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

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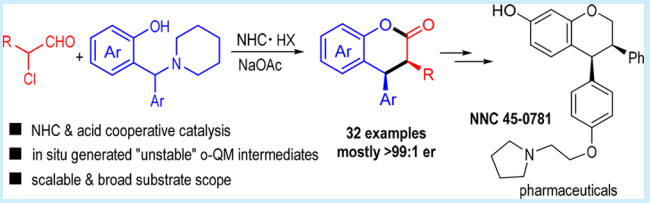
Supporting Information

**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*-hydroxybenzhydryl 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 enantioselectivities. 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 activities[2] 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] antiestrogen (**B** and **C**),[2g−i] and antiosteoporotic (**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**. 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.

Notably, the combined use of NHC[6] and Brønsted acid[7] cocatalysts have recently emerged as a useful strategy especially for better control of reaction enantioselectivities, as reported by Rovis,[8] Xu,[9] Scheidt,[10] and our own laboratory.[11] In the present study, the mild acid cocatalyst 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.[13c] 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*-hydroxylbenzhydryl amine substrates via acid catalysis for carbene-catalyzed reactions. The *o*-hydroxylbenzhydryl 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]

Key results of our reaction optimization are summarized in Table 1. We first used *o*-hydroxybenzhydryl alcohol **2a** as an *o*-

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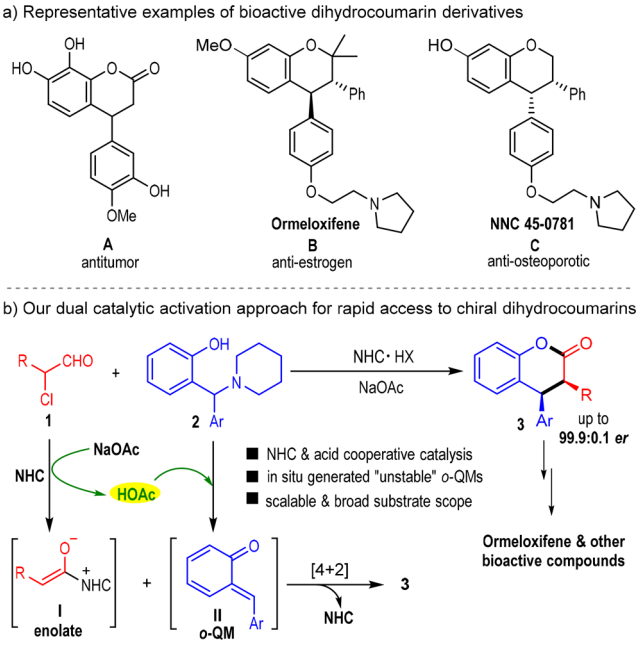
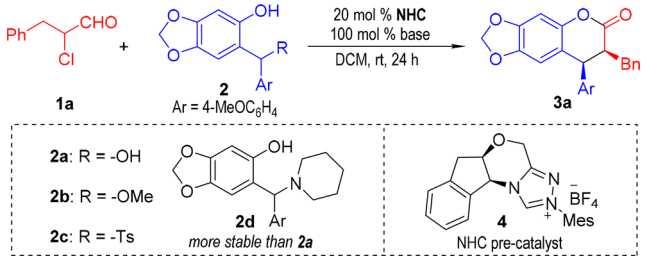



**Figure 1.** Representative examples of biologically active molecules and our synthetic strategy.

## Table 1. Optimization of Reaction Conditions[a]



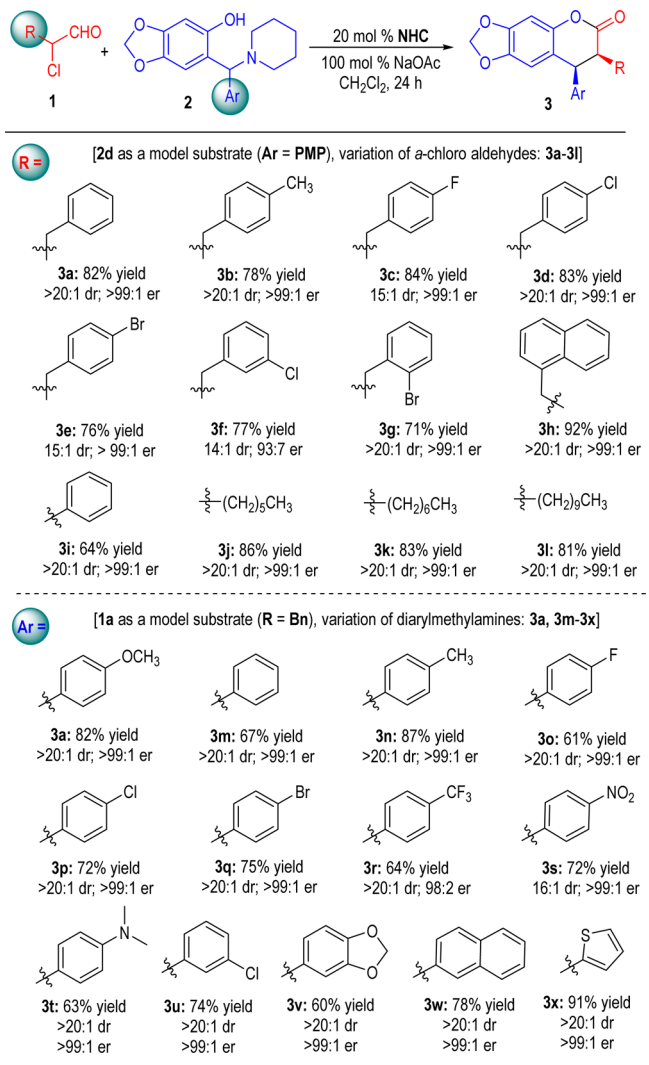

| entry | 2 | base | yield[b] (%) | er[c] | dr[c] |
|---|---|---|---|---|---|
| 1 | **2a** | TEA | 44 | >99:1 | >20:1 |
| 2 | **2b** | TEA | np | | |
| 3 | **2c** | TEA | np | | |
| 4 | **2d** | TEA | 41 | >99:1 | >20:1 |
| 5 | **2d** | DABCO | 34 | >99:1 | 13:1 |
| 6 | **2d** | DBU | 11 | 98:2 | 6:1 |
| 7 | **2d** | $K_3PO_4$ | 23 | 98:2 | 10:1 |
| 8 | **2d** | $Cs_2CO_3$ | 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 $SiO_2$ 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.

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 stereoselectivities (entry 4). With stable **2d** as the substrate, further condition optimization revealed that NaOAc as base performed a bit better than $Et_3N$ (entries 9 vs 4). Increasing 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 10). At last, when the diarylmethylamine **2d** was added portion-wise in 30 min, 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*-hydroxybenzhydryl amine **2d** as a model substrate (Scheme 1). 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

## Scheme 1. Substrate Scope [a]




[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), $CH_2Cl_2$ (1 mL), 40 °C. Yields (after $SiO_2$ column chromatography purification) based on the diarylmethylamines **2**.



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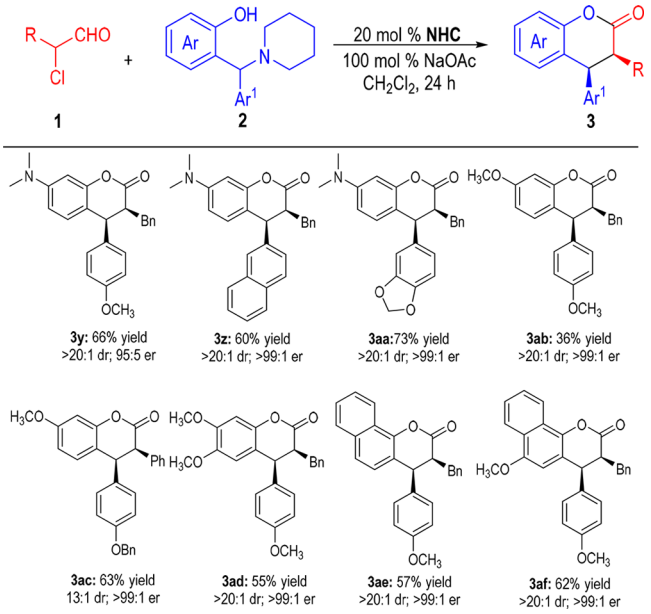
(>99:1 er). The $\alpha$-substituent of aldehyde could also be an aryl unit to give the corresponding product (**3i**) with high dr and er values, albeit with a relatively low yield (64%).

We next evaluated the scope of *o*-hydroxybenzhydryl amine **2** by using $\alpha$-chloro aldehyde **1a** as the model substrate (Scheme 1). 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 is 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 preformed *o*-QMs of this type of substrates were typically unsuccessful.[16]

The benzene unit of the core dihydrocoumarins is a critical structural motif. We then studied substitution effects and variations of this benzyl unit (Scheme 2). The substituents

**Scheme 2. Additional Examples of Diarylmethylamines 2**[a]

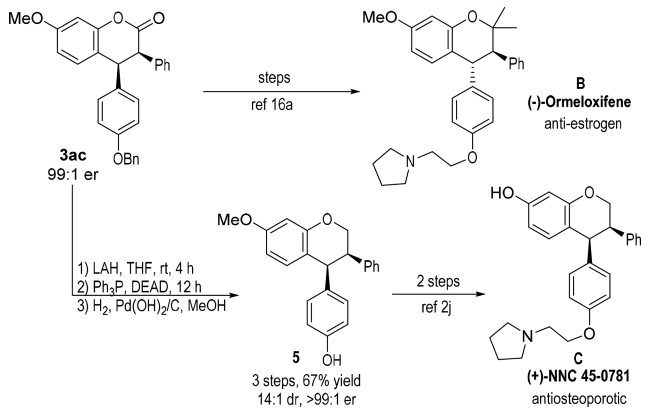



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), $CH_2Cl_2$ (1 mL), 40 °C.

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 intermediate 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 postmenopausal osteoporosis, and for the treatment of other health 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 3) reduction, intramolecular Mitsunobu reaction, and debenzyla-

**Scheme 3. Synthetic Transformations of the Product 3ac**




tion steps. The adduct **5** could be obtained with 67% overall yield from **3ac** after a three-step operation. To the best of our knowledge, the 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*-hydroxybenzhydryl 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.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02883.

Experimental procedures, characterization data, crystallographic data, and calculation details (PDF)

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### Notes

The authors declare no competing financial interest.

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