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Organocatalytic Enantioselective Higher-Order Cycloadditions of In Situ Generated Amino Isobenzofulvenes

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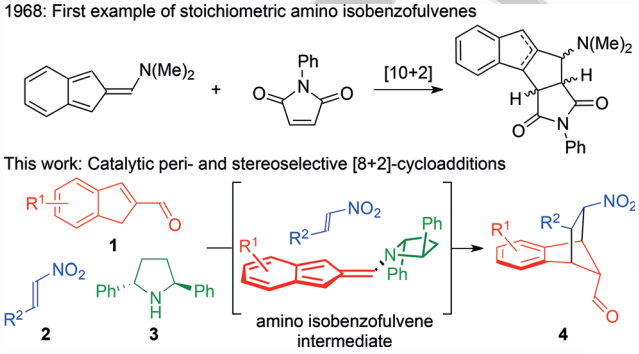
Abstract: *The [8+2] cycloaddition of indene-2-carbaldehydes and nitro olefins is described to provide benzonorbornene scaffolds in a highly peri-, diastereo-, and enantioselective fashion in the presence of a C_2-symmetric aminocatalyst. This reaction, which proceeds through a transient semi-aromatic amino isobenzofulvene, represents the first example of catalytic formation and transformation of these species. Quantum chemical calculations suggest a kinetically controlled stepwise mechanism where the stereochemistry is determined in the first bond-forming event. Beyond the useful [8+2] cycloadducts, [10+4] cycloadducts have been identified in silico as potential off-pathway intermediates.*

Higher-order cycloadditions involve more than 6π electrons and allow rapid construction of complex cyclic frameworks.[1] In these reactions, selectivity is often difficult to control owing to several competing pericyclic pathways, which has been a hindrance for their application in synthesis.[2] Aminocatalysis has recently been employed to circumvent the issue of periselectivity and promote the first enantioselective intermolecular higher-order cycloadditions.[3] Herein, the catalytic formation of amino isobenzofulvenes is described to facilitate highly stereoselective [8+2] cycloadditions[4] to afford enantioenriched benzo-norbornenes (Scheme 1). A DFT-based computational analysis accounts for the observed peri- and stereoselectivity through a stepwise [8+2] cycloaddition. An off-pathway [10+4] cycloadduct is energetically feasible and potentially in equilibrium with proposed zwitterionic structures leading to the [8+2] cycloaddition product.

In 1968, the first isobenzofulvenes were utilized in cycloadditions by Hafner and Bauer.[5] An amino substituent on the exocyclic carbon atom stabilized the isobenzofulvenes by increasing the aromatic character. The depicted amino isobenzofulvene was found to form a mixture of [10+2] cycloadducts with *N*-phenylmaleimide (Scheme 1). In the following years Warrener et al. explored the periselectivity of isobenzofulvenes and found them to react as both 8π- and 10π-electron components in [8+2], [8+6], and [10+8] cycloadditions.[6] This work represents, to the best of our knowledge, the first catalytic formation and application of 8π/10π-electron isobenzofulvene systems in cycloadditions.



Scheme 1. Cycloadditions of amino isobenzofulvenes.

Indene-2-carbaldehydes (**1**) were envisioned as precursors to activated amino isobenzofulvenes (Scheme 1). The high symmetry of both substrate and intermediate presented a challenge in relation to enantioselective catalysis. During catalyst screening and reaction optimization the C_2-symmetric 2,5-diphenylpyrrolidine[7] **3** was identified as the sole catalyst of those tested to provide acceptable conversion and enantioselectivity for the reaction with nitro olefins (**2**; see the Supporting Information). The attained benzonorbornenes **4** contain five contiguous stereocenters and the scaffold is of interest because of its presence in commercial pesticides and neurotransmitter analogues.[8]

Following optimization of the reaction conditions (see the Supporting Information), the catalyst **3** (20 mol%), in the presence of *p*-methyl-benzoic acid (20 mol%) in $CDCl_3$, facilitated the formation of the benzonorbornene **4a**■**4a** does not appear in the table. Please clarify.■ from the indene **1a** and nitrostyrene (**2a;** 2.0 equiv) in good yield and high enantioselectivity (Table 1, entry 1). For purification purposes, the alcohols **5** were isolated after one-pot reduction of the aldehyde [8+2]-adducts **4**. In all entries only one diastereoisomer was observed with small amounts (< 5%) of a Michael adduct (not shown).

Initially, the substrate scope with regards to nitro olefins was investigated. The nitrostyrenes **2b–g**, having *para* and *meta* substituents of various electronic natures, performed well in the catalytic system to afford their corresponding cycloadducts **5b–g** in decent to good yields and high enantioselectivities (Table 1, entries 2–7). However, the *ortho*-substituted **5h** was formed with low enantioselectivity while a decent yield was maintained (entry 8). The disubstituted nitrostyrene **2i** gave **5i** in a decent yield and high enantioselectivity (entry 9). Nitro olefins with heteroaromatic

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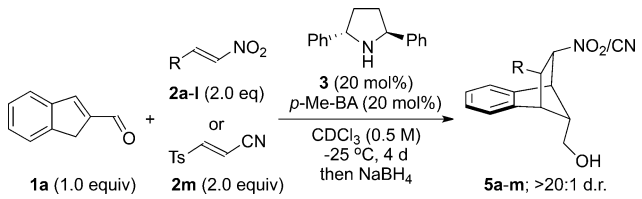
Table 1: Nitro olefin scope for [8+2]-cycloaddition.[a]



Entry	2	R	Yield [%]	*ee* [%]
1	**2a**	Ph	**5a** 73	91
2	**2b**	4-Me-C_6H_4	**5b** 74	91
3	**2c**	4-OMe-C_6H_4	**5c** 54	93
4	**2d**	4-F-C_6H_4	**5d** 64	92
5[b]	**2e**	4-Br-C_6H_4	**5e** 51	94
6	**2f**	4-NO_2-C_6H_4	**5f** 65	94
7	**2g**	3-OMe-C_6H_4	**5g** 59	90
8[c]	**2h**	2-Cl-C_6H_4	**5h** 54	22
9	**2i**	3,4-Cl_2-C_6H_3	**5i** 58	93
10[b]	**2j**	2-thiophenyl	**5j** 54	87
11[d]	**2k**	3-pyridyl	**5k** 61	98
12[d]	**2l**	*n*Bu	**5l** 20	96
13[e]	**2m**	Ts	**5m** 81	96

[a] All reactions carried out at 0.1 mmol scale (see the Supporting Information). Yields are those of the products isolated after reduction and FC■Please define.■. The *ee* value was determined by chiral-phase stationary phase UPC^2. [b] 5 d reaction time. [c] Reaction performed at 0 °C. [d] 6 d reaction time. [e] Benzoic acid (20 mol%) applied as additive. BA = benzoic acid, Ts = 4-toluenesulfonyl.

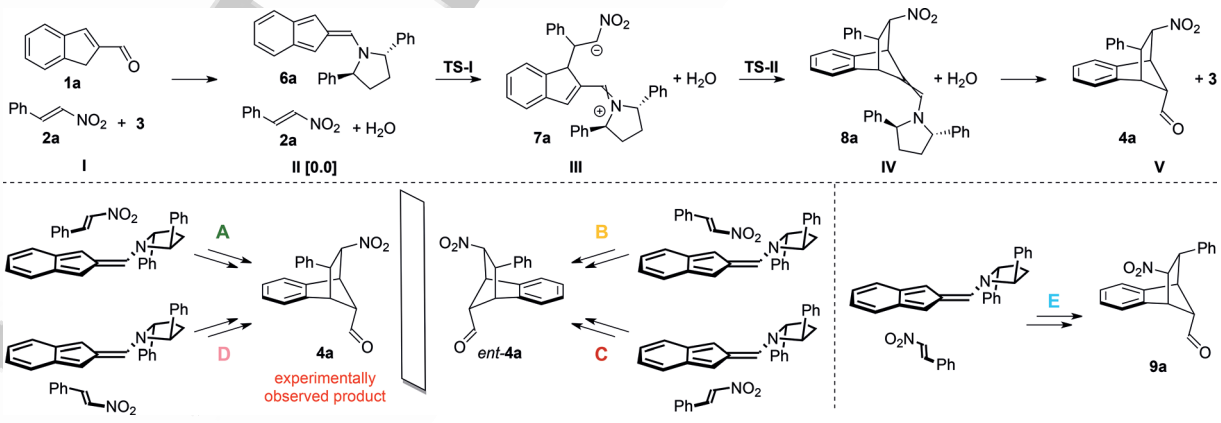
substituents performed well and delivered the products **5j**,**k** in good to excellent enantioselectivities (entries 10 and 11). An aliphatic substituent was found to lower the conversion and yield, which was not alleviated by raising the temperature, but the excellent enantioselectivity was maintained (entry 12). Finally, a 2π-electron component carrying both a nitrile and a tosyl group was found to readily participate in the [8+2] cycloaddition to afford **5m** in high yield and excellent enantioselectivity (entry 13). In contrast to the successful employment of the electron-poor olefin **2m**, related olefins afforded little or no product (see the Supporting Information). The results suggest that the olefin must be highly electron deficient and have limited steric demand to achieve the desired reactivity.

The high level of stereoselectivity achieved for the [8+2] cycloaddition employing the catalyst **3** is intriguing and a computational study to elucidate the mechanism and the origin of the selectivity was initiated.

Geometries and energies were calculated with *Gaussian09* using DFT [ωB97X-D/6–31 + G(d,p) SMD($CHCl_3$)].[9] All transition-state (TS) structures were connected to their respective minima by intrinsic reaction coordinate calculations.[10] Initially, the condensation product **6a**, derived from **3** and **1a** was located (Scheme 2 and Figure 1). It was hypothesized that this amino isobenzofulvene could display facial discrimination towards the approach of **2a**. Four approaches (A–D, Scheme 2) leading to the two enantiomers of the experimentally observed product **4a** were investigated along with the most reasonable approach in which the phenyl group of **2a** points towards the catalyst moiety (E), thus leading to an unobserved diastereoisomer.

For all approaches, the zwitterionic intermediate **7a** was found and no TS structures for concerted cycloaddition pathways were located, despite exhaustive searching. The formation of **6a** was found to be energetically unfavorable, and the barrier for reversible formation of **7a** was found to be 13.7–16.3 kcal mol^{-1}. Formation of the second C–C bond was found to be irreversible with lower barriers of 6.0–11.6 kcal mol^{-1} and affords **8a** with energies from −9.3 to −14.2 kcal mol^{-1} (reverse barriers of 24.1–28.9 kcal mol^{-1}). The enamine cycloadduct **8a** was calculated to be favored relative to **4a** by up to 4.9 kcal mol^{-1}. Based on these findings, both condensation and release of catalyst are thermodynamically disfavored, which may explain the relatively long reaction times necessary to achieve high conversion.

According to the computational results this reaction is under kinetic control and the lowest-energy approach for TS-I (A) leads to the major product enantiomer. It should be noted that while the lowest barrier is observed for A, the second lowest-energy approach (D) provides the same enantiomer of cycloadduct **4a**. The $\Delta\Delta G^{\ddagger} = 1.8$ kcal mol^{-1} preference for approach A over B (leading to the opposite enantiomer) is in line with the experimentally observed enantioselectivity of greater than 90% *ee*. The alternate approach E was found to have a higher barrier for TS-I (A vs. E; $\Delta\Delta G^{\ddagger} = 2.6$ kcal mol^{-1}), and is in accordance with the excellent level of diastereocontrol observed.



Scheme 2. Pathway and stereochemical approaches investigated computationally.

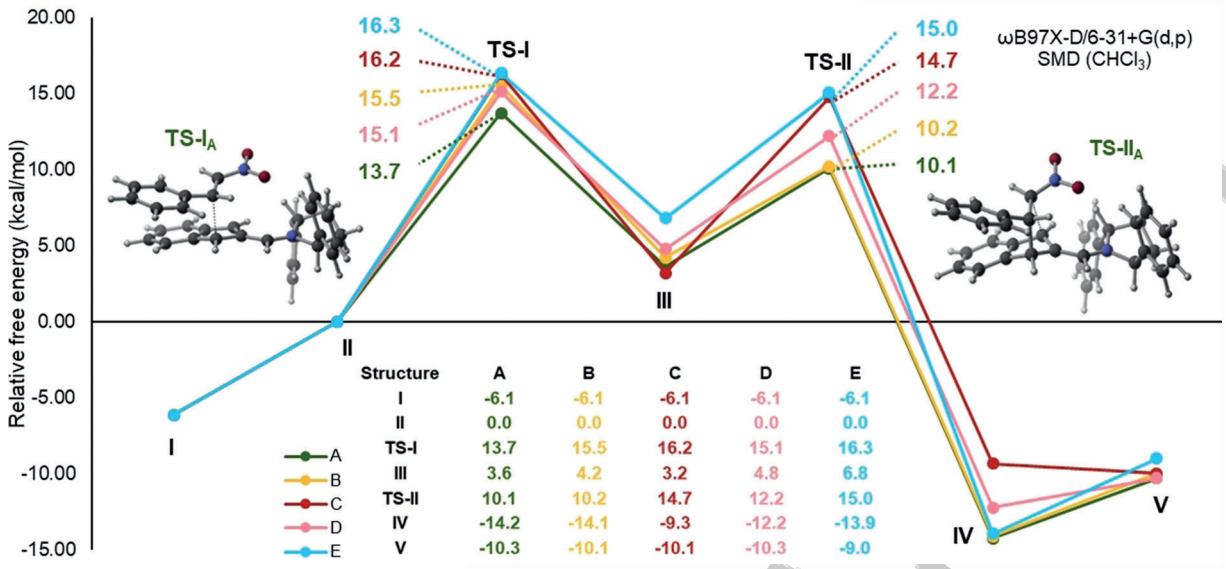


Figure 1. Relative free-energy profile and table of five approaches (A–E) for the stepwise cycloaddition of catalytically formed amino isobenzofulvene and nitrostyrene. The lowest-energy TS structures for the two C–C bond-forming steps are displayed (TS-I_A and TS-II_A).

For approaches A–D, electrostatic interactions in TS-I between an oxygen atom of the nitro group and C_{ipso} appear to be important. The O–C_{ipso} bond distance ranges from 2.73–3.01 Å, which indicates the possibility of a [10+4] cycloaddition pathway. Larger electron-withdrawing groups on the olefin may not be able to accommodate this interaction because of steric clash with the phenyl groups of the catalyst. This arrangement is in accordance with experimental results in which only nitro and cyano groups were tolerated. The electrostatic interaction is not viable for the alternate approach E, and may explain the higher predicted energy.

Single-point (SP) energies computed with a dispersion corrected functional (M06-2X/6–31 + G(d,p))[11] were in agreement with the free-energy data, while SP energies computed using functionals known to poorly treat dispersion forces (B3LYP, MPW1PW91/6–31 + G(d,p))[12] were in disagreement with the presented computed pathway (see the Supporting Information).[13] This finding suggests that dispersion forces play a significant role in governing the observed selectivity, and is in line with the account from Houk and Krenske stating that computational handling of aromatic interactions as stereocontrol elements requires effective treatment of dispersion forces.[14] SP calculations using the 6–311 + + G(2d,2p) basis set show an improved qualitative correlation, for B3LYP and MPW1PW91, to experimental data. TS-I_A was consistently predicted to be the lowest-energy structure, however, the predicted enantioselectivity does not correlate quantitatively to experimental data. Of particular note, is that B3LYP and MPW1PW91 now predict TS-I_D (which leads to the experimentally observed enantiomer and is the second lowest-energy structure in the free-energy calculations) to be the highest-energy TS.

The theoretically predicted absolute configuration of **4** was confirmed by X-ray crystallographic analysis of the TFA salt of an amine functionalized cycloadduct **4e** (see the Supporting Information).

The effect of substituents on the indene **1** was probed for a series of analogues (**1b–f;** Table 2). The 4,7-disubstituted substrate **1b** delivered the cycloadduct **5n** in decent yield and excellent diastereo- and enantioselectivity. Application of the 5-methoxy indene **1c** gave a mixture of **5o**/**5o′** in an acceptable yield with a good enantioselectivity for the major diastereomer **5o** and excellent enantioselectivity for the minor diastereomer **5o′**. The 6-methoxy indene **1d** provided the same major diastereomer **5o** in excellent diastereoselectivity and high enantioselectivity, while lower enantioselectivity was observed for the minor diastereomer **5o′**. The 5- and 6-chloro-substituted (**1e**,**f**) indenes displayed the same trend with regards to diastereo- and enantioselectivity.

The difference in enantioselectivity, depending on the substituent position in the substrates (**1c** vs. **1d** and **1e** vs. **1f**), points to the formation of two discrete amino isobenzofulvene intermediates. Under the assumption that the configuration of the exocyclic bond is retained during catalyst condensation, **1c** and **1d** would form the intermediates **6c** and **6d**, respectively (Scheme 3). Reaction of **6c** through TS-I_A/TS-I_C is expected to lead to the observed major diastereomer **4o**, while the same product from **6d** would be formed via TS-I_B/TS-I_D.

If the donating effect of the methoxy substituents is added to the calculated preference for TS-I_A in the unsubstituted system, a high diastereoselectivity would be expected for the reaction with **1c** compared to that with **1d**. However, the opposite is experimentally observed with low diastereoselectivity for **1c** and high diastereoselectivity for **1d**. This outcome is in line with an inherent preference for TS-I_D, which is negated for the intermediate **6c** and enhanced for the intermediate **6d** because of substituent positions (see the Supporting Information for schematic representations of mechanistic considerations).

To investigate the observed selectivity with substituted indenes, the computational approach which successfully

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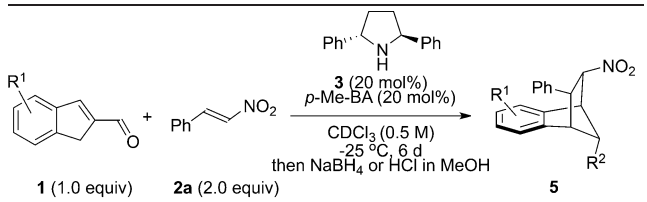
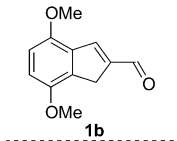
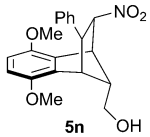
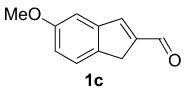
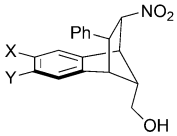
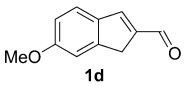
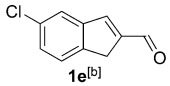
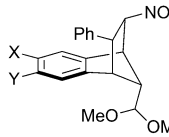
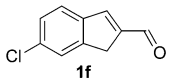
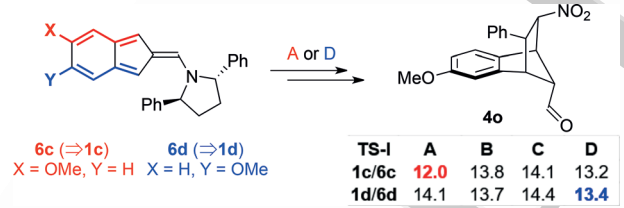
Table 2: Scope with respect to the substituted indenes **1b–f**.[a]



Substrates	Products	5/5'	Yield [%]	*ee* [%] (5/5')
 **1b**	 **5n**	-	52	95
 **1c**	 **5o**; X = H, Y = OMe **5o'**; X = OMe, Y = H	1.8:1 (2.4:1)	51	76/96
 **1d**		20:1 (>20:1)	54	94/85
 **1e**[b]	 **5p**; X = H, Y = Cl **5p'**; X = Cl, Y = H	1.3:1 (1.5:1)	62	71/n.d.[c]
 **1f**		10:1 (10:1)	47	95/n.d.[c]

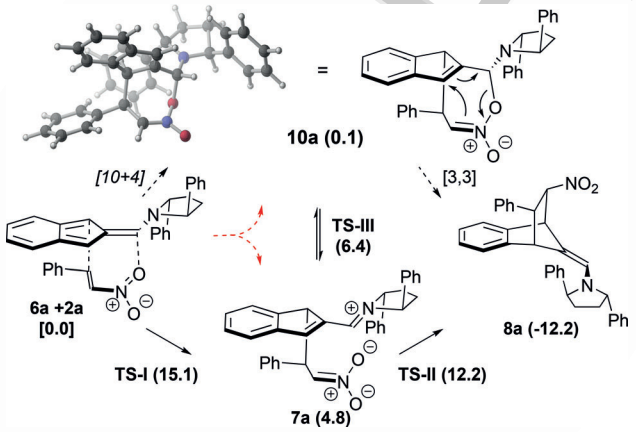
[a] Reactions performed at 0.1 mmol scale (see the Supporting Information). Yields are those of the products isolated after one-pot functionalization and FC■Please define.■. The d.r. values of the crude reaction mixture and isolated product (within parenthesis) determined by NMR spectroscopy. The *ee* value was determined by chiral-phase stationary phase UPC^2. [b] Reaction performed at 0 °C. [c] The *ee* value was determined for products obtained after hydrolysis and reduction to the corresponding alcohol.



Scheme 3. Energy profile for substituted amino isobenzofulvenes (TS-I). Relative free-energies in kcal mol^{-1} (ωB97X-D/6–31+G(d,p) SMD ($CHCl_3$)).

described the unsubstituted system was applied (Scheme 3). The results supported our expectations in that TS-I_A is favored for **1c** and TS-I_D is favored (by a small margin) for **1d**. This data qualitatively explains the formation of **4o** as the major stereoisomer for both substrates, though the relative level of diastereoselectivity is not accounted for.

While studying these electronically enriched systems in an attempt to explain this mismatch in diastereoselectivity, an interesting observation was made. Optimization of the zwitterionic intermediate from **6c** via TS-I_D yielded the oxazepine-*N*-oxide [10+4] cycloadduct **10c**■No structure for **10c** is shown; please provide IUPAC name.■. Analogous oxazine-*N*-oxides have been observed as catalyst resting states in enamine-catalyzed Michael additions of aldehydes to nitro olefins.[15] Based on this precedence, the potential intermediate was optimized for all relevant approaches and the indenes **1a**,**c**,**d** (Scheme 4 and the Supporting Information).



Scheme 4. Off-pathway [10+4] intermediate. Relative free-energies in kcal mol^{-1} for pathway D from **6a** (ωB97X-D/6–31+G(d,p) SMD ($CHCl_3$)). Potential post-TS bifurcation depicted with red reaction arrows.

The [10+4]-cycloadducts **10** were found to be 4.6–5.1 kcal mol^{-1} lower in energy than the zwitterionic intermediates **7** for reaction path D in the three systems. Moreover, the [10+4]-adducts **10** from pathway D are 3.5–4.6 kcal mol^{-1} lower in energy than the corresponding adducts **10** from path A. This difference could hint at a preference for pathway D. No concerted TS structures connecting the isobenzofulvenes **6** directly to **10** were found and could be relevant to the discrepancy in diastereoselectivity between experiment and theory. However, TS structures (TS-III, Scheme 4) connecting **7** to **10** have been located (pathways A and D). These barriers range from 0.3–3.8 kcal mol^{-1}, thus making **10** the kinetically preferred cyclization ■product■. This data suggests that these two intermediates are at the very least in equilibrium in the reaction mixture. It is possible that a single TS connects **6** and **7**, as well as **10**, via a post-TS bifurcation. The occurrence of post-TS bifurcations in higher-order cycloadditions of a pentafulvene with tropone, and nitrostyrene with cyclopentadiene, have been documented previously by Houk et al.[16] Furthermore, it was found that polarizing Lewis acid catalysts altered the potential energy surface to favor the product resulting from nitrostyrene acting as a 4π component.[16b] Analogously, the presence of the methoxy substituents in **6c**,**d**, which polarizes all structures involved in the proposed pathways, may promote **2a** to act as a 4π component. It should be stressed that while this polarizing effect of substituents could change the preferential pathway (A vs. D) and explain the observed selectivity, current experiments and calculations are inconclusive. Computationally demanding molecular dynamics studies, which could probe the possibility of a post-TS bifurcation and its potential effects on the product distribution, are beyond the

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scope of this communication. Finally, the proposed cycloadducts **10** appear to be structurally preorganized to undergo a [3,3] sigmatropic rearrangement, thus leading to the thermodynamically favored [8+2] cycloadducts **8**. The search for TS structures connecting **10** to **8** directly has not proven fruitful.

In conclusion, a highly stereoselective [8+2] cycloaddition between catalytically generated amino isobenzofulvenes and nitro olefins has been developed. DFT calculations suggest that the higher-order cycloaddition proceeds by a stepwise pathway in which the stereoselectivity is governed by the kinetics of the first step. In select cases, oxazepine-*N*-oxide [10+4] cycloadducts have been calculated to be the kinetically favored intermediates in equilibrium with the zwitterionic species from which the thermodynamically preferred benzonorbornene [8+2] cycloadducts are formed. Future studies will aim to develop asymmetric [10+4] cycloaddition reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cycloaddition · enantioselectivity · fulvenes · organocatalysis · reaction mechanisms

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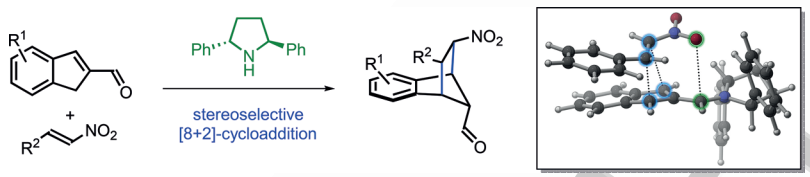
Communications

Organocatalysis

B. S. Donslund, A. Monleón, T. A. Palazzo, M. L. Christensen, A. Dahlgaard, J. D. Erickson, K. A. Jørgensen* ———— ▮▮▮▮–▮▮▮▮

Organocatalytic Enantioselective Higher-Order Cycloadditions of In Situ Generated Amino Isobenzofulvenes

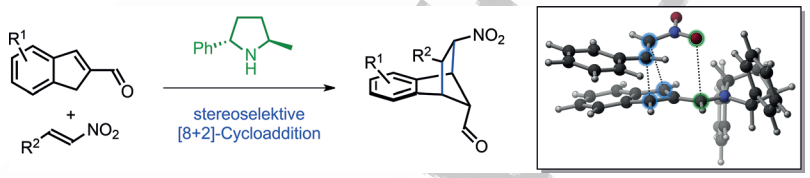


After a fashion: Experimental and computational studies detail the catalytic formation and transformation of transient amino isobenzofulvenes by stereoselective [8+2] cycloaddition reactions with electron-deficient olefins. Benzonorbornene scaffolds are obtained in a highly peri-, diastereo-, and enantioselective fashion in the presence of a C_2-symmetric aminocatalyst.

Organokatalyse

B. S. Donslund, A. Monleón, T. A. Palazzo, M. L. Christensen, A. Dahlgaard, J. D. Erickson, K. A. Jørgensen* ———— ▮▮▮▮–▮▮▮▮

Organocatalytic Enantioselective Higher-Order Cycloadditions of In Situ Generated Amino Isobenzofulvenes



Experimente und Rechnungen bestätigen die katalytische Bildung und Umwandlung transienter Aminoisobenzofulvene durch stereoselektive [8+2]-Cycloadditionen mit elektronenarmen Olefinen. Bei Verwendung eines C_2-symmetrischen Aminkatalysators werden Benzonorbornen-Gerüste hoch peri-, diastereo- und enantioselektiv aufgebaut.

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