

RESEARCH ARTICLE

[View Article Online](#)  
[View Journal](#) | [View Issue](#)



Cite this: *Org. Chem. Front.*, 2024, **11**, 1700

Received 12th December 2023,  
Accepted 12th January 2024

DOI: 10.1039/d3qo02040a

rsc.li/frontiers-organic

## Polyenolate-mediated reaction cascade initiated by higher-order-cycloaddition for the construction of polycarbocyclic scaffolds†

Adam Cieśliński, Anna Skrzynińska, Artur Przydacz and Łukasz Albrecht \*

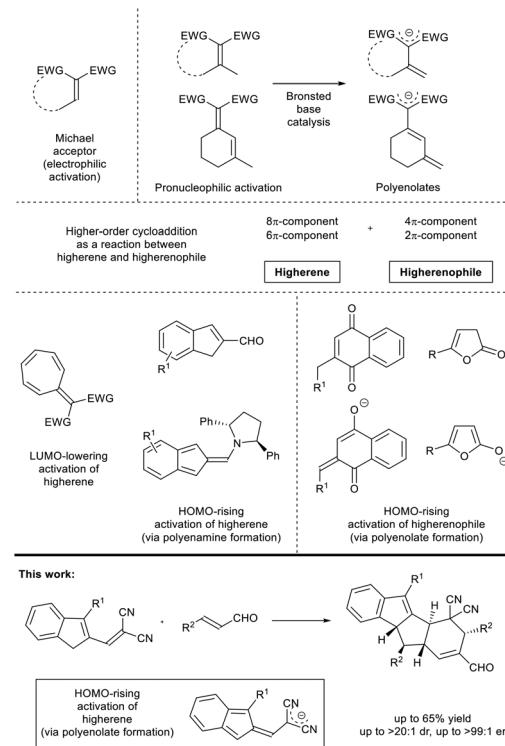
In this manuscript, the application of polyenolate chemistry for the activation of higherenes towards a higher-order-cycloaddition-initiated cascade reaction is demonstrated. This has been made possible by using alkylidenemalononitriles derived from indene-2-carbaldehydes as the higherene precursors. Their reaction with an iminium ion, generated *in situ* in the presence of a suitable amino catalyst, allowed for a cascade reaction involving [10 + 2]-higher-order cycloaddition followed by Michael addition and aldol condensation to proceed in a highly stereoselective fashion.

The introduction of two electron-withdrawing substituents on a double bond constitutes a common strategy that enables the transformation of its properties from nucleophilic into electrophilic.<sup>1,2</sup> If an enolizable alkyl group is present in a suitable position of such compounds, it becomes a pronucleophilic species that serves as a precursor of a polyenolate intermediate (Scheme 1, top).<sup>2</sup> This group of reactive intermediates, generated under Brønsted base catalysis, has recently proven its usefulness for asymmetric synthesis. Such an activation strategy of pronucleophilic species constitutes an interesting alternative to aminocatalytic polyenamine chemistry.<sup>3</sup> It is noteworthy that many reactions involving polyenolate or polyenamine intermediates proceed in a cascade manner allowing for the construction of multiple carbon–carbon and carbon–heteroatom bonds *via* a single chemical procedure.<sup>4</sup>

Chemical transformations that enable the construction of a new ring system starting from acyclic precursors are commonly referred to as cycloaddition reactions.<sup>5</sup> According to Huisgen “the concept of cycloaddition gives a formal description of an overall reaction but not a mechanistic interpretation”.<sup>6</sup> As a consequence, their mechanism can be either concerted, concerted asynchronous or stepwise, with all these transformations belonging to this specious group of chemical reactions. Cycloadditions constitute a highly reliable synthetic tool commonly employed for the preparation of both carbo- and hetero-

cyclic systems with the Diels–Alder reaction and its hetero-versions being the most prominent examples.<sup>7</sup>

Higher-order cycloadditions have been introduced already in 1970 by Woodward and Houk.<sup>8</sup> They can be described as transformations that take place with the participation of



**Scheme 1** Various activation strategies for higher-order cycloadditions and synthetic objectives of our studies.

Institute of Organic Chemistry, Faculty of Chemistry, Łódź University of Technology, Źeromskiego 116, 90-924 Łódź, Poland. E-mail: lukasz.albrecht@p.lodz.pl, anna.skrzynska@p.lodz.pl; <https://www.a-teamlab.p.lodz.pl/>

† Electronic supplementary information (ESI) available. CCDC 2279932. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3qo02040a>



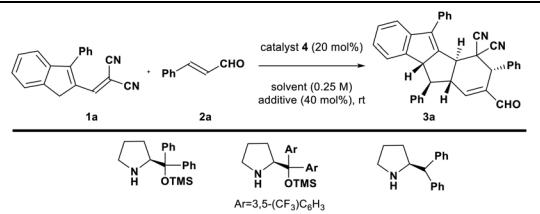
overall more than  $6\pi$ -electrons. Recently, this field of research has regained the attention of the chemical community with interesting new reports appearing in the literature, thus indicating the potential for further research.<sup>9–13</sup> In particular, the application of organocatalytic activation modes opened new possibilities in this area.<sup>10</sup> Notably, two main strategies have been adopted for the activation of higherenes towards higher-order cycloadditions (Scheme 1, middle): (1) LUMO-lowering approach (*via* introduction of electron-withdrawing substituents into their structure)<sup>11</sup> and (2) HOMO-rising approach (*via* aminocatalytic formation of polyenamine intermediates).<sup>12</sup> The application of the related HOMO-rising activation of higherenes based on polyenolate formation remains elusive.

Recently, we demonstrated that polyenolates, generated under Brønsted base catalysis, serve as a reactive group of higherenophiles for higher-order cycloadditions.<sup>13</sup> Dienolates generated from either 2-alkyl-1,4-naphthoquinones or 5-substituted-2(3*H*)-furanones reacted with 8,8-dicyanoheptafulvenes *via* an approach involving LUMO-lowering activation of higherenes. Given the lack of higherene activation strategies based on polyenolate formation, studies on such a reactivity pattern were undertaken. It was anticipated that by conversion of indene-2-carbaldehydes into alkylidenemalononitrile derivatives, access to effective polyenolate precursors should be possible. Their deprotonation under basic conditions and reaction with suitable higherenophiles should create a unique reaction manifold for the development of new reactivities.

Herein, we present our studies on the development of a cascade reaction involving alkylidenemalononitriles derived from indene-2-carbaldehydes as higherene precursors (Scheme 1, bottom). Their reaction with  $\alpha,\beta$ -unsaturated aldehydes realized under aminocatalytic conditions proceeded in a cascade manner and involved [10 + 2]-higher-order cycloaddition followed by Michael addition and aldol condensation.

Studies were initiated by testing the reaction between 2-((3-phenyl-1*H*-inden-2-yl)methylene)malononitrile **1a** and cinnamaldehyde **2a** for the synthesis of the desired **3a**. The model reaction was performed using several commercially available aminocatalysts **4** in dichloromethane as a solvent (Table 1, entries 1–3). Gratifyingly, the use of **4a** provided the expected product **3a**, but the conversion of the starting material **1a** was unsatisfactory. To improve the reaction outcome, the screening of additives was performed. Better results were observed when an organic acid was used as a co-catalyst (Table 1, entries 4 and 5). Then, a thorough evaluation of the solvent effect showed that 1,2-dichloroethane improved the conversion and afforded product **3a** in 43% yield (Table 1, entries 6–10). Additionally, the use of a chiral acidic co-catalyst increased the diastereoselectivity of the process. *R*-Mandelic acid co-catalyzed this reaction, providing product **3a** in 45% yield with excellent stereoselectivity (Table 1, entry 11). The use of *S*-mandelic acid in combination with catalyst **4a** diminished the efficiency of the reaction (Table 1, entry 12). Then, the change of the reagent's ratio showed that the application of a 2-fold excess of aldehyde **2a** did not bring a significant

**Table 1** Polyenolate-mediated reaction cascade initiated by the higher-order-cycloaddition – optimization studies<sup>a</sup>



	Solvent (catalyst)	Additive (40 mol%)	Conv. (yield) <sup>b</sup> [%]	dr <sup>c</sup>	er <sup>d</sup>
1	CH <sub>2</sub> Cl <sub>2</sub> ( <b>4a</b> )	—	20	n.d.	n.d.
2	CH <sub>2</sub> Cl <sub>2</sub> ( <b>4b</b> )	—	Trace	n.d.	n.d.
3	CH <sub>2</sub> Cl <sub>2</sub> ( <b>4c</b> )	—	Trace	n.d.	n.d.
4	CH <sub>2</sub> Cl <sub>2</sub> ( <b>4a</b> )	PhCO <sub>2</sub> H	52	4.5 : 1	>99.1
5	CH <sub>2</sub> Cl <sub>2</sub> ( <b>4a</b> )	NaOAc	Trace	n.d.	n.d.
6	CHCl <sub>3</sub> ( <b>4a</b> )	PhCO <sub>2</sub> H	49	3 : 1	>99.1
7	Et <sub>2</sub> O ( <b>4a</b> )	PhCO <sub>2</sub> H	64	4 : 1	>99.1
8	Toluene ( <b>4a</b> )	PhCO <sub>2</sub> H	36	4.5 : 1	n.d.
9	PhCF <sub>3</sub> ( <b>4a</b> )	PhCO <sub>2</sub> H	47	8 : 1	n.d.
10	Cl(CH <sub>2</sub> ) <sub>2</sub> Cl ( <b>4a</b> )	PhCO <sub>2</sub> H	>95 (43)	5 : 1	>99.1
11	Cl(CH <sub>2</sub> ) <sub>2</sub> Cl ( <b>4a</b> )	<i>R</i> -Mandelic acid	>95 (45)	15 : 1	>99.1
12	Cl(CH <sub>2</sub> ) <sub>2</sub> Cl ( <b>4a</b> )	<i>S</i> -Mandelic acid	35	20 : 1	>99.1
13 <sup>e</sup>	Cl(CH <sub>2</sub> ) <sub>2</sub> Cl ( <b>4a</b> )	<i>R</i> -Mandelic acid	>95 (50)	20 : 1	>99.1
14 <sup>f</sup>	Cl(CH <sub>2</sub> ) <sub>2</sub> Cl ( <b>4a</b> )	<i>R</i> -Mandelic acid	>95 (65)	>20 : 1	>99.1
15 <sup>g</sup>	Cl(CH <sub>2</sub> ) <sub>2</sub> Cl ( <b>4a</b> )	<i>R</i> -Mandelic acid	>95 (63)	>20 : 1	>99.1

<sup>a</sup> Reactions performed at the 0.05 mmol scale using **1a** (0.05 mmol), **2a** (0.12 mmol) and catalyst **4** (20 mol%) in 0.2 mL of the solvent for 24 h at rt. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. The yield of the isolated product **3a** after column chromatography is given in parentheses. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>d</sup> Determined by chiral UPC<sup>2</sup>. <sup>e</sup> The reaction performed using **1a** (0.05 mmol) and **2a** (0.2 mmol). <sup>f</sup> The reaction performed using **1a** (0.1 mmol) and **2a** (0.1 mmol). <sup>g</sup> Reaction performed on a 1 mmol scale for 48 h.

improvement in terms of conversion (Table 1, entry 13). However, reducing the excess of **2a** allowed us to obtain **3a** with excellent selectivity and the yield increased to 65% (Table 1, entry 14), indicating the optimized conditions for the synthesis of **3a** *via* a higher-order-cycloaddition-initiated cascade reaction. Furthermore, product **3a** could also be effectively accessed when the reaction was carried out on a 20-fold higher scale under the optimized conditions (Table 1, entry 15).

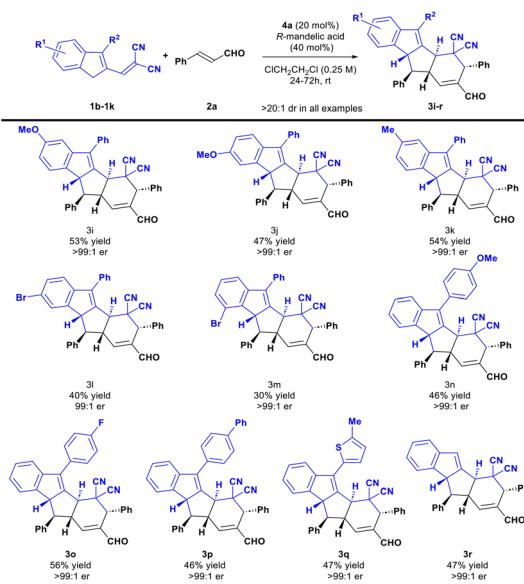
To verify the application scope of this polyenolate-mediated reaction cascade, a series of  $\alpha,\beta$ -unsaturated aldehydes **2** and alkylidenemalononitrile derivatives **1** were investigated (Table 2 and Scheme 2). As shown in Table 2, a variety of  $\alpha,\beta$ -unsaturated aldehydes **2b–h** bearing different aromatic groups successfully participated in the cascade, delivering the desired polycarbocyclic scaffolds **3b–h** in generally good yields with excellent stereoselectivities. In detail, *trans*-cinnamaldehydes **2b–f** bearing either electron-rich or electron-deficient substituents at the *para*- or *meta*-positions of the phenyl moiety underwent facile transformation into the desired products **3b–f** in moderate to good yields with high diastereo- and enantioselectivities. It is noteworthy that in the case of alde-



**Table 2** Polyenolate-mediated reaction cascade initiated by the higher-order-cycloaddition – scope of  $\alpha,\beta$ -unsaturated aldehydes **2**<sup>a</sup>

Entry	3 (2)	Ar	Yield [%]	dr <sup>b</sup>	er <sup>c</sup>
1	3a (2a)	Ph	65	>20 : 1	>99 : 1
2	3b (2b)	4-MeOC <sub>6</sub> H <sub>4</sub>	60	17 : 1	>99 : 1
3	3c (2c)	3-MeOC <sub>6</sub> H <sub>4</sub>	44	20 : 1	>99 : 1
4	3d (2d)	4-MeC <sub>6</sub> H <sub>4</sub>	59	20 : 1	>99 : 1
5	3e (2e)	4-ClC <sub>6</sub> H <sub>4</sub>	55	20 : 1	>99 : 1
6	3f (2f)	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	36	20 : 1	>99 : 1
7	3g (2g)	2-Naphthyl	50	20 : 1	>99 : 1
8	3h (2h)	2-Furyl	52	20 : 1	>99 : 1

<sup>a</sup> Reactions were performed using **1a** (0.2 mmol), **2** (0.2 mmol), *R*-mandelic acid (0.04 mmol) and catalyst **4** (0.02 mmol) in 1,2-dichloroethane (0.4 mL) at rt. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup> Determined by chiral UPC<sup>2</sup>.



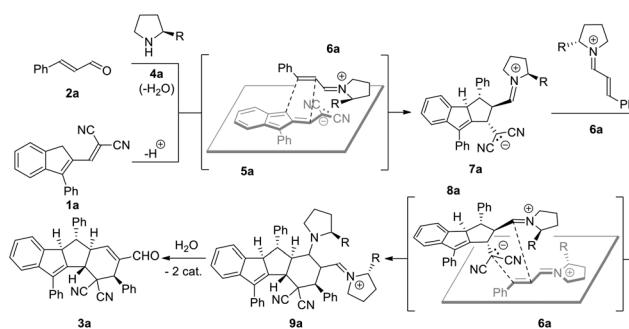
**Scheme 2** Polyenolate-mediated reaction cascade initiated by the higher-order-cycloaddition – scope of alkylidenemalononitrile derivatives **1**. Reactions were performed using **1** (0.2 mmol), **2a** (0.2 mmol), *R*-mandelic acid (0.04 mmol) and catalyst **4** (0.02 mmol) in 1,2-dichloroethane (0.4 mL) at rt. Diastereomeric ratio (dr) was determined by <sup>1</sup>H NMR of the crude reaction mixture. Enantiomeric ratio (er) was determined by chiral UPC<sup>2</sup>.

hyde **2f**, the reaction with alkylidenemalononitrile derivative **1a** provided the desired product **3f** but in a lower yield. Besides, doubly substituted **2g** was successfully utilized as a reaction partner to give the corresponding product **3g** in 50% yield and >99 : 1 er. Finally, the reactivity and stereoselectivity were hardly affected by the incorporation of the furan ring in **2h**, as the target polycyclic scaffold **3h** was effectively obtained. Moreover, under the standard conditions, the aliphatic  $\alpha,\beta$ -unsaturated aldehydes were not tolerated in this

cascade process as the formation of the desired products **3** was not detected. Unfortunately, the reaction with *ortho*-substituted aromatic  $\alpha,\beta$ -unsaturated aldehydes **2** did not lead to the desired product **3**.

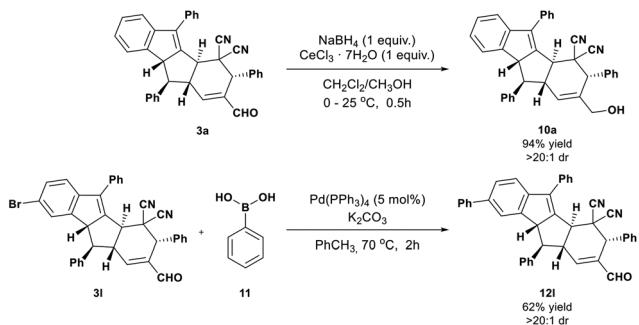
Next, the generality of the cascade reaction for alkylidene-malononitrile derivatives **1** as higherene precursors was investigated (Scheme 2). The reaction proved applicable for a series of substituted substrates **1** with different R<sup>1</sup> substituents at the C5–C7 positions of the phenyl ring. Several representative substrates **1i–m** with methyl, methoxy and bromine substituents successfully took part in the cascade reaction, providing the target products **3i–m** in moderate to good yields with perfect enantioselectivity. However, the steric hindrance of the bromine atom at the C7 position had an effect on the reactivity of **1m** and delivered a relatively low yield of product **3m** compared to other substrates. Similarly, alkylidenemalononitrile derivatives **1n–q** bearing aromatic groups of varying electronic nature at the 3-position were employed for this reaction, affording the target products **3n–q** in overall good yields. Furthermore, the unsubstituted derivative **1r** could also be effectively used as a competent higherene precursor in the presented cascade. Notably, all the products **3i–r** were generated with uniformly excellent diastereoselectivity (dr > 20 : 1). Disappointingly, when the aliphatic group was introduced at the R<sup>2</sup> position, no reaction was observed.

The absolute configuration of the polycyclic products **3a–r** was unequivocally confirmed by single crystal X-ray analysis of **3m** (for details, see the ESI†).<sup>14</sup> The stereochemistry of other products was assigned by analogy. Scheme 3 shows the detailed mechanism of the developed transformation, based on the assigned configuration of the final polycyclic products **3**. The reaction cascade begins with the formation of two key intermediates: (1) polyenolate **5a** (through deprotonation of indene derivative **2a**) and (2) iminium ion **6a** (by condensation of aldehyde **2a** and catalyst **4a**). For the first cyclization to occur, higherene **5a** approaches higherenophile **6a** from the less sterically-hindered side and in an *endo*-like fashion. The latter may be explained by the attractive interactions between the oppositely charged dicyanomethine scaffold and the pyrrolidine nitrogen atom. The resulting zwitterionic intermediate **7a** undergoes a 1,4-addition to another iminium ion **6a** fol-



**Scheme 3** Polyenolate-mediated reaction cascade initiated by the higher-order-cycloaddition – mechanistic considerations.





**Scheme 4** Polyenolate-mediated reaction cascade initiated by the higher-order-cycloaddition – selected transformations.

lowed by an intermolecular Mannich reaction. Similarly to the periselective [10 + 2]-cycloaddition step, the spatial orientation of both substrates and hence the stereochemical outcome of the second reaction sequence are controlled by the bulky substituents originating from the catalyst. The catalytic cycle is then completed by the release of two catalyst molecules through elimination and hydrolysis.

To demonstrate the potential utility of the cascade reaction products, selected transformations of **3** were attempted. Chemoselective reduction of the carbonyl group in **3a** led to the formation of alcohol **10a** in an excellent 94% yield (Scheme 4, top). The reaction was realized using NaBH<sub>4</sub> in the presence of cerium chloride as a reducing reagent. Moreover, the Suzuki coupling involving aldehyde **3I** and phenylboronic acid **11** was performed to give the desired product **12I** in a good 62% yield (Scheme 4, bottom). Both reactions occurred with the preservation of the optical purity of **3a,I** as all products were obtained as single diastereoisomers.

In conclusion, we have demonstrated that polyenolate chemistry constitutes a powerful strategy, enabling the formation of higherenes for a higher-order-cycloaddition-initiated cascade reaction. Alkylidenemalononitriles derived from indene-2-carbaldehyde derivatives upon deprotonation underwent the reaction cascade involving [10 + 2]-higher-order cycloaddition followed by Michael addition and aldol condensation that proceeded in a highly stereoselective fashion.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This project was realized within the Opus programme (grant number: UMO-2021/41/B/ST4/03385) from the National Science Centre, Poland. Thanks are expressed to Dr Lesław Sieroń (Lodz University of Technology) for the X-ray analysis. This contribution has been completed while the first author (AC) was a Doctoral Candidate in the Interdisciplinary Doctoral School of Lodz University of Technology, Poland.

## References

- For selected reviews, see: (a) H.-L. Cui and Y.-C. Chen,  $\alpha,\alpha$ -Dicyanoalkenes: versatile vinylogous nucleophiles for organic synthesis, *Chem. Commun.*, 2009, 4479; (b) Y. Zhang and W. Wang, Recent advances in organocatalytic asymmetric Michael reactions, *Catal. Sci. Technol.*, 2012, 2, 42; (c) G. Casiraghi, L. Battistini, C. Curti, G. Rassu and F. Zanardi, The Vinylogous Aldol and Related Addition Reactions: Ten Years of Progress, *Chem. Rev.*, 2011, **111**, 3076; (d) L. Battistini, C. Curti, G. Rassu, A. Sartori and F. Zanardi, Enolizable Alkylidene Heterocyclic and Carbocyclic Carbonyl Systems: Valuable Vinylogous Donor Substrates in Synthesis, *Synthesis*, 2017, 2297; (e) C. Curti, L. Battistini, A. Sartori and F. Zanardi, New Developments of the Principle of Vinylogy as Applied to  $\pi$ -Extended Enolate-Type Donor Systems, *Chem. Rev.*, 2020, **120**, 2448.
- For selected examples, see: (a) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi and G. Casiraghi, Bifunctional Cinchona Alkaloid/Thiourea Catalyzes Direct and Enantioselective Vinylogous Michael Addition of 3-Alkylidene Oxindoles to Nitroolefins, *Angew. Chem., Int. Ed.*, 2012, **51**, 6200; (b) G. Rassu, V. Zambrano, L. Pinna, C. Curti, L. Battistini, A. Sartori, G. Pelosi, F. Zanardi and G. Casiraghi, Direct Regio-, Diastereo-, and Enantioselective Vinylogous Michael Addition of Prochiral 3-Alkylideneoxindoles to Nitroolefins, *Adv. Synth. Catal.*, 2013, **355**, 1881; (c) L. Dell'Amico, L. Albrecht, T. Naicker, P. H. Poulsen and K. A. Jørgensen, Beyond Classical Reactivity Patterns: Shifting from 1,4- to 1,6-Additions in Regio- and Enantioselective Organocatalyzed Vinylogous Reactions of Olefinic Lactones with Enals and 2,4-Dienals, *J. Am. Chem. Soc.*, 2013, **135**, 8063; (d) Q. Chen, G. Wang, X. Jiang, Z. Xu, L. Lin and R. Wang, Highly Enantioselective Organocatalyzed Vinylogous Michael-Type Reaction for the Construction of Trifluoromethylated All-Carbon Quaternary Stereocenters, *Org. Lett.*, 2014, **16**, 1394; (e) T.-P. Gao, J.-B. Lin, X.-Q. Hu and P.-F. Xu, A catalytic asymmetric hetero-Diels–Alder reaction of olefinic azlactones and isatins: facile access to chiral spirooxindole dihydropyranes, *Chem. Commun.*, 2014, **50**, 8934; (f) Y. Zhong, S. Ma, Z. Xu, M. Chang and R. Wang, Organocatalytic asymmetric vinylogous Michael addition of 3-alkylidene oxindoles to  $\alpha$ -substituted  $\beta$ -nitroacrylates: facile construction of a chiral all-carbon quaternary center, *RSC Adv.*, 2014, **4**, 49930; (g) G. Rassu, V. Zambrano, L. Pinna, C. Curti, L. Battistini, A. Sartori, G. Pelosi, G. Casiraghi and F. Zanardi, Direct and Enantioselective Vinylogous Michael Addition of  $\alpha$ -Alkylidenepyrazolinones to Nitroolefins Catalyzed by Dual Cinchona Alkaloid Thioureas, *Adv. Synth. Catal.*, 2014, **356**, 2330; (h) N. Di Iorio, P. Righi, S. Ranieri, A. Mazzanti, R. G. Margutta and G. Bencivenni, Vinylogous Reactivity of Oxindoles Bearing Nonsymmetric 3-Alkylidene Groups, *J. Org. Chem.*, 2015, **80**, 7158; (i) X. Xiao, H. Mei, Q. Chen, X. Zhao, L. Lin, X. Liu and X. Feng, Direct asymmetric viny-



logous Michael addition of 3-alkylidene oxindoles to chalcones catalyzed by a chiral N,N'-dioxide ytterbium(III) complex, *Chem. Commun.*, 2015, **51**, 580; (j) J.-L. Han and C.-H. Chang, An asymmetric assembly of spirooxindole dihydropyranones through a direct enantioselective organocatalytic vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles with isatins, *Chem. Commun.*, 2016, **52**, 2322.

3 For selected reviews, see: (a) H. Jiang, L. Albrecht and K. A. Jørgensen, Aminocatalytic remote functionalization strategies, *Chem. Sci.*, 2013, **4**, 2287; (b) S. Reboreda, A. Parra and J. Alemán, Trienamines: Their Key Role in Extended Organocatalysis for Diels-Alder Reactions, *Asymmetric Catal.*, 2013, **1**, 24; (c) V. Marcos and J. Alemán, Old tricks, new dogs: organocatalytic dienamine activation of  $\alpha,\beta$ -unsaturated aldehydes, *Chem. Soc. Rev.*, 2016, **45**, 6812; (d) A. Przydacz, A. Skrzynska and L. Albrecht, Breaking Aromaticity with Aminocatalysis: A Convenient Strategy for Asymmetric Synthesis, *Angew. Chem., Int. Ed.*, 2019, **58**, 63; (e) T. J. Pawar, S. B. Mitkari, E. Peña-Cabrera, C. V. Gómez and D. C. Cruz, Polyenals and Polyenones in Aminocatalysis: A Decade Building Complex Frameworks from Simple Blocks, *Eur. J. Org. Chem.*, 2020, 6044.

4 For selected reviews, see: (a) C. Grondal, M. Jeanty and D. Enders, Organocatalytic cascade reactions as a new tool in total synthesis, *Nat. Chem.*, 2010, **2**, 167; (b) D. B. Ramachary and S. Jain, Sequential one-pot combination of multi-component and multi-catalysis cascade reactions: an emerging technology in organic synthesis, *Org. Biomol. Chem.*, 2011, **9**, 1277; (c) R. C. Wende and P. R. Schreiner, Evolution of asymmetric organocatalysis: multi- and retrocatalysis, *Green Chem.*, 2012, **14**, 1821; (d) P. Chauhan, S. Mahajan, U. Kaya, D. Hack and D. Enders, Bifunctional Amine-Squaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions, *Adv. Synth. Catal.*, 2015, **357**, 253; (e) S. Nayak, P. Panda, S. Bhakta, S. K. Mishraa and S. Mohapatra, Current advances of organocatalytic Michael-Michael cascade reaction in the synthesis of highly functionalized cyclic molecules, *RSC Adv.*, 2016, **6**, 96154; (f) T. Parvin, R. Yadav and L. H. Choudhury, Recent applications of thiourea-based organocatalysts in asymmetric multicomponent reactions (AMCRs), *Org. Biomol. Chem.*, 2020, **18**, 5513.

5 For selected reviews on cycloadditions, see: (a) H.-W. Frühauf, Metal-Assisted Cycloaddition Reactions in Organotransition Metal Chemistry, *Chem. Rev.*, 1997, **97**, 523; (b) L. Yet, Metal-Mediated Synthesis of Medium-Sized Rings, *Chem. Rev.*, 2000, **100**, 2963; (c) *Cycloaddition Reactions in Organic Synthesis*, ed. S. Kobayashi and K. A. Jørgensen, Wiley-VCH, Weinheim, 2001; (d) E. M. Carreira and L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, 2009; (e) A. Moyano and R. Rios, Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions, *Chem. Rev.*, 2011, **111**, 4703; (f) F. E. Held and S. B. Tsogoeva, Asymmetric cycloaddition reactions catalyzed by bifunctional thiourea and squaramide organocatalysts: recent advances, *Catal. Sci. Technol.*, 2016, **6**, 645; (g) L. Klier, F. Tur, P. H. Poulsen and K. A. Jørgensen, Asymmetric cycloaddition reactions catalysed by diarylprolinol silyl ethers, *Chem. Soc. Rev.*, 2017, **46**, 1080.

6 R. Huisgen, Kinetics and Mechanism of 1,3-Dipolar Cycloadditions, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633, (*Angew. Chem.*, 1963, **75**, 742).

7 For reports on Diels-Alder reactions, see: (a) O. Diels and K. Alder, Syntheses in the hydroaromatic series. I. Addition of "diene" hydrocarbons, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98; (b) O. Diels and K. Alder, Synthesen in der hydroaromatischen Reihe, II. Mitteilung: Über Cantharidin, *Ber. Dtsch. Chem. Ges.*, 1929, **62**, 554; (c) R. B. Woodward and R. Hoffmann, Stereochemistry of Electrocyclic Reactions, *J. Am. Chem. Soc.*, 1965, **87**, 395; (d) R. Hoffmann and R. B. Woodward, Orbital Symmetries and endo-exo Relationships in Concerted Cycloaddition Reactions, *J. Am. Chem. Soc.*, 1965, **87**, 4388; (e) R. Hoffmann and R. B. Woodward, Selection Rules for Concerted Cycloaddition Reactions, *J. Am. Chem. Soc.*, 1965, **87**, 2046; (f) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **81**, 797; *Frontier Orbitals and Reaction Paths: Selected Papers of Kenichi Fukui*, ed. H. Fujimoto and K. Fukui, World Scientific, Singapore, 1997. For selected reviews on Diels-Alder and related reactions, see: (g) D. L. Boger, Diels-Alder Reactions of Heterocyclic Azadienes: Scope and Applications, *Chem. Rev.*, 1986, **86**, 781; (h) K. A. Jørgensen, Catalytic Asymmetric Hetero-Diels-Alder Reactions of Carbonyl Compounds and Imines, *Angew. Chem., Int. Ed.*, 2000, **39**, 3558, (*Angew. Chem.*, 2000, **112**, 3702); (i) E. J. Corey, Catalytic Enantioselective Diels-Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, *Angew. Chem., Int. Ed.*, 2002, **41**, 1650, (*Angew. Chem.*, 2002, **114**, 1724); (j) H. Pellissier, Asymmetric hetero-Diels-Alder reactions of carbonyl compounds, *Tetrahedron*, 2009, **65**, 2839; (k) S. Reymond and J. Cossy, Copper-Catalyzed Diels-Alder Reactions, *Chem. Rev.*, 2008, **108**, 5359; (l) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne and J. Rodriguez, Enantioselective Organocatalyzed Domino Synthesis of Six-Membered Carbocycles, *Synthesis*, 2013, 1909; (m) X. Jiang and R. Wang, Recent Developments in Catalytic Asymmetric Inverse-Electron-Demand Diels-Alder Reaction, *Chem. Rev.*, 2013, **113**, 5515.

8 K. N. Houk and R. B. Woodward, Cycloaddition Reactions of Cycloheptatriene and 2,5-Dimethyl-3,4-diphenylcyclopenta-dienone, *J. Am. Chem. Soc.*, 1970, **92**, 4143.

9 For selected reviews, see: (a) T. A. Palazzo, R. Mose and K. A. Jørgensen, Cycloaddition Reactions: Why Is It So Challenging To Move from Six to Ten Electrons?, *Angew. Chem., Int. Ed.*, 2017, **56**, 10033, (*Angew. Chem.*, 2017, **129**, 10165); (b) X. Liu, H. Zheng, Y. Xia, L. Lin and X. Feng, Asymmetric Cycloaddition and Cyclization Reactions Catalyzed by Chiral N,N'-Dioxide-Metal Complexes, *Acc. Chem. Res.*, 2017, **50**, 2621; (c) T. A. Palazzo and K. A. Jørgensen, Higher-order cycloaddition reactions: A



computational perspective, *Tetrahedron*, 2018, **74**, 7381. For selected metal-catalyzed higher-order cycloadditions, see: (d) M. Xie, X. Liu, X. Wu, Y. Cai, L. Lin and X. Feng, Catalytic Asymmetric [8 + 2] Cycloaddition: Synthesis of Cycloheptatriene-Fused Pyrrole Derivatives, *Angew. Chem., Int. Ed.*, 2013, **52**, 5604, (*Angew. Chem.*, 2013, **125**, 5714); (e) A. R. Rivero, I. Fernández and M. Sierra, Regio- and Diastereoselective Stepwise [8 + 3]-Cycloaddition Reaction between Tropone Derivatives and Donor-Acceptor Cyclopropanes, *Org. Lett.*, 2013, **15**, 4928; (f) R. Tejero, A. Ponce, J. Adrio and J. C. Carretero, Ni-Catalyzed [8 + 3] cycloaddition of tropones with 1,1-cyclopropanediesters, *Chem. Commun.*, 2013, **49**, 10406; (g) T.-L. Liu, Q.-H. Li, L. Wei, Y. Xiong and C.-J. Wang, Copper(I)-Catalyzed One-Pot Sequential [3 + 2]/[8 + 2] Annulations for the (Z)-Selective Construction of Heterocyclic Diazabicyclo[5.3.0]decatrienes, *Adv. Synth. Catal.*, 2017, **359**, 1854; (h) J. Zhang, W. Xiao, H. Hu, L. Lin, X. Liu and X. Feng, Catalytic Asymmetric [8 + 3] Annulation Reactions of Tropones or Azaheptafulvenes with meso-Aziridines, *Chem. - Eur. J.*, 2018, **24**, 13428.

10 For selected reviews, see: (a) S. Frankowski, M. Romaniszyn, A. Skrzynska and Ł. Albrecht, The Game of Electrons: Organocatalytic Higher-Order Cycloadditions Involving Fulvene- and Tropone-Derived Systems, *Chem. - Eur. J.*, 2020, **26**, 2120; (b) N. I. Jessen, D. McLeod and K. A. Jørgensen, Higher-order cycloadditions in the age of catalysis, *Chem.*, 2022, **8**, 20.

11 For selected examples, see: (a) R. Mose, G. Preegel, J. Larsen, S. Jakobsen, E. H. Iversen and K. A. Jørgensen, Organocatalytic stereoselective [8 + 2] and [6 + 4] cycloadditions, *Nat. Chem.*, 2017, **9**, 487; (b) M. Romaniszyn, K. Gronowska and Ł. Albrecht, 2-Substituted 1,4-Naphthoquinones in [6 + 4]-Cycloaddition with 8,8-Dicyanoheptafulvene, *J. Org. Chem.*, 2019, **84**, 9929; (c) M. Romaniszyn, L. Sieroń and Ł. Albrecht, 5-Substituted-furan-2(3H)-ones in [8 + 2]-Cycloaddition with 8,8-Dicyanoheptafulvene, *J. Org. Chem.*, 2022, **87**, 5296.

12 For examples, see: (a) B. S. Donslund, A. Monleón, T. A. Palazzo, M. L. Christensen, A. Dahlgaard, J. D. Erickson and K. A. Jørgensen, Organocatalytic Enantioselective Higher-Order Cycloadditions of In Situ Generated Amino Isobenzofulvenes, *Angew. Chem., Int. Ed.*, 2018, **57**, 1246; (b) B. S. Donslund, N. I. Jessen, G. Bertuzzi, M. Giardinetti, T. A. Palazzo, M. L. Christensen and K. A. Jørgensen, Catalytic Enantioselective [10 + 4] Cycloadditions, *Angew. Chem., Int. Ed.*, 2018, **57**, 13182; (c) M. Giardinetti, N. I. Jessen, M. L. Christensen and K. A. Jørgensen, Organocatalytic [10 + 4] cycloadditions for the synthesis of functionalised benzo[a]azulenes, *Chem. Commun.*, 2019, **55**, 202.

13 A. Cieśliński, S. Frankowski and Ł. Albrecht, Pentaenolate activation in the organocatalytic allylic alkylation of indene-2-carbaldehydes, *Chem. Commun.*, 2023, **59**, 7655.

14 CCDC 2279932† contains the supplementary crystallographic data for this paper.

