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Pnictogen-Bonding Catalysis: An Interactive Tool to Uncover Unorthodox Mechanisms in Polyether Cascade Cyclizations

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Abstract: *Pnictogen-bonding catalysis and supramolecular σ-hole catalysis in general is currently being introduced as the non-covalent counterpart of covalent Lewis acid catalysis. With access to anti-Baldwin cyclizations identified as unique characteristic, pnictogen-bonding catalysis appeared promising to elucidate one of the hidden enigmas of brevetoxin-type epoxide opening polyether cascade cyclizations, that is the cyclization of certain trans epoxides into cis-fused rings. In principle, a shift from S_N2- to S_N1-type mechanisms could suffice to rationalize this inversion of configuration. However, the same inversion could be explained by a completely different mechanism: Ring opening with C-C bond cleavage into a branched hydroxy-5-enal and the corresponding cyclic hemiacetal, followed by cascade cyclization under conformational control, including stereoselective C-C bond formation. In this report, a pnictogen-bonding*

supramolecular Sb(V) catalyst is used to demonstrate that this unorthodox polyether cascade cyclization mechanism occurs.

Pnictogen-bonding catalysis[1,2] is currently being envisioned as the supramolecular counterpart of the intrinsically covalent[3] Lewis acid catalysis,[4] just like hydrogen-bonding catalysis is the non-covalent version of Brønsted acid catalysis (Figure 1a, b).[5] The differences between the latter are understood and appreciated.[5] In sharp contrast, more explicit evidence that σ-hole[6,7] catalysts[1,2,8] in general and pnictogen-bonding[7] catalysts[1,2] in particular are more than just weak Lewis acids[4] is needed, also to demonstrate that pnictogen-bonding catalysis really exists and matters.[1] Recently, we found that in epoxide-opening cascade cyclization,[9,10] pnictogen-bonding catalysts such as stibine **1** or stiborane **2** can break the Baldwin rules (Figure 1c).[1,11] This differs from Brønsted acid catalysts, which cyclize 1,5-diepoxide **3** into oxolane dimer **4** via the 5-*exo*-*tet* transition state **TS-1** dictated by the Baldwin rules (Figure 2a).[1] Covalent Lewis acid catalysis with $SbCl_3$ gives mixtures of constitutional isomers with little preference. Supramolecular σ-hole catalysts **1** and **2**, however, afford the *trans*-fused bicycles **5** as major products, with *trans,anti*-**5** preferred by Sb(V) **2** and *trans,syn*-**5** accessible only with Sb(III) **1** (Figure 2b).[12,13] The pnictogen-bond stabilized 6-*endo*-*tet* **TS-2** leading to **5** is against the Baldwin rules[11] but most important in biology to explain the biosynthesis of brevetoxin-like polyether natural products.[10] The isolation of intermediate **6** supported that the cascade cyclization occurs with “head-to-tail” directionality, from the alcohol nucleophile to the epoxide electrophiles.

The breaking of the Baldwin rules identified as a unique signature suggested that pnictogen-bonding catalysis could solve one of the hidden enigmas of brevetoxin-like polyether cascade cyclizations.[14] There is nothing enigmatic about the elegant Lewis acid catalyzed cascade cyclization transcribing the *trans*-diepoxide **7** into the *trans*-fused bicyclic product **8** (Figure

2c).[12,13,15] With a weaker carbonate nucleophile (compared to **3**) and much stronger covalent leaving group activation with BF_3,[14-16] this cascade cyclization is thought to occur with reversed tail-to-head directionality through an epoxonium reactive intermediate **TS-3**. The transcription of the *trans* conformation of the epoxide into a *trans*-fused bicycle is consistent with an intramolecular S_N2-type mechanism.

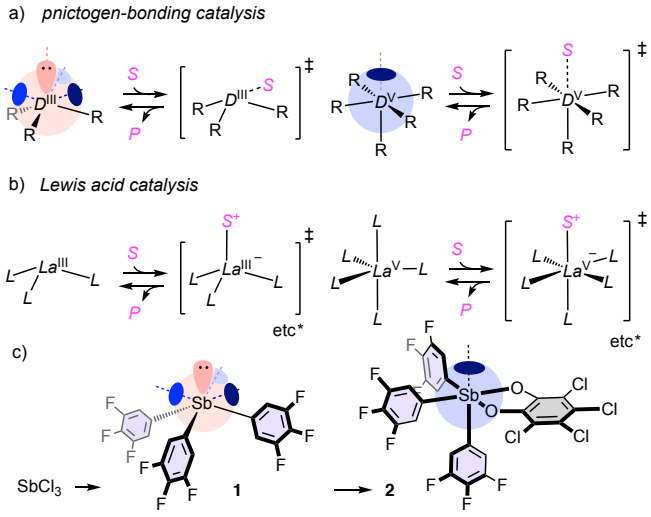

Figure 1. a) Pnictogen-bonding catalysis defined as a non-covalent counterpart of b) Lewis acid (*La*) catalysis. *D*, pnictogen-bond donors; blue circles, σ holes; R, organic substituent; *S*, substrate; *P*, product; *L*, inorganic ligand; etc*: *L* exchange, proton release from *S* upon addition to *La*. c) Structure of catalysts **1** and **2**, accessible from $SbCl_3$ in one step each.

More intriguing is the inversion of configuration during the cyclization of the shortened, 1,4 *trans*-diepoxide **9** into the *cis*-fused bicyclic product **10** (Figure 2d).[12-14] This "inversion of configuration" could be explained with a shift from S_N2- to S_N1-type mechanism of the "tail-to-head" cyclization. Opening of the epoxonium in **TS-4** could produce an achiral carbocation intermediate, but the intramolecular cyclization with the nucleophile can be expected to be stereoselective due to severe conformational constraints in **TS-5**. The occurrence of this S_N1-type epoxonium opening with the 1,4 diepoxide **9** but not 1,5 diepoxide **7** could be understood

with the higher stability of the 6-membered ring in **TS-5** obtained by the former compared to the 7-membered ring not obtained by the latter. However, the reverse transcription of *trans* epoxides into *cis*-fused bicylces could also be explained with a completely different mechanism, involving ring opening by C-C bond cleavage followed by quite spectacular ring closing cascades with C-C bond formation. In the following, non-covalent, supramolecular pnictogen-bonding catalysis is introduced as an interactive tool to demonstrate the existence and relevance of this unorthodox mechanism for epoxide-opening polyether cascade cyclizations.

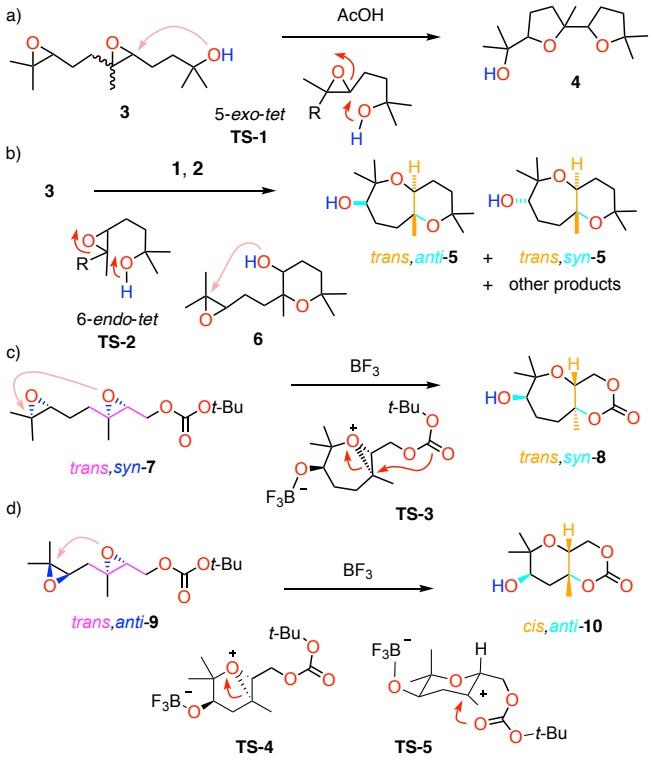

Figure 2. Previously reported a) Brønsted acid catalyzed 5-*exo*-*tet* cyclization (**TS-1**) of dimer **3** into Baldwin-product **4** and b) 6-*endo*-*tet* cyclization (**TS-2**) into *trans*-fused anti-Baldwin **5** with pnictogen-bonding catalysts **1** and **2**,[1] c) Lewis acid catalyzed S_N2-like cyclization of *trans*-**7** into *trans,anti*-**8**[15] and d) S_N1-like cyclization of *trans*-**9** into *cis,syn*-**10**.[12-14]

The enigmatic “reverse transcription” of 1,4 *trans*-epoxides into *cis-fused* products was readily confirmed with *trans*-3,6-diepoxyoctanol **11** (Figure 3a).[12,13] Cyclized with covalent Lewis acid catalysis, the *cis-fused* bicycle **12** was obtained instantaneously as the only product. However, only *cis,anti*-**12** was observed.[13] The *cis,syn*-epimer of **12** was not formed although the substrate *trans*-**11** was prepared as a mixture of *syn* and *anti* diepoxides rather than a diastereomerically pure compound.[12] This result was inconsistent with an S_N1-like mechanism through **RI-1**. This mechanism excludes changes of the stereochemistry of the secondary alcohol and should thus afford a mixture of *cis,anti*-**12** and *cis,syn*-**12**.

Supramolecular pnictogen-bonding catalysis of the cascade cyclization of *trans*-diepoxide **11** with 1 mol% **2** gave a mixture of *cis,anti*-**12** and *cis,syn*-**12** in 54% and 27% yield, respectively, that is a 2:1 ratio (Figure 3b). Moreover, the acyclic, branched hydroxy-5-enal **13** formed immediately and cyclized only slowly over 10 h into the different stereoisomers of **12**. Intermediate **13** could be isolated in 72% yield. Reaction of isolated and purified **13** with 1 mol% pnictogen-bonding catalyst **2** gave the same mixture of *cis,anti*- and *cis,syn*-**12** in a 2:1 ratio (Figure 3c). Likewise, the only product of the reaction of substrate *trans*-**11** and intermediate **13** with BF_3 was the same, i.e., *cis,anti*-**12** (Figure S27).

Enals similar to **13** have been reported previously as final by-products because they could not further cyclize.[17] The temporary appearance of acyclic **13** in pnictogen-bonding catalysis implied that the cascade cyclization of 1,4 *trans*-diepoxide **11** into **12** begins with a tail-to-head formation of an epoxonium as in **TS-6** (Figure 4). This inversion of the head-to-tail directionality with 1,5 *trans*-diepoxide **3** to the tail-to-head directionality with 1,4 *trans*-diepoxide **11** was as designed. Namely, shortening of the tether of the alcohol nucleophile from three carbons in 4-epoxyalcohol **3** to two carbons in 3-epoxyalcohol **11** should disfavor head-to-tail cyclization into the smaller, more strained rings.[18] Instead, the central epoxide oxygen opens the pnictogen-

bonding activated terminal epoxide. This tail-to-head cyclization occurs with anti-Baldwin *endo-tet* selectivity because the Baldwin isomer would be highly strained. The resulting epoxonium intermediate then opens by C-C bond cleavage as outlined in **TS-6** to afford the 5-enal intermediate **13**.

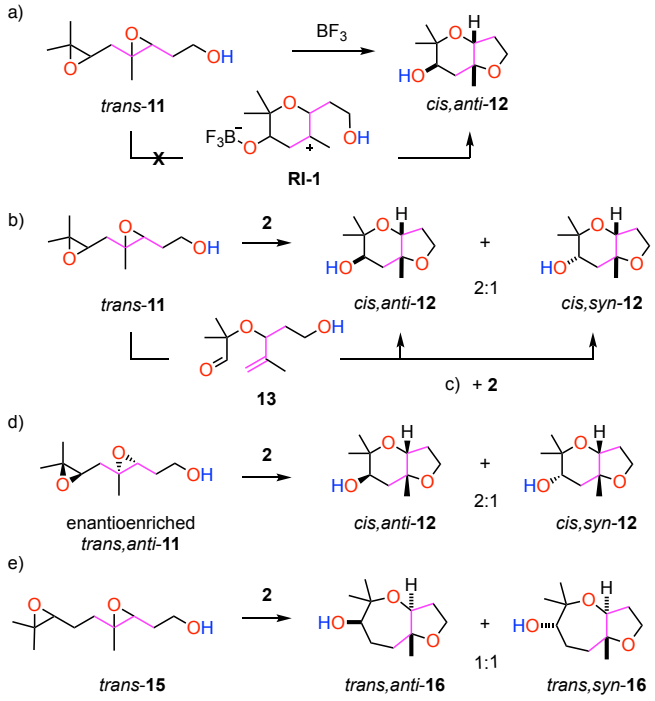

Figure 3. a) Lewis acid catalyzed, non-S_N1-like cyclization of 1,4 *trans*-diepoxide **11** into *cis,anti*-**12**. b) Unorthodox, pnictogen-bonding catalyzed cyclization of **11** into *cis,anti*- and *cis,syn*-**12** (2:1) via **13**, c) of **13** into *cis,anti*- and *cis,syn*-**12** (2:1), d) of enantioenriched *trans,anti*-**11** into *cis,anti*- and *cis,syn*-**12** (2:1), and of 1,5 *trans*-diepoxide **15** into *trans,anti*- and *trans,syn*-**16**.[12,13]

The detectability of the enal intermediate **13** in pnictogen-bonding catalysis but not in Lewis acid catalysis could be caused just by differences in velocity. However, the equally stunning different speed of formation and conversion of **13** with **2**, i.e., 5 minutes against 10 hours, and

a stereoselectivity different from BF_3 (see below) supported that also the equilibrium with the non-reactive cyclic hemiacetal **14** could be involved. In CD_2Cl_2, hydroxy-5-enal **13** and hemiacetal **14** equilibrated at a 3:2 ratio (Figures S7-S12). Recognition of the oxepane hemiacetal **14** over the acyclic enal **13** by supramolecular pnictogen-bonding catalysts was conceivable considering the additional interactions available in their binding pocket, including CH/π…O, CH/π…π or even pnictogen double or triple bonds to bind to both oxygens.[1] Such recognition of the non-reactive form **14** of the key intermediate could either inhibit the catalyst **2**, inactivate the reactive form **13**, or both. General inorganic Lewis acids such as BF_3 do not offer such secondary interactions and might thus fail to recognize **14** for the same reason they fail to catalyze the cyclization of **13** into *cis,syn*-**12** (*vide infra*).

This identification of intermediate **13** implied that its cascade cyclization into product **12** has to account for the stereospecific *cis* fusion with variable *syn*/*anti* selectivity. Considering an *anti* addition of the electrophile to the alkene, two conformations are possible, i.e., an *O-eclipsed* conformer **TS-7** leading to *cis-fused* and an *H-eclipsed* conformer **TS-7** leading to *trans-fused* products. According to the Chamberlin-Hehre model, *O-eclipsed* conformers like **TS-7** are preferred,[19,20] thus explaining the specificity for *cis* fusion.

A concerted addition to the olefin would also impose boat-like transition states **TS-9** and **TS-10**.[21] **TS-9** could be preferred simply because the resulting alcohol in *cis,anti*-**12** ends up in equatorial position.[13] Stabilization of **TS-9** leading to *cis,anti*-**12** would also be conceivable by intramolecular ion pairing of the covalent anionic OBF_3^- intermediate resulting from the aldehyde reacting with BF_3 with the positive charge accumulating on the disubstituted olefin carbon upon addition to the aldehyde. Supramolecular pnictogen-bonding catalysts do not produce similarly localized negative charge (Figure 1). The complementary **TS-10** leading to the intrinsically disfavored *cis,syn*-**12** exposes all functional groups to one side, thus allowing for the secondary

interactions with the supramolecular catalyst **2** already alluded to above for hemiacetal recognition. Similar contacts with the nearby environment have already been shown to account for anti-Baldwin polyether cascade cyclizations including **3** (Figure 2b)[1] and, absent in general Lewis acid catalysis, are commonly appreciated as advantage of supramolecular catalysis.

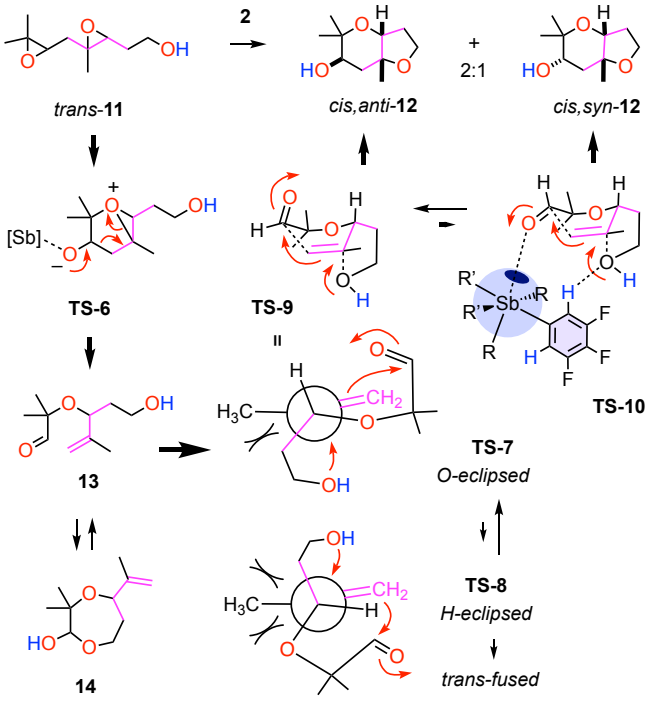

Figure 4. An unorthodox mechanism for brevetoxin-type polyether cyclizations revealed by pnictogen-bonding catalysis, characterized by transcription of *trans* epoxides into *cis* fusion and variable stereochemistry of the alcohol terminus.[12,13]

To validate this unorthodox mechanism, diastereomerically pure 1,4 *trans,anti*-**11** was prepared.[12] The stereoselective Shi epoxidation used for this purpose naturally produced the substrate also in enantioenriched form.[9] Enantioselectivity was, however, irrelevant for the

question asked and thus not further investigated. Cyclization with the supramolecular Sb(V) catalyst **2** afforded an unchanged 2:1 ratio of *cis,anti*- and *cis,syn*-**12** (Figure 3d). This result confirmed that an S_N1-type mechanism does not occur with pnictogen-bonding catalysis. The same reason, i.e., a change of stereochemistry from the epoxide terminus in the substrate to the secondary alcohol terminus in the product, already evinced that reverse transcription of *trans*-epoxide **11** into *cis*-fused **12** with covalent Lewis acid catalysis occurs also through acyclic intermediate **13** and not through an S_N1-type mechanism with intermediate **RI-1** (Figure 3a).

To confirm that the new mechanism of polyether cyclization is limited to 1,4 *trans*-diepoxides, the homologous 1,5 *trans*-diepoxide **15** was synthesized and studied as a mixture of *syn* and *anti* diastereomers.[12] Cyclization into the *trans*-fused bicycles **16** in 80% yield and a 1:1 *syn*/*anti* ratio was found for pnictogen-bonding catalysis (Figure 3e; same for BF_3, Figure S41). This conventional S_N2-behavior was consistent with the proposed mechanism, which excludes reverse transcription 1,5 *trans*-diepoxide **15** into *cis*-fused bicycles because ring opening of a homologous **TS-6** with an extra carbon between alcoholate and epoxonium is inconceivable (Figure 4).

These results add up to a new, unorthodox mechanism of epoxide-opening polyether cascade cyclization. They are compatible neither with head-to-tail cyclization by Baldwin/anti-Baldwin nucleophilic attack of the epoxides (Figure 2a, b) nor with tail-to-head cyclization by S_N2/S_N1-type opening of epoxonium intermediates (Figures 2c, d, 3a). They are compatible only with more complex C-C bond cleaving ring opening into acyclic hydroxy-5-enal followed by a C-C bond forming ring closing cascade reactions (Figures 3b-d, 4). This unorthodox epoxide-opening polyether cyclization mechanism explains the hidden enigma of brevetoxin-like polyether cyclizations, that is the reverse transcription of *trans* epoxides into *cis* fusions, with

Chamberlin-Hehre conformational control. It is limited to 1,4 *trans*-diepoxides, and general applicability remains to be demonstrated.

With these results, supramolecular pnictogen-bonding catalysis is not only confirmed to provide access to unique reactivity, here access to *cis*,*syn*-**12**, but emerges also as a practically useful tool to unravel unorthodox reaction mechanisms. These characteristics are thought to originate at least in part from pnictogen-bonding catalysts being less reactive but more interactive than their covalent Lewis acid counterparts. This is reminiscent of non-covalent hydrogen-bonding catalysis differing from covalent Brønsted acid catalysis, implying that the emergence of pnictogen-bonding catalysis and σ-hole catalysis in general could, at best, have a similar impact.

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Keywords: Pnictogen-bonding catalysis • σ-hole catalysis • epoxide-opening polyether cyclizations • cascade reactions • polyether natural products

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[12] For diepoxide substrates, the terms *cis* and *trans* are used here to designate, if applicable, the relative position of the atoms or groups attached to the two carbons of an epoxide (mostly highlighted in pink), and the terms *syn* and *anti* to designate the relation between the two epoxides (with the connecting linear alkyl chain in an extended all-*anti* conformation).

[13] For fused ring products, the terms *cis* and *trans* are used here to designate the relative position of the exocyclic atoms or groups attached to the ring junctions, and the terms *syn* and *anti* to designate the relation between the OH in the ring of interest and the O in the following ring.

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