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Application of Chiral Cationic Catalysts to Several Classical Syntheses of Racemic Natural Products Transforms Them into Highly Enantioselective Pathways

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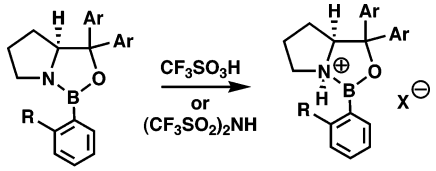
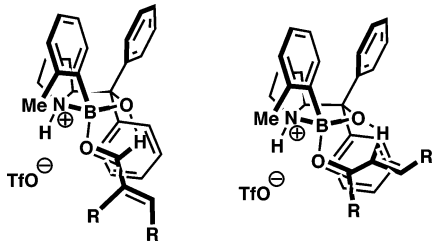
Abstract: This paper describes the application of chiral oxazaborolidinium cations of type **2** to various enantioselective Diels−Alder reactions that have served as early key steps for the syntheses of complex natural products. In the original syntheses these Diels−Alder reactions produced racemic adducts and led to racemic target molecules unless a separation of enantiomers by classical resolution was employed. By use of chiral catalysts of type **2**, chiral products were obtained directly from Diels−Alder reactions of achiral components in excellent yield and enantioselectivity and with the mechanistically predicted absolute configuration. As a result, a number of classical syntheses could be converted to enantioselective versions, including (1) cortisone/cortisol (Merck/Sarett), (2) dendrobine (Kende), (3) vitamin B_{12} (Eschenmoser), (4) myrocin C (Chu-Moyer/Danishefsky), (5) coriolin and hirsutene (Mehta), (6) dendrobatid 251F (Aubé), (7) silphinene (Ito), and (8) nicandrenone core (Stoltz/Corey).

The Diels−Alder reaction, one of the most powerful constructions for the assembly of carbon compounds, has been used as a key step in many notable syntheses of complex natural products in its original form, which converted achiral components to racemic adducts. In this paper we describe the formal conversion of eight of these classical syntheses to modern enantioselective versions. This transformation has been made possible by the recent invention of extraordinarily powerful chiral catalysts of broad scope and predictable enantio- and regioselectivity. These catalysts are generated simply by protonation of oxazaborolidines of type **1** by triflic acid, CF_3SO_3H, or triflimide, $(CF_3SO_2)_2NH$, to form the corresponding *cis*-fused oxazaborolidinium cation, **2**.[1] The face selectivity of the



1 2

enantioselective Diels−Alder reactions depends on the structural type of the dienophile component. For 2-substituted α,β-enals, formyl C−H···O hydrogen bonding leads to a preferred pathway via **3**,[1a,b,2] whereas for α,β-unsaturated esters, lactones, and ketones having an α-C−H subunit, a preference for α-C−H···O hydrogen bonding[1b,c] favors reaction via complex **4**. For 1,4-



3 4

benzoquinones a detailed set of selection rules have been developed that allows the prediction of both enantioselection and regioselection in Diels−Alder reactions promoted by the chiral catalysts **2**.[1e,3] The following sections of this paper describe the application of catalysts **2** to new enantioselective versions of Diels−Alder reactions that were first used for some of the most interesting multistep syntheses of natural products of the 20th century.

Sarett's Total Synthesis of Cortisone. The challenge of producing cortisone/cortisol, one of the most important of all modern therapeutic innovations, dominated synthetic organic chemistry for two decades following World War II. The development of the first workable total synthesis by a group at Merck headed by Sarett was one of the crowning achievements of that period.[4,5] The initial step in this cortisone synthesis was a thermal Diels−Alder reaction of **5** and the ethyl ether analogue of **6**, which produced the corresponding racemate of adduct **7** (Scheme 1). To obtain the natural enantiomer of cortisone by

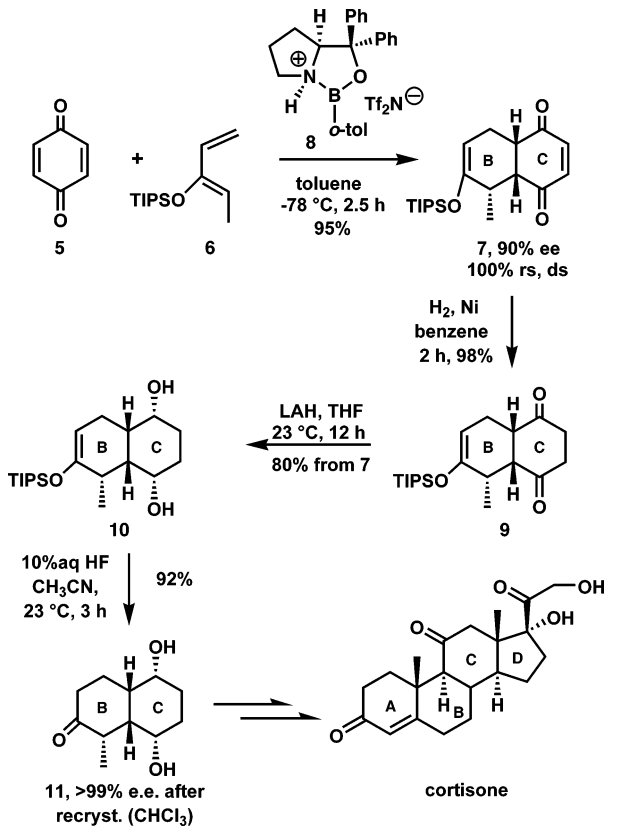
(1) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808−3809. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390. (d) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979−3982. (e) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800−4802. (f) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984−5986.

(2) Corey, E. J.; Lee, T. W. *J. Chem. Soc., Chem. Commun.* **2001**, 1321−1329.

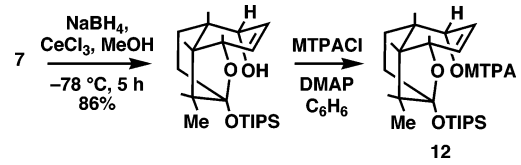
(3) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373−2376.

10.1021/ja046154m CCC: $27.50

Scheme 1

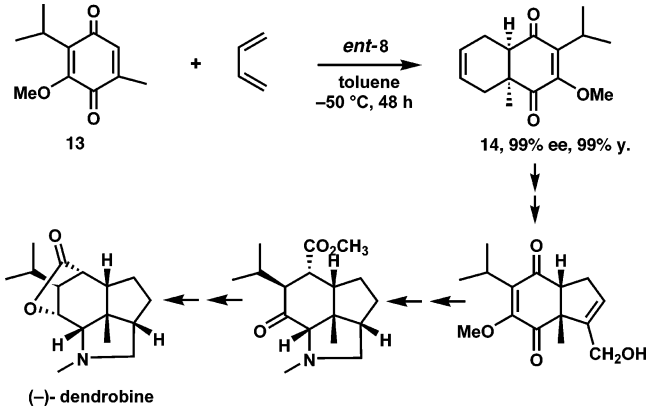


the Sarett route, conventional resolution was applied to the brucine salt of an advanced tricyclic intermediate corresponding to the A/B/C network of cortisone.[5] Partly because of the cumbersome nature of this process and the unavoidable loss of more than half of an advanced tricyclic synthetic intermediate, this leap forward in chemical synthesis still fell short of commercial application. In the present work, the key initial Diels−Alder step has been recast into a new highly efficient enantioselective version. Specifically, reaction of **5** and **6** occurred rapidly in the presence of 20 mol % chiral oxazaborolidinium catalyst **8** in toluene solution at −78 °C to give the chiral adduct **7** with 95:5 enantioselectivity and 100% regioselectivity and diastereoselectivity (rs and ds) in 95% yield after 2.5 h.[6] The chiral adduct **7** was shown to be spectroscopically and chromatographically identical with racemic **7**, produced by thermal reaction of **5** and **6**, the structure and relative stereochemistry of which had been established.[4] The orientation of the methyl group in **7** corresponds to the expected *endo* transition-state preference. Following the Merck route, adduct **7** was converted efficiently via intermediates **9** and **10** to the crystalline diol **11**, which was obtained enantiomerically pure (by gas chromatographic analysis)[7] simply by recrystallization from $CHCl_3$ (mp of pure **11**, 194−195 °C; $[\alpha]_D^{23}$ +91). The enantiomeric purity of the original Diels−Alder adduct **7** was determined after conversion in two steps to the α-methoxy-(α-trifluoromethyl)phenylacetate (MTPA, Mosher) ester **12**, as shown below, and ^1H and ^{19}F NMR analysis. The absolute configuration of **7** follows from previous studies of the closely related enantioselective reactions, for example, of 1,4-benzoquinone (**5**) with 2-triisopropylsilyloxy-1,3-butadiene.[3]



Kende's Total Synthesis of Dendrobine. In 1974 Kende and Bentley[8] described a simple total synthesis of (±)-dendrobine that derived much of its brevity from a key thermal Diels−Alder reaction of 1,3-butadiene with methoxythymoquinone **13** to produce the racemic Diels−Alder adduct **14** (Scheme 2). When we conducted the reaction of these components in the presence of 20 mol % catalyst *ent*-**8** in toluene at −50 °C for 48 h, the chiral adduct **14** was obtained with 99% enantiomeric purity in 99% yield.[7] This highly successful result opens the way for the enantioselective synthesis of (−)-dendrobine via the Kende sequence.[8] It should be noted that the synthesis of chiral **14** in Scheme 2 is the first example of the use of 1,3-butadiene as a component in an enantioselective Diels−Alder pathway to a natural product.

Scheme 2



Eschenmoser's Photochemical Route to Vitamin B_{12}. In Eschenmoser's ingenious photochemical synthesis of vitamin B_{12}, the cobryic acid core was assembled from four chiral pyrrolidones, **15**−**18**, representing the A, B, C, and D subunits of the corrin ring system (Scheme 3).[9] These intermediates, in turn, were synthesized from the enantiomeric dilactones **19** (for **15**−**17**) and **20** (for **18**). Finally, the dilactones **19** and **20** were obtained from the chiral keto acids **21** and **22**, which were produced as a racemic mixture by the Diels−Alder reaction and

(4) (a) Sarett, L. H.; Arth, G. E.; Lukes, R. M.; Beyler, R. E.; Poos, G. I.; Johns, W. F.; Constantin, J. M. *J. Am. Chem. Soc.* **1952**, *74*, 4974−4976. (b) Sarett, L. H.; Lukes, R. M.; Poos, G. I.; Robinson, J. M.; Beyler, R. E.; Vandergrift, J. M.; Arth, G. E. *J. Am. Chem. Soc.* **1952**, *74*, 1393−1397. (c) For assignment of configuration see Beyler, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 1406−1411. (d) Poos, G. I.; Arth, G. E.; Beyler, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 422−429. (e) Lukes, R. M.; Poos, G. I.; Beyler, R. E.; Johns, W. F.; Sarett, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 1707−1712. (f) Sarett, H. L.; Johns, W. F.; Beyler, R. E.; Lukes, R. M.; Poos, G. I.; Arth, G. E. *J. Am. Chem. Soc.* **1953**, *75*, 2112−2118.

(5) See also (a) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold Publishing Co.: New York, 1959; pp 711−713. (b) Blickenstaff, R. T.; Gosh, A. C.; Wolf, G. C. *Total Synthesis of Steroids*; Academic Press: New York, 1974; pp 182−187.

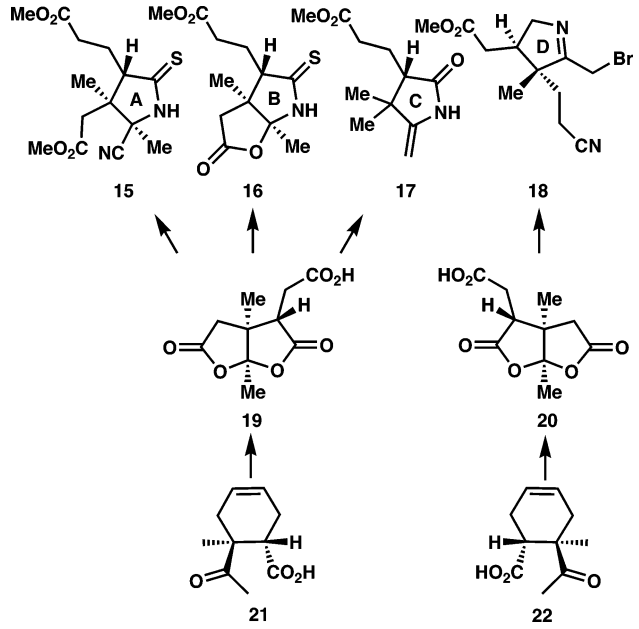
(6) On a larger scale the use of 5 mol % catalyst **8** would probably suffice since the reaction could be run at higher concentrations of the Diels−Alder components. In any event (*S*)-diphenylprolinol, from which catalyst **8** is derived, is readily recovered for reuse.

(7) Enantiomeric purity was determined by gas chromatographic analysis on a chiral γ-TA column.

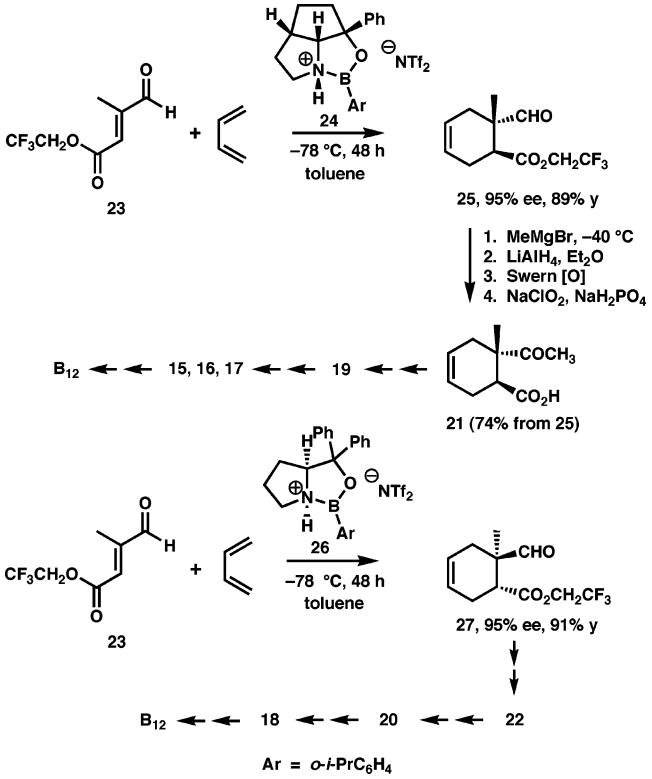
(8) Kende, A. S.; Bentley, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 4332−4334.

(9) Eschenmoser, A.; Witner, C. E. *Science* **1977**, *196*, 1410−1420.

Scheme 3

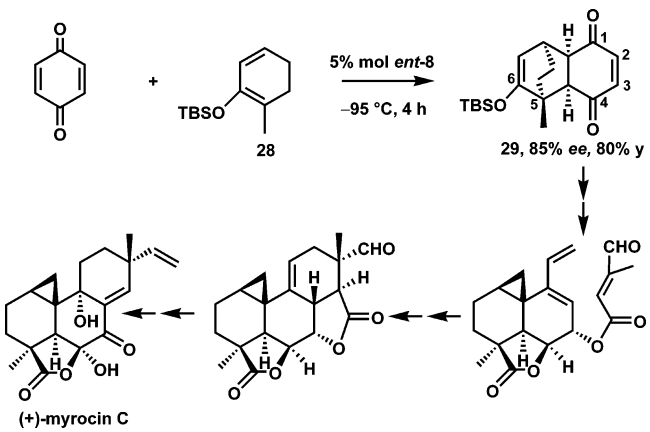


Scheme 4



obtained from that mixture by resolution of the salts with 1-phenylethylamine.[9] In this research **21** and **22** have been synthesized enantioselectively from the same components by use of two different chiral catalysts. Scheme 4 details the synthesis of the dextrorotatory keto acid **21**. Reaction of the aldehyde trifluoroethyl ester **23** with 1,3-butadiene in the presence of 20 mol % catalyst **24**[1f] [Ar = *o*-(*i*-propyl)phenyl] at −78 °C afforded the adduct **25** in 95% ee and 89% yield. The addition of methyl to the formyl group of **25** and ester reduction produced a diol which upon two-stage oxidation afforded the chiral keto acid **21** in good overall yield from **25**.

Scheme 5



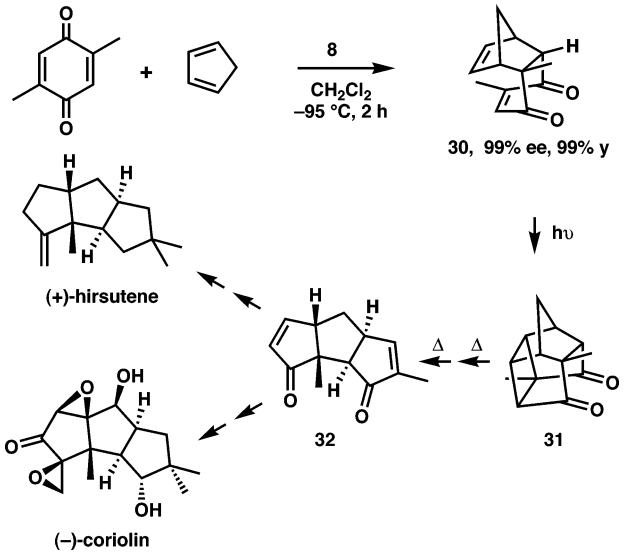
The synthetic pathway between **21** and vitamin B_{12} via **19** and **15**, **16**, and **17** has previously been established. Catalyst **24** (or its analogue **24**, Ar = *o*-$CF_3C_6H_4$) gave a significantly better level of enantioselectivity than the corresponding B-*o*-tolyl analogue (73% ee), which we have previously employed for enantioselective syntheses of estrone and desogestrel.[1f] In a similar way **23** and 1,3-butadiene were combined by use of the catalyst **26** to form adduct **27** in 95% ee and 91% yield. The transformation of **27** to **22**, the required intermediate for B_{12} synthesis via **20** and **18**, was accomplished as described just above for **25** → **21**.[10]

Chu-Moyer/Danishefsky Synthesis of (±)-Myrocin C. The complex antitumor antibiotic myrocin C has been synthesized in racemic form by Chu-Moyer and Danishefsky[11] via an impressive multistep sequence that commenced with the Diels−Alder reaction of diene **28** and 1,4-benzoquinone to form (±)-adduct **29**. We have been able to carry out this initial [4 + 2] cycloaddition enantioselectively as outlined in Scheme 5 using catalyst *ent*-**8** (20 mol %) at −95 °C for 4 h to give the chiral tricyclic dione **29** in 85% ee and 80% yield. The enantiomeric purity of **29** was ascertained by reduction ($LiAlH_4$) of the dione to the corresponding diol, conversion to the MTPA ester of the corresponding monohydroxy 4 → 6 cyclic ether, and ^{19}F NMR analysis. The Chu-Moyer/Danishefsky synthesis of (±)-myrocin C proceeded via the intermediates (racemic) shown at the bottom of Scheme 5.

G. Mehta's Synthesis of (±)-Triquinanes Including Coriolin and Hirsutene. The elegant synthetic route developed by Mehta to the triquinane family of natural products testifies eloquently to the power and versatility of the Diels−Alder reaction for the synthesis of complex molecules.[12] The reaction of cyclopentadiene with 2,5-dimethyl-1,4-benzoquinone in the presence of 20 mol % catalyst **8** in CH_2Cl_2 proceeded to completion at −95 °C in just 2 h to afford the endo adduct **30**, $[\alpha]_D^{25}$ +11.3 ($CHCl_3$) in 99% ee (by HPLC analysis) and 99% yield in an enantioselective version of Mehta's first step on the pathway to triquinanes (Scheme 6). A few of the following key

(10) The enantiomer of catalyst **26** obviously could be used for the enantioselective synthesis of **25**.
(11) (a) Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1994**, *116*, 11213−11228. (b) Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 8333−8334.
(12) (a) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443−3452. (b) Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* **1981**, 756−757.

Scheme 6

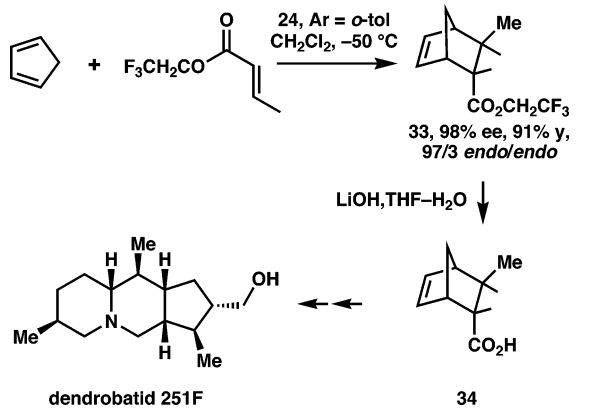


steps in the Mehta approach to racemic triquinanes are shown in Scheme 6, which also illustrates the new enantioselective modification via **31** and **32**.

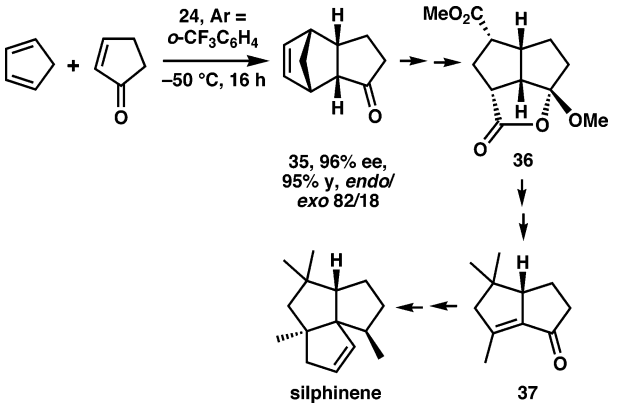
Bicyclo[2.2.1]heptene Routes to Dendrobatid 251F and Other Natural Products. Bicyclo[2.2.1]heptene intermediates that are available from Diels−Alder reactions have served as valuable intermediates for the synthesis of a number of complex molecules, for example, gibberellic acid and prostanoids.[13] In this section we illustrate the application of the cationic oxazaborolidinium catalyst **24**, Ar = *o*-tolyl, to the synthesis of intermediate **34** that has been used for the construction of various natural products including *E*- and *Z*-*β*-santalols[14] (important perfumery components) and dendrobatid 251F.[15] The previously described syntheses have employed chiral controller groups to achieve diastereoselective access to **34** in contrast to the present methodology with a chiral catalyst. Reaction of *E*-crotyl trifluoroacetate with cyclopentadiene in the presence of 10 mol % catalyst **24**, Ar = *o*-tolyl, in CH_2Cl_2 at −50 °C for 16 h produced the Diels−Alder adduct **33** in 91% yield with an endo/exo ratio of 97/3 and an enantiomeric purity of the endo product of 98% (Scheme 7). Base hydrolysis generated the corresponding acid **34** (95%), recently used for the total synthesis of dendrobatid 251F.

A more challenging test for catalysts of type **2** is the synthesis of silphinene via a bicyclo[2.2.1]heptene intermediate. The synthesis of racemic silphinene has previously been carried out from the racemic Diels−Alder adduct **35** via the intermediates **36** and **37** as indicated in Scheme 8.[16] The catalytic enantioselective synthesis of adduct **35** is especially interesting and challenging because of the relative unreactivity of 2-cyclopentenone in catalytic Diels−Alder reactions. We have examined three catalysts of type **24**, Ar = *o*-$CH_3C_6H_4$, *o*-*i*-PrC_6H_4, and *o*-$CF_3C_6H_4$, and have determined that the last of these affords the best results. The reaction of cyclopentadiene and 2-cyclopentenone in CH_2Cl_2 at −50 °C for 16 h in the presence of 10

Scheme 7



Scheme 8

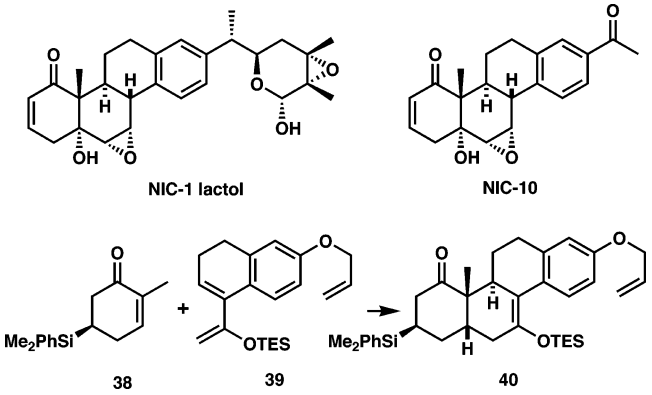


mol % catalyst **24**, Ar = *o*-$CF_3C_6H_4$, afforded **35** in 95% yield as an 82/18 mixture of endo and exo diastereomers, which were separated by column chromatography on silica gel. The endo adduct was analyzed by GC and found to be 96% enantiomerically pure.[17] This highly enantioselective synthesis of **35** provides the missing link in a formal synthesis of the naturally occurring form of silphinene.

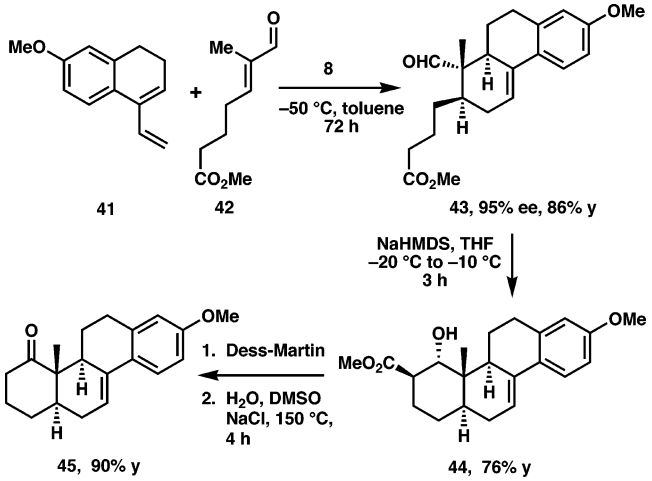
Enantioselective Synthesis of the Tetracyclic Core of the Nicandrenones. In 2000 we reported the development of an enantioselective synthesis of the nicandrenone family of potent insect antifeedants including NIC-1 lactone, NIC-1 lactol, and NIC-10.[18] An important step in the pathway of synthesis was a remarkable exo-diastereoselective Diels−Alder reaction of the chiral α,*β*-enone **38** and the achiral diene **39** to give **40** under catalysis by $MeAlCl_2$ in CH_2Cl_2 at −78 °C, as shown in Scheme 9.[18−20] We report herein a catalytic enantioselective approach to the construction of the chiral tetracyclic framework of **40** from achiral components that takes advantage of the cationic catalyst **8** and provides ready access to the core ring system of the nicandrenones. The key steps for this process are outlined in Scheme 10. Reaction of the Dane diene **41** with the α,*β*-enal ester **42** in the presence of 25 mol % catalyst **8** in toluene at −50 °C for 72 h afforded the Diels−Alder product **43** in 95% ee and 86% yield. The formation of adduct **43**, assigned on the

(13) For a recent review of such enantioselective Diels−Alder routes see Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.
(14) Krotz, A.; Helmchen, G. *Tetrahedron Asymmetry* **1990**, *1*, 537−540.
(15) Wrobleski, A.; Sahasrabuhde, K.; Aubé, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974−9975.
(16) Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83−86.
(17) The absolute configuration of adduct **35** follows from analogy with a large number of related examples (see ref 1).
(18) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044−9045.
(19) See also Ge, M.; Stoltz, B. M.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1927−1929.
(20) For the synthesis of the chiral α,*β*-enone **38**, see Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811−814.

Scheme 9

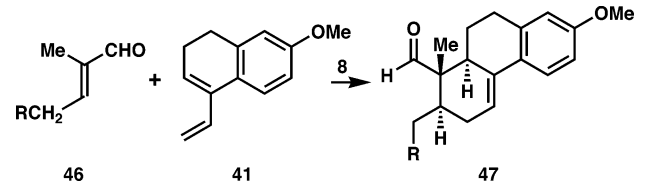


Scheme 10



basis of X-ray crystallographic analysis of the lower homologue (two CH_2 groups between the MeOOC and the tricyclic nucleus; see Table 1 below), requires an exo arrangement of **41** and **42**

Table 1. *Exo*-Selective Diels−Alder Reactions of Diene **41** and Catalyst **8**

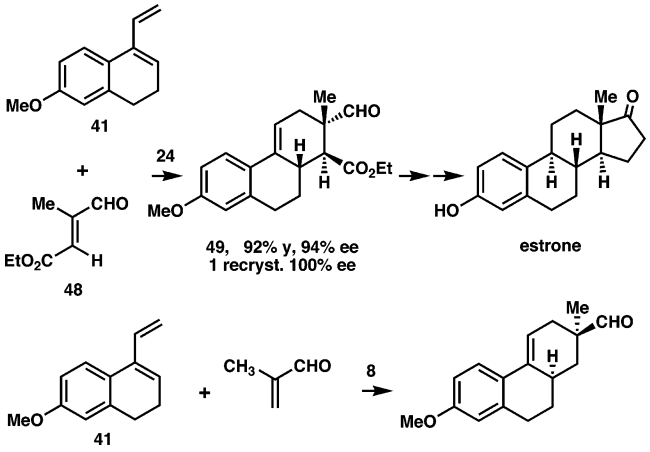


R in **46**, **47**	conditions	ee for **47**, yield (%)
−COOMe	−50 °C, 48 h	92, 80
−OTIPS	−50 °C, 48 h	93, 92
$-CH_2COOMe$	−78 to −50 °C, 56 h	98, 94
$-(CH_2)_2COOMe$	−50 °C, 72 h	95, 86

in the [4 + 2] cycloaddition transition state. As is discussed below, the exo preference over the usually favored endo pathway is a consequence of steric repulsions in the transition state between the aromatic ring of **41** and the *o*-tolyl group of the catalyst **8**. Aldol ring closure of **43** provided the β-hydroxy ester **44**, which was selectively oxidized to the corresponding β-keto ester and demethoxycarbonylated by heating with wet NaCl in dimethyl sulfoxide to give the nicandrenone core structure **45**, as shown in Scheme 10.

We have examined the Diels−Alder reactions of the Dane diene **41** with three lower homologues/analogues of α,β-enal

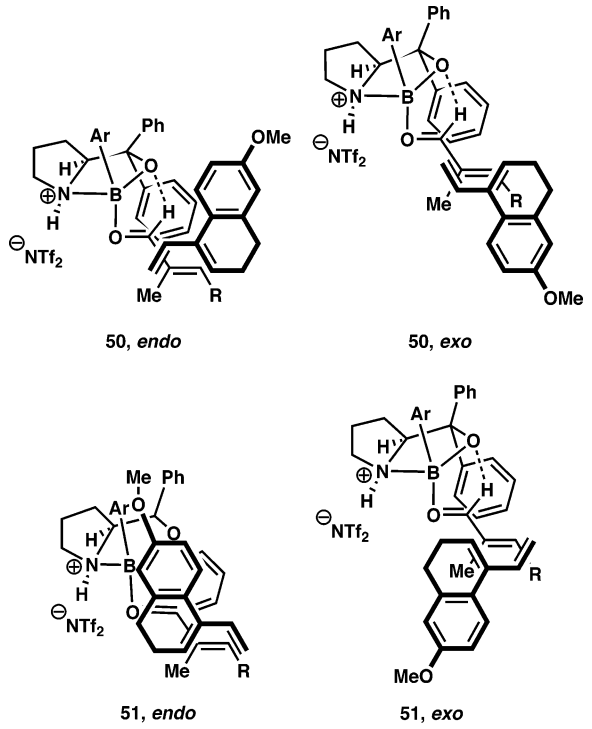
Scheme 11



42 under catalysis by **8** with the results that are summarized in Table 1. It is apparent from these data that the catalyzed reactions proceed with uniformly good yields and enantioselectivities. In the case of **47**, R = CH_2COOMe, the structure of the product was determined unambiguously to be that shown by single-crystal X-ray diffraction analysis (data included in Supporting Information). It is noteworthy not only that these reactions are exo-selective but also that they occur with the opposite regioselectivity to that with the α,β-enal **48** (see Scheme 11). The reaction of **48** with the Dane diene **41** under catalysis by **24**, Ar = *o*-tolyl, has recently been used in a short and efficient enantioselective synthesis of estrone via adduct **49** as summarized in Scheme 11.[1f] The contrasting regiopreference in the Diels−Alder reactions of **41** with **48** vs **43**, though surprising at first sight, can be rationalized in terms of subtle steric effects. First, the Dane diene **41** affords a stable cationic intermediate regardless of whether it is attacked electrophilically at the terminal CH_2 of the diene (giving a disecondary allylic cation) or at the endocyclic CH terminus (which gives a *p*-methoxybenzylic cation). Diels−Alder reactions of **41** are known to involve a delicate balance between both modes of attack and to follow different pathways with different dienophiles and Lewis acids.[21] For an asynchronous transition state, attack by a bulky electrophile would normally be favored at the terminal methylene of **41** rather than the endocyclic terminus of the diene. Therefore, the effective steric bulk of the group attached β to the formyl carbon of **46** (Table 1) relative to COOEt in **48** may account in part for the orientational divergence of **46** and **48** in the reactions with diene **41**. (Electronic differences may also play a secondary role since the complex between **48** and **8** would clearly be more electron-deficient than those between **46** and **8**, possibly leading to a more synchronous [4 + 2] cycloaddition.) Further support for the significant role of the bulk of the β-substituent in determining the regiochemistry of chiral Lewis-acid-catalyzed [4 + 2] cycloaddition to **41** comes from the study of the reaction of 2-methylacrolein with **41** under catalysis by oxazaborolidinium

(21) (a) Quinkert, G.; Grosso, D. M.; Döring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Durner, G. *Helv. Chim. Acta* **1995**, *78*, 1345−1391. (b) Stojanac, Z.; Dickinson, R. A.; Stojanac, N.; Woznow, R. J.; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 616−618. (c) Das, J.; Kubela, R.; MacAlphile, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308−3319. (d) Singh, G. *J. Am. Chem. Soc.* **1956**, *78*, 6109−6115. (e) Dane, E.; Eder, K. *Liebigs Ann. Chem.* **1939**, *539*, 207−212.

Scheme 12



reagent **8**, which follows the same regiopath as **41** + **48** → **49**, as shown in Scheme 11.

The preference for an exo-type transition state in the reaction of **41** and **42** and **8** leading to **43**, in contrast to the endo preference that is involved in the synthesis of estrone from **41** and **48**, can be explained readily in terms of the mechanistic model that has been developed for Diels−Alder reactions under oxazaborolidinium catalysis.[1] Scheme 12 displays four pre-transition-state assemblies for reactions involving catalyst **8**, the Dane diene **41**, and dienophiles of type **46** or **48**. In structures **50** of Scheme 12, which represent the regiopreference exhibited with α,β-enal **48** in the synthesis of estrone, there are no significant differences in steric repulsion between the endo and exo pathways, so it is understandable that the normally favored endo pathway (**50**, endo) is observed. In contrast for regiopreference involved in the nicandrenone synthesis (**51**), the endo pathway (*endo*-**51**) is greatly disfavored vs the exo (*exo*-**51**) by serious steric repulsion between the aryl group on boron of catalyst **8** and the aromatic ring of the diene component.

Conclusion. The recent development of catalysts for the enantioselective construction of carbon rings has dramatically changed the landscape of chemical synthesis of complex natural products. The results described in this paper demonstrate that the rapid rate of progress made over the past few decades[13] continues unabated and has, if anything, accelerated in the last three years because of the discovery of chiral catalysts of type **2**. These catalysts and others still to be invented promise important further improvements in the logic, power, and sophistication of chemical synthesis. One remarkable feature of the new catalysts is their ease of use and practicality. From an intellectual point of view, the mechanistic clarity and predictability of their catalytic action is both remarkable and unsurpassed. The examples of catalytic enantioselective Diels−Alder reactions described in this paper all followed the expected course to give the predicted major enantiomer with high selectivity and excellent yield. With the inclusion of our new enantioselective methodology, each of the classical syntheses discussed in this paper gains further luster and beauty.

Supporting Information Available: Experimental procedures for the preparation of catalysts **8**, **24**, and **26** and the reactions used for the enantioselective synthesis and analysis of Diels−Alder products displayed in Schemes 1−11; NMR spectra of Diels−Alder adducts **7**, **14**, **25**, **29**, **30**, **33**, **35**, **43**, **44**, **45**, and **47** (PDF); and X-ray crystallographic data for **47**, R = CH_2-COOMe (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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