ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

TEMPO-Mediated Aliphatic C–H Oxidation with Oximes and Hydrazones

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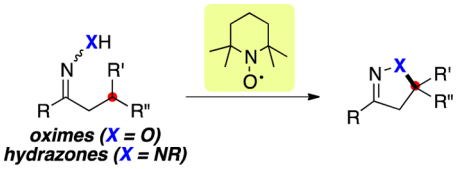
Received April 17, 2013

ABSTRACT



A method for aliphatic C–H bond oxidation of oximes and hydrazones mediated by 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) has been developed, which enables the concise assembly of substituted isoxazole and pyrazole skeletons.

The sp^3-hybridized carbon–hydrogen bonds (aliphatic C–H bonds) are ubiquitous in organic molecules, while most of them especially without activation by the adjacent functional groups (e.g., carbonyl groups) are inert even under harsh reaction conditions. As direct functionalization of such nonreactive aliphatic C–H bonds can potentially result in the atom- and step-economical assembly of functionalized chemical structures, development of chemo- and regioselective C–H oxidation strategies is one of the most challenging topics in synthetic chemistry.[1]

Transition-metal catalysts have played a significant role in state-of-the-art aliphatic C–H oxidation processes, especially in C–H oxygenation[2] and C–H amination,[3] which have actually revolutionized the retrosynthetic tactics of biologically active complex molecules.[4] On the other hand, our reaction design for the C–H oxidation was motivated by the potential of free radical reactions that could be operated under transition-metal-free conditions. A representative example of aliphatic C–H oxidation with the free-radical strategy is the Hofmann–Löffler–Freytag reaction (Scheme 1A).[5] The process is initiated by thermal or photochemical decomposition of protonated *N*-haloamines to afford nitrogen-centered radicals (N-radicals), which immediately induce a 1,5-H radical shift to provide carbon-centered radicals (C-radicals). Further chlorination of the C-radicals followed by a base-mediated intramolecular substitution reaction results in the C–N bond. However, the Hofmann–Löffler–Freytag reaction tends to afford poor product yields while being difficult to control, mainly due to the instability of the radical precursors (*N*-haloamines) and inherent high chemical reactivity of the resulting aminyl radicals. Moreover, several steps (i.e., preparation of *N*-haloamines, radical C–H halogenation, and base-mediated substitution reaction for the C–N bond construction) are required to obtain C–H amination products. Based on these backgrounds,

(1) For recent reviews on C–H oxidation, see: (a) White, M. C. *Science* **2012**, *335*, 807. (b) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (c) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147 and references therein.

(2) For recent selected reports on C–H oxygenation, see: (a) Wang, Y.-F.; Chen, H.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 11980. (b) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70. (c) McNeill, E.; Du Bois, J. *Chem. Sci.* **2012**, *3*, 1810. (d) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (e) Prat, I.; Mathieson, J. S.; Güell, M.; Ribas, X.; Luis, J. M.; Cronin, L.; Costas, M. *Nat. Chem.* **2011**, *3*, 788. (f) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat. Chem.* **2011**, *3*, 216. (g) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584. (h) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (i) McNeil, E.; Du Bois, J. *J. Am. Chem. Soc.* **2010**, *132*, 10202. (j) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654.

(3) For recent reviews on C–H amination, see: (a) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Rec.* **2012**, *45*, 911. (b) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758. (c) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (d) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347. (e) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (f) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379.

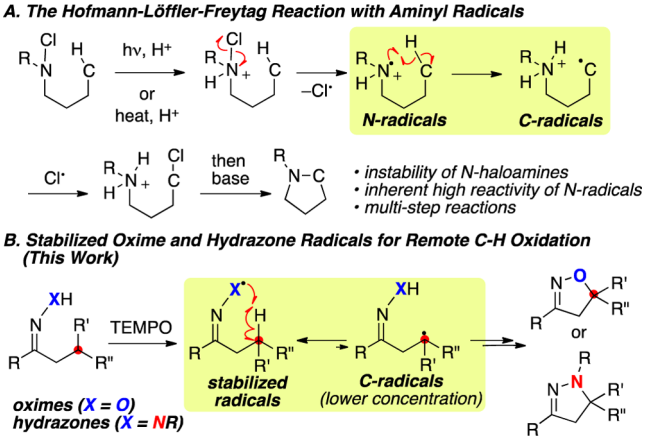
(4) For recent reviews, see: (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (b) Chen, D. Y.-K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452.

(5) (a) Titouania, S. L.; Lavergne, J.-P.; Viallefonta, P.; Jacquierb, E. *Tetrahedron* **1980**, *36*, 2961. (b) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657. (c) Löffler, K.; Freytag, C. *Ber.* **1909**, *42*, 3427. (d) Hofmann, A. W. *Ber.* **1883**, *16*, 558.

10.1021/ol4014969

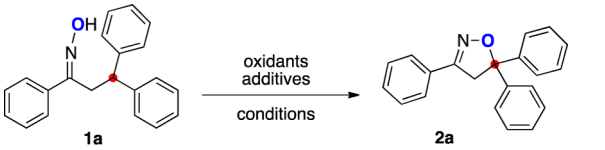
we have designed the intramolecular setting for remote C−H functionalization[6] using stabilized heteroatom-centered (O- or N-) radicals derived from oxime[7] or hydrazone[8] derivatives. It could be envisioned that these heteroatom radicals from oximes or hydrazones undergo 1,5-H-radical abstraction[9] to generate C-radicals at the β-position, where the concentration of the C-radicals could be kept lower due to the weaker reactivity of the oxime or hydrazone radicals that can potentially result in the highly selective oxidative transformation of the C-radicals (Scheme 1B). Herein, we report the realization of this concept as TEMPO-mediated oxidative aliphatic sp^3 C−H oxygenation with oximes as well as sp^3 C−H amination with hydrazones.

Scheme 1. C−H Oxidation with Radical Strategies



We commenced our investigation with the reaction of ketoxime **1a** to oxidize its tertiary C−H bond at the β-position of the oxime moiety (marked in red) using various nonmetal oxidants for generation of the corresponding iminoxyl radical under an inert (N_2) atmosphere (Table 1). When **1a** was treated with TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl, 3 equiv) in toluene,[7a] the reaction proceeded at 120 °C to afford an intramolecular C−H oxygenation product, dihydroisoxazole **2a**, in 30% yield along with 30% recovery of **1a** and some unidentified complex mixtures (entry 1). Addition of inorganic bases (2 equiv) rendered the reactions more efficient (entries 2−4). Further screening of the solvents revealed that the polar aprotic solvents (DMSO, DMF, and DMA) gave good yields of **2a** (entries 5−7), while a polar protic one (*t*-BuOH, entry 8) made the reaction sluggish. A higher reaction temperature (140 °C) in DMF and DMA resulted in the best yields of **2a** (86% and 84%, respectively), with full conversion and acceleration of the reaction rate (entries 9 and 10). The reaction with a sterically less hindered nitroxyl radical, AZADO[10] (2-adamantan-*N*-oxyl), afforded a lower yield of **2a** (entry 11). Although the reaction with DIAD[11] (diisopropyl azodicarboxylate) consumed **1a** rapidly (for 3 h), the yield of **2a** was moderate along with the formation of unidentified complex mixtures (entry 12).

Table 1. Optimization of Reaction Conditions[a]



entry	oxidants (3 equiv)	additives (2 equiv)	solvents	temp (°C)	time (h)	yield of **2a** (%)[b]
1	TEMPO	–	toluene	120	24	30 (30)[c]
2	TEMPO	K_2CO_3	toluene	120	48	68 (10)[c]
3	TEMPO	K_3PO_4	toluene	120	48	57 (25)[c]
4	TEMPO	NaOAc	toluene	120	48	56 (30)[c]
5	TEMPO	K_2CO_3	DMSO	120	48	78 (14)[c]
6	TEMPO	K_2CO_3	DMF	120	48	83 (9)[c]
7	TEMPO	K_2CO_3	DMA	120	48	78 (6)[c]
8	TEMPO	K_2CO_3	*t*-BuOH	120	48	21 (47)[c]
9	**TEMPO**	**K_2CO_3**	**DMF**	**140**	**17**	**86**
10	TEMPO	K_2CO_3	DMA	140	17	84
11	AZADO	K_2CO_3	DMF	140	23	58
12	DIAD	K_2CO_3	DMF	140	3	33

[a] The reactions were carried out using 0.25 mmol of **1a** in solvents (0.1 M). [b] Isolated yields. [c] Recovery yield of **1a**.

We next examined the generality of this TEMPO-mediated C−H oxygenation of oximes **1** for the synthesis of isoxazole derivatives **2** under the optimized reaction conditions (Table 1, entry 9). By varying the substituent R^1, various aromatic rings including both electron-rich and -deficient benzene rings as well as a thienyl unit could be installed (Scheme 2, for **2b**−**2g**).[12] The reaction of oxime **1h** bearing an ethyl moiety as R^1 also proceeded, while the yield of **2h** was moderate (in 40% yield). Oxygenation of diaryl methine moieties bearing various aromatic rings proceeded smoothly to give the corresponding 5,5-diaryl-4,5-dihydroisoxazoles in good yields (for **2i**−**2k**). The reaction of oxime **1l** (R^2 = Me; R^3 = Ph) afforded

(6) The recent reports on sp^3 C−H oxidation (oxygenation and desaturation) by Baran's group have shown the great potential of the radical strategy via remote H-radical abstraction as a key step; see: (a) Voica, A.-F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 629. (b) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (c) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247.

(7) For application of iminoxyl radicals to organic synthesis, see: (a) Han, B.; Yang, X.-L.; Fang, R.; Yu, W.; Wang, C.; Duan, X.-Y.; Liu, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 8816. (b) Ngo, M.; Larson, K. R.; Mendenhall, G. D. *J. Org. Chem.* **1986**, *51*, 5390. (c) Cornejo, J. J.; Larson, K. R.; Mendenhall, G. D. *J. Org. Chem.* **1985**, *50*, 5382.

(8) For application of hydrazonyl radicals to organic synthesis, see: (a) Zhu, M.-Z.; Chen, Y.-C.; Loh, T.-P. *Chem.—Eur. J.* **2013**, *in press* (DOI: 10.1002/chem.201203832). (b) Harej, M.; Dolenc *J. Org. Chem.* **2007**, *72*, 7214 and references therein.

(9) For reviews, see: (a) Cekovic, Z. *Tetrahedron* **2003**, *59*, 8073. (b) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095.

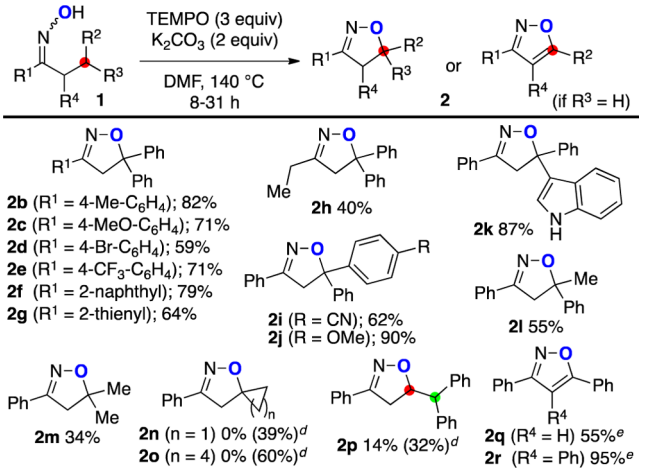
(10) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

(11) For the use of DIAD as a radical initiator, see: (a) Shan, A.; George, M. V. *Tetrahedron* **1971**, *27*, 1291. (b) Huisgen, R.; Pohl, H. *Chem. Ber.* **1960**, *93*, 527.

(12) Oximes **1g**, **1h**, and **1o** were obtained as a mixture of *E*/*Z*-isomers. No difference was observed in the yields of **2g** between treatment of *E*/*Z* mixture of **1g** and that of pure *E*-isomer **1g**, which suggested that isomerization of the N−O bond in the oxime *E*/*Z* isomers could readily occur under the present reaction conditions. See the SI for more details.

5-methyl-3,5-diphenyl-4,5-dihydroisoxazole (**2l**) in 55% yield, while that of oxime **1m** (R^2 and R^3 = Me) resulted in a moderate yield (34%) of 5,5-dimethyldihydroisoxazole **2m**. However, α-cyclopropyl- and α-cyclohexyloximes **1n** and **1o** were not converted into the desired dihydroisoxazoles at all. Oxime **1p** having a more reactive dibenzylic methine C−H bond at the 6-position (marked in green) to the oxime oxygen underwent cyclization onto the 5-position (marked in red) to give **2p** albeit in low yield. Oxygenation of a benzylic methylene moiety of **1q** and **1r** could also be achieved to give the corresponding aromatized isoxazoles **2q** and **2r**, respectively, by the reaction of oximes with TEMPO and subsequent treatment of the reaction mixture under an air atmosphere for completion of the aromatization.

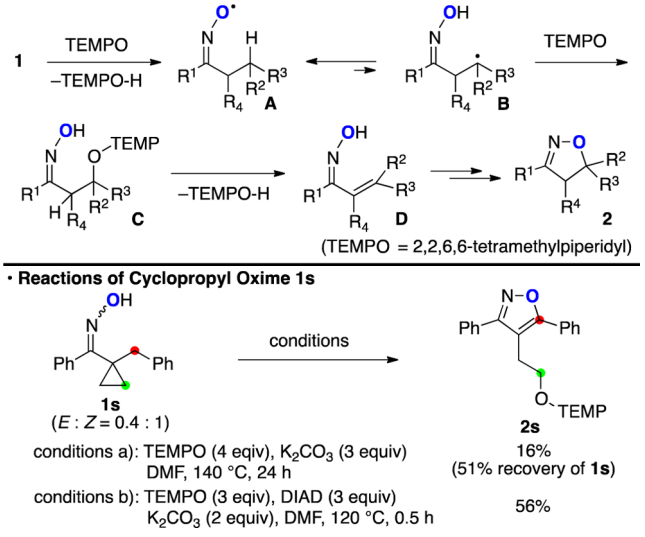
Scheme 2. TEMPO-Mediated C−H Oxygenation of Oximes **1**[a−c]



[a] Unless otherwise noted, the reactions were carried out using 0.25 mmol of oximes **1** under a N_2 atmosphere at 140 °C for 6−31 h (see the Supporting Information for more details). [b] Oximes **1** except for **1g**, **1h**, and **1r** were obtained as a pure *E*-isomer. Oximes **1g**, **1h**, and **1r** were used as an *E*/*Z* mixture for the reaction (see ref 12 and the SI for more details). [c] Isolated yields were recorded above. [d] Recovery yield of oxime **1**. [e] Upon heating under a N_2 atmosphere for 23 h, the reaction mixture was exposed to air for 3 h.

Based on these results, a proposed mechanism of this TEMPO-mediated C−H oxygenation of oximes **1** is depicted in Scheme 3. TEMPO induces generation of iminoxyl radical **A** that undergoes a rate-determining 1,5-H radical shift to give C-radical intermediate **B**. Another TEMPO traps the resulting C-radical **B** to generate β-aminoxyl oxime **C**, and successive elimination of 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPO-H)[13] affords α,β-unsaturated oxime **D**,[14] which cyclizes to give dihydroisoxazole **2** probably via both an ionic and radical 5-endo manner.[15] The presence of C-radical **B** could be speculated by the reactions of oxime **1s** bearing an α-quaternary carbon with a cycpropyl unit. While the reaction of **1s** with 4 equiv of TEMPO was very sluggish, isoxazole **2s** bearing a 2-aminoxyethyl part was formed via radical ring opening of the cyclopropane[16] followed by trapping of the resulting primary C-radical (on the carbon marked in green) with TEMPO (see the Supporting Information (SI) for the detailed reaction mechanism). It was found that the combined use of TEMPO and DIAD (3 equiv in each) could accelerate the reaction and improve the yield of **2s** to 56% yield. It is noted that the reactions of other types of α-quaternary oximes (2,2-dimethyl **1t**, cyclohexyl **1u**, and benzene tethered **1v**; see the SI) gave no desired C−H oxgenation products.

Scheme 3. A Proposed Reaction Mechanism and Reactions of **1s**



Stimulated by the structural analogy of hydrazones **3** with oximes **1**, we next examined the TEMPO-mediated reactions of hydrazones **3** for sp^3 C−H amination (Scheme 4). As expected, treatment of both *N*-phenyl and *N*-benzoyl hydrazones **3a** and **3b** with TEMPO (3 equiv) delivered the corresponding β-C−H amination products, dihydropyrazoles **4a** and **4b**, respectively in good yields.[17] Various 5,5-diaryl-4,5-dihydropyrazoles could be constructed in good yields (for **4c**−**4g**). Amination of methine C−H bonds bearing only one phenyl group (**3h**: R^2 = Me, R^3 = Ph)

(13) For the elimination of TEMPO-H from **C**, several possible pathways could be considered such as ionic *anti*-elimination with base, ionic *syn*-elimination where the N atom of the aminoxyl group works as an internal base, and radical elimination with C−O bond homolysis. For a report on ionic *syn*-elimination, see: Ananchenko, G. S.; Fischer, H. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3604. For a report on radical elimination, see: Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. *J. Am. Chem. Soc.* **2013**, *135*, 3355.

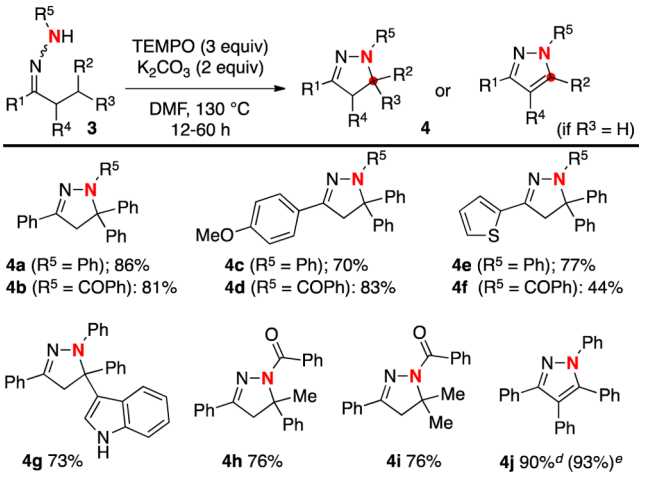
(14) While we could not observe the presence of α,β-unsaturated oxime **D** in the reaction of oximes **1** even by further lowering the reaction temperature, the corresponding α,β-unsaturated hydrazone could be isolated and characterized; see ref 17.

(15) To investigate the mechanism of the cyclization, we have prepared α,β-unsaturated oxime **1q′** (the model of intermediate **D** for the reaction of **1q** to **2q**) and examined several reactions of **1q′**. See: Shotter, R. G.; Sesardic, D.; Wright, P. H. *Tetrahedron* **1975**, *31*, 3069.

(16) (a) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

(17) The formation of *N*-benzoyl dihydropyrazole **4b** needed 39 h to complete the reaction. It was found that quenching the reaction of **3b** for 4 h provided α,β-unsaturated hydrazone **4b′** in 39% yield along with the formation of dihydropyrazole **4b** in 26% yield and recovery of **3b** in 26% yield. The isolation of α,β-unsaturated hydrazone **4b′** supported the reaction mechanism of the present C−H oxidation depicted in Scheme 2. See the Supporting Information for mode details.

Scheme 4. TEMPO-Mediated Reactions of Hydrazones 3^{a-c}

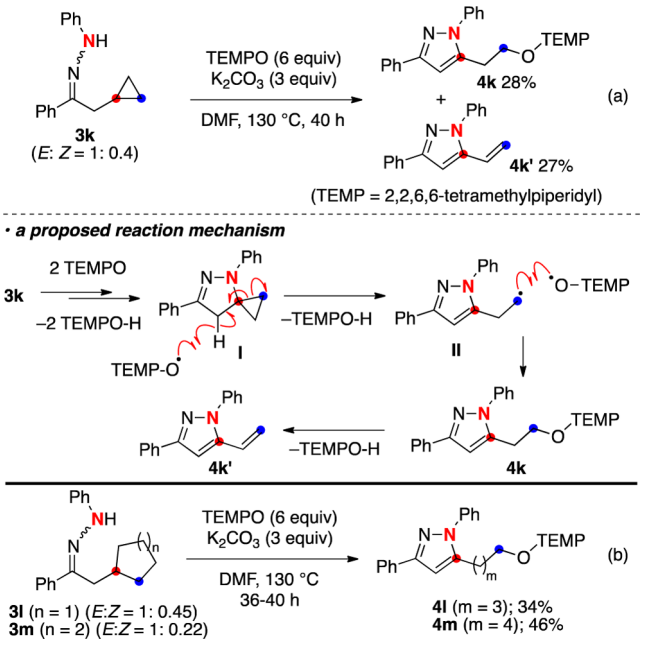


[a] Unless otherwise noted, the reactions were carried out using 0.25 mmol of hydrazones **3** under a N_2 atmosphere at 130 °C for 12−60 h (see the SI for more details). [b] Hydrazones **3** except for **3a** and **3e** were obtained as a pure *E*-isomer. Hydrazones **3a** and **3e** were used as an *E*/*Z* mixture for the reaction (see the SI for more details). [c] Isolated yields. [d] Upon heating under a N_2 atmosphere for 28 h, the reaction mixture was exposed to air for 3 h. [e] The reaction was run with 4.5 equiv of TEMPO for 28 h.

and even with a dimethyl motif (**3i**: R^2 and R^3 = Me) proceeded smoothly to give **4h** and **4i**, respectively, in good yields, which indicated that the *N*-radical species derived from hydrazones **3** could possess higher reactivity toward the targeted C−H bonds than that of the *O*-radicals from oximes **1** (by comparison with the formation of **2l** and **2m** in Scheme 2). Synthesis of 1,3,4,5-tetraphenylpyrazole (**4j**) could be realized in excellent yield by methylene C−H amination followed by further aromatization by air or excess amounts of TEMPO.

The reaction of α-cyclopropyl hydrazone **3k** with TEMPO (6 equiv) delivered aromatized pyrazoles **4k** and **4k′** (Scheme 5a). In this case, the present *β*-C−H amination generates the corresponding dihydropyrazole **I**, which might undergo radical ring opening of the cyclopropane moiety driven by aromatization to form C-radical intermediate **II**. Subsequent trapping of the C-radical **II** with TEMPO affords **4k**, which could undergo further elimination of TEMPO-H to afford **4k′**. It is worth noting that this aromatization-driven radical ring opening could be observed even for stable cyclopentane and -hexane rings of hydrazones **3l** and **3m**, affording the corresponding pyrazoles **4l** and **4m**, respectively, although the yields were moderate (Scheme 5b).

Scheme 5. Reactions of α-Cycloalkyl Hydrazones **3k**−**m**



In summary, we have developed an operationally simple TEMPO-mediated aliphatic C−H oxidation with oximes and hydrazones, which enables the concise assembly of substituted isoxazole and pyrazole skeletons under transition-metal-free conditions. The reaction mechanism in the present processes includes a 1,5-H radical shift of iminoxyl and hydrazonyl radicals generated from oxime and hydrazone derivatives, respectively, with TEMPO. We are currently engaged in further synthetic applications of this radical mediated tactic for other types of aliphatic C−H oxidation.

Acknowledgment. This work was supported by funding from Nanyang Technological University and the Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2012-T2- 1-014). Y.-F.W. is thankful for the Lee Kuan Yew postdoctoral fellowship (the LKY PDF). We acknowledge a generous gift of AZADO from Nissan Chemical Industries, Ltd. We appreciate the valuable suggestions from the referees to this work.

Supporting Information Available. Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.