

Bidentate Lewis Acid Catalyzed Domino Diels–Alder Reaction of Phthalazine for the Synthesis of Bridged Oligocyclic Tetrahydronaphthalenes

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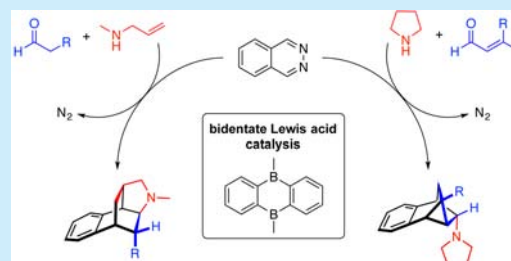
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S Supporting Information

ABSTRACT: A domino process consisting of an inverse and a normal electron-demand Diels–Alder reaction is presented for the formation of bridged tri- and tetracyclic 1,2,3,4-tetrahydronaphthalenes catalyzed by a bidentate Lewis acid. The products were synthesized in a one-pot reaction from commercially available starting materials and contain up to six stereogenic centers. The tetrahydronaphthalenes were isolated as single diastereomers and are derivatives of phenylethylamine, which is well-known as a scaffold of amphetamine or dopamine.



The ability to construct complex molecules in an economically and environmentally friendly way is highly attractive, especially in view of a shortage in energy and resources.^{1–3} Domino reactions allow streamlining the overall process by combining multiple transformations in one operation. Based on the domino methodology, large libraries can be prepared in a fast and concise manner containing, for instance, small bioactive molecules.⁴ Such low-cost libraries allow a systematic investigation of the chemical space.^{5–9} Diels–Alder reactions represent a highly potent component in this context because they enable the creation of two bonds and up to four stereogenic centers in a single diastereoselective step. It was shown that merging multiple Diels–Alder reactions increases the potential even further.¹⁰ Diels–Alder reactions can also be combined with Knoevenagel condensations¹¹ or other cycloadditions.¹² Hence, the versatility of the domino concept bears high prospects for medicinal^{13,14} as well as material sciences.¹⁵ One variant, the inverse electron-demand Diels–Alder reaction (IEDDA), has been established as a very convenient reaction for the synthesis of aromatic compounds.^{16,17} It was also introduced into domino processes with great success, as independently reported by Boger^{18,19} and Kobayashi.²⁰

During the past several years, we developed bidentate Lewis acids as effective catalysts for the IEDDA reaction of phthalazines to form substituted naphthalenes.^{21,22} We used the easily accessible 9,10-dimethyl-9,10-dihydroboranthracene (**1**) as a catalyst for these transformations. The idea was later expanded to the preparation of cyclopropane substituted

dihydronaphthalenes via a subsequent [3,9]-sigmatropic rearrangement.²³

The high capability of the method was demonstrated by the direct application of in situ generated enamines as dienophiles,²⁴ which is a powerful approach in such IEDDA reaction schemes.^{25–28} In this way, dienophiles can be produced directly from aldehydes and amines, widely broadening the scope of the reaction. Recently, the concept of bifunctional bis-boron catalysts was extended to other processes such as the reduction of carbon dioxide²⁹ or the dehydrogenation of ammonia borane.³⁰

When investigating the scope of the bidentate Lewis acid catalyzed IEDDA of phthalazine (**2**) with in situ generated enamines to form substituted naphthalenes, the α,β -unsaturated aldehyde **3** was applied as starting material. Surprisingly, the reaction did not lead to the expected vinyl naphthalene **6**.²⁴ Instead, the tricyclic 1,2,3,4-tetrahydronaphthalene **7** was formed in 77% yield (Scheme 1). The product contained five stereogenic centers and a cyclopropane as key structural elements. It was isolated as a single diastereomer.³¹ Tetrahydronaphthalene **7** is a conformationally restricted derivative of phenylethylamine. Various biologically active compounds, e.g. amphetamine, in which conformation plays an important role for activity, are based on this scaffold.^{32,33}

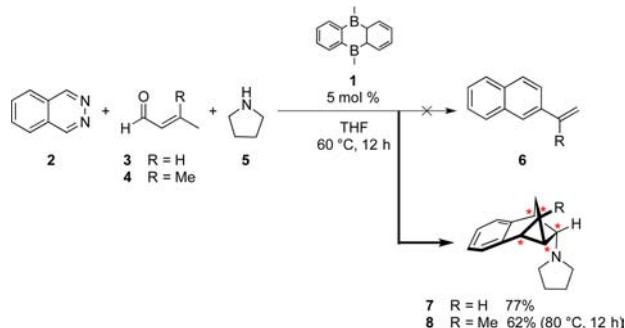
Besides crotonaldehyde (**3**) the methyl-substituted aldehyde **4** led to the corresponding methyl substituted product **8** in 62% yield. The reaction temperature had to be increased to 80 °C

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Scheme 1. Bidentate Lewis Acid Catalyzed IEDDA Reaction with in Situ Generated Enamines



due to the higher steric hindrance. No major side product was identified. In both experiments the *exo* isomer was favored and the only isolated product (determined by 2D-NMR spectroscopy). N_2 -formation was already observed at rt immediately after combining the starting materials with catalyst **1**. However, the reactions were heated overnight to achieve full conversion.

The dienophile necessary for the second Diels–Alder reaction with normal electron demand could also be introduced within the amine component (Table 1). With allyl amine **9** tricyclic products built on five- and six-membered rings were obtained in a highly selective manner. The reaction could be conducted successfully with a variety of differently substituted aldehydes and led, again, exclusively to the *exo* products. When using valeraldehyde (**10a**), full conversion and an isolated yield of 93% were achieved (Table 1, entry 1). It was also possible to apply the branched isovaleraldehyde (**10b**), which gave the target compound in 71% yield (Table 1, entry 2). The reason for the drop in yield can be found in the higher steric demand of the aldehyde component. In experiments with smaller aliphatic aldehydes, e.g. propionaldehyde, the desired product was also formed. However, yields were lower and the reaction did not proceed as cleanly. In this case, competing aldol reactions might be the cause. Aromatic residues were successfully used, such as the phenyl substituted aldehyde **10c**. With this aldehyde component, again, a very high isolated yield of 93% could be reached (Table 1, entry 3). To further increase the complexity of the tricyclic products we selected aldehydes containing a stereogenic center in the β -position (Table 1, entries 4–6). In this manner we were able to form tricyclic tetrahydronaphthalenes with six stereogenic centers. The products of these experiments were isolated as a mixture of two diastereomers, as the aldehydes were applied as racemic mixtures. The ratio of the two-formed stereoisomers varied between 1.2:1 and 1.7:1 illustrating a small excess of one isomer. As mentioned above, we observed that the yields slightly decreased upon substitution in the β -position (Table 1, entries 2, 4, and 5). Gratifyingly, the method also allowed introduction of functional groups such as esters (Table 1, entry 5). Although these groups bear the potential to coordinate to the bidentate Lewis acid, the reaction cleanly provided the desired product in 70% yield. Additionally, furan aldehyde **10f** (Table 1, entry 6) was tested. The high yield of 87% illustrates the high selectivity of the reaction, as the furan could also act as a diene in Diels–Alder reactions.

X-ray analysis of products **8** and **11e** was achieved from crystals formed by slow evaporation of *n*-pentane at -20 °C. The data illustrate the ring strain generated in the domino process (Figure 1). The tricyclic structure of product **8**

Table 1. Scope of the Bidentate Lewis Acid Catalyzed Domino IEDDA–DA Reaction

entry	aldehyde	product ^a	yield (%)
1			93
2			71
3			93
4			71 1.2:1 ^b
5			70 1.6:1 ^b
6			87 1.7:1 ^b

^aIsolated as single diastereomers. Only one enantiomer of every product is represented for clarity. ^bIsolated as a mixture of two diastereomers. The ratio was determined by NMR spectroscopy.

dominated by the cyclopropane motif contains a cyclohexane pattern with a twisted conformation and bond angles up to 119° .

A mechanism for the domino reaction is proposed in Scheme 2. In a first step the bidentate Lewis acid **1** coordinates to the phthalazine (**2**). The complexation reduces the electron density of the phthalazine facilitating the IEDDA reaction step with the in situ generated enamines **13**. It is proposed that the more electron-rich enamine acts as a dienophile in the first Diels–Alder reaction. This transformation is suggested to proceed with the more stable *E*-isomers of the enamines, which is in agreement with the *exo* conformation of the isolated products.

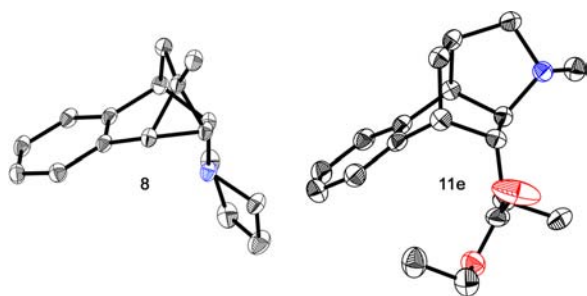
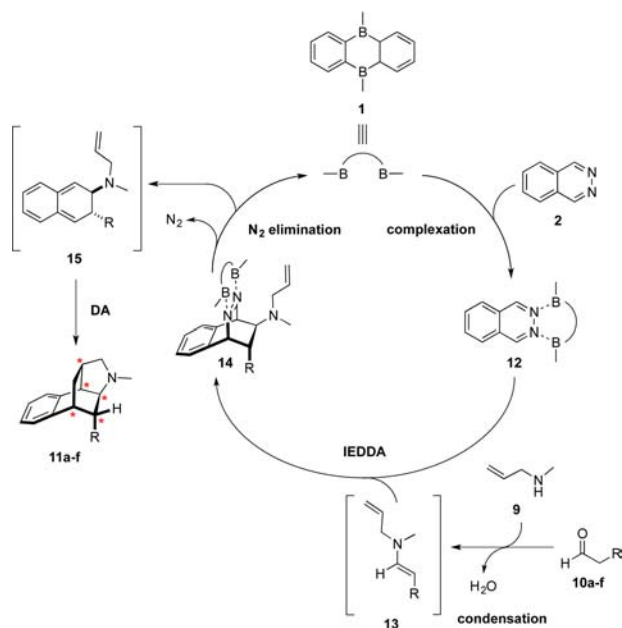


Figure 1. X-ray structures of products **8** and **11e** (thermal ellipsoids drawn at 50% probability; hydrogen atoms and water molecules omitted for clarity).

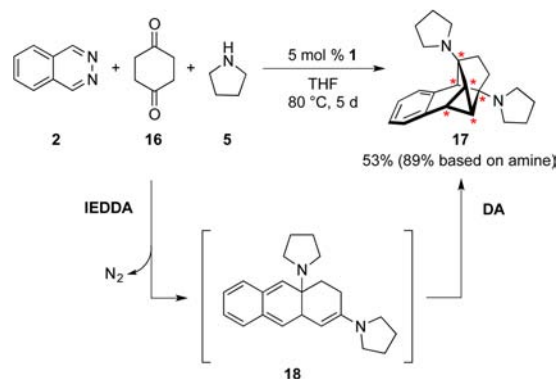
Scheme 2. Catalytic Cycle of the Domino Reaction Leading to Products **11a–f**



Interestingly, neither the amine nor the water produced in the enamine formation influenced the activity of the catalyst. Elimination of N_2 forms the highly reactive *o*-quinodimethane intermediate **15** and releases the catalyst. Such *o*-quinodimethane intermediates have biradical character^{34,35} and are described as very powerful dienes for Diels–Alder reactions.^{36,37} Consequently, an intramolecular Diels–Alder reaction terminates the sequence as the last step. Noteworthy, both bond forming events, in the inverse as well as in the normal electron-demand Diels–Alder reaction, occur at the same two carbon atoms.

The concept was further expanded by choosing 1,4-cyclohexanedione (**16**) as a bifunctional carbonyl component (Scheme 3). The reaction mixture was stirred at 80 °C for 5 days to isolate the complex tetracyclic diamine **17** in 53% yield (89% based on amine). The longer reaction time was required due to the smaller amount of enamine in the reaction mixture and the higher steric demand (ketone vs aldehyde). Dione **16** can form two enamine functionalities, with both able to act as an electron-rich dienophile. Consequently, the bis-enamine of **16** undergoes a bidentate Lewis acid catalyzed IEDDA reaction with the first enamine, which is then followed by N_2 extrusion leading to the *o*-quinodimethane intermediate **18**. Intermediate **18** undergoes the domino DA step with the second enamine

Scheme 3. Formation of Tetracyclic Product **17** in the Diastereoselective Bidentate Lewis Acid Catalyzed Domino Reaction



leading to product **17**, which contains six stereogenic centers and was formed again as a single diastereomer.

In conclusion, we developed a bidentate Lewis acid catalyzed domino IEDDA–DA process that allows the synthesis of bridged tri- and tetracyclic tetrahydronaphthalenes with up to six stereogenic centers in a single step. Commercially available amines, aldehydes/ketones, and phthalazine were used as starting materials. The initial catalyzed IEDDA reaction leads to a highly reactive *o*-quinodimethane intermediate, which enables the second intramolecular cycloaddition. The formed tetrahydronaphthalenes were isolated as single diastereomers. Only in the presence of racemic starting material with an additional stereogenic center two diastereomers were obtained, as expected. The products are complex derivatives of phenylethylamine and demonstrate that this new domino process is a suitable method to quickly build up chemical libraries containing molecules with high structural diversity. Future work will address expanding the scope of the reaction and investigating the biological activity of the products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00276.

Experimental details, analytical data and NMR spectra are provided (PDF)

X-ray crystal structure data for **8** and **11e**; the X-ray structures were deposited on the Cambridge Structural Database (CCDC 1449732 and 1449733) (CIF)

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The authors declare no competing financial interest.

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