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Lewis Acid Catalyzed Inverse Electron-Demand Diels−Alder Reaction of 1,2-Diazines

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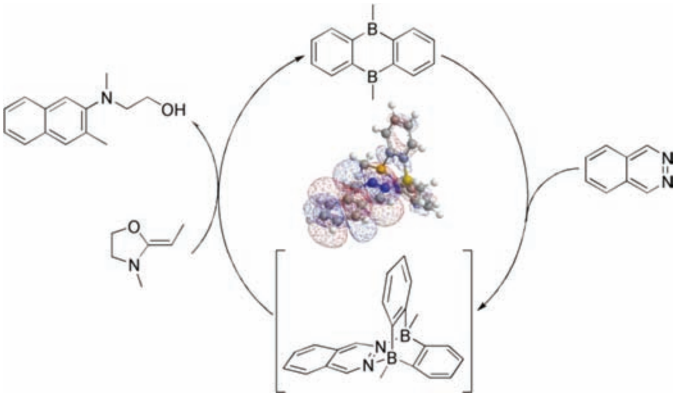
ABSTRACT



A systematic approach toward Lewis acid catalyzed inverse electron-demand Diels−Alder (IEDDA) reactions of 1,2-diazines is described. The general concept is first investigated by DFT calculations, supported by spectroscopic data, and finally proven in the experiment.

The Diels−Alder reaction with normal electron-demand has been established as one of the most utilized reaction types and offers the great advantage of installing four stereocenters at once.[1] In the shadow of this versatile reaction, the inverse electron-demand Diels−Alder (IEDDA) reaction has gradually gained in interest over the past 50 years. Nowadays it offers a broad application spectrum.[2] Following the first studies of the IEDDA reaction of 3,6-disubstituted 1,2,4,5-tetrazines,[3] a variety of substituted tetrazines and triazines have been investigated.[4] Despite this work, the reaction of 1,2-diazines with electron-rich dienophiles has received less attention. Reports in the literature are mainly on 1,2-diazines substituted by electron-withdrawing groups due to the energetically high lying LUMO of unsubstituted diazines.[4] This renders them hardly reactive even toward electron-rich dienophiles. Therefore, only one dienophile is known to react with unsubstituted pyridazine,[5] a few more to react with phthalazine **1**.[6]

Herein we describe for the first time an IEDDA reaction of an unsubstituted phthalazine catalyzed by a bidentate Lewis acid, 5,10-dimethyl-5,10-dihydroboranthrene (**7**).[7] The

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(1) (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (b) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779.

(2) For an example for an IEDDA in a total synthesis, see: Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261.

(3) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342.

(4) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. For recent examples of IEDDA reactions with triazines, see: (c) Xu, G.; Zheng, L.; Wang, S.; Dang, Q.; Bai, X. *Synlett* **2009**, 3206. (d) Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. *J. Org. Chem.* **2009**, *74*, 8343. For recent examples of IEDDA reactions with tetrazines, see: (e) Rahanyan, N.; Linden, A.; Baldridge, K. K.; Siegel, J. S. *Org. Biomol. Chem.* **2009**, *7*, 2082.

10.1021/ol101701z

idea of the catalysis of the IEDDA reaction of 1,2-diazines is based on the following rationale: a bidentate Lewis acid may complex the vicinal nitrogen atoms and thus withdraw electron density from the diazine. The simultaneous coordination should lower the LUMO of the diene and facilitate the cycloaddition step according to the FMO theory.[8]

A variety of bidentate boron-based Lewis acids have been reported in the literature.[9] Although complexation of boron-based[9b−d] and indium-based[10] bidentate Lewis acid with 1,2-diazines has been described, to the best of our knowledge, no example has been reported to exploit this phenomenon for catalysis in organic synthesis.

The complexes of 1,2-diazines with different bidentate boron Lewis acids have been geometrically optimized with DFT at the B3LYP[11] level, and the orbital energies have been calculated with HF theory, both with the 6-31G* split-valence set,[12] using Gaussian 03.[13,14]

The dihydroboranthrene system **7** was predicted to display the above desired properties combined with relatively easy synthetic accessibility. The calculations of the adduct **2** of phthalazine **1** with dimethyl dihydroboranthrene **7** predict a significant shift of the LUMO to lower energies (Figure 1). This result fully supports the initial idea for catalysis of the IEDDA reaction of diazines.

The dihydroborantherene **7** was prepared in four steps by known literature procedures (Scheme 1). The synthesis commences with a Li/Br exchange and consecutive silylation to result in 1,2-bis(trimethylsilyl)benzene (**4**).[15] One of the TMS groups was selectively substituted with BCl_3 to give the monoborinated product **5** according to a procedure published by Kaufmann.[16] The product was dimerized[17] at 135 °C, followed by methylation[7] with methyl lithium.

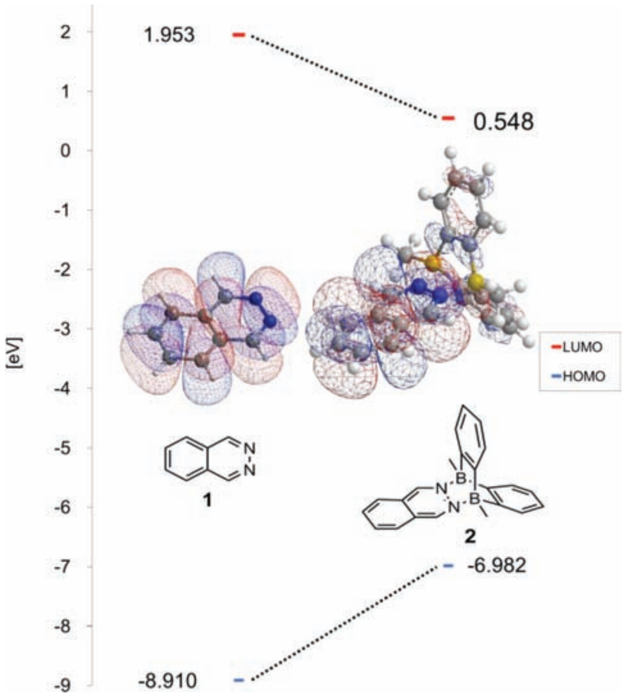
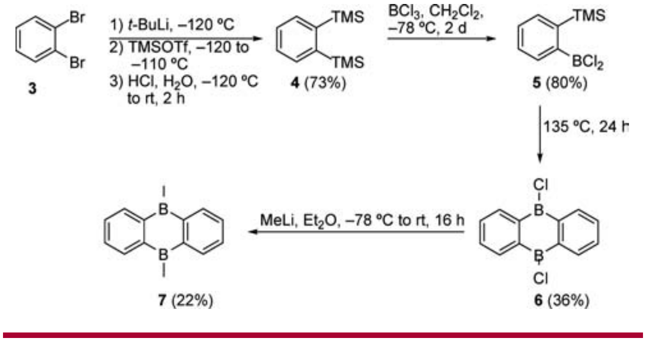


Figure 1. Relative energies of the FMOs of the uncomplexed phthalazine **1** in comparison with the 5,10-dimethyl-5,10-dihydroboranthrene phthalazine complex **2**. The graphics represent the LUMOs.

With the desired Lewis acid in hand, complexation studies with 1,2-diazines were conducted to validate the electron-withdrawing effect predicted by the calculations. Titration of phthalazine to a solution of **7** resulted in the formation of a 1:1 complex of the 1,2-diazine with the Lewis acid, as revealed by ^1H NMR spectroscopy: the electron withdrawal from the 1,2-diazine is reflected by a low field shift of the diazine protons and, accordingly, a high field shift of the protons of the Lewis acid (Figure 2). If an electron-rich dienophile such as the oxazolidine **8** is treated with the Lewis acid **7**, complexation on the N atom is observed. However, upon addition of phthalazine, the complexation of **7** is completely shifted to the 1,2-diazene.

Scheme 1. Preparation of the Bidentate Lewis Acid **7**



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(5) (a) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 6027. For intramolecular examples, see: (b) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240. (c) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415. In total syntheses: (d) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. (e) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230.

(6) Oishi, E.; Taido, N.; Iwamoto, K.; Miyashita, A.; Higashino, T. *Chem. Pharm. Bull.* **1990**, *38*, 3268.

(7) Schulz, H.; Pritzkow, H.; Siebert, W. *Chem. Ber.* **1991**, *124*, 2203.

(8) (a) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*; Wiley: Chichester, UK, 2010. (b) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(9) (a) Schulz, H.; Seyffer, H.; Deobald, B.; Pritzkow, H.; Siebert, W. *Z. Naturforsch., B: Chem. Sci.* **1994**, *49*, 465. (b) Piers, W. E.; Irvine, G. J.; Williams, W. C. *Eur. J. Inorg. Chem.* **2000**, 2131. (c) Ashe, A. J.; Kampf, J. W.; Schiesher, M. W. *Organometallics* **2003**, *22*, 203. (d) Jaska, C. A.; Emslie, D. J. H.; Bosdet, M. J. D.; Piers, W. E.; Sorensen, T. S.; Parvez, M. *J. Am. Chem. Soc.* **2006**, *128*, 10885.

(10) Gabbai, F. P.; Schier, A.; Riede, J.; Hynes, M. J. *Chem. Commun.* **1998**, 897.

(11) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(12) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650. (b) McLean, A. D.; Chandler, J. S. *J. Chem. Phys.* **1980**, *72*, 5639. (c) Curtiss, L. A.; McGrath, M. P.; Blaudeau, J.-P.; Davis, N. E.; Binning, R. C., Jr.; Radom, L. *J. Chem. Phys.* **1995**, *103*, 6104. (d) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.

(13) Frisch, M. J.; *Gaussian 03*, revision D.02; see Supporting Information.

(14) Bachrach, S. M. *Computational Organic Chemistry*; Wiley-Interscience: Hoboken, NJ, 2007.

(15) Bettinger, H. F.; Filthaus, M. *J. Org. Chem.* **2007**, *72*, 9750. Alternatively, we developed in our laboratory a new Fe-catalyzed method to access 1,2-bis(trimethylsilyl)benzenes: Bader, S.; Kessler, S. N.; Wegner, H. A. *Synthesis* **2010**, 2759.

The electron shift in the phthalazine complex **2** in comparison to their free counterparts was highlighted by means of DFT and by NMR spectroscopy. All observations support a decrease of the LUMO energy of the complexed 1,2-diazine. Hence, the cycloaddition step should be facilitated.

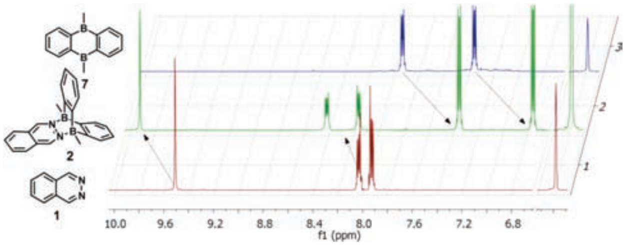

Figure 2. Stacking of the low field region of the ^{1}H NMR spectrum of the complex **2** in green (Nr. 2), the free phthalazine **1** in red (Nr. 1), and the free Lewis acid **7** in blue (Nr. 3). The singlet THF-d_8 (δ = 3.58 ppm) is used as the reference peak.

The bidentate Lewis acid **7** was tested as a catalyst in a model reaction of phthalazine **1** with oxazolidine **8**.[18] Hünig's base was added to capture any protons which might catalyze the acid promoted polymerization of the oxazolidine **8**.[18b,c] The reaction was first tested with 10 mol % of the Lewis acid complex **2**. In parallel, the same reaction mixture was carried out with 5 and 2.5 mol % of the catalyst **2** using 1.5 equiv of the oxazolidine **8** (Figure 3).

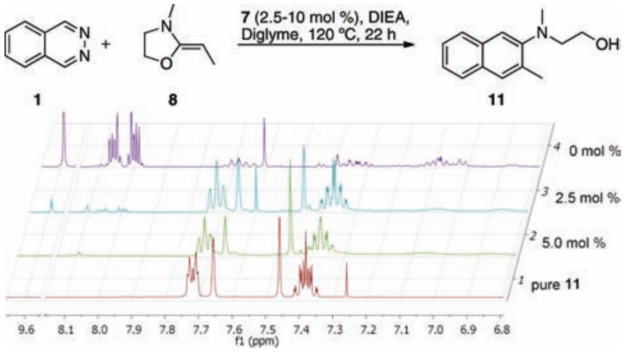

Figure 3. Stacked aromatic region of ^{1}H NMR (in $CDCl_3$) of the pure product **11** in red (Nr. 1), the catalyzed reaction with 5.0 and 2.5 mol % of catalyst **7** in green (Nr. 2) and in cyan (Nr. 3), and the uncatalyzed reaction in purple (Nr. 4).

Comparison of the catalyzed reaction and the noncatalyzed reaction clearly demonstrates the ability of the bidentate Lewis acid to promote the IEDDA of phthalazine. After the same reaction time, when nearly no conversion is observed without the catalyst, the addition of only 5 mol % of complex **2** results in full conversion according to ^{1}H NMR (isolated yield 42%). This proves an acceleration of the intended IEDDA reaction in the presence of the catalyst **7**.

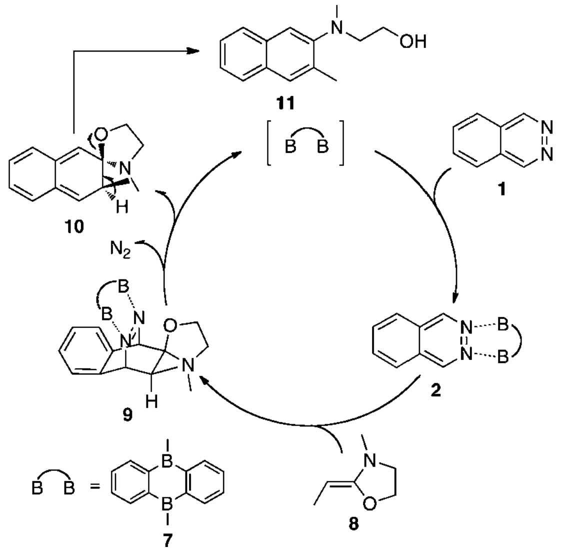

Figure 4. Proposed catalytic cycle of the IEDDA reaction of oxazolidine **8** with phthalazine **1** catalyzed by the bidentate Lewis acid **7**.

The proposed catalytic cycle is displayed in Figure 4.[19] The bidentate Lewis acid **7** forms a 1:1 complex **2** with the phthalazine **1**. This complex **2** undergoes the cycloaddition step with the dienophile resulting in the cycloadduct **9** which releases dinitrogen to the intermediate **10**. In this process also, the Lewis acid is liberated which now can re-enter the catalytic cycle by complexing the next 1,2-diazine molecule. Rearomatization of **10** yields the final product, the substituted naphthalene **11**.

The reaction of phthalazine **1** with oxazolidine **8** in the presence of a monodentate Lewis acid such as BF_3•Et_2O followed a totally different reaction path. None of the IEDDA product **11** was detected in ^{1}H NMR nor GC-MS analysis. All results suggest products resulting from a nucleophilic addition of the oxazolidine. This is similar to a nucleophilic addition of alkyl lithium reagents mediated by BF_3•Et_2O.[20]

Besides the oxazolidine **8**, a number of other electron-rich reaction partners can be used to access 2,3-substituted naphthalenes which are difficult to obtain by other means (Table. 1).[21] Enamines give in good to very good yield the desired products (Table 1, entries 2−4).[22] It is noteworthy that the enamines can be prepared in situ without disturbing the activity of the catalyst with the free amine or the water

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(16) Kaufmann, D. *Chem. Ber. Rec.* **1987**, *120*, 901.

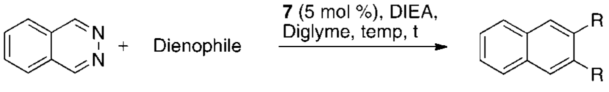
(17) Schacht, W.; Kaufmann, D. *J. Organomet. Chem.* **1987**, *331*, 139.

(18) (a) Schulze, T.; Letsch, J.; Klemm, E. *J. Polym. Sci., Part A: Polym Chem.* **1996**, *34*, 81. (b) Zhou, A.; Pittman, C. U., Jr. *Synthesis* **2006**, 37. (c) Zhou, A.; Pittman, C. U. *J. Comb. Chem.* **2006**, *8*, 262.

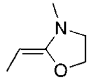
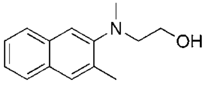
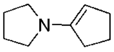
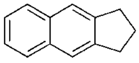
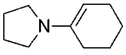
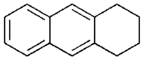
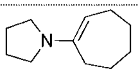
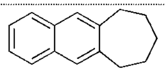
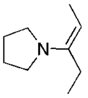
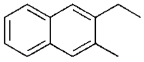
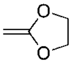
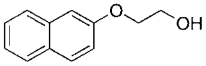
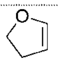
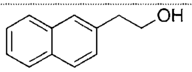
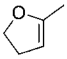
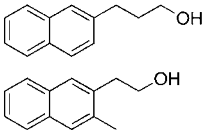
(19) (a) Hartmann, K.-P.; Heuschmann, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1267. (b) Hartmann, K.-P.; Heuschmann, M. *Tetrahedron* **2000**, *56*, 4213. (c) Ernd, M.; Heuschmann, M.; Zipse, H. *Helv. Chim. Acta* **2005**, *88*, 1491.

(20) Uno, H.; Okada, S.; Suzuki, H. *Tetrahedron* **1991**, *47*, 6231.

Table 1. IEDDA-Reaction of phthalazine catalyzed by the bidentate Lewis acid **7** with different dienophiles.[a]



1

entry	dienophile	temp/t	product/yield
1	 **8**	120 °C 20 h	 **11** (42%)
2[b]	 **12**	55 °C 2.5 d	 **13** (52%)
3	 **14**	90 °C 2.5 d	 **15** (80%)
4[b]	 **16**	80 °C 2.5 d	 **17** (85%)
5[b]	 **18**	130 °C 2.5 d	 **19** (25%)
6	 **20**	160 °C 10 h	 **21** (45%)
7	 **22**	170 °C 72 h	 **23** (43%)
8	 **24**	160 °C 48 h	 **25a/25b** (75%, 3:1)

[a] With 5 mol % of **2**, 1.5−3 equiv of dienophile, 2 equiv of DIEA, and diglyme. [b] Enamine was prepared in situ from the corresponding ketone and pyrrolidine.

formed. Using this protocol, even linear ketones can be transformed, where the enamine is difficult to isolate.[23] Also less activated dienophiles, like dihydrofurans, give in moderate to good yield the substituted naphthalenes.[24] Alkynes were, so far, not reactive in the catalyzed IEDDA reaction. In general, the reactivity of the dienophiles corresponds to the trend of the kinetic data for 1,2,4,5-tetrazines.[25]

In summary, the presented study gives first proof of principle of catalysis for an IEDDA reaction of nonactivated 1,2-diazines. Investigations to elucidate the mechanism and the applications of this new methodology are currently underway.

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Supporting Information Available: Experimental details and characterization data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) General Procedure: To a fine suspension of complex **2** (5.0 mg, 15.0 μmol, 5.00 mol %) and phthalazine **1** (39.0 mg, 0.300 mmol, 1.00 equiv) in diglyme (500 μl) and *N*,*N*-diisopropylethylamine (125 μl) was added 2-ethylidene-3-methyloxazolidine (**8**) (50.9 mg, 0.450 mmol, 1.50 equiv). The reaction mixture was heated to 120 °C for 20 h. After evaporation at 50 °C/2 mbar, it was purified by flash chromatography (silica gel; hexane/ee 19:1 → 4:1, stabilized with 1% Et_3N) to yield a colorless oil (28.4 mg, 42%).

(22) The elimination of the pyrrolidine was completed using *m*-CPBA: Chenard, B. L.; Ronau, R. T.; Schulte, G. K. *J. Org. Chem.* **1988**, *53*, 5175.

(23) (a) Carlson, R.; Nilsson, A.; Stroemqvist, M. *Acta Chem. Scand., Ser. B* **1983**, *37*, 7. (b) Snyder, D. C. *J. Organomet. Chem.* **1986**, *301*, 137. (c) For an example of an IEDDA with 1,2,4-triazenes with enamines, generated in situ, see: Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982**, *47*, 895.

(24) (a) The mixture of regioisomers in Table 1, entry 8, is caused by isomerization of the double bond to the *exo*-position: (a) Armitage, D. M.; Wilson, C. L. *J. Am. Chem. Soc.* **1959**, *81*, 2437. (b) The elimination to the aromatic product was completed using UV irradiation: (b) Sauer, J.; Bäuerlein, P.; Ebenbeck, W.; Füllhuber, H.; Gousetis, C.; Wernthaler, K. *Eur. J. Org. Chem.* **2001**, 3999.

(25) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885.