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

Damian P. Hruszkewycz,a Kelsey C. Miles,a Oliver R. Thielb and Shannon S. Stahl*a

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.

Introduction

Liquid-phase radical-chain autoxidation reactions are amongst the largest-scale oxidation reactions performed in industry (Scheme 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 autooxidation 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 autooxidation 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 bonds5,6 (Scheme 2A). The reactions are often compatible with heterocycles and other heteratom-containing functional groups, suggesting they could be well suited for use in pharmaceutical applications.

**Scheme 1** Summary of major industrial radical autoxidation processes.

**Scheme 2** Recent work on aerobic benzylic oxygenation.
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). In a representative example, Maes and coworkers developed a copper-catalysed oxygenation method, in which they contrasted successful oxygenation of 2- and 4-benzylicpyridine with the poor reactivity of 3-benzylicpyridine. A subsequent mechanistic study provided evidence for a heterolytic C–H cleavage pathway and the involvement of the benzylicpyridine enamine tautomer (Scheme 2B).

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. 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. 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. This methodology has been demonstrated in numerous oxidation reactions, including industrial applications, but the vast majority of studies have focused on simple hydrocarbon substrates.

Here, we explore Co/NHPI-catalyzed benzylic oxidation 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-ethylypyridine (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). A 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 Co²⁺ 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 1 Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>CoX₂</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Co(OAc)₂·4H₂O</td>
<td>EtOAc</td>
<td>70</td>
<td>60</td>
<td>59</td>
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<tr>
<td>2</td>
<td>—</td>
<td>EtOAc</td>
<td>70</td>
<td>&lt;1</td>
<td>&lt;1</td>
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<tr>
<td>3</td>
<td>Co(OAc)₂·4H₂O</td>
<td>MeCN</td>
<td>70</td>
<td>50</td>
<td>45</td>
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<tr>
<td>4</td>
<td>Co(OAc)₂·4H₂O</td>
<td>AcOH</td>
<td>70</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Co(OAc)₂·4H₂O</td>
<td>BuOAc</td>
<td>70</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>Co(NO₃)₂·6H₂O</td>
<td>BuOAc</td>
<td>70</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Co(acac)₂</td>
<td>BuOAc</td>
<td>70</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>8</td>
<td>CoCl₂·6H₂O</td>
<td>BuOAc</td>
<td>70</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>Co(OAc)₂·4H₂O</td>
<td>BuOAc</td>
<td>80</td>
<td>95</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>Co(OAc)₂·4H₂O</td>
<td>BuOAc</td>
<td>90</td>
<td>99</td>
<td>94</td>
</tr>
</tbody>
</table>

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

### Table 2 Comparison of catalyst systems

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst system</th>
<th>Ref.</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Co/Br²</td>
<td>14</td>
<td>51</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>Co/Mn/Br²</td>
<td>14</td>
<td>20</td>
<td>&lt;1</td>
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<tr>
<td>3</td>
<td>CuI, 1 eq. AcOH</td>
<td>6e</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4</td>
<td>FeCl₂·4H₂O</td>
<td>6e</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>Co/NHPI</td>
<td>This work</td>
<td>99</td>
<td>94</td>
</tr>
</tbody>
</table>

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)₃·4H₂O, 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), in which a bromine radical is proposed to participate in the H-atom abstraction step. We also tested representative catalyst systems 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).

The optimized reaction conditions were then tested for aerobic oxygenation of a number of pharmaceutically relevant (hetero)arene substrates (Table 3). 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 heteratom-containing functional groups, including a pyrdyl, 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, 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 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). 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. 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.
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.

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
control of reaction temperature during the deprotonation and addition (Scheme 6B).\textsuperscript{21} We envisioned an alternative, two-step route to 2s, starting from the inexpensive, commercially available precursors \( p \)-phenylene diamine and 4-fluorophenolacetic acid (Scheme 6C). The Co/NHPI-catalyzed oxygenation of 1s was performed in EtOAc (1 M) with 500 psi of 9\% O\(_2\) in N\(_2\) to maintain the O\(_2\) concentration below the limiting oxygen concentration (LOC) of ETOAc.\textsuperscript{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:\textsuperscript{25} (i) waste prevention due to high volumetric efficiency, (ii) atom economy due to use of O\(_2\) as both the terminal oxidant and oxygen atom source, (iii) use of an environmentally benign ester solvent,\textsuperscript{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/oxygenation 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.\textsuperscript{27} Reflecting this feature, the route in Scheme 6B has an estimated \( E\)-factor of >15, while the two-step condensation/oxygenation sequence can be <5.\textsuperscript{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.\textsuperscript{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.\textsuperscript{29} This opportunity warrants attention in future studies.

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**Notes and references**


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,


10 For detailed discussion of the mechanism of aerobic Co/NHPI oxidations, see ref. 8a.


12 For simplicity, the term “benzylic” is used for sites adjacent to both aryl and heteroaryl rings.


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-propylfurran, isobutylbenzene, and 2-ethylacetanilide, are presented in the ESL† See Tables S4 and S5 and associated text for details.


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 near conditions (see ref. 5d). For $E$-factor analysis, see ESL†.