Tetrahedron Letters 53 (2012) 5094–5098

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Metal-free oxidative amide formation with *N*-hydroxysuccinimide and hypervalent iodine reagents

Haoyi Yao, Yun Tang, Kana Yamamoto *

Department of Chemistry and School of Green Chemistry and Engineering, University of Toledo, 2801 W. Bancroft St., Toledo, OH 43606, United States

ARTICLE INFO

Article history:
Received 15 June 2012
Revised 3 July 2012
Accepted 6 July 2012
Available online 21 July 2012

Keywords:
Hypervalent iodine
Amide
Oxidation
N-Hydroxysuccinimide
Electron spin resonance

ABSTRACT

An oxidative amide formation using *N*-hydroxysuccinimide and hypervalent iodine reagents was developed. The method enables a wide range of aldehydes and amines to be coupled under mild reaction conditions providing amide in good to excellent yield. The radical species in the reaction mixture was observed for the first time using ESR measurement, and along with other mechanistic investigations, a plausible mechanism of the reaction was proposed.

Published by Elsevier Ltd.

Tandem reactions have drawn significant attention in recent years as an attractive green alternative to traditional multi-step processes. They avoid the isolation of intermediates and curtail the number of overall synthetic steps.[1] Among tandem reaction, oxidative esterification or amide formation of alcohols or aldehydes has become popular as a promising synthetic tool serving as an alternative to conventional approaches requiring carboxylic acid isolation. Research during the past decade resulted in significant progress in this field establishing a number of successful oxidative esterifications. On the other hand, despite numerous reported elegant strategies,[2] oxidative amide formations are less established: Most reported methods have limited substrate scope, and some use excess of coupling partners or precious metal catalysts. Current state of art methods in oxidative amide formation have been reviewed.[3] Recently, we reported the first aerobic oxidative amide formation method using a catalytic amount of $Co(OAc)_2$ in combination with *N*-hydroxysuccinimide (NHSI) (Fig. 1).[4,5] This approach involves the NHSI-mediated oxidative formation of NHSI ester **3**, which is sufficiently reactive to undergo amine displacement providing amide **5**. The reaction can be applied to both aliphatic and aromatic aldehydes, and the mild reaction conditions enable chiral amines to be introduced without racemization. However, sterically or electronically deactivated substrates were shown to suffer from competitive formation of a by-product, carboxylic acid **4**. In addition, unsaturated aldehydes were not applicable.

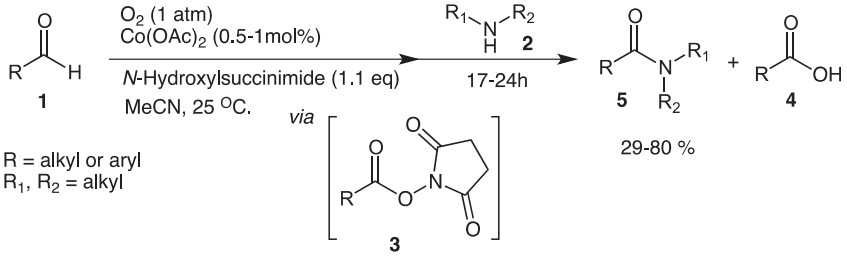


Figure 1. Aerobic oxidative amide formation.

* Corresponding author. Tel.: +1 419 530 1507; fax: +1 419 530 4033.
E-mail address: kana.yamamoto@utoledo.edu (K. Yamamoto).

0040-4039/$ - see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2012.07.024

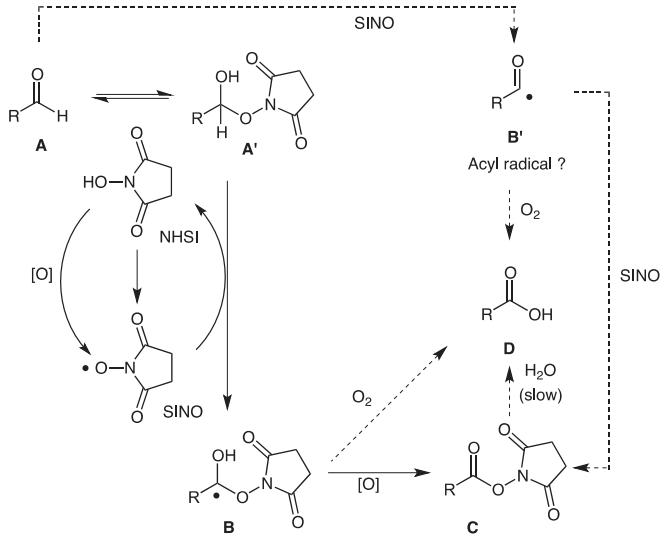


Figure 2. Aerobic oxidative amide formation.

Herein, we report the successful use of an alternative terminal oxidant, hypervalent iodine reagents ($PhI(OAc)_2$ or IBX) to effectively suppress this unwanted side reaction. These oxidants efficiently lead to amide formation via a two-step tandem reaction, delivering significantly higher yields than previously reported. Our new method also possesses broader scope demonstrated by the coupling with an α,β-unsaturated aldehyde, pivaldehyde, and aniline. In addition, a plausible mechanism is proposed based on detailed mechanistic investigation.

At the onset of our investigation, pathways to form carboxylic acid byproducts under the original aerobic conditions[4] were considered. We speculated that the reaction of NHSI with aldehydes **A** proceeds through an intermediate radical, analogous to the known nitroxide-mediated oxidations (Fig. 2).[6] This led us to two possible reaction pathways that could generate carboxylic acids involving either the reaction of radical intermediate **B** with molecular oxygen, or by hydrolysis of NHSI ester **C**. Investigation into the stability of ester **C** revealed these derivatives to be highly stable to hydrolytic conditions (see the Supplementary data), which led us to assume that the radical mediated oxidative pathway is more likely.

Thus, we embarked on screening for alternative oxidants that suppress this undesirable side reaction (Scheme 1). Aldehyde **1a** was used as a test substrate, and was treated with 1 equiv of NHSI and various oxidants. The reaction mixture was analyzed by determining the ratio of the amount of produced ester **3a** and acid **4a** by ^1H NMR analyses. While the majority of the oxidants showed an increased level of acid formation when compared to molecular oxygen, two hypervalent iodine reagents, $PhI(OAc)_2$ and IBX, exclusively provided the desired NHSI ester **3a**.[7] Using other hypervalent

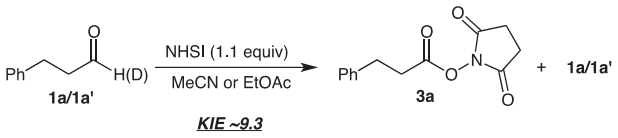


Figure 3. Kinetic isotope effect measured with Singleton method.

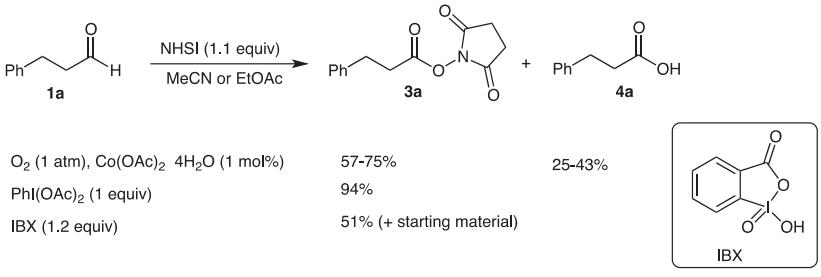
iodine reagents or the conditions catalytic in $PhI(OAc)_2$[8] were less effective (see the Supplementary data).

To gain further insights into this reaction, a series of mechanistic studies were performed using stoichiometric $PhI(OAc)_2$ (Fig. 3). Again utilizing **1a** as a representative aldehyde, the kinetic isotope effect (KIE) of the substitution of the aldehyde hydrogen with deuterium was examined using the method of Singelton.[9] A mixture of aldehyde **1a** and the deuterated aldehyde **1a′** was subjected to the reaction conditions, however the reaction was quenched before its full conversion, and the recovered starting material was analyzed for the ratio of parent and deuterated substrates. A large kinetic isotope effect (~9.3) was measured for this reaction, indicating that the abstraction of the aldehyde hydrogen is rate limiting in the formation of the NHSI ester. The recorded KIE higher than the theoretical maximum may be due to a quantum tunneling, which has been observed in related oxidative reactions that use nitroxide catalysts.[10]

To verify the presence of a radical intermediate, a series of electron spin resonance (ESR) experiments were performed under various conditions. When $PhI(OAc)_2$ and NHSI were mixed in a 2:1 ratio, a clean ESR signal corresponding to the reported succinimide *N*-oxy (SINO) radical **A**[11] was observed (Fig. 4(a)). The signal for this radical diminished within ~10 min in the absence of reactant, confirming its non-persistent nature.[6a,12] In a separate ^1H NMR experiment, the same mixture showed immediate consumption of $PhI(OAc)_2$ and the formation of PhI and AcOH upon mixing of the two reagents. Successive addition of benzaldehyde or aldehyde **1a** to this mixture diminished the original ESR signal, and new signals began to emerge as shown in (b) and (c), respectively. We attributed these spectra to hemiaminal radicals **B** and **C**. Both radicals are elusive and diminish within a few minutes. Acyl radical formation from free aldehyde was another possibility,[13,14] however it was not observed under our experimental conditions.

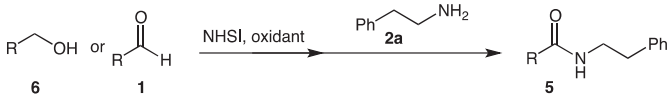
On the basis of the foregoing studies, a plausible mechanism of the oxidative NHSI ester formation is proposed (Fig. 2). Mixing of $PhI(OAc)_2$ and NHSI results in the rapid formation of SINO.[15] Addition of aldehyde **A** led to the presumably reversible formation of hemiaminal **A′**. A slow (rate-determining) hydrogen abstraction of the aminal hydrogen by SINO provides the observed hemiaminal radical **B**, which rapidly undergoes the second oxidation with $PhI(OAc)_2$, either by direct oxidation or mediated by NHSI, to provide ester **C**.[16]

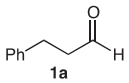
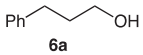
With improved reaction conditions to deliver the ester **C** now identified, we examined its compatibility to coupling with primary amines. Subjecting phenethylamine **2a** to 1 equiv each of aldehyde



Scheme 1. The screening results of alternative oxidants.

Table 1
Tandem amide formation using hypervalent iodine reagents



Entry	Aldehyde	Conditions	Yield[a] (%)
1	 **1a**	NHSI (1.1 equiv), $PhI(OAc)_2$ (1 equiv), MeCN, rt, 3–5 min; **2a** (1 equiv)	90
2		NHSI (1.2 equiv), IBX (1 equiv), EtOAc, 90 °C, 2.5 h; **2a** (2 equiv)	42
3	 **6a**	NHSI (2.5 equiv), IBX (2.2 equiv), EtOAc, 90 °C, 4.5 h; **2a** (3 equiv)	57
4	 **6b**	NHSI (2.5 equiv), IBX (2.2 equiv), EtOAc, 90 °C, 3.5 h; **2a** (4 equiv), 23.5 h	70

[a] Isolated yield.

1a, NHSI, and $PhI(OAc)_2$ resulted in a rapid reaction that delivered a multitude of unidentified products. To circumvent what we believe to be competitive amine oxidation, consumption of the oxidant needs to be completed before introduction of the amine coupling partner. As such we observed that addition of amine **2a** to the reaction mixture after formation of the active ester led to smooth displacement of NHSI with the amine to deliver the desired amide **5a** in excellent yield (Table 1, entry 1). Due to the extremely fast formation of the active ester, amine addition can be made immediately after addition of the other reagents making it a practical alternative to available oxidative amide formations. In most cases, an amine was added after stirring for 2–3 min.

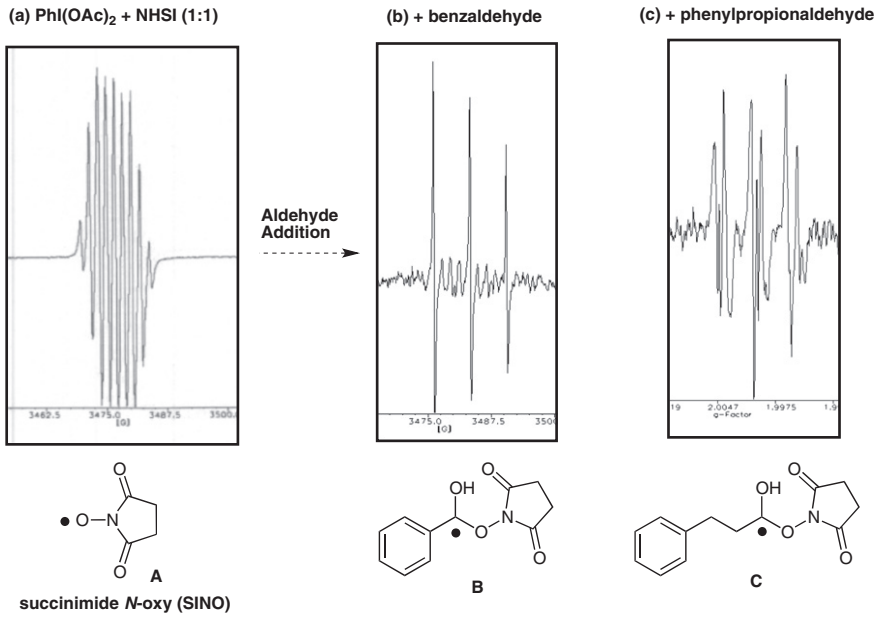
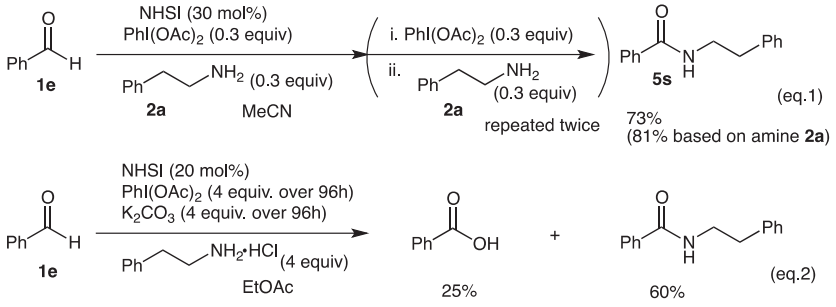
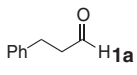
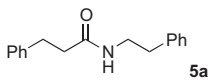
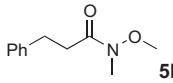
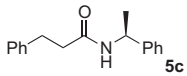
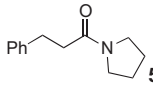
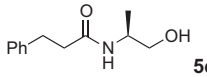
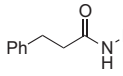
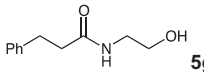
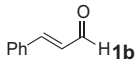
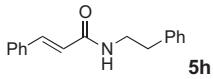
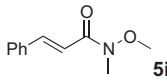
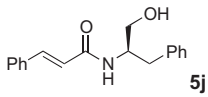
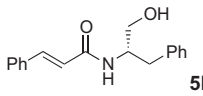
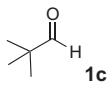
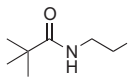
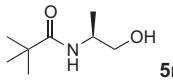
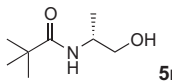
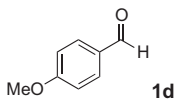
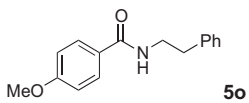
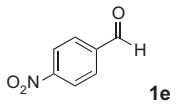
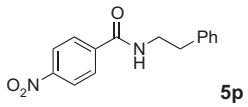
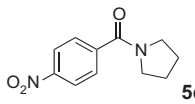


Figure 4. ESR measurements of the reaction mixture.



Scheme 2. Oxidative amide formation with a catalytic amount of NHSI using $PhI(OAc)_2$ oxidant.

Table 2
Scope of aldehydes and amines

Entry	Aldehyde	Product	Yield[b] (%)
1	 **1a**	 **5a**	90
2		 **5b**	70
3		 **5c**	84[a]
4		 **5d**	60
5		 **5e**	55[a]
6		 **5f**	69
7		 **5g**	74
8	 **1b**	 **5h**	84
9		 **5i**	56
10		 **5j**	67[a]
11		 **5k**	57[a]
12	 **1c**	 **5l**	62
13		 **5m**	66[a]
14		 **5n**	54[a]
15	 **1d**	 **5o**	58
16	 **1e**	 **5p**	61
17		 **5q**	72

[a] >99% ee (see the Supplementary data).
[b] Isolated yield.

An analogous amide formation procedure using IBX was also examined. The formation of the active ester using this reagent was not as rapid as using $PhI(OAc)_2$, and a higher temperature and/or a longer reaction time were required (entry 2). One advantage of the use of IBX is its capability to oxidize primary alcohol to aldehyde, which extends the substrate scope (entries 3–4).[17]

NHSI can be recycled multiple times after release by the amine displacement (Scheme 2). Thus, when using 0.3 equiv of NHSI, addition of 0.3 equiv each of the oxidant followed by the amine, in three separate operations furnished the desired amide in 81% yield (Eq. 1). Alternatively, to limit the oxidation of the amine, amine hydrochloride salt can be used. In the presence of a suitable base, the amine may be gradually neutralized such that it undergoes displacement at a rate that competes with its oxidation. This approach provided the desired compound with a maximum yield of 60% using 20 mol% of NHSI (Eq. 2).

We examined the scope and limitation of this approach using stoichiometric $PhI(OAc)_2$. Table 2 shows the amide formation with various amines and aldehydes. Initially, 3-phenylpropionaldehyde **1a** was examined with various amines (entries 1–7). Good to excellent yields were obtained with primary amines (entries 1, 3, 5, and 7). As expected, primary alcohols were compatible under the reaction conditions (entries 5, 7, 10, 13, and 14). Secondary amines also delivered good yields including synthetically important Weinreb amine (entry 2). Less reactive aniline also provided good yield of the amide (entry 6).

In the reaction of unsaturated aldehyde **1b**, the corresponding unsaturated amides were obtained without affecting the double bond (entries 8–11). Sterically hindered pivaldehyde **1c** also reacted smoothly under the reaction conditions (entries 12–14). The yields with these substrates are generally lower than that of **1a**, although still giving respectable yields for these challenging substrates. We have also examined aryl aldehydes with electron donating or electron-withdrawing groups (entries 15–17), and were pleased to find that these substrates participated in the amide formation under identical conditions. Finally, all the optically pure amines examined retained their optical purity (entries 3, 5, 10, 11, 13, and 14).

In conclusion, an oxidative and metal-free amide formation was developed. Hypervalent iodine reagents, $PhI(OAc)_2$ and IBX both served as stoichiometric oxidants and provided the intermediate, active ester in good to excellent yields. A plausible mechanism of the active ester formation was proposed based on a series of mechanistic investigations. The reaction was extended to tandem amide formation reaction by successive addition of reagents in one-pot, which demonstrated the recyclability of NHSI. Because of the mild nature of the oxidant,[8,18] this oxidative amide formation is widely applicable for the synthesis of structurally diverse amines and aldehydes, including aniline, pivaldehyde, and α,β-unsaturated aldehyde. The current method showed clear advantages to our previous methods, demonstrating simplicity, readily available reagents, and broad scope of applicable substrates.

Acknowledgments

This work was supported by funding from the University of Toledo (K.Y., New Faculty Start Up Fund; University of Toledo Summer Research Award, 2010). We thank Dr. Yong-Wah Kim for assistance with ESR analyses. We also thank Dr. Chao Hang of Bristol-Myers Squibb for helpful discussions on isotope effect experiments.

Supplementary data

Supplementary data (The spectral data for compounds **5f**–**5k**, **5m**, **5n**, and **5g**; Stability testing of ester **3a**; Full data for oxidant screening; ESR spectral data; NMR data for kinetic isotope effect measurements.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.024.

References and notes

1. (a) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492–8509; (b) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237–294.
2. Representative and/or recent methods. Cu-mediated: (a) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065; NHC-mediated: (b) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797; (c) Bode, J. W.; Sohn, S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799; Lanthanide mediated: (d) Seo, S.; Marks, T. J. *Org. Lett.* **2008**, *10*, 317–319; KI-TBHP: (e) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**, 3619–3622; Metal-catalysed: (f) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, *2001*, 523–528; Pd: (g) Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008**, *9*, 5732–5735; Metal-free: (h) Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429–3432; Mechanical milling: (i) Gao, J.; Wang, G. W. *J. Org. Chem.* **2008**, *73*, 2955–2958; Ru-mediated: (j) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790–792; (k) Schley, N. D.; Dobereimer, G. E.; Crabtree, R. H. *Organometallics* **2011**, *30*, 4174–4179; (l) Chen, C.; Zhang, Y.; Hong, S. H. *J. Org. Chem.* **2011**, *76*, 10005–10010; Ag-mediated: (m) Shimizu, K.; Ohshima, K.; Satsuma, A. *Chem. Eur. J.* **2009**, *15*, 9977–9980; Au-mediated: (n) Soule, J. F.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18550–18553; (o) Kegnaes, S.; Mielby, J.; Mentzel, U. V.; Jensen, T.; Fristrup, P.; Rilsager, A. *Chem. Commun.* **2012**, *48*, 2427–2429; Fe-mediated: (p) Ghosh, S. C.; Ngiam, J. S. Y.; Chai, C. L. L.; Seayad, A. M.; Dang, T. T.; Chen, A. *Adv. Synth. Catal.* **2012**, *354*, 1407–1412; Flow chemistry: (q) Liu, X.; Jensen, K. F. D. *Green Chem.* **2012**, *14*, 1471–1474; (r) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673.
3. (a) Ekoue-Kovi, K.; Wolf, C. *Chem. Eur. J.* **2008**, *14*, 6302–6315; (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471–479; (c) Christian, A.; Montalbetti, G. N.; Virginie, F. *Tetrahedron* **2005**, *61*, 10827–10852; (d) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631; (e) Allen, C. L.; Williams, J. M. *Chem. Soc. Rev.* **2011**, *40*, 3405–3415.
4. Yao, H.; Yamamoto, K. *Chem. Asian J.* **2012**, *7*, 1542–1545.
5. Non-catalyzed oxidative formation of amides using Phl(OAc)2 has been reported in the literature: Fang, C.; Qian, W.; Bao, W. *Synlett* **2008**, 2529–2531.The reported process was only applied to aryl aldehydes and require longer reaction time (20–36 h), suggesting that distinctly different mechanism from the method report herein.
6. (a) Ishii, Y.; Sakaguchi, S. *Catal. Today* **2006**, *117*, 105–113; (b) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393–427.
7. (a) Schulze, A.; Giannis, A. *Adv. Synth. Catal.* **2004**, *346*, 252–256; (b) Liu, R.; Xu, Q.; Liang, X. *Chem. Lett.* **2006**, *35*, 566–567.
8. (a) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085; (b) Thottumkara, A. P.; Bowsjer, M. S.; Vinod, T. K. *Org. Lett.* **2005**, *7*, 2933–2936; (c) Schulze, A.; Giannis, A. *Synthesis* **2006**, 257–260.
9. Singleton, D.; Thomas, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 9357–9358.
10. (a) Lee, J.; Park, E.; Cho, S.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825; (b) Koshino, N.; Saha, B.; Espenson, J. H. *J. Org. Chem.* **2003**, *68*, 9364–9370.
11. Stermitz, F. R.; Neiswander, D. W. *J. Am. Chem. Soc.* **1973**, *95*, 2630–2634.
12. (a) Sheldon, R.; Arends, I. *J. Mol. Catal. A: Chem.* **2006**, *251*, 200–214; (b) Minisci, F.; Punta, C.; Recupero, F. *J. Mol. Catal. A: Chem.* **2006**, *251*, 129–149.
13. The involvement of an acyl radical intermediate was proposed (however not observed) in an *N*-hydroxyphthalimide mediated reaction under non-aerobic conditions.[14]
14. Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2001**, 2352–2353.
15. A possible intermediate wherein NHSI displacing one of the acetates of $PhI(OAc)_2$ has been suggested.[7a] While we did not observe this type of complex in ^1H NMR spectra, its involvement is possible as a precursor to radical A.
16. Although acyl radical formation was not observed in the ESR study, it may still be involved in the reaction pathway to C as shown in Figure 2. We thank the reviewer for raising this point.
17. A reported oxidation reaction of aliphatic alcohol with $PhI(OAc)_2$[7b] was inconsistent in our hands.
18. (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358; (b) Yusubov, M. S.; Zhdankin, V. V. *Curr. Org. Synth.* **2012**, *9*, 247–272.