Boosting molecular complexity with O_2: iron-catalysed oxygenation of 1-arylisochromans via dehydrogenation, Csp^3-O cleavage and hydrogenolysis

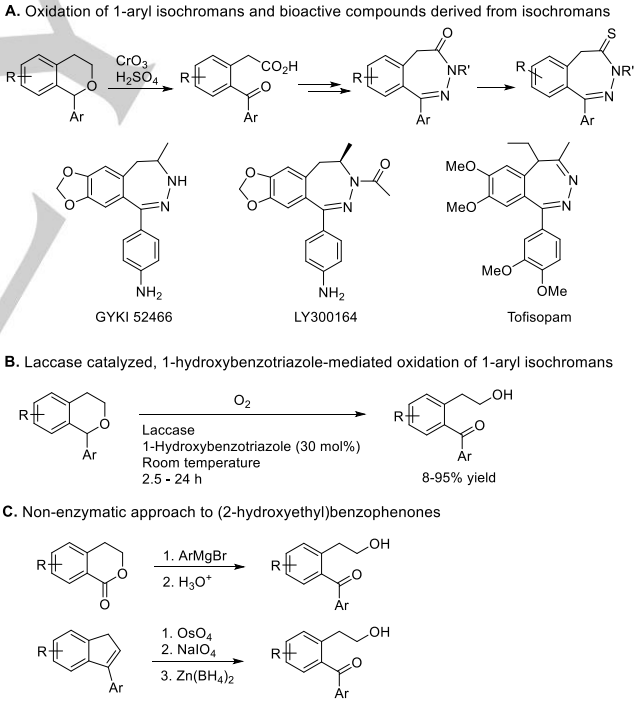
Angela Gonzalez-de-Castro,*[a,b] Craig M. Robertson[a] and Jianliang Xiao*[a]

Abstract: Oxidative cleavage of the Csp^3-O bond in 1-arylisochromans with stoichiometric oxidants such as CrO_3/H_2SO_4 has been practiced for decades in synthetic chemistry. Herein we report that a structurally well-defined Fe(II)-pyridyl(bis-imidazolidine) catalyst promotes the aerobic oxygenation of 1-arylisochromans, affording highly selectively 2-(hydroxyethyl)benzophenones, compounds of potential for neuroprotective agents. Key intermediates have been isolated, indicating that the reaction proceeds via dehydrogenative oxygenation of the isochromans at the 1 position, Csp^3-O bond cleavage at the iron center and hydrogenolysis of the resulting Fe-O bond with the H_2 generated from the dehydrogenation step. In the absence of H_2 but under the iron catalysis, the peroxide intermediate is converted into an unexpected ketal compound, which transfers into a 2-(hydroxyethyl)benzophenone when both O_2 and H_2 are admitted. The unique ability of the iron catalyst for oxygenation and hydrogenation in the same catalytic process under mild conditions allows for the stepwise preparation of a variety of isolable oxygenated products on a preparative scale, circumventing the need for using wasteful and/or toxic oxidants.

Introduction

The ether linkage is one of the most ubiquitous bonds found in nature and manmade chemicals, ranging from pharmaceuticals and agrochemicals through detergents to polluting plastics, lignin and coal, and is one of the most important means nature uses to fix carbon.[1] Oxidation of ethers can lead to value-added functional and bioactive products,[2] degradation of biomass such as lignin,[3] removal of organic pollutants and bioremediation.[4] Because of the strong C-O bond (BDE of EtO-Et, Ph-OMe: 85, 100 kcal/mol, respectively), selective oxidation of ethers necessitates catalysts. Iron is particularly attractive as catalyst, because of its low toxicity, easy availability and low cost, and when large-scale processing of cheap feedstock and environmental remediation are concerned.[5] In nature, iron-containing metalloenzymes are well-known of remarkable ability in selectively oxidizing various substrates with O_2 under mild conditions. For instance, bacteria powered by iron oxygenases enable oxidative degradation of ether linkages in agrochemicals, detergents and lignin, although often with unknown mechanism.[1,6] Inspired by nature, a wide variety of biomimetic Fe catalysts have been explored in the past a few decades, bringing about remarkable advances in selective oxidation of CH bonds.[7]

However, the development of similar catalysts for the selective aerobic oxidation of ethers, particularly the oxidative cleavage of ethereal C-O bonds, has received much less attention,[7c,8] although such reactions could provide new pathways for the synthesis of bioactive molecules and new insight into the mechanisms of ether degradation by oxygenases and drug metabolism.[9]



Scheme 1. Oxidative cleavage of Csp^3-O bond in 1-arylisochromans for the synthesis of bioactive compounds and other methods to access the key intermediate 2-(hydroxyethyl)benzophenones.

A case in point is the oxidation of isochroman and the derivatives, which can lead to products of widely ranging bioactivities but has generally been performed with toxic, expensive and/or environmentally hazardous terminal oxidants,[10,11] such as CrO_3/H_2SO_4,[12] DDQ,[13] CAN,[14] SeO_2,[15] CrO_3/H_5IO_6[16] and $KMnO_4$.[17] Of particular note is the oxidative cleavage of the endocyclic Csp^3-O bond in 1-arylisochromans,

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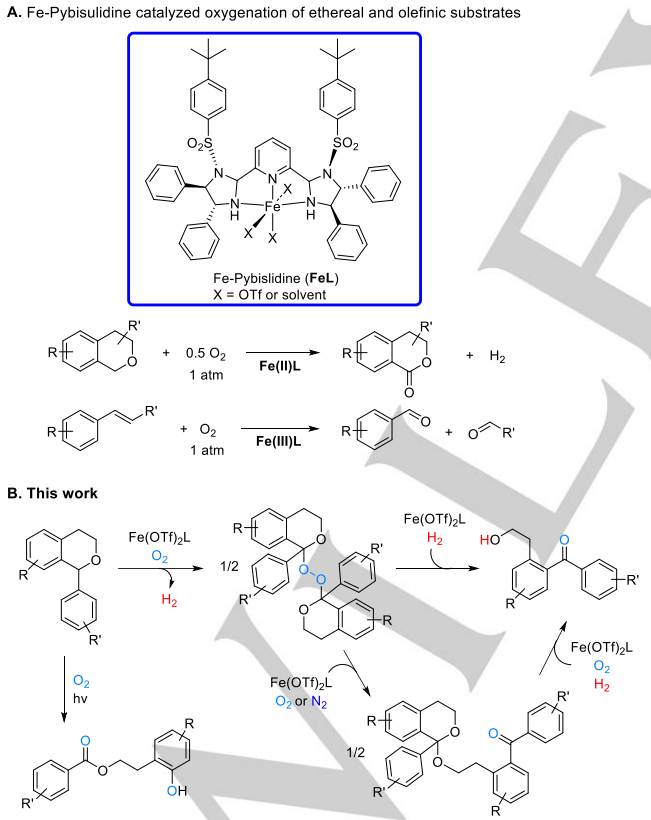
which has been exploited by medicinal chemists for the synthesis of benzodiazepines, benzodiazepinones and benzodiazepinethiones, analogues of the neuroprotective agent GYKI52466 and related LY300164 and Tofisopam (Scheme 1A).[18] Given the therapeutic potential of such compounds in treating epilepsy, spasticity, chronic pain and neurodegenerative disorders, it would be highly desirable to develop catalysts capable of aerobic oxidative cleavage of the Csp^3-O bond in 1-arylisochromans. *To the best of our knowledge, laccase enzymes appear to be the only catalysts that have been reported to promote such reactions* (Scheme 1B).[19] Non-enzymatic methods for the synthesis of 2-(hydroxyethyl)benzophenones are also known, e.g. Grignard addition and osmylation followed by periodate cleavage (Scheme 1C).[20]

Recently, we reported a novel class of iron-pyridine bis-sulfonamide (Fe-Pybisulidine) catalysts for the selective α-oxygenation of ethereal substrates[21] and for the aerobic Csp^2-Csp^2 bond cleavage of styrenes (Scheme 2A).[22] Inspired by nature's dioxygenases in cleaving inert C-C bonds under mild aerobic conditions, we set out to explore such catalysts for selective aerobic cleavage of aliphatic and unstrained C-C/C-O bonds in complex and functionalized substrates. Herein we report the aerobic cleavage of functionalized 1-arylisochromans into a variety of complex oxygenated products in a preparative scale under very mild conditions in a selective fashion with excellent atom economy (Scheme 2B).



Scheme 2. Previous work on Fe(II/III)-Pybisulidine catalyzed oxidation of isochromans and oxidative cleavage of styrenes, and the work described in this paper.

The iron catalyst was found to promote the cleavage of the endocyclic Csp^3-O bond of 1-arylisochromans under an atmosphere of O_2, furnishing valuable 2-(hydroxyethyl)benzophenones. Mechanistic studies suggest that the substrate is oxidized via a sequence of iron-catalyzed reactions, i.e. dehydrogenative oxygenation of two ethereal substrates to form a tetrasubstituted peroxide intermediate followed by peroxide cleavage and subsequent hydrogenolysis of the resulting iron-alkoxo species. Under aerobic or inert atmosphere, the peroxide was converted into a novel ketal species, which was further transformed into the 2-(hydroxyethyl)benzophenone product when exposed to the iron catalyst under an atmosphere of O_2 and H_2. In contrast, in the absence of the iron catalyst, 1-arylisochromans underwent a selective aerobic Csp^2-Csp^3 bond cleavage, resulting in the formation of valuable benzyl esters, in which both the aliphatic and the aromatic carbons were selectively oxidized (Scheme 2B).

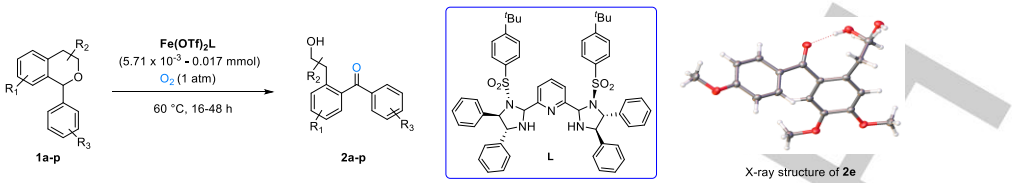
Results and Discussion

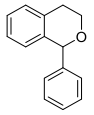
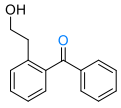
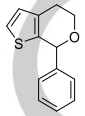
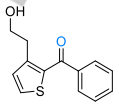
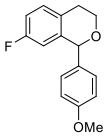
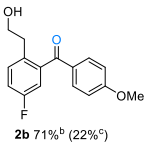
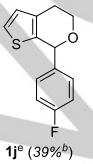
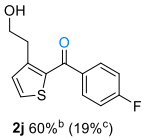
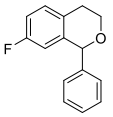
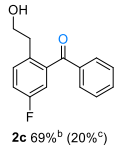
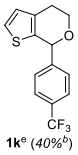
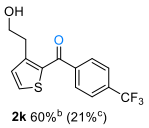
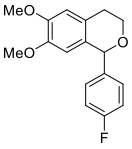
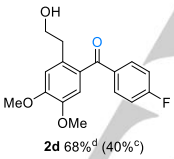
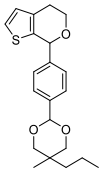
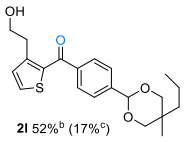
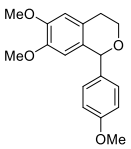
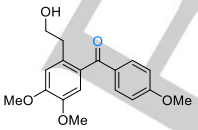
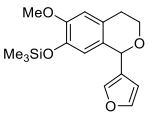
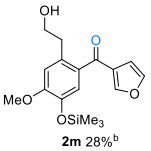
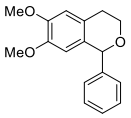
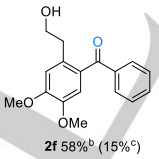
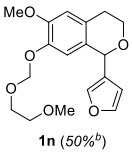
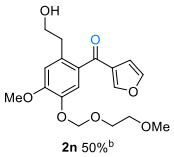
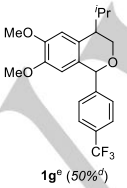
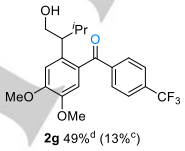
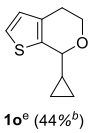
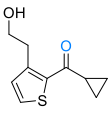
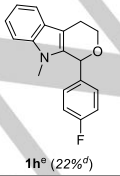
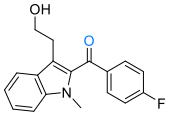
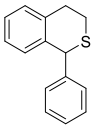
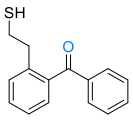
$Fe(OTf)_2$**L catalyzed aerobic cleavage of 1-aryl isochromans**

Following our investigations in the selective oxidation of isochromans to isochromanones promoted by the catalyst, $Fe(OTf)_2$**L**, formed in situ by reacting $Fe(OTf)_2$ with the pyridine bis-sulfonamide ligand **L** (Scheme 2A),[23] we set out to investigate the oxidation of 1-phenylisochroman (Table 1). To our delight, the benzophenone **2a**, resulting from cleavage of the Csp^3-O bond and oxygenation of the Csp^3 carbon, was obtained exclusively in a 21% yield after a 16 h reaction. Of practical interest is that following three consecutive additions of the catalyst over a period of 16 h each, **2a** was obtained in 70% isolated yield with the unreacted starting material being fully recovered. Subsequent catalyst additions did not increase the product yield, however. Under such reaction conditions, no over-oxidation of the primary alcohol was observed. In contrast, continued oxidation of the alcohol moiety to carboxylic acids happens when using CrO_3 as the oxidant.[12]

The excellent functional group tolerance and selectivity of the $Fe(OTf)_2$**L** catalyst is further manifested in the reaction scope (Table 1). The catalyst tolerated the presence of electron donating and electron withdrawing groups in the aromatic rings of 1-arylisochromans (entries 1-6) and the presence of substituents in the alkyl chain (entry 7). In all cases, the desired 2-(hydroxyethyl)benzophenones were obtained in preparative yields after two or three catalyst additions and with excellent selectivity and mass balance. The structure of **2e** has been confirmed by X-ray diffraction (Table 1). Notably, selective Csp^3-O cleavage was also realized in substrates incorporating N, S and O-based heterocycles with similar high yields and mass balance (entries 8 to 15), indicating that the iron centre is not poisoned by the heteroatoms. Of further interest is that competing CH bond oxygenations were not observed, even in substrates bearing electronically activated CH bonds (entries 12 and 14), and the very labile protecting group TMS was also tolerated, although the reaction yield was lower and deprotection to the phenol form (see the Supporting Information) took place during purification by column chromatography (entry 13). Significantly, the Csp^3-O cleavage of the radical-sensitive substrate **1o** bearing a cyclopropyl ring was cleanly accomplished with excellent mass balance and no substrate

Table 1. Scope of the $Fe(OTf)_2$**L** catalysed aerobic Csp^3-O cleavage of 1-arylisochromans



Entry	Substrate (rsm%)[a]	Product (isol. yield%)	Entry	Substrate (rsm%)[a]	Product (isol. yield%)
1	 **1a** (*29%*[b])	 **2a** 70%[b] (21%)[c]	9	 **1i**[e] (*39%*[b])	 **2i** 60%[b] (22%[c])
2	 **1b** (*29%*[b])	 **2b** 71%[b] (22%[c])	10	 **1j**[e] (*39%*[b])	 **2j** 60%[b] (19%[c])
3	 **1c** (*30%*[b])	 **2c** 69%[b] (20%[c])	11	 **1k**[e] (*40%*[b])	 **2k** 60%[b] (21%[c])
4	 **1d** (*32%*[d])	 **2d** 68%[d] (40%[c])	12	 **1l**[e] (*20%*[b] + *20%*[f])	 **2l** 52%[b] (17%[c])
5	 **1e** (*40%*[b])	 **2e** 60%[b] (20%[c])	13	 **1m** (*72%*[b])	 **2m** 28%[b]
6	 **1f** (*40%*[b])	 **2f** 58%[b] (15%[c])	14	 **1n** (*50%*[b])	 **2n** 50%[b]
7	 **1g**[e] (*50%*[d])	 **2g** 49%[d] (13%[c])	15	 **1o**[e] (*44%*[b])	 **2o** 56%[b] (20%[c])
8	 **1h**[e] (*22%*[d])	 **2h** 78%[d] (50%[c])	16	 **1p** (*47%*[b])	 **2p** 52%[b] (19%[c])

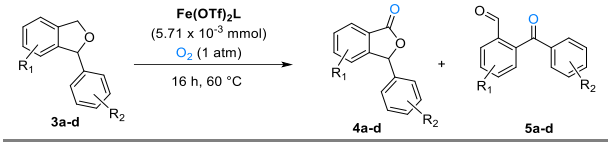
Reaction conditions: **1** (0.3 mmol) neat or in C_6H_6 (0.5 mL) under O_2 (15% v/v in N_2) (1 atm) at 60 °C. [a]rsm: recovered starting material (unoxidized). [b]Three $Fe(OTf)_2$**L** catalyst additions (5.71 x 10^{-3} mmol each), 32 h. [c]One $Fe(OTf)_2$**L** catalyst addition (5.71 x 10^{-3} mmol), 16 h. [d]Two $Fe(OTf)_2$**L** catalyst additions (5.71 x 10^{-3} mmol each), 48 h. [e]Reaction run with 2.0 mL of substrate. [f]Deprotected acetal (acetal cleavage)

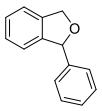
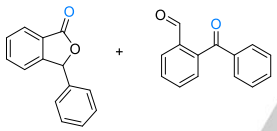
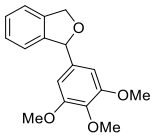
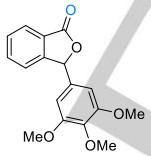
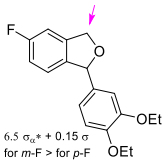
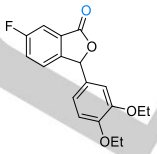
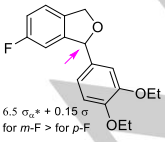
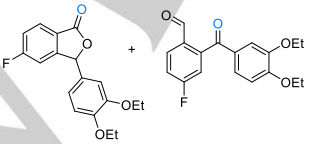
degradation. This is in contrast with the reaction involving free radicals (vide infra) and seems to indicate that either there is no radical formation at the C1 position or the Csp^3-O cleavage is much faster than the ring opening of the cyclopropyl moiety. In addition, an analogous Csp^3-S bond cleavage was also realized when **1p** was used as substrate, affording **2p** with a pendant thiol group in preparative yield.

Site selective CH_2 oxygenation vs aerobic Csp^3-O bond cleavage in 1-arylphthalans

Unlike 1-arylisochromans in which the Csp^3-H bond at the position 1 is more activated, the reaction of 1-arylphthalans brings up a question of regioselectivity. Although $Fe(OTf)_2$**L** could promote a similar aerobic Csp^3-O bond cleavage, a CH_2 oxygenation may also take place, since the Csp^3-H bond at this position is more easily accessible sterically and is activated

Table 2. Methylene oxygenation vs Csp^3-O bond cleavage in 1-arylphthalans: steric and electronic effects



Entry	Substrate (rsm%)[a]	Product (isol. yield%)
1	 **3a** (*50%*)	 **4a** 44%[b] **CH_2 oxygenation** Sterically favoured; **5a.** 6%[b] **Csp^3-O bond cleavage** Electronically favoured
2	 **3b** (*50%*)	 **4b.** 42% **CH_2 oxygenation** Sterically favoured
3	 6.5 σ_α* + 0.15 σ for *m*-F > for *p*-F **3c** (*42%*)	 **4c** 58% **CH_2 oxygenation** Sterically favoured Electronically favoured
4	 6.5 σ_α* + 0.15 σ for *m*-F > for *p*-F **3d** (*38%*)	 **4d.** 44%[b] **CH_2 oxygenation** Sterically favoured; **5d.** 21%[b] **Csp^3-O bond cleavage** Electronically favoured

Reaction conditions: $Fe(OTf)_2$ (5.71 x 10^{-3} mmol; 2.0 mg) and **L** (5.7 x 10^{-3} mmol; 5.2 mg) stirred in C_6H_6 (0.5 mL) for 1 h at 40 °C. Substrate (1.8 – 2.0 mmol) was then added and stirred under O_2 (15% v/v in N_2) (1 atm) at 60 °C for 16 h. [a]rsm: recovered starting material (unoxidized). [b]Product ratio determined by ^{1}H NMR.

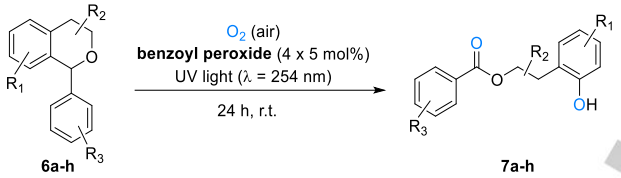
electronically by the adjacent phenyl ring. Indeed, exposure of 1-phenylphthlan **3a** to the $Fe(OTf)_2$**L** catalyst afforded the CH_2 oxidized product **4a** in 44% yield (Table 2). Formation of the Csp^3-O cleaved product **5a**, in which the benzylic alcohol is now oxidized to its aldehyde form, was observed only in a low 6% yield, indicating that steric effect overruns the electronic effect with the bulky $Fe(OTf)_2$**L** catalyst. In line with this conjecture, exposure of the catalyst to compound **3b**, in which the tertiary CH bond is somewhat more sterically hindered by the surrounding methoxy substituents, resulted in the exclusive formation of phthalide **4b** in a 42% isolated yield, although we note that the *o*-MeO moiety is slightly destabilizing towards benzylic radicals.[24] Even though para- and meta-substituents are not normally prone to exert remarkable steric effects, the Fe-**L** catalyst might be particularly sensitive to the presence of substituents in such positions. As evidenced by the X-ray structure of the Fe**L**(THF)$(OTf)_2$ complex,[21a] the THF molecule is fitted in a sterically crowded environment surrounded by two phenyl rings and two sulfone-aryl groups. Any substitution in the more rigid 1-arylphthalan substrate is very likely to weaken its coordination and thus, contribute to the significant regioselectivity difference observed between **3a** and **3b.** Phthalides are known to possess a broad spectrum of biological activities.[25]

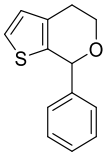
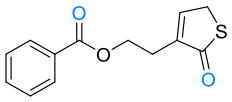
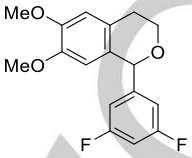
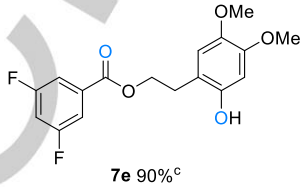
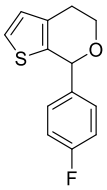
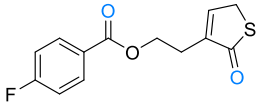
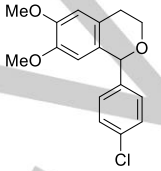
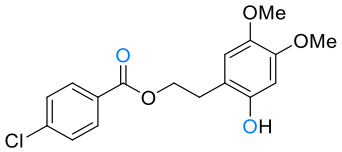
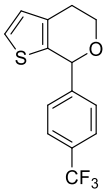
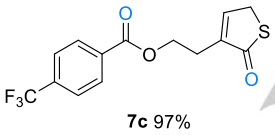
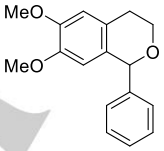
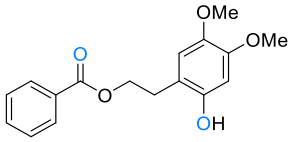
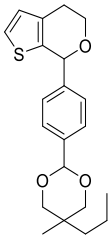
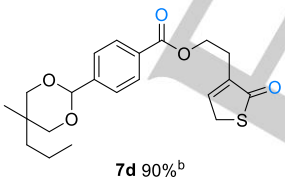
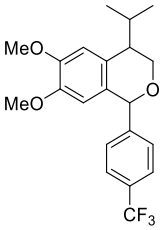
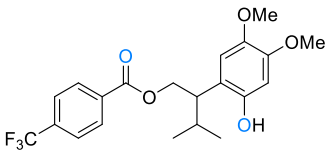
The introduction of fluorine into the aromatic ring of phthlans brings about a subtle electronic effect on the regioselectivity. Thus, substrate **3c**, in which the tertiary C-H bond is *para* to the fluorine substituent, afforded phthalide **4c** exclusively in a high 58% isolated yield. However, when the fluorine is placed *meta* to the position 1, the oxygenation of the substrate **3d** afforded the CH_2 oxygenated product **4d** as well as the Csp^3-O cleaved product **5d**, in a ratio of *c.a.* 2:1. These results can be explained by the spin delocalization-based σ_α* constants corrected to a small degree with the Hammett constant σ, which indicate that the *para*-F destabilizes a benzyl radical more than the *meta*-F does[26] (Table 2, entries 3 and 4). Consequently, the presence of the fluorine may increase the BDE of the *para* C-H bond more, rendering it more difficult to oxidize. Nonetheless, these results suggest that in the oxygenation of 1-arylphthalans, the selectivity of the $Fe(OTf)_2$**L** catalyst is strongly governed by steric constrains, predictably furnishing the CH_2 oxidized phthalides as main or exclusive reaction products. In contrast, in the oxygenation of sterically non-constrained phthalans to phthalides, the regioselectivity of the reaction could be predicted on the basis of an electronic effect.[21a]

Metal free aerobic Csp^3-Csp^2 bond cleavage of 1-arylisochromans

Upon exposure to UV light, 1*H*-isochromans are known to be auto-oxidizable to afford a mixture of peroxides and hydroperoxides.[27] However, 1-arylisochromans were early reported to be resistant to auto-oxidation under UV light irradiation[27b] and ever since, further investigations on their potential auto-oxidation reactions has rarely been attempted.[18c] Even though the structure of the substrate can play a decisive role in determining its susceptibility to the action of O_2,[28] it was surprising to us that 1-arylisochromans bearing weakened tertiary CH bonds could exhibit such inertness towards auto-oxidation processes. In an elegant, single example, Eli Lilly researchers showed that a 1-(4-nitrophenyl)-substituted isochroman could be cleanly oxidized at the 1 position via deprotonation with NaOH (50%) followed by reaction with O_2 in DMSO/DMF, leading to the synthesis of the AMPA antagonist LY300164.[18c] However, the necessity of deprotonation would

Table 3. Scope of the metal-free auto-oxidative Csp^2-Csp^3 bond cleavage of 1-arylisochromans



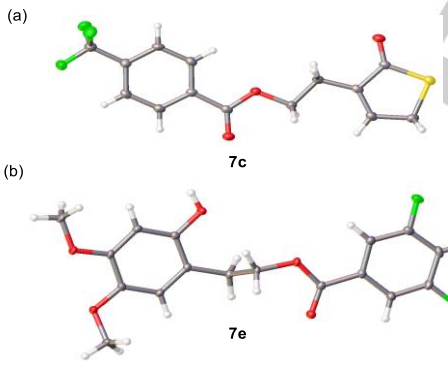
Entry	Substrate (rsm%)[a]	Product (isol. yield%)	Entry	Substrate (rsm%)[a]	Product (isol. yield%)
1	 **6a** (*1%*)	 **7a** 97%	5	 **6e** (*10%*)	 **7e** 90%[c]
2	 **6b** (*1%*)	 **7b** 97%	6	 **6f** (*8%*)	 **7f** 91%[c]
3	 **6c** (*1%*)	 **7c** 97%	7	 **6g** (*12%*)	 **7g** 87%[c]
4	 **6d** (*8%*)	 **7d** 90%[b]	8	 **6h** (*12%*)	 **7h** 43%[b]

Reaction conditions: 6 (300 µL) neat or in C_6H_6 (100 µL) stirred under air in the presence of benzoyl peroxide (Luperox) (5 mol%) at r.t. for 24 h. Three subsequent additions of Luperox (5 mol% each) and C_6H_6 (50 µL each) were done in 1 h intervals. [a]rsm: recovered starting material (unoxidized). [b]Reaction run under sunlight exposure for 14 h without Luperox. [c]Five additions of Luperox (5 x 5 mol%) and reacted for 36 h at 30 °C.

limit the reaction to 1-aryls bearing strongly electron-withdrawing groups. During our investigations, we noted that a colorless neat sample of a thienopyran **6c** evolved to orange after two days at ambient temperature (See the SI and Table 3). Exposure to air for 4 days intensified the color change and after purification by column chromatography, compound **7c** was obtained in 19% isolated yield, the structure of which was confirmed by NMR and X-ray diffraction analysis (Scheme 3). It appears that **7c** results from the auto-oxidative Csp^2-Csp^3 bond cleavage in substrate **6c**. Thus, after 14 days of exposure to air and sunlight, compound **7c** was selectively isolated in 97% yield along with the formation of a minor byproduct **7c´** (see the SI). Under UV irradiation, the aerobic Csp^2-Csp^3 bond cleavage of **6c** was accelerated, furnishing **7c** in 96% isolated yield after 10 days (see the SI). In contrast, storing the samples in darkness significantly slowed down the reaction (see the SI). Heating a sample of **6c** at 60 °C also accelerated the reaction but with eroded selectivity, with **7c** been isolated in a 60% yield after 5 days (see the SI). As maybe expected, stirring **6c** in the presence of a radical initiator benzoyl peroxide[29] (5 mol%) improved the rate of the oxidative cleavage, affording **7c** in a 28% isolated yield after 12 h. Subsequent additions of benzoyl peroxide (4 x 5 mol%) to a stirred sample of **6c** under UV irradiation afforded compound **7c** in a 96% isolated yield after 24 h. The remarkably contrasting chemoselectivity of the auto-oxidation *vs* that promoted by $Fe(OTf)_2$**L** highlights the mechanistic difference in the two systems. The scope of the auto-oxidative Csp^2-Csp^3 bond cleavage could be expanded to

other thienopyrans, which led to the selective formation of the novel benzoates **7a**-**7d** in a preparative scale (Table 3, entries 1-4). Thus, this simple protocol allows to selectively convert the easily accessible thienopyran motif into valuable 2(5H)-thienophenone derivatives. The latter motifs are, in fact, of pharmaceutical interest, showing applications as endothelin antagonists,[30] quorum-sensing inhibitors for controlling E. Coli O103:H2 virulence [31] and COX-1 inhibitors.[32] Additionally, thienophenones can be converted into their hydroxythiophene tautomers,[33] which are common motifs and building blocks into pharmaceutically active compounds.[34,35] Despite their numerous applications, traditional organic methods are often employed to synthesize these motifs.[33]

A similar Csp^2-Csp^3 bond cleavage was observed in 1-aryl-6,7-dimethoxyisochromans, furnishing valuable 2-hydroxy-4,5-dimethoxyphenethyl benzoates **7e**-**7h** in excellent yields with perfect atom economy and mass balance (entries 5-8) (Scheme 3). However, although simple and efficient for synthesizing phenols and benzoates, this auto-oxidative reaction is more limited in scope than that of the $Fe(OTf)_2$-**L** catalyzed Csp^3-O bond cleavage. Thus, when **1o** bearing the radical-sensitive cyclopropyl ring was subjected to the auto-oxidation conditions, substrate degradation was the predominant reaction observed (see the SI). More significantly, the auto-oxidation conditions appear to be applicable only to liquid and relatively electron-rich substrates. Thus, the auto-oxidation of **6h** afforded **7h** in 43% yield (entry 8) alongside side reactions that reduced the mass balance, and after exposing **1a** to air for 2 months, 1,1'-peroxybis(1-phenylisochroman) **8a** was isolated in 12% yield among a myriad of other uncharacterized products (see the SI). In contrast, under the catalysis of $Fe(OTf)_2$**L**, the Csp^3-O cleaved products **2a**, **2g** and **2o** were cleanly obtained (Table 1).

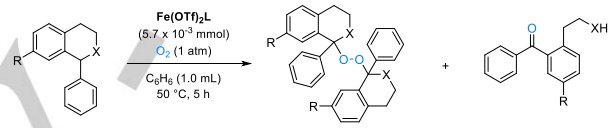


Scheme 3. X-ray structures of the benzoate products resulting from the auto-oxidation of a thienopyran (**6c)** and a 1-arylisochroman (**6e**).

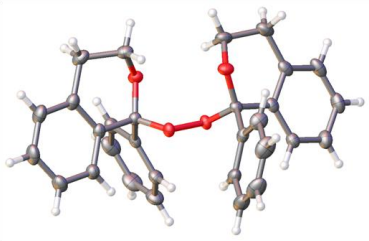
Mechanistic investigations of the $Fe(OTf)_2$L promoted aerobic cleavage of 1-arylisochromans

Isolation of peroxide intermediates

The $Fe(OTf)_2$**L** catalyzed oxygenation of ethers to esters was found to proceed by a two-step mechanism involving the formation of a 1,1'-peroxybisether intermediate, which results from the catalyst-mediated dehydrogenative oxygenation of two ether molecules.[21a] The reaction in question, i.e. the $Fe(OTf)_2$**L** catalyzed aerobic Csp^3-O bond cleavage of 1-arylisochromans, could also proceed via a similar peroxy intermediate. Indeed, when the substrate **1a** was subjected to the iron catalyst for a shorter time at a lower temperature, the peroxide species **8a** was isolated in 10% yield along with the Csp^3-O cleaved product **2a** in 5% yield. The structure of the tetrasubstituted peroxide **8a** was confirmed by NMR analysis and X-ray diffraction after its isolation by column chromatography and crystallization in an Et_2O/hexane solution (see Scheme 4 and the SI). Although 1,1'-peroxybisisochromans were easily isolable by silica gel chromatography and stable upon heating until 78 °C,[27] the peroxide **8a** was found to be a much more reactive species, even partially decomposing in the presence of silica gel or upon exposure to X-ray, which made its isolation and characterization particularly difficult. In fact, to the best of our knowledge, there is no other report in the literature of a tetrasubstituted peroxide in which a structural analysis by X-ray diffraction has been reported. Unlike **8a** and its derivative **8c**, the peroxide species **8p** derived from the less electronegative sulphur-based substrate **1p** was found more stable and could be subjected to purification by silica gel chromatography without showing significant decomposition. As indicated by previous $^{18}O_2$ labelling experiments,[21a] the formation of the peroxide intermediate does not involve the cleavage of the O-O bond in the O_2 molecule, thus discarding the formation of iron-oxo species.



1a. (R = H, X = O) *(81% rsm)* **8a.** (R = H, X = O) 10% isol. yield **2a.** (R = H, X = O) 5% isol. yield
1c. (R = F, X = O) *(80% rsm)* **8c.** (R = F, X = O) 10% isol. yield **2c.** (R = F, X = O) 5% isol. yield
1p. (R = H, X = S) *(87% rsm)* **8p.** (R = H, X = S) 9% isol. yield **2p.** (R = H, X = S) 4% isol. yield
(2.37 mmol)



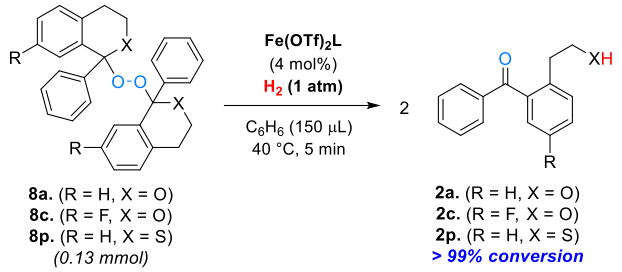
8a

Scheme 4. Identification and isolation of a peroxide intermediate during the $Fe(OTf)_2$**L** catalyzed aerobic cleavage of 1-arylisochromans. The X-ray structure of **8a** is shown.

Peroxide reaction under H_2 atmosphere

The oxygenation of isochromans to isochromanones via the 1,1'-peroxybisether intermediate catalyzed by $Fe(OTf)_2$**L** was accompanied with the release of a stoichiometric amount of H_2 gas in each step with no water formation detected.[21a] Likewise, the formation of peroxides **8a**-**8p** can be seen as the result of the iron-promoted dehydrogenative oxygenation of two ethereal molecules, from which the 2-(hydroxyethyl)benzophenone products **2a**, **2c** and **2p** resulted. Both remarkably and insightfully, exposure of **8a-8p** to the $Fe(OTf)_2$**L** catalyst under a *H_2 atmosphere* resulted in an immediate color change and after a few minutes, quantitative formation of **2a**, **2c** and **2p** was achieved, respectively (Scheme 5). These results suggest that the formation of the tetrasubstituted peroxide intermediate is also accompanied with H_2 gas release, with the released H_2 gas subsequently consumed in the $Fe(OTf)_2$**L** promoted conversion of the peroxide intermediate into the 2-(hydroxyethyl)benzophenone product. Control experiments revealed that no reaction took place in the absence of the iron catalyst (see the SI).

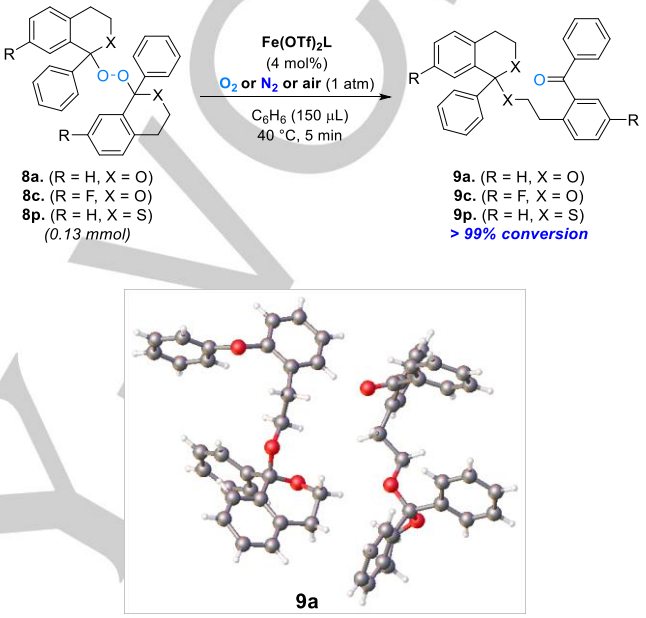
It is noted, however, that transition metal catalysts capable of activating O_2 and H_2 during the same process are rare, due to the incompatibility of most hydrogenation catalysts with O_2 and the inability of most oxygenation catalysts in activating H_2.[36] In fact, there appears to be no example in the literature of a homogeneous iron catalyst capable of activating both H_2 and O_2 during the same catalytic process. Equally, we are not aware of a homogeneous iron catalyst that promotes the hydrogenation of organic peroxides with H_2. Nonetheless, heterogeneous catalysts are known to promote such transformation.[37]



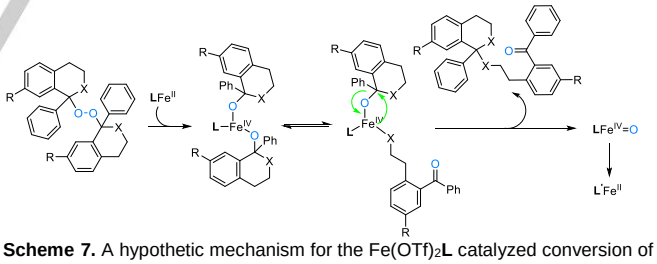
Scheme 5. Fe(OTf)$_2$**L** catalyzed conversion of the peroxide intermediate into 2-(hydroxyethyl)benzophenones under an atmosphere of H_2.

Peroxide reaction under inert and aerobic atmosphere

Interestingly, when the peroxides **8a**-**8p** were subjected to the Fe(OTf)$_2$**L** catalyst under *an atmosphere of N$_2$*, the unexpected ketal products **9a**-**9p** were obtained quantitatively and again, no reaction occurred in the absence of the iron catalyst (Scheme 6). The same products were obtained quantitatively when the reaction was performed under an atmosphere of O_2 or under air, highlighting that in the absence of H_2, the Fe(OTf)$_2$**L** catalyst is capable of promoting a different mode of reactions for the peroxide species. Interestingly, the ketal products **9a**-**9p** were not detected when the same reactions were performed under H_2 atmosphere, suggesting that their rate of formation is lower than that of **2a**, **2c** and **2p**. The structure of **9a** has been confirmed by X-ray diffraction. The conversion of a peroxy-bridged 1-arylisochroman into a benzophenone-functionalized ketal is, to the best of our knowledge, unprecedented, although peroxide bonds can be cleaved by various iron compounds[38] including biomimetic iron-porphyrin complexes.[39]
The mechanism of the reaction is not clear, however. Stoichiometrically, the conversion of the peroxides **8a**-**8p** to the ketal products **9a**-**9p** implies the loss of an oxygen atom. It was noted that the Fe(OTf)$_3$**L** complex was able to promote the oxygenation of vinyl halides into phenacyl halides with solvent participation.[22a] As no traces of oxygenated solvent molecules were detected during the conversion of **8a**-**8p** to the ketal products **9a**-**9p**, the hypothesis of solvent molecules being involved in this transformation was excluded. It is likely that the conversion of **8a**-**8p** to **9a**-**9p** is initiated by the peroxo-bond cleavage via oxidative addition to the Fe(OTf)$_2$**L** catalyst, resulting in the formation of a highly reactive Fe^{IV} intermediate species (Scheme 7). The acetal fragment of such Fe^{IV} species may easily be in equilibrium with its keto-alkoxo form. Such a reactive intermediate might lead to the formation of the ketal products **9a**-**9p** via the attack of the alkoxo fragment to the highly electrophilic acetal carbon. As a consequence, a very reactive Fe^{IV}-oxo species would be generated. In a polar protic medium, Fe^{IV}-oxo complexes behave as a strong oxidant, capable of oxidizing inert C-H bonds.[7a,7b,7c] As no oxidation of the solvent was observed and on the basis of the X-ray structure of the Fe(THF)(OTf)$_2$**L** complex,[21a] it might be plausible that the ligand somehow is involved in the reduction of such Fe^{IV}-oxo species, which could eventually lead to O-O bond formation.[40] The use of non-innocent ligands that actively participate in the catalytic cycle is nowadays well acknowledged[41] and several examples have also been shown in the arena of iron catalysis[42] and in catalytic oxidations.[43] Unfortunately, the oxygen acceptor of this reaction has not been identified and thus the mechanism postulated (Scheme 7) is merely speculative.



Scheme 6. Fe(OTf)$_2$**L** catalyzed conversion of the peroxide intermediates into ketal species in the absence of H_2. The X-ray structure of **9a** is shown.

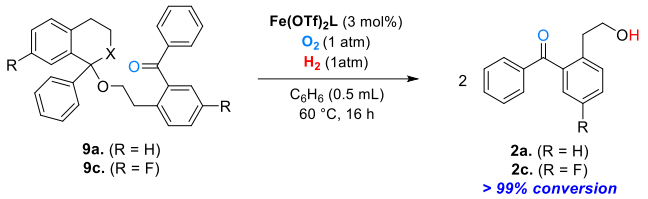


Scheme 7. A hypothetic mechanism for the Fe(OTf)$_2$**L** catalyzed conversion of the peroxide intermediates into ketal species in the absence of H_2.

Iron-catalyzed conversion of ketals

As maybe expected, upon exposure to water or moisture the ketals **9a** and **9c** were slowly hydrolyzed into the 2-(hydroxyethyl)benzophenone products **2a** and **2c**, respectively (see the SI). Surprisingly, the ketals were also transformed into the same products in a dry C_6H_6 solution of the Fe(OTf)$_2$**L** catalyst under a O_2 and H_2 atmosphere, albeit in a much longer time (ca 16 h) (Scheme 8). However, no reaction was observed in the absence of the iron catalyst, H_2 or O_2 gas, further highlighting the unique ability of the Fe(OTf)$_2$**L** catalyst to activate both O_2 and H_2 during the same catalytic process. Whilst the selective cleavage of ketals and acetals in synthetic chemistry under anhydrous,[44] oxidative[45] and reductive[46]

conditions has been developed, a methodology combining an iron-promoted aerobic cleavage and subsequent hydrogenolysis is unprecedented. Alternatively, the conversion of **9a**-**9c** into **2a**-**2c** could be mechanistically seen as a result of the Fe(OTf)$_2$**L** catalyst being able to promote the reduction of O_2 by H_2 ultimately generating water, which would cause the hydrolysis of the ketals. It was noted, however, that the Fe(OTf)$_2$**L** catalyst was unable to promote the opposite transformation (i.e. water splitting).

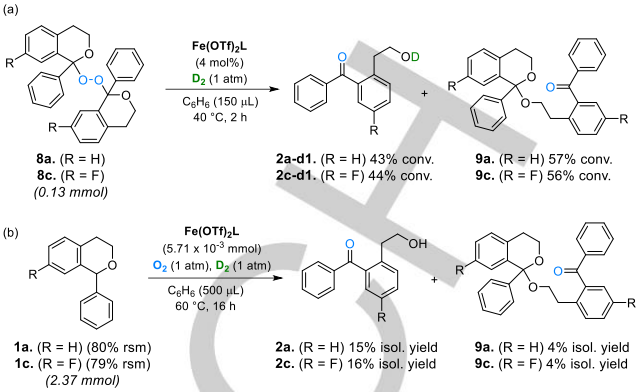


Scheme 8. Conversion of ketals into 2-(hydroxyethyl)benzophenones catalyzed by Fe(OTf)$_2$-**L** under a H_2 and O_2 atmosphere.

Reactions in the presence of D_2

To shed light on the hydrogenolysis of O-C bonds expected during the conversion of **1** to **2**, the peroxide **8a** and **8c** were exposed to the Fe(OTf)$_2$**L** catalyst under an atmosphere of D_2 (Scheme 9a). The 2-(hydroxyethyl)benzophenone-d_1 products **2a-d$_1$** and **2c-d$_1$** were formed under such conditions. The formation of **2a-d$_1$** and **2c-d$_1$** is consistent with the assertion that H_2 is generated and then consumed in the hydrogenolysis of the peroxide intermediate, affording the oxidative cleavage of **1** to give **2**. However, in contrast to using H_2 (Scheme 5), the major products were the compounds **9a** and **9c** in the case of D_2. Since the formation of these latter two requires no H_2, their dominance in the reaction could result from a kinetically slower deuterogenolysis than hydrogenolysis of **8**, which renders the cleavage of **8** to **9** favorable. (NOTE: as there is no O_2 present in the reaction, the formation of **2a-d$_1$** and **2c-d$_1$** cannot stem from the iron-promoted decomposition of **9a** and **9c**). Considering that in apolar solvents of low dielectric constant the diffusion of D_2 is slower than the diffusion of H_2,[47,48] the formation of the ketal products **9a** and **9c** in large amounts could also be attributed to the reaction of the Fe(OTf)$_2$**L** catalyst with the peroxide being faster than the diffusion of D_2 in the reaction mixture. As the isolated peroxides reacted to completion almost immediately upon exposure to the Fe(OTf)$_2$**L** catalyst, the difference in the diffusion rates of H_2 and D_2 could somewhat affect the product distribution. Therefore, from the observed kinetic isotope effect in the hydrogenolysis of the peroxides **8a** and **8c**, we cannot categorically conclude that the activation of H_2 by the iron catalyst is the rate determining step of the hydrogenolysis.

To gain more insight into the mechanism behind the formation of the 2-(hydroxyethyl)benzophenone and the ketal products, the arylisochromans **1a** and **1c** were exposed to the Fe(OTf)$_2$**L** catalyst under a O_2 and D_2 atmosphere (Scheme 9b). Under these conditions, the products **2a** and **2c** were formed predominantly albeit in a slightly lower isolated yield of *ca*. 15% (*cf* Table 1). The ketal compounds **9a** and **9c** were also obtained in a 4% isolated yield, whereas the deuterated **2a-d$_1$** and **2c-d$_1$** products were not observed. The formation of **2a** and **2c** as the major reaction products, rather than **9a** and **9c**, points towards the intermediate peroxide species and the released H_2 gas being in close proximity to the catalytically-active iron center and their ability to react much faster than D_2 activation and/or diffusion.



Scheme 9. a) Reaction of 1-arylisochrmoan peroxides upon exposure to the Fe(OTf)$_2$**L** catalyst under a D_2 atmosphere. b) Reaction of 1-arylisochromans promoted by the Fe(OTf)$_2$**L** catalyst under an atmosphere of O_2 and D_2.

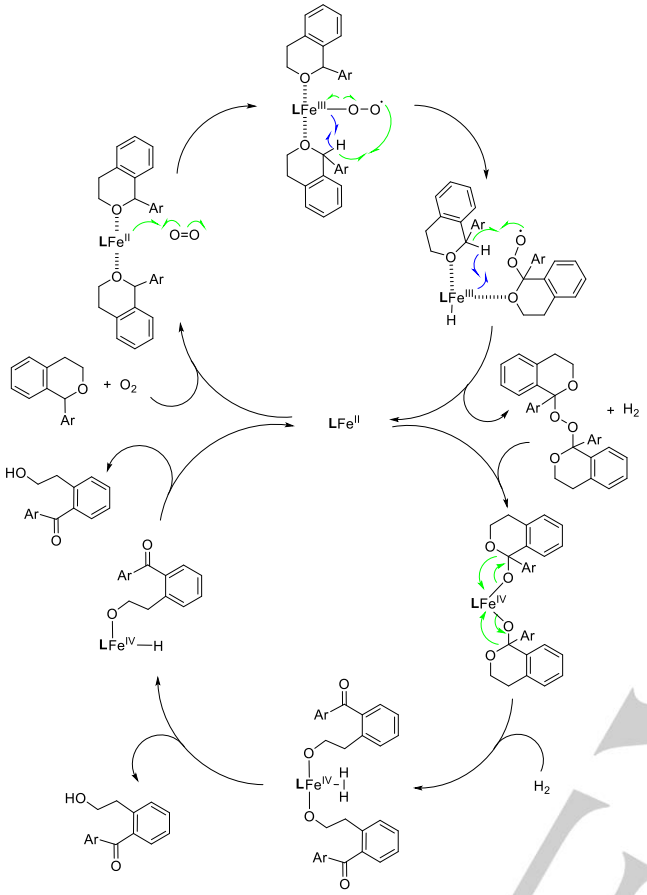
Postulated mechanism of the Fe(OTf)$_2$L promoted aerobic cleavage of 1-arylisochromans

On the basis of the experimental data, we postulate that the Fe(OTf)$_2$**L** catalyzed aerobic Csp^3-O bond cleavage of 1-arylisochromans involves two key steps, i.e. dehydrogenative formation and hydrogenative cleavage of a peroxide intermediate (Scheme 10). By analogy with the postulated mechanism for the oxygenation of isochromans to isochromanones which proceeds via a peroxide accompanied with H_2 release,[21a] initial coordination of two ethereal substrates to the iron catalyst gives rise to the formation of the peroxide intermediate. In the presence of O_2, the formation of a Fe^{III}-superoxo radical can be proposed, which is followed by the concerted attack of the superoxo radical to one of the weak α-CH bonds and the hydrogen atom transfer to the iron center. A second attack to the α-CH bond of the other ethereal molecule with a concomitant hydrogen transfer to the iron center would result in the formation of the peroxide intermediate and a LFe^{IV}-(H)$_2$ dihydride species.[21a] The latter would rapidly undergoes reductive elimination, releasing H_2 and regenerating the starting LFe^{II} catalyst.[49]

Subsequently, a concerted oxidative addition of the LFe^{II} catalyst into the weak peroxide bond takes place (Scheme 10). Containing electronically activated Csp^3-O bonds, the resulting ketal-type LFe^{IV}-dialkoxo species rearranges to the thermodynamically more stable benzophenone-containing LFe^{IV}-dialkoxo species, which is highly electrophilic and would allow the released H_2 to coordinate. Hydrogenolysis of one of the LFe^{IV}-alkoxo bonds by the η^2-H_2 could then lead to the release of one equivalent of the 2-(hydroxyethyl)benzophenone product and an intermediate LFe^{IV}-H species. Reductive elimination from this intermediate would furnish the second equivalent of the 2-(hydroxyethyl)benzophenone product and regenerate the LFe^{II} catalyst.

The hydrogenolysis of transition metal M-O bonds has been postulated as a step in many catalytic reactions.[50,51] A hypothetical hydrogenolysis would also be consistent with the formation of the 2-benzoylbenzaldeyhde products **5a** and **5d** from phthalans **3a** and **3d**, respectively (*cf*. Table 2). An alternative reaction pathway, involving β-hydride abstraction from the Fe^{IV}-dialkoxo species to afford an aldehyde intermediate, appears less likely, considering that there was no formation of C-D bond on going from **8a** and **8c** to **2a** and **2c**,

which could result from deuteration of the aldehyde (Scheme 9).[51]

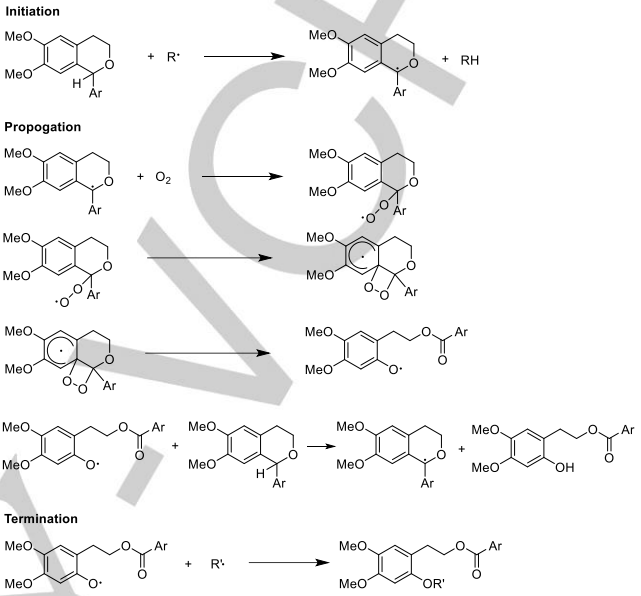


Scheme 10. Postulated mechanism for the Fe(OTf)$_2$**L** catalyzed oxidative cleavage of 1-arylisochromans.

The postulated mechanism for the Fe(OTf)$_2$**L** catalyzed oxidative cleavage of 1-arylisochromans clearly differs from the oxidation performed by Lacasse multicopper enzymes which couple the oxidation of substrates to the 4 electron reduction of O_2 to H_2O.[52] In particular, the oxidation of 1-arylisochromans to 2-(hydroxyethyl)benzophenones performed by the Lacasse/BHT system is described to occur via the formation of a benzyl radical that stems from the abstraction of the hydrogen atom from the C1 position of the isochroman ring.[19] This benzyl radical can be further oxidized to a carbocation which would react with water to generate a hemiacetal. The ring opening of the labile hemiacetal would lead to the product formation. In our case, the identification of the peroxide intermediate, the high yields observed for isochromans bearing electron withdrawing substituents and the selectivity with which the radical sensitive substrate **1o** is oxidized by Fe(OTf)$_2$**L** all appear to be in disagreement with the formation of benzyl radicals analogous to those involved in the Lacasse/BHT oxidation.

Postulated mechanism of the auto-oxidative cleavage of 1-arylisochromans

The participation of freely diffusing radical species during the Fe(OTf)$_2$**L** promoted Csp^3-O bond cleavage appears unlikely due to the high selectivity and mass balance exhibited by the catalyst even in the presence of highly activated CH bonds and a radical-sensitive cyclopropyl moiety (*cf* Table 1). In contrast, the auto-oxidative Csp^2-Csp^3 bond cleavage in electron rich 1-arylisochromans is enhanced by radiation, higher temperatures and radical initiators, indicating that the reaction proceeds through a mechanism involving free radical species.



Scheme 11. Postulated mechanism for the metal-free auto-oxidative cleavage of 1-arylisochromans.

A suggested radical chain mechanism initiated by the benzoyl peroxide additive is shown in Scheme 11. Formation of the relatively stable benzylic radical would trigger the reaction with the triplet O_2 in a fast, diffusion-controlled manner,[53] furnishing a peroxo radical. In the methoxy-substituted 1-arylisochromans, the resulting peroxo radical may add to the aromatic ring to afford a dioxetane species,[54] although the formation of the 4-membered ring could be energy-costly due to geometric strains.[55] Collapse of the dioxetane then leads to a phenoxide radical, which abstracts a hydrogen from the substrate, generating the observed product and a new benzylic radical that starts the propagation reaction again. The phenoxide radical may react with other radical species, terminating the chain reaction.

Conclusions

The oxidative cleavage of the Csp^3-O bond in 1-arylisochromans with toxic/wasteful stoichiometric oxidants has been practiced for decades, aiming particularly for bioactive compounds such as neuroprotective agents. This work shows for the first time that 1-arylisochromans can be converted into a variety of oxygenated products with a molecular iron catalyst under mild aerobic conditions and in a predictable and preparative fashion. The unique ability of the Fe(OTf)$_2$**L** catalyst in undergoing selective oxygenation and hydrogenolysis reactions during the same catalytic process allows the stepwise isolation of structurally complex oxygenated products, such as 1,1'-peroxybis(1-arylisochromans) and phenyl (2-(2-((1-phenylisochroman-1-yl)oxy)ethyl)phenyl) methanones that can be further "digested" into simpler 2-(hydroxyethyl)benzophenone compounds, resembling natural anabolic and catabolic pathways. We

anticipate that these reactions in conjunction with the mechanistic evidence presented can inspire the design of future catalytic processes in which selective oxidations/oxidative cleavages are combined with other transformations allowing for significant synthetic complexity. An additional auto-oxidative Csp^2-Csp^3 bond cleavage in electron rich substrates is also presented, which allows for the synthesis of valuable benzoates in good yields and shows that radical auto-oxidative processes can lead to complementing synthetic protocols.

Experimental Section

General procedure for the iron-catalyzed aerobic Csp^3-O cleavage of 1-arylisochromans: In a Radley's tube equipped with a magnetic stir bar, ligand **L** (5.71×10^{-3} mmol, 5.2 mg) and $Fe(OTf)_2$ (5.71×10^{-3} mmol, 2.0 mg) were added. The corresponding ether (2.0 mL) was added and the reaction tube was degassed, charged with O_2/N_2 (1 atm, 3 times) and kept under oxygen (1 atm) by using a balloon. The reaction mixture was heated to 60 °C and allowed to react for 16 h. Thereafter, a second addition of catalyst was made (5.71×10^{-3} mmol) and the reaction mixture was reacted at 60 °C for another 8 h. If needed, a third addition of catalyst was made following the same procedure with the reaction mixture heated to 60 °C for an additional 8 h. The reaction mixture was purified by silica gel column chromatography (Hexane/EtOAc, gradient: 10/1 to 4/1 or 2/1) to afford the unreacted starting material and the reaction product.

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Keywords: isochromans • oxidation • aerobic cleavage • dioxygen • iron catalyst

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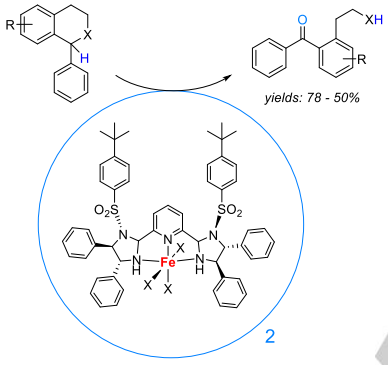
FULL PAPER

A breath of fresh air: An iron catalyst enables the selective aerobic cleavage of 1-arylsiochromans to afford valuable 2-(hydroxyethyl)benzophenones, via an unprecedented mechanism involving aerobic dehydrogenation, C-O cleavage and hydrogenolysis.



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Boosting molecular complexity with O2: iron-catalysed oxygenation of 1-arylisochromans via dehydrogenation, Csp^3-O cleavage and hydrogenolysis