A Journal of the Gesellschaft Deutscher Chemiker

Angewandte

GDCh

International Edition

Chemie

www.angewandte.org

Accepted Article

Title: Catalytic Enantioselective [10+4]-Cycloadditions

Authors: Karl Anker Jørgensen, Bjarke Donslund, Nicolaj Inunnguaq Jessen, Giulio Bertuzzi, Maxime Giardinetti, Teresa Ann Palazzo, and Mette Louise Christensen

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201807830
Angew. Chem. 10.1002/ange.201807830

Link to VoR: http://dx.doi.org/10.1002/anie.201807830
http://dx.doi.org/10.1002/ange.201807830

WILEY-VCH

10.1002/anie.201807830

WILEY-VCH

COMMUNICATION

Catalytic Enantioselective [10+4]-Cycloadditions

Bjarke S. Donslund, Nicolaj Inunnguaq Jessen, Giulio Bertuzzi, Maxime Giardinetti, Teresa A. Palazzo, Mette Louise Christensen and Karl Anker Jørgensen[a]*

Abstract: The first peri- and stereoselective [10+4]-cycloaddition between catalytically generated amino isobenzofulvenes and electron-deficient dienes is described. The highly stereoselective catalytic [10+4]-cycloaddition exhibits a broad scope with high yields reflecting a robust higher-order cycloaddition. Experimental and computational investigations support a kinetic distribution of intermediate rotamers dictating the enantioselectivity, which relies heavily on additive effects.

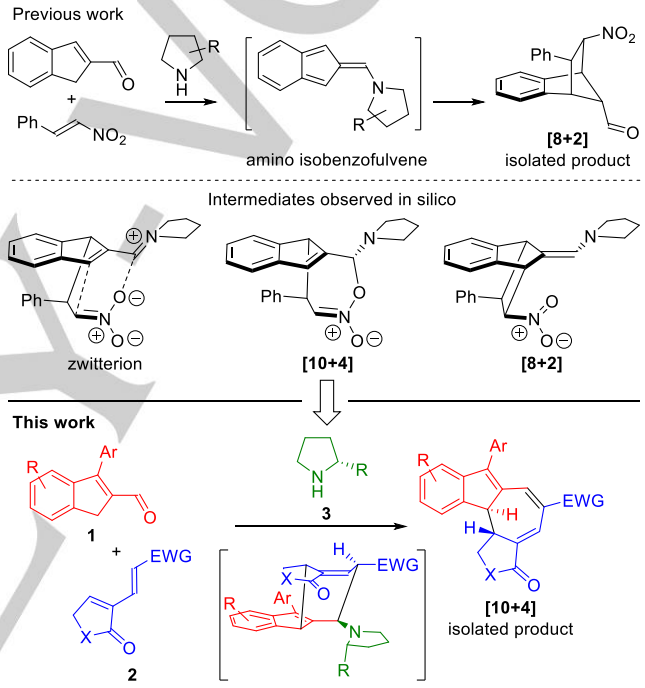
For concise and controlled construction of chiral cyclic structures, cycloadditions are recognized as highly valuable synthetic strategies. Diels-Alder reactions and dipolar cycloadditions, involving 6π-electrons, have been particularly useful and a multitude of enantioselective catalytic versions have been developed.[1] Higher-order cycloadditions are relatively underexplored although the potential for elegant construction of complex cyclic scaffolds has been demonstrated by the syntheses of *e.g.* capnellene and azulenes.[2] This is partially due to challenges regarding periselectivity and stereocontrol.[3] Intermolecular higher-order cycloadditions remained elusive in asymmetric catalysis until the first metal-catalyzed [8+2]-cycloaddition was reported in 2013.[4] The next development was organocatalyzed [6+4]- and [8+2]-cycloadditions disclosed in 2017.[5] Shortly after, organocatalyzed [6+2]- and [8+2]-cycloadditions were reported to provide cyclic scaffolds in high enantioselectivities.[6]

During the development of catalytic enantioselective [8+2]-cycloadditions through amino isobenzofulvenes with nitroolefins, computational investigations indicated the potential for a [10+4]-cycloadduct as the kinetically favored intermediate (Scheme 1, top).[6a] However, this proposed off-pathway species was not observed experimentally. Herein, the possibility to harness this reactivity and develop a catalytic enantioselective [10+4]-cycloaddition is investigated. To the best of our knowledge, [10+4]-cycloadditions have been reported in two instances in non-catalytic reactions employing dialkyl isobenzofulvenes without control of enantioselectivity.[7] Since only one example of an intermolecular [6+4]-cycloaddition has been achieved catalytically in high enantioselectivity with cyclopentenone and tropone,[4a] the development of a general procedure for a catalytic enantioselective [10+4]-cycloaddition would represent a significant step forward for controlling peri- and stereoselectivity of higher-order cycloadditions.

[a] Dr. B. S. Donslund, N. I. Jessen, G. Bertuzzi, Dr. M. Giardinetti, Dr. T. A. Palazzo, M. L. Christensen, Prof. Dr. Karl Anker Jørgensen
Department of Chemistry, Aarhus University.
Langelandsgade 140, 8000 Aarhus C (Denmark)
E-mail: kaj@chem.au.dk

Supporting information for this article is given via a link at the end of the document.

To achieve isolable [10+4]-cycloadducts and avoid catalyst trapping, an all-carbon 4π-component with judicious substitution to aid in both reactivity and eliminative catalyst release was envisioned. Electron-deficient dienes **2** were identified as promising candidates in early reactivity screenings (Scheme 1, bottom).[8]



Scheme 1. Peri- and stereoselective [8+2]- and [10+4]-cycloadditions.

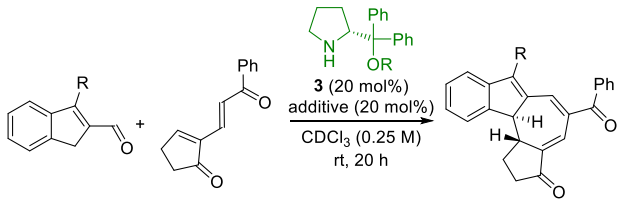
Initially, the reaction between 1*H*-indene-2-carbaldehyde **1a** and diene **2a** (1.5 eq) catalyzed by diphenylprolinol silyl ether **3a** (20 mol%) in $CDCl_3$ was investigated.[9] This afforded a complex product mixture containing mainly Michael adducts, traces of a presumed [8+2]-cycloadduct, an isolable amount of the desired [10+4]-cycloadduct **4a**, and a [10+4]-cycloadduct with a shifted indene double bond (Table 1, entry 1). Application of 3-phenyl substituted indene **1b** gave **4b** as a single diastereoisomer in higher yield and enantioselectivity with no significant formation of byproducts (entry 2). Addition of molecular sieves (MS) lowered the yield of **4b** while maintaining the enantioselectivity (entry 3). A bulkier diphenylprolinol silyl ether **3b** also facilitated the reaction, but with no major improvement in enantioselectivity (entries 4, 5). Curiously, reaction rate and enantioselectivity for the reaction with **3b** and MS was found to vary with solvent batch.

10.1002/anie.201807830

WILEY-VCH

COMMUNICATION

Table 1. Optimization of [10+4]-cycloaddition



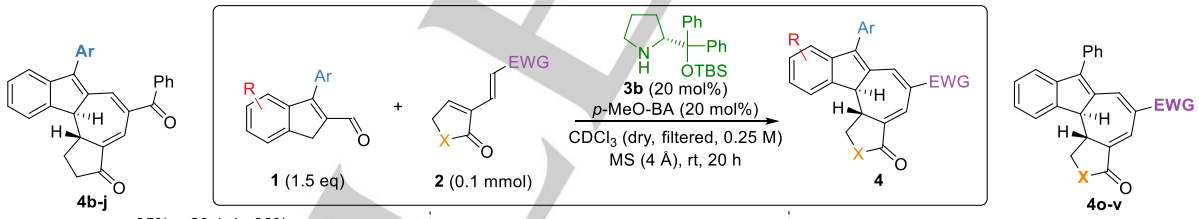
1a; R = H, **1b**; R = Ph (0.05 mmol) | **2a** (1.5 eq) | **3a**; R = TMS, **3b**; R = TBS | **4**

Entry	1	$CDCl_3$[a]	3	additive	yield (%)[b]	*ee* (%)[c]
1	**1a**	-	**3a**	-	<5	11
2	**1b**	-	**3a**	-	45	44
3	**1b**	MS	**3a**	-	36	45
4	**1b**	-	**3b**	-	17	51
5	**1b**	MS	**3b**	-	7	44
6	**1b**	MS, F	**3b**	-	<5	-
7	**1b**	MS, F	**3b**	*p*-MeO-BA	69	92
8	**1b**	MS, F	**3b**	*p*-MeO-BA	80	83
9	**1b**	MS, F	**3b**	*p*-NO_2-BA	31	78
10[d]	**1b**	MS, F	**3b**	*p*-MeO-BA	82	92
11[d]	**1b**	F	**3b**	*p*-MeO-BA	64	84

[a] MS = activated 4Å molecular sieves added, F = filtered through basic alumina. [b] Yield measured by NMR of the crude reaction mixture with $SiEt_4$ as internal standard. [c] Determined by chiral-stationary phase UPCC. [d] **2a** (1.0 eq) and **1b** (1.5 eq). BA = benzoic acid.

Application of $CDCl_3$, filtered through activated basic alumina (F in Table 1) to remove DCl traces, led only to trace product formation (entry 6). Acid additives were found to restore reactivity in a reproducible fashion. Catalyst **3b** with *p*-methoxybenzoic acid (20 mol%) provided **4b** in 69% yield and 92% *ee* (entry 7), while the less bulky catalyst **3a** gave **4b** in 80% yield and 83% *ee* (entry 8). The nature of the acid additive was important, exemplified by *p*-nitrobenzoic acid causing lower yield and selectivity (entry 9). Applying catalyst **3b** with reversed stoichiometry ensured full conversion within 20 h and increased the yield, while maintaining the enantioselectivity (entry 10). Combining the effects of MS and an acid additive was beneficial for yield and selectivity (entries 10-11, for additional results see SI).

The substrate scope was then investigated (Scheme 2). In general, excellent diastereoselectivity was observed. Phenyl groups of varying electronic nature on the 3-position of 1*H*-indene-2-carbaldehydes **1** led to the formation of [10+4]-cycloadducts **4b-e** in high yields and enantioselectivities. *ortho*-Tolyl and 1-naphthyl substituted indenes delivered **4f** and **4g**, respectively, in high yields and enantioselectivities, as 1:1 diastereomeric mixtures due to hindered axial rotation. 2-Naphthyl and 5-(1,3-(benzodioxyl)) substituted **4h**,**i** were achieved in high yields and enantioselectivities as single diastereomers. A heteroaromatic substituent was well-tolerated and **4j** was formed in excellent yield and enantioselectivity. In a 10-fold scale-up with no procedural modifications, the excellent stereoselectivity was maintained and a slight improvement to 95% yield was achieved. Unfortunately, only indenes **1** carrying aromatic substituents at position 3 were found to be reactive towards **2a** (Me-, *t*-Bu- and vinyl-substituted indenes were tested).



4b; Ph — 85%, >20:1 dr, 92% *ee*

4c; p-MeO-C_6H_4 — 89%, >20:1 dr, 92% *ee*

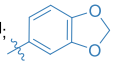
4d; p-F-C_6H_4 — 89%, >20:1 dr, 90% *ee*

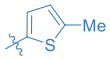
4e; p-CF_3-C_6H_4 — 84%, >20:1 dr, 92% *ee*

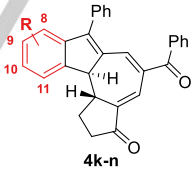
4f[a]; o-Me-C_6H_4 — 84%, 1:1 dr (rotamers), 85/84% *ee*

4g; 1-naphthyl — 82%, 1:1 dr (rotamers), 81/74% *ee*

4h; 2-naphthyl — 81%, >20:1 dr, 90% *ee*

4i[b];  — 83%, >20:1 dr, 95% *ee*

4j;  — 91%, >20:1 dr, 95% *ee*; [c]95%, >20:1 dr, 94% *ee* (0.42 g)



4k; 10-Cl — 86%, >20:1 dr, 90% *ee*

4l; 10-MeO — 83%, >20:1 dr, 95% *ee*

4m[a]; 9-MeO — 82%, >20:1 dr, 92% *ee*

4n[b]; 9-Me — 79%, >20:1 dr, 95% *ee*

4o; CO(p-Br-C_6H_4), CH_2 — 88%, >20:1 dr, 93% *ee*

4p[b]; CO(p-MeO-C_6H_4), CH_2 — 84%, >20:1 dr, 89% *ee*

4q; CO(p-NO2-C_6H_4), CH_2 — 70%, >20:1 dr, 88% *ee*

4r; COMe, CH_2 — 79%, >20:1 dr, 90% *ee*

4s; CO_2Et, CH_2 — 81%, >20:1 dr, 80% *ee*

4t; CO_2Ph, CH_2 — 89%, >20:1 dr, 83% *ee*

4u[d]; CN, CH_2 — 44%, >20:1 dr, 36% *ee*

4v[d,e]; CO_2Et, O — 27%, >20:1 dr, 76% *ee*

Scheme 2. Peri- and stereoselective [8+2]- and [10+4]-cycloadditions. Isolated yields. Diastereomeric ratio determined by NMR of crude reaction mixture. Enantiomeric excess determined by chiral-stationary phase UPCC. See SI. [a] Reaction performed at 40 °C. [b] Reaction performed with 10 mol% *p*-MeO-BA. [c] Reaction performed on 1.0 mmol scale. [d] Extensive degradation of **2** observed. [e] Indene **1b** applied as limiting reagent with 2 eq of **2**.

Successful variations of the benzofused ring were performed with indenes bearing methoxy-, chloro- and methyl substituents granting access to cycloadducts **4k-n** in high yields and enantioselectivities. An attempt to introduce a methyl

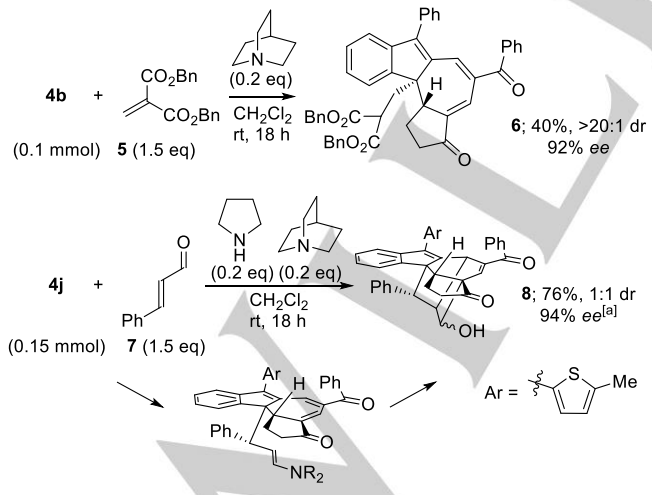
10.1002/anie.201807830

substituent at position 11 resulted only in trace product formation (results not shown).

Various 4π-components **2** were also tested and it was found that the phenyl ketone could be decorated with halogens, electron-donating, and electron-withdrawing groups affording **4o-q** in good to high yields and enantioselectivities. Similar good results were obtained with a methyl ketone (**4r**). Employment of esters as electron-withdrawing groups resulted in slightly lower enantioselectivity, however, the high yield was maintained (**4s**,**t**). The nitrile containing cycloadduct **4u** was also obtained, albeit in low yield and enantioselectivity. As an alternative to the cyclopentenone core of the 4π-component, a lactone was found to deliver cycloadduct **4v** with an enantioselectivity comparable to other esters (**4s**,**t**). However, as was observed with the nitrile substituted 4π-component, extensive degradation of the lactone substrate occurred, resulting in low yield.

The absolute configuration of **4k** was determined by X-ray crystallographic analysis and the stereochemistry of the remaining cycloadducts **4** was assigned analogously (see SI).

Having demonstrated the stereoselective formation of a range of [10+4]-cycloadducts **4**, the possibility of selectively modifying the tetracyclic products was explored (Scheme 3). Specifically, the indene moiety was targeted for application as a nucleophile. Treatment with Michael acceptor **5** in the presence of quinuclidine delivered **6** containing an all-carbon quaternary stereocenter in 40% yield, maintaining the high enantiomeric excess. The reaction of **4j** with cinnamaldehyde **7** was facilitated by a catalytic amount of pyrrolidine (necessary for reactivity) and quinuclidine. Michael addition onto iminium-ion activated cinnamaldehyde is proposed, followed by intramolecular [4+2]-cycloaddition through an enol/enamine, granting access to the multi-bridged polycyclic compound **8** in 76% yield with maintained enantiomeric excess as a mixture of two diastereoisomers. This structure is proposed based on NMR analysis and is supported by computational NMR (see SI).

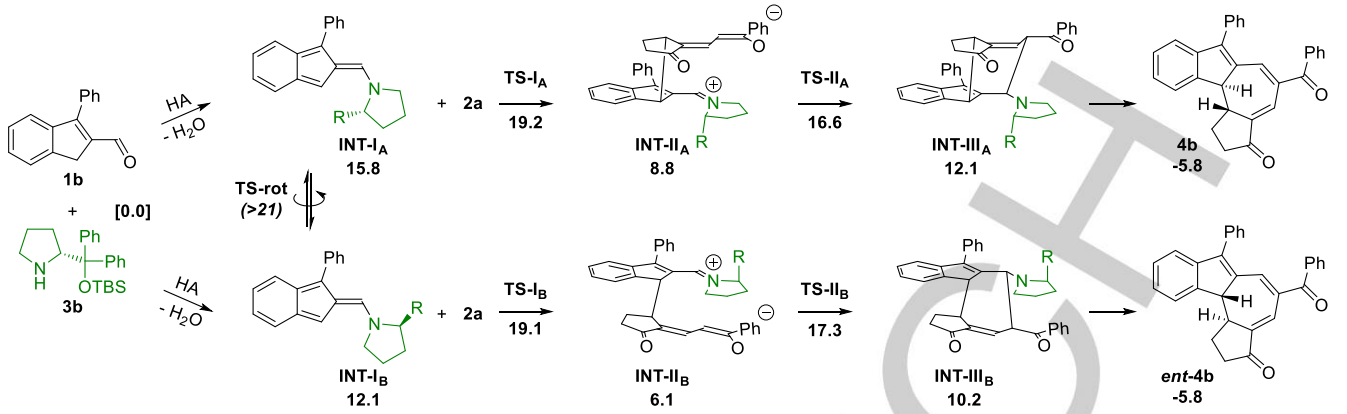


Scheme 3. Synthetic elaborations of [10+4]-cycloadducts. For details see SI. [a] Enantiomeric excess of one diastereomer determined following flash chromatography.

In the [10+4]-cycloaddition between 3-substituted 1*H*-indene-2-carbaldehydes **1** through amino isobenzofulvenes and electron-deficient dienes **2**, excellent diastereoselectivity is observed. Products **4** are formed with *anti*-configuration in agreement with the reaction proceeding through an *exo*-transition state. This is expected to be favorable in [6+4]-cycloadditions due to unfavorable interactions in the *endo*-approach.[10] However, application of symmetry rules and FMO analysis in large polyene systems is complicated.[11] A significant effect on enantioselectivity was exerted by acid additives and water in the reaction when catalyst **3b** was employed (Table 1). This was hypothesized to arise from effects on the formation and distribution of two rotamers of the amino isobenzofulvene intermediate (**INT-I$_A$**/**INT-I$_B$**, Scheme 4). Unfortunately, we have not been able to observe the intermediates by NMR analysis. Instead, the hypothesis was probed indirectly by employment of the C_2-symmetric catalyst **3c**,[12] for which **INT-I$_A$** and **INT-I$_B$** are equivalent due to the rotational symmetry axis of the catalyst (Scheme 5). Interestingly, the presence of an acid additive and water were found to have no measurable effect on the enantioselectivity when **3c** was employed. This suggests an effect on the distribution or reactivity of the two rotamers of the amino isobenzofulvene formed from catalyst **3b** and indenes **1**. The positive effect on enantioselectivity observed upon removal of water under the optimized conditions could owe to a shut-down of reversibility of iminium-ion formation and hence eliminate the potential for equilibration between **INT-I$_A$** and **INT-I$_B$**. To investigate if the rotational barrier between the two is too high to allow for direct interconversion at room temperature, the intermediate was optimized computationally. A scan of the relevant dihedral revealed a barrier of >21 kcal/mol suggesting that **INT-I$_A$** and **INT-I$_B$** are distinct intermediates (see SI). From the absolute configuration of the [10+4]-cycloadducts **4**, reaction through **INT-I$_A$** is expected to be predominant, however, **INT-I$_B$** was calculated to be 3.7 kcal/mol lower in energy. This suggests that **INT-I$_A$** is kinetically formed under the optimized reaction conditions, or that it could be a Curtin-Hammett scenario. To investigate further, the formation of **4b** and ***ent*-4b** from **INT-I$_A$** and **INT-I$_B$**, respectively, was studied computationally by reaction pathway analysis.[13] By visual inspection, it was deemed unlikely that **INT-I$_B$** could lead to **4b** with diene **2a** approaching from the sterically hindered face (see SI).

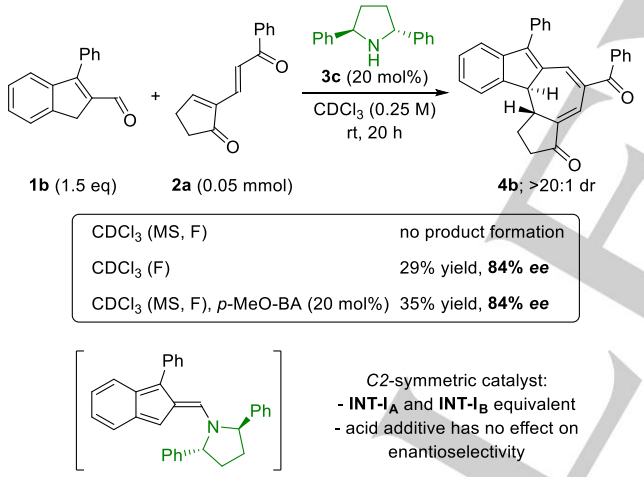
The calculations suggest that formation of either **INT-I$_A$** or **INT-I$_B$** is an endergonic process, and that conjugate addition to **2a** proceeds via low barriers and is energetically viable. No concerted pathways for the formation of **INT-III$_A$** or **INT-III$_B$** were found, suggesting a step-wise cycloaddition. Reasonable barriers for the closure of zwitterionic species **INT-II$_A$** and **INT-II$_B$** were located.

10.1002/anie.201807830



Scheme 4. Relative free energies in kcal/mol (B3LYP-gd3/6-31G(d,p) SMD ($CHCl_3$)) are presented in bold (rotational TS energy in *italics* is an electronic energy relative to **INT-I$_B$**). Calculations were performed with ***ent*-3b**, however, the relevant mirror-image structures are displayed to aid the reader. For corrected single-point electronic energies,[14] see SI.

Pathway **A** leading to **4b** contains higher energy intermediates but lower barriers, while pathway **B** leading to ***ent*-4b** contains lower energy intermediates but higher barriers. Both pathways contain reasonable barriers for reactivity at room temperature. The computed free energies suggest that the enantioselectivity is determined not by conjugate addition to **2**, but could indicate a kinetic preference for formation of amino isobenzofulvene **INT-I$_A$**.



Scheme 5. Additive effects on stereochemistry with C_2-symmetric catalyst. Yield and dr measured by NMR of the crude reaction mixture with $SiEt_4$ as internal standard. Enantiomeric excess determined by chiral-stationary phase UPCC.

This claim of kinetic control is further supported experimentally using the C_2-symmetric catalyst **3c**, which showed no dependence of enantioselectivity on acid additive or water (*vide supra*). Despite the unlikely rotation of **INT-I$_A$** to **INT-I$_B$** with **3b**, if the two intermediates were formed equally in solution, a nearly racemic mixture of **4b** and ***ent*-4b** would be expected as both pathways are energetically viable. We propose that a preferential kinetic formation of **INT-I$_A$** over **INT-I$_B$** controls the stereochemical outcome of these [10+4]-cycloadditions.

In conclusion, the first catalytic [10+4]-cycloaddition has been developed. Experimental and computational evidence suggest that the observed stereoselecitvities arise from kinetically controlled amino isobenzofulvene formation. High yields, coupled with high peri-, diastereo- and enantioselectivity, and a broad substrate scope make this methodology valuable towards the development of complex enantioenriched scaffolds.

Acknowledgements

The authors are grateful for crystallographic analysis by Line Næsborg and Jeremy D. Erickson and financial support from Carlsberg Foundation Semper Ardens, Aarhus University and DNRF.

Keywords: higher-order cycloadditions • organocatalysis • asymmetric synthesis • isobenzofulvenes • DFT calculations

[1] a) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366-5412; b) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667; c) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863-910; d) H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007-1019.

[2] a) Y. Wang, D. Mukherjee, D. Birney, K. N. Houk, *J. Org. Chem.* **1990**, *55*, 4504-4506; b) S. E. Reiter, L. C. Dunn, K. N. Houk, *J. Am. Chem. Soc.* **1977**, *99*, 4199-4201.

[3] a) T. A. Palazzo, R. Mose, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2017**, *56*, 10033-10038; b) J. H. Rigby, *Acc. Chem. Res.* **1993**, *26*, 579-585. For studies on regio- and stereoselectivity in [6+4]-cycloadditions, see *e.g.*: c) M. E Garst, V. A. Roberts, K. N. Houk, N. G. Rondan, *J. Am. Chem. Soc.* **1984**, *106*, 3882-3884; d) M. E. Garst, V. A. Roberts, C. Prussin, *Tetrahedron* **1981**, *39*, 581-589.

[4] a) M. Xie, X. Liu, X. Wu, Y. Cai, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2013**, *52*, 5604-5607; for an intramolecular asymmetric metal catalyzed [6+4]-cycloaddition, see: b) J. H. Rigby, M. Fleming, *Tetrahedron Lett.* **2002**, *43*, 8643-8646.

[5] a) R. Mose, G. Preegel, J. Larsen, S. Jakobsen, E. H. Iversen, K. A. Jørgensen, *Nat. Chem.* **2017**, *9*, 487-492; for an intramolecular asymmetric organocatalyzed [6+2]-cycloaddition, see: b) Y. Hayashi, H. Gotoh, M. Honma, K. Sankar, I. Kumar, H. Ishikawa, K. Konno, H. Yui, S. Tsuzuki, T. Uchimaru, *J. Am. Chem. Soc.* **2011,** *133*, 20175-20185.

[6] a) B. S. Donslund, A. Monleon, T. A. Palazzo, M. L. Christensen, A. Dahlgaard, J. D. Erickson, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2018**, *57*, 1246-1250; b) S. L. Wang, C. Rodríguez-Escrich, M. A. Pericàs, *Angew. Chem. Int. Ed.* **2017**, *56*, 15068-15072; c) Z. Zhou, Z. X. Wang,

Y. C. Zhou, W. Xiao, Q. Ouyang, W. Du, Y. C. Chen, *Nat. Chem.* **2017**, *9*, 590-594.

[7] a) R. N. Warrener, M. L. A. Hammond, D. N. Butler, *Synth. Commun.* **2001**, *31*, 1167-1175; b) H. Tanida, T. Irie, K. Tori, *Bull. Chem. Soc. Jpn.* **1972**, *46*, 1999-2003.

[8] B. M. Trost, S. Yamazaki, *Chem. Lett.* **1994**, 2245-2248.

[9] B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860-13874.

[10] a) R. Hoffmann, R. B. Woodward, *J. Am. Chem. Soc.* **1965**, *87*, 4388-4398; b) K. N. Houk, J. K. George, R. E. Duke, *Tetrahedron* **1974**, *30*, 523-533.

[11] R. Warrener, M. Paddon-Row, R. Russell, P. Watson, *Aust. J. Chem.* **1981**, *34*, 397-420.

[12] E. K. Kemppainen, G. Sahoo, A. Piisola, A. Hamaza, B. Kótai, I. Pápai, P. M. Pihko, *Chem. Eur. J.* **2014**, *20*, 5983-5993.

[13] a) A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378-6396; b) C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523-5527; c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652; d) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372-1377; e) C. T. Lee, W. T. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785-789; f) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104-1 - 154104-19.

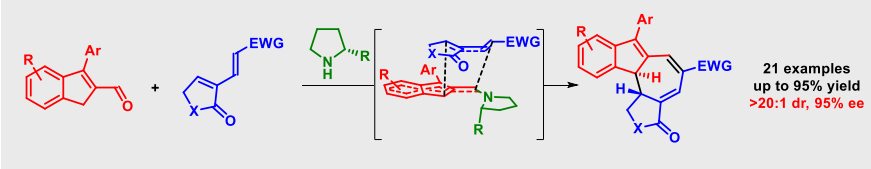
[14] a) Y. Zhao, D. G. Truhlar, *J. Chem. Theory Comput.* **2008,** *4*, 1849-1868; b) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008,** *41*, 157-167; c) J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008,** *10*, 6615-6620; d) J.-D. Chai, M. Head-Gordon, *J. Chem. Phys.* **2008,** *128*, 084106-1 – 084106-15; e) P. Yu, T. Q. Chen, Z. Yang, C. Q. He, A. Patel, Y.-h. Lam, C.-Y. Liu, K. N. Houk, *J. Am. Chem. Soc.* **2017,** *139*, 8251-8258.

10.1002/anie.201807830

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



Text for Table of Contents

*Bjarke S. Donslund, Nicolaj Inunnguaq Jessen, Giulio Bertuzzi, Maxime Giardinetti, Teresa A. Palazzo, Mette Louise Christensen and Karl Anker Jørgensen**

Page No. – Page No.

Catalytic Enantioselective [10+4]-Cycloadditions