Asymmetric Catalysis

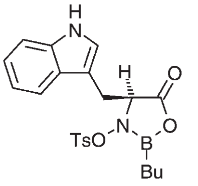
DOI: 10.1002/anie.200800574

Oxazaborolidines as Catalysts for Enantioselective Cycloadditions: Now [2+2]!

*Holger Butenschön**

asymmetric catalysis · cycloadditions · cyclobutane ·
Lewis acids · oxazaborolidine

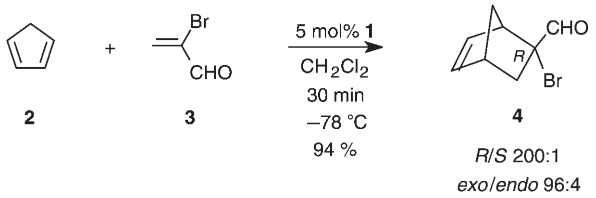
Lewis acids have been employed satisfactorily as catalysts for cycloadditions for some time, and more recently organocatalysts have also been shown to catalytically accelerate such reactions.[1–3] Catalyzed enantioselective cycloadditions, in particular, are of prime interest for organic synthesis. On the occasion of the 100th birthday of Kurt Alder, Corey summarized the field of catalyzed enantioselective Diels–Alder reactions in this journal in 2002.[4] Although a number of enantioselective homo- as well as hetero-Diels–Alder reactions are known, which are catalyzed by transition metals in the presence of bis(oxazoline), binaphthyl, or α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol(Taddol) ligands,[5,6] the research by Corey and co-workers focused on asymmetric catalysis with Lewis acids derived from aluminum, boron, or titanium. In addition, Narasaka has made important pioneering contributions to the latter field.[7–9]



1

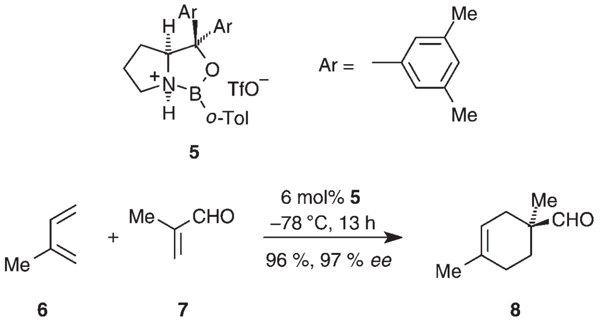
Scheme 1. Oxazaborolidine catalyst **1**. Ts = *p*-toluenesulfonyl.

Oxazaborolidine catalysts such as **1** (Scheme 1) have proven successful in the enantioselective Corey–Bakshi–Shibata(CBS) reduction[10–12] over the past 20 years.[13] Catalysts of this kind are suitable not only for reduction but also for [4+2] cycloaddition reactions. Corey and Loh showed as early as 1991 that the Diels–Alder reaction of cyclopentadiene (**2**) with 2-bromopropenal (**3**) in the presence of 5 mol % of **1** afforded cycloadduct **4** in excellent enantioselectivity (ca. 99.5 % *ee*) in 94 % yield (*exo*/*endo* 96:4, Scheme 2).[14]



Scheme 2. Enantioselective Diels–Alder reaction with catalyst **1**.

Later Corey et al. showed that protonated oxazaborolidinium triflates such as **5** have an extraordinarily broad application profile as catalysts in enantioselective Diels–Alder reactions. For example, the cycloaddition of 2-methyl-1,3-butadiene (**6**) with 2-methylpropenal (**7**) at −78 °C affords **8** in 96 % yield and 97 % *ee* (Scheme 3).[15,16]



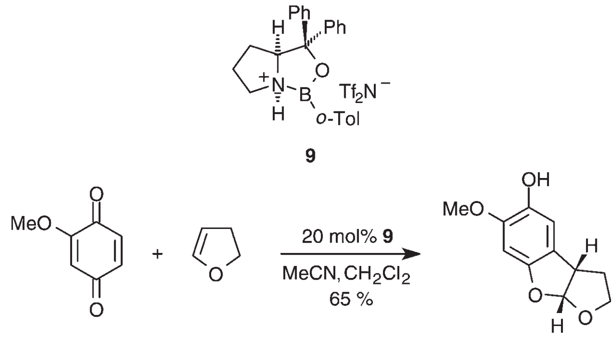
Scheme 3. Enantioselective Diels–Alder reaction catalyzed by the protonated oxazaborolidinium triflate **5**. *o*-Tol = *o*-tolyl.

The broad application profile of protonated oxazaborolidinium catalysts such as **5** has been underlined impressively by the implementation of enantioselective Diels–Alder cycloadditions into some classic syntheses of racemic natural products, resulting in the formation of the respective natural products in high enantiomeric purity.[17] In this respect, mention should be made of the cortisone synthesis by Sarett et al.,[18,19] that of vitamin B_{12} by Eschenmoser and Winter,[20] that of myrocine C by Danishefsky et al.[21] as well as the triquinane syntheses by Mehta et al. including those of corioline and hirsutene.[22,23] In addition to the implementation of enantioselective Diels–Alder reactions into known racemic syntheses, Corey and co-workers developed new syntheses of natural products and active substances based on this reaction. These include dolabellane-derived marine natural products such as dolabellatrienone and palominol,[24] fragrances such as georgyone and arborone,[25] as well as the neuroamidase inhibitor oseltamivir, which has gained impor-

---

[*] Prof. Dr. H. Butenschön
Institut für Organische Chemie
Leibniz Universität Hannover
Schneiderberg 1B, 30167 Hannover (Germany)
Fax: (+49) 511-762-4661
E-mail: holger.butenschoen@mboc.oci.uni-hannover.de
Homepage: http://www.oci.uni-hannover.de/AK_Butenschoen/startseite.htm

tance as Tamiflu in connection with medicinal treatment of infections with the bird flu virus H5N1.[26] An important expansion of the profile of protonated oxazolidinium catalysts has been realized by the application of triflimide **9** as a catalyst for an enantioselective [3+2] cycloaddition of 2-methoxyquinone (**10**) and 4,5-dihydrofuran (**11**) to give **12** within the total synthesis of aflatoxin B_2 (Scheme 4).[27]

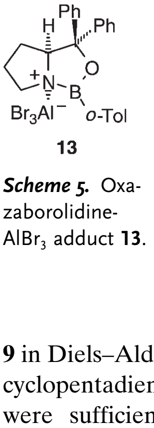


9

10 **11** **12** (92 % *ee*)

Scheme 4. Enantioselective [3+2] cycloaddition catalyzed by the protonated oxazaborolidinium triflimide **9**.

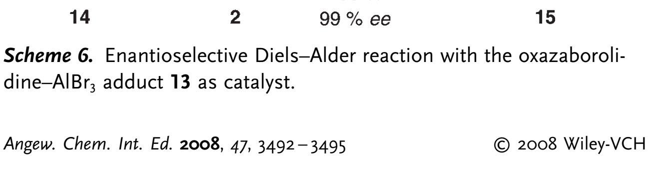
It should emphasized that the complete protonation of the oxazaborolidines requires strong acids such as trifluoromethanesulfonic acid or bis(trifluormethylsulfonyl)imide, even methanesulfonic acid or *p*-toluenesulfonic acid are insufficient. Early attempts at the formation of adducts of oxazaborolidines and Lewis acids were less than promising; however, Corey and co-workers have now reported efficient asymmetric catalyses of Diels–Alder cycloadditions and, more recently, [2+2] cycloadditions by the adduct **13** of the oxazaborolidine, which had aldready been protonated to give **9**, and aluminum tribromide (Scheme 5).[28,29]



13

Scheme 5. Oxazaborolidine-$AlBr_3$ adduct **13**.

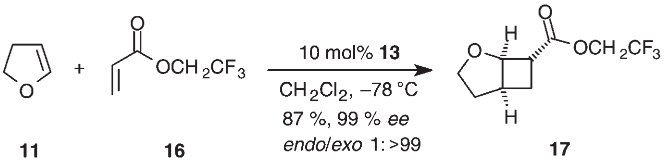
The adduct **13** was formed in situ by addition of a solution of $AlBr_3$ in dibromomethane to a cold (< -20 °C) solution of the oxazaborolidine in dichloromethane, and was identified by ^1H NMR spectroscopy; the pyrrolidine and the *o*-tolyl methyl protons showed a deshielding comparable to that in protonated oxazaborolidines. It turned out that **13** was more efficient than **9** in Diels–Alder reactions such as that of the quinone **14** and cyclopentadiene (**2**) to tricycle **15** (Scheme 6): 4 mol% of **13** were sufficient for performing the reaction under mild reaction conditions in excellent yields and enantioselectivities, whereas 10–20 mol% of **9** were required to achieve comparable results. This applies also to cycloadditions with the less reactive cyclohexadiene. The catalysis also functions with with furans, thus opening the way to valuable chiral cyclohexadienes by subsequent ring-opening of the cycloadducts by using trimethylsilyl bromide or zinc dust in acetonitrile. An additional advantage of this method for large-scale reactions is that the catalyst precursor diphenylpyrrolidinomethanol can be recovered easily in enantiomerically pure form. Remarkably, up to now only aluminum tribromide has led to such an activation of oxazolidine catalysts, $AlCl_3$ and $GaCl_3$ gave clearly worse results.[28]



14 **2** **15**

Scheme 6. Enantioselective Diels–Alder reaction with the oxazaborolidine–$AlBr_3$ adduct **13** as catalyst.

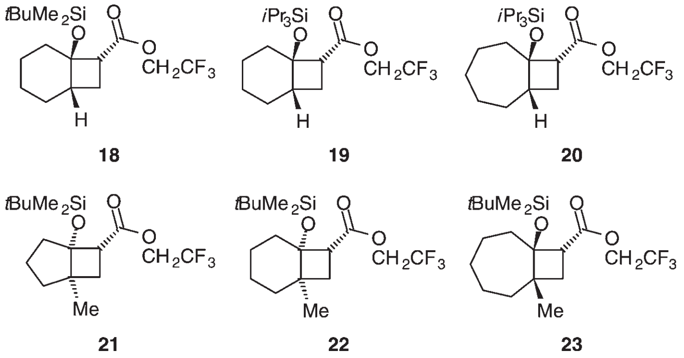
Recent review articles by Lee-Ruff and Bach on syntheses of cyclobutanes indicate that catalyzed enantioselective [2+2] cycloadditions are exceptionally rare.[30–32] Early groundbreaking contributions by Narasaka et al. include the catalyzed enantioselective [2+2] cycloaddition of α,β-unsaturated amides with various ketene thioacetals, allenyl and alkenyl sulfides in high yields and enantioselectivities in the presence of chiral Taddol ligands and dichlorodiisopropoxytitanium.[33–36] Later Engler applied the catalyst system for the [2+2] cycloaddition of quinones with styrene derivatives.[37] In a recent paper, Corey and Canales now describe the application of catalyst **13** in enantioselective [2+2] cycloadditions of cyclic enol ethers with the particularly reactive 2,2,2-trifluorethylpropenoate (**16**). The reactions take place in the presence of 10 mol% of **13** at -78 °C in 87–99% yield with high diastereoselectivity and enantiomeric excesses of the cyclobutanes formed of up to 99%. For example, the reaction of 4,5-dihydrofuran (**11**) with **16** affords the bicycle **17** in 87% yield (*endo*/*exo* = 1: > 99) and 99% *ee* in only 3 h (Scheme 7).[29]



11 **16** **17**

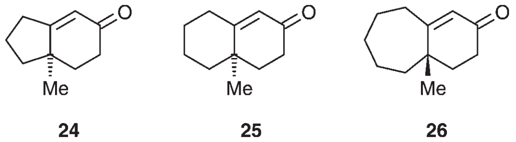
Scheme 7. Enantioselective [2+2] cycloaddition catalyzed by the oxazaborolidine–$AlBr_3$ adduct **13**.

Notably, the reaction works with *tert*-butyldimethylsilyl as well as with triisopropylsilyl enol ethers, which are well accessible from the respective ketones. The enol ethers derived from cyclohexanone undergo the cycloaddition to **18** and **19** with high *endo* selectivity (**18**: 82:18, **19**: 97:3) in 97 and 99% yield, respectively, with 92% *ee* in both cases (Scheme 8). 1-(Triisopropylsilyloxy)cycloheptene performs particularly well to give the cycloadduct **20** (*endo*/*exo* 99:1) in 99% yield and 99% *ee*. In contrast, the stereochemical course of the reaction of 2-methyl-substituted silyl enol ethers appears to be less clear: Whereas the silyl enol ethers derived from 2-methylcyclohexanone predominantly afford *exo*-cycloadducts **21** and **22** (**21**: 1:99, **22**: 10:90), the reaction of 1-(*tert*-butyldimethylsilyloxy)-2-methylcycloheptene preferentially leads to the *endo*-cycloadduct **23** (96:4). The annelated



Scheme 8. Products of the enantioselective [2+2] cycloaddition of cyclic silyl enol ethers with **16** catalyzed by **13**.

silyloxy-substituted cyclobutane derivatives thus obtained in enantiomerically pure form can be transformed in few steps with high yields into the valuable enantiomerically pure bicycloalkenones **24**–**26** (Scheme 9).[29]



Scheme 9. Enantiomerically pure bicycloalkenones obtained from [2+2] cycloadducts.

In terms of the mechanism, the authors presume an attack of the enol ether at the acrylate from the *si* face, which corresponds to the mechanistic model of the action of catalyst **13** in enantioselective Diels–Alder reactions.[15,16,38] In contrast, the facial selectivity of the silyl enol ether appears to be influenced by several different factors such as the steric bulk of the silyl group, the presence of other substituents (H, Me) at the double bond, and the ring size. For the [2+2] cycloaddition the authors presume an asynchronous process and propose, as earlier for the Diels–Alder reactions, a transition state with a bridge between the α-hydrogen atom of the acrylate and the oxygen atom of the oxazaborolidine catalyst. For the reaction with 4,5-dihydrofuran (**11**), a transition state similar to that for the [3+2] cycloaddition leading to **12** is suggested.

With the introduction of the oxazaborolidine–aluminum tribromide adduct **13** as an efficient catalyst for enantioselective Diels–Alder reactions and now also for enantioselective [2+2] cycloadditions, Corey and co-workers have succeeded in an impressive broadening of the application profile of oxazaborolidine derivatives in asymmetric catalysis. The compounds accessible by these reactions are valuable as enantiomerically pure building blocks for the synthesis of complex organic compounds. Although the classes of compounds, which according to the earlier work of Narasaka et al. and the more recent publication by Corey and Canales can be used successfully in enantioselective [2+2] cycloaddition, are still somewhat limited in scope, the results summarized here makes one expect further improvements of this important, sometimes underestimated reaction type in the near future.

---

[1] P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.

[2] P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

[3] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460.

[4] E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724–1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.

[5] D. Carmona, M. Pilar Lamata, L. A. Oro, *Coord. Chem. Rev.* **2000**, *200–202*, 717–772.

[6] K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702–3733; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588.

[7] K. Narasaka, M. Inoue, T. Yamada, *Chem. Lett.* **1986**, 1967–1968.

[8] K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, J. Sugimori, *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.

[9] K. Narasaka, H. Tanaka, F. Kanai, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387–391.

[10] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

[11] E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.

[12] E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861–2863.

[13] E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

[14] E. J. Corey, T. P. Loh, *J. Am. Chem. Soc.* **1991**, *113*, 8966–8967.

[15] E. J. Corey, T. Shibata, T. W. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 3808–3809.

[16] D. H. Ryu, T. W. Lee, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 9992–9993.

[17] Q.-Y. Hu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 13708–13713.

[18] L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns, J. M. Constantin, *J. Am. Chem. Soc.* **1952**, *74*, 4974–4976.

[19] L. H. Sarett, R. M. Lukes, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandegrift, G. E. Arth, *J. Am. Chem. Soc.* **1952**, *74*, 1393–1397.

[20] A. Eschenmoser, C. E. Wintner, *Science* **1977**, *196*, 1410–1420.

[21] M. Y. Chu-Moyer, S. J. Danishefsky, G. K. Schulte, *J. Am. Chem. Soc.* **1994**, *116*, 11213–11228.

[22] G. Mehta, A. N. Murthy, D. S. Reddy, A. V. Reddy, *J. Am. Chem. Soc.* **1986**, *108*, 3443–3452.

[23] G. Mehta, A. V. Reddy, *J. Chem. Soc. Chem. Commun.* **1981**, 756–757.

[24] S. A. Snyder, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 740–742.

[25] S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 1346–1352.

[26] Y.-Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311.

[27] G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 11958–11959.

[28] D. Liu, E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 1498–1499.

[29] E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 12686–12687.

[30] E. Lee-Ruff in *The Chemistry of Cyclobutanes, Vol. 1* (Eds.: Z. Rappoport, J. F. Liebman), Wiley, Chichester, **2005**, pp. 281–355.

[31] E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449–1483.

[32] T. Bach, *Synthesis* **1998**, 683–703.

[33] K. Narasaka, Y. Hayashi, H. Shimadzu, S. Niihata, *J. Am. Chem. Soc.* **1992**, *114*, 8869 – 8885.
[34] K. Narasaka, H. Kusama, Y. Hayashi, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471 – 1478.
[35] Y. Hayashi, S. Niihata, K. Narasaka, *Chem. Lett.* **1990**, 2091 – 2094.
[36] Y. Hayashi, K. Narasaka, *Chem. Lett.* **1990**, 1295 – 1298.
[37] T. A. Engler, M. A. Letavic, R. Iyengar, K. O. LaTessa, J. P. Reddy, *J. Org. Chem.* **1999**, *64*, 2391 – 2405.
[38] D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 6388 – 6390.