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Catalytic Migratory Oxidative Coupling of Nitrones

Shogo Hashizume, Kounosuke Oisaki,* and Motomu Kanai*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

oisaki@mol.f.u-tokyo.ac.jp; kanai@mol.f.u-tokyo.ac.jp

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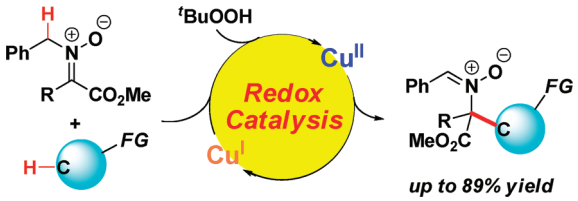
ABSTRACT



A Cu(I)-catalyzed migratory oxidative coupling between nitrones and heterocycles or a methylamine is described. Selective C−C bond-formation proceeds through cleavage of two C(sp^3)−H bonds concomitant with C=N double bond-migration. The reaction provides an alternating nitrone moiety, allowing for further synthetically useful transformations. Radical clock studies suggest that the nucleophilic addition of nitrones to an oxidatively generated carbocation is a key step.

The pursuit of novel catalytic methodologies to functionalize unactivated C−H bonds is one of the most attractive subjects in current synthetic organic chemistry.[1] Cross-dehydrogenative coupling (CDC) reactions pioneered by Li et al.[2] are direct oxidative C−C bond-formations from two different C−H bonds in the presence of terminal oxidants (hydrogen acceptors). CDC eliminates the need for preactivation and cumbersome functional group manipulations of substrates thereby contributing to environmentally benign, streamlined synthesis.[3,4] Although various CDC reactions have been reported to date, there remains much room for improvement, especially in the extension to practical complex molecule synthesis. Reported conditions usually include precious metals, high temperature, oxidants producing stoichiometric amounts of hazardous waste, and narrow substrate scope.[2,5] Here we report a catalytic migratory oxidative coupling reaction between nitrones (imine *N*-oxides) and *O*-/*N*-heterocycles or an alkylamine as a novel CDC, producing alternating nitrones, that can be used for synthetically useful transformations. This reaction is promoted by an inexpensive and abundant copper catalyst at room temperature, using *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant.[6]

Our study began with the unexpected finding that a migratory coupling product **3ac** was produced from nitrone **1a** under oxidative conditions in the presence of a copper catalyst in THF (**2c**), even at room temperature. In this reaction, multiple events proceeded sequentially: (1)

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(2) (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Scheuermann, C. J. *Chem. Asian. J.* **2010**, *5*, 436. (c) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.

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(5) Representative examples of metal-catalyzed CDC forming C-(sp^3)-C(sp^3) bonds: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (b) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173. (c) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (e) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (f) Li, Z.-P.; Yu, R.; Li, H.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (g) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901. (h) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (i) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem.* **2008**, *73*, 5859. (j) Richter, H; Mancheño, O. G. *Eur. J. Org. Chem.* **2010**, 4460. (k) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214. (l) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181.

(6) For CDCs using copper catalyst and TBHP: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (d) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. Also see refs 2, 5a, 5b, 5d, 5e, 5k, and 5l.

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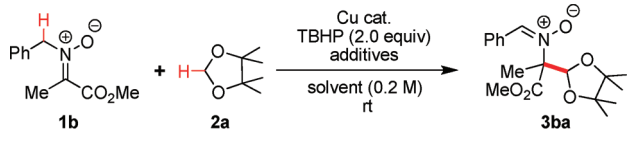
cleavage of both the benzylic C−H bond of **1a** and the methylene C−H bond adjacent to an oxygen atom of THF, (2) double bond-migration of **1a**, and (3) the site-selective C−C bond formation. The synthetic utility and reactivity of nitrones have previously been studied due to their unique structural features such as densely presented functional groups and easy availability; however, the above conversion is not found among any classical transformation.[7] This finding led us to explore the novel reactivity of nitrones under oxidative coupling conditions.

We optimized the migratory oxidative coupling reaction between nitrone **1b** (prepared via condensation of methyl pyruvate with *N*-benzyl hydroxylamine) and pinacol acetal **2a** in the presence of copper catalysts and TBHP, affording **3ba** (Table 1). First, screening of copper salts as a catalyst revealed that copper halides and cationic copper salts were less suitable than copper carboxylates, among which copper benzoate (CuOBz) produced the best results (entries 1−4).[8] Reducing the amount of TBHP to 2.0 equiv and decreasing the reaction time suppressed undesirable side reactions and improved the yield (entry 5). Polar solvents generally afforded better yields, and dimethylsulfoxide (DMSO) was the optimum solvent (entry 6). Investigation of the ligand effects on copper revealed that specific bidentate ligands comprising pyridyl moieties enhanced the reactivity. The best yield was obtained with 1,10-phenanthroline (1,10-phen) as the ligand (entries 7−9). Decreasing the catalyst loading to 5 mol %, however, produced a less satisfactory yield (entry 10). We then studied the effects of additives to enhance the reactivity. Brönsted base cocatalysts markedly enhanced the reactivity (entries 11−13). Finally, product **3ba** was obtained in 75% isolated yield with a shorter reaction time (0.5 h) by adding 20 mol % of $NaHCO_3$ (entry 13).

Under these optimized conditions, substrate scope was tested (Figure 1). Compared with previously reported room temperature CDCs,[5a−c,i,j,l] the substrate scope of the current reaction is quite broad. The reaction was not very sensitive to steric factors of the substrates, for both the nitrone (R = Me, CH_2CO_2Me) and cyclic acetal (α-Me, **2b**). Products containing tetrasubstituted carbons, including **3bb** containing highly congested contiguous tetrasubstituted carbon centers, were obtained in moderate to high yields.

Table 1. Optimization of Reaction Conditions[a]



entry	Cu cat. (mol %)	solvent	time [h]	additives (mol %)	yield[b] [%]
1[c]	CuCl (20)	CH_3CN	24	none	8
2[c]	$Cu(OAc)_2$ (20)	CH_3CN	24	none	13
3[c]	CuOAc (20)	CH_3CN	24	none	16
4[c]	CuOBz (20)	CH_3CN	24	none	20
5	CuOBz (10)	CH_3CN	6	none	40
6	CuOBz (10)	DMSO	8	none	55
7	CuOBz (10)	DMSO	6	TMEDA(12)	8
8	CuOBz (10)	DMSO	6	2,2′-bipy. (12)	57
9	CuOBz (10)	DMSO	4	1,10-phen.(12)	76
10	CuOBz (5)	DMSO	5	1,10-phen.(6)	66
11	CuOBz (5)	DMSO	5	1,10-phen. (6), pyridine (20)	61
12	CuOBz (5)	DMSO	1.5	1,10-phen.(6), K_2CO_3(20)	64
13	CuOBz (5)	DMSO	0.5	1,10-phen. (6), $NaHCO_3$ (20)	75[d]

[a] Standard conditions: **1** (0.10 mmol), **2** (0.50 mmol), Cu catalyst (0.005−0.02 mmol), TBHP (0.20 mmol), and solvent (0.5 mL) at rt for 0.5−24 h. [b] Determined by ^1H NMR using an internal standard. [c] Using 3.0 equiv of TBHP. [d] Isolated yield. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, 2,2′-bipy. = 2,2′-bipyridine, 1,10-phen. = 1,10-phenanthroline.

In addition, the reaction in the absence of base cocatalyst was tolerant of substrate **1c** containing fairly acidic methylene protons, giving **3ca**. The product **3ca** is a potentially versatile precursor of biologically relevant aspartic acid analogs. Cyclic ethers, such as tetrahydrofuran (**2c**), 1,4-dioxane (**2d**), oxepane (**2e**), cyclopentylmethyl ether (**2f**), and oxetane (**2g**) were competent substrates as well. Because direct functionalizations of medium-sized ether rings are rare, the result giving **3ag** would offer novel synthetic route and derivatization of more complex (poly)cyclic ethers, which are observed in many bioactive molecules.[9] In the case of **2f**, two regioisomers, **3af** and **3af′**, were produced in a moderate ratio with tertiary ether **3af** as the major product. Direct introduction of a strained oxetane ring (**2g**) will be useful for medicinal chemistry applications.[10] The expected coupling product was produced at the initial stage of the reaction between **2g** and **1a**. In case of extended reaction time, however, a ring-opening reaction proceeded to produce alcohol **3ag**. In contrast, the oxetane ring remained intact in the reaction between **2g** and pyruvate-derived nitrone **1b** to give **3bg**.

In addition to simple cyclic ethers, the reaction was applicable to protected 1,2-diol **2h** and morpholine **2i**. Densely functionalized **3ah** and **3ai** were produced in a convergent manner through a simple operation. The unique regioselectivity of this system is noteworthy. In cases of **2i**, oxidative coupling proceeded at the α-carbon of a nitrogen atom with complete regioselectivity. Both cyclic amines **2j**

(7) Previously reported synthetic utilities of nitrones are categorized into the following four main transformations. [2 + 3] Cyclization reaction: (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. Cyclization with cyclopropane opening reaction: (d) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (e) Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 1528. Kinugasa reaction: (f) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466. (g) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999. (h) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572. (i) Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198. Used as an electrophile: (j) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245. (k) Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Vallee, Y. *Org. Lett.* **2002**, *4*, 1463. (l) Garret, M. R.; Tarr, J. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 12944. Recently a CDC reaction using nitrones was reported: (m) Murarka, S.; Studer, A. *Org. Lett.* **2011**, *13*, 2746.

(8) Iron salts were also studied as catalysts, but the results were less satisfactory than when using copper catalysts.

(9) Review of the synthesis of a medium-sized ether ring: (a) Yet, L. *Tetrahedron* **1999**, *55*, 9349. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963.

(10) Intriguing properties of oxetanes in medicinal chemistry: Burk-hard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052.

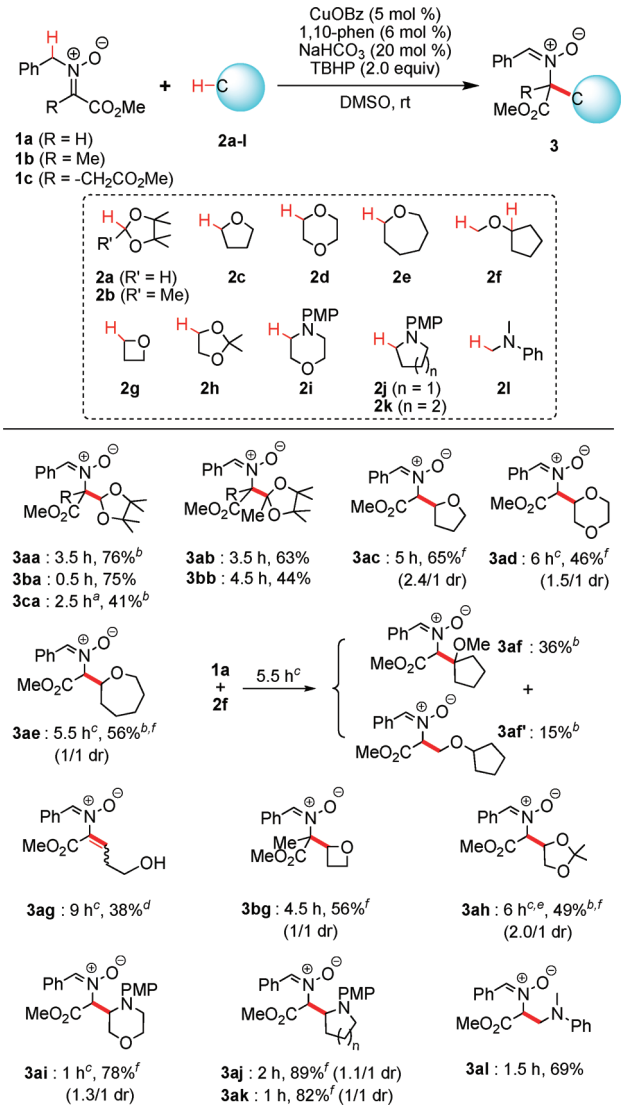
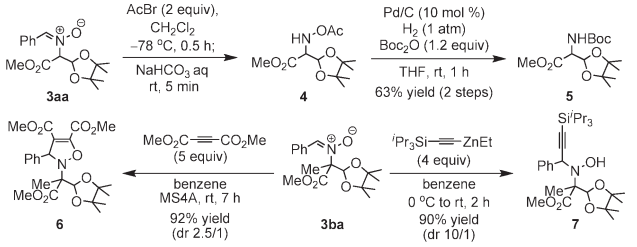


Figure 1. Catalytic migratory oxidative coupling between nitrones **1** and heterocycles **2a**–**2k** or *N*,*N*-dimethylaniline **2l**. Isolated yield is shown for each run unless otherwise noted. Diastereomeric ratio (dr) was determined from ^{1}H NMR of diastereo-mixture. [a]Reaction was conducted without $NaHCO_3$. [b]Yield was calculated from ^{1}H NMR (see Supporting Information). [c]Using 10 equiv of **2**. [d] Obtained as a mixture of geometrical isomers (6.6:1 ratio). [e]Using 3.0 equiv of TBHP. [f]Combined yield of diastereo-mixture. PMP = *p*-methoxyphenyl.

and **2k** and acyclic amine **2l** were effective substrates in the coupling with amines, affording 1,2-diamine derivatives. In general, the diastereoselectivity was not high (1:1 to 2.4:1) and requires further improvement.

(11) Nitrones, oximes, imines, and Michael acceptors are excellent carbon radical acceptors. For O_2/alkylborane-initiated radical reactions: (a) Kabalka, G. W.; Brown, H. C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* **1970**, *92*, 710. (b) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043. (c) Liu, J.-Y.; Jang, Y.-J.; Lin, W.-W.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* **2003**, *68*, 4030. For dialkylzinc-initiated radical reactions: (d) Akindele, T.; Yamada, K.-i.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345. Also see Supporting Information for our detailed investigations.

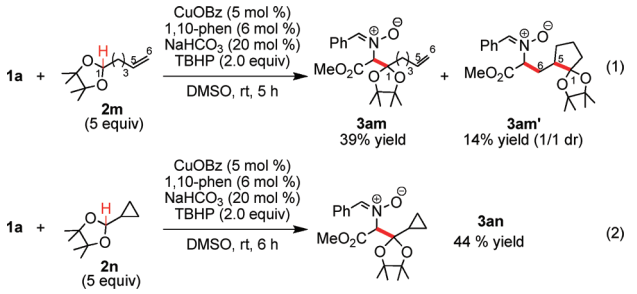
Scheme 1. Conversions of Coupling Products



The *pseudo*replication feature starting from nitrones **1** to products **3** containing an alternating nitrone functionality is also unique in this catalysis. Thus, products **3** are synthetically useful intermediates for further conversions (Scheme 1). Functional group transformation of the nitrone to an amine derivative was conducted in two steps; treatment of **3aa** with acetyl bromide at −78 °C followed by hydrolysis afforded **4**, which was converted into non-natural α-amino acid derivative **5**, through hydrogenolysis. Nitrone itself is also a reactive functional group for further structural diversification.[7] 1,3-Dipolar cycloaddition between **3ba** and electron-deficient alkyne produced isoxazoline **6** in 92% yield. Nitrones can be used as an electrophile for the addition of organometallic reagents. Thus, the addition of a zinc acetylide species[7k] to **3ba** proceeded in 90% yield.

To get insight into the reaction mechanism, "radical clock" experiments were conducted (Scheme 2). The coupling reaction with **1a** using **2m**, possessing a $\Delta^{5,6}$ C=C double bond, mainly proceeded at the acetal C-1. In this case, however, the cyclopentanone derivative **3am′** was concomitantly produced as a minor product through cyclization between C-1 and C-5, followed by intermolecular C–C bond-formation at C-6 (eq 1). The coupling reaction of acetal **2n**, containing a neighboring cyclopropane moiety, proceeded without any ring-opening (eq 2).

Scheme 2. Radical Clock Experiments



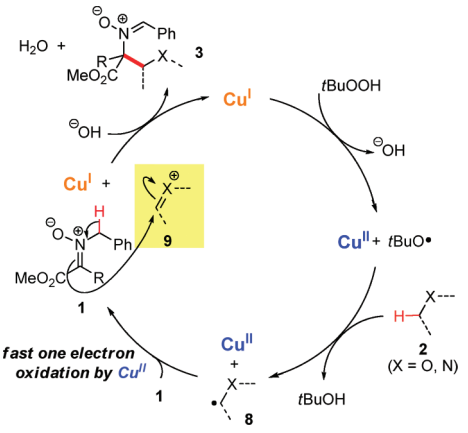
These two results suggested that the present reaction does not include attack of carbon radical species, which are catalytically generated from heterocycles in situ, to nitrones ("radicalic pathway", Scheme S1, Supporting Information).[11] If a radical was generated at the acetal methine carbon, ring-opening of cyclopropane must have been also observed, because the estimated rate constant for the

ring-opening of cyclopropylmethyl radical is much larger than that of cyclization of 5-hexenyl radical ($k = 1.3 \times 10^8$ M^{-1} s^{-1} and 1.0×10^5 M^{-1} s^{-1}, respectively, at 25 °C).[12]

We propose a possible catalytic cycle of the migratory oxidative coupling reaction partly based on those results (Scheme 3). First, a Fenton reaction between Cu(I) and TBHP produces *tert*-butyloxy radical (or hydroxy radical) and Cu(II).[13] The base cocatalyst, which exhibited marked acceleration effects, might contribute to increase the concentration of precursor for radical generation ($CuOO^tBu$) by producing peroxide anion ($^tBuOO^-$) that is more coordinating to Cu(I) than TBHP.[14] The thus-generated radical is reactive enough to subtract a hydrogen atom from a C(sp^3)–H bond α to a heteroatom of coupling partners **2** to afford carbon radical **8**. A "radicalic pathway" is not probable, based on the radical clock studies described above. As an alternative pathway, we propose the "polar pathway" involving oxonium/iminium intermediate **9** generated by fast one-electron oxidation of **8** by Cu(II).[15] Subsequent nucleophilic attack of nitrone **1** to **9** affords product **3**. This polar mechanism is consistent with all the experimental results, including the regioselectivity discussed in scope and limitations (Figure 1, **3ai**).

In conclusion, we developed a catalytic migratory oxidative coupling between nitrones and heterocycles or an alkylamine by identifying a novel reactivity of nitrones. Due to the following two characteristics, this catalysis will significantly expand the utility of CDC reactions: (1) the molecular complexity was rapidly increased in a convergent manner starting from C(sp^3)–H bonds without preactivation; (2) the reaction proceeded under mild conditions to produce densely functionalized α-amino acid derivatives, acting as versatile synthetic intermediates for further conversions. The experimental results supported that this reaction proceeds via a "polar mechanism". Further studies, especially with regard to the improvement of stereoselectivity, are ongoing in our laboratory.

Scheme 3. Possible Catalytic Cycle



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Supporting Information Available. Experimental procedures, syntheses and characterization of all new products, and supporting data for mechanistic insights. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) (a) Lal, D.; Griller, D.; Husband, S.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6355. (b) Mailard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024.

(13) Detailed mechanism of Fenton reaction is still under debate. For recent discussion: Rachmilovic-Calis, S.; Masarwa, A.; Meyerstein, N.; Meyerstein, D.; van Ekdik, R. *Chem.—Eur. J.* **2009**, *15*, 8303 and references therein.

(14) Results of other mechanistic investigations are consistent with our proposed mechanism. See Supporting Information for details.

(15) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106.