ACS Catalysis

Research Article

Cite This: ACS Catal. 2019, 9, 11125−11129

pubs.acs.org/acscatalysis

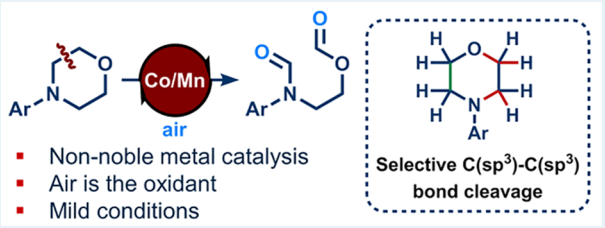
Improved Bimetallic Cobalt−Manganese Catalysts for Selective Oxidative Cleavage of Morpholine Derivatives

David K. Leonard, Wu Li, Kathrin Junge, and Matthias Beller*

Leibniz Institute for Catalysis at the University of Rostock, Albert-Einstein-Straße 29a, 18059 Rostock, Germany

Supporting Information

ABSTRACT: Catalytic methods for the site-selective scission of $C(sp^3)-C(sp^3)$ bonds remain scarcely explored in contrast to the vast literature on C−C coupling. In view of this, we report a means of oxidative C−C single-bond cleavage in morpholines, made possible by a synergy between cobalt and manganese catalysts using air as a benign oxidant. We demonstrate the synthetic utility of this system with the late-stage oxidative cleavage of Linezolid.



KEYWORDS: *manganese, cobalt, oxidation, C−C bond activation, heterocycles*

Despite being so highly prevalent in the scaffold of organic compounds, cleavage of $C(sp^3)-C(sp^3)$ bonds remains a real synthetic challenge, particularly in the presence of more reactive functional groups. C−C single bonds are kinetically stable because of steric hindrance and the directional nature of sp^n-hybridized orbitals used in covalent bonding. Additionally, oxidative addition of C−C bonds is difficult to achieve thermodynamically, as the strength of M−H bonds exceeds that of M−C bonds.[1]

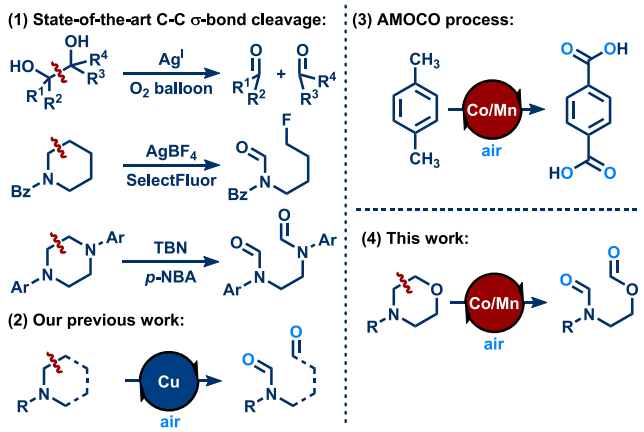
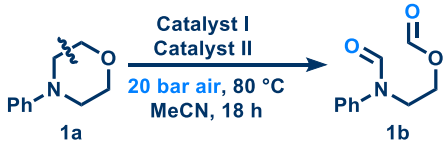


Figure 1. Selected examples of C−C bond cleavage reactions and Co/Mn-catalyzed oxidations.[9−12]

In traditional synthetic methods (e.g., the Criegee and Malaprade reactions), chemists employed oxidants, such as O_3,[2] $NaIO_4$,[3] HIO_4,[4] $Pb(OAc)_4$,[5] and $KMnO_4$, to enable C−C bond scission. Regrettably, these harsh oxidizing reagents are unsuitable for most substrates containing more reactive functional groups. Thus, mild catalytic protocols for C−C bond activations are in demand as novel deconstructive strategies and functionalizations of organic compounds.

Table 1. Co and Mn Catalysts for C−C Bond Cleavage in *N*-Phenylmorpholine[a]



entry	catalyst I	catalyst II	yield **1b** (%)[d]
1	$Mn(OAc)_2{\cdot}4H_2O$[b]		trace
2	$Mn(OAc)_2{\cdot}4H_2O$		26
3		$CoBr_2$[b]	10
4		$Co(OAc)_2{\cdot}4H_2O$	13
5	$Mn(OAc)_2{\cdot}4H_2O$	$Co(OAc)_2{\cdot}4H_2O$	60[c]
6	$Mn(OAc)_2{\cdot}4H_2O$	$Co(OAc)_2{\cdot}4H_2O$	96
7	$Mn(OAc)_2{\cdot}4H_2O$	$CoBr_2$	94
8	$Cu(OTf)_2$		55

[a]Reaction conditions: **1a** (0.5 mmol), catalyst I (5 mol %), catalyst II (5 mol %), pyridine (20 mol %), in MeCN (2 mL), 20 bar air, 80 °C. [b]Catalyst I/II (10 mol %). [c]KBr (5 mol %) added. [d]Yields determined by gas chromatograph-flame ionization detector (GC-FID) using *n*-dodecane as an internal standard.

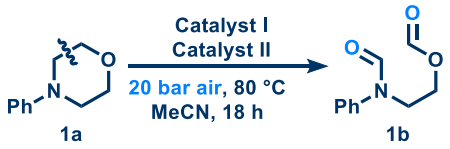
Furthermore, this field may even lead to innovative methods for breaking biomass into high-value chemicals/fuels, or to "crack" fossil fuel feedstocks with greater efficiency and improved selectivity.

In nature, several metalloenzymes are capable of aerobic C−C single-bond cleavages under mild conditions and play a key role in animal metabolism. Examples of such reactivity is shown by the diketone-cleaving enzyme (Dke 1), capable of oxidatively cleaving acetylacetone into less toxic metabolites,[6]

Received: August 16, 2019
Revised: October 22, 2019
Published: October 24, 2019

DOI: 10.1021/acscatal.9b03476
ACS Catal. 2019, 9, 11125−11129

Table 2. Variation of Catalysts and Optimization[a]



entry	catalyst I	catalyst II	ligand	yield **1b**[b] (%)
1	$Mn(OAc)_2{\cdot}4H_2O$	$Co(acac)_3$	Py	19
2	$Mn(OAc)_2{\cdot}4H_2O$	$Co(OAc)_2{\cdot}4H_2O$		54
3	$MnBr_2$	$Co(OAc)_2{\cdot}4H_2O$	Py	63
4	$Mn(acac)_2$	$Co(OAc)_2{\cdot}4H_2O$	Py	72
5	$MnCl_2$	$Co(OAc)_2{\cdot}4H_2O$	Py	92
6	$Mn(OAc)_2{\cdot}4H_2O$	$CoBr_2$	Py	94
7	$Mn(OAc)_2{\cdot}4H_2O$	$Co(OAc)_2{\cdot}4H_2O$	Py	96

[a]Reaction conditions: **1a** (0.5 mmol), catalyst I (5 mol %), catalyst II (5 mol %), ligand (20 mol %) in MeCN (2 mL), 20 bar air, 80 °C. [b]Yields determined by GC-FID using *n*-dodecane as an internal standard.

2-hydroxyethylphosphonate dioxygenase (HEPD)[7] and 2,4-dihydroxyacetophenone dioxygenase (DAD).[8] Remarkably, one of the key features of these enzymes is that they all contain iron metal ions, thus demonstrating the ability of non-noble metals to cleave C−C σ-bonds under mild conditions.

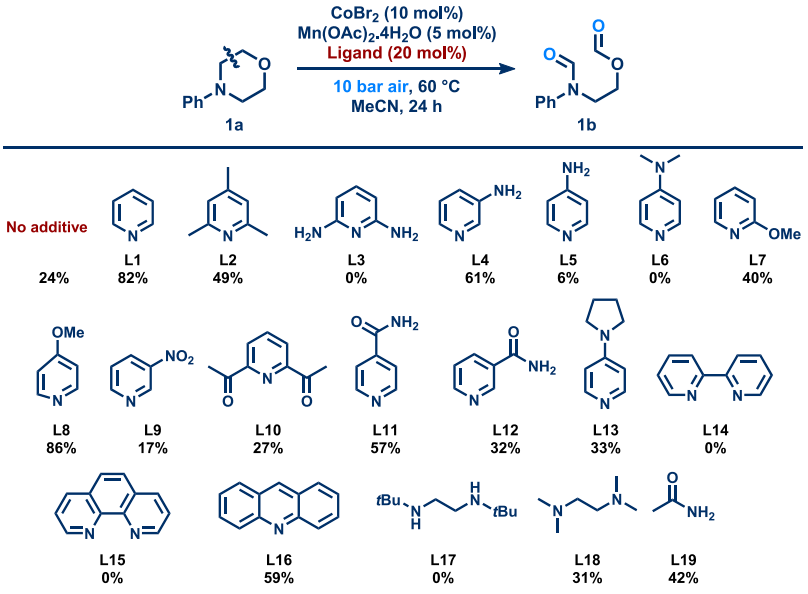
Drug compounds are also sensitive to metabolic pathways which alter their physicochemical properties and toxicity. Thus, the ability to synthesize and characterize drug metabolites may greatly benefit the pharmaceutical industry by guiding the selection of safe and viable drug candidates.

Modern developments have enabled $C(sp^3)-C(sp^3)$ bonds to be utilized as synthons for various structural diversification strategies. The state-of-the-art publications in this field include the following (Figure 1): the deconstructive fluorination of *N*-heterocycles using $AgBF_4$ and SelectFluor;[9] the AgOTf-catalyzed cleavage of 1,2-diols;[10] the Cu(I)-mediated cleavage of amines;[11] and *tert*-butyl nitrite (TBN)-enabled bond activations in diarylpiperazines.[12] In summary, these works highlight that the cleavage of C−C σ-bonds is feasible under mild conditions and need not be restricted to simple substrates.

In a similar fashion to C−C bond activations, the structural diversification of C−H bonds is hindered by their inertness and pervasiveness within the framework of organic compounds. These initial restraints have been tackled over several decades of intense focus, which has led to a number of successful industrial developments, including the AMOCO process.[13] This process has been adopted worldwide for the autoxidation of *para*-xylene to terephthalic acid,[14] a valuable precursor for condensation polymerizations. Interestingly, this reaction uses a combination of two homogeneous catalysts, in addition to a source of bromide, which acts as a promoter. The key to the success of this reaction is a unique Co/Mn/Br combination, which introduces new catalytic pathways to increase the catalyst activity by 16 times, compared to a single cobalt catalyst.[13] Reminiscently, we herein report a method for the selective cleavage of $C(sp^3)-C(sp^3)$ bonds within functionalized morpholines using a combination of cobalt and manganese catalysts under aerobic conditions (Figure 1).

From the outset we were investigating the ability of non-noble metals for the cleavage of C−C single bonds under air. Inspired by our recent work using Cu catalysts,[11] we tested various metal species for the site-selective cleavage of *N*-phenylmorpholine **1a**, applying 20 bar of air at 80 °C. While $Pd(OAc)_2$, $Ru(acac)_3$, $RuCl_3$, $Fe(OAc)_2$, $Co(OAc)_2{\cdot}4H_2O$, $CoBr_2$, $AgCF_3SO_3$, Ag_2CO_3, $Mn(OAc)_2{\cdot}4H_2O$, $Mn(acac)_2$, $MnCl_2$, and MnO_2 displayed only low activity for the desired transformation (Table S1), to our delight, we discovered that by using Mn(II) and Co(II) salts in tandem, we could realize a dramatic increase in catalytic activity. As a result, we observed an increase in the yield of 2-(*N*-phenylformamido)ethyl formate (**1b**) from 10% to 94% (Table 1). In contrast to the aforementioned AMOCO process, the addition of a bromide source (KBr) was disadvantageous here (Table 1, entry 5).

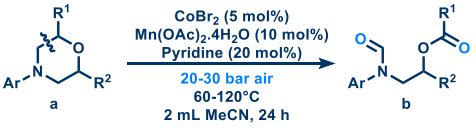
Table 3. Influence of *N*-Containing Ligands on the Benchmark Reaction[a]

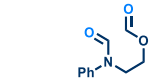
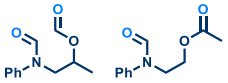
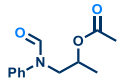
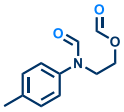
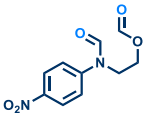
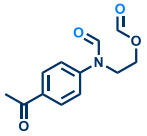
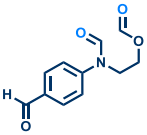
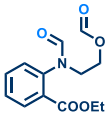
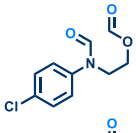
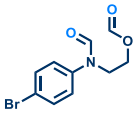
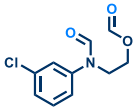
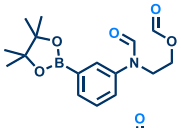
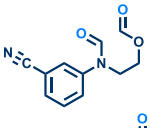
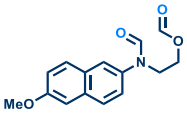
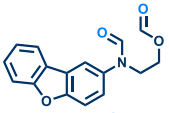
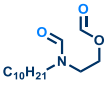


[a]Reaction conditions: **1a** (0.5 mmol), $CoBr_2$ (10 mol %), $Mn(OAc)_2{\cdot}4H_2O$ (5 mol %), ligand (20 mol %) in MeCN (2 mL), 10 bar air, 60 °C. Yields determined by GC-FID using *n*-dodecane as an internal standard.

DOI: 10.1021/acscatal.9b03476
ACS Catal. 2019, 9, 11125−11129

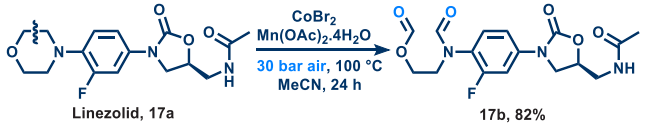
Table 4. C−C Bond Cleavage Reactions of Morpholines[a]



entry	product(s)		T (°C)	P (bar)	yield (%)[b]
1		**1b**	60	20	96
2		**2b & 2c** (2.70:1)	60	20	>99
3		**3b**	60	20	66
4		**4b**	60	20	85
5		**5b**	100	30	43
6		**6b**	100	30	77
7		**7b**	100	30	>99
8		**8b**	120	20	90
9		**9b**	60	20	90
10		**10b**	60	20	84
11		**11b**	100	30	70
12		**12b**	60	20	56
13		**13b**	100	30	81
14		**14b**	100	30	60
15		**15b**	100	30	27[c]
16		**16b**	120	20	17[c]

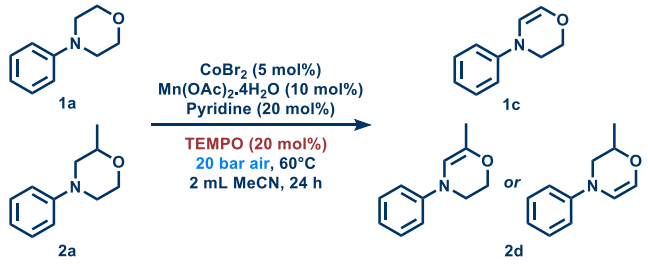
[a]Reaction conditions: **1a** (0.5 mmol), $CoBr_2$ (5 mol %), $Mn(OAc)_2{\cdot}4H_2O$ (10 mol %), pyridine (20 mol %) in MeCN (2 mL). [b]Isolated yields by column chromatography. [c]Pyridine (1 equiv).

Scheme 1. Late-Stage C−C Bond Cleavage of Bioactive Linezolid[a]



[a]Reaction conditions: **17a** (0.5 mmol), $CoBr_2$ (5 mol %), $Mn(OAc)_2{\cdot}4H_2O$ (5 mol %), pyridine (20 mol %) in MeCN (2 mL), 30 bar air, 100 °C.

Scheme 2. Putative Intermediates Detected by GC-MS[a]



[a]Reaction conditions: **1a** or **2a** (0.5 mmol), $CoBr_2$ (5 mol %), $Mn(OAc)_2{\cdot}4H_2O$ (5 mol %), pyridine (20 mol %), TEMPO (20 mol %) in MeCN (2 mL), 20 bar air, 60 °C.

Notably, significantly lower yield is observed in the presence of our previously developed Cu catalyst (Table 1, entry 8), clearly demonstrating the improved reactivity of the bimetallic system.

Spurred on by these initial findings, we investigated the activity of various Co(II) and Mn(II) salts. As shown in Table 2, the combinations $Mn(OAc)_2{\cdot}4H_2O/Co(OAc)_2{\cdot}4H_2O$, $Mn(OAc)_2{\cdot}4H_2O/CoBr_2$, and $MnCl_2/Co(OAc){\cdot}4H_2O$ all exhibited comparably excellent yields of **1b** (Table 2). It is noteworthy to highlight that, in the absence of pyridine, the reaction yield is decreased from 96% to 54%, supporting the documented positive influence of *N*-containing ligands in oxidations.[11,15]

To investigate this effect further, we tested a range of pyridines, amides, urea, and amines as alternative ligands in

DOI: 10.1021/acscatal.9b03476
ACS Catal. 2019, 9, 11125−11129

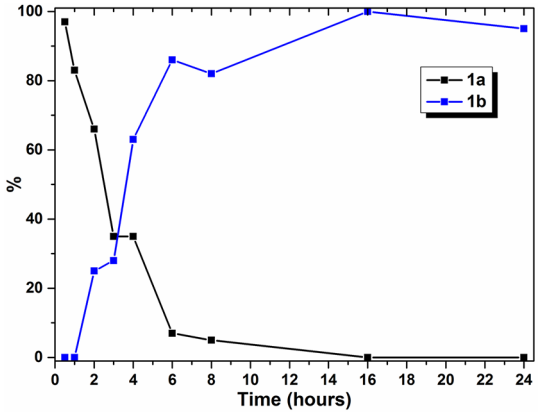


Figure 2. Reaction monitoring of C−C bond cleavage.

this reaction under mild conditions (60 °C, 10 bar air). As shown in Table 3, most substituted pyridines proved to be beneficial here. Notably, pyridine (**L1**) and 4-methoxypyridine (**L8**) were most effective in this regard, improving the yield of **1b** to 82% and 86%, respectively.

Unpredictably, chelating agents proved either disadvantageous (**L14**, **L15**, **L17**) or provided only weak activation (**L18**) for this transformation. 2,2′-bipy and phenanthroline—which are widely adopted ligands in catalysis—stopped the catalysis entirely! Ultimately, owing to its high performance, ready availability, and low cost, pyridine was chosen as an ideal ligand in this reaction.

Before proceeding, nitrous oxide (N_2O) was also considered as an alternative oxidant in this reaction,[16] as when reduced, this strong oxidant can be reduced to dinitrogen, and thus provide a beneficial entropic gain and driving force in the reaction. To our disappointment, this approach was unsuccessful and no reaction was observed (see Supporting Information for experimental details). Nevertheless, air had proven to be an effective oxidizer in our system, and thus it was utilized for all subsequent reactions.

With an effective catalyst, ligand, and oxidant in hand, we were able to obtain full conversion of **1a**, with no detectable side reactions taking place using 20 bar air at 60 °C. After isolation, **1b** was afforded with 96% yield. It is important to note that this reaction was not successful at low pressure when using a balloon filled with air, indicating the involvement of oxygen in the rate-limiting reaction step. To explore the applicability of this new system, a variety of functionalized morpholines were applied as substrates in this reaction under the optimized catalytic conditions (Table 4).

Methyl-substituted derivatives (**2a** and **3a**) were well-tolerated, despite introducing extra steric bulk directly at the reaction center. Likewise, with the inclusion of electron-withdrawing groups on the phenyl ring (e.g., NO_2, C≡N, COOEt), high yields of the desired products (**5b**, **8b**, **13b**) could be obtained. Gratifyingly, aryl halides, which are invaluable building blocks for the pharmaceutical and agrochemical industries, were able to afford high yields with the C−X bond intact. Similarly, boronate ester (**12b**), which represents a privileged substrate for Suzuki−Miyaura cross-coupling reactions, was able to be cleaved at low temperature (60 °C) with a yield of 56%.

In addition to the ester moiety, ketone (**6a**) posed no issues. Astonishingly, even under our oxidation conditions, the analogous aldehyde *para*-formylphenylmorpholine (**7a**) did not undergo oxidation to the corresponding carboxylic acid. The desired product **7b** was obtained selectively in quantitative yield! Furthermore, compounds **1b**, **4b**, **9b**, and **10b** were synthesized with high yields at only 60 °C and 20 bar air. Notably, this is a substantial improvement from our recently reported [Cu]/air protocol, which utilizes harsher conditions (80−100 °C, 20−30 bar air).[11]

To further probe the general applicability of the Co/Mn system toward functionalized molecules, we attempted the cleavage of the prescription antibiotic Linezolid. Successfully, we managed to obtain an 82% isolated yield of the expected product **17b** (Scheme 1). Therefore, we argue that this highlights the potential of this protocol for late-stage functionalization and for the introduction of valuable structural complexity to nonstrained heterocycles.

To initially probe the existence of radical intermediates, we performed cleavage of **1a** under optimized conditions in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). With addition of substoichiometric amounts of TEMPO (10 mol %) to the mixture, the reaction was stopped completely and none of the desired product was detected by GC-FID. We infer, therefore, that radical intermediates are crucial in this process. While no radical intermediates could generally be observed over the entire course of the reaction, we were able to detect trace amounts of **1c** and **2d** (Scheme 2) by GC-MS by quenching the reaction with TEMPO (20 mol %). From these data, we infer that dehydrogenation of the $C(sp^3)-C(sp^3)$ bond to a more labile $C(sp^2)-C(sp^2)$ bond occurs prior to oxidative cleavage.

On the basis of a recent report from He et al.,[12] further experiments were performed to capture some intermediates by the addition of $NaNO_2$ to the reaction mixture but without success. Similarly, using $C_{10}F_{21}I$, which easily reacts with carbon-centered radicals, was also ineffective for this purpose (see Supporting Information).

A kinetic profile was recorded to monitor the reaction. As seen on Figure 2, there is no apparent induction period needed for the catalysis. After just 30 min, the starting material is consumed and after 6 h the yield is greater than 80%. Unfortunately, we were unable to detect any intermediates by GC-FID over the entire course of the reaction.

In conclusion, we have developed a mild protocol for the cleavage of $C(sp^3)-C(sp^3)$ bonds in functionalized morpholines using a combination of cobalt and manganese salts and air as an oxidant. In addition, the system has exhibited good tolerance toward a variety of chemical moieties, including halides, nitriles, and carbonyl substrates. Importantly, this protocol has proven effective for the late-stage functionalization of the drug Linezolid, with other functional groups remaining untouched.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b03476.

Experimental procedures; characterization data for compounds prepared (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: matthias.beller@catalysis.de (M.B.).

DOI: 10.1021/acscatal.9b03476
ACS Catal. 2019, 9, 11125−11129

ORCID

Matthias Beller: 0000-0001-5709-0965

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the support from the Federal Ministry of Education and Research (BMBF) and the State of Mecklenburg-Vorpommern. Financial support by Fonds der Chemischen Industrie (Kekulé-Stipendium n. 103231) for D.K.L. is also acknowledged. We thank the analytical staff of the Leibniz-Institute for Catalysis, Rostock, for their excellent service.

■ REFERENCES

(1) (a) Sattler, A.; Parkin, G. Cleaving Carbon−Carbon Bonds by Inserting Tungsten into Unstrained Aromatic Rings. *Nature* **2010**, *463*, 523. (b) Masarwa, A.; Didier, D.; Zabrodski, T.; Schinkel, M.; Ackermann, L.; Marek, I. Merging Allylic Carbon-Hydrogen and Selective Carbon-Carbon Bond Activation. *Nature* **2014**, *505*, 199−203.

(2) (a) Saliu, F.; Orlandi, M.; Bruschi, M. *N*-Aryl Lactams by Regioselective Ozonation of *N*-Aryl Cyclic Amines. *ISRN Org. Chem.* **2012**, *2012*, 1−5. (b) Suarez-Bertoa, R.; Saliu, F.; Bruschi, M.; Rindone, B. Reaction Products and Mechanism of the Regioselective Oxidation of *N*-Phenylmorpholine by Ozone. *Tetrahedron* **2012**, *68*, 8267−8275.

(3) Binder, C. M.; Dixon, D. D.; Almaraz, E.; Tius, M. A.; Singaram, B. A Simple Procedure for C-C Bond Cleavage of Aromatic and Aliphatic Epoxides with Aqueous Sodium Periodate Under Ambient Conditions. *Tetrahedron Lett.* **2008**, *49*, 2764−2767.

(4) Malaprade, L. *Bull. Soc. Chim. Fr.* **1934**, *3*, 833.

(5) Criegee, R. Eine Oxydative Spaltung von Glykolen. *Ber. Dtsch. Chem. Ges. B* **1931**, *64*, 260−266.

(6) Straganz, G. D.; Glieder, A.; Brecker, L.; Ribbons, D. W.; Steiner, W. Acetylacetone-Cleaving Enzyme Dke1: A Novel C-C-Bond-Cleaving Enzyme from *Acinetobacter johnsonii*. *Biochem. J.* **2003**, *369*, 573−581.

(7) Peck, S. C.; Cooke, H. A.; Cicchillo, R. M.; Malova, P.; Hammerschmidt, F.; Nair, S. K.; van der Donk, W. A. Mechanism and Substrate Recognition of 2-Hydroxyethylphosphonate Dioxygenase. *Biochemistry* **2011**, *50*, 6598−6605.

(8) Keegan, R.; Lebedev, A.; Erskine, P.; Guo, J.; Wood, S. P.; Hopper, D. J.; Rigby, S. E. J.; Cooper, J. B. Structure of the 2,4′-Dihydroxyacetophenone Dioxygenase from *Alcaligenes sp*. 4HAP. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2014**, *70*, 2444−2454.

(9) Roque, J. B.; Kuroda, Y.; Göttemann, L. T.; Sarpong, R. Deconstructive Fluorination of Cyclic Amines by Carbon-Carbon Cleavage. *Science* **2018**, *361*, 171−174.

(10) Zhou, Z. Z.; Liu, M.; Lv, L.; Li, C. J. Silver(I)-Catalyzed Widely Applicable Aerobic 1,2-Diol Oxidative Cleavage. *Angew. Chem., Int. Ed.* **2018**, *57*, 2616−2620.

(11) Li, W.; Liu, W.; Leonard, D. K.; Rabeah, J.; Junge, K.; Brückner, J.; Beller, M. Practical Catalytic Cleavage of $C(sp^3)$−$C(sp^3)$ Bonds in Amines. *Angew. Chem.* **2019**, *131*, 10803−10807.

(12) He, K.; Zhang, T.; Zhang, S.; Sun, Z.; Zhang, Y.; Yuan, Y.; Jia, X. Tunable Functionalization of Saturated C-C and C-H Bonds of *N*,*N*′-Diarylpiperazines Enabled by tert-Butyl Nitrite (TBN) and $NaNO_2$ Systems. *Org. Lett.* **2019**, *21*, 5030−5034.

(13) Tomas, R. A.; Bordado, J. C.; Gomes, J. F. *p*-Xylene Oxidation to Terephthalic Acid: A Literature Review Oriented Toward Process Optimization and Development. *Chem. Rev.* **2013**, *113*, 7421−69.

(14) (a) Brill, W. Terephthalic Acid by Single-Stage Oxidation. *Ind. Eng. Chem.* **1960**, *52*, 837−840. (b) Zuo, X.; Niu, F.; Snavely, K.; Subramaniam, B.; Busch, D. H. Liquid Phase Oxidation of *p*-Xylene to Terephthalic Acid at Medium-High Temperatures: Multiple Benefits of CO_2-Expanded Liquids. *Green Chem.* **2010**, *12*, 260. (c) Raghavendrachar, P.; Ramachandran, S. Liquid-phase catalytic oxidation of p-xylene. *Ind. Eng. Chem. Res.* **1992**, *31*, 453−462.

(15) (a) Stahl, S. S. Palladium-Catalyzed Oxidation of Organic Chemicals with O_2. *Science* **2005**, *309*, 1824. (b) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev.* **2018**, *118*, 2636−2679.

(16) Ettedgui, J.; Neumann, R. *J. Am. Chem. Soc.* **2009**, *131*, 4−5.

DOI: 10.1021/acscatal.9b03476
ACS Catal. 2019, 9, 11125−11129