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Asymmetric Synthesis of 4-Aryl-3,4-dihydrocoumarins by *N*-Heterocyclic Carbene Catalyzed Annulation of Phenols with Enals

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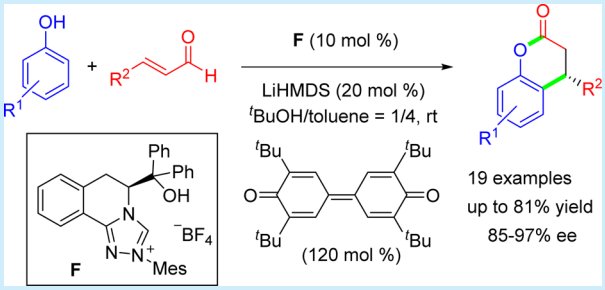
Supporting Information

ABSTRACT: The highly enantioselective synthesis of 4-aryl-3,4-dihydrocoumarins was realized through direct annulation of phenols with enals catalyzed by dihydroisoquinoline-type NHC (DHIQ-NHC), an *N*-heterocyclic carbene derived from L-phenylalanine. The catalytic reaction proceeds with a wide scope of electron-rich phenols and enals providing structurally diverse 4-aryl-3,4-dihydrocoumarins in good to excellent yields and enantioselectivity. This method was useful in the synthesis of natural products and biologically relevant compounds from readily available starting materials.



Coumarin derivatives are found in numerous natural products, pharmaceuticals, and biologically active compounds.[1] In particular, 4-aryl-3,4-dihydrocoumarins exist extensively as naturally occurring compounds from various plants (Figure 1), such as *Polygonum perfoliatum*,[2a] *Dorstenia*

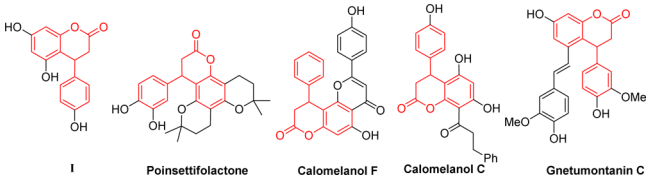
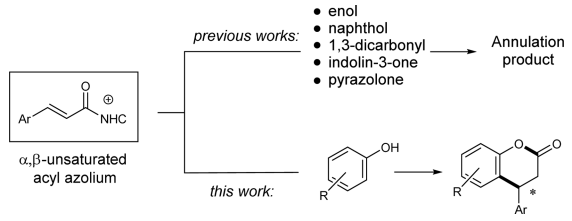


Figure 1. Selected natural products containing 4-aryl-3,4-dihydrocoumarin core.

poinsettifolia,[2b] *Pityrogramma calomelanos*,[2c] and *Gnetum montanum* Markgr. f. megalocarpum Markgr.[2d] Of particular note, these compounds have been found to possess interesting biological activities, such as antibacterial,[3a] antioxidant,[3b] antiherpetic,[3c] antiplasmodial,[3d] and hepatoprotective.[3e] In addition, 4-aryl-3,4-dihydrocoumarins are important synthetic intermediates.[4] As such, various synthetic methods toward 4-aryl-3,4-dihydrocoumarins have been developed;[5−10] however, most reported methods involve racemic syntheses. There have been only a handful of examples on the asymmetric synthesis of 4-aryl-3,4-dihydrocoumarins.[6−9] Therefore, the catalytic asymmetric syntheses of 4-aryl-3,4-dihydrocoumarins remain highly desirable.

N-Heterocyclic carbenes (NHCs) have been demonstrated as useful catalysts for the synthesis of substituted dihydrocoumarin compounds.[11] Since the introduction of α,β-unsaturated acyl azolium intermediates by the reaction of NHC with α,β-unsaturated aldehydes, various nucleophiles, such as enols,[12] naphthols,[13] heterocyclic C−H acids,[14] 1,3-dicarbonyls,[15] indolin-3-ones,[16] and pyrazolones,[17] have been successfully explored as suitable reaction partners.[18] However, phenols have been rarely utilized as the nucleophiles despite the fact that such a reaction provides direct access to 4-aryl-3,4-dihydrocoumarins.[19] As a part of our continuing interest in chiral NHC catalysis, we recently realized an NHC-catalyzed annulation reaction of 2-naphthols with α,β-unsaturated aldehydes.[13] In this paper, we report a straightforward synthesis of 4-aryl-3,4-dihydrocoumarins by NHC-catalyzed annulation reaction of enals with substituted phenols (Scheme 1).

Scheme 1. α,β-Unsaturated Acyl Azolium Involved Annulation Reactions



At the outset, we tested the reaction of 3,5-dimethoxyphenol (**1a**) with 4-methoxycinnamaldehyde (**2a**) in the presence of 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (**5**)[20] with NHCs derived from readily available triazolium salts (Table 1). To our delight, in most cases, the annulation product **3a** could be obtained. The reaction catalyzed by triazolium salt **A** derived NHC proceeded well to give annulation product **3a** in 40% yield and 63% ee (entry 1). Of particular note, DHIQ-NHC derived from triazolium salt **D** gave results similar to those of

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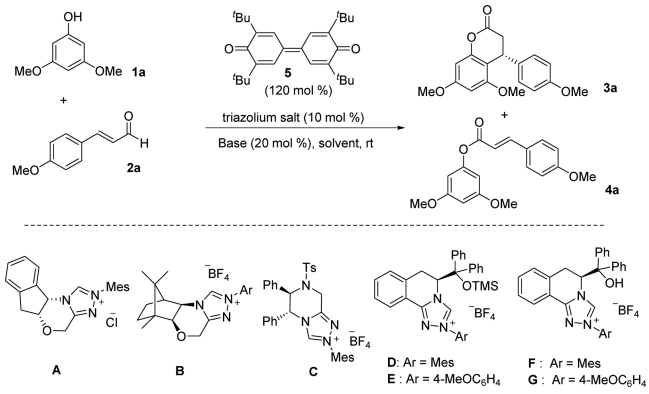
Table 1. Optimization of the Reaction Conditions[a]



entry	triazolium salt	time (h)	yield of **3a**[b] (%)	ee[c] (%)	**3a**/**4a**[d]
1	**A**	5	40	63	1/1.27
2	**B**	5	44	−5	1/1.09
3	**C**	24	<20		1/4.11
4	**D**	8	32	60	1/1.56
5	**E**	40	39	49	1/1.54
6	**F**	10	49	87	1/0.98
7	**G**	40	43	56	1/1.33
8[e]	**F**	24	71	97	1/0.39

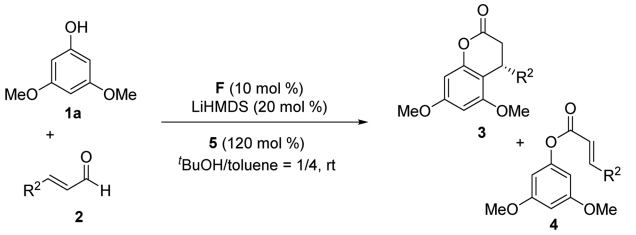
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), triazolium salt (0.02 mmol), K_3PO_4 (0.04 mmol), 3,3́,5,5́-tetra-*tert*-butyldiphenoquinone **5** (0.24 mmol) in toluene (2.0 mL) at rt. [b]Isolated yield of **3a**. [c]Determined by HPLC analysis. [d]Determined by ^{1}H NMR of the crude reaction mixture. [e]20 mol % of LiHMDS was used as base, and a mixed solvent of ^{t}BuOH/toluene (1/4) was used.

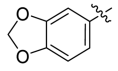
triazolium salt **A**, while the triazolium salt **F**, featuring a free hydroxyl group, gave **3a** in 87% ee (Table 1, entries 1, 4, and 6). The key role of the free hydroxyl group is also supported by the fact that triazolium salt **G** is superior to **E** (Table 1, entries 5 and 7). However, in general, the yields of **3a** are moderate due to the formation of byproduct **4a**.

With triazolium salt **F** as the NHC precursor, further optimization of the reaction conditions (bases, solvents, and additives) was carried out (Tables S1−S4).[21] The best results (**3a**, 71% yield, 97% ee) were obtained in a mixed solvent of ^{t}BuOH/toluene (1/4) and with 20 mol % of LiHMDS as base (entry 8). The conjugate addition of phenol to acyl azolium intermediate is more favorable presumably due to the existence of a hydrogen-bond interaction between ^{t}BuOH and the carbonyl group. It should be noted that the significantly increased yield of annulation product **3a** is more attributed to the use of LiHMDS.

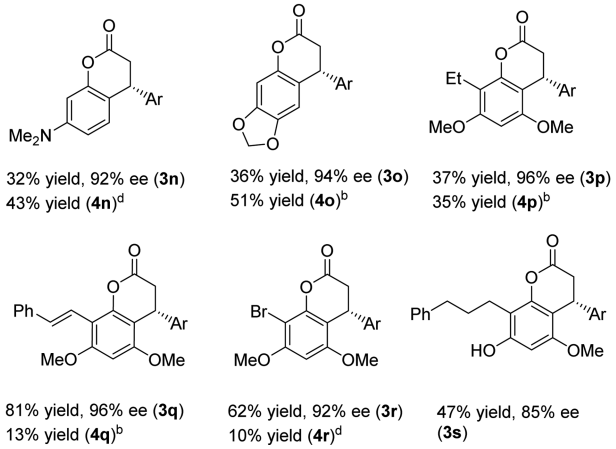
In the presence of 10 mol % of triazolium salt **F**, 20 mol % of LiHMDS, and 120 mol % of oxidant **5** in ^{t}BuOH/toluene (1/4) at room temperature (Table 1, entry 8), the reactions of various α,β-unsaturated aldehydes with substituted phenols have been tested to investigate the generality of the reaction. The results are summarized in Table 2. When 3,5-dimethoxyphenol was used, substituted cinnamaldehydes bearing either an electron-donating or electron-withdrawing group were examined. In all cases, the reaction proceeded smoothly, affording their corresponding products in excellent enantioselectivity and yields (85−97% ee for **3**, entries 1−13). In the case of a strong electron-withdrawing group incorporated substrate such as 4-nitrocinnamaldehyde, a slight decrease of enantioselectivity was observed (85% ee, entry 9). Notably, (*E*)-3-(furan-2-yl)acrylaldehyde was found to be a suitable substrate, yielding **3m** in excellent enantioselectivity (entry 13, 52% yield, 96% ee).

Table 2. Substrate Scope[a]



entry	R^2 (**2**)	time (h)	yield% (**3**)	yield% (**4**)	ee (%)[c]
1	4-MeOC$_6$H$_4$ (**2a**)	24	71 (**3a**)	27[d] (**4a**)	97
2	C$_6$H$_5$ (**2b**)	24	70 (**3b**)	18[b] (**4b**)	96
3	4-MeC$_6$H$_4$ (**2c**)	36	67 (**3c**)	27[b] (**4c**)	97
4	4-Me$_2$NC$_6$H$_4$ (**2d**)	36	61 (**3d**)	23[d] (**4d**)	94
5	4-FC$_6$H$_4$ (**2e**)	24	60 (**3e**)	24[d] (**4e**)	96
6	4-ClC$_6$H$_4$ (**2f**)	24	62 (**3f**)	23[d] (**4f**)	96
7	4-BrC$_6$H$_4$ (**2g**)	36	72 (**3g**)	17[d] (**4g**)	96
8	4-COOMeC$_6$H$_4$ (**2h**)	36	66 (**3h**)	27[b] (**4h**)	94
9	4-NO$_2$C$_6$H$_4$ (**2i**)	48	50 (**3i**)	28[b] (**4i**)	85
10	3-BrC$_6$H$_4$ (**2j**)	24	68 (**3j**)	18[d] (**4j**)	96
11	2-MeOC$_6$H$_4$ (**2k**)	48	66 (**3k**)	20[d] (**4k**)	97
12	 (**2l**)	40	59 (**3l**)	23[b] (**4l**)	96
13	2-furyl (**2m**)	40	52 (**3m**)	26[d] (**4m**)	96

Ar = 4-MeOC$_6$H$_4$



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36−0.6 mmol, 1.2−2.0 equiv), **F** (0.03 mmol), LiHMDS (0.06 mmol), **5** (0.36−0.6 mmol, 1.2−2.0 equiv) in toluene/^{t}BuOH (3.0 mL) at rt. [b]Isolated yield. [c]Determined by HPLC. [d]Determined by ^{1}H NMR.

However, the reaction of phenol **1a** with crotonaldehyde (R^2 = methyl) was sluggish, and only a trace amount of product was observed. Then different substituted phenols were also investigated. When 3-(dimethylamino)phenol and sesamol were used, the annulation products were obtained in 92−94% ee (**3n**,**o**) together with a significant amount of side products **4**. Substituents such as ethyl, styryl, and bromo at the 2-position of 3,5-dimethoxyphenol could be well tolerated (**3p**−**r**), and

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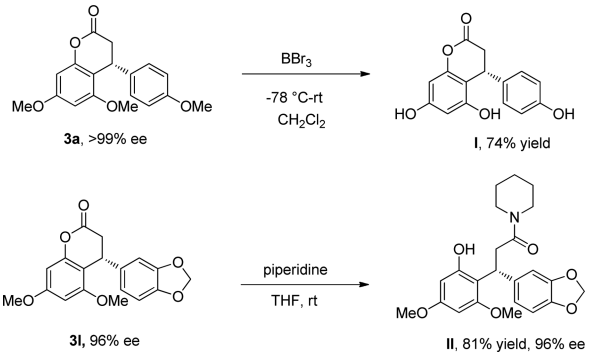
their corresponding annulation products were obtained in 37−81% yields and 92−96% ee. A substrate derived from chrysin[22] could also be utilized in this reaction to afford the annulation product **3s**, an analogue of natural product calomelanol C, in 47% yield and 85% ee. However, in all cases, byproduct **4** was inevitable under the reaction conditions. In order to determine the absolute configuration of the product, a single-crystal X-ray analysis of enantiopure **3a** was carried out, and the configuration was determioned to be *R*.

The enantioenriched products obtained here could undergo diverse transformations and could be utilized as key intermediates for highly efficient syntheses of natural products and bioactive compounds. As depicted in Scheme 2, demethylation of **3a**

Scheme 2. Transformations of 3a and 3l into Natural Product and Bioactive Compound



(>99% ee after recrystallization) by BBr_3 in CH_2Cl_2 gave naturally occurring compound (*R*)-3,4-dihydro-4-(4′-hydroxyphenyl)-5,7-dihydroxycoumarin (**I**). This represents the first enantioselective synthesis and determines its absolute configuration as *R*.[2a] Ring opening of **3l** by piperidine in THF led to an antidiabetic agent (**II**).[4,23]

In conclusion, we have developed an enantioselective *N*-heterocyclic carbene-catalyzed annulation of electron-rich phenols with enals. The NHC generated from triazolium salt **F** derived from L-phenylalanine (DHIQ-NHC) was found to be a highly efficient catalyst, providing 4-aryl-3,4-dihydrocoumarins in good yields and excellent ee. The utility of this new method has been demonstrated by the facile transformation of products into naturally occurring and bioactive compounds. The mild reaction conditions, ready availability of both starting materials, and synthetically appealing products make this methodology attractive in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00088.

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

X-ray crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(21) For complete optimizations, see the Supporting Information.

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