOH, we stirred a suspension of $Bi(OTf)_3 \cdot nH_2O$ in CH_2Cl_2 for 30 min and filtered the solids through a 0.2 μm PTFE syringe filter. The resulting solution failed to induce rearrangement of the epoxide or the addition/ISMS sequence (Table 4, entry 8). The Lewis acid/Lewis base coordination results in the loss of a ligand ($^-$OTf) from the bismuth compound and produces TfOH in situ. Consistent with the observed experimental results, molecular sieves would have no effect on the reaction under this model, while DTBMP would neutralize any HX produced by either simple hydrolysis or the interaction of substrate with $Bi(OTf)_3$.

Due to Lambert and co-workers' hypothesis[28] that $Bi(OTf)_3$-catalyzed reactions afford TMSOTf and that both species are participating in the overall mechanism, we initially presumed that TMSOTf was the active species, since at 10 mol % it promotes the reaction to afford product in moderate yield (Table 4, entry 13). Additionally, desilylation of (*Z*)-1-(trimethylsilyl)oct-1-en-4-ol (**1a**) occurs readily in the presence of TfOH to produce TMSOTf in situ. Only after addition of excess acid do reactions other than protodesilylation occur and cause significant decomposition of the starting material; this most likely occurs through formation of carbocationic intermediates from protonation of the hydroxyl moiety, as proposed by Keramane et al. in mechanistic studies of $BiCl_3$-catalyzed chlorination reactions of benzylic alcohols[35] and the benzylation of alcohols.[36] In both of these cases, however, the authors argue that the Bi(III) atoms are acting as Lewis acids.

At 10 mol % loading levels, TMSOTf, $Bi(OTf)_3 \cdot H_2O$, and $BiBr_3$ all promote the protodesilylation (GC-MS) of the olefin, generating TMSBr or TMSOTf in situ (eq 4). Since all reactivity ceases when the Lewis acid TMSOTf is added in the presence of DTBMP, Brønsted acid (TfOH) must be the actual catalyst. Any protodesilylation of the starting material results only in a small amount of TMSOTf as a byproduct.



A number of NMR experiments were also performed to further validate that the reaction is catalyzed by triflic acid. We found that $Bi(OTf)_3 \cdot nH_2O$ is insoluble in CD_2Cl_2 at room temperature even when H_2O is present in small, but detectable, amounts in the NMR solvent. No resonances were observed in the ^1H, ^{19}F, or ^{13}C NMR spectra, even with prolonged acquisition times. If any $Bi(OTf)_3 \cdot nH_2O$ is slightly soluble, it is below the limit of detection in NMR spectroscopic experiments.

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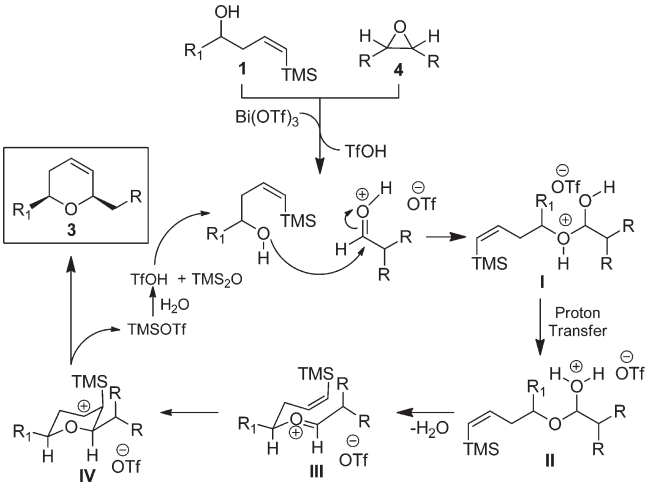
Scheme 4. Proposed Mechanism for Combined Rearrangement, Addition, and ISMS Reaction to Dihydropyrans 3



The signature ^{19}F peaks for TfOH (−76.3 ppm), TMSOTf (−77.4 ppm), and $Bu_4N^+{}^-OTf$ (−78.7 ppm) were determined using authentic standards. Upon addition of either alkenylsilane or styrene oxide to both 5 and 10 mol % $Bi(OTf)_3$ in CD_2Cl_2, a ^{19}F peak was observed corresponding to the triflate anion (−78.8 ppm). This same resonance was observed when either substrate was subjected to 10% TfOH and 10% TMSOTf.

To further test the argument that the water present in the $Bi(OTf)_3 \cdot nH_2O$ simply reacts in the reaction medium to afford TfOH in situ, a suspension of bismuth triflate was stirred rapidly at room temperature in CD_2Cl_2 for 90 min under an argon atmosphere. The suspension was then filtered through a plug of fine glass fibers to remove the suspended solids but to allow dissolved species to remain in solution. Unlike the case in which phenylacetaldehyde was added directly to an unfiltered suspension and underwent some aldol reaction, addition of the same aldehyde to the filtered solvent showed no propensity to react. When a similar experiment with filtered $Bi(OTf)_3 \cdot nH_2O$ was performed with the alkenylsilane, no desilylation was observed even after 48 h at room temperature. These two experiments once again indicate that intimate contact of the organic substrates and bismuth salt is necessary to activate the suspended $Bi(OTf)_3$ and facilitate dissolution of the solid to afford TfOH, which catalyzes either reaction. Therefore, the Lewis acidity of $Bi(OTf)_3$ does play an important role in the tandem reaction, even though the bismuth compound is not the catalytic species.

The observance of the triflate anion peak is likely due to the presence of an ion pair with the triflate anion acting as the counterion to the protonated substrate (see Scheme 4, vide infra). In order to further assess this possibility, we dissolved cyclohexanol in CD_2Cl_2 and then added 10 mol % $Bi(OTf)_3$ followed by 10 mol % TfOH. Upon addition of bismuth triflate, a ^{19}F signal was observed at −78.9 ppm; addition of TfOH to the same tube increased the intensity of this same resonance. Similar spectroscopic signals were observed for interactions of cyclohexanone with both $Bi(OTf)_3$ and TfOH. As a whole, these studies provide compelling evidence that the overall reaction is TfOH catalyzed but that the Lewis acidic nature of the $Bi(OTf)_3$ is still important as an initiation step.

Mechanistic Considerations. A key finding of our experiments is that a Lewis acid/base interaction between the substrates and $Bi(OTf)_3 \cdot nH_2O$ occurs prior to formation of any significant quantities of TfOH. Once catalytic quantities of TfOH are present, the reaction proceeds in the same manner as briefly explained in Scheme 1 (vide supra). As more completely shown in Scheme 4, protonation of the aldehyde electrophile is followed by attack of the hydroxyl moiety of the (*Z*)-*δ*-hydroxyalkenylsilane **1** to afford protonated hemiacetal **I**. Proton transfer and elimination of water generates the (*E*)-oxocarbenium ion **III**, which is completely analogous to intermediate **A** from Scheme 1. The pseudoequatorial disposition of the two side chains and pseudoaxial orientation of the silyl group[14e] all favor formation of the *cis*-2,6-disubstituted carbocation **IV**, and elimination of TMSOTf provides product **3**. Hydrolysis of the TMSOTf then regenerates TfOH and forms disiloxane (TMSOTMS) as a byproduct. As previously shown, oxocarbenium ion **III** can undergo [3,3] sigmatropic oxonia-Cope rearrangements to provide some side-chain exchange products which are certainly more prevalent when reactions are run with $Bi(OTf)_3$ instead of $BiBr_3$.[32a]

CONCLUSIONS

We have developed a convenient $Bi(OTf)_3$-initiated cascade reaction involving epoxide rearrangement to an aldehyde electrophile, intermolecular addition of the (*Z*)-*δ*-hydroxyalkenylsilane **1**, and an ISMS reaction to afford *cis*-2,6-disubstituted-3,6-dihydro-2*H*-pyrans **3** in moderate to good yields. NMR spectroscopic evaluation of $Bi(OTf)_3$ in the presence of substrates indicate that Lewis acid/base interactions are necessary to liberate TfOH, the catalytic species, in solution.

EXPERIMENTAL SECTION

Materials. All reagents and substrates were used as received unless otherwise noted. Dichloromethane was distilled from CaH_2. Trifluoromethanesulfonic acid (TfOH) was purchased from Acros Organics, Inc. Bismuth bromide and bismuth triflate were purchased from Aldrich Chemical Co., Inc. Trimethylsilyltrifluoromethanesulfonate was obtained from GFS Chemicals, Inc. Bismuth triflate tetrahydrate ($Bi(OTf)_3 \cdot 4H_2O$) was synthesized from triflic acid and triphenylbismuth.[29] Compounds **1a**−**d** were synthesized as previously described.[9] NMR spectra (^{13}C) were recorded with the aid of an APT experiment in which methylene (2H) and quaternary carbons (0H) are even (e) and methyl (3H) and methyne (1H) carbons are odd (o). Coupling constants were determined by the method outlined by Hoye and Zhao.[37] Single-crystal X-ray determinations were carried out using a Bruker SMART Apex II diffractometer with graphite-monochromated Cu Kα radiation. Chromatography was performed using 200−475 mesh silica gel. Unless otherwise noted, all experiments were conducted under an argon atmosphere. All compounds were judged to be >95% homogeneous by ^1H NMR spectroscopy.

NMR Spectroscopy Studies. ^1H and ^{13}C NMR chemical shifts are reported as δ using CD_2Cl_2 as a solvent and are referenced to dichloromethane or trimethylsilane. ^{19}F NMR chemical shifts are reported as δ using trichlorofluoromethane as an internal standard (δ 0.0). NMR samples were prepared by addition of 5−10% catalyst to a solution of substrate (25−50 mg), 0.75 mL of deuterated dichloromethane, and 10 μL of trichlorofluoromethane. In the case of the addition of multiple catalysts, the catalysts (10 mol % each addition) were added sequentially to the same NMR sample, recording both ^1H and ^{19}F spectra between additions.

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General Procedure for the Synthesis of Dihydropyrans 3a−o. The catalyst (TfOH, TMS-OTf, $BiOTf_3$, $BiBr_3$; 0.010−0.050 equiv) was weighed into a 15 mL round-bottom flask, and 5 mL of CH_2Cl_2 was added via syringe. The solution was cooled to 0 °C using an ice−water bath. δ-Hydroxyalkenylsilanes **1a**−**d** (1.0 equiv) and epoxides **4a**−**f** (1.1−2.0 equiv) were added sequentially. The mixture was warmed to room temperature slowly and stirred for 12 h. The suspension was then filtered through a small SiO_2 pipet column with CH_2Cl_2 as eluent and concentrated in vacuo again. The product was then purified by column chromatography.

*Preparation of cis-6-Benzyl-2-butyl-3,6-dihydro-2H-pyran (**3a**).* According to the general procedure, (*Z*)-1-(trimethylsilyl)oct-1-en-4-ol (**1a**; 0.100 g, 0.50 mmol, 1.00 equiv) was treated with styrene oxide (0.120 g, 1.00 mmol, 2.0 equiv) to provide 0.067 g (58%) of **3a** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.57): IR (neat) 3029 (m), 2955 (s), 2929 (s), 2860 (m), 1454 (m), 1184 (m), 1085 (s), 1064 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18−7.31 (m, 5H), 5.76−5.81 (m, 1H), 5.61 (dm, *J* = 10.3 Hz, 1H), 4.31 (m, 1H), 3.48−3.54 (m, 1H), 2.99 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.68 (dd, *J* = 13.5, 7.0 Hz, 1H), 1.92−1.98 (m, 2H), 1.22−1.64 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (e), 129.7 (o), 129.4 (o), 128.2 (o), 126.2 (o), 125.2 (o), 76.0 (o), 74.3 (o), 42.3 (e), 36.1 (e), 31.6 (e), 28.0 (e), 23.1 (e), 14.5 (o). Anal. Calcd for $C_{16}H_{22}O$ (230.35): C, 83.43; H, 9.63. Found: C, 83.51; H, 9.67.

*Preparation of cis-2-Butyl-6-isopropyl-3,6-dihydro-2H-pyran (**3b**).* According to the general procedure, (*Z*)-1-(trimethylsilyl) oct-1-en-4-ol (**1a**; 0.100 g, 0.500 mmol, 1.00 equiv) was treated with isobutylene oxide (0.072 g, 1.00 mmol, 2.0 equiv) to provide 0.057 g (63%) of **3b** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.62): IR (neat) 3031 (m), 2957 (s), 2929 (s), 2868 (s), 1465 (m), 1366 (m), 1185 (m), 1080(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80−5.85 (m, 1H), 5.66 (dq, *J* = 10.3, 1.5 Hz, 1H), 3.84−3.88 (m, 1H), 3.44−3.51 (m, 1H), 1.90−1.94 (m, 2H), 1.71−1.79 (dq, *J* = 6.6, 5.5 Hz, 1H), 1.25−1.60 (m, 6H), 0.93 (d, *J* = 5.5 Hz, 3H), 0.92 (d, *J* = 5.5 Hz, 3H), 0.90(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.6 (o), 125.6 (o), 79.8 (o), 74.0 (o), 36.2 (e), 33.0 (o), 31.8 (e), 28.1 (e), 23.1 (e), 18.3 (o), 14.5 (o). Anal. Calcd for $C_{12}H_{22}O$ (182.30): C, 79.06; H, 12.16. Found: C, 79.06; H, 12.22.

*Preparation of cis-6-Benzhydryl-2-butyl-3,6-dihydro-2H-pyran (**3c**).* According to the general procedure, (*Z*)-1-(trimethyl-silyl)oct-1-en-4-ol (**1a**; 0.100 g, 0.500 mmol, 1.00 equiv) was treated with *trans*-stilbene oxide (0.108 g, 0.55 mmol, 1.1 equiv) to provide 0.047 g (31%) of **3c** as a colorless powder, after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.43): IR (neat) 3060 (m), 3026 (m), 2954 (s), 2926 (s), 2858 (s), 1599 (m), 1495 (s), 1451 (s), 1369 (m), 1187 (m), 1094 (s), 745 (s), 699 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13−7.37 (m, 10H), 5.74−5.78 (m, 1H), 5.55 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.78−4.83 (m, 1H), 3.97 (d, *J* = 8.4 Hz, 1H), 3.52−3.59 (m, 1H), 1.88−1.99 (m, 2H), 1.18−1.54 (m, 6H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5 (e), 142.1 (e), 129.01 (o), 128.97 (o), 128.93 (o), 128.4 (o), 127.9 (o), 126.4 (o), 126.12 (o), 126.06 (o), 76.9 (o), 74.5 (o), 56.6 (o), 35.9 (e), 31.7 (e), 28.1 (e), 22.8 (e), 14.5 (o). Anal. Calcd for $C_{22}H_{26}O$ (306.44): C, 86.23; H, 8.55. Found: C, 85.85; H, 8.53.

*Preparation of cis-6-Benzyl-2-ethyl-3,6-dihydro-2H-pyran (**3d**).* According to the general procedure, (*Z*)-6-(trimethylsilyl)hex-5-en-3-ol (**1b**; 0.100 g, 0.580 mmol, 1.0 equiv) was reacted with styrene oxide (0.139 g, 1.16 mmol, 2.0 equiv) to provide 0.062 g (53%) of **3d** as a pale yellow oil, after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.52): IR (neat) 3030 (m), 2963 (s), 1496 (m), 1185 (m), 1086 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.37 (m, 5H), 5.85 (ddd, *J* = 10.2, 1.6 Hz, 1H), 5.67 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.36−4.39 (m, 1H), 3.51 (q, *J* = 6.6 Hz, 1H), 3.05 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.00−2.03 (m, 2H), 1.51−1.71 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (e), 129.8 (o), 129.6 (o), 128.3 (o), 126.3 (o), 125.3 (o), 76.0 (o), 75.6 (o), 42.3 (e), 31.0 (e), 29.2 (e), 10.1 (o); HRMS (CI) calcd for $(C_{14}H_{18}O)Na$ $(M + Na)^+$ 225.1250, found 225.1250.

*Preparation of cis-6-Benzhydryl-2-ethyl-3,6-dihydro-2H-pyran (**3e**).* According to the general procedure (*Z*)-6-(trimethylsilyl)hex-5-en-3-ol (**1b**; 0.100 g, 0.58 mmol, 1.0 equiv) was treated with *trans*-stilbene oxide (0.228 g, 1.16 mmol, 2.0 equiv) to provide 0.047 g (29%) of **3e** as colorless crystals after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.47): IR (neat) 3055 (m), 2985 (s), 2306 (s), 2306 (s), 1599 (s), 1495 (s), 1265 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16−7.37 (m, 10H), 5.74−5.79 (m, 1H), 5.56 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.80−4.83 (m, 1H), 3.98 (d, *J* = 8.2 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 1.92−1.96 (m, 2H), 1.34−1.52 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (e), 142.2 (e), 129.2 (o), 129.1 (o), 128.6 (o), 128.0 (o), 126.5 (o), 126.2 (o), 76.9 (o), 75.9 (o), 56.6 (o), 31.2 (e), 29.2 (e), 10.3 (o); HRMS (CI) calcd for $(C_{20}H_{22}O)Na$ $(M + Na)^+$ 301.1563, found 301.1563.

*Preparation of cis-6-Benzyl-2-heptyl-3,6-dihydro-2H-pyran (**3f**).* According to the general procedure (*Z*)-1-(trimethylsilyl)undec-1-en-4-ol (**1c**; 0.075 g, 0.31 mmol, 1.0 equiv) was treated with styrene oxide (0.041 g, 0.34 mmol, 1.1 equiv) to provide 0.050 g (59%) of **3f** as a pale yellow liquid after column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.56): IR (neat) 3029 (s), 2858 (s), 1604 (s), 1495 (m), 1185 (m), 1085 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19−7.31 (m, 5H), 5.79 (dm, *J* = 10.2 Hz, 1H), 5.60 (dm, *J* = 10.0 Hz, 1H), 4.29−4.33 (m, 1H), 3.48−3.54 (m, 1H), 2.99 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.68 (dd, *J* = 13.7, 7.4 Hz, 1H), 1.93−1.98 (m, 2H), 1.27−1.62 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (e), 129.8 (o), 129.6 (o), 128.3 (o), 126.3 (o), 125.3 (o), 76.0 (o), 74.3 (o), 42.3 (e), 36.3 (e), 32.0 (e), 31.5 (e), 29.8 (e), 29.5 (e), 25.7 (e), 22.9 (e), 14.4 (o); HRMS (CI) calcd for $(C_{19}H_{28}O)Na$ $(M + Na)^+$ 295.2032, found 295.2033.

*Preparation of cis-2-Heptyl-6-isopropyl-3,6-dihydro-2H-pyran (**3g**).* According to the general procedure (*Z*)-1-(trimethylsilyl)undec-1-en-4-ol (**1c**; 0.150 g, 0.62 mmol, 1.0 equiv) was treated with isobutylene oxide (0.089 g, 1.23 mmol, 2.0 equiv) to provide 0.072 g (52% yield) of **3g** and 0.018 g (11%) of inseparable 2,6-diheptyl-3,6-dihydro-2*H*-pyran as a pale yellow liquid, after column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.72): IR (neat) 3035 (s), 2972 (s), 1467 (s), 1186 (s), 1076 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80−5.86 (m, 1H), 5.67 (dq, *J* = 10.16, 1.6 Hz, 1H), 3.83−3.88 (m, 1H), 3.44−3.51 (m, 1H), 1.89−1.94 (m, 2H), 1.75 (dh, *J* = 5.5, 1.4 Hz, 1H), 1.20−1.60 (m, 12H), 0.86−0.96 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8 (o), 125.8 (o), 79.8 (o), 74.0 (o), 36.4 (e), 32.9 (o), 32.1 (e), 31.7 (e), 29.9 (e), 29.5 (e), 25.7 (e), 22.9 (e), 18.2 (o), 14.3 (o); HRMS (CI) calcd for $(C_{15}H_{28}O)_2Na$ $(2\ M + Na)^+$ 471.4173, found 471.416.

*Preparation of cis-6-Benzyl-2-phenethyl-3,6-dihydro-2H-pyran (**3h**).* According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (**1d**; 0.100 g, 0.40 mmol, 1.00 equiv) was treated with styrene oxide (0.100 g, 0.80 mmol, 2.0 equiv) to provide 0.069 g (62%) of **3h** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/diethyl ether, R_f = 0.64): IR (neat) 3062 (s), 3028 (s), 2923 (s), 2858 (s), 1603 (s), 1495 (s), 1454 (s), 1084 (s), 1064 (s), 747 (s), 699 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07−7.37 (m, 10H), 5.78−5.82 (m, 1H), 5.65 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.27−4.29 (1H, m), 3.47 (1H, ddd, *J* = 14, 9.2, 4.8 Hz), 2.98 (1H, dd, *J* = 13.4, 7.8 Hz), 2.64−2.81 (3H, m), 1.74−2.08 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4 (e), 138.9 (e), 129.8 (o), 128.7 (o), 128.5 (o), 128.3 (o), 126.4 (o), 125.8 (o), 125.3 (o), 76.0 (o), 72.9 (o), 42.3 (e), 37.7 (e), 31.7 (e), 31.5 (e).

*Preparation of cis-2-Phenethyl-6-isopropyl-3,6-dihydro-2H-pyran (**3i**).*[38] According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (**1d**; 0.100 g, 4.00 mmol, 1.00 equiv) was treated with isobutylene oxide (0.06 g, 0.80 mmol, 2.0 equiv) to provide 0.054 g (60%) of pure product **3i** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/diethyl ether; R_f = 0.67): IR (neat) 3028.0 (s), 2959.6 (s), 2649.2 (s), 2360.9 (s), 1940.7 (s), 1603.8 (m), 1096.7 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17−7.31 (5H, m), 5.80−5.84 (1H, m), 5.67 (1H, dt, *J* = 10, 1.2 Hz), 3.85 (1H, dd, *J* = 3.4, 1.4 Hz), 3.48 (1H, dddd, *J* = 14, 4.4 Hz), 2.69−2.86 (2H, m), 1.72−2.04 (5H, m), 0.97 (6H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6 (e), 129.0 (o), 128.8 (o), 128.5 (o), 125.8 (o), 125.6 (o), 79.7 (o), 72.6 (o), 37.8 (e), 33.0 (o), 31.8 (e), 31.7 (e), 18.4 (o), 18.1 (o); HRMS (CI) calcd for $(C_{16}H_{22}O)Na$ $(M + Na)^+$ 253.1563, found 253.1556.

*Preparation of cis-2-Butyl-6-(4-fluorobenzyl)-3,6-dihydro-2H-pyran (**3j**).* According to the general procedure, (*Z*)-1-(trimethylsilyl)oct-1-en-4-ol (**1a**; 0.100 g, 0.50 mmol, 1.00 equiv) was treated with 2-(4-fluorophenyl)oxirane (**4d**; 0.140 g, 1.00 mmol, 2.00 equiv) to provide 0.058 g (47%) of **3j** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.51): IR (neat) 3035 (s), 2932 (s), 2861 (s), 1601 (s), 1510 (s), 1222 (s), 1157 (s), 1072 (s), 843 (s), 713 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 6.8 Hz, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 5.79−5.84 (m, 1H), 5.61 (d, *J* = 10.2 Hz, 1H), 4.26−4.32 (m, 1H), 3.48−3.56 (m, 1H), 2.93 (dd, *J* = 7.0, 6.6 Hz, 1H), 2.70 (dd, *J* = 7.0, 6.6 Hz, 1H), 1.92−1.99 (m, 2H), 1.28−1.65 (m, 6H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (e) (C−F; q, *J* = 244.0 Hz), 134.3 (e), 131.2 (o), 131.1 (o), 129.4 (o), 125.6 (o), 115.1 (o), 114.9 (o), 75.8 (o), 74.3 (o), 41.3 (e), 36.0 (e), 31.4 (e), 27.9 (e), 22.9 (e), 14.3 (o); HRMS (CI) calcd for $(C_{16}H_{21}FO)Na$ $(M + Na)^+$ 271.1469, found 271.1462.

*Preparation of cis-2-Butyl-6-(4-chlorobenzyl)-3,6-dihydro-2H-pyran (**3k**).* According to the general procedure, (*Z*)-1-(trimethylsilyl)oct-1-en-4-ol (**1a**; 0.100 g, 0.50 mmol, 1.00 equiv) was treated with 2-(4-chlorophenyl)oxirane (0.12 mL, 1.00 mmol, 2.00 equiv), to provide 0.065 g (49%) of **3k** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.56): IR (neat) 3032 (s), 2933 (s), 2861 (s), 1493 (s), 1184 (s), 1091 (s), 833 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 14.0, 7.0 Hz, 4H), 5.76−5.82 (m, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 4.27 (s, 1H), 3.45−3.54 (m, 1H), 2.89 (dd, *J* = 7.0, 6.6 Hz, 1H), 2.68 (dd, *J* = 7.4, 6.3 Hz, 1H), 1.91−1.96 (m, 2H), 1.25−1.62 (m, 6H), 0.91 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (e), 132.1 (e), 131.1 (o), 129.4 (o), 128.3 (o), 125.7 (o), 75.6 (o), 74.3 (o), 41.5 (e), 36.0 (e), 31.4 (e), 27.9 (e), 22.9 (e), 14.3 (o); HRMS (CI) calcd for $(C_{16}H_{21}ClO)Na$ $(M + Na)^+$ 287.1173, found 287.1170.

*Preparation of cis-6-(4-Bromobenzyl)-2-butyl-3,6-dihydro-2H-pyran (**3l**).* According to the general procedure, (*Z*)-1-(trimethylsilyl)oct-1-en-4-ol (**1a**; 0.100 g, 0.50 mmol, 1.00 equiv) was treated with 2-(4-bromophenyl)oxirane (0.200 g, 1.00 mmol, 2.00 equiv) to provide 0.063 g (41%) of **3l** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/ethyl ether, R_f = 0.46): IR (neat) 3032 (s), 2959 (s), 2861 (s), 1652 (s), 1489 (s), 1368 (s), 1184 (s), 1072 (s), 1012 (s), 712(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2, Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 5.77−5.84 (m, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 4.25−4.31 (m, 1H), 3.46−3.54 (m, 1H), 2.89 (dd, *J* = 7.4, 6.3 Hz, 1H), 2.68 (dd, *J* = 7.0, 6.6 Hz, 1H), 1.92−1.97 (m, 2H), 1.25−1.63 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (e), 131.6 (o), 131.3 (o), 129.3 (o), 125.7 (o), 120.2 (e), 75.5 (o), 74.3 (o), 41.6 (e), 36.0 (e), 31.4 (e), 27.9 (e), 22.9 (e), 14.3 (o); HRMS (CI) calcd for $(C_{16}H_{21}BrO)Na$ $(M + Na)^+$ 331.0668, found 331.0664.

*Preparation of cis-6-(4-Fluorobenzyl)-2-phenethyl-3,6-dihydro-2H-pyran (**3m**).* According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (**1d**; 0.124 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-fluorophenyl)oxirane (**4d**; 0.138 g, 1.00 mmol, 2.0 equiv) to provide 0.088 g (60%) of **3m** as a colorless oil, after purification by column chromatography (95/5 petroleum ether/diethyl ether, R_f = 0.53): IR (neat) 3024 (s), 2929 (s), 1946 (s), 1889 (s), 1724 (s), 1601 (s), 1496 (s), 1157 (s), 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95−7.30 (m, 9H), 5.75−5.82 (1H, m), 5.60 (d, *J* = 10.2 Hz, 1H), 4.18−4.25 (m, 1H), 3.39−3.48 (m, 1H), 2.88 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.59− 2.77 (m, 3H), 1.70−2.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (e) (C−F; q, *J* = 243.3 Hz), 142.3 (e), 134.5 (e), 131.2 (o), 129.6 (o), 128.7 (o), 128.5 (o), 125.9 (o), 125.5 (o), 115.1 (o), 114.9 (o), 75.8 (o), 72.8 (o), 41.3 (e), 37.7 (e), 31.7 (e), 31.4 (e); HRMS (CI) calcd for $(C_{20}H_{21}FO)Na$ $(M + Na)^+$ 319.1469, found 319.1465.

*Preparation of cis-6-(4-Chlorobenzyl)-2-phenethyl-3,6-dihydro-2H-pyran (**3n**).* According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (**1d**; 0.124 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-chlorophenyl)oxirane (0.155 g, 1.00 mmol, 2.0 equiv), to provide 0.087 g (56%) of **3n** as a pale yellow oil, after purification by column chromatography (95/5 petroleum ether/diethyl ether, R_f = 0.43): IR (neat) 3024 (s), 2924 (s), 1721 (s), 1602 (s), 1493 (s), 1368 (s), 1185 (s), 1017 (s), 835 (s), 746 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09−7.32 (m, 9H), 5.77−5.83 (m, 1H), 5.62 (dt, *J* = 10.2, 1.2 Hz, 1H), 4.23−4.28 (m, 1H), 3.42−3.50 (m, 1H), 2.98 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.64−2.81 (m, 3H), 1.74−2.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3 (e), 137.3 (e), 132.1 (e), 131.2 (o), 129.5 (o), 128.7 (o), 128.5 (o), 128.4 (o), 125.9 (o), 125.6 (o), 75.6 (o), 72.9 (o), 41.5 (e), 37.7 (e), 31.7 (e), 31.4 (e); HRMS (CI) calcd for $(C_{20}H_{21}ClO)Na$ $(M + Na)^+$ 335.1173, found 335.1171.

*Preparation of cis-6-(4-Bromobenzyl)-2-phenethyl-3,6-dihydro-2H-pyran (**3o**).* According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (**1d**; 0.124 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-bromophenyl)oxirane (0.199 g, 1.0 mmol, 2.0 equiv) to provide 0.099 g (53%) of **3o** as a pale yellow oil, after purification by column chromatography (95/5 petroleum ether/diethyl ether, R_f = 0.48): IR (neat) 3024 (s), 1652 (s), 1489 (s), 1454 (s), 1368 (s), 1185 (s), 746 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08−7.50 (m, 9H), 5.78−5.83 (m, 1H), 5.61 (dm, *J* = 10.16 Hz, 1H), 4.25 (dm, *J* = 1.6 Hz, 1H), 3.42−3.55 (m, 1H), 2.60−2.95 (m, 4H), 1.72− 2.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3 (e), 137.8 (e), 131.6 (o), 131.3 (o), 129.5 (o), 128.7 (o), 128.5 (o), 125.9 (o), 125.6 (o), 120.2 (e), 75.5 (o), 72.9 (o), 41.6 (e), 37.7 (e), 31.7 (e), 31.4 (e); HRMS (CI) calcd for $(C_{20}H_{21}BrO)Na$ $(M + Na)^+$ 379.0668, found 379.0663.

■ ASSOCIATED CONTENT

Supporting Information. Figures, tables, and a CIF file giving ^1H and ^{13}C APT NMR spectra for **3a**−**o**, ^{19}F resonances for substrates and triflate species, and X-ray crystallographic data for **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 757-221-1501. Fax: 757-221-2715. E-mail: rjhink@wm.edu.

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REFERENCES

(1) (a) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. S. *Chem. Soc. Rev.* **2011**, *40*, 4649–4704. (b) Sandhu, S.; Sandhu, J. S. *Rasãyan J. Chem.* **2011**, *4*, 73–85. (c) Salvador, J. A. R.; Pinto, R. M. A.; Silvestre, S. M. *Curr. Org. Synth.* **2009**, *6*, 426–470. (d) Hua, R. *Curr. Org. Synth.* **2008**, *5*, 1–27. (e) Komatsu, N. In *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: New York, 2001; pp 371−440. (f) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517–2532. (g) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373–8397.

(2) Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215–7218.

(3) Wada, M.; Nagayama, S.; Mizutani, K.; Hiroi, R.; Miyoshi, N. *Chem. Lett.* **2002**, 248–249.

(4) Garrigues, B.; Gonzaga, F.; Robert, H.; Dubac, J. *J. Org. Chem.* **1997**, *62*, 4880–4882.

(5) Evans, P. A.; Andrews, W. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5426–5429. (b) Jung, H. H.; Seiders, J. R.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8464–8467.

(6) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883–3885.

(7) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702–14703.

(8) Wipf, P.; Hopkins, T. D. *Chem. Commun.* **2005**, 3421–3423.

(9) (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456–11457. (b) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005**, *61*, 11679–11685.

(10) Hinkle, R. J.; Lian, Y.; Speight, L. C.; Stevenson, H. E.; Sprachman, M. M.; Katkish, L. A.; Mattern, M. C. *Tetrahedron* **2009**, *65*, 6834–6839.

(11) Lian, Y.; Hinkle, R. J. *J. Org. Chem.* **2006**, *71*, 7071–7074.

(12) For the efficient rearrangement of epoxides with catalytic $Bi(OTf)_3$, see: Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129–8132.

(13) For a few recent examples, see: (a) Wender, P. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 9228–9231. (b) Gesinski, M. R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2011**, *133*, 9727–9729. (c) Lin, H.-Y.; Snider, B. B. *Org. Lett.* **2011**, *13*, 1234–1237. (d) Fenster, E.; Fehl, C.; Aubé, J. *Org. Lett.* **2011**, *13*, 2614–2617. (e) Tenenbaum, J. M.; Morris, W. J.; Custar, D. W.; Scheidt, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5892–5895. (f) Wang, J.; Crane, E. A.; Scheidt, K. A. *Org. Lett.* **2011**, *13*, 3086–3089. (g) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445. (h) Reddy, U.; Saikia, A. K. *Synlett* **2010**, 1027–1032. (i) Li, H.; Loh, T.-P. *Org. Lett.* **2010**, *12*, 2679–2681.

(14) (a) Hémery, T.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Synthesis* **2010**, 329–342. (b) Pham, M.; Allatabakhsh, A.; Minehan, T. G. *J. Org. Chem.* **2008**, *73*, 741–744. (c) Meilert, K.; Brimble, M. A. *Org. Biomol. Chem.* **2006**, *4*, 2184–2192. (d) Dobbs, A. P.; Guesné, S. J. J. *Synlett* **2005**, 2101–2103. (e) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426–3427.

(15) For Dobbs' work on Prins and silyl-Prins reactions, see: (a) Chio, F. K.; Warne, J.; Gough, D.; Penny, M.; Green, S.; Coles, S. J.; Hursthouse, M. B.; Jones, P.; Hassall, L.; McGuire, T. M.; Dobbs, A. P. *Tetrahedron* **2011**, *67*, 5107–5124. (b) Dobbs, A. P.; Guesné, S. J. J.; Martinović, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880–7883. (c) Dobbs, A. P.; Martinović, S. *Tetrahedron Lett.* **2002**, *43*, 7055–7057.

(16) For a recent example in an approach toward SCH 351448, see: Cheung, L. L.; Marumoto, S.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101–3104.

(17) Markó and co-workers developed and have extensively examined the ISMS reaction. For fundamental, representative examples, see: (a) Leroy, B.; Markó, I. E. *Tetrahedron Lett.* **2001**, *42*, 8685–8688. (b) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899–2902. (c) Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141–7156.

(18) Several researchers claim that Bi(III) salts produce H−X in situ; see: (a) Bouguerne, B.; Hoffmann, P.; Lherbet, C. *Synth. Commun.* **2010**, *40*, 915–926. (b) Pinto, R. M. A.; Salvador, J. A. R.; Le Roux, C.; Carvalho, R. A.; Beja, A. M.; Paixão, J. A. *Tetrahedron* **2009**, *65*, 6169–6178. (c) Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2004**, *45*, 825–829.

(19) Spectroscopic evidence for the role of $Bi(OTf)_3$ as a Lewis acid was recently claimed: (a) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409–413. (b) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611–1614.

(20) Kadam, S. T.; Kim, S. S. *J. Organomet. Chem.* **2009**, *694*, 2562–2566.

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

(22) Hayashi, R.; Cook, G. R. *Tetrahedron Lett.* **2008**, *49*, 3888–3890.

(23) Donnelly, S.; Thomas, E. J.; Arnott, E. A. *Chem. Commun.* **2003**, 1460–1461.

(24) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49–52.

(25) Lewis acidity is evident in Bi(III) compounds with bridging ligands: Yin, S.-F.; Shimada, S. *Chem. Commun.* **2009**, 1136–1138.

(26) Ollevier, T.; Mwene-Mbeja, T. M. *Tetrahedron Lett.* **2006**, *47*, 4051–4055.

(27) Salvador, J. A. R.; Pinto, R. M. A.; Silvestre, S. M. *Mini-Rev. Org. Chem.* **2009**, *6*, 241–274.

(28) Kelly, B. D.; Allen, J. M.; Tundell, R. E.; Lambert, T. H. *Org. Lett.* **2009**, *11*, 1381–1383.

(29) Labrouillère, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1999**, *40*, 285–286.

(30) (a) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484–493. (b) Bajwa, J. S.; Jiang, X.; Slade, J.; Prasad, K.; Repíc, O.; Blacklock, T. J. *Tetrahedron Lett.* **2002**, *43*, 6709–6713.

(31) In order to explain low yields for reactions involving *trans*-stilbene oxide, a reviewer suggested that 2,2-diphenylacetaldehyde likely exists substantially in the enol form under the reaction conditions and is, therefore, unavailable to act as an electrophile.

(32) For extensive mechanistic discussions, see: (a) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640–13648. (b) Jasti, R; Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2175–2178.

(33) Grimster, N. P.; Wilton, D. A. A.; Chan, L. K. M.; Godfrey, C. R. A.; Green, C.; Owen, D. R.; Gaunt, M. J. *Tetrahedron* **2010**, *66*, 6429–6436.

(34) (a) Ollevier, T.; Nadeau, E.; Guay-Bégin, A.-A. *Tetrahedron Lett.* **2006**, *47*, 8351–8354. (b) Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292–9295.

(35) Keramane, E. M.; Boyer, B.; Roque, J.-P. *Tetrahedron* **2001**, *57*, 1909–1916.

(36) Keramane, E. M.; Boyer, B.; Roque, J.-P. *Tetrahedron* **2001**, *57*, 1917–1921.

(37) Hoye, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014–4016.

(38) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299–1303.