ORGANIC LETTERS

2007
Vol. 9, No. 7
1275−1278

Highly Stereoselective [4 + 3] Cycloadditions of Nitrogen-Stabilized Oxyallyl Cations with Pyrroles. An Approach to Parvineostemonine†

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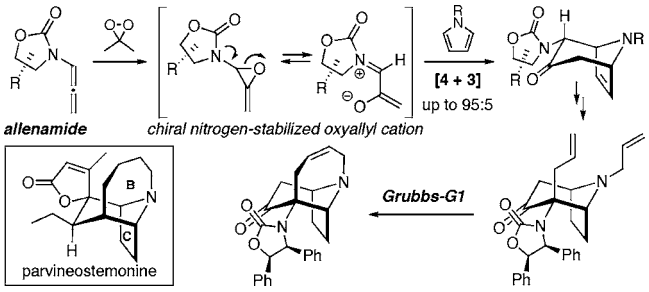
Received January 14, 2007

ABSTRACT



A highly stereoselective [4 + 3] cycloaddition of *N*-substituted pyrroles with allenamide-derived nitrogen-stabilized chiral oxyallyl cations is described here. This method provides an approach for constructing tropinone alkaloids.

Heteroatom-substituted oxyallyl cations have emerged as the most effective 1,3-dipoles in [4 + 3] cycloadditions.[1−5] In our active efforts to develop methods employing allenamides,[6−9] we have demonstrated that nitrogen-stabilized chiral oxyallyl cations **2b** derived from epoxidations of allenamides **1** can undergo highly diastereoselective inter-[10] and intramolecular[11] [4 + 3] cycloadditions with dienes (Scheme 1). Given that achieving highly stereoselective

† With deepest respect and appreciation, this paper is dedicated to Professor Gilbert Stork on the special occasion of his 85th birthday.

(1) For excellent reviews on heteroatom-substituted oxyallyl cations, see: (a) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297. (b) Harmata, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 523.

(2) For general reviews, see: (a) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934. (b) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371. (c) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595. Also see: (d) Davies, H. M. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Greenwich, 1998; Vol. 5, p 119. (e) West, F. G. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Greenwich, 1997; Vol. 4, p 1. (f) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351. (g) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.

(3) For examples of nitrogen-stabilized oxyallyl cations in [4 + 3] cycloadditions, see: (a) MaGee, D. I.; Godineau, E.; Thornton, P. D.; Walters, M. A.; Sponholtz, D. J. *Eur. J. Org. Chem.* **2006**, 3667. Also see: (b) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23. (c) Walters, M. A.; Arcand, H. R. *J. Org. Chem.* **1996**, *61*, 1478.

(4) Also see: (a) Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425. (b) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett.* **1999**, *1*, 2017. (c) Dennis, N.; Ibrahim, B.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2307.

(5) For some examples of other heteroaton-substituted oxyallyl cations, see: (a) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563. (b) Sáez, J. A.; Arnó, M.; Domingo, L. R. *Tetrahedron* **2005**, *61*, 7538. (c) Harmata, M.; Kahraman, M.; Adenu, G.; Barnes, C. L. *Heterocycles* **2004**, *62*, 583. (d) Sáez, J. A.; Arnó, M.; Domingo, L. R. *Org. Lett.* **2003**, *5*, 4117. (e) Funk, R. L.; Aungst, R. A. *Org. Lett.* **2001**, *3*, 3553. (f) Harmata, M.; Sharma, U. *Org. Lett.* **2000**, *2*, 2703. (g) Lee, K.; Cha, J. K. *Org. Lett.* **1999**, *1*, 523. (h) Masuya, K.; Domon, K.; Tanino, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 1724. (i) Harmata, M.; Elomari, S.; Barnes, C. J. *J. Am. Chem. Soc.* **1996**, *118*, 2860 and references cited therein.

(6) For a compendium on the chemistry of allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vols. 1 and 2.

(7) For reviews on the chemistry and synthesis of allenamides, see: (a) Hsung, R. P.; Wei, L.-L.; Xiong, H. *Acc. Chem. Res.* **2003**, *36*, 773. (b) Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, 2005; Chapter 21.4.

10.1021/ol070103n CCC: $37.00
Published on Web 03/03/2007

Scheme 1. [4 + 3] Cylcoadditions with Pyrroles

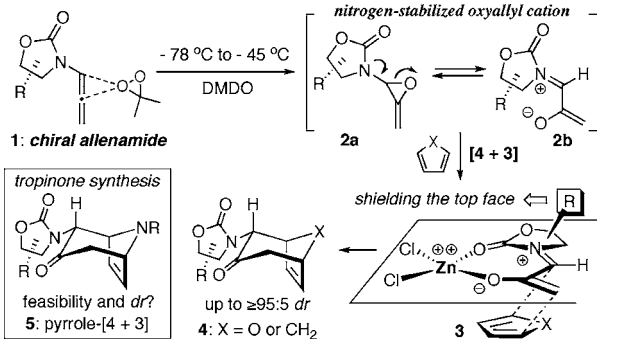
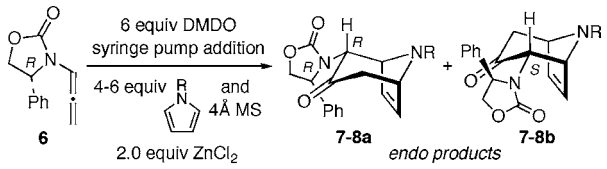


Table 1. Feasibility of the Pyrrole-[4 + 3] Cycloaddition



entry	R =	temp [°C]	solvent	time [h]	cycloadd	yield [%][a]	ratio [**a**:**b**][b]
1	H	- 78	THF	20	-	decomp	-
2	Me	- 78	THF	20	-	decomp	-
3	Boc	- 78	THF	18	**7**	10	95:5
4	Boc	- 45	CH_2Cl_2	48	**7**	76	82:18
5	Bz	- 45	CH_2Cl_2	48	**8**	86	83:17

[a] Isolated yields or decompositions of the starting allenamide and pyrroles. [b] Ratios determined by ^{1}H and/or ^{13}C NMR.

[4 + 3] cycloadditions represents a significant challenge, it has continued to attract elegant synthetic efforts,[1−2,12] and nitrogen-substituted oxyallyl cations[3,4,10,11] have proven to be a unique design in this endeavor, as evident in the fact that Harmata's[13] and our own[14] offer to date the only asymmetric variant of this powerful cycloaddition.[12j]

Despite our preliminary success, pyrroles remained precarious as a suitable diene. Pyrroles in general behave as a poor diene in cycloadditions due to competing retro-cycloaddition to regain its aromaticity, and as a result, efforts in this aspect of [4 + 3] cycloaddition have remained scarce with a few elegant exceptions.[15] Therefore, success in this endeavor would constitute a highly stereoselective entry to tropinone alkaloids (see **5**). We report here a highly stereoselective [4 + 3] cycloaddition of nitrogen-stabilized chiral oxyallyl cations with *N*-substituted pyrroles as an approach to parvineostemonine.

We were able to establish the feasibility of [4 + 3] cycloadditions of nitrogen-stabilized chiral oxyallyl cations with pyrroles via employing chiral allenamide **6** as shown in Table 1. The key elements to our ultimate success are the following: (1) The pyrrole needs to be substituted with an electron-withdrawing group such as Boc [entry 4] or Bz [entry 5] to avoid unwanted oxidation by DMDO, (2) the reaction proceeds better at −45 °C likely due to the fact that it is the temperature at which the epoxidation of allenamides occurs optimally,[16] and (3) DMDO needs to be added via a syringe pump to improve the chemoselectivity of the epoxidation in favor of the allenamide over pyrrole.

Under these conditions, cycloadducts **7** and **8**[17] were isolated in 76% and 86% yields, respectively, with isomeric ratios of 82:18 [entry 4] and 83:17 [entry 5]. However, we recognized that in comparison with respective cycloadditions using furan and cyclopentadiene,[10] the observed diastereomeric ratio here was even lower than when using 2.0 equiv of $ZnCl_2$.[10]

To improve the diastereoselectivity, we examined a range of chiral auxiliaries as shown in Figure 1. It appears that the Evans type auxiliaries[18] (see cycloadducts **9** and **11**) and Sibi's auxiliary[19] (see cycloadduct **10**) provided modest to poor ratios, whereas the Seebach's auxiliary[20] and the (1*R*,2*S*)-(+)-2-amino 1,2-diphenylethanol derived oxazolidinone auxiliary appeared to be the best, leading to cycloadducts **12** (also see **14** with the MeOCO *N*-substitution) and

(8) For our recent efforts, see: (a) Huang, J.; Ianni, J. C.; Antoline, J. E.; Hsung, R. P.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 1565. (b) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Rameshkumar, C.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038. (c) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081.

(9) For recent reports on the allenamide chemistry, see: (a) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 621. (b) Fenández, I.; Monterde, M. I.; Plumet, J. *Tetrahedron Lett.* **2005**, *46*, 6029. (c) de los Rios, C.; Hegedus, L. S. *J. Org. Chem.* **2005**, *70*, 6541. (d) Alouane, N.; Bernaud, F.; Marrot, J.; Vrancken, E.; Mangeney, P. *Org. Lett.* **2005**, *7*, 5797.

(10) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174.

(11) (a) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694. (b) Rameshkumar, C.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 615.

(12) For recent stereoselective attempts, see: (a) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2693. (b) Prié, G.; Prévost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6517. (c) Grainger, R. S.; Owoare, R. B.; Tisselli, P.; Steed, J. W. *J. Org. Chem.* **2003**, *68*, 7899. (d) Montanã, A. M.; Grima, P. M. *Tetrahedron* **2002**, *58*, 4769. (e) Beck, H.; Stark, C. B. W.; Hoffman, H. M. R. *Org. Lett.* **2000**, *2*, 883 and ref 11 cited therein. (f) Cho, S. Y.; Lee, J. C.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 3394. (g) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett.* **1999**, *40*, 1831. (h) Kende, A. S.; Huang, H. *Tetrahedron Lett.* **1997**, *38*, 3353. (i) Harmata, M.; Jones, D. E. *J. Org. Chem.* **1997**, *62*, 4885. For a recent account that constitutes an enatioselective formal [4 + 3] cycloaddition, see: (j) Dai, X.; Davies, H. M. L. *Adv. Synth. Catal.* **2006**, *348*, 2449.

(13) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

(14) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50.

(15) (a) For an elegant equivalent of pyrrole-[4 + 3] cycloaddition via a tandem cyclopropanation/Cope rearrangement en rout to tropinones, see: Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095. (b) For our preliminary communication, see: *Abstracts of Papers*, 231st ACS National Meeting of the American Chemical Society, Atlanta, GA, Spring 2006; American Chemical Society: Washington, DC, 2006; Abstract No. ORGN-192. During our efforts, MaGee and Walters reported one example of pyrrole-[4 + 3] cycloaddition employing nitrogen-stabilized oxyallyl cations derived from α-bromo-α-amido ketones, although the yield was low [see ref 3a].

(16) Rameshkumar, C.; Xiong, H.; Tracey, M. R.; Berry, C. R.; Yao, L. J.; Hsung, R. P. *J. Org. Chem.* **2002**, *67*, 1339.

(17) See the Supporting Information. Also although not specifically described in the text, the oxazolidinone auxiliary could be removed by using SmI_2 [see the Supporting Information].

(18) (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. (b) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99.

(19) For a leading reference, see: Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

(20) For a leading reference, see: Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093.

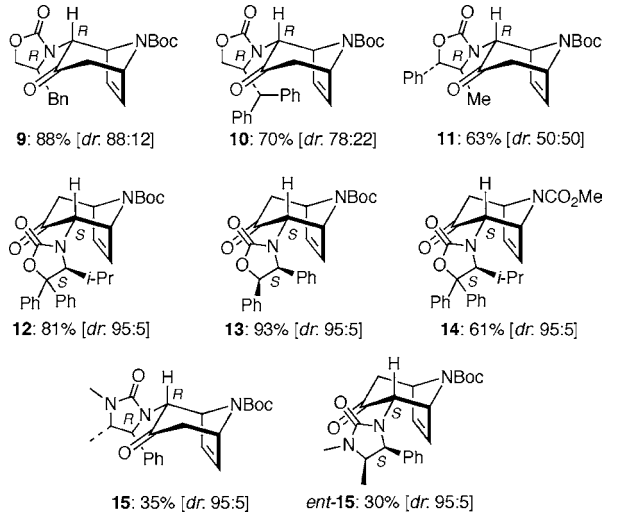


Figure 1. Product chart.

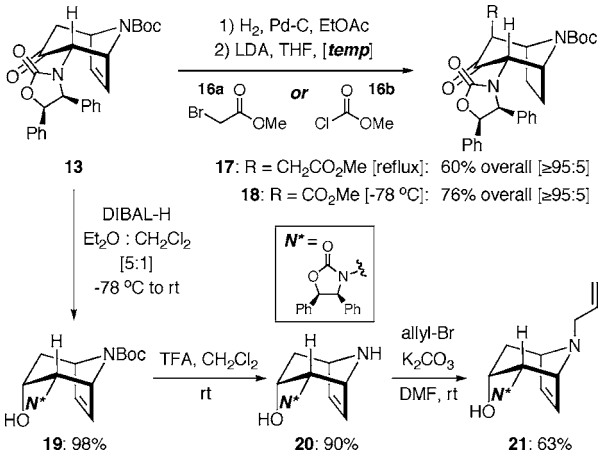
13, respectively, in good yields essentially as single diastereomers. This is unexpected as all three types of auxiliaries led to high diastereoselectivities in the cycloadditions of furan especially when applying 2.0 equiv of $ZnCl_2$.[10] We are not certain of the reason behind this difference between cycloadditions of pyrrole and furan.

Finally, although Close's auxiliary[21] led to lower yields (likely due to stability of the respective allenamide), it also provided high diastereoselectivity (Figure 1). In addition, we were able to establish that both antipodes of the cycloadduct **15** could be attained through the usage of both enantiomers of the auxiliary.

Establishing the stereochemical assignment for these cycloadducts proved to be a real challenge. We had to embark on a series of transformations to identify crystalline materials suitable for X-ray analysis. For example, deprotonation of hydrogenated cycloadduct **13** with LDA followed by additions of electrophilic reagents such as methyl α-bromoacetate[16a] and methyl chloroformate[16b] led to ester **17** and *β*-ketoester **18** in good yields as single diastereomers (Scheme 2). Unfortunately, neither was crystalline.

Consequently, a stereoselective DIBAL-H reduction of **13** provided alcohol **19** in 98% yield, and this in turn allowed us to remove the Boc group en route to amine **20**. Attempts to remove the Boc group under various acidic conditions without first reducing the ketone led to retro-Mannich fragmentation.[22] Finally, capping of amine **20** with an allyl

Scheme 2. Functionalization of the Pyrrole-[4 + 3] Cycloadduct



group afforded allyl amine **21** as a highly crystalline material that was suitable for X-ray analysis. Single-crystal X-ray structure of **21** (Figure 2) confirmed stereochemically that

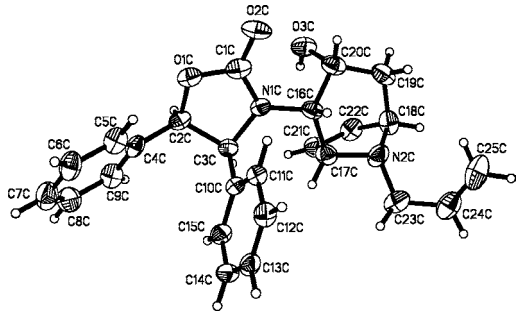


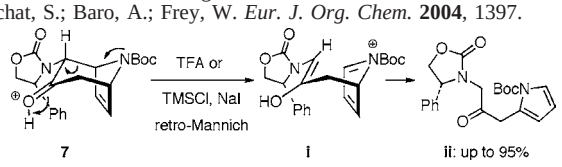
Figure 2. X-ray sturcture of allyl amine **21**.

our pyrrole-[4 + 3] cycloadditions are *endo*-selective in favor of the *endo* products as shown. Therefore, the mechanistic origin of diastereoselectivity should be similar to that proposed for cycloadditions of furan and cyclopentadiene (see **3** → **4** in Scheme 1).[10]

Our efforts in trying to establish the stereochemical assignment directed our focus to potential applications of these new tropinones as chiral templates. Specifically, we explored a synthetic sequence en route to the *aza*-tricyclic core of a new stemona alkaloid parvineostemonine (Scheme 3), featuring a ring-closing metathesis.[23] Parvineostemonine was found by Ye and co-workers from *Stemona parviflora* gathered in the Hainan Province of China and used as traditional Chinese medicine for treatment of coughing and also as insecticides.[24] While parvineostemonine contains a

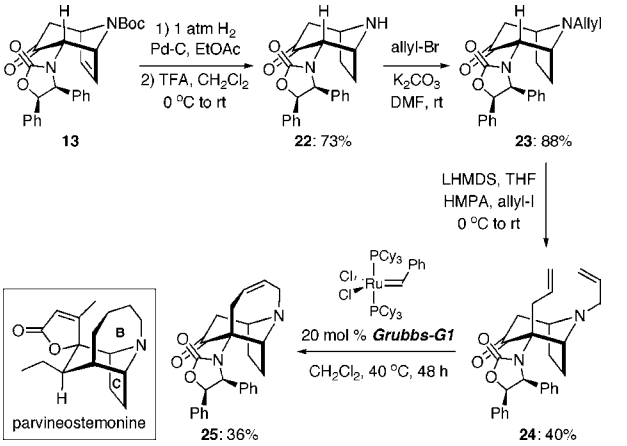
(21) Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.

(22) Acidic conditions used to remove the Boc group led to pyrrole **ii** via a retro-Mannich fragmentation followed by re-aromatization of the iminium intermediate **i**. This in essence represents an equivalent of the Type-III cycloadduct or α-arylation of a methyl ketone. For a recent elegant account related to this fragmentation, see: Cramer, N.; Juretschke, J.; Laschat, S.; Baro, A.; Frey, W. *Eur. J. Org. Chem.* **2004**, 1397.



(23) For recent reviews on RCM, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Walters, M. A. In *Prog. Heterocycl. Chem.* **2003**, *15*, 1. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (e) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912.

Scheme 3. A RCM Approach to Parvineostemonine



basic skeleton similar to other known stemona alkaloids,[25,26] it is unique as the bridging nitrogen atom is part of the 7-membered B-ring.

Hydrogenation of cycloadduct **13** followed by Boc-removal led to amine **22** in good yields (Scheme 3). It is noteworthy that the acid-catalyzed retro-Mannich[22] fragmentation does not occur when the olefin is first hydrogenated. A standard *N*-allylation gave allyl amine **23**, and a subsequent allylation of the lithium enolate generated from **23** led to diene **24**. Although this alkylation regiochemically compliments our earlier work (see Scheme 2), we are not certain as to the origin of this change of regioselectivity. Subjecting diene **24** to ring-closing metathesis conditions employing Grubbs' Gen-I catalyst[23] led to **25** containing the *aza*-tricyclic core of parvineostemonine.

We have described here a highly stereoselective [4 + 3] cycloaddition of *N*-substituted pyrroles with allenamide-derived nitrogen-stabilized chiral oxyallyl cations and demonstrated that this cycloaddition method could serve as an approach toward parvineostemonine.

Acknowledgment. The authors thank NIH-NIGMS [GM066055] and UW-Madison for financial support. The authors also thank Dr. Vic Young's [University of Minnesota] valiant efforts in obtaining and providing X-ray structural information. Finally, the authors acknowledge ChemMatCARS for attempts at obtaining a single-crystal X-ray structure. ChemMatCARS Sector 15 is principally supported by NSF/DOE under grant no. CHE0087817 and by the Illinois board of higher education.

Supporting Information Available: Experimental and ^{1}H NMR spectra and characterizations for all new compounds as well as X-ray structrural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Isolations: Ke, C. Q.; He, Z. S.; Yang, Y. P.; Ye, Y. *Chin. Chem. Lett.* **2003**, *14*, 173.

(25) For an excellent review, see: Pilli, R. A.; Oliveria, M. C. F. *Nat. Prod. Rep.* ***2000***, *17*, 117.

(26) (a) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990. (d) Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505. (e) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (f) Olivo, H. F.; Tovar-Miranda, R.; Barragan, E. *J. Org. Chem.* **2006**, *71*, 3287.