

## $\alpha'$ -Hydroxy Enones as Achiral Templates for Lewis Acid-Catalyzed Enantioselective Diels–Alder Reactions

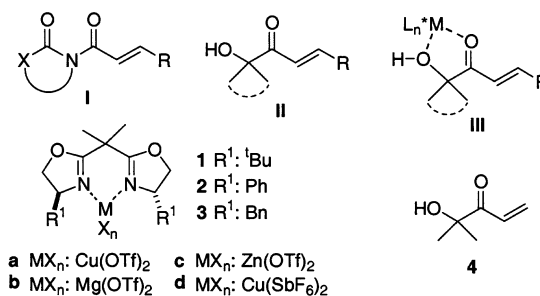
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The field of asymmetric catalysis has produced remarkable results in the area of the Diels–Alder reaction,<sup>1</sup> where a high degree of development has been achieved in both fundamentals<sup>1,2</sup> and synthetic applications.<sup>3</sup> While chiral amines have recently been applied as catalysts of Diels–Alder reactions involving enals<sup>4</sup> and enones<sup>5</sup> as dienophiles, enantioselectivity during Diels–Alder cycloadditions is most often effected by chiral ligand-bearing metal complexes. Catalysts for producing the cycloadducts in high ee's include the Evans C<sub>2</sub>-symmetric bis(oxazoline)-metal complexes<sup>6</sup> which have proven to be very successful when *N*-enoylimides **I** are employed as dienophiles. It appears that these substrates have become the standard test for new catalyst development, while other achiral templates have been much less investigated.<sup>7</sup> In this context, application of the chiral relay concept<sup>8</sup> to improve asymmetric induction has been recently realized.<sup>9</sup> Despite these advances, unmet challenges remain with regard to reactivity and selectivity for challenging substrates. For example, dienes other than the highly reactive cyclopentadiene have been less documented and, with most of the enantioselective methods so far developed, inferior results are obtained.<sup>10</sup>  $\alpha'$ -Hydroxy enones **II** constitute attractive chelating ketone dienophiles.<sup>11</sup> Chiral  $\alpha'$ -hydroxy enones (ketols) in both Lewis acid catalyzed and uncatalyzed diastereoselective Diels–Alder reactions were introduced by Masamune,<sup>12</sup> who showed that the internal hydrogen bond activation operating in these ketols is sufficient for promoting their reaction with the highly reactive cyclopentadiene. Recently, within a broad project aimed at establishing the potential of ketols as carboxylic acid surrogates in the context of diastereo- and enantioselective C–C bond forming transformations,<sup>13</sup> our group has documented the Brønsted acid-catalyzed Diels–Alder reaction of chiral  $\alpha'$ -hydroxy enones.<sup>14</sup> The remarkable efficiency of these  $\alpha'$ -hydroxy enones, even against less reactive dienes, was interpreted on the basis of an intermolecular hydrogen bond network activation. While the above observations reveal some interesting features inherent to  $\alpha'$ -hydroxy enones, to the best of our knowledge, the use of achiral  $\alpha'$ -hydroxy enones **II** as templates in enantioselective Diels–Alder reactions has not been reported yet. We envisaged that these templates may give rise to well ordered transition structures for high enantiocontrol provided that: (a) upon combination with chiral Lewis acids, tight templates as in **III**<sup>15</sup> are generated and (b) there is a substantial energy preference for the enone to adopt the *s*-cis arrangement over the *s*-trans.<sup>16</sup>

To evaluate this hypothesis, enone **4** was prepared from 1-lithio-1-methoxyallene and acetone,<sup>17</sup> and its reactivity against a variety of dienes in the presence of chiral Lewis acids was examined, Table 1. Concordant with our expectations, cycloadduct **5**, from the reaction of **4** with cyclopentadiene carried out in the presence of



**Figure 1.** *N*-Enoylimides **I** typically used as achiral templates in enantioselective Diels–Alder reactions, and the alternative enones **II**, along with the Lewis acid catalysts considered in this work.

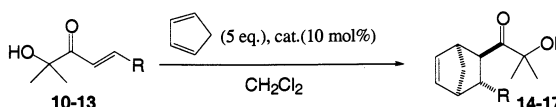
**Table 1.** Reaction of  $\alpha'$ -hydroxy Enone **4** with Representative Dienes Catalyzed by **1a** and **1d**<sup>a</sup>

diene	cat.	T, °C	t, h	isom. ratio <sup>b</sup>	endo:exo <sup>c</sup>	product	yield, %	ee % <sup>d</sup>
	<b>1a</b>	–78	2.5	--	>99:1		99	>99
	<b>1a</b>	25	2	--	>99:1		93	≥98
	<b>1a</b>	25	1.5	99:1	--		88	81
	<b>1d</b>	–20	30	>99:1	--		87	88
	<b>1d</b>	–20	14	>99:1	--		85	94
	<b>1d</b>	–20	20	>99:1	--		85	90 <sup>e</sup>
	<b>1a</b>	–20	20	--	--		75	89
	<b>1d</b>	–20	13	--	--		80	94
	<b>1d</b>	–20	20	--	--		90	90 <sup>e</sup>
	<b>1a</b>	25	8	50:50	--		--	nd
	<b>1d</b>	25	2	76:24	--		--	nd
	<b>1d</b>	–10	15	88:12	--		95	>99

<sup>a</sup> Reactions conducted at 0.5 mmol scale in CH<sub>2</sub>Cl<sub>2</sub>. Molar ratio of enone: diene:catalyst 1:5:0.1. <sup>b</sup> Ratio of regio- or *cis/trans* isomers, as applicable, determined by <sup>13</sup>C NMR. <sup>c</sup> Determined by <sup>13</sup>C NMR. <sup>d</sup> Enantiomeric excess of the major regio- or diastereoisomer, as applicable, determined by HPLC. n.d.= not determined. <sup>e</sup> Using 2 mol % of catalyst.

catalyst **1a** (10 mol %), was indeed formed with essentially perfect *endo*-selectivity and enantioselectivity at –78 °C. The less reactive cyclohexadiene did not react with **4** under the same conditions but at ambient temperature a clean reaction took place and, most notably, almost complete selectivity was achieved (*endo:exo* ratio >99:1, ee ≥ 98%). Of major significance were the results with more problematic dienes. With isoprene and catalyst **1a**, a 99:1 regioisomeric ratio and an 81% ee were obtained, a result that could be improved to >99:1 regioisomeric ratio and 88% ee by perform-

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**Table 2.** Diels-Alder Reactions of  $\beta$ -substituted Enones **10–13** with Cyclopentadiene


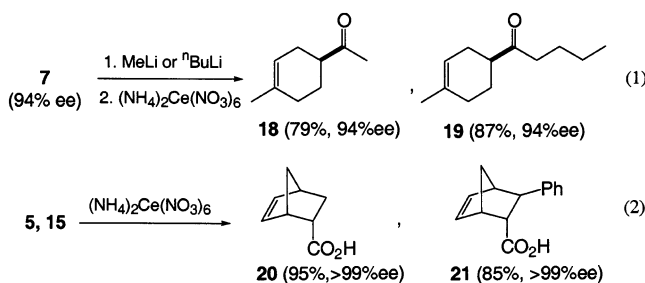
enone	R	cat.	T, °C	t, h	endo:exo <sup>a</sup>	product	yield, %	ee, % <sup>b</sup>
<b>10</b>	Et	<b>1a</b>	–20	6	95:5	<b>14</b>	93	>99
		<b>1d</b>	–78	21	>98:2		90	>99
<b>11</b>	Ph	<b>1a</b>	25	8	91:9	<b>15</b>	90	90
		<b>1d</b>	0	14	94:6		86	>99
<b>12</b>	4-ClPh	<b>1d</b>	0	2.5	95:5	<b>16</b>	85	>99
<b>13</b>	4-MeOPh <sup>c</sup>	<b>1d</b>	0	24	94:6	<b>17</b>	94	>99

<sup>a</sup> Determined by <sup>13</sup>C NMR. <sup>b</sup> Determined by HPLC. <sup>c</sup> Using 10 equiv. of diene.

ing the reaction at –20 °C. The result was most impressive when catalyst **1d** was used, which led to >99:1 regioisomeric ratio and 94% ee.<sup>18</sup> Similar levels of selectivity were obtained with other difficult dienes such as 2,3-dimethyl butadiene and piperylene, catalyst **1d** again being the most effective. Remarkably, lowering the catalyst loading from 10% to only 2% resulted in no significant loss of either regioselectivity or enantioselectivity for isoprene and 2,3-dimethylbutadiene and reaction times were only slightly longer.

Observations that supported the 1,4-metal binding activation of these enones were further attained in the reactions of  $\beta$ -substituted enones **10–13**<sup>19</sup> with cyclopentadiene.<sup>20</sup> As shown in Table 2, selectivities and ee values remained high for both  $\beta$ -alkyl and  $\beta$ -aryl substituted enones, even at the high temperatures required for the less reactive substrates. In addition, the reaction appears to be quite regular regardless of the electron-neutral, electron-rich or electron-poor nature of aryl substituents.

The excellent enantioselectivity observed in these reactions is also of particular interest since carbonyl addition and subsequent diol cleavage provides ketone adducts such as **18** and **19** (eq 1), formally derived from the Diels–Alder reaction of alkyl vinyl ketones. Similarly, treatment of adducts **5** and **15** (eq 2) with cerium ammonium nitrate (CAN) gave the corresponding carboxylic acids **20** and **21** in high yields and ee's.<sup>14</sup> Moreover, in these transformations acetone is the only byproduct formed, an additional aspect of the approach that is of practical interest.



In conclusion, we have documented a complementary approach to enantiocontrol in Diels–Alder reactions that is based upon an efficient 1,4-metal binding complexation in  $\alpha'$ -hydroxy enones. Extension of this metal-binding principle to other enantioselective transformations can be predicted and work in that direction is active in our laboratories.

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**Supporting Information Available:** Complete experimental procedures, determination of stereoisomeric mixtures, <sup>1</sup>H and <sup>13</sup>C spectra, and HPLC chromatograms. This material is available free of charge via the Internet at <http://pubs.acs.org>. See any current masthead page for ordering information and Web access instructions.

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- (19) Enones **10–13** were readily prepared by aldol condensation of the commercially available 3-hydroxy-3-methyl-2-butanone with the respective aldehyde. See Supporting Information for details.
- (20) Other less reactive dienes such as isoprene and 2,3-dimethylbutadiene did not react with  $\beta$ -substituted enones under the conditions tested.

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