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Anion- π Catalysis of Diels-Alder Reactions

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Abstract: Among concerted cycloadditions, the Diels-Alder reaction is the grand old classic. Usually achieved with acid catalysis, hydroxypyrones, oxa- and thiazolones are explored in this report because they provide access to anionic dienes. Their [4+2] cycloaddition to cyclic and acyclic dienophiles such as maleimides and fumarates affords bicyclic products with four new stereogenic centers. Bifunctional anion- π catalysts composed of amine bases next to the π surface of naphthalenediimides (NDIs) are shown to selectively stabilize the “open,” fully accessible anionic *exo* transition state on the π -acidic aromatic surface. Our results also include reactivities that are hard to access with conventional organocatalysts, such as the *exo* specific and highly enantioselective Diels-Alder reaction of thiazolones and maleimides with complete suppression of the otherwise dominant Michael addition. With increasing π acidity of the anion- π catalysts, rates, chemo-, diastereo- and enantioselectivities increase consistently. Contributions of anion- π interactions to the concerted processes are further supported by inhibition with nitrate.

The stabilization of anionic transition states and reactive intermediates with anion- π interactions^[1] on π -acidic surfaces is essentially unknown in biology and has been explicitly introduced in chemistry only four years ago.^[2] Since then, asymmetric anion- π catalysis has been reported for several reactions,^[3] and the first anion- π enzyme^[4] and electric-field-assisted anion- π catalysis^[5] have been realized. Moving on from coupled cascade cyclizations^[3] to concerted cycloadditions, the Diels-Alder reaction stands out as the grand old classic.^[6-12] The usual mechanism of Diels-Alder reactions involves activation of the dienophile with Lewis acids.^[6] However, base-catalyzed Diels-Alder reactions^[7] have been realized by activation of dienes such as 5*H*-oxazol-4-one,^[8,9] 5*H*-thiazol-4-ones^[10] and 3-hydroxy-2-pyrones.^[11,12] Several organocatalysts, often tertiary amines derived from cinchona alkaloids, have been applied to all three dienes together with several dienophiles to yield the cycloaddition product, often with excellent *endo* selectivity and high enantioselectivity.^[7-12]

The selective acceleration of the usually disfavored *exo* product of Diels-Alder reactions^[13] is an intriguing challenge that has attracted much attention. *Exo* selectivity has been achieved, for example, with catalytic antibodies raised against stable analogs of the *exo* transition state.^[14] Other unforgettable classics for *exo*-selective Diels-Alder reactions are trimeric cyclic porphyrin catalysts and self-assembled molecular flasks.^[15] The *endo/exo* selectivity of Diels-Alder reaction has further been of interest with enzymes, ribozymes, DNAzymes, cyclodextrins, hemicyptophanes, capsules, scanning

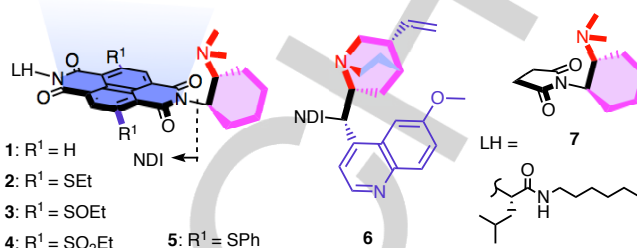


Figure 1. Structure of anion- π catalysts 1–7 used in this study.

tunneling microscopy break junctions, silica nanopores, chaotropes, ionic liquids, voltage, pressure, medium, and so on.^[16,11]

To elaborate on the selective catalysis of Diels-Alder reactions with anion- π interactions, bifunctional anion- π catalysts 1–7 composed of a tertiary amine next to the π -acidic surface of a naphthalenediimide (NDI) were prepared following reported procedures (Figure 1).^[3] All details on catalyst and substrate synthesis can be found in the Supporting Information.

Anionic [4+2] cycloadditions with 5*H*-oxazol-4-one **8** as diene were explored first (Figure 2a). In the presence of catalyst 1–5 and dienophiles **9**, the *exo* Diels-Alder products **10** were obtained in nearly quantitative yield with >20:1 *dr* and 88–94% *ee* (Table 1, entries 3–9). The brominated substrate **9b** was of interest to determine the absolute configuration of the *exo* product **10b** by x-ray crystallography (Figure 2b). Only the cinchona fusion catalyst **6** gave lower *dr* and *ee* (Table 1, entry 10). Preliminary results further indicated that replacement of the tertiary amine in **1** with a stronger guanidine base decreases rather than increases stereoselectivity. These indications confirmed that for anion- π catalysis with sufficiently acidic substrates such as oxazolone **8**, the strength of the

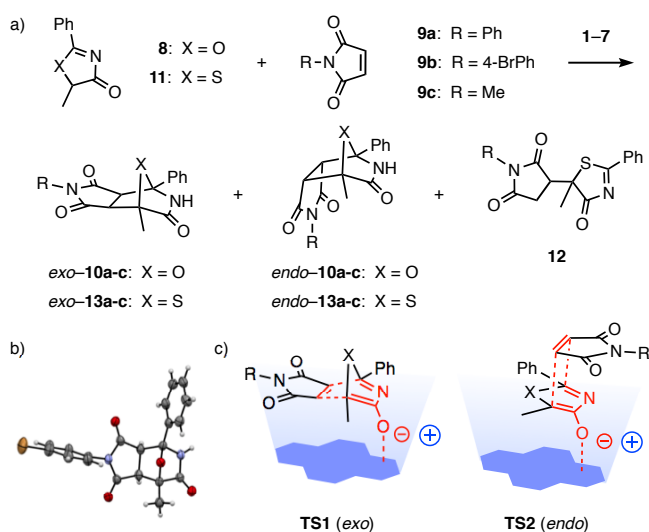


Figure 2. (a) Base-catalyzed reactions between oxazolone **8** or thiazolone **11** and maleimides **9**. (b) Crystal structure of *exo*-**10b**. (c) Notional anionic transition states **TS1** for *exo* products and **TS2** for *endo* products **10/13** (red) on π -acidic surfaces (blue). Only one arbitrary enantiomer is shown for *exo* and *endo* products **10/13** and **TS1/TS2**.

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Table 1. Diels-Alder Reactions with Oxa- and Thiazolones.^[a]

	cat ^[b]	substrates ^[c]	η [%] ^[d]	$dr_{exo/endo}$ ^[e]	ee [%] ^[f]
1	Et ₃ N	8 + 9a	86	3.0:1	Nd
2	7	8 + 9a	85	1.1:1	<3
3	1	8 + 9a	93	>20:1	94
4	1	8 + 9b	94	>20:1	88
5	1	8 + 9c	92	>20:1	90
6	2	8 + 9a	91	>20:1	90
7	3	8 + 9a	94	>20:1	92
8	4	8 + 9a	93	>20:1	93
9	5	8 + 9a	96	>20:1	93
10	6	8 + 9a	88	6.2:1	-14
11 ^[g]	Et ₃ N	11 + 9a	17 (1:4.7)	10:1	Nd
12 ^[g]	1	11 + 9a	80 (5.5:1)	>20:1	90
13	1	11 + 9a	85 (6.3:1)	>20:1	82
14	2	11 + 9a	82 (6.7:1)	>20:1	80
15	5	11 + 9a	90 (18:1)	>20:1	51
16 ^[g]	5	11 + 9a	88 (15:1)	>20:1	94

^[a]With 0.5 M diene (**8/11**), 1.0 M dienophile (**9**), 10 mol% catalyst, 20 °C, benzene-*d*₆ (or CDCl₃^[g]). ^[b]Catalysts (Figure 1). ^[c]Figure 2a. ^[d]Total yield of diastereomeric mixtures of products **10/13** determined by ¹H NMR spectroscopy after consumption of **8/11** (60 h) with dibromomethane as internal standard. Entries 11-16: The DA/M ratio of Diels-Alder and Michael products η (**13**) / η (**12**) is given in parenthesis. ^[e]Diastereomeric ratio of *exo/endo* products (Figure 2a). ^[f]Enantiomeric excess for *exo-10*, *exo-13*. ^[g]Reaction in CDCl₃ instead of benzene-*d*₆.

base is less important than the positioning relative to the π -acidic surface. Studies with guanidine-based anion- π catalysts were therefore discontinued (not shown).

Almost negligible stereoselectivity of 1.1:1 dr and <3% ee was observed with control catalyst **7** (Table 1, entry 2). The performance of Et₃N was similarly poor (Table 1, entry 1), and *endo* selectivity has been reported for conventional thiourea-based catalysts.^[8] The complete inversion of selectivity to *exo* specificity on π -acidic surfaces was consistent with anion- π interactions stabilizing the delocalized anion of the conjugate base of oxazolone **8**, the following charge delocalization in the anionic *exo* transition state **TS1** of the [4+2] cycloaddition (Figure 2c), and the final, more basic anionic tautomer of the product. Naturally, these anion- π interactions are supported by ion pairing and π - π interactions. However, the latter should be weak in isolate, neutral form and, contrary to anion- π interactions, almost disappear during the cycloaddition. The secondary orbital interactions in transition state **TS2** that account for

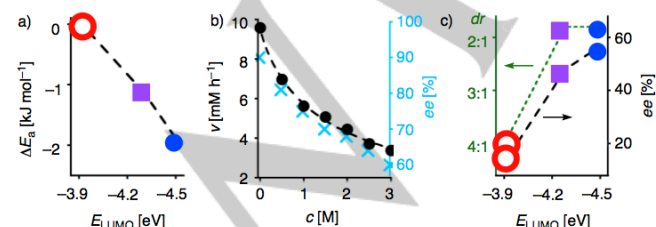


Figure 3. (a) Dependence of the activation energy ΔE_a of the reaction of **8** and **9a** on the LUMO energy of the NDIs in catalyst **2** (○), **3** (■) and **4** (●). (b) Initial velocity of the formation of product **10a** (●) and ee (X) as a function of concentration of Bu₄NNO₃, with fit to Hill equation. (c) Dependence of dr and ee of product *exo-15* on the LUMO of **2** (○), **3** (■) and **4** (●).

endo selectivity should be incompatible with the stabilization by similarly extended anion- π interactions (Figure 2c). In **TS1**, the dienophile is proposed to approach the diene from the side of the π surface to benefit also from dienophile activation by π - π interactions and preorganizing positioning of the substrates in close proximity, and to preserve anion- π stabilization of the complete system throughout the entire reaction. An alternative approach from the free side of the diene opposite the π surface would exclude initial contacts of the dienophile with the π surface and thus, compared to *endo* **TS2**, not explain the increasing *exo* selectivity found with anion- π catalysis. Such an alternative “top-down” approach would also exclude the stabilization of the full transition state on the π surface and result in decreasing anion- π interactions during the cycloaddition.

Corroborative support for these conclusions was obtained by increasing rates with increasing π acidity^[3] of the NDI in catalysts **3** and **4** compared to **2** (Figure S18). A formal transition-state stabilization by $\Delta E_a = -1.15$ kJ mol⁻¹ and $\Delta E_a = -1.96$ kJ mol⁻¹ was in the range expected^[2] for focused changes in anion- π interactions only (Figure 3a). Moreover, nitrate inhibited catalyst **1** ($IC_{50} = 1.58 \pm 0.05$ M, Figures 3b, ●, S19) with a coinciding decrease in enantioselectivity from ~90% ee down to 60% ee (Figure 3b, X).

5*H*-Thiazol-4-one **11** with a more nucleophilic α carbon was of interest because with conventional organocatalysts, the Michael addition product **12** rather than cycloaddition product **13a** is obtained (Figure 2a).^[17] A Diels-Alder/Michael (DA/M) ratio of 1:4.7 recorded with 10 mol% Et₃N was in agreement with these reports (Figure 4a, Table 1, entry 11). The DA/M ratio did not change over time, indicating that the Michael product **12** could not be transformed into the chiral 1,4-sulfur-bridged piperidinone **13a** by a subsequent Mannich ring closure (Figure S6). This observation suggested that the mechanisms leading to the two products are different, i.e., the occurrence of a concerted Diels-Alder cycloaddition to afford **13a** in 17% yield with an *exo/endo* selectivity of 10:1 (Table 1, entry 11).

In the presence of 10 mol% anion- π catalyst **1**, the Diels-Alder product *exo-13a* was obtained almost exclusively (85%, DA/M = 6.3:1), without detectable *endo-13a* and with 82% ee (Table 1, entry 13). Catalyst screening gave best results for NDI **5** (DA/M = 15:1, *exo/endo* >20:1, 94% ee , Figure 4b, Table 1, entries 15, 16). This inversion of selectivity from Michael addition to enantioselective *exo*

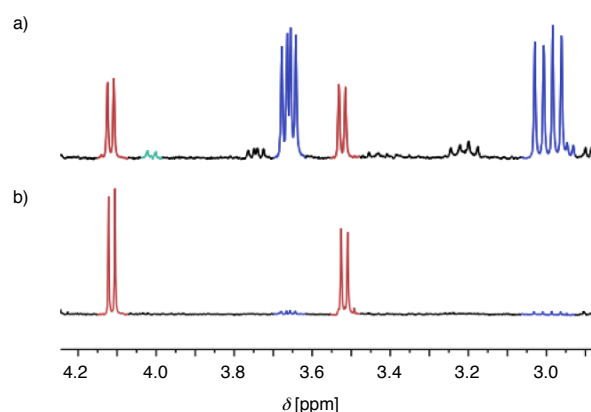


Figure 4. Diagnostic peaks in the ¹H NMR spectra of the product mixtures obtained with **11** and **9a** in the presence of 10 mol% Et₃N (a) and catalyst **5** (b); blue: **12**, red: *exo-13a*, green, 4.03 ppm: *endo-13a*, in CDCl₃ (Table 1, entries 11, 16).

Table 2. Diels-Alder Reactions with 3-Hydroxy-2-Pyrones.^[a]

	cat ^[b]	substrates ^[c]	η [%] ^[d]	$dr_{endo/exo}$ ^[e]	ee [%] ^[f]
1	Et ₃ N	9c	90	5.8:1	0
2	2	9c	83	4.0:1	13
3	3	9c	89	1.8:1	48
4	4	9c	92	1.8:1	56
5	6	9c	80	1.3:1	19
6	Et ₃ N	16	90	0.8:1	-
7	2	16	92	2.0:1	-
8	3	16	90	2.5:1	-
9	4	16	0	nd	-
10	5	16	94	3.2:1	-
11	6	16	91	2.0:1	-
12	Et ₃ N	17	98	>20:1	-
13	2	17	64	>20:1	-
14	6	17	70	>20:1	-

^[a]With 0.1 M **14**, 0.11 M dienophile, 20 mol% catalyst, CDCl₃, rt. ^[b]Catalysts (Figure 1). ^[c]Dienophiles (Figure 5a). ^[d]Total yield of **15**, **18a–c** determined by ¹H NMR after consumption of **14**: 1–4 h for **9c**; 10 days for **16**; 35 days for **17**. ^[e]Diastereomeric ratio of *endo/exo* products. ^[f]Enantiomeric excess for *exo-16*, **19a**; entries 6–14: *ee*'s not determined, acyclic dienophiles were of interest for mechanistic studies only.

Diels-Alder reaction on π -acidic surfaces was perfectly explained with the selective recognition of the *exo* transition state of the cycloaddition by π - π enhanced anion- π interactions as outlined above with *exo-TS1* (Figure 2c).

With 20 mol% Et₃N, 3-hydroxy-2-pyrone **14** and dienophile **9c** reacted with high 5.8:1 *endo/exo* selectivity (Figure 5a, Table 2, entry 1). With 20 mol% catalyst **2**, selectivity for the *endo* product increased to 4.0:1 *dr* (Table 2, entry 2). As expected for operational anion- π catalysis, increasing π acidity from **2** to **4** improved *exo* product formation from 4.0:1 to 1.8:1 *endo/exo* selectivity and enantioselectivity from 13% *ee* up to 56% *ee* (Figure 3c; Table 2, entries 2–4). Although the high intrinsic *endo* selectivity with hydroxypyrones **14** prevented inversion of diastereoselectivity, these trends were as with oxa- and thiazolones and consistent with selective anion- π catalysis via the respective analog of *exo-TS1* (Figure 2c).

With catalysts **2–4**, the addition of 3-hydroxy-2-pyrone **14** to the acyclic dimethyl fumarate **16** afforded the *anti* products **18a** and **18b** exclusively, whereas dimethyl maleate **17** gave the complementary *syn* product **18c** with equal specificity (Figure 5a). Together with the absence of Michael addition products throughout all reactions, the absence of isomerization during the cyclization (Figure 5b) provided strong support for a concerted [4+2] addition mechanism.^[11,12] For acyclic *trans* dienophiles, the assignment of *endo* and *exo* diastereomers is less obvious than with cyclic substrates (Figure 5a).^[12] With 20 mol% Et₃N, the intrinsically favored^[12] *exo* product **18b** was obtained from *trans* dienophile **16** with the expected *endo/exo* ratio of 0.8:1 (Table 2, entry 6). In the presence of 20 mol% of anion- π catalysts **2–6** except for **4**, the intrinsically disfavored *endo* product **19a** was obtained with *endo/exo* ratios 2.0:1 and beyond (Table 2, entries 7–11). Surprisingly, *endo*

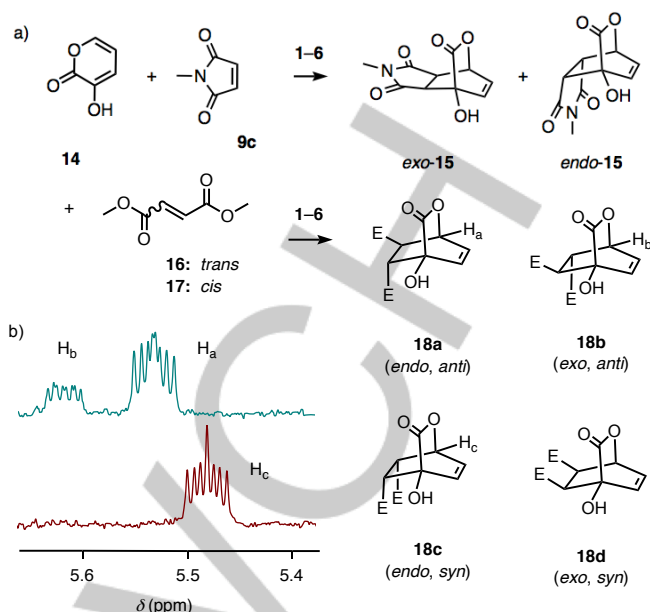


Figure 5. (a) Reactions between hydroxypyrene **14** and either maleimide **9c** or fumarates **16** or **17** (only one enantiomer shown per diastereomer). (b) Diagnostic part of representative ¹H NMR spectra of mixtures of **18a** and **18b** obtained with **16**, and **18c** obtained with **17** in the presence of catalyst **2**.

selectivity for this cycloaddition has not been reported previously. With increasing π acidity from **2** to **3**, these unique *endo/exo* ratios increased from 2.0:1 to 2.5:1 *dr* (Table 2, entry 7, 8). The strongest π acid **4** was however inefficient, probably due to instability over the very long reaction times (10 days, Table 2, entry 9). With *cis* dienophile **18**, the reaction became even much slower, and neither Et₃N nor NDI catalysts were able to overcome the intrinsic *endo* specificity (Table 2, entries 12–14).

In summary, Diels-Alder reactions with oxazolones, thiazolones, hydroxypyrones and standard cyclic and acyclic dienophiles run on π acidic surfaces excel with high rates, chemo-, diastereo- and enantioselectivity. Consistent with anion- π catalysis of this grand old classic, activities and selectivities reliably increase with π acidity and vanish in the presence of nitrate and upon removal of the π surface. Highlights are the unprecedented inversion of *endo/exo* diastereoselectivity of the [4+2] cycloaddition of hydroxypyrones to fumarates without a trace of *syn* diastereomers (Figure 5; Table 2, entries 6–11) and the equally unprecedented *exo* specific [4+2] cycloaddition of thiazolones to maleimides without the otherwise dominant Michael addition product and up to 94% *ee* (Figures 2, 4; Table 1, entries 11–16). These results are special because they support, for the first time, one of the long-term expectations from anion- π catalysis, that is to provide access to reactivities that are beyond reach of conventional catalysts.

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Keywords: Anion- π interactions – catalysis – Diels-Alder reactions – chemoselectivity – stereoselectivity

- [1] (a) A. Frontera, P. Gamez, M. Mascal, T. J. Mooibroek, J. Reedijk, *Angew. Chem. Int. Ed.* **2011**, *50*, 9564–9583; *Angew. Chem.* **2011**, *123*, 9736–9756; (b) M. Giese, M. Albrecht, K. Rissanen, *Chem. Commun.* **2016**, *52*, 1778–1795; (c) D.-X. Wang, M.-X. Wang, *Chimia* **2011**, *65*, 939–943; (d) K. Hiraoka, S. Mizuse, S. Yamabe, *J. Chem. Phys.* **1987**, *86*, 4102–4105; (e) Z. Yu, A. Erbas, F. Tantakitti, L. C. Palmer, J. A. Jackman, M. Olvera de la Cruz, N.-J. Cho, S. I. Stupp, *J. Am. Chem. Soc.* **2017**, *139*, 7823–7830; (f) G. Bélanger-Chabot, A. Ali, F. P. Gabbaï, *Angew. Chem. Ed. Engl.* **2017**, *56*, 9958–9961; *Angew. Chem.* **2017**, *129*, 10090–10093.
- [2] Y. Zhao, Y. Domoto, E. Orentas, C. Beuchat, D. Emery, J. Mareda, N. Sakai, S. Matile, *Angew. Chem. Int. Ed.* **2013**, *52*, 9940–9943; *Angew. Chem.* **2013**, *125*, 10124–10127.
- [3] L. Liu, Y. Cotelle, J. Klehr, N. Sakai, T. R. Ward, S. Matile, *Chem. Sci.* **2017**, *8*, 3770–3774.
- [4] Y. Cotelle, V. Lebrun, N. Sakai, T. R. Ward, S. Matile, *ACS Cent. Sci.* **2016**, *2*, 388–393.
- [5] M. Akamatsu, N. Sakai, S. Matile, *J. Am. Chem. Soc.* **2017**, *139*, 6558–6561.
- [6] E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667; *Angew. Chem.* **2002**, *114*, 1724–1741.
- [7] J. Shen, C.-H. Tan, *Org. Biomol. Chem.* **2007**, *6*, 3229–3236.
- [8] S. Qiu, R. Lee, B. Zhu, M.-L. Coote, X. Zhao, Z. Jiang, *J. Org. Chem.* **2016**, *81*, 8061–8069.
- [9] B. Zhu, R. Lee, J. Li, X. Ye, S.-N. Hong, S. Qiu, M.-L. Coote, Z. Jiang, *Angew. Chem. Int. Ed.* **2016**, *55*, 1299–1303; *Angew. Chem.* **2016**, *128*, 1321–1325.
- [10] (a) B. Zhu, S. Qiu, J. Li, M. L. Coote, R. Lee, Z. Jiang, *Chem. Sci.* **2016**, *7*, 6060–6067; (b) S. Qiu, C.-H. Tan, Z. Jiang, *Beilstein J. Org. Chem.* **2016**, *12*, 2293–2297.
- [11] (a) B. Chatelet, V. Dufaud, J. P. Dutasta, A. Martinez, *J. Org. Chem.* **2014**, *79*, 8684–8688; (b) H. Okamura, H. Shimizu, Y. Nakamura, T. Iwagawa, M. Nakatani, *Tetrahedron Lett.* **2000**, *41*, 4147–4150.
- [12] (a) T. Suzuki, S. Watanabe, S. Kobayashi, K. Tanino, *Org. Lett.* **2017**, *19*, 922–925; (b) M.-Q. Zhou, J.-Q. Zhao, Y. You, X.-Y. Xu, X.-M. Zhang, W.-C. Yuan, *Tetrahedron* **2015**, *71*, 3903–3908; (c) P. Zhao, C. M. Beaudry, *Angew. Chem. Int. Ed.* **2014**, *53*, 10500–10503; *Angew. Chem.* **2014**, *126*, 10668–10671; (d) K. J. Bartelson, R. P. Singh, B. M. Foxman, L. Deng, *Chem. Sci.* **2011**, *2*, 1940–1944.
- [13] R. Hoffman, R. B. Woodward, *J. Am. Chem. Soc.* **1965**, *87*, 4388–4389.
- [14] A. Heine, E. A. Stura, J. T. Yli-Kauhaluoma, C. Gao, Q. Deng, B. R. Beno, K. N. Houk, K. D. Janda, A. I. Wilson, *Science* **1998**, *279*, 1934–1940.
- [15] (a) T. Murase, S. Horiuchi, M. Fujita, *J. Am. Chem. Soc.* **2010**, *132*, 2866–2867; (b) C. J. Waiter, H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.* **1993**, 458–460.
- [16] (a) B.-S. Jeon, S.-A. Wang, M. W. Ruzsyczky, H.-W. Liu, *Chem. Rev.* **2017**, *117*, 5367–5388; (b) A. C. Aragonès, N. L. Haworth, N. Darwish, S. Ciampi, N. J. Bloomfield, G. G. Wallace, I. Diez-Perez, M. L. Coote, *Nature* **2016**, *531*, 88–91; (c) M. Chandra, S. K. Silverman, *J. Am. Chem. Soc.* **2008**, *130*, 2936–2937; (d) J. Kang, J. Rebek, *Nature* **1997**, *385*, 50–52; (e) R. Breslow, T. Guo, *J. Am. Chem. Soc.* **1988**, *110*, 5613–5617.
- [17] (a) J. Li, S. Qiu, X. Ye, B. Zhu, H. Liu, Z. Jiang, *J. Org. Chem.* **2016**, *81*, 11916–11923; (b) S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. Lopez, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851; *Angew. Chem.* **2013**, *125*, 12062–12067.

