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# Enantioselective N-Heterocyclic Carbene Catalyzed Diene Regenerative (4 + 2) Annulation

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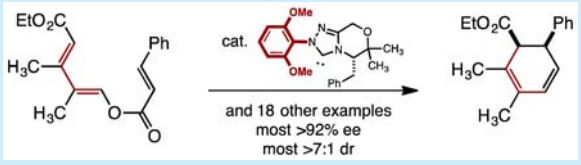
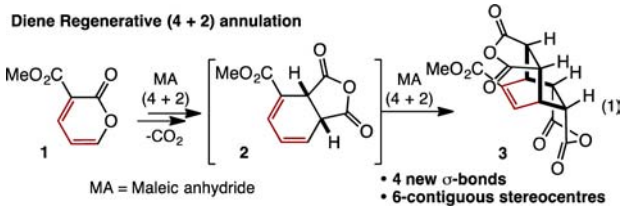
Supporting Information

**ABSTRACT:** An enantioselective N-heterocyclic carbene (NHC)-catalyzed diene regenerative (4 + 2) annulation has been achieved through the use of highly nucleophilic morpholinone-derived catalysts. The reaction proceeds with good to excellent yields, high enantioselectivity (most >92% ee), and good diastereoselectivity (most >7:1). The generality of the reaction is high, with 19 examples reported. The utility of the products has been examined with subsequent derivatization in Diels–Alder reactions using electron-poor dienophiles. Furthermore, interception of the proposed $\beta$-lactone intermediate has been achieved, allowing the synthesis of compounds bearing four contiguous stereocenters with high levels of enantio- and diastereoselectivity.




More than 80 years ago, Diels and Alder reported the double (4 + 2) cycloaddition between maleic anhydride and 2-pyranone **1**. Following an initial Diels–Alder reaction, decarboxylation regenerates diene intermediate **2** that reacts in a subsequent (4 + 2) cycloaddition (eq 1).[1a] While one-pot diene




regenerative cascades (as in eq 1) have seen limited application, stepwise and enantioselective versions have enduring significance in target-focused synthesis.[2,3]

In 2011, our group reported the diene regenerative (4 + 2) annulation of acyl fluorides (i.e., **4**) and silyl dienol ethers (i.e., **5**) (eq 2).[4a] This N-heterocyclic carbene (NHC)-catalyzed[5,6] transformation is orthogonal to pyranone (4 + 2) additions providing regioisomeric diene products (i.e., **7** cf. **2**). While the reaction is highly diastereoselective (>20:1 dr), challenges accessing the $\alpha,\beta$-unsaturated acyl azolium[7] and competing O-acylation precluded discovery of the enantioselective variant, while restricting reaction scope. To resolve these limitations, established homochiral NHCs, BAC carbenes (**A**),[8] imidazolium NHCs (**B**,[9a] **C**,[9b] and **E**[10]), and imidazoliumide NHC (**D**)[11] have been examined over the last 5 years and found wanting in the synthesis of **8** (Figure 1).[12]

Recently, we reported the (4 + 2) annulation[4c] of trienyl esters using *t*-butyl morpholinone catalyst **F1**.[13] While this reaction provides novel $\beta$-lactone products, olefin isomerization precluded diene regeneration.[14] Due to the utility of diene regenerative reactions,[1−3] we wished to overcome this limitation. Central to this would be the use of substrates less prone to olefin

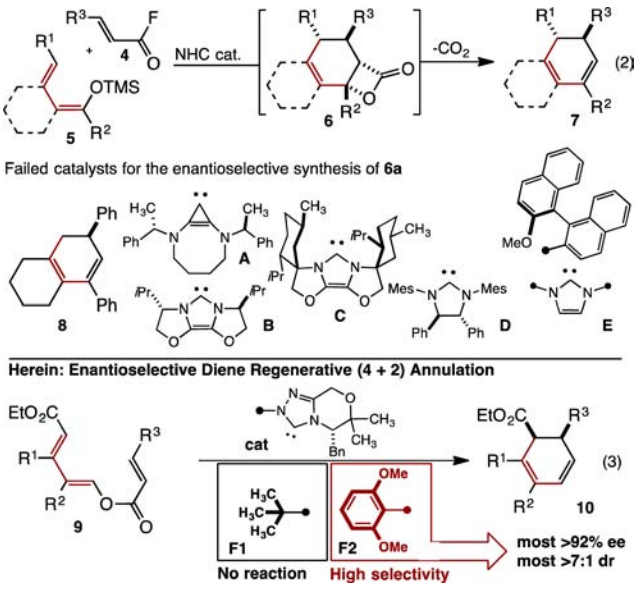



**Figure 1.** Background.

isomerization (i.e., **9**). While reaction discovery with **F1** was not possible, it was using the highly nucleophilic catalyst **F2**.[15,16] Herein, we report studies that have allowed discovery of the enantioselective NHC-catalyzed diene regenerative (4 + 2) annulation. The reaction has broad scope (>19 examples), high enantioselectivity (most >92% ee), and good diastereoselectivity (most >7:1 dr). Derivatization of the dienyl products (i.e., **10**) through subsequent Diels–Alder reactions and interception of the $\beta$-lactone intermediate are described.

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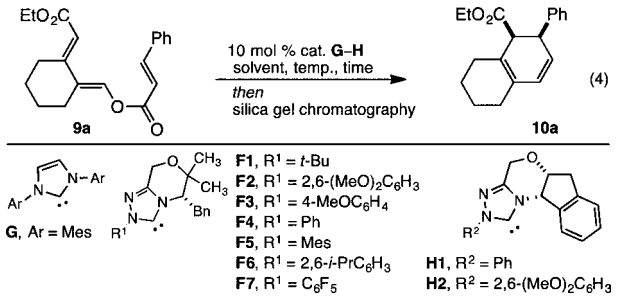
Studies commenced with triene **9a**. When exposed to IMes NHC (**G**), the (4 + 2) annulation reaction was achieved (Table 1, entry 1). While the crude residue contained both diene **10a** and $\beta$-lactone precursor (vide infra), following silica gel chromatography, decarboxylation allowed diene **10a** to be isolated in 76% yield. To develop the enantioselective variant, *N*-*t*-butyl NHC **F1**, *N*-4-methoxyphenyl **F3**, and *N*-phenyl catalyst **F4** were examined. Although **F1** and **F3** failed to provide **10a**, catalyst **F4** gave the expected product with excellent diastereoselectivity (>20:1 dr) and modest enantioselectivity (Table 1, entries 2−4). Changing to *N*-Mes **F5** (Table 1, entry 5) failed to improve the enantioselectivity; however, *N*-2,6-dimethoxyphenyl **F2**, while moderately more enantioselective at room temperature (result not shown), allowed conversion at lower temperatures, providing diene **10a** in 87% isolated yield and 65% ee after 30 min (Table 1, entry 6). In contrast, at this temperature, the reaction with catalyst *N*-Mes **F5** took 16 h to provide **10a** in 46% yield and 55% ee (Table 1, entry 7). The *N*-2,6-diisopropylphenyl NHC **F6** also allowed low-temperature reactions, however with less enantioselectivity (Table 1, entry 8), while pentafluorophenyl NHC **F7** was inactive (Table 1, entry 9). The *N*-phenyl and *N*-2,6-dimethoxyphenyl substituents were then appended to an indanol scaffold; however, catalyst **H1** was inactive, and **H2** failed to improve the selectivity (Table 1, entries 10 and 11). Similarly, performing the reaction with catalyst **F2** in toluene had little effect on the enantioselectivity (Table 1, entries 12). Although the enantioselectivity with this substrate (**9a**) was modest, this is the outlier, with other substrates (vide infra) reacting with excellent enantioselectivity (most >92% ee) under the optimized conditions (Table 1, entry 6).

**Table 1. Selected Optimization Studies**




| entry | cat.[a] | solvent | temp (°C)/time (h) | yield (%)[b] | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | **G** | THF | −78→rt/1 | 76 | >20:1 | |
| 2 | **F1** | THF | Δ/16 | NR[e] | | |
| 3 | **F3** | THF | rt/5 | NR[e] | | |
| 4 | **F4** | THF | rt/5 | 42 | >20:1 | 55 |
| 5 | **F5** | THF | rt/5 | 90 | >20:1 | 53 |
| **6** | **F2** | **THF** | **0/0.5** | **87** | **>20:1** | **65** |
| 7 | **F5** | THF | 0/16 | 46 | >20:1 | 55 |
| 8 | **F6** | THF | 0/5 | 61 | >20:1 | 62 |
| 9 | **F7** | THF | rt/5 | NR[e] | | |
| 10 | **H1** | THF | rt/5 | NR[e] | | |
| 11 | **H2** | THF | 0/5 | 79 | 9:1 | 63 |
| 12 | **F2** | toluene | 0/5 | 87 | >20:1 | 59 |

[a]Generated in situ from the salt with KHMDS; see Supporting Information. [b]Isolated yield following flash column chromatography. [c]Determined by $^1$H NMR analysis of the unpurified residue. [d]Determined by HPLC on chiral stationary phases; see Supporting Information. [e]No reaction.

The generality of the reaction was initially examined with the preparation of a series of dienyl decalans (**10a−d**) from substrates with electronically dissimilar cinnamate functionality (**9a−d**) (Figure 2). Electron-rich cinnamates reacted with higher enantioselectivity (**9c** and **d**: 78 and 84% ee) than electron-poor derivatives (**9b**, 67% ee); however, this was achieved at the expense of diastereoselectivity. While similar enantioselectivity was obtained with ring-expanded dienes (i.e., **10e**), non-annulated substrates reacted with significantly increased enantioselectivity. Thus, dimethyl cyclohexadienes derived from neutral (i.e., **9f**), electron-poor (i.e., **9g**), and electron-rich cinnamates (**9h−j**) formed with excellent enantioselectivity (93, 95, 92, 94, and 95% ee), although diastereoselectivity ranged from 3:1 to 5:1. Similarly, furan **10k** and indole **10l** were prepared in 95 and 92% ee. Longer alkyl substituents at $R^1$ and $R^2$ generally improved enantio- and diastereoselectivity. Thus, dienes **10m−q** bearing an ethyl chain at $R^1$ formed with a enantioselectivity similar to that of the dimethyl variants (94, 95, 91, 90, and 94% ee); however, the diastereoselectivity was enhanced. Furthermore, substitution with *n*-propyl and ethyl groups gave cyclohexadienes **10r** and **s** in 90 and 99% ee and 12:1 and 20:1 dr, respectively. Unfortunately, and as with other related reactions, the use of $\beta$-alkyl $\alpha,\beta$-unsaturated esters led to only traces of the expected product.

In addition to allowing the construction of two new $\sigma$-bonds and two stereogenic centers, the diene regenerative (4 + 2) annulation enables subsequent (4 + 2) annulations. Thus, a two-step process involving NHC-catalyzed (4 + 2) annulation,

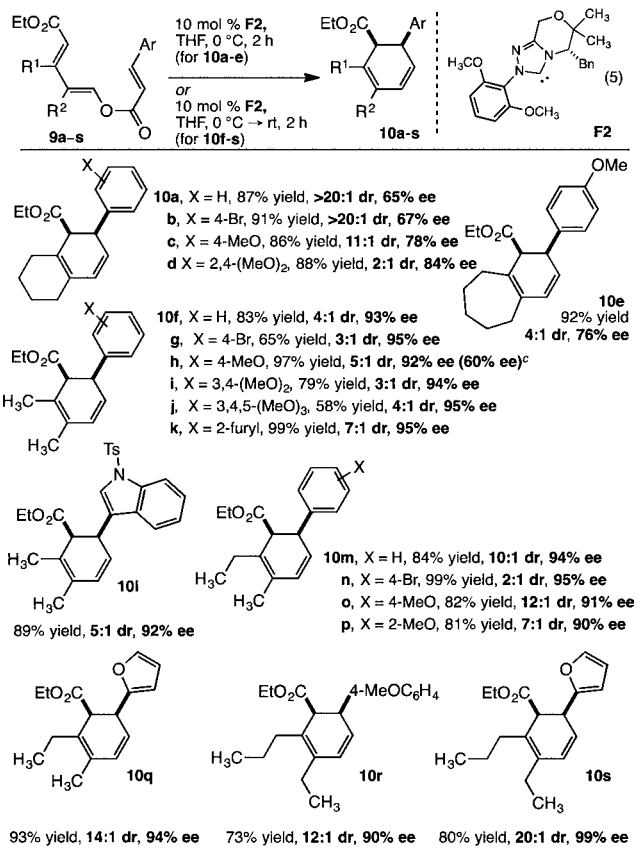



**Figure 2.** Scope of the enantioselective (4 + 2) annulation. [a]All diastereoisomers were isolated by flash column chromatography, with a combined yield of both. [b]Enantioselectivity was determined by HPLC on chiral stationary phases. [c]Minor diastereoisomer.



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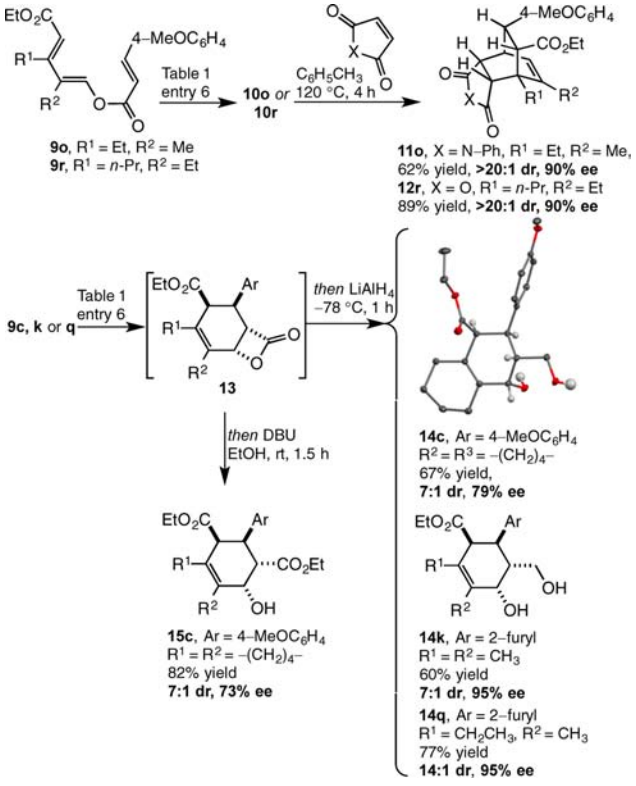
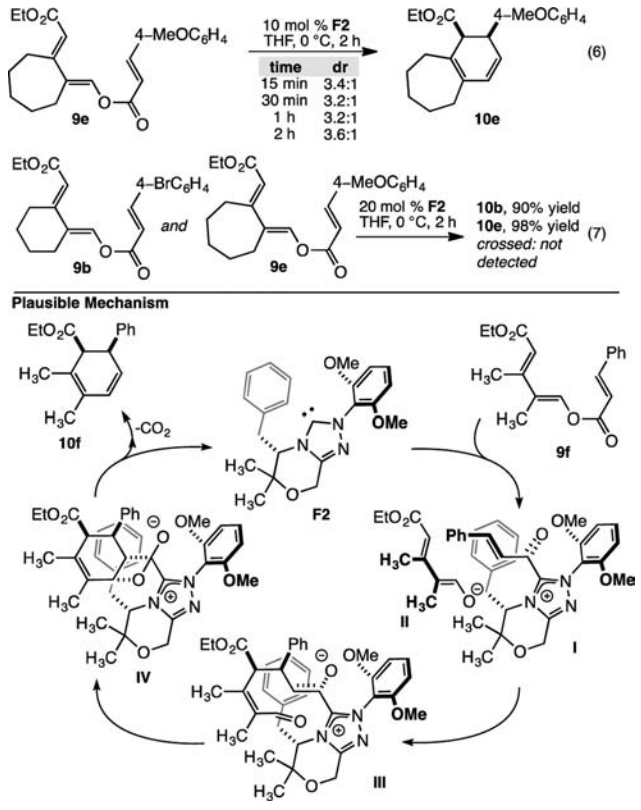
followed by a Diels–Alder reaction, can be devised to rapidly generate structural and stereochemical complexity. Demonstrating this strategy, prochiral trienyl esters **9o** and **r** were elaborated to [2.2.2]-bicyclooctanes **11o** and **12r**, bearing six contiguous stereocenters as a single diastereoisomer, in 90% ee and good overall yield and enantiomeric excess (Scheme 1).

Derivatization via the $\beta$-lactone intermediate was examined. The chemoselective reduction of the $\beta$-lactone intermediate **13** providing diol **14c**, which following single-crystal analysis, allowed absolute and relative stereochemistry to be determined.[17] In contrast to the non-enantioselective (4 + 2) annulation, which proceeds via an *endo* pretransition state reminiscent of a Diels–Alder reaction to give a *trans* arrangement of substituents, the *cis* product was formed. Similarly, diols **14k** and **q** were prepared via $\beta$-lactones **13k** and **q** with high levels of stereochemical purity. Finally, $\beta$-lactone intermediate **13** was cleaved with ethanol to afford diester **15c**, bearing four contiguous stereocenters, without significant erosion in stereochemical purity.

**Scheme 1. Derivatization**




**Scheme 2. Diastereoselectivity and Plausible Mechanism**




The variable diastereoselectivity of the reaction is striking and may be due to a lack of selectivity in the vinylogous Michael addition or epimerization following completion of the reaction. To examine these scenarios, the diastereoselectivity of the formation of **10e** was monitored and found to vary little over the reaction course (eq 6). In addition, when the enantiopurity of the minor diastereoisomer of **10h** was determined, it was found to be significantly different from that of the major diastereoisomer (Figure 2, 60 cf. 92% ee), a result inconsistent with an epimerization pathway. Next, the fragmentation was examined with a crossover experiment involving substrates **9b** and **e**. Although no crossover was observed (eq 7), we believe that fragmentation occurs, but this yields a tight ion pair, which rapidly undergoes vinylogous Michael addition. Thus, a mechanism can be proposed in which fragmentation of the enol ester substrate (i.e., **9f**) gives $\alpha,\beta$-unsaturated acyl azolium **I** and dienolate **II**. Previous computational studies have shown that the acyl unit is twisted from the plane of the triazolium ring,[13] thereby projecting away from the benzyl group. Approach of the dienolate to the diene is blocked by the N-substituent, forcing an *exo*-type approach from the opposite aspect of the Michael acceptor. These unite in an enantio- and diastereoselective vinylogous Michael addition to afford acyl azolium enolate **III**, which undergoes lactonization via **IV** to yield a $\beta$-lactone intermediate that decarboxylates to provide the cyclohexadiene products (i.e., **10f**).

1,3-Dienes are significant motifs in chemical synthesis, in large part due to their capacity to engage in the Diels–Alder reaction. Herein, we have developed a new diene regenerative reaction that allows the facile synthesis of enantio- and diastereoenriched cyclohexadienes. The strategy provides dienes that are regiosiomeric to those provided by pyranone strategies and hence creates new opportunities in complex target synthesis. The application of the dienyl products in subsequent Diels–Alder reactions has been demonstrated, allowing the synthesis of [2.2.2]-bicyclooctanes containing six contiguous stereocenters and four new $\sigma$-bonds as a single diastereomer and in 90% ee. Central to the development of this reaction was the use of the highly electron-rich *N*-2,6-dimethoxy aryl morpholinone catalyst **F2**. In previous (4 + 2) annulations, we found this catalyst to be too reactive, leading to poor yields and various side reactions. In the context of this reaction, however, the enhanced reactivity allows its application at lower temperatures, delivering a highly enantioselective reaction. The utility of the enantioselective NHC-catalyzed diene regenerative (4 + 2) annulation is



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significant, and we are conducting ongoing studies focused on the application of this reaction in multistep synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02693.

Experimental procedures and $^{1}H$ and $^{13}C$ NMR of new materials (PDF)

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### Notes

The authors declare no competing financial interest.

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