J|A|C|S
COMMUNICATIONS

Published on Web 09/21/2006

Catalytic, Enantioselective Bifunctional Inverse Electron Demand Hetero-Diels−Alder Reactions of Ketene Enolates and *o*-Benzoquinone Diimides

Ciby J. Abraham, Daniel H. Paull, Michael T. Scerba, James W. Grebinski, and Thomas Lectka*

Department of Chemistry, New Chemistry Building, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218

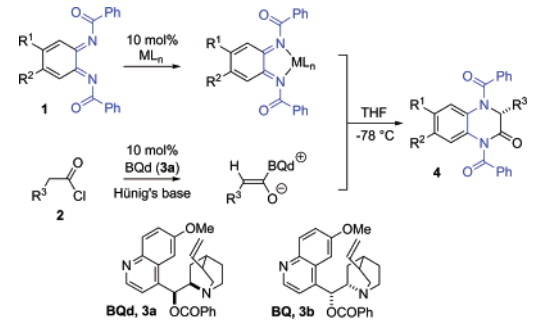
Received August 8, 2006; E-mail: lectka@jhu.edu

Catalytic, enantioselective Diels−Alder reactions ([4 + 2] cycloadditions) constitute a vital part of the synthetic repertoire.[1] Usually, they are catalyzed, through dienophile activation, by chiral Lewis acids. However, of late, a strategy involving chiral iminium ion catalysis has also emerged.[2] Less well studied are cases in which the diene is catalytically activated, and virtually unknown are cases in which both the diene and dienophile are activated in tandem. In this Communication, we report a system in which an achiral Lewis acid (activating the diene) works in concert with a chiral nucleophile (dienophile) to effect the first highly enantio- and regioselective catalytic *inverse electron demand*[3] cycloaddition reaction to form biologically active quinoxalinones from ketene enolates and *o*-benzoquinone diimides[4] (Scheme 1). Such bifunctional catalysis, especially the partnership of a Lewis acid and a Lewis base or nucleophile,[5] has been an appealing goal in organic chemistry for many years.

Quinoxalinones are useful templates for drug development because of their structural relationship to benzodiazepines.[6] However, they have been much less widely explored owing to limited means of synthesis. Quinoxalinones are also attractive targets for asymmetric catalysis as they exhibit a wide variety of biological activity, including antidiabetic[7] and antiviral effects, in particular against retroviruses such as HIV.[8] They also are inhibitors of aldose reductase,[9] partial agonists of the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex,[10] and antagonists of the AMPA and angiotensin II receptors.[11] Related 3,4-dihydroquinoxalines also possess biological activity, for example, as inhibitors of cholesteryl ester transfer proteins.[12] Quinoxalinones have been identified as desirable scaffolds for diversity oriented synthesis as they may be assembled in a modular fashion on solid-phase media.[13]

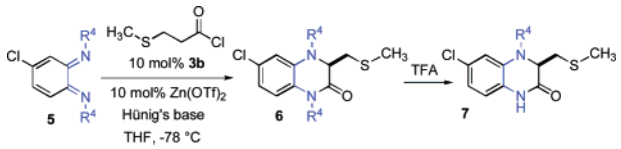
o-Benzoquinone diimides (Scheme 2) are easily synthesized through oxidation of various 1,2-dianilides by $Pb(OAc)_4$.[14] In our initial screen, we employed diimide **1a**, butyryl chloride, Hünig's base, and benzoylquinidine (**3a**) at −78 °C in THF. The reaction was sluggish, and other unidentified byproducts were formed as well as the desired quinoxalinone (**4a**). At this point, we reasoned that a metal cocatalyst, acting through putative coordination to the diimide,[15] would render it more electrophilic, thereby increasing the reaction rate. A number of metal triflates were screened as cocatalysts, including $Al(OTf)_3$ and $In(OTf)_3$, forming **4a** in 64% and 65% yield, respectively. However, $Sc(OTf)_3$ and $Zn(OTf)_2$ were found to perform the best. For example, the initial rate of reaction increased by greater than a factor of 20, and the product yield increased significantly, with less byproducts, when 10 mol % $Zn(OTf)_2$ was employed as the cocatalyst (82% for **4a**). Most importantly, the observed enantioselectivity was >99% in each case. Though aluminum and indium cocatalysts improved the reaction rate and yield relative to no metal, they did not match the effectiveness of Zn(II) and Sc(III).

Scheme 1. Bifunctional Hetero-Diels−Alder Reaction of *o*-Benzoquinone Diimides and Ketene Enolates to Form Quinoxalinones



Scheme 2. Examples of *o*-Benzoquinone Diimides

Scheme 3. Synthesis of (*R*)-Isopropyl-7-chloro-2-(methylthiomethyl)-3-oxo-3,4-dihydroquinoxaline-1(2*H*)-carboxylate, $R^4 = CO_2i$-Pr



We hypothesized that the Lewis acid cocatalysts operate cooperatively; that is, they increase the electrophilicity of the diimide without interfering with the nucleophilic enolate. We tested our notion that the metal acts through coordination to the diimide by monitoring the IR band shift difference of **1b** with and without Zn(II) in $CHCl_3$, at room temperature. In the absence of metal, **1b** shows imine and carbonyl IR bands at 1609, 1632, and 1691 cm^{-1}, while in the presence of $Zn(OTf)_2$, the IR shows bands at 1575, 1608, and 1682 cm^{-1}. When Sc(III) was tested, IR bands shifted to 1559, 1604, and 1675 cm^{-1}. These shifts in the IR spectrum support our proposal that Zn(II) and Sc(III) coordinate to the diimide.[16] Because of its inexpense, $Zn(OTf)_2$ was used in subsequent reactions.

To demonstrate the utility of our methodology, we synthesized compound **7** (Scheme 3), which exhibits very strong antiviral activity against HIV.[8] The synthesis of **7** was easily accomplished by the enantioselective (and remarkably regioselective) cycloaddition reaction between **5** and 3-methylthiopropionyl chloride mediated by cocatalysts BQ (**3b**) and $Zn(OTf)_2$ to give the (*R*)-enantiomer **6**, in >99% ee and 62% yield. Subsequent deprotection by TFA forms **7** in 94% yield with full retention of ee. We also

10.1021/ja065754d CCC: $33.50

Scheme 4. Synthesis of 2-Ethyl-1,2,3,4-tetrahydroquinoxaline

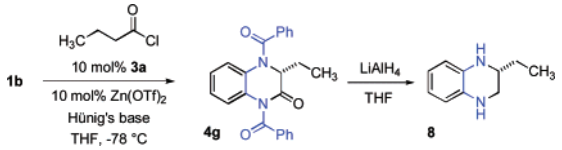


Table 1. 3,4-Dihydroquinoxalin-2-one Products[a]

entry		R^1	R^2	R^3	% ee	% yield
1	**4a**	Cl	Cl	Et	>99	82
2	**4b**	Cl	Cl	*i*-Pr	>99	79
3	**4c**	Cl	Cl	CH_2SMe	>99	84
4	**4d**	Cl	Cl	$(CH_2)_3Cl$	>99	81
5	**4e**	Cl	Cl	Bn	>99	85
6	**4f**	Cl	Cl	CH_2phthalimide	>99	93
7	**4g**	H	H	Et	>99	76
8	**4h**	H	H	*i*-Pr	>99	71
9	**4i**	H	H	*i*-Bu	>99	73
10	**4j**	H	H	Bn	>99	83
11	**4k**	CF_3	H	Et	>99	81
12	**4l**	CF_3	H	*i*-Pr	>99	79
13	**4m**	CF_3	H	*i*-Bu	>99	83
14	**4n**	CF_3	H	Bn	>99	77
15	**4o**	CF_3	H	*p*-Br−Bn	>99	78
16	**4p**	COPh	H	Et	>99	84
17	**4q**	COPh	H	*i*-Pr	>99	84
18	**4r**	COPh	H	*i*-Bu	>99	84
19	**4s**	COPh	H	CH_2SMe	>99	92
20	**4t**	COPh	H	$(CH_2)_3Cl$	>99	87
21	**4u**	COPh	H	Bn	>99	86
22	**4v**	COPh	H	CH_2phthalimide	>99	90
23	**4w**	COPh	H	*p*-Br−Bn	>99	69
24*	**4x**	COPh	H	*p*-Br−Bn	>99	72

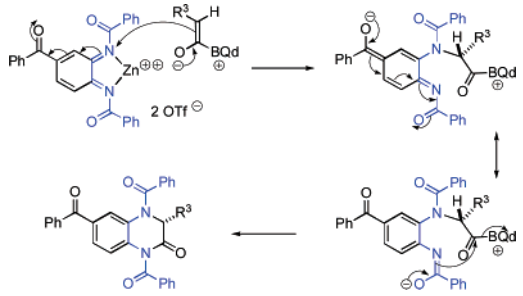
[a] Reactions employed cocatalysts BQd (**3a**) and $Zn(OTf)_2$ (0.032 mmol each), acid chloride (0.64 mmol), Hünig's base (0.64 mmol), and slow addition of diimide solution, (0.32 mmol) via syringe pump over a range of 6−10 h at −78 °C in THF. (∗) Reaction run using BQ (**3b**) as cocatalyst.

extended our methodology by synthesizing compound **8**, an inhibitor of cholesteryl ester transfer protein,[12] as an example of the quinoxaline class of biologically active compounds (Scheme 4). Cycloaddition between **1b** and butyryl chloride with cocatalysts BQd (**3a**) and $Zn(OTf)_2$ gave the (*R*)-enantiomer **4g**, in nearly optically pure form. Remarkably, LAH[17] cleaves the benzoyl groups while reducing the ring carbonyl, affording **8** in quantitative yield with complete retention of ee.

Each of these reactions shown in Table 1 gave the (*R*)-enantiomer (except that **4c**, **4s**, and **4x** gave (*S*)-enantiomer) in virtually enantiomerically pure form with good to excellent yields. When BQ (**3b**) was used instead of BQd (**3a**), the opposite enantiomer was obtained with similarly high enantioselectivity and yield for all cycloaddition reactions. In fact, for almost every chiral reaction assayed, the other enantiomer *was not* detected by HPLC.

Reactions of unsymmetrical diimides (**1c** and **1d**) illustrate the notable regioselectivity of the reaction. The specific regioisomer and enantiomer were assigned based on X-ray crystallography performed for **4o** and **4w**. The observed regiochemistry is consistent with the proposed stepwise mechanism[4] (Scheme 5), where the reaction is initiated by nucleophilic attack on the more electrophilic nitrogen.

Scheme 5. Proposed Mechanism of Regioselective Cycloaddition



In conclusion, we have demonstrated a highly enantioselective bifunctional catalyst system for the cycloaddition of quinoxalinones from *o*-benzoquinone diimides and acid chlorides. The highly biologically active cycloadducts will be useful scaffolds for drug development and are useful synthetic intermediates as well.

Acknowledgment. T.L. thanks the NIH (Grant GM064559), the Sloan and Dreyfus Foundations, and Merck & Co. for support.

Supporting Information Available: Procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) For review, see Carmona, D.; Pilar Lamata, M.; Oro, L. A. *Coord. Chem. Rev.* **2000**, *200*−*202*, 717−772. (b) For a recent example, see Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336−1337.
(2) For review, see List, B. *Chem. Commun.* **2006**, *8*, 819−824.
(3) (a) Marko, I. E.; Evans, G. R.; Seres, P.; Chelle, I.; Janousek, Z. *Pure Appl. Chem.* **1996**, *68*, 113−122. (b) Boger, D. L.; Patel, M. *Prog. Heterocycl. Chem.* **1989**, *1*, 30−64.
(4) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635. (b) Bekele, T.; Shah, M. H.; Wolfer, J.; Abraham, C. J.; Weatherwax, A.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 1810−1811.
(5) (a) DiMauro, E. F.; Mamai, A.; Kozlowski, M. C. *Organometallics* **2003**, *22*, 850−855. (b) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206−1215. (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, *10*, 1491−1508.
(6) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930 and references therein.
(7) Gupta, D.; Ghosh, N. N.; Chandra, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1019−1022.
(8) Rösner, M.; Billhardt-Troughton, U.-M.; Kirsh, R.; Kleim, J.-P.; Meichsner, C.; Riess, G.; Winkler, I. U.S. Patent 5,723, 461, 1998.
(9) a) Sarges, R.; Lyga, J. W. *J. Heterocycl. Chem.* **1988**, *25*, 1475−1479. (b) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997−10998.
(10) Lee, L.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874−3879 and references therein.
(11) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172−1177.
(12) Jones, Z.; Groneberg, R.; Drew, M.; Eary, C. T. U.S. Patent 20050282812, 2005.
(13) (a) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874−3879. (b) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **1999**, *64*, 2555−2557.
(14) Adams, R.; Way, J. W. *J. Am. Chem. Soc.* **1954**, *76*, 2763−2769.
(15) For review, see Nair, V.; Dhanya, R.; Rajesh, C.; Devipriya, S. *Synlett* **2005**, *16*, 2407−2419.
(16) The experimental values are consistent with PM3 vibrational analyses performed by the Spartan program (version 5.0.3).
(17) Ikeda, M.; Ohno, K.; Uno, T.; Tamura, Y. *Tetrahedron Lett.* **1980**, *21*, 3403−3406.

JA065754D