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Functional-Group-Tolerant Catalytic Migratory Oxidative Coupling of Nitrones

Shogo Hashizume,[a, b] Kounosuke Oisaki,*[a, b] and Motomu Kanai*[a, b]

Abstract: A copper-catalyzed migratory oxidative-coupling reaction between nitrones and various ethers/amines exhibited high functional-group tolerance. Even in aqueous media, the reaction proceeded efficiently. For practical use of this catalysis, a unique sequential Huisgen cycloaddition was demonstrated. Mechanistic investigations revealed that the reaction proceeded through oxidative catalytic activation of ethers/amines to afford iminium/oxonium intermediates by concurrent dual one-electron abstractions by copper(II) and oxyl radicals.

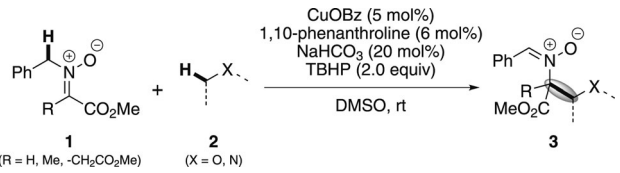
Keywords: C–C bond formation · C–H activation · copper · cycloaddition · nitrones

Introduction

New, efficient, and sustainable catalytic methods for the construction of carbon skeletons of organic molecules are essential for advancing synthetic organic chemistry. The direct catalytic transformation of unreactive and ubiquitous carbon–hydrogen bonds into carbon–carbon bonds is a rapidly emerging, powerful synthetic tool because cumbersome preactivation steps and functional-group manipulations can be omitted, thereby minimizing the number of synthetic steps and chemical waste.[1] Cross-dehydrogenative coupling (CDC) reactions, pioneered by Li among others, involve the direct oxidative formation of C–C bonds by coupling the C–H bonds of two distinct coupling partners in the presence of a terminal oxidant.[2] CDC reactions generate a C–C bond with an escalation of the molecular oxidation level, which contributes to an environmentally benign, streamlined synthesis that is endowed with all aspects of "synthetic economy" (atom economy,[3] step economy,[4] and redox economy[5]). Chemoselective CDC reactions can potentially realize a convergent coupling between the late-stage fragments of a synthesis that contain other functional groups without the need for protecting groups.[6] Furthermore, "water-tolerant" CDC[7] reactions might be extended to future applications in bio-orthogonal reactions,[8] which are used for labeling biologically relevant molecules, such as proteins, lipids, and sugars.

Many catalytic CDC reactions have been reported to date,[9] but there is still much room for improvement, especially in their extension to the potential applications described above. Moreover, the use of precious-metal catalysts and/or wasteful oxidants, harsh reaction conditions, narrow substrate scope, and low functional-group compatibility are typical drawbacks of the current CDC reactions.

We have previously reported the migratory oxidative-coupling reaction between nitrones and various ethers/amines that was promoted by an inexpensive and abundant copper catalyst and *tert*-butylhydroperoxide (TBHP) as a terminal oxidant (Scheme 1).[10] This reaction involves multiple steps:



Scheme 1. Catalytic migratory oxidative coupling of nitrones.

1) selective cleavage of two distinct C_{sp^3}–H bonds (benzylic C–H bonds in nitrones and C_α–H bonds in ethers/amines); 2) migration of the C=N double bond in nitrones; and 3) site-selective C–C bond-formation between nitrones and ethers/amines. Mild reaction conditions (room temperature and near-neutral pH) allow for the rapid synthesis of unique, unnatural α-amino-acid derivatives that contain various functional groups. The pseudoreplicated nitrone could be used as a foothold for further chemical transformations, such as [2+3] cycloaddition reactions and the nucleophilic addition of organometallic reagents.[11]

Herein, we report that this oxidative-coupling reaction can be applied to multifunctional substrates without the use of protecting groups, even in aqueous media. Mechanistic

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201200359.

studies revealed that the coupling reaction proceeded through the nucleophilic attack of nitrones to form oxonium/iminium cationic intermediates that were oxidatively generated from ethers/amines. We propose a unique two-electron-oxidation mechanism of ethers/amines through concurrent dual one-electron abstractions by catalytic copper(II) and oxyl radicals.

Results and Discussion

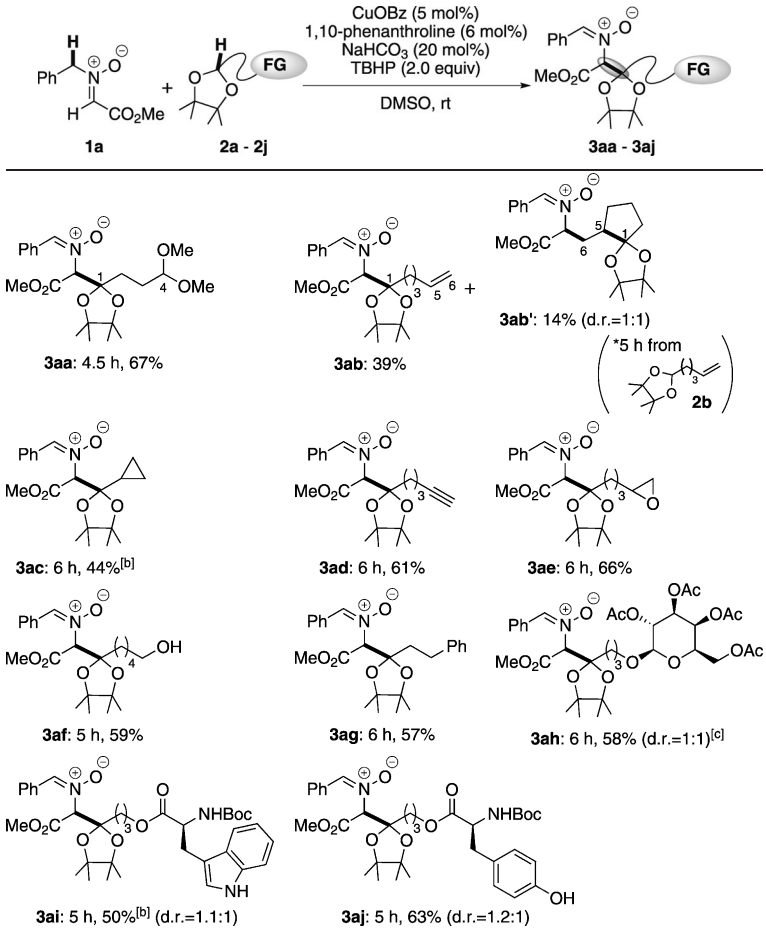
Coupling Reactions between Nitrones and Functionalized Substrates

The catalytic migratory oxidative-coupling reaction proceeds under mild conditions. This property motivated us to investigate the functional-group tolerance and chemoselectivity of this reaction. Cyclic acetals **2a**–**2g**, which possessed various functional groups, were tested as coupling partners in the reactions with nitrone **1a** (Table 1).

The reaction of compound **2a** with two distinct acetal groups proceeded exclusively at the cyclic acetal moiety (C1), thereby affording compound **3aa** as the sole coupling product. The coupling product at the dimethylacetal center (C4) was not observed in this case. The reaction of compound **2b**, which possesses a C5=C6 double bond, mainly proceeded at the acetal C1 moiety, thus affording compound **3ab**. However, in this case, compound **3ab′** was also produced as a minor product through a 5-membered cyclization reaction between the C1 and C5 atoms, followed by intermolecular C–C bond formation at the C6 position with the nitrone. The reaction of acetal **2c**, which containing a neighboring cyclopropane moiety, proceeded without ring-opening of the cyclopropane (**3ac**). These two results (the production of a mixture of compounds **3ab** and **3ab′** versus compound **3ac**) provided an important insight into the reaction mechanism (see below). Acetal **2d**, which possessed an C_{ω}≡C triple bond, afforded the expected coupling product (**3ad**); none of the potential side-reactions, such as cyclization (analogous to compound **3ab′**), [2+3] cycloaddition between the nitrone and the triple bond, Glaser coupling,[12] or alkynylation of the nitrones, were observed, although copper–acetylide species should be generated through C_{sp}–H bond activation. The reactions of acetals **2e**–**2g**, which contained an epoxide, an unprotected primary hydroxy group, and a benzylic C–H bond, respectively, proceeded in synthetically useful yields without opening of the epoxide or oxidation of the alcohol or the benzylic C–H bond. Acetal **2h**, which contained an acetylated sugar moiety, was successfully coupled with the nitrone at the predicted position to leave the sugar moiety intact. Acetals **3i** and **3j**, which were ligated with *N*-Boc-tryptophan and -tyrosine (Boc = *tert*-butoxycarbonyl), respectively, were also successful as coupling partners. Although these two amino acids contained oxidatively labile functional groups (unprotected indole and phenol groups, respectively), the desired reactions proceeded chemoselectively in moderate-to-good yield to afford their convergent products, compounds **3ai** and **3aj**, respectively.

Thus, this catalytic migratory oxidative-coupling reaction is compatible with a wide range of functional groups without the need for protecting groups. This characteristic is advan-

Table 1. Coupling reactions between nitrone **1a** and functionalized substrates **2a**–**2j**.[a]



[a] Standard reaction conditions: compound **1a** (0.3 mmol), compound **2** (1.5 mmol), CuOBz (0.015 mmol), 1,10-phenanthroline (0.018 mmol), $NaHCO_3$ (0.06 mmol), and TBHP (0.6 mmol) in DMSO (1.5 mL) at room temperature. Yields are of the isolated products unless otherwise noted. Ratios in parenthesis are the diastereomeric ratios. [b] Yield was determined by ^{1}H NMR spectroscopy of inseparable mixture of the product and the byproducts or the starting material (see the Experimental Section). [c] Reaction was conducted on a 0.15 mmol scale.

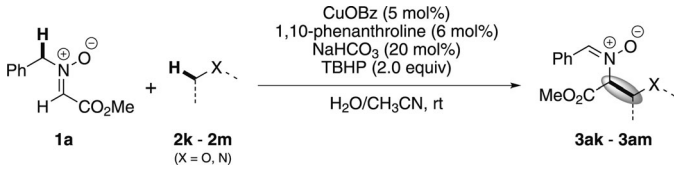
Abstract in Japanese:
銅触媒によるニトロン転移型酸化カップリング反応は優れた官能基許容性を持ち、水系溶媒中においても効率よく反応は進行した。また反応機構解析実験により、以前提唱されたカチオン中間体を経由する機構はより確実なものであると示唆された。

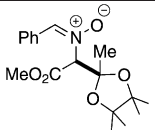
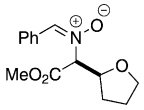
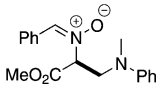
tageous for its application in late-stage convergent coupling reactions in the synthesis of complex molecule.

Catalysis under Aqueous Conditions

The direct modification of unprotected hydrophilic drug-like molecules and biomolecules in aqueous media through a C–H functionalization process will be a useful and attractive method in medicinal chemistry and chemical biology. However, catalytic C–H functionalization in aqueous media is rare, especially for C_{sp^3}–H bonds.[13] Encouraged by the excellent functional-group tolerance of our catalytic conditions, especially for an unprotected hydroxy group (Table 1, **3af**), we expected that the reaction would even proceed efficiently in aqueous media. Indeed, the yields that were produced in aqueous solvent (H_2O/CH_3CN, 1:1) were very similar to those in non-aqueous solvent (DMSO, Table 2). Therefore, this oxidative-coupling reaction of nitrones can be potentially used as a bio-orthogonal reaction.

Table 2. Coupling reactions under aqueous conditions.[a]

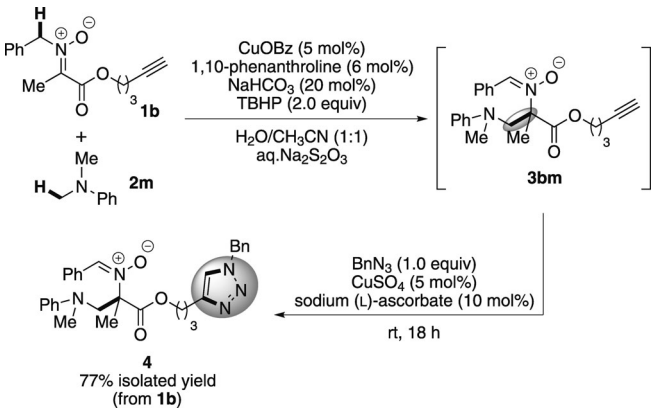


Entry	Product (**3**)		Aqueous conditions[b]		Non-aqueous conditions[b,c]	
			t [h]	Yield [%]	*t* [h]	Yield [%]
1		**3ak**	5.5	67	3.5	63
2		**3al**	6.5	51 (1.2:1)	5	65 (2.4:1)
3		**3am**	1	66	1.5	69

[a] Standard reaction conditions: compound **1a** (0.3 mmol), compound **2** (1.5 mmol), CuOBz (0.015 mmol), 1,10-phenanthroline (0.018 mmol), $NaHCO_3$ (0.06 mmol), and TBHP (0.6 mmol) in H_2O/CH_3CN (1:1, 1.5 mL) at room temperature. [b] Yield of isolated product; the ratio in parenthesis is the diastereomeric ratio (entry 2). [c] Data taken from Ref. [10].

Encouraged by these results, we planned a sequential one-pot oxidative-coupling reaction of nitrone **1b**, which contained a terminal C≡C triple bond, followed by Huisgen cycloaddition, under aqueous conditions. The copper-catalyzed Huisgen reaction is a powerful method that can couple a terminal C≡C triple bond and an azide with excellent chemoselectivity and functional-group tolerance, even under aqueous conditions.[14] Based on the compatibility of our oxidative-coupling reaction with a terminal C≡C triple bond (Table 1) we expected that a sequential combination of these two convergent steps would provide a unique method to rapidly increase the molecular size and structural complexity starting from a nitrone, an amine/ether, and an azide in aqueous media. Because both reactions are promoted by a copper catalyst, we investigated a sequential one-pot reaction of nitrone **1b**, amine **2m**, and BnN_3 (Bn = benzyl).

After the CuOBz-catalyzed oxidative coupling reaction between compounds **1b** and **2m** had been completed, BnN_3 was added into the reaction mixture to effect the Huisgen-cycloaddition reaction. The desired product (**4**) was obtained in moderate yield (56%) but about 20% of compound **3bm** remained. Considering that the Huisgen-cycloaddition reaction is promoted by a copper(I) catalyst (a reduced form), we added reductants of copper(II) prior to the addition of the azide. However, unexpectedly, the use of sodium ascorbate as a reductant lowered the yield (11%). On the other hand, the addition of an aqueous solution of $Na_2S_2O_3$, followed by the addition of a catalytic amount of $CuSO_4$, sodium ascorbate, and BnN_3, afforded triazole **4** in 77% yield (Scheme 2). This highly chemoselective sequential transformation in aqueous media is potentially useful for labeling bioactive molecules.[15]



Scheme 2. Sequential "one-pot" catalytic migratory oxidative-coupling/Huisgen-cycloaddition reactions.

Mechanistic Investigations

To elucidate the reaction mechanism, we performed various control experiments. Initially, we considered a "radical-type" mechanism (Scheme 3a) in which carbon radical **5**, which was catalytically generated from ether/amine **2**, attacks nitrone **1** to form the C–C bond; this mechanism was plausible for two reasons: First, the combination of copper(I) and hydroperoxide produces copper(II) species and a hydroxyl or alkoxyl radical (Fenton reaction).[16] This oxyl radical has sufficient activity to cleave the C_α–H bond of ether/amine **2** in a radical-type manner (hydrogen-radical abstraction). Second, nitrones are effective acceptors of carbon-radical species in general.[17] The resulting aminoxyl

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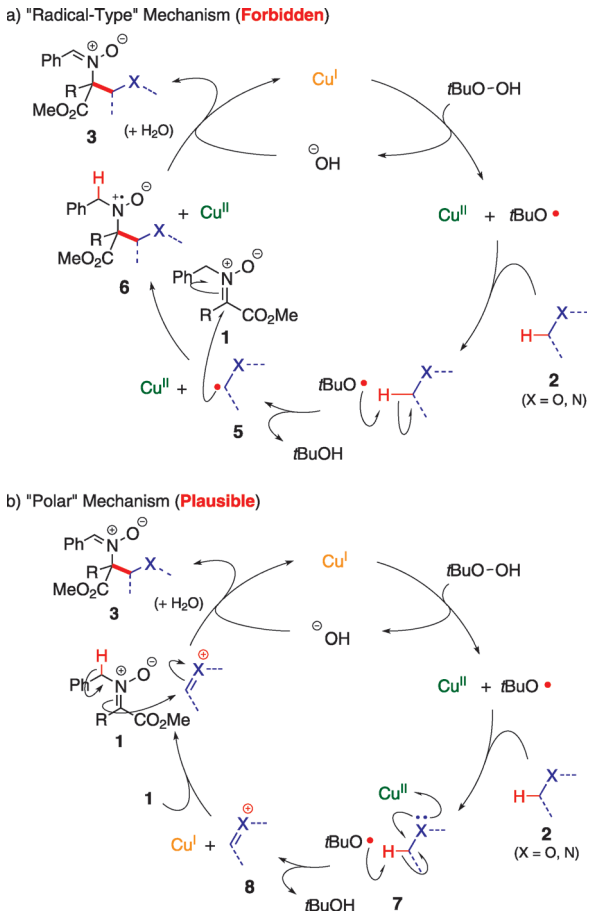
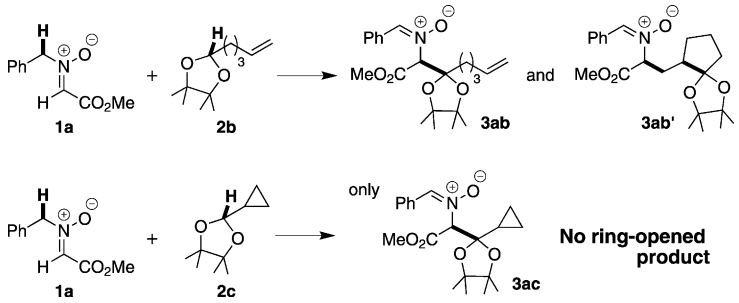


Scheme 3. a) "Radical-type" mechanism (forbidden) and b) "polar" mechanism (plausible).

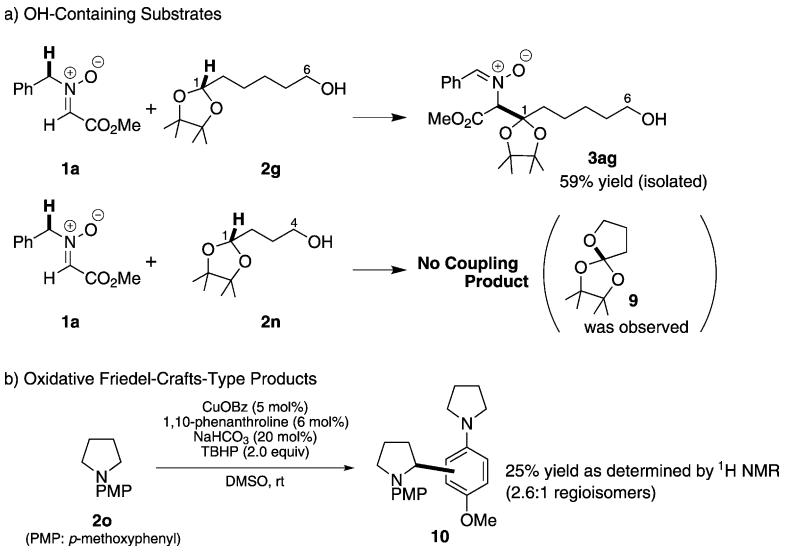
radical (**6**) that is generated through attack of carbon radical **5** on compound **1** would be oxidized by copper(II), thereby producing coupling product **3**.

However, the results of our mechanistic experiments contradicted this hypothesis. Ingold and co-workers reported rate constants of various radical-isomerization reactions that were used as "radical clocks".[18] The estimated rate constant of the ring-opening reaction of the cyclopropylmethyl radical was much larger than that of the ring-closing reaction of a 5-hexenyl radical ($k = 1.3 \times 10^8\ M^{-1}s^{-1}$ and $1.0 \times 10^5\ M^{-1}s^{-1}$, respectively, at 25 °C). As shown in Table 1, the reaction between nitrone **1a** and acetal **2b**, which contained a C5=C6 double bond, afforded a mixture of the expected product (**3ab**) and cyclized byproduct **3ab′**. In contrast, when using acetal **2c**, which contained a neighboring cyclopropane ring, the expected product (**3ac**) was obtained without any cyclopropane ring-opening side-reactions (Scheme 4). These two results strongly suggest that the reaction does not involve a carbon-radical species (**5**).



Scheme 4. Radical clock experiments.

In addition, subsequent control experiments also contradicted this "radical-type" mechanism. First, we performed the reactions of compound **1a** with acetals **2g** and **2n**, which possessed hydroxy groups at the 6- and 4-positions, respectively (Scheme 5a). As shown in Table 1 , acetal **2f** produced the expected product (**3af**). However, acetal **2n** did not produce its corresponding coupling product; instead, orthoester **9** was obtained as the major side-product. Orthoester **9** could not be produced through the α-carbon-radical intermediate (**5**) that was hypothesized in the "radical-type" mechanism. Thus, compound **9** must have been formed through intramolecular nucleophilic attack of the 4-hydroxy group onto an oxidatively generated oxonium-cation intermediate. The five-membered cyclization reaction should be faster than the intermolecular oxidative-coupling reaction. The oxidative-coupling product (**3ag**) was produced in the case of acetal **2g** because the formation of the 7-membered ring was kinetically unfavorable.



Scheme 5. Control experiments.

Second, the reaction between compound **1a** and *N*-PMP-protected amine **2o** (PMP = *para*-methoxyphenyl), led to the formation of homo-coupled byproducts (**10**). Thus, we subjected compound **2o** to the reaction conditions in the absence of nitrone **1a** and an oxidative Friedel–Crafts reaction proceeded to afford compound **10** in 25% yield (Scheme 5b). Dimeric compound **10** was presumably produced through nucleophilic attack of the electron-rich arene onto an iminium-cation intermediate. Together, cationic intermediates **8** were generated from ether/amine substrates **2** in this present catalytic cycle.

Based on these experimental results, we propose a "polar" mechanism that involves an oxonium/iminium intermediate (**8**), which is generated from the in situ oxidation of ethers/amines **2** by the copper/TBHP system (Scheme 3b), as an active species.[19,20] Subsequent nucleophilic attack of nitrone **1** onto cation **8** produces product **3**. The detailed mechanism of the oxidation step (cation-generation step) remains unclear. Considering the fact that both copper(II) and the *tert*-butoxyl radical are generated by a Fenton reaction and that these two species are generally one-electron oxidants, we hypothesize that the oxidation of compound **2** proceeds through the simultaneous radical-type cleavage of the C_α–H bond by hydroxyl or alkoxyl radicals and by one-electron oxidation from the lone pair of heteroatoms in compound **2** with a copper(II) species (Scheme 3b, **7**).[20] In this mechanism, the two-electron oxidation of ethers/amines **2** to afford oxonium/iminium intermediates (**8**) proceeds through two one-electron abstractions without generating a radical-type intermediate (a concurrent dual one-electron abstraction mechanism). This hypothesis is consistent with the current experimental data.

Conclusions

The copper-catalyzed migratory oxidative-coupling reaction between nitrones and ethers/amines exhibits remarkable functional-group tolerance. Furthermore, this reaction can be performed in aqueous media under mild conditions (at room temperature and at near-neutral pH). These two characteristics of this system are favorable for its future extension to convergent- and protecting-group-free CDC reactions, as well as for the chemical labeling of biologically relevant molecules. As a unique application, the sequential one-pot catalytic oxidative-coupling/Huisgen-cycloaddition reactions of an amine, a nitrone, and an azide were demonstrated in aqueous solvent. Mechanistic investigations strongly suggest that the polar mechanism is more plausible. The reactive cationic intermediate (oxonium/iminium cation) is likely generated through a concurrent dual one-electron-abstraction mechanism. This mechanistic foundation will be useful for the future development of synthetically useful, chemoselective oxidative-coupling reactions.

Experimental Section

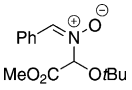
General

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-LA500, JNM-ECX500, and JNM-ECA500 spectrometers that were operating at 500 MHz (^{1}H) and 125.65 MHz (^{13}C). Chemical shifts were reported downfield of TMS ($\delta = 0$ ppm) in the ^{1}H NMR spectra and relative to the solvent as an internal reference in the ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 410 Fourier-transform IR spectrophotometer. MS (ESI) was performed on a Waters ZQ4000 spectrometer and HRMS (ESI) was performed on a JEOL JMS-T100 LC AccuTOF spectrometer. Column chromatography was performed on silica gel (Merck 60, 230–400 mesh ASTM). In general, the reactions were performed under an argon atmosphere. Reagents were prepared as described in the Supporting Information or purchased from Sigma–Aldrich, TCI (Tokyo Chemical Industry Co., Ltd.), Kanto Chemical Co., Inc., and Wako Pure Chemical Industries, Ltd. and used without purification.

*General Procedure for the Migratory Oxidative-Coupling Reactions between Nitrones and Functionalized Substrates (Table 1, for Compound **3aa**)*

Dry DMSO (1.5 mL) was added into a flame-dried test tube that was charged with CuOBz (2.8 mg, 0.015 mmol; bz = benzoyl), 1,10-phenanthroline (3.2 mg, 0.018 mmol), and $NaHCO_3$ (5.0 mg, 0.060 mmol). The mixture was stirred at room temperature until the copper salt had completely dissolved (approximately 10 min). Next, nitrone **1a** (58.0 mg, 0.30 mmol) and cyclic acetal **2a** (356 μL, 348 mg, 1.50 mmol) were added into the test tube and the inside of the test tube was flushed with argon gas. TBHP (5.5 M in *n*-decane, 109 μL, 0.60 mmol) was added to the mixture with a syringe and the mixture was stirred at room temperature for 4.5 h before being quenched with solid $Na_2S_2O_3$. The mixture was directly purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:2) to afford compound **3aa** (85.3 mg, 0.201 mmol, 67% yield). For compounds **3ac**, **3ai**, and **3aj**, the product was inseparable from the starting material (**1a**) or the byproduct (**11**; for characterization of compound **11**, see our previous report, Ref. [10a]). The yield was calculated by ^{1}H NMR spectroscopy of the mixture of compound **3** with compound **1a** or compound **11**.

General Procedure for the Coupling Reactions under Aqueous Conditions (Table 2, entry 1)



11

Distilled water and CH_3CN (0.75 mL each) were added into a dried test tube that was charged with CuOBz (2.8 mg, 0.015 mmol), 1,10-phenanthroline (3.2 mg, 0.018 mmol), and $NaHCO_3$ (5.0 mg, 0.060 mmol). The mixture was stirred at room temperature until the copper salt had completely dissolved (approximately 10 min). Next, nitrone **1a** (58.0 mg, 0.30 mmol) and acetaldehyde pinacolacetal **2k** (207 μL, 216 mg, 1.50 mmol) were added into the test tube and the inside of the test tube was flushed with argon gas. TBHP (5.5 M in *n*-decane, 109 μL, 0.60 mmol) was added into the mixture with a syringe and the mixture was stirred at room temperature for 5.5 h before being quenched with a saturated solution of aqueous $Na_2S_2O_3$. After diluting this mixture with water, the aqueous layer was extracted three times with EtOAc. The combined organic phase was dried with anhydrous Na_2SO_4, filtered, and evaporated to give a crude mixture. ^{1}H NMR spectroscopy of the crude mixture was performed to determine the diastereomeric ratio (for Table 2, entry 2). The crude mixture was purified by column chromatography on silica gel (acetone/*n*-hexane, 1:4) to afford compound **3ak** (67.2 mg, 0.200 mmol, 67% yield).

General Procedure for the Sequential One-Pot Catalytic Migratory Oxidative-Coupling/Huisgen-Cycloaddition Reactions under Aqueous Conditions (Scheme 2)

Distilled water and CH_3CN (0.75 mL each) were added into a dried test tube that was charged with CuOBz (2.8 mg, 0.015 mmol), 1,10-phenan-

throline (3.2 mg, 0.018 mmol), and $NaHCO_3$ (5.0 mg, 0.060 mmol). The mixture was stirred at room temperature until the copper salt had completely dissolved (approximately 10 min). Next, nitrone **1b** (77.8 mg, 0.30 mmol) and *N*,*N*-dimethylaniline **2m** (189 μL, 182 mg, 1.50 mmol) were added into the test tube. Finally, TBHP (5.5 M in *n*-decane, 109 μL, 0.60 mmol) was added with a syringe and the reaction mixture was stirred at room temperature for 5 h. The oxidative-coupling reaction was quenched with a couple of drops of saturated solution of aqueous $Na_2S_2O_3$ to quench the TBHP. After stirring for several minutes, $CuSO_4$ (2.4 mg, 0.015 mmol) and sodium ascorbate (5.9 mg, 0.030 mmol) were added and the inside of the test tube was again flushed with argon. Finally, benzyl azide (37.3 μL, 0.30 mmol) was added with a syringe. The reaction mixture was stirred at room temperature for 18 h and the Huisgen reaction was quenched with a saturated solution of aqueous NH_4Cl. The resulting mixture was extracted three times with EtOAc. The combined organic layer was dried with anhydrous Na_2SO_4, filtered, and evaporated to give a crude mixture. The crude mixture was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:1 to 2:1) to afford compound **4** (119 mg, 0.233 mmol, 77% yield).

Acknowledgements

This work was supported by a Grant in-Aid for Young Scientist B from the JSPS (K.O.) and by ERATO from the JST (M.K.)

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Received: April 20, 2012
Published online: July 4, 2012

