

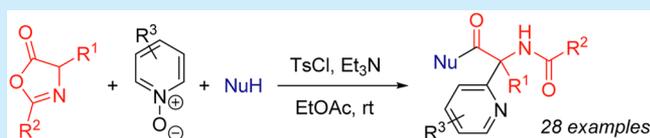
Precious-Metal-Free Heteroarylation of Azlactones: Direct Synthesis of α -Pyridyl, α -Substituted Amino Acid Derivatives

Tarn C. Johnson and Stephen P. Marsden*

School of Chemistry and Institute of Process Research and Development, University of Leeds, Leeds, LS2 9JT, U.K.

S Supporting Information

ABSTRACT: A one-pot, three-component synthesis of α -pyridyl, α -substituted amino acid derivatives is described. The key transformation is a direct, precious-metal-free heteroarylation of readily available, amino acid derived azlactones with electrophilically activated pyridine *N*-oxides. The resulting intermediates can be used directly as efficient acylating agents for a range of nucleophiles, leading to the heteroarylated amino acid derivatives in a single vessel.



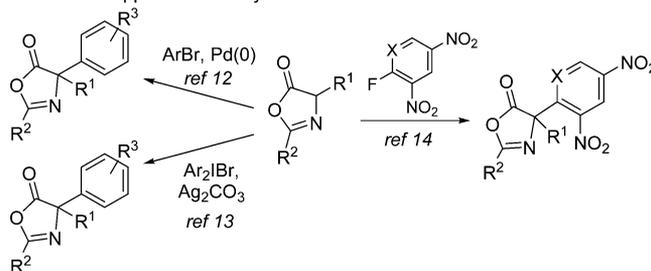
α,α -Disubstituted amino acids are found in many biologically active compounds, both naturally occurring and man-made.¹ The incorporation of such motifs into peptides and peptidomimetics confers conformational preferences (frequently inducing β -turns) as well as hydrolytic stability on the resulting peptides.² Among these structures, α -pyridyl, α -substituted amino acid derivatives have attracted interest as potent and selective inhibitors of proteases such as cathepsin³ and β -secretase,⁴ the latter as potential treatments for Alzheimer's disease. Additionally, the hydrogen-bond accepting capability of the pyridine nitrogen atom promotes well-defined conformational behavior upon short peptides containing α -2-pyridyl, α -substituted amino acids.⁵

Building on our interest in quaternary amino acids,⁶ we wished to develop a direct, convergent approach to α -pyridyl, α -substituted amino acids based upon heteroarylation of readily available α -amino acids. The intermolecular arylation of amino acid enolates or their equivalents is nontrivial. There are only isolated reports of the arylation of nonstabilized amino acid enolates by S_NAr reactions⁷ or oxidative coupling to nitroarenes.⁸ The arylation of stabilized enolates derived from amino acid aldimines is limited to S_NAr substitution of fluoro-nitroarenes⁹ and (fluoroarene)chromium(0) carbonyl complexes,¹⁰ or to direct coupling with arylbismuth reagents.¹¹ By contrast, the use of azlactones as relatively acidic amino acid enolate equivalents has been exploited in a broader range of arylation reactions (Scheme 1, panel A), including palladium-catalyzed cross-coupling to aryl halides,¹² direct condensation with diaryliodonium salts,¹³ and S_NAr reactions with nitrohaloarenes,¹⁴ as well as direct Michael addition/aromatization reactions with quinones.¹⁵ Among all of these examples, there are only isolated reports of the synthesis of α -pyridyl, α -substituted amino acids.^{8c,12b,14}

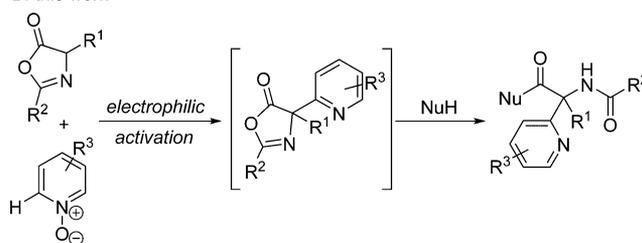
Londregan and colleagues at Pfizer have recently demonstrated the *in situ* activation/substitution of pyridine *N*-oxides using PyBroP with a range of nucleophiles,^{16–18} including carbon-based nucleophiles such as β -dicarbonyls (malonates, ketoesters, diketones, and cyanoacetate)¹⁷ and silyl ketene acetals.¹⁸ Given the similar pK_a of azlactones (ca. 9–10)¹⁹ and

Scheme 1. Arylation of Azlactones

A: Previous approaches to arylation of azlactones



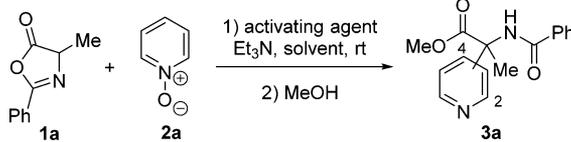
B: this work



the carbon acids (and other nucleophiles such as phenols) examined by Londregan, we anticipated that they might act as competent nucleophiles for the activated pyridine *N*-oxide, facilitating the direct, precious-metal-free synthesis of α -pyridyl, α -substituted amino acid derivatives (Scheme 1, Panel B).²⁰ Moreover, the azlactones can be regarded as activated acylating agents, the nucleophilic ring opening of which would lead directly to diverse α -pyridyl, α -substituted amino acid derivatives. This strategy is particularly significant and advantageous given the documented issues with facile decarboxylation of α -pyridyl amino acids,²¹ compounding the known poor electrophilicity of activated α,α -disubstituted amino acids. We report herein the successful demonstration of this strategy,

Received: September 11, 2016

Table 1. Screening of Electrophilic Activating Agents



entry	reagent	solvent	ratio C2:C4	isolated yield (%)
1	PyBroP	THF	1:0.7	53
2	TsCl	THF	1:2.2	68
3	4-NsCl	THF	1:1.7	11
4	MsCl	THF	1:3.8	16
5	Ac ₂ O	THF	n/a	0
6	AcCl	THF	n/a	0
7	TsCl	2-MeTHF	1:1.6	51
8	TsCl	EtOAc	1:1.5	68 (67 ^b)
9	TsCl	PhMe	1:1.6	67
10	TsCl	PhOMe	1:1.4	57
11	TsCl	TBME	1:1.4	47
12	TsCl	MeCN	1:1.7	42

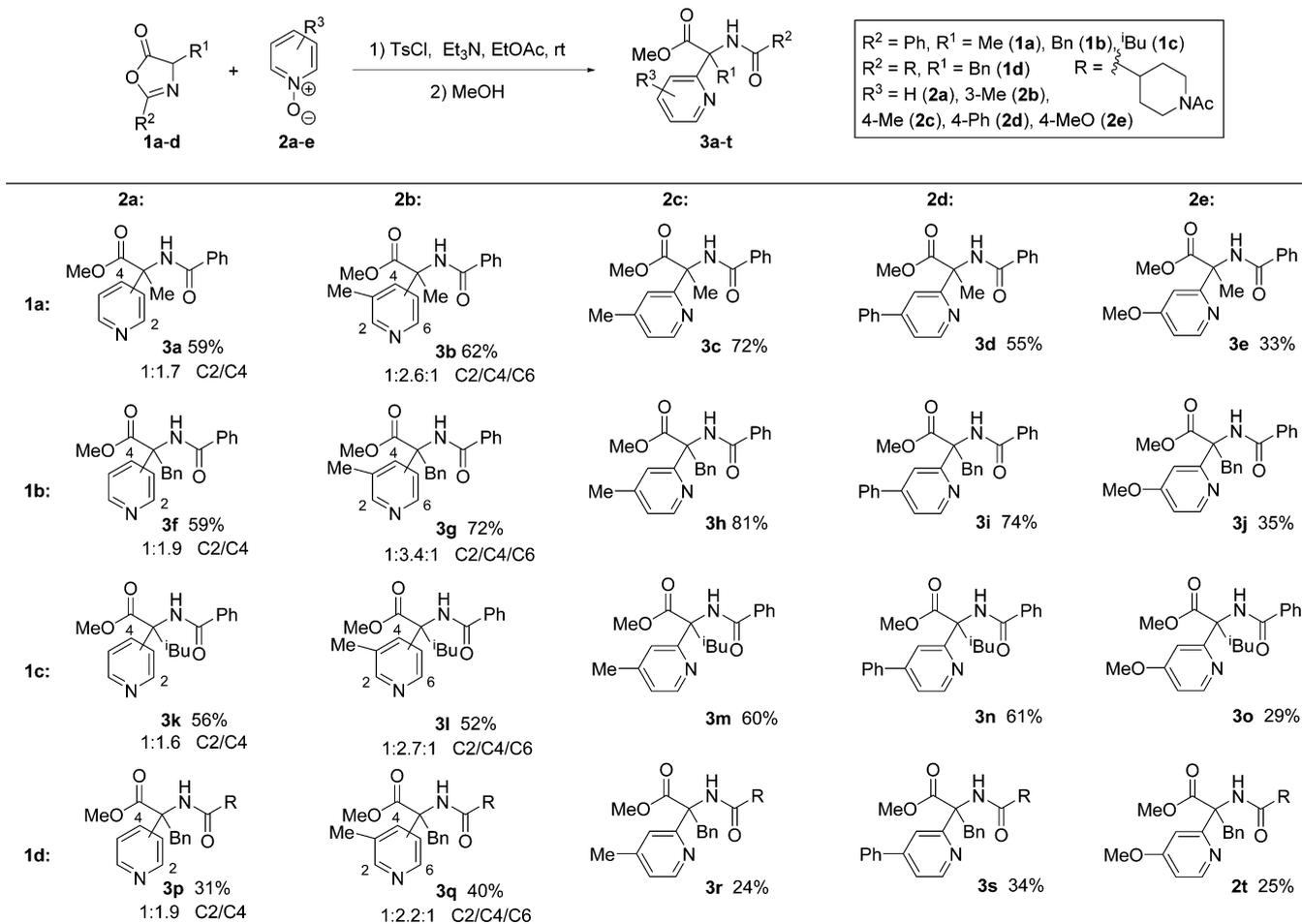
^aConditions: Azlactone (0.29 mmol), pyridine *N*-oxide (0.32 mmol), activating agent (0.32 mmol), NEt₃ (0.86 mmol), and solvent (1.4 mL) at rt for 16 h followed by addition of MeOH (1 mL) and stirring for a further 3 h. ^b0.61 mmol of NEt₃.

exemplified in the one-pot, three-component synthesis of a wide range of α -pyridyl quaternary amino acid derivatives.²²

We commenced our study with a screen of electrophilic activating agents for the direct coupling of 4-methyl-2-phenyloxazol-5-one **1a** with pyridine *N*-oxide **2a**; for ease of analysis, after a standard reaction time of 16 h the presumed intermediate azlactones were subjected to methanolysis to generate the α -methyl, α -pyridyl amino acid ester **3a** as a mixture of C2- and C4-regioisomers.

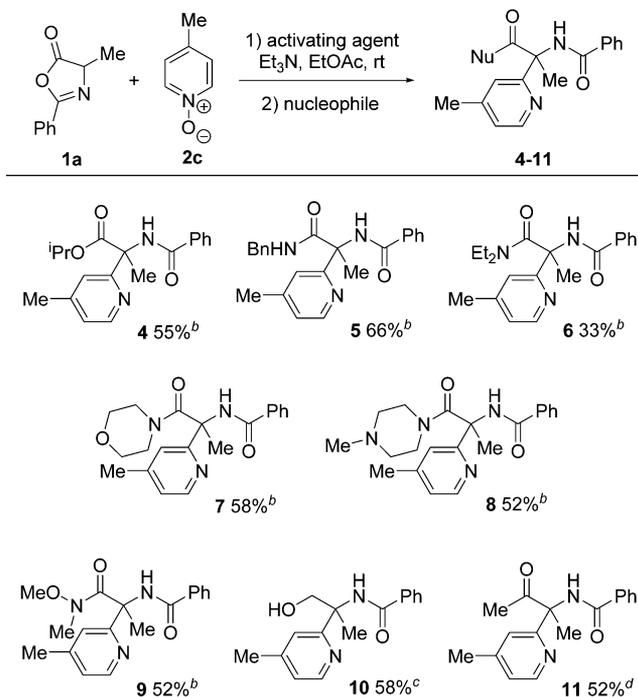
A screen of potential activating agents in THF (Table 1, entries 1–6) revealed that both PyBroP and TsCl were competent reaction partners, with the former showing modest C2 selectivity and the latter a higher level of selectivity in favor of the C4 isomer. Mindful that THF is regarded as problematic in industrially led analyses of solvents,²³ we screened a variety of more favorable solvents in conjunction with TsCl (entries 7–12). Pleasantly, a comparable yield to that achieved in THF was obtained using ethyl acetate (a “recommended” solvent²³), albeit with a slightly reduced regioselectivity (entry 8). Additionally, the charge of triethylamine base could also be reduced to 2 equiv versus the *N*-oxide/activating agent without detriment. Other bases (KOAc, K₃PO₄, K₂CO₃) were unsuccessful in the reaction.

We next applied these optimized conditions to a substrate scoping study, utilizing a matrix combination of azlactones **1a**–

Scheme 2. Substrate Scope in the One-Pot, Three-Component Synthesis of α -Pyridyl, α -Substituted Amino Acid Methyl Esters

^aConditions: azlactone (0.50 mmol), *N*-oxide (0.55 mmol), TsCl (0.55 mmol), NEt₃ (1.05 mmol), and EtOAc (2.5 mL) at rt for 16 h followed by NaOMe (1.10 mmol) and MeOH (1 mL) and stirring for a further 3 h.

Scheme 3. Scope of Nucleophilic Ring Opening



^aConditions: azlactone (0.50 mmol), *N*-oxide (0.55 mmol), TsCl (0.55 mmol), NEt₃ (1.05 mmol), and EtOAc (2.5 mL) at rt for 7 h. ^bNucleophile and stirring for 16–24 h. ^cNaBH₄ (0.50 mmol) and 5:1 THF/MeOH (6 mL) at 0 °C for 1 h. ^d3 M MeMgBr in Et₂O (0.51 mmol) and THF (5 mL) at –40 °C for 3 h.

d and pyridine *N*-oxides **2a–e**, again with methanolytic ring opening of the presumed intermediate azlactone. The results are shown in Scheme 2. Variation of the azlactone C4-substituent (which becomes the α -alkyl group of the amino acid products **3**) was well tolerated, with little variation in average yield across five pyridine *N*-oxide substrates for R¹ = methyl (56%), benzyl (64%), or isobutyl (52%). Changing the azlactone C2-substituent from aromatic (R² = Ph) to aliphatic (R² = *N*-acetyl-4-piperidinyl), was less well tolerated: although each of the reactions was still successful, the average yield dropped from 64% to 31% (with R¹ = Bn). Regarding the pyridine *N*-oxide, the reactions of the parent reagent **2a** all gave similar regioselectivities in favor of the C4 isomer (1.6:1 to 1.9:1). Reaction of 3-methylpyridine *N*-oxide **2b** gave rise to a mixture of 2,3-, 3,4-, and 2,5-disubstituted products, but with the 3,4-disubstitution product dominating in all cases. The reaction of 4-substituted pyridine *N*-oxides **2c–e** gives rise to good yields of the 2,4-disubstituted products as expected. Alkyl or aryl substituents were well tolerated, though the presence of an electron-donating 4-methoxy group in **2e** leads to systematically lower yields. Overall, though, the reaction shows excellent robustness, with the full matrix of 20 substrate pairings giving products in an average yield for the three-component coupling of >50%.

We next turned our attention to the range of nucleophiles that could be used to open the intermediate arylated azlactones. The formation of peptides and peptidomimetics from α,α -disubstituted amino acids is not straightforward,²⁴ with *N*-functionalization limited by the poor nucleophilicity of the hindered amine and *C*-functionalization slowed by the difficulty of forming adjacent quaternary centers in the tetrahedral

intermediate for acyl substitution. An additional complication in attempting *C*-functionalization of α -pyridyl, α -substituted amino acids is that the free acids undergo facile decarboxylation, accelerated by the potential for charge delocalization into the pyridyl ring;²¹ we have already exploited this in a direct two-component synthesis of 2-(1-amidoalkyl)pyridines by arylation/decarboxylative ring opening of azlactones.²² Direct access to a range of *C*-functionalized α -pyridyl, α -substituted amino acids by nucleophilic opening of the azlactones would therefore be synthetically valuable. The results are shown in Scheme 3.

While methanol had already been used for azlactone opening (Scheme 2), we were pleased to see that a more hindered secondary alcohol (isopropanol) was also a competent nucleophile. The use of amines was examined: primary and cyclic secondary aliphatic amines gave good yields of the diamide products. The use of more hindered, less nucleophilic acyclic secondary amines gave a lower yield, as might be expected, though the Weinreb amide **9** was obtained in reasonable yield.

Treatment with sodium borohydride in methanol/THF led to reductive ring opening, giving the amino alcohol derivative **10**, while the use of a Grignard reagent was also successful, leading to ketone **11**. A broad range of nucleophiles is therefore compatible with the one-pot, three-component coupling.

In summary, we have described a new synthetic approach to α -pyridyl, α -substituted amino acid derivatives by direct pyridylation of azlactones with readily available pyridine *N*-oxides, followed by ring opening with diverse nucleophiles. The reaction shows good robustness (average yield 51%, range 25–81% across 28 examples), while the one-pot, three-component nature of the reaction should be readily applicable to array synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02731.

Experimental procedures, analytical data, and crystallographic information for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: s.p.marsden@leeds.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research for this work has received funding from the Innovative Medicines Institute joint undertaking project CHEM21 under Grant Agreement No. 115360, the resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

■ REFERENCES

- (1) For recent reviews of synthetic approaches to α,α -disubstituted amino acids, see: (a) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1–7. (b) Vogt, H.; Brase, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430.

- (c) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623.
- (2) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152.
- (3) Anselm, L.; Banner, D.; Haap, W.; Kuhn, B.; Luebbbers, T.; Peters, J.-U.; Spinnler, B. *PCT Int. Appl.* **2013**, WO 2013117512.
- (4) (a) Malamas, M. S.; Barnes, K.; Johnson, M.; Hui, Y.; Zhou, P.; Turner, J.; Hu, Y.; Wagner, E.; Fan, K.; Chopra, R.; Olland, A.; Bard, J.; Pangalos, M.; Reinhart, P.; Robichaud, A. J. *Bioorg. Med. Chem.* **2010**, *18*, 630–639. (b) Zhou, P.; Li, Y.; Fan, Y.; Wang, Z.; Chopra, R.; Olland, A.; Hu, Y.; Magolda, R. L.; Pangalos, M.; Reinhart, P. H.; Turner, M. J.; Bard, J.; Malamas, M. S.; Robichaud, A. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2326–2329.
- (5) Hanyu, M.; Ninomiya, D.; Yanagihara, R.; Murashima, T.; Miyazawa, T.; Yamada, T. *J. Pept. Sci.* **2005**, *11*, 491–498. (b) Yamada, T.; Ichino, T.; Hanyu, M.; Ninomiya, D.; Yanagihara, R.; Miyazawa, T.; Murashima, T. *Org. Biomol. Chem.* **2004**, *2*, 2335–2339. (c) Hanyu, M.; Murashima, T.; Miyazawa, T.; Yamada, T. *Tetrahedron Lett.* **2004**, *45*, 8871–8874.
- (6) (a) Watson, E. L.; Marsden, S. P.; Raw, S. A. *Tetrahedron Lett.* **2009**, *50*, 3318–3320. (b) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905–2908. (c) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kundig, E. P. *Chem. Commun.* **2008**, 4040–4042. (d) Jones, M. C.; Marsden, S. P. *Org. Lett.* **2008**, *10*, 4125–4128. (e) Jones, M. C.; Marsden, S. P.; Muñoz-Subtil, D. M. *Org. Lett.* **2006**, *8*, 5509.
- (7) (a) Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Org. Lett.* **2014**, *16*, 432–435. (b) Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Tetrahedron* **2015**, *71*, 5814–5823.
- (8) (a) Makosza, M.; Surowiec, M.; Szczepanska, A.; Sulikowski, D.; Maltsev, O. *Synlett* **2007**, *2007*, 470–474. (b) Makosza, M.; Sulikowski, D.; Maltsev, O. *Synlett* **2008**, *2008*, 1711–1713. (c) Sulikowski, D.; Makosza, M. *Eur. J. Org. Chem.* **2010**, *2010*, 4218–4226.
- (9) (a) O'Connor, S. J.; Liu, Z. *Synlett* **2003**, 2135–2138. (b) Shirakawa, S.; Yamamoto, K.; Tokuda, T.; Maruoka, K. *Asian J. Org. Chem.* **2014**, *3*, 433.
- (10) (a) Rose-Munch, F.; Aniss, K.; Rose, E. *J. Organomet. Chem.* **1990**, *385*, C1–C3. (b) Chaari, M.; Jenhi, A.; Lavergne, J.-P.; Viallefont, P. *J. Organomet. Chem.* **1991**, *401*, C10–C13. (c) Chaari, M.; Lavergne, J.-P.; Viallefont, P. *Synth. Commun.* **1989**, *19*, 1211–1216. (d) Shirakawa, S.; Yamamoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 838–840.
- (11) O'Donnell, M. J.; Bennett, W. D.; Jacobsen, W. N.; Ma, Y.-a. *Tetrahedron Lett.* **1989**, *30*, 3913–3914.
- (12) (a) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, *5*, 1915–1918. (b) Arylation of hydantoins leading to α -aryl, α -amino acids derivatives: Fernandez-Nieto, F.; Mas Rosello, J.; Lenoir, S.; Hardy, S.; Clayden, J. *Org. Lett.* **2015**, *17*, 3838–3841.
- (13) Chai, Z.; Wang, B.; Chen, J.-N.; Yang, G. *Adv. Synth. Catal.* **2014**, *356*, 2714–2718.
- (14) D'Anello, M.; Erba, E.; Gelmi, M. L.; Pocar, D. *Chem. Ber.* **1988**, *121*, 67.
- (15) Li, G.; Sun, W.; Li, J.; Jia, F.; Hong, L.; Wang, R. *Chem. Commun.* **2015**, *51*, 11280–11282.
- (16) (a) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2010**, *12*, 5254–5257. (b) Lian, Y.; Coffey, S. B.; Li, Q.; Londregan, A. T. *Org. Lett.* **2016**, *18*, 1362–1365.
- (17) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2011**, *13*, 1840–1843.
- (18) Londregan, A. T.; Burford, K.; Conn, E. L.; Hesp, K. D. *Org. Lett.* **2014**, *16*, 3336–3339.
- (19) De Jersey, J.; Zerner, B. *Biochemistry* **1969**, *8*, 1967–1974.
- (20) For the activation/substitution of quinoline *N*-oxide by nitropropionate using acetic anhydride, see: Caldwell, R. D.; Guckian, K. M.; Kumaravel, G.; Lee, W.-C.; Lin, E. Y.-S.; Llu, X.; Ma, B.; Scott, D. M.; Shl, Z.; Thomas, J.; Taveras, A. G.; Zheng, G. Z. U.S. Pat. Appl. Publ., 20140100195, 2014.
- (21) Edgar, M. T.; Pettit, G. R.; Krupa, T. S. *J. Org. Chem.* **1979**, *44*, 396–400.
- (22) Johnson, T. C.; Marsden, S. P. *Beilstein J. Org. Chem.* **2016**, *12*, 1–4.
- (23) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. *Green Chem.* **2016**, *18*, 288–296.
- (24) Schaefer, G.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1526–1529.