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N-Heterocyclic Carbene-Catalyzed Enantioselective Annulations: A Dual Activation Strategy for a Formal [4+2] Addition for Dihydrocoumarins

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Abstract

A highly efficient asymmetric formal [4+2] annulation for the synthesis of dihydrocoumarins has been developed via an *in situ* activated NHC catalysis. Both electrophilic and nucleophilic species are generated *in situ* simultaneously whereby acyl imidazoles facilitated rapid formation of an NHC-enolate intermediate to afford the [4+2] dihydrocoumarin adducts.

Coumarins and their substituted derivatives are found in numerous natural products and pharmaceuticals.¹ In particular, 3,4-dihydrocoumarins are prevalent in nature and have shown interesting biological activities such as aldose reductase and protein kinase inhibition, as well as anti-herpetic, anti-inflammatory, anti-oxidative, anti-aging and anti-cancer properties.² Given the significance of these compounds as important structural scaffolds in natural products and drug candidates, the synthesis of chiral dihydrocoumarin derivatives through catalytic and stereoselective processes is a high value endeavor. Most currently deployed conventional approaches for the synthesis of dihydrocoumarins require the use of transition metal catalysis.³ However, there are opportunities to go beyond these processes and generate new, potentially more sustainable and selective approaches with complementary substrate scope and/or activation strategies. Within the area of organocatalysis, the Zeidler group reported an *N*-heterocyclic carbene (NHC)-catalyzed redox lactonization for the synthesis of unsubstituted, achiral dihydrocoumarins using *o*-hydroxycinnamaldehydes.⁴ Our group has also reported an NHC-catalyzed domino elimination/conjugate addition/acylation process for the synthesis of substituted coumarins.⁵ Recently, the Hong group synthesized dihydrocoumarin derivatives including quaternary carbon center via asymmetric domino Michael/acetalization reactions and oxidation reaction using 2-hydroxynitrostyrene and 2-oxocyclohexanecarbaldehyde.⁶ More recently, the Jørgensen group reported an asymmetric synthesis of 3,4-dihydrocoumarins by merging aminocatalysis with an NHC-catalyzed internal redox process.⁷ Lastly, the deracemization process of α -aryl hydrocoumarins using chiral phosphoric acids was reported by the List group.⁸ However, a convergent and efficient asymmetric strategy for the synthesis of the

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dihydrocoumarin scaffold starting from simple starting compounds is currently underdeveloped: reports for straightforward approaches such as enantioselective α -alkylations or α -allylations are surprisingly limited.⁹

N-heterocyclic carbenes represent a potent class of catalysts for the formation of key C–C and C–X bonds via nontraditional *Umpolung* reactivity.¹⁰ The development of novel approaches using NHC catalysis by employing activation strategies has drawn significant attention over the last few years. For example, the Chi group has demonstrated the ability to access NHC enolates through the acylation of carbenes with highly activated aryl esters.¹¹ Recently, our group has employed a strategy which invokes the in situ formation of acyl azolium enolates^{12,13} for the synthesis of dihydroquinolones.^{14,15} In this study, carboxylic acids as simple and accessible starting materials provided an intermediate acyl imidazole for subsequent addition of an NHC.¹⁶ By using an acyl imidazole generated *in situ*, the undesired enal dimerization pathway that is a common concern in NHC catalysis can be avoided.¹⁷ Additionally, this approach offers a complimentary and potentially more general strategy vs. NHC-enolate generation via disubstituted ketenes reported by Ye.¹⁸ Encouraged by this work and our continuing interest in the synthesis of bioactive-relevant heterocyclic compounds employing asymmetric NHCs catalysis, we have explored an enantioselective formal [4+2] annulation reaction for the synthesis of dihydrocoumarins. Herein, we report the first general method for the highly efficient asymmetric synthesis of substituted dihydrocoumarins from simple precursors (Scheme 1).

We have been exploring new strategies to enhance NHC reactivity and selectivity through the integration of Lewis base catalysis with other activation modes, including Lewis acids,^{11b,19,20} Brønsted acids^{21,22} and additional Lewis bases.²³ In this endeavour, we have developed additional activation modes such as Lewis base-promoted in situ electrophile generation. A key aspect of this “dual activation” approach is to productively integrate the in situ creation of reactive electrophiles during the NHC process (e.g., see *o*-quinone methide, or *o*-QM, formation, Scheme 1, A). Using this concept, we demonstrated a formal [4+3] annulation reaction for the synthesis of enantioenriched 2-benzoxepinones using enals and *o*-QMs *via* dual Lewis base activation strategy (see Scheme 1, B).^{23,24} The desired products were obtained in high yields and excellent enantioselectivities (up to 99:1 e.r.), however, it was found that the enal-derived NHC-homoenolate species²⁵ were unable to undergo a formal [4+2] process after protonation to afford the dihydrocoumarins (Scheme 1, B). Undaunted by this lack of specific reactivity, we envisaged that the [4+2] annulation pathway could be promoted by the use of acyl imidazoles as NHC-enolate precursors. To test this hypothesis, we designed a model reaction using acyl imidazole **1a** and benzyl bromide derivative **2a** as nucleophilic and electrophilic precursors, respectively (Table 1). Various NHC pre-catalysts were screened, and the chiral 5,5-triazolium catalyst **A** was found to most effectively catalyze the addition of acyl imidazole **1a** to **2a** (data not shown, see SI for more detail).

Acyl imidazole **1a** underwent decomposition at 23 °C under the reaction conditions, therefore the reaction was carried out at 4 °C. Various silyl protecting and desilylating reagents were evaluated on **2a**, and optimal rate of *o*-QM generation was achieved with the use of an equimolar combination of crown ether and cesium fluoride in conjunction with the

tert-butyldimethylsilyl (TBS)-protected phenol substrate (see SI for more detail). The use of more labile silyl groups (TMS, TES) result in very poor yields, presumably due to the balance of generating both electrophile and nucleophile at productive concentrations. Further investigations are ongoing.

Interestingly, the choice of chloride and bromide leaving groups on substrate **2a** is essentially insignificant in terms of reactivity and enantioselectivity (See SI for more detail). However, the measurement of enantiomeric excess over the course of the reaction in the presence of strong bases such as Cs₂CO₃ and CsOAc revealed slow racemization of the products (Figure 1). Consequently, *the principal synthetic challenges associated with these compounds are derived from both the difficulty associated with effective control of o-QM formation and sensitivity of the products to racemization.*

To address this racemization, we speculated that altering base strength and/or stoichiometry would likely improve enantioselectivity. While the product was fully racemized when we employed 2.5 equivalents of Cs₂CO₃ and CsOAc as the base (entries 1 and 2), decreasing the amounts of base improved the enantioselectivity at the expense of yield (entries 3 and 4). However, by employing weaker bases, we were able to improve both the yield and enantioselectivity (entries 6 and 7). Optimal results were obtained in terms of reactivity and enantioselectivity when we introduced 1.0 equivalent of potassium acetate as the base; the desired product was obtained in 75% yield and 85:15 e.r. (entry 7). Sodium acetate also provided the product with high enantioselectivity (85:15 e.r.), however, the reaction yield was low and did not improve with additional equivalents of base (entries 9–11). To little surprise, the reaction did not proceed in the absence of 18-crown-6 and/or CsF (entries 12 and 13), both necessary for the formation of the *o*-QM.^{23,26}

With the optimized reaction conditions in hand, the scope of this formal [4+2] annulation was explored (Table 2). The reaction was found to be tolerant of both electron-rich and electron-deficient acyl imidazoles (**1**). The desired dihydrocoumarins were obtained in good yield (56–80%) and high enantioselectivity (up to 93:7 e.r.) with benzyl (**3a–3c**, **3g**, **3j**, **3m–3n**), aliphatic (**3d–3f**, **3h–3i**, **3k–3l**) and hetero alkyl (**3o**) substituted acyl imidazoles. In most cases, similar reactivity and enantioselectivity were observed, although slightly improved enantioselectivity was obtained with isovaleryl acyl imidazole **3e** (92:8 e.r.).

Tolerance to substitution on the benzyl bromide derivative **2** was also investigated. Various substituents were tolerated at the C-3, C-4, and C-5 positions affording the desired products **3g–3n** in good to high yields and high enantioselectivities. However, the bromides including electron-withdrawing groups at C-5 positions were not suitable substrates, and no desired products were obtained (See SI for more details). In addition, no product was isolated when using C-6 substituted benzyl bromides since many of these potential substrates were not stable under the reaction conditions. The products derived from electron-rich substituted bromides were obtained with slightly higher enantioselectivity (**3g** vs **3j** or **3m**, **3h** vs **3k**), however, the reaction yields of both electron rich and deficient substituted bromides were similar. In the case of chloro-substituted benzyl bromide **3m**, diminished yields and enantioselectivities were observed along with the generation of several unknown by-products. We assumed that the formation of *o*-QM does not take place properly under the

reaction condition and this might be a main reason for the diminished yield. The absolute configuration of compound **3d** was determined to be (*S*)-configuration by comparison with the reported optical rotation value.²⁷

The proposed reaction pathways are shown in Scheme 2. The initial addition of the NHC (**A**) to the acyl imidazole **1** generates NHC-enolate equivalent **I** after tautomerization. Two different reaction pathways are hypothesized for the formation of dihydrocoumarin **3** from enol **I**: (1) a concerted [4+2] process, (2) a formal [4+2] process involving a stepwise Michael addition and annulation. In the [4+2] pathway, concerted addition of *in situ* generated *o*-QM **2** and NHC enolate **I** via **II** (via either endo or exo transition states) could provide the desired product **3**. On the other hand, in the Michael addition/acylation pathway, carbon-carbon bond formation through the less sterically demanding transition state (**III**) would take place to afford acyl azolium intermediate **IV**, which then undergoes N-acylation to provide **3** and the NHC catalyst **A** ready the next catalytic cycle.

In conclusion, we have developed a highly efficient enantioselective formal [4+2] annulation reaction using simple starting compounds for the synthesis of dihydrocoumarin derivatives via NHC catalysis. This new method employs a dual activation strategy using *in situ* electrophilic and nucleophilic species generated simultaneously during the course of the reaction. The desired dihydrocoumarins were obtained in high yields and enantioselectivities. This platform facilitates rapid access to chiral α -substituted dihydrocoumarins and further studies on the synthesis of biologically active heterocycles via *in situ* activated NHC catalysis are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Racemization in the presence of 1.0 equiv. of CsOAc as the base (Table 1, entry 3).

A. *in situ* generated *o*-quinone methide **B. Dual Activation Strategy****Previous work** **This work**

Scheme 1.
Dual activation NHC strategy.

Scheme 2.
Proposed Reaction Pathways.¹⁴

Table 1 Optimization of asymmetric reaction conditions.^{a)}

Entry	Base	Equiv.	Yield (%) ^{b)}	e.r. ^{c)}
1	Cs ₂ CO ₃	2.5	65	50:50
2	CsOAc	2.5	70	50:50
3	CsOAc	1.0	68	67:33
4	CsOAc	0.5	32	84:16
5	K ₂ CO ₃	1.0	60	59:41
6	KOAc	1.5	74	67:33
7	KOAc	1.0	75	85:15
8	KOAc	0.5	40	85:15
9	NaOAc	1.0	40	85:15
10	NaOAc	0.5	11	85:15
11	NaOAc	2.5	44	85:15
12 ^{d)}	KOAc	1.0	no rxn	-
13 ^{e)}	KOAc	1.0	no rxn	-

^{a)} Conditions: **1a** (0.05 mmol, 1.0 equiv), **2a** (2.0 equiv), triazolium **A** (0.2 equiv), 18-crown-6 (2.0 equiv), CsF (2.0 equiv) at 4 °C for 15 h.^{b)} Determined by NMR analysis with 1,3,5- trimethoxybenzene as an internal standard.^{c)} Determined by HPLC analysis.^{d)} Reaction conducted in the absence of CsF and 18-crown-6.^{e)} Reaction conducted in the absence of 18-crown-6.

Table 2

Substrate Scope.

Reactions were performed at 0.2 mmol with **1** (1 equiv), **2** (2 equiv), triazolium **A** (0.2 equiv), KOAc (1 equiv), CsF (2 equiv), and 18-crown-6 (2 equiv) in CPME (0.125 M). Yields are of isolated product after column chromatography. Enantiomeric ratio was determined by HPLC analysis.