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Breaking Symmetry with Symmetry: Bifacial Selectivity in the Asymmetric Cycloaddition of Anthracene Derivatives

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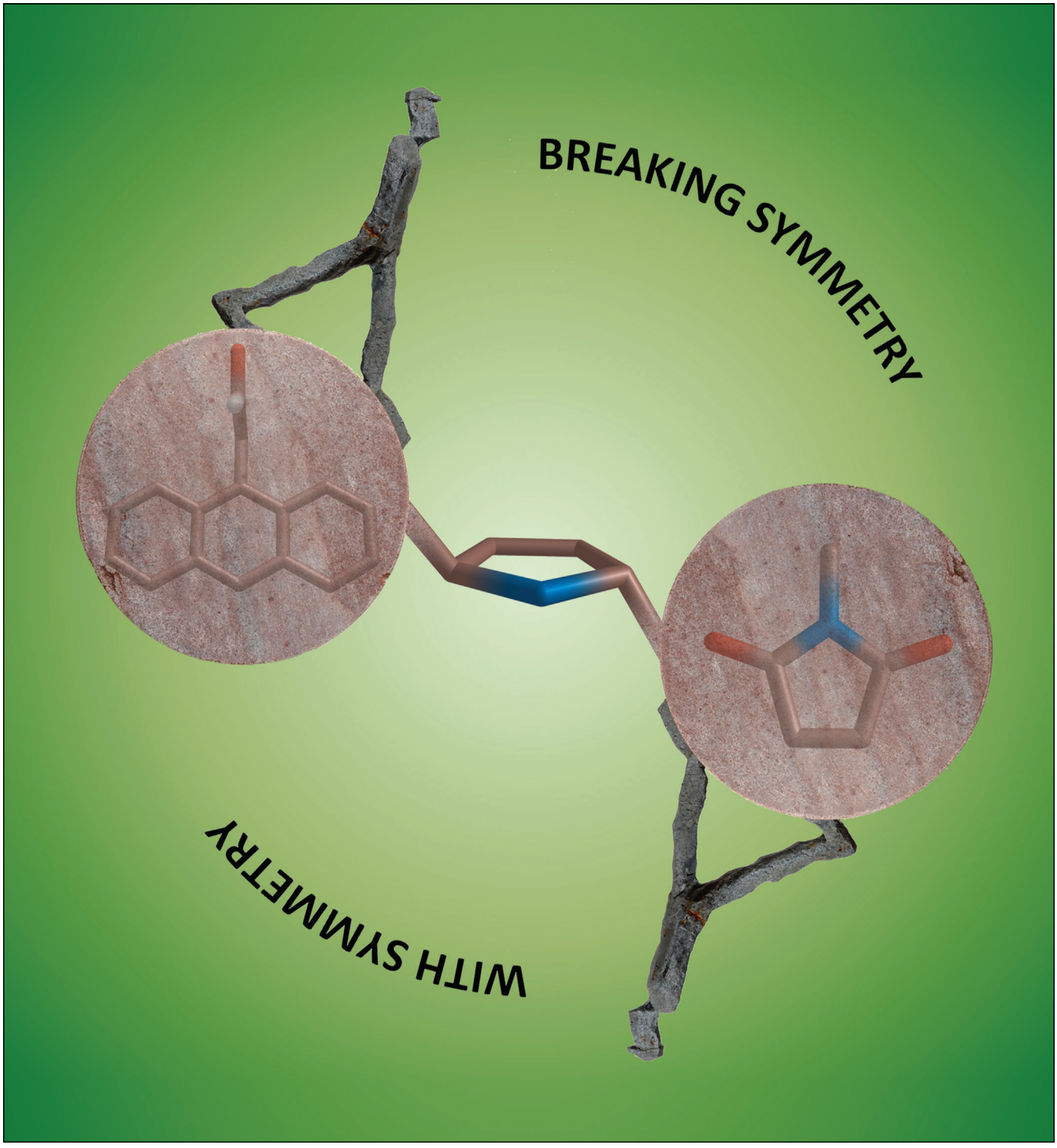
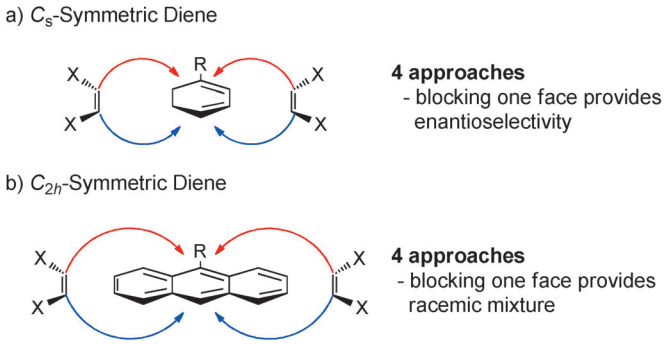


The selectivities in Diels–Alder reactions are determined by a set of well-understood orbital interactions, which account for the experimentally observed regioselectivity and *endo*/*exo* selectivity in these cycloadditions.[1] By combining the governing interactions with a chiral catalyst, high enantioselectivity can be achieved.[2] However, when employing symmetrical dienes and dienophiles, the enantioselectivity in Diels–Alder reactions is difficult to control (Scheme 1a). In order to achieve good enantioselectivity, the chiral catalyst must be able to direct the approach of the dienophile. This challenge is exemplified in the Diels–Alder reactions of anthracene derivatives,[3,4] in which the dienophile has to discriminate between two approaches on each face of the anthracene ring[5] (Scheme 1b). Previously, we have described a method in which a hydrogen-bond-donating secondary-amine catalyst can direct the approach of the hydrogen-bond-accepting dienophile to one face of the anthracene.[6] However, with this approach, good enantioselectivities were limited to systems in which both the diene and the dienophile are activated by the catalyst.



Scheme 1. Stereoselectivities in Diels–Alder reactions of C_s-symmetric dienes and C_{2h}-symmetric dienes (anthracenes).

The intermediate of 2-(anthracen-9-yl)acetaldehyde and a nonsymmetric aminocatalyst is shown in Figure 1a. For such an intermediate, three different approaches of the symmetric maleimide to the diene in the central ring of the anthracene moiety are possible. However, this is expected to result in low enantioselectivity. We envisioned a C_2-symmetric catalyst that would take advantage of the symmetry of the anthracene ring system by directing the approach of the dienophile on both faces, giving rise to the same enantiomeric product (Figure 1b). The symmetry of such a catalyst should provide the chirality necessary to obtain the product in high enantioselectivity.

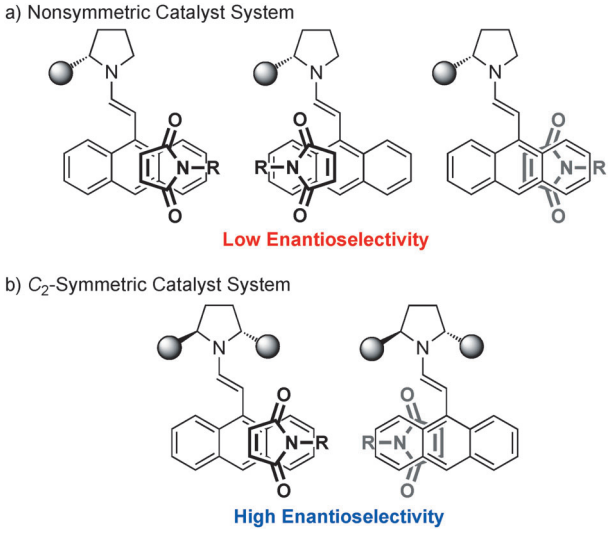


Figure 1. Rationalization of the superiority of a C_2-symmetric catalyst.

Initial development of this method was accomplished with a combination of synthesis and DFT calculations. It was observed that the C_2-symmetric catalyst (2*R*,5*R*)-2,5-diphenylpyrrolidine (**3a**) could catalyze the reaction between 2-(anthracen-9-yl)acetaldehyde (**1a**) and *N*-methylmaleimide to give the desired Diels–Alder product in 85% yield and 75% *ee* at room temperature.

DFT calculations were used to rationalize the stereocontrol provided by C_2-symmetric catalyst **3a** with **1a**.[7] All structures were optimized at the wB97xd/6-31G(d) level and activation energies were obtained with wB97xd/6-311+G(2df,2p) single points in chloroform.[8,9] Solvent effects were estimated with the integral equation formalism polarizable continuum model (IEFPCM).[10] Frequency calculations were performed for all stationary points to identify them as local minima or first-order saddle points and to obtain the zero-point energies (ZPEs) and thermochemical corrections for the free energies. All of the reported values are free energies at 298 K.

To understand the selectivity of this enantioselective reaction, we examined the cycloaddition of the reactive intermediate with *N*-methylmaleimide approaching from both the left and the right. Calculations suggest that both reaction pathways are concerted and highly exothermic.[11] Examination of the transition-state structures for both approaches of the *N*-methylmaleimide shows a clear energetic preference for one approach over the other (Figure 2). To our surprise, the selectivity of this system does not appear to be based on steric shielding of one side of the anthracene, as the phenyl rings are almost perpendicular to the anthracene ring system, allowing them to take advantage of T-shaped, π-stacking interactions. The selectivity appears to be largely the result of distortions in the C1-C2-C3-C4 dihedral angle (Figure 2, top). In **TS-A**, steric repulsion between the ap-

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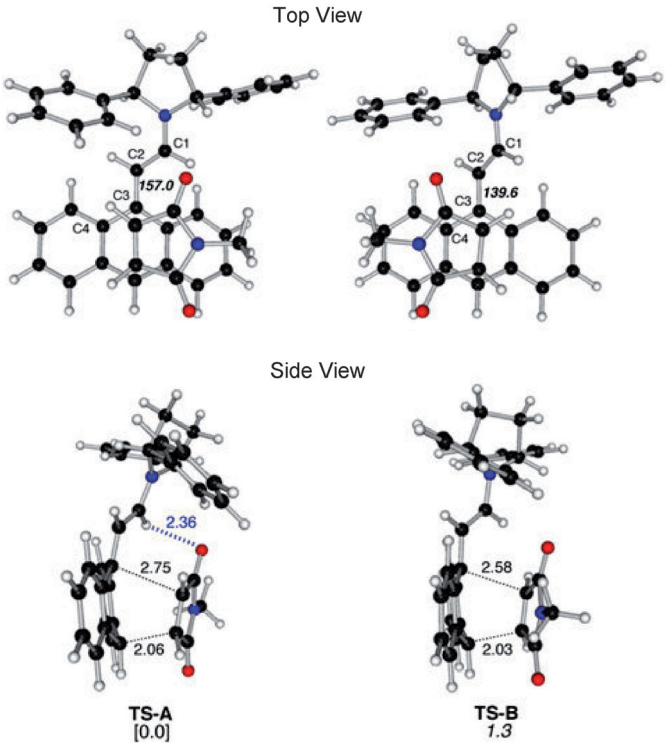
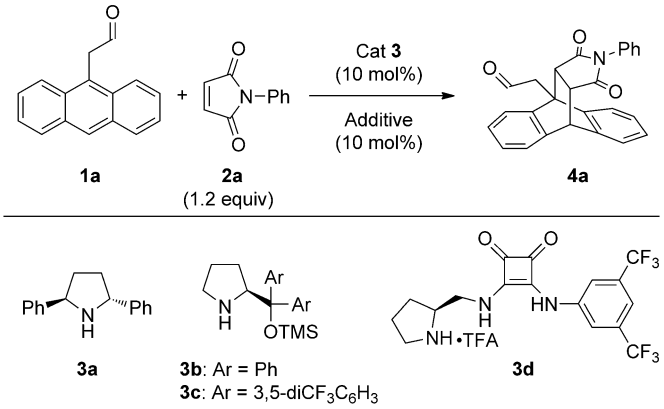


Figure 2. Transition-state structures for both approaches of the *N*-methylmaleimide. Activation energies are Gibbs free energies from wB97xd/6-311+G(2df,2p)//wB97xd/6-31G(d) single points in chloroform. Bond lengths are in [Å]. Dihedral angles [°] are reported in bold and italics.

Table 1. Optimization of the reaction conditions.[a]



	Cat	Solvent	Additive[b]	T [°C]	t [h][c]	*ee* [%][d]
1	**3a**	$CHCl_3$	BA	RT	1	86
2	**3b**	$CHCl_3$	BA	RT	0.5	77
3	**3c**	$CHCl_3$	BA	RT	6	14
4	**3d**	$CHCl_3$	DEA[e]	RT	10	34
5	**3a**	CH_2Cl_2	BA	RT	2	77
6	**3a**	PhMe	BA	RT	2	81
7	**3a**	EtOH	BA	RT	5	74
8	**3a**	$CHCl_3$	BA	−30	24	92

[a] Reactions carried out on a 0.1 mmol scale. [b] DEA = *N*,*N*-diethylacetamide; BA = benzoic acid. [c] Indicates the approximate time to full conversion. [d] Determined by chiral ultraperformance convergence chromatography (UPC²). [e] 1.0 Equivalent of additive employed.

proaching maleimide and the enamine subunit pushes the enamine into conjugation with the anthracene subunit, resulting in increased HOMO activation of the diene fragment in the anthracene system.[12] It should also be noted that in **TS-A** the carbonyl oxygen atom of the maleimide is able to form a favorable C–H···O interaction with the hydrogen atom of the enamine, further contributing to the energetic preference for this approach. In **TS-B**, steric repulsion between the maleimide and the phenyl ring of the catalyst forces the latter to rotate, pushing the enamine out of conjugation with the anthracene subunit. The gain and loss of conjugation in the two transition-state structures leads to an energy difference of 1.3 kcal mol^{-1}. This difference in energy is in good agreement with the initial experimentally observed enantioselectivity.

Based on the initial synthetic and computational results, the cycloaddition of 2-(anthracen-9-yl)acetaldehyde (**1a**) and *N*-phenylmaleimide (**2a**) was investigated. The C_2-symmetric catalyst **3a** provided the Diels–Alder product **4a** in 86% *ee* (Table 1, entry 1). To ensure that the C_2-symmetry of the catalyst was important for the selectivity of the reaction, the nonsymmetric aminocatalysts **3b** and **c** and the dual activation catalyst **3d**[13] were tested in this reaction. In all of these cases, lower selectivities were observed (Table 1, entries 2–4). Further screening showed that $CHCl_3$ proved superior to other solvents both in terms of reaction rate and enantioselectivity (Table 1, entries 1,5–7). Several other additives (or absence thereof) were screened, but none of these provided an improvement of the results obtained compared to benzoic acid. It should also be noted that the reaction rates were unusually high for an organocatalytic process. Therefore, to achieve the best selectivities without compromising the reactivity, temperature is a crucial factor. Gratifyingly, conducting the reaction at −30°C, full conversion was achieved within 24 h to furnish **4a** in 92% *ee*.

Once the reaction conditions had been optimized, we decided to test the generality of the system. A series of aromatic maleimides were found to undergo [4+2] cycloaddition to furnish cycloadducts **4a**–**e** (Table 2). Remarkably, the reaction worked with electron-poor, heteroaromatic, polycyclic, and electron-rich maleimides with excellent yields and enantioselectivities. Moreover, the absolute configuration of **4b** could be unambiguously determined by single-crystal X-ray diffraction[14] (Figure 3). The remaining products were assigned by analogy. Non-aromatic maleimides also reacted smoothly: for example, methoxycarbonyl male-

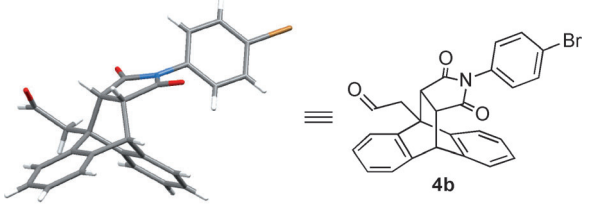
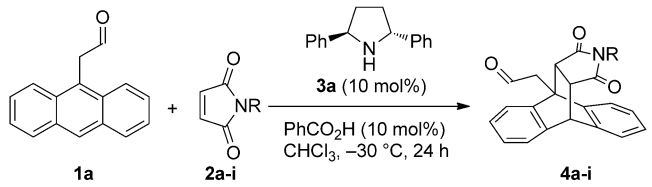
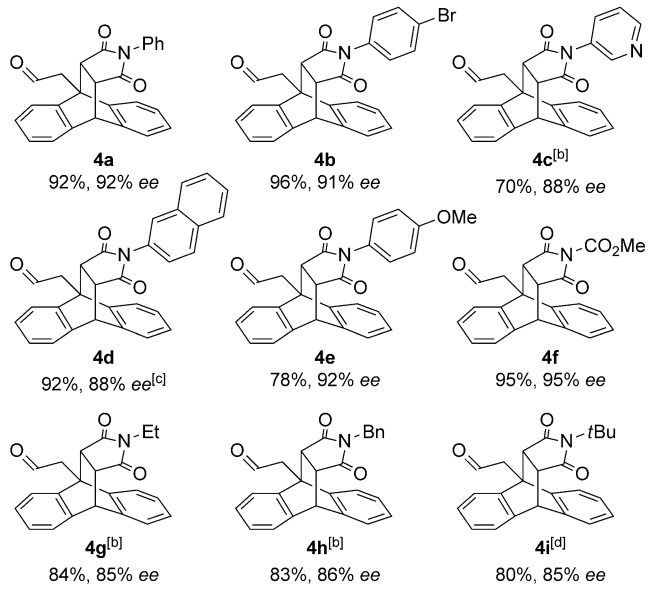


Figure 3. X-ray structure of **4b**.

Table 2. Dienophile scope.[a]



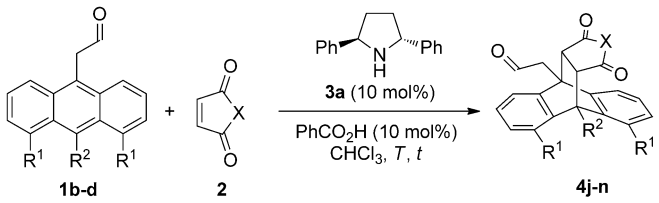


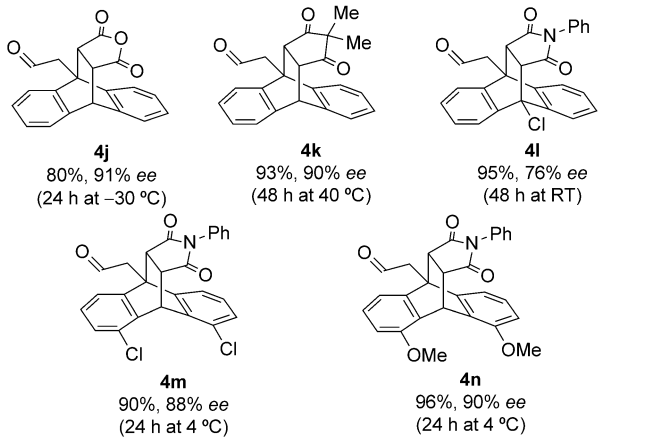
[a] All reactions were carried out at a 0.2 mmol scale in 1 mL of $CHCl_3$. [b] Reaction carried out at −30 °C for 40 h. [c] Determined after reduction to the alcohol. [d] Reaction carried out at RT for 40 h.

imide **2f** gave the desired cycloadduct **4f** in 95% yield and 95% *ee*. As for the *N*-alkyl maleimides, the reactions were somewhat slower and the stereoselectivities decreased slightly, although the enantioselectivities were always ≥85% *ee*. It is worth emphasizing that, even though the aminocatalytic α-addition of aldehydes to maleimides via an enamine has been described,[15] no such products were observed in the course of our study.

To our delight, the scope was not limited to maleimides (Table 3). While noncyclic dienophiles (*cis* or *trans*) proved unreactive, maleic anhydride also participated in the reaction and the corresponding cycloadduct **4j** was isolated in 80% yield and 91% *ee*. As for the cyclopentenedione, it required mild heating and longer reaction times to drive the reaction to completion (40 °C for 2 d), but cycloadduct **4k** was obtained in 93% yield and 90% *ee*. With the dienophile scope established, we turned our attention to the anthracene derivative. The introduction of an electron-withdrawing group in the 10-position entailed a loss in reactivity. The reaction could be driven to completion after 48 h at room temperature, but the stereoselectivity in **4l** dropped to 76% *ee*. However, when these substituents were located on the outer rings, the Diels–Alder cycloaddition products **4m** and **n** were obtained in 90–96% yield and 88–90% *ee*.

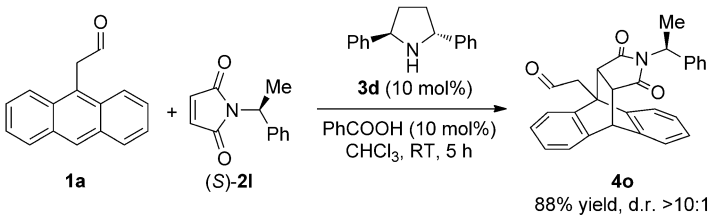
Table 3. Scope of the anthracene derivative.[a]





[a] All reactions were carried out at a 0.2 mmol scale in 1 mL of $CHCl_3$.

In an attempt to study the influence of the catalyst on the overall process, we decided to test a case of double stereoselection. Thus, we were pleased to observe that **3a** was able to promote the reaction between the enantiopure maleimide **2l** and **1a** in a highly diastereoselective fashion (d.r. > 10:1, Scheme 2). In contrast, the reaction in the presence of *ent*-**3a** is sluggish, indicating a mismatched case. However, a competition experiment using **3a** and two equivalents of (±)-**2l** indicated only a slight preference for the **2l** over its enantiomer, resulting in a 2:1 diasteromeric mixture of the cycloadduct **4o**.



Scheme 2. Double stereoselective reaction: matched case.

In summary, a new catalytic strategy for the activation of anthracene derivatives has been successfully developed using a combination of synthetic and computational methods. Using a C_2-symmetric aminocatalyst **3a**, the cycloaddition reaction takes place with excellent yields and stereoselectivities. This selectivity was not the result of steric shielding, as originally envisioned, but was instead due to the gain or loss of conjugation between the enamine and the anthra-

cene in the two transition-state structures. The low temperatures required and high reactivity observed shows that aminocatalysis is an efficient strategy for aromatic activation and may expand the use of anthracene derivatives in enantioselective cycloaddition reactions.

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Keywords: anthracene activation · asymmetric catalysis · density functional calculations · Diels–Alder reaction · organocatalysis

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[14] CCDC-898222 (**4b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See Supporting Information for details.

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