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TEMPO-Mediated Allylic C-H Amination with Hydrazones

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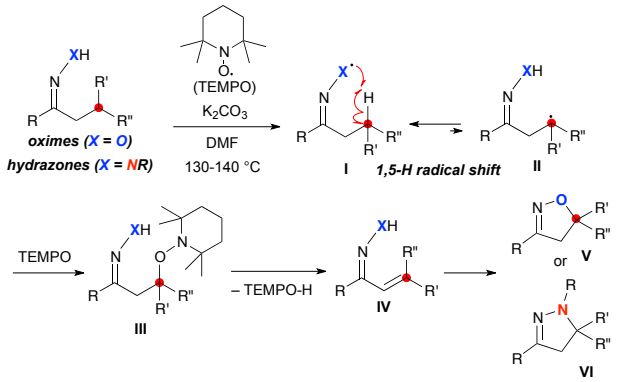
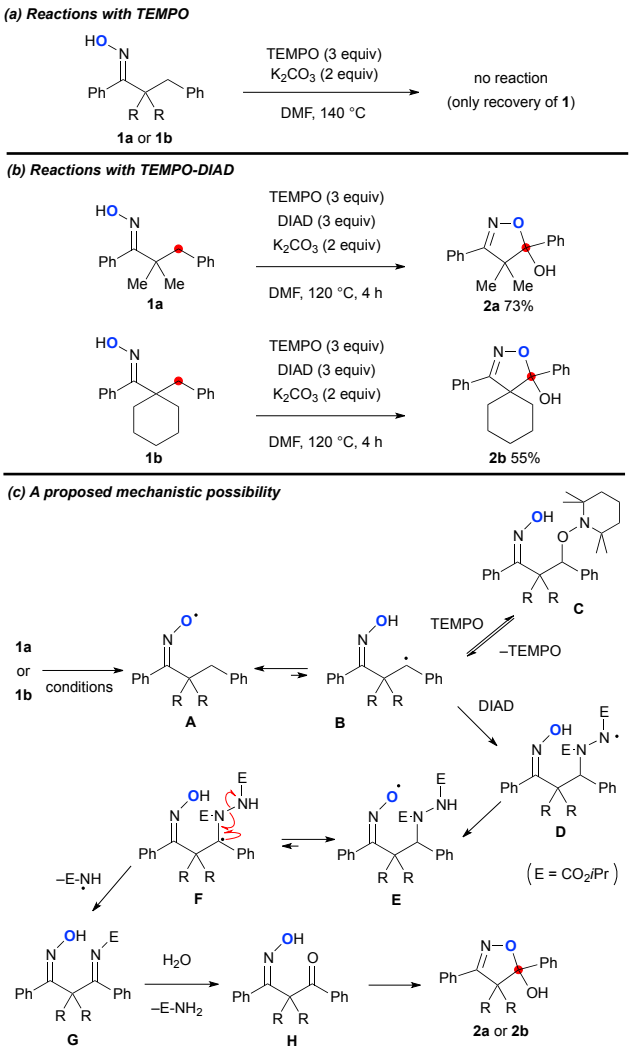
TEMPO-mediated reactions of alkenyl hydrazones afforded azaheterocycles via sp^3 C-H allylic amination. The transformation is featured by sequence of remote allylic H-radical shift and allylic homolytic substitution with hydrazone radicals.

Development of methods for oxidative functionalization of sp^3 C-H bonds, that provide direct and step-economical approaches to construct functionalized organic structures, has been one of the hottest trends in the area of synthetic organic chemistry.[1] To realize this goal in regio- and chemo-selective manner, use of organometallic intermediates as well as metal-carbene and -nitrene species with various transition-metal-catalysts has prevailed. On the other hand, free-radical mediated sp^3 C-H bond functionalization by remote H-radical shift[2] has been recognized for a long time as represented by the Hofmann-Löffler-Freytag reaction,[3] while the inherent violent chemical reactivity of the free radical species often renders these processes of dyscontrol along with undesired side reactions such as fragmentation and intermolecular H-radical abstraction.

Our group has been interested in use of stabilized O- and N-radicals derived from oximes and hydrazones, respectively, for remote sp^3 C-H bond oxidation, and recently reported β-sp^3-C-H oxygenation and amination with oximes and hydrazones mediated by 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (Scheme 1).[4-6] In β-sp^3-C-H oxygenation with oximes (**X** = O), the process is initiated by 1,5-H-radical shift of the putative oxime O-radicals **I**, giving β-C-radicals **II** that are subsequently trapped with TEMPO. The resulting β-aminoxyl oximes **III** undergo elimination of 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPO-H) to form α,β-unsaturated oximes **IV**, that finally cyclize to deliver dihydroisoxazoles. The analogous mechanism could be proposed for β-sp^3-C-H amination with hydrazones (**X** = N). Therefore, the presence of at least one α-hydrogen atom is indispensable to realize this β-sp^3-C-H oxidation via α,β-unsaturated oxime or hydrazone intermediates **IV**.



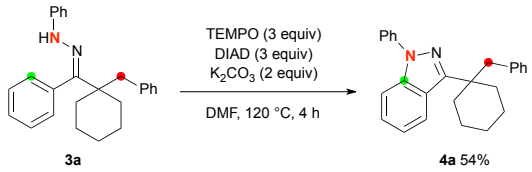
Scheme 1 TEMPO-medaited β-C-H oxidation of oximes and hydrazones



Scheme 2 β-C-H oxygenation of α-quaternary oximes **1a** and **1b**

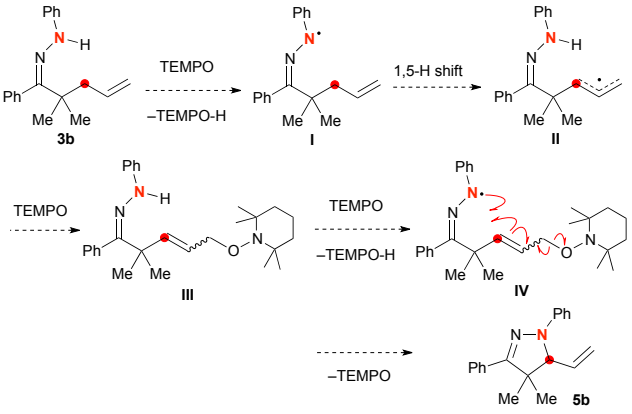
It is therefore inherent that the β-C-H oxygenation of α-quaternary oximes such as **1a** and **1b** with TEMPO did not proceed at all (Scheme 2-a). In sharp contrast, treatment of these oximes with TEMPO and diisopropyl azodicarboxylate (DIAD) (3 equiv, each) delivered β-keto oximes, which were isolated as the hemiacetal forms **2a** and **2b**, respectively (Scheme 2-b). Although we are not certain as to the reaction mechanism of this β-oxygenation reaction, tentative speculation of the reaction course was described in Scheme 2-c. In the presence of only TEMPO, the resulting carbon radical **B** might be trapped by TEMPO to give β-aminoxyl oxime **C**. However, the C-O bond of oxime **C** undergoes thermal homolysis to be back to the carbon radical **B**,[7] that is further converted into more stable imonoxyl radical **A**. On the other hand, in the presence of both TEMPO and DIAD, the carbon-radical **B** could be trapped by DIAD[8] to give aminyl radical **D** and this process should not be reversible under the present reaction conditions. The resulting aminyl radical re-generates iminoxyl radical **E**, which undergoes 1,5-H radical shift to give carbon-radical **F**. Further radical fragmentation of **F** with N-N bond cleavage generates *N*-acylimine **G** and further hydrolysis of the imine moiety generate β-keto oxime **H** that cyclzes to form hemiacetal **2a** or **2b**.[9]

However, this TEMPO-DIAD system could not be adopted for the reaction of α-quaternary hydrazones such as **3a** (Scheme 3). In this case, amination proceeded not onto the β-sp^3 C-H bond but onto the sp^2 aromatic C-H bond to give the correspinding indazole **4a** in 54% yield.[10,11]



Scheme 3 The reaction of α-quaternary hydrazone **3a**

These results stimulated us to develop remote sp^3-C-H amination process with hydrazones that could be realized regardless of degree of the α-substitution. We wondered if γ,δ-unsaturated hydrazone **3b** can be used for allylic C-H amination,[12] in which the resulting allylic radical **II** by 1,5-H shift of the corresponding hydrazone radical **I** might trap TEMPO to give β,γ-unsaturated-δ-aminoxyl oxime **III** that undergo further

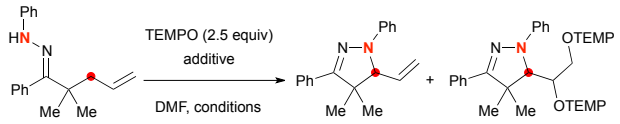


Scheme 4 Allylic C-H amination with γ,δ-unsaturated hydrazone **3b**

intramolecular radical allylic substitution reaction[13,14] with hydrazone radical **IV** to afford the allylic C-H amination products **5b** (Scheme 4).

Based on the hypothesis outlined in Scheme 4, we began our investigation with hydrazone **3b** (Table 1). Recently, Han et al. has reported that the reactions of γ,δ-unsaturated hydrazones such as **3b** with 4 equiv of TEMPO and 1 equiv of DIAD in toluene at 100 °C provided dihydropyrazole **5b'** as a sole product, that was formed via 5-exo radical cyclization of the putative intermediate **IV** followed by trap of the resulting C-radical with TEMPO.[5b] On the other hand, the reaction of **3b** with 2.5 equiv of TEMPO in DMF at 130 °C delivered dihydropyrazole **5b** in 77% yield as a sole product (entry 1). In the presence of the inorganic base such as K_2CO_3 or K_3PO_4, the reactions were performed with slightly lower yield (entries 2 and 3). Lowering the reaction temperature from 130 °C to 80 °C render the process sluggish, giving a mixture of dihydropyrazoles **5b** and **5b'** in 24% and 11% yields, respectively along with recovery of **3b** in 56% yield (entry 4). These results implicated that higher temperature (130 °C) is indispensable to realize the homolytic allylic substitution reaction selectively to form **5b**.

Table 1 Allylic C-H amination: optimization of the reaction conditions [a,b]

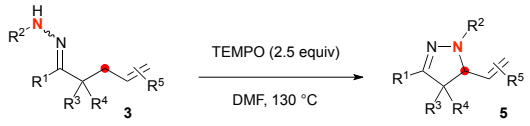


entry	additive (equiv)	temp (°C)	time (h)	yields (%)[b] 5b	5b'
1	–	130	24	77	0
2[c]	K_2CO_3 (3)	130	30	72	0
3	K_3PO_4 (3)	130	30	68	0
4	–	80	45	24 (56)[c]	11

[a] The reactions were carried out using 0.20 mmol of **3b** in DMF (0.1 M) under Ar atmosphere. [b] Isolated yields were recorded. [c] Recovery yield of hydrazone **3b**.

Having optimized the reaction conditions, we next examined scope and limitation of this allylic C-H amination using a series of γ,δ-unsaturated hydrazones **3**. By varying the substituent R^2 on the hydrazone nitrogen, 4-methoxy- and 4-bromophenyl groups were introduced to give the desired dihydropyrazoles **5c** and **5d**, respectively, in good yields (entries 1 and 2). The method allowed to construct spirocyclic dihydropyrazole **5e** in 62% yield (entry 3). The reactions of α-mono-substituted-γ,δ-unsaturated hydrazones **3f-h** proceeded in diastereoselective manner, delivering 4,5-*trans*-dihydropyrazoles **5f-h** in good to moderate yields (entries 4-6). Of worthy to note is that hydrazone **3h** having allylic (marked in red) and benzylic (marked in green) C-H bonds exclusively selected allylic one (entry 6). The reaction of γ,δ-unsaturated hydrazone **3i** having no substituent at the α-position with 2.5 equiv of TEMPO resulted in formation of an inseparable mixture of aromatized pyrazole **5i** and the corresponding dihydropyrazole.[15] Use of 4.5 equiv of TEMPO could complete aromatization to give pyrazole **5i** in 80% yield (entry 7). Installation of a methyl group onto the alkene (either γ- or δ-position) did not retard the allylic C-H amination, affording the corresponding dihydropyrazoles (entries 8 and 9).

Table 2. Scope on allylic C-H amination with hydrazones **3** [a]



entry	Hydrazones	Time (h)	products	yields (%)[b]
1	**3c**: R^2 = 4-MeOC$_6$H$_4$	12	**5c**	73
2	**3d**: R^2 = 4-BrC$_6$H$_4$	16	**5d**	74
3	**3e**	6	**5e**	62
4	**3f**: R^3 = Ph	20	**5f**	80
5	**3g**: R^3 = Me	20	**5g**	53
6	**3h**	20	**5h**	72
7[c]	**3i**	20	**5i**	80
8	**3j**	23	**5j**	86
9	**3k** (*E*:*Z* = 6:1)	6	**5k** (*E*:*Z* = 25:1)	56

[a] The reactions were carried out using 0.28-0.35 mmol of **3** with TEMPO (2.5 equiv) in DMF (0.1 M) at 130 °C under an Ar atmosphere. [b] Isolated yields were recorded above. [c] The reaction was conducted using 4.5 equiv of TEMPO.

The present strategy could be extended further for construction of tetrahydropyridazine skeletons **5l-n** from δ,ε-unsaturated hydrazones **3l-n** by rendering their β-position quaternary to prevent the 1,5-H radical shift (Scheme 5-a). Similarly, the present method enabled to synthesize dihydrophthalazine **5o** from benzene-tethered hydrazone **3o**, while the yield was moderate (Scheme 5-b).

In summary, we have developed TEMPO-mediated radical sp^3-allylic amination with hydrazones for synthesis of azaheterocycles such as dihydropyrazoles and tetrahydropyridazines. The process involves sequence of remote H-radical shift and allylic homolytic substitution that could be enabled by the putative hydrazone radical. This method should be readily adopted for synthesis of various azaheterocycles valuable in pharmaceutical and material-based applications.

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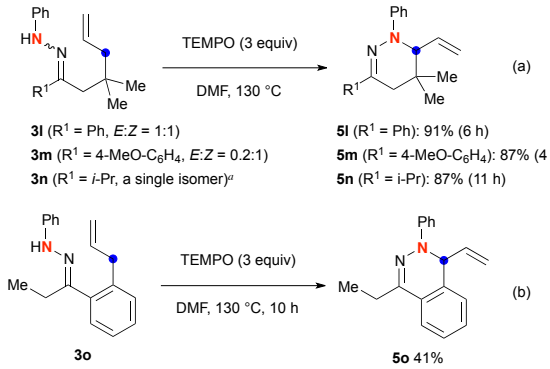

Scheme 5 Formation of 6-membered rings: The reactions were conducted using 0.30 mmol of **3** in DMF (0.1 M) under an Ar atmosphere. [a] The stereochemistry of the hydrazone moiety of **3n** was not determined.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of products, and copies of ^{1}H and ^{13}C NMR spectra.. See DOI: 10.1039/b000000x/

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