Chiral amine/chiral acid as an excellent organocatalytic system for the enantioselective tandem oxa-Michael-aldol reaction†

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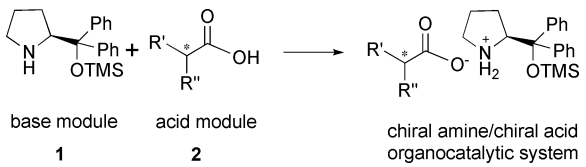
The asymmetric tandem oxa-Michael-aldol reaction of salicylic aldehyde derivatives with α,β-unsaturated aldehydes catalyzed by a chiral amine/chiral acid organocatalytic system was investigated. The organocatalytic system of (*S*)-diphenylpyrrolinol trimethylsilyl ether with chiral shift reagent (*S*)-Mosher acid presented a synergistic effect in the improvement of reaction performance and offered an efficient steric effect in the transformation. The tandem oxa-Michael-aldol reaction proceeded with high yields (up to 90%) and with excellent ee values (up to 99%) to give the corresponding chromene derivatives. The structure of the chiral ammonium salt formed *in situ* and the corresponding mechanism were also studied by ^{1}H NMR.

Introduction

The chiral chromene skeleton, which is often found in natural products, is a widespread unit that has a broad and interesting range of biological activities.[1] The synthesis of chiral chromenes has been a major object of research,[2] and a number of synthetic strategies have been described, such as enzyme-catalyzed kinetic resolution,[3] derivatization of chiral precursors,[4] and metal-catalyzed asymmetric reactions.[5] However, the development of efficient asymmetric methods has proven to be a challenging task. An enantioselective tandem oxa-Michael-aldol reaction for C2-chiral chromenes catalyzed by chiral pyrrolidine derivatives has recently been independently reported by five groups.[6–10] This cascade reaction of simple α,β-unsaturated aldehydes with salicylaldehydes has opened a green and efficient route toward these "privileged" structural motifs.[11] In these studies, it was noted that the acidity and the structure of the organic acidic additives were important properties relevant to their catalytic activity and enantioselectivity of the tandem oxa-Michael-aldol reaction.[6–8]

Organocatalysis has become a field of central importance for asymmetric catalysis.[12] Novel modes of substrate activation, such as SOMO,[13] dienamine,[14] chiral primary amine activation[15] and asymmetric counterion-directed catalysis (ACDC)[16] have been exploited. In our study of ammonium salt organocatalysts, we envisioned that the acid–base interaction between chiral aminocatalysts and chiral organic acid additives may be beneficial in the tandem oxa-Michael-aldol reaction of simple α,β-unsaturated aldehydes and salicylaldehydes. For example, by using the (*S*)-diphenylpyrrolinol trimethylsilyl ether **1** as the reaction center and the base module, a series of chiral organic acids **2** can replace nonchiral organic acids as the acid module, forming a chiral acid/chiral base ammonium salt (Scheme 1). The chiral organic acids should accelerate the catalytic tandem reaction, and moreover, fine-tuning of the catalytic environment by modifying the chiral acid/chiral base ammonium salt should enable improvement of the enantioselectivity. To the best of our knowledge, there has been no report of a chiral amine/chiral acid organocatalytic system in the direct asymmetric tandem oxa-Michael-aldol reaction.



Scheme 1 The chiral amine/chiral acid organocatalytic system.

Results and discussion

In our initial investigation, (*S*)-diphenylpyrrolinol trimethylsilyl ether **1**, which exhibited the best catalytic ability in the tandem Michael-aldol reaction in the literature[7–10] was selected as the base module. Organic acids **2** with a chiral center near the acidic group were chosen as the acid module. To explore the proposed chiral amine/chiral acid organocatalytic system in the tandem process, a model reaction between *trans*-cinnamaldehyde **3a** and salicylaldehyde **4a** in toluene at room temperature was evaluated. Meanwhile, molecular sieves were added to remove water from the reaction medium, which could increase the rate of aldol condensation and push the equilibrium towards product formation. Several chiral amine/chiral acid catalyst systems were tested and the results are shown in Table 1.

Compared with only organocatalyst **1**, the chiral amine/chiral acid organocatalytic system not only accelerated the reaction, but also efficiently increased the enantioselectivity in the same conditions. Moreover, compared with the reported nonchiral benzoic acid **2a**,[7] (*S*)-*N*-Boc phenylalanine **2b** as the chiral acid module increased the conversion of the reaction from 65% to 96% and the enantioselectivity of the reaction was enhanced from 36% to 68% (Table 1, Entries 2 and 3). Notably, the (*S*)-phenylalanine derivative as the acid module gave better results than the (*R*)- analogue (Table 1, Entries 3 and 4). These results indicated

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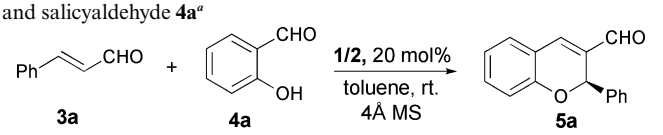
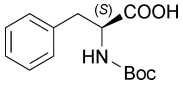
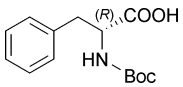
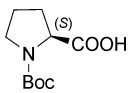
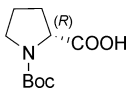
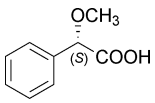
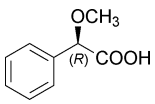
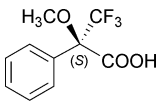
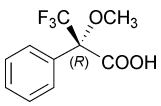
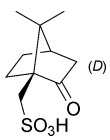
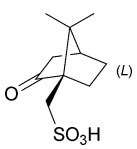
Table 1 Different chiral amine/chiral acid organocatalytic systems for the tandem oxa-Michael-aldol reaction between *trans*-cinnamaldehyde **3a** and salicyaldehyde **4a**[a]

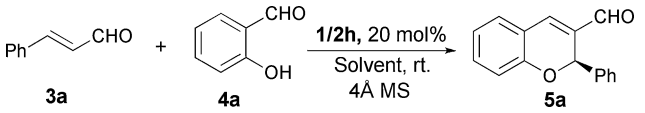


Entry	Acid module		Time (h)	Yield (%)[b]	ee (*syn*) (%)[c]
1	None		48	14	8
2	**2a**	PhCOOH	48	65	36
3	**2b**		48	96	68
4	**2c**		48	82	59
5	**2d**		48	70	78
6	**2e**		48	57	31
7	**2f**		48	60	50
8	**2g**		48	41	47
9	**2h**		**12**	**94**	**80**
10	**2i**		12	90	71
11	**2j**		48	40	48
12	**2k**		48	35	45

[a] A mixture of salicylaldehyde (0.25 mmol), *trans*-cinnamaldehyde (0.25 mmol) and chiral amine/chiral acid organocatalytic system **1/2** (20 mol%) was stirred at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 396 nm).

that the synergistic ionic interaction of chiral amine with chiral acid was formed *in situ* in the catalytic system, and that the (*S*)-organic acid could form a steric shield more efficiently with chiral amine **1**, enhancing the conversion as well as the enantioselectivity of the reaction.

Table 2 Solvent screening for the tandem oxa-Michael-aldol reaction between *trans*-cinnamaldehyde **3a** and salicyaldehyde **4a**[a]



Entry	Solvent	Time (h)	Yield (%)[b]	ee (*syn*) (%)[c]
1	Toluene	12	94	80
2	DMSO	48	—	—
3	DMF	48	2	—
4	CH_3CN	48	15	65
5	*i*-PrOH	48	41	36
6	THF	48	58	69
7	Xylene	48	66	67
8	CH_2Cl_2	48	27	80
9	**Et_2O**	**24**	**88**	**90**
10	Hexane	48	61	83

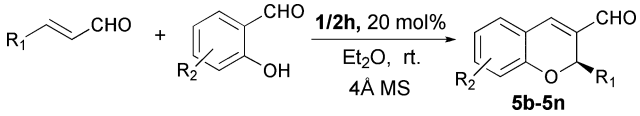
[a] A mixture of salicylaldehyde (0.25 mmol), *trans*-cinnamaldehyde (0.25 mmol), chiral amine/chiral acid organocatalytic system **1/2h** (20 mol%) in the solvent indicated was stirred at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 396 nm).

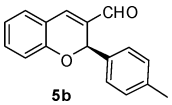
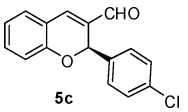
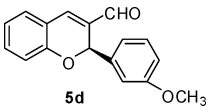
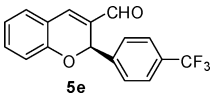
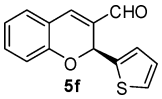
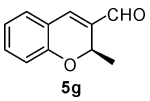
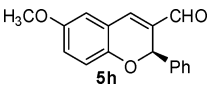
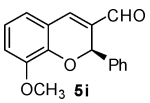
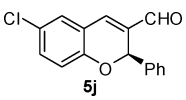
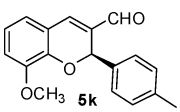
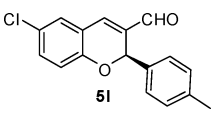
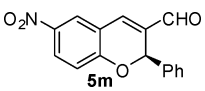
These results encouraged us to study more chiral amine/chiral acid organocatalytic systems of chiral amine **1** with diverse chiral acids, and similar results were observed. The acidity of the acid module was also important. In carboxylic acids, strong acidity in particular tended to generate good yields (Table 1, Entries 2–10), but (*D*)- or (*L*)-camphorsulfonic acids failed to accelerate the tandem reaction (Table 1, Entries 11 and 12). However, to our delight, using the (*S*)-Mosher acid **2h** gave the product, chromene-3-carbaldehyde, with 94% yield and 80% ee in just 12 h (Table 1, Entry 9). (*S*)-Mosher acid **2h**, which is often used as a NMR chiral shift reagent for the determination of enantiomeric excesses of chiral compounds, not only shows a suitable acidity compared to benzoic acid derivatives, but also has a favorable chiral structure that may help to result in a highly efficient chiral environment with chiral amine **1**.

Having established the optimal chiral amine/chiral acid organocatalytic system for the tandem oxa-Michael-aldol reaction of *trans*-cinnamaldehyde **3a** and salicyaldehyde **4a**, we probed the effect of different solvents on the reaction. The results are summarized in Table 2. More polar or aprotic solvents seemed to suppress the reactivity of the system, and the reaction essentially did not occur in DMSO or DMF (Table 2, Entries 2 and 3). However, in nonpolar solvents, such as toluene, CH_2Cl_2, Et_2O and hexane, both yields and enantioselectivities were higher than in polar solvents (Table 2, Entries 1 and 7–10). Moreover, the desired product chromene-3-carbaldehyde was obtained with the highest enantioselectivity (90% ee) in Et_2O (Table 2, Entry 9).

We next examined the scope of the tandem oxa-Michael-aldol process by using a variety of α,β-unsaturated aldehydes and salicylic aldehyde derivatives under the optimal reaction conditions. As the results in Table 3 show, the reaction tolerated a broad scope of substrates, giving the desired products in moderate to excellent yields (45–90%) and with good to excellent enantioselectivities (70–99%) in 24–48 h. Compared with previously reported catalytic systems,[6,7c,8c] the better yields and

Table 3 Tandem oxa-Michael-aldol reactions between α,β-unsaturated aldehydes and salicylic aldehyde derivatives[a]



Entry	R_1	R_2	Product	Time (h)	Yield (%)[b]	ee (*syn*) (%)[c]
1	4-Me-C_6H_4	H	 **5b**	24	90	99
2	4-Cl-C_6H_4	H	 **5c**	24	90	99
3	3-MeO-C_6H_4	H	 **5d**	24	70	91
4	4-F_3C-C_6H_4	H	 **5e**	48	56	89
5	Thiophen-2-yl	H	 **5f**	36	68	87
6	Me	H	 **5g**	48	45	70
7	Ph	5-MeO	 **5h**	24	70	82
8	Ph	3-MeO	 **5i**	24	90	90
9	Ph	5-Cl	 **5j**	24	85	90
10	4-Me-C_6H_4	3-MeO	 **5k**	24	90	90
11	4-Me-C_6H_4	5-Cl	 **5l**	24	90	94
12	Ph	5-NO_2	 **5m**	48	55	77

[a] A mixture of salicylic aldehyde derivatives (0.25 mmol), α,β-unsaturated aldehydes (0.25 mmol), and the chiral amine/chiral acid organocatalytic system **1/2h** (20 mol%) was stirred at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

higher ee values indicate that the **1/2h** system has a synergistic effect in the improvement of reaction performance, and provides an efficient steric effect in the transformation. α,β-Unsaturated aldehydes bearing electron-donating groups afforded the desired products with high yield (up to 90%) and enantioselectivity (up to 99%) (Table 3, Entries 1–3), while results were not so good for an α,β-unsaturated aldehyde with an electron-withdrawing group (Table 3, Entry 4). *trans*-3-(Thiophen-2-yl)acrylaldehyde was also a suitable substrate, leading to the product in 68% yield and 87% ee (Table 3, Entry 5). *trans*-But-2-enal, being α,β-unsaturated aliphatic aldehyde, was a less active substrate, giving the product in 45% yield and 70% ee (Table 3, Entry 6). Salicylic aldehyde derivatives bearing electron-donating groups underwent this tandem process efficiently, with higher yields and ee values than those bearing electron-withdrawing groups (Table 3, Entries 7–11 *vs.* Entry 12). The steric effect of the substrate was also observed: 3-methoxysalicylic aldehyde gave the product with 90% yield and 90% ee, while 5-methoxysalicylic aldehyde gave the product with 70% yield and 82% ee (Table 3, Entries 7 and 8).

The NMR chemical shifts of amines usually change in the base–acid conjugation process, because the electronic and chemical environments can be affected by the close association of the ammonium salt formed *in situ*. Hence the stereocontrol process of the chiral amine/chiral acid organocatalytic system formed by (*S*)-diphenylpyrrolinol trimethylsilyl ether **1** and (*S*)-Mosher acid **2h** was studied by ^{1}H NMR.[17] As Fig. 1 shows, because of the ionic interaction of **1** with the carboxylic acid of **2h**, the active hydrogens (the NH proton at 1.872 ppm and the COOH proton at 7.670 ppm) disappeared (Fig. 1A and B). More importantly, the protons of **1**, especially the hydrogens on the pyrrolidine backbone, were shifted when the stable ionic pair was formed. For example, the proton in the second position of the pyrrolidine ring (H1) was shifted downfield to 4.869 ppm from 4.130 ppm by the deshielding effect of **2h**. Two methylene protons in the fourth position of the pyrrolidine ring (H6 and H7) were diastereotopic, and the difference between the peak positions of two protons increased from 0.060 ppm to 0.776 ppm. All changes of chemical shift are probably due to the electronic effects of the newly formed ammonium salt, as well as the conformational changes in the pyrrolidine backbone. These changes of chemical environments may influence the catalytic environment and enhance the catalytic performance of **1**.

The mechanism of the tandem oxa-Michael-aldol reactions was also studied. When the *trans*-cinnamaldehyde was added to the **1/2h** system, the iminium ion intermediate was detected by ^{1}H NMR and mass spectroscopy (Fig. 1D and Fig. 2). However, this phenomenon was not found in the **1/2a** system under the same conditions (Fig. 1C). All these results indicate that the formation rate of the iminium ion is affected by the acidity of the acid module. The chiral shift reagent (*S*)-Mosher acid **2h** shows a strong co-catalytic ability to accelerate the formation of the iminium ion. Moreover, based on the above study, (*S*)-Mosher acid **2h** interacted with chiral amine **1** to give a highly efficient chiral environment. As the proposed transition state model (Fig. 3) shows, the (*S*)-diphenylpyrrolinol trimethylsilyl ether **1** and the (*S*)-Mosher acid **2h** form a stable ionic pair on the less sterically hindered side of the pyrrolidine ring of **1**, so the secondary amine catalyst **1** was flanked on both sides by chirality-directing groups. After activation by this chiral amine/chiral acid organocatalytic system, the *Si* face of the *trans*-cinnamaldehyde was shielded efficiently by the phenyl group of the (*S*)-Mosher acid and the chiral framework of **1**. The hydroxyl group of the salicylic aldehyde then only attacks the β-carbon atom from the *Re* face of the *trans*-cinnamaldehyde. Since the Michael addition is the key stereocontrol step in the tandem oxa-Michael-aldol reaction, this leads to the desired product with high enantioselectivity.

Conclusions

In summary, we have discovered an efficient chiral amine/chiral acid organocatalytic system for the tandem oxa-Michael-aldol reaction between α,β-unsaturated aldehydes and salicylic aldehyde derivatives. Significantly better catalytic performance was provided by the tandem reaction in terms of yield (up to 90%) and enantioselectivity (up to 99%). Further investigations of this organocatalytic system, as well as the development of other enantioselective tandem reactions, are ongoing in our laboratory.

Experimental

General

All starting chemicals were commercial products (Aldrich or J&K Chemica) of analytical grade. Organic solvents were dried and purified before use by the usual methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian NMR. Chemical shifts of ^{1}H and ^{13}C are given in ppm relative to tetramethylsilane (TMS). Coupling constants *J* are given in Hz. GC–MS experiments were performed on an Agilent 6890 N GC system with a 5973 N mass selective detector. HPLC experiments were carried out using a JASCO LC-2000 Plus system consisting of an MD detector.

Experimental procedure

Typical experimental procedure for the tandem oxa-Michael-aldol reaction: To a stirred solution of (*S*)-diphenylpyrrolinol trimethylsilyl ether (20 mol%, 0.05 mmol) and (*S*)-Mosher acid (20 mol%, 0.05 mmol) in Et_2O (0.5 mL) at room temperature, *trans*-cinnamaldehyde **3a** (0.25 mmol) and salicyaldehyde **4a** (0.25 mmol) were added. The reaction mixture was stirred for the time given in the tables. The generated compound was directly purified by silica gel chromatography (pentane–EtOAc mixtures) to give the corresponding chromene-3-carbaldehyde. The ee values of the products were determined by chiral HPLC analysis with an MD detector.

Spectroscopic data

(*R*)-2-Phenyl-2*H*-chromene-3-carbaldehyde (5a). Isolated yield 88%. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 396 nm): t_R = 12.36 min (minor), 11.15 min (major). IR ν(film)/cm^{-1}: 3061, 3032, 2931, 2813, 1673, 1633, 1603, 1568, 1456, 1212, 1159, 991, 756, 698. ^{1}H NMR (500 MHz, $CDCl_3$): 9.63 (s, 1H), 7.39 (s, 1H), 7.35–7.34 (m, 2H), 7.28–7.23 (m, 5H), 6.95–6.92 (t, *J* = 7.5 Hz, 1H), 6.87–6.85 (d, *J* = 8.5 Hz, 1H), 6.33 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 154.9, 140.8, 139.1, 133.8, 133.7, 129.4, 128.7, 128.6, 126.8, 121.8, 120.0, 117.2, 74.3. MS (EI): 51(97), 63(43), 77(100), 89(17),

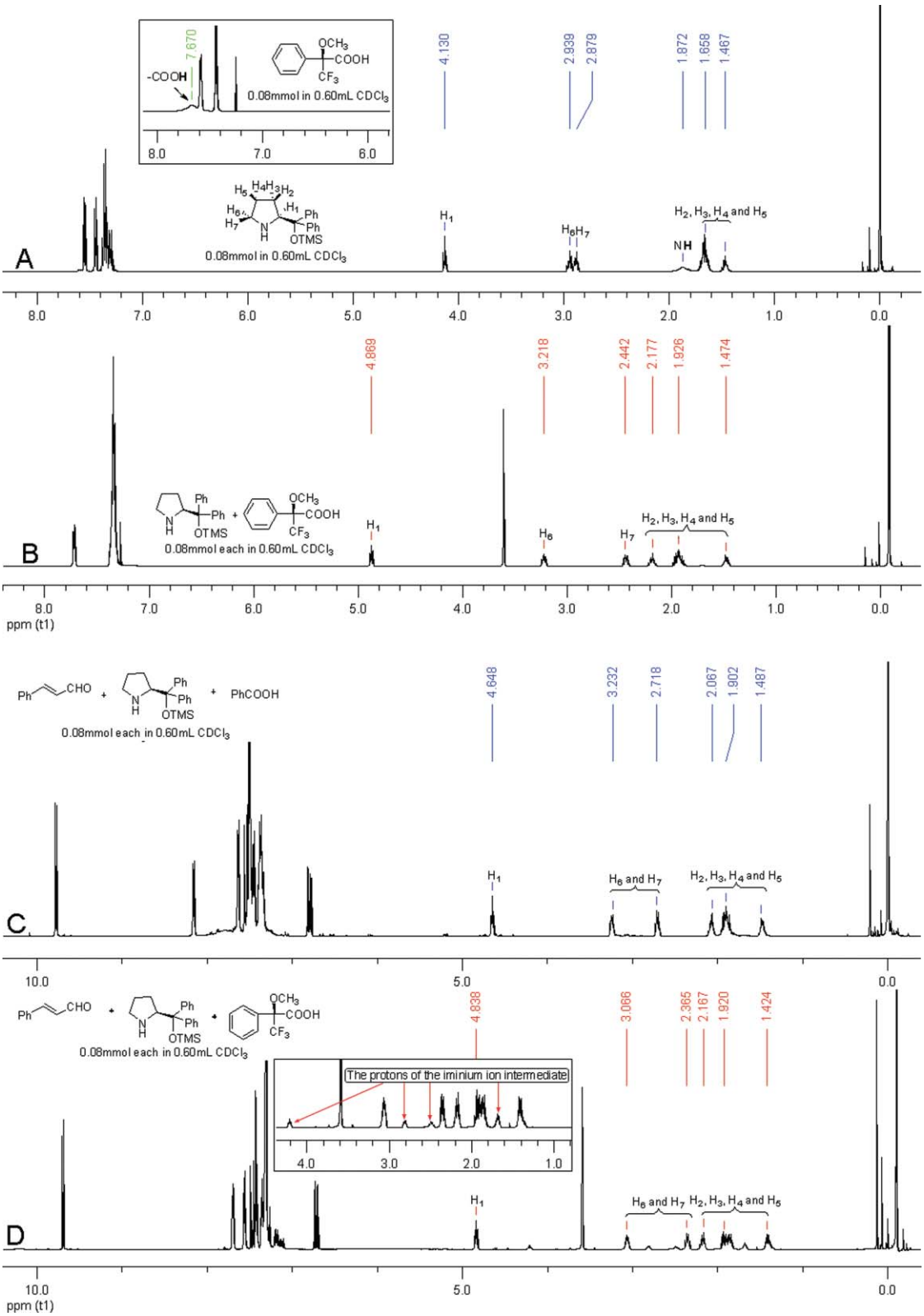


Fig. 1 ^{1}H NMR spectra.

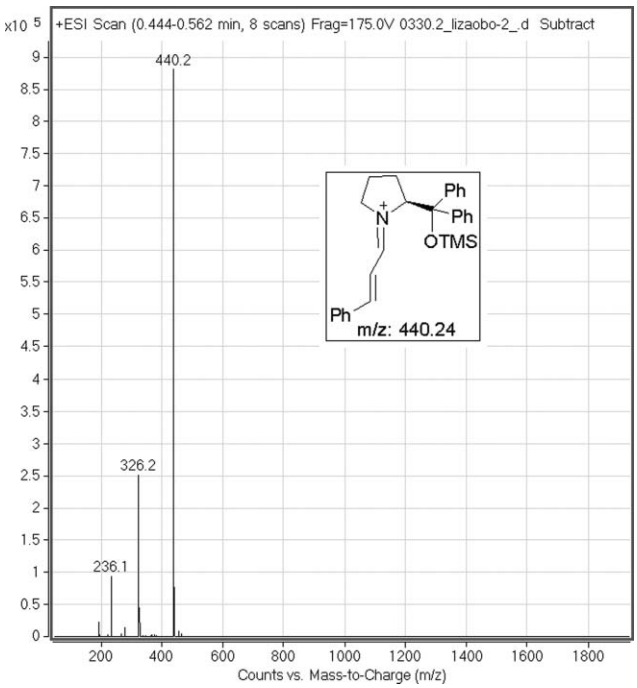


Fig. 2 The ESI-MS spectrum of the iminium ion intermediate.

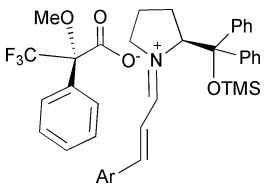


Fig. 3 Proposed transition state model.

102(39), 115(19), 131(17), 152(22), 178(40), 189(2), 207(46), 236(12).

(*R*)-2-*p*-Tolyl-2*H*-chromene-3-carbaldehyde (5b). Isolated yield 90%. HPLC (Daicel Chiralpak OD-H, hexane–*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 380 nm): t_R = 14.91 min (minor), 12.76 min (major). IR ν(film)/cm^{-1}: 3028, 2924, 2856, 2812, 1677, 1630, 1604, 1568, 1512, 1211, 1158, 987, 818, 757. ^{1}H NMR (500 MHz, $CDCl_3$): 9.62 (s, 1H), 7.39 (s, 1H), 7.27–7.22 (m, 4H), 7.08–7.06 (d, J = 8.5 Hz, 2H), 6.94–6.91 (t, J = 8.5 Hz, 1H), 6.85–6.83 (d, J = 8.5 Hz, 1H), 6.29 (s, 1H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 154.9, 140.6, 138.5, 136.1, 133.9, 133.6, 129.3, 129.2, 126.8, 121.7, 120.0, 117.2, 74.2, 21.1. MS (EI): 51(7), 63(7), 77(11), 91(7), 102(6), 115(9), 126(9), 131(6), 141(1), 159(11), 178(30), 189(8), 205(7), 221(100), 235(15), 250(23). HRMS calc. for $C_{17}H_{14}O_2$: 250.0994, found 250.1008.

(*R*)-2-(4-Chlorophenyl)-2*H*-chromene-3-carbaldehyde (5c). Isolated yield 90%. HPLC (Daicel Chiralpak OD-H, hexane–*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 384 nm): t_R = 13.99 min (minor), 12.65 min (major). IR ν(film)/cm^{-1}: 3049, 2929, 2814, 1672, 1631, 1603, 1568, 1489, 1211, 1158, 951, 823, 758. ^{1}H NMR (500 MHz, $CDCl_3$): 9.63 (s, 1H), 7.41 (s, 1H), 7.31–7.27 (m, 3H), 7.25–7.22 (m, 3H), 6.97–6.94 (t, J = 9.0 Hz, 1H), 6.87–6.85 (d, J = 8.5 Hz, 1H), 6.29 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.9, 154.6, 140.9, 137.6, 134.5, 133.9, 133.4, 129.4, 128.7, 128.2, 122.0, 119.8, 117.2, 73.5. MS (EI): 51(13), 63(10), 75(15), 89(7), 102(10), 111(6), 131(8), 149(3), 159(17), 178(42), 205(19), 241(100), 270(38).

(*R*)-2-(3-Methoxyphenyl)-2*H*-chromene-3-carbaldehyde (5d). Isolated yield 70%. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 380 nm): t_R = 13.55 min (major), 14.88 min (minor). IR ν(film)/cm^{-1}: 3053, 3003, 2937, 2835, 1673, 1634, 1604, 1569, 1269, 1159, 992, 876, 799, 760, 695. ^{1}H NMR (500 MHz, $CDCl_3$): 9.63 (s, 1H), 7.38 (s, 1H), 7.30–7.26 (m, 1H), 7.25–7.22 (m, 1H), 7.19–7.16 (t, J = 8.0 Hz, 1H), 6.95–6.91 (m, 3H), 6.88–6.87 (d, J = 8.5 Hz, 1H), 6.80–6.78 (dd, J_1=8.5 Hz, J_2=3.0 Hz, 1H), 6.31 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 159.7, 154.9, 140.8, 140.6, 133.7, 129.6, 129.4, 121.8, 120.0, 119.0, 117.1, 113.9, 112.7, 74.0, 55.2. MS (EI): 63 (24), 76 (20), 102 (16), 131 (18), 159 (26), 165 (26), 166 (21), 194 (32), 237 (100), 266 (45). HRMS calc. for $C_{17}H_{14}O_3$: 266.0943, found 266.0932.

(*R*)-2-(4-(Trifluoromethyl)phenyl)-2*H*-chromene-3-carbaldehyde (5e). Isolated yield 56%. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 388 nm): t_R = 10.44 min (minor), 11.24 min (major). IR ν(film)/cm^{-1}: 3049, 2929, 2855, 1676, 1632, 1605, 1569, 1480, 1326, 1211, 1163, 1125, 1068, 947, 822, 759. ^{1}H NMR (500 MHz, $CDCl_3$): 9.66 (s, 1H), 7.54–7.52 (m, 2H), 7.48–7.46 (m, 2H), 7.44 (s, 1H), 7.35–7.31 (m, 1H), 7.27–7.26 (m, 1H), 6.99–6.96 (t, J = 8.5 Hz, 1H), 6.92–6.90 (d, J = 8.5 Hz, 1H), 6.38 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.9, 154.6, 143.1, 141.2, 134.0, 133.2, 130.8, 129.6, 127.0, 125.6, 125.5, 122.2, 119.8, 117.4, 73.4. MS (EI): 51 (22), 75 (14), 102 (10), 131 (41), 178 (38), 199 (7), 275 (100), 304 (58). HRMS calc. for $C_{17}H_{11}F_3O_2$: 304.0711, found 304.0704.

(*S*)-2-(Thiophen-2-yl)-2*H*-chromene-3-carbaldehyde (5f). Isolated yield 68%. HPLC (Daicel Chiralpak OD-H, hexane–*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 352 nm): t_R = 28.03 min (major), 30.34 min (minor). IR ν(film)/cm^{-1}: 3105, 2927, 2853, 1671, 1610, 1569, 1458, 1207, 1158, 963, 760, 708. ^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (s, 1H), 7.41 (s, 1H), 7.29–7.27 (m, 2H), 7.17–7.16 (dd, J_1=5.0 Hz, J_2=1.5 Hz, 1H), 6.99–6.96 (m, 2H), 6.89–6.86 (m, 2H), 6.54 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): 190.0, 160.3, 152.8, 141.0, 140.3, 133.1, 132.7, 129.3, 126.4, 121.8, 119.8, 119.0, 116.6, 67.9. MS (EI): 51(28), 63(35), 77(31), 89(12), 102(25), 115(23), 126(9), 139(17), 152(23), 184(28), 195(3), 213(100), 242(11). HRMS calc. for $C_{14}H_{10}O_2S$: 242.0402, found 242.0400.

(*R*)-2-Methyl-2*H*-chromene-3-carbaldehyde (5g). Isolated yield 45%. HPLC (Daicel Chiralpak OD-H, hexane–*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 384 nm): t_R = 7.32 min (minor), 7.83 min (major). IR ν(film)/cm^{-1}: 3043, 2973, 2928, 2854 1673, 1632, 1604, 1568, 1459, 1213, 1162, 943, 757. ^{1}H NMR (500 MHz, $CDCl_3$): 9.55 (s, 1H), 7.32–7.29 (m, 1H), 7.21–7.19 (m, 2H), 6.96–6.93 (t, J = 7.0 Hz, 1H), 6.88–6.87 (d, J = 8.0 Hz, 1H), 5.44–5.40 (q, J = 6.5 Hz, 1H), 1.37–1.36 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 154.5, 140.2, 136.3, 133.4, 129.2, 121.6, 120.0, 117.4, 69.9, 19.9. MS (EI): 51 (8), 63 (8), 77 (12), 91 (8), 102 (7), 115 (23), 131 (13), 145 (24), 159 (100), 174 (23).

(*R*)-6-Methoxy-2-phenyl-2*H*-chromene-3-carbaldehyde (5h). Isolated yield 70%. HPLC (Daicel Chiralpak OD-H, hexane–*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 424 nm): t_R = 19.53 min (major), 15.01 (minor). IR ν(film)/cm^{-1}: 3015, 2971, 2945, 2834, 1659, 1637, 1576, 1485, 1210, 1155, 994, 899, 819, 767, 702. ^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (s, 1H), 7.35 (s, 1H), 7.34–7.32 (m, 2H), 7.26–7.25 (m, 3H), 6.87–6.85 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1H), 6.81–6.79 (m, 1H), 6.77–6.76 (d, J = 3.0 Hz, 1H), 6.29 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 154.2, 148.8, 140.9, 138.9, 134.3, 128.5, 128.4, 126.7, 120.4, 119.8, 117.9, 113.0, 73.9, 55.7. MS (EI): 63 (6), 77 (4), 89 (7), 115 (8), 139 (10), 165 (30), 178 (8), 194 (20), 237 (100), 266 (53).

(*R*)-8-Methoxy-2-phenyl-2*H*-chromene-3-carbaldehyde (5i). Isolated yield 90%. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 384 nm): t_R = 11.33 min (major), 13.33 min (minor). IR ν(film)/cm^{-1}: 3057, 2938, 2840, 2813, 1667, 1635, 1601, 1478, 1264, 1098, 997, 771, 730, 697. ^{1}H NMR (500 MHz, $CDCl_3$): 9.66 (s, 1H), 7.39–7.36 (m, 3H), 7.26–7.25 (m, 3H), 6.93–6.87 (m, 3H), 6.43 (s, 1H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.1, 148.5, 144.1, 140.8, 139.0 134.0, 128.5, 126.5, 121.5, 121.3, 120.7, 119.6, 116.1, 74.1, 56.3. MS (EI): 51 (6), 63 (9), 77 (6), 89 (7), 115 (9), 139 (8), 152 (11), 165 (41), 178 (11), 194 (17), 237 (100), 266 (50).

(*R*)-6-Chloro-2-phenyl-2*H*-chromene-3-carbaldehyde (5j). Isolated yield 85%. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 396 nm): t_R = 11.65 min (minor), 9.89 min (major). IR ν(film)/cm^{-1}: 3065, 2933, 2822, 1674, 1640, 1597, 1563, 1473, 1207, 1159, 975, 819, 754, 699. ^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (s, 1H), 7.32–7.31 (m, 3H), 7.28–7.27 (m, 3H), 7.22–7.20 (m, 2H), 6.81–6.79 (d, J = 8.0 Hz, 1H), 6.32 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.7, 153.3, 139.1, 138.5, 134.6, 133.1, 128.9, 128.6, 128.4, 126.8, 126.5, 121.2 118.6, 74.5. MS (EI): 51 (9), 63 (7), 75 (10), 89 (8), 102 (8), 115 (4), 152 (11), 165 (9), 178 (45), 193 (14), 205 (12), 241 (100), 270 (50).

(*R*)-8-Methoxy-2-*p*-tolyl-2*H*-chromene-3-carbaldehyde (5k). Isolated yield 90%. HPLC (Daicel Chiralpak OD-H, hexane–*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 216 nm): t_R = 22.60 min (minor), 28.61 min (major). IR ν(film)/cm^{-1}: 3007, 2937, 2840, 1672, 1634, 1604, 1574, 1480, 1260, 1099, 981, 774, 733. ^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (s, 1H), 7.38 (s, 1H), 7.26–7.24 (d, J = 9.0 Hz, 2H), 7.06–7.05 (m, 2H), 6.90–6.87 (m, 3H), 6.39 (s, 1H), 3.81 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 148.5, 144.1, 140.7, 138.4, 135.9, 134.0, 129.1, 126.6, 124.5, 121.4, 119.5, 116.1, 74.0, 56.3, 21.1. MS (EI): 51(3), 63(5), 76(4), 89(8), 102(2), 115(5), 128(3), 139(4), 152(5), 165(22), 178(9), 189(9), 208(11), 221(4), 237(11), 251(100), 280(36). HRMS calc. for $C_{18}H_{16}O_3$: 280.1099, found 280.1082.

(*R*)-6-Chloro-2-*p*-tolyl-2*H*-chromene-3-carbaldehyde (5l). Isolated yield 90%. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 396 nm): t_R = 15.29 min (major), 14.35 min (minor). IR ν(film)/cm^{-1}: 3036, 2925, 2823, 1675, 1640, 1599, 1563, 1473, 1315, 1206, 1160, 953, 821, 723. ^{1}H NMR (500 MHz, $CDCl_3$): 9.64 (s, 1H), 7.33 (s, 1H), 7.23–7.19 (m, 4H), 7.09–7.07 (m, 2H), 6.79–6.77 (d, J = 8.5 Hz, 1H), 6.28 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 189.7, 153.3, 139.0, 138.9, 135.5, 134.7, 133.1, 129.4, 128.4, 126.8, 126.5, 121.2, 118.6, 74.5, 21.2. MS (EI): 51(5), 63(6), 75(6), 87(2), 101(6), 115(7), 127(4), 139(3), 152(4), 165(10), 178(10), 192(13), 205(7), 219(5), 241(9), 255(100), 269(12), 284(27). HRMS calc. for $C_{17}H_{13}ClO_2$: 284.0604, found 284.0606.

(*R*)-6-Nitro-2-phenyl-2*H*-chromene-3-carbaldehyde (5m). Isolated yield 55%. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 284 nm): t_R = 26.03 min (minor), 22.15 min (major). IR ν(film)/cm^{-1}: 3061, 3028, 2925, 2854, 1678, 1585, 1518, 1492, 1339, 1289, 1089, 976, 752, 701. ^{1}H NMR (500 MHz, DMSO-d_6): 9.69 (s, 1H), 8.48–8.47 (d, J = 2.5 Hz, 1H), 8.20–8.17 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1H), 8.04 (s, 1H), 7.35 (s, 5H), 7.08–7.06 (d, J = 7.5 Hz, 1H), 6.45 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): 190.8, 158.8, 141.7, 138.8, 137.9, 133.9, 129.2, 128.8, 128.6, 127.0, 125.3, 120.0, 117.5, 75.1. MS (EI): 51 (10), 63 (6), 76 (10), 89 (7), 102 (10), 115 (7), 158 (12), 178 (24), 206 (57), 234 (9), 252 (100), 281 (72). HRMS calc. for $C_{16}H_{11}NO_4$: 281.0688, found 281.0689

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