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Organocatalytic stereoselective [8+2] and [6+4] cycloadditions

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Cycloadditions that involve more than six π electrons are termed higher-order cycloadditions and are an excellent tool for solving complex synthetic challenges, as they provide direct access to polycyclic scaffolds that contain medium-sized rings. They have interesting synthetic potential for the discovery of new bioactive molecules and in natural product synthesis. It is peculiar that stereocontrolled [8+2] and [6+4] cycloadditions have been largely neglected for the past 50 years. Here we demonstrate a cross-dienamine activation of 2-cyclopentenone and the unprecedented endocyclic linear-dienamine activation of 2-cyclohexenones and 2-cycloheptenones. These dienamine intermediates undergo aminocatalytic stereoselective [8+2], [6+4] and formal [4+2] cycloadditions with various heptafulvenes. The periselectivities of the cycloadditions are controlled based on the ring size of the 2-cycloalkenones and the substitution patterns of the heptafulvenes. The chiral products obtained undergo various chemical and photochemical single-step transformations that give access to other classes of all-carbon polycyclic scaffolds.

The seminal paper by Woodward and Hoffmann in 1965 stating a simple set of rules for pericyclic reactions was the onset of a new era in chemistry[1]. In addition to the [8+2] cycloaddition reported in 1960, they proposed that [6+4] cycloadditions would also be symmetry allowed[2–4]. Furthermore, based on the orbital symmetry rules, the [6+4] cycloaddition was predicted to proceed with *exo*-selectivity, whereas the [8+2] and [4+2] cycloadditions should both be *endo*-selective. A proof of concept was provided the following year when the first [6+4] cycloaddition was demonstrated by the reaction of tropone with cyclopentadiene[5].

Higher-order cycloadditions (cycloadditions that involve more than six π electrons) often suffer from a lack of periselectivity as several competitive reaction pathways are possible. For example, tropone has been reported to react as a 2π component in [2+4] (ref. 6) cycloadditions, a 4π component in [4+2] (refs 7–9) and [4+6] (ref. 10) cycloadditions, a 6π component in [6+3] (refs 11–13), [6+4] (refs 5,14–18) and [6+6] (ref. 19) cycloadditions, and as an 8π component in [8+2] (ref. 20) cycloadditions. Although no general guidelines to control the reaction pathway of higher-order cycloadditions are known, it is highly desirable to be able to perform periselective reactions for synthetic applications.

Numerous examples of the thermally allowed [8+2] and [6+4] cycloadditions have been reported over the past 50 years, but there is a remarkable lack of their enantioselective equivalents. A singular example of a catalytic intramolecular [6+4] cycloaddition exists (80% yield, 40% e.e.)[14,21], and a metal-catalysed enantioselective *aza*-[8+2] cycloaddition was reported only recently[22]. In addition, enantioselective versions of the [4+2] cycloadditions with heptafulvenes have also received limited attention[9].

The aminocatalytic activation of 2-cycloalkenones provides a mixture of dienamine species that consists of a cross dienamine, an endocyclic linear dienamine and an exocyclic linear dienamine (only for 3-alkyl-2-cycloalkenones) (Fig. 1a). The thermodynamic distribution of the dienamine mixtures lies in favour of the endo- or exocyclic linear dienamines for 3-alkyl-2-cycloalkenones and towards the endocyclic linear dienamine for 2-cycloalkenones, whereas the cross dienamine is generally not observed or only found in small quantities[23–25]. The thermodynamic distributions of the dienamine mixtures are not reflected in the aminocatalytic reactions and 3-alkyl-2-cycloalkenones react through either cross-dienamine[26–29] or exocyclic linear-dienamine intermediates[29–31], whereas 2-cycloalkenones are known to react through cross-dienamine intermediates[27–29,32]. In contrast, the catalytic γ functionalization via an endocyclic linear dienamine is uncommon and has only been observed for 3-phenyl-2-cyclopentenone[33].

We envisioned that stereoselective [8+2], [6+4] and [4+2] cycloadditions could be accessed via aminocatalysis[34]. The periselectivities of these reactions are considered to be determined by the possibility that 2-cycloalkenones can generate different catalytic dienamine intermediates by reaction with an aminocatalyst. As outlined in Fig. 1b, it is postulated that a cross-dienamine intermediate[35] will lead to a [6+4] cycloaddition, whereas a linear dienamine can undergo either an [8+2] or formal [4+2] cycloaddition.

We initiated our studies by investigating the reaction of 2-cyclopentenone **2a** with tropone **3A** catalysed by cinchona alkaloid primary amines **1** (ref. 36) (screening and optimization results are given in Supplementary Table 1). With catalyst **1c** the [6+4] cycloadduct **4aA** was readily formed in 51% yield and excellent stereoselectivities (95% e.e., >20:1 d.r.) and represents the first catalytic stereoselective intermolecular [6+4] cycloaddition (Table 1, entry 1). Surprisingly, no reaction was observed when heptafulvenes **3B** and **3C** were applied under Conditions A (Table 1, footnotes); however, the [6+4] cycloadduct **4aB** was formed in 50% yield, >20:1 d.r. and 42% e.e. after the tuning of several reaction parameters (Table 1, entry 2).

When cycloadditions between 2-cyclohexenone **2b** with tropone **3A** and dicyanoheptafulvene **3B** were attempted, the formal inverse-electron-demand [4+2] cycloadducts **6bA** and **6bB** were isolated instead of the expected [6+4] cycloadducts (Table 1, entries 4 and 5). This observation is notable, as 2-cyclohexenones are known to react via cross-dienamine intermediates[27–29,32], but the catalytic γ functionalization via an endocyclic linear dienamine had not been observed previously[33]. We hypothesized that the [4+2] cycloadducts were formed by an initial [8+2] cycloaddition followed by a rearrangement into the [4+2] cycloadducts (Fig. 2c)[37]. Thus, when

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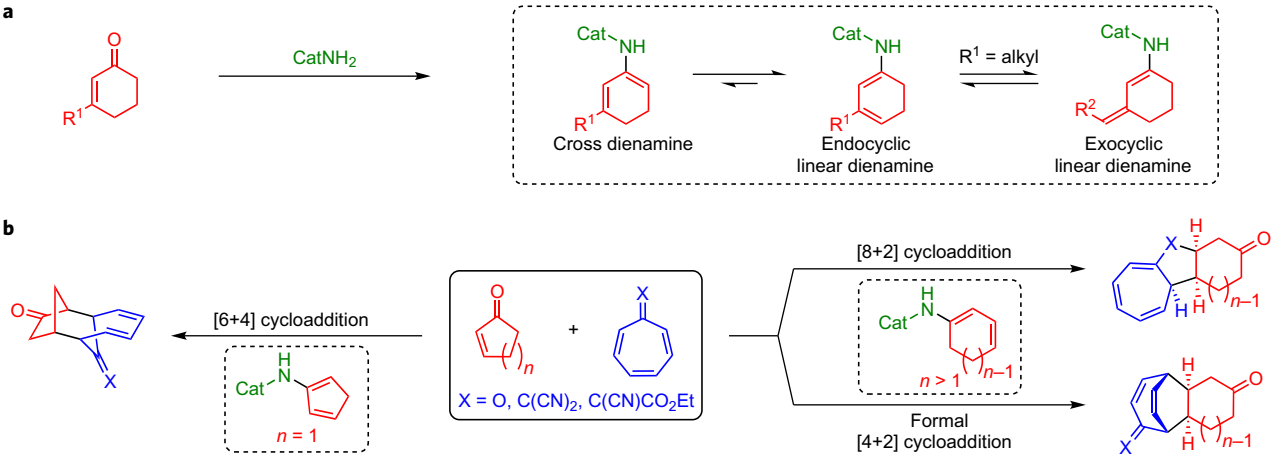
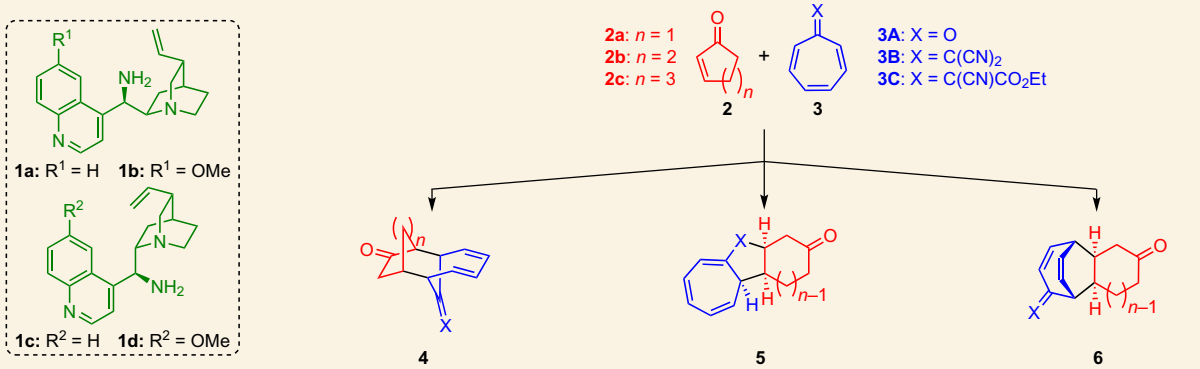


Figure 1 | Aminocatalytic dienamine activation of 2-cycloalkenones and their applications in higher-order cycloadditions. a, Aminocatalytic activations of enones provide mixtures of dienamine species. Reactivity is usually observed through the cross-dienamine or exocyclic linear-dienamine species. **b**, Work presented herein; mixtures of 2-cycloalkenones and heptafulvenes can undergo various cycloadditions. 2-cyclopentenone reacts through a cross-dienamine intermediate in a [6+4] cycloaddition, whereas reactions with 2-cyclohexenone and 2-cycloheptenone provide an [8+2] or formal [4+2] cycloadduct through an endocyclic linear-dienamine intermediate. $CatNH_2$, chiral primary amine catalyst.

Table 1 | Organocatalytic enantioselective reaction of 2-cycloalkenones 2a–2c with heptafulvenes 3A–3C.



Entry	*n*	X	[6+4] cycloadduct	[8+2] cycloadduct	[4+2] cycloadduct
1*	1	O	**4aA**; 51% yield, 95% e.e., >20:1 d.r.	–	–
2†	1	$C(CN)_2$	**4aB**; 50% yield, 42% e.e., >20:1 d.r.	–	–
3*,†	1	$C(CN)CO_2Et$	NR	NR	NR
4*	2	O	–	–	**6bA**; 72% yield, 71% e.e., >20:1 d.r.
5†	2	$C(CN)_2$	–	–	**6bB**; 56% yield, 87% e.e., >20:1 d.r.
6†	2	$C(CN)CO_2Et$	–	**5bC**; 58% yield, 98% e.e., 85:15 d.r.	–
7*,†	3	O	NR	NR	NR
8†	3	$C(CN)_2$	**4cB**; 5% yield, 52% e.e., >20:1 d.r.	**5cB**; 48% yield, >99% e.e., 9:1 d.r.	–
9†,‡	3	$C(CN)CO_2Et$	–	**5cC**; 61% yield, 99% e.e., >20:1 d.r.	–

*Conditions A: **1c** (0.02 mmol), **2** (0.2 mmol), **3A** (0.1 mmol) and (–)-CSA (0.04 mmol) in 1,4-dioxane (0.1 ml) at 60 °C. †Conditions B: **1b** (0.02 mmol), **2** (0.2 mmol), **3B** or **3C** (0.1 mmol) and $EtCO_2H$ (0.02–0.06 mmol) in toluene (0.1 ml) at 60 °C (Supplementary Information gives the details). ‡Performed at 80 °C. NR, no reaction; dashes indicate that no product was observed.

the less electron-poor cyanoesterheptafulvene **3C** was applied, the [8+2] cycloadduct **5bC** was isolated in good yield (58%) and excellent stereoselectivities (98% e.e., 85:15 d.r.) (Table 1, entry 6).

2-Cycloheptenone **2c** did not react with tropone **3A**, whereas it underwent an [8+2] cycloaddition with both heptafulvenes **3B** and **3C** in 48–61% yield and excellent stereoselectivities (9:1 to >20:1 d.r., 99 to >99% e.e.) (Table 1, entries 7–9). The only reaction not being completely periselective was the reaction between 2-cycloheptenone **2c** and dicyanoheptafulvene **3B**, which gave the [6+4] cycloadduct **4cB** as a by-product (Table 1, entry 8).

Whereas tropone **3A** readily reacted with **2a** and **2b** under Conditions A, only moderate results were obtained under Conditions B (**3A** + **2a**: 48% yield, >20:1 d.r., 65% e.e. and for **3A** + **2b** no reaction was observed). In addition, no reactions were observed when Conditions A were applied to the reactions of dicyanoheptafulvene **3B** and cyanoesterheptafulvene **3C** with the 2-cycloalkenones **2**. In general, all the reactions reported in Table 1 do not reach full conversion of the starting materials and the products are only isolated in moderate-to-good yields. Prolonged reaction times only led to degradation of the starting materials without improvements in the yield of the reactions. No or few by-products were observed by ^{1}H NMR spectroscopy on the crude reaction mixtures and the apparent disappearance of the starting materials is ascribed to polymerization reactions.

At this point, the reaction pathways for the formation of the products were not clear. The products might be formed by three

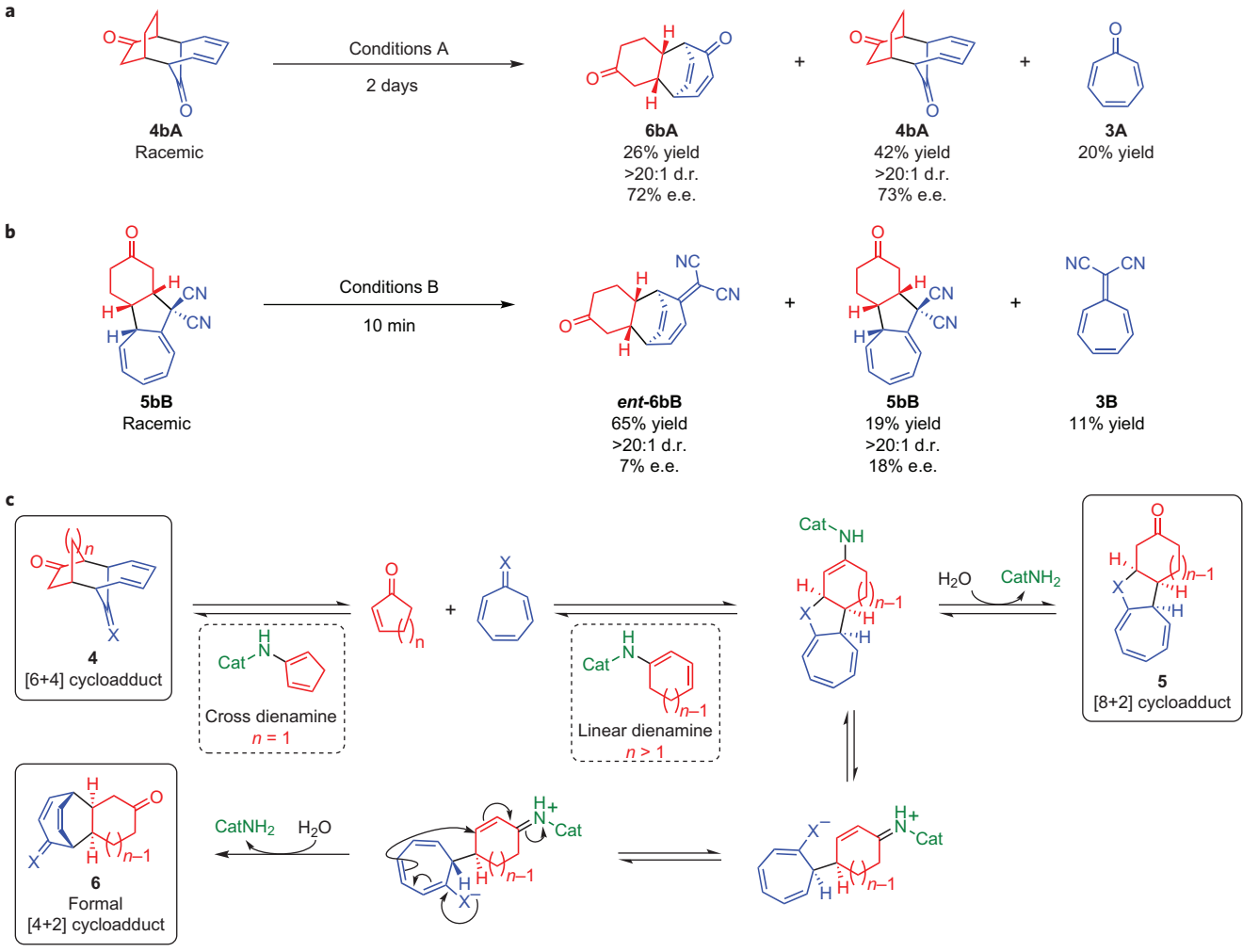


Figure 2 | Elucidating the reaction pathway. a, Equilibration of **4bA** to the thermodynamically most stable cycloadduct **6bA**. **b**, Equilibration of **5bB** to the thermodynamically most stable cycloadduct **6bB**. **c**, The reaction pathways in accordance with the equilibration experiments. Cross-dienamine activation of a 2-cycloalkenone leads to a [6+4] cycloaddition with the heptafulvene, whereas-linear dienamine activation leads to an [8+2] cycloaddition. The formal [4+2] cycloadducts were formed by an initial [8+2] cycloaddition followed by a rearrangement to give the formal [4+2] cycloadducts. Conditions A and B are given in the footnotes to Table 1.

distinct cycloadditions, or by interconversion of the cycloadducts; for example, interconversion of [6+4] and [8+2] cycloadducts via a [3,3]-sigmatropic rearrangement/oxy-Cope rearrangement[38,39], or interconversion of [8+2] and [4+2] cycloadducts via zwitterionic intermediates[37,40]. In an attempt to elucidate the reaction pathways, racemic samples of the [8+2] cycloadduct **5bB** and [6+4] cycloadduct **4bA** were prepared (we were unable to obtain **4bB** and **5bA**) because their respective [4+2] cycloadducts **6bA** and **6bB** have lower potential energies (vide infra). Under Conditions A, used for the formation of the [4+2] cycloadduct **6bA**, the racemate of the [6+4] cycloadduct **4bA** was converted into the [4+2] cycloadduct **6bA** with similar stereoselectivities as for the reaction between 2-cyclohexenone **2b** and tropone **3A** (Fig. 2a). Furthermore, unreacted [6+4] cycloadduct **4bA** was recovered in a high optical purity (the e.e. of the recovered **4bA** was dependent on the reaction time), which indicates a resolution of the racemic starting material. These results show that the organocatalyst is involved in a retro [6+4] cycloaddition of **4bA** followed by the formation of the cycloadduct **6bA**. To investigate the [8+2] to [4+2] interconversion, a racemic sample of [8+2] cycloadduct **5bB**, which was not observed in the organocatalytic reaction (Table 1, entry 5), was subjected to Conditions B used for the formation of the [4+2] cycloadduct **6bB** (Fig. 2b). The reaction was significantly faster (ten minutes) compared with the reaction of 2-cyclohexenone **2b** with dicyanoheptafulvene **3B** (18 hours) and yielded the enantiomer of **6bB** with a very low 7% e.e. In addition, the interconversion of racemic **5bB** to *ent*-**6bB** was completely retarded in the absence of the aminocatalyst. These results show that the aminocatalyst is involved in the interconversion of the [8+2] cycloadduct **5bB** into the [4+2] cycloadduct **6bB** and that the interconversion does not proceed via 2-cyclohexenone **2b** and dicyanoheptafulvene **3B**. The results are summarized in Fig. 2c.

In accordance with the results in Table 1 and the proposed reaction pathway in Fig. 2c, both 2-cyclohexenone **2b** and 2-cycloheptenone **2c** underwent an initial [8+2] cycloaddition with the heptafulvenes **3A**–**3C** through a linear-dienamine intermediate (Table 1, entries 4–9). All the reactions with cyanoesterheptafulvene **3C** were found to give the [8+2] cycloadducts, whereas both tropone **3A** and dicyanoheptafulvene **3B** produced [4+2] cycloadducts with 2-cyclohexenone **2b** through an unobserved [8+2] cycloadduct intermediate.

To investigate the influence of the electronic properties of the 2-cyclohexenone on the periselectivity of the reaction, a series of substituted 2-cyclohexenones **7** was prepared and reacted with tropone **3A**, dicyanoheptafulvene **3B** and cyanoesterheptafulvene **3C** (Fig. 3). It was observed that **3A** did not react with **7** under either Conditions A or B, whereas a formal [4+2] cycloaddition

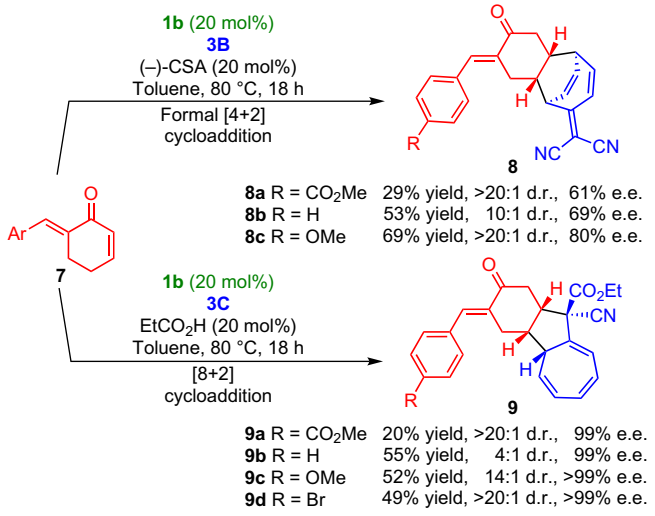


Figure 3 | Control of formal [4+2] and [8+2] periselectivity of the cycloadditions of 2-cyclohexenones 7 by reactions with heptafulvenes. Using the common starting material **7**, one can obtain either the [4+2] or [8+2] product. By varying the nature of the acid used, synthetically useful yields of products with a variety of substituents can be obtained with excellent diastereo- and enantioselectivity.

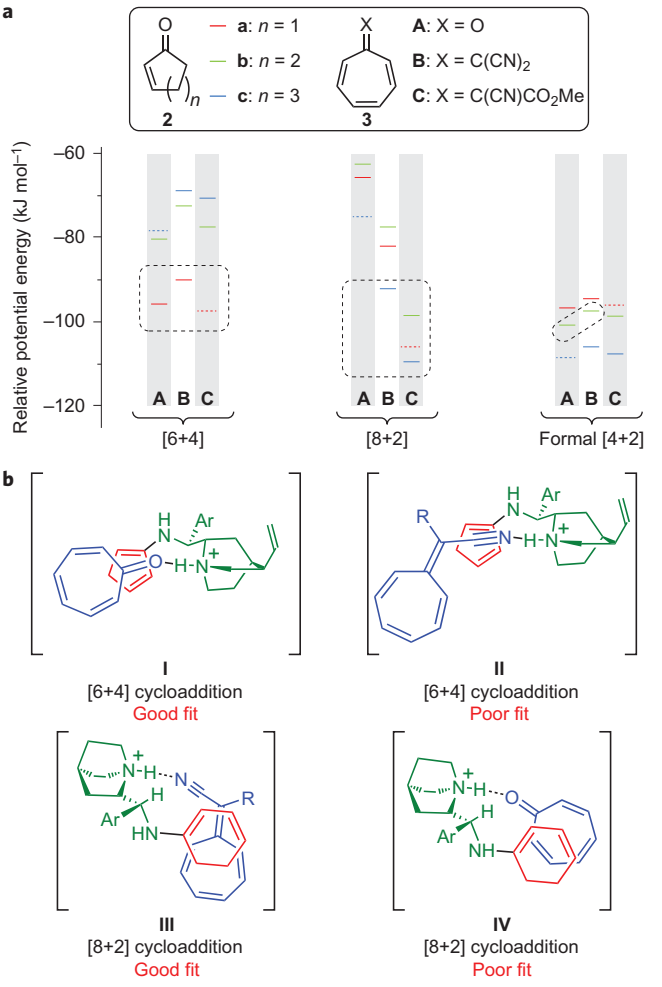


Figure 4 | Rationalization of peri- and stereoselectivities. a, Relative potential energies of [6+4] cycloadducts **4**, [8+2] cycloadducts **5** and [4+2] cycloadducts **6** to their respective starting materials. The observed products are marked within dotted boxes. Density functional theory calculations were performed using the ωb97X-D functional and the pc-2 basis set. **b**, Proposed transition-state structures for the aminocatalytic [6+4] and [8+2] cycloadditions.

proceeded with dicyanoheptafulvene **3B** to yield the cycloadduct **8b** under Conditions B (27% yield, 10:1 d.r., 49% e.e.). Improvements in yield and enantioselectivity were found when (–)-CSA (CSA, camphorsulfonic acid) was used as the acid additive to form **8b** (53% yield, 10:1 d.r., 69% e.e.). In the reactions to generate the [4+2] cycloadducts **8**, yields and stereoselectivities were found to be dependent on the electronic properties of the substituents in **7**. Improvements in yield and enantioselectivity were observed when the 2-cyclohexenone **7** is more electron rich (Fig. 3, top reaction). When the 2-cyclohexenones **7** were reacted with cyanoesterheptafulvene **3C** under Conditions B an [8+2] cycloaddition was realized in all cases (Fig. 3, bottom reaction). For this reaction path the different substituents did not have any significant influence on the enantioselectivities (99 to >99% e.e.), but resulted in variations of the diastereoselectivities (4:1 to >20:1). These results demonstrate that the periselectivity of the cycloaddition reactions of 2-cyclohexenones depends solely on the nature of the heptafulvene **3** and not on the electronic properties of the 2-cyclohexenone.

The moderate-to-good enantioselectivities for the formation of the [4+2] cycloadducts **8** (Fig. 3, top reaction) can be rationalized based on the reaction pathway in Fig. 2c. The catalyst performs the [8+2] to [4+2] rearrangement most rapidly for the minor enantiomer of the [8+2] cycloadduct, which rearranges to **8** (extrapolated from Fig. 2b). As the [8+2] cycloaddition is assumed to be reversible, the decreased nucleophilicities of the linear dienamines from **7** compared with the linear dienamines from **2b** (80 °C for reactions of **7** versus 60 °C for reactions of **2b**) lead to a deterioration of the enantioselectivity of the reaction when **7** becomes less electron rich because of a slower [8+2] to [4+2] rearrangement.

To obtain a better understanding of the periselectivity of these higher-order cycloadditions, the potential energies of all classes of products **4**, **5** and **6** were calculated relative to their respective starting compounds. Figure 4a displays the relative potential energies of the possible products obtained from the reactions of 2-cycloalkenones **2a**–**2c** with heptafulvenes **3A**–**3C** and the observed products are marked within dotted boxes (see Supplementary Table 2 for specific values). For 2-cyclopentenone **2a** the [6+4] cycloadditions are more exothermic (~20 kJ mol^{-1}) compared with the [6+4] cycloadditions with 2-cyclohexenone **2b** and 2-cycloheptenone **2c**. The two [6+4] cycloaddition products obtained are lower in potential energy relative to the [8+2] cycloaddition products, but are in the same range as the formal [4+2] cycloaddition products. Thus, the calculations predict the formation of a mixture of [6+4] and [4+2] cycloadducts under thermodynamic conditions. Interestingly, only the [6+4] cycloadducts were observed, which suggests a kinetic preference for this reaction. In two cases, the formation of the [4+2] cycloadducts was observed. These [4+2] cycloadducts were formed under the thermodynamic conditions shown in Fig. 2 and also supported by the calculations (>20 kJ mol^{-1} preference for the [4+2] cycloadducts over the [6+4] and [8+2] cycloadducts). Finally, the observed [8+2] cycloadducts **5bC**, **5cB** and **5cC** were calculated to have lower relative potential energies than their respective [6+4] cycloadducts (>20 kJ mol^{-1}). These [8+2] cycloadducts are thermodynamically less stable or similar in energy to the [4+2] cycloadducts. As the [4+2] cycloadducts were not observed in these reactions, the activation barrier for the [8+2] to [4+2] cycloadduct rearrangement is predicted to be too high to proceed under the reaction conditions.

To sum up, the periselectivity of the cycloadditions can be explained as follows: for cases in which the activation barrier for the [8+2] to [4+2] cycloadduct rearrangement is too high to proceed under the reaction conditions, the [6+4] or [8+2]

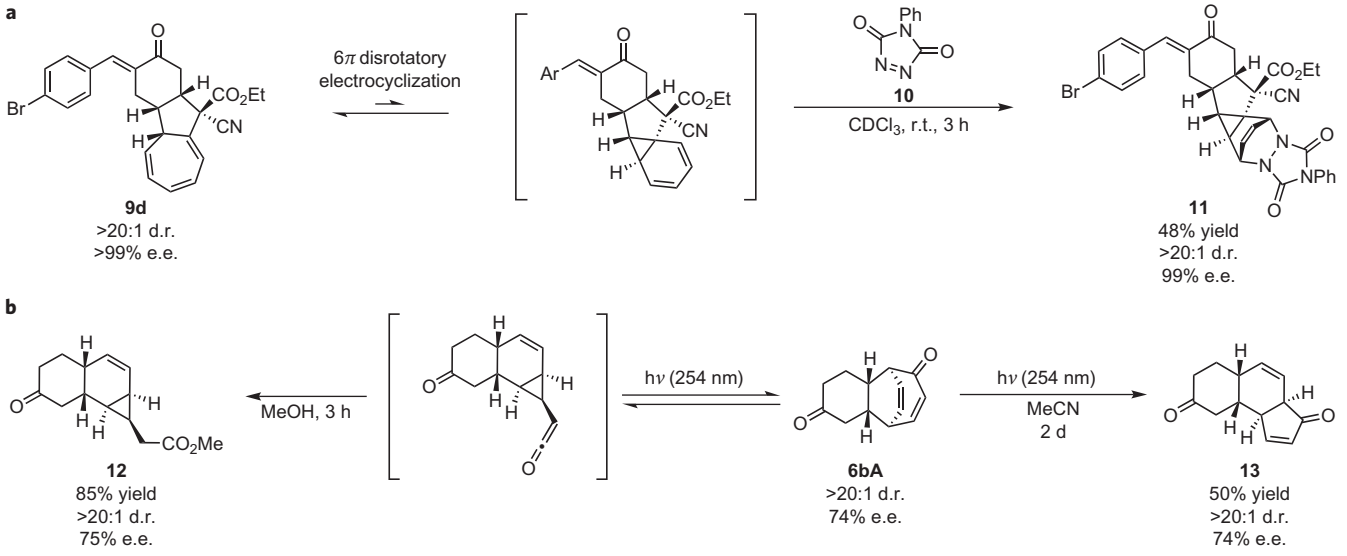


Figure 5 | Selected transformations. a, Cycloheptatrienes exist in equilibrium with their norcaradiene tautomer, which can be trapped selectively in a Diels–Alder reaction. **b**, The formal [4+2] cycloadduct **6bA** can undergo either a photochemical [3,3]-sigmatropic rearrangement or a photochemical 1,3-acyl shift. The reaction pathway can be controlled by the selection of a nucleophilic/non-nucleophilic solvent.

cycloadduct with the lowest relative potential energy is formed, whereas when the [8+2] to [4+2] cycloadduct rearrangement readily proceeds, the thermodynamically most stable [6+4], [8+2] or [4+2] cycloadduct is formed.

The mechanistic aspects of the reactions catalysed by cinchona alkaloid primary amines **1** have been investigated recently by Houk and co-workers[41,42]. Based on these mechanistic investigations, we are able to propose transition-state models for the [6+4] and [8+2] cycloadditions that rationalize the results presented in Table 1 (Fig. 4b).

The [6+4] cycloaddition is initiated by the condensation of 2-cyclopentenone **2a** with the aminocatalyst **1**. This intermediate, in its protonated form, is set up for hydrogen bonding to tropone **3A** as it places the 6π component of tropone for the *exo*-selective interactions with the 4π component of the cross-dienamine intermediate (Fig. 4b, **I**). Spatial considerations of the transition state account for the stereochemical outcome of the reaction, which is in accordance with the absolute configuration obtained by X-ray analysis of the [6+4] cycloadduct. Whereas tropone **3A** can easily be placed in close proximity to the cross dienamine in an *exo*-transition state when being activated and directed through hydrogen bonding to the catalyst, dicyanoheptafulvene **3B** does not fit this model well, as hydrogen bonding to the cyano group places the heptafulvene moiety too far away from the cross dienamine (Fig. 4b, **II**). These different approaches are reflected in the high (95% e.e.) and low (42% e.e., 52% e.e.) enantioselectivities of the reactions (Table 1, entries 1, 2 and 8).

The [8+2] and [4+2] cycloadducts are formed through reactions of a linear dienamine intermediate (Fig. 2c). As the catalyst directs the approach of the heptafulvene **3B** or **3C** through hydrogen bonding to the cyano group, the 8π component of the heptafulvene and the 2π component of linear dienamine are placed in an *endo*-transition state (Fig. 4b, **III**). This provides a rationale for the absolute configuration of the cycloadducts obtained. For reactions that take place via a linear dienamine, the nucleophilic double bond of the dienamine is placed further away from the catalyst compared with that of the cross dienamine. Hydrogen bonding between the catalyst and the cyano group of **3B** and **3C** places the heptafulvene in an optimal spatial orientation towards an *endo*-selective [8+2] cycloaddition (Fig. 4b, **III**), whereas tropone is moved too close to the catalyst and away from the nucleophilic double bond on hydrogen bonding to the catalyst (Fig. 4b, **IV**). These considerations are reflected in the stereoselectivities of the reactions (Table 1, entries 4–9).

To demonstrate the synthetic potential of these cycloadducts, selected transformations were performed to show the ease with which they can be turned into other molecular scaffolds. Cycloheptatrienes can co-exist in equilibrium with small amounts of their norcaradiene tautomer through a thermally allowed 6π disrotatory electrocyclization. The norcaradiene tautomer of **9d** could be trapped through a Diels–Alder reaction with triazolinedione **10** to form the hexacyclic compound **11** (Fig. 5a). The [4+2] cycloadduct **6bA** was found to undergo a photochemical [3,3]-sigmatropic shift to form a ketene intermediate that could be trapped with methanol to form **12** (Fig. 5b). Alternatively, in the absence of a nucleophile, product **13** was formed through the less efficient 1,3-acyl shift.

The absolute configurations of **11**, tribrominated **4aA** and monobrominated **6bB** were unambiguously determined by single-crystal X-ray diffraction and the configurations of all the remaining products were assigned by analogy (Supplementary Information).

In conclusion, we have developed novel and unprecedented organocatalytic asymmetric higher-order cycloaddition reactions exemplified by intermolecular [8+2], [6+4] and formal [4+2] cycloadditions. The reactions proceed with excellent stereoselectivities for 2-cycloalkenones that reacted with heptafulvenes in the presence of cinchona alkaloid primary amines as catalysts. The periselectivity can be controlled by the ring size of the 2-cycloalkenones and the substitution pattern of the heptafulvenes. This set of reactions provides an easy set-up for the generation of a variety of polycyclic scaffolds from commercial or readily available starting materials. In addition, it was demonstrated that the products from the cycloaddition reactions can undergo simple one-step transformations to give access to other all-carbon polycyclic compounds.

Data availability

X-ray crystallographic data for compounds **4aA**, **11**, **15** and **16** are freely available from the Cambridge Crystallographic Data Centre (CCDC 1434123, 1469731, 1457777 and 1470038, respectively).

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Author contributions

R.M. and G.P. optimized the reactions. R.M., G.P., J.L. and E.H.I. performed the experiments. S.J. performed the calculations. R.M. and K.A.J. wrote the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to K.A.J.

Competing financial interests

The authors declare no competing financial interests.