OL Organic Letters

pubs.acs.org/OrgLett Letter

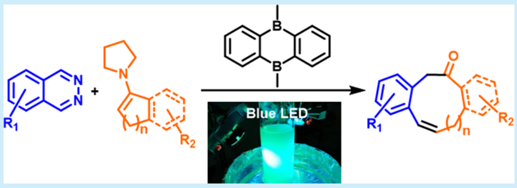
Synthesis of Medium-Sized Carbocycles via a Bidentate Lewis Acid-Catalyzed Inverse Electron-Demand Diels–Alder Reaction Followed by Photoinduced Ring-Opening

Julia Ruhl, Sebastian Ahles, Marcel A. Strauss, Christopher M. Leonhardt, and Hermann A. Wegner*

Cite This: *Org. Lett.* 2021, 23, 2089–2093 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

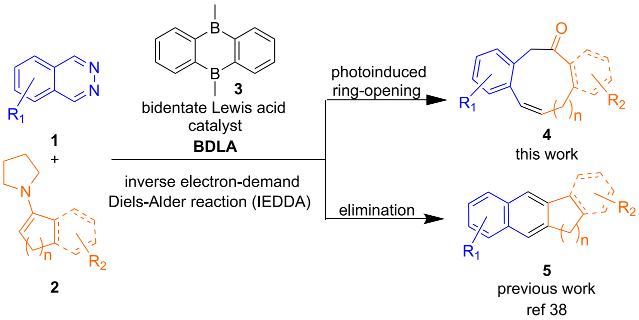
ABSTRACT: The combination of a Lewis acid-catalyzed inverse electron-demand Diels–Alder (IEDDA) reaction with a photoinduced ring-opening (PIRO) reaction in a domino process has been established as an efficient synthetic method to access medium-sized carbocycles. From readily available electron-rich and electron-poor phthalazines and enamines, respectively, as starting materials, various 9- and 11-membered carbocycles were prepared. This versatile transition-metal-free tool will be valuable for broadening the structural space in biologically active compounds and functional materials.



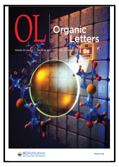
Medium-sized carbon rings (7- to 11-membered) are the structural core motif of various biologically active natural products and medicinally effective synthetic compounds.[1,2] The challenge in creating these medium-sized rings is mostly due to both the ring strain (enthalpy) and the competition between intra- and intermolecular reactions (entropy) during their preparation.[3] Olefin metathesis has been shown to be a very effective method to build these medium-sized rings with either molybdenum (Schrock's)[4,5] or ruthenium (Grubb's)[6,7] catalysts.[8,9] Additionally, it is possible to form medium-sized carbocycles using other metal-catalyzed cyclization, cross-coupling, ring-expansion, and ring-opening reactions as well as free-radical cyclization reactions that rely on metals, such as gallium,[10] platinum,[11,12] cobalt,[13,14] samarium,[15−19] molybdenum,[20] ruthenium,[21,22] indium,[23] manganese,[24,25] iron,[26,27] chromium,[28] copper,[29] palladium,[30,31] silver,[32,33] or gold.[32,34] Further, Nicolaou et al. used a McMurry coupling of a dialdehyde with titanium(III)-chloride in the presence of a zinc−copper couple to build a medium-sized ring system in the total synthesis of taxol.[35] An efficient metal-free method would provide a convenient alternative to access such systems, especially in view of the shortage of resources and sustainability.

In the past, we established bidentate Lewis acids (**BDLA**) as effective catalysts for the inverse electron-demand Diels–Alder (IEDDA) reaction of diazines with various dienophiles.[36] After the initial IEDDA step, a reactive quinodimethane **9** is formed that serves as the ideal base for transformations to various products, such as substituted naphthalenes or complex oligocyclic alkaloid-type structures.[37] The specific outcome of the reaction depends on the conditions chosen and the substitution pattern of the dienophile.[38−41] Recently, we showed that a photoinduced ring-opening (PIRO) reaction of the quinodimethane intermediate **9** by irradiation leads to *ortho*-substituted styrenes. The PIRO reaction of this quinodimethane intermediate **9** proceeds according to the Woodward–Hoffmann rules in a 10π conrotatory pericyclic ring-opening.[42,43] We envisioned that the use of cyclic enamines should deliver medium-sized carbocycles in the same fashion. This would present a metal-free alternative to otherwise difficult-to-prepare targets. Based on our bidentate Lewis acid-catalyzed domino IEDDA/PIRO reaction, we present a modular and transition-metal-free strategy for the synthesis of medium-sized ring systems (Scheme 1).

Scheme 1. Domino Lewis Acid-Catalyzed Inverse Electron-Demand Diels–Alder and Photoinduced Ring-Opening Reaction with Phthalazines 1 and Cyclic Enamines 2



Received: January 21, 2021
Published: February 25, 2021



https://dx.doi.org/10.1021/acs.orglett.1c00249

To realize such a strategy, the **BDLA** catalyst was applied to phthalazine (**1a**) and enamine **2a** under irradiation. First, the reaction mixture was subjected to 448 nm light at different temperatures (see the Supporting Information). Fortunately, the desired 9-membered ring system **4a** was isolated with the eliminated product **5a** as only a minor component. The best yield of 73% was obtained at 80 °C. At higher temperatures, the eliminated IEDDA product **5a** was predominantly formed, decreasing the yield of the photo product **4a**. At temperatures below 80 °C, the IEDDA reaction did not proceed, and the starting material was recovered.

Subsequently, the wavelength was scanned at the optimized temperature of 80 °C. The experiments show that yields above 70% can be achieved with an irradiation between 405 and 500 nm, with an optimum irradiation at 425 nm. As previously shown, the **BDLA** catalyst was partially decomposed at shorter wavelengths (405 nm), significantly reducing the yield.[42] Longer wavelengths between 425 to 500 nm only marginally changed the yield. Hence, a temperature of 80 °C and an irradiation wavelength of 470 nm were chosen as the optimal reaction conditions. At 470 nm, the product was only isolated in a 1% lower yield than at 425 nm, but the purification was much easier due to the formation of fewer side products. As a range of wavelengths from 425 to 500 nm was tolerated, two LEDs were used in some cases to increase the energy density.

To show the scope and high modularity of the IEDDA/PIRO reaction, the reaction was performed with differently substituted starting materials. In the case of 5,8-difluorophthalazine (**1b**), we obtained only the eliminated product under the standard reaction conditions (Figure 1). Due to the lower energy of the lowest unoccupied molecular orbital (LUMO), the IEDDA reaction was expected to proceed much faster. Therefore, the conditions for 5,8-fluorophthalazine (**1b**) were amended to room temperature and an irradiation of 448 and 470 nm. This way, the IEDDA reaction was slower and the PIRO reaction could compete with the elimination. With the same refinement, the reaction of 6-fluorophthalazine (**1c**) was performed at 30 °C with an irradiation of 425 and 470 nm. For the same reason, the IEDDA/PIRO reactions with 6-(trifluoromethyl)phthalazine (**1d**) and 6-chlorophthalazine (**1e**) were done at the same irradiation wavelengths and lower temperatures compared to those of the unsubstituted phthalazine (**1a**). Due to the lower reaction temperatures for the electron-poor phthalazines **1b**−**d**, the corresponding eliminated products were not obtained. In these cases, the remaining phthalazine starting materials **1b**−**d** were recovered. In case of 6-chlorophthalazine **1e**, the reaction temperature had to be raised to 50 °C for an optimal yield. This produced the eliminated product **5e** as a side product. For all electron-deficient phthalazines **1b**−**e**, the corresponding 9-membered carbocycles **4b**−**e** were obtained in good to very good yields. The IEDDA/PIRO reaction with the electron-rich 6-methoxyphthalazine (**1f**) had to be performed at 130 °C and an irradiation of 425 and 448 nm. However, the corresponding photo product **4f** was only obtained in a yield of 5%. Because of the higher LUMO energy of the 6-methoxyphthalazine (**1f**), more energy (higher temperature) was needed for the initial IEDDA reaction, favoring the elimination reaction. Additionally, we used 6-methylphthalazine, 6,7-dimethylphthalazine, and 6,7-dimethoxyphthalazine in the IEDDA/PIRO reaction. However, only the starting materials were reisolated in all three cases. Due to the energetically higher LUMO energy of the phthalazine derivatives, the IEDDA reaction did not proceed for these starting materials.

Next, different cyclic enamines **2b**−**f** were screened (Figure 2). All enamines **2a**−**f** were synthesized following a known procedure reported by Thompson et al.[44] The PIRO reaction proceeded smoothly with unsubstituted 1-(1-cyclopenten-1-yl)pyrrolidine (**2b**). Due to the lower steric hindrance of enamine **2b**, it was possible to obtain the (7*Z*)-bicyclo[7.4.0]-trideca-1(13),7,9,11-tetraen-3-one (**4g**) product in an excellent yield of 93%. Additionally, electron-rich and electron-deficient

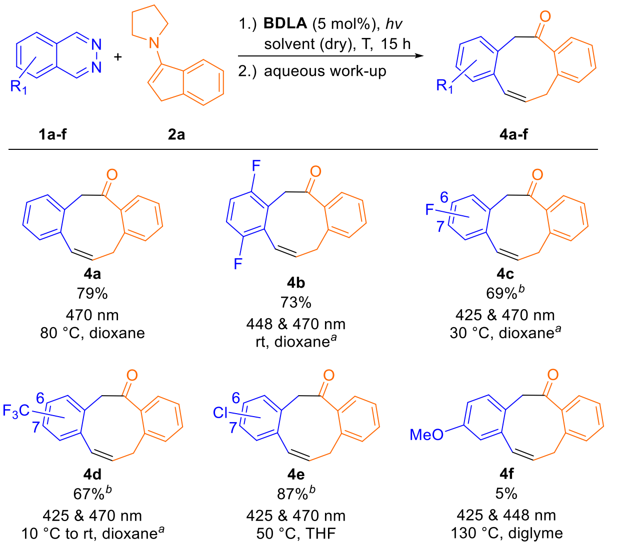


Figure 1. Screening of the phthalazines **1a**−**f** in the IEDDA/PIRO reaction with enamine **2a**. Reaction conditions are as follows: phthalazines (**1a**−**f**) (1.0 mmol, 1.0 equiv), **BDLA** (50 μmol, 5.0 mol %), enamine **2a** (2.9 mmol, 2.9 equiv), and dry solvents (10 mL, 100 mM). [a]The corresponding eliminated product was not obtained under these reaction conditions. [b]Isolated yield as mixture of C6 and C7 constitutional isomers.

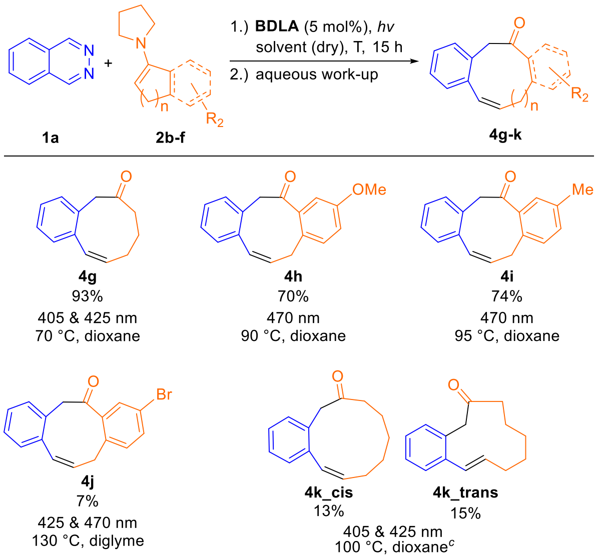


Figure 2. Screening of the cyclic enamines **2b**−**f** in the IEDDA/PIRO reaction with phthalazine **1a**. Reaction conditions are as follows: phthalazine (**1a**) (1.0 mmol, 1.0 equiv), **BDLA** (50 μmol, 5.0 mol%), enamines **2b**−**f** (2.9 mmol, 2.9 equiv), and dry solvents (10 mL, 100 mM). [c]**BDLA** (0.10 mmol, 10 mol %) was used as a catalyst.

enamines could be used in the IEDDA/PIRO reaction; 1-(6-methoxy-3*H*-inden-1-yl)pyrrolidine (**2c**) and 1-(6-methly-3*H*-inden-1-yl)pyrrolidine (**2d**), respectively, were converted to the corresponding photo products **4h** and **4i** in good yields. For the 5-bromo-substituted enamine **2e**, the reaction temperature was increased to 130 °C and the irradiation was done at 425 and 470 nm. Again, the elimination reaction was preferred in this case due to the harsher conditions, and the corresponding photo product **4j** was only isolated in a yield of 7%.

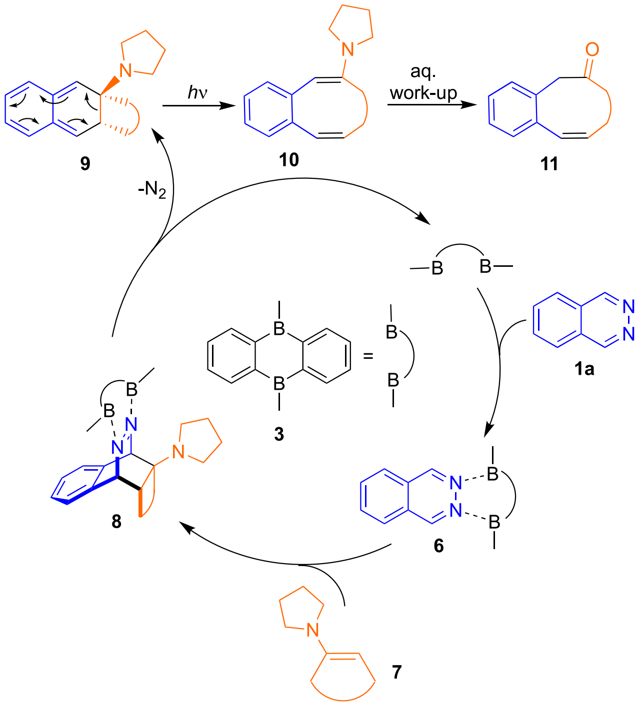
Enamines with an increased ring size would give access to even larger carbocycles. For example, the IEDDA/PIRO reaction of phthalazine (**1a**) and 1-(1-cyclohepten-1-yl)-pyrrolidine (**2f**) provided the 11-membered carbocycle **4k**, although in lower yields and as both double-bond isomers. To obtain a better understanding of why the synthesis of **4k** yielded both isomers and that of **4g** yielded a single isomer, a computational analysis was conducted. Therefore, conformer ensembles of compounds **4k_cis**, **4k_trans**, **4g_cis**, and the theoretical **4g_trans** were computed with the Conformer−Rotamer Ensemble Sampling Tool (CREST)[45,46] developed by Grimme and co-workers. The structures of the conformer with the lowest energy were further optimized on the PBE0[47] level of theory with a def2-TZVP[48] basis set and the D3-BJ[49,50] dispersion correction. High-level single-point corrections were computed at the DLPNO−CCSD(T)[51] level, also using the def2-TZVP basis set. This computational analysis showed that the difference in ΔG° between **4k_cis** and **4k_trans** was merely 0.37 kcal/mol. For **4g** and its theoretical *trans*-isomer, this difference increased to 4.20 kcal/mol due to the higher ring strain, clearly favoring the formation of a bowl-shaped structure of the *cis*-isomer over the less favorable *trans*-isomer (see the Supporting Information for more details). The lower yield can be rationalized by the decomposition of the **BDLA** over time, as the IEDDA reaction proceeded much slower.[42] Furthermore, both 1-(1-cyclohexen-1-yl)pyrrolidine and 1-(1-cycloocten-1-yl)pyrrolidine were tested in the IEDDA/PIRO reaction. However, these substrates did not react in the IEDDA, probably due to the increased steric demand of these enamines. In previous publications, we also showed that these enamines need higher temperatures to undergo the IEDDA reaction and form the corresponding eliminated products.[38,52] Therefore, we also tested the IEDDA/PIRO reaction with the two isomeric six-membered enamines 1-(3,4-dihydronaphth-1-yl)pyrrolidine and 1-(3,4-dihydronaphth-2-yl)pyrrolidine. These reaction partners should have more planar ring systems than 1-(1-cyclohexen-1-yl)pyrrolidine, reducing the steric hindrance. However, the IEDDA reaction also did not proceed in these cases.

The method can easily be carried out on a gram scale. The reaction of phthalazine (**1a**) and enamine **2b** was set up in a Schlenk tube, and the reaction mixture was irradiated with two LEDs (470 and 500 nm). However, the larger diameter of the reaction vessel reduced the penetration depth of the light, favoring side reactions. Hence, the photo product **4a** was obtained in a lower yield of 57% compared to that of the small scale.

Additionally, the IEDDA/PIRO reaction of phthalazine (**1a**) and enamine **2a** was performed with the air-stable variant of the bidentate Lewis acid catalyst recently developed by us (see Supporting Information for details).[53] In this case, the reaction temperature was slightly increased to 90 °C to speed up the exchange of the coordinated pyridazine on the bidentate Lewis acid with the phthalazine reactant (**1a**). Nevertheless, the desired photo product **4a** was isolated in a 61% yield.

Based on previous studies of the IEDDA reaction, the following mechanistic proposal is put forward for the IEDDA/PIRO reaction. In the first step of the catalytic cycle, the bidentate Lewis acid **3** coordinates to the phthalazine (**1a**) to form complex **6**.[37] The activated phthalazine can now react with an electron-rich dienophile, in this case enamine **7**, to form the intermediate **8** via an IEDDA reaction. The elimination of nitrogen regenerates the BDLA and leads to the quinodimethane intermediate **9**.[37,40] For the ring-opening, a visible-light-promoted opening of the quinodimethane intermediate **9** to enamine **10** is hypothesized.[42] With 10π electrons involved, this photo electrocyclization reaction has to proceed conrotatory according to the Woodward−Hoffmann rules.[43,54] The cyclic enamine **10** is transformed to the corresponding cyclic ketone **11** during aqueous workup (Scheme 2).

Scheme 2. Catalytic Cycle of the Domino Bidentate Lewis Acid-Catalyzed IEDDA Reaction of Phthalazine (1a) and an Electron-Rich Dienophile 7[a]



[a] The catalytic cycle was followed by the photoinduced ring-opening (PIRO) reaction.

In summary, we established the IEDDA/PIRO reaction of phthalazines and cyclic enamines as a powerful tool for the synthesis of medium-sized carbocycles. The scope of this reaction was shown by screening differently substituted phthalazines **1a−f** and cyclic enamines **2a−f**. We demonstrated that the electron-rich enamines **2c** and **2d** and especially the electron-deficient phthalazines **1b−e** provided the corresponding medium-sized carbocycles in good to very good yields. However, the electron-rich phthalazine **1f** and electron-deficient enamine **2e** only reacted sluggishly in the domino IEDDA/PIRO reaction. By using enamines with different ring-sizes, it was shown that sterics also influence the IEDDA/PIRO reaction. Over all, the IEDDA/PIRO reaction offers a new transition-metal-free and stereoselective synthesis strategy for 9- and 11-membered carbocycles, which will contribute to the efficient expansion of the molecular space for biological and materials applications.[55−57]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00249.

> Experimental details, analytical data, NMR spectra, and computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hermann A. Wegner − *Institute of Organic Chemistry, Justus Liebig University Giessen, 35392 Giessen, Germany; Center for Materials Research (LaMa), Justus Liebig University Giessen, 35392 Giessen, Germany;* orcid.org/0000-0001-7260-6018; Email: hermann.a.wegner@org.chemie.uni-giessen.de

Authors

Julia Ruhl − *Institute of Organic Chemistry, Justus Liebig University Giessen, 35392 Giessen, Germany; Center for Materials Research (LaMa), Justus Liebig University Giessen, 35392 Giessen, Germany;* orcid.org/0000-0002-3062-9227

Sebastian Ahles − *Institute of Organic Chemistry, Justus Liebig University Giessen, 35392 Giessen, Germany; Center for Materials Research (LaMa), Justus Liebig University Giessen, 35392 Giessen, Germany;* orcid.org/0000-0002-3954-5513

Marcel A. Strauss − *Institute of Organic Chemistry, Justus Liebig University Giessen, 35392 Giessen, Germany; Center for Materials Research (LaMa), Justus Liebig University Giessen, 35392 Giessen, Germany;* orcid.org/0000-0001-8152-9421

Christopher M. Leonhardt − *Institute of Organic Chemistry, Justus Liebig University Giessen, 35392 Giessen, Germany; Center for Materials Research (LaMa), Justus Liebig University Giessen, 35392 Giessen, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00249

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Heike Hausmann (Justus Liebig University, Giessen) for NMR support and Edgar Reitz (Justus Liebig University, Giessen) for the design and construction of the LED devices.

■ REFERENCES

(1) Hussain, A.; Yousuf, S. K.; Mukherjee, D. Importance and synthesis of benzannulated medium-sized and macrocyclic rings (BMRs). *RSC Adv.* **2014**, *4*, 43241−43257.

(2) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century. *Angew. Chem., Int. Ed.* **2000**, *39*, 44−122.

(3) Galli, C.; Mandolini, L. The Role of Ring Strain on the Ease of Ring Closure of Bifunctional Chain Molecules. *Eur. J. Org. Chem.* **2000**, *2000*, 3117−3125.

(4) Schrock, R. R. Multiple metal-carbon bonds for catalytic metathesis reactions (Nobel Lecture). *Angew. Chem., Int. Ed.* **2006**, *45*, 3748−3759.

(5) McConville, D. H.; Wolf, J. R.; Schrock, R. R. Synthesis of chiral molybdenum ROMP initiators and all-cis highly tactic poly(2,3-(R)2norbornadiene) (R = CF3 or CO2Me). *J. Am. Chem. Soc.* **1993**, *115*, 4413−4414.

(6) Grubbs, R. H. Olefin-metathesis catalysts for the preparation of molecules and materials (Nobel Lecture). *Angew. Chem., Int. Ed.* **2006**, *45*, 3760−3765.

(7) Ogba, O. M.; Warner, N. C.; O'Leary, D. J.; Grubbs, R. H. Recent advances in ruthenium-based olefin metathesis. *Chem. Soc. Rev.* **2018**, *47*, 4510−4544.

(8) Yet, L. Metal-mediated synthesis of medium-sized rings. *Chem. Rev.* **2000**, *100*, 2963−3008.

(9) Maier, M. E. Synthesis of Medium-Sized Rings by the Ring-Closing Metathesis Reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077.

(10) Kim, S. M.; Lee, S. I.; Chung, Y. K. GaCl3-catalyzed formation of eight-membered rings from enynes bearing a cyclic olefin. *Org. Lett.* **2006**, *8*, 5425−5427.

(11) Fürstner, A.; Davies, P. W. Catalytic carbophilic activation: catalysis by platinum and gold pi acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449.

(12) Añorbe, L.; Domínguez, G.; Pérez-Castells, J. Reorganization of enynes catalyzed by platinum salts. *Chem. - Eur. J.* **2004**, *10*, 4938−4943.

(13) Bradley, A.; Motherwell, W. B.; Ujjainwalla, F. A concise approach towards the synthesis of steganone analogues. *Chem. Commun.* **1999**, 917−918.

(14) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. Tandem Use of Cobalt-Mediated Reactions to Synthesize (+)-Epoxydictymene, a Diterpene Containing a Trans -Fused 5−5 Ring System. *J. Am. Chem. Soc.* **1997**, *119*, 4353−4363.

(15) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. Investigations on 1,2-, 1,3-, and 1,4-asymmetric induction in intramolecular Reformatskii reactions promoted by samarium(II) iodide. *J. Am. Chem. Soc.* **1991**, *113*, 8036−8045.

(16) Molander, G. A.; Harris, C. R. Sequenced Reactions with Samarium(II) Iodide. Tandem Intramolecular Nucleophilic Acyl Substitution/Intramolecular Barbier Cyclizations. *J. Am. Chem. Soc.* **1995**, *117*, 3705−3716.

(17) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. Efficient construction of 8-membered ring framework of vinigrol through SmI2-induced coupling cyclization. *Tetrahedron* **1999**, *55*, 14369−14380.

(18) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. New Samarium Diiodide-Induced Ketyl Couplings - From Analogous Reactions to Serendipitously Discovered Processes. *Synlett* **2004**, 422−438.

(19) Molander, G. A.; McKie, J. A. Samarium(II) iodide-induced reductive cyclization of unactivated olefinic ketones. Sequential radical cyclization/intermolecular nucleophilic addition and substitution reactions. *J. Org. Chem.* **1992**, *57*, 3132−3139.

(20) Yin, J.; Liebeskind, L. S. Enantiocontrolled [5 + 2] Cycloaddition to η 3 -Pyranylmolybdenum π-Complexes. Synthesis of Substituted Oxabicyclo[3.2.1]octenes of High Enantiopurity. *J. Am. Chem. Soc.* **1999**, *121*, 5811−5812.

(21) Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. Rhodium-Catalyzed [5 + 2] Cycloadditions of Allenes and Vinylcyclopropanes. *Org. Lett.* **1999**, *1*, 137−140.

(22) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. First Studies of the Transition Metal-Catalyzed [5 + 2] Cycloadditions of Alkenes and Vinylcyclopropanes. *J. Am. Chem. Soc.* **1998**, *120*, 1940−1941.

(23) Cintas, P. Synthetic Organoindium Chemistry. *Synlett* **1995**, *1995*, 1087−1096.

(24) Snider, B. B. Manganese(III)-Based Oxidative Free-Radical Cyclizations. *Chem. Rev.* **1996**, *96*, 339−364.

(25) Snider, B. B.; Merritt, J. E. Formation of seven- and eight-membered rings by Mn(III)-based oxidative free-radical cyclization. *Tetrahedron* **1991**, *47*, 8663−8678.

(26) Booker-Milburn, K. I.; Thompson, D. F. Iron(III) mediated transformations of cyclopropyltrimethylsilyl ethers. Part 1. Free radical tandem ring expansion−cyclisation reactions for the rapid construction of [n.3.0] bicyclic ring systems. *J. Chem. Soc., Perkin Trans. 1* **1995**, *45*, 2315−2321.

(27) Christoffers, J. Iron(III) catalysis of an intramolecular Michael reaction. *Tetrahedron Lett.* **1998**, *39*, 7083−7084.

(28) Fürstner, A. Carbonminus signCarbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev.* **1999**, *99*, 991−1046.

(29) de Campo, F.; Lastécouères, D.; Verlhac, J.-B. New and improved catalysts for transition metal catalysed radical reactions. *Chem. Commun.* **1998**, *1998* (19), 2117−2118.

(30) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. Palladium(0)-catalyzed synthesis of medium-sized heterocycles by using bromoallenes as an allyl dication equivalent. *J. Am. Chem. Soc.* **2004**, *126*, 8744−8754.

(31) Denmark, S. E.; Yang, S.-M. Sequential ring-closing metathesis/Pd-catalyzed, Si-assisted cross-coupling reactions. *Tetrahedron* **2004**, *60*, 9695−9708.

(32) Watson, I. D. G.; Ritter, S.; Toste, F. D. Asymmetric synthesis of medium-sized rings by intramolecular Au(I)-catalyzed cyclopropanation. *J. Am. Chem. Soc.* **2009**, *131*, 2056−2057.

(33) Muñoz, M. P. Silver and platinum-catalysed addition of O-H and N-H bonds to allenes. *Chem. Soc. Rev.* **2014**, *43*, 3164−3183.

(34) Jiménez, T.; Carreras, J.; Ceccon, J.; Echavarren, A. M. Gold(I)-Catalyzed Inter- and Intramolecular Additions of Carbonyl Compounds to Allenenes. *Org. Lett.* **2016**, *18*, 1410−1413.

(35) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. Total synthesis of taxol. *Nature* **1994**, *367*, 630−634.

(36) Schweighauser, L.; Wegner, H. A. Bis-Boron Compounds in Catalysis: Bidentate and Bifunctional Activation. *Chem. - Eur. J.* **2016**, *22*, 14094−14103.

(37) Schweighauser, L.; Bodoky, I.; Kessler, S. N.; Häussinger, D.; Donsbach, C.; Wegner, H. A. Bidentate Lewis Acid Catalyzed Domino Diels-Alder Reaction of Phthalazine for the Synthesis of Bridged Oligocyclic Tetrahydronaphthalenes. *Org. Lett.* **2016**, *18*, 1330−1333.

(38) Kessler, S. N.; Neuburger, M.; Wegner, H. A. Bidentate Lewis Acids for the Activation of 1,2-Diazines - A New Mode of Catalysis. *Eur. J. Org. Chem.* **2011**, *2011*, 3238−3245.

(39) Kessler, S. N.; Neuburger, M.; Wegner, H. A. Domino inverse electron-demand Diels-Alder/cyclopropanation reaction of diazines catalyzed by a bidentate Lewis acid. *J. Am. Chem. Soc.* **2012**, *134*, 17885−17888.

(40) Kessler, S. N.; Wegner, H. A. One-pot synthesis of phthalazines and pyridazino-aromatics: a novel strategy for substituted naphthalenes. *Org. Lett.* **2012**, *14*, 3268−3271.

(41) Ahles, S.; Götz, S.; Schweighauser, L.; Brodsky, M.; Kessler, S. N.; Heindl, A. H.; Wegner, H. A. An Amine Group Transfer Reaction Driven by Aromaticity. *Org. Lett.* **2018**, *20*, 7034−7038.

(42) Ahles, S.; Ruhl, J.; Strauss, M. A.; Wegner, H. A. Combining Bidentate Lewis Acid Catalysis and Photochemistry: Formal Insertion of o-Xylene into an Enamine Double Bond. *Org. Lett.* **2019**, *21*, 3927−3930.

(43) Woodward, R. B.; Hoffmann, R. Stereochemistry of Electrocyclic Reactions. *J. Am. Chem. Soc.* **1965**, *87*, 395−397.

(44) Thompson, H. W.; Huegi, B. S. Stabilised enamine anions. Generation and alkylation of anions stabilised as cyclopentadienide enamine systems. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1603−1607.

(45) Pracht, P.; Bohle, F.; Grimme, S. Automated exploration of the low-energy chemical space with fast quantum chemical methods. *Phys. Chem. Chem. Phys.* **2020**, *22*, 7169−7192.

(46) Grimme, S. Exploration of Chemical Compound, Conformer, and Reaction Space with Meta-Dynamics Simulations Based on Tight-Binding Quantum Chemical Calculations. *J. Chem. Theory Comput.* **2019**, *15*, 2847−2862.

(47) Adamo, C.; Barone, V. Toward reliable density functional methods without adjustable parameters. *J. Chem. Phys.* **1999**, *110*, 6158−6170.

(48) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.

(49) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* **2011**, *32*, 1456−1465.

(50) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104.

(51) Riplinger, C.; Sandhoefer, B.; Hansen, A.; Neese, F. Natural triple excitations in local coupled cluster calculations with pair natural orbitals. *J. Chem. Phys.* **2013**, *139*, 134101.

(52) Balcar, J.; Chrisam, G.; Huber, F. X.; Sauer, J. Reaktivität von stickstoff-heterocyclen genenüber cyclooctin als dienophil. *Tetrahedron Lett.* **1983**, *24*, 1481−1484.

(53) Hong, L.; Ahles, S.; Heindl, A. H.; Tiétcha, G.; Petrov, A.; Lu, Z.; Logemann, C.; Wegner, H. A. An air-stable bisboron complex: a practical bidentate Lewis acid catalyst. *Beilstein J. Org. Chem.* **2018**, *14*, 618−625.

(54) Woodward, R. B.; Hoffmann, R. The Conservation of Orbital Symmetry. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781−853.

(55) Rabinovitz, M.; Willner, I.; Gamliel, A.; Gazit, A. Benzannelated [9] and [13] annulenes. *Tetrahedron* **1979**, *35*, 667−673.

(56) Rabinovitz, M.; Willner, I. Aromatic linearly annelated dibenzocyclononatetraenyl anion. *Tetrahedron Lett.* **1974**, *15*, 4447−4450.

(57) Kajioka, T.; Ikai, M.; Fujikawa, H.; Taga, Y. Disubstituted 1,6-methano[10]annulene derivatives for use in organic light-emitting diodes. *Tetrahedron* **2004**, *60*, 6183−6187.