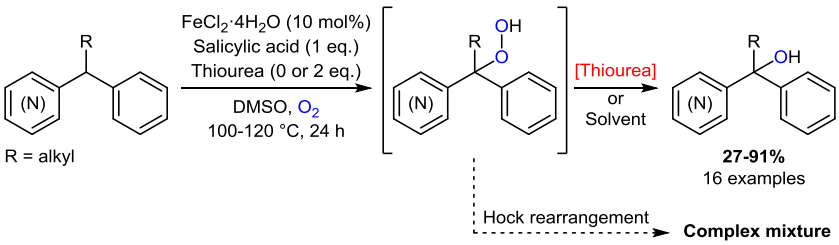
Iron-catalyzed aerobic oxidation of (Alkyl)(aryl)azinylmethanes

Iron Catalyzed Aerobic Oxidation of (Alkyl)(aryl)azinylmethanes

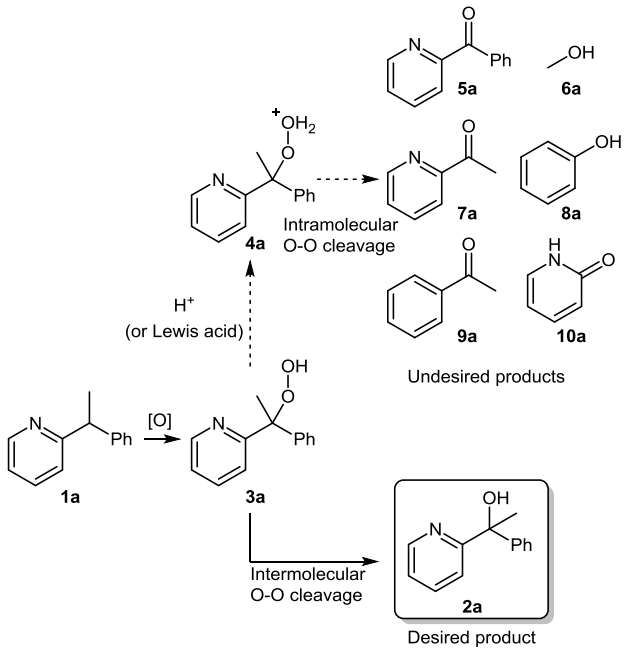
Hans Sterckx, Carlo Sambiagio, Filip Lemière, Kourosch Abbaspour Tehrani, Bert U. W. Maes*

[a] Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium.
bert.maes@uantwerpen.be



Abstract An iron catalyzed aerobic oxidation of (alkyl)(aryl)azinylmethanes has been developed leading to tertiary alcohols in moderate to good yields. Hock rearrangement was identified as a major side reaction leading to a complex mixture of undesired products. Addition of thiourea sometimes allows inhibiting this side reaction and steers the reaction towards the desired products.

Since the turn of the millennium the number of papers in the field of aerobic oxidation has started growing exponentially.[1] This growth can in part be explained by the emergence of green chemistry in the late 1990s which promotes the use of molecular oxygen as a terminal oxidant.[2] Furthermore, the progress in the mechanistic understanding of these oxidation processes has allowed researchers to improve existing and design new catalytic systems,[3] thereby increasing substrate scope and limiting side reactions such as overoxidation and catalyst deactivation.[4] The work of our group[5] in this area has focused on copper- and iron catalyzed oxygenation of benzylic C(sp^3)-H leading to the formation of ketones.[6] In 2012 we reported a base metal catalyzed oxygenation of (aryl)azinylmethanes.[5a] Two years later a similar catalytic system was used by Sekar in the intramolecular direct oxidative C-H amination of 2-benzhydryl(di)azines yielding (di)azino[1,2-*a*]indoles.[7,8] In this oxidase reaction the authors noted the formation of the corresponding triarylmethanol as a side product and adjusted their reaction conditions accordingly to get the alcohol, resulting from oxygenase type reaction, as the sole product. We wondered whether a synthetic protocol could be developed for tertiary methane substrates featuring one alkyl, namely (alkyl)(aryl)azinylmethanes. These substrates are particularly challenging as Hock rearrangement on the intermediate hydroperoxide is expected to be a competitive reaction (Scheme 1, exemplified for **1a**).[9] As three different groups are able to transfer to oxygen in **3a**, several ketones (**5a**, **7a**, **9a**) and alcohols (**6a**, **8a**, **10a**) can be expected if Hock rearrangement occurs.



Scheme 1 Two competitive pathways from tertiary hydroperoxide **3a** *in situ* formed from **1a** and O_2.

The target (alkyl)(aryl)azinylmethanols are interesting reaction products as derivatives of these appear in a number of active pharmaceutical ingredients (APIs) (Figure 1).

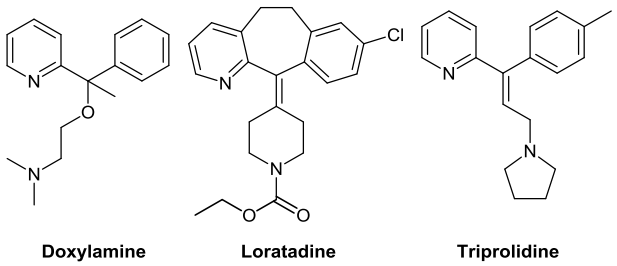
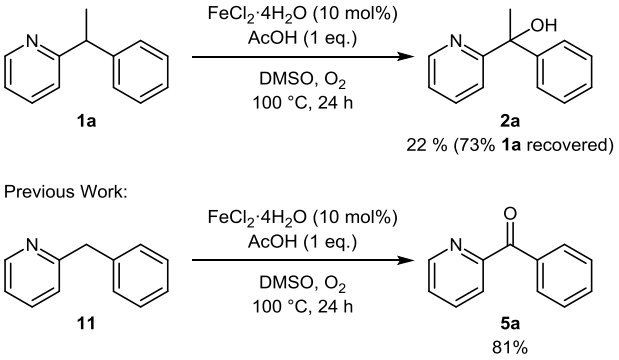


Figure 1 Representative examples of APIs that can be derived from (alkyl)(aryl)azinylmethanols.

As a model substrate 2-(1-phenylethyl)pyridine (**1a**) was chosen. The starting materials can easily be obtained from the corresponding (aryl)azinylmethanes[10] by deprotonation and alkylation using alkyl halides or by cross-coupling[11]. When **1a** was brought under the optimal conditions, previously developed for the oxidation of (aryl)azinylmethanes into the corresponding ketone[5a], 1-phenyl-1-(pyridin-2-yl)ethanol (**2a**) was formed in 22% yield with 73% of starting material recovered (Scheme 2).



Scheme 2 Fe catalyzed aerobic oxidation of **1a** under reaction conditions optimized for **11** (reference 5a).

As we have previously found that the pK_a of the acid additive has a large effect on the overall reaction rate of the methylene oxidation,[5b] a set of benzoic- and salicylic acids were screened. When plotting their respective yields *versus* their pK_a values (Figure 2), a beneficial effect of the acidity on the conversion of the reaction revealed. A maximum is reached around a pK_a of 2.70, which corresponds to salicylic acid (2.77), 4-chlorosalicylic acid (2.71), 4-fluorosalicylic acid (2.85), 5-fluorosalicylic acid (2.70), 5-chlorosalicylic acid (2.59) and 3,5-dinitrobenzoic acid (2.67).[12] When the acidity is increased further the conversion drops again. It should be noted that mass balances for this screening were typically between 70 and 90% indicating that most of the starting material was recovered and not lost due to undesired oxidative side reactions.

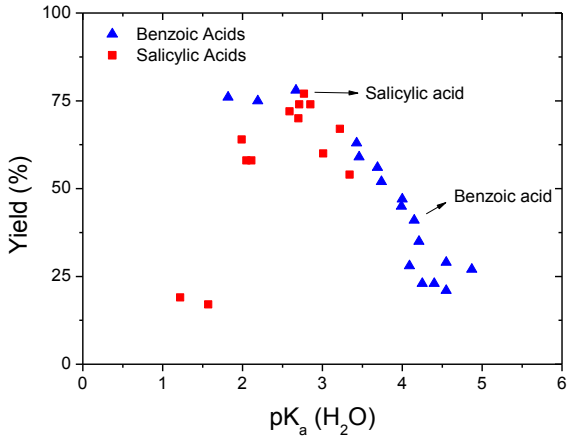
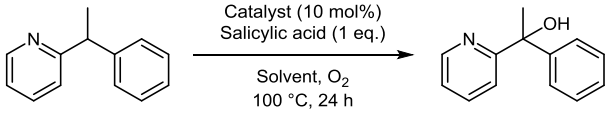


Figure 2 Effect of the pK_a of different benzoic- and salicylic acids on the NMR yield of the aerobic oxidation of **1a**. Conditions used: **1a** (0.5 mmol), Acid (0.5 eq.), $FeCl_2 \cdot 2H_2O$ (10 mol%), O_2 (balloon), DMSO (1 mL), 100 °C, 24 h. 1,3,5-Trimethoxybenzene was used as an internal standard.

Considering price and availability of the different acids, salicylic acid was chosen as the optimal additive. To achieve a reasonable reaction rate, 1 equivalent of acid was used in the reaction. Using these conditions full conversion and 88% yield of **2a** could be achieved in DMSO (Table 1, entry 1). Use of $FeCl_3 \cdot 6H_2O$ as catalyst also provided the product in a yield of 81% (entry 2) showing that the oxidation state of the iron salt added is of less importance as it is likely initially oxidized *in-situ* to Fe^{III}. Remarkably the use of CuI under these conditions resulted in no product whatsoever but instead caused full degradation of the starting material (entry 3). The same was true for $CuCl_2 \cdot 2H_2O$ (entry 4), a catalytic system which was recently found to work very well for the aerobic oxidation of picolines.[4b] Omitting the acid or catalyst does not provide any reaction product proving that both are necessary in this reaction (entries 5 and 6). A small solvent screening revealed DMSO to be the only viable solvent for this reaction as the use of other solvents gave low yields and degradation (*vide infra*) of substrate as less than 10% of starting material could be recovered in all cases (entries 7-10).

Table 1 Catalyst and solvent screening for the aerobic oxidation of **1a**[a]



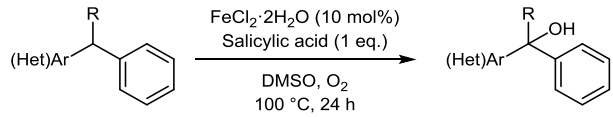
1a **2a**

Entry	Catalyst	Solvent	Yield (%)[b]
1	$FeCl_2{\cdot}4H_2O$	DMSO	88
2	$FeCl_3{\cdot}6H_2O$	DMSO	81
3	CuI	DMSO	Trace
4	$CuCl_2{\cdot}2H_2O$	DMSO	Trace
5	$FeCl_2{\cdot}4H_2O$	DMSO	Trace[c]
6	/	DMSO	Trace
7	$FeCl_2{\cdot}4H_2O$	*n*-BuOAc	30
8	$FeCl_2{\cdot}4H_2O$	*n*-BuOH	22
9	$FeCl_2{\cdot}4H_2O$	Anisole	21
10	$FeCl_2{\cdot}4H_2O$	Toluene	29

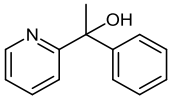
[a] Conditions: **1a** (0.5 mmol), salicylic acid (1 eq.), catalyst (10 mol%), O_2 (balloon), solvent (1 mL), 100 °C, 24 h.
[b] Isolated yield
[c] No salicylic acid was added

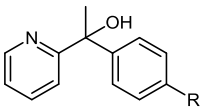
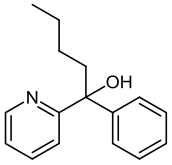
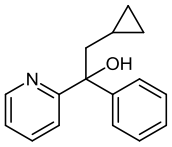
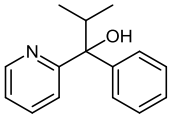
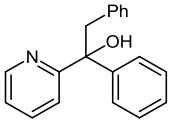
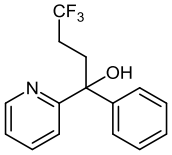
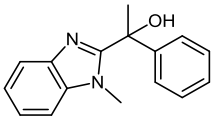
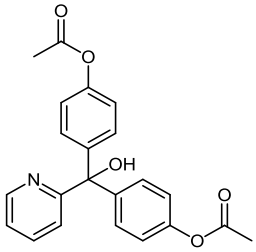
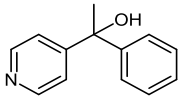
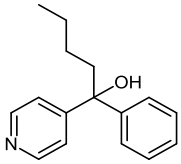
We then investigated the scope of this transformation using the optimal conditions (Table 2). Substrates featuring different electron donating and withdrawing groups on the phenyl ring were screened. No additional oxidation of sulfur was seen when 2-{1-[4-(methylthio)phenyl]ethyl}pyridine (**1b**) was used as substrate (entry 2) but the product could only be isolated in a moderate yield of 47%. Substrate **1c** bearing a *p*-OMe group provided only 27% of alcohol target product (entry 3) and also gave 33% of elimination product 2-[1-(4-methoxyphenyl)vinyl]pyridine (**12c**). Substrates **1d-f** bearing electron withdrawing groups Cl, F, CN gave respectively 91, 88 and 74% of reaction product (entries 4-6), showing that the oxidation reaction works better when electron withdrawing groups are present. The protocol extended quite easily to longer and bulkier alkyl chains (entries 7–11) than methyl although a higher temperature (120 °C) was required to reach full conversion. Interestingly selective oxidation of the tertiary over the secondary benzylic center was observed in the oxidation of 2-(1,2-diphenylethyl)pyridine (**1j**). Adding a trifluoromethyl group to the alkyl chain (**1k**) did not hamper the oxidation (entry 11). Changing the pyridinyl for a benzimidazolyl moiety (**1l**) is also possible and yielded the oxidation product **2l** in 70% yield (entry 12). The API bisacodyl which is used as a laxative drug was easily oxidized to tertiary alcohol **2m** in a good yield of 72% (entry 13).[13] Surprisingly no hydrolysis of the esters was seen under the reaction conditions. As anticipated at the start, competitive decomposition can be an issue. When 4-(1-phenylethyl)pyridine (**1n**), the regioisomer of **1a**, was used (entry 14) the reaction provided only degradation of the starting material and no desired product. 4-Benzoylpyridine (14%) was isolated in this case. Furthermore, LC-MS analysis of the crude reaction mixture confirmed the presence of phenol, acetophenone, 4-acetylpyridine and 4-pyridone, clearly pointing to Hock rearrangement. Using the conditions of Sekar on **1n** also resulted in complete degradation (not shown). This degradation seems to be general for the 4-benzylpyridine substrates as the same problem occurred with 4-(1-phenylpentyl)pyridine (**1o**) (entry 15).

Table 2 Scope of the Fe-catalyzed aerobic oxidation method[a]



1a-o **2a-o**

Entry		Product	Yield (%)[b]
1	**2a**		88

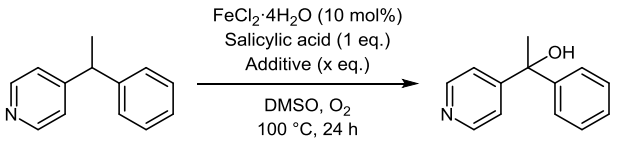
				
2	**2b**	R = SMe		47
3	**2c**	R = OMe		27[d]
4	**2d**	R = Cl		91
5	**2e**	R = F		88
6	**2f**	R = CN		74
7	**2g**			70[c]
8	**2h**			84[c]
9	**2i**			72[c]
10	**2j**			77[c]
11	**2k**			79[c]
12	**2l**			70
13	**2m**			72
14	**2n**			0
15	**2o**			0

[a] Conditions: **1a-o** (0.5 mmol), salicylic acid (1 eq.), $FeCl_2 \cdot 2H_2O$ (10 mol%), O_2 (balloon), DMSO (1 mL), 100 °C, 24 h
[b] Isolated yield
[c] At 120 °C
[d] 33 % of 2-[1-(4-methoxyphenyl)vinyl]pyridine (12c) was also isolated

As both the desired and the Hock rearrangement products form *via* the same hydroperoxide intermediate (**3**), Hock rearrangement initiated by protonation or coordination of Lewis acid will always be a side-reaction of our oxidation protocol (Scheme 1). The yield of the desired product will therefore depend upon the relative rates. To this end we decided to screen additives that could promote O-O bond cleavage in

hydroperoxides intermoleculary in order to steer the process into the desired direction (Table 3). The superiority of DMSO as a solvent for this reaction can be explained by considering such an active role in the O-O bond cleavage through nucleophilic attack of the sulfur, resulting in the formation of dimethylsulfone. Crude ^{1}H-NMR of the reaction mixture does indeed show significant dimethylsulfone formation. It should be noted that this may also arise from the direct oxidation of DMSO with O_2 under the reaction conditions. Hydroperoxides are however known to easily oxidize sulfides to sulfoxides and sulfones supporting our hypothesis.[14] Sulfur based additives therefore seem likely reagents of choice to suppress Hock rearrangement. This screening was performed on 4-(1-phenylethyl)pyridine (**1n**) as this substrate only gave degradation under the standard reaction conditions without additive.

Table 3 Screening of additives on the Fe catalyzed aerobic oxidation of **1n**[a]



1n **2n**

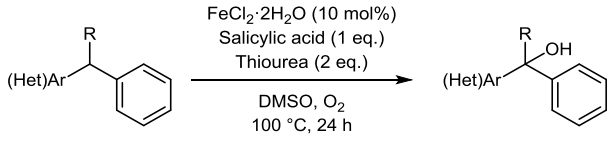
Entry	Additive	Equivalents	Yield (%)[b]	5n (%)[b,c]
1	$Na_2S_2O_3$	1	0[d]	N.D.
2	Na_2SO_3	1	0[d]	N.D.
3	Na_2S	1	15	7
4	Thiosalicylic acid[e]	1	8	11
5	$(Bu)_2S$	1	12	15
6	Thiomorpholine	1	15	6
7	1,3-dithiane	1	15	13
8	NaI	1	23	4
9	Me_2S_2	1	17	29
10	Me_2S_2	co-solvent[f]	(46)	18
11	Me_2S_2	solvent	(72)	10
12	Thiourea	1	54 (48)	8
13	Thiourea	2	75 (63)	7
14	Me_4-thiourea	1	14	22

[a] Conditions: **1n** (0.5 mmol), salicylic Acid (1 eq.), additive (x eq.), $FeCl_2 \cdot 2H_2O$ (10 mol%), O_2 (balloon), DMSO (1 mL), 100 °C, 24 h
[b] NMR yield using 1,3,5-trimethoxybenzene as internal standard, isolated yield between brackets
[c] **5n** = 4-benzoylpyridine
[d] at 120°C
[e] No salicylic acid was added
[f] 0.5 mL Me2S2:0.5 mL DMSO

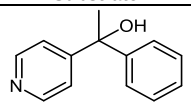
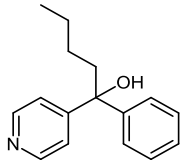
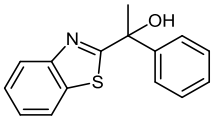
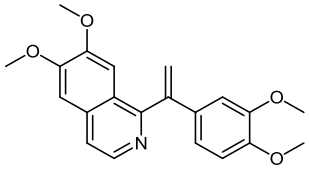
While known peroxide quenchers such as $Na_2S_2O_3$ and Na_2SO_3 failed to give any desired product (entries 1 and 2), we had more success with Na_2S which gave 15% of **2n** (entry 3). Replacing salicylic acid with thiosalicylic acid, which could potentially fulfill the role of both acid additive and O-O cleavage reagent, gave a disappointing yield of 8% (entry 4). Addition of thioethers such as dibutylsulfide (entry 5) or thiomorpholine (entry 6) and the dithioacetal, 1,3-dithiane (entry 7) resulted in comparable yields (12-15%) as for Na_2S. Sodium iodide worked slightly better giving 23% of **2n** (entry 8). Dimethyldisulfide (DMDS) is an interesting reagent as it occurs naturally in certain foods (Cabbage, Brussels sprouts, onions, garlic) and can also be used as a solvent. The addition of 1 equivalent of DMDS only provided the product in 17% yield (entry 9), adding it as a co-solvent or using it as solvent however, provided the product in 46% (entry 10) and 72% (entry 11) isolated yield, respectively. Finally, thiourea proved to be the best reagent and provided the product in 48% isolated yield when adding 1 equivalent (entry 12) or in 63% when adding 2 equivalents (entry 13).[15] The presence of the free N-H bonds in thiourea proved to be important as *N*,*N*,*N*',*N*'-tetramethyl thiourea provided only 14% of product (entry 14). The altered conditions were applied to a set of difficult substrates to further broaden the scope of the reaction (Table 4). While the addition of 2 equivalents of thiourea inhibited Hock rearrangement for substrate **1n** and provided the product in 63% yield (entry 1), it proved ineffective when applied to **1o** (entry 2). For this substrate the Hock

rearrangement is likely too fast relative to the desired reaction. For 2-(1-phenylethyl)benzo[*d*]thiazole (**1p**) the addition of thiourea greatly improved the selectivity and yielded the desired product **2p** in 74% yield (entry 3) as well as 19% of Hock degradation product benzo[*d*]thiazol-2(3*H*)-one (**10p**). When the thiourea was omitted only 24% of **2p** and 33% of **10p** were isolated. In the case of **1q**, a papaverine analog, the oxidation reaction was followed by spontaneous elimination of water and yielded alkene **12q** in 54% yield. Without the addition of thiourea 16% of alkene **12q** and 38% of alcohol was isolated.

Table 4 Scope of the Fe catalyzed aerobic oxidation using thiourea additive[a]

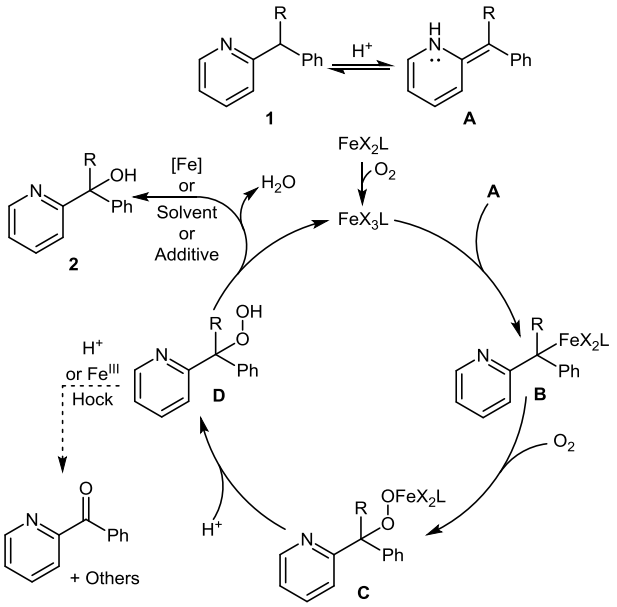


1n-q **2n-q**

Entry		Substrate	Yield (%)[b]
1	**2n**		63
2	**2o**		0
3	**2p**		74[c]
4	**12q**		54

[a] Conditions: **1n-q** (0.5 mmol), salicylic Acid (1 eq.), thiourea (2 eq.), $FeCl_2 \cdot 2H_2O$ (10 mol%), O_2 (balloon), DMSO (1 mL), 100 °C, 24 h
[b] Isolated yield
[c] 19 % of benzo[d]thiazol-2(3H)-one (**10p**) was isolated

The mechanism of the Cu-catalyzed benzylic oxygenation of (aryl)azinylmethanes with oxygen has been previously reported by our group.[3a] While that reaction involved the formation of ketones instead of tertiary alcohols, the same mechanistic principles can be applied in this case as the reaction also requires acid. A simplified mechanism is proposed in Scheme 3. The first step is the acid catalyzed imine-enamine tautomerization of **1** into **A**. The pK_a of the acid catalyst is of great importance to achieve a decent reaction rate (*vide supra*). Enamine species **A** is able to attack an electrophilic Fe^{III}-species, generated *in-situ* through reaction of O_2 with $FeCl_2$, resulting in the formation of species **B**. Species **B** will in turn undergo insertion of O_2 forming intermediate **C**. Protonation of this intermediate leads to the organic hydroperoxide **D** which can undergo the desired process of O-O bond cleavage leading to the product **2**. The actual O-O bond cleavage can be transition metal catalyzed or can be mediated by the solvent or the additive.[15] Alternatively, protonation of, or coordination with Fe^{III}, of hydroperoxide **D** can trigger a Hock rearrangement (Scheme 2) leading to several undesired ketone and alcohol compounds.



Scheme 3 Proposed mechanism of the Fe catalyzed aerobic oxidation of **1a**

In conclusion, we have developed an iron catalyzed aerobic oxidation of tertiary benzylic centers leading to tertiary alcohols. The study of the substrate scope revealed that Hock rearrangement is often a competitive process leading to a complex mixture of undesired products. Both the desired and undesired products result from a common intermediate hydroperoxide. A screening of additives showed that the addition of 2 equivalents of thiourea can often steer the reaction towards the desired products by promoting inter- versus intramolecular O-O cleavage.

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(16) **Typical procedure for Fe catalyzed aerobic C-H oxygenation of 1a:**

A 10 mL vial was charged with $FeCl_2 \cdot 4H_2O$ (9.94 mg, 0.050 mmol), 2-(1-phenylethyl)pyridine (**1a**) (0.092 g, 0.5 mmol), salicylic acid (0.069 g, 0.500 mmol) and 1 mL of DMSO. The vial was flushed for 10 seconds with O_2, capped with an aluminum crimp cap with septum and stirred at 100 °C for 24 hours with an O_2 balloon through the septum. After cooling down to room temperature, the content of the vial was transferred into a separation funnel and the vial was rinsed with dichloromethane (20 mL). Aq. saturated $NaHCO_3$ (10 mL) was added and the organic phase was separated. The aqueous phase was extracted twice with dichloromethane (10 mL). The combined organic fractions were washed with brine (20 mL), dried on $MgSO_4$ and filtered. Further purification was achieved by automated column chromatography (Heptane/EtOAc) to give 1-phenyl-1-(pyridin-2-yl)ethanol (**2a**) in 88% yield.

Characterization data for 2a

HRMS (ESI) for $C_{13}H_{14}NO$ $[M+H]^+$, calcd 200.1070, found 200.1080; Colourless oil; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H: 8.51 (d, 1H, *J* = 4.6 Hz), 7.62 (dt, 1H, *J* = 7.8, 1.4 Hz), 7.47 (d, 2H, *J* = 7.4 Hz), 7.34-7.25 (m , 3H), 7.25-7.11 (m, 2H), 5.80 (s, 1H), 1.92 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ_C: 164.8 [C], 147.4 [CH], 147.2 [C], 136.9 [CH], 128.2 [CH], 127.0 [CH], 125.9 [CH], 122.0 [CH], 120.3 [CH], 75.1 [C], 29.3 [CH_3].

Characterization data for 2m

HRMS (ESI) for $C_{22}H_{20}NO_5$ $[M+H]^+$, calcd 378.1336, found 378.1342; Colourless viscous oil; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H: 8.58 (d, 1H, *J* = 4.5 Hz), 7.65 (dt, 1H, *J* = 7.7, 1.3 Hz), 7.29 (d, 4H, *J* = 8.6 Hz), 7.26-7.21 (m, 1H), 7.12 (d, 1H, *J* = 7.9 Hz), 7.02 (d, 4H, *J* = 8.6 Hz), 6.29 (bs, 1H), 2.28 (s, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ_C: 169.3 [C], 162.7 [C], 150.0 [C], 147.8 [CH], 143.4 [C], 136.6 [CH], 129.3 [CH], 122.9 [CH], 122.6 [CH], 121.0 [CH], 80.2 [C], 21.2 [CH_3].