Organic LETTERS

Letter

pubs.acs.org/OrgLett

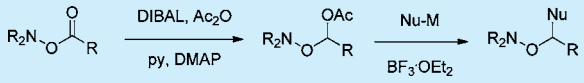
Synthesis of *N,N,O*-Trisubstituted Hydroxylamines by Stepwise Reduction and Substitution of *O*-Acyl *N,N*-Disubstituted Hydroxylamines

Sandeep Dhanju and David Crich*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States

Supporting Information

ABSTRACT: Diverse *N,N,O*-trisubstituted hydroxylamines, an under-represented group in compound collections, are readily prepared by partial reduction of *N*-acyloxy secondary amines with diisobutylaluminum hydride followed by acetylation and reduction of the so-formed *O*-acyl-*N,N*-disubstituted hydroxylamines with triethylsilane and boron trifluoride etherate. Use of carbon nucleophiles in the last step, including allyltributylstannane, silyl enol ethers, and 2-methylfuran, gives *N,N,O*-trisubstituted hydroxylamines with branching α- to the *O*-substituent. *N,N*-Disubstiuted hydroxylamines are conveniently prepared by reaction of secondary amines with dibenzoyl peroxide followed by diisobutylaluminum hydride reduction.



The hydroxylamine moiety is an interesting functional group with the potential to enrich compound collections, in which it is currently under-represented,[1] by increasing the fraction of sp^3-hybridized atoms (Fsp^3)[2] without the synthetic complication of an additional stereogenic center. This is because the low basicity of the hydroxylamine function (pK_a hydroxylamine in water = 5.93)[3,4] and the modest barrier to inversion (~15 kcal·mol^{-1})[5−8] together ensure that at physiological pH the pyramidal nitrogen is not protonated in aqueous solution and undergoes rapid inversion of configuration. As such, hydroxylamines carrying two different nitrogen substituents can be considered as surrogates of chiral alcohols and ethers that avoid the need for asymmetric synthesis. Indeed, we have recently prepared and evaluated as β-(1→3)-glucan mimetics a series of mono-, di-, and trimeric *N*-alkoxyimino sugars in which the hydroxylamine nitrogen replaces the anomeric carbon and eliminates the need for diastereoselective glycosidic bond formation.[9] On the other hand, the low basicity of the *N*-alkoxyimino sugars and of oxazines, unlike their *N*-alkyl counterparts, render them poor analogues of glycosyl oxocarbenium ions and correspondingly poor glycosidase inhibitors.[8,10]

The paucity of hydroxylamines in compound collections is due in part to current criteria for compound selection, which with a view to limiting false positives in biochemical screens, exclude molecules containing heteroatom−heteroatom bonds on the grounds of their weakness and electrophilicity.[11−13] In particular, *N*-aryl- and *N*-heteroarylhydroxylamines are genotoxic because of their ability to form adducts with nucleic acid bases following activation by *O*-acetylation or *O*-sulfonation.[14−18] However, with computed[19] and experimentally derived[20] N−O bond dissociation energies ranging from 55 to 65 kcal·mol^{-1} depending on substituent pattern, and lacking the ability to undergo activation by acylation or sulfation, trisubstituted hydroxylamines are neither particularly thermally unstable nor electrophilic. Although not common,[21] the hydroxylamine moiety is found in biologically active natural products and their analogues, such as the anticancer calicheamicins and esperamicins,[22,23] the potent bacterial tRNA synthase inhibitor SB-219383,[24] and a recent selective inhibitor of human neuraminidase isoenzymes.[25]

Before the broader application of trisubstituted hydroxylamines can be investigated, improved methods for their synthesis are required. Thus, while several methods exist for the preparation of acyclic hydroxylamines,[26,27] only a relatively limited number of methods are available for the synthesis *N,N,O*-trisubstituted systems,[8,9,27−31] other than by the 2,3-Meisenheimer rearrangement of allylic tertiary amine *N*-oxides with its inherent limitation to the formation of the *O*-allylated hydroylamines.[32−36] In particular, the *O*-alkylation of *N,N*-disubstituted hydroxylamines to give *N,N,O*-trisubstituted systems is only described with simple, potent electrophiles.[26] We considered the latter problem as analogous to the synthesis of ethers from alcohols, for which a number of creative methods have been devised recently,[37,38] and focused on the development of methods based on the reduction of *O*-acyl-*N,N*-disubstituted hydroxylamines to the trisubstituted hydroxylamines without concomitant reductive cleavage of the N−O bond (Scheme 1). We report here on the reduction of this concept to practice and on the synthesis of a number of diversely trisubstituted hydroxylamines.

Synthesis of *N,N*-disubstituted hydroxylamines for acylation was best achieved by adaptation of the Ganem protocol[39] for the formation of *N*-(benzoyloxy)amines followed by diisobutylaluminum hydride (DIBAL) reduction (Table 1). Alternatively, aza-Michael addition of a secondary amine to acrylonitrile, followed by *N*-oxide formation and Cope elimination,[40] also was found to be effective (Scheme 2). *O*-Acylhydroxylamines were synthesized (Table 2) from *N,N*-

Received: February 27, 2016
Published: April 7, 2016

DOI: 10.1021/acs.orglett.6b00556
Org. Lett. 2016, 18, 1820−1823

Scheme 1. Synthesis of Trisubstituted Hydroxylamines from *N*-Acyloxyamines

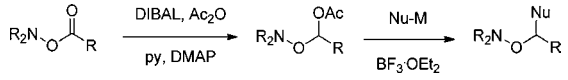
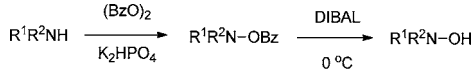


Table 1. Synthesis of *N,N*-Disubstituted Hydroxylamines



1a-d 2a-d 3a-d

entry	amine, **1**	**2** % yield[a]	**3** % yield[b]
1	**1a**, $R^1 = R^2 =$ Bn	**2a**, 81	**3a**, 90
2	**1b**, R^1 = Me, R^2 = Bn	**2b**, 82	**3b**, 93
3	**1c**, piperidine	**2c**, 86	**3c**, 63
4	**1d**, 4-methylpiperidine	**2d**, 82	**3d**, 84

[a]Stirring with $(BzO)_2$ (1.1 equiv) and K_2HPO_4 (1.5 equiv) in DMF at rt for 1−22 h. [b]Stirring with DIBAL (2.5 equiv) in CH_2Cl_2 at 0 °C for 15 min.

Scheme 2. Alternative Synthesis of *N*-(Acyloxy)amines Exemplified for *N*-4-(Phenylbutyroyl)pyrrolidine

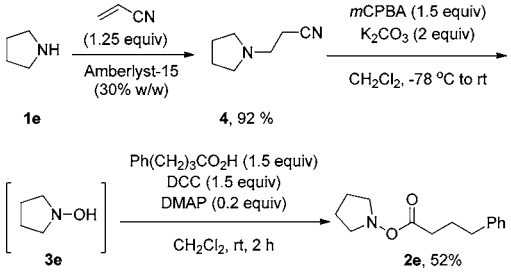
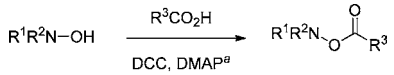


Table 2. Synthesis of *N*-(Acyloxy)amines



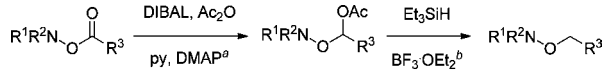
3 2f-m

entry	R^1	R^2	R^3	% yield
1	Bn	Bn	$Ph(CH_2)_3$	**2f**, 98
2	Bn	Bn	$C_{10}H_{15}$	**2g**, 72
3	Bn	Bn	$tBuCH_2$	**2h**, 63
4	Bn	Me	$Ph(CH_2)_4$	**2i**, 93
5	-$(CH_2)_5$-		$Ph(CH_2)_3$	**2j**, 93
6	-$(CH_2)_2CHMe(CH_2)_2$-		$Ph(CH_2)_3$	**2k**, 91
7[b]	Bn	Bn	2-NpOCH$_2$	**2l**, 89
8	Bn	Bn	3-C_5H_4N	**2m**, 97

[a]R_3CO_2H (1.25−2.5 equiv), DCC (1.25−2.5 equiv), DMAP (0.2 equiv), CH_2Cl_2, RT, 0.5−30 h. [b]2-Np = 2-naphthalenyl.

disubstituted hydroxylamines and the corresponding carboxylic acids with the aid of dicyclohexyl carbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP).[41] In view of the mechanism for the genotoxicity of *N*-aryl- and *N*-heteroarylhydroxylamines, which are rendered electrophilic at nitrogen by *O*-

Table 3. Synthesis of Trisubstituted Hydroxylamines



2 5 6

entry	**2**	**5**, % yield	**6**, % yield
1	**2a**	**5a**, -[c]	**6a**, 50[d]
2	**2b**	**5b**, -[c]	**6b**, 53[d]
3	**2e**	**5e**, 63	**6e**, 77
4	**2f**	**5f**, 88	**6f**, 83
5	**2g**	**5g**, 65	**6g**, 89
6	**2h**	**5h**, 75	**6h**, 81
7	**2i**	**5i**, 89	**6i**, 85
8	**2j**	**5j**, 55	**6j**, 75
9	**2k**	**5k**, 84	**6k**, 76
10[e]	**2l**	**5l**, 90	**6l**, 38
11	**2m**	**5m**, -[c]	**6m**, 42[d]

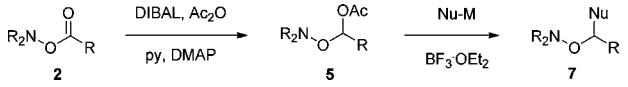
[a](i) DIBAL (1.25−2 equiv), CH_2Cl_2, −78 °C, time; (ii) Ac_2O (6 equiv), Py (3 equiv), DMAP (2 equiv), CH_2Cl_2, −78 to 0 °C. [b]Et_3SiH (2.5−5 equiv), BF_3·OEt_2 (2.5−6.25 equiv), CH_2Cl_2, −78 °C to rt. [c]Not isolated. [d]Yield over two steps. [e]2-Np = 2-naphthalenyl.

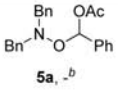
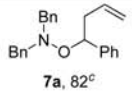
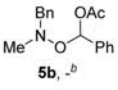
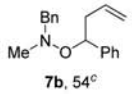
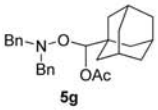
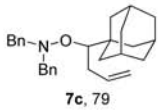
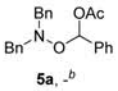
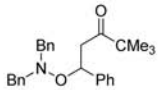
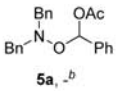
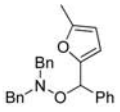
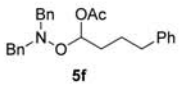
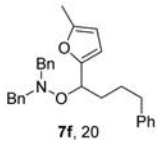
acylation or sulfation,[14−18] it is noteworthy that the nucleophilic attack on the more highly substituted *O*-acylhydroxylamines by DIBAL reported in Table 1 takes place at the carbonyl group and leaves the N−O bond intact. Selective reduction of the carbonyl group in hydroxamic acid derivatives, i.e., *N*-acylhydroxylamines, has also been described.[27]

Adapting Rychnovsky's protocol for the synthesis of ethers from esters,[37] the *O*-acylhydroxylamines were then reduced with diisobutylaluminum hydride (DIBAL) at −78 °C and the intermediate aluminum alkoxides trapped in situ with acetic anhydride in the presence of pyridine and DMAP followed by warming to 0 °C to give a diverse range of *O*-(α-acetoxyalkyl)

DOI: 10.1021/acs.orglett.6b00556
Org. Lett. 2016, 18, 1820−1823

Table 4. Synthesis of Trisubstituted Hydroxylamines with Concomitant CC Bond Formation



entry	ester	5[a]	reagent, conditions	7, % yield
1	**2a**	 **5a**, -[b]	$Bu_3SnCH_2CH{=}CH_2$ (2.5 equiv) BF_3OEt_2 (2.5 equiv), CH_2Cl_2, -78 to 0 °C	 **7a**, 82[c]
2	**2b**	 **5b**, -[b]	$Bu_3SnCH_2CH{=}CH_2$ (2.5 equiv) BF_3OEt_2 (2.5 equiv), CH_2Cl_2, -78 to 0 °C	 **7b**, 54[c]
3	-	 **5g**	$Bu_3SnCH_2CH{=}CH_2$ (2.5 equiv) BF_3OEt_2 (2.5 equiv), CH_2Cl_2, -78 to 0 °C	 **7c**, 79
4	**2a**	 **5a**, -[b]	$CH_2{=}C(OTMS)CMe_3$, (2.5 equiv) BF_3OEt_2 (2.5 equiv), CH_2Cl_2, -78 to 0 °C	 **7d**, 66[c]
5	**2a**	 **5a**, -[b]	2-methylfuran (2.5 equiv) BF_3OEt_2 (2.5 equiv), CH_2Cl_2, -78 °C	 **7e**, 51[c]
6	-	 **5f**	2-methylfuran (2.5 equiv) BF_3OEt_2 (2.5 equiv), CH_2Cl_2, -78 to 0 °C	 **7f**, 20

[a](i) DIBAL (2 equiv), CH_2Cl_2, −78 °C; (ii) Py (3 equiv), DMAP (2 equiv), Ac_2O (6 equiv), CH_2Cl_2, −78 to 0 °C. [b]Not isolated. [c]Two steps.

N,N-dialkylhydroxylamines **5** in good to excellent yield (Table 3). In particular, it is noteworthy that the reaction is compatible with alkyl and aryl groups in both the *N*- and *O*-substituents and is tolerant of branching at the α- and β-positions of the acyl groups undergoing reduction (Table 3, **6g**, **6h**). Treatment of the *O*-(α-acetoxyalkyl)hydroxylamines with triethylsilane and boron trifluoride ethereate in dichloromethane at −78 °C followed by warming to 0 °C gave the anticipated *O*-alkyl-*N,N*-dialkylhydroxylamines in good yield (Table 3). As some *O*-(α-acetoxyarylmethyl)hydroxylamines were found to be relatively unstable, the final reduction with Et_3SiH and $BF_3{\cdot}OEt_2$ was best conducted without isolation, when good overall yield of the hydroxylamines was obtained for the two-step process (Table 3, **6a**, **6b**, **6m**). Monitoring by thin-layer chromatography revealed the actual temperature of the Lewis acid mediated reduction of the *O*-(α-acetoxyalkyl) hydroxylamines by triethylsilane to be substrate dependent, reflecting the stability of the presumed intermediate aminoxocarbenium ions. The β-(2-naphthyloxy)-ethyl system **6l** provides an extreme example of the effect of substituent on reduction, requiring stirring with multiple equivalents of silane and Lewis acid at room temperature over 7 days in order to achieve a 38% isolated yield of hydroxylamine. The relative slowness of this particular reduction reflects the destabilizing influence of alkoxy groups on oxocarbenium ion like intermediates such as is widely appreciated in carbohydrate chemistry.[42−44]

The scope of the hydroxylamine-forming process was further expanded by the replacement of triethylsilane in the final reduction by other suitable nucleophiles. Thus, adapting literature methods for *C*-glycoside formation[45−49] and for the reductive allylation of α-acetoxy ethers,[50,51] DIBAL-mediated reductive acetylation of **2a** and **2b** was followed by treatment of the intermediate *O*-(α-acetoxybenzyl)hydroxylamines **5a** and **5b** with allyltributylstannane in the presence of $BF_3{\cdot}OEt_2$ between −78 and 0 °C to give the trisubstituted hydroxylamines **7a** and **7b** in 82% and 54% isolated yields, respectively, for the two step protocol (Table 4, entries 1 and 2). The reductive allylation could also be conducted in high yield with the isolated and sterically hindered *O*-(α-acetoxyalkyl)-hydroxylamines **2g** (Table 4, entry 3). A silyl enol ether also proved to be a satisfactory nucleophile (Table 4, entry 4) for capture of the intermediate aminoxocarbenium ion (Table 4, entry 4) as observed previously with glycosyl[52] and simple acyclic oxocarbenium ions derived from the corresponding acetates.[53] Finally, 2-methylfuran was also found to be a suitable nucleophile enabling the synthesis of the complex hydroxylamines **7e** and **7f** in moderate yield (Table 4, entries 5 and 6).

Overall, a straightforward method for the synthesis of *N,N,O*-trisubstituted hydroxylamines has been developed on the basis of the acylation and subsequent two-step reduction of *N,N*-disubstituted hydroxylamines, which themselves are readily accessible by the reaction of secondary amines with dibenzoyl peroxide followed by reductive deacylation. Replacement of the hydride source in the reductive deacetoxylation of the intermediate *O*-(α-acetoxyalkyl)hydroxylamines by suitable carbon nucleophiles enables the formation of trisubstituted hydroxylamines branched α- to the oxygen atom. These methods, which proceed via the intermediacy of amino-

DOI: 10.1021/acs.orglett.6b00556
Org. Lett. 2016, 18, 1820−1823

xocarbenium ions, considerably extend the range of fully substituted hydroxylamines currently available and should permit the wider application of this underutilized functional group in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00556.

Full experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dcrich@chem.wayne.edu.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Axerio-Cilies, P.; Castaneda, I. P.; Mirza, A.; Reynisson, J. *Eur. J. Med. Chem.* **2009**, *44*, 1128.
(2) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.
(3) Mollin, J.; Kasparek, F.; Lasovsky, J. *Chem. Zvesti* **1975**, *29*, 39.
(4) Bartmess, J. E. In *Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; Rappoport, Z., Liebman, J. F., Eds.; Wiley: Chichester, 2011; Vol. 2, p 115.
(5) Riddell, F. G.; Turner, E. S.; Boyd, A. *Tetrahedron* **1979**, *35*, 259.
(6) Hassan, A.; Wazeer, M. I. M.; Perzanowski, H. P.; Ali, S. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 411.
(7) Raban, M.; Kost, D. *Tetrahedron* **1984**, *40*, 3345.
(8) Malik, G.; Ferry, A.; Guinchard, X.; Cresteil, T.; Crich, D. *Chem. - Eur. J.* **2013**, *19*, 2168.
(9) Ferry, A.; Malik, G.; Guinchard, X.; Vetvicka, V.; Crich, D. *J. Am. Chem. Soc.* **2014**, *136*, 14852.
(10) Bach, P.; Bols, M. *Tetrahedron Lett.* **1999**, *40*, 3461.
(11) Rishton, G. M. *Drug Discovery Today* **2003**, *8*, 86.
(12) Sink, R.; Gobec, S.; Pecar, S.; Zega, A. *Curr. Med. Chem.* **2010**, *17*, 4231.
(13) Bruns, R. F.; Watson, I. A. *J. Med. Chem.* **2012**, *55*, 9763.
(14) Fan, L.; Schut, H. A. J.; Snyderwine, E. G. *Carcinogenesis* **1995**, *16*, 775.
(15) Sadrieh, N.; Davis, C. D.; Snyderwine, E. G. *Cancer Res.* **1996**, *56*, 2683.
(16) Williams, J. A.; Stone, E. M.; Fakis, G.; Johnson, N.; Cordell, J. A.; Meinl, W.; Glatt, H.; Sim, E.; Phillips, D. H. *Pharmacogenetics* **2001**, *11*, 373.
(17) Benigni, R.; Giuliani, A.; Franke, R.; Gruska, A. *Chem. Rev.* **2000**, *100*, 3697.
(18) Novak, M.; Chakraborty, M. In *Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; Rappoport, Z., Liebman, J. F., Eds.; Wiley: Chichester, 2011; Vol. 2, p 577.
(19) Yu, B.; Reynisson, J. *Eur. J. Med. Chem.* **2011**, *46*, 5833.
(20) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, 2003.
(21) Ashani, Y.; Silman, I. In *The Chemistry of Hydroxylamines, Oximes, and Hydroxamic Acids, Part 1*; Rappoport, Z., Liebman, J. F., Eds.; Wiley: Chichester, 2009; p 609.
(22) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.
(23) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.
(24) Berge, J. M.; Copley, R. C. B.; Eggleston, D. S.; Hamprecht, D. W.; Jarvest, R. L.; Mensah, L. M.; O'Hanlon, P. J.; Pope, A. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1811.
(25) Zhang, Y.; Albohy, A.; Zou, Y.; Smutova, V.; Pshezhetsky, A. V.; Cairo, C. W. *J. Med. Chem.* **2013**, *56*, 2948.
(26) Melman, A. In *The Chemistry of Hydroxylamines, Oximes, and Hydroxamic Acids, Part 1*; Rappoport, Z., Liebman, J. F., Eds.; Wiley: Chichester, 2009; p 117.
(27) Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6369.
(28) Malik, G.; Guinchard, X.; Crich, D. *Org. Lett.* **2012**, *14*, 596.
(29) Sun, L.; Li, P.; Amankulor, N.; Tang, W.; Landry, D. W.; Zhao, K. *J. Org. Chem.* **1998**, *63*, 6472.
(30) Elboray, E. E.; Gao, C.; Grigg, R. *Tetrahedron* **2012**, *68*, 3103.
(31) Barnes, K. L.; Chen, K.; Catalano, V. J.; Jeffrey, C. S. *Org. Chem. Front.* **2015**, *2*, 497.
(32) Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett.* **1991**, *32*, 4481.
(33) Enders, D.; Kempen, H. *Synlett* **1994**, 969.
(34) Davies, S. G.; Smyth, G. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2467.
(35) Bao, H.; Qi, X.; Tambar, U. K. *Synlett* **2011**, 1789.
(36) Theodorou, A.; Limnios, D.; Kokotos, C. G. *Chem. - Eur. J.* **2015**, *21*, 5238.
(37) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.
(38) Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082.
(39) Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537.
(40) O'Neil, I. A.; Cleator, E.; Tapolczay, D. J. *Tetrahedron Lett.* **2001**, *42*, 8247.
(41) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(42) Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429.
(43) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734.
(44) Martin, A.; Arda, A.; Désiré, J.; Martin-Mingot, A.; Probst, N.; Sinaÿ, P.; Jiménez-Barbero, J.; Thibaudeau, S.; Blériot, Y. *Nat. Chem.* **2016**, *8*, 186.
(45) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
(46) Kozikowski, A. P. *Tetrahedron Lett.* **1982**, *23*, 2281.
(47) Danishefsky, S. J.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.
(48) Keck, G. E.; Enholm, E. J.; Kachensky, D. F. *Tetrahedron Lett.* **1984**, *25*, 1867.
(49) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479.
(50) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317.
(51) Kadota, I.; Uyehara, H.; Yamamoto, Y. *Tetrahedron* **2004**, *60*, 7361.
(52) Ogawa, T.; Pernet, A. G.; Hanessian, S. *Tetrahedron Lett.* **1973**, *14*, 3543.
(53) Rychnovsky, S. D.; Cossrow, J. *Org. Lett.* **2003**, *5*, 2367.

DOI: 10.1021/acs.orglett.6b00556
Org. Lett. 2016, 18, 1820−1823