Catalytic, Enantioselective Bifunctional Inverse Electron Demand Hetero-Diels–Alder Reactions of Ketene Enolates and o-Benzooquinone Diimides

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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 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 demand3 cycloaddition reaction to form biologically active quinoxalinones from ketene enolates and o-benzoquinone diimides4 (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 antidiabetic7 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-dihydroquinoxalinones 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-Benzooquinone 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, Hüning’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).
extended our methodology by synthesizing compound 8, an inhibitor of cholesterol ester transfer protein, to 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, LAH²⁻ 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 (Scheme 5), where the reaction is initiated by nucleophilic attack on the more electrophilic nitrogen.

In conclusion, we have demonstrated a highly enantioselective bifunctional catalyst system for the cycloaddition of quinoxalines 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.

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

**References**

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(16) The experimental values are consistent with PM3 vibrational analyses performed by the Spartan program (version 5.0.3).

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