Catalytic, Enantioselective [4 + 2]-Cycloadditions of Ketene Enolates and o-Quinones: Efficient Entry to Chiral, α-Oxygenated Carboxylic Acid Derivatives

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The use of chiral, catalytically derived zwitterionic “ketene” enolates has brought forth powerful methodology for the synthesis of a diverse variety of optically enriched products. Chiral ketene enolate intermediates are well-known for undergoing highly enantioselective [2 + 2]-cycloadditions with both aldehydes and amines to produce β-lactones and β-lactams, respectively.1 However, cases in which ketene enolates engage in formal [4 + 2]-cycloaddition reactions are almost unknown. The products of these [4 + 2] reactions would be useful in their own right, while significantly expanding the synthetic utility of ketene enolate reactions in general. Accordingly, we report catalytic, enantioselective [4 + 2]-cycloadditions of o-quinones with chiral ketene enolates that are derived from readily available acid chlorides and a cinchona alkaloid-based catalyst. Additionally, the chiral cycloadducts can be derivatized to provide a flexible synthesis of α-oxygenated carboxylic acid derivatives (Scheme 1).

The reasons for the absence of the [4 + 2]-manifold in ketene enolate-based reactions may be due to a number of factors, including a kinetic preference for the creation of four-membered rings and the relative unreactivity of the enolates themselves toward various heterodienes. A strategy to overcome these obstacles would be to employ more energetic substrates such as o-quinones to achieve the desired higher-order asymmetric cycloadditions.2 The driving force for these reactions would be, in large part, the restoration of aromaticity to the products.

The chemistry of o-quinones has been extensively outlined.4 In some cases o-quinones are commercially available, such as o-chloranil 1a,5 and 9,10-phenanthrenequinone 1c (Chart 1). We envisioned the standard transformation of an acid chloride into a chiral ketene enolate (10 mol % of a cinchona alkaloid derivative, stoichiometric base, toluene or THF solvent, low temperature) that then reacts with the o-quinone to produce a chiral adduct. Follow-up reactions with nucleophiles should occur smoothly (the products

Scheme 1. Synthesis of Cycloadducts and Carboxylic Acid Derivatives

Chart 1. o-Quinones Screened

would also be activated esters6), and CAN “deprotection” would then unmask the α-hydroxylated product (Scheme 1).

Our initial screen employed o-quinones 1a–1d (Chart 1) and butyryl chloride (2a, R = Et) as the reagents. Triethylamine (1.1 equiv.) served as both the dehydrohalogenating agent and the catalyst. We initially employed o-chloranil 1a, but to our disappointment, no desired product was obtained in THF or toluene even at room temperature.7 However, when we employed our chiral “shuttle base” system (10 mol % benzoylquinidine (“BQd”, 3), 1.0 equiv Proton Sponge in toluene at −78 °C), surprisingly, after 4 h reaction time, we isolated the desired product in 40% yield and 93% enantiomeric excess (ee) (eq 1). The very dark color of the reaction was a cause for concern—precedent suggests that a charge-transfer complex between o-chloranil and Proton Sponge may be reducing the yield.8 By replacing Proton Sponge with Hünig’s base in THF at −78 °C, the yield and the ee rose significantly (to 91% and 99% respectively, 4a, Table 1).

Thenceforth, we employed these conditions with all substrates. We also screened o-bromanil (1b), which was found to form product in high ee (95%), and 90% yield (4g, Chart 2).9,10-Phenanthrenequinone (1c) was screened using similar conditions; its reactivity proved to be much lower than that of o-chloranil. However, when the reaction temperature was raised to 0 °C, reaction occurred sluggishly to afford product. On the other hand, 4,5-dimethoxy-o-quinone 1d failed to provide appreciable product under any conditions.

Given the superiority of o-chloranil (1a) in our screen, we decided to investigate its reaction with a variety of acid chlorides. For example, the aliphatic 3-methylbutyryl chloride (2h, Table 1)
afforded product 4b in 75% yield and 93% ee (entry 2). An aromatic substrate, phenylacetyl chloride (2c), afforded product 4c in 90% ee and also in excellent yield (90%, entry 3). Dihydrocinnamoyl chloride (2d) performed similarly, affording product 4d in high ee (99%). Additionally, other α-arylacetyl chlorides proved to be excellent substrates. For example, (p-methoxyphenyl)acetyl chloride (2e) generated product in very high (99%) ee (entry 5). Using BQd as catalyst, the (R)-enantiomers were formed preferentially. The (S)-enantiomers are made using benzoylquinine (BQ) as catalyst instead.

The α-chloranil-derived cycloadducts can be derivatized to chiral, α-oxygenated carboxylic acid derivatives. For example, methanolation of 4f followed by CAN oxidation affords (+)-methylmandelate 8e in excellent (95%) yield (90% ee). This result confirmed the sense of induction in our products, which is consistent with the stereochemical model we devised for related β-lactam and halogenation reactions. Several other cycloadducts (4a–4d) were likewise converted to optically active α-hydroxyesters (Chart 3).

In each case, the alcoholysis/oxidation sequence proceeds in high yield, under mild conditions, and with full preservation of optical activity, comparing favorably with other methods for the synthesis of chiral α-hydroxyesters.

In future work, we intend to expand the scope of the α-quinone [4 + 2] reaction and investigate other α-quinone derivatives as well.

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Note Added after ASAP Publication. After this paper was published ASAP on January 21, 2006, changes were made in the Table 1 footnote. The corrected version was published January 26, 2006.

Supporting Information Available: General procedures for the catalytic synthesis of the cycloadducts and compound characterization. This information is available free of charge via the Internet at http://pubs.acs.org.

References


(7) Under these conditions, undesired ketene dimers are usually isolated.


(9) 4-Chlorobromine was added slowly to the reaction mixture over 6 h.

(10) Absolute configurations of the products were determined by conversion to the corresponding α-hydroxyesters of known configuration through sequential methanolysis/CAN oxidation. See Supporting Information for details.

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