

Spontaneous Oxygenation of Siloxy-*N*-silylketenimines to α -Ketoamides

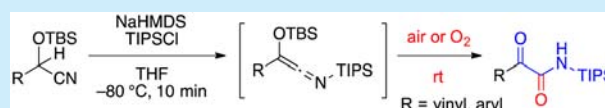
Michiko Sasaki,^{*,†} Masafumi Ando,[†] Masatoshi Kawahata,[‡] Kentaro Yamaguchi,[‡] and Kei Takeda[†]

[†]Department of Synthetic Organic Chemistry, Institute of Biomedical & Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8553, Japan

[‡]Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan

S Supporting Information

ABSTRACT: Siloxy-*N*-silylketenimines generated in situ from *O*-silyl cyanohydrins were converted to α -ketoamides by brief exposure to air or oxygen. Oxidation under extremely mild conditions can be explained by assuming the intermediacy of a 3-imino-1,2-dioxetane derivative generated via triplet–singlet intersystem crossing after the reaction of siloxy-*N*-silylketenimines with triplet oxygen.

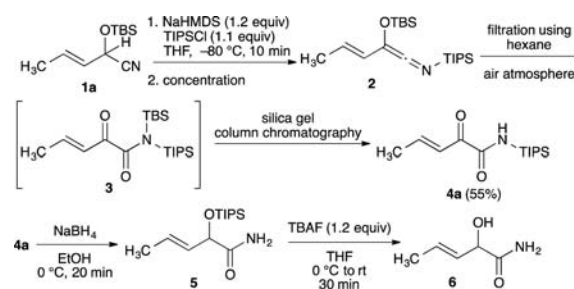


α -Ketoamides have attracted the interest of synthetic chemists because they constitute a basic structural unit of biologically important compounds such as cyclotheonamide, RAR γ agonist, and FK506,¹ providing numerous synthetic methods for their preparation. Approaches to the preparation of α -ketoamides can be classified into four categories: (1) amidation of α -keto acids,² (2) double carbonylation of amines,³ (3) oxidation of precursor molecules such as α -hydroxyamides,⁴ α -cyanoamides,⁵ α -aminoamides,⁶ and ynamides,⁷ and (4) oxidative coupling of amines with isocyanides,⁸ aldehydes,⁹ methylketones,¹⁰ alkynes,¹¹ or α -carbonyl aldehydes.¹² The latter two methods using molecular oxygen, an ideal oxidant, as the oxygen source have received much attention. Although these approaches are very attractive, most of the approaches require transition metals such as copper, making the method environmentally less friendly. We are aware of only one example involving molecular oxygen as an oxidant without any additives.¹³ There, Kumar et al. reported the oxidation of 2,2-dibromo-1-aryl ethanones to α -ketoamides in the presence of air or oxygen and secondary amines. However, long reaction times (18–26 h) and heating at 40–50 °C are required and the substrate scope is also limited to aryl derivatives. Another problem in the synthesis of α -ketoamides is that only a few methods are applicable to the parent *N*-unsubstituted derivatives.^{8a,10d} Herein, we report a new straightforward approach to the preparation of α -ketoamides that involves oxidation of siloxy-*N*-silylketenimines, generated in situ from *O*-silyl cyanohydrins, with atmospheric air or molecular oxygen at room temperature in the absence of any transition metals.

During our attempts to generate enantioenriched *N*-protected ketenimines,^{14,15} in which no chiral elements other than an axial chirality is present, by a center-to-axial chirality transfer from chiral α -nitrile carbanions,¹⁶ we had the opportunity to prepare *N*-silylketenimines from *O*-silyl cyanohydrin and to examine their chemical behavior. According to the procedures reported by Cunico and Kuan^{15c} and the modified one reported for *O*-*tert*-butyl derivatives by Denmark

and co-workers,¹⁷ when *O*-silyl cyanohydrin of α,β -unsaturated aldehyde **1a** was treated with NaHMDS (1.2 equiv) in the presence of *i*-Pr₃SiCl (TIPSCl) (1.1 equiv) in THF at –80 °C for 10 min and then concentrated after warming to room temperature, an essentially pure sample of siloxy-*N*-silylketenimine **2** was obtained, and it showed a characteristic signal for the sp carbon atom of ketenimines at 211.0 ppm in the ¹³C NMR (Scheme 1).¹⁸ Filtration of the sample through Celite

Scheme 1. Transformation of *O*-Silyl Cyanohydrin to α -Ketoamide via *N*-Silylketenimine



using *n*-hexane under exposure to air to remove inorganic salts, however, resulted in the complete disappearance of **2** in contrast to the results reported by Denmark.¹⁷ On the basis of comparisons of its spectral data with those reported for analogous compounds, the major product was suggested to be α -ketoamide **3**, of which purification via column chromatography on silica gel resulted in the formation of an *N*-monosilyl derivative **4a**. The structure of **4a** was confirmed on the basis of X-ray analysis of *O*-silyl- α -hydroxyamide derivative **5** that was obtained by NaBH₄ reduction and silyl transfer to afford **6**.¹⁹

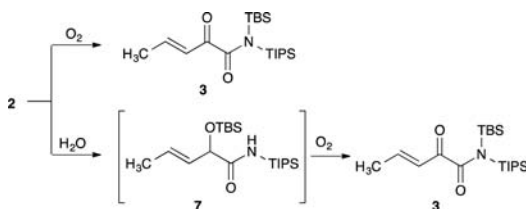
The formation of α -ketoamide **3** indicates the intervention of an oxidation process during the filtration, suggesting direct

Received: February 17, 2016

Published: March 17, 2016

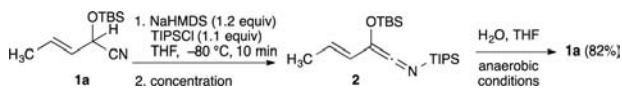
oxygenation of ketenimine **2** by an atmospheric oxygen or hydrolysis by atmospheric moisture to β -hydroxyamide **7** followed by air oxidation (Scheme 2).

Scheme 2. Possible Pathways for Oxidation



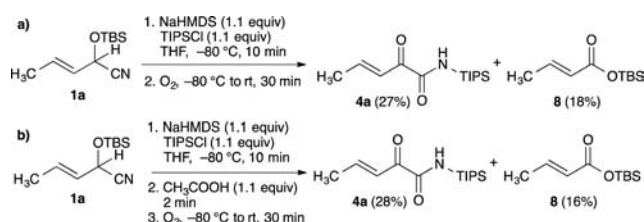
To gain an insight into the mechanism for the formation of an oxidation product **3**, we examined the chemical behavior of siloxy-*N*-silylketenimine **2** toward water and air. Exposure of **2** obtained by concentration of the reaction mixture to water and THF under anaerobic conditions gave back **1a** in 82% yield, indicating that the α -ketoamide is not formed under conditions without oxygen and that hydrolysis of α -ketoamide does not precede the oxidation (Scheme 3).

Scheme 3. Hydrolysis of *N*-Silylketenimine



On the other hand, when **1a** was treated with NaHMDS and TIPSCl under a nitrogen atmosphere at $-80\text{ }^{\circ}\text{C}$ for 10 min and then the nitrogen supply was replaced by oxygen and the solution was allowed to warm to room temperature followed by hydrolytic workup, α -ketoamide **4a** was obtained in 27% yield together with a silyl ester derivative **8** in 18% yield. Relatively low conversion yields are probably due to hydrolysis of the ester group in **8** during the aqueous workup and purification using column chromatography on silica gel (Scheme 4a). The

Scheme 4. Oxidation of *N*-Silylketenimine

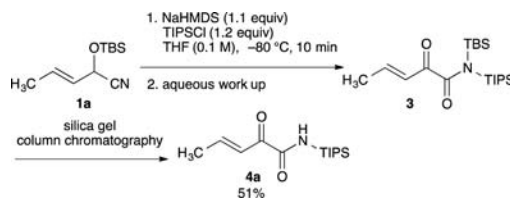


structure of **8** was confirmed by comparison with a separately prepared authentic sample from crotonic acid. When acetic acid (1.1 equiv), which should cause immediate protonation of the base, a sodiocarbanion, and/or an *N*-sodioketenimine if they remain unreacted, was added before replacement of nitrogen to oxygen atmosphere at $-80\text{ }^{\circ}\text{C}$, almost the same yields of **4a** (28%) and **8** (16%) as those without addition of acetic acid were obtained with no detectable amount of **1a** (Scheme 4b). This observation indicates that the formation of siloxy-*N*-silylketenimine **2** was completed at $-80\text{ }^{\circ}\text{C}$ within 10 min.²⁰

In fact, quenching the reaction at $-80\text{ }^{\circ}\text{C}$ followed by the usual aqueous workup and then silica gel chromatographic purification resulted in the formation of α -ketoamide **4a** in an acceptable yield (Scheme 5). The result suggests that the rate of

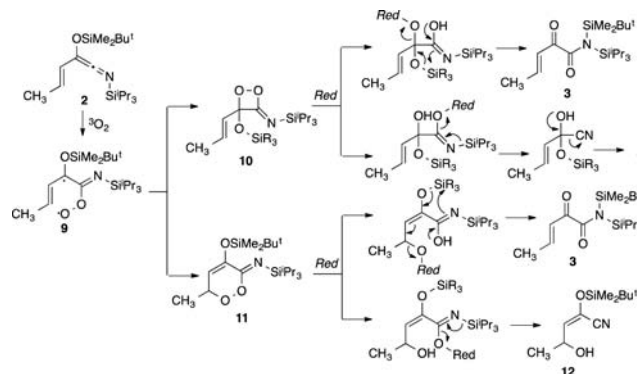
oxidation of **2** by atmospheric oxygen is much faster than that for giving back **1a** by hydrolysis.

Scheme 5. Synthesis of α -Ketoamide from *O*-Silylcyanohydrin



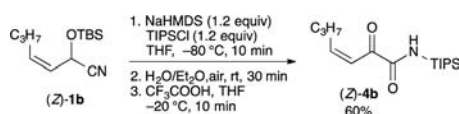
Since reaction of atmospheric oxygen, a triplet dioxygen $^3\text{O}_2$, with singlet organic molecules is a spin-forbidden process, for the spontaneous occurrence of a reaction, generally, either $^3\text{O}_2$ or organic substrates should be activated photochemically.²¹ However, it is known that a particular type of organic substrate such as a strained acetylene can be involved without any activation in the formation of typical products generated via a singlet oxygen.²² Turro and co-workers reported that diphenylketene undergoes a direct reaction with a triplet oxygen to give diradical and/or zwitterionic intermediates, which are collapsed to benzophenone via a 1,2-dioxetanone intermediate after a triplet–singlet intersystem crossing.^{22j} This and other reports^{22a,b} led us to speculate a similar type of reaction pathway involving an intersystem crossing as shown in Scheme 6. Thus, the addition of triplet oxygen to siloxy-*N*-

Scheme 6. Possible Reaction Pathways



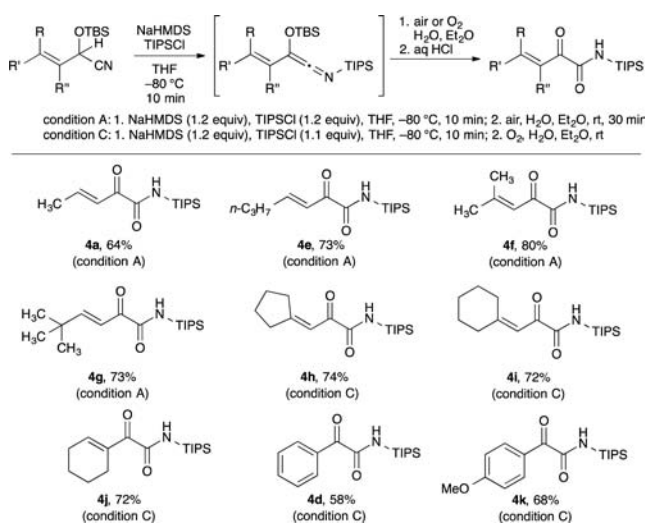
silylketenimine **2** would afford a biradical intermediate **9** that leads to a 3-imino-1,2-dioxetane derivative **10**²³ or an 3-imino-1,2-dioxane derivative **11** via triplet–singlet intersystem crossing and then collapse to α -ketoamide **3** and silyl ester **8** as well as **3** and allyl alcohol derivative **12** via reductive cleavage of the peroxide bond by the participation of an easily oxidizable species such as hexamethyldisilazane in the system, respectively.²⁴ The formation of a silyl ester **8** is compatible with the former pathway but not with the latter. The fact that a *Z*-to-*E* isomerization of the double bond was not observed in the reaction of (*Z*)-**1b** indicates that the possibility of a pathway via 3-imino-1,2-dioxane **11** is unlikely (Scheme 7).

To delineate the structural requirements for the reaction, reactions of alkyl-substituted and phenyl-substituted derivatives **1c** and **1d** were conducted under the same conditions as those used for **1a** (Table 1). While the starting material was recovered in the case of **1c**, the reaction of **1d** proceeded to give **4d** in 6% yield along with recovery of the starting material

Scheme 7. Transformation of *O*-Silylcyanohydrin (Z)-1b to α -Ketoamide (Z)-4bTable 1. Synthesis of α -Ketoamide from *O*-Silyl Cyanohydrin

entry	1	R	A/B	yield (%)	sm (%)
1	1a	(<i>E</i>)-CH ₃ CH=CH ₂ -	A	64	5
2	1c	PhCH ₂ CH ₂ -	A	0	97
3	1d	Ph-	A	6	87
4	1a	(<i>E</i>)-CH ₃ CH=CH ₂ -	B	45	
5	1c	PhCH ₂ CH ₂ -	B	0	66
6	1d	Ph-	B	45	19

Scheme 8. Substrate Scope



(87%) (entries 2 and 3). In the latter case, the yield was improved to 45% by carrying out the reaction in an oxygen atmosphere (entry 6). The formation of oxidation products in phenyl derivatives is also incompatible with the intermediacy of 1,2-dioxane 11.

Although further experimental and theoretical study is required to propose a detailed mechanism, the above-mentioned results suggest a process that involves 1,2-dioxetane intermediates and a triplet-singlet thermal intersystem crossing.

Aside from the mechanistic aspect of their formation, the oxidation reaction has the following unique and interesting features from a synthetic point of view: (1) the starting *O*-silyl cyanohydrins are readily available, (2) the reaction proceeds under very mild conditions that do not require an elevated temperature and transition metals such as copper, and (3) the parent *N*-unsubstituted derivatives can be readily prepared unlike most of the known methods. Therefore, we proceeded to evaluate the scope of the reaction using *O*-silyl cyanohydrins derived from α,β -unsaturated aldehydes. After conversion of *O*-

silyl cyanohydrins to an *N*-silylketenimine 2 by reaction with NaHMDS and TIPSCl at $-80\text{ }^{\circ}\text{C}$ for 10 min, Et₂O and water were added, and then the reaction mixture was kept open to air (condition A) or under an oxygen atmosphere (condition C) (Scheme 8). The oxidation reactions that proceeded sluggishly under an air atmosphere were improved by carrying out the reaction under oxygen atmosphere.

In conclusion, we have demonstrated that α,β -unsaturated siloxy-*N*-silylketenimines, readily derived from the corresponding aldehydes, can be transformed to α -ketoamides by brief exposure to air or oxygen. Not only does the process offer a very convenient and efficient procedure for the synthesis of α -ketoamides, particularly *N*-unsubstituted ones, due to its operational simplicity, mild reaction conditions, and the ready availability of the starting aldehydes but also it provides a further example of organic substrates that can react spontaneously with ³O₂ without photochemical activation and afford products typical of ¹O₂ involvement.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00455.

Experimental and analytical data (PDF)

Crystallographic data for 5 (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: misasaki@hiroshima-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was partially supported by a Grant-in-Aid for Scientific Research (C) 25460015 (M.S.), a Grant-in-Aid for Challenging Exploratory Research 15K14929 (K.T.) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Hoan Sha Foundation (M.S.), the Takeda Science Foundation (M.S.), and the Naito Foundation Natural Science Scholarship (M.S.). We thank the staff of the Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University, for the use of their facilities.

■ REFERENCES

- (1) (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (b) Fusetani, N.; Matsunaga, S.; Matsumoto, H.; Takebayashi, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7053. (c) Stein, M. L.; Cui, H.; Beck, P.; Dubiella, C.; Voss, C.; Krüger, A.; Schmidt, B.; Groll, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1679.
- (2) (a) Heaney, F.; Fenlon, J.; McArdle, P.; Cunningham, D. *Org. Biomol. Chem.* **2003**, *1*, 1122. (b) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063. (c) Bou-Hamdan, F. R.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2403. (d) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Am. Chem. Soc.* **2009**, *131*, 10390. (e) Igarashi, T.; Tayama, E.; Iwamoto, H.; Hasegawa, E. *Tetrahedron Lett.* **2013**, *54*, 6874.
- (3) (a) Ozawa, F.; Soyama, H.; Yanagihara, H. *J. Am. Chem. Soc.* **1985**, *107*, 3235. (b) des Abbayes, H.; Salaiün, J.-Y. *Dalton Trans.* **2003**, 1041. (c) Tsukada, N.; Ohba, Y.; Inoue, Y. *J. Organomet. Chem.* **2003**, *687*, 436. (d) Iizuka, M.; Kondo, Y. *Chem. Commun.* **2006**, 1739.

- (e) Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734. (f) Liu, J.; Zhang, R.; Wang, S.; Sun, W.; Xia, C. *Org. Lett.* **2009**, *11*, 1321. (g) Genelot, M.; Villandier, N.; Bendjeriou, A.; Jaithong, P.; Djakovitch, L.; Dufaud, V. *Catal. Sci. Technol.* **2012**, *2*, 1886.
- (4) (a) Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, 985. (b) Nakamura, M.; Inoue, J.; Yamada, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2807. (c) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769.
- (5) Zhu, J.; Wong, H.; Zhang, Z.; Yin, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *Tetrahedron Lett.* **2005**, *46*, 3587.
- (6) El Kaïm, L.; Gamez-Montañón, R.; Grimaud, L.; Ibarra-Rivera, T. *Chem. Commun.* **2008**, 1350.
- (7) (a) Schank, K.; Beck, H.; Himbert, G. *Synthesis* **1998**, 1998, 1718. (b) Al-Rashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 8780. (c) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661. (d) Li, H.; Antoline, J. E.; Yang, J.-H.; Al-Rashid, Z. F.; Hsung, R. P. *New J. Chem.* **2010**, *34*, 1309. (e) Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. *Org. Lett.* **2011**, *13*, 1556. (f) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, 47, 379. (g) Huang, H.; He, G.; Zhu, X.; Jin, X.; Qiu, S.; Zhu, H. *Eur. J. Org. Chem.* **2014**, 2014, 7174.
- (8) (a) Grassot, J.-M.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 947. (b) Bouma, M.; Masson, G.; Zhu, J. *J. Org. Chem.* **2010**, *75*, 2748.
- (9) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11088.
- (10) (a) Du, F.-T.; Ji, J.-X. *Chem. Sci.* **2012**, *3*, 460. (b) Lamani, M.; Prabhu, K. R. *Chem. - Eur. J.* **2012**, *18*, 14638. (c) Mai, W.-P.; Wang, H.-H.; Li, Z.-C.; Yuan, J.-W.; Xiao, Y.-M.; Yang, L.-R.; Mao, P.; Qu, L.-B. *Chem. Commun.* **2012**, 48, 10117. (d) Zhang, Z.; Su, J.; Zha, Z.; Wang, Z. *Chem. Commun.* **2013**, 49, 8982. (e) Zhang, X.; Wang, L. *Green Chem.* **2012**, *14*, 2141.
- (11) (a) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (b) Deshidi, R.; Kumar, M.; Devari, S.; Shah, B. A. *Chem. Commun.* **2014**, 50, 9533. (c) Sagadevan, A.; Ragupathi, A.; Lin, C.-C.; Hwu, J. R.; Hwang, K. C. *Green Chem.* **2015**, *17*, 1113.
- (12) (a) Zhang, C.; Zong, X.; Zhang, L.; Jiao, N. *Org. Lett.* **2012**, *14*, 3280. (b) Shaw, A. Y.; Denning, C. R.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 4151. (c) Mupparapu, N.; Khan, S.; Battula, S.; Kushwaha, M.; Gupta, A. P.; Ahmed, Q. N.; Vishwakarma, R. A. *Org. Lett.* **2014**, *16*, 1152.
- (13) Shanmugapriya, D.; Shankar, R.; Satyanarayana, G.; Dahanukar, V. H.; Kumar, U. K. S.; Vembu, N. *Synlett* **2008**, 2008, 2945.
- (14) For reviews of *N*-silylketenimines, see: (a) Denmark, S. E.; Wilson, T. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9980. (b) Lu, P.; Wang, Y. *Chem. Soc. Rev.* **2012**, *41*, 5687.
- (15) (a) Watt, D. S. *Synth. Commun.* **1974**, *4*, 127. (b) Watt, D. S. *J. Org. Chem.* **1974**, *39*, 2799. (c) Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1992**, *57*, 1202.
- (16) (a) Kotomori, Y.; Sasaki, M.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2015**, *80*, 11013. (b) Sasaki, M.; Takegawa, T.; Sakamoto, K.; Kotomori, Y.; Otani, Y.; Ohwada, T.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 12956. (c) Sasaki, M.; Fujiwara, M.; Kotomori, Y.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Tetrahedron* **2013**, *69*, 5823. (d) Sasaki, M.; Takegawa, T.; Ikemoto, H.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Chem. Commun.* **2012**, 48, 2897. (e) Sasaki, M.; Shirakawa, Y.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Chem. - Eur. J.* **2009**, *15*, 3363. (f) Sasaki, M.; Kawanishi, E.; Shirakawa, Y.; Kawahata, M.; Masu, H.; Yamaguchi, K.; Takeda, K. *Eur. J. Org. Chem.* **2008**, 2008, 3061.
- (17) Denmark, S. E.; Wilson, T. W. *Nat. Chem.* **2010**, *2*, 937.
- (18) Attempted further purification by distillation resulted in decomposition.
- (19) Osprian, I.; Fechter, M. H.; Griengl, H. *J. Mol. Catal. B: Enzym.* **2003**, *24–25*, 89.
- (20) A typical literature procedure^{15c,17} for preparation of oxy-substituted *N*-silylketenimines involves treatment of nitrile anions with silyl chlorides in THF at -78°C for 2 h followed by warming to ambient temperature and then concentration without aqueous workup before distillation.
- (21) Sawyer, D. T. *Oxygen Chemistry*; Oxford University Press: New York, 1991.
- (22) (a) Drujon, D.; Rahmani, R.; Héran, V.; Blanc, R.; Carissan, T.; Tuccio, B.; Commeiras, L.; Parrain, J.-L. *Phys. Chem. Chem. Phys.* **2014**, *16*, 7513. (b) Kholdeeva, O. A.; Ivanchikova, I. D.; Zalomaeva, O. V.; Sorokin, A. B.; Skobelev, I. Y.; Talsi, E. P. *J. Phys. Chem. B* **2011**, *115*, 11971. (c) Najjar, F.; André-Barrés, C.; Lauricella, R.; Gorrichon, L.; Tuccio, B. *Tetrahedron Lett.* **2005**, *46*, 2117. (d) Clark, K. B.; Howard, J. A.; Oyler, A. R. *J. Am. Chem. Soc.* **1997**, *119*, 9560. (e) Chou, C.-H.; Trahanovsky, W. S. *J. Org. Chem.* **1995**, *60*, 5449. (f) Huang, C.-S.; Peng, C.-C.; Chou, C.-H. *Tetrahedron Lett.* **1994**, *35*, 4175. (g) Seip, M.; Brauer, H.-D. *J. Am. Chem. Soc.* **1992**, *114*, 4486. (h) Turro, N. J. *Tetrahedron* **1985**, *41*, 2089. (i) Turro, N. J.; Chow, M.-F.; Rigaudy, J. *J. Am. Chem. Soc.* **1981**, *103*, 7218. (j) Turro, N. J.; Chow, M.-F.; Ito, Y. *J. Am. Chem. Soc.* **1978**, *100*, 5580. (k) Turro, N. J.; Ramamurthy, V.; Liu, K.-C.; Krebs, A.; Kemper, R. *J. Am. Chem. Soc.* **1976**, *98*, 6758. (l) Barton, D. H. R.; Haynes, R. K.; Leclerc, G.; Magnus, P. D.; Menzies, I. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2055. (m) Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, *14*, 3181. (n) Criegee, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 519.
- (23) For related 3-imino-1,2-dioxetane derivatives, see: (a) Adam, W.; De Lucchi, O.; Quast, H.; Reckterwald, R.; Yany, F. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 788. (b) Ito, Y.; Yokoya, H.; Kyono, K.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1980**, 898.
- (24) (a) Adam, W.; Heil, M. *J. Am. Chem. Soc.* **1992**, *114*, 5591. (b) Adam, W.; Blancafort, L. *J. Org. Chem.* **1997**, *62*, 1623. (c) Kelly, D. R.; Bansal, H.; Morgan, J. J. *Tetrahedron Lett.* **2002**, *43*, 9331.