

# Diastereodivergent Enantioselective [8+2] Annulation of Tropones and Enals Catalyzed by N-Heterocyclic Carbenes

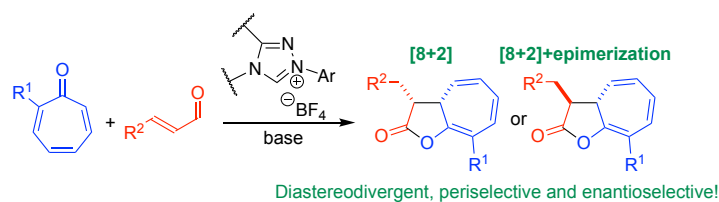
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Supporting Information Placeholder



**ABSTRACT:** N-Heterocyclic carbene (NHC) catalysts are used for the first time to mediate asymmetric [8+2] cycloadditions of enals with tropones. The kinetic [8+2] *cis*-cycloadducts can be epimerized to their *trans* analogues by simply using increased amounts of base and longer reaction times. Substituted tropones are also tolerated, and the cycloaddition products can be derivatized by hydrogenation or methanolysis. The main stereochemical features of the process have been rationalized by microkinetic modeling based on the results of DFT calculations.

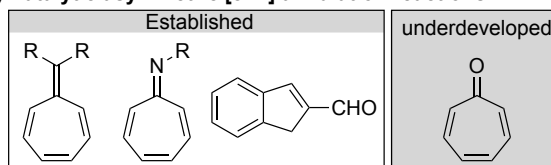
Chiral catalyst development has given rise to an ever growing toolkit that allows to cover a wide range of chemical space through myriad transformations. However, the stress is usually placed in selectivity rather than versatility.<sup>1</sup> In other words, synthesis of a different isomer, where possible, usually requires changing the catalyst or the reaction. However, in some particular cases subtle changes in the reaction conditions can give rise to either the kinetic or the thermodynamic product. If this approach is successful, it significantly expands the chemical space covered by a given catalyst, thus increasing its versatility.<sup>2</sup> However, reaching good levels of selectivity for both isomers is generally challenging, so the number of such methodologies is relatively scarce.

Enantioselective higher order cycloadditions<sup>3-4</sup> (HOCs) are inherently difficult transformations due to the fact that control of periselectivity represents another challenge that adds up to diastereo- and enantioselectivity. However, a few authors have shown that it is indeed a feasible approach, which gives rise to very interesting compounds bearing unusual scaffolds.<sup>5-17</sup> Within the realm of HOCs, several examples on [8+n] annulation reactions have been reported,<sup>18-32</sup> albeit the asymmetric variant has been limited to heptafulvenes,<sup>33</sup> and azaheptafulvenes<sup>34-35</sup> (Scheme 1a). Indeed, enantioselective [6+n]<sup>5-11,33</sup> and [4+2]<sup>12,36</sup> processes involving tropones have been described, but this substrate remained essentially unexplored as an 8π component for catalytic enantioselective transformations<sup>37</sup> (Scheme 1b) until this year, when Feng and co-workers published the [8+3] annulation of tropones and azaheptafulvenes

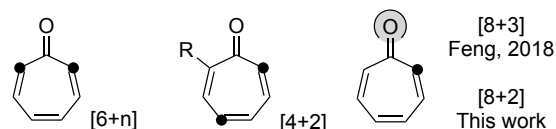
with meso-aziridines.<sup>38</sup> In this work, we report the first examples of NHC-catalyzed asymmetric [8+2] processes between tropones derivatives and enals (Scheme 1c).

## Scheme 1. Catalytic enantioselective [8+n] cycloadditions.

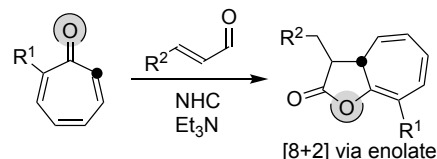
### (a) Catalytic asymmetric [8+n] annulation reactions



### (b) Catalytic asymmetric transformations of tropones

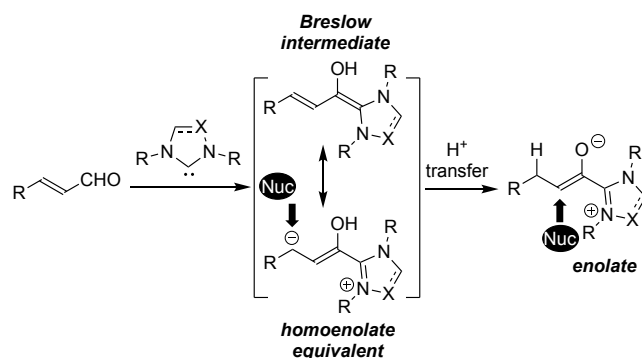


### (c) This work: NHC-catalyzed [8+2] annulation of tropones



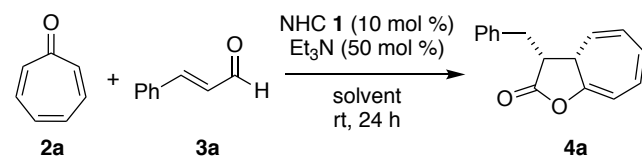
We have recently reported that isothiourea catalysts are able to mediate highly stereo- and periselective [8+2] annulations of azaheptafulvenes, leading to [5.3.0] bicyclic products.<sup>35</sup> However, some limitations remained, such as the fact that tropones proved unreactive and only arylacetic acid derivatives were tolerated as the 2 $\pi$  component. Thus, we started investigating whether NHC catalysts might also be able to promote these HOCs and whether this might expand the substrate scope. NHC catalysts<sup>39-43</sup> are known to provide chiral azolium enolate species upon reaction with ketenes,  $\alpha$ -functionalized aldehydes and  $\alpha,\beta$ -unsaturated aldehydes.<sup>44-46</sup> We reasoned that the latter, given their wide availability and stability, would be more interesting as substrates for an annulation process.<sup>47</sup> In this case, the Breslow intermediate undergoes proton transfer to render an azolium enolate, which plays the role of the 2 $\pi$  component, in a redox neutral process (Scheme 2).

### Scheme 2. Generation of an enolate equivalent by reaction of an NHC catalyst and an $\alpha,\beta$ -unsaturated aldehyde



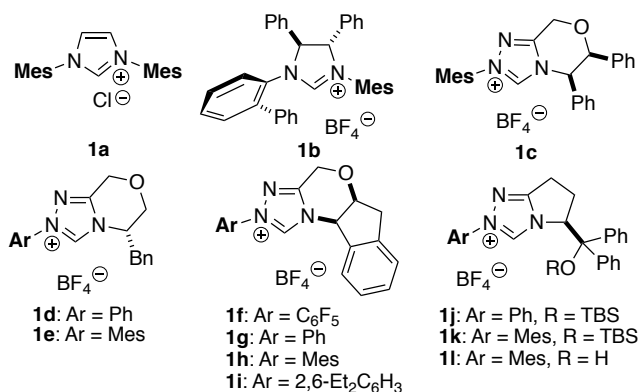
To assess the viability of the strategy, we selected tropone **2a** and enal **3a** as the benchmark substrates (Table 1). To our delight, achiral NHC precursor **1a** was able to furnish the annulated product **4a** (entry 1). Despite the low yield and dr, this result served as a proof of concept, which encouraged us to screen the behavior of a battery of chiral NHC precursors **1b-1l** (entries 2-12). As a general trend, mesityl-containing NHC precursors performed better than analogues with less bulky groups, which is in agreement with the rationalization made by Bode et al.<sup>48</sup> The most promising of these experiments, which entailed the use of triazolium salt **1h**, furnished the bicyclic product **4a** in good yield and dr and with excellent enantioselectivity (98%). Subsequent solvent screening (entries 13-17) and optimization of the reaction time led us to conclude that the use of DCE and 48 h reaction time were optimal for this particular example. These observations contrast with the previous report by Nair et al. in which similar starting materials and an achiral NHC catalyst give rise to the corresponding [8+3] product, presumably via homoenolate.<sup>49</sup>

**Table 1.** Optimization of the reaction conditions for the [8+2] annulation of tropone derivatives with enals.<sup>a</sup>



entry	NHC precursor	solvent	conv. [%] <sup>b</sup>	dr <sup>b</sup>	ee [%] <sup>c</sup>
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1	<b>1a</b>	CH <sub>2</sub> Cl <sub>2</sub>	20	1:2	–
2	<b>1b</b>	CH <sub>2</sub> Cl <sub>2</sub>	<10	–	–
3	<b>1c</b>	CH <sub>2</sub> Cl <sub>2</sub>	37	2:1	97
4	<b>1d</b>	CH <sub>2</sub> Cl <sub>2</sub>	<10	–	–
5	<b>1e</b>	CH <sub>2</sub> Cl <sub>2</sub>	48	2:1	76
6	<b>1f</b>	CH <sub>2</sub> Cl <sub>2</sub>	trace	–	–
7	<b>1g</b>	CH <sub>2</sub> Cl <sub>2</sub>	<10	1:1	93
8	<b>1h</b>	CH <sub>2</sub> Cl <sub>2</sub>	62	4:1	98
9	<b>1i</b>	CH <sub>2</sub> Cl <sub>2</sub>	35	5:1	98
10	<b>1j</b>	CH <sub>2</sub> Cl <sub>2</sub>	trace	–	–
11	<b>1k</b>	CH <sub>2</sub> Cl <sub>2</sub>	<10	–	–
12	<b>1l</b>	CH <sub>2</sub> Cl <sub>2</sub>	<10	–	–
13	<b>1h</b>	DCE	64	5:1	98
14	<b>1h</b>	CHCl <sub>3</sub>	48	4:1	98
15	<b>1h</b>	Tol	<10	2:1	97
16	<b>1h</b>	THF	41	3:1	97
17	<b>1h</b>	CH <sub>3</sub> CN	39	2:1	95
18 <sup>d</sup>	<b>1h</b>	DCE	73	4:1	98

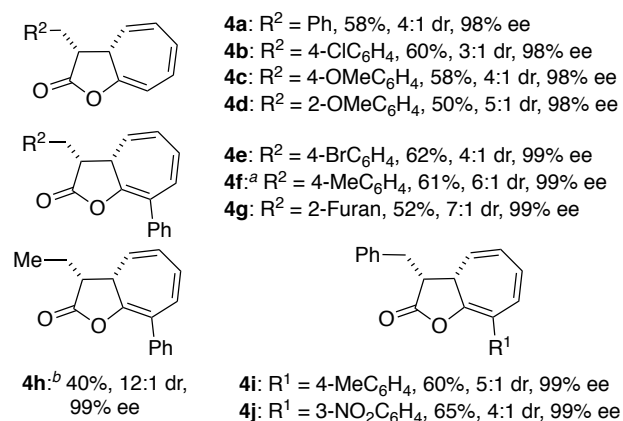
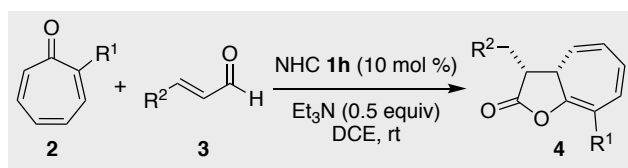


<sup>a</sup> Reactions performed on a 0.1 mmol scale. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> reaction time was 48 h.

Identifying the optimal reaction conditions allowed us to study the scope of this [8+2] annulation, as shown in Scheme 3. Pristine tropone reacted with several  $\alpha,\beta$ -unsaturated aldehydes giving the corresponding products (**4a-4d**) in decent yields, moderate to good dr's and excellent enantioselectivities, a general trend in most of the examples to be discussed. 2-Phenyltropone also proved to be a good substrate for this transformation, leading to bicyclic products **4e-4g**, bearing aromatic and

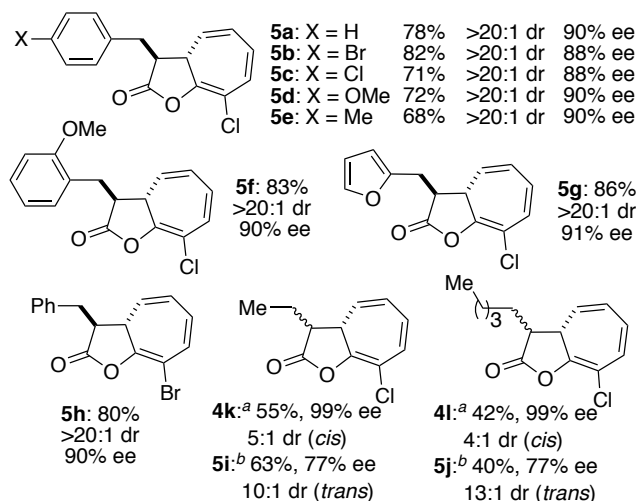
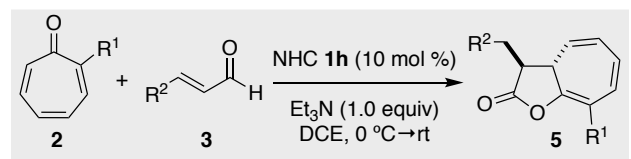
heteroaromatic substituents. Even crotonaldehyde, a usually challenging substrate, could react with 2-phenyltroponone furnishing **4h** in rather low yield (40%) but excellent stereoselectivity (12:1 dr, 99% ee). As for the 2-aryltroponone, it could be modified with electron-donating and electron-withdrawing substituents without affecting its behavior (**4i-4j**). The absolute configuration of cycloadducts **4** was based on the X-ray diffraction of **4e**.<sup>50</sup> During the optimization of reaction conditions we found that a selectivity switch was taking place if stoichiometric amounts of base and extended reaction times were applied, providing **5** (the *trans*-diastereomer) as the major compound. The substrate scope for reactions leading to **5** is summarized in Scheme 4. For instance, 2-chlorotroponone reacted with a variety of para-substituted cinnamaldehydes (**5a-5e**), furnishing the cycloadducts in good yields, excellent dr's and good ee's (88-90%). The absolute configuration of **5b**<sup>50</sup> was established by X-ray diffraction, the rest being assigned by analogy. *o*-Methoxycinnamaldehyde provided the desired product **5f**, whereas introduction of a 2-furyl substituent rendered **5g** in similarly good results. The brominated analog **5h** could also be produced from 2-bromotroponone in very good yield, dr and ee. As a token of the versatility of this approach, when crotonaldehyde and heptenal were reacted at 0 °C for 48 h the *cis*-isomers (**4r** and **4t**) were obtained as the main product. However, simply warming up to rt and extending the reaction times for a further 72 h gave the *trans* cycloadducts (**5i** and **5j**). Such a selectivity switch, from the kinetic to the thermodynamic product, allows to cover a wider chemical space with practically the same reaction conditions. The epimerization observed could also be carried out with an isolated substrate, as shown by treating **4e** with 2 equivalents of Et<sub>3</sub>N, which provided **5k** in moderate diastereo- but excellent enantioselectivity (Scheme 5a). Derivatization of the cycloadducts was also proved feasible. For instance, hydrogenation of **5a** gave rise to **6** in very good yield and chemoselectivity (Scheme 5b). On the other hand, treatment with methanol effected a ring opening-elimination sequence to yield **7**, with only marginal erosion of the enantiomeric excess.

### Scheme 3. Scope of the [8+2] annulation reaction under optimized conditions.



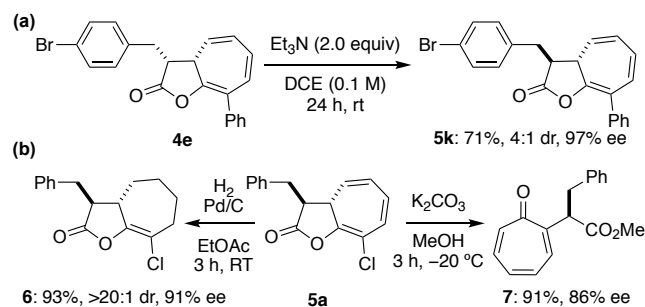
<sup>a</sup> 1.0 equiv of Et<sub>3</sub>N. <sup>b</sup> 3.0 equiv of enal and 1.0 equiv of Et<sub>3</sub>N.

### Scheme 4. Scope of the [8+2] annulation-epimerization reaction



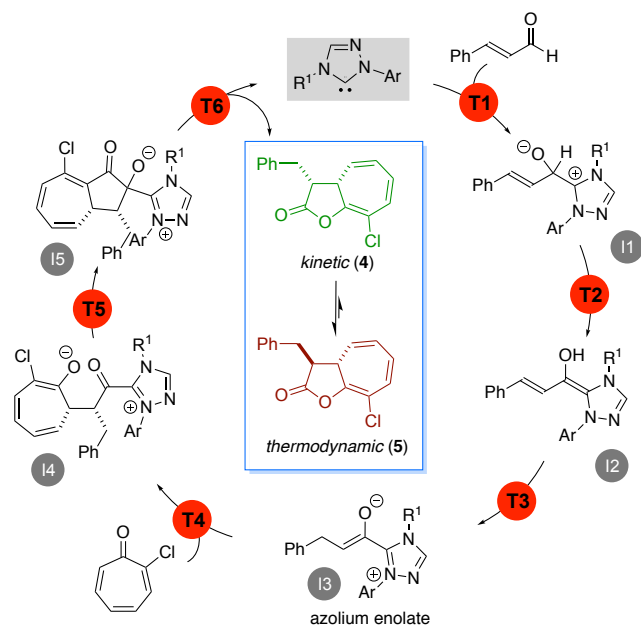
<sup>a</sup> At 0 °C for 48 h. <sup>b</sup> At 0 °C for 48 h; then, at rt for 72 h.

### Scheme 5. Derivatization of the [8+2] adducts

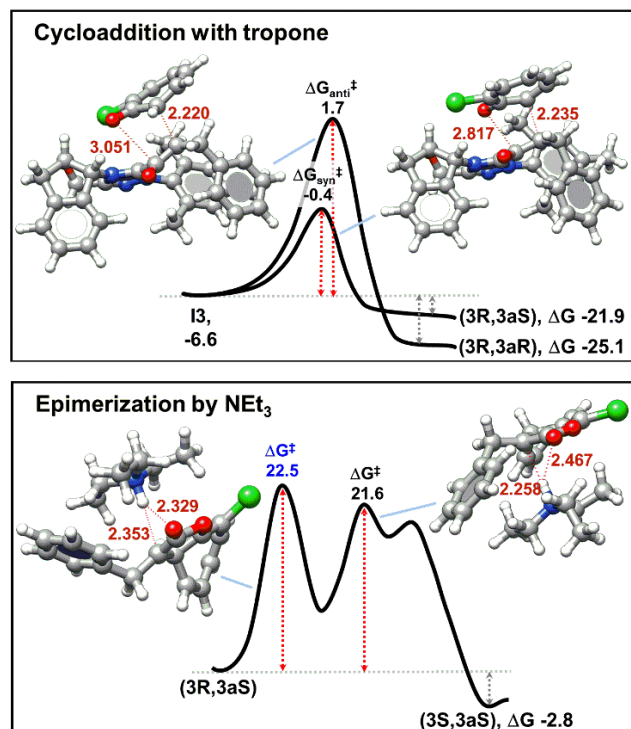


In order to explain the origin of the selectivity in the reaction, we decided to study the system with DFT methodology,<sup>51</sup> which has proved to afford reliable results for organocatalytic processes.<sup>56-57</sup> Besides gaining a general view on the factors that determine the sense of stereoinduction, we aimed at understanding the effect of the nature of the β-substituent of the reacting aldehyde on the diastereoselectivity (compare **4a** and **4h**), rationalizing the effect of a 2-chloro substituent in troponone on the observed diastereoselectivity under kinetic control [from 4:1 for R<sup>1</sup> = H (**4a** in Scheme 3) to 1:1.5 for R<sup>1</sup> = Cl (see Table S5)], and understanding the course of the base-mediated epimerization. To this end, we selected the combinations of reactants leading to **5a**, **4a**, **4e** and **4h**, with **1h** as catalyst precursor. The calculated reaction profile is in all cases qualitatively the same, and fits with the catalytic cycle represented in Figure 1 for the reaction leading to **5a**. The triazolium salt (**1h**) is deprotonated by NEt<sub>3</sub>, and the so-formed NHC catalytic species then attacks the carbonyl of cinnamaldehyde through transition state **T1**, evolving through intermediates **I1**, **I2** (which is the Breslow intermediate<sup>58-60</sup>) and **I3**.<sup>46-47</sup> This intermediate then undergoes a rapid and irreversible 1,8-addition to the troponone derivative<sup>61</sup> through transition state **T4** (Figure 2, top), which determines both the enantio- and the diastereoselectivity of the process. The resulting intermediate **I4** further evolves, ultimately releasing the product and regenerating the NHC catalyst. In a relevant step outside

the catalytic cycle, also shown in Figure 1, the cycloaddition product can experience  $\text{NEt}_3$  catalyzed epimerization leading to the more thermodynamically stable *trans* diastereomer.



**Figure 1.** Relevant intermediates (**I**) and transition states (**T**) in the calculated reaction profile NHC catalyzed [8+2] cycloaddition of tropones with enals. The sequence leading to **5a** is shown, and the base has been omitted for clarity



**Figure 2.** Relevant steps in the mechanistic pathway leading to **5a**

Since only the *Z* configuration of the enolate in intermediate **I3** is energetically available, the cycloaddition can only lead to the products with *(3R,3aS)* and *(3R,3aR)* configurations, depending on the face (*Re* or *Si*, respectively) of the tropone reactant involved in the process. For the four studied cases, catalyst **1h** always biases

stereoselectivity at **T4** towards the production of *(3R,3aS)* furanone as the major kinetic product. This is likely because of the easier sterical accommodation of the oxygen of the tropone against the mesityl group of the catalytic pocket in the TS leading to that configuration. According to the studied cycloaddition step, the four systems should have a similar behavior, leading to **4a**, **4e**, **4h** and **5a** with only minor differences in the diastereomeric composition (see Table S19). However, while this is true in the first three cases, the prediction is completely wrong for **5a** where the *trans* diastereomer predominates. A possible explanation for this behaviour can be found taking into consideration the experimentally observed base catalyzed epimerization, that could transform the *(3R,3aS)* *cis* diastereomer into the *(3S,3aS)* *trans* one. Interestingly, the calculated barrier to epimerization is lower for **5a** (22.5 kcal.mol<sup>-1</sup>) than for **4h**, **4a** and **4e**, (25.0, 26.9 and 23.2 kcal.mol<sup>-1</sup>, respectively). The reason of the enhanced epimerization rate of **5a** is likely related to the presence of the chlorine substituent that stabilizes the approach of the base through H...Cl interactions (Figure 2, bottom). In any case, it is not obvious that this subtle difference in the epimerization barrier can account in a quantitative manner for the differential course of the reaction leading to **5a**. To overcome this limitation, we decided to run microkinetic modeling calculations,<sup>62</sup> which translate activation barriers and initial concentrations into concentrations after a given reaction time, thus providing the most accurate insight into real reacting systems. Full details of these calculations are provided in the SI, and the final results have been summarized in Table 2. As it can be seen, not only the major stereoisomer formed in the reaction is correctly predicted when the full reaction possibilities are considered, but also an almost perfect agreement with the experimental results in the four studied cases.

**Table 2.** Comparison of experimental and calculated (microkinetic modeling) stereoselectivities for all investigated systems at 298 K in DCE

	Abs. config.	Exp. dr	Calcd. dr	Exp. ee [%]	Calcd. ee [%]
<b>4h<sup>a</sup></b>	<i>(3R,3aS)</i>	92:8	100:0	99	100
<b>4a<sup>a</sup></b>	<i>(3R,3aS)</i>	80:20	90:10	98	98
<b>4e<sup>a</sup></b>	<i>(3R,3aS)</i>	80:20	83:17	99	100
<b>5a<sup>b</sup></b>	<i>(3S,3aS)</i>	94:6	98:2	87	81

<sup>a</sup> Under optimized conditions (Scheme 3). <sup>b</sup> Under the conditions of entry 5 in Table S6 (DCE, 1 eq Et<sub>3</sub>N, 24h, rt).

In summary, we have been able to exploit the particular reactivity of enals vs. tropones with NHC catalysts to carry out higher order cycloadditions leading to cyclohepta[b]furan-2-ones in high enantiomeric purity. Interestingly, the reaction can be directed to different diastereomers of the [8+2] adducts through small modification of reaction conditions leading to a shift from kinetic to thermodynamic control. DFT computational kinetic modeling strongly corroborates the experimental findings in terms of periselectivity and stereoselectivity.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxxxxxx.

General information, screening conditions, general procedures, compound characterizations, epimerization studies, HPLC chromatograms, and <sup>1</sup>H and <sup>13</sup>C NMR spectra. Computational remarks on free energy hypersurfaces for selected cycloaddition examples, non-corrected and corrected absolute and relative thermochemical parameters for all stationary points, kinetic models, cartesian coordinates and vibrations for all the stationary points (PDF).

## Accession Codes

CCDC 1870414 and 1870415 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest

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