Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

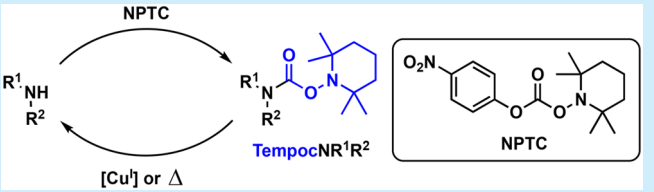
2,2,6,6-Tetramethylpiperidin-1-yloxycarbonyl: A Protecting Group for Primary, Secondary, and Heterocyclic Amines

Joseph R. Lizza,[†] Maximilian Bremerich,[‡] Stephanie R. McCabe,[†] and Peter Wipf*[,†]

[†]Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States
[‡]Institute of Organic Chemistry, RWTH Aachen University, Aachen, Germany

Supporting Information

ABSTRACT: The 2,2,6,6-tetramethylpiperidin-1-yloxycarbonyl (Tempoc) protecting group is readily introduced by the reaction of amines with a new acyl transfer reagent, 4-nitrophenyl (2,2,6,6-tetramethylpiperidin-1-yl) carbonate (NPTC). Tempoc has a reactivity profile that complements the commonly used *t*-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) protecting groups. Deprotection can be achieved under mild reductive conditions with *in situ* generated Cu(I) species or by thermolytic cleavage at 135 °C. Mechanistic studies on the deprotection of Tempoc-indole suggest a combination of ionic and radical fragmentation pathways under thermal conditions.



Synthetic efficiency in routes toward complex target molecules, including natural products, strives to minimize the use of protecting groups; however, basic amines are frequently incompatible with transition metal catalysis and oxidative conditions and often require protection during these transformations.[1−3] Furthermore, protecting groups continue to play a critical role in peptide synthesis[4] and carbohydrate chemistry.[5] Therefore, the development of new protecting groups remains an important goal in organic and biological chemistry. Orthogonal protecting groups that allow for selective manipulations in molecules with multiple functionalities are particularly useful in this context.[6−9] Amines are among the most common functionalities found in both pharmaceuticals and natural products.[10,11] While trifluoroacetyl,[12] tosyl,[13] nosyl,[14,15] phthaloyl,[16] and trityl[17] are frequently used for amine protection, carbamates with *t*-butoxycarbonyl (Boc),[18] benzyloxycarbonyl (Cbz),[18] 9-fluorenylmethoxycarbonyl (Fmoc),[19] and allyloxycarbonyl (Aloc or Alloc)[20] substituents are among the most common and versatile amine protecting groups used across all branches of chemistry. Carbamates offer robustness, ease of introduction and removal, and opportunities for orthogonal deprotections, and new variants are continually being developed.[21,22] Typical deprotection conditions involve acidic (Boc), basic (Fmoc), hydrogenolytic (Cbz), and transition metal catalyzed (Alloc) conditions. However, often reagents such as TFA,[23] HCl,[24] H_2/Pd,[25] Et_3SiH/Pd,[26] and Mg/MeOH[27] can promote side reactions such as over-reductions,[28] rearrangements,[29] and epimerizations.[30]

In our recent total synthesis of (−)-cycloclavine,[31] a base stable amine-protecting group was required that should be resistant to a tin−lithium transmetalation−enone 1,2-addition sequence and subsequently thermally cleavable during a Diels−Alder reaction (Figure 1). The Boc group did not provide satisfactory results, and after considerable optimization, we identified the 2,2,6,6-tetramethylpiperidin-1-yloxycarbonyl ("Tempoc") group as a superior protective group for this transformation.[31] We are now presenting studies that illustrate that Tempoc is of general utility for amine protection.

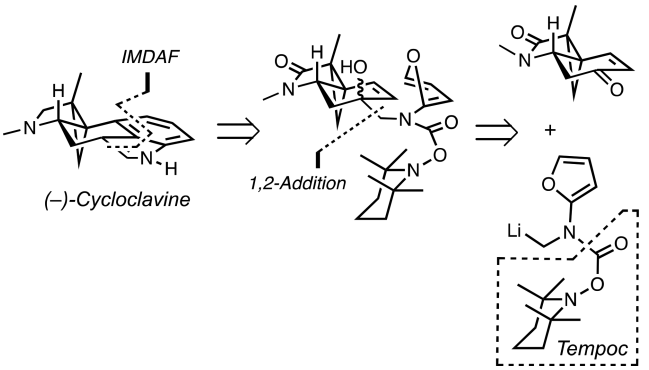


Figure 1. Use of a Tempoc-protected lithium reagent for a selective 1,2-addition.[31]

We first developed a suitable reagent for the introduction of Tempoc on amines (Scheme 1). Reduction of the stable nitroxide Tempo (**1**) with sodium ascorbate (SA)[32] and *O*-acylation of the intermediate hydroxylamine with *p*-nitrophenyl chloroformate provided the Tempoc transfer reagent **2** ("NPTC"). Under the optimized conditions, treatment of 2-phenethylamine (**3**) with 1.2 equiv of NPTC in DMF at room temperature in the presence of 3 equiv of triethylamine provided the Tempoc-protected carbamate **4** in 94% yield. Other suitable solvents and bases include THF, dichloro-

Received: September 8, 2018

DOI: 10.1021/acs.orglett.8b02874
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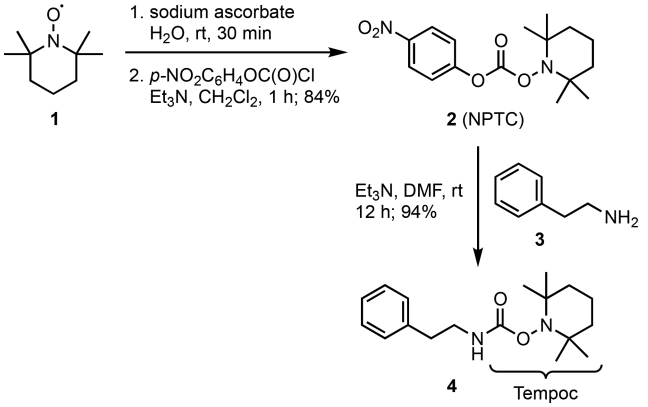
Scheme 1. Preparation of *p*-Nitrophenol Tempo Carbonate (NPTC) and Protection of 2-Phenethylamine



methane, methanol, pyridine, sodium bicarbonate, and potassium carbonate, but in this particular case, these reagents led to slightly reduced yields of **4** (Supporting Information (SI), Table 1). Several alternatives to NPTC were also identified (see Supporting Information (SI), reagents **S1**−**S4**), but NPTC consistently provided the highest yields and was also readily accessible at an ∼100 g scale. Differential scanning calorimetry (DSC) of NPTC showed an exotherm of 70 cal/g at an onset temperature of 135 °C, suggesting that, in spite of the presence of a nitro group and a weak N−O bond, **4** is a relatively stable compound.[33,34] However, we have not yet pursued shock sensitivity studies that would provide an additional safety parameter.

Under the optimized conditions (i.e., amine (1 equiv), NPTC (1.2 equiv), and triethylamine (3 equiv), in DMF (0.5 M, rt, 12 h)), primary amines were converted to the Tempoc derivatives **5**−**16** in high yields, with the exception of the sterically hindered *t*-butylamine **15** (Figure 2). Branching in the α-position led to a slight decrease in yields for **6** and **11** to 72% and 75%, respectively, but the sterically less hindered cyclohexylamine **13** was obtained in 87%.

Interestingly, anilines proved unreactive toward NPTC, which was used as an advantage for diamine **12**, where only benzyl amine protection was observed in the presence of 1.2 equiv of NPTC. Similarly, no acylation of the indole nitrogen was found for tryptamine **5** under these conditions. Attempted preparation of naphthylamine **18** and protection of other anilines also failed even under more forcing conditions and with a larger excess of NPTC reagent. Preliminary evidence suggests that it is necessary to deprotonate anilines in order to achieve the level of nucleophilicity necessary for acylation with the carbonate, and we are still exploring suitable bases for this purpose. In agreement with this finding, we observed that alcohol functions were well tolerated in the absence of strong bases, even allowing the use of methanol as a solvent, and exclusive selectivity for amine carbamoylation was achieved for amino alcohols **6** and **16**. With a 2:1 ratio of hydrazine vs NPTC, the monoprotected hydrazide reagent **17** was isolated in 95% yield. Furthermore, the use of 2.6 equiv of NaH as a base in the presence of 2.4 equiv of NPTC induced double *N*-acylation to give phenethylamine **19** in 90% yield.

The protection of secondary amines in **20**−**27** was also generally accomplished in excellent yields (Figure 3). Both linear and cyclic amines behaved uniformly well, with the exception of dipropylamine derivative **25**, which could only be

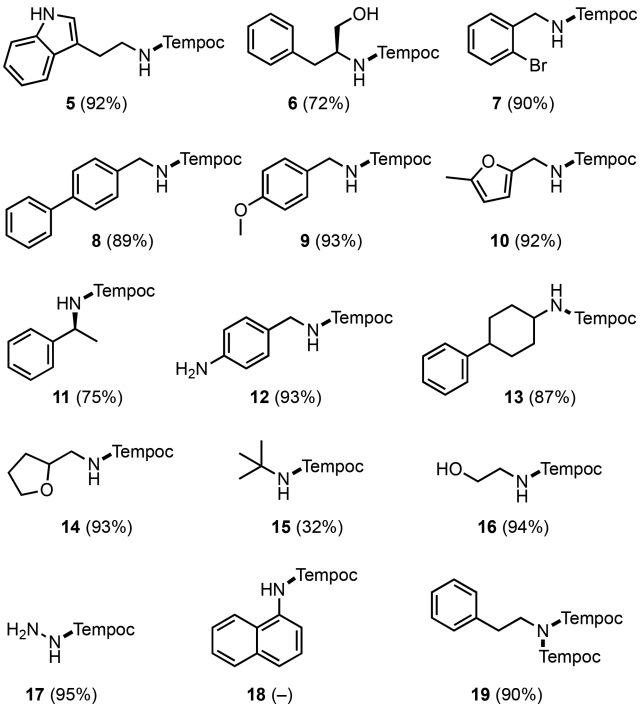


Figure 2. Products of Tempoc protection of primary amines (isolated yields).

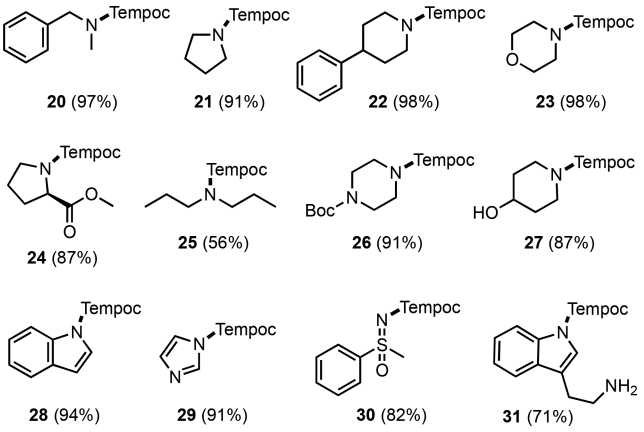


Figure 3. Products of Tempoc protection of secondary amines (isolated yields).

obtained in 56% yield. We repeated this reaction several times but were unable to substantially increase the yield, possibly a consequence of the subtle decrease in amine nucleophilicity caused by the steric hindrance of the two flexible propyl chains.

Four equiv of triethylamine were used for the Tempoc protection of proline methyl ester, providing **24** in 87% yield. Alcohol groups were still tolerated in the presence of secondary amines, as shown for **27**. Imidazole was also converted under standard conditions to the Tempoc derivative **29**, whereas the use of 1.3 and 1.1 equiv of NaH, respectively, allowed for the protection of indole and sulfoximine[35] nitrogens in **28** and **30**. The use of 1.3 equiv of NaH as a base also allowed for a selective protection of the indole nitrogen in tryptamine to give **31** in 71% yield (Figure 3).

In the synthesis of (−)-cycloclavine, we had employed a thermolysis in toluene at 135 °C for 68 h for Tempoc removal.[31] Our current investigations revealed considerable

DOI: 10.1021/acs.orglett.8b02874
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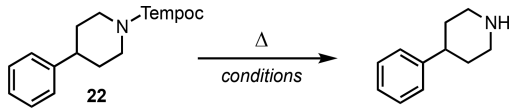
differences in thermal stabilities depending on the nature of the protected amine. Microwave heating of a 0.1 M solution of Tempoc-piperidine **22** in chlorobenzene or pyridine at 165−175 °C for 1 h only led to trace product (Table 1, entries 1 and 2). In contrast, Tempoc was cleanly removed in propionitrile in 48% yield after 2 h at 165 °C (Table 1, entry 3). In the more

Table 1. Thermolytic Deprotection of Secondary Amine 22

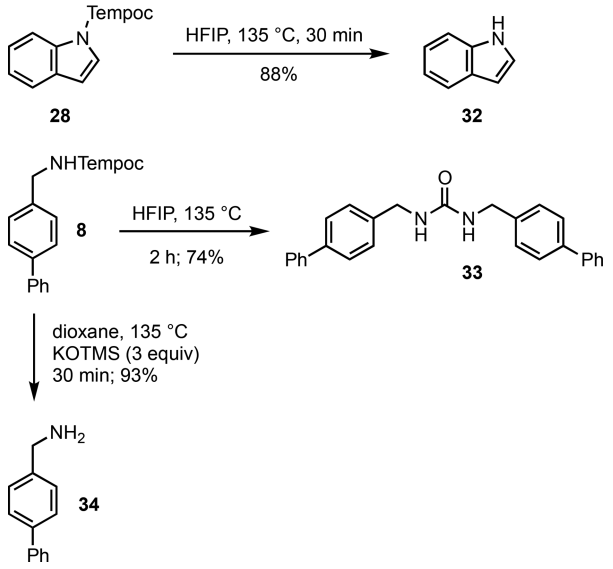


entry	solvent	temp (°C)	time (h)	yield (%)
1	PhCl	165	1	trace
2	pyridine	175	1	trace
3	EtCN	165	2	48
4	TFE	135	6	30
5	HFIP	135	6	73
6	HFIP	135	8	85

polar, protic solvent trifluoroethanol (TFE), deprotection was more facile, yielding 30% of 4-phenylpiperidine after 6 h at 135 °C (entry 4). Hexafluoroisopropanol (HFIP), which has previously been used to cleave carbamates,[36,37] further accelerated Tempoc removal and provided 4-phenylpiperidine in 73 and 85% yields after 6 and 8 h, respectively (entries 5 and 6).

Optimized thermolytic conditions were applied to indole **28** and primary amine **8** (Scheme 2). While the indole was

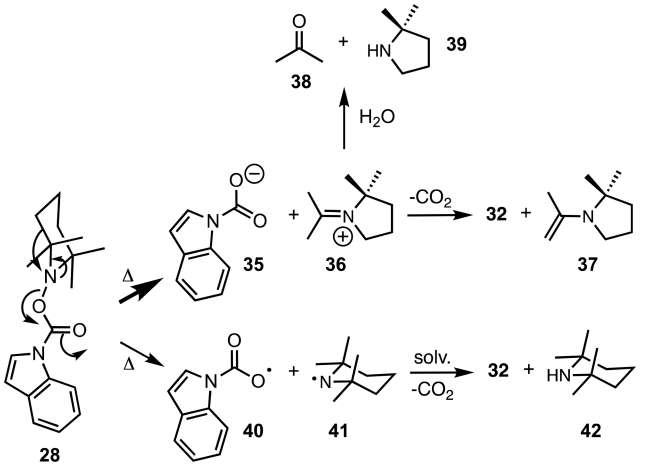
Scheme 2. Thermolytic Tempoc Deprotection of Indole and Primary Amine



deprotected in 88% yield after 30 min in HFIP at 135 °C, thermolysis of **8** under analogous conditions generated the symmetrical urea **33**. In the presence of 3 equiv of potassium trimethylsilanolate (KOTMS) in dioxane at 135 °C,[38] however, the desired primary amine **34** was formed in 30 min and 93% yield.

Since the literature information on the thermal breakdown of *O*-acyl hydroxylamines is sparse,[39] we searched for intermediates formed in the thermolysis of Tempoc-indole **28** (Scheme 3). We hypothesized that a heterolytic cleavage of the N−O bond would initially produce carbamic acid anion **35**

Scheme 3. Proposed Ionic and Radical Pathways for Tempoc Deprotection under Thermal Conditions



and iminium ion **36**,[39] which, after proton exchange and decarboxylation, would form indole **32** and pyrrolidine enamine **37**. Alternatively, a homolytic N−O bond breakage would generate radical pair **40** and **41**, which would likely produce indole **28** and piperidine **42** after hydrogen atom abstractions from solvent. Experimentally, when heated at 150 °C in toluene-d_8, **28** was found to generate a 3.6:1 ratio of pyrrolidine **39** and piperidine **42**, in addition to indole **32**. This ratio did not substantially change in the presence of 4 equiv of H_2O, but when the reaction was performed under nitrogen, a 2.3:1:1 ratio of **39**, **37**, and **42** was observed. Furthermore, when the temperature was lowered to 135−140 °C, the ratio of **39** to **42** also decreased to 1.8:1. These NMR analyses suggested that the ionic rearrangement pathway shown in Scheme 3 was the major source of the desired deprotected compound but that the homolytic N−O bond cleavage also participated in the cleavage of the Tempoc group, in particular under low-temperature conditions. Yet another possibility is a radical [1,2]-shift of **41** leading to **36** after electron transfer.

N−O bonds are known to undergo facile copper(I)-catalyzed reduction in the presence of stoichiometric reductants,[40−42] and therefore we also explored a redox cleavage of the Tempoc group. In the presence of 2.2 equiv of Cu(I)Cl, a 0.1 M solution of Tempoc-indole **28** in acetonitrile at room temperature was readily converted to indole **32** in 83% yield (Table 2, entry 1). Interestingly, under the same conditions, Cu(I)-iodide did not generate product (entry 2), and 1.1 equiv of $Cu(II)Cl_2$ only gave 2% of **32** (entry 3). Reducing the amount of Cu(II) salt to 0.2 equiv, but performing the reaction in the presence of the stoichiometric reductant sodium ascorbate (SA) or ascorbic acid (Asc) and water as a cosolvent, increased the yield to a still modest 29% after 24 h reaction time (entries 4 and 5). A significant increase in yield to 63% was observed when acetonitrile was changed to MeOH (entry 6), and a 5:1 mixture of DMF and water produced 84% of **32** (entry 7). This conversion was independent of the Cu(II) salt used and was repeated with $CuSO_4{\cdot}5H_2O$ (entry 8), as well as $Cu(OAc)_2$, $Cu(ClO_4)_2$, and $Cu(OTf)_2$ (not shown). Furthermore, Tempoc-protected piperidine **22** and indole **28** were also deprotected in >90%

DOI: 10.1021/acs.orglett.8b02874
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Table 2. Copper-Catalyzed Conversion of Tempoc-indole 28 to Indole 32

entry	CuX (equiv)	reductant (equiv)	solvent	yield (%)[a]
1	CuCl (2.2)	–	MeCN	83
2	CuI (2.2)	–	MeCN	trace
3	$CuCl_2$ (1.1)	–	MeCN	2
4	$CuCl_2$ (0.20)	SA (1.1)	MeCN/H_2O (2:1)	29
5	$CuCl_2$ (0.20)	Asc (5)	MeCN/H_2O (2:1)	29
6	$CuCl_2$ (0.20)	Asc (5)	MeOH/H_2O (5:1)	63
7	$CuCl_2$ (0.20)	Asc (5)	DMF/H_2O (5:1)	84, 82[b]
8	$CuSO_4$ (0.20)	Asc (5)	DMF/H_2O (5:1)	84
9	$CuCl_2$ (0.05)	Asc (2)	DMF/H_2O (5:1)	67[c]
10	$CuCl_2$ (0.05)	Asc (2)	MeCN/THF/H_2O (4:1:1)	83[c]
11	$CuCl_2$ (0.10)	Asc (2)	MeCN/THF/H_2O (4:1:1)	84[b]

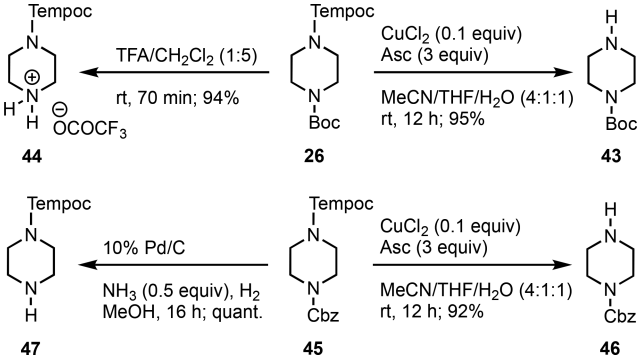
[a]HPLC yield. [b]Isolated yield after 12 h. [c]Isolated yield after 24 h.

isolated yield under these conditions. Cyclohexyl amine **13** required mild heating at 40 °C for deprotection in 91% yield.

When Cu(II) loading was reduced from 0.20 to 0.05 equiv, the conversion of **28** to **32** slowed down considerably, and only 67% product was isolated after 24 h in aqueous DMF (Table 2, entry 9). Switching the solvent to a ternary 4:1:1 mixture of MeCN, THF, and H_2O increased the yield back to 83% (entry 10). At 0.10 equiv of Cu(II) loading, an equivalent yield was obtained after only 12 h reaction time (entry 11) that could be further increased to 91% in the presence of 3 equiv of Asc. It is likely that the cosolvent acetonitrile inhibits the disproportionation of Cu(I) to Cu(II) and Cu(0)[43] and thus facilitates the reduction of the N−O bond and slows the precipitation and loss of the catalytic metal at low copper loadings.

Finally, we were able to demonstrate that a Tempoc group has orthogonal deprotection properties compared to two of the most popular carbamates, the Boc and Cbz groups (Scheme 4). Bis-protected piperazines **26** and **45** were readily converted

Scheme 4. Orthogonal Deprotections of Tempoc-, Boc-, and Cbz-Amines



to the Boc-amine **43** and the Cbz-amine **46**, respectively, under the Cu(I)-catalyzed Tempoc removal conditions. Alternatively, the Tempoc TFA salt **44** was obtained in 94% yield by removing the Boc group from **26** with TFA in dichloromethane (1:5), and its corresponding free base **47** was generated by hydrogenolysis of **45** in the presence of 0.5 equiv of methanolic ammonia.

In conclusion, our studies demonstrate that the 2,2,6,6-tetramethylpiperidin-1-yloxycarbonyl (Tempoc) group is an effective new protecting group for primary, secondary, and heterocyclic amines, with excellent orthogonality to Boc- and Cbz-carbamates, including resistance to acidic and hydrogenolytic conditions. Treatment with the crystalline *p*-nitrophenol Tempo carbonate (NPTC) reagent is a convenient way to introduce Tempoc in high yield and generally excellent chemoselectivity. For deprotections, two main reaction conditions are feasible: thermolysis occurs in HFIP at 135 °C, or alternatively, catalytic Cu(I) conditions release the amine at room temperature in an organic/aqueous solvent mixture. Previously, we have already demonstrated that a Tempoc-protected indole is resistant to strongly basic and nucleophilic reaction conditions.[31] Accordingly, we suggest that the Tempoc amine protective group is likely to be of significant utility in the synthesis of functionalized natural and unnatural target molecules and organic building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02874.

Experimental procedures, compound characterizations, NMR spectra, and DSC analysis (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pwipf@pitt.edu

ORCID

Stephanie R. McCabe: 0000-0001-9773-4796
Peter Wipf: 0000-0001-7693-5863

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by discretionary funding from Boehringer−Ingelheim Pharmaceuticals Inc., Ridgefield, CT, and a Dietrich School of Arts & Sciences Fellowship (JRL). The authors would also like to thank D. Crocker, T. Maskrey (University of Pittsburgh) for technical assistance, J. Aubé (University of North Carolina) for stimulating discussions, and D. K. Achary and B. Godugu (University of Pittsburgh) for NMR and HRMS analyses, respectively. JRL would also like to thank L. W. Whaley (Rowan University) for his mentorship, and MB thanks M. Kerner (University of Pittsburgh) for insightful discussions.

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DOI: 10.1021/acs.orglett.8b02874
Org. Lett. XXXX, XXX, XXX−XXX