ORGANIC LETTERS

2009
Vol. 11, No. 11
2345−2348

Intramolecular H-Atom Abstraction in γ-Azido-Butyrophenones: Formation of 1,5 Ketyl Iminyl Radicals

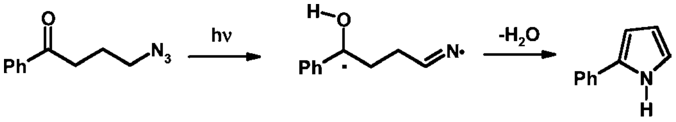
Sivaramakrishnan Muthukrishnan,[†] Jagadis Sankaranarayanan,[†] Rodney F. Klima,[†] Tamara C. S. Pace,[‡] Cornelia Bohne,[‡] and Anna D. Gudmundsdottir*,[†]

Department of Chemistry, University of Cincinnati, PO Box 210172,
Cincinnati, Ohio 45221, and Department of Chemistry, University of Victoria,
Victoria, Canada V8W 3V6

Anna.Gudmundsdottir@uc.edu

Received April 7, 2009

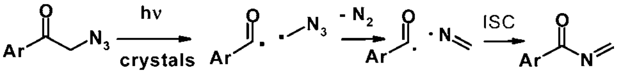
ABSTRACT



Photolysis of γ-azidobutyrophenone derivatives yields 1,4 ketyl biradicals via intramolecular H-atom abstraction. The 1,4 ketyl biradicals expel a nitrogen molecule to form 1,5 ketyl iminyl biradicals, which decay by ring closure to form a new carbon−nitrogen bond. The 1,5 ketyl iminyl biradicals were characterized with transient spectroscopy. In argon/nitrogen-saturated solutions, the biradicals have $\lambda_{max} \approx 300$ nm and $\tau = 15$ μs. DFT-TD calculations were used to support the proposed mechanism for formation of the 1,5 ketyl iminyl radicals.

Formation of carbon−carbon bonds through radical combination is a valuable tool in organic synthesis. In comparison, nitrogen−carbon bonds are generally not produced from radicals even though nitrogen radicals hold similar promise as carbon radicals in synthesis.[1−3] The limited use of nitrogen radicals in synthesis is mainly due to the lack of methods for selectively yielding nitrogen centered radicals. Recently, we demonstrated that iminyl radicals can be formed selectively by irradiating α-azidoacetophenones in the solid-state.[4] The α-azidoacetophenones undergo α-cleavage to form an azido alkyl and benzoyl radical pair, but the azido alkyl radicals expel nitrogen molecules to form iminyl radicals. By irradiating the α-azidoacetophenones in the solid-state, the benzoyl and iminyl radical pairs are held in close proximity and combine to form a new carbon−nitrogen bond (Scheme 1).

Scheme 1



We have further advanced our methodology of using radicals to form carbon−nitrogen bonds. In this communication, we demonstrate that 1,5 nitrogen−carbon biradicals can be used to form carbon−nitrogen bonds in high selectivity in solution. Thus, these 1,5 biradicals have the potential to make five-membered heterocyclic derivatives in synthetic applications. The 1,5 biradicals are formed by irradiating

---

[†] University of Cincinnati.

[‡] University of Victoria.

(1) (a) El Kaim, L.; Meyer, C. *J. Org. Chem.* **1996**, *61*, 1556. (b) Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838.

(2) Zard, S. S. *Chem. Soc. Rev.* **2008**, *37*, 1603.

(3) (a) McNab, H. *Aldrichimica Acta* **2004**, *31*, 19. (b) Hickson, C. L.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1569. (c) Hickson, C. L.; McNab, H. *Synthesis* **1981**, 464. (d) Bucher, G.; Scaiano, J. C.; Sinta, R.; Barclay, G.; Cameron, J. *J. Am. Chem. Soc.* **1995**, *117*, 3848. (e) Bencivenni, G.; Lanza, T.; Leardini, T.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2008**, *73*, 4721. (f) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G.; Rizzoli, C. *Org. Lett.* **2004**, *6*, 417. (g) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *J. Org. Chem.* **1997**, *62*, 5846.

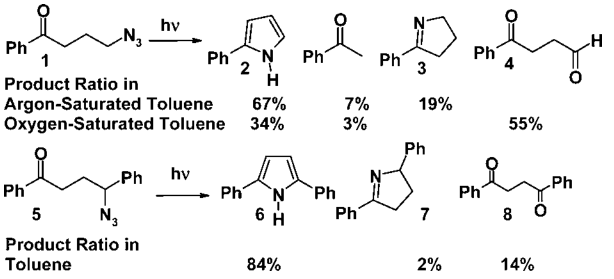
(4) Mandel, S. M.; Singh, P. N. D.; Muthukrishnan, S.; Chang, M.; Krause, J. A.; Gudmundsdottir, A. D. *Org. Lett.* **2006**, *8*, 4207.

10.1021/ol900754a CCC: $40.75

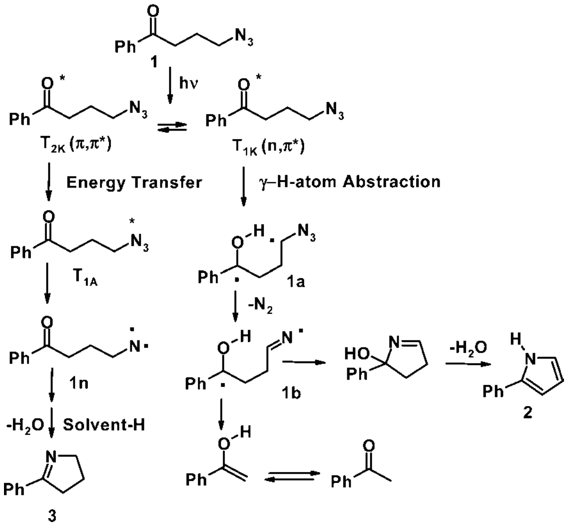
γ-azido butyrophenone derivatives, which consequently undergo efficient intramolecular γ-H-atom abstraction to yield 1,4 ketyl biradicals. Expulsion of nitrogen molecules from the 1,4 biradicals results in the 1,5 ketyl iminyl biradicals. We used transient spectroscopy, trapping studies and density functional theory (DFT) calculations to characterize the 1,5 ketyl iminyl biradicals and to support the proposed mechanism for formation of these biradicals.

Photolysis of **1** in argon-saturated toluene yields **2** as the major product and smaller amounts of acetophenone and **3** (Scheme 2), whereas photolysis of **1** in oxygen-saturated toluene results mainly in **4**, **2** and trace amounts of acetophenone. We propose that the lowest excited triplet ketone (T_{1K}) of **1**, that presumably has a (n,π^*) configuration, abstracts a γ-H-atom to form biradical **1a** (Scheme 3). Expulsion of a nitrogen molecule from **1a** results in iminyl radical **1b**, which cyclizes and dehydrates to give **2**. However, a small fraction of **1a** must cleave to form 1-phenylethenol, which tautomerizes to acetophenone. Based on the comparison with valerophenone derivatives, where the first two triplet states are close in energy,[5] we theorize that the second excited state of the triplet ketone (T_{2K} (π,π^*)) of **1** undergoes energy transfer to form the triplet excited state of the azido chromophore (T_{1A}) of **1**, which falls apart to yield triplet alkyl nitrene **1n** and eventually results in formation of **3** (Scheme 3).

Scheme 2



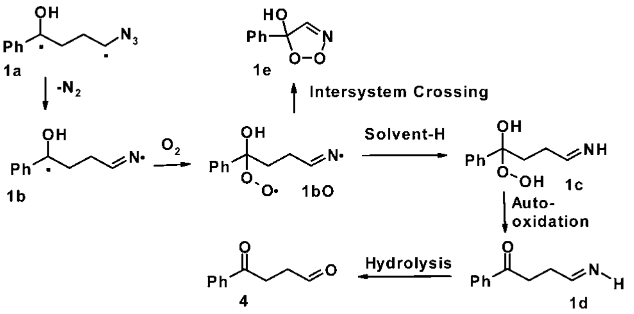
Scheme 3



Similarly, photolysis of **5** in toluene yields mainly **6** and trace amounts of **7** and **8**. Thus, **5** also reacts mainly by intramolecular H-atom abstraction to form **6**, further indicating that irradiation of γ-azidobutyrophenone derivatives generally yield pyrroles.

We theorize that in oxygen-saturated toluene, biradical **1b** must be intercepted with oxygen to form **1bO** (Scheme 4).

Scheme 4



Biradical **1bO** presumably decays by abstracting H-atoms from the solvent, followed by autoxidation to form **1d**, which is hydrolyzed to **4**.

We used calculations to validate the reaction mechanisms shown in Schemes 3 and 4. The calculations were done using Gaussian03 at B3LYP level of theory and 6-31+G(d) as the basis set.[6,7] We optimized the structures of **1** and T_{1K} of **1** and calculated their IR spectra. We found that the T_{1K} of **1** is 69 kcal/mol above S_0. The T_{1K} C=O bond is elongated to 1.32 Å (compared to 1.22 Å in S_0) and has a vibrational stretch at 1394 cm^{-1}. The progression of the C−O bond and its IR vibrational stretch fits well with the T_{1K} of **1** having a (n,π^*) configuration.[8] The energy of the T_{1K} of **1** is considerably lower than the measured energy of T_{1K} in the analog valerophenone, which has a T_{1K} that is 74 kcal/mol

---

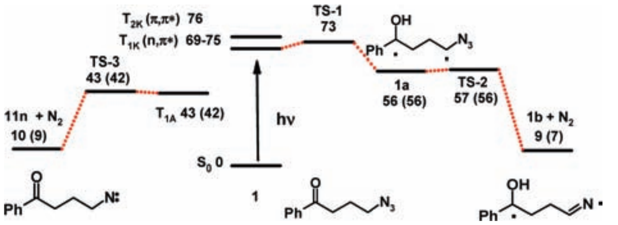
(5) Wagner, P. J.; Kemppainen, A. E.; Schott, H. N. *J. Am. Chem. Soc.* **1973**, *95*, 5604.

(6) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(7) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian03*, Revisions A.1 and C.02; Gaussian, Inc.: Wallingford, CT, 2004.

above S_0.[9] However, we have previously shown that DFT underestimates the energy of triplet ketones with a (n,π^*) configuration.[10] In comparison, time dependent density functional theory (TD-DFT)[11] calculations show that the T_{1K} and T_{2K} of **1** are 76 and 77 kcal/mol above S_0, respectively. We plotted stationary points on the triplet energy surface of **1** to form **1b** and **1n** in Scheme 5. The transition state (TS-1) for the intramolecular H-atom abstraction from the T_{1K} of **1** to form **1a** is located 4 kcal/mol above the T_{1K} of **1**. The transistion state (TS-2) for **1a** expeling a nitrogen molecule to yield **1b** is only 1.1 kcal/mol above **1a**, indicating that formation of **1b** is very feasible at ambient temperature. It is important to note that the energy for TS-1 is lower than the energy for T_{2K} making this mechanistic pathway energetically feasible. Finally, the T_{1A} of **1** is 43 kcal/mol above its S_0, and the transition state (TS-3) for the T_{1A} to form **1n** and a nitrogen molecule is only 0.4 kcal/mol above T_{1A}.

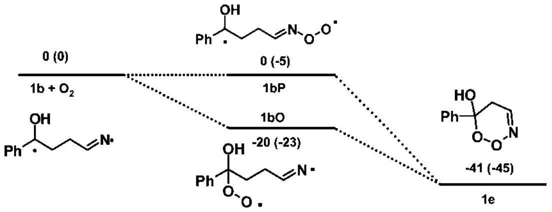
Scheme 5[a]



[a] Calculated energies are in kcal/mol. Numbers in parentheses are the calculated energies in methanol.

We calculated stationary points on the triplet energy surface of the reaction of **1** with oxygen (Scheme 6). The calculations support the idea that **1b** reacts efficiently and irreversibly with oxygen to form **1bO**, whereas formation of **1bP** must be reversible since the nitrogen−oxygen bond is weaker than the carbon−oxygen bond in **1bO**. Since we did not observe **1e** (Scheme 4), we conclude that **1bO** does not undergo intersystem crossing to form **1e**. Rather, **1bO** must decay by H-atom abstraction from the solvent and autoxidation to form **1d**.

Scheme 6[a]



[a] Calculated energies are in kcal/mol. Numbers in parentheses are the calculated energies in methanol.

We used laser flash photolysis to further support the proposed mechanism for the photoreactivity of **1**. Laser flash photolysis (Excimer laser, $\lambda = 308$ nm, 17 ns; YAG lasers, $\lambda = 355$ nm, 15 ns)[12] of **1** in nitrogen-saturated acetonitrile and methanol produced a transient spectrum with $\lambda_{\max} \approx 300$ nm (Figure 1). This transient absorption was formed immediately after the laser pulse and the lifetime of this transient (as determined by its monoexponential decay at 300 nm) was ~15 μs in methanol and acetonitrile (Figure 1A). We assigned this transient absorption to **1b** based on TD-DFT calculations. In acetonitrile, the most intense band is calculated to be at 297 nm ($f = 0.1152$) and is due to the transition of an electron from the half full p-orbital of the carbon atom of the hydroxyl group into the π^* orbital (Figure 2). The calculations also show less intense electronic transitions at 290, 315, 340, and 374 nm (Figure 2). Furthermore, the TD-DFT calculations rule out assignment of this absorption to **1a** (see Supporting Information where an absoption between 360 and 400 nm was predicted).

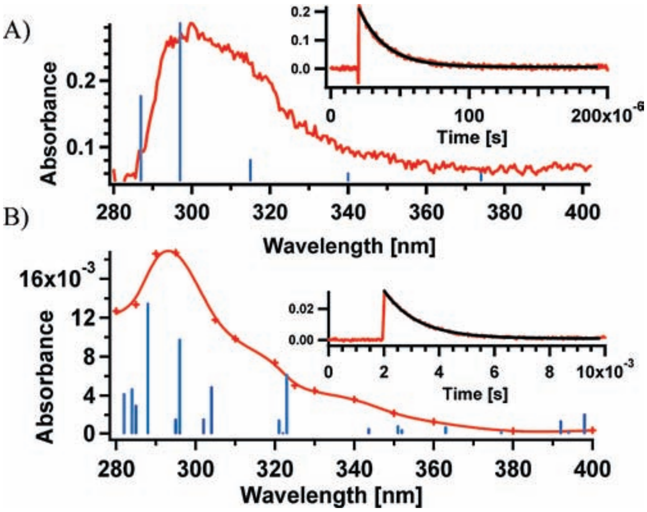


Figure 1. Transient spectra of (A) **1b** in nitrogen-satured acetonitrile. (Inset) Decay of **1b** at 300 nm. (B) **1bO** in oxygen-saturated acetonitrile. (Inset) Decay of **1bO** at 290 nm. The blue bars are calculated electronic transitions for **1b** (×4) and **1bO**.

---

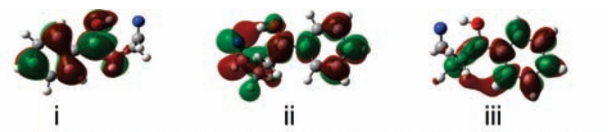
(8) (a) Srivastava, S.; Yourd, E.; Toscano, J. P. *J. Am. Chem. Soc.* **1998**, *120*, 6173. (b) He, H.-Y.; Fang, W.-H.; Phillips, D. L. *J. Phys. Chem. A* **2004**, *108*, 5386. (c) Fang, W.-H.; Phillips, D. L. *Chem. Phys. Chem.* **2002**, *3*, 889. (d) Fang, W.-H.; Phillips, D. L. *J. Theor. Comput. Chem.* **2003**, *2*, 23.

(9) Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*; Marcel Dekker: New York, 1993.

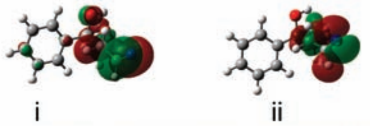
(10) (a) Muthukrishnan, S.; Mandel, S. M.; Hackett, J. C.; Singh, P. N. D.; Hadad, C. M.; Krause, J. A.; Gudmundsdottir, A. D. *J. Org. Chem.* **2007**, *72*, 2757. (b) Klima, R. F.; Jadhav, A. V.; Singh, P. N. D.; Chang, M.; Vanos, C.; Sankaranarayanan, J.; Vu, Mai; Ibrahim, N.; Ross, E.; McCloskey, S.; Murthy, R. S.; Krause, J. A.; Ault, B. S.; Gudmundsdottir, A. D. *J. Org. Chem.* **2007**, *72*, 6372.

(11) (a) *Density Functional Methods in Chemistry*; Labanowski, J., Ed.; Springer-Verlag: Heidelberg, 1991. (b) Parr, R. G.; Weitao, Y. *Density-Functional Theory in Atoms and Molecules*; Oxford University Press: New York, 1989. (c) Bauernschmitt, R. *Chem. Phys. Lett.* **1996**, *256*, 454. (d) Stratmann, R. *J. Chem. Phys.* **1998**, *109*, 8218. (e) Foresman, J. *J. Phys. Chem.* **1992**, *96*, 135.

(12) (a) Liao, Y.; Bohne, C. *J. Phys. Chem.* **1996**, *100*, 734. (b) Gritsan, N. P.; Zhai, H. B.; Yuzawa, T.; Karwiek, D.; Brooke, J.; Platz, M. S. *J. Phys. Chem. A* **1997**, *108*, 3783. (c) Cosa, G.; Scaiano, J. C. *Photochem. Photobiol.* **2004**, *80*, 159. (d) See Supporting Information.



A) Orbtials involved in electronic transition in **1b** at 297 nm (i → ii and iii).



B) Orbitals involved in elctronic transition in **1bO-A** at 304 nm (i → ii).

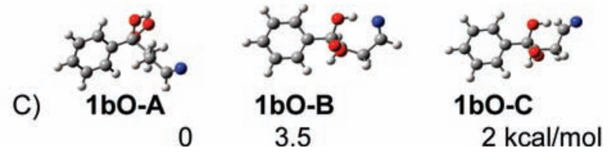


Figure 2. Major elecronic transitions in (A) **1b** and (B) **1bO**. (C) Minimal energy conformers of **1bO**.

We did not observe **1a** or the T_{1K} of **1**, presumably because their lifetimes are less than the time resolution of the laser flash apparatus (17 ns). We attribute the short lifetime of T_{1K} of **1** to the fact that the transition state for H-atom abstraction to form **1a** is located only a few kcal/mol above T_{1K} of **1**. Similarly, **1a** is short-lived because the transition state for it to form **1b** is less than 1 kcal/mol above **1a** and thus **1b** is formed very efficiently at ambient temperature.

Laser flash photolysis of **1** in the oxygen-saturated solutions produced a different transient spectrum than in the nitrogen-saturated solution. This transient spectrum has $\lambda_{max} \approx 295$ nm and its lifetime (as determined by its monoexponential decay at 290 nm) was 1.2 ms and 650 μs in acetonitrile and methanol, respectively. We assign this transient absorption to **1bO** based on TD-DFT calculations. TD-DFT of the lowest energy conformer **A** of **1bO** has two of the most intense bands at 304 nm ($f = 0.0048$) and 285 nm ($f = 0.0029$). The band at 304 nm is due to an electronic transition from the π-orbital of C═N to the antibonding orbital of the O−O bond, whereas the 284 nm band is due to an electronic excitation from the π-orbital of O−O to its antibonding orbital (Figure 2). The TD-DFT calculations were affected somewhat by the conformer of **1bO** (see Supporting Information). Thus, we calculated the electronic transition for the conformers **B** and **C** of **1bO** (see Figure 2) and included the electronic transition for these 3 conformers in Figure 1B. The lifetime of **1bO** being shorter in methanol than in acetonitrile supports the idea that **1bO** decays by H-atom abstraction to form **1d**. Furthermore, the observed transient absorption in oxygen-saturated solutions cannot be due to **1e** because its calculated absorption spectrum has no absorption bands above 290 nm (see Supporting Information).

Thus, product studies, calculations and transient spectroscopy support the idea that γ-azidobutyrophenones undergo intramolecular H-atom abstraction from the T_{1K} state with a (n,π*) configuration to form 1,4 biradicals, which efficiently expel nitrogen molecules to form 1,5-ketyl iminyl biradicals. In the absence of oxygen, the ketyl iminyl biradicals decay by intramolecular cyclization, whereas they are efficiently trapped with oxygen in oxygen-saturated solutions. In comparison, β-azidopropiophenone derivatives undergo efficient intramolecular energy transfer from their T_{2K} state (π,π*) to form triplet alkyl nitrenes in solution, because intramolecular H-atom abstraction of β-H-atoms is less feasible than for γ-H-atoms.[13] Similarly, α-azidoacetophenone derivatives undergo intramolecular energy transfer to form triplet alkyl nitrenes from their triplet ketone with a (π,π*) configuration and α-azidoacetophenones also undergo α-cleavage from their triplet ketones with a (n,π*) configuration to form benzoyl and azido alkyl radicals. However, the α-cleavage is not selective in solution. In constrast, the γ-H-atom abstraction reaction described here leads to good selectivity for the ring closed products.We expect this methodology to be applicable for the synthesis of 2-arylpyrroles with numerous functional groups and thus be complementary to metal catalyzed functionlization of pyrroles.[14]

Acknowledgment. This work was supported by the NSF (CHE-0703920) and the Ohio Supercomputer Center. C.B. and T.C.S.P. thank the Natural Science and Engineering Research Council (NSERC) for funding at Victoria and T.C.S.P. thanks NSERC for a CGS-D scholarship. We thank Prof. M. S. Platz at The Ohio State Univ. and J. C. Scaiano at the Univ. of Ottawa for use of their instrumentation.

Supporting Information Available: Experiments and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900754A

---

(13) (a) Singh, P. N. D.; Mandel, S. M.; Sankaranarayanan, J.; Muthukrishnan, S.; Chang, M.; Robinson, R. M.; Lahti, P. M.; Ault, B. S.; Gudmundsdottir, A. D. *J. Am. Chem. Soc.* **2007**, *129*, 16263. (b) Sankaranarayanan, J.; Bort, L.; Krause, J. A.; Mandel, S. M.; Chen, P.; Brooks, E. E.; Tsang, P.; Gudmundsdottir, A. D. *Org. Lett.* **2008**, *10*, 937.

(14) (a) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.