Highly Enantioselective Diels−Alder Reactions of 1-Amino-3-siloxy-dienes Catalyzed by Cr(III)-Salen Complexes

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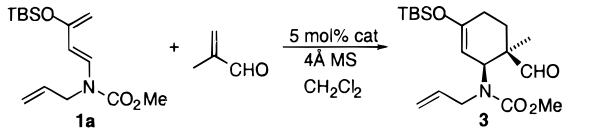
The Diels−Alder (DA) reaction is perhaps the most powerful method for the stereocontrolled synthesis of complex molecules.[1] In a single step it produces six-membered carbocycles and heterocycles with from one to as many as four stereocenters. Among the many advances with this reaction,[2−4] of particular significance are the numerous chiral Lewis acid-catalyzed cycloadditions.[5,6] A large percentage of successful enantioselective DA reactions reported involve the use of a cyclic diene, most commonly cyclopentadiene.[5b] Of the acyclic dienes reported, most are monosubstituted butadienes.[7] Surprisingly, enantioselective DA reactions of multiply heteroatom-substituted dienes, such as Danishefsky's diene,[8] appear to not have been reported despite their tremendous usefulness in complex molecule synthesis.[9] In connection with our interest in the chemistry of 1-amino-3-siloxy-1,3-butadienes,[10] we have explored the chiral Lewis acid catalyzed cycloadditions of these dienes. We report here that the reactions of 1-amino-3-siloxy-1,3-butadienes with various acroleins catalyzed by chromium (III)-salen catalysts proceed with exceptionally high enantioselectivity to afford highly functionalized cyclohexene derivatives.

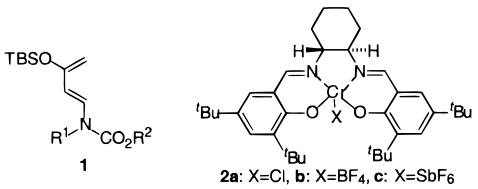
The enantioselective catalysis of 1-amino-3-siloxybutadienes in DA reactions was particularly promising since the uncatalyzed cycloaddition with α-substituted acroleins were known to proceed with excellent regio- and endoselectivities.[10] Thus of the eight possible cycloadducts, only the two enantiomeric endo adducts were expected. The task of the chiral catalyst was to select between these two adducts.

Table 1. Effect of Solvent and Catalyst Counterion[a]



entry	cat	solv	temp (°C)	time	yield (%)[b]	ee (%)[c]
1	**2a**	MTBE	−30−0	5.5 d	60	81
2	**2a**	toluene	−30−0	4.5 d	62	77
3	**2a**	CH_2Cl_2	−30	26 h	78	79
4	**2b**	CH_2Cl_2	−40	2 d	93	90
5	**2c**	CH_2Cl_2	−40	2 d	94	93

[a] Reactions were carried out at 1.0 M in solvent with 2 equiv of methacrolein, 5 mol % of **2** and oven-dried 4 Å MS (0.8 g/1 mmol of **1a**). [b] Isolated yield based on **1a**. [c] Determined by NMR analysis of a Mosher ester derivative, see ref 12 and Supporting Information for details.



Among the chiral Lewis acid catalysts examined for the reaction of methacrolein and diene **1a**,[10c] used for the pivotal DA reaction in our tabersonine synthesis, Jacobsen's Cr(III)-salen catalyst afforded the most encouraging results.[11] Early studies showed that the DA reaction was efficiently catalyzed using 5 mol % of (*R,R*)-chromium (III) catalyst **2a** in methyl *tert*-butyl ether (MTBE) in the presence of 4 Å molecular sieves (MS) and afforded cycloadduct **3**, exclusively the endo isomer, as determined by ^{1}H NMR analysis of the crude reaction mixture. The product was obtained in 60% yield and with 81% enantiomeric excess (ee), the predominant enantiomer being that shown (Table 1, entry 1).[12,13] The rate of the cycloaddition was appreciably faster in CH_2Cl_2 than in either MTBE or toluene (entries 1−3), although the enantioselectivities were comparable. The nature of the counterion impacted the enantioselectivity. When the reaction was carried out using 5 mol % of catalyst **2b**, bearing the less

(1) (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 5, pp 315−399. (b) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873−3905.

(2) Stoichiometric processes with chirally modified dienophiles: (a) Jurczak, J.; Bauer, T.; Chapuis, C. In *Stereoselective Synthesis*; Houben-Weyl, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Verlag: Stuttgart, 1995; Vol. E21c, pp 2735−2871. (b) Rück-Braun, K.; Kunz, H. *Chiral Auxiliaries in Cycloadditions*, Wiley-VCH. New York, 1999.

(3) Chiral dienes: (a) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023−1035. (b) Barluenga, J.; Suárez-Sobrino, A.; López, L. A. *Aldrichimica Acta* **1999**, *32*, 4−15.

(4) Antibody catalyzed Diels−Alder: Gouverneur, V. E.; Houk, K. N.; Pascual-Teresa, B.; Beno, B.; Janda, K. D.; Lerner, R. A. *Science* **1993**, *262*, 204−208.

(5) General reviews on catalyzed asymmetric reactions: (a) Noyori, R. *Asymmetric Catalysts in Organic Synthesis*; Wiley: New York, 1994. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (c) Yamamoto, H. *Lewis Acid Reagents*; Oxford: Oxford University Press: 1999. (d) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: 1999; Vols. I−III.

(6) (a) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289−332. For an in-depth discussion of catalytic asymmetric DA reactions, see: (b) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, pp 1177−1235.

(7) For noteworthy exceptions, see: (a) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987−2989. (b) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611−3612.

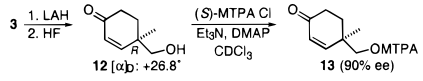
(8) Enantioselective hetero-Diels−Alder reactions of Danishefsky's diene have been reported: (a) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405. (b) Simonsen, K. B.; Svenstrup, N.; Robertson, M.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 123−128 and references therein.

(9) (a) Jurczak, J.; Bauer, T.; Chapuis, C. In *Stereoselective Synthesis*; Houben-Weyl, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Verlag: Stuttgart, 1995; Vol. E21c, pp 2905−2952. (b) Tietze, L. F.; Kettschau, K. *Top. Curr. Chem.* **1997**, *189*, 1−120.

(10) (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252−5253. (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165−7166. (c) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523−13524. (d) Kozmin, S. A.; Janey, J. M.; Rawal, V. H., *J. Org. Chem.* **1999**, *64*, 3039−3052. (e) Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045−8047. (f) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562−9573.

(11) (a) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898. Although catalysis of a Diels−Alder reaction using a Cr salen catalyst has not been reported, catalysis of hetero-Diels−Alder reactions is known: see ref 8a.

(12) The enantiomeric excesses were determined by ^{1}H NMR analysis of the Mosher ester **13**, obtained through the sequence shown below. See Supporting Information for details. The absolute stereochemistry of **3** was determined to be 6*R* by comparison of the specific rotation of **12** with the reported value.[10b,f] The absolute stereochemistry of **4**−**7** was determined in the same manner.[10b,f]



(13) General procedure for the DA reactions: To a stirred mixture of 5 mol % (based on **1**) of **2** and oven-dried powdered 4 Å MS (0.8 g) in CH_2Cl_2 (1 mL) cooled to −40 °C was added the dienophile (2.0 mmol). Diene **1** (1 mmol) was added neat, and the mixture was stirred at −40 °C. The solids were removed by filtration through Celite and washed with CH_2Cl_2. The filtrate was concentrated and the residue purified by flash chromatography on silica gel.

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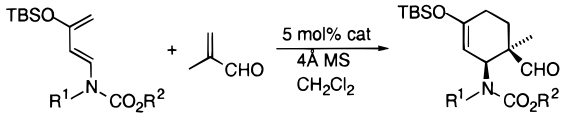
Table 2. Effect of Carbamate Group Size and Temperature[a]



entry		diene R^1	R^2	cat	temp (°C)	time	yield[b] (%)	ee[c] (%)
1[d]	**1a**	allyl	Me	**2b**	−40	2 d	**3** (93)	90
2	**1b**	Me	Me	**2b**	−40	2 d	**4** (89)[e]	78[f]
3	**1c**	$-(CH_2)_2-$		**2b**	−40	2 d	**5** (85)	92
4	**1d**	benzyl	Me	**2b**	−40	2 d	**6** (95)	95
5	**1d**	benzyl	Me	**2c**	−40	2 d	**6** (93)	97
6	**1d**	benzyl	Me	**2b**	rt	8 h	**6** (80)	93
7	**1d**	benzyl	Me	**2c**	rt	16 h	**6** (92)	91

[a] Reactions were carried out at 1.0 M in CH_2Cl_2 with 2 equiv of methacrolein, 5 mol % of **2** and oven-dried 4 Å MS (0.8 g/1 mmol of **1**). [b] Isolated yield based on **1**. [c] Determined by ^{1}H NMR analysis of the Mosher ester, See Supporting Information for details. [d] Listed from Table 1, entry 4. [e] endo:exo = 94:6, calculated by ^{1}H NMR. [f] For endo adduct.

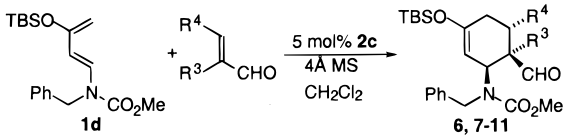
coordinating BF_4^- counterion, the adduct was obtained 93% yield and 90% ee (entry 4). The ee of the product increased further to 93% using catalyst **2c**,[14] possessing SbF_6^- counterion (entry 5).[15]

An analysis of the asymmetric induction capability of the chiral scaffold (vide infra) pointed to an important role for the carbamate alkyl group (Table 2, entries 1−4). Indeed, compared to the allyl substituted diene (**1a**), the smaller methyl substituted diene (**1b**, entry 2) gave poorer results. The endo-exo selectivity of the cycloaddition was lower (94:6) as was the enantioselectivity (78% ee for the endo isomer). The oxazolidinone substituted diene **1c** (entry 3) gave quite satisfactory results (92% ee). The best result was obtained with the benzyl substituted diene **1d** (95% ee). The use of catalyst **2c** for this reaction improved the enantioselectivity to 97% ee (entry 5). It should be noted that the benzyl substituted dienes underwent cycloaddition with high enantioselectivity even at room temperature (cf. entries 4−7).

The optimized set of conditions shown in entry 5 of Table 2 proved to be quite general. The cycloadditions of diene **1d** with a range of acrolein derivatives catalyzed by salen **2c** proceeded in high yield and with excellent enantioselectivity (Table 3).[12] All of these reactions were highly endo selective, with no evidence of the exo adduct in the crude product (by NMR). Simple α-alkyl-substituted acroleins gave cycloadducts with ≥97% ee (entries 1−3). Entry 5 is interesting in that it is also an enol ether. Nevertheless, it participates very effectively in the cycloaddition, affording the α-siloxycarboxaldehyde cycloadduct in >97% ee. The reaction shown in entry 6 is noteworthy in that the product is a functionalized hydrindane derivative, formed in good yield and 96% ee. The cycloadducts of the reactions shown are functionalized, versatile intermediates with a quaternary chiral center. Such compounds have clear potential for use in complex molecule synthesis.[10c,f]

The high enantioselectivities observed in this study are remarkable given the seemingly flat topography of the salen scaffold. A consideration of the above results in conjunction with a careful analysis of the salen scaffold suggests the following rationale for the observed asymmetric induction. Coordination of the chromium with the carbonyl lone pair that is *anti* to the R^3 group is expected to activate the dienophile.[16] The diene can approach the dienophile from the more open surface on the scaffold, which is believed to

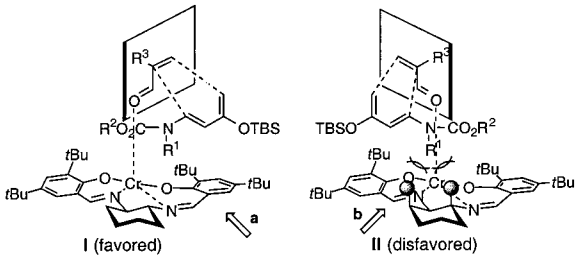
Table 3. Catalytic Asymmetric Diels−Alder Reactions[a]



entry	dienophile R^3	dienophile R^4	temp (°C)	time	yield[b] (%)	ee[c] (%)
1[d]	Me	H	−40	2 d	**6** (93)	97
2	Et	H	−40	2 d	**7** (91)	97
3	isopropyl	H	−40	5 d	**8** (92)	>97
4	$TBSO(CH_2)_2$	H	−40	2 d	**9** (93)	95
5	TBSO	H	−40	2 d	**10** (86)	>97
6	$-(CH_2)_3-$		−40−rt	5 d	**11** (76)	96

[a] Reactions were carried out at 1.0 M in CH_2Cl_2 using 2 eq of a dienophile, 5 mol % of **2c** and oven-dried 4 Å MS (0.8 g/1 mmol of **1**). [b] Isolated yield based on **1d**. The absolute stereochemistry of **8**−**11** was estimated on the basis of the reaction mechanism, see also ref 12. [c] Determined by ^{1}H NMR analysis of the Mosher ester, see Supporting Information for details. [d] Listed from Table 2, entry 5.

be over the imine linkages, away from bulky *tert*-butyl groups.[17] Of the different possible endo transition states for the DA reaction, the two shown (**I** and **II**) appear to involve the fewest nonbonding interactions between the diene-dienophile complex, particularly the R^1 group of the carbamate, and the chiral framework. Transition state **I** (path **a**) seems more favorable than **II**, which suffers from steric interactions between R^1 and the axial hydrogens shown.[18]



In summary, we have found that 1-amino-3-siloxy-1,3-butadienes undergo highly enantioselective DA reactions with various acroleins catalyzed by Cr(III) salen complexes. The high endo-selectivity of the DA reactions as well as the substituents on the 1-position of the diene are important for the success of this process.

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Supporting Information Available: General experimental procedure for Diels−Alder reactions, spectroscopic data and specific rotations of new cycloadducts (**3**−**11**), and general experimental procedure for Mosher ester analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) This catalyst was prepared by stirring **2a** and $AgSbF_6$ in MTBE for ~5 h followed by removal of the precipitated AgCl and concentration of the solution (see also ref 8a).

(15) The corresponding Mn(III)-salen complex is also effective in catalyzing the DA reaction, but affords lower enantioselectivities. Oxo(Mn)-salen complexes are known to catalyze the asymmetric DA reactions of cyclopentadiene and acroleins: Yamashita, Y.; Katsuki, T. *Synlett* **1995**, 829−830.

(16) (a) Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945−6948. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133−3139. See also ref 6b.

(17) (a) Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N. *Chem. Eur. J.* **1996**, *2*, 974−980, and references therein. (b) Kuroki, T.; Hamada, T.; Katsuki, T. *Chem. Lett.* **1995**, 339−340.

(18) The carboxylate group on the nitrogen is expected to be oriented *s-trans* to the diene during the DA reactions, see: (a) Menezes, R. F.; Zezza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295−3298. (b) Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J. *Tetrahedron Lett.*, **1995**, *36*, 9533−9536.