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Cite this: *Chem. Sci.*, 2017, 8, 1282

Co/NHPI-mediated aerobic oxygenation of benzylic C–H bonds in pharmaceutically relevant molecules†

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A simple cobalt(II)/*N*-hydroxyphthalimide catalyst system has been identified for selective conversion of benzylic methylene groups in pharmaceutically relevant (hetero)arenes to the corresponding (hetero)aryl ketones. The radical reaction pathway tolerates electronically diverse benzylic C–H bonds, contrasting recent oxygenation reactions that are initiated by deprotonation of a benzylic C–H bond. The reactions proceed under practical reaction conditions (1 M substrate in BuOAc or EtOAc solvent, 12 h, 90–100 °C), and they tolerate common heterocycles, such as pyridines and imidazoles. A cobalt-free, electrochemical, NHPI-catalyzed oxygenation method overcomes challenges encountered with chelating substrates that inhibit the chemical reaction. The utility of the aerobic oxidation method is showcased in the multigram synthesis of a key intermediate towards a drug candidate (AMG 579) under process-relevant reaction conditions.

Received 26th August 2016
Accepted 6th October 2016

DOI: 10.1039/c6sc03831j

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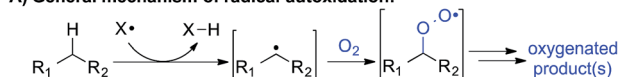
Introduction

Liquid-phase radical-chain autoxidation reactions are amongst the largest-scale oxidation reactions performed in industry (Scheme 1).¹ Prominent examples include the Co/Mn/Br-

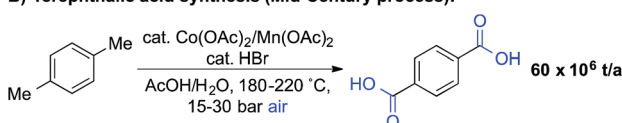
catalyzed oxidation of *p*-xylene to terephthalic acid in variations of the Mid-Century process (Scheme 1B),² autoxidation of cumene *en route* to phenol and acetone in the Hock process (Scheme 1C)³ and radical-chain autoxidation of cyclohexane to a mixture of cyclohexanone and cyclohexanol ("KA oil", Scheme 1D).⁴ In contrast to these prominent large-scale applications, aerobic oxidations and radical autoxidation reactions, in particular, are rarely used for the production of pharmaceuticals or related complex molecules.

A number of groups have recently reported methods for aerobic oxygenation of benzylic C–H bonds^{5,6} (Scheme 2A). The reactions are often compatible with heterocycles and other heteroatom-containing functional groups, suggesting they could be well suited for use in pharmaceutical applications.

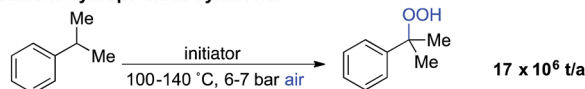
A) General mechanism of radical autoxidation:



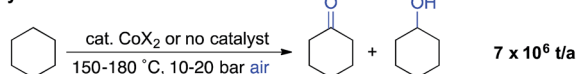
B) Terephthalic acid synthesis (Mid-Century process):



C) Cumene hydroperoxide synthesis:

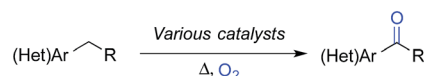


D) Cyclohexane oxidation to KA oil:

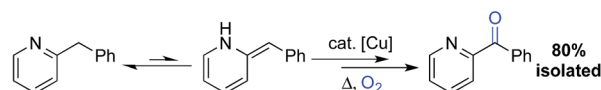


Scheme 1 Summary of major industrial radical autoxidation processes.

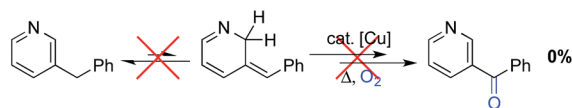
A) Aerobic benzylic oxygenations



B) Implications of heterolytic C–H cleavage pathway (cf. Maes, ref. 4e):



2-benzylpyridine: Imine-enamine tautomerization precedes oxygenation



3-benzylpyridine: Tautomerization inaccessible

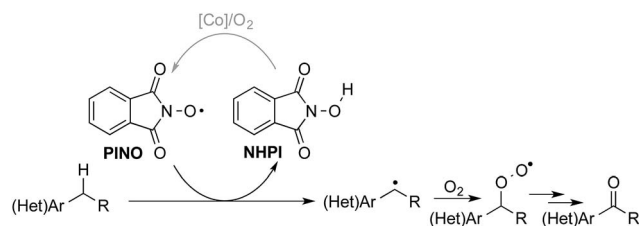
Scheme 2 Recent work on aerobic benzylic oxygenation.

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† Electronic supplementary information (ESI) available: Screening data, experimental protocols, characterization data. See DOI: 10.1039/c6sc03831j





Scheme 3 Simplified mechanism depicting C–H abstraction by phthalimido-*N*-oxyl (PINO) and radical oxygenation by O₂.

Further studies have shown that heterocycles can play an important role in promoting the reaction by facilitating formation of an enamine or related tautomer that is more susceptible to aerobic oxygenation (Scheme 2B).⁷ In a representative example, Maes and coworkers developed a copper-catalysed oxygenation method, in which they contrasted successful oxygenation of 2- and 4-benzylpyridine with the poor reactivity of 3-benzylpyridine.^{6e} A subsequent mechanistic study provided evidence for a heterolytic C–H cleavage pathway and the involvement of the benzylpyridine enamine tautomer (Scheme 2B).^{6f}

The “heterolytic” C–H oxygenation reactions show broad synthetic appeal, but the mechanism limits their utility to substrates with relatively acidic benzylic C–H bonds. In this context, we sought an alternative method that could bypass this limitation, and our attention was drawn to the *N*-hydroxyphthalimide (NHPI)-based C–H oxygenation reactions.⁸ In the 1990s, Ishii and coworkers showed that use of redox-active metal salts, such as Co(OAc)₂, in combination with O₂ enable efficient conversion of NHPI into the phthalimido-*N*-oxyl (PINO) radical.⁹ PINO then mediates selective abstraction of weak C–H bonds (Scheme 3) to generate an organic radical that can react with O₂ to afford the oxygenated products.¹⁰ This methodology has been demonstrated in numerous oxidation reactions, including industrial applications,⁸ but the vast majority of studies have focused on simple hydrocarbon substrates.¹¹

Here, we explore Co/NHPI-catalyzed benzylic¹² oxygenation reactions of substrates bearing common heterocycles, such as pyridines, benzimidazoles and thiophenes, and benzylic ketones are often obtained in good-to-excellent yield. Notably, the radical autoxidation pathway enables oxygenation of non-acidic substrates that are ineffective with catalyst systems that mediate oxygenation *via* a heterolytic pathway. For reactions that appear to be inhibited by heterocycle chelation to the Co co-catalyst, we show that a Co-free, electrochemical NHPI-mediated method offers a promising alternative approach. Finally, we demonstrate the practicality and scalability of the Co/NHPI catalytic conditions in the multigram synthesis of a pharmaceutical intermediate.

Results and discussion

We began our studies by evaluating the oxygenation of 3-ethylpyridine (**1a**) to 3-acetylpyridine (**2a**) (Table 1). This reaction is expected to be problematic for many of the recently reported oxygenation methods. First, we used Co(OAc)₂ as the cobalt source and compared solvents that have been considered previously in Ishii-type oxidation reactions (entries 1–4).¹³ A

Table 1 Optimization of reaction conditions^a

Entry	CoX ₂	Solvent	Temp (°C)	Conv. ^b (%)	Yield ^b (%)
1	Co(OAc) ₂ ·4H ₂ O	EtOAc	70	60	59
2	—	EtOAc	70	<1	<1
3	Co(OAc) ₂ ·4H ₂ O	MeCN	70	50	45
4	Co(OAc) ₂ ·4H ₂ O	AcOH	70	35	30
5	Co(OAc) ₂ ·4H ₂ O	BuOAc	70	61	59
6	Co(NO ₃) ₂ ·6H ₂ O	BuOAc	70	35	35
7	Co(acac) ₃	BuOAc	70	<1	<1
8	CoCl ₂ ·6H ₂ O	BuOAc	70	14	14
9	Co(OAc) ₂ ·4H ₂ O	BuOAc	80	95	89
10	Co(OAc)₂·4H₂O	BuOAc	90	99	94

^a 1 mmol scale, orbital mixing. ^b GC yields with benzonitrile as an internal standard.

superior yield was obtained using EtOAc (entry 1), and a similar yield was obtained with the higher boiling ester solvent, *n*-BuOAc (entry 5). The identity of the counterion in the CoX₂ co-catalyst had a marked effect on catalytic efficiency (entries 5–10). The best yields were obtained with Co(OAc)₂·4H₂O and other Co^{II}-carboxylate salts (see Tables S1 and S2 in the ESI† for full screening data). Use of BuOAc solvent enabled access to higher reaction temperatures (entries 9 and 10), and an excellent yield of **2a** was achieved at 90 °C (94%, entry 10).

A comparison of the optimized Co/NHPI reaction conditions with previously reported benzylic oxygenation methods in

Table 2 Comparison of catalyst systems^a

Entry	Catalyst system	Ref.	Conv. ^b (%)	Yield ^b (%)
1	Co/Br ^c	14	51	19
2	Co/Mn/Br ^d	14	20	<1
3	CuI, 1 eq. AcOH ^e	6e	5	<1
4	FeCl ₂ ·4H ₂ O, 1 eq. AcOH ^f	6e	7	<1
5	Co/NHPI^g	This work	99	94

^a 1 mmol scale, orbital mixing. ^b GC yields with benzonitrile as an internal standard. ^c 1 mmol **1a**, 1 mL AcOH, 10 mol% Co(OAc)₂·4H₂O, 10 mol% HBr, 12 h, 100 °C. ^d 1 mmol **1a**, 1 mL AcOH, 5 mol% Co(OAc)₂·4H₂O, 5 mol% Mn(OAc)₂·4H₂O, 10 mol% HBr, 12 h, 100 °C. ^e 0.5 mmol **1a**, 1 mL DMSO, 10 mol% CuI, 1 eq. AcOH, 1 atm O₂, 24 h, 100 °C. ^f 0.5 mmol **1a**, 1 mL DMSO, 10 mol% FeCl₂·4H₂O, 1 eq. AcOH, 24 h, 100 °C. ^g 1 mmol **1a**, 1 mL BuOAc, 1 mol% Co(OAc)₂·4H₂O, 20 mol% NHPI, 12 h, 90 °C.



Table 2 highlights the potential utility of the new conditions. Poor yields and mass balances were obtained using two Mid-Century-type radical autoxidation methods (entries 1 and 2),¹⁴ in which a bromine radical is proposed to participate in the H-atom abstraction step. We also tested representative catalyst systems^{6c} for “heterolytic” aerobic C–H oxygenation, corresponding to the methods noted in Scheme 2. As expected from the precedents, 3-ethylpyridine **1a** is not a viable substrate with these catalyst systems (entries 3 and 4).¹⁵

The optimized reaction conditions were then tested for aerobic oxygenation of a number of pharmaceutically relevant (hetero)arene substrates (Table 3).¹⁶ In general, pyridines are well tolerated, with good-to-excellent yields obtained for products **2a–f**. This collection of substrates includes 3-substituted pyridine derivatives (**1a**, **1c**, **1f**), which are ineffective with heterolytic C–H oxygenation methods, as well as 2- and 4-substituted pyridines, which are compatible with the heterolytic methods. Excellent yields were obtained for the benzimidazole derivatives **1g** and **1h**. Ethylbenzene derivatives bearing remote heteroatom-containing functional groups, including a pyridyl, an imidazole and an acetamide group (**1i**, **1j** and **1k**), also underwent successful oxygenation.

The standard reaction conditions in Table 3 proved to be ineffective for certain substrates,¹⁷ and two different approaches were identified to address some of these limitations. In the first case, the simple hydrocarbon, *n*-butylbenzene (**1l**) (Table 4), as well as the sulphur-containing heterocyclic substrates **1m**, **1n** and **1o** (Table 5) led to poor results (42%, 3%, 7% and 31% yields, respectively). In the reaction of **1l**, benzoic acid was observed as the major side product, arising from cleavage of the alkyl chain. Subsequent empirical studies showed that use of pyridine as a co-solvent attenuated this alkyl chain cleavage and enabled higher yields and mass balance in the oxygenation of **1l**. The optimal 7 : 3 BuOAc : pyr solvent mixture (77% yield of

Table 4 Enhanced selectivity for formation of **2l** in the presence of pyridine cosolvent^a

Entry	Vol% pyr	Conv. ^b (%)	Yield ^b (%)
1	0	>99	42
2	10	98	74
3	20	95	76
4	30	90	77
5	40	84	73
6	50	74	66

^a 1 mmol scale, orbital mixing. ^b GC yields with benzonitrile as an internal standard.

2l, entry 4) proved to be similarly beneficial for the oxygenation of the sulphur-heterocycle substrates **1m**, **1n** and **1o**, as well as the *N*-methylated benzimidazole **1p** (Table 5).¹⁸ The latter substrates underwent oxygenation in 65%, 50%, 72% and 94% yields, respectively. The reactions with pyridine co-solvent have a dark red color, consistent with pyridine coordination to cobalt.¹⁹ We speculate that this coordination might attenuate unproductive cobalt-mediated side reactions in these substrates.

The second case involved 2-ethylpyridine (**1q**) and 2-ethylbenzimidazole (**1r**), in which the benzylic C–H bonds of the ethyl substituent is directly adjacent to a coordinating group. Under the standard conditions, the benzylic ketones **2q** and **2r** were obtained in only 48% and 15% yields, respectively (Scheme 4A). This poor reactivity contrasts the good reactivity observed with analogous doubly benzylic substrates **1b**, **1g** and **1h** in Table 3. We hypothesized that, in these reactions, the product could chelate the cobalt co-catalyst and inhibit further product formation. To test this hypothesis, we investigated the reaction of an effective substrate, 4-ethylpyridine **1e**, in the presence and absence of 4-acetylpyridine **2e** or 2-acetylpyridine **2q**

Table 3 Oxygenation of polar (hetero)arenes^a

2a 84%	2b 93%	2c 92%	2d 89%
2e 56%	2f 60%	2g , R = H 94%	2h , R = OMe 92%
2i 87%	2j 66%	2k 74%	

^a 1 mmol scale, isolated yields.

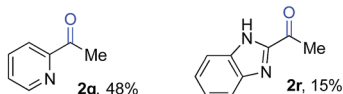
Table 5 Use of pyridine co-solvent for improved selectivity^a

2m 65% (65%) w/o pyr 3%	2n 50% (48%) w/o pyr 7%
2o 72% (64%) w/o pyr 31%	2p 94% (80%) w/o pyr 58%

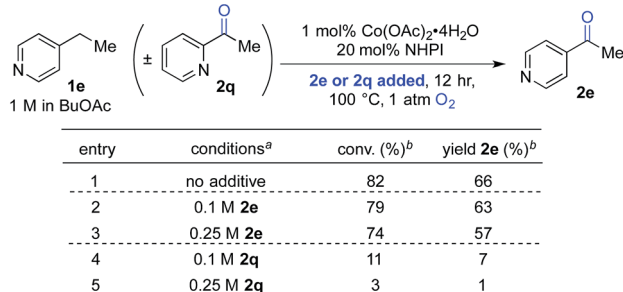
^a 1 mmol scale. Yields were determined by ¹H NMR spectroscopy. Isolated yields in parentheses.



A) Results under standard conditions (cf. Table 3)



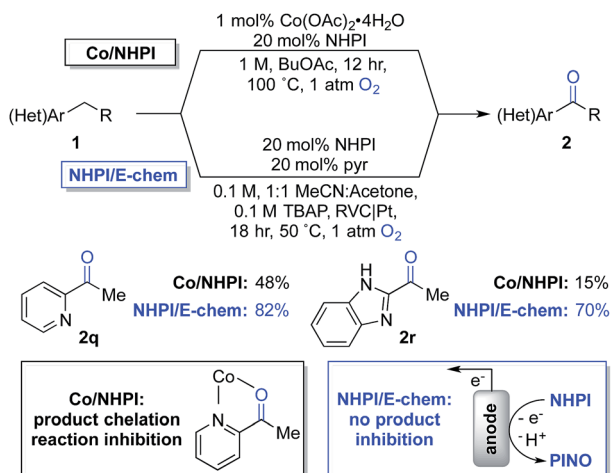
B) Product inhibition studies



Scheme 4 Product-inhibition studies in Co/NHPI-catalyzed oxygenation. ^a1 mmol scale, orbital mixing. ^bGC yields with chlorobenzene as an internal standard.

(Scheme 4B). The results show that 2e has minimal impact on the reaction (Scheme 4B, entries 1–3), whereas the presence of 2q significantly lowers the yield in the oxygenation of 1e (Scheme 4B, entries 1, 4 and 5).

The observations in Scheme 4 prompted us to consider cobalt-free electrochemical aerobic oxygenation reactions, originally reported by Masui and coworkers in the 1980s.^{20,21} These methods generate PINO *via* electrochemical oxidation of NHPI (*i.e.*, in the absence of cobalt ions) and, therefore, should not be susceptible to chelate-inhibition by the product. Preliminary studies validated this hypothesis. Optimization of Masui's reported electrochemical conditions with 1q and 1r enabled formation of the ketone products 2q and 2r in 82% and 70% yields, respectively. These results represent substantial improvements over those obtained with the chemical conditions (Scheme 5). Further studies will be needed to explore the full scope and limitations of the electrochemical method.

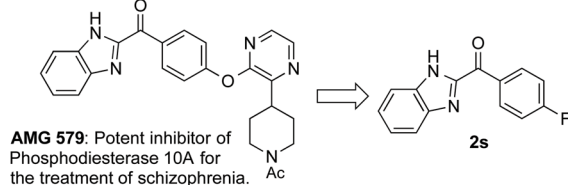


Scheme 5 Overcoming a limitation in Co/NHPI chemistry through the electrochemical generation of PINO.

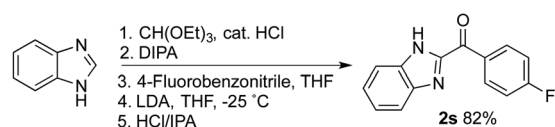
Preliminary studies with other substrates (*e.g.*, with 1b and 1g) suggest that the chemical conditions will be superior to the electrochemical conditions in other cases. These observations together with the ease of reaction set up and performance of the Co/NHPI/O₂ oxygenations suggest that the aerobic reactions will be advantageous in most cases. Nonetheless, the results with the oxygenation of 1q and 1r demonstrate that electrochemical NHPI-mediated reactions could be a valuable complement to Co/NHPI reactions in strategic situations.

The standard Co/NHPI/O₂ conditions developed here exhibit a number of features that are appealing from a process chemistry perspective, including a low cobalt catalyst loading and a high reaction concentration, which minimizes solvent volume. The relatively high NHPI loading (20 mol%) is offset by its extraordinarily low cost (<\$5 per kg on commercial scale). In an effort to demonstrate the potential utility of this method for larger-scale applications, we targeted a streamlined route to the heterocyclic ketone 2s (Scheme 6A), an intermediate *en route* to AMG 579.²² The latter compound is a clinical candidate for the treatment of neurological conditions such as schizophrenia and Huntington's disease. The reported multi-step route to 2s is effective, but it is operationally complex and requires careful

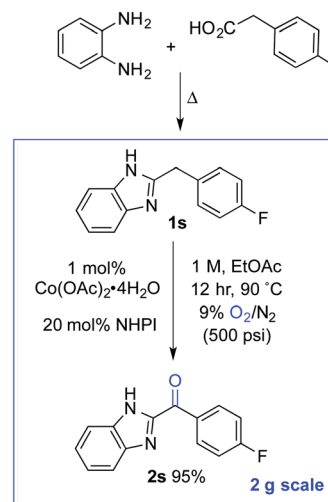
A) Retrosynthesis of AMG 579



B) Amgen process route to access the ketone 2s



C) Co/NHPI oxygenation route to 2s



Scheme 6 Streamlined synthetic route toward AMG 579 *via* Co/NHPI-catalyzed benzylic oxygenation.

control of reaction temperature during the deprotonation and addition (Scheme 6B).²³ We envisioned an alternative, two-step route to **2s**, starting from the inexpensive, commercially available precursors *o*-phenylene diamine and 4-fluorophenylacetic acid (Scheme 6C). The Co/NHPI-catalyzed oxygenation of **1s** was performed in EtOAc (1 M) with 500 psi of 9% O₂ in N₂ to maintain the O₂ concentration below the limiting oxygen concentration (LOC) of EtOAc.²⁴ Operation of this reaction on 2 g scale resulted in near quantitative isolated yield of **2r** (95%).

This route to **2s** incorporates a number established green chemistry principles:²⁵ (i) waste prevention due to high volumetric efficiency, (ii) atom economy due to use of O₂ as both the terminal oxidant and oxygen atom source, (iii) use of an environmentally benign ester solvent,²⁶ (iv) use of an earth-abundant metal catalyst, (v) application of practical reaction conditions with respect to temperature and pressure, as well as (vi) application of inherently safe reaction conditions (*i.e.*, below the LOC of EtOAc). Although more thorough analysis would be required to compare the overall process viability of the two routes, the two-step condensation/oxidation sequence in Scheme 6C should have a much smaller environmental footprint, owing to the formation of water as a only stoichiometric by-product in each of the two reactions.²⁷ Reflecting this feature, the route in Scheme 6B has an estimated *E*-factor of >15, while the two-step condensation/oxidation sequence can be <5.²⁸

Conclusions

The results described herein show that Co/NHPI-catalyzed, radical-mediated, benzylic aerobic oxygenation reactions are quite effective with pharmaceutically relevant heterocyclic substrates. The comparatively non-polar nature of the H-atom transfer step mediated by PINO plays an important role in expanding the scope of aerobic benzylic oxygenation to substrates that are ineffective with complementary heterolytic oxygenation methods.^{5,6} The chemistry and reaction conditions identified herein are sufficiently practical that these methods could be compelling for large-scale application. In addition to the low *E*-factors associated with these reactions, the homogeneous reaction conditions (*i.e.*, lacking solid reagents or additives) suggest that they are excellent candidates for continuous-flow applications.²⁹ This opportunity warrants attention in future studies.

Acknowledgements

Financial support was provided by the NIH (F32GM113399, D. P. H.), the DOE (DE-FG02-05ER15690, S. S. S.), and Merck Research Laboratories–Rahway (K. C. M., electrochemical studies). Spectroscopic instrumentation was partially supported by the NIH (S10 OD020022) and the NSF (CHE-1048642).

Notes and references

- 1 H. J. Teles, I. Hermans, H. G. Franz and R. A. Sheldon, Oxidation in *Ullmann's Encyclopedia of Industrial Chemistry, Electronic Release*, Wiley-VCH, Weinheim, 2015.

- 2 (a) W. Partenheimer, *Catal. Today*, 1995, **23**, 69; (b) R. A. F. Tomas, J. C. M. Bordado and J. F. P. Gomes, *Chem. Rev.*, 2013, **113**, 7421; (c) V. A. Adamian and W. H. Gong in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives*, ed. S. S. Stahl and P. L. Alsters, Wiley-VCH, Weinheim, 2016, pp. 41–66.
- 3 M. Weber, M. Weber and M. Kleine-Boymann, Phenol in *Ullmann's Encyclopedia of Industrial Chemistry, Electronic Release*, Wiley-VCH, 2004.
- 4 M. T. Musser, Cyclohexanol and Cyclohexanone in *Ullmann's Encyclopedia of Industrial Chemistry, Electronic Release*, Wiley-VCH, 2011.
- 5 For metal-free conditions: (a) K. K. Park, L. K. Tsou and A. D. Hamilton, *Synthesis*, 2006, 3617; (b) C. Qi, H. Jiang, L. Huang, Z. Chen and H. Chen, *Synthesis*, 2011, 387; (c) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Tetrahedron*, 2012, **68**, 5258; (d) A. Dos Santos, L. El Kaim and L. Grimaud, *Org. Biomol. Chem.*, 2013, **11**, 3282; (e) L. Ren, L. Wang, Y. Lv, G. Li and S. Gao, *Org. Lett.*, 2015, **17**, 2078; (f) K. Bao, F. Li, H. Liu, Z. Wang, Q. Shen, J. Wang and W. Zhang, *Sci. Rep.*, 2015, **5**, 10360.
- 6 For metal-catalyzed examples: (a) F. M. Moghaddam, Z. Mirjafary, H. Saeidian and M. J. Javan, *Synlett*, 2008, 892; (b) X. Fan, Y. He, X. Zhang, S. Guo and Y. Wang, *Tetrahedron*, 2011, **67**, 6369; (c) X. Fan, Y. He, Y. Wang, Z. Xue, X. Zhang and J. Wang, *Tetrahedron Lett.*, 2011, **52**, 899; (d) Y.-F. Wang, F.-L. Zhang and S. Chiba, *Synthesis*, 2012, **44**, 1526; (e) J. De Houwer, K. Abbaspour Tehrani and B. U. W. Maes, *Angew. Chem., Int. Ed.*, 2012, **51**, 2745; (f) C. Menendez, S. Gau, S. Ladeira, C. Lherbet and M. Baltas, *Eur. J. Org. Chem.*, 2012, 409; (g) B. Pieber and C. O. Kappe, *Green Chem.*, 2013, **15**, 320; (h) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti and R. Verdiglione, *Synthesis*, 2013, **45**, 1701; (i) Y. Jeong, Y. Moon and S. Hong, *Org. Lett.*, 2015, **17**, 3252; (j) J.-W. Yu, S. Mao and Y.-Q. Wang, *Tetrahedron Lett.*, 2015, **56**, 1575; (k) G. Zheng, H. Liu and M. Wang, *Chin. J. Chem.*, 2016, **34**, 519; (l) H. Sterckx, J. De Houwer, C. Mensch, I. Caretti, K. A. Tehrani, W. A. Herrebout, S. Van Doorslaer and B. U. W. Maes, *Chem. Sci.*, 2016, **7**, 346; (m) H. Sterckx, J. De Houwer, C. Mensch, W. Herrebout, K. A. Tehrani and B. U. W. Maes, *Beilstein J. Org. Chem.*, 2016, **12**, 144; (n) Q. Li, Y. Huang, T. Chen, Y. Zhou, Q. Xu, S.-F. Yin and L.-B. Han, *Org. Lett.*, 2014, **16**, 3672; (o) Y. Huang, T. Chen, Q. Li, Y. Zhou and S.-F. Yin, *Org. Biomol. Chem.*, 2015, **13**, 7289; (p) M. Liu, T. Chen and S.-F. Yin, *Catal. Sci. Technol.*, 2016, **6**, 690; (q) H. Xie, Y. Liao, S. Chen, Y. Chen and G.-J. Deng, *Org. Biomol. Chem.*, 2015, **13**, 6944; (r) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 11088; (s) Z. Xu, C. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 11367; (t) C. Zhang, L. Zhang and N. Jiao, *Adv. Synth. Catal.*, 2012, **354**, 1293.
- 7 This pathway is analogous to aerobic oxygenation reactions adjacent to carbonyl groups. For examples, see: (a) F.-T. Du and J.-X. Ji, *Chem. Sci.*, 2012, **3**, 460; (b) X. Xu, W. Ding, Y. Lin and Q. Song, *Org. Lett.*, 2015, **17**, 516; (c) X. Huang,



- X. Li, M. Zou, J. Pan and N. Jiao, *Org. Chem. Front.*, 2015, **2**, 354; (d) H. Cheng and C. Bolm, *Synlett*, 2016, **27**, 769.
- 8 (a) Y. Ishii, S. Sakaguchi and T. Iwahama, *Adv. Synth. Catal.*, 2001, **343**, 393; (b) F. Recupero and C. Punta, *Chem. Rev.*, 2007, **107**, 3800; (c) L. Melone and C. Punta in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives*, ed. S. S. Stahl and P. L. Alsters, Wiley-VCH, Weinheim, 2016, pp. 253–266.
- 9 (a) Y. Ishii, T. Iwahama, S. Sakaguchi, K. Nakayama and Y. Nishiyama, *J. Org. Chem.*, 1996, **61**, 4520; (b) Y. Yoshino, Y. Hayashi, T. Iwahama, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 1997, **62**, 6810.
- 10 For detailed discussion of the mechanism of aerobic Co/NHPI oxygenations, see ref. 8a.
- 11 Studies of substrates potentially relevant to pharmaceutical applications are rare and have met with limited success: (a) A. Shibamoto, S. Sakaguchi and Y. Ishii, *Org. Process Res. Dev.*, 2000, **4**, 505; (b) B. B. Wentzel, M. P. J. Donners, P. L. Alsters, M. C. Feiters and R. J. M. Nolte, *Tetrahedron*, 2000, **56**, 7797; (c) S. Sakaguchi, A. Shibamoto and Y. Ishii, *Chem. Commun.*, 2002, 180; (d) L. Schmieder-van de Vondervoort, S. Bouttemy, F. Heu, K. Weissenbock and P. L. Alsters, *Eur. J. Org. Chem.*, 2003, 578.
- 12 For simplicity, the term “benzylic” is used for sites adjacent to both aryl and heteroaryl rings.
- 13 T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2000, **65**, 6502.
- 14 For similar reaction conditions for Mid Century-type autoxidation, see: (a) A. S. Hay and H. S. Blanchard, *Can. J. Chem.*, 1965, **43**, 1306; (b) B. Gutmann, P. Elsner, D. Roberge and C. O. Kappe, *ACS Catal.*, 2013, **3**, 2669.
- 15 See also: J. Liu, X. Zhang, H. Yi, C. Liu, R. Liu, H. Zhang, K. Zhuo and A. Lei, *Angew. Chem., Int. Ed.*, 2015, **54**, 1261.
- 16 Pyridines and imidazoles are amongst the most commonly occurring N-heterocycles in F.D.A.-approved pharmaceuticals. See: E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
- 17 A “robustness screen” in which the reaction of **1a** was carried out in the presence of additives bearing potentially interesting functional groups, together with independent reactions of 2-propylfuran, isobutylbenzene, and 2-ethylacetanilide, are presented in the ESI.† See Tables S4 and S5† and associated text for details.
- 18 For a review on thiophene-containing pharmaceuticals, see: D. Gramec, L. Peterlin Masic and M. Sollner Dolenc, *Chem. Res. Toxicol.*, 2014, **27**, 1344.
- 19 (a) H. Henschel, J.-P. Kloeckner, I. A. Nicholls and M. H. Prosenc, *J. Mol. Struct.*, 2012, **1007**, 45; (b) A. B. P. Lever and D. Ogden, *J. Chem. Soc. A*, 1967, 2041.
- 20 M. Masui, S. Hara, T. Ueshima, T. Kawaguchi and S. Ozaki, *Chem. Pharm. Bull.*, 1983, **31**, 4209.
- 21 For electrochemical, PINO-mediated oxygenation of allylic C–H bonds, see: (a) M. Masui, K. Hosomi, K. Tsuchida and S. Ozaki, *Chem. Pharm. Bull.*, 1985, **33**, 4798; (b) E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate and P. S. Baran, *Nature*, 2016, **533**, 77.
- 22 E. Hu, N. Chen, M. P. Bourbeau, P. E. Harrington, K. Biswas, R. K. Kunz, K. L. Andrews, S. Chmait, X. Zhao, C. Davis, J. Ma, J. Shi, D. Lester-Zeiner, J. Danao, J. Able, M. Cueva, S. Talreja, T. Kornecook, H. Chen, A. Porter, R. Hungate, J. Treanor and J. R. Allen, *J. Med. Chem.*, 2014, **57**, 6632.
- 23 O. R. Thiel, J. R. Huckins, D. B. Brown, E. A. Bercot, J. T. Colyer, B. Riahi, R. R. Milburn, S. M. Shaw and J. Tomaskevitch, *ACS Symp. Ser.*, 2014, **1181**, 269.
- 24 The LOC is defined as the minimum partial pressure of oxygen that supports a combustible mixture. Below the LOC, combustion is not possible. P. M. Osterberg, J. K. Niemeier, C. J. Welch, J. M. Hawkins, J. R. Martinelli, T. E. Johnson, T. W. Root and S. S. Stahl, *Org. Process Res. Dev.*, 2015, **19**, 1537.
- 25 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.
- 26 (a) R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, *Green Chem.*, 2011, **13**, 854; (b) D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, *Org. Process Res. Dev.*, 2013, **17**, 1517; (c) D. Prat, J. Hayler and A. Wells, *Green Chem.*, 2014, **16**, 4546.
- 27 Another attractive feature of the reaction is that the NHPI and its decomposition products are readily separated from the reaction mixture through hydrolysis with aqueous NaOH.
- 28 The condensation step was not optimized, but literature precedents suggest these reactions can proceed in near-quantitative yield under neat conditions (see ref. 5d). For E-factor analysis, see ESI.†
- 29 For leading references to continuous-flow aerobic oxidation chemistry, see ref. 6g and 14b, and the following: (a) X. Ye, M. D. Johnson, T. Diao, M. H. Yates and S. S. Stahl, *Green Chem.*, 2010, **12**, 1180; (b) H. P. L. Gemoets, V. Hessel and T. Noel, in *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives*, ed. S. S. Stahl and P. L. Alsters, Wiley-VCH, Weinheim, 2016, pp. 399–417.

