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Broadly Effective Enantioselective Diels–Alder Reactions of 1-Amino-substituted-1,3-butadienes

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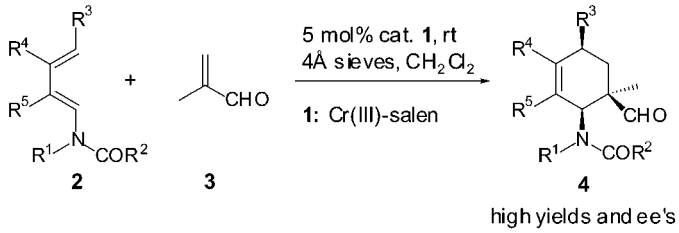
ABSTRACT



A broad range of substituted 1-amino-1,3-butadienes undergo enantioselective Diels–Alder reactions with methacrolein in the presence of 5 mol % of Cr(III)-salen complex 1. The reactions are carried out conveniently, at room temperature, and they afford the cycloadducts in high yields and excellent ee's.

The clear importance of the Diels−Alder (DA) reaction to complex molecule synthesis has stimulated considerable interest in the development of enantioselective catalysts for this transformation.[1] Despite numerous and significant advances in this area, the overall scope of this reaction remains limited. Whereas many chiral scaffolds engender high enantioselectivity in these cycloadditions, a relatively small range of dienes and dienophiles give useful results.[2] Few examples of successful enantioselective DA reactions of heteroatom-substituted dienes, arguably the most useful for natural product synthesis applications,[3] have been reported, and until recently these had been limited primarily to mono-alkoxy- or -acyloxy-substituted butadienes.[4] Our recent report on enantioselective DA reactions of 1-amino-3-siloxy dienes[5,6] provided not only the first examples of the use of doubly heteroatom-substituted dienes in this process but also one of the earliest examples of amine-substituted dienes.[7−10] As a significant advance of our earlier report,[5] we found that the chiral Lewis acid-catalyzed DA reactions between a broad range of Oppolzer−Overman[11]

(1) Reviews on catalytic enantioselective Diels−Alder reactions: (a) Kagan, H. B.; Riant, O. *Chem. Rev*. **1992**, *92*, 1007−1019. (b) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289−332. (c) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalyst*, Vol. III; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; pp 1177−1235.

(2) Of the successful (>90% ee, see ref 1c) DA's reported, the vast majority involve the use of cyclopentadiene, butadiene, or their alkyl-substituted derivatives.

(3) Cf.: (a) Danishefsky, S.; Hershenson, F. M. *J. Org. Chem.* **1979**, *44*, 1180−1181. (b) Overman, L. E.; Petty, C. B.; Doedens, R. J. *J. Org. Chem.* **1979**, *44*, 4183−4185. (c) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454−1456. (d) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373−5379. (e) Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441−4444.

(4) For reactions involving mono-alkoxy- or -acyloxy-substituted butadienes, see: (a) Marshall, J. A.; Xie, S. J. *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, also see ref 1c.

(5) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843−7844.

(6) Other applications of amino-siloxy dienes: (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. (g) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059−9068. (h) Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*, 160−168. (i)Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321−3323.

(7) Reviews on Diels−Alder reaction of amino-substituted 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.

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type 1-carbamate-substituted dienes and α-substituted acroleins proceed with complete diastereoselectivities, high enantioselectivities, and good to excellent yields.[12]

We had previously reported[5] that 1-amino-3-siloxybutadienes undergo DA reactions with a wide range of α-substituted acroleins catalyzed by Jacobsen's chiral Cr(III)-salen catalyst,[13−15] to give cycloadducts in excellent yield (>90%) and up to 97% ee. The primary cycloadducts are readily hydrolyzed, providing quick entry into synthetically useful 4-substituted or 4,5-disubstituted cyclohexenones.[5,6] Upon further consideration of the early results and the model put forth to explain the observed enantioselectivity, we hypothesized that although the enol ether moiety may enhance the reactivity of the diene (by raising the HOMO energy), it is unlikely to play a role in the enantiodifferentiation (Figure 1). The crucial factor favoring one of the two possible endo

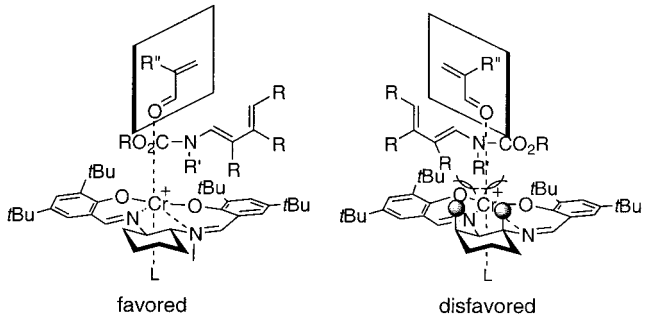
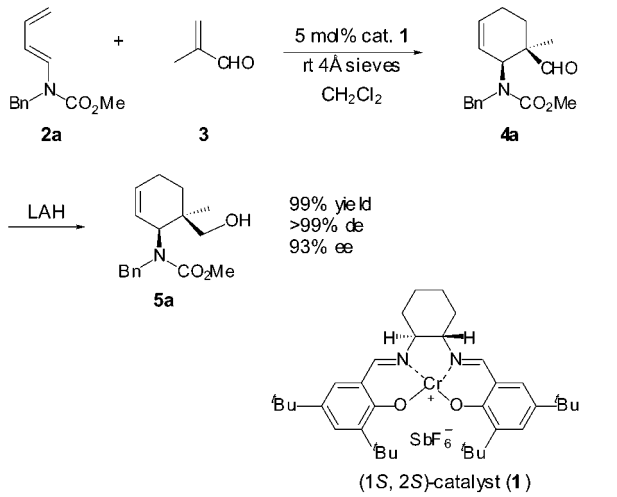


Figure 1. Proposed transition states for the facial selectivity.

transition states appeared to be the steric interaction between the axial hydrogens in the salen diaminocyclohexane and the alkyl group on the carbamate moiety. This analysis implied that the reaction might not be limited to the specific diene used in the original study but could be applicable to a broad range of 1-carbamate-substituted dienes, thereby greatly expanding the scope and usefulness of the catalyzed asymmetric DA reaction.

In an initial exploratory study, the Oppolzer−Overman[11] type of diene (**2a**) was allowed to react at room temperature with 2 equiv of methacrolein (**3**) and 5 mol % of the hexafluoroantimonate derivative of Jacobsen's Cr(III)-salen catalyst (**1**) in the presence of 4 Å molecular sieves (Scheme 1). A clean, rapid reaction ensued, affording exclusively the

Scheme 1. Eantioselective Diels−Alder Reaction between 1-Aminobutadiene and Methacrolein



endo diastereomer (**4a**) in quantitative yield after 21 h. Mosher ester analysis of its reduction product (**5a**) established that the cycloadduct had formed in 93% enantiomeric excess. The success of this enantioselective cycloaddition represents a major advance over our previous work. Unlike the earlier results, adducts such as **4** are not prone to eliminative hydrolysis to enones, yet they possess varied functionality that can be elaborated further for natural products synthesis applications.

The above chiral salen-catalyzed DA reaction was found to be remarkably general. We have examined this process using a variety of dienes and have obtained uniformly good results, summarized in Table 1. Unlike the low temperature required for many enantioselective processes, these reactions

(8) The sole example of a Lewis acid-catalyzed enantioselective DA reaction of a simple amino-substituted diene (i.e., of the Oppolzer−Overman type) predating our work was that of Evans, who observed high enantioselectivity for the cycloaddition between *N*-Cbz-amino-1,3-butadiene and *N*-acrolyloxazolidinone. The latter is capable of two-point binding to the chiral catalyst. See: Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582−7594.

(9) After the Evans report, Wipf and Wang reported the same transformation using Kobayashi's scandium catalyst: Wipf, P.; Wang, X. *Tetrahedron Lett.* **2000**, *41*, 8747−8751.

(10) The antibody-catalyzed enantioselective DA reaction of 1-amine-substituted dienes has been reported: (a) Romesberg, F. E.; Spiller, B.; Schultz, P. G.; Stevens, R. C. *Science* **1998**, *279*, 1929−1933. (b) Heine, A.; Stura, E. A.; Yli-Kauhaluoma, J. T.; Gao, C.; Deng, Q.; Beno, B. R.; Houk, K. N.; Janda, K. D.; Wilson, I. A. *Science* **1998**, *279*, 1934−1940.

(11) (a) Oppolzer, W.; Fröstl, *Helv. Chim. Acta* **1975**, *58*, 587−589. (b) Oppolzer, W.; Fröstl, *Helv. Chim. Acta* **1975**, *58*, 590−593. (c) Oppolzer, W.; Fröstl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593−595. (d) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352−2354. (e) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164−2167. (f) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 4537−4540, and references therein. See also: (g) Terada, A.; Murata, K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1644−1649.

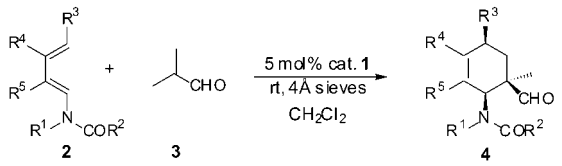
(12) The synthetic significance of the present work stems from the paucity of enantioselective DA reactions of amine-substituted butadienes and the demonstrated usefulness of 1-aminobutadiene Diels−Alder reactions in natural product synthesis. See reports cited in ref 3. See also: (a) Chigr, M.; Fillion, H.; Rougny, A. *Tetrahedron Lett.* **1987**, *28*, 4529−4532. (b) Chigr, M.; Fillion, H.; Rougny, A.; Berlion, M.; Riondel, J.; Beriel, H. *Chem. Pharm. Bull.* **1990**, *38*, 688−691.

(13) For leading references of (salen)Cr(III) catalyst, see: (a) Larkworthy, L. F.; Nolan, K. B.; O'Brien, P. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1987; Vol. 3, Chapter 35.4.8. (b) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *227*, 936−938. (d) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420−7421 and references cited therein.

(14) Cr(III)-(salen) catalyst was used in enantioselective hetero-Diels−Alder reactions by Jacobsen: Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405.

(15) Welker has reported the use of Jacobsen's salen as a stoichiometric chiral auxiliary for dienes: Chapman, J. J.; Day, C. S.; Welker, M. E. *Eur. J. Org. Chem.* **2001**, 2273−2282 and references therein.

Table 1. Enantioselective Diels−Alder Reaction with Various 1-Aminobutadienes



entry[a]	diene	R^1	R^2	R^3	R^4	R^5	time	prod	yield st(%)[b]	ee (%)[d]
1	**2a**	Bn	MeO	H	H	H	21 h	**4a**	99	93
2	**2b**	Alkyl	MeO	H	H	H	24 h	**4b**	95	89
3	**2c**	Me	MeO	H	H	H	22 h	**4c**	96	79
4	**2d**	Bn	t-BuO	H	H	H	23 h	**4d**	99	92
5	**2e**	Bn	Me	H	H	H	25 d	**4e**	85 (95)[c]	91
6	**2f**	Bn	MeO	Me	H	H	22 h	**4f**	94	93
7	**2g**	Bn	MeO	Ph	H	H	5 d	**4g**	63 (78)[c]	93
8	**2h**	Bn	MeO	H	Me	H	15 h	**4h**	93	95
9	**2i**	Bn	MeO	H	H	Me	4 d	**4i**	81 (97)[c]	95
10	**2j**	Bn	MeO	Me	H	Me	9.5 d	**4j**	40 (93)[c]	92

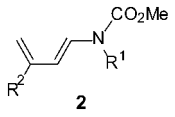
[a] Reactions were carried out at room temperature in CH_2Cl_2 (1.0 M) with 2 equiv of methacrolein, 5 mol % of catalyst **1**, and oven-dried 4 Å sieves (0.8 g/mmol of diene **2**). [b] Isolated yield based on **2**. [c] Yield based on recovered starting material. [d] Determined by NMR analysis of a Mosher ester derivative.

were carried out at room temperature. In every case, none of the exo diastereomer was discernible in the NMR of the crude reaction mixture. Consistent with our previous observations, the size of the alkyl group on the nitrogen (R^1) correlated with the enantioselectivity of the product. The *N*-allyl and *N*-methyl dienes (entries 2 and 3) gave cycloadducts with lower ee's than the *N*-benzyl diene. The size of R^2 appears not to be important for high enantioselectivity (entries 4 and 5). Both the *tert*-butyl carbamate (**2d**) and the acetamide (**2e**) dienes gave the corresponding adducts in high yields and ee's. The longer reaction time for the latter is understandable given the stronger electron withdrawing ability of the acetyl group compared to the alkoxycarbonyl group.

Dienes with substituents at the 2-, 3-, or 4-positions were good substrates for this reaction (entries 6−10). Dienes possessing a substituent at the 2-position were measurably less reactive than the other dienes (entries 9 and, 10). Presumably, 1,3-allylic strain twists the carbamate group out of planarity with the conjugated diene, rendering it less electron-rich. Although sluggish, these reactions were clean and gave high ee's, and the yields based on recovered starting material were above 90%. The reduced reactivity of the phenyl-substituted diene can be attributed to a combination of steric and electronic effects (entry 7). The rates, and hence the yields, of several of these reactions could be increased by slightly raising the reaction temperature.

The cycloadditions described here proceed at a good rate (Table 2). When the reaction between diene **2a** and methacrolein was quenched after only 1 h, the product was obtained in 74% isolated yield, with complete recovery of the unreacted diene (entry 1). The product yield rose to 85% after 2 h and to 94% after 6 h (entries 2 and 3). The ee of the product of each experiment was the same as that obtained for the 21 h reaction (entry 4). While the ee's of the

Table 2. Temperature Effect on Reaction Rate and Enantioselectivity



2a: R^1= benzyl, R^2=H
2b: R^1=allyl, R^2=H
2c: R^1=methyl, R^2=H

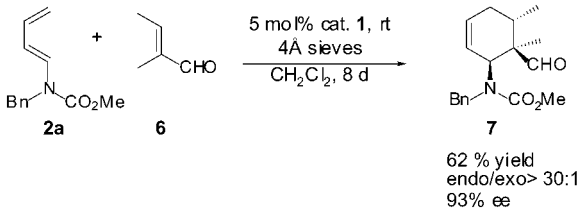
entry	diene	temp	time	yield[a] (%)	ee (%)
1	**2a**	rt	1 h	74 (100)	93
2	**2a**	rt	2 h	85 (100)	93
3	**2a**	rt	6 h	94 (100)	93
4	**2a**	rt	21 h	99	93
5	**2a**	0 °C	26 h	94	95
6	**2a**	−20 °C	3 d	85 (94)	97
7	**2b**	rt	22 h	95	89
8	**2b**	−20 °C	3.5 d	70 (91)	92
9	**2c**	rt	24 h	96	79
10	**2c**	−20 °C	3.5 d	87 (91)	85

[a] Isolated yields. Yields in parentheses are based on recovered starting materials.

cycloadditions have been consistently good, they can be improved by carrying out the reactions at a lower temperature. Thus, when the above reaction was carried out at 0 °C, the product was formed with 95% ee (26 h, 94% yield, entry 5). The ee increased to 97% at −20 °C, but the reaction did not go to completion, even after 3 days (entry 6). The same improvement in ee was observed for two other dienes (entries 7−10).

A final example highlights the capability of the salen-catalyzed DA reaction. Diene **2a** reacted under the standard conditions with tiglic aldehyde (**6**), a trisubstituted dienophile, to afford the expected endo adduct (**7**) in good yield and high ee (Scheme 2). The effectiveness of the salen catalyst

Scheme 2. Enantioselective Diels−Alder Reaction of 1-Aminobutadiene and Tiglic Aldehyde



in all these reactions is noteworthy since both the diene and the DA product possess carbamate groups, the carbonyl oxygens of which are expected to be more Lewis basic—hence better ligands—than that from the dienophile.

The present study has uncovered the immense potential of the enantioselective Diels−Alder reaction of 1-amino-substituted butadienes and α-substituted acroleins catalyzed by Jacobsen's chiral Cr(III)-salen complex. The reactions are conveniently performed, remarkably tolerant of substituents at different positions of the diene framework, and afford cycloadducts with almost complete endo-selectivity in good

yields and high ee's. This simple process provides ready access to richly functionalized cyclohexenylamines possessing a quaternary chiral center. The application of this chemistry to complex targets is currently under investigation.

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Supporting Information Available: Preparation of Cr(III)-salen catalysts, general experimental procedure for Diels−Alder reactions, and spectroscopic data and specific rotations of new cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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