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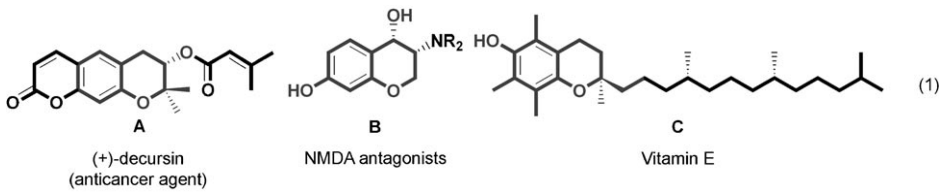
Direct Catalytic Asymmetric Synthesis of Highly Functionalized 2-Methylchroman-2,4-diols via Barbas–List Aldol Reaction

Dhevalapally B. Ramachary* and Rajasekar Sakthidevi[a]

Chromanes and chromenes are an important class of heterocycles, which display a very large spectrum of biological activities and are widely used as drug intermediates and ingredients in pharmaceuticals [see Eq. (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-methylchroman-2,4-diols, which can serve as good intermediates for the functionalized chromanes and chromenes. Herein, we reported for the first time the organocatalytic approach to the asymmetric synthesis of functionalized 2-methylchroman-2,4-diol products via "Barbas–List aldol reactions".[3]



(1)

Recently Barbas, List and co-workers discovered the novel technology of amino acid catalyzed intermolecular aldol reactions of ketones/aldehydes with a variety of carbonyls to provide a general route to several diverse aldol products in good yields with high enantioselectivity, which is known as the Barbas–List aldol (BLA) reaction.[3] The advent of amino acid catalyzed aldol reaction technology triggered a burst of activity in the synthesis of a huge variety of chiral pool of aldol products through biomimetic enamine chemistry thus providing a high potential for the development of cellular-type cascade reactions.[4]

The amino acid catalyzed aldol reaction of ketones/aldehydes **1** with functionalized 2-hydroxybenzaldehydes **2** has not been described thus far although the resulting aldol products **4** and **5** have a wide range of potential applications in pharmaceutical chemistry [see Eq. (1) and (2)]; also, there is no direct methodology available to date to prepare these compounds by classical reaction strategies. We report herein a metal-free, novel and green technology for the synthesis of highly substituted 2-methylchroman-2,4-diols **5** using organocatalytic BLA reactions from commercially available 2-hydroxybenzaldehydes **2**, ketones **1** and amines/amino acid **3** [Eq. (2)]. We describe the existence of fast dynamic equilibrium between 2-methylchroman-2,4-diols [lactol] **5** and 4-hydroxy-4-(2-hydroxyphenyl)-butan-2-one [δ-hydroxyketone] **4** under the normal reaction conditions.[5]

Over the last few years, we have been interested in amine/amino acid mediated multicatalysis reactions from multiple components and multiple catalysts for the generation of highly functionalized molecules via C–C, C–H, C–O and C–N bonds formation in one-pot reactions.[6] During our investigations of new reactive species for such multicatalytic processes, we decided to explore the potential ability of 2-hydroxybenzaldehydes **2** to participate in an amine/amino acid catalyzed BLA reaction with acetone **1a**. We expected that the reaction of 2-hydroxybenzaldehyde **2a** with in situ generated enamine from acetone **1a** would lead to 4-hydroxy-4-(2-hydroxyphenyl)butan-2-one (**4aa**). However, aldol product **4aa** was not only detected; instead product **4aa** showed the existence of a fast dynamic equilibrium with 2-methylchroman-2,4-diol **5aa** under standard reaction conditions. This unexpected result represents a novel methodol-

[a] Prof. Dr. D. B. Ramachary, R. Sakthidevi
School of Chemistry, University of Hyderabad
Hyderabad 500046 (India)
Fax: (+91) 40-23012460
E-mail: ramsc@uohyd.ernet.in

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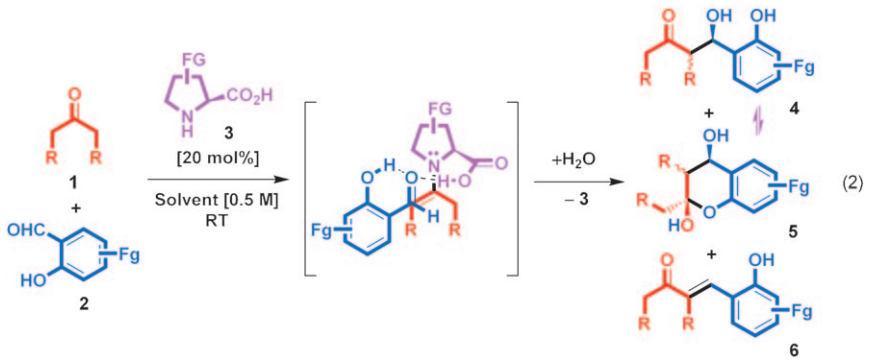


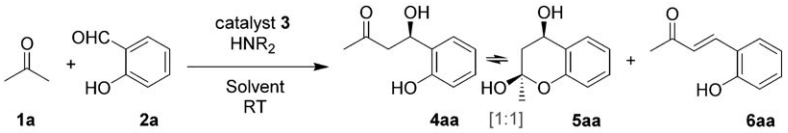
ogy for the preparation of 2-methylchroman-2,4-diols and a new reactivity for amino acid catalysts. Herein, we report our results of these new BLA reactions.

We started our original studies on the BLA reactions by screening a number of known and novel organocatalysts for the aldolization of 2-hydroxybenzaldehyde **2a** by 14 to 28 equivalents of acetone **1a**. A few representative results are shown in Table 1. Interestingly, reaction of **2a** with 28 equiv of acetone **1a** in DMF under 20 mol% of L-proline (**3a**) catalysis furnished a 1:1 ratio of the aldol↔lactol product **4aa/5aa** in 50% yield with only 17% *ee* and byproduct enone **6aa** in 20% yield (Table 1, entry 1). The same reaction in DMSO with 20 mol% of **3a** also furnished a 1:1 ratio of aldol↔lactol product **4aa/5aa** in 50% yield with only 19% *ee* and enone **6aa** in 30% yield (Table 1, entry 2). Reaction of **2a** with 28 equiv of **1a** in *N*-methylpyrrolidone (NMP) with 20 mol% **3a** furnished a 1:1 ratio of **4aa/5aa** in 50% yield with increased an (36%) *ee* value and enone **6aa** in 20% yield (Table 1, entry 3). Reaction of **2a** with 14 equiv of **1a** with 20 mol% D- **3a** in NMP for 38 h furnished the 1:1 ratio of **4aa/5aa** in 60% yield with decreased (11%) *ee* and byproduct **6aa** in 20% yield (Table 1, entry 4). Interestingly, L-proline-catalyzed BLA reaction of **1a** with **2a** in H_2O furnished the expected aldol↔lactol product **4aa/5aa** in 50% yield with 0% *ee* (Table 1, entry 5).

Proline-catalyzed BLA reaction of **1a** with **2a** is a solvent-dependent reaction, which performs well in aprotic and protic polar solvents such as DMSO, DMF, NMP, and H_2O; however, only <5% conversion was observed in other solvents such as CH_3CN, CH_2Cl_2, $CH_3C_6H_5$, and [bmim]BF_4 (results not shown). Bifunctional catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine·TFA (**3b**) and L-thiaproline (**3c**) also catalyzed the BLA reaction of **1a** with **2a** in NMP at −10 or 25°C to furnish **4aa/5aa** with moderate yields and increased *ee* values compared with **3a** as shown in Table 1, entries 6–7. Interestingly, reaction of **2a** with 14 equiv of **1a** and 20 mol% of *trans*-4-OH-L-proline (**3d**) in NMP for 24 h furnished a 1:1 ratio of (+)-**4aa/5aa** in 70% yield with 77% *ee*; but the same reaction under *trans*-4-OTBS-L-proline (**3e**) catalysis furnished **4aa/5aa** and byproduct **6aa** with low results (50% yield/33% *ee* and 40% yield, Table 1, entries 8–11). We also tested a number of primary and secondary amines such as L-Trp-OH (**3f**), L-Ala-OH (**3g**), L-Val-OH (**3h**), L-aminophenylacetic acid (**3i**), L-Thr(O*t*Bu)-OH (**3j**), 4-benzyl-1-methylimidazolidine-2-carboxylic acid (**3k**), L-DPP (**3l**) and L-DPPOTMS (**3m**) as catalysts for the BLA reaction of **1a** with **2a** in NMP or H_2O though the conversion was very poor (results not shown in Table 1). We envisioned the optimized condition as 25°C in NMP using 20 mol% **3d** to furnish highly substituted 1:1 ratio of (+)-**4aa/5aa** in 70% yield with 77% *ee* (Table 1, entry 8).

After successful demonstration of the asymmetric BLA reaction of **1a** with **2a** under amino acid catalysis, we decided to investigate the amino acid catalyzed BLA reaction of **1a** with the other functionalized 2-hydroxybenzaldehydes **2b–k** in H_2O to study the library generation of achiral **4/5** in good yields and also to furnish the further support for the

Table 1. Reaction optimization for the BLA reaction of **1a**, **2a** and **3**.



Entry	Catalyst **3** [20 mol%]	Solvent [1.0 M–0.25 M]	*t* [h]	Product yield [%][a]		*ee* **4aa/5aa**[b]
				4aa/5aa	**6aa**	
1[c]	L-proline **3a**	DMF	24	50	20	17
2[c]	L-proline **3a**	DMSO	6	50	30	19
3[c]	L-proline **3a**	NMP	4	50	20	36
4[d]	D-proline **3a**	NMP	38	60	20	11
5[d]	L-proline **3a**	H_2O	24	50	5	0
6[d,e]	diamine·TFA **3b**	NMP	48	50	30	50
7[d]	L-thiaproline **3c**	NMP	24	20	2	69
8[d]	*trans*-4-OH-L-proline **3d**	NMP	24	70	2	77
9[d]	*trans*-4-OH-L-proline **3d**	DMSO	17	45	10	50
10[d]	*trans*-4-OH-L-proline **3d**	DMF	23	20	6	63
11[d]	*trans*-4-OTBS-L-proline **3e**	NMP	12	50	40	33
12[d]	*trans*-4-OH-L-proline **3d**	–	72	<5	–	–

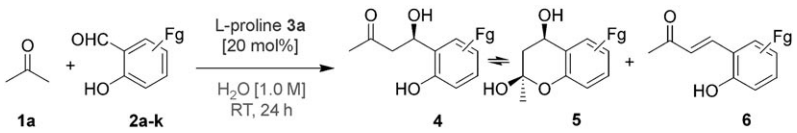
[a] Yield refers to the column-purified product. [b] *ee* determined by CSP HPLC analysis. [c] Reactions were carried out in solvent (0.25 M) with 28 equiv of **1a** relative to the **2a** (0.5 mmol) in the presence of 20 mol% of catalyst **3**. [d] Reactions were carried out in solvent (1.0 M) with 14 equiv of **1a** relative to the **2a** (0.5 mmol) in the presence of 20 mol% of catalyst **3**. [e] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine·TFA **3b** and reaction was carried out at −10°C.

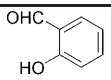
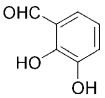
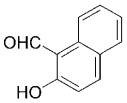
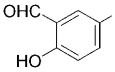
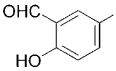
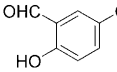
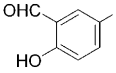
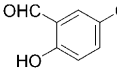
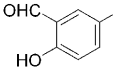
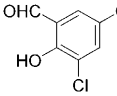
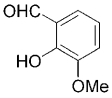
existence of fast dynamic equilibrium between **4** and **5** as shown in Table 2. The results in Table 2 give strong support to the existence of rapid equilibrium between aldol **4** and lactol **5** products in solution and also provide the best method to synthesize racemic **4/5** in good yields. Rapid equilibrium between aldol **4** and lactol **5** products in solution was confirmed by NMR analysis on **4ad/5ad** and also finally confirmed by X-ray structure analysis (see next section). ^{1}H NMR analysis on **4ad/5ad** in $CDCl_3$ at different temperatures (50, 25, 0, −15, −30, and −45 °C) and also in $CDCl_3$ + D_2O at 25 °C indicate that the resulting compound is bearing four OH groups, that is, two secondary, one tertiary and one phenolic OH. Interestingly, equilibrium between aldol **4** and lactol **5** products were controlled by electronic factors as shown in Table 2 (entries 3 and 9). Reaction of 2-hydroxynaphthalene-1-carbaldehyde (**2c**) with acetone **1a** under proline catalysis furnished lactol **5ac** as the major product and 2-hydroxy-5-nitrobenzaldehyde (**2i**) with acetone **1a** under proline catalysis produced aldol **4ai** as the major product (Table 2, entries 3 and 9).

With the optimized reaction conditions in hand, the scope of the amino acid catalyzed asymmetric BLA reactions was investigated. A series of substituted 2-hydroxybenzaldehydes **2a**–**k** was reacted with 14 equivalents of **1a** catalyzed by 20 mol% **3d** at 25 °C in NMP (Table 3). Neutral, electron-withdrawing and electron-donating compounds generated the expected BLA products **4/5** with excellent yields and *ee* values (Table 3). BLA reaction byproducts **6aa**–**ad** were obtained in very poor yields and **6ae**–**ak** were not observed. Fascinatingly, reaction of 2-hydroxynaphthalene-1-carbaldehyde (**2c**) with acetone **1a** and **3d** furnished lactol (−)-**5ac** as the major product, but unfortunately only 26% *ee* were observed (Table 3, entry 3). Interestingly, BLA reaction of 2-hydroxy-5-nitrobenzaldehyde (**2i**) with **1a** and **3d** furnished aldol (+)-**4ai** as major product with 85% yield and 52% *ee* (Table 3, entry 9). A deuterated 1:1 ratio of chiral (+)-**4bg/5bg** was furnished in 50% yield with 86% *ee* (Table 3, entry 12). Equilibrium between aldol **4** and lactol **5** of BLA products **4aa**–**ak/5aa**–**ak** was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (+)-**5ag** and (+)-**4ai** as shown in Figures S1 and S2 (see Supporting Information).[7]

After successful demonstration of the *trans*-4-OH-L-proline-catalyzed asymmetric BLA reactions of **1** with **2**, we decided to explore the utilization of the aldol↔lactol isomerization in the synthesis of functionalized molecules via acid/base catalysis in a one-pot reaction as shown in Equations (3–4). BLA reaction of **1a** with **2a** under **3d** catalysis at 25 °C in NMP furnished (+)-**4aa/5aa** in 70% yield with 77% *ee*, which upon treatment with *p*-TsCl and Et_3N in a one-pot reaction furnished the selectively tosylated product (+)-**7aa** in 50% yield with 77% *ee* as shown in Equation (3). In a similar manner, treatment of reaction inter-

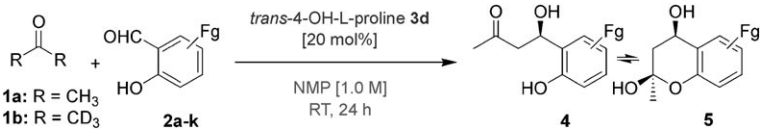
Table 2. Synthesis of achiral aldol↔lactol products **4/5**.[a]

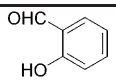
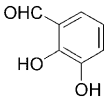
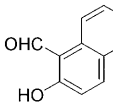
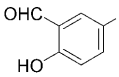
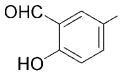
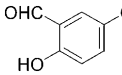
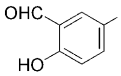
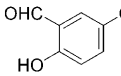
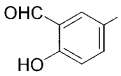
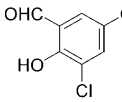
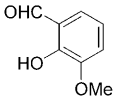
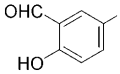


Entry	2-Hydroxybenzaldehydes **2**	Products [**4/5**]	Ratio[b] [**4/5**]	Products yield [%][c] **4/5**	**6**
1	 **2a**	**4aa/5aa**	1:1	50	5
2	 **2b**	**4ab/5ab**	1:1	56	4
3	 **2c**	**4ac/5ac**	1:99	50	5
4	 **2d**	**4ad/5ad**	1:1	65	–
5	 **2e**	**4ae/5ae**	1:1	85	-
6	 **2f**	**4af/5af**	1:1	65	3
7	 **2g**	**4ag/5ag**	1:1	70	2
8	 **2h**	**4ah/5ah**	1:1	70	2
9	 **2i**	**4ai/5ai**	99:1	85	–
10	 **2j**	**4aj/5aj**	3:1	90	–
11	 **2k**	**4ak/5ak**	5:1	40	–

[a] Reactions were carried out in H_2O (1.0 M) with 14 equiv of **1a** relative to the **2a**–**k** (0.5 mmol) in the presence of 20 mol% of catalyst **3a**. [b] Ratio is based on NMR analysis. [c] Yield refers to the column purified product.

Table 3. Synthesis of chiral aldol↔lactol products **4/5**.[a]

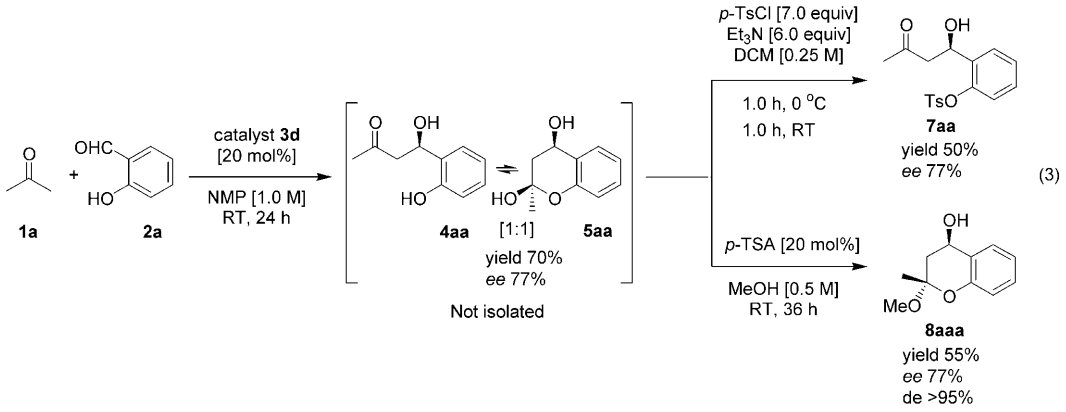


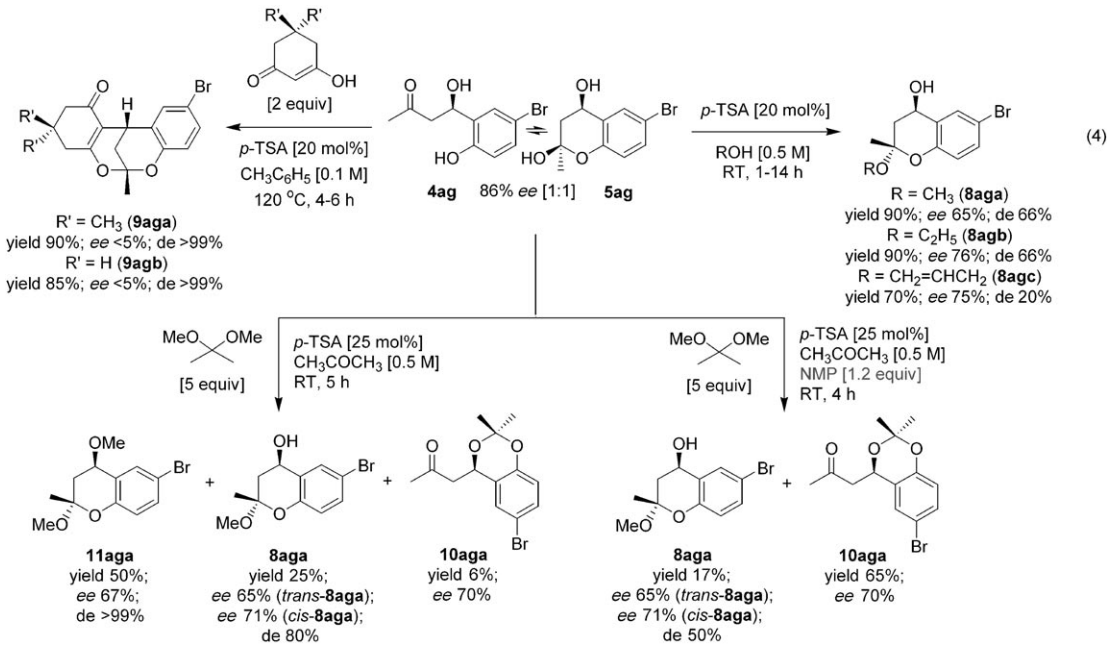
Entry	2-Hydroxy-benzaldehydes **2**	Products [**4**/**5**]	Ratio[b] [**4**/**5**]	Yield [%][c] **4**/**5**	*ee* **4**/**5** [d]
1[e]	 **2a**	**4aa**/**5aa**	1:1	70	77
2[e]	 **2b**	**4ab**/**5ab**	1:1	65	90
3[e]	 **2c**	**4ac**/**5ac**	1:99	50	26
4[e]	 **2d**	**4ad**/**5ad**	1:1	65	89
5	 **2e**	**4ae**/**5ae**	1:1	65	87
6	 **2f**	**4af**/**5af**	1:1	65	88
7	 **2g**	**4ag**/**5ag**	1:1	70	86
8	 **2h**	**4ah**/**5ah**	1:1	70	87
9	 **2i**	**4ai**/**5ai**	99:1	85	52
10	 **2j**	**4aj**/**5aj**	3:1	90	86
11	 **2k**	**4ak**/**5ak**	5:1	40	75
12[f]	 **2g**	**4bg**/**5bg**	1:1	50	86

[a] Reactions were carried out in NMP (1.0 M) with 14 equiv of **1a** relative to the **2a**–**k** (0.5 mmol) in the presence of 20 mol% of catalyst **3d**. [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] Byproducts **6aa**–**6ad** was obtained in 5–10% yields. [f] CD_3COCD_3 **1b** (14 equiv) was used and reaction time is 48 h.

mediate (+)-**4aa**/**5aa** with *p*-TSA in MeOH (**a**) at 25°C in a one-pot reaction furnished selectively *trans*-2-methoxy-2-methylchroman-4-ol [(+)-**8aaa**] in 55% yield with 77% *ee* and >95% de as shown in Equation (3).

With synthetic and pharmaceutical applications in mind, we further extended the application of acid-catalyzed lactonization methodology to pure isolated (+)-**4ag**/**5ag** with various alcohols **a**–**c**, CH acids and 2,2-dimethoxypropane as shown in Equation (4). All expected 2-alkoxy-2-methylchroman-4-ols (+)-**8aga**–(+)–**agc** were furnished in very good yields with good de values from the reaction of (+)-**4ag**/**5ag** with methanol **a**, ethanol **b** and allyl alcohol **c** under acid catalysis [see Eq. (4)]. Acid-catalyzed lactonization of aldol↔lactol product (+)-**4ag**/**5ag** is further applied in the presence of CH acids like dimedone and cyclohexane-1,3-dione. Interestingly, reaction of (+)-**4ag**/**5ag** with 2 equiv of dimedone under *p*-TSA catalysis in toluene at 120°C for 4–6 h furnished the unexpected tetracyclic product **9aga** in 90% yield with <5% *ee* and >99% de instead of simple chiral addition product and there is no reaction observed at 25°C. Generation of unexpected tetracyclic product from acid catalysis on (+)-**4ag**/**5ag**





(4)

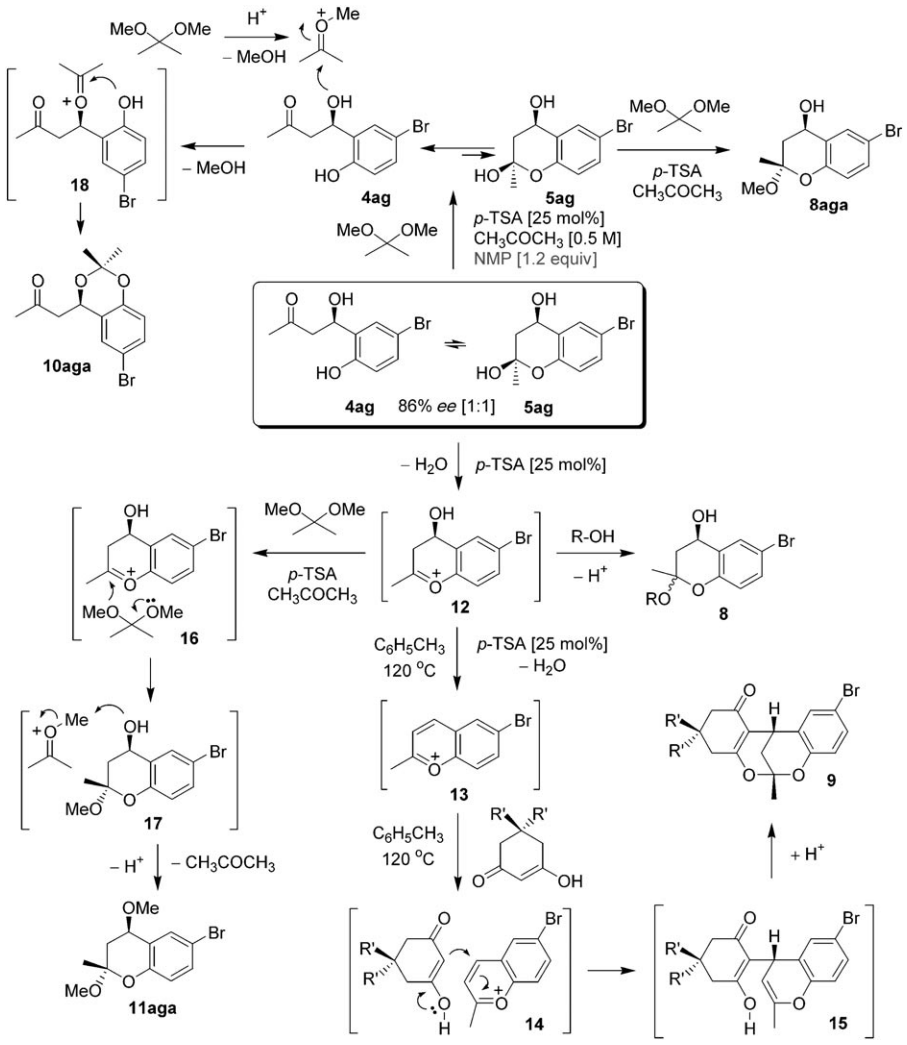
with CH acid was confirmed by one more example as shown in Equation (4) and furnished **9agb** in 85% yield with <5% *ee* and >99% *de*. Structure and regiochemistry of cascade products **9** were confirmed by X-ray structure analysis on **9aga** (Figure S3, see Supporting Information).[7]

2,2-Dimethoxypropane is known to serve as a source of methyl esterification, methylation, acetonation of acids and alcohols, respectively,[8] and herein we utilized this reagent for the acetonation of BLA product (+)-**4ag**/**5ag**. Interestingly, reaction of (+)-**4ag**/**5ag** with 5 equiv of 2,2-dimethoxypropane and 1.2 equiv of NMP under *p*-TSA catalysis in acetone (0.5 M) at 25°C for 4 h furnished acetonation product (+)-**10aga** in 65% yield with 70% *ee* as shown in Equation (4). In this reaction, 17% of *trans*-2-methoxy-2-methylchroman-4-ol [(+)-**8aga**] was isolated as byproduct with 50% de [see Eq. (4)]. The same reaction without NMP as co-solvent furnished three products as *trans*-6-bromo-2,4-dimethoxy-2-methylchroman [(+)-**11aga**] in 50% yield with >99% *de* and 67% *ee*, *trans*-2-methoxy-2-methylchroman-4-ol [(+)-**8aga**] in 25% yield with 80% *de* and acetonation product (+)-**10aga** in 6% yield as shown in Equation (4). The 2,2-disubstituted 2*H*-1-benzopyran structural unit [compounds **8** and **11**] is found in many natural products and designed products which exhibit a wide range of biological activities.[1q] This reaction is an ideal example for the trapping of both forms of aldol **4** and lactol **5** from fast dynamic equilibrium and utilization of 1.2 equiv of NMP as co-solvent is crucial for the generation of acyclic product (+)-**10aga** in good yield as shown in Equation (4) and Scheme 1. Unfortunately the optical purity of products **8**, **10** and **11** was decreased by 10–20% and products **9** were decreased by 80% starting from 86% optical purity of (+)-**4ag**/**5ag** under acid catalysis as shown in Equation (4).

The possible reaction mechanism for the synthesis of functionalized compounds **8**–**11** through reaction of BLA product (+)-**4ag**/**5ag** with alcohols, CH acids, and 2,2-dimethoxypropane under *p*-TSA catalysis is illustrated in Scheme 1. In the first step, catalyst *p*-TSA selectively reacts with (+)-**4ag**/**5ag** to generate substituted chroman oxonium ion **12** via a dehydration reaction in the solvents such as alcohols, toluene and acetone (**4**/**5**→**12**). In the following second step, in situ generated chroman ion **12** selectively reacts with different nucleophiles as shown in Scheme 1. Direct selective addition of variety of alcohols to chroman ion **12** leads to the formation of compounds **8**. In situ reaction of **12** with *p*-TSA at 120°C in toluene generates racemic 6-bromo-2-methylbenzopyrylium tosylate (**13**), which upon treatment with 1,3-diones at 120°C in toluene generates the cyclic intermediates **15** via transition state **14**, which upon further treatment with *p*-TSA furnishes the expected products **9**. Reaction of **12** with 2,2-dimethoxypropane generates compounds **8** and methyloxonium ion via methoxy-transfer reaction (see **16**), which on further intermolecular methyl-transfer reaction through **17** generates **11aga** with high selectivity. Interestingly, the reaction of (+)-**4ag**/**5ag** with *p*-TSA in 2,2-dimethoxypropane and NMP as the co-solvent gave different results than without NMP, so that we assume that the 1:1 ratio of **4ag** ↔ **5ag** is shifted towards aldol compound **4ag** due to the basic nature of NMP and major isomer diol **4ag** is transformed into acetonation product **10aga** via **18** as shown in Scheme 1. Minor isomer **5ag** is also transformed into compounds **8aga** via **12**→**16**→**8aga** sequence as shown in Scheme 1.

In summary, we describe for the first time the synthesis of the *trans*-4-OH-L-proline **3d** catalyzed asymmetric BLA reaction of acetone with 2-hydroxybenzaldehydes at ambient conditions. The BLA reaction proceeds in good yields with

Keywords: aldol reaction · amino acids · heterocycles · organocatalysis



Scheme 1. Proposed reaction mechanism for acid-catalyzed reactions on aldol↔lactol product **4ag/5ag**.

high selectivity using *trans*-4-OH-L-proline as the catalyst. Furthermore, we have demonstrated the application of chiral aldol↔lactol products **4/5** in the synthesis of highly functionalized molecules. Further work is in progress to utilize chiral 2-methylchroman-2,4-diols as intermediates for the bioactive molecules synthesis.

Experimental Section

Experimental procedures, characterization data for new products, X-ray crystal structures and complete details about the synthesis of new products are available in the Supporting Information.

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[1] a) G. P. Ellis, *Chromenes, Chromanones, and Chromones (Chemistry of Heterocyclic Compounds), Vol. 31*, Wiley, New York, **1977**, pp. 11–141; b) K. Hase, S. Kadota, P. Basnet, J. Li, S. Takamura, T. Namba, *Chem. Pharm. Bull.* **1997**, *45*, 567–569; c) S. R. Trenor, A. R. Shultz, B. J. Love, T. E. Long, *Chem. Rev.* **2004**, *104*, 3059–3077; d) K. S. Atwal, P. Wang, W. L. Rogers, P. Sleph, H. Monshizadegan, F. N. Ferrara, S. Traeger, D. W. Green, G. J. Grover, *J. Med. Chem.* **2004**, *47*, 1081–1084; e) R. Frédérick, S. Robert, C. Charlier, J. Ruyck, J. Wouters, B. Pirotte, B. Masereel, L. Pochet, *J. Med. Chem.* **2005**, *48*, 7592–7603; f) W. B. Turner, *J. Chem. Soc. Perkin Trans. 1* **1978**, 1621–1621; g) P. W. Manley, U. Quast, H. Andrea, K. Bray, *J. Med. Chem.* **1993**, *36*, 2004–2010; h) Y. Kang, Y. Mei, Y. Du, Z. Jin, *Org. Lett.* **2003**, *5*, 4481–4484; i) S. A. Ross, G. N. N. Sultana, C. L. Burandt, M. A. ElSohly, J. P. J. Marais, D. Ferreira, *J. Nat. Prod.* **2004**, *67*, 88–90; j) J. A. Burlison, L. Neckers, A. B. Smith, A. Maxwell, B. S. J. Blagg, *J. Am. Chem. Soc.* **2006**, *128*, 15529–15536; k) Y-.L. Shi, M. Shi, *Org. Biomol. Chem.* **2007**, *5*, 1499–1504; l) E. M. K. Wijeratne, T. J. Turbyville, A. Fritz, L. Whitesell, A. A. L. Gunatilaka, *Bioorg. Med. Chem.* **2006**, *14*, 7917–7923; m) T. Rezanka, K. Sigler, *J. Nat. Prod.* **2007**, *70*, 1487–1491; n) M. Isaka, S. Palasarn, K. Kocharin, J. Saenboonrueng, *J. Nat. Prod.* **2005**, *68*, 945–946; o) M. M. Wagenaar, J. Clardy, *J. Nat. Prod.* **2001**, *64*, 1006–1009; p) K. Hase, S. Kadota, P. Basnet, J. Li, S. Takamura, T. Namba, *Chem. Pharm. Bull.* **1997**, *45*, 567–569; q) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953.

[2] a) K. Takahashi, O. Fukuoka, *Jpn. Kokai Tokkyo Koho* **1988**, 8, JP 63203677A 19880823; *Chem. Abstr.* **1988**, *110*, 75320, (patent written in Japanese); b) S. Jegham, F. Puech, P. Burnier, D. Berthon, *PCT Int. Appl.* **1997**, 49, WO 9717347A1 19970515 [*Chem. Abstr.* **1997**, *127*, 34207], (patent written in French); c) T. W. Butler, J. F. Blake, J. Bordner, P. Butler, B. L. Chenard, M. A. Collins, D. DeCosta, M. J. Ducat, M. E. Eisenhard, F. S. Menniti, M. J. Pagnozzi, S. B. Sands, B. E. Segelstein, W. Volberg, W. F. White, D. Zhao, *J. Med. Chem.* **1998**, *41*, 1172–1184; d) G. S. Ahn, H. G. Han, S. Y. Jung, H. H. Kim, I. H. Kim, J. D. Lim, *Kongkae Taeho Kongbo* **2002**, KR 2002003940A 20020116 [*Chem. Abstr.* **2002**, *142*, 113796], (patent written in Korean); e) J. E. Yeo, X. Yang, H. J. Kim, S. Koo, *Chem. Commun.* **2004**, 236–237; f) B. Lesch, S. Braese, *Angew. Chem.* **2004**, *116*, 118–120; *Angew. Chem. Int. Ed.* **2004**, *43*, 115–118; g) B. Wang, G. Walkinshaw, J. Chen, X. Jin, J. Song, W. Zhang, *U. S. Pat. Appl. Publ.* **2005**, 48, US 2005065149A1 20050324 [*Chem. Abstr.* **2005**, *142*; 336251], (patent written in English); h) C. F. Nising, U. K. Ohnemuel-

ler, A. Friedrich, B. Lesch, J. Steiner, H. Schnoeckel, M. Nieger, S. Braese, *Chem. Eur. J.* **2006**, *12*, 3647–3654; i) U. K. Ohnemueller (née Schmid), C. F. Nising, M. Nieger, S. Braese, *Eur. J. Org. Chem.* **2006**, 1535–1546; j) Y. Fang, C. Li, *J. Org. Chem.* **2006**, *71*, 6427–6431; k) R. Rios, H. Sunden, I. Ibrahem, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 2181–2184; l) K. A. Sangita, D. P. Sahu, S. Ray, *Indian Pat. Appl.* **2007**, 11, IN 2003DE00305A 20070413 [*Chem. Abstr.* **2007**, *148*, 285051], (patent written in English); m) Z. Zhang, C. Pan, Z. Wang, *Chem. Commun.* **2007**, 4686–4688; n) N. Saito, A. Ryoda, W. Nakanishi, T. Kumamoto, T. Ishikawa, *Eur. J. Org. Chem.* **2008**, 2759–2766; o) K. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem.* **2008**, *120*, 5911; *Angew. Chem. Int. Ed.* **2008**, *47*, 5827–5829; p) L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith, C. Große, *Chem. Eur. J.* **2008**, *14*, 8956–8963.

[3] a) G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas III, *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132; b) B. List, R. A. Lerner, C. F. Barbas III, *Org. Lett.* **1999**, *1*, 59–62; c) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; d) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; e) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; f) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575; g) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283; h) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912; i) A. Cordova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301–303; j) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; k) A. Bogevig, K. Juhl, N. Kumaragurubaran, K. A. Jorgensen, *Chem. Commun.* **2002**, 620–621; l) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167–8177; m) P. Kotrusz, I. Kmentova, B. Gotov, S. Toma, E. Solcaniova, *Chem. Commun.* **2002**, 2510–2511; n) T. Darbre, M. Machuqueiro, *Chem. Commun.* **2003**, 1090–1091; o) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16–17; p) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479; q) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839–5842; r) C. Allemann, R. Gordillo, F. R. Clemente, P. H-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569; s) S. Chandrasekhar, C. Narsihmulu, N. R. Reddy, S. S. Sultana, *Chem. Commun.* **2004**, 2450–2451; t) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474–2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; u) J. T. Suri, D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1383–1385; v) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735; w) Y. Zhou, Z. Shan, *J. Org. Chem.* **2006**, *71*, 9510–9512; x) M. Raj, V. Maya, S. K. Ginotra, V. K. Singh, *Org. Lett.* **2006**, *8*, 4097–4099; y) V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593–2595; z) J. Huang, X. Zhang, D. W. Armstrong, *Angew. Chem.* **2007**, *119*, 9231–9235; *Angew. Chem. Int. Ed.* **2007**, *46*, 9073–9077; aa) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857–7870; ab) C. L. Chandler, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6737–6739; ac) S. Källström, A. Erkkilä, P. M. Pihko, R. Sjöholm, R. Sillanpää, R. Leino, *Synlett* **2005**, 751–756.

[4] For recent reviews on organocatalytic cascade and multi-component reactions, see: a) H. C. Guo, J. A. Ma, *Angew. Chem.* **2006**, *118*, 362–375; *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366; b) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143–2173; c) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1–21; d) J. Gerencsér, G. Dorman, F. Darvas, *QSAR Comb. Sci.* **2006**, *25*, 439–448; e) G. Guillena, D. J. Ramon, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693–700; f) D. Enders, C. Grondal, Matthias, R. M. Huettl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; g) For the excellent review on iminium-ion induced cascade reactions, see: A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.

[5] For the fast dynamic equilibrium between lactol and δ-hydroxyketone, see: a) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105–5107; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955–4957; b) M. V. Novotny, B. Jemiolo, D. Wiesler, W. Ma, S. Harvey, F. Xu, T.-M. Xie, M. Carmack, *Chem. Biol.* **1999**, *6*, 377–383; c) P. Bravo, C. Ticozzi, D. Maggi, *J. Chem. Soc. Chem. Commun.* **1976**, 789b–790b.

[6] For multi-catalysis reactions, see: a) D. B. Ramachary, M. Kishor, K. Ramakumar, *Tetrahedron Lett.* **2006**, *47*, 651–656; b) D. B. Ramachary, M. Kishor, G. Babul Reddy, *Org. Biomol. Chem.* **2006**, *4*, 1641–1646; c) D. B. Ramachary, G. Babul Reddy, *Org. Biomol. Chem.* **2006**, *4*, 4463–4468; d) D. B. Ramachary, M. Kishor, *J. Org. Chem.* **2007**, *72*, 5056–5068; e) D. B. Ramachary, G. Babul Reddy, M. Rumpa, *Tetrahedron Lett.* **2007**, *48*, 7618–7623; f) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *J. Org. Chem.* **2007**, *72*, 1458–1463; g) D. B. Ramachary, M. Kishor, Y. V. Reddy, *Eur. J. Org. Chem.* **2008**, 975–998; h) D. B. Ramachary, Y. V. Reddy, B. V. Prakash, *Org. Biomol. Chem.* **2008**, *6*, 719–726; i) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.* **2008**, *6*, 2488–2492; j) D. B. Ramachary, M. Kishor, *Org. Biomol. Chem.* **2008**, *6*, 4176–4187; k) D. B. Ramachary, Y. V. Reddy, M. Kishor, *Org. Biomol. Chem.* **2008**, *6*, 4188–4197; l) D. B. Ramachary, V. V. Narayana, K. Ramakumar, *Eur. J. Org. Chem.* **2008**, 3907–3911; m) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, *14*, 9143–9147.

[7] CCDC 710263 for (+)-**5ag**, 710264 for (+)-**4ai** and 710265 for (−)-**9aga** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for crystal structures.

[8] a) M. P. Nguyen, J. N. Arnold, K. E. Peterson, R. S. Mohan, *Tetrahedron Lett.* **2004**, *45*, 9369–9371, and references therein; b) Y. Ueno, K. Hori, R. Yamauchi, M. Kiso, A. Hasegawa, K. Kato, *Carbohydr. Res.* **1981**, *89*, 271–278; c) R. Shaw, W. H. Elliott, *J. Lipid Res.* **1978**, *19*, 783–787; d) J. R. Rachele, *J. Org. Chem.* **1963**, *28*, 2898.

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