JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Flexible and Chemoselective Oxidation of Amides to α-Keto Amides and α-Hydroxy Amides

Aurélien de la Torre,[†] Daniel Kaiser,[†] and Nuno Maulide*

Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna, Währinger Straße 38, 1090 Vienna, Austria

Supporting Information

ABSTRACT: A suite of flexible and chemoselective methods for the transition-metal-free oxidation of amides to α-keto amides and α-hydroxy amides is presented. These highly valuable motifs are accessed in good to excellent yields and stereoselectivities with high functional group tolerance. The utility of the method is showcased by the formal synthesis of a potent histone deacetylase inhibitor.

Selective oxidation reactions are highly sought in organic chemistry.[1] As a ubiquitous motif in bioactive molecules as well as a uniquely reactive ambident proelectrophile and pronucleophile, the α-keto amide function has attracted the interest of the scientific community.[2−4] Similarly, α-hydroxy carbonyl derivatives are important and widespread motifs in organic synthesis.[5]

The most straightforward approach to access an α-keto amide motif would arguably be the direct α-oxidation of an amide substrate. Surprisingly, methods to achieve this transformation are scarce. Indeed, to the best of our knowledge, the oxidation of amides to α-keto amides is limited to the specific case of α-aryl amides (thus being effectively a benzylic oxidation) (Figure 1a).[6] On the other hand, the oxidation of carbonyl compounds to α-hydroxy carbonyl compounds is well-described, mainly using enol or enolate chemistry, including the venerable Rubottom oxidation (Figure 1b).[5,7] However, as the amide function is the least prone to enolate formation (lowest α-CH acidity among all carbonyl and carboxyl derivatives), the selective oxidation of amides to α-hydroxy amides in the presence of other carbonyl compounds remains an unsolved challenge.

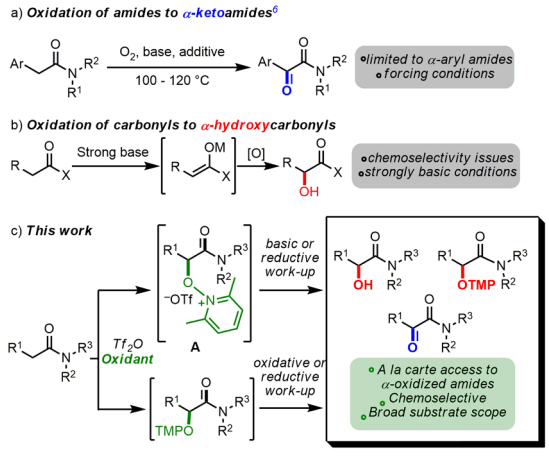


Figure 1. Strategies for α-oxidation of amides.

Triflic anhydride-mediated activation of amides is a powerful synthetic tool to enhance the intrinsic electrophilicity of amides.[8] This approach has been exploited by various research groups, allowing amides to undergo cycloadditions and nucleophilic additions in a chemoselective fashion.[9] We recently disclosed the use of an electrophilic enolonium species,[10] based on amide activation and trapping with an *N*-oxide, to trigger umpolung reactivity at the α-position of amides.[10] Precedent for this reactivity dates back to work by Ghosez and co-workers, forming particular α,β-unsaturated amides and α-chloroamides.[11] We posited that this intermediate might be coerced to undergo a second attack by the *N*-oxide species. The resulting oxapyridinium species **A** (Figure 1c) should be a versatile intermediate: following basic workup, it might afford the corresponding *α-keto* amide, while a reductive workup could lead to the corresponding *α-hydroxy* amide (Figure 1c). Herein we report the development of a flexible approach for the α-oxidation of amides to α-hydroxy and α-keto amides.

After extensive optimization using amide **1f** (see the Supporting Information (SI)), we identified 2,6-lutidine-*N*-oxide (LNO) as the ideal oxidant and the use of molecular sieves (3 Å) as beneficial for achieving high conversions and reproducible yields. The reaction is simply quenched using aqueous NaOH to afford the corresponding keto amide **2f**.

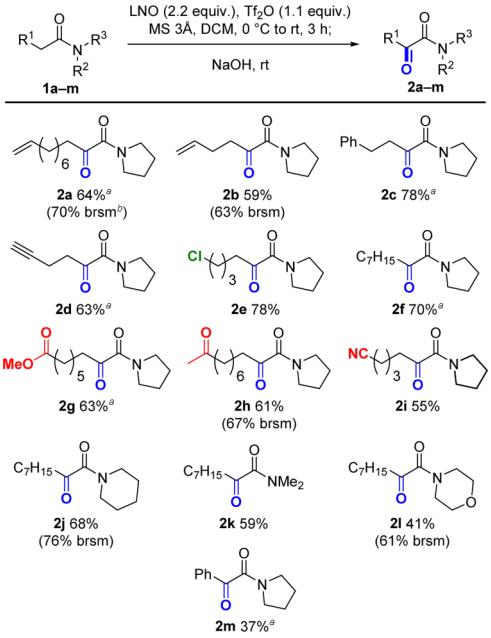
As shown in Scheme 1, several aliphatic amides could be oxidized to the corresponding α-keto amides in good yields. Various functional groups were tolerated under the reaction conditions, including alkenes (**2a**, **2b**), alkynes (**2d**), and halides (**2e**). Moreover, the oxidation is chemoselective for amides in the presence of esters, ketones, and nitriles (**2g−i**). The nitrogen substituents could also be modified to some extent. Piperidine, dimethyl, and morpholine amides could be oxidized in moderate to good yields (**2j−l**). However, α-aryl amides proved to be reluctant under those oxidation conditions (**2m**), as were sterically hindered amides (not shown). Additionally, the α-oxidation of secondary amides did not proceed to yield the desired products. As previous work has shown, electrophilically activated secondary amides form the corresponding nitrilium ions and therefore cannot undergo the reactions described herein.[8b,9c]

Exchanging the basic quench for reductive conditions allowed the synthesis of the corresponding α-hydroxy amides. We

Received: March 25, 2017

DOI: 10.1021/jacs.7b02983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

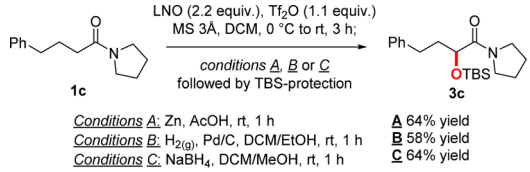
Scheme 1. Scope of the Amide to α-Keto Amide Oxidation



[a]Reaction time = 12 h. [b]brsm = based on recovered starting material.

identified three orthogonal reductive conditions leading to the desired products (Scheme 2). For convenience of isolation, the

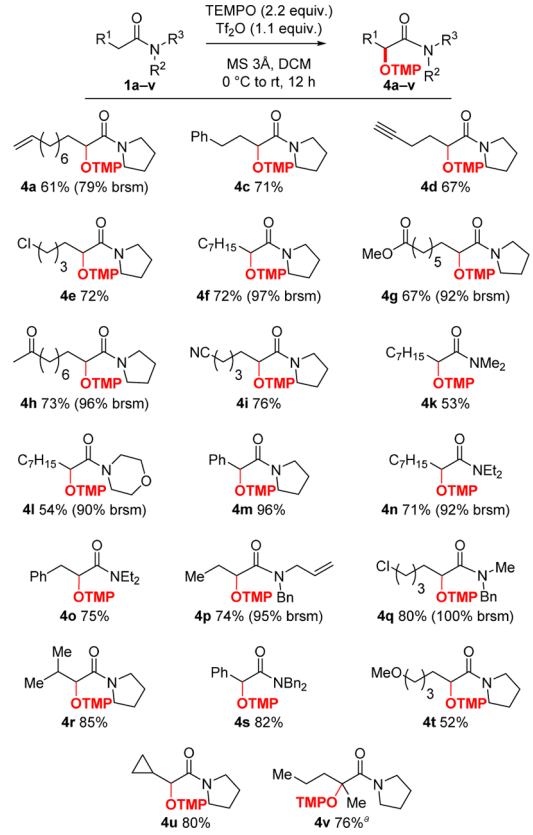
Scheme 2. Reductive Workup Leading to an α-Hydroxy Amide



α-hydroxy amide was directely TBS-protected. By the use of either zinc and acetic acid, hydrogen and catalytic palladium on carbon, or sodium borohydride, protected α-hydroxyamide **3c** was isolated in good yield (Scheme 2) in a highly flexible manner.

Aware that the limitations in the scope of our transformation could hamper its synthetic utility, we decided to explore a complementary approach for the cases giving low yields. In the course of our investigations, we made the remarkable observation that treating the amide with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and triflic anhydride led to the formation of the corresponding α-(tetramethylpiperidin-1-yl)oxyamide.[12] This intermediate product is particularly interesting because the tetramethylpiperidine (TMP) moiety can be considered as a protecting group for the hydroxy function,[13] and we decided to explore the scope of the formation of α-OTMP amides (Scheme 3; additional substrates are shown in the SI). To our delight, the amides oxidized using LNO could also be oxidized using TEMPO, affording **4a–l** in good yields. In this reaction, the chemoselectivity of the oxidation of amides was preserved, and the reaction could be conducted in the presence of esters, ketones, and nitriles as well as unsaturations and halides. More importantly, phenylacetamide **1m** could now be oxidized to the corresponding α-OTMP amide **4m** in excellent yield (compare **2m** in Scheme 1, 37% yield with **4m** in Scheme 3, 96% yield). Other amides containing ethyl (**1n**, **1o**), allyl (**1p**), and benzyl

Scheme 3. Scope of the Amide to α-OTMP Amide Oxidation

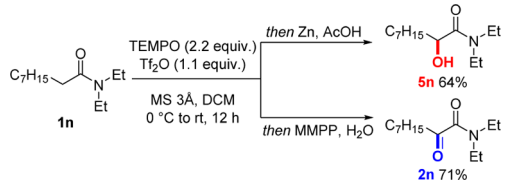


[a]1 equiv of 2-fluoropyridine was added to the reaction mixture.

(**1q**) substituents on nitrogen could also be oxidized in good yields. Sterically hindered amides were also easily oxidized, as exemplified by isovalerylamide **1r** and dibenzylamide **1s**. Methyl ethers did not affect the reaction (cf. **1t**). An α-cyclopropyl substituent was also tolerated, affording **4u** in good yield without cleavage of the cyclopropyl moiety (vide infra). Finally, an α,α-disubstituted amide could also be oxidized to form protected tertiary alcohol **4v** in good yield.

The synthetic flexibility of these products is illustrated in Scheme 4. A simple reductive workup using zinc and acetic acid

Scheme 4. One-Pot Synthesis of α-Hydroxy Amides and α-Keto Amides from the α-OTMP Precursor



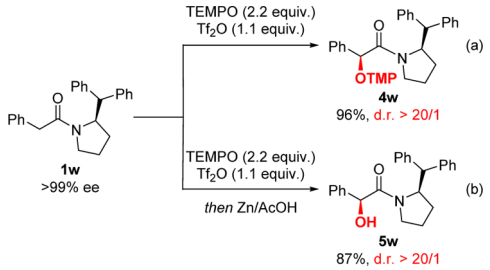
afforded α-hydroxy amide **5n** in good yield.[13d] Similarly, using magnesium monoperoxyphthalate (MMPP) hexahydrate as a cheap and mild oxidant for the quench,[14] we could perform the oxidation of **1n** to α-keto amide **2n** in good yield. Remarkably, no significant loss of yield was observed in this transformation compared to the formation of the α-OTMP amide **4n**.

We were subsequently intrigued as to whether the addition of TEMPO to simple amides could be performed in a diastereoselective fashion. Pleasingly, we found that exposure of chiral amide **1w** to Tf_2O and TEMPO afforded the desired

DOI: 10.1021/jacs.7b02983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

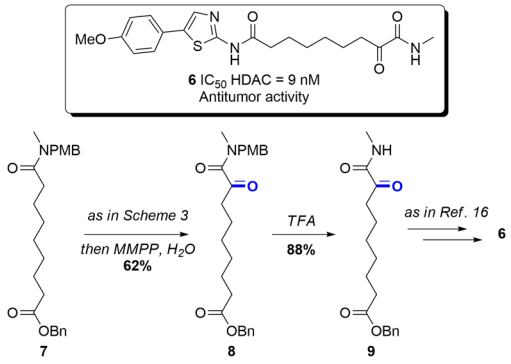
product in nearly quantitative yield with an excellent diastereomeric ratio (Scheme 5a).[15] Additionally, one-pot reduction of this product efficiently afforded the free alcohol **5w** without erosion of the diastereoselectivity (Scheme 5b).

Scheme 5. Diastereoselective Synthesis of Both an α-OTMP Amide and an α-Hydroxy Amide



The synthetic utility was further demonstrated by targeting α-keto amide **6**, a potent histone deacetylase inhibitor that has been found to have significant anticancer activity in an in vivo tumor model.[16] Application of our oxidation conditions to the simple azelaic acid-derived amide **7** smoothly led to the formation of keto amide **8** (Scheme 6).[17] Subsequent acid-mediated cleavage

Scheme 6. Synthesis of Bioactive Compound 6

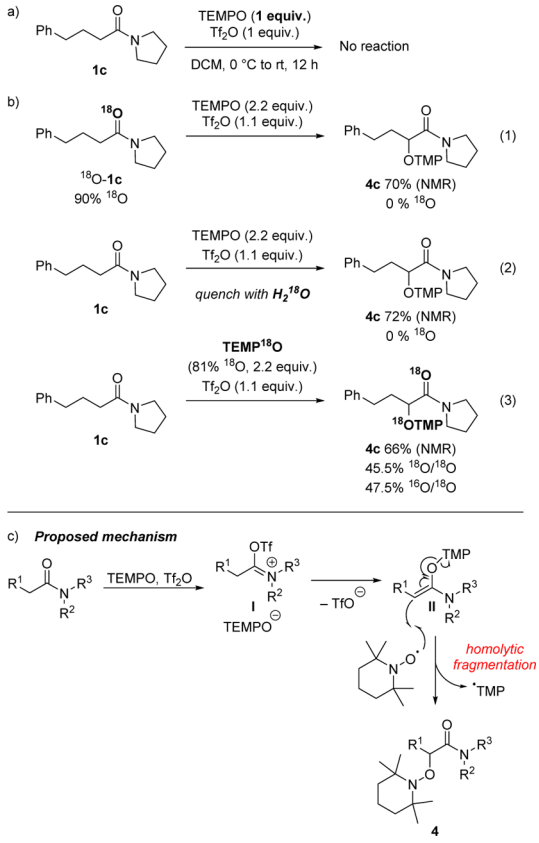


of the *p*-methoxybenzyl (PMB) protecting group led to the formation of secondary keto amide **9**, an intermediate in the previous synthesis of **6**. This application showcases the synthetic utility of our methodology by shortening the eight-step synthesis of **6** by two synthetic steps (see the SI for the synthesis of **7**).

Although the mechanism of the reaction of activated amides with LNO (serving as the oxidant and oxygen donor) could be easily understood on the basis of previous work,[10] the reactivity of TEMPO was much less obvious to us. In particular, the formation of **4u** without opening of the cyclopropyl ring (see Scheme 3) strongly argues against the possible intermediacy of an α-carbonyl radical species.

Performing the reaction of **1c** with only 1 equiv of TEMPO led to full recovery of the starting material and no observable oxidation product (Scheme 7a).[18] While amide activation is undisputable, despite several additional experiments (see the SI for details) it remains unclear which reactions precede or effect it. Possibilities include (a) the formation of an intermediate species derived from the reaction of TEMPO and triflic anhydride, itself capable of activating the amide, (b) a pre-equilibrium between a nonreactive species formed by the reaction of TEMPO with triflic anhydride and the reagents, and (c) direct activation of the amide with triflic anhydride. In order to shed light onto the

Scheme 7. Mechanistic Experiments and Proposed Mechanism



second half of the reaction mechanism, isotopic labeling studies were additionally performed (Scheme 7b, eqs 1–3; see the SI for further details). Neither the use of ^{18}O-labeled **1c** (Scheme 7b, eq 1) nor quenching the reaction with $H_2{}^{18}O$ (Scheme 7b, eq 2) led to incorporation of the label in the final product. On the other hand, the use of ^{18}O-labeled TEMPO afforded the pivotal $^{18}O/^{18}O$ product **4c** (Scheme 7b, eq 3). We are therefore inclined to propose initial electrophilic amide activation and formation of **I** with concomitant reduction of TEMPO to anionic $TEMPO^-$. Nucleophilic substitution of $TEMPO^-$, replacing TfO^-, leads to the formation of intermediate **II** (Scheme 7c).[19] Homolytic fragmentation of this intermediate—consistent with incorporation of the TEMPO oxygen into the amide carbonyl—subsequently affords the α-oxidation product **4**. This preliminary rationale effectively constitutes a polar-radical crossover that is unprecedented in the field of amide activation.

In conclusion, we have described a novel flexible and chemoselective approach for the oxidation of amides to α-keto and α-hydroxy amides. Notably, this is the first example of a synthetically useful and general direct oxidation of aliphatic amides to the corresponding α-keto amides. Our strategy relies on chemoselective amide activation using triflic anhydride along with the use of an oxidant. In the case of nonhindered aliphatic amides, the use of LNO as the oxidant led to the formation of various keto amides. α-Hydroxy amides could also be synthesized by quenching the reaction with a reductant. The scope of the reaction could be extended to virtually any kind of amide by switching to TEMPO as the oxidant. A wide range of α-OTMP amides could be synthesized, and it was shown that the latter could be converted to the corresponding α-keto and α-hydroxy amides by quenching the reaction under oxidative and reductive

DOI: 10.1021/jacs.7b02983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

conditions, respectively. The reaction could also be performed in a diastereoselective fashion using a chiral auxiliary, leading to the formation of the product with excellent diastereocontrol. Our reaction could be applied to the formal synthesis of a potent histone deacetylase inhibitor. Preliminary mechanistic observations led us to propose a polar-radical crossover, which is unprecedented in the field of amide activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02983.

Experimental procedures and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*nuno.maulide@univie.ac.at.

ORCID

Nuno Maulide: 0000-0003-3643-0718

Author Contributions

†A.d.l.T. and D.K. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Vienna for continued support of our research program. Support of this research by the ERC (StG FLATOUT and CoG VINCAT) and the DFG (Grants MA-4861/4-1 and 4-2) is acknowledged. D.K. is the recipient of a DOC Fellowship of the Austrian Academy of Sciences.

■ REFERENCES

(1) White, M. C. *Science* **2012**, *335*, 807.

(2) For general reviews of the synthesis of α-keto amides, see: (a) De Risi, C.; Pollini, G. P.; Zanirato, V. *Chem. Rev.* **2016**, *116*, 3241. (b) Kumar, D.; Vemula, S. R.; Cook, G. R. *ACS Catal.* **2016**, *6*, 4920.

(3) For selected examples of α-keto amide synthesis, see: (a) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (b) Du, F.-T.; Ji, J.-X. *Chem. Sci.* **2012**, *3*, 460. (c) Deshidi, R.; Kumar, M.; Devari, S.; Shah, B. A. *Chem. Commun.* **2014**, *50*, 9533. (d) Liu, L.; Du, L.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2014**, *16*, 5772. (e) Li, W.; Duan, Z.; Zhang, X.; Zhang, H.; Wang, M.; Jiang, R.; Zeng, H.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 1893. (f) Wang, Z.; Liu, C.; Huang, Y.; Hu, Y.; Zhang, B. *Chem. Commun.* **2016**, *52*, 2960. (g) Nagaki, A.; Takahashi, Y.; Yoshida, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 5327. (h) Ma, F.; Liu, H.; Chen, J. *Tetrahedron Lett.* **2016**, *57*, 5246. (i) Wan, J.-P.; Lin, Y.; Cao, X.; Liu, Y.; Wei, L. *Chem. Commun.* **2016**, *52*, 1270.

(4) For selected synthetic applications of α-keto amides, see: (a) Kou, K. G.M.; Le, D. N.; Dong, V. M. *J. Am. Chem. Soc.* **2014**, *136*, 9471. (b) Goudedranche, S.; Pierrot, D.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Chem. Commun.* **2014**, *50*, 15605. (c) Echave, H.; López, R.; Palomo, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 3364. (d) Xu, X.-M.; Zhao, L.; Zhu, J.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2016**, *55*, 3799. (e) Chen, Q.; Tang, Y.; Huang, T.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 5286. (f) Du, Y.; Yu, A.; Jia, J.; Zhang, Y.; Meng, X. *Chem. Commun.* **2017**, *53*, 1684.

(5) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, *62*, 1.

(6) Song, B.; Wang, S.; Sun, C.; Deng, H.; Xu, B. *Tetrahedron Lett.* **2007**, *48*, 8982. (b) Shao, J.; Huang, X.; Wang, S.; Liu, B.; Xu, B. *Tetrahedron* **2012**, *68*, 573.

(7) For general reviews, see: (a) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (b) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917.

(8) (a) Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879. (b) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694.

(9) (a) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592. (b) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (c) Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341. (d) Mewald, M.; Medley, J. W.; Movassaghi, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 11634. (e) White, K. L.; Mewald, M.; Movassaghi, M. *J. Org. Chem.* **2015**, *80*, 7403. (f) White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383. (g) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18. (h) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817. (i) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228. (j) Xiao, K.-J.; Wang, A.-E.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 8314. (k) Peng, B.; Geerdink, D.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 14968. (l) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J.; Wang, Y.; Xia, Y.-E. *J. Org. Chem.* **2015**, *80*, 2861. (m) Lumbroso, A.; Behra, J.; Kolleth, A.; Dakas, P.-Y.; Karadeniz, U.; Catak, S.; Sulzer-Mossé, S.; De Mesmaeker, A. *Tetrahedron Lett.* **2015**, *56*, 6541. (n) Kolleth, A.; Lumbroso, A.; Tanriver, G.; Catak, S.; Sulzer-Mossé, S.; De Mesmaeker, A. *Tetrahedron Lett.* **2016**, *57*, 2697. (o) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J. *J. Org. Chem.* **2016**, *81*, 9020. (p) Kaiser, D.; Maulide, N. *J. Org. Chem.* **2016**, *81*, 4421. (q) Tona, V.; de la Torre, A.; Padmanaban, M.; Ruider, S.; González, L.; Maulide, N. *J. Am. Chem. Soc.* **2016**, *138*, 8348.

(10) (a) Patil, D. V.; Kim, S. W.; Nguyen, Q. H.; Kim, H.; Wang, S.; Hoang, T.; Shin, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 3670. (b) Kaiser, D.; de la Torre, A.; Shaaban, S.; Maulide, N. *Angew. Chem., Int. Ed.* **2017**, DOI: 10.1002/anie.201701538. (c) Chen, X.; Ruider, S. A.; Hartmann, R. W.; González, L.; Maulide, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 15424.

(11) Da Costa, R.; Gillard, M.; Falmagne, J. B.; Ghosez, L. *J. Am. Chem. Soc.* **1979**, *101*, 4381.

(12) This reaction could be accelerated by using 1 equiv of 2-fluoropyridine. However, in most cases similar results were obtained without this additive.

(13) (a) Inokuchi, T.; Kawafuchi, H. *Tetrahedron* **2004**, *60*, 11969. (b) Jahn, U.; Dinca, E. *Chem. - Eur. J.* **2009**, *15*, 58. (c) Jahn, U.; Dinca, E. *J. Org. Chem.* **2010**, *75*, 4480. (d) Dinca, E.; Hartmann, P.; Smrcek, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, *2012*, 4461.

(14) Hayashi, M.; Shibuya, M.; Iwabuchi, Y. *Synlett* **2012**, *23*, 1025.

(15) Reducing the size of the chiral auxiliary to a 2-methylpyrrolidine produced the desired product in 96% yield with a d.r. of 4.6/1 (see the SI).

(16) (a) Curtin, M. L.; Dai, Y.; Davidsen, S. K.; Frey, R. R.; Guo, Y.; Heyman, H. R.; Holms, J. H.; Ji, Z.; Michaelides, M. R.; Vasudevan, A.; Wada, C. K. Inhibitors of histone deacetylase and their therapeutic use. U.S. Patent 0,177,594, Nov 28, 2002. (b) Wada, C. K.; Frey, R. R.; Ji, Z.; Curtin, M. L.; Garland, R. B.; Holms, J. H.; Li, J.; Pease, L. J.; Guo, J.; Glaser, K. B.; Marcotte, P. A.; Richardson, P. L.; Murphy, S. S.; Bouska, J. J.; Tapang, P.; Magoc, T. J.; Albert, D. H.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3331.

(17) Because of the increased steric demand of the PMB substituent on nitrogen, the TEMPO conditions had to be used in lieu of LNO oxidation.

(18) In separate experiments, a reaction between TEMPO and triflic anhydride could be observed and substantiated by changes in the ^{1}H and ^{19}F NMR spectra. However, characterization and identification of the resulting species were inconclusive. See the SI for further details.

(19) The substitution of **I** leading to **II** could also conceivably result from attack of TEMPO$^{\bullet}$ and release of TfO$^{\bullet}$. However, this type of reaction is mechanistically unprecedented in amide activation.

DOI: 10.1021/jacs.7b02983
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX