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Biomimetic Synthesis

$Et_2SBr{\cdot}SbCl_5Br$: An Effective Reagent for Direct Bromonium-Induced Polyene Cyclizations**

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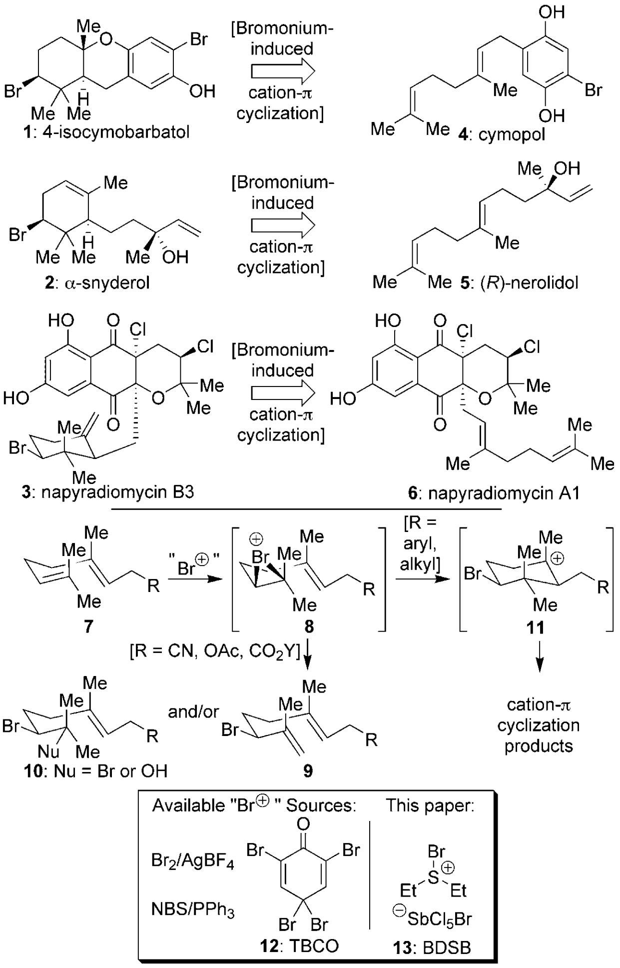
Although biomimetic polyene cyclizations[1] have been honed into powerful tools for complex molecule construction in the half-century since the pioneering efforts of Stork and Eschenmoser,[2] several limitations remain. For instance, while nature can deploy heme- or vanadium-based enzymes[3] to enantioselectively fashion an array of natural products, such as **1**–**3** (Scheme 1),[4] from a broad range of appropriate precursors, such as **4**–**6**,[5] laboratory efforts to mirror the same reactivity in racemic form with standard electrophilic bromine sources, such as Br_2, *N*-bromosuccinimide (NBS) or 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO, **12**), broadly fail.[6–8] Electron-deficient forms of **7**, for example, are typically converted into elimination products (**9**) and/or materials that incorporate exogenous nucleophiles such as water or bromide (**10**), due to the low rate of intramolecular cyclization within intermediate **8**;[6a–d] attempts to counter these results by precipitating bromide with added silver salts[7] or by enhancing the electrophilicity of the halogen through complexation (NBS/Ph_3P)[9] are, at best, modestly successful. Only a few electron-rich terpenes have been directly cyclized in synthetically useful yields,[6f,g,9] though many materials in this class,[6e,i] such as protected forms of cymopol (**4**), remain challenging substrates (with typical cation–π product yields ranging around 35 %).[8,10] Here, we describe a simple and readily handled reagent, **13**, that overcomes these deficiencies and smoothly effects bromonium-induced cation–π cyclizations with a diverse set of compounds derived from geraniol, farnesol, and nerol, including electron-deficient systems and a protected form of cymopol (**4**).

Our efforts began with the search for novel classes of brominating reagents under the operating assumption that a highly activated, cationic source of electrophilic bromine free from any additional nucleophilic species might have the best chance to enable controlled bromonium-induced cyclization of a variety of terpenes, particularly those possessing electron-deficient olefin nucleophiles.



Scheme 1. Natural products with rings that likely result from direct, bromonium-induced cation–π cyclizations and the challenges in achieving those reactions.

An extensive search of the literature revealed the existence of a Br_2 complex with Me_2S and $SbCl_5$ that potentially fit these criteria; however, while structurally characterized over 25 years ago, its reactivity with olefins, or any other nucleophile, had not been explored.[11] Accordingly, we prepared a number of compounds of this general type, and discovered that admixing Br_2 with a slight excess of $SbCl_5$ and Et_2S in 1,2-dichloroethane at −30 °C led to the immediate precipitation of an orange powder. Recrystallization afforded pure **13** as an orange, plate-like solid.[12] With this nearly odor-free, stable, and easily handled reagent in

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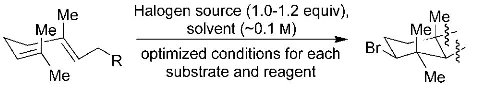
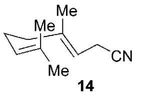
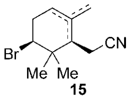
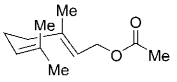
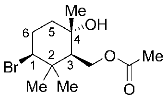
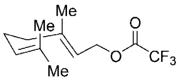
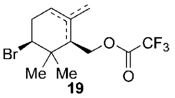
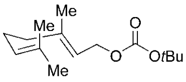
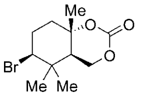
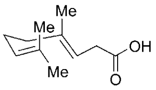
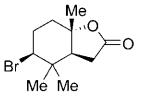
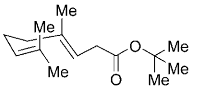
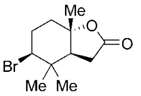
hand,[13] we then proceeded to test its reactivity with a diverse set of terpene-derived substrates.

Table 1: Exploration of the generality of direct, bromonium-induced cation–π cyclizations using reagent **13** and available alternatives with electron-deficient substrates.



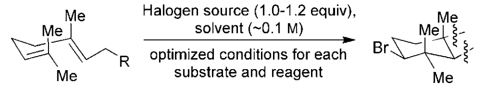
	Starting material	Product	Yield [%] (reaction temperature) (time)			
			13 (BDSB), CH_3NO_2	Br_2/ $AgBF_4$, CH_3NO_2	TBCO, CH_3CN	NBS/ Ph_3P, CH_2Cl_2
1	 **14**	 **15**	73[a] (25 °C) (5 min)	8[b] (25 °C) (5 min)	< 5[b] (25 °C) (15 min)	< 5[b] (–40 °C) (6 h)
2	 **16**	 **17**	80[c] (0 °C) (5 min)	22 (0 °C) (5 min)	< 5 (0 °C) (15 min)	< 5 (–40 °C) (6 h)
3	 **18**	 **19**	56[a] (25 °C) (5 min)	< 5 (25 °C) (5 min)	< 5 (25 °C) (15 min)	< 5 (–40 °C) (6 h)
4	 **20**	 **21**	65[d] (–25→ 25 °C) (30 min)	18 (–25→ 25 °C) (30 min)	< 5 (–5→ 25 °C) (60 min)	< 5 (–40 °C) (6 h)
5	 **22**	 **23**	73 (–25 °C) (5 min)	28 (–25 °C) (5 min)	< 5 (–25 °C) (60 min)	< 5 (–40 °C) (6 h)
6	 **24**	 **23**	79 (0 °C) (5 min)	23 (0 °C) (5 min)	17 (0 °C) (15 min)	< 5 (–40 °C) (6 h)

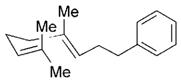
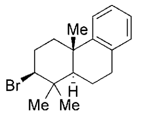
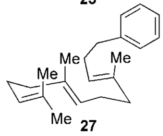
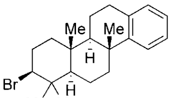
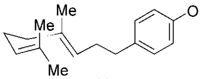
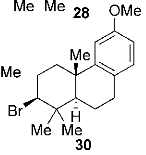
[a] Isolated as a mixture of alkene stereoisomers. [b] All yields deriving from this reagent were determined by NMR analysis using nitrobenzene as an internal standard since the desired material co-elutes with undesired side products. [c] Produced as a 3.8:1 mixture of separable diastereomers at the C-4 position favoring the drawn product. [d] Produced as a 4.8:1 mixture of separable diastereomers at the bridgehead methyl favoring the drawn product.

As indicated in Table 1, a variety of electron-deficient polyenes derived from geraniol[14] were smoothly cyclized following the rapid addition of a CH_3NO_2 solution of **13** (1.0 equiv) to 0.1 mmol of the alkene starting material in CH_3NO_2 (yielding a final reaction concentration of 0.1M). In all cases, the bromonium-induced cation–π cyclization was complete within 5 min, with the reaction temperature employed in each case dictated by the nucleophilicity of the internal alkene; a prolonged reaction was employed for substrate **20** (entry 4) to effect the second, oxygen nucleophile-based, cyclization. In an effort to obtain a quantitative sense of the value and unique reactivity profile of **13** (BDSB) over available alternatives, we next attempted to initiate cation–π cyclizations of the same substrates with each of the other major methods known in the literature[15] under either the same reaction conditions ($Br_2/AgBF_4$ and TBCO) or previously optimized protocols (NBS/PPh_3).[9] In all cases, **13** provided far superior yields, the fastest and cleanest reactions, and the simplest product purifications. Among these results, entry 3 is perhaps the most significant as **13** alone proved capable of cyclizing the highly electron-deficient **18** in any measurable yield. It should be noted that every reaction using these alternate methods was driven to completion, and that the yields for these experiments derive from NMR analyses of crude reaction mixtures since product isolation proved challenging and/or impossible to achieve; as such, these yields are likely artificially high relative to those observed with **13** since those numbers reflect yields of isolated compounds.[16]

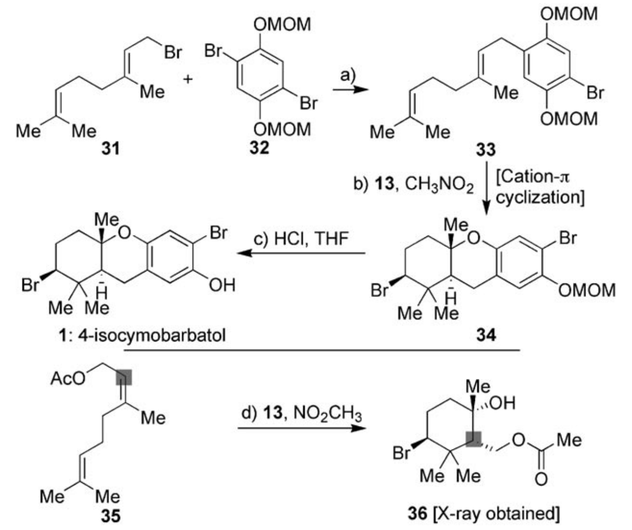
Similar facility in initiating cation–π reactions was observed when we exposed electron-rich substrates derived from both geraniol and farnesol (Table 2) to the action of BDSB (**13**).[14] For instance, not only was a polycyclization smoothly achieved in 58 % yield (entry 2), but even a substrate bearing a highly electron-rich aromatic ring was cyclized in 76 % isolated yield without significant amounts of competing aryl halogenation following 5 min of reaction time at –25 °C.[17] As shown in Scheme 2, reagent **13** worked equally well with even more complex and highly electron-rich substrates such as **33**,[18] providing in this case the means to complete an efficient total synthesis of the natural product 4-isocymobarbatol (**1**) with the cation–π cyclization step proceeding in 74 % yield (53 % overall yield from commercial

Table 2: Exploration of the generality of direct, bromonium-induced cation-π cyclizations using reagent **13** and available alternatives with electron-rich substrates.



	Starting material	Product	Yield [%] (reaction temperature) (time)			
			13 (BDSB), CH_3NO_2	Br_2/ $AgBF_4$, CH_3NO_2	TBCO, CH_3CN	NBS/ Ph_3P, CH_2Cl_2
1	 **25**	 **26**	75[a] (–25 °C) (5 min)	9[b] (–25 °C) (5 min)	27[b] (–25 °C) (60 min)	13[b,c] (–78 °C, 24 h; 40 °C, 6 h)
2	 **27**	 **28**	58[a,d] (–25 °C) (5 min)	< 5[d] (–25 °C) (5 min)	14[a,d] (–25 °C) (60 min)	< 5[d] (–78 °C, 24 h; 40 °C, 6 h)
3	 **29**	 **30**	76 (–25 °C) (5 min)	11 (–25 °C) (5 min)	27 (–25 °C) (60 min)	20[c] (–78 °C, 24 h; 40 °C, 6 h)

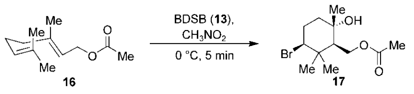
[a] Generated alongside some very minor diastereomers; [b] All yields deriving from this reagent were determined by NMR analysis using nitrobenzene as an internal standard since the desired material co-elutes with undesired side products; [c] Yield includes partially cyclized material; [d] Complete cyclization promoted by the addition of CH_3SO_3H at the end of the reaction.



Scheme 2. Total synthesis of 4-isocymobarbatol (**1**) and a reaction with nerol-derived substrate **35** using BDSB (**13**) to effect a biomimetic cation–π cyclization: a) **32** (2.0 equiv), *n*BuLi (1.3 M in hexanes, 1.7 equiv), THF, −78 °C, 30 min; then added to **31** (1.0 equiv), THF, −40 °C to 0 °C, 2 h, 75 %; b) **13** (1.1 equiv), CH_3NO_2, −25 °C, 5 min, 74 %; c) HCl (concentrated, excess), THF, 25 °C, 5 h, 97 %; d) **13** (1.1 equiv), CH_3NO_2, 0 °C, 5 min, 71 %. MOM = methoxymethyl.

materials). It also smoothly cyclized a terpene possessing an alternate olefin geometry, namely polyene **35** derived from nerol; as such, this result, coupled with those in both Table 1 and Table 2, illustrate that each of these BDSB-initiated cyclizations proceeds through a tight, chair-like transition state where the initial alkene geometry is expressed in the relative stereochemistry of the products (i.e. the isoprene cyclization rule is followed).[19,20] It is also worth noting that while all of the reactions mentioned above were conducted on a relatively small scale (0.1 mmol), we have been able to successfully and smoothly perform the same transformation on far larger quantities of material (5.0 mmol) for each of the two substrates that we have attempted thus far (**16** and **25**). As shown in Table 3, in our efforts to explore the large-scale conversion of **16** into **17**, the key to success is reaction concentration, with far more dilute solutions providing superior yields and diastereoselectivities. Additionally, electron-rich substrate **25** was smoothly cyclized to tricycle **26** in 67 % yield on 5.0 mmol scale under the same reaction concentration as that of entry 8 in Table 3 at a reaction temperature of −25 °C.[21]

Table 3: Exploration of scaleability of BDSB-induced cyclizations with substrate **16**.



	Scale [mmol]	Concentration [M]	BDSB equiv.	Yield [%]	d.r.
1	0.1	0.100	1.0	80	3.8:1
2	0.5	0.100	1.0	61	4.3:1
3	0.5	0.025	1.0	70	4.7:1
4	0.5	0.025	1.0[a]	71	4.6:1
5	0.5	0.025	1.1	74	4.3:1
6	0.5	0.010	1.0	78	5.1:1
7	0.5	0.010	1.1	84	5.0:1
8	5.0	0.010	1.1	75	5.3:1

[a] Inverse order of addition (by adding a solution of **16** to a solution of BDSB in CH_3NO_2).

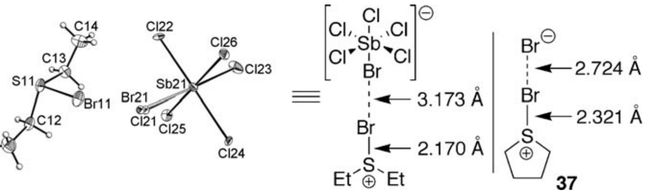


Figure 1. Preliminary X-ray crystal structure of BDSB (**13**) and comparison to a known, related structure (**37**): a possible explanation for superior reactivity.

Finally, although we do not yet fully understand the basis for the unique chemical reactivity profile of BDSB (**13**) in successfully initiating cation–π cyclizations far more smoothly over available electrophilic bromine alternatives,[22] a few initial observations are worth mentioning at this juncture. As indicated in Figure 1, a preliminary X-ray crystal structure[23] of **13** reveals significantly tighter binding between the sulfur atom and its electrophilic bromine counterpart relative to other published Br_2·sulfur adducts such as **37**;[24] this alternate distance is the likely basis for its unique reactivity, since **37** has proven to be a source of molecular Br_2 and ineffective for cation–π cyclizations in our hands. Interestingly, though the bromide atom that is part of the $SbCl_5Br$ anion within **13** is oriented towards the electrophilic bromine atom attached to sulfur, the extended bond distances suggest that it is effectively sequestered. In terms of general capability to effect other reactions, such as electrophilic aromatic substitution, BDSB appears to be very comparable to NBS in terms of its reaction with substrates that we have previously explored.[25] However, NBS is more prone to provide small quantities of overhalogenated materials that are absent in the analogous reactions using BDSB.

In conclusion, we have demonstrated that BDSB (**13**) is a powerful reagent for electrophilic bromination, one that finally enables the direct formation of cation–π cyclization products with essentially every class of standard terpene substrate in the absence of the difficult to separate side-adducts formed with more classical reagents, as well as with predictable stereoselectivity. Efforts to further explore the complete reactivity profile of **13**, render this transformation asymmetric, and apply the lessons learned to analogous chlorine- and iodine-based reactions, are the subject of current study.

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Keywords: biomimetic synthesis · bromine · isocymobarbatol · polyene cyclization · terpene

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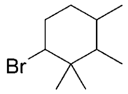

Of these, many have potent biological activity, including antitumor, antibacterial, and anti-HIV activity. For selected examples, see: d) G. R. Pettit, C. L. Herald, M. S. Allen, R. B. Von Dreele, L. D. Vanell, J. P. Y. Kao, W. Blake, *J. Am. Chem. Soc.* **1977**, *99*, 262–263; e) S. Loya, M. Bakhanashvili, Y. Kashman, A. Hizi, *Arch. Biochem. Biophys.* **1995**, *316*, 789–796; f) C. S. Vairappan, M. Suzuki, T. Ishii, T. Okino, T. Abe, M. Masuda, *Phytochemistry* **2008**, *69*, 2490–2494.

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[8] A. Tanaka, T. Oritani, *Biosci. Biotechnol. Biochem.* **1995**, *59*, 516–517. A graphical summary of all of the bromonium-induced cyclizations in Refs. [6–8] can be found at the end of the Supporting Information to provide a full sense of the true state-of-the-art in these reactions in racemic format.

[9] A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900–903. It should be noted that this paper describes asymmetric iodonium-induced cyclizations of three structurally similar geraniol-derived substrates possessing electron-rich alkene nucleophiles; attempts to extend the developed system directly to bromine afforded products in poor enantiomeric excess, revealing that the problem of inducing asymmetry in this transformation is far from a trivial one; these challenges, of course, are in addition to those described for effecting bromonium-induced cyclizations in racemic format as already described.

[10] Available two-step alternatives include iodonium-based cyclization followed by lithium exchange and bromine capture with retention of configuration (cf. Ref. [9]), cyclization of bromohydrin precursors, or stoichiometric Hg^{II}-based cyclizations followed by bromine replacement: a) E. A. Couladouros, V. P. Vidali, *Chem. Eur. J.* **2004**, *10*, 3822–3835; b) A. Murai, A. Abiko, T. Masamune, *Tetrahedron Lett.* **1984**, *25*, 4955–4958; c) T. R. Hoye, M. J. Kurth, *J. Org. Chem.* **1979**, *44*, 3461–3467.

[11] a) G. J. Goetz-Grandmont, M. J. F. Leroy, *J. Chem. Res.* **1982**, 160–161; b) H. F. Askew, P. N. Gates, A. S. Muir, *J. Raman Spectrosc.* **1991**, *22*, 265–274. Related reagents with different Lewis acidic counterions have been known for far longer, though again, their reactivity with olefins or other nucleophilies remains unreported: c) H. Böhme, E. Boll, *Z. Anorg. Allg. Chem.* **1957**, *290*, 17–23; d) R. Minkwitz, V. Gerhard, A. Werner, *Z. Anorg. Allg. Chem.* **1989**, *575*, 137–144; e) R. Minkwitz, B. Baeck, *Z. Naturforsch. B* **1993**, *48*, 694–696; f) B. Regelmann, K. W. Klinkhammer, A. Schmidt, *Z. Anorg. Allg. Chem.* **1997**, *623*, 1633–1638.

[12] Use of Me_2S and iPr_2S leads to competent reagents for cation–π cyclization; however, **13** is the most easily prepared and crystallized. We propose giving compound **13** the acronym of BDSB for bromodiethylsulfonium bromopentachloroantimonate.

[13] **13** has proven stable in a vial stored in a −20°C refrigerator for several months with no depreciation in chemical reactivity. It appears only to be sensitive to prolonged exposure to moisture-rich air. In terms of its solubility profile, **13** is fully soluble at ambient temperature in CH_3NO_2, $CH_3CH_2NO_2$, MeCN, DMSO, DMF, and EtOAc, moderate to slightly soluble in CH_2Cl_2, 1,2-dichloroethane, chloroform, and toluene, and insoluble in benzene, hexanes, and pentane. We have observed that **13** is soluble in acetone, methanol, ethanol, and THF, but reacts with these solvents.

[14] For the synthesis of these substrates, see the Supporting Information.

[15] Although not reported to initiate cation–π cyclizations, bis(collidine)halonium triflate and perchlorate salts have been utilized as sources of electrophilic halogen. For selected examples, see: a) R. U. Lemieux, A. R. Morgan, *Can. J. Chem.* **1965**, *43*, 2190–2197; b) J. W. Lown, A. V. Joshua, *Can. J. Chem.* **1977**, *55*, 122–130; c) Y. Tamaru, S. Kawamura, Z. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 2885–2888; d) R. D. Evans, J. W. Magee, J. H. Schauble, *Synthesis* **1988**, 862–868; e) A. A. Neverov, R. S. Brown, *J. Org. Chem.* **1998**, *63*, 5977–5982; f) X.-L. Cui, R. S. Brown, *J. Org. Chem.* **2000**, *65*, 5653–5658. We prepared the bis(collidine)bromonium triflate reagent and explored its reactivity with homogeranyl benzene (**25**) in CH_3NO_2 at −25°C, finding that a complex mixture of products was formed after 5 min of reaction time with ca. 20% being the desired cation–π product (**26**). In CH_2Cl_2, the yield of **26** was much lower.

[16] As a point of internal calibration to verify that our results with these alternate reagents are valid and have not been skewed in any way, we note that three of the yields in Table 1 directly parallel literature precedent, namely entries 2 and 5 for Br_2/$AgBF_4$ and entry 1 for TBCO. Each of these precedents is fully elucidated in the Supporting Information.

[17] A substrate related to **29** was reported in Ref. [9] to cyclize with NBS/Ph_3P under the utilized conditions in 71% yield; we have been unable to achieve similar results despite several attempts. Rather than offer any questioning of this precedent, we would argue instead here that our protocol provides for easier execution since temperature control over the course of 30 h is not required.

[18] Compound **33** has also been prepared by using the cuprate nucleophile derived from **32**; see Ref. [6i]. We observed that the lithiated form was better yielding overall for this bond construction with none of the very difficult to separate S_N2' adducts generated.

[19] In all cases, the stereochemistry of products was confirmed by NMR analysis as well as comparison to published characterization data. In particular, at least in terms of NMR analyses, any alteration in the axial or equatorial disposition of groups attached to the carbocycle are highly diagnostic signals. To verify the nerol cyclization case, we obtained a crystal structure for **36** (a picture of which is shown in the Supporting Information) since precedent for cyclizations with these substrates is sparse.

[20] Products **17** and **36** are believed to result upon work-up through a reaction between water and the acetate-bridged cationic intermediate formed following cation–π cyclization. This mechanism was first advanced by Faulkner in his group's studies with compound **16** using Br_2/$AgBF_4$ (cf. Ref. [7a]).

[21] For the reaction of **25**, as well as all the other substrates in Table 2, one minor and characterizable side-product, that of proton-initiated cation–π cyclization, was observed in each case in up to 12% overall yield. On large scale, this side-product could be suppressed to $<5\%$ by using dilute reaction concentrations (0.01 M) and adding 2 equivalents of pulverized $CaCO_3$ to the reaction media prior to BDSB addition. It could also be suppressed by adding a cold solution of BDSB very quickly to the substrate.

[22] Conceptually, the reagent described herein can be defined as Lewis base activation of a Lewis acid. For a review on this important mode of promoting reactivity from one of its leading practitioners, see: S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584–1663; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638. For a recent paper on the use of this approach to attempt enantioselective addition of chalcogens such as sulfur onto alkenes, see: S. E. Denmark, W. R. Collins, M. D. Cullin, *J. Am. Chem. Soc.* **2009**, *131*, 3490–3492.

[23] The crystal structure of **13** is noted as preliminary since disorder resulting from halide exchanges between the halogen atoms attached to the antimony counterion prevents a consistent unit cell.

[24] G. Allegra, G. E. Wilson, E. Benedetti, C Pedone, R. Albert, *J. Am. Chem. Soc.* **1970**, *92*, 4002–4007.

[25] a) S. A. Snyder, A. L. Zografos, Y. Lin, *Angew. Chem.* **2007**, *119*, 8334–8339; *Angew. Chem. Int. Ed.* **2007**, *46*, 8186–8191; b) S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, *J. Am. Chem. Soc.* **2009**, *131*, 1753–1765.