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Multicomponent *cis*- and *trans*-Aziridinatons in the Syntheses of All Four Stereoisomers of Sphinganine

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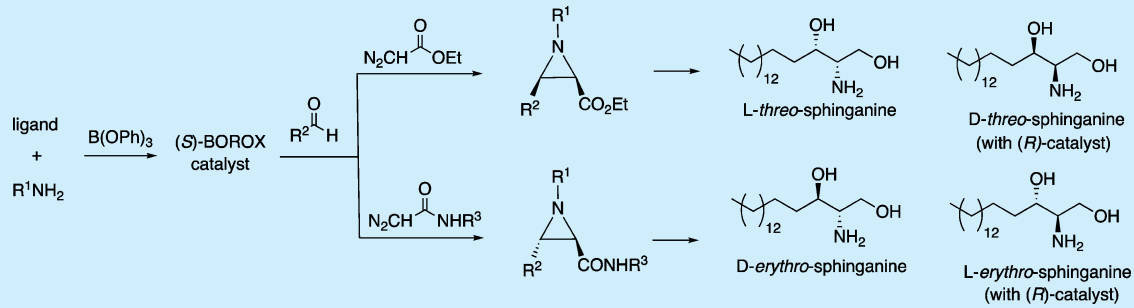
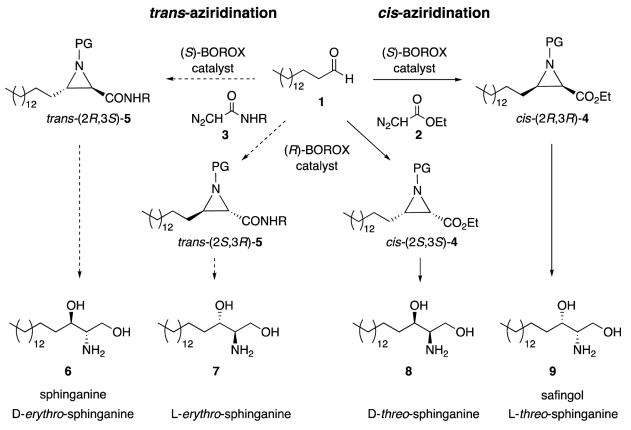
Supporting Information



ABSTRACT: All four stereoisomers of sphinganine can be synthesized by a multicomponent aziridination of an aldehyde, an amine and an α-diazo carbonyl compound mediated by a BOROX catalyst with high asymmetric induction ($\geq$96% ee). The threo isomers are available from ring-opening of *cis*-aziridines by an oxygen nucleophile with inversion at the C-3 position and the erythro-isomers are likewise available from *trans*-aziridines.

Sphinganine is one of three core structures present in sphingolipids, which exist in several subclasses and are involved in many aspects of cell structure and regulation.[1−3] Errors in sphingolipid metabolism have led to several inherited human diseases including diabetes,[4] cancers,[5] Alzheimer's disease,[6] heart disease and an array of neurological syndromes.[7] Sphingolipids are involved in nearly all aspects of cell regulation, including proliferation, differentiation, adhesion, neuronal repair, and signal transduction.[8] The natural configuration of sphinganine is the D-*erythro* configuration **6**, however, it has been found that the stereochemistry can play a large role in their bioactivity. For example, the L-*threo* diastereomer of sphinganine (safingol **9**) is an antineoplastic and antipsoriatic drug[9] and has been investigated for its ability to inhibit protein kinase C.[10] As a consequence of this and other differences in bioactivities, all of the isomers of sphinganines have been prepared and their biological properties investigated.[1−3]

Scheme 1. Sphinganines via *cis*- and *trans*-Aziridination



The history of the synthesis of sphinganines has been quite extensive[11,12] and dates back to the first synthesis in 1951.[13] The most successful applications with asymmetric catalysis involve the use of either the Sharpless asymmetric dihydroxylation[14] the Sharpless asymmetric epoxidation[15] and the Sharpless kinetic resolution of allylic alcohols,[16] although it has not been demonstrated if these methods can be used for all four of the stereoisomers of the sphinganines. Other catalytic asymmetric methods utilized in the synthesis sphinganines are asymmetric hydrogenation of β-oxo esters,[17] a proline based Mannich reaction,[18] and again, it has not been demonstrated that either can be used for the preparation of all four of the stereoisomers of sphinganine. A catalytic asymmetric nitro aldol reaction (Henry reaction) with a lanthanum BINOL complex between 2-nitroethanol and hexadecanal has also been reported but is limited to the *threo*-isomers.[19] Likewise, an organocatalytic based catalyst with a prolinol derivative has been reported[12c] but is also limited to the *threo*-isomers (sphinganine itself is *erythro*).

The goal of the present work is to demonstrate that the asymmetric catalytic aziridination reaction can be adapted to the synthesis of all four sphinganines (Scheme 1). We have

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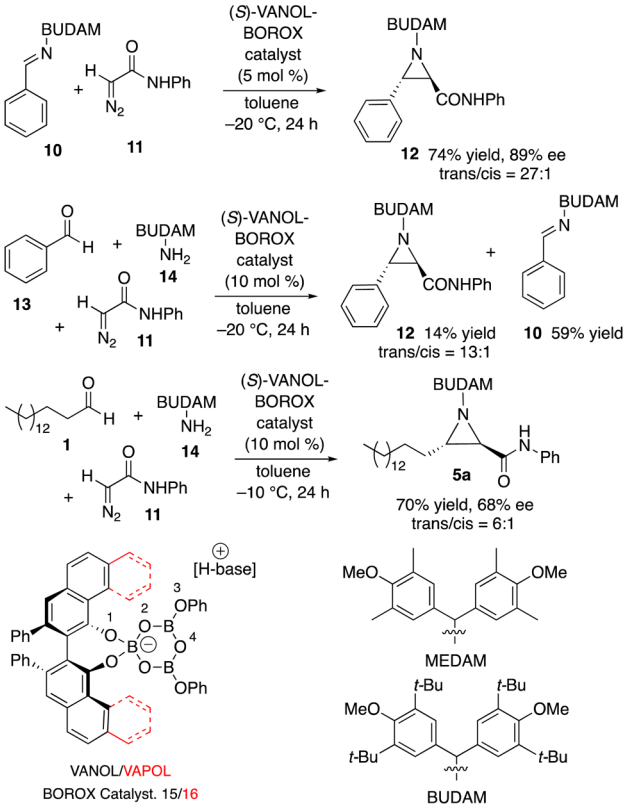
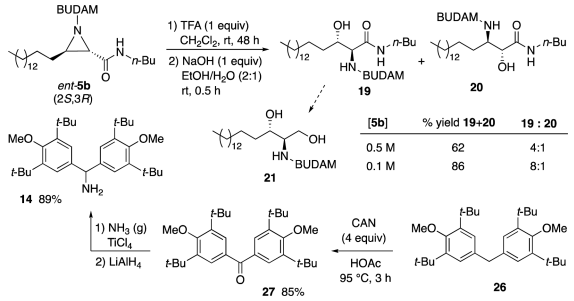
Scheme 2. Multicomponent *trans*-Aziridination of Aryl and Aliphatic Aldehydes



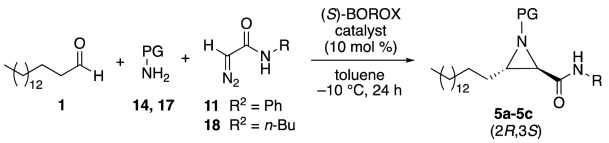
Scheme 3. Ring-Opening of Aziridine 5b and Recycling of BUDAM amine 14



previously reported[20] the synthesis of the *threo*-sphinganines from *cis*-aziridines which were generated by the catalytic asymmetric multicomponent *cis*-aziridination[21] of hexadecanal, an amine and ethyl diazoacetete mediated by a BOROX catalyst. The *cis*-aziridines were ring-opened at the C-3 position by an oxygen nucleophile with inversion. In this work access to the *erythro*-sphinganines was also achieved from the *cis*-aziridines in a multistep process involving the removal of the *N*-protecting group and then installation of an *N*-Boc group, ring expansion to an oxazolidinone (with retention at C-3), and then hydrolysis to an amino alcohol. However, it was envisioned that the *erythro*-sphinganines could be obtained directly from *trans*-aziridines via ring-opening at the C-3 position by an oxygen nucleophile with inversion. The diastereo-selectivity of the aziridination can be switched from *cis*- to *trans*- by changing the diazo substrate from a diazo acetate to a diazo acetamide beginning from preformed imines.[22] We present here the first examples of the multicomponent *trans*-aziridination of aldehydes with an amine and a diazoacetamide using a BOROX catalyst and its application to the synthesis of *erythro*-sphinganines.

We have previously reported that switching the diazo compound from a diazo acetate to a 2° diazo acetamide will produce *trans*-aziridines rather than *cis*-aziridines from preformed imines with a BOROX catalyst generated from either the VANOL or VAPOL ligand.[22,23] As an example, the BUDAM imine **10** prepared from benzaldehyde and BUDAM amine **14** reacts with the *N*-phenyl diazoacetamide **11** to give the *trans*-aziridine **12** in 74% yield with 89% ee and with a 27:1 selectivity for the *trans*-isomer (Scheme 2).[24] We had previously determined that both amines and imines are basic enough to cause self-assembly of the BOROX catalyst from a molecule of the ligand and three equivalents of $B(OPh)_3$.[25] However, our initial attempts at translation of this reaction into a multicomponent version from aryl aldehydes were not successful. For example, the reaction of benzaldehyde, BUDAM amine **14** and diazo acetamide **11** only gave the aziridine **12** in 14% yield along with the imine **10** in 59% yield. Given this

Table 1. Optimization of the Multicomponent *trans*-Aziridination of Aliphatic Aldehyde 1[a]



entry	amine	PG	ligand	R	aziridine	*trans*/*cis*[b]	% yield trans aziridine[c]	% ee trans aziridine[d]
1	**14**	BUDAM	(*S*)-VANOL	Ph	**5a**	6:1	70	68
2	**14**	BUDAM	(*S*)-VANOL	*n*-Bu	**5b**	24:1	85	96
3	**14**	BUDAM	(*S*)-VANOL	*n*-Bu	**5b**	28:1	88	96[e]
4	**14**	BUDAM	(*R*)-VANOL	*n*-Bu	**5b**	30:1	86	−96[e,f]
5	**14**	BUDAM	(*S*)-VAPOL	*n*-Bu	**5b**	14:1	91	91
6	**17**	MEDAM	(*S*)-VANOL	*n*-Bu	**5c**	8:1	67	88
7	**17**	MEDAM	(*S*)-VAPOL	*n*-Bu	**5c**	15:1	79	86

[a]Unless otherwise specified, all reactions were performed at 0.2 M in amine in toluene with 0.2 mmol of amine and 1.1 equiv of **1** and 1.2 equiv of diazo compound with 10 mol % catalyst, which was prepared by heating 0.1 equiv of ligand, 0.3 equiv of $B(OPh)_3$ and 1.0 equiv of amine in toluene at 80 °C for 30 min. The catalyst was cooled to rt, and then the aldehyde and 4 Å molecular sieves were added, and then the mixture was immediately cooled to −10 °C, and the diazo compound was added. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield of purified *trans*-aziridine. [d]Determined on purified *trans*-aziridine by HPLC. [e]Reaction run on 3.0 mmol scale. [f](2*S*,3*R*)-**5b** is produced.

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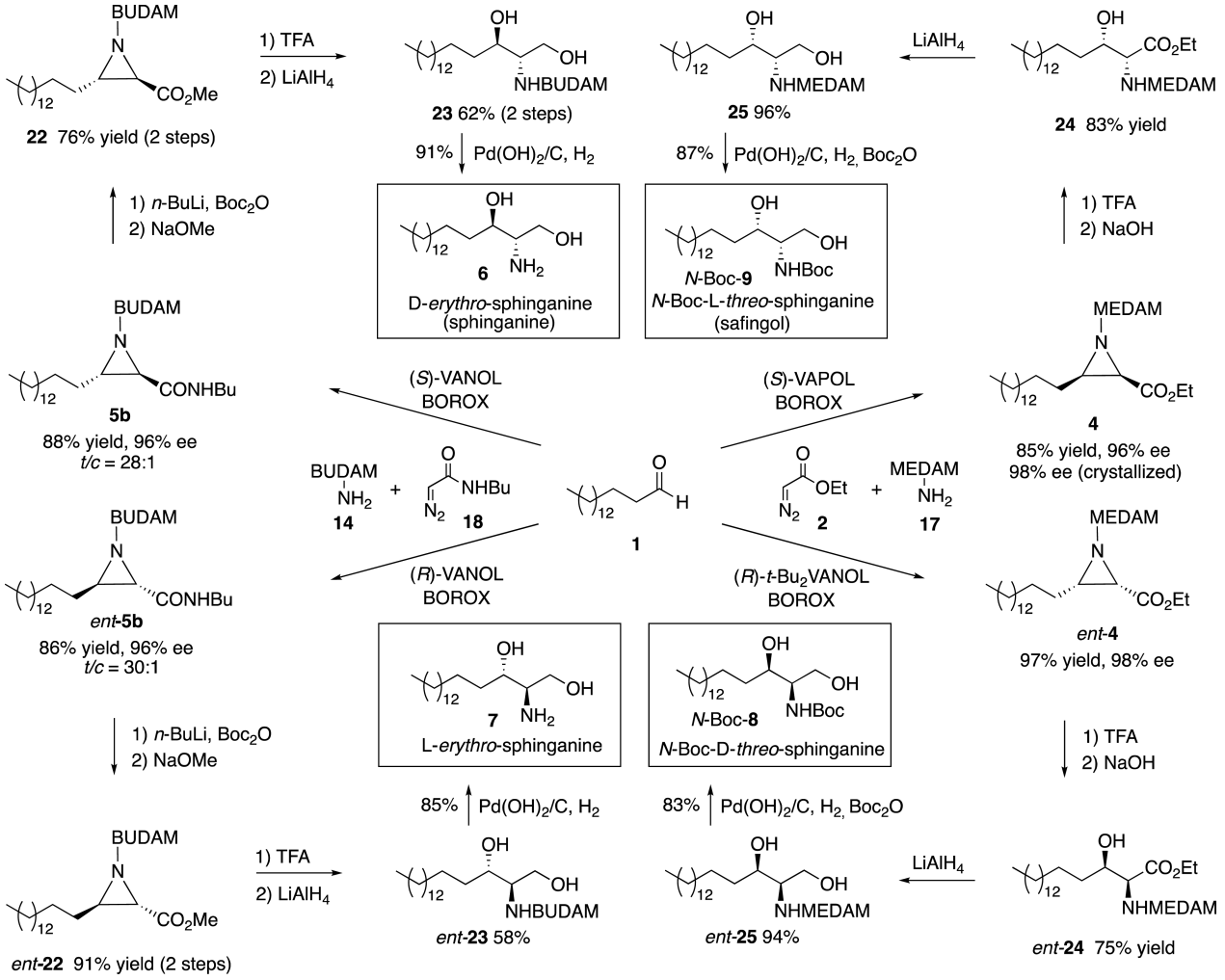
Scheme 4. Synthesis of all Four Stereoisomers of Sphinganine via Asymmetric Catalytic Multicomponent *cis*- and *trans*-Aziridinations



result, it was surprising to find that the same multicomponent reaction with the aliphatic aldehyde hexadecanal **1** gave the *trans*-aziridine **5a** in 70% yield and in 68% ee with a 6:1 trans/cis ratio.

With the successful multicomponent *trans*-aziridination of hexadecanal, attention was turned to its optimization (Table 1). It was found that if the *N*-substituent on the diazo was an *n*-butyl instead of phenyl, the asymmetric induction increased to 96% ee (Table 1, entry 2). This reaction could be scaled up 15-fold to give 2.12 g of aziridine (2*R*,3*S*)-**5b** in 96% ee and 88% yield with a *trans*:*cis* ratio of 28:1 (entry 3). With the (*R*)-BOROX catalyst the aziridine (2*S*,3*R*)-**5b** was obtained in 86% yield and 96% ee (entry 4). The corresponding VAPOL-BOROX catalyst was also effective but gave slightly lower diastereo- and enantioselectivity (Table 1, entries 2 vs 5). The VANOL and VAPOL catalysts were also compared with the MEDAM amine but both were slightly less effective than BUDAM amine (Table 1, entries 2 vs 6 and 5 vs 7).

We had previously shown that *cis*-aziridine-2-carboxylate esters would undergo ring-opening with trifluoroacetic acid to give exclusive opening at the C-3 position.[20] We had not previously examined the ring-opening of the *trans*-aziridine-2-carboxamides with oxygen nucleophiles. The reaction of aziridine (2*R*,3*S*)-**5b** with trifluoroacetic acid actually gave a mixture of the regioisomers **19** and **20** (Scheme 3). Fortunately, the major regioisomer resulted from nucleophilic opening at the C-3 position in a 4:1 ratio which could be enhanced to 8:1 by decreasing the concentration (Scheme 3). From compound **19**, the most straightforward route to the sphinganines would involve reduction of the amide to the alcohol to give compound **21**. Unfortunately, the screening of a host of reducing agents including $BH_3{\cdot}NH_2Li$[26] did not lead to the clean conversion of **19** to **21** but rather to complex mixtures of compounds. This lack of selectivity was thought to be due to the bulk of the BUDAM group and not to the presence of the *β*-hydroxy group.[26]

A change in tactics then involved the conversion of the *trans*-amide *ent*-**5b** to the *trans*-ester *ent*-**22** prior to the ring-opening (Scheme 4). Ring-opening of the *trans*-ester *ent*-**22**, like that of the *trans*-amide *ent*-**5b**, did not give a single regioisomer but rather a mixture of opening at C-3 and C-2 (2.5:1). The regioisomers could be separated after the reduction of the ester to give the amino diol *ent*-**23** in 58% yield for 2 steps. The regioisomer of *ent*-**23** could be isolated in 23% yield and thus the ring-opening of the *trans*-ester *ent*-**22** is less regioselective (2.5:1) than for the trans-amide *ent*-**5b** (8:1). Finally, the amino group in *ent*-**23** could be deprotected to give L-*erythro*-sphinganine **7** in 85% yield. In a similar manner, the aziridine **5b** could be converted to D-*erythro*-sphinganine (Scheme 4). It is to be noted that the final cleavage of the BUDAM group in

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ent-**23** (and also for **23**) leads to the recovery of the bis-aryl methane **26**. BUDAM amine **14** can be recycled from **26** by oxidation[27] to the benzophenone **27** (85%) and then reductive amination (89%) (Scheme 3).

We have described here the first examples of the multicomponent *trans*-aziridination of aldehydes and, together with the multicomponent *cis*-aziridination, the synthesis of all four stereoisomers of sphinganine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00697.

Experimental protocols, characterization procedures (PDF)

Spectral data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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