Sequential combination of Michael and acetalization reactions: direct catalytic asymmetric synthesis of functionalized 4-nitromethyl-chromans as drug intermediates†

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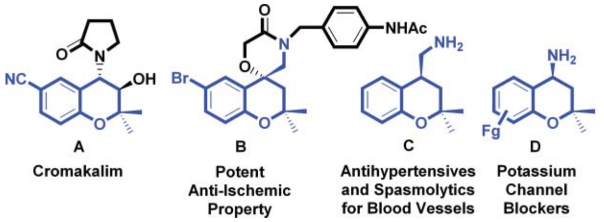
Functionalized chiral 4-nitromethyl-chromans as drug intermediates were achieved for the first time through sequential combination of Michael and acetalization reactions on 2-(2-nitro-vinyl)-phenols with acetone and alcohols in the presence of a catalytic amount of 9-amino-9-deoxyepiquinine and Ph$_2$CHCO$_2$H followed by *p*-TSA.

Functionalized chromans display broad spectrum of biological activities and are widely used as drug intermediates and ingredients in pharmaceuticals (see eqn (1)).[1] As such, the development of new and more general catalytic asymmetric methods for their preparation is of significant interest.[2] Interestingly, to the best of our knowledge there is no report on the direct catalytic asymmetric method for the synthesis of functionalized 2-hydroxy-2-methyl-4-nitromethyl-chromans, which can serve as good intermediates for the functionalized chromans as demonstrated in this communication. Herein, first time we reported the metal-free approach to the asymmetric synthesis of functionalized 2-hydroxy-2-methyl-4-nitromethyl-chromans *via* "sequential Michael and acetalization (SMA) reactions".[3]



(1)

Recently Barbas and co-workers discovered the novel technology of amine or amino acid-catalyzed intermolecular Michael reactions of ketones/aldehydes with a variety of active olefins to provide a general route to a variety of Michael adducts in good yields with high enantioselectivity.[4] The advent of this enamine based Michael technology triggered a burst of activity in the synthesis of a huge chiral pool of Michael adducts through biomimetic enamine chemistry.[4]

However, the amine-catalyzed Michael reaction of ketones **1** with 2-(2-nitro-vinyl)-phenols **2** was not known and the resulting products **4–6** have a wide range of uses in pharmaceutical chemistry (see eqn (1) and (2)). Furthermore, there is no methodology available to prepare achiral compounds **4–6**. We have reporting a metal-free and novel technology for the asymmetric synthesis of substituted 2-hydroxy-2-methyl-4-nitromethyl-chromans **5/6** and 2-alkoxy-2-methyl-4-nitromethyl-chromans **8/9** using organocatalytic SMA reactions from easily available 2-(2-nitro-vinyl)-phenols **2**, ketones **1**, amines/amino acid **3** and alcohols **7** (eqn (2)). In this communication, we report the existence of a fast dynamic equilibrium between the pair of pseudo-diastereomeric hemiketals of 2-hydroxy-2-methyl-4-nitromethyl-chromans **5/6** and 4-(2-hydroxy-phenyl)-5-nitro-pentan-2-one **4** under normal conditions.[5]

During our investigation of new reactive species for the development of MCC processes,[6] we decided to explore the potential ability of the 2-(2-nitro-vinyl)-phenols **2** to participate in an amine-catalyzed SMA reaction with acetone **1**. We expected that the reaction of 2-(2-nitro-vinyl)-phenol **2a** with *in situ* generated enamine from acetone **1** would lead to 4-(2-hydroxy-phenyl)-5-nitro-pentan-2-one **4a**. However, Michael adduct **4a** was not only detected; instead product **4a** showed the existence of a fast dynamic equilibrium with both *cis*-2-hydroxy-2-methyl-4-nitromethyl-chroman **5a** and *trans*-2-hydroxy-2-methyl-4-nitromethyl-chroman **6a** under the standard reaction conditions. This unexpected result represents a novel methodology for the preparation of 2-hydroxy-2-methyl-4-nitromethyl-chromans **5/6** and a new reactivity for amines or amino acid catalysts. Herein, we report our findings regarding these new sequential reactions.

We initiated our studies of the SMA reactions by screening a number of organocatalysts for the Michael reaction of 2-(2-nitro-vinyl)-phenol **2a** with 14 equiv. of acetone **1** and some important results are shown in Table 1. Interestingly, reaction of **2a** with 14 equiv. of acetone **1** in DMSO under 20 mol% of L-proline **3a**-catalysis furnished a 1 : 1 : 1 ratio of Michael↔*cis*-lactol↔*trans*-lactol products **4a/5a/6a** in 92% yield with only ≤7% ee (see eqn (2) and Table 1, entry 1). Rapid equilibrium between Michael **4a** and lactols **5a/6a** in solution was confirmed by NMR analysis and also finally confirmed by acetalization with methanol. For the clear understanding of the fast dynamic equilibrium between **4a** and **5a/6a**, and also for clear HPLC separation, we transformed the crude product **4a/5a/6a** into two easily separable SMA products *cis*-**8aa** and *trans*-**9aa** in a 1 : 1 ratio with 92% yield *via* *p*-TSA-catalyzed acetalization reaction in MeOH **7a** at 25 °C for 2 h (see Table 1). In a further optimization, reaction of **1** and **2a** in DMSO under catalysis by 20 mol% of L-Thr(O*t*Bu)–OH **3b** followed by *p*-TSA-catalysis in MeOH furnished a 1 : 1 ratio of products **8aa** and **9aa** in only <30% yield (Table 1, entry 2). Reaction of **1** with **2a** in DMSO under catalysis by 20 mol% of L-2-methoxymethyl-pyrrolidine **3c**/PhCO$_2$H followed by *p*-TSA-catalysis in MeOH furnished a

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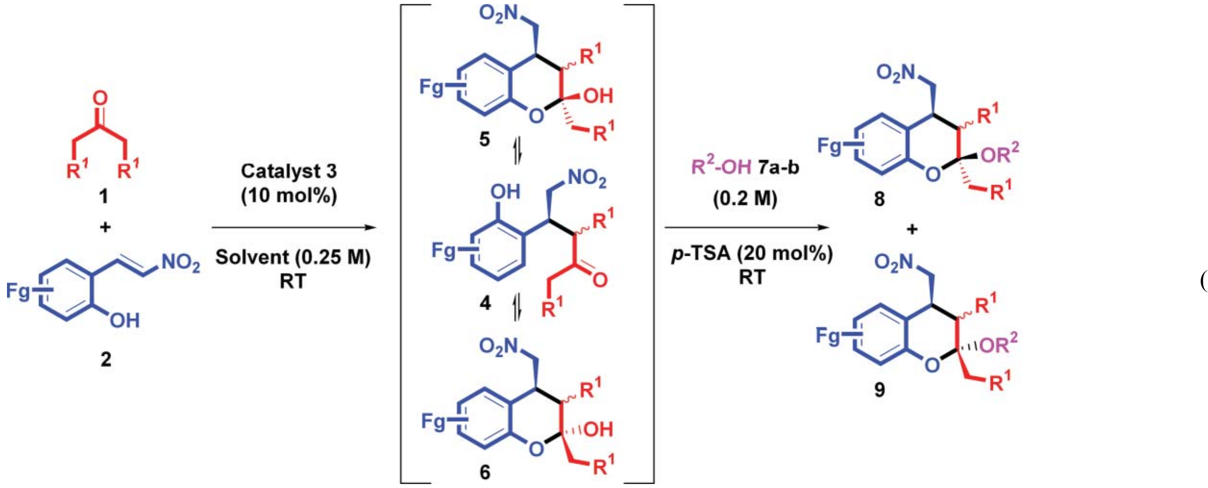
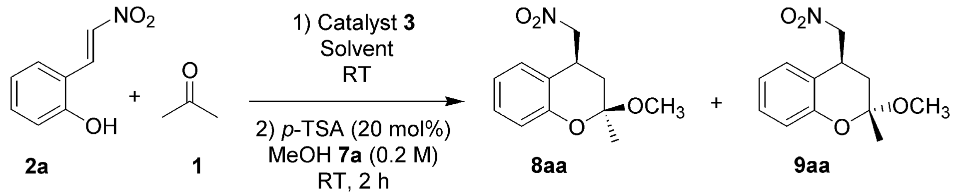
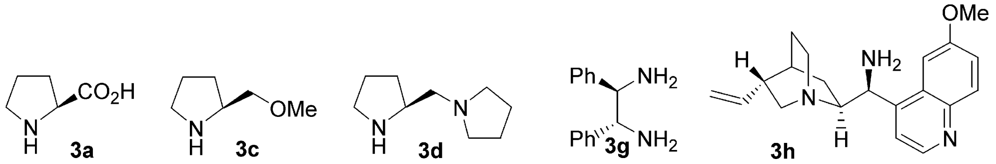
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. CCDC reference numbers 777137 for (+)-**8ba**, 765267 for (−)-**8ga** and 765268 for (-)-**9ha**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00189a



(2)

Table 1 Reaction optimization for the SMA reaction of **1**, **2a** and **7a**





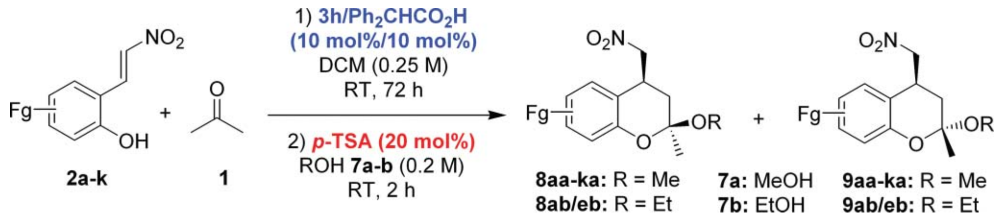
Entry	Catalyst **3** (20 mol%)	Solvent 0.25 M)	Time/h	Products yield (%)[a]		ee(%)[b]	
				8aa	**9aa**	**8aa**	**9aa**
1	L-Proline **3a**	DMSO	5	46	46	−7	−7
2	L-Thr(O*t*Bu)-OH **3b**	DMSO	48	<15	<15	ND	ND
3	**3c**/$PhCO_2H$	DMSO	1	47	47	−18	−16
4[c]	**3d**/D-CSA	DMSO	2	45	45	−22	−22
5	**3d**/Ph_2CHCO_2H	DCM	24	47	48	−25	−21
6[d]	L-DPPOTMS **3e**/D-CSA	DMSO	96	—	—	—	—
7[e]	L-Pyrrolidin-2-ylmethyl-thiourea **3f**	DMSO	24	<15	<15	−30	−30
8	**3g**/AcOH	DMSO	24	40	40	<5	<5
9	**3h**	$C_6H_5CH_3$	24	35	35	18	18
10	**3h**/$PhCO_2H$	$C_6H_5CH_3$	24	42	43	60	58
11	**3h**/Ph_2CHCO_2H	DCM	72	47	42	84	82
12[f]	**3h**/Ph_2CHCO_2H	DCM	72	40	42	82	82

[a] Yield refers to the column-purified product. [b] Ee determined by CSP HPLC analysis. [c] Similar results obtained without co-catalyst. [d] (*S*)-α,α-Diphenylprolinol trimethylsilyl ether (L-DPPOTMS). [e] (*S*)-1-(3,5-Bis-trifluoromethyl-phenyl)-3-pyrrolidin-2-ylmethyl-thiourea. [f] Reactions were carried out with each 10 mol% of **3h** and Ph_2CHCO_2H.

1 : 1 ratio of products **8aa** and **9aa** in 94% yield with increased (18%) ee (Table 1, entry 3). The same reaction under catalysis by 20 mol% of L-diamine **3d**/Ph_2CHCO_2H in DCM for 24 h followed by *p*-TSA-catalysis in MeOH furnished a 1 : 1 ratio of products **8aa**/**9aa** in 95% yield with increased (25%/21%) ee (Table 1, entry 5). Interestingly, there is no product formation under catalysis by (*S*)-α,α-diphenylprolinol trimethylsilyl ether (L-DPPOTMS)/D-CSA in DMSO as shown in Table 1, entry 6. Results are not fruitful with even bifunctional catalyst (*R*,*R*)-1,2-diphenylethane-1,2-diamine **3g**/AcOH and L-(3,5-bis-trifluoromethyl-phenyl)-3-pyrrolidin-2-ylmethyl-thiourea **3f** (Table 1, entries 7–8).

SMA Reaction of **1**, **2a** and **7a** is a catalyst and solvent dependent reaction. After unsuccessful results with chiral pyrrolidines **3a–g** as catalyst [many of the results with lower ee's are not shown in Table 1], we were interested in further screening alkaloid based primary amines like 9-amino-9-deoxyepiquinine **3h** as catalysts for the SMA reaction (see Table 1).[7] Interestingly, reaction of **2a** with 14 equiv. of **1** under catalysis by 20 mol% of **3h** in toluene for 24 h followed by *p*-TSA-catalysis in methanol furnished a 1 : 1

Table 2 Synthesis of chiral SMA products **8** and **9**[a]



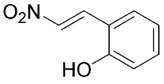
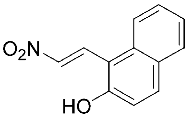
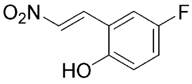
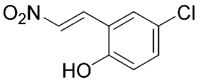
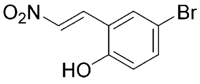
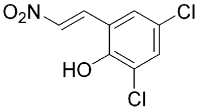
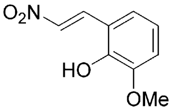
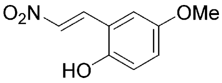
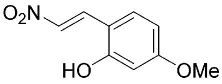
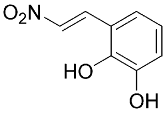
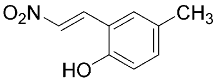
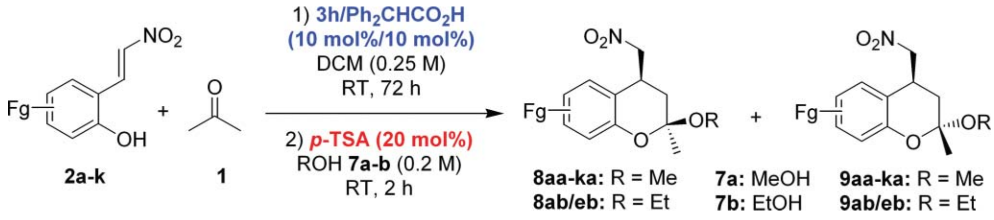
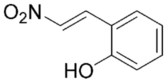
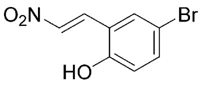
			ROH	Products	Ratio[b]	Product yield (%)[c]		Ee (%)[d]	
Entry	2-(2-Nitro-vinyl)-phenols **2**		**7a/7b**	**8/9**	**(8/9)**	**8**	**9**	**8**	**9**
1		**2a**	**7a**	**8aa/9aa**	1 : 1	42	42	82	82
2		**2b**	**7a**	**8ba/9ba**	99 : 1	72	< 1	98	—
3		**2c**	**7a**	**8ca/9ca**	1 : 1	43	43	82	76
4		**2d**	**7a**	**8da/9da**	1 : 1	40	40	69	70
5		**2e**	**7a**	**8ea/9ea**	1 : 1	41	41	87	86
6		**2f**	**7a**	**8fa/9fa**	1 : 1	41	41	88	91
7		**2g**	**7a**	**8ga/9ga**	1 : 1	38	38	79	79
8		**2h**	**7a**	**8ha/9ha**	1 : 1	33	38	79	79
9		**2i**	**7a**	**8ia/9ia**	1 : 1	37	37	80	80
10		**2j**	**7a**	**8ja/9ja**	1 : 1	38	38	83	82
11		**2k**	**7a**	**8ka/9ka**	1 : 1	44	44	92	89
12[e]		**2k**	**7a**	**8ka–d$_5$/9ka–d$_5$**	1 : 1	37	37	89	89

Table 2 *(Contd.)*



Entry	2-(2-Nitro-vinyl)-phenols 2		ROH 7a/7b	Products 8/9	Ratio[b] (8/9)	Product yield (%)[c] 8	 9	Ee (%)[d] 8	 9
13		**2a**	**7b**	**8ab/9ab**	1 : 1	44	44	80	80
14		**2e**	**7b**	**8eb/9eb**	1 : 1	40	40	88	82

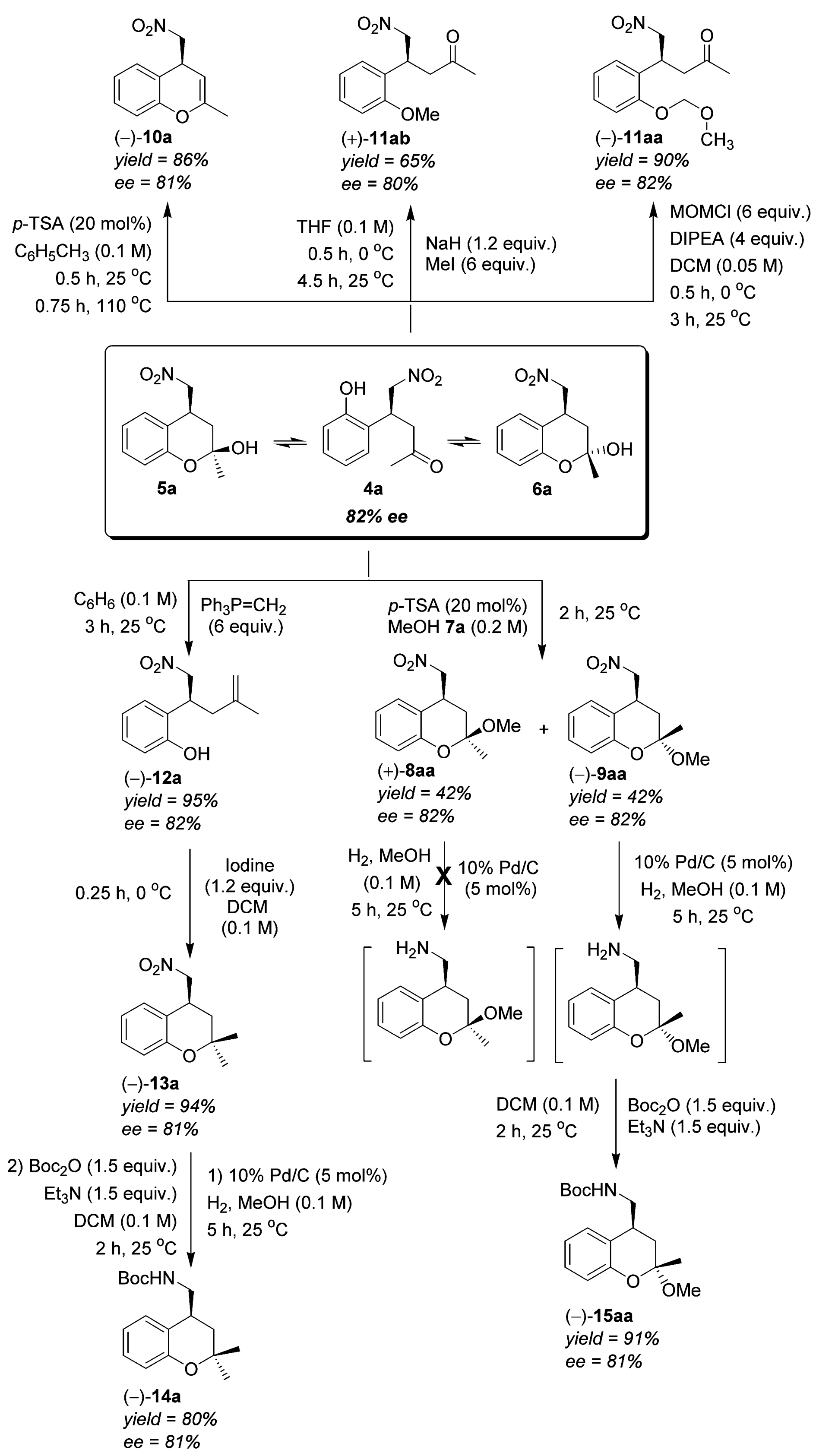
[a] Reactions were carried out in DCM (0.25 M) with 14 equiv. of **1** relative to **2a–k** (0.5 mmol) in the presence of 10 mol% of catalyst **3h**/Ph_2CHCO_2H and the reaction mixture was stirred at 25 °C for 72 h. After aqueous workup, the crude product was treated with *p*-TSA (20 mol%) in solvent ROH **7** (0.2 M), and the reaction mixture was stirred at 25 °C for 2 h. [b] Ratio is based on NMR analysis. [c] Yield refers to the column-purified product. [d] Ee determined by CSP HPLC analysis (see SI). [e] CD_3COCD_3 **1**-d_6 (14 equiv.) was used.

ratio of products **8aa** and **9aa** in 70% yield each with 18% ee; but the same reaction under catalysis by $PhCO_2H$ salt of 9-amino-9-deoxyepiquinine **3h** furnished the SMA products (+)-**8aa** in 42% yield with 60% ee and (–)-**9aa** in 43% yield with 58% ee as shown in Table 1, entries 9–10. After this interesting result, we screened a number of acids as co-catalysts with **3h** for the high asymmetric induction in SMA reaction of **1**, **2a** and **7a** in different solvents at 25 °C for 72 h (Table S1, see Supporting Information†). After thorough investigation, we envisioned the optimized conditions to be 25 °C in DCM under catalysis by 10 mol% of Ph_2CHCO_2H salt of 9-amino-9-deoxyepiquinine **3h** followed by *p*-TSA-catalysis in methanol to furnish a 1 : 1 ratio of highly substituted SMA products (+)-**8aa** in 40% yield with 82% ee and (–)-**9aa** in 42% yield with 82% ee (Table 1, entry 12). We also tested number of other primary amines like 9-amino-9-deoxyepicinchonidine **3i**, 9-amino-9-deoxyepiquinidine **3j**, 9-amino-9-deoxyepihydroquinine **3k** and 9-amino-9-deoxyepihydroquinidine **3l** as catalysts for the SMA reaction of **1** with **2a** in DCM solvent but results are no better compared to **3h**-catalysis (Table S1, see Supporting Information†).

With the optimized reaction conditions in hand, the scope of the amine-catalyzed asymmetric SMA reactions was investigated.[8] A series of substituted 2-(2-nitro-vinyl)-phenols **2a–k** were reacted with 14 equiv. of acetone **1** catalyzed by 10 mol% of **3h**/Ph_2CHCO_2H at 25 °C in DCM for 72 h followed by acetalization on crude products **4/5/6** with alcohols **7a–b** under *p*-TSA-catalysis at 25 °C for 2 h (Table 2). The chiral products **8aa**–**eb** and **9aa**–**eb** were obtained in a 1 : 1 ratio with excellent yields and ee's. Electronic factors had little influence: neutral, electron-withdrawing and electron-donating substituted 2-(2-nitro-vinyl)-phenols **2a–k** generated the expected products **8aa**–**eb** and **9aa**–**eb** in excellent yields and ee's (see Table 2). Fascinatingly, reaction of 1-(2-nitro-vinyl)-naphthalen-2-ol **2b** with acetone **1** under **3h**/Ph_2CHCO_2H-catalysis furnished the *cis*-chroman (+)-**5b** as the major product in 80% yield with 98% ee, which on further acetalization with methanol also furnished the *cis*-chroman (+)-**8ba** as the major product with 98% ee (Table 2, entry 2). The high stereoselectivity in the synthesis of *cis*-chromans (+)-**5b**/(+)-**8ba** can be explained using $A^{(1,3)}$-strain as highlighted by Johnson and Hoffman in their reviews.[9] Maybe due to $A^{(1,3)}$-strain, the relatively larger nitromethyl group in **5b**/**8ba** existed in the axial position in the cyclohexane conformation, which prevented another large group from approaching on the same side to minimize 1,3-*syn*-diaxial repulsions. Without showing much influence from kinetic factors, deuterated products (+)-**8ka–d**$_5$ and (–)-**9ka–d**$_5$ were furnished in 37% yield with 89% ee as shown in Table 2, entry 12. The structure and stereochemistry of SMA products **8aa**–**eb**/**9aa**–**eb** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (+)-**8ba**, (–)-**8ga** and (–)-**9ha** as shown in Figures S1 to S3 (see Supporting Information†).

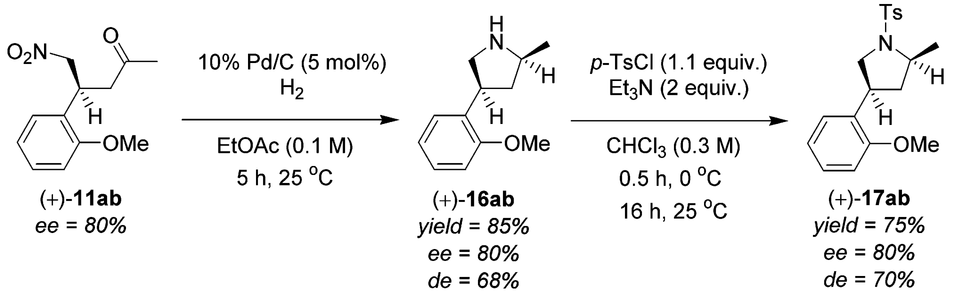
After successful demonstration of the **3h**/Ph_2CHCO_2H-catalyzed asymmetric SMA reactions of **1** with **2**, we decided to explore the utilization of δ-hydroxyketone↔lactol isomerization in the synthesis of functionalized chiral molecules *via* acid/base-catalysis in a sequential manner as shown in eqn (3). Reaction of pure δ-hydroxyketone↔lactol products (+)-**4a**/**5a**/**6a** with 20 mol% of *p*-TSA in toluene at 110 °C for 0.75 h furnished the selectively cyclized 2-methyl-4-nitromethyl-4*H*-chromene product (–)-**10a** in 86% yield with 81% ee as shown in eqn (3). Treatment of reaction intermediate (+)-**4a**/**5a**/**6a** with MOM–Cl (**a**) under DIPEA-catalysis in DCM at 0 °C→25 °C for 3.5 h furnished the selectively protected 4-(2-methoxymethoxy-phenyl)-5-nitro-pentan-2-one (–)-**11aa** in 90% yield with 82% ee as shown in eqn (3). In a similar manner, treatment of (+)-**4a**/**5a**/**6a** with MeI (**b**) under NaH in THF at 0 °C→25 °C for 5 h furnished the selectively protected 4-(2-methoxy-phenyl)-5-nitro-pentan-2-one (+)-**11ab** in 65% yield with 80% ee as shown in eqn (3).

With synthetic and pharmaceutical applications in mind, we further extended the application of acid-catalyzed lactonization



(3)

methodology to pure isolated δ-hydroxyketone↔lactol product (+)-**4a/5a/6a** under various conditions as shown in eqn (3). Interestingly, reaction of (+) - **4a/5a/6a** with 6 equiv. of methylenetriphenylphosphorane in benzene (0.1 M) at 25 °C for 3 h furnished the olefin phenol (−)-**12a** in 95% yield with 82% ee. Treatment of (−)-**12a** with 1.2 equiv. of iodine in DCM at



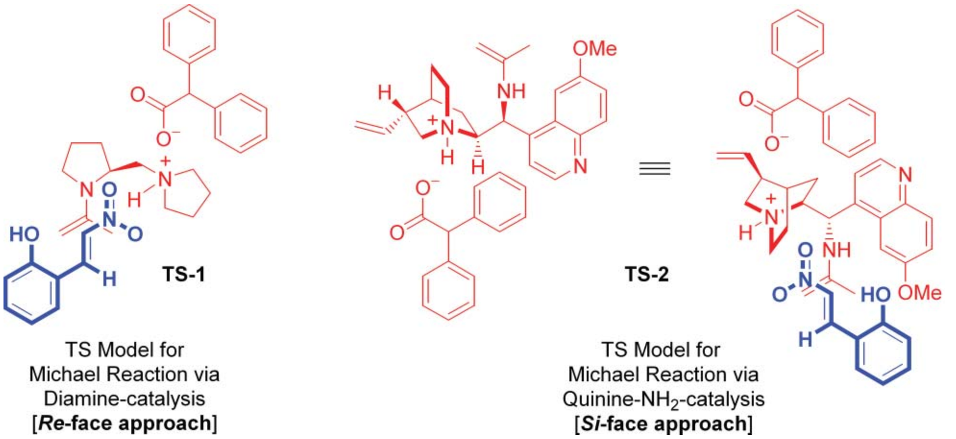
(4)

0 °C for 0.25 h furnished the selectively cyclized 2,2-dimethyl-4-nitromethyl-chroman product (–)-**13a** in 94% yield with 81% ee as shown in eqn (3). Hydrogenation of (–)-**13a** with 10% Pd/C in methanol at 25 °C for 5 h furnished the primary amine, which on protection with Boc_2O in DCM at 25 °C for 2 h furnished protected amine (–)-**14a** in 80% yield with 81% ee. In a similar manner, hydrogenation of (–)-**9aa** with 10% Pd/C in methanol at 25 °C for 5 h furnished the primary amine, which on protection with Boc_2O in DCM at 25 °C for 2 h furnished protected amine (–)-**15aa** in 91% yield with 81% ee. But interestingly, we did not observe hydrogenation reaction of the *cis*-isomer (+)-**8aa** under similar conditions as shown in eqn (3), possibly due to steric hindrance. Cascade hydrogenation–reductive amination of (+)-**11ab** with H_2 under Pd-catalysis followed by protection with *p*-TsCl under amine-catalysis furnished the stereoselectively substituted pyrrolidine-sulfonamide (+)-**17ab** in 64% overall yield with 80% ee and 70% de as shown in eqn (4). These reactions are ideal examples for the trapping of both forms of SMA products **4**/**5**/**6** from fast dynamic equilibrium as shown in eqn (3) and eqn (4).

Molecule (–)-**14a** and analogue (–)-**15aa** are important compounds as they have potent anti-ischemic properties, and as anti-hypertensives, spasmolytics for blood vessels and potassium channel blockers (**A**–**D**, see eqn (1)), which emphasizes the value of this SMA approach to the pharmaceuticals.[1] Also functionalized pyrrolidine-sulfonamide (+)-**17ab** and their analogues are useful drugs as modulators of serotonin 5HT6 receptors and dopamine D3 receptors for the treatment of CNS disorders.[1g] In addition, the disubstituted-2*H*-1-benzopyran structural unit (**14** and **15**) is found in many natural products and designed products which exhibit a wide range of biological activities.[2a]

Even though further studies are needed to firmly elucidate the mechanism of these asymmetric SMA reactions through **3h**/Ph_2CHCO_2H-catalysis, the reaction likely proceeds *via* an enamine mechanism (see eqn (5)). In the case of the addition of acetone to 2-(2-nitro-vinyl)-phenols **2** *via* diamine-catalysis (Table 1, entries 4–5), we can rationalize the observed stereochemistries through a favoured transition state where the 2-(2-nitro-vinyl)-phenol **2** approaches the enamine from the less hindered *Re* face as shown in **TS-1**. In the case of **3h**/Ph_2CHCO_2H-catalysis, the observed opposite selectivity may be explained by model **TS-2**, in which there are favourable electrostatic interactions between the partially positive nitrogen of the quinine and the partially negative nitro group, and also between the partially positive phenolic OH and the partially negative quinine OMe in the transition state (eqn (5)). The observed stereochemistries of the products **4** could be explained by approach of the nitro olefin from the less hindered *Si* face to the enamine as shown in **TS-2**.

In summary, first time we have developed the 9-amino-9-deoxyepiquinine **3h**/Ph_2CHCO_2H-catalyzed asymmetric SMA reaction of acetone with 2-(2-nitro-vinyl)-phenols under ambient conditions. The sequential asymmetric reaction proceeds in good yields with high selectivity using **3h**/Ph_2CHCO_2H as the catalyst. Furthermore, we have demonstrated the application of chiral δ-hydroxyketone↔lactol products **4**/**5**/**6** in the synthesis of highly functionalized chroman and pyrrolidine molecules. Further work is in progress to utilize chiral 2-hydroxy-2-methyl-4-nitromethyl-chromans as intermediates for the bio-active molecule synthesis.



TS Model for
Michael Reaction via
Diamine-catalysis
[***Re*-face approach**]

TS Model for
Michael Reaction via
Quinine-NH_2-catalysis
[***Si*-face approach**]

(5)

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Notes and references

1 (*a*) S. R. Trenor, A. R. Shultz, B. J. Love and T. E. Long, *Chem. Rev.*, 2004, **104**, 3059–3077; (*b*) S. A. Buckner, I. Milicic, A. Daza, R. Davis-Taber, V. E. S. Scott, J. P. Sullivan and J. D. Brioni, *Eur. J. Pharmacol.*, 2000, **400**, 287–295; (*c*) A. Coi, A. M. Bianucci, V. Calderone, L. Testai, M. Digiacomo, S. Rapposelli and A. Balsamo, *Bioorg. Med. Chem.*, 2009, **17**, 5565–5571; (*d*) M. C. Breschi, V. Calderone, A. Martelli, F. Minutolo, S. Rapposelli, L. Testai, F. Tonelli and A. Balsamo, *J. Med. Chem.*, 2006, **49**, 7600–7602; (*e*) A. Widdig, H. J. Kabbe, A. Knorr and U. Benz, *Ger. Offen.*, 1984, 77, DE 3300004 A1 19840712 (*Chem. Abstr.*, 1984, **102**, 6203) (patent written in German); (*f*) S. Khelili, X. Florence, M. Bouhadja, S. Abdelaziz, N. Mechouch, Y. Mohamed, P. D. Tullio, P. Lebrun and B. Pirotte, *Bioorg. Med. Chem.*, 2008, **16**, 6124–6130; (*g*) R. Grandel, W. M. Braje, A. Haupt, S. C. Turner, U. Lange, K. Drescher, L. Unger and D. Plata, *PCT Int. Appl.*, 2007, 113, WO 2007118899 A1 20071025 (*Chem. Abstr.*, 2007, **147**, 486320) (patent written in English).

2 (*a*) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939–9953 and references therein; (*b*) B. Lesch and S. Braese, *Angew. Chem., Int. Ed.*, 2004, **43**, 115–118; (*c*) L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith and C. Große, *Chem.–Eur. J.*, 2008, **14**, 8956–8963; (*d*) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.*, 2009, **11**, 1627–1630; (*e*) H. Li, J. Wang, T. E-Nunu, L. Zu, W. Jiang, S. Wei and W. Wang, *Chem. Commun.*, 2007, 507–509; (*f*) M. M. Biddle, M. Lin and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 3830–3831.

3 For recent papers on sequential Michael and lactonization reactions, see: (*a*) S. Belot, K. A. Vogt, C. Besnard, N. Krause and A. Alexakis, *Angew. Chem., Int. Ed.*, 2009, **48**, 8923–8926; (*b*) M. Rueping, E. Merino and E. Sugiono, *Adv. Synth. Catal.*, 2008, **350**, 2127–2131; (*c*) P. Buchgraber, T. N. Snaddon, C. Wirtz, R. Mynott, R. Goddard and A. Fürstner, *Angew. Chem., Int. Ed.*, 2008, **47**, 8450–8454.

4 For selected recent papers on enamine-based Michael reaction of carbonyl compounds with β-nitrostyrenes, see: (*a*) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260–5267; (*b*) J. M. Betancort, K. Sakthivel, R. Thayumanavan and C. F. Barbas III, *Tetrahedron Lett.*, 2001, **42**, 4441–4444; (*c*) J. M. Betancort and C. F. Barbas III, *Org. Lett.*, 2001, **3**, 3737–3740; (*d*) B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423–2425; (*e*) N. Mase, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2004, **6**, 2527–2530; (*f*) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Synthesis*, 2004, 1509–1521; (*g*) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw and S. V. Ley, *Chem. Commun.*, 2004, 1808–1809; (*h*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212–4215; (*i*) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861–863; (*j*) P. García-García, A. Ladépêche, R. Halder and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 4719–4721; (*k*) P. Dinér, A. Kjærsgaard, M. A. Lie and K. A. Jørgensen, *Chem.–Eur. J.*, 2008, **14**, 122–127; (*l*) X. Zhu, F. Tanaka, R. A. Lerner, C. F. Barbas III and I. A. Wilson, *J. Am. Chem. Soc.*, 2009, **131**, 18206–18207; (*m*) H. Uehara and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2009, **48**, 9848–9852.

5 For the fast dynamic equilibrium between lactol and δ-hydroxyketone, see: (*a*) N. Halland, T. Hansen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4955–4957; (*b*) D. B. Ramachary and R. Sakthidevi, *Chem.–Eur. J.*, 2009, **15**, 4516–4522.

6 For selected recent papers on multi-catalysis cascade (MCC) reactions, see: (*a*) D. B. Ramachary, Y. V. Reddy and B. V. Prakash, *Org. Biomol. Chem.*, 2008, **6**, 719–726; (*b*) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2008, **6**, 2488–2492; (*c*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4176–4187; (*d*) D. B. Ramachary, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4188–4197; (*e*) D. B. Ramachary and Y. V. Reddy, *J. Org. Chem.*, 2010, **75**, 74–85.

7 For selected recent papers on 9-amino-9-deoxyepiquinine **3h**-catalyzed asymmetric reactions, see: (*a*) C. M. Reisinger, X. Wang and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 8112–8115; (*b*) M. W. Paixao, N. Holub, C. Vila, M. Nielsen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2009, **48**, 7338–7342; (*c*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2010, **8**, 2859–2867 and references therein.

8 For organocatalytic synthesis of substituted 2-(2-nitro-vinyl)-phenols **2a–k** and racemic products **8aa**–**eb** and **9aa**–**eb** in good yields, see Tables S2–S3 in Supporting Information.

9 For excellent reviews on A$^{(1,3)}$-strain, see: (*a*) F. Johnson, *Chem. Rev.*, 1968, **68**, 375–413; (*b*) R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841–1860.