Remote, Late-Stage Oxidation of Aliphatic C–H Bonds in Amide-Containing Molecules

Takeshi Nanjo,‡ Emilio C. de Lucca, Jr.,‡ and M. Christina White*†

Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana—Champaign, Urbana, Illinois 61801, United States

Supporting Information

ABSTRACT: Amide-containing molecules are ubiquitous in natural products, pharmaceuticals, and materials science. Due to their intermediate electron-richness, they are not amenable to any of the previously developed N-protection strategies known to enable remote aliphatic C–H oxidations. Using information gleaned from a systematic study of the main features that makes remote oxidations of amides in peptide settings possible, we developed an imidate salt protecting strategy that employs methyl trifluoromethanesulfonate as a reversible alkylating agent. The imidate salt strategy enables, for the first time, remote, nondirected, site-selective C(sp3)–H oxidation with Fe(PDP) and Fe(CF3PDP) catalysis in the presence of a broad scope of tertiary amides, anilide, 2-pyridone, and carbamate functionality. Secondary and primary amides can be masked as N-Ns amides to undergo remote oxidation. This novel imidate strategy facilitates late-stage oxidations in a broader scope of medicinally important molecules and may find use in other C–H oxidations and metal-mediated reactions that do not tolerate amide functionality.

INTRODUCTION

Nitrogen-containing functionalities append notable physical and bioactivity properties to organic molecules. Among them, amides are considered a privileged scaffold in medicinal chemistry, natural products, and materials science. Therefore, the development of a method to selectively oxidize inert remote C(sp3)–H bonds on amide-containing molecules would be a powerful tool for late-stage functionalization of important organic structures.

Site-selective and -divergent oxidation of tertiary (3°) and secondary (2°) C–H bonds has been demonstrated with small-molecule catalysts Fe(PDP) 1 and Fe(CF3PDP) 2, respectively. Such catalysts are thought to proceed via a biomimetic, stepwise mechanism. A highly electrophilic Fe oxidant [likely an Fe(oxo)carboxylate] affects C–H cleavage via a late, product-like transition state where its capacity to differentiate among C–H bonds on the basis of their electronics, sterics, and stereoelectronics properties controls site-selectivities. Recently, these catalysts were shown to oxidize remote C–H bonds in the presence of basic amines and electron-poor imides. Electron-rich amines, previously used as directing groups, promoted remote C–H oxidations after protonation by a strong Brønsted acid (i.e., HBF4) and complexation with an oxidatively stable Lewis acid (BF3). The electronically deactivated ammonium salts and BF3 adducts provided strong inductive deactivation of hyperconjugatively activated α-C–H bonds.

Herein, we describe an imidate salt strategy that promotes remote, nondirected, site-selective aliphatic C–H oxidation in amide-containing molecules.
amide-containing molecules with electrophilic Fe(PDP) \(^1\) and Fe(CF\(_3\)PDP) \(^2\) catalysis.

### RESULTS AND DISCUSSION

A significant deviation from the reactivity trend in Figure 1 is seen in peptides which can be spontaneously oxidized at both tertiary and secondary aliphatic C–H bonds with Fe(PDP) \(^1\) and Fe(CF\(_3\)PDP) \(^2\) catalysis without protection of the amide moiety.\(^{12}\) With the goal of elucidating whether the steric or electronic properties of the substituents flanking the peptide amide bond make it well suited toward remote C(sp\(^3\))–H oxidations, we systematically deconstructed dipeptide \(3a\) to determine which of its features is important for maintaining selectivity for remote tertiary C–H bond oxidation over other deleterious oxidation pathways (Scheme 1). Removal of the methyl steric element on C-terminus slightly decreased the yield and selectivity (\(4b\), 50% yield, 67% selectivity). Replacement of the methyl ester (CO\(_2\)Me) by a methyl group, however, significantly decreased the yield and selectivity for remote oxidation product (\(4c\), 10% yield, 12% selectivity), likely due to \(\alpha\)-oxidation of the adjacent tertiary C–H bond promoted by the amide nitrogen. When the \(\alpha\)-C–H bond is replaced with a methyl group, removing the alternate proximal site of oxidation, the yield and selectivity for remote oxidation are restored (\(4d\), 45% yield, 67% selectivity). Evaluation of groups flanking the carbonyl of the amide moiety showed a strong dependence on electronics: replacing the electron-withdrawing \(N\)-Ns substituent with a more sterically demanding methyl group\(^{13}\) furnished the remote oxidation product \(4e\) in moderate yield (37%) and low selectivity (43%). Collectively, these results suggest that electron-withdrawing substitution flanking both sides of the amide bonds in peptides are most effective for enabling remote oxidations. We therefore sought to find a way to reversibly electronically deactivate the amide bond in simple amides where such adjacent electron-withdrawing groups are not native.

In the absence of protection on nitrogen, 3\(^{\circ}\) and 2\(^{\circ}\) lactams \(5a\) and \(5b\), containing a remote tertiary site of oxidation, yielded no desired product due to the competitive oxidation of \(\alpha\)-C–H bonds (Table 1, entries 1 and 6). Previous complexation strategies using Bronsted or Lewis acids, such as HBF\(_4\), H\(_2\)SO\(_4\), and BF\(_3\), provided no improvement of the reaction due to the reversible nature of the complexation (entries 2–4).\(^{5,14}\) We envisioned that nonbasic, but nucleophilic amides would react with an alkylating reagent to form a stable imidate salt. Previously, imidate salts had only been employed as intermediates to activate unreactive amides toward nucleophilic substitutions.\(^{15}\) We hypothesized that under these weakly acidic, mild oxidation conditions with short reaction times, these imidate salts would be stable. Moreover, the cationic functionality would provide strong electronic deactivation to neighboring sites to promote remote C–H oxidation with the electrophilic oxidant generated with Fe(PDP) and H\(_2\)O\(_2\).\(^4\) Based on this concept, using methyl trifluoromethanesulfonate (MeOTf) as additive we observed the desired oxidation product \(6a\) in excellent yield after a mild decomplexation with sodium iodide (NaI) at room temperature (Table 1, entry 5, and Scheme 2, eq 1, 59% isolated yield over three steps),\(^{16}\) providing the first example of remote oxidation in the presence of a simple tertiary amide.

In the case of 2\(^{\circ}\) amides, more conventional electron-withdrawing protecting groups on nitrogen may prevent deleterious \(\alpha\)- and \(N\)-oxidation and promote remote oxidations. Whereas the reaction of Boc-protected lactam \(5c\) was not effective (entry 7), 4-nitrobenzenesulfonyl (Ns) protection provided remote oxidized product \(6d\) in 62% yield (entry 8). Interestingly, \(N\)-Ns protection in secondary amines furnishes \(\alpha\)-oxidation products whereas for secondary amides remote oxidation is observed.\(^{12}\) The remote oxidation strategies for 3\(^{\circ}\) and 2\(^{\circ}\) amides shown above could be also used for methylene C–H oxidation with Fe(CF\(_3\)PDP) \(^2\) (entries 9 and 10).

### Table 1. Reaction Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactam</th>
<th>R</th>
<th>Additive</th>
<th>Yield [%] (rsm)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>Me</td>
<td>-</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>Me</td>
<td>HBF(_4)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>5a</td>
<td>Me</td>
<td>H(_2)SO(_4)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>Me</td>
<td>BF(_3)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>Me</td>
<td>MeOTf(^{12})</td>
<td>59 (10)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Scheme 1. C–H Oxidation of Peptides**

**Table 1. Reaction Optimization**

**A. Remote 3\(^{\circ}\) C–H Oxidation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactam</th>
<th>R</th>
<th>Additive</th>
<th>Yield [%] (rsm)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>5e</td>
<td>Me</td>
<td>MoOTf(^{12})</td>
<td>56 (12)</td>
<td>&gt; 20.1 (\gamma)</td>
</tr>
<tr>
<td></td>
<td>10(^{\circ})</td>
<td>5f</td>
<td>Ns</td>
<td>-</td>
<td>54 (14)</td>
</tr>
</tbody>
</table>

**B. Remote 2\(^{\circ}\) C–H Oxidation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactam</th>
<th>R</th>
<th>Additive</th>
<th>Yield [%] (rsm)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5g</td>
<td>Me</td>
<td>MoOTf(^{12})</td>
<td>66% (66%, (\beta) = 5.11 (13%))</td>
<td>-</td>
</tr>
</tbody>
</table>

*Slow addition: 15 mol% \(\pm\) 1 or 25 mol% \(\pm\) 2, \(\mathrm{AcOH}\) (5.0 equiv.), \(\mathrm{H}_{2}\)\(\mathrm{O}_{2}\) (9.0 equiv.), \(\mathrm{MeCN}\). syringe pump (80 min). \(^{\circ}\)Estimated yield is average of three runs, \% rac is given in parentheses. \(^{\circ}\) Slow addition: 25 mol% \(\pm\) 1, \(\mathrm{AcOH}\) (5.0 equiv.), \(\mathrm{H}_{2}\)\(\mathrm{O}_{2}\) (9.0 equiv.), \(\mathrm{MeCN}\). syringe pump (80 min). \(^{\circ}\)Graded material recycled 3. \(^{\circ}\) Selectivity = yield/conversion. \(^{\circ}\) NMR yield using MeOTf as an internal standard. \(^{\circ}\) Based on isolation. \(^{\circ}\) Starting material recycled 3. \(^{\circ}\) Pretreatment with MeOTf prior to the NaI-mediated decomplexation is necessary to quench excess of \(\mathrm{H}_{2}\)\(\mathrm{O}_{2}\) and ensure reproducibility.
Significantly, the imidate salt strategy gave better site-selectivities for remote δ oxidation than Ns protection, suggesting that the cationic nature of the imidate salt provides stronger electronic deactivation than Ns protection. This feature of the imidate protection strategy promotes highly site-selective remote oxidations with electrophilic Fe(PDP)\textsubscript{1} and Fe(CF\textsubscript{3}PDP)\textsubscript{2} oxidants, previously elucidated to have a strong preference for oxidizing the most electron-rich site in substrates.\textsuperscript{3,5} In both the 3° and 2° oxidized products 6d and 6f, the N-Ns-protected amide could be readily deprotected via K\textsubscript{2}CO\textsubscript{3}/PhSH in 90% and 88% yield, respectively (See Supporting Information). N-Nosyl protection is also useful for 1° amides: N-Ns-protected hexanamide 5g was oxidized at a remote site to form the desired product 6g in good yield and 5:1 site-selectivity.

Typically, the imidate salt can be deprotected via an SN\textsubscript{2} reaction mediated by NaI (Scheme 2, eq 1). However, these intermediates may also be intercepted with other nucleophiles. The Fe(CF\textsubscript{3}PDP)\textsubscript{2}-catalyzed oxidation of lactam 5e followed by treatment of the crude imidate salt with lithium prop-2-en-1-olate underwent a Meerwein−Eschenmoser [3,3]-rearrangement to provide the allylated compound 7 in 26% overall yield for three steps (64% yield per step) (Scheme 2, eq 2).\textsuperscript{18}

Substituted lactams are prevalent substructures in natural products and medicinal agents.\textsuperscript{1} Five- and six-membered ring lactams with N-alkyl chains uniformly provided remote 3° and 2° C−H bond oxidation products in high yields and selectivities (Table 2, 8−11). The inductive effect of the imidate salt enabled high site-selectivities for Fe(CF\textsubscript{3}PDP)\textsubscript{2}-catalyzed oxidation at alkyl substitution α to the amide carbonyl: cyclopentyl substituted 5- and 6-membered lactams were oxidized with Fe(CF\textsubscript{3}PDP)\textsubscript{2} at the methylene sites most remote from this electron-withdrawing moiety to furnish ketones 12 and 13. Medium-sized lactams (7- and 8-membered) showed analogous reactivity and selectivity trends (14−18). Significantly, no ring oxidations were observed even with the eight-membered lactams (15 and 17).

The imidate salt strategy can be applied to acyclic amides to equal effect. In a series of dialkyl amides of varying steric bulk (Me, Et, and i-Pr), remote tertiary C−H hydroxylation with Fe(PDP)\textsubscript{1} provided the oxidized products (19−21) in excellent overall yields (avg. 54% for three steps), suggesting that formation and stability of the imidate salt is not significantly impacted by steric at the nitrogen. Interestingly, pyrrolidine amides, general structures in medicinal compounds, also provided remote 3° and 2° C−H oxidation products (22−24) in excellent yields.

We proceeded to challenge the efficiency of these amide-protection strategies in the context of more complex medicinally relevant core structures. The fused tricyclic lactam, containing a quinolizidine-2-one moiety that is a prevalent unit in alkaloids, such as matrine, was evaluated for oxidation using the imidate salt strategy.\textsuperscript{19} The imidate underwent Fe(CF\textsubscript{3}PDP)\textsubscript{2} oxidation to furnish ketone 25 on the most remote methylene site in good yield and excellent site-selectivity (only one oxidized product observed). The quinolizidinone core, that may have been susceptible to oxidation, remained unaffected.

Notably, β-lactams, the most prevalent lactam core in pharmaceuticals such as antibiotics,\textsuperscript{12,20} were amenable to this protection strategy, despite the potential ring strain introduced during imidate formation. 3-Carene- and α-pinene-derived β-lactams underwent Fe(CF\textsubscript{3}PDP)\textsubscript{2} catalyzed remote methylene oxidations at their N-alkyl side chains to afford 26 and 27 in excellent yields.
good yields and selectivities. Significantly, their sensitive terpene cores were shielded from C–H cleavage via the strong inductive deactivation afforded by the imidate salt formed at the fused β-lactam ring.

We questioned the generality of this strategy for other nitrogen functionality of intermediate electron-richness. The challenging anilide motif, which is easily oxidized by strong oxidants due to the electron-richness of the aromatic ring, was effectively protected as an imidate salt to provide remote tertiary hydroxylated product 28 with Fe(CF₃PDP) 1 oxidation in 46% overall yield. 2-Pyridone, which exists in a variety of bioactive compounds and incorporates a very sensitive moiety known to be oxidized by monooxygenases, was effectively protected from oxidation with this strategy and underwent Fe(CF₃PDP) 1 oxidation to afford remote methylene oxidation ketone 29 in 51% overall yield and 5:3:1 site-selectivity. The diminished site-selectivity for compound 29—relative to analogous products derived from amide imidates—is attributed to the dampened positive charge of the imidate due to delocalization around the conjugated ring. Carbamates, which promote α-heterorotam oxidation under standard conditions, furnish remote methylene oxidized ketone 30 with Fe(CF₃PDP) 1 2 catalysis in 53% overall yield using this imidate salt strategy. It has been previously reported that imides promote remote aliphatic C=H oxidations without protection. Using the nosyl protection strategy, a more electron-rich uracil analogue was successfully oxidized remotely with Fe(PDP) 1 to afford alcohol 31 in 64% yield.

Finally, the robustness of this strategy was evaluated in the late-stage oxidation of a series of amide-containing natural product derivatives. Palasoninimide B, bearing an interesting cantharimide core, is a natural product recently isolated from Mylabis phalerata Palla and found to be a potent inhibitor of hepatitis B virus (HBV). The Fe(CF₃PDP) 1 oxidation of the nosylated palasoninimide B analogue 32 resulted in remote oxidation product 33 in 64% yield and 6:1 selectivity with the cyclic ether cantharimide substructure untouched (Scheme 3A). For N-methyl derivative 34, the higher nucleophilicity of the amide nitrogen versus that of the imide led it to preferentially reacting with the alkylating reagent to form a stable imidate salt. The Fe(CF₃PDP) 1 oxidation resulted in only the remote oxidized product 35 in 54% overall yield (>20:1). 'H NMR, 82% (step). The higher site-selectivity in Fe(CF₃PDP) 2 methylene oxidation with the imidate salt versus N-Ns protection strategies is consistent with previous trends observed on simpler substrates (Table 1B).

Finasteride, known as a type II and type III 5α-reductase inhibitor, is a medication used for the treatment of enlarged prostate and pattern hair loss. The azasteroid structure contains two amides: one in the A-ring of the steroidal core and the other a t-Bu amide on the D-ring (Scheme 3B). We envisioned that only the sterically exposed A-ring lactam of finasteride derivative 36 would react with MeOTf to form the imidate salt 37. Based on our studies with the t-Bu amide of peptide 3d, we envisioned that this unprotected amide moiety would not inhibit productive catalysis (Scheme 1). Using the previously developed quantitative reactivity model, we predicted that oxidation of 37 using the sterically sensitive Fe(CF₃PDP) 2 catalyst would afford primarily D-ring oxidation due to strong electronic deactivation of A- and B-rings by the cationic imidate moiety and steric congestion at the C-ring (see Supporting Information). Treatment of finasteride analogue 36 with MeOTf formed imidate salt 37. Fe(CF₃PDP) 2 oxidation and decomposition with NaI provided C15 ketone 38 in 32% yield over three steps (68% per step) from 36 as a single regiosomer (Scheme 3B). Despite the lack of imidate and amide moieties in the model’s training set, this was the predicted major site of oxidation with Fe(CF₃PDP) 2. Significantly, this reaction provides the first example of non-directed, aliphatic C–H oxidation at the D-ring of a steroid with a small-molecule catalyst.

Sublactam, a β-lactamase inhibitor used as antibiotic, contains an amide moiety electronically reminiscent of a peptide: it is flanked with two strongly electron-withdrawing moieties, an ester and a sulfone group (Scheme 3C). We hypothesized that given this, undesired α-nitrogen oxidation would be disfavored in sulbactam ester 39 without any amide protection. Aliphatic C–H oxidation with electrophilic Fe(PDP) 1 catalyst 1 occurred remotely from the innately electron-withdrawing sulbactam core at the most electron-rich tertiary C–H bond to furnish product 40 in 54% yield and 69% selectivity.

**CONCLUSION**

We have demonstrated remote Fe(PDP)-catalyzed tertiary and methylene oxidation in a range of amide-containing molecules by employing an imidate salt formation strategy. We envision this strategy will be highly beneficial in the late-stage...
functionalization of bioactive molecules and assist in the rapid evaluation of their metabolites. Moreover, we envision that this novel amide protecting strategy may find uses in other C–H oxidations and metal-mediated reactions where α-oxidation and/or catalyst deactivation is problematic.

**EXPERIMENTAL PROCEDURES**

**General Procedure for Protection with MeOTf.** To a stirring solution of amide-containing molecule (1.0 equiv) in CH2Cl2 (0.2 M) at 0 °C was added MeOTf (1.2 equiv) dropwise, and the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure and left on high vacuum overnight (12–24 h) to yield an imidate salt which was either used in the next step without further purification (if imidate salt is a liquid) or recrystallized in Et2O (if imidate salt is a solid).

**General Procedure for C–H Oxidation Using the Slow Addition Protocol.** The imidate salt (1.0 equiv) and AcOH (5.0 equiv) were dissolved in MeCN (0.5 M). A 1 mL syringe was charged with a solution of Fe(PDP) (0.15 equiv) or Fe(CF3PDP) (0.25 equiv) in MeCN [0.11 M for Fe(PDP) or 0.19 M for Fe(CF3PDP)]. A 10 mL syringe was charged with a solution of H2O2 (9.0 equiv) in MeCN (0.75 M). Both syringes were fitted with 25G needles, and solutions were added simultaneously into the stirring reaction mixture via a syringe pump over 1 h. For 0.300 mmol scale the addition rate would be 3.6 mL/h. The reaction solution was stirred for 30 min after the addition, for a total reaction time of approximately 1.5 h.

**General Procedure for Imidate Salt Deprotection.** After the oxidation, the reaction mixture was cooled to 0 °C, and MnO2 (0.5 equiv) was added to quench the excess H2O2. After being stirred for 1 h, the mixture was warmed to room temperature and stirred overnight. The mixture was filtered, and concentrated under reduced pressure. Pretreatment with MnO2 prior to the NaI-mediated decomplexation is necessary to quench and concentrated under reduced pressure. The residue was partitioned in CHCl3 and saturated aqueous solution of NaHCO3. The organic phase was reduced pressure, and the residue was partitioned in CHCl3 and saturated aqueous solution of NaHCO3. The organic phase was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to afford the desired oxidation product.

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07665.

Experimental procedures and analytical data (1H and 13C NMR, HRMS) for all new compounds (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**
*mcwhite7@illinois.edu*

**ORCID**

Emilio C. de Lucca Jr.: 0000-0002-7732-3559

M. Christina White: 0000-0002-9563-2523

**Author Contributions**
*T.N. and E.C.L. contributed equally.

**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


(13) Although the A-value for NH2 is unknown, the A-value for NHTs is 0.7, which is significantly smaller than for a methyl group (A-value = 1.7): Pozharliev, I. G.; Mikhailov, S. Izv. Otdelenieto Khim. Nauki 1970, 3, 133.


(17) We could not isolate the C–H oxidized imidate salts. However, in cases where we isolated the imidate salt prior to C–H oxidation, the yields were uniformly greater than 90%. Considering that Fe(PDP)
and Fe(CF₃PDP) oxidations generally proceed in 50–70% yield (see ref 3–5), we can assume that the NaI-mediated deprotection goes in excellent yield, making the overall yield very representative of the C–H oxidation.