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Manganese Dioxide–Methanesulfonic Acid Promoted Direct Dehydrogenative Alkylation of sp^3 C–H Bonds Adjacent to a Heteroatom

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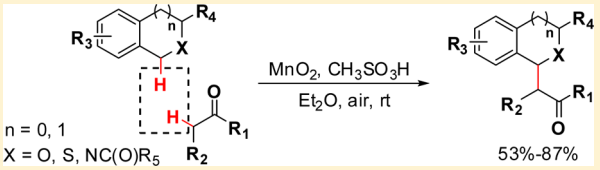
Supporting Information

ABSTRACT: A manganese dioxide (MnO_2)–methanesulfonic acid (CH_3SO_3H) oxidation system has been developed to efficiently promote direct coupling of benzylic ethers and carbamates with simple ketones via oxidative C–H bond activation. The alkylation proceeds smoothly under air atmosphere to afford the corresponding products in good to excellent yields (53–87%). The employment of the combination of MnO_2 and CH_3SO_3H is attractive on the basis of economical and environmental issues.

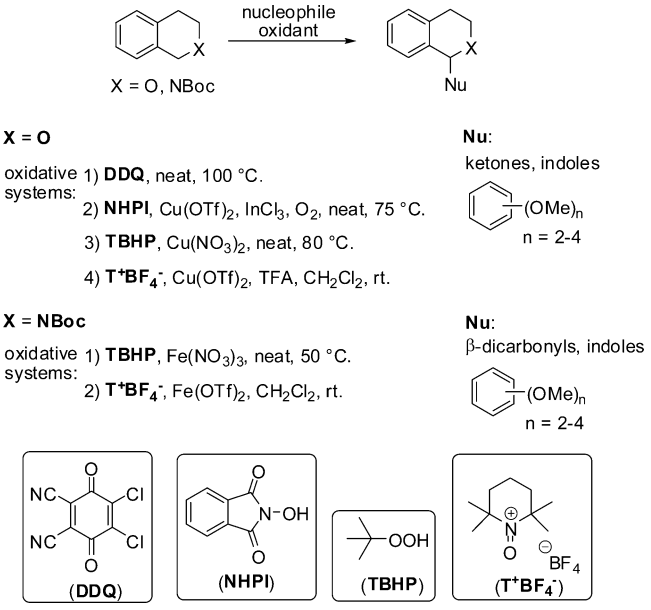


INTRODUCTION

Carbon–carbon (C–C) bond forming reactions are fundamental transformations in organic synthesis. While these processes are most frequently achieved through reactive functional group transformations, precise one step substitution of carbon–hydrogen (C–H) bonds, the most ubiquitous bonds in organic molecules, with C–C bonds opens a new synthetic strategy for modern synthesis.[1−4] Among these, the cross-dehydrogenative coupling (CDC) reaction, namely, the direct coupling of two different C–H bonds between two reactants, has attracted much interest in recent years.[5−10] The majority of such CDC reactions involve oxidative alkylation of benzylic C–H bonds adjacent to an *N*-aryl group.[11−26] In sharp contrast, for the oxidation of corresponding less reactive benzylic C–H bonds next to an oxygen atom or an *N*-acyl group, only a few oxidation systems have been reported so far (Scheme 1). The four oxidants utilized for isochroman substrates are 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[27−34] NHPI (*N*-hydroxyphthalimide),[35] organic peroxides,[36,37] and TEMPO oxoammonium salt ($T^+BF_4^-$);[38,39] the two oxidants for *N*-acyl THIQs are organic peroxides[36,37] and $T^+BF_4^-$.[38,39] These oxidation systems required either intensive heating or expensive reagents. While moderate to high reaction efficiency (up to 81%) was observed for *N*-acyl THIQs, only low to moderate reaction efficiency (23–52%) was reported for isochromans when using either *tert*-butyl hydroperoxide (*t*BHP) or $T^+BF_4^-$ as the oxidant. Considering that isochroman moieties are core units within a multitude of biologically active compounds,[40−44] and the synthetic efficiencies of such compounds through CDC are still far from satisfactory, the development of a mild, economic and efficient oxidation system is still a worthwhile project to pursue.

Manganese moieties like manganese(III) porphyrins and (salen)manganese(III) complexes have long been known to selectively catalyze benzylic hydroxylation through a P450-like

Scheme 1. Four Reported Oxidation Systems for CDCs between Isochroman or *N*-Acyl THIQ and Carbon Nucleophiles



C–H oxidation mechanism (Scheme 2).[45−49] However, direct C–C bond formations have not been achieved via such systems to date. Activated MnO_2 is an inexpensive, less toxic, easily handled, and environmentally benign reagent.[50,51] It has been utilized as an efficient and mild reagent for selective oxidation of activated alcohols (benzylic, allylic, propargylic, etc.).

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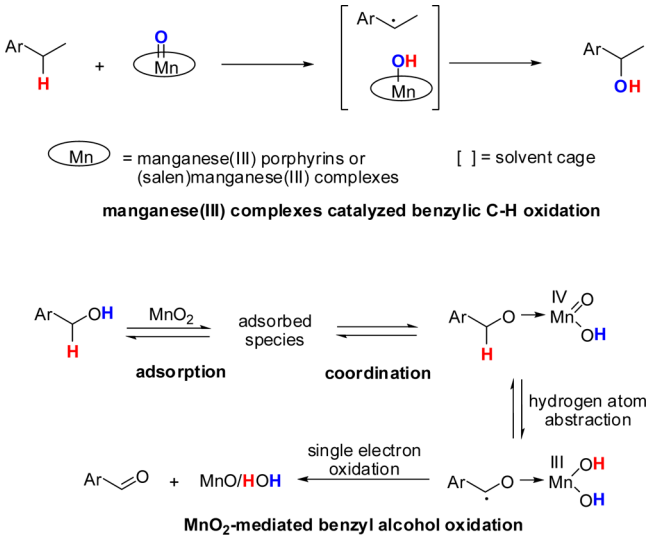
Scheme 2. Well-Accepted Mechanisms of Manganese-Species-Induced Benzylic C−H Oxidation

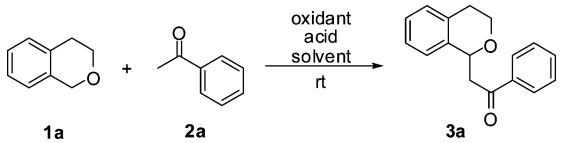


However, to the best of our knowledge, MnO_2 has not been reported to promote corresponding oxidation of activated ethers, leading to C−C bond formation.[52] While the mechanism of benzylic alcohol oxidation is not fully understood, a widely accepted rationale[53−55] involves an adsorption and coordination of the alcohol onto MnO_2, followed by a rate-determining hydrogen abstraction to produce a free benzylic radical, and subsequent a one-electron oxidation to afford the desired aldehyde (Scheme 2). Utilizing the mechanistic rationale, we proposed that a suitable acid might be able to activate MnO_2 thereby initiating a C−H oxidation of the benzylic ether. Herein, we document a MnO_2-mediated oxidative cross-coupling of cyclic benzylic ethers and carbamates with simple ketones in the presence of CH_3SO_3H at room temperature.

RESULTS AND DISCUSSION

We selected the coupling of isochroman and acetophenone as a starting point for our initial studies. Isochroman was known to be readily oxidized when exposed to the air, especially in an acidic environment and under elevated oxygen pressure.[56−59] Therefore, reactions were conducted under a nitrogen atmosphere in a glovebox to get rid of the involvement of oxygen. A variety of Brønsted acids as well as Lewis acids were applied to the model reaction employing activated MnO_2 as the oxidant in CH_2Cl_2 (Table 1). Lewis acids like $BF_3{\cdot}OEt_2$ and Brønsted acids like AcOH and *p*-toluenesulfonic acid (PTSA) resulted in no reaction at all (entries 2−4, Table 1). Camphorsulfonic acid (CSA), trifluoroacetic acid (TFA) and trifluoromethanesulfonic acid (TfOH) can promote the coupling, and CH_3SO_3H proved to be the best choice for the coupling (entries 5−8). No reaction took place if MnO_2 or CH_3SO_3H alone was employed (entries 1 and 9). Subsequently, various metal oxidants were investigated for the reaction. While manganese-based candidates like $Mn(OAc)_3$,[60] $Mn(OAc)_2{\cdot}4H_2O$ and $Ba(MnO_4)_2$ can also effect the coupling, MnO_2 worked best and was selected for further reaction optimization (entries 10−17). The reaction was also highly dependent on the solvent choice. Solvents such as hexane, THF and 1,4-dioxane inhibited the reaction (entries 18, 20 and 21); CH_2Cl_2 afforded a fair amount of the desired product at the beginning stage, but product decomposition was observed during the reaction, giving irreproducible results (entry 8); products in toluene and Et_2O were well compatible with the oxidation system, and Et_2O proved to be the best choice (entries 19 and 22). Reaction optimization experiments identified decreased MnO_2 (300 mol %) and CH_3SO_3H (0.3 mL) as ideal conditions (entry 25), although a prolonged reaction time was necessary. The involvement of oxygen did not bring down the reaction efficiency. Even after four days, little conversion was observed when the reaction was performed under atmospheric pressure of oxygen in the absence of MnO_2 (entry 27). When MnO_2 was introduced to the oxygen atmosphere, the reaction went to completion to give an 82% yield (entry 28). The reaction under air afforded comparable result, and this optimized condition will be applied for further studies for convenience (entry 29). Addition of substoichiometric amounts (50 mol %) of a radical inhibitor,

Table 1. Optimization of the Oxidation System[a]



entry	oxidant	acid	solvent	time (h)	yield (%)[b]
1	MnO_2	–	CH_2Cl_2	12	0
2	MnO_2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	12	0
3	MnO_2	AcOH	CH_2Cl_2	12	0
4	MnO_2	PTSA	CH_2Cl_2	12	0
5	MnO_2	CSA	CH_2Cl_2	12	15
6	MnO_2	TFA	CH_2Cl_2	3	28
7	MnO_2	TfOH	CH_2Cl_2	3	33
8	MnO_2	CH_3SO_3H	CH_2Cl_2	2	45
9	–	CH_3SO_3H	CH_2Cl_2	12	<5
10	$Mn(OAc)_3$	CH_3SO_3H	CH_2Cl_2	3	38
11	$Mn(OAc)_2$	CH_3SO_3H	CH_2Cl_2	3	15
12	$Ba(MnO_4)_2$	CH_3SO_3H	CH_2Cl_2	3	36
13	$FeCl_3$	CH_3SO_3H	CH_2Cl_2	3	<5
14	$RuCl_3$	CH_3SO_3H	CH_2Cl_2	3	<5
15	CoF_3	CH_3SO_3H	CH_2Cl_2	3	<5
16	$CuCl_2$	CH_3SO_3H	CH_2Cl_2	3	<5
17	$PdCl_2$	CH_3SO_3H	CH_2Cl_2	3	<5
18	MnO_2	CH_3SO_3H	hexane	3	<5
19	MnO_2	CH_3SO_3H	toluene	4	77
20	MnO_2	CH_3SO_3H	THF	4	<5
21	MnO_2	CH_3SO_3H	1,4-dioxane	4	10
22	MnO_2	CH_3SO_3H	Et_2O	3	83
23[c]	MnO_2	CH_3SO_3H	Et_2O	8	81
24[d]	MnO_2	CH_3SO_3H	Et_2O	24	63
25[e]	MnO_2	CH_3SO_3H	Et_2O	24	80
26[f]	MnO_2	CH_3SO_3H	Et_2O	48	57
27[e,g]	–	CH_3SO_3H	Et_2O	96	<5
28[e,g]	MnO_2	CH_3SO_3H	Et_2O	24	82
29[e,h]	MnO_2	CH_3SO_3H	Et_2O	24	81
30[e,h,i]	MnO_2	CH_3SO_3H	Et_2O	24	<5

[a]General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (600 mol %), acid (0.4 mL), solvent (1.5 mL) in a glovebox, unless stated otherwise. [b]Isolated yield. [c]CH_3SO_3H (0.3 mL). [d]CH_3SO_3H (0.2 mL). [e]CH_3SO_3H (0.3 mL) and MnO_2 (300 mol %). [f]CH_3SO_3H (0.3 mL) and MnO_2 (200 mol %). [g]Reaction under O_2. [h]Reaction under air. [i]50 mol % BHT added.

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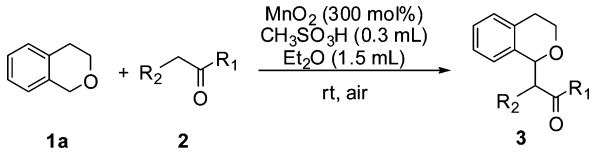
2,6-di-*tert*-butyl-4-methylphenol (BHT) completely blocked the transformation (entry 30).

With the optimized oxidative cross-coupling conditions in hand, the effect of various nucleophiles on the transformation was studied (Table 2). A variety of ketones with electronically

Table 2. Cross-Coupling between Isochroman and Ketone Derivatives[a]



1a 2 3

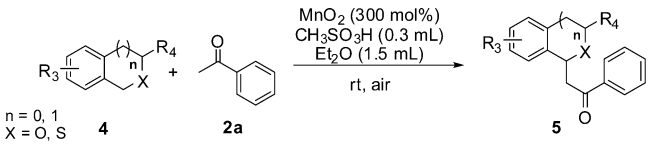
entry	series	ketone	yield (%)[b]
1	**2a**	acetophenone	81
2	**2b**	4′-methylacetophenone	75
3	**2c**	4′-methoxyacetophenone	71
4	**2d**	4′-bromoacetophenone	87
5	**2e**	2′-chloroacetophenone	75
6	**2f**	propiophenone	71
7	**2g**	2-furyl methyl ketone	53
8	**2h**	3-pentanone	30
9	**2i**	cyclopentanone	13

[a]General conditions: **1a** (0.2 mmol), **2** (0.4 mmol), MnO_2 (300 mol %), acid (0.3 mL), Et_2O (1.5 mL) under air for 24 h. [b]Isolated yield.

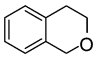
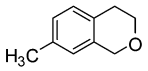
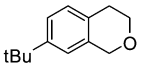
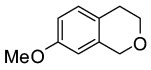
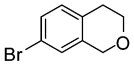
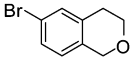
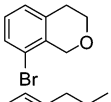
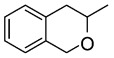
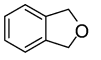
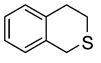
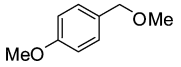
varied aromatic and heteroaromatic substituents, as well as propiophenone, were accommodated. The coupling reaction was found to be sensitive to the electronic substituents. Electron-rich ketones provided products in slightly reduced yields relative to acetophenone (entries 1−3, Table 2), while electron-deficient ones like 4′-bromoacetophenone afforded a better result (entry 4). The reaction efficiency was also influenced by the steric encumbrance of the nucleophile, which well explained the mild decrease in yields for 2′-chloroacetophenone and propiophenone (entries 1 and 4−6). A heteroaromatic ketone like 2-furyl methyl ketone was also compatible with the system, though only a moderate yield was observed (entry 7). Aliphatic ketones proved to be less effective than the aromatic ones, and relatively low yields were obtained (entries 8 and 9).

The substituent effect of isochroman on the coupling reaction was subsequently investigated (Table 3). Alkyl-substituents like methyl and *tert*-butyl at C7 of isochroman performed equally well as the model reaction (entries 1−3, Table 3). In accordance with Todd's result,[28] the methoxy substituent afforded no reaction (entry 4). This can be explained by Floreancig's mechanistic studies,[61] that substrates with lower oxidation potentials have higher bond dissociation energy of the scissile C−H bond, if reactions proceed through a radical mechanism. The reaction went smoothly when a bromo-substituent was placed at C7 position, and 72% yield was obtained (entry 5). A bromo-substituent at C6 position resulted in a slightly reduced yield (entry 6), and the yield of substituent at C8 dropped to 55% (entry 7), probably because of the increased steric bulk. The compatibility of a bromo-substituent with the oxidation system will be beneficial for further diversifications. The reaction of 3-substituted isochroman with acetophenone gave the product in 78% yield (entry 8). Other active methylene compounds were also applied to the protocol. Phthalan and isothiochroman can be oxidized by the protocol (entries 9 and 10), although both of them proved to

Table 3. Cross-Coupling between Acetophenone and Isochroman Derivatives[a]



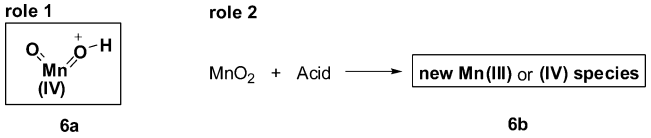
n = 0, 1
X = O, S 4 2a 5

entry	series	isochroman derivatives	yield (%)[b]
1	4a		81
2	4b		76
3	4c		74
4	4d		0
5	4e		72
6	4f		66
7	4g		55
8	4h		78
9	4i		40
10	4j		18
11	4k		0

[a]General conditions: **4** (0.2 mmol), **2a** (0.4 mmol), MnO_2 (300 mol %), acid (0.3 mL) in Et_2O (1.5 mL) under air for 24 h. [b]Isolated yield.

be less reactive than isochroman. No desired product was observed when acyclic benzylic ether **4k** was subjected to the reaction (entry 11).

The presence of a suitable acid is the key issue to the coupling. Although the exact role of the acid is still unclear, we proposed two possible roles in which MnO_2 and acid acted in the oxidation (Figure 1). In the first one, MnO_2 is the real



6a 6b

Figure 1. Proposed roles of MnO_2 and the acid in the coupling.

oxidant and the role of the acid is activating the MnO_2 like **6a**.[62] In the other one (**6b**), the acid might react with MnO_2 to form a new reactive manganese species, which might be the essential oxidant.[63] Although the formula of **6b** is unclear, the fact that manganese species like $Mn(OAc)_3$ and $Ba(MnO_4)_2$ afforded comparable results to MnO_2 in the presence of CH_3SO_3H in CH_2Cl_2 (entries 8, 10 and 12, Table 1), and the precedent[64]

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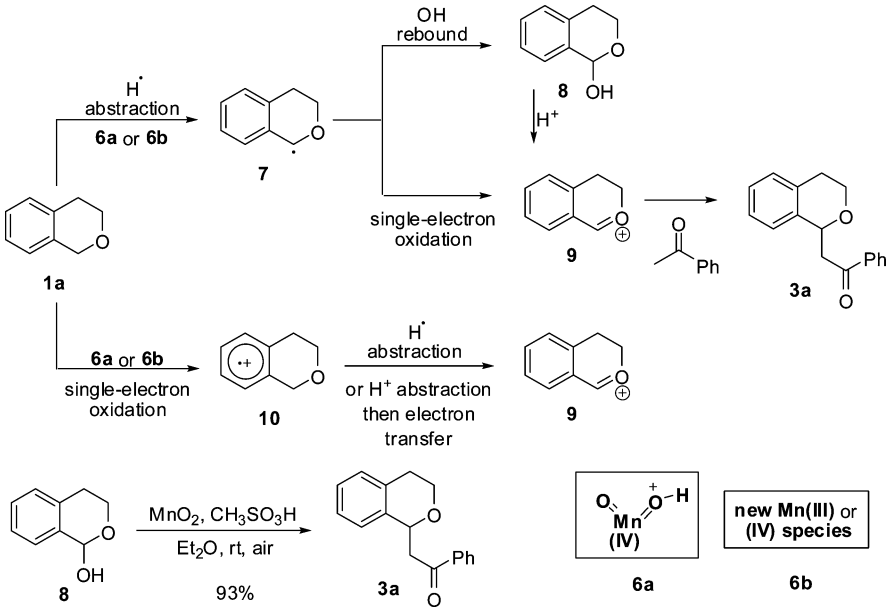
Scheme 3. Proposed Mechanism for MnO_2-Mediated Oxidative Cross-Coupling

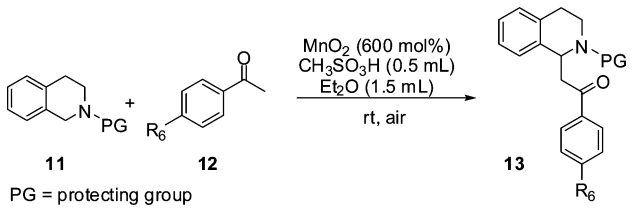


that $Mn_2(SO_4)_3$ is a reasonably stable one-electron oxidant, indicates that the presence of **6b** should be possible. According to the above analysis, the reactivity difference of a variety of acids in Table 1 could be well explained. For example, enough acidity and solubility are required for the acid to activate or react with the MnO_2 to initiate the oxidation process, which could explain the reactivity difference between AcOH and TFA (entries 3 and 6, Table 1), and PTSA and CSA (entries 4 and 5, Table 1), respectively. TfOH is less effective than CH_3SO_3H for the process (entries 7 and 8, Table 1), which could be attributed to the strong acidity of TfOH, resulting in a poor compatibility of TfOH with reactive intermediates or products; moreover, in reactive species **6b**, the counterion of the acid like sulfonate (methanesulfonate for $CH_3SO_3^-$ and trifluoromethanesulfonate for TfOH) could affect the reactivity of **6b** by coordinating to the manganese center. This counterion effect could also explain the observation that CSA is not as efficient as CH_3SO_3H for the process (entries 5 and 7, Table 1), probably because the coordination of a bulky counterion to the manganese center might result in a less reactive oxidant.[65]

While the mechanism is not yet fully understood, radical intermediates should be involved in the reaction since substoichiometric amounts (50 mol %) of BHT completely blocked the transformation (entry 30, Table 1); therefore, one-step hydride transfer process from isochroman to the oxidant should be excluded. Two mechanisms have been postulated for the generation of stabilized carbocation **9** through MnO_2–CH_3SO_3H mediated C–H oxidation (Scheme 3). The first pathway proceeds through an initial benzylic hydrogen atom abstraction from **1a** to **6a** or **6b** to form free radical **7**;[66] the radical diverges either via hydroxyl rebound to form **8** or one-electron oxidation to directly generate cationic intermediate **9**. Indeed, employing synthesized **8** as a substrate under the standard oxidation conditions[67] provided the alkylation product **3a** in 93% yield (Scheme 3), indicating that **8** could be a potential intermediate. The other pathway proceeds through an initial electron transfer from isochroman to **6a** or **6b** to form the radical cation **10**.[68] Carbocation **9** can then be accessed through hydrogen atom abstraction or proton abstraction followed by a second electron transfer.[68,69]

The success of the MnO_2/CH_3SO_3H system on ether alkylation led us to explore the corresponding nitrogenated substrates because tetrahydroisoquinoline (THIQ) derivatives are common subunits in numerous natural products and pharmaceutically active compounds.[70−72] *N*-Alkyl and *N*-aryl THIQs proved to be incompatible with the acid system, and substrate decomposition occurred immediately after the additions (entries 1 and 2, Table 4). Protecting groups bearing carbonyl functions were also investigated (entries 3−6). While similar decomposition was observed with the *tert*-butyl carbamate (Boc) substituent (entry 3), benzyl carbamate (Cbz) and amide moieties like acyl (Ac) and benzoyl (Bz) gave the corresponding alkylation products (entries 4−6); among these, the Cbz protecting group worked the best. Cbz-

Table 4. Cross-Coupling between THIQ Derivatives and Ketones[a]



entry	PG	R	yield (%)[b]
1	Bn	H	–[c]
2	Ph	H	–[c]
3	Boc	H	–[c]
4	Cbz	H	60
5	Ac	H	20
6	Bz	H	16
7	Cbz	Br	65
8	Cbz	MeO	62

[a]General conditions: **11** (0.2 mmol), **12** (0.4 mmol), MnO_2 (600 mol %), CH_3SO_3H (0.5 mL) in Et_2O (1.5 mL) under air. [b]Isolated yield. [c]Decomposition.

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protected THIQ displayed lower reactivity compared to the oxygenated analogues, and more MnO_2 and CH_3SO_3H were required for reaction completion. 4′-Bromo and 4′-methoxyacetophenone were selected to simply test the nucleophilic scope, and both of them afforded desired products in good chemical yields (entries 7 and 8). While the C−H functionalization of *N*-arylated THIQs was well-studied, a vital limitation of such protocols is the difficulty in removing the *N*-aryl group, often requiring harsh conditions[73−75] and therefore resulting in poor functional group tolerance and synthetic applications. In sharp contrast, although the Cbz group can be easily removed under a variety of mild conditions,[36,76−78] only two examples of such couplings were reported, probably because of the reduced reactivity (Scheme 1).[36,37,39] While moderate to good chemical yields (up to 81%) were achieved using *t*BHP or $T^+BF_4^-$ as the oxidant, either intensive heating or the expensive $T^+BF_4^-$ was requisite for the coupling. Herein, the successful alkylation of *N*-Cbz THIQs under very mild conditions affords efficient access to structurally diverse THIQs through further functionalization.

CONCLUSION

In summary, we have developed an oxidative cross-coupling protocol simply employing the inexpensive reagents CH_3SO_3H and MnO_2 under air at room temperature. The oxidation system efficiently promotes the alkylation of isochroman and Cbz-protected THIQ derivatives with simple ketones in good to excellent yields with high functional group tolerance on both reactants. The low cost, negligible toxicity, and ease of handling combined with the absence of hazardous byproducts, are attractive. The method does not require intensive heating, and the workup consists of simple filtration and solvent evaporation. To the best of our knowledge, this is the first example of the use of MnO_2 to promote benzylic ether or carbamate oxidation, leading to C−C bond formation. The development of potential manganese(III)-catalyzed oxidative alkylation of benzylic ethers and carbamates is currently under investigation and will be disclosed in due course.

EXPERIMENTAL SECTION

General Experimental Methods. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 600 and 125 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) or the solvent peak was used as a reference value: for ^{1}H NMR, TMS (in $CDCl_3$) = 0.00 ppm; for ^{13}C NMR, TMS (in $CDCl_3$) = 0.00. Infrared spectra were recorded on a FT-IR spectrometer with KBr discs. Analytical TLC was performed on precoated silica gel GF_{254} plates. HRMS were carried out on an Orbitrap analyzer. Active MnO_2 was heated at 200 °C under a vacuum before use.

General Procedure A for Oxidative Couplings between Benzylic Ethers with Ketones. To a solution of benzylic ethers (0.2 mmol, 1.0 equiv) and ketones (0.4 mmol, 2.0 equiv) in Et_2O (1.5 mL) were added activated MnO_2 (52.2 mg, 3.0 equiv) followed by CH_3SO_3H (0.3 mL) dropwise under air. The reaction mixture was stirred at rt until TLC analysis showed complete starting material consumption. The above mixture was directly purified by flash chromatography to give the desired products.

*2-(Isochroman-1-yl)-1-phenylethanone (**3a**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 81% yield (40.8 mg) as colorless 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; IR ν_{max} 1685, 1596, 1579, 1493, 1449, 1427, 1399, 1366, 1340, 1282, 1203, 1181, 1160, 1107, 1073, 1039, 1013, 1002, 986 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{16}O_2$ [M + H]$^+$ 253.1223, found 253.1222.

*2-(Isochroman-1-yl)-1-(p-tolyl)ethanone (**3b**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 75% yield (39.9 mg) as colorless 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; IR ν_{max} 1700, 1590, 1566, 1492, 1468, 1432, 1365, 1339, 1286, 1200, 1106, 1078, 1037, 990, 960, 799 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{18}O_2$ [M + H]$^+$ 267.1380, found 267.1382.

*2-(Isochroman-1-yl)-1-(4-methoxyphenyl)ethanone (**3c**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 71% yield (40.1 mg) as colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.01 (d, J = 7.8 Hz, 2H), 7.20 (s, 2 H), 7.14 (d, J = 6.0 Hz, 2 H), 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, 130.3, 129.0, 126.5, 126.2, 124,6, 113.7, 72.8, 63.5, 55.5, 45.1, 28.9; IR ν_{max} 1675, 1600, 1575, 1511, 1455, 1421, 1366, 1260, 1171, 1106, 1028, 987, 846,754 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{18}O_3$ [M + H]$^+$ 283.1329, found 283.1328.

*1-(4-Bromophenyl)-2-(isochroman-1-yl)ethanone (**3d**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 87% yield (57.6 mg) as colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.88 (d, J = 6.6 Hz, 2H), 7.62 (d, J = 6.6 Hz, 2 H), 7.26−7.05 (m, 4 H), 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 197.3, 137.2, 135.9, 134.0, 131.8, 129.9, 129.1, 128.3, 126.7, 126.29, 124.4, 72.7, 63.5, 45.3, 28.9; IR ν_{max} 1686, 1581, 1495, 1396, 1368, 1283, 1196, 1174, 1105, 1070, 1012, 990, 847, 805, 754 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{15}BrO_2$ [M + H]$^+$ 331.0328, found 331.0331.

*1-(2-Chlorophenyl)-2-(isochroman-1-yl)ethanone (**3e**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 75% yield (43.0 mg) as colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.55 (d, J = 6.0 Hz, 1H), 7.44−7.32 (m, 3H), 7.26−7.05 (m, 4H), 5.37 (s, 1H), 4.15−4.07 (m, 1H), 3.82−3.74 (m, 1H), 3.49 (s, 2H), 2.99−2.93 (m, 1H), 2.71 (d, J = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 139.5, 136.9, 133.9, 131.7, 130.7, 130.3, 129.4, 129.1, 127.0, 126.7, 126.3, 124.5, 72.8, 63.1, 49.7, 28.7; IR ν_{max} 1680, 1606, 1572, 1492, 1453, 1406, 1366, 1339, 1284, 1200, 1181, 1106, 1039, 1013, 983, 805 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{15}ClO_2$ [M + H]$^+$ 287.0833, found 287.0835.

*2-(Isochroman-1-yl)-1-phenylpropan-1-one (**3f**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 71% yield (37.8 mg, dr = 3:1): ^{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, 64.0, 63.3, 47.3, 47.8, 29.3, 28.9, 13.6, 9.9; IR ν_{max} 1722, 1686, 1597, 1579, 1492, 1451, 1426, 1374, 1343, 1276, 1240, 1220, 1161, 1114, 1075, 1061, 976 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{18}O_2H$ [M + H]$^+$ 267.1380, found 267.1382.

*1-(Furan-2-yl)-2-(isochroman-1-yl)ethanone (**3g**).* The general procedure A for the oxidative coupling was followed, affording the

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title compound in 50% yield (24.2 mg) as 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; IR ν_{max} 1721, 1663, 1563, 1493, 1468, 1430, 1393, 1342, 1294, 1246, 1164, 1100, 1057, 1030, 1006, 987, 911, 881 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{14}O_3$ $[M + H]^+$ 243.1016, found 243.1015.

*2-(Isochroman-1-yl)pentan-3-one (**3h**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 30% yield (13.1 mg) as 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; IR ν_{max} 1710, 1604, 1580, 1494, 1453, 1411, 1373, 1284, 1192, 1160, 1113, 1073, 1042, 980, 942, 906, 804, 748 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{18}O_2$ $[M + H]^+$ 219.1380, found 219.1377.

*2-(Isochroman-1-yl)cyclopentanone (**3i**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 13% yield (5.6 mg) as 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; IR ν_{max} 1741, 1604, 1493, 1452, 1427, 1404, 1376, 1329, 1278, 1158, 1111, 1060, 1010, 983, 944 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{16}O_2$ $[M + H]^+$ 217.1223, found 217.1221.

*2-(7-Methylisochroman-1-yl)-1-phenylethanone (**5b**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 76% yield (40.4 mg) as 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; IR ν_{max} 1679, 1596, 1578, 1504, 1446, 1366, 1284, 1263, 1202, 1095, 1060, 1010, 809, 758 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{18}O_2$ $[M + H]^+$ 267.1380, found 267.1382.

*2-(7-(tert-Butyl)isochroman-1-yl)-1-phenylethanone (**5c**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 74% yield (45.6 mg) as colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.03 (d, J = 7.8 Hz, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.26 (d, J = 7.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 5.53 (d, J = 9.0 Hz, 1H), 4.15−4.07 (m, 1H), 3.81 (dd, J = 9.6, 16.8 Hz, 1H), 3.66 (dd, J = 9.0, 15.6 Hz, 1H), 3.30 (d, J = 16.2 Hz,1H), 3.03−2.95 (m, 1H), 2.70 (d, J = 16.2 Hz 1H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5, 149.2, 137.4, 137.0, 133.1, 131.0, 128.7, 128.6, 128.4, 123.8, 121.2, 73.0, 63.4, 45.6, 34.5, 31.3, 28.5; IR ν_{max} 1726, 1685, 1597, 1580, 1503, 1449, 1364, 1280, 1202, 1102, 1073, 1018, 988, 930, 821 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{24}O_2$ $[M + H]^+$ 309.1849, found 309.1846.

*2-(7-Bromoisochroman-1-yl)-1-phenylethanone (**5e**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 72% yield (47.7 mg) as 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; IR ν_{max} 1685, 1596, 1580, 1483, 1402, 1368, 1331, 1280, 1109, 1017, 987, 919, 813, 691 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{15}BrO_2$ $[M + H]^+$ 331.0328, found 331.0330.

*2-(6-Bromoisochroman-1-yl)-1-phenylethanone (**5f**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 66% yield (43.7 mg) as 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; IR ν_{max} 1731, 1685, 1596, 1562, 1451, 1439, 1403, 1355, 1280, 1203, 1177, 1100, 1059, 1005, 965, 905, 816, 767 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{15}BrO_2$ $[M + H]^+$ 331.0328, found 331.0331.

*2-(8-Bromoisochroman-1-yl)-1-phenylethanone (**5g**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 55% yield (36.4 mg) as 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; IR ν_{max} 1731, 1673, 1595, 1484, 1449, 1431, 1359, 1336, 1280, 1238, 1106, 1080, 1038, 967, 888, 825 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{15}BrO_2$ $[M + H]^+$ 331.0328, found 331.0330.

*2-(3-Methylisochroman-1-yl)-1-phenylethanone (**5h**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 78% yield (41.5 mg, dr = 1:1) as colorless oil. First isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.03 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1 H), 7.48 (t, J = 7.2 Hz, 2 H), 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; IR ν_{max} 1725, 1687, 1597, 1492, 1450, 1357, 1279, 1207, 1146, 1108, 1083, 1042, 987, 955, 822, 750 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{18}O_2$ $[M + H]^+$ 267.1380, found 267.1381. Second isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.01 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1 H), 7.49 (t, J = 7.2 Hz, 2 H), 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; IR ν_{max} 1725, 1682, 1597, 1492, 1450, 1383, 1355, 1281, 1204, 1123, 1107, 1076, 1039, 984, 940, 815 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{18}O_2$ $[M + H]^+$ 267.1380, found 267.1380.

*2-(1,3-Dihydroisobenzofuran-1-yl)-1-(furan-2-yl)ethanone (**5i**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 40% yield (18.3 mg) as 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, 1 H), 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; IR ν_{max} 1700, 1682, 1599, 1476, 1450, 1361, 1281, 1231, 1208, 1107, 1042, 983, 936, 878 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{14}O_2$ $[M + H]^+$ 239.1067, found 239.1066.

*2-(Isothiochroman-1-yl)-1-phenylethanone (**5j**).* The general procedure A for the oxidative coupling was followed, affording the title compound in 18% yield (9.7 mg): ^{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), 3.01−2.95 (m, 1H), 2.90−2.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125

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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; IR ν_{max} 1677, 1594, 1491, 1445, 1410, 1357, 1299, 1274, 1238, 1205, 1186, 977, 913 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{16}SO$ $[M + H]^+$ 269.0995, found 269.0996.

General Procedure B for Oxidative Couplings between Tetrahydroisoquinoline (THIQ) Derivatives and Ketones. To a solution of THIQ derivatives (0.2 mmol, 1.0 equiv) and ketones (0.4 mmol, 2.0 equiv) in Et_2O (1.5 mL) were added activated MnO_2 (104 mg, 6.0 equiv) followed by CH_3SO_3H (0.5 mL) dropwise. The reaction mixture was stirred at rt until TLC analysis showed complete starting material consumption. The reaction was quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired products.

*Benzyl-1-(2-oxo-2-phenylethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**13a**).* The general procedure B for the oxidative coupling was followed, affording the title compound in 60% yield (46.3 mg): ^1H NMR ($CDCl_3$, 600 MHz, rotamers seen) δ 8.01 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 6.6 Hz, 1H), 7.60−7.30 (m, 5H), 7.30−7.10 (m, 7H), 5.85 (d, J = 4.8 Hz, 1H), 5.14 (s, 1H), 5.09 (d, J = 12.6 Hz, 0.5H), 4.95 (d, J = 12.6 Hz, 0.5H), 4.18 (d, J = 12.6 Hz, 0.5H), 3.99−3.89 (m, 0.5H), 3.77−3.53 (m, 1H), 3.47 (d, J = 9.6 Hz, 1H), 3.37 (dd, J = 6.0, 15.0 Hz, 1H), 3.05−2.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, rotamers seen) δ 197.3, 155.0, 137.0, 136.8, 136.7, 136.6, 136.3, 134.2, 133.1, 129.0, 128,6, 128.4, 128.3, 128.1, 127.9, 127.9, 127.2, 127.1, 126.9, 129.4, 67.3, 51.9, 46.5, 38.8, 28.3; IR ν_{max} 1687, 1607, 1492, 1454, 1381, 1333, 1275, 1205, 1095, 1075, 1051, 1006, 995, 957, 917, 776 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{23}NO_3$ $[M + H]^+$ 386.1751, found 386.1740.

*Benzyl-1-(2-(4-bromophenyl)-2-oxoethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**13b**).* The general procedure B for the oxidative coupling was followed, affording the title compound in 65% yield (60.1 mg) as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz, rotamers seen) δ 7.87 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.42−7.28 (m, 4H), 7.26−7.10 (m, 5H), 5.79 (d, J = 6.0 Hz, 1H), 5.13 (s, 1H), 5.08−4.95 (m, 1H), 4.21−4.15 (m, 0.5H), 3.95−3.89 (m, 0.5H), 3.61 (s, 0.5H), 3.55−3.37 (m, 1.5H), 3.34−3.28 (m, 1H), 3.04−2.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, rotamers seen) δ 196.2, 154.9, 136.6, 136.2, 136.1, 135.7, 135.4, 134.2, 132.0, 129.9, 129.6, 129.1, 128.7, 128.4, 128.0, 127.9, 127.2, 127.1, 126.8, 126.4, 67.4, 52.0, 46.5, 38.7, 28.3; IR ν_{max} 1697, 1584, 1453, 1425, 1327, 1294, 1225, 1204, 1120, 1097, 1006, 947, 834, 753 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{22}BrNO_3$ $[M + H]^+$ 464.0856, found 464.0837.

*Benzyl-1-(2-(4-methoxyphenyl)-2-oxoethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**13h**).* The general procedure B for the oxidative coupling was followed, affording the title compound in 62% yield (51.5 mg) as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz, rotamers seen) δ 8.02 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.41−7.23 (m, 5H), 7.22−7.12 (m, 4H), 6.95 (d, J = 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.82 (m, 1H), 5.14 (s, 1H), 5.08 (d, J = 12.6 Hz, 0.5H), 4.96 (d, J = 12.0 Hz, 0.5H), 4.22−4.16 (m, 0.5H), 3.96−3.90 (m, 0.5H), 3.87 (s, 3H), 3.65−3.29 (m, 2H), 3.32−3.24 (m, 1H), 3.04−2.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, rotamers seen) δ 195.8, 163.5, 155.1, 136.7, 136.6, 136.5, 134.2, 130.7, 130.5, 130.1, 129.9, 129.0, 128.6, 128.4, 128.0, 127.2, 127.1, 126.4, 113.8, 67.3, 55.5, 52.2, 46.3, 38.7, 28.4; IR ν_{max} 1698, 1600, 1454, 1425, 1294, 1258, 1227, 1170, 1119, 1026, 1003, 839 cm^{-1}; HRMS (EI) m/z calcd for $C_{26}H_{25}NO_4$ $[M + H]^+$ 416.1856, found 416.1844.

General Procedure C for the Synthesis of Isochroman Derivatives (4b−h, 4j). Substrates **4b−h**, **4j** were prepared following Johansen[79] and Watson[80] protocols. A mixture of the substituted phenylethyl alcohol (1.0 equiv), (2-methoxyethoxy)methyl (MEM) chloride (1.5 equiv) and *N*,*N*-diisopropylethylamine (1.5 equiv) in dry CH_2Cl_2 (120 mL) was stirred under N_2 for 2.5 h at rt. The reaction mixture was then washed with 1 M HCl and dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by flash chromatography to provide the desired acetal for next step.

To the MEM acetal (1.0 equiv) in CH_3CN at 0 °C was added TMSOTf (0.25 equiv) dropwise. After striing at rt for 10 h, it was quenched by saturated aqueous $NaHCO_3$. The CH_3CN was removed under reduced pressure, and the resulting mixture was diluted with saturated aqueous $NaHCO_3$ and then partitioned with Et_2O. The ethereal layer was dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by flash chromatography to afford the corresponding isochroman derivatives as colorless oil.[21]

*7-Methylisochroman (**4b**).* The general procedure C was followed, affording the title compound in 80% yield (1.2 g) over two steps as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.10−6.98 (m, 2H), 6.82 (s, 1H), 4.76 (s, 2H), 3.98 (d, J = 5.4 Hz, 2H), 2.84 (d, J = 4.8 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.5, 134.7, 130.1, 128.7, 127.2, 124.8, 67.9, 65.5, 27.9, 21.1; IR ν_{max} 1506, 1461, 1448, 1430, 1377, 1337, 1269, 1227, 1152, 1126, 1104, 1069, 1005, 986, 946, 916, 853, 810, 747 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_{12}O$ $[M + H]^+$ 149.0960, found 149.0957.

*7-(tert-Butyl)isochroman (**4c**).* The general procedure C was followed, affording the title compound in 80% yield (1.5 g) over two steps as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.25 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 4.84 (s, 2H), 4.02 (t, J = 5.4 Hz, 2H), 2.88 (t, J = 5.4 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ148.9, 134.3, 130.2, 128.5, 123.5, 121.0, 68.2, 65.4, 34.4, 31.3, 31.3, 31.3, 27.9; IR ν_{max} 1506, 1462, 1376, 1362, 1266, 1194, 1138, 1105, 1067, 989, 945, 878, 824, 810 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{18}O$ $[M + H]^+$ 191.1430, found 191.1426.

*7-Methoxyisochroman (**4d**).* The general procedure C was followed, affording the title compound in 40% yield (600 mg) over two steps as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.05 (d, J = 8.4 Hz, 1H), 6.75 (dd, J = 1.8, 8.4 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 4.76 (s, 2H), 3.97 (t, J = 6.0 Hz, 2H), 3.78 (s, 3H), 2.80 (t, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 135.8, 129.8, 125.2, 112.7, 109.0, 68.0, 65.6, 55.2, 27.5; IR ν_{max} 1725, 1612, 1589, 1504, 1464, 1429, 1320, 1271, 1253, 1226, 1098, 1035, 991, 850, 814 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_{12}O_2$ $[M + H]^+$ 165.0944, found 165.0938.

*7-Bromoisochroman (**4e**).* The general procedure C was followed, affording the title compound in 40% yield (750 mg) over two steps as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.28 (m, 1H), 7.14 (s, 1H), 7.00 (d, J = 8.4 Hz, 1H), 4.73 (s, 2H), 3.96 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.0, 132.1, 130.5, 129.4, 127.3, 119.4, 67.4, 65.1, 27.8; IR ν_{max} 1484, 1426, 1412, 1190, 1101, 986, 944, 877, 807 cm^{-1}; HRMS (EI) m/z calcd for C_9H_9BrO $[M + H]^+$ 212.9910, found 212.9905.

*6-Bromoisochroman (**4f**).* The general procedure C was followed, affording the title compound in 15% yield (200 mg) over two steps as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.38 (d, J = 7.8 Hz, 1H), 7.11−7.03 (m, 2H), 4.71 (s, 2H), 3.94 (t, J = 6.0 Hz, 2H), 2.86 (t, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.1, 134.0, 130.0, 127.9, 127.6, 120.7, 68.6, 64.8, 28.3; IR ν_{max} 1566, 1461, 1434, 1200, 1111, 1067, 1003, 954, 823, 771 cm^{-1}; HRMS (EI) m/z calcd for C_9H_9BrO $[M + H]^+$ 212.9910, found 212.9905.

*8-Bromoisochroman (**4g**).* The general procedure C was followed, affording the title compound in 45% yield (600 mg) over two steps as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.27 (d, J = 6.0 Hz, 2H), 6.85 (d, J = 8.4 Hz, 1H), 4.71 (s, 2H), 3.95 (t, J = 5.4 Hz, 2H), 2.83 (t, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.4, 133.7, 131.6, 129.0, 126.0, 119.8, 67.5, 64.9, 28.0; IR ν_{max} 1592, 1573, 1481, 1431, 1379, 1327, 1231, 1103, 1066, 1005, 990, 943, 865, 810 cm^{-1}; HRMS (EI) m/z calcd for C_9H_9BrO $[M + H]^+$ 212.9910, found 212.9907.

*3-Methylisochroman (**4h**).* The general procedure C was followed, affording the title compound in 80% yield (1.2 g) over two steps as colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.20−7.14 (m, 2H), 7.11 (s, 1H), 7.01 (d, J = 2.4 Hz, 1H), 4.88−4.82 (m, 2H), 3.84 (dd, J = 5.4, 11.4 Hz, 1H), 2.73 (d, J = 7.2 Hz, 2H), 1.37 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.6, 133.5, 128.7, 126.3, 125.9, 124.1, 70.9, 68.1, 35.7, 21.6; IR ν_{max} 1497, 1451, 1383, 1369, 1203, 1139, 1124, 1103, 1084, 1040, 821 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_{12}O$ $[M + H]^+$ 149.0961, found 149.0956.

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*Isothiochroman (**4j**).* The general procedure C was followed, affording the title compound in 40% yield (400 mg) over two steps as colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.26−7.10 (m, 4H), 3.77 (s, 2H), 3.04 (t, J = 6.0 Hz, 2H), 2.92 (t, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.8, 135.0, 129.2, 127.6, 126.8, 126.2, 30.4, 29.2, 26.4; IR ν_{max} 1696, 1579, 1492, 1446, 1423, 1289, 1189, 1102, 1046, 945, 903, 814, 744 cm^{-1}; HRMS (EI) m/z calcd for $C_9H_{10}S$ [M + H]$^+$ 151.0554, found 151.0548.

*Isochroman-1-ol (**8**).* The title compound was prepared through the Harling route:[81] ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37−7.31 (m, 1H), 7.30−7.23 (m, 2H), 7.15 (d, J = 7.2 Hz, 1H), 5.99 (d, J = 5.4 Hz, 1H), 4.23 (td, J = 3.6, 12.6 Hz, 1H), 3.97 (ddd, J = 2.4, 5.4, 11.4 Hz, 1H), 3.02 (d, J = 5.4 Hz, 1H), 2.70 (d, J = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.9, 134.1, 128.5, 128.3, 127.3, 126.5, 91.5, 58.3, 28.0; IR ν_{max} 3377, 1606, 1494, 1458, 1424, 1384, 1269, 1199, 1078, 1066, 1011, 984, 950, 938, 885, 784, 740, 664, 572, 439 cm^{-1}; HRMS (EI) m/z calcd for $C_9H_{10}O_2$ [M + H]$^+$ 151.0754, found 151.0748.

*2-(Isochroman-1-yl)-1-phenylethanone (**3a**).* To a solution of hemiacetal **8** (30.0 mg, 0.2 mmol) and acetophenone (46.7 uL, 0.4 mmol) in Et_2O (1.5 mL) were added activated MnO_2 (52.2 mg, 0.6 mmol) followed by CH_3SO_3H (0.3 mL) dropwise under air. The reaction mixture was stirred at rt for 3 h, and the above mixture was directly purified by flash chromatography to give the desired product **3a** (46.9 mg, 93%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds in Tables 2, 3, and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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§Liu and Sun made an equal contribution to this work.

Notes

The authors declare no competing financial interest.

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