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COMMUNICATION

Observation of neighboring *ortho*-hydroxyl group participation in organocatalytic asymmetric sequential Michael-lactonization reactions: synthesis of highly substituted chiral spirodihydrocoumarins†‡

Dhevalapally B. Ramachary,* R. Madhavachary and M. Shiva Prasad

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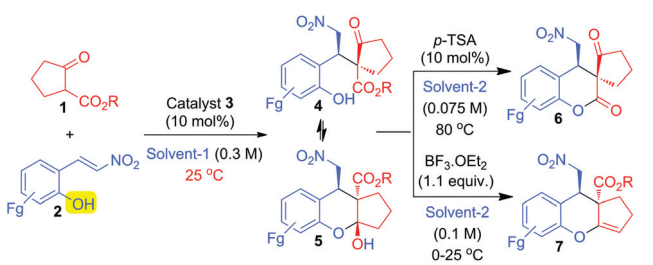
A general approach to asymmetric synthesis of highly substituted spirodihydrocoumarins with a quaternary stereocenter was achieved through neighboring *ortho*-hydroxyl group induced sequential Michael–lactonization reactions on 2-(2-nitrovinyl)phenols with alkyl cyclopentanone-2-carboxylates in the presence of a catalytic amount of quinine–*N*H–thiourea followed by *p*-TSA.

Despite rapid progress in asymmetric organocatalytic sequential one-pot reactions,[1] mimicking cellular and highly efficient asymmetric sequential one-pot approaches remain in high demand. An ideal asymmetric sequential one-pot multi-catalysis reaction would be atom-economical, rapid, have a high substrate scope, and performed under the mild conditions to yield quantitative and enantiomerically pure drug-like products with a vast library of catalysts and substrates. Recently the organocatalytic aldol, Michael, Mannich or Diels–Alder reactions have become triggering reactions for a combination of other reactions like Michael, Henry, alkylation, amination, aldol, epimerization or acetalization in a sequential one-pot manner for the synthesis of complex chiral molecules.[2] The development of new and highly efficient cellular-type organocatalytic sequential one-pot approaches based on the high-yielding asymmetric reactions to form drug-like molecules is significant. Herein, we describe an unusual efficient neighboring *ortho*-hydroxyl group induced asymmetric organocatalytic sequential one-pot reaction for the synthesis of drug-like chiral spirodihydrocoumarins from simple substrates and catalysts by using sequential Michael–lactonization reactions.

Chromanes and 3,4-dihydrocoumarins are important classes of heterocyclic cores found in many natural products and are widely used as drug intermediates and ingredients in pharmaceuticals.[3] Therefore, high-yielding asymmetric syntheses of these heterocycles have been extensively studied in recent years and provided many efficient methods.[4] Recently, our group, Enders *et al.*, Gong *et al.*, and Hong *et al.* have independently developed an organocatalytic Michael–acetalization–oxidation/reduction reaction sequence for the efficient synthesis of chromanes and 3,4-dihydrocoumarins in a highly enantioselective manner.[5] However, there is no suitable asymmetric method to prepare spirodihydrocoumarins in enantiomerically pure form with more functional diversity. As a continuation of our research in this area, we envisaged (*E*)-2-(2-nitrovinyl)phenols and alkyl cyclopentanone-2-carboxylates as the potential substrates for a newly designed Michael–lactonization (M–L) reaction (Scheme 1).[6]

As our group is working on the development of asymmetric sequential one-pot synthesis of drug-like compounds,[7] herein we propose that medicinally important spirocyclic dihydrocoumarins **6** and tetrahydrocyclopenta[*b*]chromenes **7** with a quaternary stereocenter could be constructed through newly designed neighboring *ortho*-hydroxyl group induced asymmetric sequential Michael–lactonization (M–L) reactions between alkyl cyclopentanone-2-carboxylates **1** and (*E*)-2-(2-nitrovinyl)phenols **2** with suitable organocatalysts **3** followed by *p*-TSA or $BF_3{\cdot}OEt_2$-catalysis (Scheme 1).

As we were interested in investigating the role of neighboring *ortho*-hydroxyl group participation in organocatalytic asymmetric reactions, we decided to explore the 2-(2-nitrovinyl) phenols **2** as Michael acceptors in an amine-catalyzed M–L reaction with keto-esters **1**.[8] We expected that the reaction of 2-(2-nitrovinyl)phenol **2a** with *in situ* generated enolate from keto-ester **1a** under the standard reaction conditions would lead to



Scheme 1 Design of a new sequential M–L reaction for the asymmetric synthesis of spirodihydrocoumarins.

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India. E-mail: ramsc@uohyd.ernet.in; Fax: +91-40-23012460

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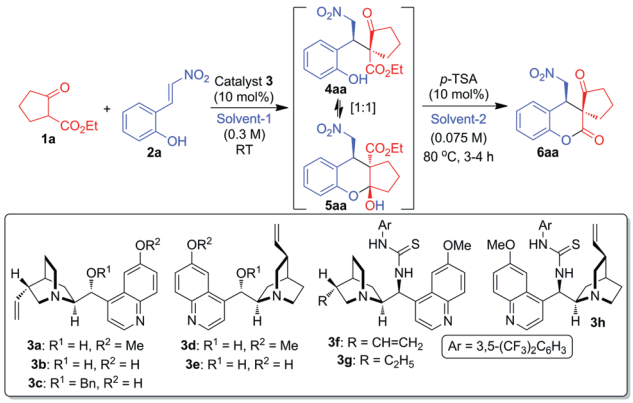
‡Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. CCDC 856223. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob07122c

Table 1 Optimization for the sequential M–L reaction



Entry	Catalyst **3** (10 mol%)	Solvent-1 (0.3 M)	Time (h)	Solvent-2 (0.075 M)	Yield[a] (%) **4aa/5aa**	Yield[b] (%) **6aa**	ee[c] (%) **6aa**	de[c] (%) **6aa**
1	**3a**	Toluene	24	Toluene	90	70	−31	>99
2	**3d**	Toluene	24	Toluene	90	73	38	>99
3	**3a**	DCE	24	DCE	95	70	−51	>99
4	**3d**	DCE	24	DCE	95	73	47	>99
5	**3a**	DCM	20	DCE	98	70	−49	>99
6	**3b**	DCE	8	DCE	95	70	−61	>99
7	**3c**	DCE	14	DCE	95	76	−85	>99
8	**3e**	DCE	8	DCE	95	70	91	>99
9	**3f**	**DCM**	**3**	**DCE**	**98**	**75**	**>99.9**	**>99**
10	**3g**	DCM	4	DCE	90	60	97	>99
11	**3h**	**DCM**	**3**	**DCE**	**98**	**75**	**−98**	**>99**
12[d]	**3f**	**DCM**	**3**	**DCE**	**99% conv.**	**70**	**91**	**>99**

[a] Yield refers to the quickly filtered product. [b] Yield refers to the column-purified product. [c] ee and de determined by CSP HPLC analysis. [d] Reaction performed in a cascade one-pot manner.

Michael adduct **4aa** with high ee. However, Michael adduct **4aa** was not detected alone and instead it has shown the existence of fast dynamic equilibrium with lactol **5aa** with high ee under the modified conditions. This unexpected result represents a novel methodology for the preparation of **4**/**5** and a new reactivity for amine-catalysts. Herein, we report our findings regarding these new sequential reactions.

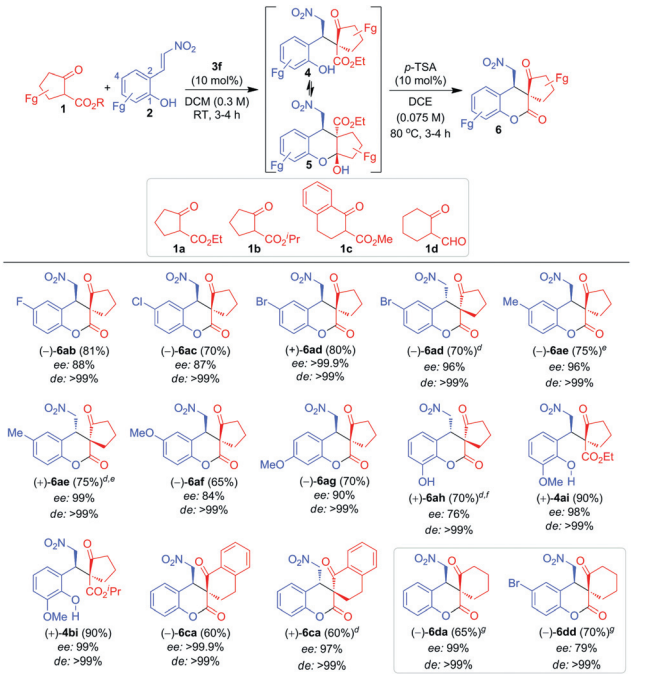
For the optimization of designed M–L reaction, we screened a number of organocatalysts for the reaction of 2-(2-nitrovinyl) phenol **2a** with 1.3 equiv. of keto-ester **1a** and some important results are shown in Table 1. Interestingly, reaction of **2a** with 1.3 equiv. of **1a** under 10 mol% of quinine **3a**-catalysis in toluene at 25 °C for 24 h furnished the 1 : 1 ratio of **4aa** and **5aa** in 90% yield with only 31% ee and >99% de (Table 1, entry 1). Structure and fast dynamic equilibrium between **4aa**↔**5aa** was confirmed by IR, ^{1}H and ^{13}C NMR analysis of pure **4aa**↔**5aa**. The ^{1}H and ^{13}C NMR spectra exhibited two set of signals for **4aa**↔**5aa** including broad singlet at δ 6.61 due to the phenolic-O*H*, a broad singlet at δ 4.56 due to the *tert*-O*H* group, a quaternary carbon resonance at δ 214.4 due to the carbonyl carbon (*C*═O) of the ketone, and a quaternary carbon at δ 106.3 due to the ketal carbon (O–*C*–OH) confirmed the equilibrium structures of the **4aa**↔**5aa**. For a clear understanding of diastereoselectivity and also for clear HPLC separation, we transformed the quickly filtered products **4aa**/**5aa** into easily separable and also very important spirodihydrocoumarin *cis*-**6aa** with 70–76% yield *via* *p*-TSA-catalyzed lactonization in toluene or DCE at 80 °C for 3–4 h (see Table 1). In a further optimization, reaction of **1a** and **2a** in DCE with 10 mol% of quinine **3a** catalyst at 25 °C for 24 h followed by *p*-TSA-catalyzed lactonization in DCE at 80 °C for 3–4 h furnished the product *cis*-**6aa** in 70% yield with only 51% ee and >99% de (Table 1, entry 3). Interestingly, reaction of **1a** with **2a** in DCE under 10 mol% of HO–Q–OH **3b**-catalysis at 25 °C for 8 h furnished the products **4aa**/**5aa** in 95% yield, which on further lactonization with *p*-TSA-catalysis furnished the product *cis*-(+)-**6aa** in 70% yield with 61% ee and >99% de (Table 1, entry 6). Same reaction under 10 mol% of HO–Q–OBn **3c**-catalysis in DCE for 14 h furnished the products **4aa**/**5aa** in 95% yield, which on further lactonization with *p*-TSA catalyst furnished the spirodihydrocoumarin *cis*-(+)-**6aa** in 76% yield with 85% ee and >99% de (Table 1, entry 7). In a further optimization, sequential M–L reaction of **1a** with **2a** in DCE using 10 mol% of HO–QD–OH **3e** catalyst at 25 °C for 8 h furnished the products **4aa**/**5aa** in 95% yield, which on further lactonization with *p*-TSA catalyst in DCE furnished the product *cis*-(−)-**6aa** in 70% yield with 91% ee and >99% de (Table 1, entry 8). Correlation of these results with simple (2-nitrovinyl)benzene reveals that the outcome of product selectivity and reactivity is controlled by neighboring group (O–H) participation in the transition state along with the catalyst.[8i]

To further improve the asymmetric sequential M–L reaction, especially to decrease the reaction time to <5 h and increase the

ee/de to >99%, for the first time we tested the M–L reaction of **1a** and **2a** catalyzed by quinine–*N*H–thiourea catalysts **3f–h**[9] followed by *p*-TSA-catalysis. Interestingly, sequential M–L reaction of **1a** with **2a** in DCM using 10 mol% of quinine–*N*H–thiourea **3f** catalyst at 25 °C for 3 h furnished the products **4aa/5aa** in 98% yield, which on further lactonization with *p*-TSA catalyst furnished the *cis*-(−)-**6aa** in 75% yield with >99.9% ee and >99% de (Table 1, entry 9). After achieving the successful result with **3f** as the catalyst, we screened alkaloid based primary amine thioureas like **3g** and **3h** as the catalysts for the M–L reaction to monitor the outcome of reaction rate and selectivity (Table 1, entries 10–11). Results from sequential M–L reaction of **2a** with 1.3 equiv. of **1a** in DCM using 10 mol% of **3g** or **3h** catalyst followed by lactonization are not superior as compared to catalyst **3f** (Table 1, entries 10–11). Finally, we envisioned the optimized conditions to be 25 °C in DCM using 10 mol% of quinine–*N*H–thiourea **3f** catalyst followed by *p*-TSA induced lactonization to furnish the spirodihydrocoumarin *cis*-(−)-**6aa** in 75% yield with >99.9% ee and >99% de (Table 1, entry 9). Surprisingly, the same reaction when performed in cascade one-pot manner furnished the product *cis*-(−)-**6aa** with reduced yield and ee as shown in entry 12, Table 1. Structure and absolute stereochemistry of M–L products **4aa/5aa** and **6aa** was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (−)-**6aa** as shown in Fig. S1 (see ESI‡).[10]

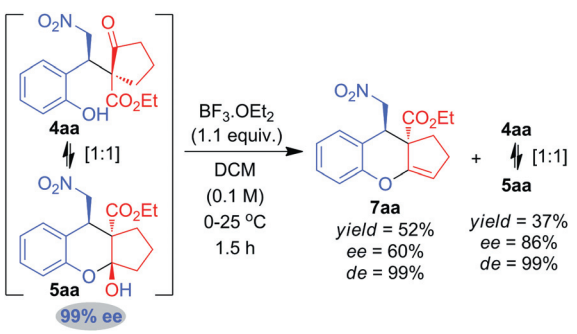
With the optimized reaction conditions in hand, the scope of the quinine–*N*H–thiourea/*p*-TSA-catalyzed asymmetric sequential M–L reactions was investigated.[11] A series of substituted 2-(2-nitrovinyl)phenols **2b–i** were reacted with 1.3 equiv. of keto-esters **1a–c** and keto-aldehyde **1d** catalyzed by 10 mol% of **3f** or **3h** at 25 °C in DCM for 3–12 h to furnish chiral products **4ab–dd/5ab–dd** with very good yields, ee's and de's, which on further lactonization with *p*-TSA catalyst or oxidation with PCC furnished the chiral products **6ab–6dd** respectively (Table 2).[12] Without showing much effect of electronic factors; neutral, electron-withdrawing and electron-donating substituted 2-(2-nitrovinyl)phenols **2b–i** generated the expected products **4ab–dd/5ab–dd** and **6ab–dd** with excellent yields, ee's and de's (see Table 2). Surprisingly, reaction of (*E*)-3-(2-nitrovinyl)benzene-1,2-diol **2h** with keto-ester **1a** using catalyst **3h** followed by lactonization furnished the *cis*-(+)-**6ah** as the major product in 70% yield with only 76% ee and >99% de (Table 2, entry 9). Observation of lower ee in this reaction may be due to the involvement of a second *OH* group in the transition state of the Michael reaction. Fascinatingly, 2-methoxy-6-(2-nitrovinyl)phenol **2i** were reacted with keto-esters **1a–b** catalyzed by 10 mol% of **3f** at 25 °C in DCM for 3–4 h to furnish chiral Michael products (+)-**4ai** and (+)-**4bi** with very good yields, ee's and de's, which on further lactonization with catalyst *p*-TSA in DCE for 5–6 h at 80 °C didn't furnish the cyclized products **6ai–bi** respectively (Table 2). Reaction of (*E*)-2-(2-nitrovinyl)phenol **2a** with keto-ester **1c** using **3f** or **3h** catalyst followed by lactonization furnished the pure two enantiomers *cis*-(−)-**6ca** and *cis*-(+)-**6ca** in each 60% yield with >99.9/97% ee and >99% de respectively (Table 2). Interestingly, reaction of (*E*)-2-(2-nitrovinyl)phenol **2a** with methyl 2-oxocyclohexanecarboxylate using catalyst **3f** or **3h** didn't furnish the expected Michael product, but the same reaction with 2-oxocyclohexanecarbaldehyde **1d** in DCM for 2 h at 25 °C followed by PCC mediated oxidation furnished the

Table 2 Synthesis of chiral M–L products **6**[abc]



[a] Reactions were carried out in DCM (0.3 M) with 1.3 equiv. of **1a–d** relative to the **2b–i** (0.3 mmol) in the presence of 10 mol% of catalyst **3f** or **3h** at 25 °C for 3–12 h. After one quick filtration, resulting products **4/5** were treated with 10 mol% of *p*-TSA in DCE (0.075 M) for 3–4 h at 80 °C. [b]Yield refers to the column-purified product. [c]Ee and de were determined by CSP HPLC analysis. [d]Reaction performed with 10 mol% of **3h** as catalyst. [e]Time taken for Michael reaction was 8 h. [f]Time taken for Michael reaction was 12 h. [g]PCC mediated oxidation was utilized for the cyclization reaction

functionalized spiro[chroman-3,1′-cyclohexane]-2,2′-dione *cis*-(−)-**6da** in 65% yield with 99% ee and >99% de (Table 2, entry 14). In a similar manner, another chiral spiro[chroman-3,1′-cyclohexane]-2,2′-dione *cis*-(−)-**6dd** was also furnished in 70% yield with 79% ee and >99% de from **1d** and **2d** (Table 2, entry 15). Structure and stereochemistry of M–L products **4ab–dd/5ab–dd** and **6ab–dd** were confirmed by NMR analysis.



(1)

With synthetic applications in mind, we decided to explore the utilization of dynamic equilibrium products **4**↔**5** in the synthesis of functionalized chiral chromanes and chromenes *via* Lewis acid-catalysis as shown in eqn (1). Reaction of the pure chiral products (+)-**4aa**/**5aa** (99% ee) with 1.1 equiv. of $BF_3{\cdot}OEt_2$ in DCM at 0–25 °C for 1.5 h furnished the cyclized ethyl

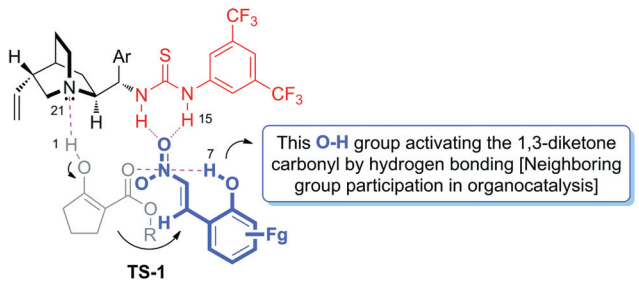
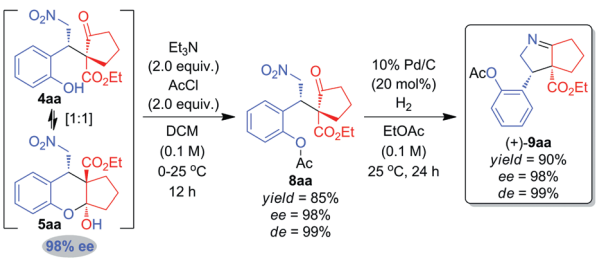


Fig. 1 Proposed transition state for the asymmetric Michael reactions.

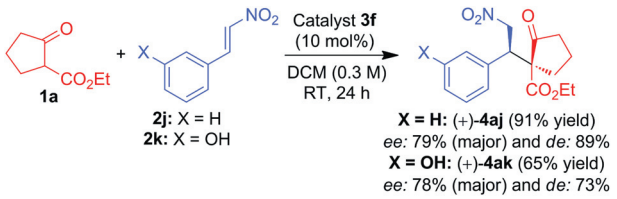
9-(nitromethyl)-1,2,9,9a-tetrahydrocyclopenta[*b*]chromene-9a-carboxylate *trans*-(−)-**7aa** in 52% yield with only 60% ee and unreacted products (+)-**4aa/5aa** in 37% yield with 86% ee as shown in eqn (1). Formation of less ee product in this reaction may be due to the decomposition or racemization of **4aa↔5aa** or **7aa** through retro-Michael and Michael reaction under the Lewis acid-catalysis.



(2)

Treatment of dynamic equilibrium products (−)-**4aa↔5aa** with AcCl using Et_3N catalyst in DCM at 0 °C → 25 °C for 12 h selectively furnished the protected open product (−)-**8aa** in 85% yield with 98% ee and >99% de as shown in eqn (2). Hydrogenation of (−)-**8aa** with 10% Pd/C in ethyl acetate at 25 °C for 24 h furnished the partially hydrogenated imine (+)-**9aa** in 90% yield with 98% ee and >99% de (see eqn (2)). Compounds (−)-**6ab** to (−)-**6dd**, (−)-**7aa**, (−)-**8aa** and (+)-**9aa** are drug-like molecules; these types of molecules are used for the treatment of potent anti-ischemic properties, anti-hypertensives, aldose reductase, spasmolytics for blood vessels, potassium channel blockers and also as HIV-1 reverse transcriptase, which emphasizes the value of this M–L approach to the pharmaceutical industry.[3] In addition, the presently discovered sequential M–L reaction will be suitable to develop substituted 3,4-dihydrocoumarins unit, which is found in many natural products and designed drug molecules.[3,4]

With controlled experimental data in hand, herein we firmly elucidate the mechanism of neighboring *ortho*-hydroxyl group involvement in an asymmetric Michael reaction through 21-membered supramolecular assembly by **3f**-catalysis, the reaction most likely proceeds *via* a **TS-1** mechanism (Fig. 1).[13] In the case of the addition of keto-esters **1a–d** to substituted 2-(2-nitrovinyl)phenols **2a–i** *via* quinine–*N*H–thiourea **3f**-catalysis, we can rationalize the observed stereochemistries through a favoured 21-membered supramolecular transition state where the less hindered *si*-face of **2a–i** approaches the *si*-face of *in situ* generated enol as shown in **TS-1**.[13] The outcome of high selectivity and reactivity for the keto-ester **1** addition to the 2-(2-nitrovinyl) phenols **2** could be explained by neighboring group participation of Ar–**O**–**H** through hydrogen-bonding with carbonyl of **1** as shown in Fig. 1. The asymmetric Michael reaction between simple (*E*)-(2-nitrovinyl)benzene **2j** and (*E*)-3-(2-nitrovinyl) phenol **2k** with keto-ester **1a** *via* **3f**-catalysis in DCM, furnished the expected Michael products (+)-**4aj** and (+)-**4ak** with moderate yields, ee's and de's under longer reaction times as shown in eqn (3). The observed moderate selectivity for the products (+)-**4aj** and (+)-**4ak** could be explained due to the lack of neighboring *ortho*-hydroxyl group participation and also the catalyst quinine–*N*H–thiourea **3f** is activating both the substrates in the transition state, which is not enough to control the selectivity as like in other substrates **2a–i**.



(3)

In summary, for the first time we have developed the quinine–*N*H–thiourea **3f** and *p*-TSA-catalyzed asymmetric sequential M–L reaction of keto-esters **1** with 2-(2-nitrovinyl)phenols **2**. The sequential asymmetric M–L reaction proceeds with very good yields and high selectivity through a favoured 21-membered supramolecular transition state using **3f** followed by *p*-TSA as the catalyst. Furthermore, we have demonstrated the application of chiral products **4**/**5** in the synthesis of functionalized chiral spirochromans. Further work is in progress to utilize chiral products **4–9** as intermediates for bio-active molecules synthesis.

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