

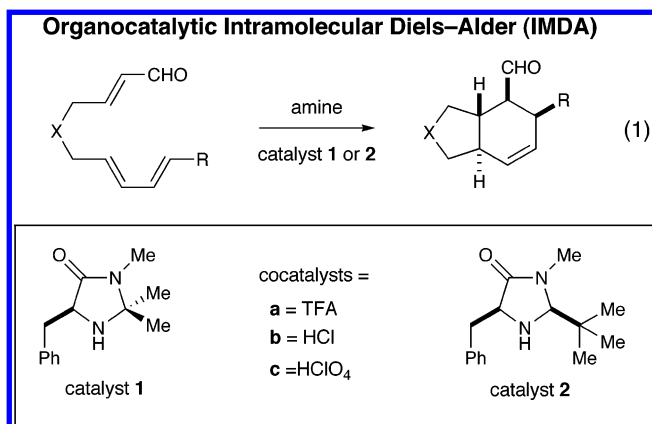
## Enantioselective Organocatalytic Intramolecular Diels–Alder Reactions. The Asymmetric Synthesis of Solanapyrone D

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Over the last 20 years, considerable research efforts have been directed toward the development of enantioselective catalytic variants of the Diels–Alder reaction.<sup>1</sup> During this time, remarkable advances in both catalyst design and substrate tolerance have been accomplished within the *intermolecular* class of [4 + 2] cycloadditions. In contrast, few catalysts have been reported that achieve high levels of enantiocontrol in the *intramolecular* Diels–Alder (IMDA) reaction,<sup>2,3</sup> a notable deficiency in light of the numerous examples of diastereoselective IMDA reactions.<sup>4</sup> Our laboratory has recently established that the LUMO-lowering activation of  $\alpha,\beta$ -unsaturated carbonyls via the reversible formation of iminium ions is a valuable platform for the development of a variety of enantioselective cycloadditions,<sup>5</sup> Friedel–Crafts alkylations,<sup>6</sup> conjugate additions,<sup>7</sup> and hydrogenations.<sup>8</sup> In this communication, we further advance this iminium activation strategy to establish the first example of an organocatalytic intramolecular Diels–Alder reaction (eq 1). Moreover, we demonstrate the utility of this new organocatalytic technology via the total synthesis of the marine metabolite solanapyrone D.



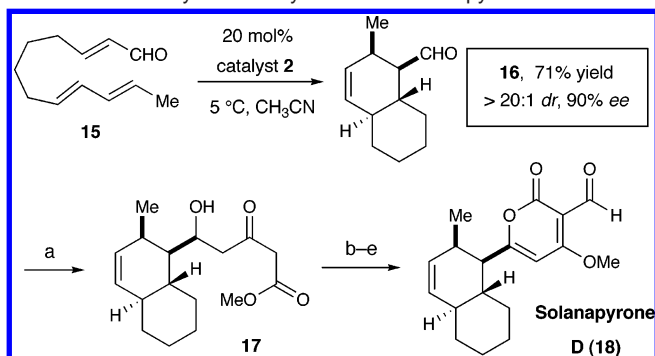
Our LUMO-lowering organocatalytic strategy has proven to be effective for the enantioselective cycloisomerization of a range of trienal aldehydes (Table 1). In general, use of our documented “second generation” imidazolidinone catalyst **2**<sup>6b</sup> resulted in superior yields and enantioselectivities in comparison with imidazolidinone catalyst **1**.<sup>5a</sup> Thus, in the presence of catalytic amounts of imidazolidinone **2a**, both phenyl- and crotyl-substituted decatrienals (**3** and **5**) underwent facile cycloaddition to provide the corresponding [4.3.0] bicyclic aldehyde products, **4** and **6**, in high yield and with excellent enantio- and diastereoselectivity (Table 1, entry 2, 85% yield, >20:1 *endo/exo*, 93% ee, and entry 4, 75% yield, >20:1 *endo/exo*, 94% ee). Surprisingly, in contrast to the success of the crotyl-substituted decatrienal, the allyl-congener **7** failed to provide cycloadduct **8** using either catalyst **1** or **2** (Table 1, entries 5 and 6). We attribute this limitation to substrate sensitivity, as the tetraene starting material was not recovered from these experiments.

**Table 1.** Organocatalyzed Intramolecular Diels–Alder Reaction

entry	triene <sup>a</sup>	amine catalyst <sup>b</sup>	product	% yield <sup>c</sup>	<i>endo/exo</i>	% ee
1		<b>1a</b>		84	>20:1	77
2		<b>2a</b>		85	>20:1	93
3		<b>1a</b>		47	4:1	87
4		<b>2a</b>		75	>20:1	94
5		<b>1</b>		<10	--	--
6		<b>2</b>		<10	--	--
7		<b>1b</b>		76	1:>20	94
8		<b>2c</b>		70	1:2.5	97
9		<b>1c</b>		79	>20:1	94
10		<b>2c</b>		84	>20:1	93
11		<b>1</b>		<10	--	--
12		<b>2c</b>		70	>20:1	92

<sup>a</sup> Trienes **3**, **5**, **9**, and **13** were contaminated with 15% of the *Z,E*-diene diastereomer. These *Z,E*-dienes were uniformly inert to this catalytic IMDA.  
<sup>b</sup> 20 mol % catalyst. <sup>c</sup> Yields reported are based on the conversion of the *E,E*-diene substrate to IMDA product. See Supporting Information for details regarding solvent, temperature, and reaction times for each transformation.

We were delighted to find that our organocatalytic IMDA protocol is effective at generating cycloadducts that incorporate quaternary carbon functionality. Indeed, using 3-methyl-10-phenyl-2,7,9-decatrien-1-al **9**, we were able to obtain the corresponding bicyclic adduct **10**, which exhibits an angular quaternary methyl group. Interestingly, adduct **10** was obtained regardless of the geometric composition of the dienophile starting material in accord with our recently reported hydrogenation studies.<sup>8</sup> Indeed, we have observed rapid equilibration of the *E*- and *Z*-isomers of aldehyde **9**, and as such, adduct **10** presumably arises via cyclization of *E*-**9** in an *endo* transition topography with subsequent epimerization of the  $\alpha$ -formyl stereocenter to minimize transannular interactions. It is important to note that, in this case, catalyst **1** provided superior levels of diastereocontrol in comparison to amine **2** (entry 7, >20:1 *exo/endo*, 94% ee).

**Scheme 1.** Catalytic Total Synthesis of Solanapyrone D<sup>a</sup>

<sup>a</sup> Key: (a) Methyl acetoacetate bis(trimethylsilyl) enol ether, TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 75%. (b) Dess–Martin Periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 71%. (c) DBU, benzene, 60 °C, 87%. (d) Methyl *p*-toluenesulfonate, K<sub>2</sub>CO<sub>3</sub>, DMF, room temperature, 81%. (e) LDA, THF, -78 °C to 0 °C; methyl formate, -78 °C, 57% (91% based on recovered starting material).

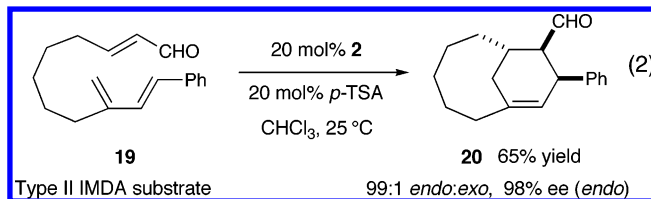
It has been established that IMDA cycloadditions of substrates incorporating heteroatoms in the tether have traditionally been problematic for Lewis acid catalysis. However, we have found that ether-aldehyde **11** readily undergoes cycloisomerization using our organocatalytic protocol to provide oxabicyclic adduct **12** in excellent yield and stereoselectivity (Table 1, entries 9 and 10). Moreover, we have found that Decalin ring systems can be readily assembled using this iminium activation method. For example, catalyst **2c** effects the [4 + 2] addition of undecatrienal **13** to efficiently provide cycloadduct **14** with excellent levels of enantiocontrol (Table 1, entry 12, 70% yield, >20:1 *endo/exo*, 93% ee). Notably, our “first generation” imidazolidinone **1** proved to be catalytically ineffective in this case (entry 11). This dramatic change in cycloaddition rate as a function of [4.4.0] versus [4.3.0] ring formation has been previously established in a number of diastereoselective IMDA studies.<sup>3</sup>

To demonstrate the chemical utility of our organocatalytic IMDA reaction, we undertook the total synthesis of the marine metabolite solanapyrone D (**18**), a phytotoxic polyketide isolated from the fungus *Atenaria solani*.<sup>9</sup> Solanapyrone D has previously been constructed in 19 steps by Hagiwara and co-workers.<sup>10</sup> Recognizing that the *trans*-fused Decalin backbone of solanapyrone D is an ideal IMDA retron, we sought to test the scope and limitations of this new bicyclic ring-forming protocol in a complex target setting. As shown in Scheme 1, cycloaddition of trienal **15** in the presence of 20 mol % **2**·TfOH afforded Decalin aldehyde **16** in 71% yield<sup>11</sup> and 90% ee. Importantly, all four stereocenters of solanapyrone D were efficiently installed in this single catalytic operation. Aldehyde **16** was then elaborated to pyrone **18** via the aldol adduct **17**. Methyl ether formation, followed by *ortho*-lithiation with formylative trap then completed the synthesis of (–)-solanapyrone D (**18**) in only six steps from trienal **15**, and nine steps from commercial materials.

Finally, we sought to extend our newly developed protocol to the cyclization of Type II IMDA substrates. The Type II IMDA (in which the dienophilic function is tethered to the 3-position of the diene) is an extremely powerful transformation that allows for the formation of medium ring cycloadducts containing up to three stereocenters and an anti-Bredt olefin.<sup>12</sup> To our knowledge, no examples of enantioselective catalytic Type II IMDA reactions have previously been documented.

We were pleased to find that, upon treatment with 20 mol % **2**·*p*TSA in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, Type II IMDA substrate **19** underwent cyclization to afford [5.3.1] cycloadduct **20** in 65% yield (72% yield based on 10% recovered diene). Remarkably, this

product was formed as a single diastereomer and with excellent levels of enantioselectivity (98% ee).



In summary, we have developed a powerful new enantioselective catalytic variant of the intramolecular Diels–Alder reaction using our LUMO-lowering iminium activation strategy. The synthetic utility of this new protocol has been demonstrated by the preparation of cycloadducts incorporating ether and quaternary carbon functionality and via the total synthesis of the marine metabolite solanapyrone D (**18**). Moreover, we have further extended this technology to execute the first enantioselective, catalytic Type II IMDA reaction.

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**Supporting Information Available:** Experimental procedures for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) For recent reviews of enantioselective Diels–Alder reactions, see: (a) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, p 1177 and references therein. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol 5. (c) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (d) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289.
- (2) For examples of enantioselective IMDA reactions, see: (a) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (c) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920. (d) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947. (e) Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron: Asymmetry* **1991**, *2*, 1305. (f) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786. (g) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979.
- (3) For reviews, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 4.4. (b) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (c) Fallis, A. G. *Can. J. Chem.* **1983**, *62*, 183. (d) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.
- (4) For examples of diastereoselective IMDA reactions using a chiral auxiliary, see: (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29. (b) Mukaiyama, M. *J. Org. Chem.* **1983**, *23*, 4441. (c) Oppolzer, W.; Dupuis, D. *Tetrahedron Lett.* **1985**, *26*, 5437. (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (e) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
- (5) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.
- (6) (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (b) Austin, J. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.
- (7) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.
- (8) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.
- (9) (a) Oikawa, H.; Yokota, T.; Ichihara, A.; Sakamura, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1284. (b) Oikawa, H.; Yokota, T.; Sakano, C.; Suzuki, Y.; Naya, A.; Ichihara, A. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2016.
- (10) Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M.; Okamoto, T.; Kobayashi, M.; Yamamoto, I.; Ohtsubo, S.; Kato, M.; Uta, H. *J. Org. Chem.* **2002**, *67*, 5969.
- (11) Diene **15** was contaminated with 15% of the *Z,E*-diene isomer. Yield reported based on the conversion of the *E,E*-diene substrate to IMDA product.
- (12) For an excellent review of the Type II IMDA, see: Bear, B. R.; Sparks, S. M.; Shea, K. *J. Angew. Chem., Int. Ed.* **2001**, *40*, 821.

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