Organocatalytic Annulation of Aldehydes and *o*-Quinone Methides: A Facile Access to Dihydrocoumarins

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Organocatalytic Annulation of Aldehydes and *o*-Quinone Methides: A Facile Access to Dihydrocoumarins

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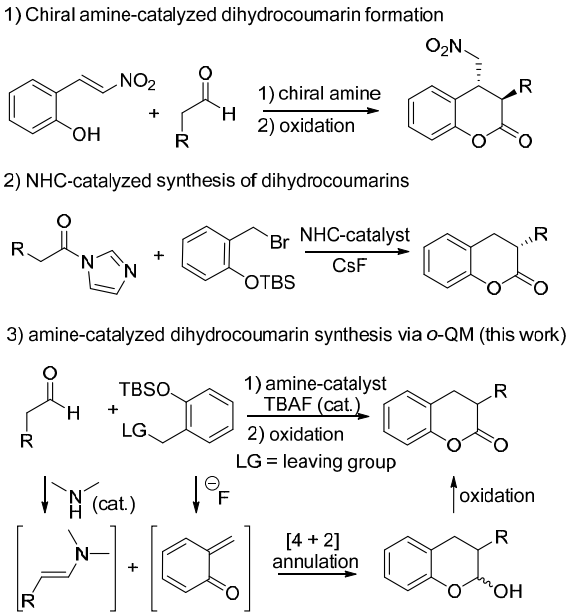
ABSTRACT

A [4+2] annulation of aldehydes and *o*-quinone methides catalyzed by a secondary amine is developed. This process leads to biologically important dihydrocoumarins in moderate to good yields after oxidation. In addition, the employment of a chiral secondary amine catalyst allows access to optically active dihydrocoumarins with up to 64% ee.

ortho-Quinone methides (*o*-QMs) are a class of highly reactive intermediates and have been employed in the synthesis of a wide variety of natural products and biologically intriguing molecules.[1] Recently, by the ingenious combination of organocatalysis,[2] the chemistry of *o*-QMs was further expanded, especially in the field of asymmetric catalysis.[3] Chiral Brøsted acids have proved to be among the most useful catalysts in the enantioselective reactions of *o*-QMs, presumably due in large part to their ability to accelerate the generation of *o*-QMs and activate nucleophiles simultaneously.[4] *N*-Heterocyclic carbene (NHC) catalysts,[5] as well as cinchona alkaloids-based catalysts[6] and substituted chiral binapthols,[7] have also been demonstrated as efficient promoters. The well-established aminecatalysts, however, were surprisingly less explored in the *o*-QMs-involved processes.

Dihydrocoumarins are structurally important motifs found in a large number of pharmaceuticals and natural occurring compounds.[8] Attracted by the intriguing biological properties of dihydrocoumarin-containing molecules (e.g., anti-cancer, anti-microbial, anti-aging, etc.),[9] organic chemists have devoted considerable efforts on the development of new synthetic methods and great progress has been achieved, particularly on the construction of dihydrocoumarins mediated by organocatalysts. The use of NHC-based catalysts has been extensively investigated.[5a,10,5b] Furthermore, chiral amines were also explored for the preparation of 3,4-disubstituted hydrocoumarins from



Scheme. 1. Organocatalytic synthesis of dihydrocoumarins

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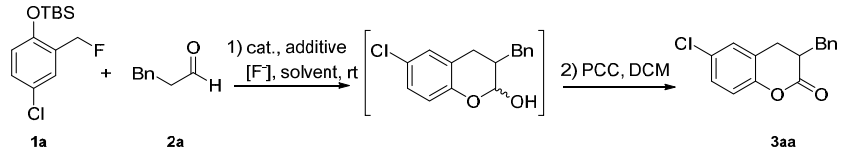
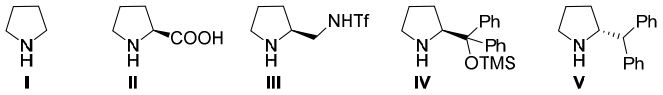
Table 1 Optimization of reaction conditions[a]



Entry	Cat.	[F⁻] (equiv.)	Additive (equiv.)	Solvent	Time (h)	Yield (%)[b]
1	**I**	KF (0.5)	18-C-6 (0.1)	DCM	12	<5[c]
2	**I**	TBAF (0.1)	-	DCM	12	36
3	**I**	TBAF (0.1)	TFA (0.1)	DCM	5	82
4	**I**	TBAF (0.1)	*p*-Nitrophenol (0.1)	DCM	5	70
5	**I**	TBAF (0.1)	AcOH (0.1)	DCM	5	87 (40)[d]
6	**II**	TBAF (0.1)	AcOH (0.1)	DCM	5	74
8	**I**	TBAF (0.1)	AcOH (0.1)	Toluene	5	77
9	**I**	TBAF (0.1)	AcOH (0.1)	THF	5	49
10	**I**	TBAF (0.1)	AcOH (0.1)	CH_3CN	5	46
11	**I**	TBAF (0.05)	AcOH (0.1)	DCM	6	85
12[e]	**I**	TBAF (0.1)	AcOH (0.1)	DCM	5	69

[a] Unless otherwise noted, reactions were conducted with **1a** (0.073 mmol), **2a** (0.22 mmol, 3 equiv.), amine catalyst (0.015 mmol, 20 mol%), additive (0.007 mmol, 10 mol%) and fluoride reagent in solvent (0.4 mL) at rt. [b] Isolated yields for two steps. [c] Yield of hemiacetal estimated by TLC [d] With Fetizon's reagent instead of PCC as oxidant. [e] With **2a** (0.11 mmol, 1.5 equiv.). TBAF: Tetrabutylammonium fluoride; PCC: pyridinium chlorochromate; TFA: trifluoroacetic acid.

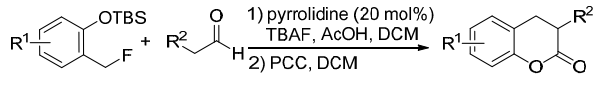


aldehydes and nitroalkenes (Scheme 1)[11]. Very recently Scheidt *et al.* described an elegant NHC-catalyzed asymmetric annulation of *o*-QMs and acyl imidazoles, resulting in optically active dihydrocoumarins with up to 86% ee.[5d] In this context, taking advantage of the *o*-QM chemistry, we wish to report a new secondary amine-catalyzed [4 + 2] annulation of aldehydes for the synthesis of dihydrocoumarins.

As illustrated in Scheme 1, we envision that *in situ*-forming *o*-QM and enamine intermediates synergistically react in [4 + 2] annulation manner. To achieve this goal, we selected fluoro-containing **1a** as *o*-QM precursor, which can be conveniently transformed to *o*-QM in the presence of a catalytic amount of fluoride, while aldehyde **2a** was activated by pyrrolidine. Initial attempt using potassium fluoride and 18-crown-6 to trigger the formation of *o*-QM failed to deliver the desired product likely due to the low solubility of potassium fluoride in dichloromethane (Table 1, entry 1). Therefore, we switched to organic solvable tetrabutylammonium fluoride (TBAF) (entry 2). We were delightful to observe the formation of hemiacetal, and upon oxidation by pyridiniumchlorochromate (PCC), dihydrocoumarin **3aa** was obtained in 36% yield over two steps. The addition of trifluoroacetic acid (TFA) to the reaction significantly increased the yield of dihydrocoumarin to 82% (entry 3). Further screening identified acetic acid as the optimal additive (entry 5). On the other hand, proline (**II**) proved to be less efficient for this transformation, affording **3aa** in lower yield (74%, entry 6). Besides DCM, other solvents (e.g. toluene, THF, CH_3CN, etc.) were also examined, but all failed to show any significant improvements (entries 8-10).

Having established the optimal reaction conditions, we then explored the generality of this [4 + 2] annulation process. A survey of aldehydes revealed that this pyrrolidine-mediated reaction is compatible with a range of substituents on acetaldehydes (Table 2). in addition to aldehyde **2a**, analogues with electron-rich (**2b**) or electron-deficient (**2c**) groups were all

Table 2 Scope of reactions

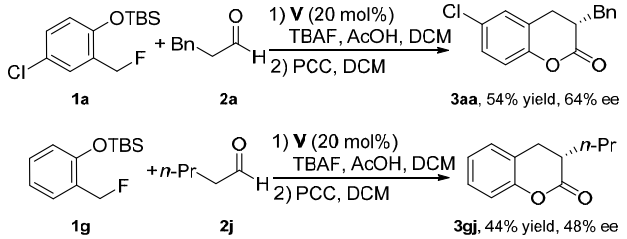


Entry	R^1	R^2	Product	Yield (%)[a]
1	4-Cl, **1a**	Bn, **2a**	**3aa**	87
2	4-Cl, **1a**	PMB, **2b**	**3ab**	66
3	4-Cl, **1a**	CH_2Ph(4'-COOEt), **2c**	**3ac**	58
4	4-Cl, **1a**	Me, **2d**	**3ad**	79
5	4-Cl, **1a**	*n*-Bu, **2e**	**3ae**	77
6	4-Cl, **1a**	*n*-C_8H_{17}, **2f**	**3af**	66
7	4-Cl, **1a**	*i*-Pr, **2g**	**3ag**	76
8	4-Cl, **1a**	Ph, **2h**	**3ah**	62
9	4-F, **1b**	Bn, **2a**	**3ba**	81
10	4-F, **1b**	*n*-Bu, **2e**	**3be**	75
11	4-Br, **1c**	Bn, **2a**	**3ca**	81
12	4-Br, **1c**	*n*-Bu, **2e**	**3ce**	75
13	4-Me, **1d**	Bn, **2a**	**3da**	55
14	6-Me, **1e**	Me, **2d**	**3ed**	48
15	4-*t*Bu, **1f**	Me, **2d**	**3fd**	54
16	H, **1g**	Bn, **2a**	**3ga**	71
17	H, **1g**	Me, **2d**	**3gd**	63
18	H, **1g**	Ph, **2h**	**3gh**	65
19	H, **1g**	*n*-Bu, **2e**	**3ge**	82
20	H, **1g**	*i*-Pr, **2g**	**3gg**	71
21	H, **1g**	Et, **2i**	**3gi**	75

[a] Isolated yields for two steps.

tolerated, giving dihydrocoumains **3ab** and **3ac** in 66% and 58% yield, respectively (entries 2, and 3). Aliphatic aldehydes (**2d**-**2g**), as well as 2-phenylacetaldehyde (**2h**), can also furnish substituted dihydrocoumarins in moderate to good yields over the two-step transformation (entries 4-8). 2-Ethylhaxanal, a α substituted aldehyde, however, is incompatible with current protocol, resulting in no desired production formation.

The scope of *o*-QM precursor was also investigated. *o*-QM precursors with both electron-neutral (R^1 = H) and electro-withdrawing groups (R^1 = F, Cl, Br) can all participate the [4 + 2] annulation process smoothly, leading to substituted dihydro-coumarins in comparable yields after oxidation (entries 9-12, 16-21). On the other hand, *o*-QM precursors with electron-donating groups (R^1 = Me, ^{t}Bu) gave slightly lower yields (entries 13-15). But *o*-QM precursors with stronger electron-donating groups (e.g., R^1 = OMe) were not amenable to this pyrrolidine-catalyzed transformation as current synthetic method failed to produce this type of less stable precursors.

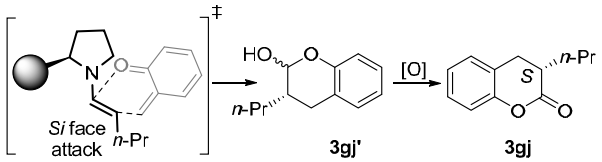


Scheme. 2 Asymmetric synthesis of dihydrocoumarins catalyzed by chiral amine

Chiral amines have proven to be highly efficient catalysts in a vast range of aldehyde/ketone-involved asymmetric transformations by forming reactive enamines or iminiums intermediates,[12] for instance, aldol reaction, Mannich reaction, Michael addition reaction. As pyrrolidine can facilitate this [4 + 2] annulation of aldehydes and *o*-QMs, we envisaged that chiral secondary amine might be able to catalyze this reaction in an asymmetric manner. To test the feasibility of this hypothesis, we screened a series of *L*-proline derivatives in this process. *L*-Proline (**II**) and catalyst **III**[13] were less efficient in the enantio-control of product, which supposedly arose from the relatively small size of chiral substituents on these catalysts. Well-studied diphenylprolinol TMS ether (**IV**)[14] was also examined, but, unfortunately, resulted in no expected adduct formation. Finally, catalyst **V**[15] was identified as the optimal catalyst, furnishing dihydrocoumarin **3aa** with 64% ee, albeit in diminished yield (54%, Scheme 2). Similarly, dihydrocoumarins **3ej** can also be synthesized in 44% yield and with 48% ee.

By comparison with the reported optical rotary data, the absolute configuration of compound **3ej** is assigned to be *S* and compound **3aa** is determined analogously. To rationalize the observed stereochemical outcome, a transition state model is proposed.[16] As depicted in Scheme 3, the substituent on the pyrrolidine ring blocks the approach of electrophilic *o*-QM from the *Re* face of enamine, leaving the *Si* face to be accessible to form the *S*-adduct as major product. Based on current investigation of this reaction, both the concerted Hetero-Diels-Alder (H-D-A) process and the stepwise Michael addition-cyclization domino process are possible for this [4 + 2] annulation reaction.

To summary, we have disclosed a new amine promoted [4 + 2] annulation of aldehydes and *o*-quinonemethides. Upon further oxidation with PCC, this protocol allows facile access to biologically interesting dihydrocoumarins in moderate to good



Scheme. 3 Proposed transition state model for enantioselection.

yields. Furthermore, the application of chiral secondary amine catalyst in this process can furnish optically active dihydrocoumarins with up to 64% ee.

Acknowledgments

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Supplementary data

Experimental procedures, characterizations, ^{1}H NMR and ^{13}C NMR spectra, HPLC traces are available in the online version.

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17 General procedure: To a solution of *o*-QM precursor **1** (0.21 mmol), aldehyde **2** (0.63 mmol) and AcOH (0.021 mmol) in dichloromethane (0.9 mL)were added pyrrolidine (0.042 mmol) and TBAF (1M in THF, 0.021 mmol), subsequently. The reaction mixture were then stirred at room temperature until completion of the reaction (monitored by TLC). Chromatography on a short silica gel column (eluting with petroleum ether/ethyl acetate) was used to give the [4 + 2] annulation adduct as crude product, which was then treated with pyridine chlorochromate (1.26 mmol) in dichloromethane (2.0 mL) at room temperature. Upon completion of the reaction, dihydrocoumarin**3** was obtained after chromatography on silica gel column (eluting with petroleum ether/ethyl acetate).

Graphical Abstract

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Organocatalytic Annulation of Aldehydes and *o*-Quinone Methides: A Facile Access to Dihydrocoumarins

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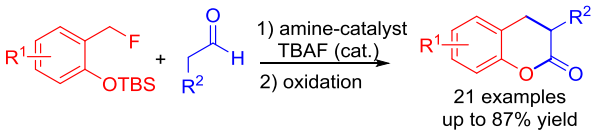

Research highlights

- [4 + 2] Annulation of aldehydes and *o*-quinone methides
- Facile synthesis of dihydrocoumarins
- Use of simple secondary amine as catalyst