

Asymmetric Lewis Acid-Catalyzed Diels–Alder Reactions of α,β -Unsaturated Ketones and α,β -Unsaturated Acid Chlorides

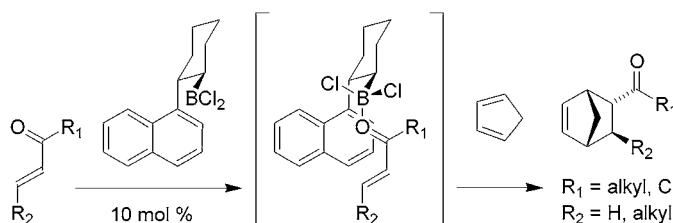
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Received August 12, 2003

ABSTRACT



Conformational analysis, van der Waals attractions, and transition structure calculations are combined to design an asymmetric Lewis acid-catalyzed Diels–Alder reaction for simple acyclic α,β -unsaturated ketones and α,β -unsaturated acid chlorides, giving up to 83 and 92% ee, respectively. The two-point-binding chiral recognition mechanism, Lewis acid–Lewis base coordination with boron and a van der Waals attraction with the naphthyl group, uses the inherent enone unit of simple α,β -unsaturated carbonyl compounds, ending the need for auxiliary oxygen binding sites on the dienophile.

Asymmetric Lewis acid-catalyzed reactions of α,β -unsaturated ketones are challenging due to nonselective metal coordination of the carbonyl oxygen lone pairs. This indiscriminate binding of the typically sterically and electronically similar lone pairs allows reaction from multiple isomeric transition states, resulting in poor enantiocontrol.^{1,2} Here we describe the combined use of conformational analysis, van der Waals attractions, and transition structure calculations to design an asymmetric Lewis acid-catalyzed Diels–Alder reaction for simple acyclic α,β -unsaturated ketones.^{3,4} Generalizing this analysis, we further present the first enantioselective asymmetric Lewis acid-catalyzed Diels–Alder reactions of α,β -unsaturated acid chlorides.

(1) For a detailed discussion, see: Northrup, A. B.; MacMillan, D. W. *J. Am. Chem. Soc.* **2002**, *11*, 2458.

(2) For the preferential coordination of electronically differentiated substituted benzophenone lone pairs allowing maximum π -electron donation in an asymmetric reduction system, see: Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.

We previously described enantioselective Diels–Alder reactions of α,β -unsaturated esters catalyzed by asymmetric Lewis acid **1** with up to 99.5% ee.^{5,6} Aromatic alkyl-dichloroborane **1** was designed to bind and activate α,β -unsaturated esters via conformation **2**, with approach of the dienophile from the top face opposite the naphthalene moiety. Active conformation **2** was predicted by conformational analysis and supported by measurements reflecting the solid state (a series of five dienophile–catalyst crystal structures),⁶ solution state

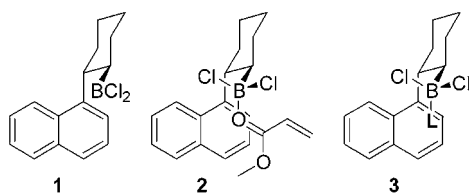
(3) MacMillan recently described the use of organocatalysts to replace the selective lone pair binding problem by iminium geometry control, thus providing the first reported enantioselective catalytic Diels–Alder reactions with simple ketone dienophiles.¹

(4) Corey recently described an enantioselective Lewis acid-catalyzed Diels–Alder reaction with ethyl vinyl ketone: Ryu, D. H.; Lee, T. L.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

(5) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794.

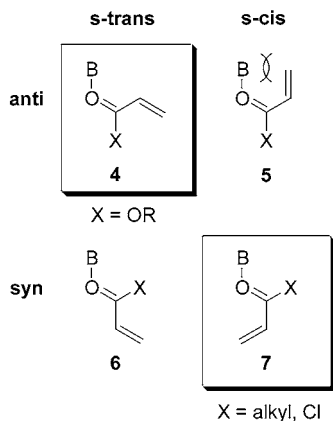
(6) Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657.

(selective shielding of dienophile protons by the arene),⁵ and transition state (degree and sense of asymmetric induction under Curtin–Hammett conditions).^{5,6}



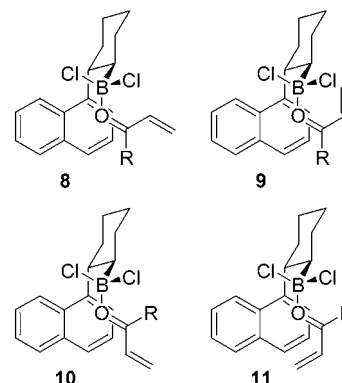
The binding of a planar, polarized, and electron-deficient ligand **L** to **1** via preferred general conformation **3** can be understood in terms of the chair cyclohexane and peri interactions present in the carbon framework, a staggered C–B bond connecting the chiral carbon framework to the coordinated metaloid, and an electrostatic and dipole–induced dipole attraction between the boron-activated ligand **L** and the electron-rich and polarizable arene of the catalyst. For ligand **L** corresponding to an α,β -unsaturated carbonyl compound, four conformations are possible, **4–7**. The boron may bind anti or syn to the nonolefinic group **X**, and the enone unit may be *s-trans* or *s-cis*. For α,β -unsaturated esters, the ester alkyl fragment **R** preferentially resides syn peri planar to the carbonyl oxygen, blocking binding of the **B** syn to **X** = OR (conformations **6** and **7**). The binding of **B** anti to OR further blocks *s-cis* conformation **5** on steric grounds, thus favoring anti *s-trans* conformation **4**. A staggered O–B bond should also be favored in **4**, and combining ester fragment **4** with catalyst fragment **3** leads to preferred reactive conformation **2**, as observed.^{5,6}

For α,β -unsaturated ketones, superimposing carbonyl fragments **4–7** on catalyst fragment **3** with a staggered B–O bond and positioning of the polar complexed carbonyl over the polarizable arene gives conformations **8–11**. Conformation **11** is sterically preferred over conformation **9** for small **R** groups, and conformation **8**⁷ gives the same product enantiomer as conformation **11**, with diene approach opposite the naphthalene in each case. Thus, the main competition for enantiocontrol for α,β -unsaturated ketones is between conformations **11** and **10**.



For α,β -unsaturated carbonyl compounds such as ketones lacking a pronounced steric preference for an *s-cis* or *s-trans*

conformation, transition structure calculations by Houk predict an inherent electronic preference for an *s-cis* conformation in the transition state. Calculated Diels–Alder transition structures for the reaction between acrolein complexed with BH_3 and butadiene show a preference for *s-cis* geometries over *s-trans* geometries by 1.9 (endo) and 2.7 (exo) kcal/mol due to a smaller separation of induced charge.⁸ Thus, theory predicts a preference for transition states resulting from *s-cis* conformation **11** over *s-trans* conformation **10**.



The dipole–induced dipole attraction between the polarized and electron-deficient boron-activated α,β -unsaturated ketone and the polarizable and electron-rich naphthalene built into catalyst **1** should further enhance reaction through *s-cis* conformation **11** over *s-trans* conformation **10** since the entire enone unit lies over the naphthalene in **11**. Thus, both Houk's calculations for a general electronic preference for *s-cis* transition states and the secondary van der Waals attraction designed into catalyst **1** predict **1** to enantioselectively catalyze Diels–Alder reactions of α,β -unsaturated ketones by approach of the diene from the top face of conformation **11** with optimum asymmetric induction for small **R** groups.

To test this hypothesis, Diels–Alder reactions between four different α,β -unsaturated ketones and cyclopentadiene were performed under catalysis by chiral Lewis acid **1** (Table 1, entries 1–4).^{9,10} Enantioselectivities up to 83% were obtained with very high endo selectivities. In each case, the

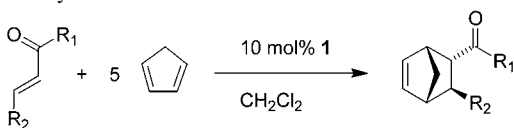
(7) Crystal structure of the benzylidene acetone· BF_3 complex shows BF_3 coordination to the lone pair on the carbonyl oxygen syn to the α,β -double bond in an *s-trans* conformation.⁴ This is analogous to conformation **8** except that the B–O bond is eclipsed in the BF_3 complex. An attractive H–F interaction in this eclipsed conformation is proposed for these BF_3 complexes.⁴

(8) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.

(9) **Representative Procedure.** Catalyst **1** (29 mg, 0.10 mmol, 10 mol %) was dissolved in 0.90 mL of dry CH_2Cl_2 under argon and cooled to -74°C . Methyl vinyl ketone (70 mg, 1.0 mmol) was added with stirring, followed by 0.45 mL (5.7 mmol, 5.7 equiv) of cyclopentadiene. After 1 h, the reaction was quenched by the addition of 1 mL of saturated NaHCO_3 (aq) and warmed to room temperature. The reaction mixture was diluted with ether, washed with NaHCO_3 (aq) and water, dried (Na_2SO_4), and concentrated to a clear oil, 81% ee according to GC (J&W Cyclodex-B column). Silica chromatography yielded 82 mg (63%) of clear oil, $[\alpha]_{\text{D}}^{25} +65.6^\circ$ (*c* 4.36, ethanol). Products were characterized by ^1H NMR, ^{13}C NMR, and high-resolution mass spectra. Acid chloride reactions were quenched with an excess of 25% TEA/methanol to give the corresponding methyl esters.

(10) Cyclohexadiene reacts considerably slower than cyclopentadiene with methyl vinyl ketone under the conditions of Table 1.

Table 1. Asymmetric Diels–Alder Reactions of α,β -Unsaturated Ketones and α,β -Unsaturated Acid Chlorides Catalyzed by **1**



entry	R ₁	R ₂	temp, time	yield (%)	endo:exo	% ee
1	Me	H	−74 °C, 1 h	63	>100:1	81 ^{a,b}
2	Et	H	−78 °C, 24 h	92	>100:1	83 ^{a,c}
3	ⁱ Pr	H	−30 °C, 20 h	81	32:1	16 ^{b,d}
4	Me	Me	−30 °C, 20 h	73	32:1	71 ^{a,c}
5	Cl	Me	−20 °C, 52 h	88 ^e	>10:1 ^e	92 ^f
6	Cl	Et	−18 °C, 48 h	64 ^e	>10:1 ^e	76 ^{a,g}
7	Cl	CH ₂ Br	−18 °C, 72 h	60 ^e	>10:1 ^e	80 ^h

^a Enantiomeric excess determined by chiral stationary phase GC. ^b Absolute configuration correlated by comparison to the literature optical rotation: Nakazaki, M; Naemura, K.; Kondo, Y. *J. Org. Chem.* **1976**, *41*, 1229. ^c Absolute configuration correlated with the corresponding methyl ester (ref 5) by addition of EtMgBr (entry 2) or MeLi (entry 4) to the ketone and ester and comparing optical rotations of the resulting tertiary alcohols. ^d Enantiomeric excess determined by comparison to the literature optical rotation (see footnote b). ^e Isolated as the corresponding methyl esters. ^f Enantiomeric excess determined by chiral stationary phase GC of the corresponding aldehyde. Correlated vs the corresponding methyl ester (ref 5). ^g Same enantiomer favored as for reaction of the corresponding methyl ester (95% ee). ^h Enantiomeric excess and correlation determined as for entry 5 after reduction of the bromide and ester followed by oxidation to the aldehyde.

absolute configuration of the product corresponds to the approach of cyclopentadiene from the predicted top open face of conformation **11**. Small ketone groups R₁ = Me and Et are well tolerated (entries 1, 2, and 4), but R₁ = ⁱPr significantly lowers the enantioselectivity (entry 3), consistent with the congested positioning of R in conformation **11**. Vinyl substituent R₂ = H or Me is well tolerated (entries 1, 2, and 4), consistent with the open space around the trans vinyl position in conformation **11**. Thus, α,β -unsaturated ketones behave according to the model proposed above.

This model can be extended to α,β -unsaturated acid chlorides by considering potential reactive conformations **8–11**, R = Cl. As discussed above for R = small alkyl, conformation **11** should be favored over conformation **9** on the basis of steric effects and favored over conformation **10** on the basis of electronic effects (s-cis transition state and maximized van der Waals attraction between the enone unit and the arene). Crystal structures generally show the binding of acid chlorides to metals at the carbonyl oxygen syn to chlorine, further supporting conformation **11**.¹¹ Any reaction through conformation **8** gives the same enantiomer as

reaction from conformation **11**; thus, catalyst **1** is predicted to enantioselectively catalyze Diels–Alder reactions of α,β -unsaturated acid chlorides with approach of the diene from the top face of conformation **11**, R = Cl.

To test this hypothesis, three different of α,β -unsaturated acid chlorides were treated with cyclopentadiene and catalyst **1** (Table 1, entries 5–7). Crotonyl chloride gives 92% ee with an absolute configuration consistent with approach of the diene from the predicted open face of conformation **11** (entry 5). γ -Substituted species give 76–80% ee, again consistent with model **11** (entries 6–7). Thus, α,β -unsaturated acid chlorides behave according to the model proposed above, providing the first asymmetric Lewis acid-catalyzed Diels–Alder reactions of α,β -unsaturated acid chlorides.

We have described asymmetric Lewis acid-catalyzed Diels–Alder reactions of simple acyclic α,β -unsaturated ketones and α,β -unsaturated acid chlorides giving up to 83 and 92% ee, respectively. Like the reactions of α,β -unsaturated esters reported previously,^{5,6} these reactions are catalyzed by alkyldichloroborane **1** with readily understandable chiral recognition mechanisms involving two-point-binding asymmetric catalysis: Lewis acid–Lewis base coordination with boron and a van der Waals attraction with the naphthalene. This form of two-point-binding uses the inherent enone unit of simple α,β -unsaturated carbonyl compounds, ending the need for auxiliary oxygen binding sites on the dienophile.¹² Alkyldichloroborane **1** was designed not only to provide the enantioselectivities described here for three different carbonyl systems but more importantly to serve as a well-defined framework for the exploration of chiral recognition mechanisms for asymmetric catalysis. Our work has shown that judicious conformational constraints, van der Waals attractions, and charge effects in the transition state can be applied to both design and promote novel enantioselectivities. Extension of these concepts to the more reactive dibromo congener of **1**, including α,β -unsaturated anhydride dienophiles, will be described shortly.

Acknowledgment. We thank Professor MacMillan for a preprint of his work^{1,3} and helpful discussions. Chemistry at Berkeley was supported by the NSF (Presidential Young Investigator Award, CHE-8857453), the Camille and Henry Dreyfus Foundation (Teacher–Scholar Award), and the Smith Kline & French Laboratories (Fellowship for S.L.).

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(11) For crystal structures of acid chloride complexes with AlCl₃, see: Rasmussen, S. E.; Broch, N. C. *Acta Chem. Scand.* **1966**, *20*, 1351 (benzoyl chloride). Chevrier, P. B.; Le Carpentier, J.-M.; Weiss, R. *Acta Crystallogr. B* **1972**, *28*, 2659 (toluoyl chlorides). Le Carpentier, J.-M.; Weiss, R. *Acta Crystallogr. B* **1972**, *28*, 1437 (propionyl chloride).

(12) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.