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Intramolecular Diels–Alder Reactions of Cycloalkenones: Translation of High *Endo* Selectivity to *Trans* Junctions

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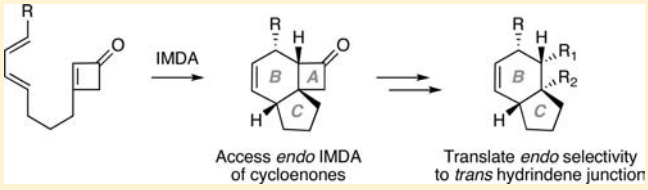
Supporting Information

ABSTRACT: Intramolecular Diels–Alder reactions of cyclobutenone and larger cycloalkenones are described. High levels of *endo* addition attained from Lewis acid catalysis translate to *trans* hydrindene junctions upon fragmentation of the tricyclic adducts.



INTRODUCTION

The role of the Diels–Alder reaction in organic chemistry is well appreciated.[1,2] Its particular impact on complex targeted natural product synthesis arises, in the first instance, from its capacity to deliver extensively functionalized six-membered rings with defined sites of unsaturation and functional group placements. Moreover, it provides the basis for coordinating stereogenic centers in the emerging cyclohexene. These configurational relationships are governed by the apparently universal suprafacial nature of the Diels–Alder reaction, and by the less universal mode of mutual presentation of its diene and the dienophilic components (i.e., *endo* vs *exo* addition).

Thus, in the formation of cyclohexene **3** by Diels–Alder logic, the relationships at C_1 and C_4 reflect the incident stereochemistry of diene **1** (Figure 1, shown with Z-hydrogens

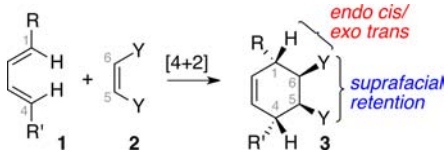


Figure 1. Stereochemistry of Diels–Alder reactions.

at C_1 and C_4), which is transmitted to **3** via suprafacial cycloaddition. The same governing principle dictates the emerging relative configurations at C_5 and C_6 arising from dienophile **2** (shown for illustration with two *cis* Y groups). The mutual relationship of C_1/C_6 and C_4/C_5 reflects the outcome of *endo* vs *exo* preference.

Generally, in thermally mediated intermolecular Diels–Alder reactions with typical dienophilic activation, *endo* presentation tends to be favored. Not infrequently, Lewis acid catalysis enhances *endo* selectivity in Diels–Alder reactions.[3]

Intramolecular variations of the Diels–Alder reaction (IMDA) are similarly recognized for their capacity to deliver high-complexity cycloaddition products.[4] Stereochemical connectivity in the IMDA reaction is dictated by the same arguments discussed above. In cases where the tethering element is sufficiently flexible to allow for either *endo* or *exo* presentation, *endo*/*exo* selectivity can be problematic (Figure 2).

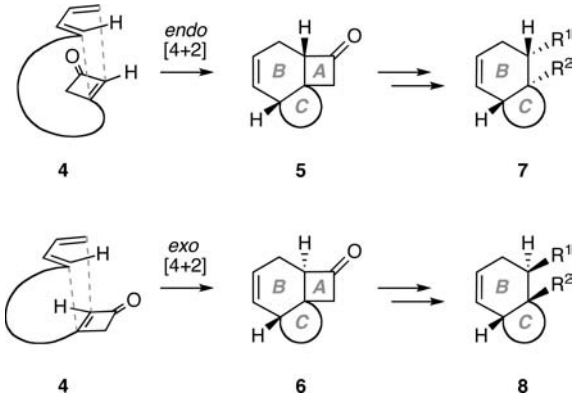


Figure 2. Cyclobutenone IMDA concept.

In an earlier study, we had demonstrated the powerful dienophilicity of cyclobutenone in the context of intermolecular Diels–Alder reactions.[5] In those explorations, it was found that the parent cyclobutenone not only is quite reactive, but also exhibits high levels of *endo* control, even in uncatalyzed settings. Following those findings, we wondered about the utility of a cyclobutenone dienophilic moiety in the context of IMDA reactions. To deal with this question, it would be necessary to synthesize probe substrates with a 1,3-diene suitably tethered to a carbon center of a dienophilic cyclobutenone. We would attempt to demonstrate the anticipated cycloaddition. Assum-

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ing IMDA reaction did occur, we would hope to determine *endo*/*exo* preferences in both catalyzed and uncatalyzed modes. Finally, this study would compare the IMDA characteristics of a cyclobutenone moiety with those of more traditional cyclopentenone- and cyclohexenone-type dienophiles. Though these cycloalkenones might be powerful Diels–Alder synthons on paper, the latter two are notoriously sluggish dienophiles.[6−9]

For reasons of design and synthetic convenience, we proposed to place the diene-containing tether at C_3 of the cyclobutenone (see system **4**, Figure 2). In addition to exploring this uncharted IMDA reaction type, and addressing several questions of interest to students of the Diels–Alder reaction, there was another consideration. Figure 2 spells out the stereochemical consequences of the *endo* vs *exo* modalities of diene/dienophile presentations, leading to **5** and **6**, respectively. It was hoped that the ketone function of the IMDA product would provide a site for cleavage of the cyclobutanone A-ring. This possibility is generalized in the form of the respective bicyclic degradation products **7** and **8**, to be retrieved from **5** and **6**, respectively. Thus, while the cycloaddition, per se, creates the AB fusion, it is the coalescence of the tether, the γ-carbon of the diene, and the β-carbon of the activated dienophile which gives rise to a new ring. In our construction, this peripherally formed ring is referred to as the C-ring. It is also fused to the B-ring.

Herein, we report the following: (i) reduction to practice of the central cyclobutenone IMDA hypothesis, (ii) high levels of *endo* stereoselection and extension even with the more classical cyclopentenone and cyclohexenone dienophilic moieties in the β-tethering arrangement employed here, and (iii) an illustrative method for obtaining *trans*-fused hydrindenes from the resultant tricyclic IMDA products.

It is easily recognized that the *trans* ring junction found in **7**, and the nonparallel relationship of the double bond at the BC junction, are inaccessible from conventional Diels–Alder reaction logic. In the case of *cis*-fused **8**, the double bond is, again, nonparallel to the junction. Thus, **8** is also not *directly* accessible by a classical [4+2] step.

A complementary motivation underlying these studies was that of enhancing the reach of the pattern recognition analysis (PRA) approach to retrosynthetic design.[10] We view PRA as an aid to the powerful dominant logic of prioritized strategic bond disconnections formulated by Corey and associates.[11−13] In PRA, one seeks to identify subunits, i.e. *motifs*, within a more complex target. Identification of such patterns may bring to light a strategic framework for building outward from the pattern in advancing to the target. Alternatively, one might identify several recognizable patterns that can be melded by appropriate chemistry.

Of course, for PRA to aid in retrosynthetic analysis, the patterns must themselves be accessible by synthesis. Thus, it was anticipated that, by identifying useful motifs for PRA and by charting new pathways for their synthesis (utilizing new insights and new protocols), the potential applicability of PRA as a resource in retrosynthetic analysis would be significantly enhanced. In terms of PRA, **7** corresponds to a *trans*-iso-Diels–Alder motif, while **8** can be seen as a *cis*-iso-Diels–Alder structure.

RESULTS AND DISCUSSION

Two routes for producing the required tethered probe structures to facilitate the study were employed. Starting with the case of cyclobutenone (Figure 3), we selected an

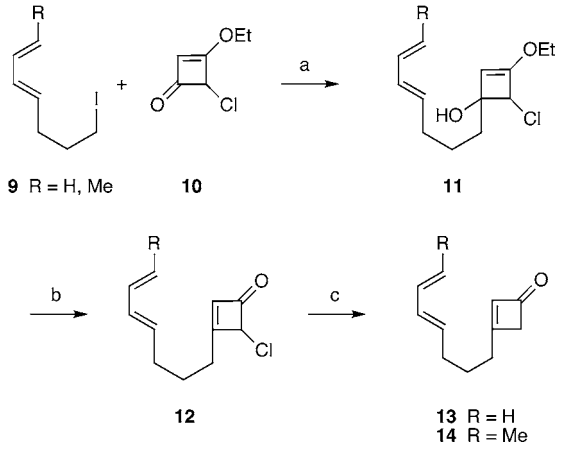

Figure 3. Preparation of cyclobutenone substrates. Key: (a) *t*-BuLi, **9**, then **10**; (b) TFAA/$NaHCO_3$ or trace $BF_3{\cdot}OEt_2$, 56–66% yield; (c) Zn, AcOH, TMEDA, MeOH, 64–69% yield.

arrangement where the diene was to be separated from the β-carbon of the cyclobutenone moiety by a tether of three methylene groups. Following the IMDA reaction, a five-membered C-ring would be produced by the coalescence described in Figure 2. The method of synthesis of such precursor substrates centered on reaction of a lithium derivative of the type **9** (R = H or Me) with the known 4-chloro-3-ethoxycyclobutenone **10**.[14] Following 1,2-addition and unraveling mediated by trifluoroacetic acid (TFAA) or trace $BF_3{\cdot}OEt_2$, there was obtained the pre-IMDA substrate **12**, which could be reductively dechlorinated by the action of zinc in acetic acid, tertiary amine, and alcoholic solvent.[15] Two probe substrates **13** and **14**, prepared by this method, were to be studied in detail as to their performance in IMDA reactions (vide infra).

As the study was expanded to include cyclopentenone and cyclohexenone as the dienophiles in the IMDA reaction, a second protocol was adopted (Figure 4). Reaction of **9** with the

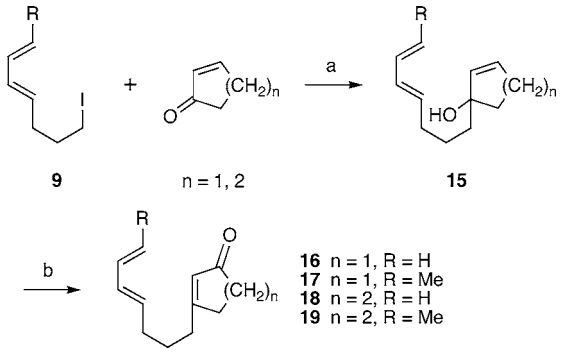

Figure 4. Preparation of IMDA substrates. Key: (a) *t*-BuLi, **9**, then cycloalkenone; (b) PCC, 58–69% yield over two steps.

appropriate cycloalkenone gave rise to the expected allylic tertiary alcohols **15**. After oxidative transposition of these intermediates,[16] probe systems **16**–**19** were in hand. Subsequently, this method was extended to cover the cases of **9** with four methylene groups in the cyclobutenone, as well as cyclopentenone and cyclohexenone settings (vide infra).

We first examined the cyclobutenone-containing dienophile **13** (Figure 5). It was found that, under $BF_3{\cdot}OEt_2$ mediation, IMDA reaction occurred in good yield, giving rise to **20** with high levels of stereoselection. Thus, *endo* selection in the

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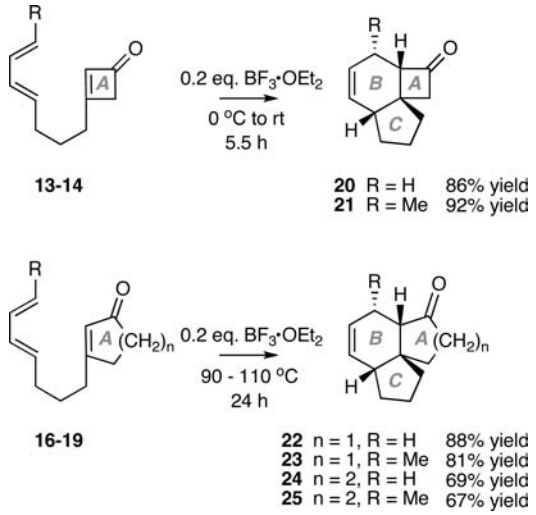

Figure 5. Lewis acid (LA)-catalyzed IMDA reactions.

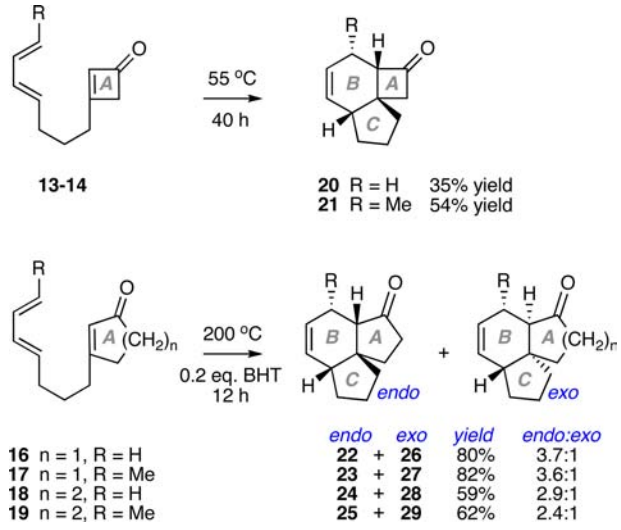

Figure 6. Thermal IMDA reactions.

cycloaddition step, giving rise to the *cis* AB junction, had also established the *trans* BC relationship. Similarly, the terminal pentadienyl compound **14** also underwent IMDA reaction mediated by $BF_3{\cdot}OEt_2$. Once again, the process was highly *endo* selective, giving rise to **21** in high yield. In both cases there seemed to be some decomposition of these vulnerable substrates. We found no indication for formation of a closely related stereoisomeric (*exo*) product as a factor in yield erosion.

It was of interest to determine whether the finding of strict *endo* cycloaddition, in the cases of **13** and **14**, extends to more traditional dienophilic cycloalkenones, which are significantly less reactive than is cyclobutenone.[17] Moreover, in the few literature cases where the performance of five- and six-membered cycloalkenone dienophiles in IMDA reactions were evaluated (though in a different tethering mode), levels of *endo* selectivity were not easily interpretable, let alone predictable.[18−20]

Happily, $BF_3{\cdot}OEt_2$ catalysis of substrates **16**−**19** also gave rise to apparently single cycloaddition products (**22**−**25**, Figure 5). Though rather more forcing conditions were required, and somewhat diminished yields were observed in the larger cycloalkenone IMDA reactions, the logic described above does serve well to provide excellent means of generating peripheral (BC) *trans* junctions. Perhaps this advance could be used toward the development of enantioselective catalysis conditions for cycloalkenones in the future.

We next asked whether the high yields and margins of *endo* stereoselection manifested in these BF_3-mediated IMDA reactions would extend to uncatalyzed conditions (Figure 6). As above, the two cyclobutenone tethered cases **13** and **14** produced **20** and **21**, respectively. Again, these were the only products found. Not surprisingly, absent catalysis, significantly higher temperatures were required to effect IMDA reaction. The yields of IMDA products **20** and **21** were reduced to 35% and 54%, respectively. Substrate decomposition, rather than product instability, was shown to be the cause of the diminished yields, since **20** and **21**, on resubjection to the reaction conditions, were actually quite stable.

A more complicated situation arose following IMDA reactions of dienylcycloenones **16**−**19** under thermal conditions. Here, again, we obtained IMDA products in each case. However, high temperatures were required in uncatalyzed reactions (ca. 200 °C) along with antioxidant 2,6-bis(1,1-dimethylethyl)-4-methylphenol (butylated hydroxytoluene, or BHT). Diastereomeric mixtures were encountered in the ratios indicated (see *exo* isomers **26**−**29**, in addition to the major *endo* products **22**−**25**). In summary, then, as regards the IMDA reactions in the cases studied thus far, only Lewis acid-catalyzed protocols provide yields and stereospecificities suitable for further development.

The tethering described in systems **13**−**19** has involved three methylene groups between the diene and dienophilic elements of the IMDA reaction. Thus, the collateral C-ring formed in the Lewis acid-directed mode is five-membered and *trans*-fused to the concurrently emerging B-ring; i.e., a "*trans* hydrindenoid" submotif is elaborated. We wondered about extending the size of the tether by one methylene group, thereby providing access to a six-membered collateral C-ring. Following degradation of the A-ring (see Figure 2), a *trans*-fused octalin would emerge. Toward that end, we prepared compounds **30**−**32**,[21] using much the same chemistry described earlier (see **13**, **14**, and **16**−**19**).

We were most surprised to find that, upon reaction of compound **30**, which we expected to be the best prospect of these substrates under Lewis acid-catalyzed conditions (first with zinc chloride as the catalyst), *the previously described compound* **21** was obtained (in 53% yield, Figure 7). When the reaction was conducted, as before, with $BF_3{\cdot}OEt_2$ as the catalyst, the same product was produced, but now only in 22% yield. Further, **21** was also the only product obtained, albeit in poor yield, from thermal IMDA reactions of **30**. Under both conditions, no isomerized **14** was recovered; the mass balance

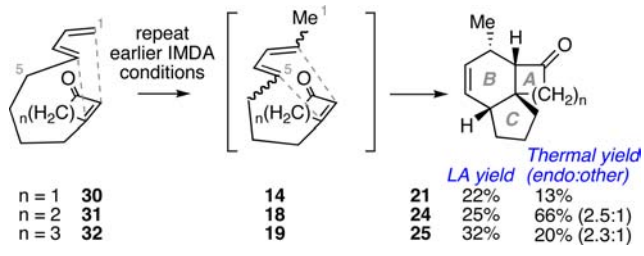

Figure 7. Tandem diene migration−IMDA. Thermal and Lewis acid (LA)-catalyzed IMDA conditions for the appropriate dienophile ring size are as shown in Figures 5 and 6.

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loss was from substrate decomposition. Apparently, Lewis acid or thermolysis provoked isomerization of the butadienyl four-carbon tether, providing the pentadienyl three-carbon tether (see compound **14**). This tandem diene migration–IMDA process was at the time unexpected but is, in retrospect, not unprecedented.[22−26]

While four *E,Z* stereopermutations of **14** are theoretically possible, apparently only the *E,E* isomer undergoes cycloaddition under these conditions, thereby affording the previously observed **21** in low yield. It should be recognized that, in the case of our earlier three-carbon tether substrate compounds, similar isomerization was also in principle possible. Such a migration, for instance in the case of **13**, would have generated a two-carbon tether of the cyclobutenone, which was independently confirmed to not undergo isomerization or IMDA reaction under the conditions employed in this study.[21] Since the conversion of **13**→**20** had occurred in fairly high yield, diene migration must be much slower than cycloaddition. Assuming that the migration is roughly independent of the differing tether size (i.e., **13** and **30** might be seen as equally prone to double bond migration), the direct IMDA reaction in the case of **30** (as opposed to **13**) is far slower than in the analogous double bond migration. Put differently, in changing the tether from three to four methylene groups, *the rate of IMDA cycloaddition is dramatically attenuated*.

Given this interesting, albeit nonhelpful sequence in cyclobutenone substrate **30**, it was not surprising that the same behavior was observed from the four-methylene-tethered cyclopentenone and cyclohexenone systems **31** and **32**. In these cases, cycloaddition under thermal conditions or Lewis acid mediation gave rise, in reduced yields, to the previously encountered *endo* IMDA products **24** and **25** arising from precursors **18** and **19**, respectively.

Finally, we address the issue of exposing the target angularly substituted and functionalized hydrindenes. As discussed earlier, the plan was to exploit the ketone found in the A-ring corresponding to the original dienophile (see **4**→**5**, Figure 2). There are a variety of ways by which ring disconnection or derivatization could be accomplished. Here, for initial demonstration purposes, we chose a sequence consisting of Baeyer–Villiger oxidation to produce the erstwhile A-ring as a lactone, followed by reductive cleavage to generate a diol with differentiable primary and secondary alcohols (Figure 8). In practice, in the compounds bearing no methyl groups in the B-ring (i.e., **20**, **22**, and **24**), this chemistry occurred quite smoothly. Regiospecific-type Baeyer–Villiger oxidations could be conducted without complications. In the case of the cyclobutenone-containing product tricyclic **21** containing an A-ring methyl group, facile Baeyer–Villiger oxidation of the cyclobutenone could be accomplished with hydrogen peroxide as in substrate **20**. However, in the cases of **23** and **25**, attempted Baeyer–Villiger oxidations with *m*CPBA were frustrated by epoxidation of the resident carbon–carbon double bond. In the case of **23**, the desired Baeyer–Villiger oxidation could be achieved through the use of bis-(trimethylsilyl) peroxide (BTSP) with 5 mol % $Bi(OTf)_3$.[27,28] However, the seemingly obvious extension to **25** took a surprising turn: There was observed, transiently, what appeared to be a nonproductive Baeyer–Villiger peroxide intermediate, eventually giving rise to the isoable α-hydroxyketone **43**. Clearly, in principle, there are a wealth of methods for degrading cyclic ketones or α-hydroxyketones to unveil diversity in the *trans* hydrenoid iso-Diels–Alder pattern. One could also retain the tricycle or otherwise transform the product, for example by carbon- or nitrogen-based ring expansions.

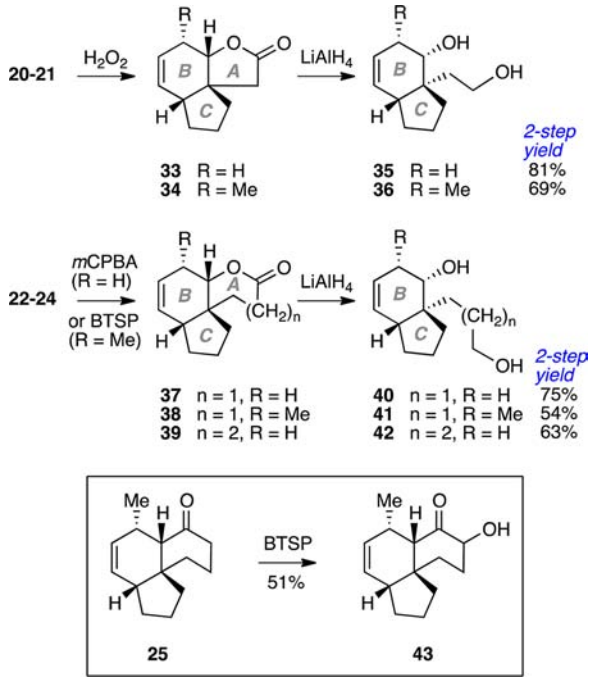

Figure 8. Illustrative fragmentation of A-ring to *trans* BC hydrindenes.

■ CONCLUSION

In summary then, the proposed logic at the core of the proposal been reduced to practice. The first examples of cyclobutenone as an IMDA dienophile are described. As in bimolecular Diels–Alder reactions, cyclobutenone is more reactive and *endo*-selective than are analogous larger cycloalkenone dienophiles. A remarkably high level of *endo* stereogovernance in the Lewis acid-catalyzed IMDA reaction was observed. These advances provide an exploitable route to otherwise difficultly accessible *trans* hydrindenoid systems, of interest in our laboratory.[29−32] The resident double bond in such structures provides additional opportunities for diversification. Given the stereoselectivity now attainable, the idea of using IMDA reactions to generate peripheral *trans* fusions is apt to be a resource in the retrosynthetic analysis of contemporary targets.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; spectral and other characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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