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Copper(II) catalyzed cross-dehydrogenative coupling of cyclic benzylic ethers with simple carbonyl compounds by $Na_2S_2O_8$

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ABSTRACT

Copper(II) catalyzed cross-dehydrogenative coupling of cyclic benzylic ethers with a variety of simple carbonyl compounds mediated by $Na_2S_2O_8$ is developed. The scope of carbonyl components is broad, including simple aldehydes as well as ketones. The use of $Na_2S_2O_8$ as the oxidant for the CDC reaction is attractive based on economical and environmental factors.

1. Introduction

α-Substituted cyclic ethers are one of the most common structural motifs spread across biologically active natural products and synthetic pharmaceuticals, and significant efforts have been devoted to their synthesis.[1] During the past few years, the direct cross-dehydrogenative coupling (CDC) reactions to construct new C–C bond by utilizing two C–H bonds have emerged as an elegant alternative to the traditional functional group chemistry.[2,3] Such strategy avoids the steps of functional group installation, and therefore makes the synthetic schemes shorter and more efficient.[4] Although remarkable progress including new types of synthetic transformations as well as oxidation systems has been achieved in this area, especially in the functionalization of the sp^3 C–H bond adjacent to a heteroatom, the majority of such couplings involve the functionalization of electron-rich amines.[5] For the corresponding ether compounds, important molecules in both academic and industrial research, the development of CDC reactions is still far from satisfactory. Till now, five terminal oxidations have been reported to promote the CDC reactions of benzylic ethers, including DDQ (2,3-dichloro-5,6-dicyanobenzoquinone),[6] *tert*-butyl hydroperoxide (TBHP),[7] NHPI (*N*-hydroxyphthalimide),[8] TEMPO oxoammonium salt ($T^+BF_4^-$),[9] and MnO_2/CH_3SO_3H.[10] Moderate to good reaction efficiency was achieved by utilizing these oxidants together with suitable metal catalysts. However, the majority of the systems suffer from either economic or environmental issues. For example, as the most universal oxidant in terms of the nucleophile scope, DDQ is moderately expensive, with a cost of $666/mol according to the 2013–2014 Aldrich catalog. In addition to concerns about cost, DDQ also poses modest toxicity concerns (LD_{50}=82 mg/kg),[11] the potential for HCN liberation upon exposure to H_2O, and the purification difficulties. As another example, TBHP in decane costs about $273/mol, and can cause severe skin burns, eye damage, and an allergic skin reaction. NHPI and $T^+BF_4^-$ do not have above problems, though the latter is not commercially available, and need to be prepared in the bench. While MnO_2 only costs $47/mol, the oxidation requires strong acid to occur, which results in poor functional group compatibility and also incurs environmental issue. According to the state of art of existing protocols, the development of an economic and environmentally benign oxidation system is still an attractive project to pursue.

The use of peroxydisulfate ($S_2O_8^{2-}$) together with a metal catalyst has long been known to oxidize the benzylic C–H bonds initiated by a single electron transfer process.[12] The oxidant is inexpensive, less toxic, and easily handled. The price of peroxydisulfate salt like $Na_2S_2O_8$ is only $8.3/mol, with a LD_{50} of 930 mg/kg.[11] Additionally, the byproduct can be easily removed with

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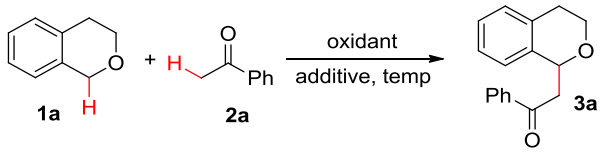
a simple filtration over Celite. To the best of our knowledge, such oxidation system has not yet been applied to CDC reactions of ethers to date. Given the importance of cyclic benzylic ethers in biologically relevant molecules, we herein report a copper(II) catalyzed CDC reaction of cyclic benzylic ethers with a variety of C–H nucleophiles employing sodium persulfate as the terminal oxidant.

2. Results and discussion

Initially, the coupling of isochroman **1a** with acetophenone **2a** was examined using $Na_2S_2O_8$ as the oxidant. The desired product **3a** was observed when the reaction was performed in CH_3CN at 80 °C (entry 1, Table 1). Inspired by the result, several solvents were screened for the optimization, and the coupling was found to be dependent on the solvent choice. While THF, hexane, CH_2Cl_2, and 1,4-dioxane inhibited the reaction, conducting the reaction without any solvent provided the best conversion (entries 1–3). As peroxydisulfate was most commonly employed with the combination of a metal catalyst, different additives were investigated next. Generally speaking, the involvement of metal catalyst afforded high efficiency compared to that using $Na_2S_2O_8$ alone, though $Cu(OAc)_2$ and $Cu(OTf)_2$ did not effect the reaction at all (entries 5 and 6). Among all the metal additives, $CuBr_2$ proved to be the best choice for the model coupling, affording **3a** in 75% yield (entries 4–16). No reaction occurred if $CuBr_2$ alone was employed even under the atmosphere of molecular oxygen (entry 17). The counter ion effect of peroxydisulfate was then studied. The results showed that $Na_2S_2O_8$ worked the best, and was selected for the further optimization (entries 10, 18 and 19). Either increasing the temperature to 100 °C or lowering it to 60 °C gave an inferior yield (entries 10, 20, and 21). Microwave-assisted reaction did not give any improvement (entry 22). Reaction optimization experiments identified increased $Na_2S_2O_8$ (3 equiv) at 80 °C as ideal conditions in the presence of $CuBr_2$ (20 mol %) without any solvent (entry 23). Stoichiometric amounts (100 mol %) of 2,6-di-*tert*-butyl-4-methylphenol (BHT), completely blocked the oxidative coupling (entry 24).

With the optimized conditions in hand, the nucleophile scope of the CDC reaction was explored (Table 2). Various simple ketones were efficiently coupled with isochroman. Electron-rich ketones like **2b** and **2c** afforded comparable results to that of acetophenone, while electron-deficient one like **2d** gave a reduced yield. Propiophenone **2e** was also a suitable substrate for the oxidative reaction, delivering the desired **3e** in 69% yield with a diastereomeric ratio of 1:1. Heteroaromatic ketone **2f** was also compatible with the oxidative condition, resulting in a moderate yield. Besides the aromatic ketones, aliphatic ones like linear **2g** and cyclic **2h** and **2i** were all tolerated with good to excellent efficiency. In addition to the ketone moieties, we also studied the alkylation of aldehydes, which would afford the isochroman with multiple stereogenic centers. Both linear pentanal **2j** and sterically hindered branched

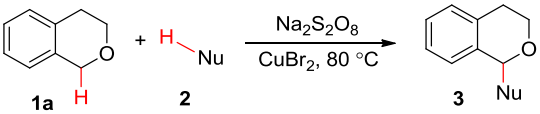
Table 1
Reaction condition optimization[a]



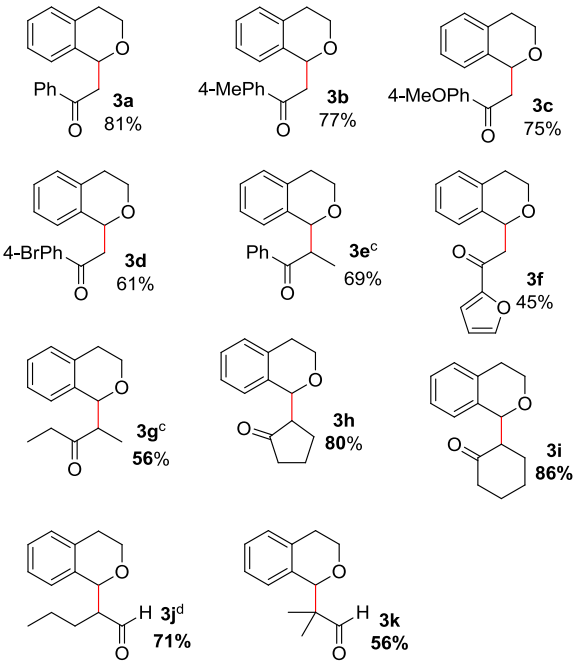
Entry	Oxidant	Additive	Yield[b] (%)
1[c]	$Na_2S_2O_8$	—	11
2[d]	$Na_2S_2O_8$	—	<5
3	$Na_2S_2O_8$	—	25
4	$Na_2S_2O_8$	$CuSO_4$	50
5	$Na_2S_2O_8$	$Cu(OTf)_2$	<5
6	$Na_2S_2O_8$	$Cu(OAc)_2$	<5
7	$Na_2S_2O_8$	$Cu_3(PO_4)_2$	29
8	$Na_2S_2O_8$	$CuCl_2$	56
9	$Na_2S_2O_8$	$Cu(C_2O_4)_2$	63
10	$Na_2S_2O_8$	$CuBr_2$	75
11	$Na_2S_2O_8$	CuOTf	46
12	$Na_2S_2O_8$	CuCl	35
13	$Na_2S_2O_8$	CuBr	38
14	$Na_2S_2O_8$	CuI	31
15	$Na_2S_2O_8$	$FeSO_4$	38
16	$Na_2S_2O_8$	$AgNO_3$	29
17	—	$CuBr_2$	<5
18	$K_2S_2O_8$	$CuBr_2$	36
19	$(NH_4)_2S_2O_8$	$CuBr_2$	21
20[e]	$Na_2S_2O_8$	$CuBr_2$	53
21[f]	$Na_2S_2O_8$	$CuBr_2$	62
22[g]	$Na_2S_2O_8$	$CuBr_2$	40
23[h]	$Na_2S_2O_8$	$CuBr_2$	81
24[i]	$Na_2S_2O_8$	$CuBr_2$	<5

[a] General conditions: **1a** (0.25 mmol), **2a** (1.25 mmol), oxidant (0.5 mmol), additive (0.05 mmol) at 80 °C for 24 h, unless stated otherwise.
[b] Isolated yield.
[c] CH_3CN as the solvent.
[d] THF, hexane, CH_2Cl_2, and 1,4-dioxane as solvents.
[e] Reaction at 60 °C.
[f] Reaction at 100 °C.
[g] Microwave at 100 °C for 1 h.
[h] 0.75 mmol oxidant used.
[i] 1 equiv of BHT added.

Table 2
Scope of the simple carbonyl components[a,b]



Carbonyl Scope



[a] General conditions: **1a** (0.25 mmol), **2** (1.25 mmol), oxidant (0.75 mmol), additive (0.05 mmol) at 80 °C for 24 h, unless stated otherwise.
[b] Isolated yield.
[c] dr = 1:1.
[d] dr = 3:1.

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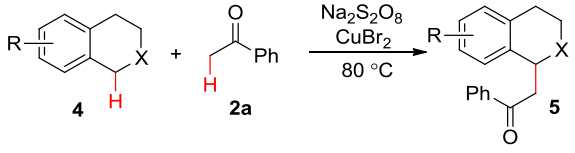
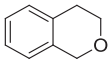
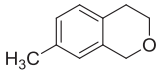
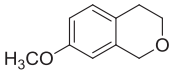
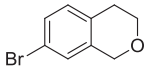
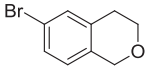
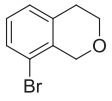
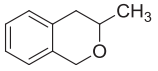
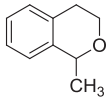
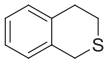
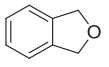
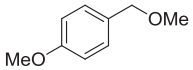
isobutyraldehyde **2k** were found to be competent substrates towards the standard conditions.

Next we turned to investigate the scope of benzylic ethers (Table 3). Isochroman variants with different electronically varied substituents reacted with acetophenone smoothly under the standard conditions to afford the desired products in good yields, though a methoxy substituent at C_7 did not effect any reaction (entries 1–6, Table 3). This observation was identical to that of DDQ/$CuCl_2$ mediated arylation of isochroman by Todd.[6b] The result can be explained according to the Floreancig's mechanistic studies of DDQ-mediated ether functionalizations involving a radical pathway, in which substrates with lower oxidation potentials were found to possess higher bond dissociation energy of the scissile C–H bond.[13] Therefore, the similar intermediate might also exist in our reaction pathway. The tolerance of a bromosubstituent towards the reaction condition will be beneficial for further manipulations. C_3-methyl substituted isochroman **4g** was suitable substrate to give the product **5g** in 76% yield with a diastereomeric ratio of 1:1 (entry 7). A methyl substituent at the C_1 position failed to deliver **5h** probably due to the increased steric bulk (entry 8). In addition to substituted isochroman, other cyclic ethers were also explored. Isothiochroman **4i** afforded the desired products **5i** in reasonable yields (entry 9). Phthalan **4j** was found to be much less reactive than isochroman **4a** with respect to the reaction conversion, providing mono-substituted **5j** in 18% yield (entry 10).[14] No reaction took place when acyclic substrate **4k** was applied to the oxidation condition (entry 11).

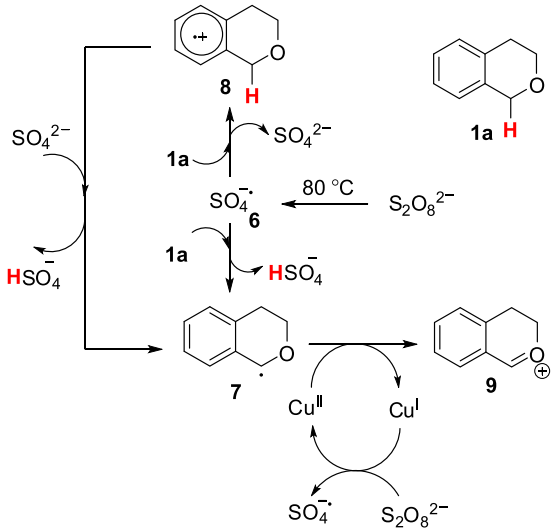
Table 3
Scope of the benzylic ethers[a,b]



Entry	Series	Benzylic ethers	Yield[b] (%)
1	**4a**		81
2	**4b**		78
3	**4c**		0
4	**4d**		70
5	**4e**		62
6[c]	**4f**		43
7	**4g**		76
8	**4h**		0
9	**4i**		39
10	**4j**		18
11	**4k**		0

[a] General conditions: **4** (0.25 mmol), **2a** (1.25 mmol), oxidant (0.75 mmol), additive (0.05 mmol) at 80 °C for 24 h, unless stated otherwise.
[b] Isolated yield.
[c] dr=1:1.

While the mechanism is not yet fully understood, radical intermediates should be involved in the reaction since stoichiometric amounts (1 equiv) of BHT completely blocked the transformation (entry 24, Table 1). This observation indicates that single step hydride transfer pathway from isochroman **1a** to the oxidant should not be applicable to our system (Scheme 1). The oxocarbenium ion **9** was envisioned to be the intermediate for the subsequent nucleophilic addition process. A proposed mechanism for the formation of carbocation intermediate **9** is shown in Scheme 1. Under thermal conditions, persulfate may decompose to generate 2 equiv of SO_4 radical anion **6**. Two mechanisms have been postulated for the generation of the carbocation **9** from **1a**. The first pathway proceeds through an initial benzylic hydrogen atom abstraction from **1a** to **6** to give free radical **7** together with 1 equiv of HSO_4^-. Cu(II) is a well-known oxidant for the carbon-centered radicals.[15] Therefore, the radical **7** then undergoes one electron oxidation to generate intermediate **9** together with the generation of Cu(I). Cu(I) then mediates the collapse of persulfate ion to regenerate Cu(II) and **6**. Alternatively, an initial electron transfer from **1a** to **6** affords the radical cation **8** with SO_4^{2-}. Then **8** undergoes proton abstraction to provide radical **7** that will be further oxidized by Cu(II) to afford intermediate **9**.



Scheme 1. Proposed catalytic cycle.

3. Conclusion

In summary, we have developed an efficient copper(II)-catalyzed oxidative cross-coupling reaction of cyclic benzylic ethers with a variety of simple carbonyl compounds employing the inexpensive reagent $Na_2S_2O_8$ as the terminal oxidant. The low cost, negligible toxicity, and ease of handling of the oxidant combined with the absence of hazardous byproducts, are attractive. The method does not require any solvent, and the workup consists of simple filtration. To the best of our knowledge, this is the first example of the use of $Na_2S_2O_8$/Cu(II) to promote CDC reaction with

ethers, leading to C–C bond formation. The development of other peroxydisulfate-mediated oxidative coupling reactions is currently under investigation and will be disclosed in due course.

4. Experimental section

4.1. General procedure for the CDC reaction of benzylic ethers with carbonyl compounds

To a solution of 1 or 4 (0.25 mmol, 1 equiv), 2 (1.25 mmol, 5 equiv) and $CuBr_2$ (0.05 mmol, 0.2 equiv) was added $Na_2S_2O_8$ (0.75 mmol, 3 equiv). Then the mixture was stirred at 80 °C until the starting material disappeared monitored by TLC. After that, the above mixture was directly purified by flash chromatography (ethyl acetate/petroleum ether as eluent) to give the desired product 3 or 5.

4.1.1. 2-(Isochroman-1-yl)-1-phenylethanone ***3a***.[10] Yield 81%; light yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.03 (d, J=7.8 Hz, 2H), 7.59 (t, J=7.2 Hz, 2H), 7.49 (t, J=7.8 Hz, 1H), 7.23–7.19 (m, 2H), 7.18–7.14 (m, 1H), 7.15–7.11(m, 1H), 5.52 (dd, J=3.0, 9.0 Hz, 1H), 4.13 (ddd, J=3.6, 7.2, 9.6 Hz, 1H), 3.83 (ddd, J=3.6, 9.6, 11.4 Hz, 1H), 3.63 (dd, J=8.4, 16.2 Hz, 1H), 3.34 (dd, J=3.0, 16.2 Hz, 1H), 3.06–3.02 (m, 1H), 2.73 (dt, J=3.0, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.2, 137.5, 137.2, 134.0, 133.2, 129.1, 128.6, 128.3, 126.5, 126.3, 124.5, 72.7, 63.5, 45.5, 28.9; HRMS (EI) m/z calcd for $C_{17}H_{17}O_2$ $[M+H]^+$ 253.1223, found 253.1222.

4.1.2. 2-(Isochroman-1-yl)-1-(p-tolyl)ethanone ***3b***.[10] Yield 77%; light yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.92 (d, J=7.2 Hz, 2H), 7.28 (d, J=7.2 Hz, 2H), 7.20 (s, 2H), 7.15 (s, 1H), 7.12 (s, 1H), 5.51 (d, J=1.8 Hz, 1H), 4.15–4.09 (m, 1H), 3.85–3.79 (m, 1H), 3.60 (dd, J=9.0, 16.2 Hz, 1H), 3.31 (d, J=16.2 Hz, 1H), 3.06–3.00 (m, 1H), 2.72 (d, J=16.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 144.0, 137.7, 134.7, 134.0, 129.3, 129.0, 128.5, 126.5, 126.3, 124.6, 72.7, 63.5, 45.4, 28.9, 21.7; HRMS (EI) m/z calcd for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1380, found 267.1382.

4.1.3. 2-(Isochroman-1-yl)-1-(4-methoxyphenyl)ethanone ***3c***.[10] Yield 75%; light yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.01 (d, J=7.8 Hz, 2H), 7.20 (s, 2H), 7.14 (d, J=6.0 Hz, 2H), 6.85 (d, J=7.2 Hz, 2H), 5.50 (d, J=7.8 Hz, 1H), 4.16–4.08 (m, 1H), 3.88 (s, 3H), 3.82 (t, J=10.2 Hz, 1H), 3.62–3.54 (m, 1H), 3.27 (d, J=16.2 Hz, 1H), 3.07–2.99 (m, 1H), 2,72 (d, J=16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.6, 163.5, 137.7, 134.0, 130.7, 130.32, 129.0, 126.5, 126.2, 124.6, 113.7, 72.8, 63.5, 55.5, 45.1. 28.9; HRMS (EI) m/z calcd for $C_{18}H_{19}O_3$ $[M+H]^+$ 283.1329, found 283.1328.

4.1.4. 1-(4-Bromophenyl)-2-(isochroman-1-yl)ethanone ***3d***.[10] Yield 61%; light yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.88 (d, J=6.6 Hz, 2H), 7.62 (d, J=6.6 Hz, 2H), 7.26–7.05 (m, 4H), 5.48 (d, J=7.2 Hz, 1H), 4.15–4.07 (m, 1H), 3.81 (t, J=10.2 Hz, 1H), 3.58 (dd, J=10.2, 15.6 Hz, 1H), 3.29 (d, J=15.6 Hz, 1H), 3.04 (dd, J=4.8, 8.4 Hz, 1H), 2.72 (d, J=16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.4, 137.2, 135.9, 134.0, 131.8, 129.9, 129.1, 128.3, 126.7, 126.3, 124.4, 72.7, 63.5, 45.3, 28.9; HRMS (EI) m/z calcd for $C_{17}H_{16}BrO_2$ $[M+H]^+$ 331.0328, found 331.0331.

4.1.5. 2-(Isochroman-1-yl)-1-phenylpropan-1-one ***3e***.[10] Yield 69%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) of the mixture, δ 8.03–7.93 (m, 2H), 7.61–7.53 (m, 1H), 7.53–7.43 (m, 2H), 7.25–7.02 (m, 4H), 5.33–5.23 (m, 1H), 4.17–4.09 (m, 1H), 4.08–3.96 (m, 1H), 3.71–3.57 (m, 1H), 3.08–2.90 (m, 1H), 2.69–2.56 (m, 1H), 1.24–1.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) of the mixture δ 202.6, 201.8, 137.2, 136.7, 136.1, 135.5, 135.0, 134.9, 132.7 (two peaks), 129.1, 128.7, 128.6, 128.5, 128.4 (two peaks), 126.6, 126.5, 126.4, 125.8 (two peaks), 124.5, 77.5, 76.6, 63.9, 63.3, 47.3, 47.8, 29.3, 28.9, 13.6, 9.9; HRMS (EI) m/z calcd for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1380, found 267.1382.

4.1.6. 1-(Furan-2-yl)-2-(isochroman-1-yl)ethanone ***3f***.[9] Yield 45%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.62 (s, 1H), 7.26 (s, 1H), 7.20 (s, 2H), 7.14 (d, J=15.0 Hz, 2H), 6.56 (s, 1H), 5.47 (d, J=9.0 Hz, 1H), 4.13 (d, J=7.2 Hz, 1H), 3.85–3.76 (m, 1H), 3.49–3.41 (m, 1H), 3.20 (d, J=15.6 Hz, 1H), 3.04–2.96 (m, 1H), 2.73 (d, J=16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.0, 153.0, 146.6, 137.2, 134.0, 129.1, 126.6, 126.3, 124.6, 117.8, 112.4, 72.6, 63.2, 45.3, 28.8; HRMS (EI) m/z calcd for $C_{15}H_{15}O_3$ $[M+H]^+$ 243.1016, found 243.1015.

4.1.7. 2-(Isochroman-1-yl)pentan-3-one ***3g***.[10] Yield 56%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.24–7.02 (m, 4H), 5.32 (s, 0.75H), 4.99 (s, 0.25H), 4.21–4.09 (m, 1H), 3.75–3.64 (m, 1H), 3.14–2.95 (m, 2H), 2.72–2.24 (m, 3H), 1.22 (d, J=4.2 Hz, 0.75H), 1.11 (s, 2.25H), 0.96 (d, J=5.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.6, 212.5, 136.0 (two peaks), 134.9, 134.4, 129.0, 126.6, 126.3 (two peaks), 126.0, 125.2, 124.3, 77.8, 76.7, 64.0, 63.6, 51.7, 51.5, 35.0, 33.9, 29.0, 28.9, 13.8 (two peaks), 9.1, 7.8 (two peaks), 7.6; HRMS (EI) m/z calcd for $C_{14}H_{19}O_2$ $[M+H]^+$ 219.1380, found 219.1377.

4.1.8. 2-(Isochroman-1-yl)cyclopentanone ***3h***.[10] Yield 80%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.22–7.02 (m, 4H), 5.30 (s, 1H), 4.12 (dd, J=6.0, 10.8 Hz, 1H), 3.72 (t, J=11.4 Hz, 1H), 3.12–2.96 (m, 1H), 2.81–2.68 (m, 1H), 2.64–2.54 (m, 1H), 2.39–2.29 (m, 1H), 2.28–1.98 (m, 2H), 1.97–1.83 (m, 1H), 1.82–1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 220.0, 218.9, 136.5, 135.8, 134.9, 134.7, 128.9, 126.4, 126.3, 126.1, 124.6, 124.1, 75.6, 75.4, 64.5, 64.2, 55.3, 53.5, 39.5, 29.3, 29.0, 25.3, 23.3, 20.8, 20.6; HRMS (EI) m/z calcd for $C_{14}H_{17}O_2$ $[M+H]^+$ 217.1223, found 217.1221.

4.1.9. 2-(Isochroman-1-yl)cyclohexanone ***3i***. Yield 86%; colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23–7.14 (m, 2H), 7.11 (d, J=6.8 Hz, 1H), 7.01 (d, J=7.0 Hz, 1H), 5.48 (s, 1H), 4.16 (dd, J=11.0, 5.4 Hz, 1H), 3.75 (t, J=11.3 Hz, 1H), 3.05–2.97 (m, 1H), 2.75 (dd, J=11.1, 5.6 Hz, 1H), 2.62–2.53 (m, 2H), 2.3–2.30 (m, 1H), 1.99 (dd, J=8.2, 4.8 Hz, 1H), 1.89–1.82 (m, 1H), 1.76 (ddd, J=32.4, 20.4, 12.8 Hz, 2H), 1.64 (d, J=7.1 Hz, 1H), 1.54 (t, J=12.5 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 210.8, 136.6, 135.5, 128.9, 126.3, 126.2, 123.9, 73.7, 64.3, 55.7, 42.0, 29.3, 26.1, 25.2, 24.5; IR$_{\nu max}$ 2938, 2847, 1706, 1493, 1450, 1426, 1377, 1320, 1280, 1145, 1111, 1054, 981, 748, 717 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{19}O_2$ $[M+H]^+$ 231.1380, found 231.1386.

4.1.10. 2-(Isochroman-1-yl)pentanal ***3j***.[16] Yield 71%, dr=3:1; colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.25–7.17 (m, 2H), 7.14 (dd, J=7.0, 2.9 Hz, 2H), 5.04 (s, 1H), 4.20 (ddd, J=11.2, 5.7, 1.5 Hz, 1H), 3.72 (td, J=11.3, 3.0 Hz, 1H), 3.09–3.01 (m, 1H), 2.86–2.81 (m, 1H), 2.65 (d, J=16.1 Hz, 1H), 1.97–1.88 (m, 1H), 1.68 (ddd, J=13.8, 10.1, 6.1 Hz, 1H), 1.50–1.41 (m, 2H), 1.00 (t, J=7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 204.2, 136.0, 134.8, 129.4, 127.0, 126.8, 125.0, 76.1, 64.8, 56.9, 29.4, 28.5, 20.8, 14.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.20 (d, J=2.6 Hz, 2H), 7.14 (d, J=6.3 Hz, 1H), 7.05 (d, J=6.5 Hz, 1H), 5.31 (s, 1H), 4.15 (dd, J=10.9, 5.6 Hz, 1H), 3.70 (t, J=11.4 Hz, 1H), 3.11–3.03 (m, 1H), 2.73 (d, J=9.8 Hz, 1H), 2.60 (d, J=16.1 Hz, 1H), 1.86 (dt, J=14.4, 9.8 Hz, 1H), 1.37–1.31 (m, 1H), 1.22–1.09 (m, 2H), 0.81 (t, J=6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.3, 135.6, 135.3, 129.4, 126.8, 126.7, 124.3, 76.6, 64.7, 56.8, 29.2, 25.3, 21.5, 14.3; HRMS (EI) m/z calcd for $C_{14}H_{19}O_2$ $[M+H]^+$ 219.1380, found 219.1376.

4.1.11. 2-(Isochroman-1-yl)-2-methylpropanal ***3k***. Yield 56%; colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.23–7.11 (m, 3H), 7.05 (d, J=7.2 Hz, 1H), 5.12 (s, 1H), 4.13 (dd, J=10.3, 4.5 Hz, 1H), 3.57 (t, J=11.3 Hz, 1H), 3.04–2.95 (m, 1H), 2.56 (d, J=15.9 Hz, 1H), 1.10 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.4, 136.5, 134.0,

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129.1, 126.8, 126.0, 126.0, 79.4, 64.0, 52.8, 30.2, 19.1, 17.4; HRMS (EI) m/z calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1219.

4.1.12. 2-(7-Methylisochroman-1-yl)-1-phenylethanone ***5b***.[10] Yield 78%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.03 (d, J=7.8 Hz, 2H), 7.58 (t, J=7.2 Hz, 1H), 7.49 (d, J=7.2 Hz, 2H), 7.04 (q, J=7.2 Hz, 2H), 6.93 (s, 1H), 5.48 (d, J=8.4 Hz, 1H), 4.15–4.07 (m, 1H), 3.80 (dd, J=3.0, 12.0 Hz, 1H), 3.62 (dd, J=9.0, 16.2 Hz, 1H), 3.36–3.30 (m, 1H), 3.31–2.95 (m, 1H), 2.68 (d, J=16.2 Hz 1H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.2, 137.3, 137.2, 135.8, 133.1, 131.0, 128.9, 128.6, 128.4, 127.5, 125.0, 72.7, 63.6, 45.6, 28.6, 21.2; HRMS (EI) m/z calcd for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1380, found 267.1382.

4.1.13. 2-(7-Bromoisochroman-1-yl)-1-phenylethanone ***5d***.[10] Yield 70%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05–7.99 (m, 2H), 7.59 (t, J=7.2 Hz, 1H), 7.49 (t, J=7.8 Hz, 2H), 7.33 (dd, J=1.2, 8.4 Hz, 1H), 7.26 (s, 1H), 7.03 (d, J=7.2 Hz, 1H), 5.45 (dd, J=1.8, 7.8 Hz, 1H), 4.12 (ddd, J=3.6, 5.4, 9.0 Hz, 1H), 3.78 (ddd, J=3.6, 9.6, 14.4 Hz, 1H), 3.62 (dd, J=9.0, 16.2 Hz, 1H), 3.30 (dd, J=3.6, 16.2 Hz, 1H), 3.00–2.92 (m, 1H), 2.67 (dt, J=3.6, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.6, 139.7, 137.0, 133.3, 133.0, 130.7, 129.7, 128.6, 128.3, 127.5, 119.8, 72.2, 63.4, 45.2, 28.4; HRMS (EI) m/z calcd for $C_{17}H_{16}BrO_2$ $[M+H]^{|+}$ 331.0328, found 331.0330.

4.1.14. 2-(6-Bromoisochroman-1-yl)-1-phenylethanone ***5e***.[10] Yield 62%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.06 (d, J=7.8 Hz, 2H), 7.59 (t, J=7.2 Hz, 1H), 7.49 (t, J=7.8 Hz, 2H), 7.44 (d, J=7.8 Hz, 1H), 7.15–7.07 (m, 2H), 5.66 (d, J=9.6 Hz, 1H), 4.10 (ddd, J=4.2, 12.0, 12.6 Hz, 1H), 3.88–3.84 (m, 1H), 3.71 (d, J=15.6 Hz, 1H), 3.44 (dt, J=10.2, 16.2 Hz, 1H), 2.96–2.90 (m, 1H), 2.80 (dt, J=4.2, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.3, 136.9, 136.8, 136.48, 133.1, 131.1, 128.6, 128.4, 128.3, 128.1, 121.2, 71.6, 59.8, 42.6, 28.6; HRMS (EI) m/z calcd for $C_{17}H_{16}BrO_2$ $[M+H]^+$ 331.0328, found 331.0331.

4.1.15. 2-(8-Bromoisochroman-1-yl)-1-phenylethanone ***5f***.[10] Yield 43%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.01 (d, J=7.8 Hz, 2H), 7.59 (t, J=7.8 Hz, 1H), 7.48 (t, J=7.8 Hz, 2H), 7.31 (d, J=9.6 Hz, 2H), 6.99 (d, J=8.4 Hz, 1H), 5.44 (d, J=6.0 Hz, 1H), 4.13–4.07 (m, 1H), 3.82–4.76 (m, 1H), 3.60 (dd, J=8.4, 16.2 Hz, 1H), 3.29 (dd, J=3.6, 16.2 Hz, 1H), 3.04–2.96 (m, 1H), 2.70 (d, J=16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 137.0, 136.6, 136.4, 133.3, 131.8, 129.37, 128.6, 128.3, 126.3, 120.3, 72.4, 63.2, 45.2, 28.7; HRMS (EI) m/z calcd for $C_{17}H_{16}BrO_2$ $[M+H]^+$ 331.0328, found 331.0335.

4.1.16. 2-(3-Methylisochroman-1-yl)-1-phenylethanone ***5g***.[10] Yield 76%, dr=1:1; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.03 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.2 Hz, 1H), 7.48 (t, J=7.2 Hz, 2H), 7.19 (d, J=1.8 Hz, 2H), 7.11 (s, 2H), 5.51 (s, 1H), 3.91–3.81 (m, 1H), 3.59 (dd, J=7.8, 16.2 Hz, 1H), 3.39 (d, J=16.2 Hz, 1H), 2.80–2.67 (m, 2H), 1.28 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.4, 137.7, 137.4, 134.4, 133.0, 128.9, 128.5, 128.4, 126.6, 126.2, 124.1, 73.5, 70.6, 45.9, 36.5, 21.7; HRMS (EI) m/z calcd for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1380, found 267.1381; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.01 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.2 Hz, 1H), 7.49 (t, J=7.2 Hz, 2H), 7.20 (m, 2H), 7.13 (s, 2H), 5.64 (d, J=9.0 Hz, 1H), 4.12–4.06 (m, 1H), 3.75 (dd, J=9.6, 15.6 Hz, 1H), 3.23 (d, J=9.6 Hz, 1H), 2.77 (d, J=15.6 Hz, 1H), 2.67 (dd, J=9.6, 15.6 Hz, 1H), 1.22 (d, J=5.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.4, 137.7, 137.4, 134.4, 133.0, 128.9, 128.5, 128.4, 126.6, 126.2, 124.1, 73.5, 70.6, 45.9, 36.5, 21.7; HRMS (EI) m/z calcd for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1380, found 267.1380.

4.1.17. 2-(Isothiochroman-1-yl)-1-phenylethanone ***5i***.[10] Yield 39%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.98 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.2 Hz, 1H), 7.48 (t, J=7.8 Hz, 2H), 7.22–7.14 (m, 4H), 4.71–4.65 (m, 1H), 3.74 (dd, J=9.0, 17.4 Hz, 1H), 3.49 (dd, J=3.0, 17.4 Hz, 1H), 3.10 (t, J=6.0 Hz, 2H), 3.01–3.95 (m, 1H), 2.90–2.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.3, 137.8, 136.8, 136.7, 133.3, 129.6, 128.7, 128.2, 127.3, 126.9, 126.6, 47.1, 36.1, 30.9, 24.7; HRMS (EI) m/z calcd for $C_{17}H_{17}SO$ $[M+H]^+$ 269.0995, found 269.0996.

4.1.18. 2-(1,3-Dihydroisobenzofuran-1-yl)-1-phenylethanone ***5j***.[10] Yield 18%; colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.00 (d, J=7.8 Hz, 2H), 7.58 (t, J=7.2 Hz, 1H), 7.47 (t, J=7.8 Hz, 2H), 7.33–7.22 (m, 4H), 5.91 (s, 1H), 5.16 (d, J=12.6 Hz, 1H), 5.10 (d, J=12.0 Hz, 1H), 3.55 (dd, J=7.2, 16.2 Hz, 1H), 3.36 (dd, J=5.4, 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 141.4, 139.2, 137.0, 133.3, 128.6, 128.3, 127.8, 127.4, 121.5, 121.0, 80.1, 72.6, 45.6; HRMS (EI) m/z calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ 239.1067, found 239.1066.

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Supplementary data

The spectra of the compounds in Tables 2 and 3 in this manuscript can be found. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.074.

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