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Carbene and Acid Cooperative Catalytic Reactions of Aldehydes and *o*-Hydroxybenzhydriyl Amines for Highly Enantioselective Access to Dihydrocoumarins

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ABSTRACT: A highly enantioselective method for quick access to dihydrocoumarins is reported. The reaction involves a cooperative catalytic process with carbene and in situ generated Brønsted acid as the catalysts. α -Chloro aldehyde and readily available and stable *o*-hydroxybenzhydriyl amine substrates were used to generate reactive azolium ester enolate and *ortho*-quinone methide (*o*-QM) intermediates, respectively, to form dihydrocoumarins with exceptionally high diastereo- and enantio-selectivities. The catalytic reaction products can be easily transformed to valuable pharmaceuticals and bioactive molecules.

Coumarins and their derivatives are widely found in natural products and bioactive synthetic molecules.¹ In particular, molecules containing 3,4-dihydrocoumarin moieties exhibit important biological activities² and thus receive much attention. Several examples of 3,4-dihydrocoumarin-based bioactive compounds and commercially used pharmaceuticals are illustrated in Figure 1a. These molecules have shown antitumor (A),^{2f} anti-estrogen (B and C),^{2g-i} and anti-osteoporotic (C) properties.^{2j} At present, metal-free asymmetric access to optically enriched 3,4-dihydrocoumarin remains challenging. For example, the commercially used chiral pharmaceutical compounds *Ormeloxifene* and *NNC 45-0781* (Figure 1a, B and C; selective estrogen receptor modulators) were obtained via a chiral resolution process from its racemic form after chemical synthesis.^{3a-b, 2j}

We report a carbene-catalyzed reaction for highly enantioselective access to 3,4-dihydrocoumarins with up to 99.9:0.1 er and excellent diastereoselectivities (Figure 1b). The reaction involves simultaneous activation of two substrates by two organic catalysts. Specifically, the reaction of carbene catalyst with α -chloro aldehyde substrate generates an azolium ester enolate intermediate **I**.⁴ This carbene catalytic process also releases a Brønsted acid (H^+) that activates diarylmethyl amine in situ to generate a transient *ortho*-quinone methide (*o*-QM)⁵ intermediate **II** (Figure 1b). Reactions of intermediates **I** and **II** eventually afford 3,4-dihydrocoumarin products with high stereo- and enantioselectivities. The products from our catalytic reaction can be readily converted to enantiomerically enriched commercial pharmaceutical compound and bioactive molecule such as *NNC 45-0781* (Figure 1a).

Notably, the combined use of NHC⁶ and Brønsted acid⁷ co-catalysts have recently emerged as a useful strategy especially for

Figure 1. Representative examples of biologically active molecules and our synthetic strategy

better control of reaction enantioselectivities, as reported by Rovis,⁸ Xu,⁹ Scheidt¹⁰ and our own laboratory.¹¹ In the present study, the mild acid co-catalyst is critical for the formation of *o*-QMs as a key reaction intermediate. *o*-QMs involved in our reactions are versatile intermediates with wide use in organic synthesis.¹² They are highly unstable species, although a number of research groups have managed to prepare them in advance and use them as starting materials in carbene catalysis, as reported by

Ye^{13a,b} and Yao.^{3c} In the area of carbene catalysis, the Scheidt group has pioneered in using the in situ generated *o*-QM (generated under basic conditions) for several elegant reactions.^{14e-f, j} The instability of *o*-QMs has made it difficult to expand reaction scopes or scales. A better approach is to generate *o*-QMs in situ from stable and readily available starting materials.^{5, 14} Here, we generated *o*-QM intermediate in situ from *o*-hydroxybenzhydriyl amine substrates via acid catalysis for carbene-catalyzed reactions. The *o*-hydroxybenzhydriyl amine substrates used for our in situ generation of *o*-QMs intermediates can be readily prepared in large scale as nice crystalline solids without column chromatography.^{14f, 15}

Table 1. Optimization of Reaction Conditions^a

entry	2	base	yield ^b (%)	er ^c	dr ^c
1	2a	TEA	44	>99:1	>20:1
2	2b	TEA	np	--	--
3	2c	TEA	np	--	--
4	2d	TEA	41	>99:1	>20:1
5	2d	DABCO	34	>99:1	13:1
6	2d	DBU	11	98:2	6:1
7	2d	K ₃ PO ₄	23	98:2	10:1
8	2d	Cs ₂ CO ₃	18	99:1	16:1
9	2d	NaOAc	48	>99:1	>20:1
10	2d	NaOAc, 40 °C	61	>99:1	>20:1
11	2d	NaOAc, 40 °C	82^d	>99:1	>20:1

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), base (0.1 mmol), NHC **4** (0.02 mmol), DCM (1 mL). ^b Isolated yield (after SiO₂ column chromatography purification) based **2**. ^c The er and dr were determined by chiral HPLC. ^d The substrate **2d** was added portion-wise in 30 min. np = No product. TEA = Triethyl amine. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. DABCO = 1,4-diazabicyclo[2.2.2]octane.

Key results of our reaction optimization are summarized in Table 1. We first used *o*-hydroxybenzhydryl alcohol **2a** as an *o*-QM precursor to react with α -chloro hydrocinnamaldehyde **1a**, and were delighted to find the formation of proposed product **3a** in 44% yield and excellent er and dr (entry 1). However, further efforts to improve the reaction yield using **2a** was unsuccessful due to its instability. *o*-Hydroxybenzhydryl alcohol **2a** can quickly turn to a complex mixture in a few hours at room temperature under our typical reaction conditions. We next moved to identify a better *o*-QM precursor. Replacing the hydroxyl unit of **2a** with a methoxy (**2b**) or *p*-toluenesulfonyl (**2c**) led to no formation of **3a**. We then found the easily accessible and stable *o*-hydroxybenzhydryl amine (**2d**) could be used to give **3a** in 41% yield and excellent stereo-selectivities (entry 4). With stable **2d** as the substrate,

Scheme 1. Scope of α -Chloro Aldehydes 1^a

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), CH₂Cl₂ (1 mL), 40 °C. Yields (after SiO₂ column chromatography purification) based on the diarylmethylamines **2**.

further condition optimization revealed that NaOAc as base performed a bit better than Et₃N (entries 9 vs 4). Increase the reaction temperature to 40 °C led to a further increase on the reaction yield without loss of er or dr value of the product (entry

Scheme 2. Scope of Diarylmethylamines 2^a

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), CH₂Cl₂ (1 mL), 40 °C.

10). At last, when the diarylmethylamine **2d** was added portion-wise in 30 minutes, product **3a** could be obtained in 82% yield, > 99:1 er, and > 20:1 dr (entry 11).

With an acceptable condition (Table 1, entry 11) in hand, we proceeded to examine the generality of the reaction with respect to α -chloro aldehydes **1** by using *o*-hydroxybenzhydriyl amine **2d** as a model substrate (Scheme 1, variation of α -chloro aldehyde substrates). The **R** substituents at the α -carbon of aldehydes can be various alkyl units, leading to the corresponding products (**3a-h**, **3j-l**) with good to excellent yields. In nearly all these reactions, the products were isolated as a single diastereomer with exceptionally high enantioselectivity (>99:1 er). The α -substituent of aldehyde could also be an aryl unit to give the corresponding product (**3i**) with high dr and er values, albeit with a relatively low yield (64%).

We next evaluated the scope of *o*-hydroxybenzhydriyl amine **2** by using α -chloro aldehyde **1a** as the model substrate (Scheme 2, variation of *o*-hydroxybenzhydriyl amines). Installation of different substituents at the *para*-position of the phenyl unit of diarylmethylamine **2** were well tolerated (**3a**, **3m-t**). The reactions also worked effectively when substituents were placed on the *meta*-position of phenyl ring of **2** (**3u**, **3v**). Naphthyl and heteroaryl units could also be used to replace the aryl unit of **2** (**3w**, **3x**). It's worth to note that *o*-QMs intermediates derived from electron-deficient substrates (such as those for **3r** and **3s**) were highly unstable, and thus literature attempts in using pre-formed *o*-QMs of this type of substrates were typically unsuccessful.¹⁶

Scheme 3. Additional Examples of Diarylmethylamines **2**^a

^a Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), CH₂Cl₂ (1 mL), 40 °C.

The benzene unit of the core dihydrocoumarins is a critical structural motif. We then studied substitution effects and variations of this benzyl unit (Scheme 3). The substituents studied here were well tolerated. Although the reaction yields were moderate, in all cases the products were obtained with exceptional dr and er values. As a technical note, all these products (**3y-3af**) were hard to access previously due to the high instability of the corresponding *o*-QM intermediates.¹⁶ Notably, to generate the *o*-QM inter-

mediate efficiently under the present reaction condition, an electron-donating substituent on the 2-hydroxyphenyl group is necessary.

Optically enriched 3,4-dihydrocoumarin and their derivatives can be used as bioactive molecules and medicines. Our catalytic reactions provide enantiomerically enriched dihydrocoumarins that can be readily transformed to useful molecules. For example, adduct **3ac** could be converted to pharmaceutical *Ormeloxifene* in a few steps using known protocols.^{17a} *NNC 45-0781*, currently in clinical development, is a promising candidate for the prevention of post-menopausal osteoporosis, and for the treatment of other healthy issues related to the loss of endogenous estrogen production.^{2j} Adduct **3ac** could be converted to bioactive *NNC 45-0781* via a five-step operation (Scheme 4). It is worth noting that column chromatography

Scheme 4. Synthetic transformations of the product **3ac**

purifications were not needed in the LiAlH₄ reduction, intramolecular Mitsunobu reaction, and debenzoylation steps. The adduct **5** could be obtained with 67% overall yield from **3ac** after a three-step operation. To the best of our knowledge, asymmetric route to *NNC 45-0781* has not been developed previously. The current protocols for *NNC 45-0781* relies on a chiral resolution process after the racemic product is prepared.^{2j, 17b}

In summary, we have developed a cooperative catalytic method for highly enantioselective access to 3,4-dihydrocoumarin.¹⁸ The key transient *o*-QM intermediates are generated in situ from readily available and stable *o*-hydroxybenzhydriyl amine substrates via an acid catalytic process. The products from our catalytic reactions were obtained with exceptionally high dr and er values. Applications of our reaction products allow enantiomeric access to commercially available pharmaceuticals and bioactive functional molecules.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Experimental procedures, characterization data, crystallographic data and calculation details.

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(18) The absolute configuration of the stereogenic center in compound **3q** was unambiguously determined by X-ray crystallographic analysis (see SI). The configurations of other products were assigned on the assumption of a uniform mechanistic pathway. CCDC 1520379 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table of Contents and Abstract Graphics