



## Diels–Alder routes to angularly halogenated cis-fused bicyclic ketones: readily accessible cyclonone intermediates

Jun Hee Lee<sup>a,\*</sup>, Woo Han Kim<sup>b</sup>, Samuel J. Danishefsky<sup>a,b,\*</sup>

<sup>a</sup> Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, NY 10027, United States

<sup>b</sup> Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10065, United States

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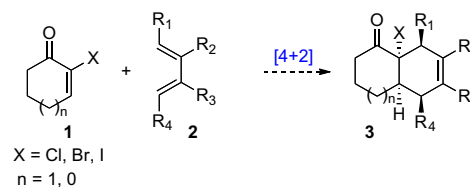
### ABSTRACT

We have developed an efficient Lewis acid-catalyzed Diels–Alder route to a series of cis-fused bicyclic ketones bearing quaternary halogenation at the angular position. We have also developed a Diels–Alder-based one-flask method for the regioselective preparation of TBS-protected 6-hydroxy tetralone and 5-hydroxy indanone derivatives.

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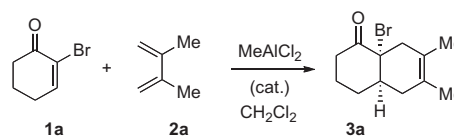
Our laboratory has a longstanding interest in expanding the capacities of the Diels–Alder reaction to the synthesis of complex and difficultly accessible molecular architectures. In this regard, cis-fused bicyclic ketones of the type **3**, bearing angular halogenation  $\alpha$  to the carbonyl function, represent a valuable substructure in organic synthesis. In principle, Diels–Alder reaction of a 2-halocycloalk-2-enone (cf. **1**)<sup>1</sup> with an appropriately substituted diene (**2**) could serve as a strategically efficient means by which to access this generic motif (Scheme 1). However, previous studies had indicated that tin(IV) chloride-catalyzed Diels–Alder cycloaddition of 2-bromocyclohex-2-enone (**1a**) with various simple dienes, such as 2,3-dimethyl-1,3-butadiene (**2a**) and isoprene (**2b**), proceeds in low yields and with incomplete conversions, even following prolonged reaction times.<sup>2</sup> In the case of diene **2a**, product decomposition served to further mitigate the reaction efficiency. Accordingly, we sought to develop an improved Diels–Alder-based method which would provide for more ready access to  $\alpha$ -halogenated bicyclic motifs of the type **3**.<sup>3</sup>

In light of our recent successes in achieving MeAlCl<sub>2</sub>-catalyzed Diels–Alder reactions of the parent compound, cyclohex-2-enone, with a series of simple dienes,<sup>4</sup> we hypothesized that the same catalytic system might be applied to the target system at hand. We note that each of the 2-halocycloalk-2-enone substrates (cf. **1**) were readily prepared according to standard procedures (see Supplementary data for details). In preliminary explorations, we observed that, in the presence of 20 mol % MeAlCl<sub>2</sub> at 0 °C, substrates **1a** and **2a** smoothly underwent the desired [4+2] addition to provide an adduct **3a** in 74% yield (Table 1, entry 1).<sup>5</sup> When the catalyst loading was dropped to 10 mol % and the temperature decreased to –10 °C, excellent yields of the cycloadduct were obtained once more (entry 2). Importantly, this reaction could be



Scheme 1.

Table 1  
MeAlCl<sub>2</sub>-catalyzed Diels–Alder reaction of **1a** and **2a**<sup>a</sup>



Entry	MeAlCl <sub>2</sub> (mol %)	Temperature (°C)	Yield (%)
1	20	0	74
2	10	–10	91
3	10	–10	89 (gram-scale) <sup>b</sup>

<sup>a</sup> Reactions were carried out using 4 equiv diene at 0.2 M in CH<sub>2</sub>Cl<sub>2</sub> with respect to enone.

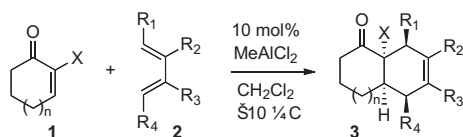
<sup>b</sup> Using 6.00 mmol (1.05 g) of **1a**.

achieved even on a gram scale with comparable levels of efficiency (entry 3).

We next sought to evaluate the scope of the Diels–Alder reaction with respect to structural variations in both the diene and the dienophile components. Thus, as outlined in Table 2, we were pleased to find that our Diels–Alder conditions were able to accommodate a range of dienophile and diene-coupling partners. Thus, cyclohex-2-enones bearing both  $\alpha$ -chloro (**1b**) and  $\alpha$ -iodo (**1c**) functionalities readily participate in the cycloaddition with 2,3-dimethyl-1,3-butadiene to afford bicyclic products in excellent yields

\* Corresponding authors. Tel.: +1 212 639 5501; fax: +1 212 772 8691 (S.J.D.).  
E-mail address: s-danishefsky@ski.mskcc.org (S.J. Danishefsky).

**Table 2**  
MeAlCl<sub>2</sub>-catalyzed [4+2] reaction of 2-halocycloalk-2-enones<sup>a</sup>



Entry	Enone	Diene	Product	Yield (%)
1				94
2				90 <sup>b</sup>
3				91
4				72 <sup>c</sup>
5				90
6				70 <sup>d</sup>
7				87 <sup>e</sup>

<sup>a</sup> Unless otherwise indicated, the reactions were carried out at –10 °C for 2 h, using 10 mol % MeAlCl<sub>2</sub> and 4 equiv diene at 0.2 M in CH<sub>2</sub>Cl<sub>2</sub> with respect to enone.

<sup>b</sup> Reaction was carried out in the dark, since cycloadduct **3c** is light-sensitive.

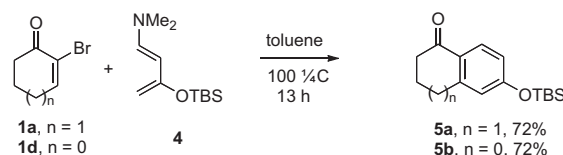
<sup>c</sup> Reaction was carried out at 0 °C for 1 h.

<sup>d</sup> Reaction was carried out at –20 °C for 3.5 h; the *exo*-cycloadduct (not shown) was also isolated, in 12% yield.

<sup>e</sup> Reaction was carried out at –7 °C for 6 h, using 30 mol % MeAlCl<sub>2</sub>.

(entries 1 and 2). Moreover, 2-bromocyclopent-2-enone (**1d**) and 2-chlorocyclopent-2-enone (**1e**) display good levels of reactivity, providing cycloadducts **3d** and **3e** in 91% and 72% yields, respectively (entries 3 and 4). The reaction is also amenable to variation in diene substitution. Thus, reaction of **1a** with diene **2b** delivered the bicyclic adduct **3f** as a single regioisomer (entry 5). Substrate **2c**, bearing methyl substitution at the 1-position of the diene, also participated in the cycloaddition with apparently complete regioselectivity, although a mixture of *endo*:*exo* adducts (6:1) was observed (entry 6). The two diastereomers were readily separated by chromatographic means.<sup>6</sup> Finally, even the relatively unreactive butadiene (**2d**) effectively participated in the Diels–Alder reaction with **1a**, in the presence of 30 mol % MeAlCl<sub>2</sub>, to furnish adduct **3h** in 87% yield within 6 h (entry 7).

Finally, having established the optimal conditions for the Diels–Alder reaction of 2-halocycloalk-2-enones (**1a–e**) with simple dienes (**2a–d**), we sought to evaluate the cycloaddition of this class of dienophile with an electron-rich synergistic diene. Interestingly,



**Scheme 2.**

under thermal conditions, the Rawal diene (**4**)<sup>7</sup> and bromocyclohexenone **1a** undergo cycloaddition followed by a spontaneous elimination of the dimethylamine and hydrogen bromide moieties, to cleanly deliver the aromatic bicyclic adduct **5a**<sup>8</sup> as a single regioisomer in 72% yield (Scheme 2). The bromocyclopentenone **1d** undergoes an analogous sequence to provide compound **5b**. All attempts to isolate the direct cycloaddition product were unsuccessful, presumably due to its strong propensity to undergo aromatization. Clearly, in couplings with electron-rich dienes of the type **4**, the  $\alpha$ -bromocycloenone can function as a readily available equivalent of a cycloalkynone. We note that the original concept of a cyclohexynone equivalent was articulated by Corey in 1981.<sup>9</sup> In the Corey example, the cyclohexynone was of opposite effective polarity to the cycloalkynones shown here. Not surprisingly, this procedure gives rise to oxygenated tetralones with different structures from the Corey case.

In conclusion, we have developed an operationally simple method for the preparation of a series of cis-fused bicyclic ketone derivatives bearing angular  $\alpha$ -halogenation. We have also developed a one-flask, highly regioselective method for the preparation of TBS-protected 6-hydroxy tetralone and 5-hydroxy indanone derivatives. Ongoing research in our laboratory is focused on further adaptation of these functionalized Diels–Alder adducts.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.135.

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- All the new compounds gave satisfactory analytical data (mp, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and high resolution mass). See Supplementary data for experimental and analytical details.
- Relative stereochemistry of both cycloadducts was confirmed by extensive 1D and 2D NMR analyses such as <sup>1</sup>H, <sup>13</sup>C, DEPT-135, DEPT-90, COSY, HSQC, and NOESY. See Supplementary data for details.
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