Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1967–1971

Oxidative entry to α-oxy *N*-acyl aminals and hemiaminals: efficient formation of 2-(*N*-acylaminal) substituted tetrahydropyrans

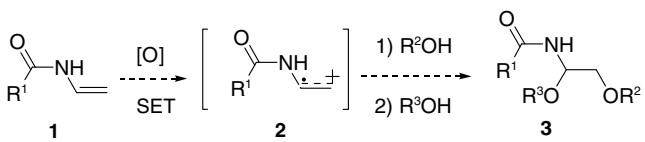
Xianhai Huang,* Ning Shao, Anandan Palani and Robert Aslanian

Department of Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ 07033, USA

Received 12 December 2006; accepted 15 January 2007
Available online 18 January 2007

Abstract—An efficient new method to synthesize α-oxy *N*-acyl aminals and hemiaminals in a single step from readily synthesized *N*-acyl enamines has been developed using $PhI(OAc)_2$ as the oxidant. The reaction conditions are very mild and the products are obtained in good yields (65–92%). A possible mechanistic pathway is laid out.

α-Alkyloxy or acyloxy *N*-acyl aminals and hemiaminals **3** (Scheme 1) are seemingly unusual substrates due to their presumed chemical instability. However, they are very important motifs present in numerous biologically active natural products,[1] for example, Psymberin, Zampanolide, and Lucilactaene are potent cytotoxins against a number of cancer cell lines (Fig. 1). The total synthesis of these natural products has attracted significant attention from the chemistry community.[2] The construction of the α-oxy *N*-acyl aminal and hemiaminal unit (**3**) has posed significant synthetic challenges and usually requires several chemical transformations in the synthesis of natural products. The generally used methods are stepwise processes and involve the introduction of the α-oxy functionality prior to the introduction of the more synthetically challenging *N*-acyl aminal and hemiaminal. There are quite a few synthetic methods available



Scheme 1. Possible oxidative entry to form *N*-acyl aminal.

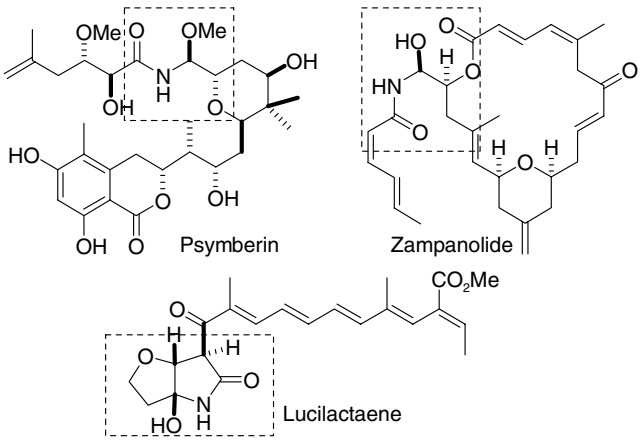


Figure 1. Representative natural products containing α-oxy *N*-acyl aminals and hemiaminals.

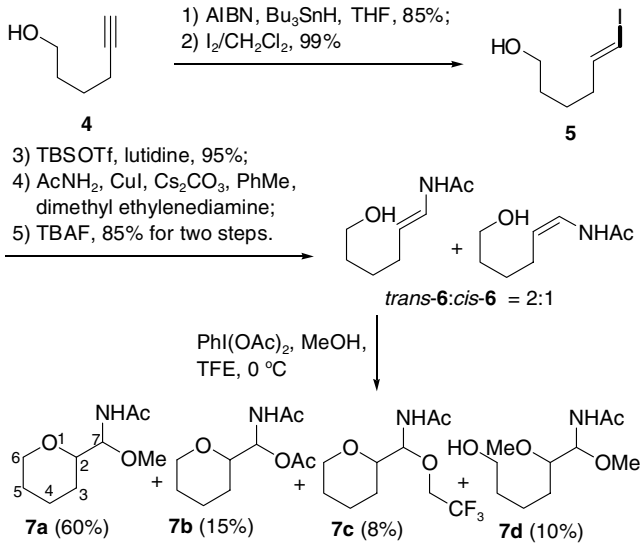
to synthesize *N*-acyl aminals and hemiaminals, which usually require further modification of functional groups such as nitrile,[2a] α-oxy carboxylic acid and aldehyde,[2e,c,3] *N*-acyl imidate, acyloxy acetal, or *N*-acyl amino acid.[4] In light of these synthetic studies, we feel that a more convergent method to prepare this functional unit is highly desirable. Herein, we report a one step oxidative preparation of α-alkyloxy or acyloxy *N*-acyl aminals and hemiaminals from readily synthesized *N*-acyl enamines (**1**),[5] which enables the simultaneous introduction of the α-oxy group and the *N*-acyl aminal and hemiaminal. We decided to study the possibility of employing an electron transfer process to generate radical cation **2** from

Keywords: (Diacetoxyiodo)benzene; *N*-Acyl enamines; α-Oxy *N*-acyl aminals and hemiaminals.
* Corresponding author. Tel.: +1 908 740 3487; fax: +1 908 740 7664; e-mail: xianhai.huang@spcorp.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.069

N-acyl enamine **1** with the hope that this process would differentiate the electrophilicity of the two vinyl carbons (Scheme 1). We choose to use the polyvalent iodine reagent (diacetoxyiodo)benzene ($PhI(OAc)_2$, DIB), which is known to react with electron rich aromatic systems to generate radical cations and has been used in numerous oxidation processes.[6]

To test this idea, *N*-acyl enamine **6** was prepared as shown in Scheme 2. There are two reasons for using **6** as the test substrate: (1) compound **6** incorporates an intramolecular nucleophile that will help to differentiate the two ends of the double bond; (2) the products, 2-(*N*-acylaminal) substituted tetrahydropyrans, are important motifs in *N*-acyl aminal containing natural products.[1] Compound **6** is readily prepared from 5-hexyn-1-ol as shown in Scheme 2 with trans and cis isomers separable by flash chromatography in a 2:1 ratio. With **6** in hand, we first tried the reaction of *trans*-**6** with 2.2 equiv of DIB and 50 equiv of MeOH in trifluoroethanol (TFE) at 0 °C. To our delight, the desired product **7a** was obtained in 60% yield as a 3.5:1 mixture of the *anti*- and *syn*-diastereomers, along with three other products **7b–d** which were isolated in 15%, 8%, and 10% yield, respectively (Scheme 2).



Scheme 2. Preparation of **6** and its reaction with $PhI(OAc)_2$.

In order to improve the yield of the desired product **7a**, we screened a series of different reaction conditions by varying the solvent and oxidant (Table 1). The solvent plays a very important role in the success of the reaction. THF, dioxane, DMF, DMSO, and *tert*-butanol are not good solvents for this reaction. MeCN (Table 1, entry 1) is an acceptable solvent and gives the product in 45% yield. With CH_2Cl_2 as a solvent, **7a** and **7b** were isolated in 35% and 30% yields, respectively (Table 1, entry 2). However, some additional unidentified more polar by-products were observed. The amount of nucleophile clearly affects the products distribution although the desired **7a** remains the major product (Table 1, entries 3–5). When less MeOH is used (4.4 equiv), the formation of open chain product **7d** is minimized, but the amount of **7b** and **7c** increases to a total of 50%. When a large excess of MeOH is used (400 equiv), **7d** is isolated in 35% yield, while **7b** and **7c** are not formed. Finally, the best conditions (Table 1, entries 6 and 7) are achieved using 20 equiv of MeOH with hexafluoroisopropanol (HFI)[6e] as the solvent. Under these conditions, the desired product **7a** is obtained in 82% yield with **7b** as the only major by-product which is readily separable by silica gel chromatography. DIB (2.2 equiv) is not essential for the success of the reaction, as the reaction proceeds equally well with 1.2 equiv of DIB (Table 1, entry 7). To further improve the yield of **7a** and to minimize the amount of **7b**, $PhI(OTFA)_2$ (BTI)[7] was used as the oxidant. The reaction proceeds smoothly to give the desired product **7a** in good yield (Table 1, entries 8–9) when MeCN and HFI are used as the solvents. Although the overall yield is slightly lower than when DIB is used as the oxidant, the amount of product incorporating trifluoroacetate is indeed reduced to a negligible amount. Noteworthy, the ratio of *anti*-**7a** to *syn*-**7a** has changed to 1:1 simply by using this more electron deficient oxidant. When $PhI(OCOt\text{-}Bu)_2$ was used as the oxidant in HFI, the reaction went smoothly to give the desired product in excellent yield, and the ratio of *anti*-**7a** to *syn*-**7a** improved to 6.5/1 (Table 1, entry

Table 1. Optimization of reaction conditions for the oxidative formation of *N*-acyl aminal

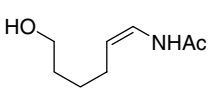
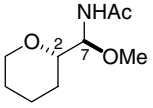
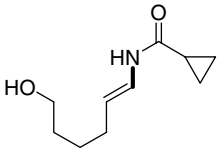
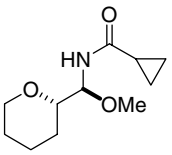
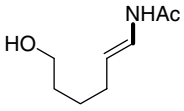
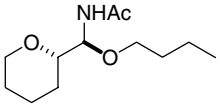
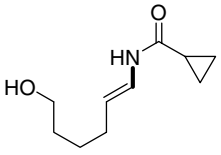
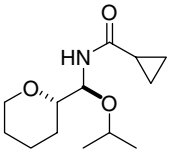
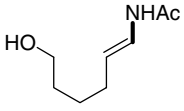
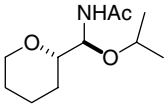
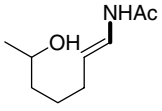
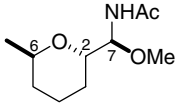
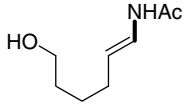
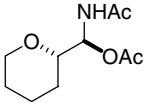
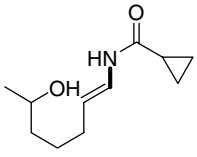
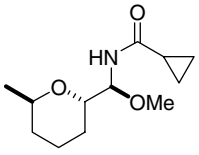
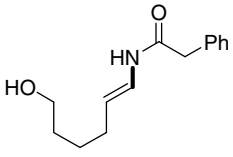
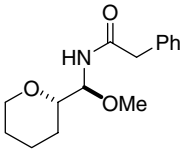
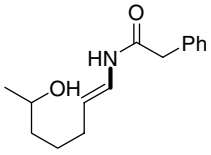
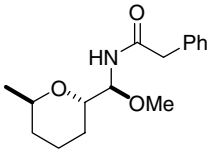
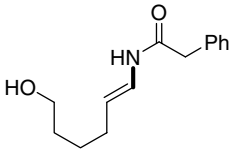
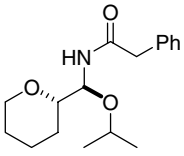
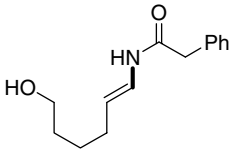
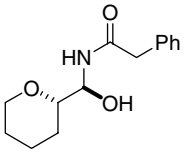
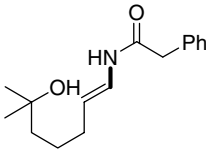
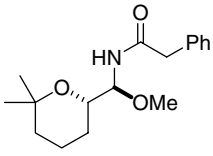
Entry	Oxidant[a]	MeOH (equiv)	Solvent	Yield (%)[c] **7a** (dr)	Yield (%)[d] **7b/7c/7d**
1	$PhI(OAc)_2$	50	CH_3CN	45 (2.5/1)	—
2	$PhI(OAc)_2$	20	CH_2Cl_2	35 (1/1)	30/0/<5
3	$PhI(OAc)_2$	4.4	TFE	45 (4/1)	25/25/0
4	$PhI(OAc)_2$	400	TFE	52 (4/1)	0/0/35
5	$PhI(OAc)_2$	20	TFE	68 (3.5/1)	15/10/<5
6	**$PhI(OAc)_2$**	**20**	**HFI**	**82 (4/1)**	**10/0/<5**
7	**$PhI(OAc)_2$**[b]	**20**	**HFI**	**77 (4/1)**	**5/0/<5**
8	$PhI(OTFA)_2$	20	HFI	66 (1/1)	<5[e]/0/<5
9	$PhI(OTFA)_2$	20	MeCN	64 (1.2/1)	<5[e]/0/<5
10	$PhI(OCO\text{-}t\text{-}Bu)_2$	20	HFI	85 (6.5/1)	10[f]/0/<5

[a] 2.2 equiv of oxidant used.
[b] 1.2 equiv of oxidant used.
[c] Isolated yield, dr = diastereomer ratio of *anti*/*syn* isomers which is determined by 2D NMR.
[d] Based on the NMR of crude product and isolated yield, relative stereochemistry is not determined.
[e] Where OAc = $OCOCF_3$.
[f] Where OAc = OCO-*t*-Bu.

10). The solvent also seems to play an important role in terms of the diastereoselectivity, since in non-polar solvents such as CH_2Cl_2, the ratio of the *anti* and *syn* isomers is 1:1 in contrast to 2.5:1 and 4:1, respectively, when MeCN and HFI are used as the solvent (Table 1, entries 1, 2, and 6). We next looked into oxidants other than hypervalent iodine reagents, such as Cu^{II}-2-ethylhexanoate and ferrocenium hexafluorophosphonate.[8] Those reagents are not effective in this reaction. When NIS is used as the oxidant, only a complex mixture was produced.

With the reaction conditions optimized, we next tested the scope of this reaction (Table 2). Different substrates were prepared using the same procedure as **6**. Surprisingly, the geometry of the enamine does not affect the

Table 2. Oxidative formation of 2-(*N*-acyl aminal) tetrahydropyrans

Entry	Substrate[a]	Product[b] (yield, dr)	Entry	Substrate[a]	Product[b] (yield, dr)
1	 ***cis*-6**	 **7a** (82%, 3/1)	8	 **14**	 **15** (85%, 3.5/1)
2	 **6** (*n*-BuOH, 20 eq.)	 **8** (82%, 4/1)	9	 **14** (IPA, 20 eq.)	 **16** (75%, 4/1)
3	 **6** (IPA, 20 eq.)	 **9** (77%, 4/1)	10	 **17**	 **18** (81%, 4.6/1/1/4.6[c])
4	 **6** (no added nucleophile)	 **7b** (92%, 4/1)	11	 **19**	 **20** (89%, 4/1/1/4[c])
5	 **10**	 **11** (86%, 3/1)	12	 **21**	 **22** (82%, 3/1/1/3[c])
6	 **10** (IPA, 20 eq.)	 **12** (75%, 3/1)	13	**21** (MeCN, BTI)	**22** (40%, 1/1/1/1[c])
			14	**21** (HFI, BTI)	**22** (62%, 1/1/1.2/0.8[c])
7	 **10** (H_2O, 20 eq.)	 **13** (65%, 3.5/1)	15	 **23**	 **24** (85%, 4.3/1[b])

[a] 2.2 equiv of $PhI(OAc)_2$ used as oxidant with 20 equiv of MeOH as nucleophile in HFI in all cases except where otherwise indicated.

[b] Isolated yield, relative stereochemistry of the major isomer is shown, dr = diastereomer ratio of 2,7-*anti*/2,7-*syn* isomers, the ratio and configuration are determined by NMR.

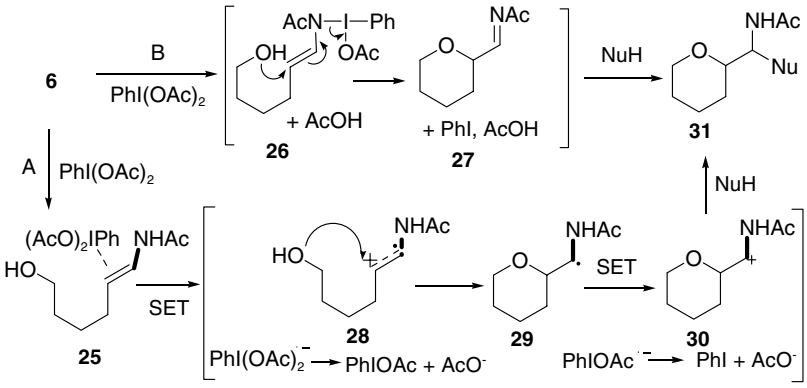
[c] Relative stereochemistry of the 2,6-*trans*-2,7-*anti* isomer is shown, dr = diastereomer ratio of 2,6-*trans*-2,7-*anti*/2,6-*trans*-2,7-*syn*/2,6-*cis*-2,7-*syn*/2,6-*cis*-2,7-*anti* isomers.

outcome of the reaction at all. When *cis*-**6** is used as the starting material (Table 2, entry 1), the reaction proceeds smoothly to give **7a** in excellent yield with a similar diastereoselectivity (*anti*/*syn* = 3/1) (Table 2, entry 1). Based on this result, we used other substrates without separation of the *N*-acyl enamine isomers. As shown in Table 2, different acyl enamines such as benzyl and cyclopropyl acyl enamines **10** and **14** react efficiently to give the desired tetrahydropyran products in excellent yields. The phenyl ring and the cyclopropyl groups are not affected under the reaction conditions. Nucleophiles including long chain primary alcohols and secondary alcohols work equally well in this reaction to give the desired products in very good yields (Table 2, entries 2, 3, 6, and 9). When there is no added nucleophile, the acetate group from DIB can act as the nucleophile and give the desired *O*-acyl *N*-acyl aminal **7b** in excellent yield (Table 2, entry 4), which provides an efficient way to generate this type of substrate. Moreover, water can act as a nucleophile as well to give *N*-acyl heminal **13** in good yield as illustrated in entry 7 (Table 2). Surprisingly, this type of hemiaminal is stable and can be readily purified with silica gel flash column chromatography. Considering the abundance of *N*-acyl hemiaminal containing natural products, this method will be very useful for the synthesis of this type of structural units.

To further demonstrate the usefulness of this new reaction, secondary and tertiary alcohols were also prepared and tested as substrates for these cyclizations (Table 2, compounds **17**, **19**, **21**, **23**). As listed in Table 2, both secondary and tertiary alcohols work very well to give the desired products in very good yields. For secondary alcohols, the stereochemical outcome is consistent with primary alcohols. When DIB is used as the oxidant, the 2,7-*anti* to 2,7-*syn* ratio is about 4:1, and the ratio becomes 1:1 when BTI is used as the oxidant. In both cases, the stereochemistry at C2 and C6 is the same with a 2,6-*cis*/2,6-*trans* ratio of 1:1. Considering the difficulties to synthesize trans 2,6-substituted tetrahydropyrans,[9] this method provides a quick access to the trans isomers in about 50% ratio. Further improvement of the stereoselectivity of this new method is ongoing.

A possible mechanistic pathway for the reaction is given in Scheme 3. Three observations made during the reaction support a radical cation pathway: (1) primary, secondary and tertiary alcohols work equally well for the cyclization reaction; (2) the bulkiness of the polyvalent iodine reagents does not dramatically affect the reaction, and the reaction yields are very comparable; (3) protic polar non-nucleophilic solvents clearly facilitate the reaction. TFE is known to be an especially good solvent for radical cation reactions.[10] Based on these results, we propose a radical cation reaction pathway (pathway A, Scheme 3). In this case, the electron rich *N*-acyl enamine first coordinates with DIB (**25**), and the reactive radical cation **28** is then generated through a single electron transfer (SET) process which is trapped by the intramolecular nucleophile to form a stabilized radical **29**. At this point, another SET process takes place from radical **29** to DIB or acetyl iodobenzene generated from the previous step to give the stabilized cation **30**. This reactive intermediate then reacts with nucleophiles to give the final product **31**. Presently, we cannot rule out an S_N2' type of reaction pathway (pathway B, Scheme 3) in which the *N*-acyl enamine first reacts with DIB to give intermediate **26**. Intermediate **26** undergoes intramolecular nucleophilic attack of the double bond to give a possible intermediate *N*-acyl imine **27**, which then reacts with the nucleophile to give the final product **31**. Further studies to fully understand the reaction pathway are ongoing.

In conclusion, an efficient new method to synthesize α-oxy *N*-acyl aminals and hemiaminals in a single step from readily synthesized *N*-acyl enamines has been developed using $PhI(OAc)_2$ as the oxidant. This method not only provides quick access to *N*-acyl aminals and hemiaminals, which normally requires several chemical transformations with reported procedures, but also generates substituted tetrahydropyrans with functionality at the C2 position available for further chemical transformation. A possible reaction pathway is laid out and preliminary results support a radical cation process when the reaction is carried out in protic non-nucleophilic polar solvents. Further studies to extend this strategy to synthesize other ether ring systems bearing *N*-acyl aminals and hemiaminals, improve the stereoselectivity of the reaction, understand the mechanistic pathway of the reaction, and apply this method in the total synthesis of natural products[1] are in progress, and the results will be reported in due course.



Scheme 3. Possible reaction pathway for the oxidative formation of *N*-acyl aminal.

Acknowledgements

During the course of this study, Professor Paul Floreancig at University of Pittsburgh presented a seminar at SPRI detailing a different methodology towards the synthesis of acyclic aminals using similar nucleophiles. We would like to thank him for sharing this information. We thank Drs. Alexei Buevich and Ross Yang for NMR spectrometry and mass spectrometry assistance, respectively; Dr. Chad Bennett for proof-reading of the manuscript; and Drs. Catherine Strader, John Piwinski, and Satwant Narula for their strong support of the postdoctoral program.

Supplementary data

Experimental details and spectral data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.069.

References and notes

1. For some representative examples: (a) Kakeya, H.; Kageyama, S.-I.; Nie, L.; Onose, R.; Okada, G.; Beppu, T.; Norbury, C. J.; Osada, H. *J. Antibiot.* **2001**, *54*, 850; (b) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535; (c) Benz, F.; Knusel, F.; Nuesch, J.; Treichler, H.; Voser, W. *Helv. Chim. Acta* **1974**, *57*, 2459–2477; (d) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951, and references cited therein; (e) Pettit, G. R.; Xu, J. P.; Chapuis, J. C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149.
2. For some selected examples: (a) Jiang, X.; Garcia-Fortanet, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254; (b) Coleman, R. S.; Walczak, M. C.; Campbell, E. L. *J. Am. Chem. Soc.* **2005**, *127*, 16038; (c) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102; (d) Sohn, J.-H.; Waizumi, N.; Zhong, M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290, and references cited therein; (e) Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *8*, 875.
3. Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem.* **2004**, *116*, 5945; Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821.
4. Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 991, and references cited therein.
5. (a) Shen, R.; Lin, C.-T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650; (b) Shen, R.; Porco, J. A. Jr. *Org. Lett.* **2000**, *2*, 1333; (c) Jiang, V.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.
6. (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123, and references cited therein; (b) Moriarty, R. M.; Chany, C. J., II; Kosmeder, J. W., II; Du Bois, J. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Crich, D., Fuchs, P. L., Molander, G., Eds.; John Wiley & Sons, 2006; (c) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137; (d) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377; (e) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397; (f) Streuff, J.; Hovelmann, C. H.; Niegar, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586; (g) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690; (h) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672; (i) Shi, L.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 6939; (j) Toumieux, S.; Compain, P.; Martin, O. R.; Selkti, M. *Org. Lett.* **2006**, *8*, 4493.
7. (a) Moriarty, R. M.; Kosmeder, J. W., II. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Crich, D., Fuchs, P. L., Molander, G., Eds.; John Wiley & Sons, 2001; (b) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316.
8. Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem.* **2005**, *117*, 615; *Angew. Chem., Int. Ed.* **2005**, *44*, 609, and references cited therein.
9. McDonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683, and references cited therein.
10. (a) Newcomb, M.; Miranda, N.; Huang, X.; Crich, D. *J. Am. Chem. Soc.* **2000**, *122*, 6128; (b) Horner, J. H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* **2004**, *126*, 14979.