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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 imines 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).[2]

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.[3] 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 would also be activated esters[6]), and CAN "deprotection" would then unmask the α-hydroxylated product (Scheme 1).

Scheme 1. Synthesis of Cycloadducts and Carboxylic Acid Derivatives

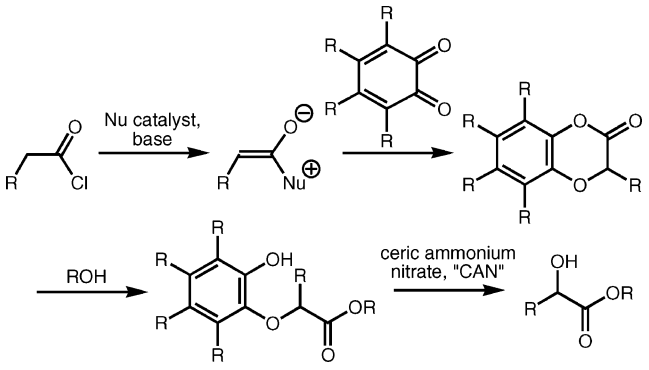
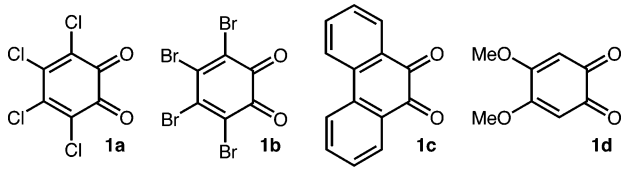
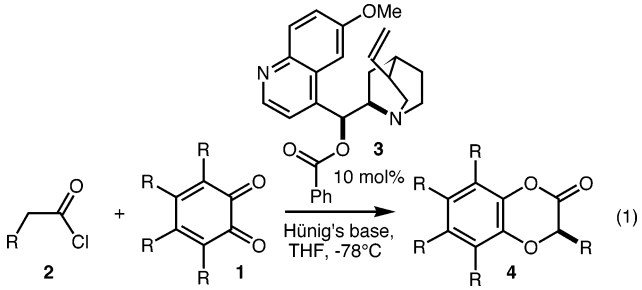


Chart 1. *o*-Quinones Screened



Our initial screen employed *o*-quinones **1a**−**1d** (Chart 1) and butyryl chloride (**2a**, R = Et) as the reactants. 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



(1)

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] 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 (**2b**, Table 1)

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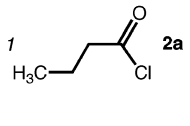
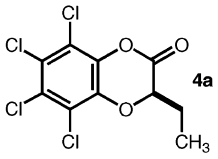
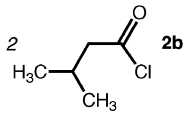
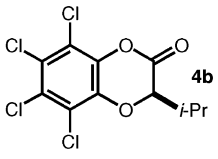
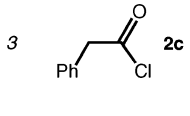
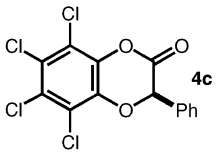
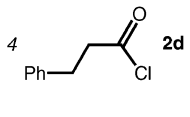
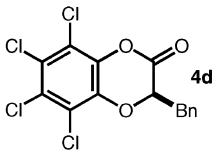
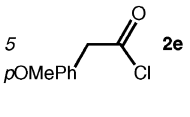
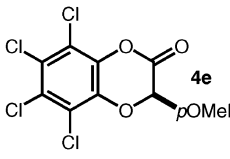
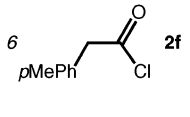
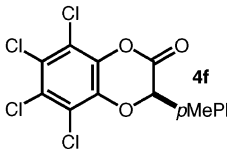
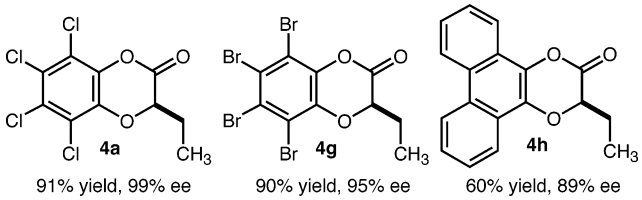
Table 1. Synthesis of *o*-Chloranil-Derived Cycloadducts

entry	acid chloride	product	% ee	% yield[a]
1	 **2a**	 **4a**	99	91
2	 **2b**	 **4b**	93	75
3	 **2c**	 **4c**	90	90
4	 **2d**	 **4d**	99	72
5	 **2e**	 **4e**	99	58
6	 **2f**	 **4f**	93	75

[a] Reactions run with 10 mol % catalyst, 0.55 mmol Hunig's base, 0.55 mmol acid halide, and 0.55 mmol **1a** at −78 °C with slow addition of the acid halide over 5 h employed for α-aryl acid halides (**2c**, **e**, **f**). Yields given are for isolated products.

Chart 2. Various Chiral *o*-Quinone Adducts



91% yield, 99% ee | 90% yield, 95% ee | 60% yield, 89% ee

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.[10] The (S)-enantiomers are made using benzoylquinine (BQ) as catalyst instead.

The *o*-chloranil-derived cycloadducts can be derivatized to chiral, α-oxygenated carboxylic acid derivatives. For example, methanolysis of **4c** followed by CAN oxidation affords (+)-methylmandelate **8c** 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.[5a] Several other cycloadducts (**4a**−**4d**) were likewise converted to optically active α-hydroxyesters (Chart 3).

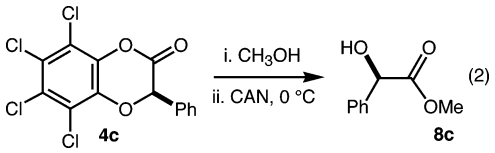
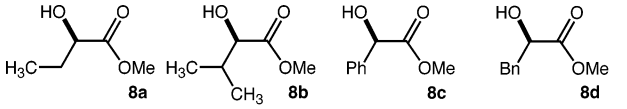


Chart 3. Conversion of Cycloadducts to α-Hydroxyesters



86% yield, 99% ee | 74% yield, 93% ee | 95% yield, 90% ee | 88% yield, 99% ee

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 *o*-quinone [4 + 2] reaction and investigate other *o*-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.

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(9) *o*-Bromanil 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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