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Article

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Enantioselective Synthesis of Chromanones Bearing Quaternary Substituted Stereocentres Catalyzed by (*1R*)-Camphor-Derived *N*-Heterocyclic Carbenes

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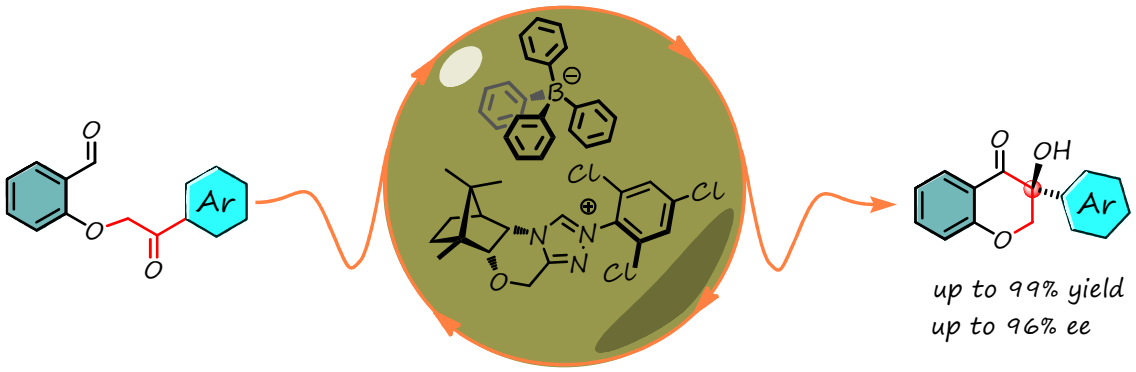


* derived from cheap and commercially available camphor
* the highest enantioselective access to 3-hydroxy-4-chromanone derivatives with quaternary stereogenic centres

Abstract: A catalytic asymmetric intramolecular crossed-benzoin reaction for the synthesis chromanones by novel camphor-derived NHCs is described. The corresponding chromanones bearing quaternary stereogenic centres were isolated in high yields with high to excellent enantioselectivity.

Keywords: N-heterocyclic carbenes, camphor, benzoin, chromanones, organocatalysis

Introduction

The chromanone core is one of the characteristic structural motifs in a variety of biologically active natural products and numerous pharmaceuticals (Figure 1).[1,2]

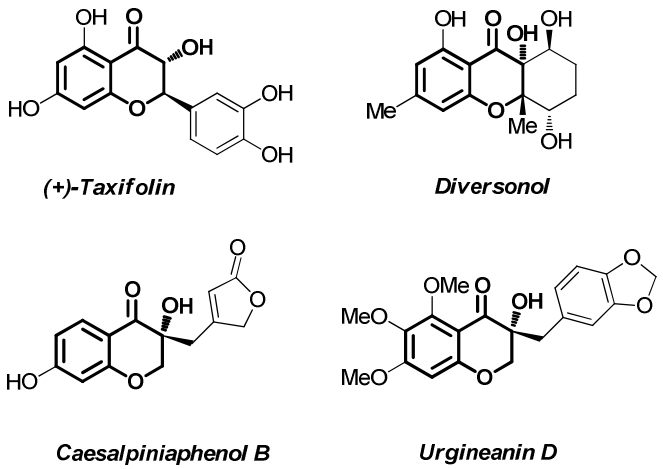
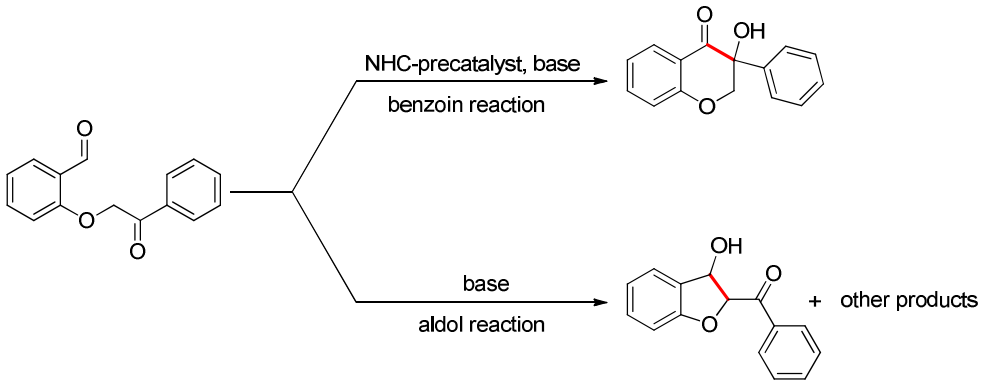


Figure 1. Selected natural products containing 3-hydroxy-4-chromanone core.

N-Heterocyclic carbene-catalyzed crossed benzoin reaction is a rapidly emerging area of organocatalysis because of the unique reaction model and significant importance of the products. For instance, Suzuki and co-workers successfully used intramolecular crossed-aldehyde-ketone benzoin reaction in an elegant synthesis of functionalized preanthraquinones.[3] In 2006, Enders applied this reaction for the synthesis of α-hydroxy tetralones, generating quaternary stereocenter in high enantioselectivity.[4] This nice aldehyde-ketone-based approach, proved successful in a number of interesting reactions.[5] In the context of NHC-mediated chromanone synthesis, this strategy was first explored by Suzuki in 2007 for the total synthesis of (+)-sappanone B.[6] However, the competing intramolecular aldol side reaction, induced by a base, in some cases resulted in significantly lower yield, and hampers separation of the main product from the side products (Scheme 1).

Scheme 1. Possible Reaction Pathways



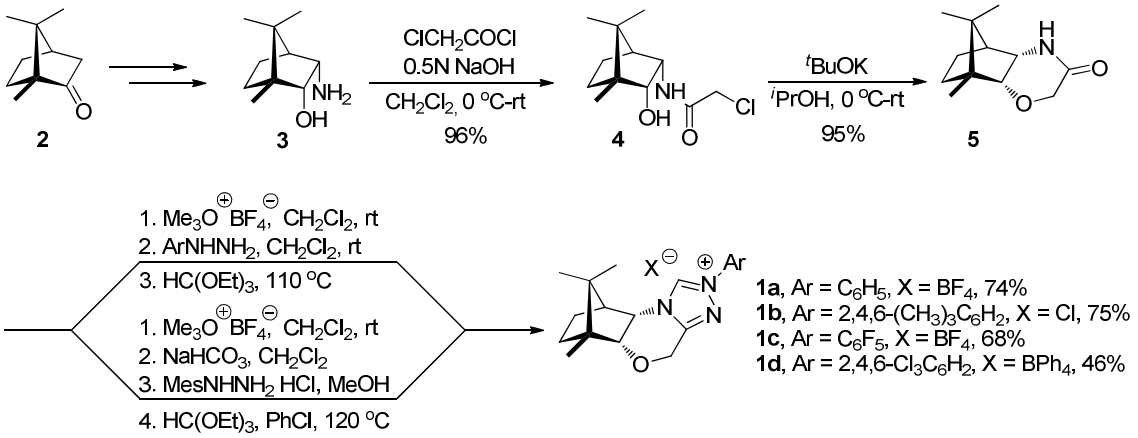
Very recently, You and co-workers devised tetracyclic triazolium salts **1**, derived from (-)-3-*exo*-aminoisoborneol backbone, and found them highly efficient in aldehyde-ketone

benzoin reactions with O- and N-tethered substrates,[7] Stetter-type Michael additions,[8] and desymmetrization reaction.[9] However, in the case of chromanones, enantioselectivities are not yet optimal (mostly below 90% ee) and the substrate scope is still limited. Despite the recent advances in this field the efficient catalysts for this reaction are also limited. Therefore the development of a novel NHC catalysts derived from natural chiral pool with improved reactivity profiles, having fine-tuned steric and electronic environment around the carbene centre is highly desirable. In a continuation of our ongoing efforts in the development of new *N*-heterocyclic carbene catalysts, derived from monoterpenes and their applications to organocatalytic reactions,[10] we report our preliminary results on the synthesis of novel chiral triazolium salts from (1*R*)-camphor and their application to the enantioselective intramolecular crossed-benzoin reaction.

Results and Disscusion

Our present study began with the synthesis of various triazolium salts as outlined in Scheme 2. (1*R*)-Camphor **2** was easily transformed into (–)-3-*endo*-aminoborneol **3** according to the reported method.[11] The morpholinone **5** was prepared using an optimized two-step procedure involving the formation of amide **4**, followed by cyclization with potassium *tert*-butoxide in excellent overall yields. A series of novel homologous triazolium salts **1a**-**d** were then obtained following procedures developed independently by Rovis[12] and Bode.[13] Additionally, their preparation does not require chromatographic purification.

Scheme 2. Synthesis of tetracyclic triazolium salts from (1*R*)-camphor



The configuration of triazolium salt **1a** was confirmed by X-ray crystallographic analysis as shown in Fig. 2.[14]

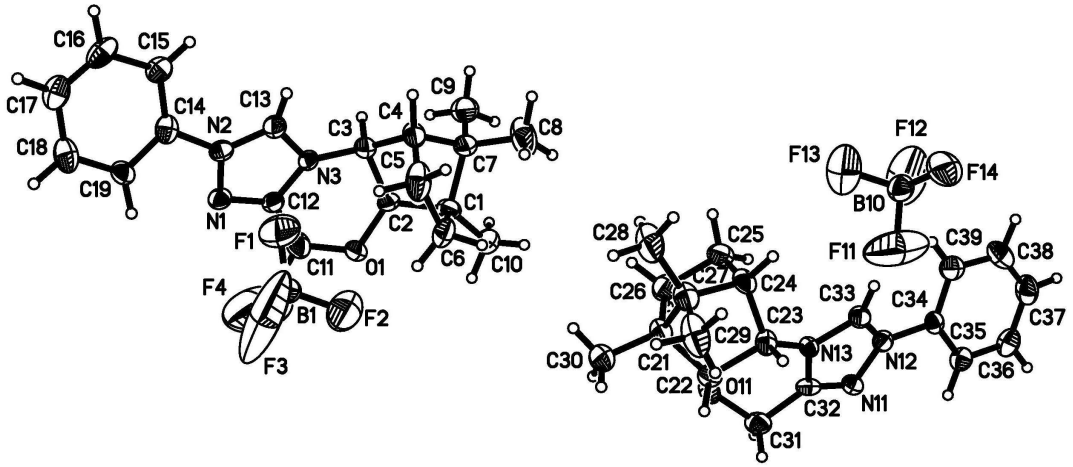
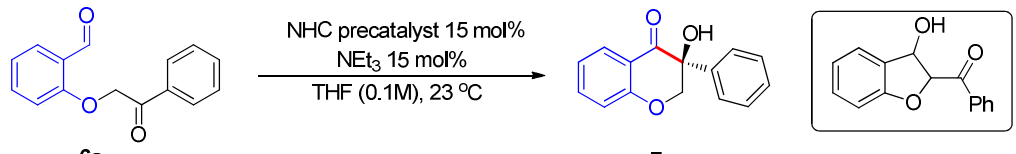


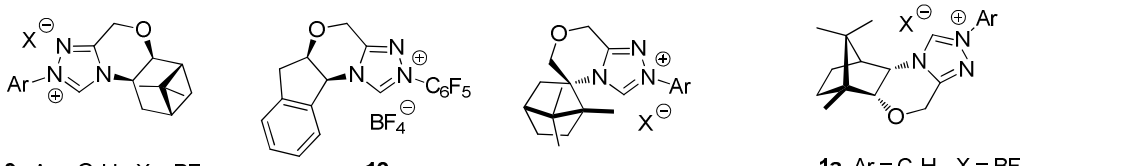
Figure 2. Crystal structure of **1a** with the thermal ellipsoids plotted at 30% probability.

The potential of four new catalysts and several readily available chiral NHC precursors in the enantioselective intramolecular crossed-benzoin reaction was tested. O-Tethered substrate **6a** reacted in the presence of NHC precatalysts **1a-d**, **9a-c**,[10a] **11a-c**[10b] (15 mol%) and triethylamine as a base (15 mol%) in THF for 20 h. As expected, the application of electron-deficient triazolium derived carbenes **1c-d, 9b**, **10**, **11b** were crucial in this type of reaction, while other structures proved completely inactive (Table 1). When the pinene-based NHC catalyst **9b** was used, **7a** was obtained in excellent 99% isolated yield (entry 2), albeit the enantioselectivity was moderate (76:24 er). Spirocyclic NHC **11b** enabled to obtain the phenyl-substituted acryloin **7a** almost quantitatively (99% yield) but with only low enantioselectivity (60:40 er, entry 6, Table 1). To our great delight, under the same conditions, application of novel camphor-based catalyst **1c** showed excellent reactivity and very promising asymmetric induction (98% yield of **7a**, 90:10 er, entry 10). Replacing the pentafluorophenyl group of **1c** with the trichlorophenyl substituent led to α-ketol **7a** with further increase of enantiomeric excess with unchanged yield (98%, 93:7 er, entry 11, Table 1). It is worth noting that for all tested terpene-based NHC precursors, the aldol reaction product **8** was not formed. Interestingly, the same reaction catalyzed by the aminoindanol derived catalyst **10** afforded the desired cyclization product **7a** in 90% yield, however low enantioselectivity was observed (65:35 er, entry 4). Moreover, as in the case of previously described Suzuki's modified aminoindanol precatalyst, the aldol product **8** was also present in the crude products,[6] and purification is difficult because of similar polarities.

Table 1. Screening of Chiral NHC Catalysts[a]



6a 7a 8



9a Ar = C_6H_5, X = BF_4
9b Ar = C_6F_5, X = BF_4
9c Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = Cl

10

11a Ar = C_6H_5, X = BF_4
11b Ar = C_6F_5, X = BF_4
11c Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = Cl

1a, Ar = C_6H_5, X = BF_4
1b, Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = Cl
1c, Ar = C_6F_5, X = BF_4
1d, Ar = 2,4,6-$Cl_3C_6H_2$, X = BPh_4

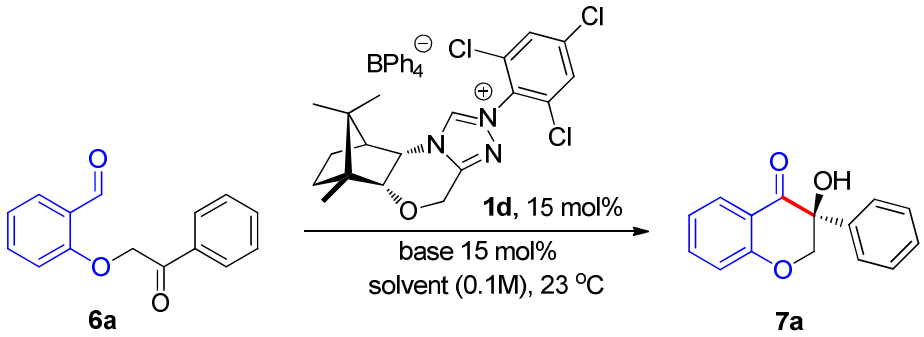
Entry	NHC precat.	yield (%)[b]	er[c]
1	**9a**	<5	ND
2	**9b**	99	76:24
3	**9c**	<5	ND
4	**10**	90[d]	65:35
5	**11a**	<5	ND
6	**11b**	99	60:40
7	**11c**	<5	ND
8	**1a**	<5	ND
9	**1b**	<5	ND
10	**1c**	98	90:10
11	**1d**	98	93:7

[a]Reaction condition: **6a** (0.1 mmol), precatalyst 15 mol%, triethylamine 15 mol%, THF 1 mL (0.1 M), 23 °C. [b]Isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase. [d]The corresponding aldol product was observed.

Next, we focused our attention on additional optimization to improve reaction enantioselectivity was carried using various bases and solvents (Table 2). In this regard, all the tested organic bases were tolerable and gave the desired α-ketol **7a** in high enantioselectivity and excellent yields. In the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) or 4-(dimethylamino)pyridine (DMAP), the reaction proceed smoothly, albeit a slight erosion of the er value was observed (entries 6-7, Table 2). Surprisingly, when the phosphazene base BEMP was used, the reaction went also smoothly to give the desired 3-

hydroxychromanone **7a** in almost quantitative yield and excellent enantioselectivity within 30 minutes (98% yield, 92% ee, entry 11, Table 2). Among the various solvent screened, the reaction in TAME, *o*-xylene and MTBE resulted in comparable results (entry 13-15), whereas the reaction in polar protic and aprotic solvents such as ethanol, DMF and octafluorotoluene, the desired product was not obtained. Finally, cyclopentyl methyl ether was found to be the optimal solvent, and **7a** was obtained in less than 1 h in 99% yield, with a slightly improved er (96.5:3.5).

Table 2. Reaction Optimization[a]



6a **7a**

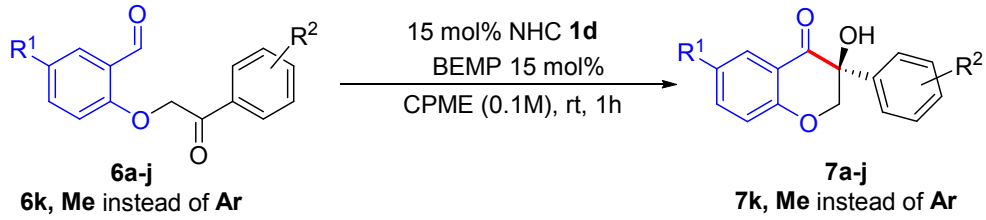
entry	solvent	base	time (h)	yield (%)[b]	er[c]
1	THF	NEt_3	20	98	93:7
2	THF	DIPEA	20	99	93:7
3	THF	DCyEA	20	98	94:6
4	THF	Pempidine	20	98	90:10
5	THF	DBU	20	93	94:6
6	THF	DABCO	20	90	89:11
7	THF	DMAP	20	91	86:14
8	THF	KHMDS	20	92	92:8
9	THF	P_2-Et	20	98	92:8
10	THF	P_2-^{t}Bu	20	98	92:8
11	THF	BEMP	0.5	99	96:4
12	CH_2Cl_2	BEMP	18	99	92.5:7.5
13	MTBE	BEMP	2	97	95:5
14	TAME	BEMP	2	99	95:5
15	*o*-xylene	BEMP	0.5	99	94:6
16	**CPME**	**BEMP**	**0.75**	**99**	**96.5:3.5**

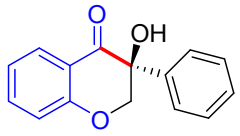
17	DMF	BEMP	48	<5	ND
18	OFT	BEMP	48	NR	------
19	EtOH	BEMP	48	NR	------

[a]Reaction condition: **6a** (0.1 mmol), precatalyst 15 mol%, base 15 mol% in 0.1 M in solvent (1 mL), and at rt. [b]Isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase. BEMP: 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine, OFT: octafluorotoluene; DCyEA: dicyclohexylethylamine; CMPE: cyclopentyl methyl ether; TAME: *tert*-amyl methyl ether.

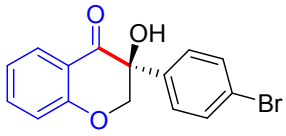
Encouraged by these results, the scope of the reaction was explored using a series of aryl substituted O-tethered substrates. The results are shown in Scheme 3. The reaction performed with both electron-withdrawing (4-BrC_6H_5-**7b**, 4-FC_6H_5-**7c** and 4-$CF_3OC_6H_5$-**7d**) and electron-donating substituents (**7f**) on the phenyl group could be well tolerated, afforded the cross-benzoin products in high yields and enantiomeric excess. However, due to the lower reactivity in the case of electron-withdrawing groups (**7b**, **7c** and **7i**) we used modified protocol by replacing BEMP with diisopropylethylamine, but the desired products are still obtained with high stereocontrol. Cyclization of 2,4-disubstituted aryl ketone (**7h**) occurred also efficiency with high yield, however a slightly lower enantioselectivity was observed. Replacing the phenyl group with naphtyl gave the desired chromanone **7e** with excellent yield and very high enantioselectivity (97% yield, 95% ee). The use of a large 4-phenyl aryl ketone also worked well, affording the desired product **7j** with high stereocontrol (98:2 er). Unfortunately, when the aryl group was replaced with small methyl, cyclization product **7k** was afforded with decreased selectivity (72:28 er) although the yield remained excellent (99% yield within 20 min.)

Scheme 3. Scope of the Cross-Benzoin Reaction[a]

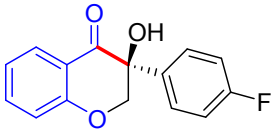




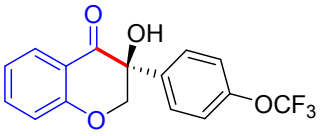
7a: 99% yield
96.5:3.5 er



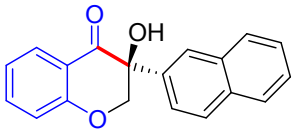
7b: 91% yield[b]
96:4 er



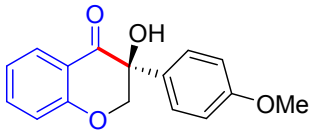
7c: 81% yield[b]
97:3 er



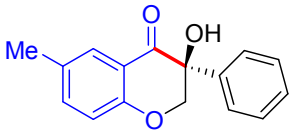
7d: 91% yield
95:5 er



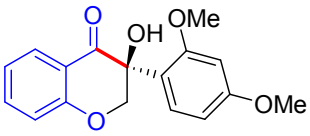
7e: 99% yield
97.5:2.5 er



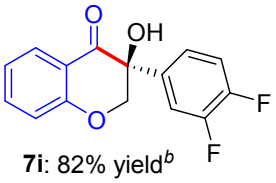
7f: 98% yield
97:3 er



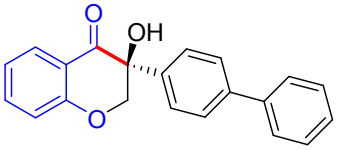
7g: 98% yield
93:7 er



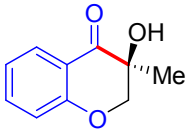
7h: 97% yield
91:9 er



7i: 82% yield[b]
95:5 er



7j: 98% yield
98:2 er



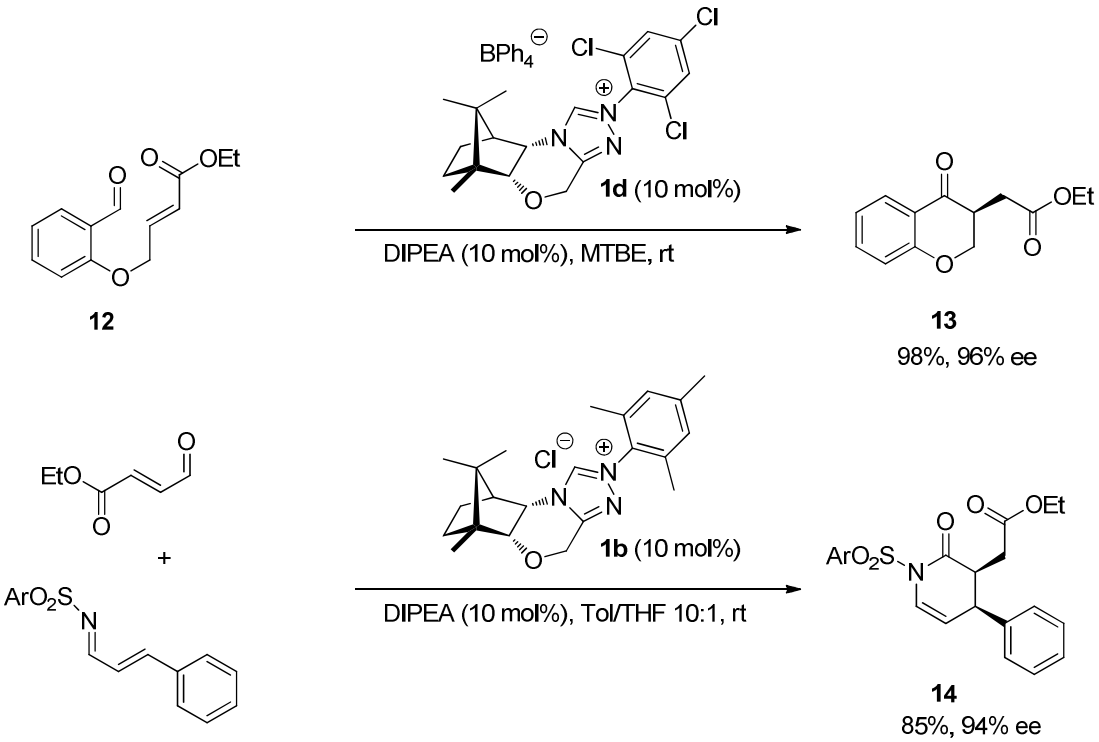
7k: 99% yield
72:28 er

[a]Unless otherwise noted, all reactions were performed with keto-aldehyde substrate (0.2 mmol), NHC precatalyst **1d** 15 mol%, BEMP 15 mol% in CPME (2 mL) at rt for 1 h. Yields of isolated product after column chromatography. The er values were determined by HPLC analysis using a chiral stationary phase.[b] For electron-withdrawing substituents DIPEA (100 mol%) instead BEMP was used. The reaction proceeded for 20 h.

We have carried out additional experiments to show the usefulness of triazolium salts **1b,d** in the Stetter reaction and aza-diene Diels-Alder reaction.[15] Cyclization of salicylaldehyde-

derived substrate **12** occurred very efficiency to give the chromanone **13** in a excellent yield with 95% ee. The reaction of enal and an α,β-unsaturated imine catalyzed by NHC-**1b**, proceeded smoothly to afford dihydropiridinone **14** with high yield and excellent enantioselectivity (Scheme 4).

Scheme 4. Application of NHC Precursors 1b,d in Other Reactions



Conclusion

In summary, a series of novel chiral NHC precursors derived from readily available (1*R*)-camphor for enantioselective cross-benzoin reaction with O-tethered substrates was developed. Various substituted 3-hydroxy-3-aryl-4-chromanone derivatives having a quaternary stereogenic centre were obtained with high to excellent yield and stereocontrol. Moreover, the excellent reactivity of substrates with electron-donating substituent on the phenyl group is noteworthy, since all reactions were completed within 1 h. Notable, the generally better enantioselectivities for the chromanone-derived products facilitated by our catalytic system were observed. Further application of the methodology in organic synthesis, and development of new enantioselective catalytic reactions using these camphor-derived triazolium salts are currently underway.

Experimental section

General information: Reactions involving moisture sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques. All glassware used was flame dried and cooled under vacuum. Anhydrous diethyl ether, *tert*-butyl methyl ether, cyclopentyl methyl ether, *tert*-amyl methyl ether, THF, DME, toluene, *o*-xylene and were distilled from sodium and benzophenone Anhydrous dichloromethane was obtained by distillation over calcium hydride. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F_{254}silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. Column chromatography was performed with silica gel 70-230 mesh. NMR spectra were recorded on either 700 (^{1}H, 700 MHz; ^{13}C, 176 MHz) or 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), using $CDCl_3$ as solvent, and were reported in ppm relative to $CHCl_3$ (δ 7.26) for ^{1}H NMR and relative to the central $CDCl_3$ (δ 77.00) resonance for ^{13}C NMR. Coupling constants (*J*) in ^{1}H NMR are in Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets)and dtd (doublet of triplets of doublets). Melting points were obtained in open capillary tubes using a micro melting point apparatus and were uncorrected. Optical rotations were measured using a 1.0 mL cell with a 0.1 dm path length. Low-resolution mass spectra (LRMS) were recorded using the ESI mode (TOF). All other reagents were purchased from commercial suppliers. Catalyst **1a-d** were prepared according to the known methods.[10a-b,12-13] Starting materials **4**, **5** were prepared according to the known method.[10a] For **1c**, in the ^{13}C NMR fluorine couplings are not included due to the complexity of the perfluoro couplings.

2-Chloro-N-((1*S*,2*S*,3*R*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide (4). White solid, 96% yield. M.p. 57-60 °C. $[\alpha]_D^{21}$ = +4.9 (c 2.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.89 (s, 3H), 0.94 (s, 3H), 0.96 (s, 3H), 1.21 (dtd, *J* = 12.8, 4.4, 2.0 Hz, 1H), 1.37 (dddd, *J* = 22.8, 13.6, 9.6, 4.4 Hz, 1H), 1.47-1.56 (m, 1H), 1.85 (dddd, *J* = 22.4, 14.0, 9.6, 4.8 Hz, 1H), 2.06 (t, *J* = 4.0 Hz, 1H), 2.32 (d, *J* = 4.8 Hz, 1H), 4.03 (ddd, *J* = 9.6, 4.8, 2.0 Hz, 1H), 4.08 (s, 2H), 4.19-4.24 (m, 1H), 7.35 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 18.3, 19.6, 19.9, 25.3, 42.8, 45.4, 48.5, 49.7, 49.8, 73.5, 166.0. LRMS (ESI): Mass calcd for $[M+Na+MeOH]^+$ $C_{13}H_{24}ClNO_3Na$: 300.1; found 300.4. Anal. calcd for $C_{12}H_{20}ClNO_2$: C, 58.65; H, 8.20; Found: C, 58.77; H, 8.30.

(4a*S*,5*S*,8*R*,8a*R*)-8,9,9-Trimethylhexahydro-2H-5,8-methanobenzo[b][1,4]oxazin-3(4H)-one (5). White solid, 95% yield. M.p. 179-181 °C. $[\alpha]_D^{21}$ = −6.5 (c 2.1, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$) δ: 0.96 (s, 3H), 0.98 (s, 3H), 0.99 (s, 3H), 1.29 (dtd, *J* = 12.6, 4.9, 1.4 Hz, 1H), 1.53-1.58 (m, 1H), 1.64-1.78 (m, 1H), 1.83 (t, *J* = 4.9 Hz, 1H), 2.01 (dddd, *J* = 22.4, 13.3, 9.8, 4.2 Hz, 1H), 3.82 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.86 (d, *J* = 9.1 Hz, 1H), 3.90 (d, *J* = 15.4 Hz, 1H), 4.20 (d, *J* = 15.4 Hz, 1H), 5.76 (bs, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 13.8, 18.6, 18.9, 20.0, 26.6, 46.8, 49.0, 49.6, 51.0, 66.6, 78.7, 173.2. LRMS (ESI): Mass calcd for $[2M+Na]^+$ $C_{24}H_{38}N_2O_4Na$: 441.3; found 441.5. Anal. calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; Found: C, 68.95; H, 9.22.

(5a*R*,6*R*,9*S*,9a*S*)-6,11,11-Trimethyl-2-phenyl-5a,6,7,8,9,9a-hexahydro-4H-6,9-methanobenzo-[b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate (1a). White solid, 74% yield. M.p. 274-277 °C. $[\alpha]_D^{21}$ = +5.2 (c 1.3, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$) δ: 0.88-0.93 (m, 1H), 0.95 (s, 3H), 0.97 (s, 3H), 1.00 (s, 3H), 1.29-1.33 (m, 1H), 1.65-1.71 (m, 1H), 1.83 (dddd, *J* = 22.4, 13.3, 9.1, 4.2 Hz, 1H), 2.70 (t, *J* = 4.2 Hz, 1H), 4.23 (d, *J* = 9.1 Hz, 1H), 4.82 (d, *J* = 15.4 Hz, 1H), 4.87 (dd, *J* = 4.2, 9.1 Hz, 1H), 5.10 (d, *J* = 15.4 Hz, 1H), 7.46-7.53 (m, 3H), 7.84-7.87 (m, 2H), 10.08 (s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 14.5, 19.3, 20.4, 20.5, 27.4, 48.2, 48.7, 51.1, 56.6, 60.6, 80.1, 121.6 (2C), 131.2 (2C), 131.7, 135.9, 140.2, 154.0. LRMS (ESI): Mass calcd for $[M]^+$ $C_{19}H_{24}N_3O$: 310.4; found 310.4. Anal. calcd for $C_{19}H_{24}BF_4N_3O$: C, 57.45; H, 6.09; Found: C, 57.40; H, 6.07.

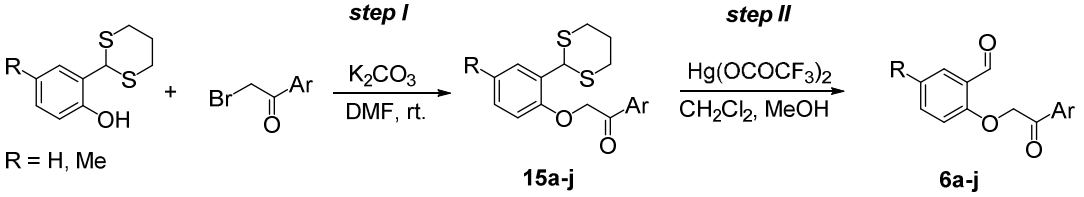
(5a*R*,6*R*,9*S*,9a*S*)-2-Mesityl-6,11,11-trimethyl-5a,6,7,8,9,9a-hexahydro-4H-6,9-methanobenzo-[b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium chloride (1b). White solid, 75% yield. M.p. = 307-310 °C. $[\alpha]_D^{21}$ = +7.3 (c 1.0, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$) δ: 0.85 (dddd, *J* = 23.1, 14.0, 9.1, 4.9 Hz, 1H), 1.03 (s, 3H), 1.04 (s, 3H), 1.11 (s, 3H), 1.37 (dt, *J* = 11.9, 4.9 Hz, 1H), 1.73-1.79 (m, 1H), 1.87 (dddd, *J* = 22.4, 12.6, 9.1, 4.9 Hz, 1H), 2.14 (s, 6H), 2.35 (s, 3H), 3.12 (m, 1H), 4.25 (d, *J* = 8.4 Hz, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 5.14-5.17 (m, 2H), 7.01 (s, 2H), 11.67 (s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 14.5, 18.7, 19.6, 20.4 (2C), 20.5, 22.2, 27.5, 48.2, 49.6, 51.4, 56.8, 60.6, 80.4, 130.8 (2C), 132.1, 135.8, 143.0 (2C), 146.3, 153.0. LRMS (ESI): Mass calcd for $[M]^+$ $C_{22}H_{30}N_3O$: 352.2; found 352.3. Anal. calcd for $C_{22}H_{30}ClN_3O$: C, 68.11; H, 7.79; Found: C, 68.20; H, 7.85.

(5a*R*,6*R*,9*S*,9a*S*)-6,11,11-Trimethyl-2-(perfluorophenyl)-5a,6,7,8,9,9a-hexahydro-4H-6,9-methanobenzo[b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate (1c). Pale yellow solid, 68% yield. M.p. 110-114 °C. $[\alpha]_D^{21}$ = +1.8 (c 1.0, $CHCl_3$). ^1H NMR (700 MHz,

$CDCl_3$) δ: 0.85 (dddd, *J* = 23.1, 14.0, 9.8, 5.6 Hz, 1H), 1.03 (s, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.36 (dt, *J* = 11.9, 4.9 Hz, 1H), 1.71-1.77 (m, 1H), 1.86 (dddd, *J* = 23.1, 14.0, 9.8, 4.2 Hz, 1H), 2.52 (t, *J* = 4.2 Hz, 1H), 4.28 (d, *J* = 9.1 Hz, 1H), 4.85 (d, *J* = 15.4 Hz, 1H), 4.93 (dd, *J* = 7.0, 4.2 Hz, 1H), 5.09 (d, *J* = 15.4 Hz, 1H), 9.97 (s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 14.4, 19.3, 20.4, 20.5, 27.3, 48.3, 48.8, 51.0, 56.9, 60.4, 79.9, 111.8, 138.3, 138.8, 139.7, 143.6, 145.0, 146.6, 154.9. LRMS (ESI): Mass calcd for $[M]^+$ $C_{19}H_{19}F_5N_3O$: 400.4; found 400.4. Anal. calcd for $C_{19}H_{19}BF_9N_3O$: C, 46.84; H, 3.93; Found: C, 46.89; H, 3.99.

(5a*R*,6*R*,9*S*,9a*S*)-6,11,11-Trimethyl-2-(2,4,6-trichlorophenyl)-5a,6,7,8,9,9a-hexahydro-4H-6,9-methanobenzo[b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetraphenylborate (1d). White solid, 46% yield. M.p. 145-147 °C. $[\alpha]_D^{21}$ = −5.4 (c 1.2, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.41 (dddd, *J* = 23.1, 14.0, 9.1, 4.8 Hz, 1H), 0.93 (s, 3H), 0.96 (s, 3H), 1.04 (s, 3H), 1.20-1.27 (m, 1H), 1.53-1.62 (m, 2H), 2.33 (t, *J* = 4.8 Hz, 1H), 2.45 (dd, *J* = 9.1, 4.8 Hz, 1H), 3.74 (d, *J* = 9.1 Hz, 1H), 4.46 (d, *J* = 15.4 Hz, 1H), 5.00 (d, *J* = 15.4 Hz, 1H), 5.66 (s, 1H), 6.68-6.93 (m, 12H), 7.36-7.42 (m, 8H), 7.65 (s, 1H), 7.70 (s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 13.3, 18.7, 19.1, 19.6, 25.8, 47.1, 47.8, 50.0, 54.5, 59.1, 79.2, 122.2 (4C), 125.7 (8C), 129.0, 129.4, 130.2, 133.9, 134.7, 136.3 (8C), 139.8, 144.8, 152.3, 163.1, 163.6, 164.1, 164.6. LRMS (ESI): Mass calcd for $[M]^+$ $C_{19}H_{21}Cl_3N_3O$: 412.1; found 412.4. Anal. calcd for $C_{43}H_{41}BCl_3N_3O$: C, 70.46; H, 5.64; Found: C, 70.55; H, 5.53.

General procedure for the preparation of keto-aldehyde 6a-j



Step I: To a solution of the dithiane[16] (9.4 mmol) in dimethylformamide (9.5 mL) was added K_2CO_3 (1.5 g, 10.8 mmol). After stirring for 0.5 h, ω-bromoacetophenone derivative (9.4 mmol) was added and the mixture was stirred at room temperature overnight. After completion (monitored by TLC), water was added to the solution, and the mixture was extracted with ethyl acetate. The combined ethyl acetate extract was washed with brine, dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified by column chromatography (Petroleum ether/EtOAc, 8:2).

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-phenylethanone (15a). Yellow solid, 92% yield (2.86 g). M.p. = 95-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.89-2.00 (m, 1H), 2.13-2.20 (m, 1H), 2.87-2.92 (m, 2H), 3.03-3.11 (m, 2H), 5.31 (s, 2H), 5.79 (s, 1H), 6.84 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.03 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.25 (dddd, *J* = 15.6, 8.4, 7.6, 1.6 Hz, 1H), 7.50-7.55 (m, 2H), 7.62-7.66 (m, 2H), 8.02-8.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 32.4 (2C), 44.0, 72.0, 112.7, 122.3, 128.3 (2C), 128.4, 128.8 (2C), 129.4, 129.5, 133.8, 134.7, 154.2, 194.4. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{18}H_{18}S_2O_2Na$: 353.1; found 353.3. Anal. calcd for $C_{18}H_{18}S_2O_2$: C, 65.42; H, 5.49; Found: C, 65.31; H, 5.38.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-(4-bromophenyl)ethanone (15b). Ochre solid, 98% yield (3.77 g). M.p. = 107-109 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.92-1.99 (m, 1H), 2.15-2.21 (m, 1H), 2.90-2.93 (m, 2H), 3.02-3.08 (m, 2H), 5.24 (s, 2H), 5.73 (s, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 7.25-7.28 (m, 1H), 7.64 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.66-7.69 (m, 2H), 7.90-7.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 32.4 (2C), 44.0, 72.0, 112.5, 122.4, 128.3, 129.0, 129.4, 129.5, 130.0 (2C), 132.1 (2C), 133.4, 154.0, 193.8. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{18}H_{17}BrS_2O_2Na$: 431.0; found 431.1. Anal. calcd for $C_{18}H_{17}BrS_2O_2$: C, 52.81; H, 4.19; Found: C, 52.71; H, 4.12.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-(4-fluorophenyl)ethanone (15c). Yellow solid, 99% yield (3.24 g). M.p. = 153-155 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.92-1.99 (m, 1H), 2.16-2.20 (m, 1H), 2.90-2.93 (m, 2H), 3.04-3.09 (m, 2H), 5.26 (s, 2H), 5.76 (s, 1H), 6.83 (d, *J* = 9.1 Hz, 1H), 7.05 (t, *J* = 7.0 Hz, 1H), 7.18-7.21 (m, 2H), 7.25-7.28 (m, 1H), 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.09-8.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 32.4 (2C), 44.0, 72.0, 112.5, 115.9, 116.1, 122.4, 128.3, 129.4 (d, *J* = 4.7 Hz, 2C), 131.1 (d, *J* = 3.1 Hz), 131.2 (d, *J* = 9.5 Hz, 2C), 154.0, 165.0 (d, *J* = 254.4 Hz), 193.0. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{18}H_{17}FS_2O_2Na$: 371.1; found 371.1. Anal. calcd for $C_{18}H_{17}FS_2O_2$: C, 62.04; H, 4.92; Found: C, 61.93; H, 4.85.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-(4-(trifluoromethoxy)phenyl)ethanone (15d). Yellow oil, 75% yield (2.92 g). ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.92-1.98 (m, 1H), 2.16-2.19 (m, 1H), 2.89-2.93 (m, 2H), 3.02-3.06 (m, 2H), 5.26 (s, 2H), 5.73 (s, 1H), 6.85 (dd, *J* = 1.4, 8.4 Hz, 1H), 7.07 (dt, *J* = 7.7, 0.7 Hz, 1H), 7.27 (ddd, *J* = 16.1, 7.7, 1.4 Hz, 1H), 7.34-7.37 (m, 2H), 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.13-8.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 32.3 (2C), 44.0, 72.0, 112.4, 120.0 (q, *J* = 257.5 Hz), 120.5, 122.5, 128.3, 129.5, 129.6 (2C), 130.7 (2C), 132.9, 153.0, 153.9, 193.3. LRMS (ESI): Mass calcd for $[M+Na]^+$

$C_{19}H_{17}F_3S_2O_3Na$: 437.0; found 437.3. Anal. calcd for $C_{19}H_{17}F_3S_2O_3$: C, 55.06; H, 4.13; Found: C, 55.18; H, 4.16.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-(naphthalen-2-yl)ethanone (15e). Yellow solid, 87% yield (3.11 g). M.p. = 154-157 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.86-1.92 (m, 1H), 2.05-2.10 (m, 1H), 2.80-2.84 (m, 2H), 2.91-2.96 (m, 2H), 5.39 (s, 2H), 5.77 (s, 1H), 6.89 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.03 (dt, *J* = 7.0, 0.7 Hz, 1H), 7.24-7.27 (m, 1H), 7.55-7.58 (m, 1H), 7.62-7.64 (m, 2H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.07 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.60 (d, *J* = 0.7 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 24.9, 32.0 (2C), 43.6, 71.8, 112.1, 122.0, 123.4, 126.5, 127.5, 127.9, 128.3, 128.5, 129.0, 129.1, 129.4, 130.1, 131.6, 132.0, 135.5, 153.7, 194.1. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{22}H_{20}S_2O_2Na$: 380.1; found 380.2. Anal. calcd for $C_{22}H_{20}S_2O_2$: C, 69.44; H, 5.30; Found: C, 69.35; H, 5.21.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-(4-methoxyphenyl)ethanone (15f). Yellow solid, 96% yield (3.25 g). M.p. = 89-90 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.93-2.00 (m, 1H), 2.17-2.21 (m, 1H), 2.90-2.93 (m, 2H), 3.08-3.12 (m, 2H), 3.92 (s, 3H, OCH_3), 5.27 (s, 2H), 5.80 (s, 1H), 6.84 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.99-7.01 (m, 2H), 7.04 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.25 (dddd, *J* = 15.4, 9.1, 7.7, 1.4 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.05-8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 32.4 (2C), 44.0, 55.6, 71.8, 112.6, 114.0 (2C), 122.2, 127.7, 128.3, 129.3, 129.4, 130.7 (2C), 154.2, 164.0, 192.8. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{19}H_{20}S_2O_3Na$: 383.1; found 383.2. Anal. calcd for $C_{19}H_{20}S_2O_3$: C, 63.30; H, 5.59; Found: C, 63.35; H, 5.48.

2-(2-(1,3-Dithian-2-yl)-4-methylphenoxy)-1-phenylethanone (15g). Brown solid, 88% yield (2.85 g). M.p. = 108-111 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.89-2.00 (m, 1H), 2.13-2.20 (m, 1H), 2.28 (s, 3H), 2.86-2.90 (m, 2H), 3.02-3.07 (m, 2H), 5.26 (s, 2H), 5.74 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 7.02 (m, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.48-7.51 (m, 2H), 7.60-7.63 (m, 1H), 8.00-8.05 (m, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 21.5, 26.4, 33.4 (2C), 45.1, 73.3, 113.9, 129.1, 129.3 (2C), 129.8 (2C), 130.8, 130.9, 132.8, 134.7, 135.8, 153.1, 195.6. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{19}H_{20}S_2O_2Na$: 367.1; found 367.1. Anal. calcd for $C_{19}H_{20}S_2O_2$: C, 66.24; H, 5.85; Found: C, 66.30; H, 5.92.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-(2,4-dimethoxyphenyl)ethanone (15h). Pink solid, 87% yield (3.19 g). M.p. = 138-140 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.93-1.99 (m, 1H), 2.16-2.20 (m, 1H), 2.90-2.93 (m, 2H), 3.09-3.14 (m, 2H), 3.91 (s, 3H; OCH_3), 3.93 (s, 3H;

OCH_3), 5.26 (s, 2H), 5.83 (s, 1H), 6.14 (d, *J* = 2.1 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.75 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.00 (dt, *J* = 8.4, 1.4 Hz, 1H), 7.22 (ddd, *J* = 9.1, 7.0, 1.4 Hz, 1H), 7.63 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.01 (d, *J* = 9.1 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 26.4, 33.4 (2C), 44.1, 56.6, 56.7, 76.0, 99.1, 106.8, 113.5, 119.3, 122.6, 129.0, 130.2 (2C), 134.1, 155.7, 162.2, 166.2, 194.4. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{20}H_{22}S_2O_4Na$: 413.1; found 413.2. Anal. calcd for $C_{20}H_{22}S_2O_4$: C, 61.51; H, 5.68; Found: C, 61.58; H, 5.76.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-(3,4-difluorophenyl)ethanone (15i). Yellow solid, 82% yield (2.82 g). M.p. = 76-79 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.93-2.00 (m, 1H), 2.18-2.22 (m, 1H), 2.92-2.95 (m, 2H), 3.05-3.10 (m, 2H), 5.23 (s, 2H), 5.74 (s, 1H), 6.84 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.07 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.27 (m, 1H), 7.30-7.34 (m, 1H), 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.86-7.90 (m, 1H), 7.95 (dddd, *J* = 18.2, 10.5, 7.7, 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 32.4 (2C), 44.0, 72.0, 112.4, 117.8 (d, *J* = 18.2 Hz), 118.0 (d, *J* = 18.2 Hz), 122.6, 125.8 (dd, *J* = 7.9, 4.0 Hz) 128.3, 129.5, 129.6, 131.7 (t, *J* = 4.0 Hz), 150.5 (dd, *J* = 249.6, 12.6 Hz), 153.8, 154.0 (dd, *J* = 256.7, 12.6 Hz), 192.4. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{18}H_{16}F_2S_2O_2Na$: 389.0; found 389.3. Anal. calcd for $C_{18}H_{16}F_2S_2O_2$: C, 59.00; H, 4.40; Found: C, 59.13; H, 4.47.

2-(2-(1,3-Dithian-2-yl)phenoxy)-1-([1,1'-biphenyl]-4-yl)ethanone (15j). Light orange solid, 89% yield (3.40 g). M.p. = 112-114 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.92-1.99 (m, 1H), 2.16-2.20 (m, 1H), 2.90-2.93 (m, 2H), 3.07-3.11 (m, 2H), 5.35 (s, 2H), 5.82 (s, 1H), 6.88 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.07 (dt, *J* = 7.0, 0.7 Hz, 1H), 7.28 (dddd, *J* = 15.4, 8.4, 7.7, 1.4 Hz, 1H), 7.44-7.46 (m, 1H), 7.50-7.53 (m, 2H), 7.65-7.68 (m, 3H), 7.74-7.77 (m, 2H), 8.12-8.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 32.4 (2C), 44.1, 72.1, 112.7, 122.4, 127.3 (2C), 127.4 (2C), 128.3, 128.5, 129.0 (2C), 129.1 (2C), 129.4, 129.5, 133.4, 139.7, 146.4, 154.2, 194.0. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{24}H_{22}S_2O_2Na$: 429.1; found 429.2. Anal. calcd for $C_{24}H_{22}S_2O_2$: C, 70.90; H, 5.45; Found: C, 70.93; H, 5.48.

Step II. To a solution of keto-dithane (7.0 mmol) in dichloromethane (82 mL) and methanol (1.2 mL) was added mercury trifluoroacetate (4.9 g, 10.5 mmol, 1.5 equiv) and the resulting cloudy solution was stirred until reaction was judged to be complete by TLC. The reaction mixture was then filtered through Celite pad and the resulting solution was concentrated in vacuo. The desired product was purified by crystallization with a solution of petroleum ether and ethyl acetate.

2-(2-Oxo-2-phenylethoxy)benzaldehyde (6a). Ochre solid, 88% yield (1.48 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.45 (s, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.50-7.56 (m, 3H), 7.64-7.69 (m, 1H), 7.89 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.00-8.03 (m, 2H), 10.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.9, 112.8, 121.7, 125.4, 128.0 (2C), 128.7, 129.0 (2C), 134.2, 134.3, 135.7, 160.3, 189.6, 193.6. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{12}O_3Na$: 263.1; found 263.1. Anal. calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; Found: C, 75.06; H, 5.09.

2-(2-(4-Bromophenyl)-2-oxoethoxy)benzaldehyde (6b). Beige solid, 99% yield (2.21 g). M.p. = 155-158 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.40 (s, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 7.10-7.13 (m, 1H), 7.55 (dddd, *J* = 16.1, 8.4, 7.0, 2.1 Hz, 1H), 7.68-7.72 (m, 2H), 7.89-7.92 (m, 3H), 10.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.9, 113.7, 122.9, 126.4, 129.9, 130.5, 130.6 (2C), 133.4 (2C), 133.9, 136.8, 161.1, 190.4, 198.8. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{11}BrO_3Na$: 343.2; found 343.2. Anal. calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Found: C, 56.56; H, 3.52.

2-(2-(4-Fluorophenyl)-2-oxoethoxy)benzaldehyde (6c). Yellowish solid, 99% yield (1.79 g). M.p. = 121-122 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.41 (s, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 7.11-7.13 (m, 1H), 7.21-7.24 (m, 2H), 7.55 (dddd, *J* = 16.1, 8.4, 7.7, 2.1 Hz, 1H), 7.91 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.06-8.09 (m, 2H), 10.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.8, 112.8, 116.2 (d, *J* = 22.1 Hz, 2C), 121.8, 125.3, 128.7, 130.6 (d, *J* = 3.2 Hz), 130.8 (d, *J* = 9.5 Hz, 2C), 135.8, 160.2, 161.1 (d, *J* = 255.2 Hz), 189.5, 192.1. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{11}FO_3Na$: 281.1; found 281.2. Anal. calcd for $C_{15}H_{11}FO_3$: C, 69.76; H, 4.29; Found: C, 69.82; H, 4.40.

2-(2-Oxo-2-(4-(trifluoromethoxy)phenyl)ethoxy)benzaldehyde (6d). White solid, 89% yield (2.02 g). M.p. = 143-145 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.40 (s, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 7.0 Hz, 1H), 7.38 (d, *J* = 8.4, 2H), 7.53-7.56 (m, 1H), 7.92 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.09-8.12 (m, 2H), 10.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.9, 112.7, 120.3 (q, *J* = 258.0 Hz), 120.7 (2C), 121.9, 125.4, 128.9, 130.3 (2C), 132.4, 135.8, 153.3, 160.1, 189.4, 192.2. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{16}H_{11}F_3O_4Na$: 347.1; found 347.3. Anal. calcd for $C_{16}H_{11}F_3O_4$: C, 59.27; H, 3.42; Found: C, 59.40; H, 3.49.

2-(2-(Naphthalen-2-yl)-2-oxoethoxy)benzaldehyde (6e). Ochre solid, 92% yield (1.87 g). M.p. = 146-148 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.60 (s, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.10-7.13 (m, 1H), 7.54-7.57 (m, 1H), 7.62-7.64 (m, 1H), 7.67-7.70 (m, 1H), 7.92 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H),

8.07 (dd, *J* = 8.4, 2.1 Hz, 1H), 8.58 (s, 1H), 10.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.0, 121.7, 123.4, 125.4, 127.2, 127.9, 128.8, 129.0, 129.1, 129.6, 130.0, 131.6, 132.4, 135.8, 136.0, 160.4, 189.6, 193.5. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{19}H_{14}O_3Na$: 313.1; found 313.3. Anal. calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86; Found: C, 78.72; H, 4.78.

2-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzaldehyde (6f). Beige solid, 97% yield (1.83 g). M.p. = 130-131 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.92 (s, 3H), 5.40 (s, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.00-7.10 (m, 2H), 7.08-7.11 (m, 1H), 7.51-7.55 (m, 1H), 7.90 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.01-8.03 (m, 2H), 10.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.6, 71.8, 113.8, 115.2 (2C), 122.6, 126.3, 128.2, 129.6, 131.5 (2C), 136.8, 161.4, 165.3, 190.6, 193.1. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{16}H_{14}O_4Na$: 293.1; found 293.3. Anal. calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; Found: C, 71.18; H, 5.34.

5-Methyl-2-(2-oxo-2-phenylethoxy)benzaldehyde (6g). Beige solid, 91% yield (1.62 g). M.p. = 107-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 5.41 (s, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.51-7.57 (m, 2H), 7.53-7.70 (m, 2H), 7.99-8.03 (m, 2H), 10.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3, 71.0, 112.9, 125.0, 128.0 (2C), 128.7, 129.0 (2C), 131.2, 134.1, 134.3, 136.4, 158.5, 189.8, 193.8. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{16}H_{14}O_3Na$: 277.1; found 277.2. Anal. calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; Found: C, 75.46; H, 5.43.

2-(2-(2,4-Dimethoxyphenyl)-2-oxoethoxy)benzaldehyde (6h). Pink solid, 87% yield (1.83 g). M.p. = 111-113 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.92 (s, 3H), 3.99 (s, 3H), 5.37 (s, 2H), 6.53 (d, *J* = 2.1 Hz, 1H), 6.64 (dd, *J* = 2.1, 9.1 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 7.05-7.07 (m, 1H), 7.49-7.51 (m, 1H), 7.90 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 10.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 55.7, 74.3, 98.1, 106.1, 113.0, 117.8, 121.0, 125.2, 128.3, 133.2, 135.6, 161.1, 161.4, 165.6, 190.0, 192.5. Mass calcd for $[M+H]^+$ $C_{17}H_{17}O_5$: 301.1; found 301.4. Anal. calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37; Found: C, 68.06; H, 5.33.

2-(2-(3,4-Difluorophenyl)-2-oxoethoxy)benzaldehyde (6i). Yellow solid, 86% yield (1.66 g). M.p. = 138-141 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.39 (s, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.12-7.14 (m, 1H), 7.33-7.37 (m, 1H), 7.55 (dddd, *J* = 16.1, 8.4, 7.0, 2.1 Hz, 1H), 7.83-7.85 (m, 1H), 7.88 (dddd, *J* = 18.2, 9.8, 7.0, 2.1 Hz, 1H), 7.91 (dd, *J* = 7.7, 2.1 Hz, 1H), 10.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.9, 112.7, 117.7 (dd, *J* = 18.2, 1.6 Hz), 118.0 (d, *J* = 17.4 Hz), 122.0, 125.3 (dd, *J* = 7.1, 3.9 Hz), 125.4, 129.0, 131,7 (t, *J* = 4.7 Hz), 135.8, 150.7

(dd, *J* = 250.4, 12.6 Hz), 154.1 (dd, *J* = 257.5, 12.6 Hz), 159.9, 189.3, 191.4. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{10}F_2O_3Na$: 299.1; found 299.2. Anal. calcd for $C_{15}H_{10}F_2O_3$: C, 65.22; H, 3.65; Found: C, 65.31; H, 3.61.

2-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethoxy)benzaldehyde (6j). Beige solid, 97% yield (2.15 g). M.p. = 145-147 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.49 (s, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.11-7.13 (m, 1H), 7.45-7.47 (m, 1H), 7.51-7.56 (m, 3H), 7.66-7.68 (m, 2H), 7.77-7.79 (m, 2H), 7.92 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.01-8.12 (m, 2H), 10.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.0, 112.9, 121.7, 125.4, 127.3 (2C), 127.6 (2C), 128.6, 128.7 (2C), 128.8, 129.1 (2C), 132.9, 135.8, 139.5, 146.9, 160.3 189.6, 193.2. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{21}H_{16}O_3Na$: 339.1; found 339.4. Anal. calcd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10; Found: C, 79.67; H, 5.15.

Typical procedure for the NHC-catalyzed crossed intramolecular benzoin reactions

A flame dried round bottom flask was charged with triazolium salt **1d** (10.8 mg, 0.015 mmol, 15 mol%) and 1.0 mL of cyclopentyl methyl ether (0.1 M). Then to this solution was added BEMP (4.3 μL, 0.015 mmol, 15 mol%) via syringe and the solution was allowed to stir at ambient temperature for 30 minutes. After this time keto-aldehyde (0.1 mmol) was added and the resulting solution was allowed to stir at ambient temperature and monitored by TLC. The reaction mixture was placed directly onto a silica gel column and eluted with a suitable solution of hexane and ethyl acetate (8:2). Evaporation of solvent afforded analytically pure product.

(*S*)-3-Hydroxy-3-phenylchroman-4-one (7a).[7a] White solid, 99% yield (23.5 mg). M.p. = 77-79 °C. $[\alpha]_D^{20} = -10.8$ (c 1.8, CH_2Cl_2). Chiral HPLC analysis Phenomenex Lux Cellulose-1 (90:10 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R major (*S*) 16.4 min., t_R minor (*R*) 19.8 min., 93% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.18 (bs, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.88 (d, *J* = 11.6 Hz, 1H), 6.97-7.00 (m, 1H), 7.07-7.11 (m, 1H), 7.32-7.37 (m, 3H), 7.47-7.57 (m, 3H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.4, 73.8, 118.1, 119.2, 122.0, 126.0 (2C), 127.6, 128.7 (2C), 128.8, 136.8, 138.5, 161.6, 194.6. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{12}O_3Na$: 263.1; found 263.3. Anal. calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; Found: C, 75.13; H, 5.08.

(*S*)-3-(4-Bromophenyl)-3-hydroxychroman-4-one (7b). Light yellow solid, 91% yield (29.1 mg). M.p. = 98-101 °C. $[\alpha]_D^{20} = -4.2$ (c 1.2, CH_2Cl_2). Chiral HPLC analysis Chiralpak

OJ (95:5 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R major (*S*) 36.7 min., t_R minor (*R*) 40.9 min., 92% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.24 (bs, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 6.99 (d, *J* = 8.4, 0.8 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 7.35-7.38 (m, 2H), 7.44-7.48 (m, 2H), 7.55 (dddd, *J* = 15.6, 8.8, 7.2, 2.0 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.0, 73.7, 118.1, 119.0, 122.2, 123.1, 127.7, 127.8 (2C), 131.9 (2C), 137.1, 137.6, 161.5, 194.0. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{11}BrO_3Na$: 341.0; found 341.1. Anal. calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Found: C, 56.36; H, 3.36.

(*S*)-3-(4-Fluorophenyl)-3-hydroxychroman-4-one (7c). Yellow solid, 81% yield (20.6 mg). M.p. = 77-78 °C. $[\alpha]_D^{20}$ = −4.4 (c 5.4, CH_2Cl_2). Chiral HPLC analysis Chiralpak OJ (95:5 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R major (*S*) 37.7 min., t_R minor (*R*) 42.3 min., 94% *ee*. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.20 (bs, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 6.97-7.02 (m, 3H), 7.07-7.09 (m, 1H), 7.43-7.47 (m, 2H), 7.53 (dddd, *J* = 15.4, 8.4, 7.7, 2.1 Hz, 1H), 7.92 (dd, *J* = 8.4, 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.0, 73.8, 115.7 (d, *J* = 21.3 Hz, 2C), 118.1, 119.0, 122.1, 127.7, 128.0 (d, *J* = 7.9 Hz, 2C), 134.3 (d, *J* = 4.0 Hz), 137.0, 161.4, 162.8 (d, *J* = 246.4 Hz), 194.3. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{11}FO_3Na$: 281.1; found 281.2. Anal. calcd for $C_{15}H_{11}FO_3$: C, 69.76; H, 4.29; Found: C, 69.68; H, 4.38.

(*S*)-3-Hydroxy-3-(4-(trifluoromethoxy)phenyl)chroman-4-one (7d). Light yellow oil, 91% yield (29.3 mg). $[\alpha]_D^{20}$ = −4.6 (c 1.1, CH_2Cl_2). Chiral HPLC analysis Chiralpak OJ (98:2 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R minor (*R*) 34.0 min., t_R major (*S*) 43.6 min., 90% *ee*. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.26 (bs, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 6.98 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.10 (dt, *J* = 7.7, 0.7 Hz, 1H), 7.16 (dd, *J* = 9.1, 0.7 Hz, 2H), 7.50-7.53 (m, 2H), 7.55 (dddd, *J* = 16.1, 9.1, 7.7, 2.1 Hz, 1H), 7.93 (dd, *J* = 8.4, 2.1 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 73.9, 74.8, 119.2, 119.9, 121.4 (q, *J* = 258.0 Hz), 122.0 (2C), 123.2, 128.7 (2C), 128.7, 138.1, 138.2, 150.4, 162.5, 195.0. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{16}H_{11}F_3O_4Na$: 347.0; found 347.1. Anal. calcd for $C_{16}H_{11}F_3O_4$: C, 59.27; H, 3.42; Found: C, 59.33; H, 3.51.

(*S*)-3-Hydroxy-3-(naphthalen-2-yl)chroman-4-one (7e). Ochre solid, 99% yield (28.5 mg). M.p. = 108-110 °C. $[\alpha]_D^{20}$ = −7.5 (c 1.6, CH_2Cl_2). Chiral HPLC analysis Chiralpak OJ (80:20 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R minor (*R*) 80.8 min., t_R major (*S*) 87.3 min., 95% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.34 (bs, 1H), 4.58 (d, *J* = 12.0 Hz,

1H), 5.03 (d, *J* = 12.0 Hz, 1H), 6.98-7.00 (m, 1H), 7.07-7.11 (m, 1H), 7.46-7.54 (m, 3H), 7.62 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.77-7.82 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.94 (m, 1H), 7.99 (dd, *J* = 7.6, 0.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.6, 73.7, 118.1, 119.2, 122.0, 123.6, 125.5, 126.3, 126.7, 127.6, 127.7, 128.4, 128.7, 133.0, 132.3, 135.7, 136.9, 161.5, 194.6. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{19}H_{14}O_3Na$: 313.1; found 313.2. Anal. calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86; Found: C, 78.69; H, 4.95.

(*S*)-3-Hydroxy-3-(4-methoxyphenyl)chroman-4-one (7f).[7a] Yellow oil, 98% yield (26.4 mg). $[\alpha]_D^{20}$ = −5.2 (c 4.6, CH_2Cl_2). Chiral HPLC analysis Chiralpak OJ (90:10 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R minor (*R*) 66.4 min., t_R major (*S*) 100.9 min., 94% *ee*. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 4.16 (bs, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.84 (d, *J* = 11.9 Hz, 1H), 6.83- 6.86 (m, 2H), 6.94 (d, *J* = 7.7 Hz, 1H), 7.04-7.07 (m, 1H), 7.38-7.41 (m, 2H), 7.50 (dddd, *J* = 16.1, 9.1, 7.7, 1.4 Hz, 1H), 7.92 (dd, *J* = 7.7, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.2, 73.1, 73.6, 114.1 (2C), 118.0, 119.2, 121.9, 127.4 (2C), 127.6, 130.3, 136.7, 159.9, 161.4, 194.7. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{16}H_{14}O_4Na$: 293.1; found 293.2. Anal. calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; Found: C, 71.14; H, 5.33.

(*S*)-3-Hydroxy-6-methyl-3-phenylchroman-4-one (7g). Ochre solid, 98% yield (24.8 mg). M.p. = 98-99 °C. $[\alpha]_D^{21}$ = −5.7 (c 1.1, CH_2Cl_2). Chiral HPLC analysis Chiralpak OJ (90:10 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R minor (*R*) 44.5 min., t_R major (*S*) 59.1 min., 86% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (bs, 3H), 4.22 (s, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.30-7.36 (m, 4H), 7.46-7.52 (m, 2H), 7.74 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.4, 73.4, 73.9, 117.9, 118.8, 126.0 (2C), 127.1, 128.7 (2C), 128.8, 131.5, 138.0, 138.7, 159.7, 194.7. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{16}H_{14}O_3Na$: 277.1; found 277.2. Anal. calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; Found: C, 75.45; H, 5.42.

(*S*)-3-(2,4-Dimethoxyphenyl)-3-hydroxychroman-4-one (7h). Light yellow solid, 97% yield (29.0 mg). M.p. = 108-110 °C. $[\alpha]_D^{20}$ = +4.4 (c 1.4, CH_2Cl_2). Chiral HPLC analysis Chiralcel OD-H (90:10 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R major (*S*) 21.3 min., t_R minor (*R*) 65.7 min., 82% *ee*. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.70 (s, 3H), 3.78 (s, 3H), 3.83 (bs, 1H), 4.30 (d, *J* = 11.9 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 6.45-6.48 (m, 2H), 6.95 (d, *J* = 9.1 Hz, 1H), 7.04-7.06 (m, 1H), 7.41 (d, *J* = 9.1 Hz, 1H), 7.46-7.48 (m, 1H), 7.94 (dd, *J* = 7.7, 2.1 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 56.4, 56.6, 74.7, 75.1, 100.7, 105.8, 118.8, 120.1, 121.0, 122.8, 128.8, 129.4, 136.7, 159.0, 161.9, 162.3, 193.7. LRMS (ESI):

Mass calcd for $[M+Na]^+$ $C_{17}H_{16}O_5Na$: 323.1; found 323.3. Anal. calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37; Found: C, 68.12; H, 5.48.

(*S*)-3-(3,4-Difluorophenyl)-3-hydroxychroman-4-one (7i). Yellow solid, 82% yield (22.6 mg). M.p. = 100-101 °C. $[\alpha]_D^{20}$ = −2.6 (c 1.7, CH_2Cl_2). Chiral HPLC analysis Chiralpak OJ (97:3 hexane/IPA, flow rate 0.7 mLmin^{-1}, 254 nm, 25 °C) t_R major (*S*) 47.3 min., t_R minor (*R*) 53.2 min., 90% *ee*. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.22 (bs, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 6.99 (d, *J* = 9.1 Hz, 1H), 7.08-7.12 (m, 2H), 7.18-7.21 (m, 1H), 7.35 (dddd, *J* = 2.1, 7.7, 11.2, 18.9 Hz, 1H), 7.55-7.57 (m, 1H), 7.92 (dd, *J* = 7.7, 2.1 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ: 73.6, 74.8, 116.6 (d, *J* = 19.4 Hz), 118.5 (d, *J* = 16.7 Hz), 119.2, 119.8, 123.3 (m), 123.4, 128.8, 136.7 (t, *J* = 4.0 Hz), 138.3, 151.3 (dd, *J* = 248.3, 12.3 Hz), 151.5 (dd, *J* = 251.0, 12.5 Hz), 162.4, 194.6. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{15}H_{10}F_2O_3Na$: 299.0; found 299.2. Anal. calcd for $C_{15}H_{10}F_2O_3$: C, 65.22; H, 3.65; Found: C, 65.34; H, 3.53.

(*S*)-3-([1,1'-Biphenyl]-4-yl)-3-hydroxychroman-4-one (7j). Light yellow solid, 98% yield (29.9 mg). M.p. = 97-99 °C. $[\alpha]_D^{20}$ = −4.2 (c 1.2, CH_2Cl_2). Chiral HPLC analysis Chiralpak OJ (90:10 hexane/IPA, flow rate 1.0 mLmin^{-1}, 254 nm, 25 °C) t_R major (*S*) 37.0 min., t_R minor (*R*) 42.2 min., 96% *ee*. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.20 (bs, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.91 (d, *J* = 11.9 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 7.08-7.11 (m, 1H), 7.32-7.35 (m, 1H), 7.40-7.43 (m, 2H), 7.52-7.54 (m, 3H), 7.55 (m, 4H), 7.96 (dd, *J* = 8.4, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.3, 73.8, 118.1, 119.2, 122.1, 126.5 (2C), 127.1 (2C), 127.5 (2C), 127.6, 127.7, 128.8 (2C), 136.9, 137.4, 140.4, 141.7, 161.6, 194.5. LRMS (ESI): Mass calcd for $[M+Na]^+$ $C_{21}H_{16}O_3Na$: 339.1; found 339.2. Anal. calcd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10; Found: C, 79.80; H, 5.17.

Supporting Information

Copies of ^{1}H and ^{13}C spectra for all new compounds, HPLC scans and X-ray crystallographic data of compound **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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