C5-Disubstituted Meldrum's Acid Derivatives as Platform for the Organocatalytic Synthesis of C3-Alkylated Dihydrocoumarins

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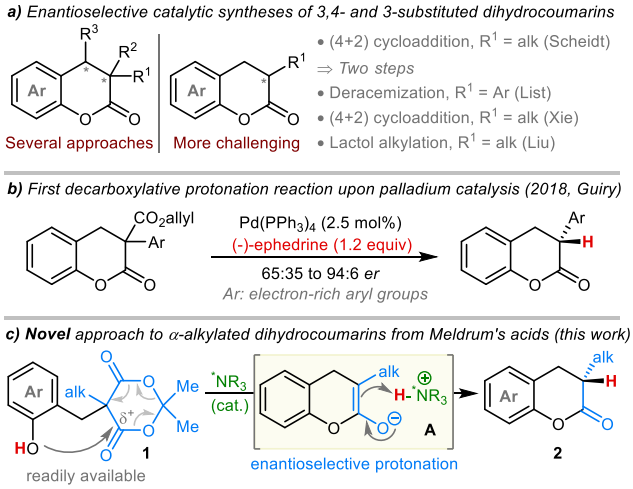
Abstract. C5-disubstituted Meldrum's acid precursors were shown to be a useful platform for the synthesis of an array of 3-alkylated dihydrocoumarins with up to 93:7 *er*, thanks to an enantioselective domino cyclization-decarboxylative-protonation reaction triggered by an unprecedented benzhydryl-derived cupreine organocatalyst. This cyclization sequence was extended to an emerging organocatalytic decarboxylative-chlorination reaction in the presence of trichloroquinolinone and by means of a bifunctional cinchona derived Brønsted base which gave rise to the formation of dihydrocoumarins (up to 79:21 *er*) with a tertiary chlorinated stereocenter.

Keywords: Coumarin; organic catalysis; synthetic method; Meldrum's acid; Decarboxylative protonation

Amongst the privileged coumarin scaffolds in medicinal chemistry, the dihydrocoumarin derivatives are widely distributed within naturally occurring molecules and bioactive compounds.[1] Consequently, several groups have developed catalytic enantioselective syntheses of 3,4-disubstituted chroman-2-ones[2] and, to a much lesser extent, 3,3-disubstituted homologues (Scheme 1).[3] Nevertheless, the construction of enantioenriched 3-substituted derivatives turned out to be more challenging. To the best of our knowledge, the group of Scheidt has reported the single one-step asymmetric construction of 3-substituted dihydrocoumarins upon NHC organocatalysis eliciting a (4+2)-cycloaddition reaction with *er* ranging from 75:25 to 93:7.[4] Beside the elegant but two steps enamine-based approaches developed by Xie and Liu,[5a-e] requiring the final oxidation of a lactol intermediate, List and co-workers have pioneered the challenging enantioselective delivery of a small proton atom to ketene dithioacetals.[5f] One of the obtained product was hydrolyzed into an α-phenyl dihydrocoumarin with high enantiomeric excess. In view of this background, an expedious synthetic sequence furnishing C3-substituted dihydrocoumarin remains desirable.

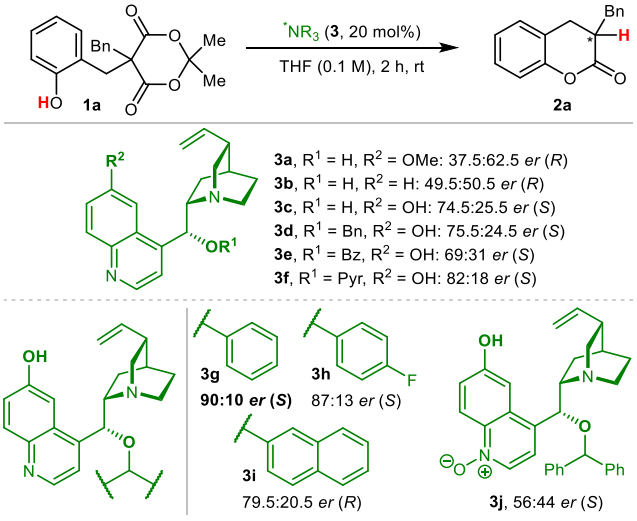
Very recently, the group of Guiry achieved the synthesis of a series of 3-aryl dihydrocoumarins with *er* ranging from 65:35 to 94:6 (Scheme 1b).[6] This functionalization strategy takes advantage of the palladium-catalyzed decarboxylative protonation reaction[7] in the presence of ephedrine as a chiral stoichiometric source of proton. Although several teams ventured into this convenient enantioselective protonation (EP) strategy, mostly from hemimalonic esters in organocatalysis, only the groups of Brunner, Rouden, Zhang and Song succeeded in getting good *er* (rarely > 95:5) albeit at the expense of the use of high catalyst loading (up to 1 equiv).[8],[9]



Scheme 1. Context of the investigation.

We recently introduced disubstituted Meldrum's acid (MA) derivatives as stable alternatives to hemimalonic esters for the enantioselective decarboxylative protonation reaction upon phase-transfer catalytic conditions,[10] while this architecture also affords new synthetic opportunities in heterocycle formation.[11] We reasoned that a novel and readily available MA platform **1** (Scheme 2),[12] may undergo the intramolecular nucleophilic addition of the phenol moiety thanks to the electrophilic character of the carbonyl groups. Then, the fragmentation-decarboxylation events would afford a transient enolate species **A** which would undergo the key enantioselective protonation. Overall, an original organocatalytic proton shuttle from the phenol part to the final product **2** would occur. We are pleased to report herein that a novel bifunctional organocatalyst (R_3N^*) allows this unprecedented catalytic route to enantioenriched 3-alkylated dihydrocoumarins **2**. Furthermore, by means of these MA-based platforms, a proof of concept of a sparingly reported asymmetric decarboxylative chlorination reaction was demonstrated allowing the construction of chiral C3-chlorinated dihydrocoumarins.[13]

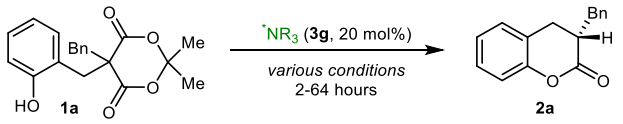
This investigation began with the phenol **1a** as a model substrate (Scheme 2, see SI for full-details). A screening of an array of chiral Brønsted bases revealed that quinine **3a** achieved the domino transformation into the desired **2a** in smooth conditions (rt, 2 hours), in a complete conversion and promising 37.5:62.5 *er*. The functional group modulation on catalysts **3** highlighted that cupreine bifunctional organocatalysts provided better selectivity with *er* increasing from 74.5:25.5 to 82:18 in line with steric hindrance at the C9-ether moiety (see R^1 for **3c**-**3f**).[14] Eventually, a novel benzhydryl-derived cupreine **3g** was synthesized and furnished excellent 90:10 *er*. Preliminary structure activity investigations by modulating the benzhydryl moiety, by *para*-fluorophenyl (**3h**) or 2-naphtyl (**3i**) pendants, together with the evaluation of the *N*-oxide catalyst **3j** led to lower selectivities.



Scheme 2. Proof of principle.

During the rapid survey of reaction conditions (Table 1 and see SI), THF proved to be the most suitable solvent both for *er* and the reaction efficiency (entries 1-5). Eventually, the enantiomeric ratio was improved to 93:7 *er* by carrying out the reaction at 5 °C (entries 8-10) in a more concentrated fashion (0.5 M – entries 6-7). This outcome provides one of the highest enantioselection for the synthesis of 3-benzyl dihydrocoumarin derivatives of type **2a**,[4],[5d] while successfully demonstrating the challenging enantioselective delivery of a small proton atom to an enolate intermediate along a complex domino process.

Table 1. Conditions optimization. [a]

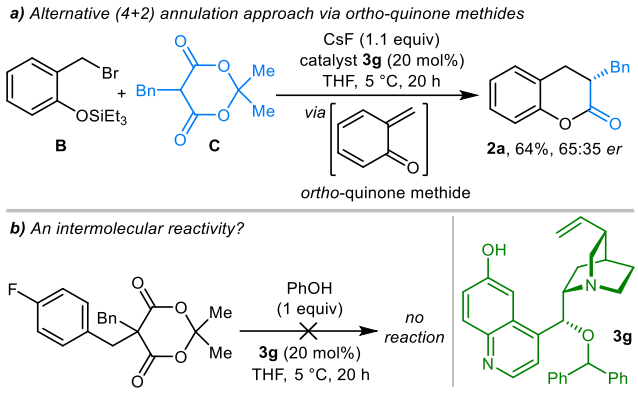


Entry	Solvent	T, time (°C, h)	Conc. (mol/l)	Conv.[b] (%)	*er*[c]
1	THF	rt, 2	0.1	99	90:10
2	PhMe	rt, 2	0.1	25	71:29
3	MeCN	rt, 2	0.1	56	71:29
4	CH_2Cl_2	rt, 2	0.1	27	61.5:38.5
5	Et_2O	rt, 2	0.1	64	87:13
6	THF	rt, 2	0.2	98	91:9
7	THF	rt, 2	0.5	98	92:8
8	THF	10, 20	0.5	99[d]	92.5:7.5
9	THF	5, 20	0.5	99[d]	93:7
10	THF	-5, 64	0.5	78[e]	93:7

[a] Reaction performed on 0.05 mmol of phenol **1a**. [b] Determined on the crude product by ^{1}H NMR. [c] Determined by chiral HPLC.

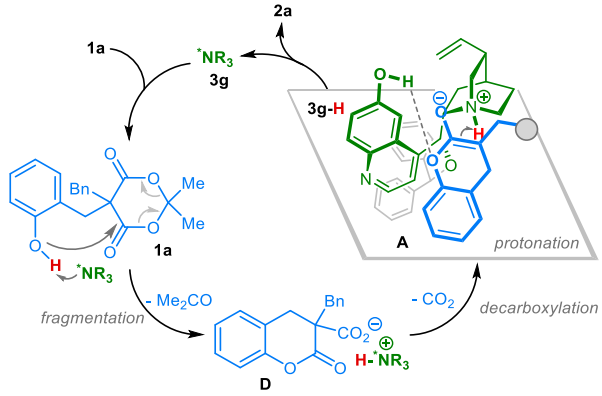
As depicted in Scheme 3a, one could envisage the annulation process between a transient unsubstituted *ortho*-quinone methide and benzyl MA **C** to give C-3 benzyl coumarin **2a**. Interestingly, Fochi and Bernardi reported the synthesis of C-4-arylated dihydrocoumarins,[15] based on the key enantioselective conjugate addition of unsubstituted Meldrum's acid to substituted *ortho*-quinone methides generated from benzylic sulfones in basic conditions. However, the non-asymmetric decarboxylative-cyclization final steps required a heating step (APTS, toluene, 100 °C). In our conditions (catalyst **3g**, THF, 5 °C), making use of the *in-situ* fluoride-promoted formation of the unsubstituted *ortho*-quinone methide generated from OTES-benzyl bromide **B** (Scheme 3a),[4],[5d] a smooth formal (4+2) cycloaddition and the subsequent decarboxylative-protonation reaction occurred. Unfortunately, the product **2a** was obtained in 64% yield and only 65:35 *er*. Contrary to the successful strategy from the suitable phenol platform **1a** (Scheme 2), the final stereoselective protonation during the (4+2) cycloaddition approach (Scheme 3a) may compete with other processes among which the racemic protonation by the rather acidic MA starting material **C** (pK_a = 4.8).[12] Eventually, it was shown

that neither the intermolecular addition of phenol nor the direct addition event of catalyst **3g** occurred (Scheme 3b).[16]



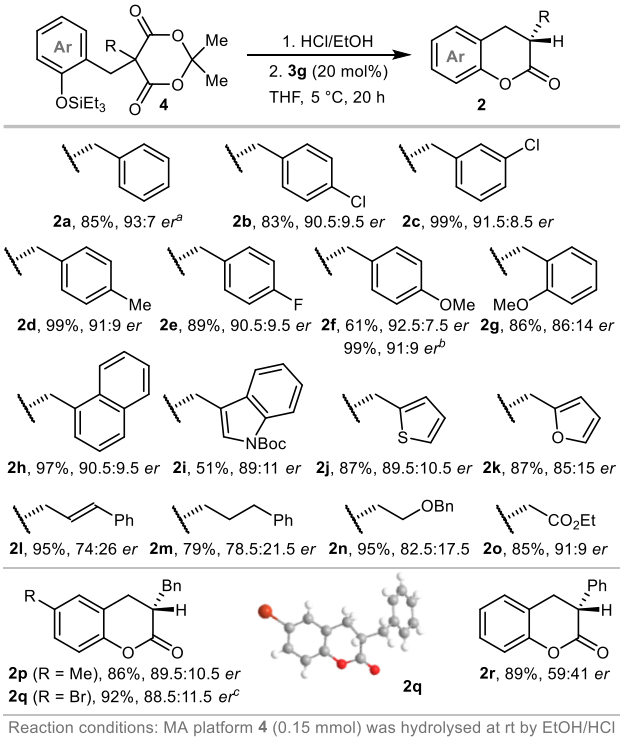
Scheme 3. Reactivity investigations.

In this context, we propose that the intramolecular attack of the phenol moiety to the electrophilic MA platform **1a** is promoted by the Brønsted base **3g** (Scheme 4), and the facile fragmentation-decarboxylation process *via* **D** to lead to the rather stable tetrasubstituted enolate intermediate **A** (Scheme 1).[17] Then, the bifunctional protonated-cupreine organocatalyst **3g-H** would deliver the proton to the rear-face of the enolate **A** to give **2a**, through a hydrogen-bonding manifold by means of the hydroxyl-quinoline part in the Transition State (see SI for TS-proposal discussion).[14]



Scheme 4. Proposed catalytic cycle and transition state.

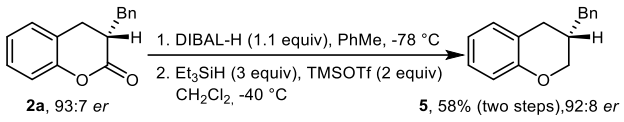
As phenol **1a** was difficult to purify, the readily available silylated precurors **4** (see SI) were used to study the scope and limitations of this novel transformation (Scheme 5). Indeed, the corresponding phenols **1** were thus generated after a simple acidic deprotection of the O-silyl moiety of **4** and used without further purification. By means of cupreine catalyst **3g** for 20 hours at 5 °C, C3-benzylated dihydrocoumarin derivatives **2a-2f** and **2h**, with phenyl-moiety flanked by *para*- or *meta*-substituents, were uneventfully formed with 61-99% yields over two-steps and *er* between 90.5:9.5 to 93:7. The yield of the *para*-methoxy derivative **2f** was improved from 61 to 99% in 60 hours of reaction albeit with a slight decrease in *er* to 91:9 (previously 92.5:7.5). *Ortho*-methoxy aryl derivative **2g** led to 86% yield with a 86:14 *er*. Heterocyclic pendants were tolerated but the corresponding products **2i-2k** were obtained with *er* ranging from 85:15 to 89.5:10.5. Precursors with alkyl-chain substituents led to moderate *er* (**2l-2n**, 79-95%, 74:26-82.5:17.5 *er*) except the counterpart **2o**, bearing a versatile ester functional group, which was synthesized in 85% yield and 91:9 *er*. The precursors having substituents on the phenol moiety were cyclized into products **2p-2q**[18] in 89.5:10.5 and 88.5:11.5 *er* respectively and excellent yields (86-92%). However, although this strategy allows the straightforward construction of 3-phenyl derivative **2r**, a low enantiomeric ratio (59:41 *er*) was measured due to racemization events of this more acidic product.



Reaction conditions: MA platform **4** (0.15 mmol) was hydrolysed at rt by EtOH/HCl (2% v/v) in 1 hour and extracted. The crude phenol product **1**, THF (0.5 M), catalyst **3g** (20 mol%), 5 °C, 20 h - yields over two-steps after purification by silica gel column chromatography. [a] On 2.2 mmol scale leading to 77%, 90.5:9.5 *er* (90% BRSM). [b] Carried out in 60 h. [c] Absolute configuration determined after single-crystal X-ray diffraction (CCDC 1870775).

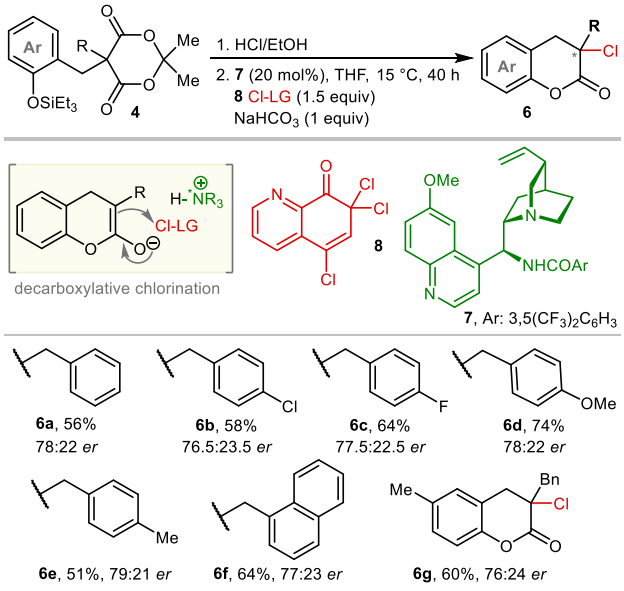
Scheme 5. Scope and limitations of the decarboxylative protonation reaction.[a-b]

In order to illustrate the utility of these dihydrocoumarins, the unprecedented synthesis of the enantioenriched C3-benzyl chroman **5** was undertaken, as these derivatives (as racemic) have potent antirhinovirus properties (Scheme 6).[19] To our delight, the desired chroman **5** was obtained in 58% yield over a two-step reduction sequence of coumarin **2a** with virtually no erosion of *er*.



Scheme 6. Useful synthetic transformation.

Next, we wondered whether it could be possible to take advantage of the reactivity of the readily available Meldrum's acid platforms **4**, for the construction of more substituted dihydrocoumarin derivatives. At the onset, we considered the beautiful and unprecedented enantioselective decarboxylative chlorination reaction recently reported by Shibatomi *et al.*[13],[20] This strategy applied to our domino cyclization-decarboxylative process would provide an unprecedented entry to dihydrocouramins **6** having a C3-chlorinated tetrasubstituted stereocenter (Scheme 7).



Reaction conditions: MA platform **4** (0.15 mmol) was hydrolysed at rt by EtOH/HCl (2% v/v) in 1 hour and extracted. The crude phenol product **1**, THF (0.25 M), trichloroquinolinone **8** (1.5 equiv), $NaHCO_3$ (1 equiv) and catalyst **7** (20 mol%), 15 °C, 40 h - yields over two-steps after purification by silica gel column chromatography; ratio of chlorinated:protonated products **6**:**2** ranging from 83:17 to 80:20 was mesured on the crude product by proton NMR.

Scheme 7. A decarboxylative chlorination approach [a-b]

Pleasingly, the chlorination reaction occurred with more efficiency with the bifunctional organocatalyst **7**,[21] derived from 9-*epi*-aminoquinine. Next, better enantiomeric excesses were observed in the presence of the trichloroquinolinone **8**, originally developed by Bartoli, Melchiorre and co-workers as chlorinated agent (see SI).[22] Under these conditions (THF, 15 °C, 40 hours) a series of novel chlorinated coumarin derivatives **6a**-**6g** were obtained as major products with isolated yields between 51 to 74%. The presence of the minor protonated products **2** was observed on the crude reaction mixture (**6**:**2** ≈ 80:20). Worthy of note, it was proven that the catalytic chlorination reaction did not occur on the coumarin product **2a**. At that stage, albeit moderate, the *er* were uniformly measured between 76:24 to 79:21 (**6a**-**6g**) for this proof of principle and novel domino cyclization-decarboxylative chlorination reaction. Furthermore, this approach allows the elaboration of unprecedented α,α-disubstituted coumarins[3] with a versatile tertiary chlorinated stereocenter.[20]

In conclusion, we have highlighted the reactivity of C5-disubstituted Meldrum's acid derivatives as novel platforms for the enantioselective organocatalytic synthesis of medicinally relevant 3-alkylated dihydrocoumarins in up to 93:7 *er*, thanks to a domino cylization-decarboxylative protonation reaction trigerred by a novel cuprein organocatalyst. The versatility of these platforms was demonstrated through an original (second report to date) enantioselective decarboxylative chlorination reaction towards the construction of chroman-2-ones with a tertiary chlorinated stereocenter with up to 79:21 *er*. The synthesis of other heterocycles based upon the Meldrum's acid platforms is currently under investigation.

Experimental Section

General decarboxylative protonation reaction procedure: 5-Benzyl-2,2-dimethyl-5-(2-((triethylsilyl)oxy)benzyl)-1,3-dioxane-4,6-dione **4a** (68.1 mg, 0.15 mmol) was diluted in EtOH (3 mL) and 37% aqueous HCl solution (0.06 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 1 hour. The mixture was quenched with water and extracted twice with CH_2Cl_2. The combined organic phases were dried over MgSO4, and concentrated *in vacuo*. The residue was diluted in dry THF (0.5 M), stirred at 5 °C for 10 minutes, then organocatalyst **3g** (20 mol%) was added. The mixture was stirred at 5 °C for 20 hours, filtered on a pad of silica gel [eluent: Petroleum Ether/EtOAc (8/2) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford the desired enantioenriched (*S*)–3–Benzylchroman–2–one **2a** in 85% yield and 93:7 *er*.

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