

# A general approach to high-yielding asymmetric synthesis of chiral 3-alkyl-4-nitromethylchromans *via* cascade Barbas–Michael and acetalization reactions†

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A general approach to the high-yielding asymmetric synthesis of chiral 3-alkyl-4-nitromethylchromans as drug intermediates was achieved through cascade Barbas–Michael and acetalization (BMA) reactions on 2-(2-nitrovinyl)phenols with aldehydes in the presence of a catalytic amount of (*R*)-DPPOTMS and PhCO<sub>2</sub>H. Herein, we have also demonstrated the application of chiral BMA products in the synthesis of functionalized chromanes and chromenes in very good yields with high optical purity, which are very useful compounds in medicinal chemistry.

## Introduction

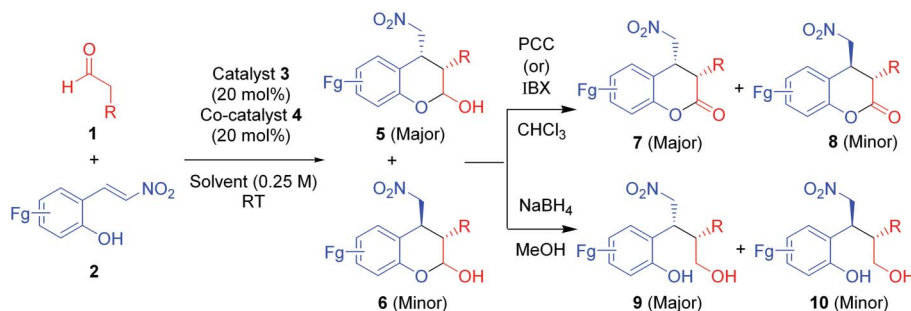
Chromanes and chromenes are important classes of the benzopyran structural unit found in many natural products and are widely used as drug intermediates and ingredients in pharmaceuticals.<sup>1</sup> Chiral benzopyran represents a privileged structural unit that is available in a range of natural products and drug molecules with vast biological applications. Thus, it is very much urgent to develop sustainable asymmetric strategies to construct optically pure chromans and chromenes.<sup>2</sup> Interestingly, to the best of our knowledge there is no report on the direct catalytic asymmetric method for the synthesis of chiral 3-alkyl-4-nitromethylchromans. Herein, we are reporting the metal-free approach to the asymmetric synthesis of functionalized 3-alkyl-4-nitromethylchroman-2-ols and 3-alkyl-

4-nitromethylchroman-2-ones *via* cascade “Barbas–Michael and acetalization (BMA) reactions”.<sup>3</sup>

Recently Barbas *et al.* discovered the modern technology of amine-catalyzed Michael reactions of ketones/aldehydes with variety of active olefins to provide a variety of Michael adducts in good yields with high enantioselectivity, which has become the “Barbas–Michael reaction”.<sup>4</sup> The advent of this bio-mimetic enamine based technology triggered a burst of activity in the synthesis of a huge variety of chiral pool of 1,4-adducts.<sup>4</sup>

However, the amine-catalyzed Michael reaction of aldehydes **1** with 2-(2-nitrovinyl)phenols **2** was not known and resulting products **5/6** have a wide range of uses in pharmaceutical chemistry (see Scheme 1) and also there is no methodology available to prepare even achiral compounds **5/6**.<sup>5</sup> Herein, we have reported a metal-free technology for the asymmetric synthesis of substituted 3-alkyl-4-nitromethylchroman-2-ols **5/6**, 3-alkyl-4-nitromethylchroman-2-ones **7/8** and 2-(3-hydroxy-2-alkyl-1-nitromethylpropyl)phenols **9/10** by using organocatalytic BMA, oxidation and reduction reactions from easily available aldehydes **1**, 2-(2-nitrovinyl)phenols **2**, amines **3**, acids **4**, PCC or IBX and NaBH<sub>4</sub> (Scheme 1).

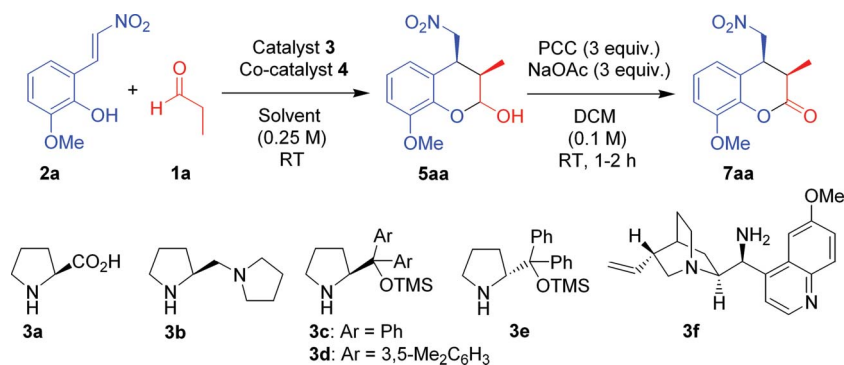
In a continuation of our investigation for new reactive species for the development of green asymmetric cascade reactions,<sup>6</sup>



Scheme 1 Direct organocatalytic asymmetric cascade BMA reactions.

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† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS and HPLC) for all new compounds. CCDC reference number 795663. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00861c

**Table 1** Reaction optimization for the cascade BMA reaction of **1a** and **2a**

Entry	Catalyst 3/4 (20/20 mol%)	Solvent (0.25 M)	Time (h)	Product yield (%) <sup>a</sup>		ee (%) <sup>b</sup>		de (%) <sup>b</sup>	
				<b>5aa</b>	<b>7aa</b>	<b>7aa</b>	<b>7aa</b>		
1	<b>3a</b>	DMSO	8	52	50	31	90		
2	<b>3b</b> /PhCO <sub>2</sub> H <b>4a</b>	DCM	4	70	50	46	63		
3	<b>3c</b>	Hexane	10	76	63	97	88		
4	<b>3c</b> / <b>4a</b>	Hexane	18	93	63	99	95		
5	<b>3c</b> / <b>4a</b>	Et <sub>2</sub> O	4	65	50	87	66		
6	<b>3c</b> / <b>4a</b>	Toluene	4	60	50	96.7	81		
7	<b>3c</b> /MeCO <sub>2</sub> H <b>4b</b>	DCM	2	92	50	97	69		
8	<b>3c</b> /Ph <sub>2</sub> CHCO <sub>2</sub> H <b>4c</b>	DCM	2	80	40	97.8	66		
9	<b>3c</b> / <b>4a</b>	<b>DCM</b>	<b>1</b>	<b>89</b>	<b>65</b>	<b>98</b>	<b>82</b>		
10	<b>3d</b> / <b>4a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	2	87	50	96.6	76		
11	<b>3d</b> / <b>4a</b>	DCM	2	87	50	98	79		
12	<b>3e</b> / <b>4a</b>	<b>DCM</b>	<b>1</b>	<b>96</b>	<b>60</b>	<b>-99.9</b>	<b>95</b>		
13 <sup>c</sup>	<b>3e</b> / <b>4a</b>	<b>DCM</b>	<b>0.5</b>	<b>95</b>	<b>70</b>	<b>-99.9</b>	<b>93</b>		
14	<b>3f</b> / <b>4a</b>	DCM	24	72	50	-87	43		
15	<b>3f</b> / <b>4a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	36	70	50	-85	32		

<sup>a</sup> Yield refers to the column-purified product. <sup>b</sup> ee and de determined by CSP HPLC analysis. <sup>c</sup> Oxidation was carried out with 1.5 equiv. of IBX in CHCl<sub>3</sub> at 65 °C for 15–24 h.

we decided to explore the 2-(2-nitrovinyl)phenols **2** as an active olefin in an amine-catalyzed BMA reaction with aldehydes **1**. We thought that the reaction of 2-(2-nitrovinyl)phenols **2** with *in situ*-generated enamine from aldehydes **1** would lead to 3-(2-hydroxyphenyl)-2-alkyl-4-nitrobutyraldehydes. However, Michael adducts were not detected and instead it has shown the completely cyclized lactol product of 3-alkyl-4-nitromethylchroman-2-ols **5/6** under the standard reaction conditions. This interesting result represents a novel tool for the preparation of chiral lactols **5/6** and a new reactivity for amine catalysts. Herein, we report our findings regarding these new cascade asymmetric reactions.

## Results and discussion

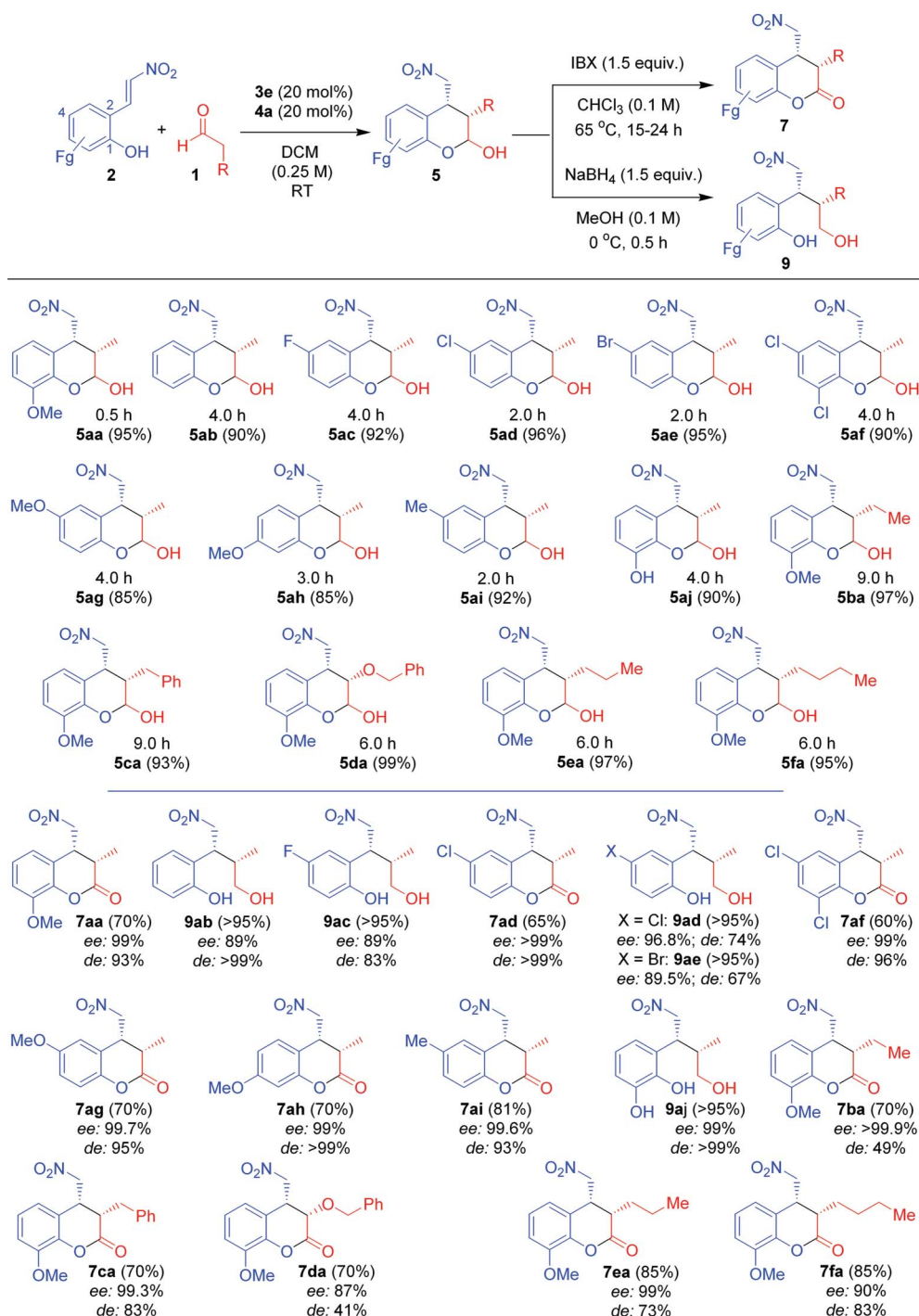
### Direct amine-catalyzed asymmetric cascade BMA reaction of propionaldehyde with 2-methoxy-6-(2-nitrovinyl)phenol: reaction optimization

For the optimization of designed BMA reaction, we screened a number of organocatalysts for the reaction of 2-methoxy-6-(2-nitrovinyl)phenol **2a** with 10 equiv. of propionaldehyde **1a** and some important results are shown in Table 1. Interestingly, reaction of **2a** with 10 equiv. of **1a** in DMSO under 20 mol% of L-proline **3a**-catalysis furnished the 1 : 1 ratio of *cis*-lactol/*trans*-lactol of major product *syn*-**5aa** in 52% yield with 31% ee and 90% de along with minor isomer *anti*-**6aa** (see Scheme 1 and Table 1, entry 1). For the clear understanding of diastereoselectivity between **5aa** and **6aa**;

and also for the clear HPLC separation, we transformed the crude product **5aa/6aa** into two easily separable products *cis*-**7aa** and *trans*-**8aa** with 50% yield *via* PCC oxidation in DCM at 25 °C for 1–2 h (see Table 1). In a further optimization, reaction of **1a** and **2a** in DCM under 20 mol% of diamine/PhCO<sub>2</sub>H **3b/4a**-catalysis followed by PCC oxidation furnished the major product *cis*-(-)-**7aa** in 50% yield with only 46% ee and 63% de (Table 1, entry 2). Interestingly, reaction of **1a** with **2a** in hexane under 20 mol% of (*S*)- $\alpha,\alpha$ -diphenylprolinol trimethylsilyl ether (L-DPPOTMS) **3c**-catalysis at 25 °C for 10 h furnished the lactols **5aa/6aa** in 76% yield, which on further oxidation with PCC furnished the major product *cis*-(-)-**7aa** in 63% yield with 97% ee and 88% de (Table 1, entry 3). The same reaction under 20 mol% of L-DPPOTMS/PhCO<sub>2</sub>H **3c/4a**-catalysis in hexane for 18 h furnished the lactols **5aa/6aa** in 93% yield, which on further PCC oxidation furnished the major product *cis*-(-)-**7aa** in 63% yield with 99% ee and 95% de (Table 1, entry 4).

To further improve the asymmetric BMA reaction, especially for decreasing the reaction time to <1 h and increasing the ee/de to >99.9%, we tested the BMA reaction of **1a** and **2a** catalyzed by **3c** and **3d** with different acids **4a–c** as co-catalysts in various solvents. But none of these results are superior compared to entry 4 except in decreasing the reaction time (Table 1, entries 5–11). Interestingly, cascade BMA reaction of **1a** with **2a** in DCM under 20 mol% of D-DPPOTMS/PhCO<sub>2</sub>H **3e/4a**-catalysis at 25 °C for 1 h furnished the lactols **5aa/6aa** in 96% yield, which on further oxidation with PCC furnished the major product *cis*-(+)-**7aa** in

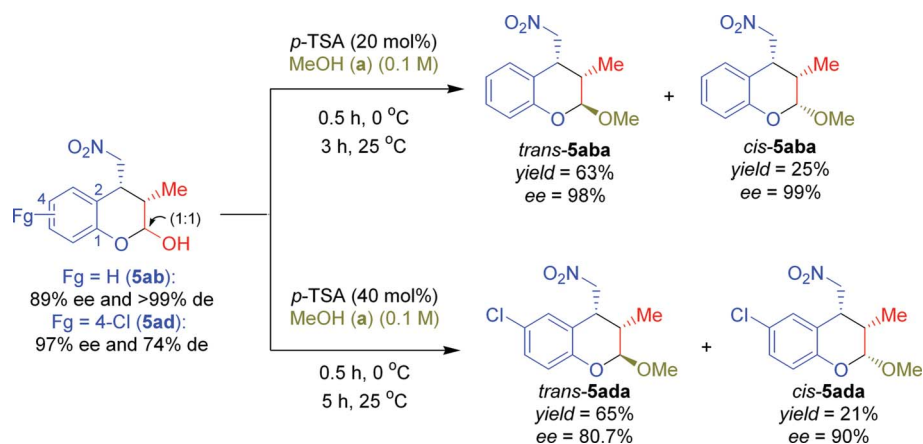
**Table 2** High-yielding synthesis of chiral *BMA* products **5**, **7** and **9**<sup>abc</sup>



<sup>a</sup> Reactions were carried out in DCM (0.25 M) with 10 equiv. of **1a** or 1.5 equiv. of **1b–f** relative to the **2a–j** (0.5 mmol) in the presence of 20 mol% of catalyst **3e/4a**. <sup>b</sup> Yield refers to the column-purified product. <sup>c</sup> ee and de were determined by CSP HPLC analysis (see SI†).

60% yield with 99.9% ee and 95% de (Table 1, entry 12). The yield of the oxidation product *cis*-(+)-**7aa** was improved by treating crude **5aa/6aa** with 1.5 equiv. of IBX in CHCl<sub>3</sub> at 65 °C for 15–24 h as shown in Table 1, entry 13. After successful results with chiral D-DPPOTMS **3e** as a catalyst, we were interested in screening alkaloid based primary amines like 9-amino-9-deoxyepiquinine **3f** as the catalyst for the *BMA* reaction to monitor the outcome of

selectivity (Table 1, entries 14–15).<sup>7</sup> Interestingly, *BMA* reaction of **2a** with 10 equiv. of **1a** under 20 mol% of **3f/4a**-catalysis in DCM or toluene for 24/36 h, followed by oxidation, furnished the major product *cis*-(+)-**7aa** in 50% yield with only 87/85% ee and 43/32% de, respectively (Table 1, entries 14–15). Finally we envisioned the optimized condition to be 25 °C in DCM under 20 mol% of D-DPPOTMS/PhCO<sub>2</sub>H **3e/4a**-catalysis followed by IBX



**Scheme 2** Synthesis of chromanes with three contiguous stereocenters.

oxidation to furnish the highly substituted cascade BMA product *cis*-(+)-**7aa** in 70% yield with 99.9% ee and 93–95% de (Table 1, entry 13). Structure and absolute stereochemistry of cascade BMA products **5aa/6aa** and **7aa/8aa** was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (–)-**7aa** as shown in Figure S1 (see Supporting Information†).<sup>8</sup>

#### Diversity-oriented synthesis of chiral BMA products 5–9

With the optimized reaction conditions in hand, the scope of the amine-catalyzed asymmetric cascade BMA reactions was investigated.<sup>9</sup> A series of substituted 2-(2-nitrovinyl)phenols **2a–j** were reacted with 10 equiv. of propionaldehyde **1a** catalyzed by 20 mol% of **3e/4a** at 25 °C in DCM, for 0.5–4 h, to furnish chiral cascade BMA products **5aa–aj** with very good yields, ee's and de's, which on further oxidation with IBX or reduction with NaBH<sub>4</sub>, furnished the products **7** and **9**, respectively (Table 2).<sup>10</sup> The chiral cascade products **5aa–aj**, **7aa–aj** and **9aa–aj** were obtained as major isomers with excellent yields, ee's and de's. Without showing much of electronic factors, neutral, electron-withdrawing and electron-donating substituted 2-(2-nitrovinyl)phenols **2a–j** generated expected products **5aa–aj**, **7aa–aj** and **9aa–aj** with excellent yields, ee's and de's (see Table 2). Fascinatingly, reaction of 2-(2-nitrovinyl)phenol **2b** with propionaldehyde **1a** under **3e/4a**-catalysis furnished the *cis*-lactol (+)-**5ab** as the major product in 90% yield, which on further reduction with NaBH<sub>4</sub> furnished the diol (+)-**9ab** as the major product with >95% yield with 89% ee and >99% de (Table 2, entry 2). In a similar manner, 2-methoxy-6-(2-nitrovinyl)phenol **2a** was reacted with a series of aldehydes **1b–f**, catalyzed by 20 mol% of **3e/4a** at 25 °C in DCM for 6–9 h, to furnish chiral cascade BMA products **5ba–fa** with very good yields, ee's and de's, which on further oxidation with IBX or reduction with NaBH<sub>4</sub>, furnished the products **7ba–fa** and **9ba–fa**, respectively (Table 2). Structure and stereochemistry of BMA products **5aa–fa**, **7aa–fa** and **9aa–fa** was confirmed by NMR analysis.

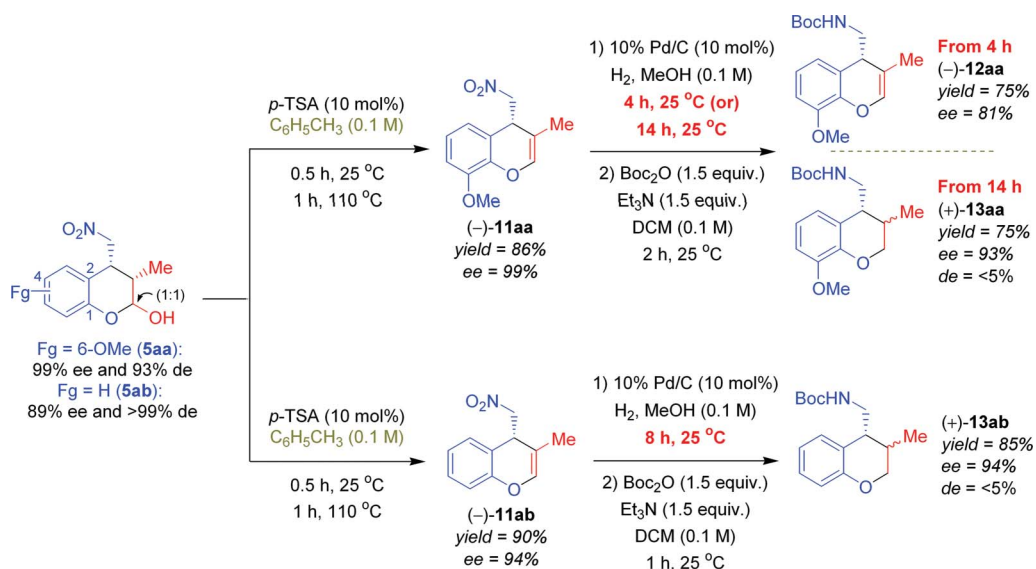
#### Applications of chiral BMA products

**Synthesis of functionalized chiral chromanes and chromenes based on the BMA platform.** With synthetic and pharmaceutical applications in mind, we decided to explore the utilization of *cis*-

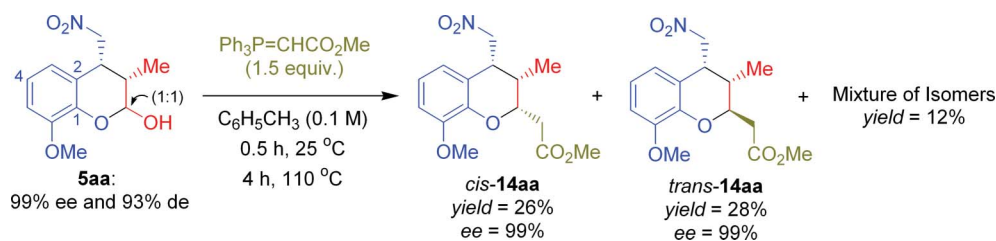
lactols **5** in the synthesis of functionalized chiral chromanes and chromenes *via* acid-catalysis as shown in Schemes 2–4. Reaction of pure lactol (+)-**5ab** with 20 mol% of *p*-TSA in polar protic solvent of MeOH (**a**) at 0 °C for 0.5 h, and 25 °C for 3 h, furnished the cyclized 2-methoxy-3-methyl-4-nitromethylchromane *trans*-(–)-**5aba** in 63% yield with 98% ee and *cis*-(+)-**5aba** in 25% yield with 99% ee as shown in Scheme 2. In a similar manner, reaction of (+)-**5ad** with 40 mol% of *p*-TSA in MeOH (**a**) at 0 °C for 0.5 h, and 25 °C for 5 h, furnished the cyclized 6-chloro-2-methoxy-3-methyl-4-nitromethylchromane *trans*-(–)-**5ada** in 65% yield with 81% ee and *cis*-(+)-**5ada** in 21% yield with 90% ee as shown in Scheme 2. Interestingly, isomers of chiral chromanes *cis*-**5aba–ada**/*trans*-**5aba–ada** containing three contiguous stereocenters are easily separated from simple column chromatography and also diversity-oriented synthesis of these chiral chromanes could be obtained from sequential one-pot operation for synthetic applications.

Interestingly, a similar type cyclization reaction on *cis*-lactol (+)-**5aa** with 5–10 mol% of *p*-TSA in nonpolar aprotic solvent of toluene at 110 °C for 1 h furnished the selectively cyclized 8-methoxy-3-methyl-4-nitromethyl-4*H*-chromene (–)-**11aa** in 86% yield with 99% ee as shown in Scheme 3. Hydrogenation of (–)-**11aa** with 10% Pd/C in methanol at 25 °C for 4 h followed by base-induced Boc<sub>2</sub>O protection furnished the partially hydrogenated amine (–)-**12aa** in 75% yield with 81% ee. The same hydrogenation on (–)-**11aa** for a longer reaction time (14 h) followed by base-induced Boc<sub>2</sub>O protection furnished the completely hydrogenated amine (+)-**13aa** in 75% yield with <5% de and each 93% ee as shown in Scheme 3. In a similar manner, reaction of *cis*-lactol (+)-**5ab** with 10 mol% of *p*-TSA in toluene at 110 °C for 1 h furnished the selectively cyclized 3-methyl-4-nitromethyl-4*H*-chromene (–)-**11ab** in 90% yield with 94% ee as shown in Scheme 3. Double hydrogenation of (–)-**11ab** with 10% Pd/C in methanol at 25 °C for 8 h followed by base-induced Boc<sub>2</sub>O protection furnished the completely hydrogenated amine (+)-**13ab** in 85% yield with <5% de and 94% ee as shown in Scheme 3.

As illustrated in Scheme 4, highly functionalized chromane acetates containing three contiguous stereocenters could be produced through cascade Wittig reaction followed by intramolecular oxa-Michael addition (W/OM) on the BMA compound of (+)-**5aa** with Ph<sub>3</sub>P=CHCO<sub>2</sub>Me. The two isomers *cis*-**14aa** and *trans*-**14aa** were furnished in 26% yield with 99% ee and 28% yield with 99% ee, respectively, as shown in Scheme 4.



**Scheme 3** Synthesis of chiral chromenes and their applications.



**Scheme 4** Synthesis of chiral chromane acetates *via* cascade W/OM reactions on BMA products.

Structure and stereochemistry of cascade W/OM products **14aa** was confirmed by NMR analysis and also finally confirmed by <sup>1</sup>H-<sup>1</sup>H COSY analysis on (+)-*cis*-**14aa** (see Supporting Information†). Functionalized chiral methyl chromane acetates **14** could be suitable starting materials for the synthesis of vitamin E analogues.

Compounds (-)-**5ada**, (-)-**12aa** and (+)-**13aa** are drug-like molecules; these types of molecules are used for the treatment of potent anti-ischemic property, anti-hypertensives, spasmolytics for blood vessels and also as potassium channel blockers, which emphasizes the value of this BMA approach to pharmaceuticals.<sup>1</sup> In addition, the presently discovered cascade BMA technology will be suitable to develop the substituted benzopyran structural unit, which is found in many natural products and designed drug molecules.<sup>2a</sup>

### Mechanistic insights

Although further studies are needed to firmly elucidate the mechanism of the phenol group involvement in an asymmetric BMA reaction through **3e/4a**- or **3f/4a**-catalysis, the reaction most likely proceeds *via* an enamine mechanism (see Fig. 1). In the case of the addition of aldehydes **1a-f** to substituted 2-(2-nitrovinyl)phenols **2a-j** *via* D-DPPOTMS/PhCO<sub>2</sub>H **3e/4a**-catalysis, we can rationalize the observed stereochemistries through a favoured transition state where the less hindered *re*-face of **2a-j** approaches the *re*-face of enamine as shown in **TS-1**. In the case of **3f/4a**-catalysis, the observed similar enantioselectivity and poor diastereoselectivity may be explained by model **TS-2**, in which there are favourable

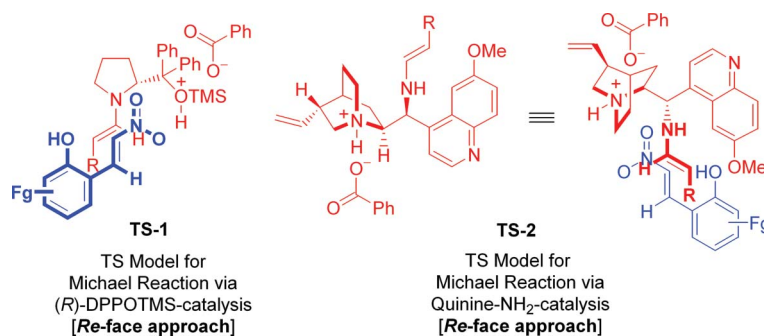
electrostatic interactions between the partially positive nitrogen of the quinone and the partially negative nitro group, and also between the partially positive phenolic OH and the partially negative quinone OMe in the transition state (Fig. 1). The observed stereochemistries of the products **5** could be explained by approach of the **2a-j** from the less hindered *re*-face to the *re*- or *si*-face of enamine as shown in **TS-2**.

### Conclusions

In summary, we have developed the D-DPPOTMS/PhCO<sub>2</sub>H **3e/4a**-catalyzed asymmetric cascade BMA reaction of aldehydes with 2-(2-nitrovinyl)phenols at ambient conditions. The cascade asymmetric reaction proceeds in very good yields with high selectivity using **3e/4a** as the catalyst. Furthermore, we have demonstrated the application of chiral lactol products **5** in the synthesis of functionalized chromanes and chromenes, which are very useful compounds in medicinal chemistry. Further work is in progress to utilize chiral lactols **5** as intermediates for the bio-active molecules synthesis.

### Experimental

**General methods.** The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (δ = 0) for <sup>1</sup>H NMR and relative to the central CDCl<sub>3</sub> resonance (δ = 77.0) for <sup>13</sup>C NMR. *In the <sup>13</sup>C NMR spectra, the nature of the carbons*



**Fig. 1** Proposed transition states for the cascade BMA reactions.

(C, CH, CH<sub>2</sub> or CH<sub>3</sub>) was determined by recording the DEPT-135 experiment, and is given in parentheses. The coupling constants *J* are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GC-MS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. LC-MS mass spectra were recorded on either a VG7070H mass spectrometer using EI technique or a Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-K $\alpha$  ( $\lambda = 0.71073$  Å) radiation with CAD4 software, or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K $\alpha$  fine-focus sealed tube ( $\lambda = 0.71073$  Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H<sub>2</sub>SO<sub>4</sub> (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

**Materials.** All solvents and commercially available chemicals were used as received.

#### General experimental procedures for the cascade BMA reactions

**General procedure for amine-catalyzed asymmetric cascade BMA reaction of aldehydes 1 with 2-(2-nitrovinyl)phenols 2.** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of D-DPPOTMS **3e** (0.1 mmol) and PhCO<sub>2</sub>H **4a** (0.1 mmol) in DCM (2.0 mL), was added propionaldehyde **1a** (5.0 mmol, 10 equiv.) or aldehydes **1b–f** (0.75 mmol, 1.5 equiv.) and 2-(2-nitrovinyl)phenols **2a–j** (0.5 mmol). After stirring the reaction mixture at 25 °C as shown in Tables 1–2, the crude reaction mixture was worked up with aqueous NH<sub>4</sub>Cl solution and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Pure chiral products **5/6** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

**General procedure for the oxidation of cascade BMA products with IBX.** In an oven dried round bottom flask, to the lactol **5/6** (0.3 mmol), added dry CHCl<sub>3</sub> (3.0 mL), and IBX (0.45 mmol,

1.5 equiv.). After stirring the reaction mixture at 65 °C for 15–24 h, it was brought to 25 °C and the crude reaction mixture was passed through a pad of celite and concentrated to dryness. Pure chiral products **7** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

#### General procedure for the reduction of cascade BMA products.

In an oven dried round bottom flask, to the lactol **5/6** (0.3 mmol), dry MeOH (3.0 mL), and NaBH<sub>4</sub> (0.45 mmol, 1.5 equiv.) was added. After stirring the reaction mixture at 0 °C for 0.5 h, it was brought to 25 °C and the crude reaction mixture was worked up with aqueous NH<sub>4</sub>Cl solution. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Pure chiral products **9** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

#### Bronsted acid-catalyzed hydrolysis of cascade BMA products.

In an oven dried round bottom flask, to the lactol **5/6** (0.3 mmol), dry toluene (3.0 mL), and *p*-TSA·H<sub>2</sub>O (3.5 mg, 10 mol%) was added. After heating the reaction mixture to 110 °C for 1 h, it was brought to 25 °C and the crude reaction mixture was worked up with aqueous NaHCO<sub>3</sub> solution. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Pure chiral products **11** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

**Hydrogenation followed by protection of nitro products.** In an oven dried round bottom flask, activated (10%) Pd/C (7 mg, 10 mol%) was taken with compound (–)-**11aa** (0.3 mmol), dissolved in dry MeOH (3.0 mL) and stirred under H<sub>2</sub> atmosphere at 25 °C for 4 or 14 h. The reaction mixture was passed through a pad of celite and concentrated to dryness. The crude mixture was taken in a dry oven dried round bottom flask in dry DCM (3.0 mL) and dry triethylamine (60  $\mu$ L, 0.4 mmol) and di-*tert*-butyl carbonate (86 mg, 0.4 mmol) was successively at 0 °C. The resulting mixture was stirred at 25 °C for 2 h and then worked up with aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Pure product (–)-**12aa** or (+)-**13aa** was obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

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- CCDC-795663 for (–)-**7aa** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or <mailto:deposit@ccdc.cam.ac.uk>. See supporting information for crystal structure†.
- For organocatalytic synthesis of substituted 2-(2-nitrovinyl)phenols **2a–j**, see: D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2010, **8**, 4259–4265.
- For organocatalytic high-yielding synthesis of racemic products **5aa–fa**, **7aa–fa** and **9aa–fa** from **1a–f** and **2a–j** through DL-proline-catalysis, see Table S1 in Supporting Information-I.† For, the *ee* and *de*'s of minor compounds **6/8/10**, see Supporting Information-I and II†.