Radical Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201607223
Internationale Ausgabe: DOI: 10.1002/anie.201607223

Nitroxyl-Radical-Catalyzed Oxidative Coupling of Amides with Silylated Nucleophiles through N-Halogenation

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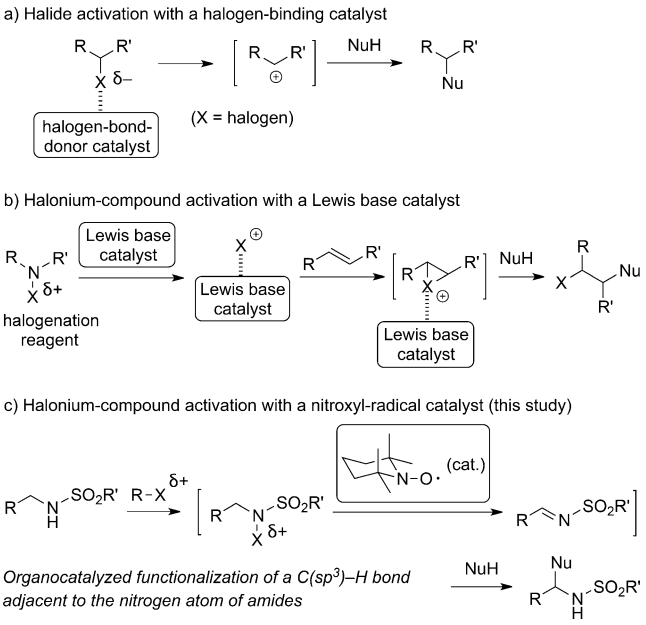
Abstract: *A nitroxyl-radical-catalyzed oxidative coupling reaction between amines with an N-protecting electron-withdrawing group (EWG) and silylated nucleophiles was developed to furnish coupling products in high yields, thus opening up new frontiers in organocatalyzed reactions. This reaction proceeded through the activation of N-halogenated amides by a nitroxyl-radical catalyst, followed by carbon–carbon coupling with silylated nucleophiles. Studies of the reaction mechanism indicated that the nitroxyl radical activates N-halogenated amides, which are generated from N-EWG-protected amides and a halogenation reagent, to give the corresponding imines.*

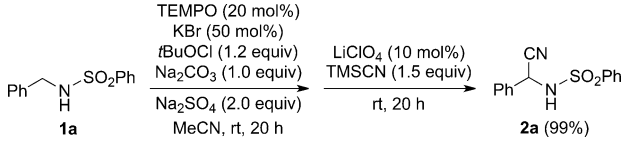
The organocatalytic activation of halogen-containing substrates by the dissociation of a halogen atom has received much attention. Halide-binding catalysts have emerged, including hydrogen-bond catalysts, such as thiourea[1] and oligotriazole catalysts,[2] and halogen-bond catalysts, which are exemplified by electron-deficient iodine catalysts.[3] These catalysts recognize an electrically negative halogen atom through a halogen-bond interaction between the halogen atom and the halogen-bond-donor groups on the catalyst to generate highly reactive cationic species (Scheme 1 a). Lewis base organocatalysts that recognize halonium ions (X^+) have also been designed that activate a halogenation reagent to promote chemoselective halogenation (Scheme 1 b).[4] On the other hand, nitroxyl radicals bearing an unpaired electron, such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), have been used to activate some transformations.[5] However, nitroxyl-radical-catalyzed transformations have narrow scope in spite of the high activity of the nitroxyl moiety.[6] Among them, it is noteworthy that nitroxyl radical is oxidized into oxoammonium cation through one-electron oxidation with NaOCl for the oxidation of alcohols (Anelli method).[7] Otherwise, studies of the association between nitroxyl radicals and halogen compounds have been limited to physicochemical characterization and crystal engineering,[8] and there have been no reports of organoradical-catalyzed reactions of halogen compounds with a nitroxyl-radical catalyst.

We anticipated that a nitroxyl radical could be used as an organocatalyst for the oxidation of amides to imines N-protected with an electron-withdrawing group (EWG) through the dissociation of the electropositive halogen atom on N-halogenated amides (Scheme 1 c). The catalytic oxidative coupling of amines through the oxidation of the $C(sp^3)$–H bond adjacent to the nitrogen atom is an elegant method for amine functionalization, and some ingenious methods have been developed.[9] In contrast, the development of catalytic systems for such an oxidation of amides is challenging, because the nitrogen atom of an amide has much lower electron density than that of an amine. Accordingly, to the best of our knowledge, there are no known examples of the catalytic oxidation of amides to *N*-EWG-protected imines, even though the protected nitrogen units are very useful because the protecting group can be cleaved readily under mild conditions. Herein we report a nitroxyl-radical-catalyzed oxidative coupling reaction of amides with silylated nucleophiles that proceeds by the transformation of N-halogenated amides, which are generated from amides with a halogenation reagent in situ, into imines.



Scheme 1. Activation of halogen-containing compounds with organocatalysts.

First, we chose the α-cyanation of *N*-benzylbenzenesulfonamide (**1a**) as a model reaction and screened for oxidants, bases, and additives in the presence of TEMPO as the catalyst in MeCN (see Table S1 in the Supporting Information). The optimum reaction conditions were found to include **1a**, TEMPO (20 mol%), KBr (50 mol%), *t*BuOCl (1.2 equiv), and Na_2CO_3 (1.0 equiv) in the presence of Na_2SO_4 (2.0 equiv) as a desiccant in MeCN for 20 h, followed by the addition $LiClO_4$ (10 mol%) as a Lewis acid catalyst[10] and TMSCN (1.5 equiv). Under these conditions, the α-cyano adduct **2a** was obtained in 99% yield (Scheme 2).



Scheme 2. TEMPO-catalyzed α-cyanation of sulfonamide **1a** with TMSCN. TMS = trimethylsilyl.

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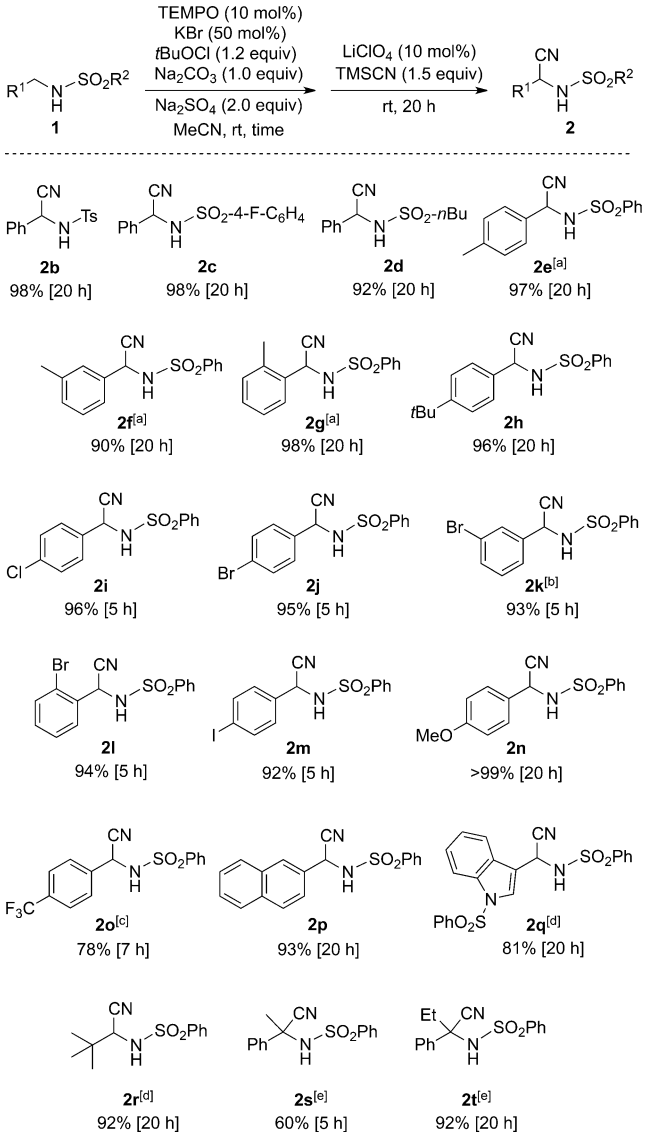
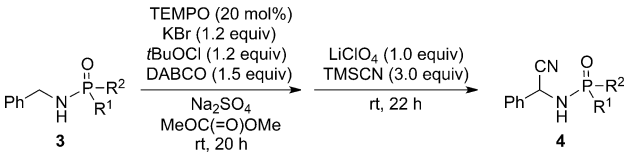
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201607223.

To explore the scope of the TEMPO-catalyzed α-cyanation, we examined a range of sulfonamides **1** under the optimum conditions (Scheme 3). The reaction of substrates bearing various sulfonamide groups (substrates **1b–d**) and benzyl groups with substituents on the aromatic ring (substrates **1e–p**) proceeded successfully, and the corresponding α-cyano adducts **2b–p** were obtained in high yields (78 to >99%). The N-heterocycle-containing sulfonamide **1q** and sulfonamide **1r** with an N-aliphatic group were also converted into the desired products **2q** and **2r** in high yields of 81 and 92%. The oxidative α-cyanation of sulfonamides **1s** and **1t** with a secondary N-substituent provided α-cyano adducts **2s** and **2t** bearing a quaternary carbon center in 60 and 92% yield, respectively, when AZADO[11] was used instead of TEMPO as the catalyst.



Scheme 3. TEMPO-catalyzed α-cyanation of sulfonamides **1** with TMSCN. [a] TEMPO (20 mol%) was used. [b] KBr (1.2 equiv) was used. [c] The reaction was carried out at 0°C. [d] TEMPO (30 mol%) was used. [e] KBr (1.2 equiv) and AZADO (20 mol%) were used. AZADO = 2-azaadamantane-*N*-oxyl, Ts = *p*-toluenesulfonyl.

We examined the nitroxyl-radical-catalyzed oxidative α-cyanation of *N*-benzylphosphinamides **3** and found that the symmetric phosphinamide **3a** and asymmetric phosphinamide **3b** could be converted into the desired products **4a** and **4b** (d.r. 64:36) in 97 and 90% yield, respectively, under modified reaction conditions, whereas under the optimum conditions for sulfonamides **1**, the reaction did not proceed at all (Scheme 4).[12] Fortunately, the use of *tert*-butylphenylphosphinamide **3c** in the oxidative coupling reaction resulted in the formation of α-cyano product **4c** with good diastereoselectivity (d.r. 80:20).

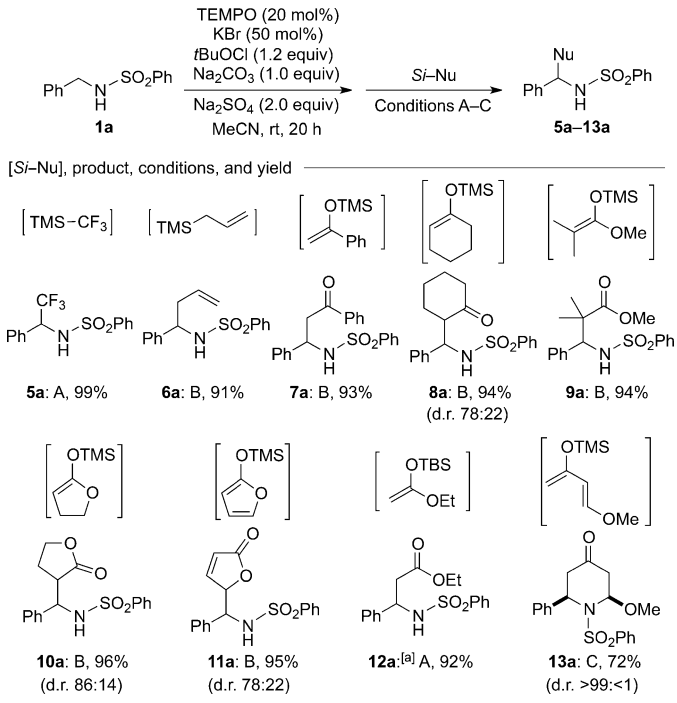


Product (**4**)	Yield [%]
$R^1 = R^2 =$ Ph (**4a**)	97
$R^1 =$ Me, $R^2 = i$Pr$_3$C$_6$H$_2$ (**4b**)	90[a] (d.r. 64:36)
$R^1 = t$Bu, $R^2 =$ Ph (**4c**)	71 (d.r. 80:20)

Scheme 4. TEMPO-catalyzed α-cyanation of *N*-benzylphosphinamides **3** with TMSCN. [a] The second step was carried out in CH_2Cl_2 instead of dimethyl carbonate. DABCO = 1,4-diazabicyclo[2.2.2]octane.

We investigated the nitroxyl-radical-catalyzed oxidative coupling reaction of sulfonamide **1a** with various silylated nucleophiles (Scheme 5). The oxidative coupling of **1a** with $TMSCF_3$ and allyltrimethylsilane as nucleophiles proceeded smoothly to give the corresponding adducts **5a** and **6a** in high yields; the reactions involved trifluoromethylation with a catalytic amount of LiOAc[13] and allylation[14] with TMSOTf. A Mukaiyama-type reaction[15] and a vinylogous reaction[16] with silyl enol ethers and ketene silyl acetals also gave coupling products **7a–11a** in high yields (93–96%). The reaction of sterically hindered ethyl *tert*-butyldimethylsilyl ketene acetal was also promoted by a Lewis base catalyst to give the desired product **12a** in 92% yield. Whereas the aza-Diels–Alder reaction of imines with the Danishefsky diene is generally used for the formation of dihydropyridones,[17] the present oxidative coupling reaction with the catalyst TBAI[18] provided the unprecedented 2-methoxy-4-piperidinone derivative **13a** in 72% yield.

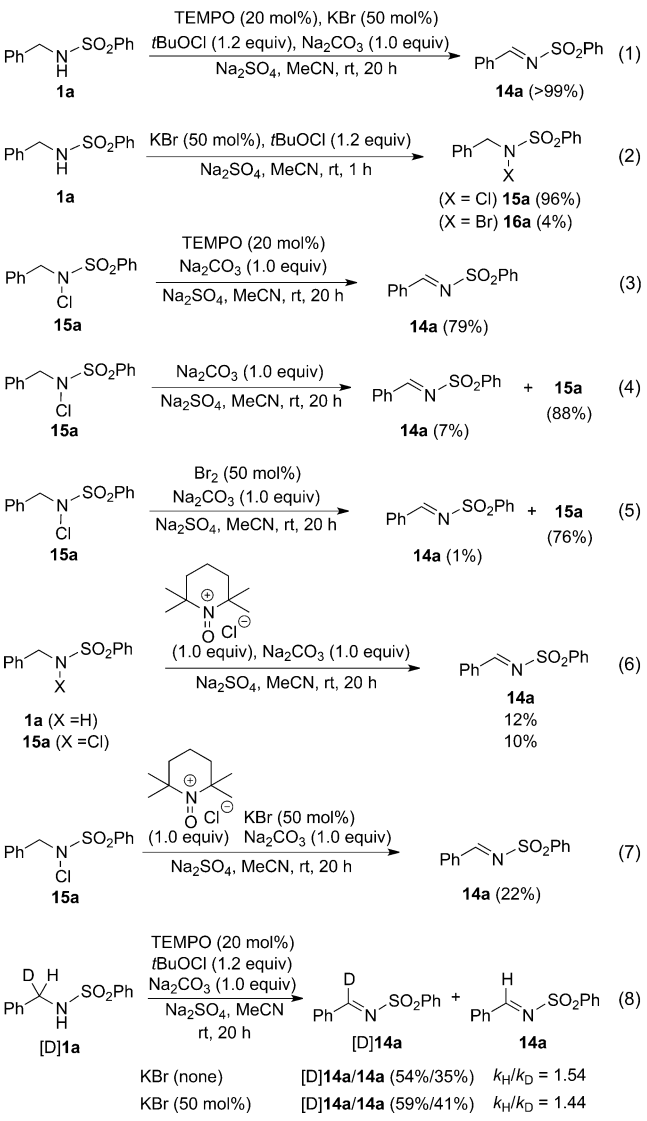
To determine the reaction mechanism of the nitroxyl-radical-catalyzed oxidative coupling reaction, we conducted a number of supporting experiments (Scheme 6). The reaction of **1a** without a silylated nucleophile under the present conditions provided the corresponding aldimine **14a** in quantitative yield [Eq. (1)]. Furthermore, the treatment of **1a** with KBr and *t*BuOCl readily furnished N-halogenated products **15a** and **16a** [Eq. (2)], and **15a** was oxidized to aldimine **14a** with a catalytic amount of TEMPO under basic conditions [Eq. (3)]. However, the attempted transformation of **15a** into **14a** without TEMPO hardly proceeded at all [Eq. (4)]. The oxidation of **15a** with Br_2 under basic conditions provided almost none of the corresponding imine **14a** [Eq. (5)]. These results indicate that TEMPO is essential



Scheme 5. TEMPO-catalyzed α-substitution reaction of sulfonamide **1a** with silylated nucleophiles. Reaction conditions for the second step: Conditions A: LiOAc (20 mol%), *Si*–Nu (1.5 equiv), DMF, −20 °C, 17 h; conditions B: TMSOTf (1.1 equiv), *Si*–Nu (1.5 equiv), CH_2Cl_2, −78 °C, 48 h; conditions C: TBAI (20 mol%), *Si*–Nu (3.0 equiv), MeCN, room temperature, 22 h. [a] The reaction was carried out at room temperature. DMF = *N*,*N*-dimethylformamide, TBAI = tetrabutylammonium iodide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

to promote the transformation of N-halogenated amides into imines. The use of an oxoammonium chloride in the reaction of **1a** or **15a** produced a small amount of **14a**, thus indicating that the TEMPO catalyst promoted the present oxidation via an active species different from that involved in the TEMPO-catalyzed oxidation of alcohols[6,7,19] and oxidative transformations with oxoammonium salts[9g,h,20] [Eq. (6)]. The presence of KBr in the reaction with oxoammonium chloride did not affect the oxidation of **15a** [Eq. (7)]. Moreover, the deuterium kinetic isotope effect on the TEMPO-catalyzed oxidation was evaluated with substrate [D]**1a** labeled with deuterium at the benzylic position. Reactions in the presence or absence of KBr showed small k_H/k_D values of 1.54 and 1.44, respectively, which indicate that the abstraction of a benzylic hydrogen atom is not the rate-determining step in the oxidation of amides [Eq. (8)].[19,20]

To confirm the further details of the oxidation of **15a** with the nitroxyl-radical catalyst, we determined the time course of the reaction of **15a** and TEMPO in a 5:1 molar ratio in MeCN under basic conditions by Raman spectroscopic analysis[21] (Figure 1). After 1.5 h, peaks assignable to oxoammonium chloride were observed (553.8 and 695.7 cm^{-1}) together with those of **14a** (541.2 and 797.4 cm^{-1}), but peaks attributable to the reduced form of TEMPO (TEMPOH; 669.6 and 782.1 cm^{-1}) were not detected at all (see the Supporting Information).



Scheme 6. Mechanistic study of the nitroxyl-radical-catalyzed oxidative coupling reaction.

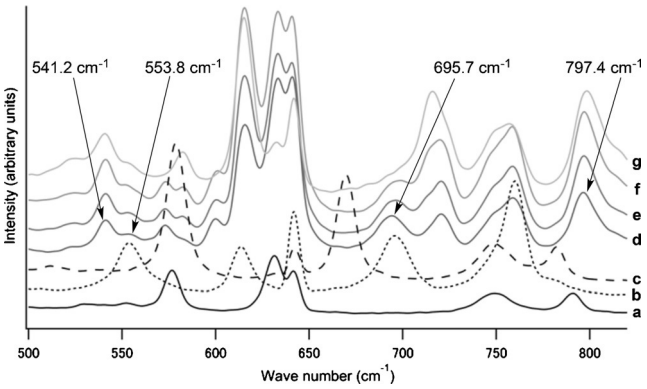
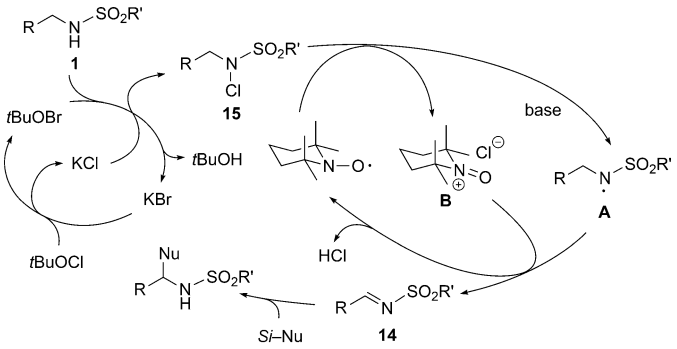


Figure 1. Time-course Raman spectroscopy of a solution of **15a** and TEMPO (5:1) in MeCN in the presence of Na_2CO_3. a) TEMPO in MeCN; b) oxoammonium chloride in MeCN; c) TEMPOH in MeCN; d–f) time-course spectra after 1.5 h (d), 3 h (e), 5 h (f), and 22 h (g).

On the basis of these mechanistic experiments, we propose a reaction mechanism for the nitroxyl-radical-catalyzed oxidative coupling reaction of amides with silylated nucleophiles (Scheme 7). Sulfonamide **1** are readily con-



Scheme 7. Plausible reaction mechanism.

verted into N-halogenated compounds **15** by halogenation of the amide group with *t*BuOCl and KBr. Notably, KBr forms the more powerful oxidant *t*BuOBr[22] in situ to promote the halogenation of **1**. Subsequently, dissociation of the chlorine atom in **15** by the nitroxyl-radical catalyst generates the corresponding amidyl-radical intermediate **A** together with oxoammonium chloride **B**, which immediately oxidizes **A** to an EWG-protected aldimine **14** with the simultaneous regeneration of the nitroxyl radical under basic conditions. The final C–C bond-forming reaction of **14** with a silylated nucleophile proceeds under the corresponding optimum conditions.

In conclusion, we have developed a nitroxyl-radical-catalyzed oxidative coupling reaction of *N*-EWG-protected amines (amides) with silylated nucleophiles by the N-halogenation of *N*-EWG-protected amides with a halogenation reagent in situ. The transformation gave the desired coupling products in high yields. We believe that nitroxyl radicals could be used as organocatalysts in various transformations based on the activation of halogen compounds. The development of further nitroxyl-radical-catalyzed reactions is under way in our laboratory.

Acknowledgements

Financial support from the Ministry of Education, Culture, Sports, Science and Technology of Japan in the form of a Grant-in-Aid for Scientific Research (No.20550033; K.M.) and from the Naito Foundation (K.M.) is gratefully acknowledged.

Keywords: amides · C–C coupling · nitroxyl radicals · organocatalysis · oxidation

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 14546–14551
Angew. Chem. **2016**, *128*, 14766–14771

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Received: July 26, 2016
Revised: August 19, 2016
Published online: September 29, 2016

