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Carbene-Catalyzed Activation of Formyl-phenylacetic Esters for Access to Chiral Dihydroisoquinolinones

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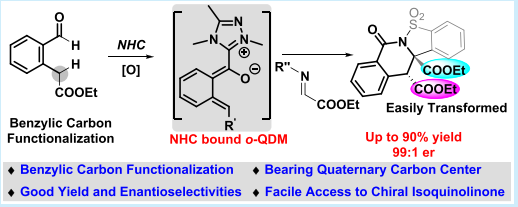
ABSTRACT: A carbene-catalyzed reaction to synthesize chiral dihydroisoquinolinones via an *o*-quinodimethane (*o*-QDM) intermediate is disclosed. *o*-QDM reacts with cyclic sulfonic imines via annulation to afford highly enantioenriched dihydroisoquinolinone products. ESI-HRMS studies suggest a stepwise Mannich addition and acylation reaction pathway, and the pathways of the catalytic and uncatalyzed background reactions are evaluated via DFT calculations.



Dihydroisoquinolinone is a common structural motif in bioactive molecules,[1] including natural products[2] and pharmaceuticals[3] (Figure 1). For example, dihydroisoquinoli-

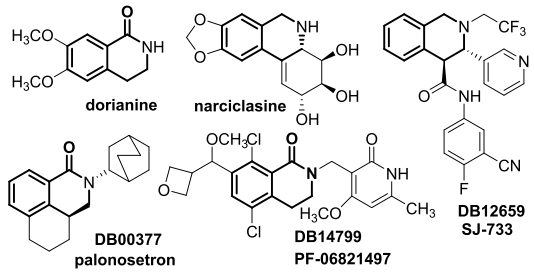


Figure 1. Bioactive and drug molecules containing isoquinolinone scalfolds.

none-containing palonosetron is an antagonist of 5-HT3 receptors for the treatment of chemotherapy-induced nausea and vomiting.[4] SJ-733 has been evaluated in clinical trials to treat malaria.[5] Dihydroisoquinolinone-fused PF-06821497 is an orally active enhancer of the zeste homologue 2 inhibitor, which inhibits tumor growth.[6] One promising approach to constructing dihydroisoquinolinone and their analogues starts with *o*-quinodimethane (*o*-QDM) intermediates[7] bearing aromatic rings. These *o*-QDM intermediates are traditionally generated via a photochemical reaction, an elimination reaction, and thermal decomposition.[8]

An *N*-heterocyclic carbene (NHC) catalyst was recently used to generate an *o*-QDM intermediate for asymmetric synthesis.[9] In 2013, we reported the first functionalization of the benzylic carbon of heteroaryl aldehydes through NHC organocatalysis; however, the benzaldehyde analogue was nonproductive in the reaction.[10] In 2016, Glorius succeeded in the realization of the in situ formation of *o*-QDM using NHC catalysis and *ortho*-bromomethyl-benzaldehyde.[11] At almost the same time, Rovis developed a highly enantioselective [4 + 2] annulation of 2-(bromomethyl)-benzaldehydes and fluorinated ketones by the action of chiral NHC and Brønsted acid cooperative catalysis.[12] In 2018, we reported that by using 2-[(trimethylsilyl)-methyl]benzoate as the substrate, the addition of a carbene catalyst to the ester can activate the remote C−Si bond and then a F^- anion attached the Si atom to form NHC-bound *o*-QDM.[13] In the same year, Yao reported the NHC-catalyzed reaction of 2-methyl-3,5-dinitrobenzoic acid with peptide coupling reagents to form *o*-QDM.[14] The all-carbon aryl aldehyde remote benzylic carbon activation is more challenging, as recognized by Glorius, Rovis, Yao, and our laboratories (Figure 2). In particular, a highly enantioselective strategy for such reactions remains underdeveloped to date. In these reactions, the benzylic carbon was converted to a methylene unit (CH_2) in the final product without any substituents, which limited the utility and further synthetic transformation of these products. However, it is known that introducing substituents (such as a methyl group) to the benzylic carbon of these substrates leads to diminished reactivities.[15]

Here we disclosed a new type of aryl substrates that can be activated by NHCs to generate *o*-QDM intermediates (Figure 2). In our approach, a carboxylic ester substituent was introduced to the benzylic carbon. This ester substituent can increase the reactivity (acidity of the benzylic C−H bond) of the benzylic carbon and thus allow for catalytic activation under mild conditions. Additionally, ester substituents can be readily transformed into other functional groups. The NHC-bound *o*-QDM intermediates from our approach undergo

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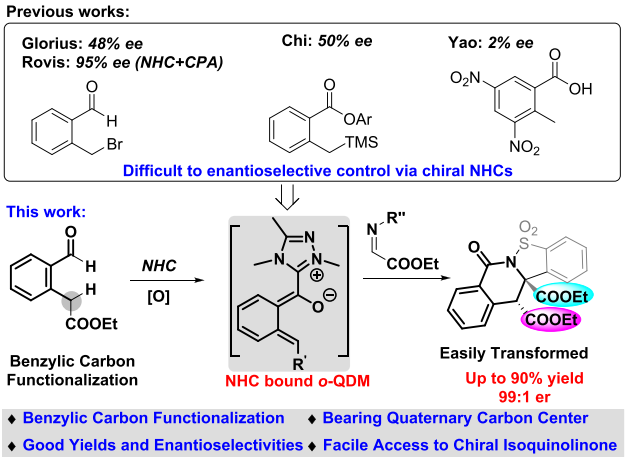
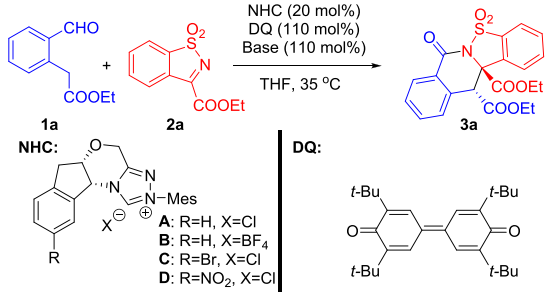


Figure 2. NHC-catalyzed formation of the *o*-QDM intermediate.

enantioselective reactions with cyclic imines to form dihydroisoquinolinone derivatives bearing multiple rings, a quaternary carbon center, and two ester groups.

We initiated our studies on benzylic carbon functionalization using aryl aldehyde **1a** as the acylazolium precursor to react with cyclic sulfonic imine **2a**. After evaluating NHC precatalysts **A**–**D** (Table 1, entries 1 to 4, respectively),[16] we found that catalyst **C** bearing a bromo group on the benzene ring gave the product **3a** in a 50% yield and 85:15 er (Table 1, entry 3). The enantioselectivity could be enhanced using Et_3N, and **3a** was obtained in a 70% yield and 92:8 er (Table 1, entries 5–8). In addition, the solvents had a strong

Table 1. Initial Studies and Condition Optimization[a]



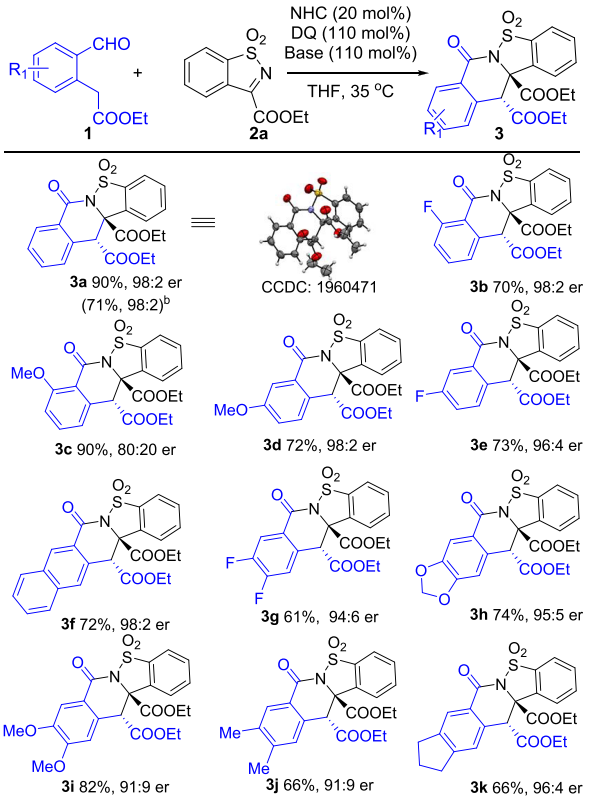
entry	Cat	Base	Solvent	Yield(%)[b]	er[c]
1	**A**	K_2CO_3	THF	51	83:17
2	**B**	K_2CO_3	THF	64	76:24
3	**C**	K_2CO_3	THF	50	85:15
4	**D**	K_2CO_3	THF	NR	-
5	**C**	Cs_2CO_3	THF	50	81:19
6	**C**	Na_2CO_3	THF	NR	-
7	**C**	DABCO	THF	35	92:8
8	**C**	Et_3N	THF	70	92:8
9	**C**	Et_3N	DCM	50	87:13
10	**C**	Et_3N	EtOAc	65	89:11
11	**C**	Et_3N	ACN	NR	-
12	**C**	Et_3N	toluene	77	90:10
13[d]	**C**	Et_3N	THF	90	98:2

[a]General conditions (unless otherwise specified) are as follows: **1a** (0.11 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), DQ (0.11 mmol), base (0.11 mmol), solvent (2.0 mL), 35 °C, 12 h. [b]Isolated yield of **3a**. [c]The er values were determined via HPLC on a chiral stationary phase. [d]As an additive, 50 mg of 4 Å MS was used.

impact on enantioselectivity, and switching THF to other solvents led to drop in the er value (Table 1, entries 9 to 12). Finally, using 4 Å molecular sieves (MS) as an additive (Table 1, entry 13) gave the product **3a** in a good yield and excellent enantioselectivity (98:2 er). The product **3a** formed in this chiral catalytic process was isolated as a single diastereomer.

Having identified the optimal reaction conditions, we evaluated the reaction scope using substrates **1** and **2** with different substitutions. Initially, we studied the reaction scope of aryl aldehydes **1** (Scheme 1). A diverse set of substituents

Scheme 1. Scope of Aldehydes 1[a]



[a]General conditions (unless otherwise specified) are as follows: **1a** (0.11 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), DQ (0.11 mmol), base (0.11 mmol), solvent (2.0 mL), 4 Å MS (50 mg), 35 °C, 12 h. [b]The reaction was carried out on at a 1.0 mmol scale based on **2a**.

(OCH_3, CH_3, halogens, etc.) at the *para*-, *meta*- or *ortho*-positions of the benzaldehyde were well-tolerated (**3a**–**3k**), and the corresponding products were obtained in moderate to good yields with good er values. However, the er value of the product **3c** decreased when a methoxyl substituent was introduced to the C-6 position of the aryl aldehyde. The possible reason was steric hindrance caused by the C-6 substituent.

The reaction scope of cyclic sulfonic imines **2** with aryl aldehyde **1a** (Scheme 2) was also examined. It was found that both electron-withdrawing (**3l**–**3p**) and electron-donating (**3q**–**3u**) substituents were well-tolerated, and the desired products were produced in good to excellent yields and high enantioselectivities. Changing the ethyl ester to a methyl ester also resulted in an excellent yield and enantioselectivity (**3v**). However, using a phenyl ketone instead of an ethyl ester led to no reaction.

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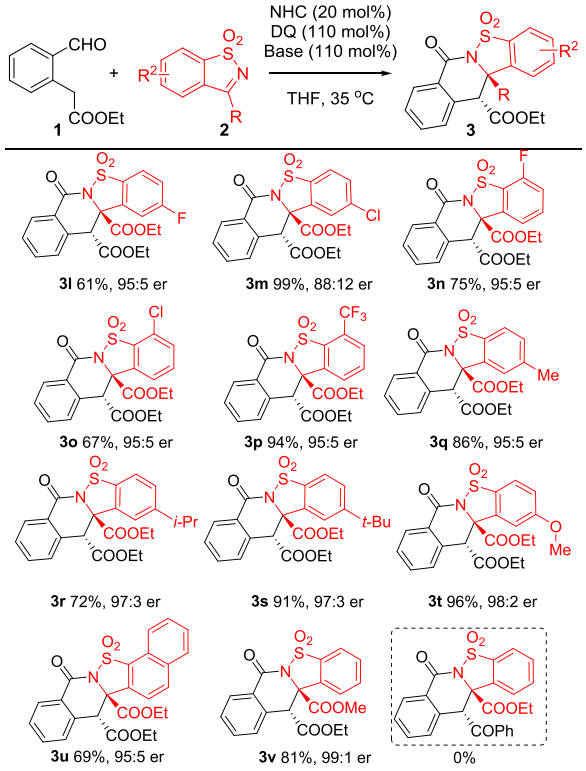
Scheme 2. Scope of Imines 2[a]



[a]General conditions (unless otherwise specified) are as follows: **1a** (0.11 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), DQ (0.11 mmol), base (0.11 mmol), solvent (2.0 mL), 4 Å MS (50 mg), 35 °C, 12 h.

Additionally, the obtained chiral dihydroisoquinolinone product **3a** was easily transformed into various derivatives through simple protocols (Figure 3). For instance, the two

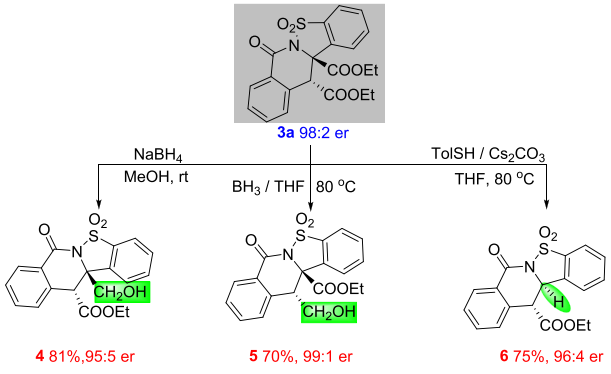


Figure 3. Synthetic transformations of **3a**.

carboxylates in **3a** were reduced to form the corresponding alcohols **4** and **5** with good yields and excellent er values. Interestingly, **3a** was reduced by $NaBH_4$ to form alcohol **4**. However, replacing $NaBH_4$ with BH_3/THF led to the formation of the alcohol **5**, indicating an excellent regioselectivity in the reduction process. Moreover, **3a** was converted to product **6** in a high yield and good er value through a decarboxylation reaction under a high temperature.

It has been reported that the NHC-catalyzed annulation reactions could go through a [4 + 2] concerted pathway or a stepwise Mannich addition and acylation, but the exact reaction mechanism is still unclear.[17] We investigated the detailed mechanism of the reaction by ESI-HRMS. As shown in Figure 4a, the reaction began with the addition of a carbene

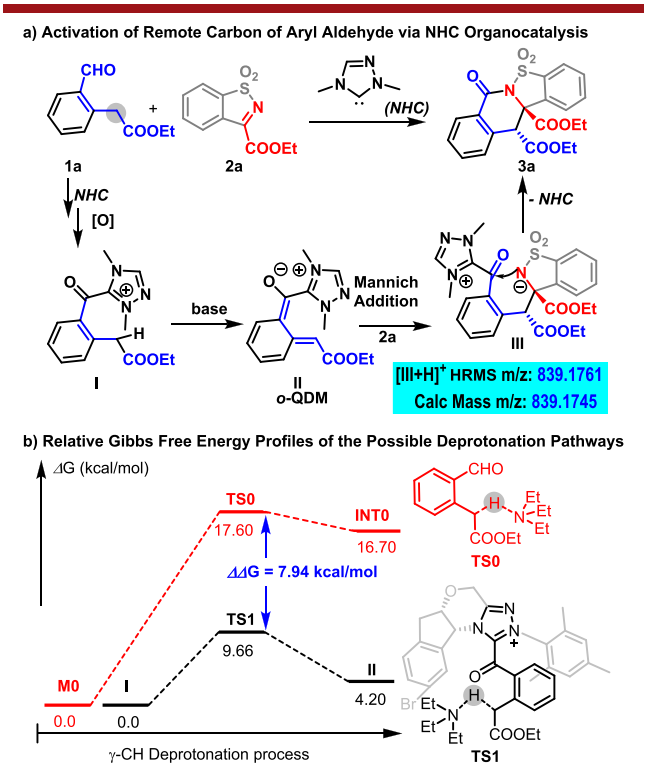


Figure 4. Proposed reaction mechanism and relative Gibbs free energy profiles.

catalyst to the aryl aldehyde moiety. Under oxidative conditions, the carbene-addition reaction forms acylazolium intermediate **I**. The benzylic carbon atom is selectively activated through the deprotonation of intermediate **I** to form the *o*-QDM intermediate **II**. An enantioselective reaction of the *o*-QDM intermediate **II** with a cyclic sulfonic imine substrate took place to form intermediate **III**, followed by intramolecular amide formation to afford the final dihydroisoquinolinone product. Notably, the key intermediate **III**, which was detected by HRMS (see the SI), indicated that this process is a stepwise Mannich addition; however, the [4 + 2] cycloaddition pathway could not be excluded.

To further investigate the direct activation of benzylic carbon, density functional theory (DFT) calculations were performed at the SMD (THF)-M06-2X/def2-TZVPP//SMD-(THF)-M06-2X/def2-SVP level[18] of theory using the Gaussian 16 program.[19] As shown in Figure 4b, triethylamine acts as the base to deprotonate the benzylic carbon of intermediate **I** via transition state **TS1** to form the *o*-QDM intermediate **II**, and the Gibbs free energy barrier is 9.66 kcal mol^{-1}. In addition, the pathway in the absence of the NHC catalyst shows a Gibbs energy barrier of 17.60 kcal mol^{-1} via the transition state **TS0**. Obviously, the energy barrier is much higher than that of **TS1** ($\Delta\Delta G$ = 7.94 kcal mol^{-1}), which is the most favorable NHC-mediated benzylic carbon activated pathway to form the *o*-QDM intermediate **II**.

In summary, we have developed an efficient stereoselective strategy for obtaining highly enantioenriched dihydroisoquinolinones. Through a deprotonation process under oxidative conditions, the NHC-catalyzed activation of the benzylic carbon led to the generation of the key the *o*-QDM

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intermediate. The subsequent formal addition reaction with cyclic sulfonic imines formed the final dihydroisoquinolinone products in excellent yields and er values. To understand the mechanism of the annulation reaction, we applied a combined approach of ESI-HRMS and DFT calculations. The available mechanistic data support the stepwise Mannich addition and acylation mechanism and the most favorable NHC-mediated benzylic carbon-activated pathway to form the *o*-QDM intermediate. Moreover, various derivatives can be easily obtained from the chiral dihydroisoquinolinone products by simple derivatization. Studies on the bioactivities of the heterocyclic compounds are in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02676.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1960471, 1969305, 1974009, and 2058361−2058362 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

⊥S.W., J.X., and R.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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