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Stereoselective Intermolecular Nitroaminoxylation of Terminal Aromatic Alkynes: Trapping Alkenyl Radicals by TEMPO

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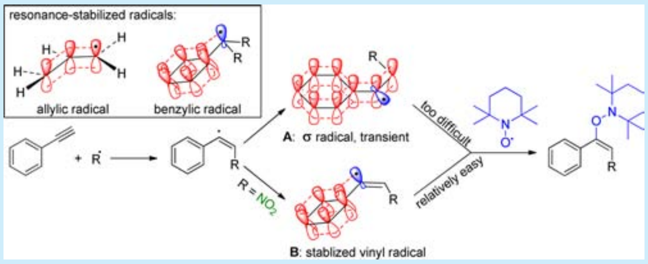
Supporting Information

ABSTRACT: The vinyl radical is one of the most unstable organic radicals. It is demonstrated that a nitro radical attacks phenylacetylene and makes the phenyl ring deconjugated with a double bond so that the resulting vinyl radical may be stabilized by delocalization to the phenyl ring's π orbital and easily trapped by TEMPO. It is noteworthy that all desired products were obtained in moderate to good yields in an (*E*)-configuration.



Radical chemistry has recently played a vital role in organic chemistry as an approach widely used in C−H functionalization,[1,2] cascade cyclization,[1b,e,3] and photochemical reactions.[4] TEMPO is usually used as a radical scavenging to trap radicals or inhibit reactions. This proves that the mechanisms of these reactions proceed through a radical pathway.[5] Olefins are a series of good radical acceptors. When they are attacked by radicals, alkyl radicals are formed which can be trapped by TEMPO and produce useful aminoxylative products. Significant work on intermolecular aminoxylative of olefins has also been reported (Figure 1, eqs 1 and 2).[6−10]Further, the benzylic and allylic radical are relatively stable in comparison to alkyl radicals because of *p*-π-conjugation. In contrast, a vinyl radical (eq 3, **A**) belongs to σ radicals that cannot disperse the electron density; therefore, it is highly unstable and has high reactivity and a short lifetime. Additionally, the vinyl radical can undergo hydrogen abstraction reactions. Therefore, trapping vinyl radicals remains challenging.[3a,11] We envisage that an appropriate radical attack on phenylacetylene will result in the phenyl ring deconjugated with a double bond and the resulting vinyl radical is stabilized by delocalization to the phenyl ring's π orbital.[12] It may extend the radical's lifetime and increase the possibility for trapping.

On the basis of our assumption, we began our study by reacting phenylacetylene with a lot of known radicals. After several unsuccessful attempts, we finally found that when a nitro radical source[13] was used, the vinyl radical is successfully trapped by TEMPO (eq 3, **B**). To the best of our knowledge, it is the first time vinyl radicals have been trapped by TEMPO. The X-ray structure of **3aa** is shown in Figure 2. The phenyl ring no longer conjugates with the double bond. The nitro group and the double bond are in the same plane which is approximately perpendicular to the phenyl ring. The length of N1−C8 is 1.43 Å, which is between the C−N single bond (1.47 Å) and C−N double bond (1.28 Å). That means the nitro group is possibly conjugated with a C−C double bond. It suggests that the π-system of the phenyl ring is orthogonal to the π-system of the double bond. Also, the angle of the phenyl ring and double bond is approximately equal to the angle C6−C7−C8 which is 129°. The value is larger than expected for the sp^2 hybridization. It is indicated that the vinyl radical is between a bent type (120°) and a linear π-type (180°) resonance stabilized structure.[12a]

These results were encouraging, and therefore a variety of nitro sources were screened. Inorganic nitrates gave the aminoxylative product in poor yields (Table 1, entries 1−4). Gratifyingly, *tert*-butyl nitrite is the ideal nitro source, affording **3aa** in 73% yield (Table 1, entry 5). Increasing and decreasing the temperature reduced the yields (Table 1, entries 6 and 7). During our studies, we found that solvents had an adverse effect on the reactions. No product was formed when alcoholic solvents were used due to oxidative side reactions of the solvent[14] (Table 1, entry 8). The yield was slightly lower when 1,4-dioxane, acetonitrile, and cyclohexane were used, while a slight increase was noted when toluene was used (Table 1, entries 9−12). THF proved to be the best solvent giving a yield as high as 80% (Table 1, entry 13). Ultimately, the use of 1.3 equiv of TEMPO gave the best yield (92%, Table 1, entry 14).

A number of alkynes were tested under the optimized test conditions. The results are displayed in Figure 3. Both *para*-substituted methoxy and methyl phenylacetylenes gave the corresponding products **3ba** and **3ca** in excellent yields. *Para*-substituted electron-withdrawing groups, such as fluoride, chloride, and bromide, slightly decreased the reactivities, offering the desired nitroaminoxylative product in 85%, 86%, and 85% yield, respectively. The yields of *para*-substituted alkyl or alkoxyl phenylacetylenes decreased. A decrease in yields is also observed when the length of the alkyl or alkoxyls is

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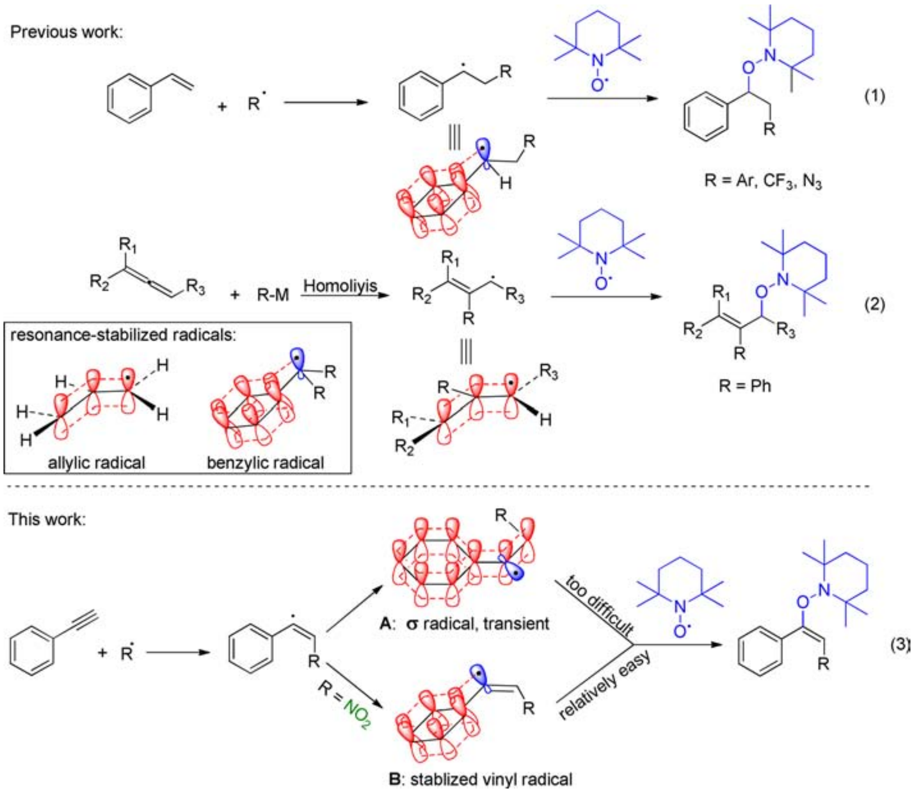


Figure 1. Trapping alkyl radicals and alkenyl radical by TEMPO.

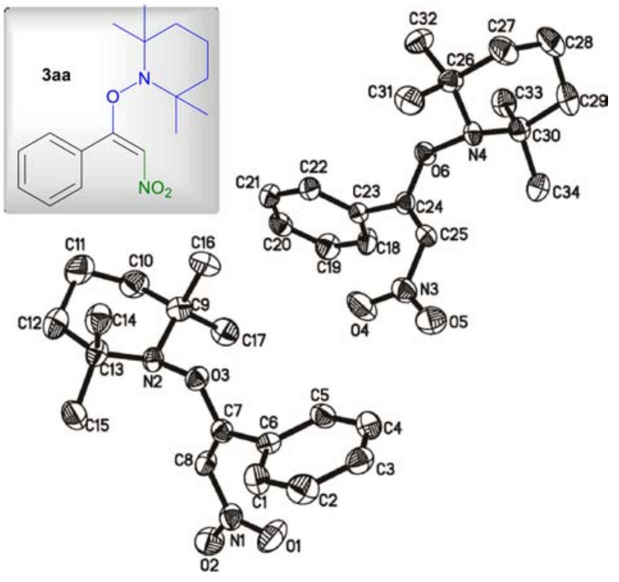
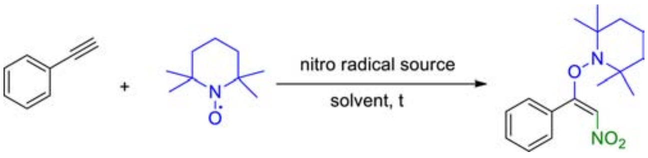


Figure 2. X-ray structure of **3aa**.

increased (**3ga**–**3ia** vs **3ba** and **3ca**). *Ortho-* and *meta-*substituted phenylacetylenes were also studied in our system. 2-Fluoride phenylacetylene showed slightly better reactivity than 4-fluoride phenylacetylene, and the desired product **3ja** was recovered in 88% yield. To our delight, 3-bromide phenylacetylene was a very suitable substrate. The corresponding product **3ka** resulted in as high as a 90% yield. However, 3-methyl phenylacetylene was a poorer substrate as compared to 4-methyl phenylacetylene, producing the 3-methyl product **3la** in 87% yield. To be noted, heterocyclic acetylenes afforded the corresponding nitroaminoxylative product (**3ma**–**3oa**) in moderate to good yields. The reactivity of alkyl alkynes was seen to be poor as compared to the other substrates. Despite this, the desired alkyl products (**3pa**–**3ra**) were generated in poor yields as expected owing to the poor σ-*p*-hyperconjugation of alkyl groups with alkenyl radicals.

Table 1. Optimazation of Nitroaminoxylation of Phenylacetylene[a]



entry	nitro radical source	solvent	t (°C)	yield (%)
1	$AgNO_3$	DCE	70	35
2	$Cu(NO_3)_2{\cdot}3H_2O$	DCE	70	7
3	$(NH_4)_2Ce(NO_3)_6$	DCE	70	45
4	$Co(NO_3)_2{\cdot}6H_2O$	DCE	70	trace
5	*t*-BuONO	DCE	70	73
6	*t*-BuONO	DCE	80	60
7	*t*-BuONO	DCE	60	49
8	*t*-BuONO	ethanol	70	0
9	*t*-BuONO	acetonitrile	70	68
10	*t*-BuONO	cyclohexane	70	69
11	*t*-BuONO	1,4-dioxane	70	71
12	*t*-BuONO	toluene	70	75
13	*t*-BuONO	THF	70	80
14[b]	*t*-BuONO	THF	70	91

[a]Conditions: phenylacetylene (0.3 mmol), nitro radical source (0.6 mmol), TEMPO (0.3 mmol), 24 h. [b]TEMPO (1.3 equiv).

Furthermore, diphenyl acetylene was employed as the substrate. The result showed that it was not a suitable substrate

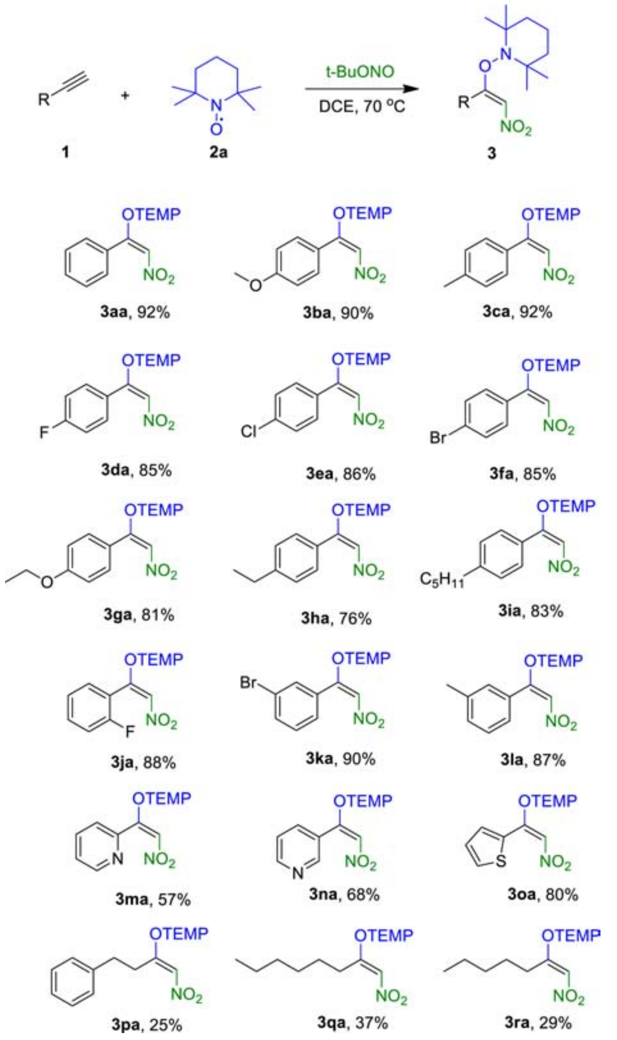
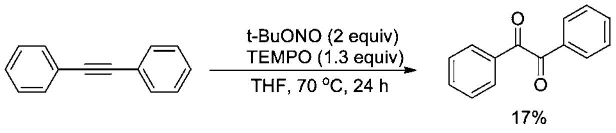


Figure 3. Nitroaminoxylation of various terminal alkynes with TEMPO. Conditions: Terminal alkyne (0.3 mmol), TEMPO (1.3 equiv), *t*-BuONO (2 equiv), THF (2 mL), 24 h. Isolated yield.

under the test conditions due to its large steric hindrance.[11b] Only benzil was isolated in 17% yield as shown in Scheme 1.

Scheme 1. Oxidation of Diphenyl Acetylene in Standard Conditions



We then investigated the kinds of derivatives of TEMPO under the optimized conditions, and the related results are listed in Figure 4. The 4-acetylamino TEMPO represents a moderate trapping ability for radicals and just gave **3ab** in 72% yield. 4-Hydroxyl, 4-alkoxyl, and 4-acetoxyl TEMPO were excellent substrates producing corresponding products (**3ac**–**3af**) in as high as 93% to 99% yields. However, 4-oxy TEMPO was less reactive and the nitroaminoxylative product **3ag** was obtained in 69% yield.

Notably, (*E*)-products were obtained exclusively. No isomerization was obviously observed between stereoisomers from the ^{1}H NMR spectra. The proposed mechanism was demonstrated in Figure S1. Explanation of stereoselectivity depends on the computational study of the mechanism. The relevant work is in progress.

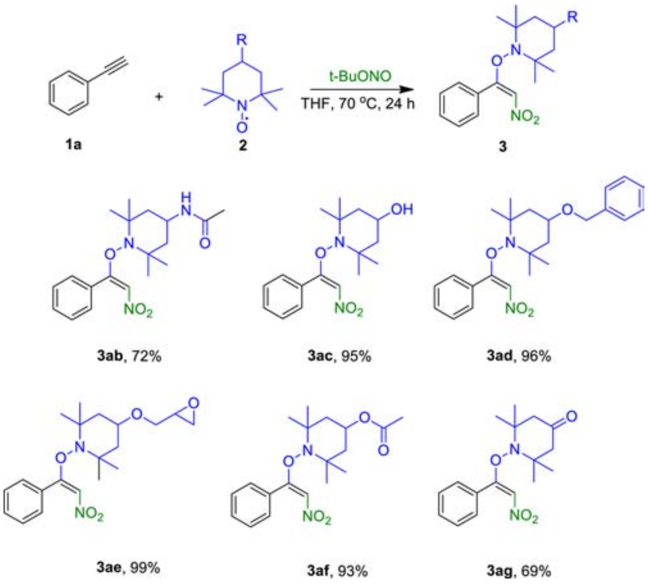
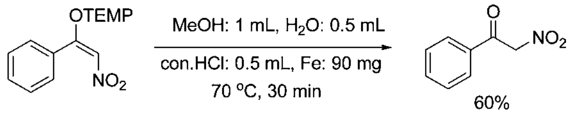


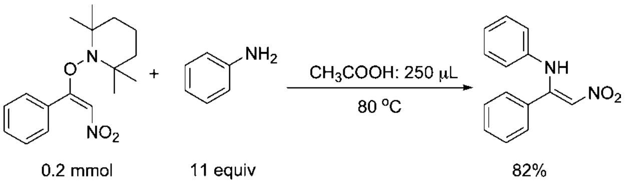
Figure 4. Nitroaminoxylation of phenylacetylene with various TEMPOs. Conditions: Phenylacetylene (0.3 mmol), TEMPO (1.3 equiv), *t*-BuONO (2 equiv), THF (2 mL), 24 h. Isolated yield.

Alkenyl aminoxylative compounds were a series of special compounds in view of the reactive N–O bond and the enol type structure. For instance, mild hydrolysis of a nitroaminoxylative product produced the α-nitroketone in 60% yield as shown in Scheme 2. Additionally, another particularly useful transformation of the alkenyl aminoxylative compound was aminolysis in glacial acetic acid, which afforded the β-nitroenamine in 82% yield as shown in Scheme 3.[15]

Scheme 2. Hydrolysis of 3aa To Prepare α-Nitroketone



Scheme 3. Aminolysis of 3aa To Prepare β-Nitroenamine



In summary, we have demonstrated for the first time that vinyl radicals can be trapped by TEMPO. The nitroaminoxylation reactions were successfully carried out under transition-metal-free conditions, and only *E*-products were obtained in moderate to good yields. The alkenyl nitroaminoxylative product was easily converted to useful building blocks under mild conditions. More studies to expand the utility of these products and computation of the mechanism are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, characterization data for all new compounds, and crystallographic data in CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent references for C−H funtionalization, see: (a) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2256−2259. (b) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972−3976. (c) Liu, W.; Groves, J. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6024−6027. (d) Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 626−629. (e) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638−3641.

(2) For references on C−H funtionalization via a radical process in our group, see: (a) Yang, H.; Sun, P.; Zhu, Y.; Yan, H.; Lu, L.; Qu, X.; Li, T.; Mao, J. *Chem. Commun.* **2012**, *48*, 7847−7849. (b) Yang, H.; Yan, H.; Sun, P.; Zhu, Y.; Lu, L.; Liu, D.; Rong, G.; Mao, J. *Green Chem.* **2013**, *15*, 976−981.

(3) For selected recent references for cyclization, see: (a) Wille, U. *Chem. Rev.* **2013**, *113*, 813−853. (b) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12975−12979. (c) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12655−12658. (d) Zhang, B.; M.-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792−10795.

(4) For selected recent references for photochemical reactions, see: (a) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338−3341. (b) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 539−542. (c) Winston, M. S.; Wolf, W. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 7777−7782. (d) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593−1596. (e) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 6858−6861.

(5) (a) Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756−10759. (b) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950−8958. (c) Han, B.; Yang, X.-L.; Fang, R.; Yu, W.; Wang, C.; Duan, X.-Y.; Liu, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 8816−8820. (d) Duan, X.-Y.; Zhou, N.-N.; Fang, R.; Yang, X.-L.; Yu, W.; Han, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 3158−3162.

(6) Heinrich, M. R.; Wetzel, A.; Kirschstein, M. *Org. Lett.* **2007**, *9*, 3833−3835.

(7) Hartmann, M.; Li, Y.; Studer, A. *J. Am. Chem. Soc.* **2012**, *134*, 16516−16519.

(8) Li, Y.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221−8224.

(9) Zhang, B.; Studer, A. *Org. Lett.* **2013**, *15*, 4548−4551.

(10) Itoh, T.; Shimizu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 2736−2739.

(11) (a) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. *J. Am. Chem. Soc.* **2013**, *135*, 11481−11484. (b) Coyle, R.; McArdle, P.; Aldabbagh, F. *J. Org. Chem.* **2014**, *79*, 5903−5907. (c) Hari, D. P.; Hering, T.; König, B. *Org. Lett.* **2012**, *14*, 5334−5337.

(12) (a) Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* **1997**, *62*, 4072−4077. (b) Neilson, G. W.; Symons, M. C. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1405−1410.

(13) For selected references on the nitro radical source, see: (a) Yan, G.; Yang, M. *Org. Biomol. Chem.* **2013**, *11*, 2554−2566. (b) Jovel, I.; Prateeptongkum, S.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2493−2497. (c) Taniguchi, T.; Fujii, T.; Ishibashi, H. *J. Org. Chem.* **2010**, *75*, 8126−8132. (d) Taniguchi, T.; Yajima, A.; Ishibashi, H. *Adv. Synth. Catal.* **2011**, *353*, 2643−2647. (e) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun.* **2013**, *49*, 514−516. (f) Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* **2012**, *14*, 1736−1739. (g) Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. *J. Am. Chem. Soc.* **2013**, *135*, 3355−3358. (h) Manna, S.; Jana, S.; Saboo, T.; Maji, A.; Maiti, D. *Chem. Commun.* **2013**, *49*, 5286−5288. (i) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384−3387. (j) Naveen, T.; Maity, S.; Sharma, U.; Maiti, D. *J. Org. Chem.* **2013**, *78*, 5949−5954. (k) Shen, T.; Yuan, Y.; Jiao, N. *Chem. Commun.* **2014**, *50*, 554−556.

(14) Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 12462−12463.

(15) (a) Rao, V. V. R.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1232−1235. (b) Nguyen, H. H.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 362−365. (c) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417−2420.