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Domino Inverse Electron-Demand Diels–Alder/Cyclopropanation Reaction of Diazines Catalyzed by a Bidentate Lewis Acid

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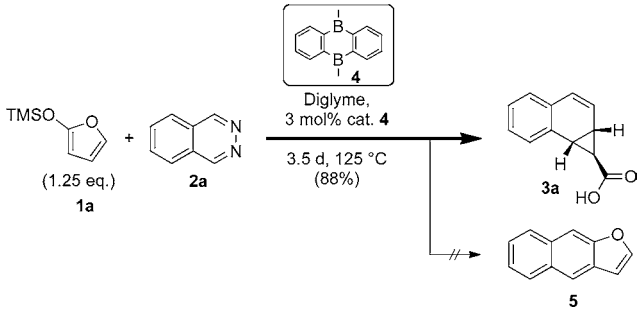
Supporting Information

ABSTRACT: A domino inverse electron-demand Diels–Alder (IEDDA)/cyclopropanation reaction of diazines was discovered by applying electron-rich furans in the bidentate Lewis acid catalyzed IEDDA reaction. This process produces benzonorcaradienes in excellent yields with a low loading of a bidentate Lewis acid catalyst of 2 to 5 mol %. We demonstrate the broad applicability by 20 examples with different dienophiles and a variety of dienes. A detailed mechanism is proposed supported by DFT calculations.

Currently, the efficient use of resources, as well as the minimization of waste and production costs, is more important than ever. Therefore, an organic synthesis procedure where one could form several bonds in one sequence would lead to a tremendous benefit over usual stepwise procedures. Domino reactions represent a highly potential approach to address the above-mentioned criteria.[1,2] Especially the incorporation of Diels–Alder reactions into Domino sequencies allows quick access to molecular complexity.[3] The inverse electron-demand Diels–Alder (IEDDA) reaction emerged in recent decades[4,5] as a powerful synthetic tool featured in the preparation of complex molecules.[6−12] In 2010 we reported the first catalytic activation of diazines by a bidentate Lewis acid for an IEDDA reaction.[13] More recently also a silver catalyzed formal IEDDA reaction of phthalazine and siloxy alkynes was published by Rawal and co-workers.[14] Furthermore, we showed the broad application spectrum of the IEDDA reaction of phthalazines with a variety of dienophiles, such as enamines and dihydrofurans.[15,16]

During the investigations of electron-rich furans **1a** in the catalytic IEDDA reaction, we discovered a novel bidentate Lewis acid catalyzed domino IEDDA/cyclopropanation reaction (Scheme 1). The application of these dienophiles did not yield the anticipated annellated ring system. Instead the cycloaddition intermediate was further transformed to the cyclopropane annellated benzonorcaradiene. In Nature the benzonorcaradiene framework is for instance found in salvipuberulin.[17,18] Additionally, such highly functionalized compounds containing small rings are useful building blocks for further transformations to quickly access complex target structures especially in the context of new drugs. Lately, two transition metal catalyzed reactions[19,20] and a Diels–Alder reaction[21,22] of a tungsten-tetra-ene complex have been published forming benzonorcaradiene with either no or a limited range of aromatic substituents.

Scheme 1. Reaction Path of the Catalyzed Domino IEDDA/Cyclopropanation Reaction of an Electron-Rich Furan and a Diazine



We started our investigation with the reaction of phthalazine and differently substituted oxyfurans **1a–e**, to display the scope of dienophiles in the Lewis acid catalyzed domino reaction (Table 1). Thereby, we found that all substrates did not show any reaction in the absence of catalyst even if heated to 160 °C for 1 day. Both steric and electronic factors play an important role in the reactivity of oxyfurans. The most reactive oxy-substituent is the trimethylsilyl (TMS) moiety due to polar effects followed by the methyl substituent, and the least reactive, the triisopropylsilyl (TIPS) group due to steric reasons (Table 1, entries 1–3). Oxyfuran **1a** directly yielded the free acid **3a** after purification on silica gel (SiO_2), while **1b** and **1c** gave access to stable esters **3b** and **3c**.

The methyl substituent on the furan core accounts for another positive inductive effect while also adding steric bulk, which counteract depending on the position of the Me group. A methyl-substituent in the 3-position as in **1d** is beneficial for the reaction allowing the reaction to proceed at lower temperature in a shorter time compared to the unsubstituted analog **1a** (Table 1, entry 4). If the methyl substituent is placed in position 5, it seems to sterically interfere with the reactive site resulting in permitting the reaction with only the more reactive dichlorophthalazine **2b** (Table 1, entry 5). No reaction was observed with less electron-deficient phthalazine **2a**. This reactivity can be explained by the steric interference of the methyl residue in furan **1e** with the Lewis acid **4** in complex **6**[15] during the IEDDA reaction (Figure 1).

To demonstrate the scope of dienes, a variety of differently substituted diazines and trimethylsilyloxyfuran **1a** have been employed in the Lewis acid catalyzed domino IEDDA/

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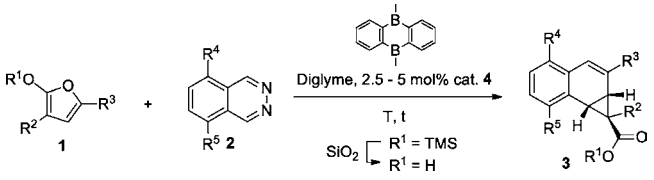
Table 1. Scope of Dienophiles in the Domino IEDDA/ Cyclopropanation Reaction



entry	1	2 R4	2 R5	product	t / d	T / °C	yield
1	1a	H	H	3a	3.5	125	88%
2	1b	H	H	3b	4	140	80%
3	1c	H	H	3c	2.5	155	99%
4	1d	H	H	3d	1.5	115	90%
5	1e	Cl	Cl	3e	1.5	115	90%

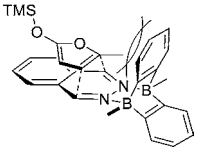
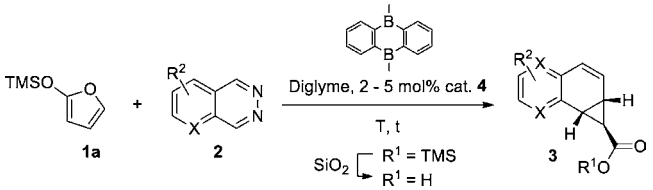


Figure 1. Steric interaction of methyl group in **1e** with Lewis acid moiety of complex **6**.

cyclopropanation reaction (Table 2). The substituted diazines can be accessed by a one-pot synthesis from aldehydes developed in our laboratory.[23] Moreover, we used alkyllithium chemistry to form dichloro- and difluorophthalazine **2b** and **2d**, also in one pot in good yields (see Supporting Information). Since in an IEDDA reaction an electron-deficient diene is preferred over an electron-rich one, the reactivity of substituted phthalazines decreases in the following order of substituents: F > Cl > MeS > Me > MeO (Table 2). Therefore, the reaction temperature can be lowered to 80 °C in the case of dichlorophthalazine **2b** and has to be increased to 160 °C with a prolonged duration in the case of dimethoxyphthalazine **2h**. Even pyridopyridazine **2k** and benzophthalazine **2l** were reactive in this transformation. The complete desilylation of the labile trimethylsilyl ester was accomplished by slightly acidic eluation on silica forming the carboxylic acid.

Furthermore, we were able to synthesize other TIPS-esters **3q**–**3s** showing good applicability of **1c** in the reaction of electron-poor phthalazine **2b**, **2c**, and **2e** (Table 3). The reaction of methoxyfuran **1b** with pyridopyridazine **2k** gave the methylester **3t** (Table 3, entry 4). These additional examples

Table 2. Scope of Dienes in the Domino IEDDA/ Cyclopropanation Reaction



entry	2	products	t / d	T / °C	yield (3xa:3xb)
1	2c	3fa 3fb	1	105	88% (1.1:1)
2	2d	3g	14	95	quant.
3	2e	3ha 3hb	1	130	quant. (1:1.1)
4	2f	3ia 3ib	4	120	quant. (1:1.3)
5	2b	3j	1.5	80	98%
6	2g	3ka 3kb	3	120	78% (1:1.5)
7	2h	3l	11	160	93%
8	2i	3ma 3mb	3.5	145	95% (1.2:1)
9	2j	3na 3nb	3.5	150	92% (1:1)
10	2k	3oa 3ob	1	105	92% (1:1.4)
11	2l	3pa 3pb	3	160	83% (2:1)

demonstrate not only the high atom economy merely producing N_2 as a side product but also the versatility of the procedure.

In cases of nonsymmetrical phthalazine substrates the IEDDA/cyclopropanation reaction produces mostly regioisomers of both Diels–Alder adducts in similar amounts

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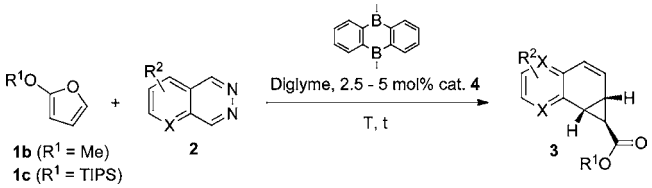
Table 3. Domino IEDDA/Cyclopropanation Reactions Forming Isolable Esters

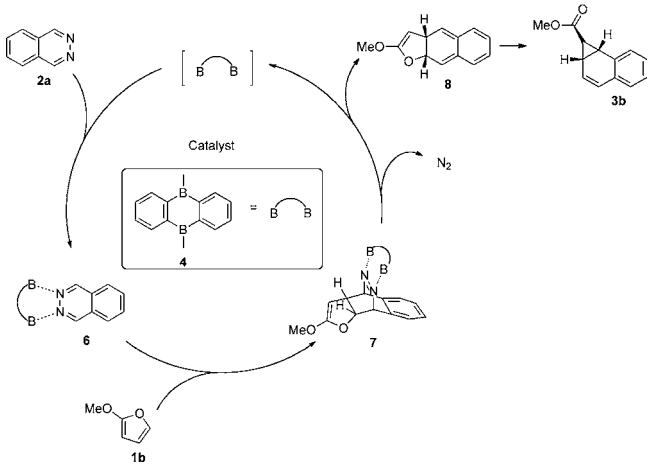


entry	2	product	t / d	T / °C	yield (3xa:3xb)
1	2c	3qa + 3qb	1	130	96% (1.3:1)
2	2e	3ra + 3rb	1	135	99% (1.1:1)
3	2b	3s	1	90	91%
4	2k	3ta + 3tb	0.5	120	91% (1:1.1)

(Tables 2 and 3). Substitution in the 5−8-position on the phthalazine hardly influences the ratio of the regioisomers.

Mechanistic Considerations. The proposed catalytic cycle[13,15] derived from Heuschmann and co-workers[24−27] starts with the complexation of phthalazine **2** by the bidentate Lewis acid **4** to activate the diazine for the following IEDDA reaction. The cycloaddition of complex **6** with methoxyfuran **1b** gives intermediary complex **7**. The elimination of molecular nitrogen regenerates the Lewis acid catalyst **4**, and the proposed dihydronaphthalene intermediate **8** is formed. Intermediate **8** rearranges to *endo*-cyclopropane **3′**, and *endo*-to-*exo* isomerization[28−30] leads to the final product **3b** (Scheme 2).[13,15] By the nature of the IEDDA cycloaddition, the domino reaction is diastereoselective resulting in only the *exo*-cyclopropane proven

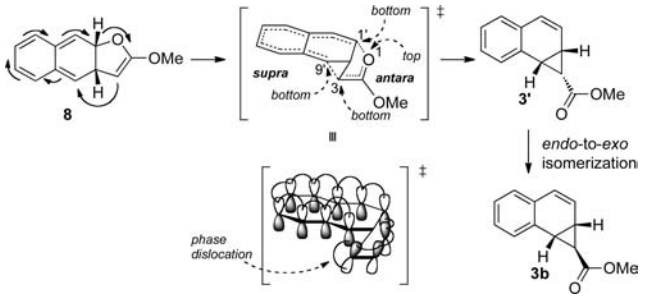
Scheme 2. Proposed Catalytic Cycle



by 2D-NMR as well as X-ray analysis (see Supporting Information).

The intermediary formed dihydronaphthalene **8** represents an *o*-quinodimethane type, which is a well-known highly reactive intermediate.[31−35] Recently, we were also able to trap such an *o*-quinodimethane intermediate by an intramolecular Diels−Alder reaction consecutive to the Lewis acid catalyzed IEDDA reaction.[16] Stable *o*-quinodimethanes have been unambiguously characterized and expose a substantial double bond with some biradical character indicated by calculations.[36,37] Dihydronaphthalene **8** reacting as tetraene species undergoes the final rearrangement to form the cyclopropanaphthalene **3**. The same observations were made starting from a tungsten−tetraene complex.[21,22] From dihydronaphthalene **8** we propose the occurrence of a sigmatropic rearrangement according to the Woodward−Hoffmann rules.[38,39] A σ-bond is moved from position 1 to 3 on one site and from 1′ to 9′ on the other side (Scheme 3). The

Scheme 3. Proposed [3,9] Sigmatropic Rearrangement



simplified 3-atom and 9-atom fragments can be divided into their topologies. On the 3-atom fragment the migration of the σ-bond occurs on the opposite face and on the nine-membered fragment on the same leading to an 'allowed' antara-suprafacial [3,9]-sigmatropic rearrangement involving $4n$ (n = 3) electrons. Alternatively, the transformation can be described by the model according to Dewar[40] and Zimmerman.[41] This way one phase dislocation occurs, representing a Möbius topology which in the case of $4n$ electrons describes an 'allowed' transition state.

The antarafacial [3,9]-sigmatropic rearrangement of furan **8** to cyclopropane **3′** is supported via DFT calculations on the B3LYP level with a basis set of 6-31g(d,p) (Figure 2). The transition state was located in the gas phase resulting in a free energy of activation as low as $\Delta^{\ddagger}G^{\circ}_{(T=298)}$ = 11.9 kcal/mol and a

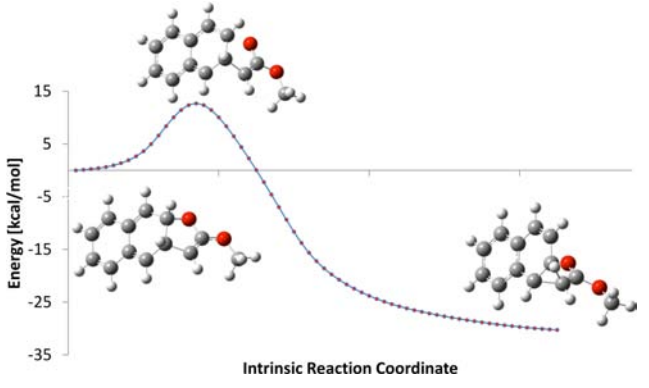


Figure 2. Intrinsic reaction coordinates of the sigmatropic rearrangement.

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high Gibbs free energy of reaction $\Delta_r G^\circ_{(T=298)}$ = −30.3 kcal/mol (Figure 2; −39.1 kcal/mol for the ester in *trans*-conformation). The high thermodynamic driving force of the rearrangement results from the formation of the ester resonance and the aromatic stabilization which has been lost in the dihydronaphthalene intermediate **8** by the elimination of molecular nitrogen springloading the molecule and easily accounting for the strain energy of the cyclopropane formation. Despite the evidence for a rearrangement, an ionic mechanism cannot be ruled out.

In conclusion, we discovered a new method to produce cyclopropanated naphthalenes in a diastereoselective fashion by a bidentate Lewis catalyzed domino process starting with an IEDDA reaction proceeding with elimination of nitrogen and concluding with an antarafacial [3,9]-sigmatropic rearrangement. A wide variety of substituents are allowed on the diazine as well as on the oxyfuran providing a very versatile entry to substituted aromatonorcaradiene in excellent yields with a low catalyst loading of 2−5 mol %. Further studies will address the selectivity issue in the reaction with unsymmetrical phthalazines, e.g. by using diboron species with different substituents as catalysts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data for **2b**, **2d**, and all products **3**, as well as X-ray data for **3g**, **3l** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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