ChemPubSoc Europe

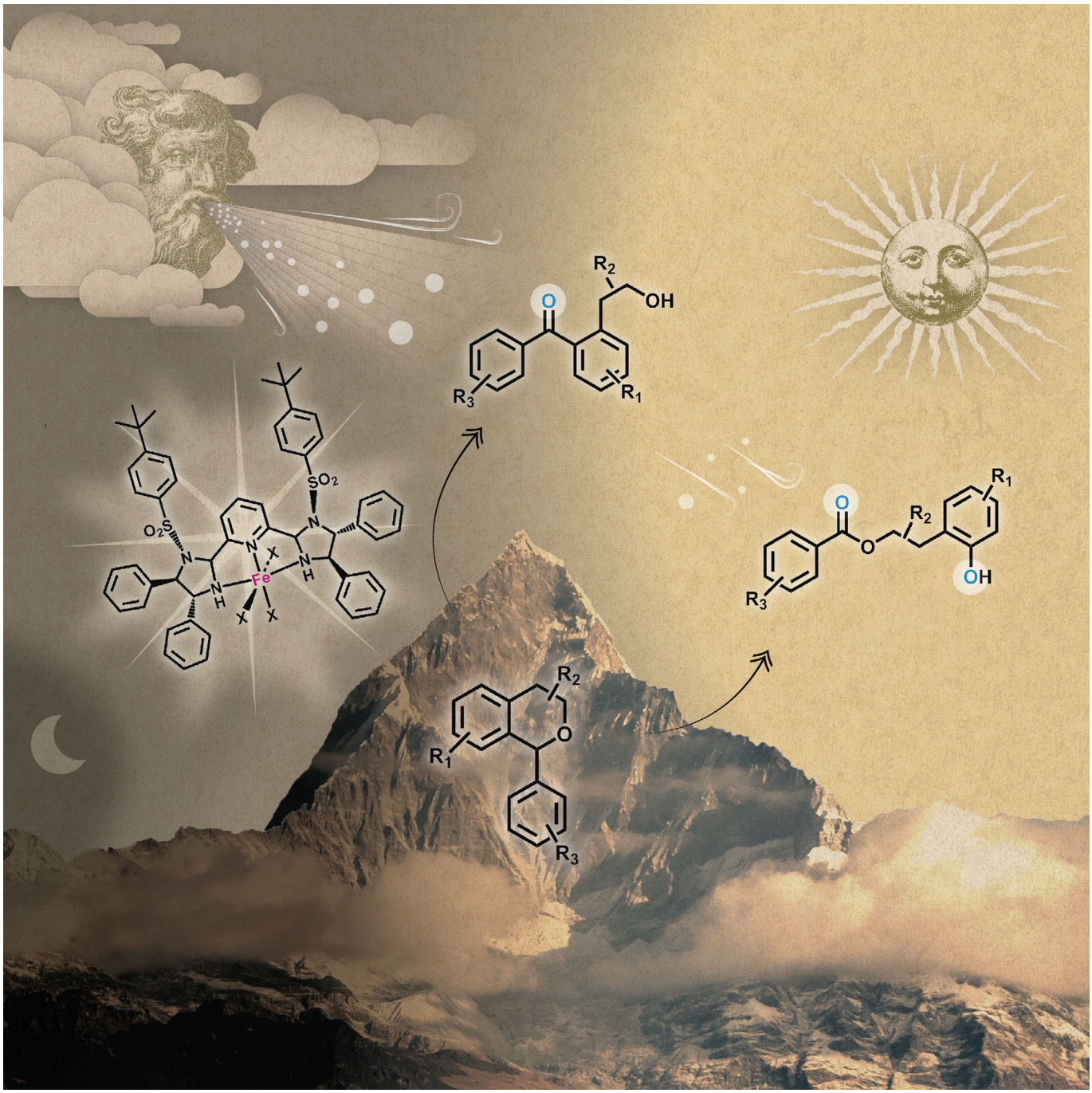
DOI: 10.1002/chem.201806117

CHEMISTRY A European Journal Full Paper

Catalyzed Oxygenation |*Hot Paper*|

Boosting Molecular Complexity with O_2: Iron-Catalysed Oxygenation of 1-Arylisochromans through Dehydrogenation, Csp^3–O Bond Cleavage and Hydrogenolysis

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



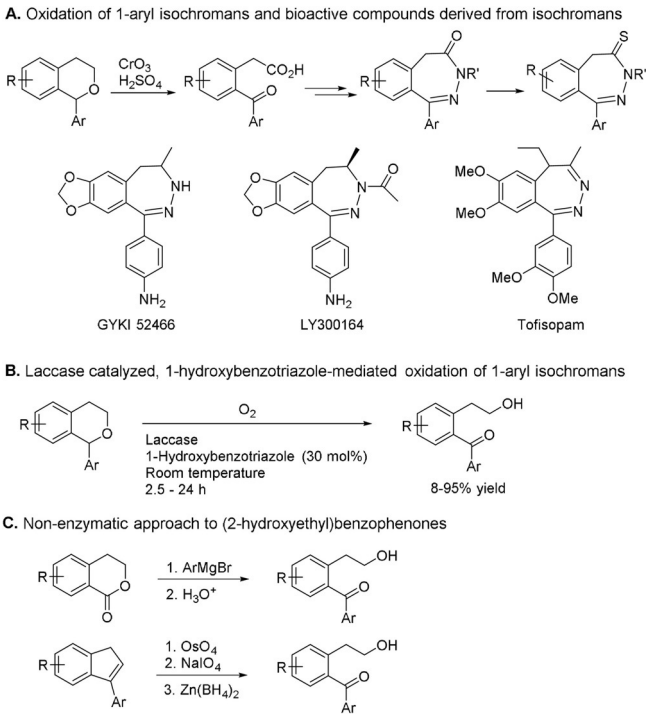
Abstract: Oxidative cleavage of the Csp^3–O bond in 1-arylisochromans with stoichiometric oxidants, such as CrO_3/H_2SO_4, has been practiced for decades in synthetic chemistry. Herein, we report that a structurally well-defined Fe^{II}–pyridyl(bis-imidazolidine) catalyst promotes the aerobic oxygenation 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 through dehydrogenative oxygenation of the isochromans at the 1-position, Csp^3–O bond cleavage at the iron centre 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 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 (bond-dissociation energy (BDE) of EtO–Et and Ph–OMe: 85 and 100 kcal mol^{-1}, 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 for their remarkable ability in selectively oxidising 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 decades, bringing about remarkable advances in the 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]

A case in point is the oxidation of isochroman and its 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] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[13] ceric ammonium nitrate (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, which has been exploited by medicinal chemists for the synthesis of benzodiazepines, benzodiazepinones and benzodiazepinethiones, analogues of the neuroprotective agent GYKI52466 and the related LY300164 and tofisopam (Scheme 1 A).[18] Given the therapeutic potential of such compounds in treating epilepsy, spasticity, chronic pain and neurodegenerative disorders, it would be highly desirable to develop



Scheme 1. Oxidative cleavage of the 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] *Dr. A. Gonzalez-de-Castro, Dr. C. M. Robertson, Prof. Dr. J. Xiao*
Department of Chemistry, University of Liverpool
Liverpool L69 7ZD (UK)
E-mail: j.xiao@liv.ac.uk

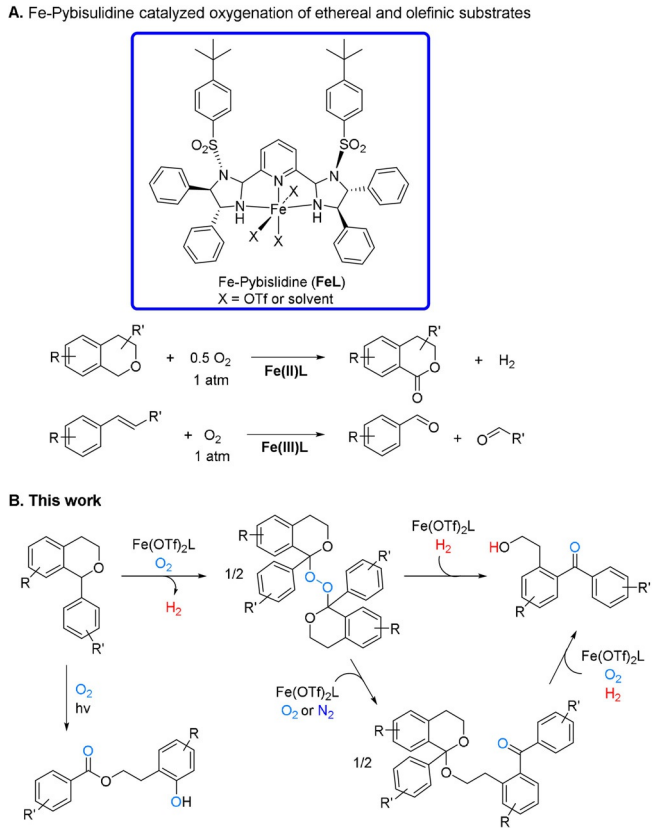
[b] *Dr. A. Gonzalez-de-Castro*
Innosyn B.V. P.O. Box 18, 6160 MD Geleen (The Netherlands)
E-mail: angela.gonzalez-de-castro@innosyn.com

The ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/chem.201806117.

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 1 B).[19] Non-enzymatic methods for the synthesis of 2-(hydroxyethyl)benzophenones are also known, for example, Grignard addition and osmylation followed by periodate cleavage (Scheme 1 C).[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 2 A).[22] Inspired by nature's dioxygenases in cleaving inert C–C bonds under mild aerobic conditions, we set out to explore such catalysts for the selective aerobic cleavage of aliphatic and unstrained C–C/C–O bonds in complex and functionalised substrates. Herein, we report the aerobic cleavage of functionalised 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 2 B).

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 oxidised through a sequence of iron-catalysed reactions, that is, dehydrogenative oxygenation of two ethereal substrates to form a tetra-substituted peroxide intermediate followed by peroxide cleavage and subsequent hydrogenolysis of the resulting iron–alkoxo species. Under an 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 carbon atoms were selectively oxidised (Scheme 2 B).



Scheme 2. Previous work on the $Fe^{(II/III)}$–Pybisulidine-catalysed oxidation of isochromans and the oxidative cleavage of styrenes, and the work described in this paper.

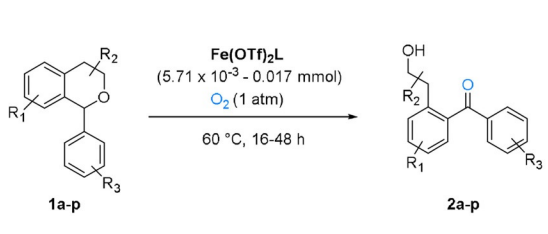
Results and Discussion

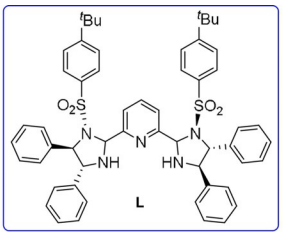
$[Fe(OTf)_2L]$-catalysed aerobic cleavage of 1-aryl isochromans

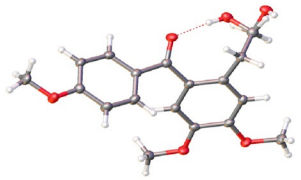
Following our investigations in the selective oxidation of isochromans to isochromanones promoted by the catalyst $[Fe(OTf)_2L]$ formed in situ by reacting $Fe(OTf)_2$ (OTf = triflate) with the pyridine bis-sulfonamide ligand L (Scheme 2 A),[23] we set out to investigate the oxidation of 1-phenylisochroman (Table 1). To our delight, the benzophenone **2a**, resulting from cleavage of the Csp^3–O bond and oxygenation of the Csp^3 carbon atom, was obtained exclusively in a yield of 21% 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 overoxidation 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 $[Fe(OTf)_2L]$ 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 the 1-arylisochromans (Table 1, entries 1–6) and the presence of substituents in the alkyl chain (Table 1, 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 realised in substrates incorporating N-, S- and O-based heterocycles with similar high yields and mass balance (Table 1, entries 8–15), 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 (Table 1, entries 12 and 14), and the very labile protecting group trimethylsilyl (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 (Table 1, entry 13). Significantly, the $Csp^3 < C- < O$ bond cleavage of the radical-sensitive substrate **1o** bearing a cyclopropyl ring was cleanly accomplished with excellent mass balance and no substrate degradation. This is in contrast with the reaction involv-

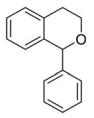
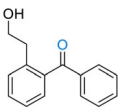
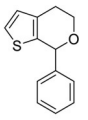
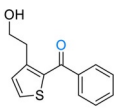
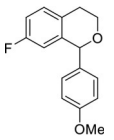
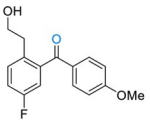
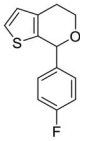
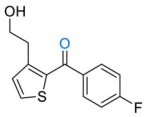
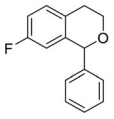
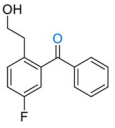
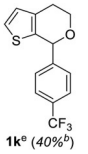
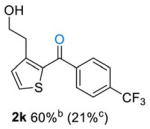
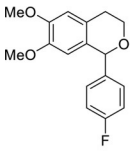
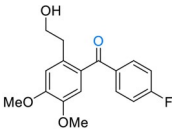
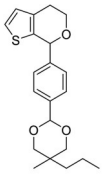
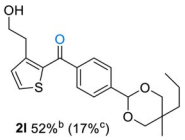
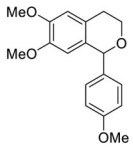
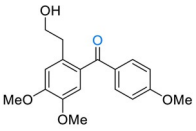
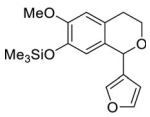
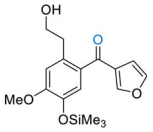
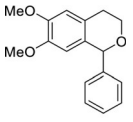
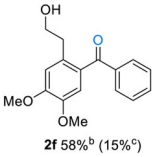
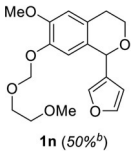
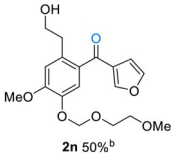
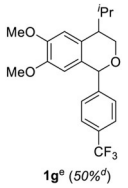
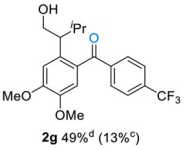
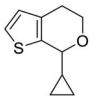
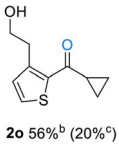
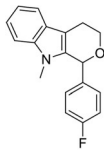
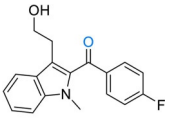
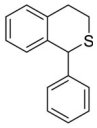
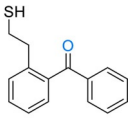
Table 1. Scope of the [Fe(OTf)$_2$L]-catalysed aerobic Csp^3–O cleavage of 1-arylisochromans.[g]







X-ray structure of **2e**

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})

[a] rsm = recovered starting material (unoxidised). [b] Three [Fe(OTf)$_2$L] catalyst additions (5.71 × 10^{-3} mmol each), 32 h. [c] One [Fe(OTf)$_2$L] catalyst addition (5.71 × 10^{-3} mmol), 16 h. [d] Two [Fe(OTf)$_2$L] catalyst additions (5.71 × 10^{-3} mmol each), 48 h. [e] Reaction run with 2.0 mL of substrate. [f] Deprotected acetal (acetal cleavage). [g] 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.

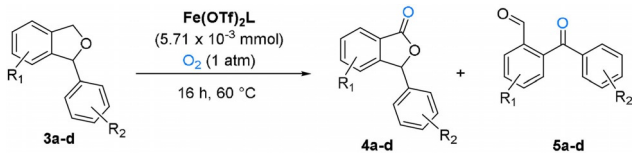
ing free radicals (see below) and seems to indicate that either there is no radical formation at the C1 position or the Csp^3–O bond cleavage is much faster than the ring-opening of the cyclopropyl moiety. In addition, an analogous Csp^3–S bond cleavage was also realised when **1p** was used as substrate,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

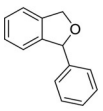
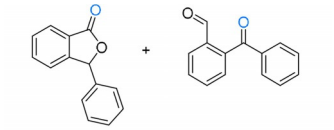
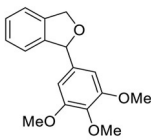
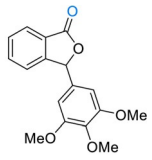
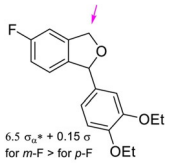
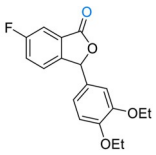
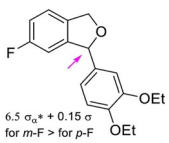
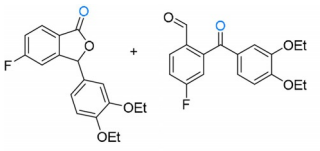
Site-selective CH_2 oxygenation versus aerobic Csp^3–O bond cleavage in 1-arylphthalans

Unlike 1-arylisochromans in which the Csp^3–H bond at the 1-position is more activated, the reaction of 1-arylphthalans brings up a question of regioselectivity. Although $[Fe(OTf)_2L]$ could promote a similar aerobic Csp^3–O bond cleavage, a CH_2 oxygenation may also take place, because the Csp^3–H bond at this position is more easily accessible sterically and is activated electronically by the adjacent phenyl ring. Indeed, exposure of 1-phenylphthlan (**3a**) to the $[Fe(OTf)_2L]$ catalyst afforded the CH_2 oxidised product **4a** in 44% yield (Table 2). Formation of the Csp^3–O bond-cleaved product **5a**, in which the benzylic alcohol is now oxidised to its aldehyde form, was observed only in a low yield of 6%, indicating that the steric effect overruns the electronic effect with the bulky $[Fe(OTf)_2L]$ 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 the phthalide **4b** in an isolated yield of 42%, although we note that the *o*-MeO moiety is slightly destabilising 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 $[FeL(thf)(OTf)_2]$ 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, contributes 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 at 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 isolated yield of 58%. However, when the fluorine is placed *meta* to the 1-position, the oxygenation of the substrate **3d** afforded the CH_2-oxygenated product **4d** as well as the Csp^3–O bond-cleaved product **5d**, in a ratio of approximately 2:1. These results can be explained by the spin-delocalisation-based σ_α^* constants corrected to a small degree with the Hammett constant σ, which indicate that the *para* F destabilises a benzyl radical more than a *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 oxidise. Nonetheless, these results suggest that in the oxygenation of 1-arylphthalans, the selectivity of the $[Fe(OTf)_2L]$ catalyst is strongly governed by steric constrains, predictably furnishing the CH_2-oxidised 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 electronic effects.[21a]

Table 2. Methylene oxygenation versus Csp^3–O bond cleavage in 1-arylphthalans: steric and electronic effects.[c]



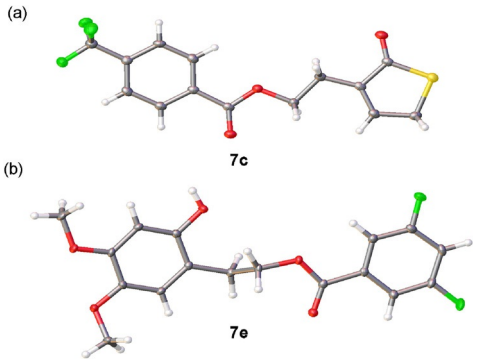
Entry	Substrate (rsm [%])[a]	Product (isol. yield [%])
1	 **3a** (*50%*)	 **4a** 44%[b] CH_2 oxygenation; Sterically favoured — **5a.** 6%[b] Csp^3-O bond cleavage; Electronically favoured
2	 **3b** (*50%*)	 **4b.** 42% CH_2 oxygenation; Sterically favoured
3	 6.5 σ_α* + 0.15 σ for *m*-F > for *p*-F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

[a] rsm = recovered starting material (unoxidised). [b] Product ratio determined by ^1H NMR spectroscopy. [c] Reaction conditions: $Fe(OTf)_2$ (5.71×10^{-3} mmol, 2.0 mg) and L (5.7×10^{-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.

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

Upon exposure to UV light, 1*H*-isochromans are known to be autoxidisable to afford a mixture of peroxides and hydroperoxides.[27] However, 1-arylisochromans were early reported to be

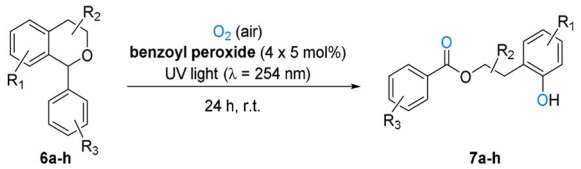
resistant to autoxidation under UV-light irradiation[27b] and ever since, further investigations on their potential autoxidation reactions has rarely been attempted.[18c] Even though the structure of the substrate can play a decisive role in determining its susceptibility to the action of O_2,[28] it was surprising to us that 1-arylisochromans bearing weakened tertiary CH bonds could exhibit such inertness towards autoxidation processes. In an elegant, single example, Eli Lilly researchers showed that a 1-(4-nitrophenyl)-substituted isochroman could be cleanly oxidised at the 1-position through 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 limit the reaction to 1-aryls bearing strongly electron-withdrawing groups. During our investigations, we noted that a colourless neat sample of the thienopyran **6c** evolved to orange after two days at ambient temperature (see the Supporting Information and Table 3). Exposure to air for four days intensified the colour change and after purification by column chromatography, compound **7c** was obtained in 19% isolated yield, the structure of which was confirmed by NMR spectroscopy and X-ray diffraction analysis (Scheme 3). It appears that **7c** results from the autoxidative



Scheme 3. X-ray structures of the benzoate products resulting from the autoxidation of the thienopyran **6c** and the 1-arylisochroman **6e**.

Csp^2–Csp^3 bond cleavage in substrate **6c**. Thus, after fourteen days of exposure to air and sunlight, compound **7c** was selectively isolated in 97% yield along with the formation of the minor byproduct **7c′** (see the Supporting Information). Under UV irradiation, the aerobic Csp^2–Csp^3 bond cleavage of **6c** was accelerated, furnishing **7c** in 96% isolated yield after ten days

Table 3. Scope of the metal-free autoxidative Csp^2–Csp^3 bond cleavage of 1-arylisochromans.[d]



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]

[a] rsm = recovered starting material (unoxidised). [b] Reaction run under sunlight exposure for 14 h without Luperox. [c] Five additions of Luperox (5× 5 mol%) and reacted for 36 h at 30 °C. [d] 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 RT for 24 h. Three subsequent additions of Luperox (5 mol% each) and C_6H_6 (50 μL each) were done in 1 h intervals

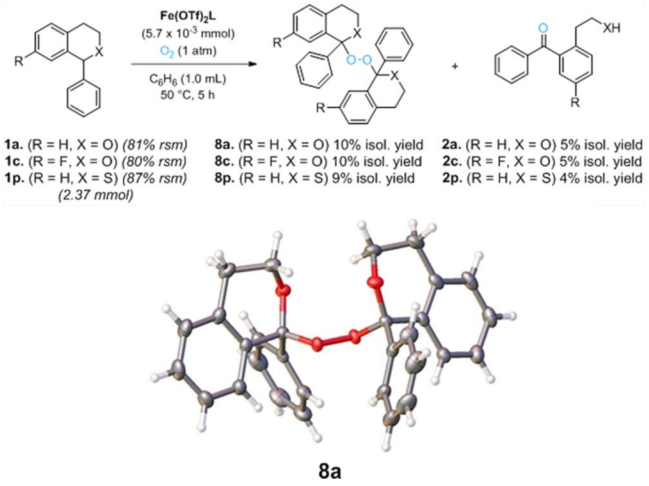
(see the Supporting Information). In contrast, storing the samples in darkness significantly slowed down the reaction (see the Supporting Information). Heating a sample of **6c** at 60 °C also accelerated the reaction but with eroded selectivity, with **7c** been isolated in a 60% yield after five days (see the Supporting Information). As may be expected, stirring **6c** in the presence of the radical initiator benzoyl peroxide[29] (5 mol%) improved the rate of the oxidative cleavage, affording **7c** in an isolated yield of 28% after 12 h. Subsequent additions of benzoyl peroxide (4×5 mol%) to a stirred sample of **6c** under UV irradiation afforded compound **7c** in an isolated yield of 96% after 24 h. The remarkably contrasting chemoselectivity of the autoxidation versus that promoted by $[Fe(OTf)_2L]$ highlights the mechanistic difference in the two systems. The scope of the autoxidative 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(5*H*)-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 for pharmaceutically active compounds.[34,35] Despite their numerous applications, traditional organic methods are often employed to synthesise these motifs.[33]

A similar Csp^2–Csp^3 bond cleavage was observed in 1-aryl-6,7-dimethoxyisochromans, furnishing the valuable 2-hydroxy-4,5-dimethoxyphenethyl benzoates **7e**–**7h** in excellent yields with perfect atom economy and mass balance (Table 3, entries 5–8, Scheme 3). However, although simple and efficient for synthesising phenols and benzoates, this autoxidative reaction is more limited in the scope than the $[Fe(OTf)_2L]$-catalysed Csp^3–O bond cleavage. Thus, when **1o** bearing the radical-sensitive cyclopropyl ring was subjected to the autoxidation conditions, substrate degradation was the predominant reaction observed (see the Supporting Information). More significantly, the autoxidation conditions appear to be applicable only to liquid and relatively electron-rich substrates. Thus, the autoxidation of **6h** afforded **7h** in 43% yield (Table 3, entry 8) alongside side reactions that reduced the mass balance, and after exposing **1a** to air for two months, 1,1′-peroxybis(1-phenylisochroman) (**8a**) was isolated in 12% yield among a myriad of other uncharacterised products (see the Supporting Information). In contrast, under the catalysis of $[Fe(OTf)_2L]$, the Csp^3–O bond-cleaved products **2a**, **2g** and **2o** were cleanly obtained (Table 1).

Mechanistic investigations of the $[Fe(OTf)_2L]$-promoted aerobic cleavage of 1-arylisochromans

Isolation of peroxide intermediates

The $[Fe(OTf)_2L]$-catalysed 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, that is, the $[Fe(OTf)_2L]$-catalysed aerobic Csp^3–O bond cleavage of 1-arylisochromans, could also proceed through 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 bond-cleaved product **2a** in 5% yield. The structure of the tetra-substituted peroxide **8a** was confirmed by NMR analysis and X-ray diffraction after its isolation by column chromatography and crystallisation in an Et_2O/hexane solution (see Scheme 4 and the Supporting Information). 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 characterisation particularly difficult. In fact, to the best of our knowledge, there is no other report in the literature of a tetra-substituted peroxide for 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 sulfur-based substrate **1p** was found to be 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.

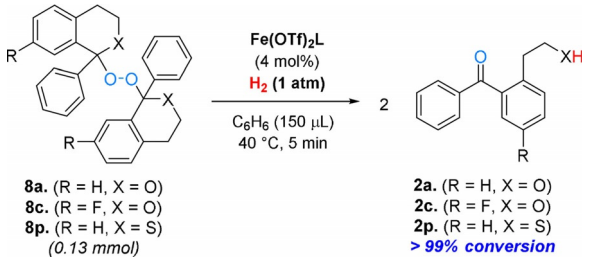


Scheme 4. Identification and isolation of a peroxide intermediate during the $[Fe(OTf)_2L]$-catalysed aerobic cleavage of 1-arylisochromans. The X-ray structure of **8a** is shown.

Peroxide reaction under H_2 atmosphere

The oxygenation of isochromans to isochromanones through the 1,1′-peroxybisether intermediate catalysed by $[Fe(OTf)_2L]$ 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 the 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**, **8c**, and **8p** the $[Fe(OTf)_2L]$ catalyst under a H_2 atmosphere resulted in an immediate colour 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 tetra-substituted peroxide intermediate is also accompanied with H_2 gas release, with the released H_2 gas subsequently consumed in the $[Fe(OTf)_2L]$-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 Supporting Information).

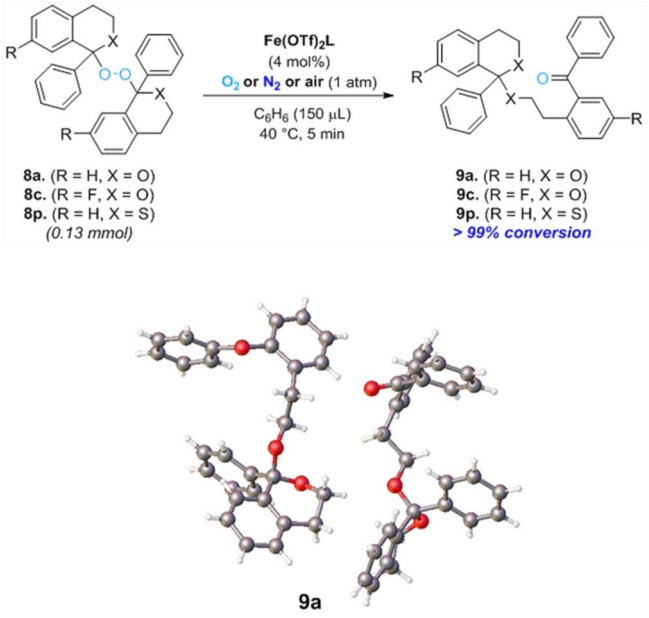


Scheme 5. $[Fe(OTf)_2L]$-catalysed conversion of the peroxide intermediates into 2-(hydroxyethyl)benzophenones under an atmosphere of H_2.

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]

Peroxide reaction under inert and aerobic atmospheres

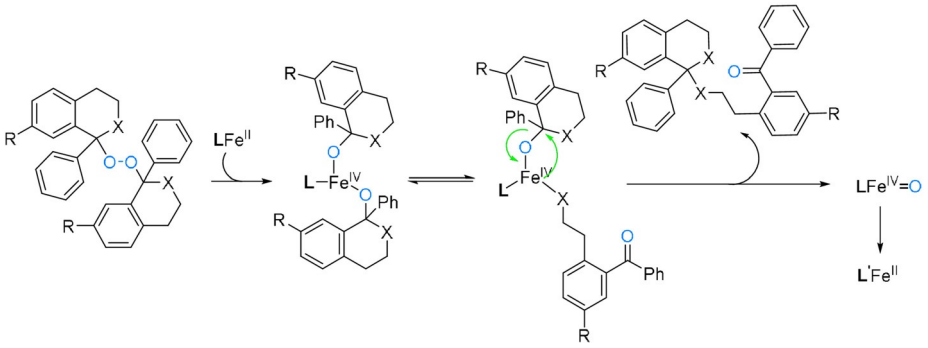
Interestingly, when the peroxides **8a**, **8c** and **8p** were subjected to the $[Fe(OTf)_2L]$ catalyst under an atmosphere of N_2, the unexpected ketal products **9a**, **9c** and **9p** were obtained quantitatively and again, no reaction occurred in the absence of the iron catalyst (Scheme 6). The 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 $[Fe(OTf)_2L]$ catalyst is capable of promoting a different mode of reactions for the peroxide species. Interestingly, the ketal products **9a**, **9c** and **9p** were not detected when the same reactions were performed under a 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



Scheme 6. $[Fe(OTf)_2L]$-catalysed conversion of the peroxide intermediates into ketal species in the absence of H_2. The X-ray structure of **9a** is shown.

by X-ray diffraction. The conversion of a peroxy-bridged 1-arylisochroman into a benzophenone-functionalised 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**, **8c** and **8p** to the ketal products **9a**, **9c** and **9p** implies the loss of an oxygen atom. It was noted that the $[Fe(OTf)_3L]$ 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**, **8c** and **8p** to the ketal products **9a**, **9c** and **9p**, the hypothesis of solvent molecules being involved in this transformation was excluded. It is likely that the conversion of **8a**, **8c** and **8p** to **9a**, **9c** and **9p** is initiated by the peroxo-bond cleavage through oxidative addition to the $[Fe(OTf)_2L]$ 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**, **9c** and **9p** through the attack of the alkoxo fragment to the highly electrophilic acetal carbon atom. As a consequence, a very reactive Fe^{IV}–oxo species would be generated. In a polar protic medium, Fe^{IV}–oxo complexes behave as strong oxidants, capable of oxidising inert C–H bonds.[7a–c] As no oxidation of the solvent was observed and on the basis of the X-ray structure of the $[Fe(thf)(OTf)_2L]$ 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

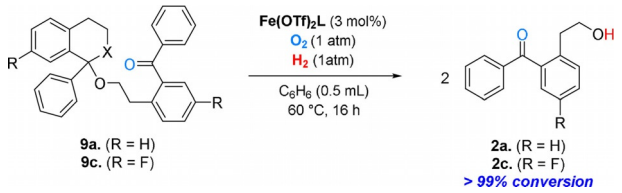


Scheme 7. A hypothetic mechanism for the [Fe(OTf)$_2$L]-catalysed conversion of the peroxide intermediates into ketal species in the absence of H_2.

the area 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.

Iron-catalysed conversion of ketals

As may be expected, upon exposure to water or moisture the ketals **9a** and **9c** were slowly hydrolysed into the 2-(hydroxyethyl)benzophenone products **2a** and **2c**, respectively (see the Supporting Information). 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 (≈16 h) (Scheme 8). However, no reaction

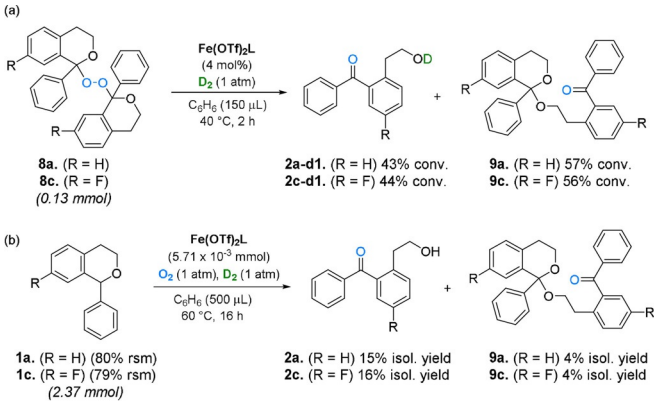


Scheme 8. Conversion of ketals into 2-(hydroxyethyl)benzophenones catalysed by [Fe(OTf)$_2$L] under a H_2 and O_2 atmosphere.

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. Whereas 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** and **9c** into **2a** and **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).

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



Scheme 9. a) Reaction of 1-arylisochroman 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.

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 the use of H_2 (Scheme 5), the major products were compounds **9a** and **9c** in the case of D_2. Considering that 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** favourable. (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 with low dielectric constants 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 perox-

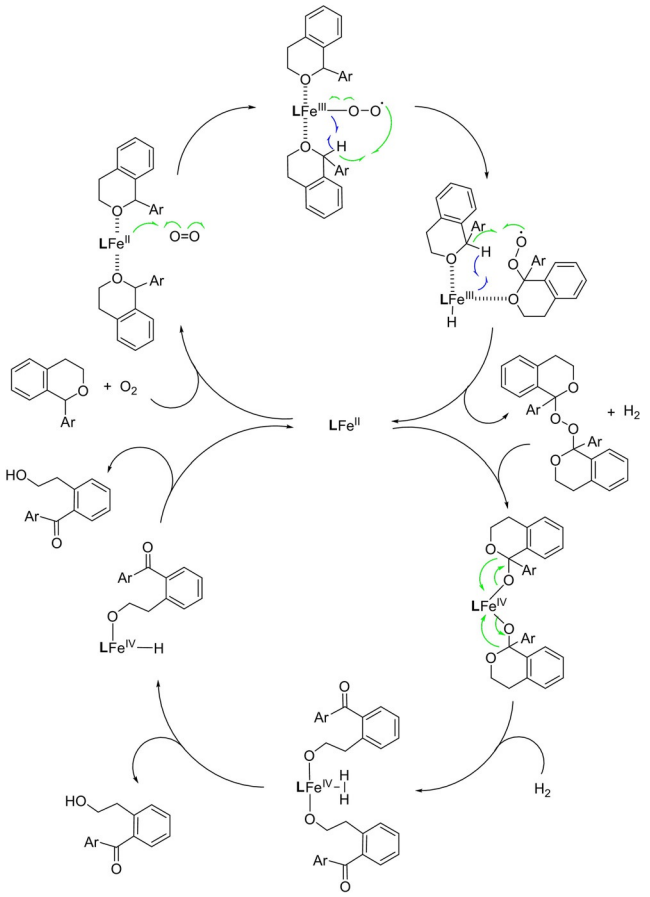
ides reacted to completion almost immediately upon exposure to the [Fe(OTf)$_2$L] catalyst, the difference in the diffusion rates of H_2 and D_2 could somewhat affect the product distribution. Therefore, from the observed kinetic isotope effect in the hydrogenolysis of the peroxides **8a** and **8c**, 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 approximately 15% (see Table 1). The ketal compounds **9a** and **9c** were also obtained in an isolated yield of 4%, whereas the deuterated products **2a-d$_1$** and **2c-d$_1$** 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 centre and their ability to react much faster than D_2 activation and/or diffusion.

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]-catalysed aerobic Csp^3–O bond cleavage of 1-arylisochromans involves two key steps, that is, 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 centre. A second attack to the α-CH bond of the other ethereal molecule with a concomitant hydrogen transfer to the iron centre would result in the formation of the peroxide intermediate and a LFe^{IV}–(H)$_2$ dihydride species.[21a] The latter would rapidly undergoe 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.



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

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 the phthalans **3a** and **3d**, respectively (see 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 C–D bond formation on going from **8a** and **8c** to **2a** and **2c**, respectively, which could result from deuteration of the aldehyde (Scheme 9).[51]

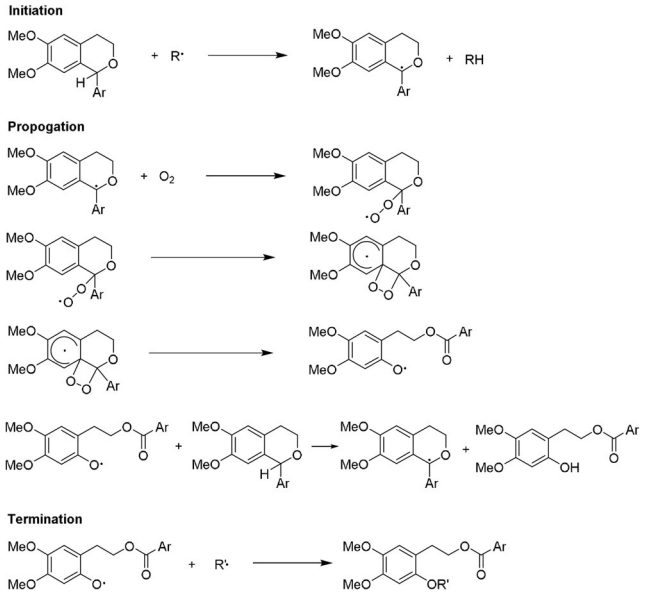
The postulated mechanism for the [Fe(OTf)$_2$L]-catalysed oxidative cleavage of 1-arylisochromans clearly differs from the oxidation performed by laccase multicopper enzymes, which couple the oxidation of substrates to the four-electron reduction of O_2 to H_2O.[52] In particular, the oxidation of 1-arylisochromans to 2-(hydroxyethyl)benzophenones performed by the laccase/butylated hydroxytoluene (BHT) system is described to occur through 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 oxidised 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 **1 o** is oxidised by $[Fe(OTf)_2L]$ all appear to be in disagreement with the formation of benzyl radicals analogous to those involved in the laccase/BHT oxidation.

Postulated mechanism of the autoxidative cleavage of 1-arylisochromans

The participation of freely diffusing radical species during the $[Fe(OTf)_2L]$-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 (see Table 1). In contrast, the autoxidative 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.

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 four-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 atom from the substrate, thereby 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.



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

Conclusion

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 $[Fe(OTf)_2L]$ 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 autoxidative 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 autoxidative processes can lead to complementing synthetic protocols.

Experimental Section

General procedure for the iron-catalysed aerobic Csp^3–O bond cleavage of 1-arylisochromans: In a Radleys tube equipped with a magnetic stir bar, the 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 (15% v/v) (1 atm, three times) and kept under O_2/N_2 (15% v/v) (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 being heated to 60 °C for 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.

Acknowledgements

We are grateful to the University of Liverpool for funding (AGdC). We also want to express our gratitude to the Analytical Services of the Department of Chemistry at the University of Liverpool for product analyses.

Conflict of interest

The authors declare no conflict of interest.

Keywords: autoxidation · dioxygen · iron · isochromans · oxidation

[1] G. F. White, N. J. Russell, E. C. Tidswell, *Microbiol. Rev.* **1996**, *60*, 216.
[2] a) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro, M. R. Prinsep, *Nat. Prod. Rep.* **2014**, *31*, 160; b) T. Janecki, *Natural Lactones and Lactams: Synthesis Occurrence and Biological Activity*, Wiley-VCH, Weinheim, **2013**; c) N. M. Xavier, A. P. Rauter, Y. Queneau, *Top. Curr. Chem.* **2010**, *295*, 19; d) J. J. Beck, S.-C. Chou, *J. Nat. Prod.* **2007**, *70*, 891.
[3] a) S. R. Collinson, W. Thielemans, *Coord. Chem. Rev.* **2010**, *254*, 1854; b) K. Kervinen, H. Korpi, M. Leskelä, T. Repo, *J. Mol. Catal. A* **2003**, *203*, 9; c) V. Alves, E. Capanema, C.-L. Chen, J. Gratzl, *J. Mol. Catal. A* **2003**, *206*, 37; d) T. K. Kirk, R. L. Farrell, *Annu. Rev. Microbiol.* **1987**, *41*, 465; e) U. Tuor, H. Wariishi, H. E. Schoemaker, M. H. Gold, *Biochemistry* **1992**, *31*, 4986; f) E. Odier, C. Rolando, *Biochimie* **1985**, *67*, 191.
[4] a) T. J. Collins, *Acc. Chem. Res.* **2002**, *35*, 782; b) M. Alexander, *Biodegradation and Bioremediation*, 2nd ed., Academic Press, London, **1999**; c) Y.-H. Kim, K.-H. Engesser, *Appl. Environ. Microbiol.* **2004**, *70*, 4398; d) C. M. Sales, A. Grostern, J. V. Parales, R. E. Parales, L. Alvarez-Cohen, *Appl. Environ. Microbiol.* **2013**, *79*, 7702.
[5] General iron catalysis: a) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170; b) B. Plietker, *Iron Catalysis in Organic Chemistry. Reactions and Applications*, Wiley- VCH, Weinheim **2008**; c) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778. Recent reviews on catalysed oxidations: d) Y. Liang, J. Wei, X. Qiu, N. Jiao, *Chem. Rev.* **2018**, *118*, 4912; e) G. Olivo, O. Cussó, M. Borrell, M. Costas, *J. Biol. Inorg. Chem.* **2017**, *22*, 425; f) E. B. Bauer, *Isr. J. Chem.* **2017**, *57*, 1131; g) S. Sahu, D. P. Goldberg, *J. Am. Chem. Soc.* **2016**, *138*, 11410.
[6] a) R. ten Have, P. J. M. Teunissen, *Chem. Rev.* **2001**, *101*, 3397; b) T. D. Bugg, M. Ahmad, E. M. Hardiman, R. Rahmanpour, *Nat. Prod. Rep.* **2011**, *28*, 1883.
[7] a) L. Que, Jr., W. B. Tolman, *Nature* **2008**, *455*, 333; b) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783; c) M. S. Chen, M. C. White, *Science* **2010**, *327*, 566; d) P. E. Gormisky, M. C. White, *J. Am. Chem. Soc.* **2013**, *135*, 14052; e) K. Suzuki, P. D. Oldenburg, L. Que, Jr., *Angew. Chem. Int. Ed.* **2008**, *47*, 1887; *Angew. Chem.* **2008**, *120*, 1913; f) P. D. Oldenburg, C. Y. Ke, A. A. Tipton, A. A. Shteinman, L. Que, Jr., *Angew. Chem. Int. Ed.* **2006**, *45*, 7975; *Angew. Chem.* **2006**, *118*, 8143; g) K. Chen, L. Que, Jr., *J. Am. Chem. Soc.* **2001**, *123*, 6327; h) K. Chen, M. Costas, J. Kim, A. K. Tipton, L. Que, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 3026; i) M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194; j) I. Prat, J. S. Mathieson, M. Güell, X. Ribas, J. M. Luis, L. Cronin, M. Costas, *Nat. Chem.* **2011**, *3*, 788; k) O. Cussó, I. Garcia-Bosch, X. Ribas, J. Lloret-Fillol, M. Costas, *J. Am. Chem. Soc.* **2013**, *135*, 14871; l) I. Garcia-Bosch, X. Ribas, M. Costas, *Chem. Eur. J.* **2012**, *18*, 2113; m) J. M. Howell, K. Feng, J. R. Clark, L. J. Trzepkowski, M. C. White, *J. Am. Chem. Soc.* **2015**, *137*, 14590; n) O. Cussó, M. Cianfanelli, X. Ribas, R. J. M. Klein Gebbink, M. Costas, *J. Am. Chem. Soc.* **2016**, *138*, 2732; o) D. Font, M. Canta, M. Milan, O. Cussó, X. Ribas, R. J. M. Klein Gebbink, M. Costas, *Angew. Chem. Int. Ed.* **2016**, *55*, 5776; *Angew. Chem.* **2016**, *128*, 5870; p) G. Olivo, O. Cussó, M. Costas, *Chem. Asian J.* **2016**, *11*, 3148.
[8] a) M. Aresta, C. Fragale, E. Quaranta, I. Tommasi, *J. Chem. Soc. Chem. Commun.* **1992**, *0*, 315; b) G. Olivo, O. Lanzalunga, L. Mandolini, S. Di Stefano, *J. Org. Chem.* **2013**, *78*, 11508; c) L. Gómez, I. García-Bosch, A. Company, J. Bene *t*Buchholz, A. Polo, X. Sala, X. Ribas, M. Costas, *Angew. Chem. Int. Ed.* **2009**, 48, 5720; *Angew. Chem.* **2009**, *121*, 5830; d) P. Spannring, I. Prat, M. Costas, M. Lutz, P. C. A. Bruijnincx, B. M. Weckhuysen, J. M. K. Gebbink, *Catal. Sci. Technol.* **2014**, *4*, 708.
[9] a) C. J. Allpress, L. M. Berreau, *Coord. Chem. Rev.* **2013**, *257*, 3005; b) B. Chakraborty, T. K. Paine, *Angew. Chem. Int. Ed.* **2013**, *52*, 920; *Angew. Chem.* **2013**, *125*, 954; c) M. M. Bittner, S. V. Lindeman, A. T. Fiedler, *J. Am. Chem. Soc.* **2012**, *134*, 5460; d) C. J. Allpress, K. Grubel, E. Szajna-Fuller, A. M. Arif, L. M. Berreau, *J. Am. Chem. Soc.* **2013**, *135*, 659.
[10] E. A. Markaryan, A. G. Samodurova, *Russ. Chem. Rev.* **1989**, *58*, 479.
[11] Oxidative coupling of isochromans with nucleophiles has also been reported, in which strong stoichiometric oxidants are generally used. See, for instance: a) W. Muramatsu, K. Nakano, C. J. Li, *Org. Lett.* **2013**, *15*, 3650; b) J. Feng, M. F. Lv, G. P. Lu, C. Cai, *Org. Chem. Front.* **2015**, *2*, 60; c) W. Muramatsu, K. Nakano, *Org. Lett.* **2015**, *17*, 1549; d) L. Liu, P. Floreancig, *Org. Lett.* **2010**, *12*, 4686; e) W. Muramatsu, K. Nakano, *Org. Lett.* **2014**, *16*, 2042.
[12] a) R. Gitto, M. Zappalà, G. De Sarro, A. Chimirri, *Il Farmaco* **2002**, *57*, 129; b) F. Gatta, D. Piazza, M. R. Del Giudice, M. Massotti, *Farmaco Ed. Sci.* **1985**, *40*, 942; c) B. Elger, A. Huth, R. Neuhaus, E. Ottow, H. Schneider, B. Seilheimer, L. Turski, *J. Med. Chem.* **2005**, *48*, 4618; d) G. Ábrahám, S. Sólyom, E. Csuzdi, P. Berzsenyi, I. Ling, I. Tarnawa, T. Hámori, I. Pallagi, K. Horváth, F. Andrási, G. Kapus, L. G. Hársing, Jr., I. Király, M. Patthy, G. Horváth, *Bioorg. Med. Chem.* **2000**, *8*, 2127.
[13] M. Guiso, C. Marra, F. Piccioni, *Nat. Prod. Res.* **2010**, *24*, 331.
[14] K. Isobe, N. Takeda, K. Mohri, Y. Tsuda, *Chem. Pharm. Bull.* **1989**, *37*, 3390.
[15] O. N. Srivastava, D. N. Chaudhury, *J. Org. Chem.* **1962**, *27*, 4337.
[16] S. Yamazaki, *Org. Lett.* **1999**, *1*, 2129.
[17] Y. Nagao, S. Tanaka, K. Hayashi, S. Sano, M. Shiro, *Synlett* **2004**, *3*, 481.
[18] a) L. Niu, *Acta Pharm. Sin. B* **2015**, *5*, 500; b) A. Chimirri, G. De Sarro, A. De Sarro, R. Gitto, S. Grasso, S. Quartarone, P. Giusti, V. Libri, A. Constanti, A. G. Chapman, *J. Med. Chem.* **1997**, *40*, 1258; c) B. A. Anderson, M. M. Hansen, A. R. Harkness, C. L. Henry, J. T. Vicenzi, M. J. Zmijewski, *J. Am. Chem. Soc.* **1995**, *117*, 12358; d) A. Chimirri, G. De Sarro, A. De Sarro, R. Gitto, S. Quartarone, M. Zappalà, A. Constanti, V. Libri, *J. Med. Chem.* **1998**, *41*, 3409; e) S. M. Leventer, K. Raudibaugh, C. L. Frissora, N. Kassem, J. C. Keogh, J. Phillips, A. W. Mangel, *Aliment. Pharmacol. Ther.* **2008**, *22*, 197; f) K. G. Guimarães, R. P. de Freitas, A. L. T. G. Ruiz, G. F. Fiorito, J. E. de Carvalho, E. F. F. da Cunha, T. C. Ramalho, R. B. Alves, *Eur. J. Med. Chem.* **2016**, *111*, 103; g) V. Hampl, I. Wetzel, F. Bracher, J. Krauss, *Sci. Pharm.* **2011**, *79*, 21.
[19] R. Bernini, F. Crisante, F. D'Accunzo, P. Gentili, E. Ussia, *New J. Chem.* **2016**, *40*, 3314.
[20] M. C. Pirrung, B. G. Roy, S. Gadamsetty, *Tetrahedron* **2010**, *66*, 3147.
[21] a) A. Gonzalez-de-Castro, C. M. Robertson, J. Xiao, *J. Am. Chem. Soc.* **2014**, *136*, 8350; b) M. Canta, M. Rodriguez, M. Costas in *Recent Advances in the Selective Oxidation of Alkyl C–H Bonds Catalyzed by Iron Coordination Complexes* (Ed.: T. Kawabata), *Site-Selective Catalysis. Topics in Current Chemistry, Vol 372* **2015**,, Springer, Heidelberg; c) G. Olivo, O. Lanzalunga, S. Di Stefano, *Adv. Synth. Catal.* **2016**, *358*, 843.
[22] a) A. Gonzalez-de-Castro, J. Xiao, *J. Am. Chem. Soc.* **2015**, *137*, 8206. For a theoretical study of the reaction, see: b) Y. Jiang, X. Zhang, Q. Mao, H. Tan, X. Li, G. Chen, Z. Jia, *Dalton Trans.* **2017**, *46*, 3825.
[23] For the X-ray characterisation of $[FeL(thf)(OTf)_2]$ see reference [21a].
[24] X. Creary, *J. Org. Chem.* **1980**, *45*, 280.
[25] R. Karmakar, P. Pahari, D. Mal, *Chem. Rev.* **2014**, *114*, 6213.
[26] J. M. Dust, D. R. Arnold, *J. Am. Chem. Soc.* **1983**, *105*, 1221.
[27] a) S. Siegel, S. Coburn, *J. Am. Chem. Soc.* **1951**, *73*, 5494; b) A. Rieche, E. Schmitz, *Chem. Ber.* **1957**, *90*, 1082.
[28] N. A. Milas, *Chem. Rev.* **1932**, *10*, 295.
[29] E. Berl, K. Winnacker, *Z. Physik. Chem.* **1930**, *148*, 261.
[30] K. A. Berryman, A. M. Doherty, J. J. Edmunds, W. C. Patt, M. S. Plummer, J. T. Repine, Warner-Lambert Company, **1993**, WO1995005376A1.
[31] I. L. Witsø, T. Benneche, L. K. Vestby, L. L. Nesse, J. Lönn-Stensrud, A. A. Scheie, *Foodborne Pathog. Dis.* **2014**, *70*, 297.
[32] M. S. Lawless, M. Waldman, R. Franczkiewicz, R. D. Clark in *Using Cheminformatics in Drug Discovery: New Approaches to Drug Discovery*, Springer, Heidelberg, **2016**, Part III, p. 161.
[33] S. Gronowitz, A. B. Hornfeld in *Syntheses, Physical Properties and Reactions of Compounds Containing Thiophene-Oxygen Bonds, The Chemistry of Heterocyclic Compounds, Vol. 44*, Wiley, New York, **2008**, Part I, pp. 2–125.
[34] Selected examples of available building blocks and drugs bearing hydroxythiophene moieties*:* effient (initial metabolite of prasugrel), hydroxytiagabine (human metabolite of tiagabine), methyl 3-hydroxythiophene-2-carboxylate (precursor for tenoxicam).
[35] F. F. Frickel, G. Philipsborn, D. M. Von Claus, L. Dieter (BASF-SE), , **1979**, EP0030688A2.
[36] a) W.-X. Pan, W.-K. Wong, X.-Q. Qiu, F.-W. Lee, *Catal. Lett.* **2004**, *92*, 25; b) Z. M. Heiden, T. B. Rauchfuss, *J. Am. Chem. Soc.* **2007**, *129*, 14303; c) K. Ishiwata, S. Kuwata, T. Ikariya, *J. Am. Chem. Soc.* **2009**, *131*, 5001; d) S. Fukuzumi, T. Kobayashi, T. Suenobu, *J. Am. Chem. Soc.* **2010**, *132*, 11866.
[37] R. L. Augustine *Heterogeneous Catalysis for the Synthetic Chemist*, Marcel Dekker, New York, **1996**.

[38] P. M. O'Neil in *The Chemistry of Peroxides* (Eds.: S. Patai, J. F. Liebman, A. Greer, Z. Rappoport, I. Marek), 1st ed., Wiley, New York, **2006**.
[39] a) W. Nam, H.-J. Han, S.-Y. Oh, Y.-J. Lee, M.-H. Choi, S.-Y. Han, C. Kim, S. K. Woo, W. Shin, *J. Am. Chem. Soc.* **2000**, *122*, 8677; b) K. A. Lee, W. Nam, *J. Am. Chem. Soc.* **1997**, *119*, 1916.
[40] M. Guo, Y.-M. Lee, R. Gupta, M. S. Seo, T. Ohta, H.-H. Wang, H.-Y. Liu, S. N. Dhuri, R. Sarangi, S. Fukuzumi, W. Nam, *J. Am. Chem. Soc.* **2017**, *139*, 15858.
[41] V. Lyaskovskyy, B. de Bruin, *ACS Catal.* **2012**, *2*, 270.
[42] a) B. de Bruin, E. Bill, E. Bothe, T. Weyhermüller, K. Wieghardt, *Inorg. Chem.* **2000**, *39*, 2936; b) P. H. M. Budzelaar, B. de Bruin, A. W. Gal, K. Wieghardt, J. H. van Lenthe, *Inorg. Chem.* **2001**, *40*, 4649; c) K. T. Sylvester, P. J. Chirik, *J. Am. Chem. Soc.* **2009**, *131*, 8772.
[43] a) C. A. Lippert, S. A. Arnstein, C. D. Sherrill, J. D. Soper, *J. Am. Chem. Soc.* **2010**, *132*, 3879; b) P. Chaudhuri, M. Hess, U. Flörke, K. Wieghardt, *Angew. Chem. Int. Ed.* **1998**, *37*, 2217; *Angew. Chem.* **1998**, *110*, 2340.
[44] C. Johnstone, W. J. Kerr, J. S. Scott, *Chem. Commun.* **1996**, 341.
[45] a) W. Panchan, S. Chiampanichayakul, D. L. Snyder, S. Yodbuntung, M. Pohmakotr, V. Reutrakul, T. Jaipetch, C. Kuhakarn, *Tetrahedron* **2010**, *66*, 2732; b) P. S. Kumar, A. Banerjee, S. Baskaran, *Angew. Chem. Int. Ed.* **2010**, *49*, 804; *Angew. Chem.* **2010**, *122*, 816.
[46] a) W. Shaozu, R. Tianhui, Z. Yulan, *Bull. Soc. Chim. Belg.* **2010**, *100*, 357; b) A. Srikrishna, R. Viswajanani, *Tetrahedron* **1995**, *51*, 3339; c) B. Fleming, H. I. Bolker, *Can. J. Chem.* **1974**, *52*, 888.
[47] M. Ross, J. H. Hildebrand, *J. Chem. Phys.* **1964**, *40*, 2397.
[48] At 20 °C the dielectric constants of pure CCl_4 and pure C_6H_6 have very similar values (2.238 and 2.284, respectively).
[49] Dihydrogen can be released from peroxides under thermal conditions: a) R. Czochara, G. Litwinienko, H.-G. Korth, K. U. Ingold, *Angew. Chem. Int. Ed.* **2018**, *57*, 9146; *Angew. Chem.* **2018**, *130*, 9284; b) W. R. Thiel, *Eur. J. Org. Chem.* **2004**, 3108, and references therein. We thank Dr. Joaquim Henrique Teles of BASF for discussion.
[50] a) C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* **2008**, *108*, 2916; b) J. R. Webb, C. Munro-Leighton, A. W. Pierpont, J. T. Gurkin, T. B. Gunnoe, T. R. Cundari, M. Sabat, J. L. Petersen, P. D. Boyle, *Inorg. Chem.* **2011**, *50*, 4195; c) J. S. Thompson, S. L. Randall, J. D. Atwood, *Organometallics* **1991**, *10*, 3906.
[51] G. R. Fulmer, A. N. Herndon, W. Kaminsky, R. A. Kemp, K. I. Goldberg, *J. Am. Chem. Soc.* **2011**, *133*, 17713.
[52] S. M. Jones, E. I. Solomon, *Cell. Mol. Life Sci.* **2015**, *72*, 869.
[53] M. Lucarini, G. F. Pedulli, *Chem. Soc. Rev.* **2010**, *39*, 2106.
[54] a) J. L. Bolland, G. Gee, *Trans. Faraday Soc.* **1946**, *42*, 244; b) C. Engler, W. Wild, *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1669; c) A. Shiroudi, M. S. Deleuze, *Comput. Theor. Chem.* **2015**, *1074*, 26.
[55] a) G. Salomon, *Trans. Faraday Soc.* **1936**, *32*, 153; b) L. R. G. Treloar, *Proc. Phys. Soc. London* **1943**, *55*, 345.

Manuscript received: December 10, 2018
Revised manuscript received: January 16, 2019
Accepted manuscript online: February 4, 2019
Version of record online: March 8, 2019