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Synthesis of 2,6-disubstituted dihydropyrans via an efficient BiBr₃-initiated three component, one-pot cascade

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ABSTRACT

The rapid synthesis of *cis*-2,6-disubstituted dihydropyrans is achieved in a three-component, one-pot cascade reaction. BiBr₃-mediated addition of ketene silyl acetals or silyl enol ethers to β,γ -unsaturated *cis*-4-trimethylsilyl-3-butenal provides a Mukaiyama aldol adduct containing a vinylsilane moiety tethered to a silyl ether. Addition of a second aldehyde initiates a domino sequence involving intermolecular addition followed by an intramolecular silyl-modified Sakurai (ISMS) reaction. Isolated yields of this one-pot reaction vary from 44 to 80% and all compounds were isolated as the *cis*-diastereomers (10 examples).

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1. Introduction

In efforts to reduce environmental impacts, increase atom economy as well as overall efficiency and convergence of experimental protocols, one-pot, multi-component reactions (MCRs)¹ have become increasingly common in organic synthesis. Efforts toward a number of natural products have resulted in the development of several protocols in which formation of an initial adduct is required to provide the substrate for a subsequent reaction. The literature has alternatively referred to such processes as tandem, multi-component, cascade, or domino reactions, although the precise meaning of each adjective has not been entirely consistent.²

As part of a program to further develop the uses of environmentally-benign^{3,4} Bi(III) compounds in organic synthesis, we recently described⁵ the BiBr₃-initiated intermolecular addition followed by intramolecular silyl-modified Sakurai reaction (ISMS)^{6,7} toward 2,6-disubstituted dihydropyrans (DHPs) with *cis*-diastereoselectivity (Eq. 1). Similar DHPs were either present in, or could be used as intermediates toward syntheses of a number of

biologically active natural products such as ambruticin⁸, the phorbazoles,⁹ leucascandrolide¹⁰, kendomycin,¹¹ neopeltolide,¹² the clavisolides,¹³ and the diosponins.¹⁴ The prevalence of DHPs, and derivatives thereof, has led to a large number of concise and selective methods for their synthesis.^{15–18}

More specifically, the utility of a DHP moiety attached to the α -position of a carbonyl compound¹⁹ prompted us to further investigate a three-component, one-pot cascade reaction involving an initial Mukaiyama aldol reaction followed by an addition/ISMS sequence as shown in the retrosynthetic analysis below (Scheme 1). Given how rapidly molecular complexity is increased in this short sequence, we examined the utility of several silane nucleophiles, **1**, and aldehydes (R'CHO). Herein, we report further examples of this multi-component, one pot reaction and details of our optimization studies.

Scheme 1. Retrosynthetic analysis of 2,6-disubstituted DHPs.

2. Results and discussion

In order to evaluate the feasibility of the first step of the three-component process, we prepared aldehyde, (*Z*)-**2**, in two, straightforward steps from commercially-available 4-trimethylsilyl-3-buten-1-ol.²⁰

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Reduction under nickel catalyzed conditions (P-2)^{16k} was most convenient as it led to the best (*Z*):(*E*) ratios (>95:5) with little or no over-reduction to the alkane. As expected, the resulting β,γ -unsaturated aldehyde, **2**,⁵ is particularly sensitive, and Dess–Martin periodinane²¹ was the only oxidant that afforded the desired substrate in sufficient purity to study the three-component sequence. We chose to focus on using the (*Z*)-vinylsilane due to recent work by Meilert and Brimble²² as well Dobbs et al.²³ showing that the *cis*-vinylsilane isomers efficiently participated in intramolecular reactions.

The initial Mukaiyama aldol^{24–26} between **2** and the commercially-available methyl trimethylsilyldimethyl-ketene acetal (**1**; R=OMe, R¹=H) readily occurred at room temperature (Scheme 2) in the presence of 10 mol % BiBr₃ in CH₂Cl₂ (~0.1 M). Crude ¹H NMR spectroscopic analyses and TLC indicated that the initial Mukaiyama aldol reaction cleanly affords the sensitive silylated aldol adduct, **A**, which is an effective nucleophile for the second addition/silyl-Prins step (ISMS).⁵ Although the free alcohol corresponding to **A** could be isolated by column chromatography, in practice, we carried **A** onto

the next step without isolation or purification. Mukaiyama aldol reactions involving Bi(III) are also efficient in CH₃CN, but we chose CH₂Cl₂ as the solvent since our previous studies indicated that the intermolecular addition and ISMS occurred more efficiently in this solvent versus CH₃CN.⁵ Addition of a second aldehyde (R²CHO) and 10 mol % more BiBr₃ results in an intermolecular addition of **A** to the second aldehyde (R²CHO) to afford the *E*-oxocarbenium ion, **B**. An intramolecular silyl-Prins reaction then affords **3a–3j** via the intermediate stabilized cation, **C**.

When using 1.1–1.4 equiv of ketene acetal (Table 1, entries 1–4 and 11), the initial aldol reaction occurs very rapidly at temperatures down to –20 °C in CH₂Cl₂ or CH₃CN. During optimization, we did find that the single most important variable for clean formation of the Mukaiyama adduct, **A**, was the specific commercial samples of ketene silyl acetal. Although we examined individual samples by ¹H and ¹³C NMR spectroscopy and found no significant impurities, some reactions required up to 1.4 equiv of the ketene silyl acetal nucleophile whereas another was effectively used with as little as 1.1 equivalents. This is most likely due to variations in trace water content and competing hydrolysis reactions during the Mukaiyama aldol step.

In all cases in which silyl enol ethers were used instead of the more nucleophilic ketene silyl acetals²⁷ at the same concentration (entry 3 vs 5), the reaction was much slower at room temperature and did not proceed to completion unless the BiBr₃ was activated by sonication in the presence of NaI as reported by Le Roux et al.²⁸ This presumably affords the more reactive BiI₃ salt in situ. We later found, however, that activation and sonication could be avoided, albeit less efficiently, if the aldol was conducted at ~0.2 M instead of ~0.1 M without NaI activation (entries 6 vs 7 and 8 vs 9).

In all cases where the hydrogens adjacent to the oxygen in the ring system could be sufficiently separated in the ¹H NMR spectrum, qualitative ¹H NOE spectra indicated that the *cis*-isomers²⁹ of DHPs **3a–j** were the only diastereomers observed in agreement with other silyl-Prins type cyclizations (Fig. 1).^{22,23}

Scheme 2. Reaction sequence for the three-component, one-pot synthesis of dihydropyrans.

Table 1
Three-component, one-pot reaction to 2,6-disubstituted dihydropyrans

Entry	R	R ¹	R ²	Product	dr (<i>cis</i> : <i>trans</i>) ^a	Yield ^b (%)
1	MeO–	–Me	PhCH ₂ –	3a	>99:1	64
2	MeO–	–Me	<i>i</i> -Pr–	3b	>99:1	53
3	MeO–	–Me	<i>n</i> -C ₅ H ₁₁ –	3c	>99:1	64
4	MeO–	–Me	<i>ortho</i> -CHOC ₆ H ₄ –	3d	>99:1	55
5	Ph–	–H	<i>n</i> -C ₅ H ₁₁ –	3e	>99:1	76 ^c
6	Ph–	–H	1-ethylpropyl–	3f	>19:1	66 ^c
7	Ph–	–H	1-ethylpropyl–	3f	>19:1	56 ^d
8	<i>tert</i> -Bu–	–H	<i>n</i> -C ₇ H ₁₅ –	3g	>19:1	80 ^c
9	<i>tert</i> -Bu–	–H	<i>n</i> -C ₇ H ₁₅ –	3g	>19:1	55 ^d
10	<i>tert</i> -Bu–	–H	PhCH ₂ CH ₂ –	3h	>19:1	52 ^d
11	MeO–	–Me	PhCH ₂ CH ₂ –	3i	>19:1	63
12	Ph–	–H	Ph–	3j	>19:1	44 ^d

^a Diastereoselectivities were determined by ¹H NMR or GC–MS analysis of crude reaction mixtures prior to chromatographic separation.

^b Yields are reported for pure, isolated *cis*-compounds characterized by ¹H NMR and ¹³C NMR spectroscopy, IR spectrometry and HRMS or elemental analysis.

^c Initial Mukaiyama aldol carried out at ~0.1 M with added NaI and sonication.

^d Initial Mukaiyama aldol carried out at ~0.2 M with neither added NaI, nor sonication.

Figure 1. Observed qualitative NOE enhancement.

We were particularly interested in syntheses using β,β -unsaturated enol ethers as nucleophiles since these resulting intermediates and products might be prone to aldol reactions or eliminations via putative enols or enolates. We were gratified to isolate several products with enolizable hydrogens α - to the carbonyl moiety; these were obtained in yields ranging from 52% to 80% (entries 5–10). The lowest yield was observed for product **3j** (entry 12) even though both the initial Mukaiyama aldol and the subsequent addition/silyl-Prins reactions appeared clean by TLC analysis and ^1H NMR spectroscopic evaluation of the crude product. This particular product appeared less stable than the other nine and prolonged reaction times led to complex mixtures while storage at room temperature also caused decomposition. This instability is likely due to the fact that the phenyl substituent (R^2) promotes ring opening under the reaction conditions via a benzylic cation.

Although we attempted cyclizations using (*E*)-vinylsilanes due to reports that the (*E*)-vinylsilanes provided *trans*-2,6-diastereomers,^{16k} we found that in the two-component case analogous to that in Eq. 1, only trace quantities of cyclization products were afforded (GC–MS) using (*E*)-vinylsilanol.⁵ This result is consistent with the stereoelectronic stabilization of the developing cation by the axial trimethylsilyl moiety in intermediates **B** and **C** (Scheme 2) as described by Speckamp^{16k} and Roush¹⁶ⁱ for DHPs as well as Overman³⁰ and Tanner³¹ for iminium ion cyclizations.

The exact role(s) of Bi(III) compounds as catalysts in organic synthesis is still debated in numerous papers. Whereas BiX_3 compounds are often described as weak Lewis acids,^{3,32,33} and investigators have attributed their reactivity to this property, we³⁴ and others³⁵ believe that BiX_3 species are progenitors of Brønsted acids and that these contribute to the activities of BiX_3 salts. Even in cases where Brønsted acids have been shown to be involved, their specific role is not always clear,^{36,37,38} especially in the presence of Lewis acids.³⁹

Bismuth(III) halides are known to rapidly hydrolyze to H-X and bismuthoxy halides (X-Bi=O) which are insoluble in CH_2Cl_2 .⁴⁰ In the cases of silyl enol ethers (Table 1, entries 5–10 and 12), the solutions become homogeneous after addition of the second aldehyde (R^2CHO), so insoluble Br-Bi=O does not accumulate. In addition, ligand exchange reactions involving the kinetically-labile Bi(III) center can produce reactive intermediates in acylation and other reactions.^{36,37,38} Finally, Mukaiyama aldol reactions occur with addition of 100 mol % methyl di-*tert*-butylpyridine (DTBP) in the presence of 15 mol % of BiBr_3 . Regardless of the explicit and potentially complex role(s) of BiBr_3 , use of this salt in catalytic quantities is convenient and inexpensive.

In short, we have developed an efficient, diastereoselective one-pot, three component Mukaiyama aldol/addition/ISMS reaction to afford valuable 2,6-disubstituted dihydropyran products. Both ketene silyl acetals and silyl enol ethers are effective nucleophiles with β,γ -unsaturated aldehyde, **1**. Aliphatic, benzylic and aromatic aldehydes were all useful as the second electrophile (R^2CHO), although benzaldehyde provided the lowest yield. We are in the process of further optimizing reactions with aromatic aldehydes, establishing the role(s) of BiBr_3 in the reaction sequence as well as applying this methodology toward more substituted products.

3. Experimental section

3.1. General

All reagents were used as received unless otherwise noted. Dichloromethane was distilled from CaH_2 and THF was purified via a Solv-Tek[®] solvent purification system. Benzaldehyde, phthaldehyde, isobutyraldehyde as well as 2-ethylbutyraldehyde were purchased from Acros Organics. Dess–Martin periodininane, hexanal, octanal, bismuth bromide, methyl trimethylsilyl dimethylketene acetal, (2,2-dimethyl-1-methylenepropoxy)trimethylsilane, and

1-phenyl-1-trimethylsiloxyethylene were purchased from Aldrich Chemical Company. 4-Trimethylsilyl-3-butyne-1-ol was purchased from GFS Chemical. ^{13}C NMR spectra were recorded with the aid of an APT sequence in which methylene and quaternary carbons=even (e) and methyl and methine carbons=odd (o). Coupling constants were determined by the method of Hoyer.⁴¹ Thin layer chromatography was performed on Sorbent Technologies general-purpose silica gel on glass and flash chromatography was performed using Sorbent Technologies chromatographic silica gel (200–475 MESH). All compounds were judged to be homogeneous by ^1H and ^{13}C NMR spectroscopy.

3.2. General procedure

3.2.1. Preparation of methyl *cis*-2-(6-benzyl-3,6-dihydro-2H-pyran-2-yl)-2,2-dimethyl propanoate (**3a**)

BiBr_3 (45 mg, 0.10 mmol, 0.10 equiv) was weighed into 25 mL round bottom flask and 10 mL CH_2Cl_2 was added via syringe. (*Z*)-4-(trimethylsilyl)but-3-enal, **2**⁵ (0.142 g, 1.00 mmol, 1.00 equiv) and methyl trimethylsilyl dimethylketene acetal (0.192 g, 1.10 mmol, 1.10 equiv) were added by syringe simultaneously. The mixture was stirred at room temperature until (*Z*)-4-(trimethylsilyl)but-3-enal, **2** was consumed by TLC (3 h). Additional BiBr_3 (45 mg, 0.010 mmol, 0.10 equiv) and phenylacetaldehyde (0.24 g, 2.0 mmol, 2.0 equiv) were added and the mixture was stirred for 12 h at rt. The solution was concentrated in vacuo, filtered through a small SiO_2 pipette column with CH_2Cl_2 as eluent and concentrated in vacuo again. The product was purified by column chromatography (9:1 petroleum ether: Et_2O , $R_f=0.34$) to provide 0.175 g (64%) of *cis*-isomer as a colorless oil: IR (neat) 3031 (s), 2982 (s), 2940 (s), 2879 (m), 1735 (s), 1451 (m), 1267 (s), 1140 (s), 1086 (s), 751 (m); ^1H NMR (400 MHz, CDCl_3) δ 7.17–7.28 (m, 5H), 5.77–5.82 (m, 1H), 5.63 (dm, $J=10.3$ Hz, 1H), 4.27 (br, 1H), 3.77 (dd, $J=11.0$, 3.3 Hz, 1H), 3.55 (s, 3H), 2.83 (dd, $J=13.9$, 8.1 Hz, 1H), 2.70 (dd, $J=13.9$, 8.1 Hz, 1H), 2.06–2.15 (m, 1H), 1.77–1.85 (m, 1H), 1.21 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (APT) (100 MHz, CDCl_3) δ 177.2 (e), 138.7 (e), 129.72 (o), 129.69 (o), 128.0 (o), 126.1 (o), 125.0 (o), 78.4 (o), 76.5 (o), 52.0 (o), 46.6 (e), 42.1 (e), 25.4 (e), 21.3 (o), 20.4 (o). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3$ (274.35): C 74.42, H 8.08; found: C 74.53, H 8.30.

3.2.2. Preparation of methyl *cis*-2-(6-isopropyl-3,6-dihydro-2H-pyran-2-yl)-2,2-dimethyl propanoate (**3b**)

Using the general procedure, **3b** was prepared from BiBr_3 (45 mg, 0.10 mmol, 0.10 equiv), (*Z*)-4-(trimethylsilyl)but-3-enal **2** (0.142 g, 1.00 mmol, 1.00 equiv), methyl trimethylsilyl dimethylketene acetal (0.192 g, 1.10 mmol, 1.10 equiv), isobutyraldehyde (0.182 mL, 2.00 mmol, 2.00 equiv), and BiBr_3 (45 mg, 0.10 mmol, 0.10 equiv). The product was purified by column chromatography (9:1 petroleum ether: Et_2O , $R_f=0.52$) to provide 0.120 g (53%) of *cis*-isomer as a colorless oil: IR (neat) 2961 (s), 1737 (s), 1458 (w), 1368 (w), 1258 (m), 1136 (m), 1084 (m); ^1H NMR (400 MHz, CDCl_3) δ 5.80–5.85 (m, 1H), 5.63 (dm, $J=10.3$ Hz, 1H), 3.86 (br, 1H), 3.75 (dd, $J=10.6$, 2.9 Hz, 1H), 3.67 (s, 3H), 2.04–2.12 (m, 1H), 1.76–1.83 (m, 1H), 1.70 (dt, $J=7.0$, 7.0, 5.1 Hz, 1H), 1.22 (s, 3H), 1.14 (s, 3H), 0.90 (d, $J=7.0$ Hz, 3H), 0.86 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (APT) (100 MHz, CDCl_3) δ 177.4 (e), 128.9 (o), 125.1 (o), 80.0 (o), 77.9 (o), 52.0 (o), 46.7 (e), 32.9 (o), 25.5 (e), 21.2 (o), 20.4 (o), 18.6 (o), 17.5 (o). Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_3$ (226.31): C 68.99, H 9.80; found: C 68.29, H 9.61.

3.2.3. Preparation of methyl *cis*-2-(6-pentyl-3,6-dihydro-2H-pyran-2-yl)-2,2-dimethyl propanoate (**3c**)

This compound was prepared according to the general procedure described for **3a** using BiBr_3 (45 mg, 0.10 mmol, 0.10 equiv), (*Z*)-4-(trimethylsilyl)but-3-enal, **2** (0.142 g, 1.00 mmol, 1.00 equiv), methyl trimethylsilyl dimethylketene acetal (0.192 g, 1.10 mmol, 1.10 equiv), hexanal (0.14 mL, 2.0 mmol, 2.0 equiv) and BiBr_3

(45 mg, 0.10 mmol, 0.10 equiv). The product was purified by column chromatography (9:1 petroleum ether:Et₂O, *R_f*=0.52) to provide 0.163 g (64%) of *cis*-isomer as a colorless oil: IR (neat) 3032 (m), 2953 (s), 2934 (s), 2861 (s), 1737 (s), 1469 (m), 1368 (w), 1265 (s), 1190 (m), 1134 (m), 1083 (m); ¹H NMR (400 MHz, CDCl₃) δ 5.74–5.80 (m, 1H), 5.59 (dm, *J*=10.3 Hz, 1H), 4.05 (br, 1H), 3.76 (dd, *J*=10.9, 2.3 Hz, 1H), 3.67 (s, 3H), 2.05–2.14 (m, 1H), 1.76–1.84 (m, 1H), 1.23–1.48 (m, 8H), 1.22 (s, 3H), 1.13 (s, 3H), 0.88 (t, *J*=7.0 Hz, 3H); ¹³C NMR (APT) (100 MHz, CDCl₃) δ 177.4 (e), 130.8 (o), 124.3 (o), 78.2 (o), 75.5 (o), 52.0 (o), 46.6 (e), 35.5 (e), 32.0 (e), 25.5 (e), 25.1 (e), 23.0 (e), 21.1 (o), 20.5 (o), 14.4 (o). Anal. Calcd for C₁₅H₂₆O₃ (254.37): C 70.83, H 10.30; found: C 70.63, H 10.27.

3.2.4. Preparation of methyl *cis*-2-(6-(2-formylphenyl)-3,6-dihydro-2H-pyran-2-yl)-2,2-dimethyl-propanoate (**3d**)

This compound was prepared according to the general procedure using BiBr₃ (22 mg, 0.05 mmol, 0.10 equiv), (Z)-4-(trimethylsilyl)but-3-enal, **2** (0.071 g, 0.50 mmol, 1.00 equiv), methyl trimethylsilyl dimethylketene acetal (0.096 g, 0.55 mmol, 1.10 equiv), phthalaldehyde (0.134 g, 1.00 mmol, 2.00 equiv), and additional BiBr₃ (22 mg, 0.05 mmol, 0.10 equiv). The product was purified by column chromatography (8:2 petroleum ether:Et₂O, *R_f*=0.22) to provide 0.079 g (55%) of *cis*-isomer as a colorless oil: IR (neat) 3743 (w), 2980 (w), 1733 (s), 1698 (s), 1558 (m), 1464 (m), 1266 (m), 1195 (m), 1139 (m), 1077 (m), 760 (m); ¹H NMR (400 MHz, CDCl₃) δ 10.33 (s, 1H), 7.88 (dd, *J*=7.7, 1.1 Hz, 1H), 7.56–7.63 (m, 2H), 7.47 (td, *J*=7.3, 1.5 Hz, 1H), 5.90–5.95 (m, 1H), 5.85–5.88 (m, 1H), 5.78–5.82 (dm, *J*=10.3 Hz, 1H), 4.13 (dd, *J*=11.0, 3.3 Hz, 1H), 3.70 (s, 3H), 2.27–2.38 (m, 1H), 1.97–2.04 (dm, *J*=17.2 Hz, 1H), 1.29 (s, 3H), 1.22 (s, 3H); ¹³C NMR (APT) (100 MHz, CDCl₃) δ 192.7 (o), 177.0 (e), 143.6 (e), 134.0 (o), 133.6 (e), 131.4 (o), 129.7 (o), 128.0 (o), 127.8 (o), 124.7 (o), 78.8 (o), 75.5 (o), 52.2 (o), 46.7 (e), 25.1 (e), 21.4 (o), 20.6 (o); HRMS (ESI) calcd for C₁₇H₂₀O₄Na (M+Na⁺) 311.1254, found 311.1251.

3.2.5. Preparation of *cis*-2-(6-pentyl-3,6-dihydro-2H-pyran-2-yl)-1-phenylethanone (**3e**)

BiBr₃ (22 mg, 0.05 mmol, 0.10 equiv) and NaI (23 mg, 0.15 mmol, 0.30 equiv) were weighed into 15 mL round bottom flask and 10 mL CH₂Cl₂ was added via syringe. After sonicating for 1 h at rt, (Z)-4-(trimethylsilyl)but-3-enal, **2** (0.071 g, 0.50 mmol, 1.00 equiv) and 1-phenyl-1-trimethylsilyloxyethylene (0.106 g, 0.55 mmol, 1.10 equiv) were added by syringe simultaneously. The mixture was stirred until (Z)-4-(trimethylsilyl)but-3-enal, **2**, was consumed by TLC analysis (2 h). Hexanal (0.134 g, 1.00 mmol, 2.00 equiv) and additional BiBr₃ (22 mg, 0.05 mmol, 0.10 equiv) were added and the mixture was stirred for 12 h. The solution was concentrated in vacuo, filtered through a small SiO₂ pipette column with CH₂Cl₂ as eluent and concentrated in vacuo again. The product was purified by column chromatography (9:1 petroleum ether:Et₂O, *R_f*=0.38) to provide 0.104 g (76%) of *cis*-isomer as a colorless oil: IR (neat) 3743 (w), 2929 (s), 2861 (s), 1686 (s), 1452 (m), 1371 (m), 1336 (m), 1281 (m), 1217 (m), 1181 (m), 1075 (m), 993 (m), 751 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.98–8.01 (m, 2H), 7.56 (tt, *J*=7.3, 1.5 Hz, 1H), 7.44–7.48 (m, 2H), 5.77–5.82 (m, 1H), 5.64 (dm, *J*=10.3 Hz, 1H), 4.16–4.23 (m, 1H), 4.08–4.14 (m, 1H), 3.40 (dd, *J*=15.7, 6.6 Hz, 1H), 2.98 (dd, *J*=15.7, 6.6 Hz, 1H), 2.02–2.18 (m, 2H), 1.18–1.50 (m, 8H), 0.85 (t, *J*=6.7 Hz, 3H); ¹³C NMR (APT) (100 MHz, CDCl₃) δ 198.5 (e), 137.5 (e), 133.1 (o), 130.6 (o), 128.6 (o), 128.4 (o), 124.2 (o), 75.2 (o), 71.0 (o), 45.4 (e), 35.8 (e), 32.1 (e), 31.6 (e), 25.1 (e), 22.9 (e), 14.4 (o). Anal. Calcd for C₁₈H₂₄O₂ (272.38): C 79.37, H 8.88; found: C 79.22, H 9.01.

3.2.6. Preparation of *cis*-2-(6-(pentan-3-yl)-3,6-dihydro-2H-pyran-2-yl)-1-phenylethanone (**3f**)

BiBr₃ (45 mg, 0.10 mmol, 0.10 equiv) and NaI (50 mg, 0.15 mmol, 0.30 equiv) were weighed into 15 mL round bottom

flask and 5 mL CH₂Cl₂ was added via syringe. After sonicating for 1 h at rt, (Z)-4-(trimethylsilyl)but-3-enal, **2** (0.142 g, 1.00 mmol, 1.00 equiv) and 1-phenyl-1-trimethylsilyloxyethylene (0.212 g, 1.10 mmol, 1.10 equiv) were added by syringe simultaneously. The mixture was stirred until (Z)-4-(trimethylsilyl)but-3-enal, **2**, was consumed (2 h). 2-Ethylbutyraldehyde (0.182 mL, 1.47 mmol, 1.47 equiv) and BiBr₃ (45 mg, 0.10 mmol, 0.10 equiv) were added and the mixture was stirred for 12 h. The solution was concentrated in vacuo, filtered through a small SiO₂ pipette column with CH₂Cl₂ as eluent and concentrated in vacuo again. The product was purified by column chromatography (9:1 petroleum ether:Et₂O, *R_f*=0.40) to provide 0.179 g (66%) of *cis*-isomer as a light yellow oil: IR (neat) 3032 (m), 2961 (s), 2932 (s), 2874 (s), 1684 (s), 1449 (m), 1279 (m), 1214 (m), 1184 (m), 1072 (s), 992 (m), 752 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.98–8.01 (dm, *J*=8.3 Hz, 2H), 7.56 (app. tm, *J*=7.3 Hz, 1H), 7.44–7.48 (m, 2H), 5.81–5.86 (m, 1H), 5.63 (dm, *J*=10.3 Hz, 1H), 4.12–4.19 (m, 2H), 3.36 (dd, *J*=15.7, 6.6 Hz, 1H), 2.94 (dd, *J*=15.7, 6.6 Hz, 1H), 2.01–2.16 (m, 2H), 1.16–1.40 (m, 5H), 0.84 (t, *J*=7.0 Hz, 3H), 0.83 (t, *J*=7.0 Hz, 3H); ¹³C NMR (APT) (100 MHz, CDCl₃) δ 198.9 (e), 137.6 (e), 133.0 (o), 129.4 (o), 128.6 (o), 128.5 (o), 124.8 (o), 76.6 (o), 71.2 (o), 46.0 (o), 45.5 (e), 31.7 (e), 22.5 (e), 22.2 (e), 12.38 (o), 12.36 (o). Anal. Calcd for C₁₈H₂₄O₂ (272.38): C 79.37, H 8.88; found: C 79.71, H 8.96.

3.2.7. Preparation of *cis*-1-(6-heptyl-3,6-dihydro-2H-pyran-2-yl)-3,3-dimethylbutan-2-one (**3g**)

BiBr₃ (45 mg, 0.10 mmol, 0.10 equiv) and NaI (50 mg, 0.15 mmol, 0.30 equiv) were weighed into 15 mL round bottom flask and 5 mL CH₂Cl₂ was added via syringe. After sonicating for 1 h at rt, (Z)-4-(trimethylsilyl)but-3-enal, **2** (0.142 g, 1.00 mmol, 1.00 equiv) and (2,2-dimethyl-1-methylenepropoxy)trimethylsilane (0.190 g, 1.10 mmol, 1.10 equiv) were added by syringe simultaneously. The mixture was stirred until (Z)-4-(trimethylsilyl)but-3-enal, **2**, was consumed (2 h). Octanal (0.313 mL, 2.00 mmol, 2.00 equiv) and BiBr₃ (45 mg, 0.10 mmol, 0.10 equiv) were added and the mixture was stirred for 24 h. The solution was concentrated in vacuo, filtered through a small SiO₂ pipette column with CH₂Cl₂ as eluent and concentrated in vacuo again. The product was purified by column chromatography (9:1 petroleum ether:Et₂O, *R_f*=0.43) to provide 0.225 g (80%) of *cis*-isomer as a colorless oil: IR (neat) 3032 (m), 2957 (s), 2929 (s), 2858 (s), 1708 (s), 1465 (m), 1367 (m), 1185 (m), 1076 (s), 994 (m), 840 (w); ¹H NMR (400 MHz, CDCl₃) δ 5.63–5.68 (m, 1H), 5.51 (dm, *J*=10.3 Hz, 1H), 3.93–4.05 (m, 2H), 2.81 (dd, *J*=16.8, 7.0 Hz, 1H), 2.36 (dd, *J*=16.8, 7.0 Hz, 1H), 1.79–1.97 (m, 2H), 1.10–1.40 (m, 12H), 1.04 (s, 9H), 0.77 (t, *J*=6.7 Hz, 3H); ¹³C NMR (APT) (100 MHz, CDCl₃) δ 213.8 (e), 130.6 (o), 124.2 (o), 75.2 (o), 70.7 (o), 44.6 (e), 43.3 (e), 35.9 (e), 32.1 (e), 31.3 (e), 29.9 (e), 29.6 (e), 26.4 (o), 25.5 (e), 23.0 (e), 14.5 (o). Anal. Calcd for C₁₈H₃₂O₂ (280.45): C 77.09, H 11.50; found: C 76.81, H 11.31.

3.2.8. Preparation of *cis*-3,3-dimethyl-1-(6-phenethyl-3,6-dihydro-2H-pyran-2-yl)butan-2-one (**3h**)

BiBr₃ (48 mg, 0.11 mmol, 0.10 equiv) was weighed into 15 mL round bottom flask and 5.0 mL CH₂Cl₂ was added via syringe. After stirring the BiBr₃ suspension for 5 min, (Z)-4-(trimethylsilyl)but-3-enal, **2** (0.152 g, 1.07 mmol, 1.00 equiv) and (2,2-dimethyl-1-methylenepropoxy)trimethylsilane (0.206 g, 1.17 mmol, 1.09 equiv) were separately dissolved in 0.25 mL CH₂Cl₂ and added by syringe simultaneously. The mixture was stirred until (Z)-4-(trimethylsilyl)but-3-enal, **2**, was consumed by TLC analysis (2 h). BiBr₃ (51 mg, 0.11 mmol, 0.10 equiv) and 3-phenylpropanal (0.281 mL, 2.14 mmol, 2.00 equiv) were then added and the mixture was stirred for 14 h. The solution was concentrated in vacuo, filtered through a small SiO₂ column with CH₂Cl₂ as eluent and concentrated in vacuo again. The product was purified by column

chromatography (95:5 to 9:1 petroleum ether:Et₂O, *R_f*=0.50 in 9:1 hexanes:EtOAc) to provide 0.158 g (52%) of the *cis*-isomer as a colorless oil: IR (neat) 3062 (m), 3027 (s), 2967 (vs), 2933 (m), 2869 (s), 1705 (vs), 1087 (vs), 1068 (vs); ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.32 (m, 2H), 7.16–7.21 (m, 3H), 5.81 (dddd, *J*=9.9, 7.3, 4.8, 2.2 Hz, 1H), 5.62 (dddd, *J*=10.3, 4.0, 2.7, 1.5 Hz, 1H), 4.09–4.15 (m, 2H), 2.97 (dd, *J*=16.5, 7.3 Hz, 1H), 2.62–2.79 (m, 2H), 2.47 (dd, *J*=16.5, 5.1 Hz, 1H), 1.94–2.10 (m, 2H), 1.74–1.82 (m, 2H), 1.19 (s, 9H); ¹³C (APT) (100 MHz, CDCl₃) δ 213.6 (e), 142.3 (e), 130.3 (o), 128.6 (o), 128.4 (o), 125.8 (o), 124.6 (o), 74.1 (o), 70.7 (o), 44.6 (e), 43.2 (e), 37.6 (e), 31.7 (e), 31.3 (e), 26.4 (o). Anal. Calcd for C₁₉H₂₆O₂ (286.41): C 79.68, H 9.15; found: C 79.64, H 9.18.

3.2.9. Preparation of methyl 2-methyl-2-(6-phenethyl-3,6-dihydro-2H-pyran-2-yl)propanoate (**3i**)

BiBr₃ (58 mg, 0.13 mmol, 0.10 equiv) was weighed into 15 mL round bottom flask and 5.0 mL CH₂Cl₂ was added via syringe. After stirring the BiBr₃ suspension for 5 min, (Z)-4-(trimethylsilyl)but-3-enal, **2** (0.180 g, 1.27 mmol, 1.00 equiv) and methyl trimethylsilyl dimethylketene acetal (0.295 g, 1.69 mmol, 1.33 equiv) were separately dissolved in 0.25 mL CH₂Cl₂ and added by syringe simultaneously. The mixture was stirred until (Z)-4-(trimethylsilyl)but-3-enal, **2** was consumed by TLC analysis (1.5 h). BiBr₃ (58 mg, 0.13 mmol, 0.10 equiv) was then added followed by 3-phenylpropanal (0.340 mL, 2.52 mmol, 1.98 equiv) and the mixture was stirred for 14 h. The solution was concentrated in vacuo, filtered through a small SiO₂ pipette column with CH₂Cl₂ as eluent and concentrated in vacuo again. The product was finally purified by column chromatography (95:5 to 9:1 petroleum ether:Et₂O, *R_f*=0.48 in 9:1 hexanes:EtOAc) to provide 0.237 g (65%) of the *cis*-isomer as a colorless oil: IR (neat) 3028 (vs), 2980 (vs), 2874 (vs), 1728 (vs); ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.29 (m, 2H), 7.14–7.20 (m, 3H), 5.80 (dddd, *J*=9.9, 4.2, 2.0, 2.0 Hz, 1H), 5.58 (dddd, *J*=9.9, 2.9, 1.5, 1.5 Hz, 1H), 4.08 (br s, 1H), 3.80 (dd, *J*=10.8, 3.1 Hz, 1H), 3.70 (s, 3H), 2.62–2.80 (m, 2H), 2.08–2.17 (m, 1H), 1.68–1.74 (m, 3H), 1.26 (s, 3H), 1.16 (s, 3H); ¹³C (APT) (100 MHz, CDCl₃) δ 177.3 (e), 142.5 (e), 130.4 (o), 128.7 (o), 128.3 (o), 125.7 (o), 124.7 (o), 78.1 (o), 74.3 (o), 52.0 (o), 46.6 (e), 37.4 (e), 31.5 (e), 25.5 (e), 21.2 (o), 20.5 (o); Anal. Calcd for C₁₈H₂₄O₃ (286.41): C 74.97, H 8.39; found: C 74.92, H 8.44.

3.2.10. Preparation of 2-(6-phenyl-3,6-dihydro-2H-pyran-2-yl)-1-phenylethanone (**3j**)

BiBr₃ (48 mg, 0.11 mmol, 0.10 equiv) was weighed into 15 mL round bottom flask and 3.5 mL CH₂Cl₂ was added via syringe. After stirring the BiBr₃ suspension for 5 min, (Z)-4-(trimethylsilyl)but-3-enal, **2** (0.153 g, 1.07 mmol, 1.00 equiv) and 1-phenyl-1-trimethylsiloxyethylene (0.237 g, 1.23 mmol, 1.15 equiv) were dissolved separately in 0.25 mL CH₂Cl₂ and added by syringe simultaneously. The mixture was stirred until (Z)-4-(trimethylsilyl)but-3-enal, **2** was consumed by TLC analysis (1.5 h). BiBr₃ (50 mg, 0.11 mmol, 0.10 equiv) and benzaldehyde (0.218 mL, 2.15 mmol, 2.01 equiv) were then added and the mixture was stirred for 4 h. The solution was concentrated in vacuo, filtered through a small SiO₂ pipette column with CH₂Cl₂ as eluent and concentrated in vacuo again. The product was finally purified by column chromatography (95:5 to 9:1 petroleum ether:Et₂O, *R_f*=0.16 with 9:1 petroleum ether:Et₂O) to provide 0.131 g (44%) of the *cis*-isomer as a light yellow oil: IR (film) 3062 (m), 3033 (m), 2922 (m), 1683 (vs), 1598 (vs), 1450 (vs); ¹H NMR (400 MHz, CDCl₃) δ 7.97 (dm, *J*=8.1 Hz, 2H), 7.52–7.58 (m, 1H), 7.42–7.48 (m, 2H), 7.32–7.38 (m, 4H), 7.24–7.30 (m, 1H), 5.91–5.97 (m, 1H), 5.77 (dm, *J*=10.3 Hz, 1H), 5.24 (br s, 1H), 4.46 (dddd, *J*=9.9, 6.2, 4.0, 4.0 Hz, 1H), 3.47 (dd, *J*=16.5, 6.2 Hz, 1H), 3.10 (ddd, *J*=16.5, 6.2, 0.7 Hz, 1H), 2.15–2.33 (m, 2H); ¹³C (APT) (100 MHz, CDCl₃) δ 198.0 (e), 141.4 (e), 137.3 (e), 133.2 (o), 130.0 (o), 128.7 (o), 128.6 (o), 128.4 (o), 127.9 (o), 127.3 (o), 124.6 (o), 77.9 (o), 71.0 (o),

45.3 (e), 31.1 (e); HRMS (ESI) calcd for C₁₉H₁₈O₂Na (M+Na⁺) 301.1199, found 301.1195.

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Supplementary data

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References and notes

1. *Multicomponent Reactions*; Zhu, J., Beinaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.
2. Multi-step reactions relying upon the formation and conversion of initial reaction products to subsequent compounds have been called tandem reactions, cascade reactions, and, more recently, domino reactions. *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, 2006.
3. (a) Hua, R. *Curr. Org. Synth.* **2008**, 5, 1–27; (b) Komatsu, N. In *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: New York, NY, 2001; pp 371–440; (c) Gaspard-Loughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 12, 2517–2532; (d) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, 58, 8373–8397.
4. The LD₅₀ of BiCl₃ is listed as 3334 mg/kg (oral, rat) and 2250 mg/kg (oral, mouse) in the MSDS provided by Sigma-Aldrich Chemical, St. Louis, MO.
5. Hinkle, R. J.; Lian, Y. J. *Org. Chem.* **2006**, 71, 7071–7074.
6. Jacques, T.; Markó, I. E.; Pospíšil, J. in ref. 1: In *Multicomponent Reactions*; Zhu, J., Beinaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 398–452.
7. Markó developed and has extensively examined the ISMS reaction. For representative examples, see: (a) Leroy, B.; Markó, I. E. *Tetrahedron Lett.* **2001**, 42, 8685–8688; (b) Markó, I. E.; Dobbs, A. P.; Scheirrmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, 34, 2899–2902; (c) Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, 50, 7141–7156; (d) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, 34, 6595–6598; (e) Mekhalifa, A.; Markó, I. E.; Adams, H. *Tetrahedron Lett.* **1991**, 32, 4783–4786.
8. Ringel, S. M.; Greenough, R. C.; Roemer, S.; Connor, D.; Gutt, A. L.; Blair, B.; Kanter, G.; von Strandtmann, M. *J. Antibiot.* **1977**, 30, 371–375.
9. (a) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, 118, 9422–9423; (b) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, 117, 8126–8131.
10. D'ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, 79, 51–60.
11. Funahashi, Y.; Kawamura, N.; Ishimaru, T. JP Patent 08231551 [A2960910], 1996.
12. Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, 70, 412–416.
13. (a) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, 65, 386–388; (b) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, 65, 1303–1306.
14. Yin, J.; Kouda, K.; Tezuka, Y.; Le Tran, Q.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med.* **2004**, 70, 54–58.
15. Recent reviews of synthetic methods toward a number of natural products containing cyclic ethers: (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053; (b) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, 105, 4348–4378.
16. For a variety of methods for the synthesis of dihydropyran ring systems, see: (a) Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, 11, 761–764; (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, 10, 3813–3816; (c) Sherry, B. D.; Maus, L.; Lafortezza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, 128, 8132–8133; (d) Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Org. Lett.* **2005**, 7, 1113–1116; (e) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.* **2004**, 126, 8642–8643; (f) Vares, L.; Rein, T. *J. Org. Chem.* **2002**, 67, 7226–7237; (g) Brimble, M. A.; Pavia, G. S.; Stevenson, R. J. *Tetrahedron Lett.* **2002**, 43, 1735–1738; (h) Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002**, 4, 293–295 and refs. therein; (i) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955–959; (j) Viswanathan, G. S.; Yang, J.; Li, C. *Org. Lett.* **1999**, 1, 993–995; (k) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, 62, 3426–3427.
17. For recent examples of dihydropyran preparations involving intramolecular reactions of alkynes, see: (a) Furman, B.; Dziedzic, M.; Justyniak, I. *Tetrahedron*

- 2008, 64, 3103–3110; (b) Miranda, P. O.; Ramirez, M. A.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, 8, 1633–1636.
18. Prins reactions have also been used extensively in the formation of tetrahydropyrans: (a) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, 130, 13177–13181; (b) Furman, B.; Dziedzic, M. *Tetrahedron Lett.* **2008**, 49, 678–681; (c) Liu, F.; Loh, T.-P. *Org. Lett.* **2007**, 9, 2063–2066; (d) Jasti, R.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, 71, 3176–3183; (e) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, 7, 4491–4494.
19. Panek et al. used a 2,6-disubstituted dihydropyran in their synthesis of leucascandrolide A: Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2007**, 72, 2–24.
20. GFS Chemical Corporation.
21. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 48, 4155–4156.
22. Meilert, K.; Brimbel, M. A. *Org. Biomol. Chem.* **2006**, 4, 2184–2192.
23. Dobbs, A. P.; Guesne, S. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, 68, 7880–7883 and refs. therein.
24. BiX₃-mediated Mukaiyama aldol reactions were first reported in 1988: Ohki, H.; Wada, M.; Akiba, K. *Tetrahedron Lett.* **1988**, 29, 4719–4721.
25. (a) Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* **1998**, 1249–1251; (b) Peidro, L.; Le Roux, C.; Laporterie, A.; Dubac, J. *J. Organomet. Chem.* **1996**, 521, 397–399.
26. For a recent account of a diastereoselective BiX₃-mediated vinylogous Mukaiyama aldol reaction, see: Ollevier, T.; Bouchard, J.-E.; Desyroy, V. *J. Org. Chem.* **2008**, 73, 331–334.
27. Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, 36, 66–77.
28. Le Roux, D.; Gaspard-Illoughmane, H.; Dubac, J.; Jaud, J.; Vignaux, P. *J. Org. Chem.* **1993**, 58, 1835–1839.
29. See the supporting information for qualitative NOE spectra.
30. (a) Castro, P.; Overman, L. E. *Tetrahedron Lett.* **1993**, 34, 5243–5246; (b) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, 44, 3919–3930; (c) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, 86, 857–873.
31. Kvaernø, L.; Norrby, P.-O.; Tanner, D. *Org. Biomol. Chem.* **2003**, 1, 1041–1048.
32. Spectroscopic evidence for the role of Bi(OTf)₃ as a Lewis acid was recently claimed: Quin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, 128, 1611–1614.
33. (a) Hayashi, R.; Cook, G. R. *Tetrahedron Lett.* **2008**, 49, 3888–3890; (b) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. *Org. Lett.* **2005**, 7, 4729–4731; (c) Keramane, E. M.; Boyer, B.; Roque, J.-P. *Tetrahedron* **2001**, 57, 1917–1921.
34. Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, 125, 11456–11457.
35. Ollevier, T.; Nadeau, E. *Org. Biomol. Chem.* **2007**, 5, 3126–3134.
36. (a) Mazières, S.; Le Roux, C.; Peyronneau, M.; Gornitzka, H.; Rogues, N. *Eur. J. Inorg. Chem.* **2004**, 2823–2826; (b) Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2004**, 45, 825–829; (c) Répichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J.-R. *Eur. J. Org. Chem.* **1998**, 2743–2746.
37. Triflic acid in the absence of BiCl₃ was found to be a poor catalyst for methane-sulfonylation of arenes. The authors noted a synergistic effect involving ligand exchange reactions: Peyronneau, M.; Boisdon, M.-T.; Roques, N.; Mazières, S.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 4636–4640.
38. Although TfOH and Bi(OTf)₃·nH₂O each catalyze Mannich reactions, diastereoselectivity results indicate that the Bi(OTf)₃ is involved as more than just a progenitor of TfOH: Ollevier, T.; Nadeau, E.; Guay-Bégin, A.-A. *Tetrahedron Lett.* **2006**, 47, 8351–8354.
39. In cases where Brønsted and Lewis acids are present, a number of interactions are possible, including Brønsted acid assisted Lewis acid catalysts (BLA), etc. See: Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, 44, 1924–1942.
40. Bajwa, J. S.; Jiang, X.; Slade, J.; Prasad, K.; Repí, O.; Blacklock, T. J. *Tetrahedron Lett.* **2002**, 43, 6709–6713.
41. Hoyer, T. R.; Zhao, H. *J. Org. Chem.* **2002**, 67, 4014–4016.