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Catalytic Migratory Oxidative Coupling of Nitrones through an Outer-Sphere C(sp^3)-H Activation Process

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ABSTRACT: Outer-sphere redox catalysis is key to efficient C-H activation, which has attracted increased interest in organic chemistry. In this account, we describe a Cu^I-catalyzed oxidative coupling between nitrones and various ethers or amines as an example. Predictable site-selective C-C bond formation was achieved through activation of the C-H bonds in each coupling partner and the migration of a C-N double bond. Mechanistic studies strongly suggested that the reaction proceeded via an oxonium/iminium cation species as the key intermediate. The mechanistic information allows for future extension of outer-sphere redox catalysis. **DOI 10.1002/tcr.201100024**

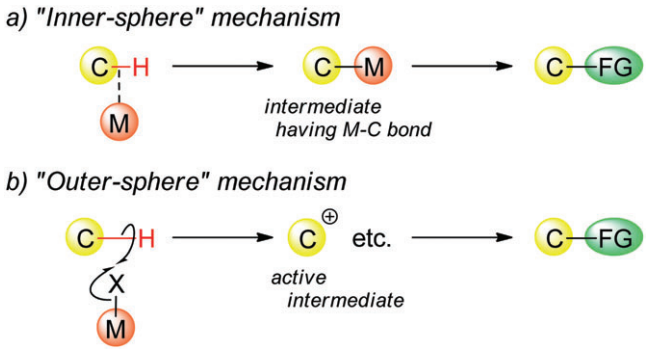
Keywords: oxidative C-C coupling; C-H activation; copper catalysis; nitrones; outer-sphere catalysis

Introduction

A novel methodology for carbon-carbon bond construction is currently in high demand in organic chemistry. Catalytic C-C bond formation through the activation of unreactive and ubiquitous C-H bonds is quite valuable,[1,2] because cumbersome pre-functionalizations of substrates and the generation of unfavorable chemical waste can be minimized, which thereby contributes to efficient synthesis and green chemistry.

Several catalytic C-H activation methods have been reported. Recent significant advances rely mainly on C-H activation through an "inner-sphere mechanism"[1b,3] (Scheme 1a). This mode of C-H activation allows for the generation of reactive organometallic intermediates. The formation of a metal-carbon bond is, however, thermodynamically and entropically unfavorable, and often requires harsh conditions, precious and expensive second- or third-row transition metals, and/or directing groups. In particular, the activation of sterically hindered C-H bonds (secondary or tertiary C(sp^3)-H bonds) through an inner-sphere mechanism is severely limited. Moreover, the resulting organometallic intermediates containing highly hindered carbon-metal bonds are generally not stable and, once formed, are vulnerable to β-hydride elimination. These inherent characteristics hamper the application of catalytic inner-sphere C(sp^3)-H activation for complex molecule synthesis. An alternative catalysis proceeding through an "outer-sphere mechanism",[1b,3] however, is a promising approach (Scheme 1b). In this type of catalysis, C-H bond cleavage occurs without the formation of a covalent bond between the substrate and metal center. This characteristic of an outer-sphere mechanism is especially favorable for C-H activation at hindered points.

Herein, we describe a Cu^I-catalyzed oxidative coupling between nitrones and various ethers or amines. This reaction is



Scheme 1. C-H activation through an "inner-sphere mechanism" and an "outer-sphere mechanism".[1b]

among the recently emerging cross-dehydrogenative coupling (CDC) reactions pioneered by Li et al.[4] Our reaction, however, significantly advances the CDC field because it proceeds under mild conditions in a convergent manner and affords synthetically useful multifunctional products containing sensitive chemical species, such as nitrones. The substrate scope and mechanistic studies strongly suggest that our reaction proceeds through a unique outer-sphere redox process, involving the catalytic generation of carbocation species from ethers and amines. This reaction is an important key to developing new catalytic late-stage fragment couplings to realize ideal and streamlined convergent syntheses through C(sp^3)-H activation.

Catalytic Migratory Oxidative Coupling of Nitrones

Recently, we developed a novel catalytic CDC reaction between nitrones **1** and various ethers or amines **2**, which are coupled in an oxidative and site-selective manner to produce products **3** possessing double bond-migrated nitrones.[5] Nitrones are easily accessible, densely functionalized, and thus useful units for some chemical transformations, but their use as

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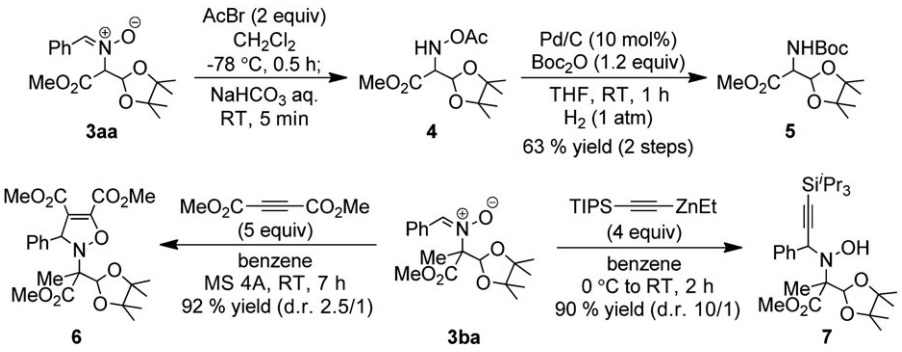

Scheme 2. Conversions of products **3**.

substrates is relatively limited by their instability under harsh conditions.[6] Our reaction proceeds smoothly even at room temperature in the presence of an inexpensive and abundant copper catalyst and *tert*-butylhydroperoxide (TBHP) as a terminal oxidant.[7] Furthermore, the substrate scope is quite broad compared with previously reported CDC reactions.

Optimization studies revealed that product **3** was obtained in the highest yield using a copper benzoate (CuOBz)–1,10-phenanthroline (1,10-phen) catalyst and a base co-catalyst ($NaHCO_3$) in DMSO as the solvent. Under the optimized conditions, various substrates were tested as a nitrone coupling partner (Table 1). Cyclic acetals **2a** and **2b** were coupled with nitrone **1a**-**c** in moderate to good yield (entries 1–5). In particular, highly congested contiguous tetrasubstituted carbon centers could be constructed in this catalysis (entry 5). Simple cyclic ethers such as THF **2c**, 1,4-dioxane **2d**, and oxepane **2e**, were also good coupling partners (entries 6–8). Direct introduction of a functional group into oxepane leads to a novel method for the functionalization of medium-sized ether rings, which frequently appear in bioactive compounds.[8] Cyclopentylmethyl ether **2f** was coupled at two different positions, producing **3af** as the major product (entry 9). Oxetane rings have recently attracted interest for medicinal chemistry applications.[9] Direct functionalization of strained oxetane ring **2g** was accomplished in the coupling with nitrone **1b**, although subsequent ring opening of the product occurred when coupled with nitrone **1a** (entries 10 and 11). A 1,2-diol moiety **2h** was introduced in the same manner (entry 12). This catalysis was also applicable to cyclic and acyclic amines **2i**-**l** (entries 13–16). PMP-protected morpholine **2i** with C-H bonds adjacent to the oxygen atom, was selectively coupled to nitrogen at α-position (entry 13). Generally, the diastereoselectivity was not high, and its improvement is one of our current focuses.

Another unique feature of this reaction is the pseudo-replication of the nitrone functionality. This feature motivated us to attempt further product transformations (Scheme 2).[6] Hydrolysis of the benzylidene group after treatment with acetyl bromide followed by hydrogenative cleavage of the N-O bond produced protected unnatural α-amino acid **5**, which is a potentially valuable building unit for medicinal chemistry. [2+3]-Dipolar cycloaddition is a common transformation of nitrones. We treated product **3ba** with an electron-deficient

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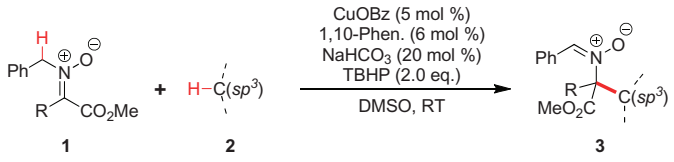
Table 1. Catalytic migratory oxidative coupling between nitrones **1** and ethers/amines **2**.[a]



1 **2** **3**

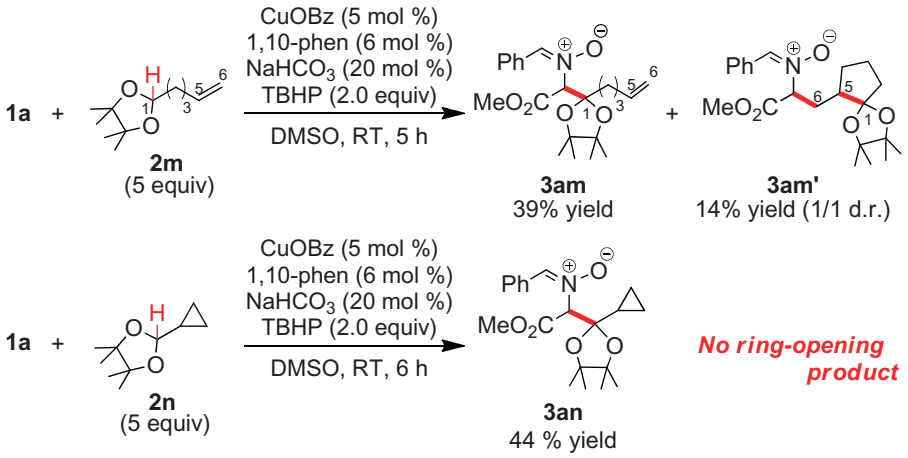
entry	R (**1**)	**2**	time [h]	products **3**	yield[b] [%] (d.r.[c])
1	H (**1a**)	**2a**	3.5	**3aa**	76[g]
2	Me (**1b**)		0.5	**3ab**	75
3[d]	-CH_2CO_2Me (**1c**)		2.5	**3ac**	41[g]
4	**1a**	**2b**	3.5	**3ba**	63
5	**1b**		4.5	**3bb**	44
6	**1a**	**2c**	5	**3ac**	65 (2.4/1)
7[e]	**1a**	**2d**	6	**3ad**	46 (1.5/1)
8	**1a**	**2e**	5.5	**3ae**	56[g] (1/1)
9[e]	**1a**	**2f**	5.5	**3af** / **3af'**	**3af**: 36[g] **3af'**: 15[g]
10	**1a**	**2g**	9	**3ag**	38
11	**1b**		4.5	**3bg**	56 (1/1)
12[e,f]	**1a**	**2h**	6	**3ah**	49[g] (2.0/1)
13	**1a**	**2i**	1.5	**3ai**	69
14	**1a**	**2j** (n = 1)	2	**3aj**	89 (1.1/1)
15	**1a**	**2k** (n = 2)	1	**3ak**	82 (1/1)
16	**1a**	**2l**	1.5	**3al**	69

[a]Standard reaction conditions; **1** (0.3 mmol), **2** (1.5 mmol), CuOBz (0.015 mmol), 1,10-phen. (0.018 mmol), $NaHCO_3$ (0.06 mmol), TBHP (0.6 mmol), DMSO (1.5 mL). [b]Isolated yield. [c]Determined by ^1H NMR of diastereo mixtures. [d]Without $NaHCO_3$. [e]With 10 equiv of **2**. [f]With 3 equiv of TBHP. [g]Calculated by ^1H NMR. PMP = *p*-methoxyphenyl.

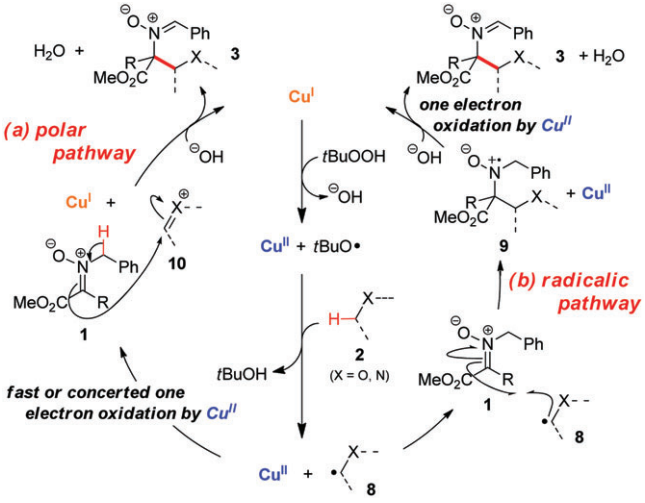
alkyne to produce isoxazoline **6** in excellent yield. Nitrones can be also used as electrophiles against several organometallic reagents. Nucleophilic addition of zinc acetylide to product **3ba** produced propargyl hydroxylamine **7** in excellent yield with good diastereoselectivity.

Mechanistic Insights

To gain insight into the mechanism, "radical clock" experiments were performed,[10] as shown in Scheme 3. Cyclic acetal **2m** possessing a 5-pentenyl group mainly coupled with nitrone **1a** directly at the α-carbon atom of the acetal. Ring-closure concomitantly occurred, however, to produce cyclopentane derivative **3am'** as a minor product. In contrast, cyclic acetal **2n** possessing a cyclopropyl group coupled directly at the α-carbon atom of the acetal without any ring-opening. The results conflict with the "radicalic mechanism," which we initially considered based on the ability of nitrones to function as good acceptors for carbon radicals[11] (Scheme 4, path b). The estimated rate constant of the cyclopropylmethyl radical ring opening is much greater than that of the 5-hexenyl radical ring closing processes ($k = 1.3 \times 10^8$ M^{-1} s^{-1} and 1.0×10^5 M^{-1} s^{-1} at 25 °C, respectively).[10a,b] An alternative rationalization of the results is the "polar mechanism," in which the reaction proceeds via a carbocation intermediate **10** generated from heterocycles **2** (Scheme 4, path a).[12] Carbocation **10** is produced through the oxidation of α–C-H bond to oxygen/nitrogen in heterocycles **2**, which is then attacked by nitrone **1** in a nucleophilic manner. Although the mechanism of carbocation gen-



Scheme 3. Radical clock experiments.



Scheme 4. Proposed catalytic cycle.

eration remains unclear, the initial step should be radicalic C-H cleavage by an oxy radical, because the reaction to produce an oxy radical from hydroperoxide and Cu^{I} is classically known as the Fenton reaction.[13] Successful fast one-electron oxidation by concomitantly produced Cu^{II} species would produce the carbocation.

The proposed mechanism of oxidative generation of a carbocation intermediate, in which two chemical species (oxy radical and Cu^{II}) work concertedly, is consistent with the outer-sphere mechanism. Diastereoselectivity is generally not high, even with a copper catalyst possessing a ligand, suggesting that the reaction proceeds away from the metal center. Furthermore, a tertiary C-H bond is more reactive than primary C-H bonds as shown in case of cyclopentylmethyl ether **2f** (Table 1, entry 9). These fundamental mechanisms imply that the present catalysis can be extended to other reaction patterns that involve cationic intermediates generated through an outer-sphere C-H activation mechanism.

Summary and Perspective

We developed a new CDC reaction using nitrones as substrates through the activation of various C(sp^3)-H bonds adjacent to oxygen or nitrogen atoms. The mild reaction conditions allow us to use functional group enriched molecules. We believe that the unique mechanism initiated from radicalic C-H cleavage with cooperation of two kinds of one-electron redox processes is a key factor that enables orthogonal transformation against existing polar functional groups. From this viewpoint, the chemoselectivity to generate carbocations can be also predicted in parallel with the selectivity of the initial radicalic C-H bond cleavage.

As we partially discuss in the scope and limitations, the concept of outer-sphere catalysis is potentially applicable to chemoselective activation of a wide range of C(sp^3)-H activations at hindered points. CDC reactions through outer-sphere C-H activation will realize convergent C-C bond formation with a linear escalation of the oxidation state between large functionalized fragments,[14] which enables us to propose retrosyntheses with disconnections of unreactive C(sp^3)-C bonds at a late stage of synthesis. This will not only maximize the efficiency and convergence of the synthetic route, but also offers additional freedom and diversity in complex molecule synthesis. On the other hand, however, stereoselectivity will require a new concept in the outer-sphere catalysis, because the reactive species are separated from the metal catalyst. This topic is part of our ongoing research in this field.

The use of molecular oxygen as a terminal oxidant is another possible approach toward the "genuine" green cataly-

sis. Although some CDC reactions using molecular oxygen have been reported,[15] the substrate scopes are limited to compounds possessing highly activated C(sp^3)-H bonds, such as benzylic C-H bonds. Broadening the substrate scope based on a unique catalyst design is an attractive strategy and another area of our current research focus.

Acknowledgements

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