JOC The Journal of Organic Chemistry

Article

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Iodide-Catalyzed Synthesis of *N*-Nitrosamines via C−N Cleavage of Nitromethane

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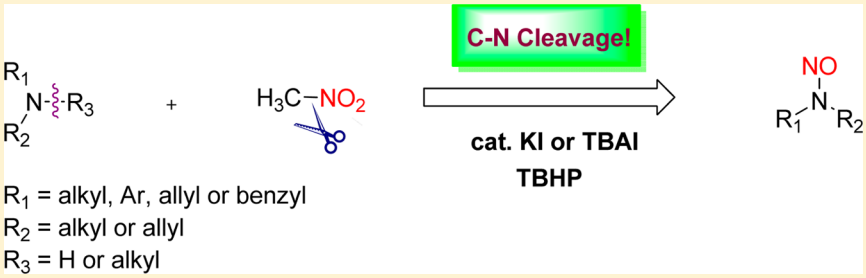
Supporting Information



ABSTRACT: An iodide-catalyzed process to synthesize *N*-nitrosamines has been developed using TBHP as the oxidant. The mild catalytic system succeeded in cleaving the carbon−nitrogen bond in nitromethane. This methodology uses commercially available, inexpensive catalysts and oxidants and has a wide substrate scope and operational simplicity.

INTRODUCTION

Transition-metal-catalyzed C−N cleavage is a synthetically significant process and has been extensively studied. A variety of transition metals, including Pd,[1a−e] Ru,[1f−i] Rh,[1j] Cu,[1k−m] Fe,[1n,o] Co,[1p] Ni,[1q,r] Nb,[1s] Ta,[1t] Zr,[1u] and Mo,[1v] have been shown to catalyze this process. Notably, Kakiuchi[1g,h] and co-workers reported the first catalytically unreactive aryl C−N cleavage for C−C bond formation on a ruthenium center. It is worth pointing out that the use of transition metals has some inherent drawbacks, such as cost and toxicity, though it is a powerful means of effecting organic reactions.

C−N bonds have also been cleaved under transition-metal-free conditions, such as photochemistry,[2a−c] acids,[2d] bases,[2e−g] strong oxidants,[2h−j] reducing reagents,[2i,k] and other agents (CsF[2l]). Recently, Tian developed a series of sulfonyl-activated benzylic C−N cleavages with stoichiometric agents, such as LDA[2e] and *n*-BuLi.[2f] Unfortunately, stoichiometric bond-breaking agents are usually required in most cases. Therefore, a mild, transition-metal-free catalytic system to break C−N bonds is highly desirable.

Nitrosation chemistry has drawn continuing interest from mechanistic organic and biological chemists.[3] It has found many applications in synthetic chemistry.[4] The most general reagent for the nitrosation of amines is nitrous acid, generated in situ from sodium nitrite and a strong acid.[5] In addition, alkyl nitrites,[6] nitrogen oxides,[7] Fremy's salt,[8] trichloronitromethane,[9] nitrosonium tetrafluoroborate,[10] oxyhyponitrite,[11] and bis(triphenylphosphine)nitrogen(1+) nitrite[12] have also been developed as efficient nitrosating agents. Recently, Hou and co-workers reported the synthesis of *N*-nitrosamines using nitromethane as the source of the nitroso group.[2j] Unfortunately, some shortcomings in this method were revealed, as it required the expensive *o*-iodoxybenzoic acid (IBX) as an oxidant, and the substrates were limited to aromatic amines. Continuing our recent studies in TBAI (tetrabutylammonium iodide)-catalyzed chemical transformation,[13a−f] we have developed an iodide-catalyzed process to synthesize *N*-nitrosamines using TBHP, which has the advantages of using a green oxidant, a wide substrate scope, and mild reaction conditions.

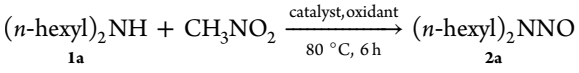
RESULTS AND DISCUSSION

At the beginning, we explored an iodide-catalyzed process to synthesize *N*-nitrosamines with secondary aliphatic amines. A mixture of dihexylamine **1a**, KI (5 mol %), and TBHP (1.5 equiv, 70% aqueous) in nitromethane at 80 °C for 6 h gave the desired product **2a** in 85% yield (Table 1, entry 1). When other oxidants were used, no **2a** was detected (Table 1, entries 2−5). Replacing KI with either KBr or KCl halted the formation of *N*-nitrosamines (entries 6 and 7). No reaction occurred in the absence of KI or TBHP (entries 8 and 9). A comparable yield was achieved when TBAI was used as the catalyst (entry 12). It is worth noting that a longer time did not improve the yield of the reaction (entry 13). This reaction was also carried out in water, leading to the desired product in low (20%) yield (entry 14).[13x,w]

Encouraged by these results, we applied this methodology to a series of secondary aliphatic amines as shown in Table 2.

Received: August 29, 2013
Published: October 15, 2013

Table 1. Optimization of Reaction Conditions for Secondary Aliphatic Amines[a]



1a 2a

entry	catalyst	oxidant	yield (%)
1	**KI**	**TBHP**	**85**
2	KI	H_2O_2	trace
3	KI	oxone	N.D.[b]
4	KI	*m*-CPBA	N.D.
5	KI	O_2	N.D.
6	KBr	TBHP	N.D.
7	KCl	TBHP	N.D.
8		TBHP	N.D.
9	KI		N.D.
10	LiI	TBHP	83
11	I_2	TBHP	76
12	Bu_4NI	TBHP	84
13	KI	TBHP	84[c]
14	KI	TBHP	20[d]

[a]Conditions (unless stated otherwise): 0.5 mmol of dihexylamine **1a**, 5 mol % of catalyst, 1.5 equiv of oxidant in 2.0 mL of nitromethane at 80 °C for 6 h. [b]Not detected. [c]8 h. [d]Conditions: 0.5 mmol of dihexylamine **1a**, 5 mol % of KI, 1.5 equiv of TBHP, 2.0 equiv of nitromethane in 2.0 mL of H_2O at 80 °C for 6 h.

Both chain and cyclic amines are suitable reaction partners for this transformation. This protocol exhibits a high level of functional group tolerance, including hydroxyl, halide, methoxyl, benzyl, allyl, phenyl, pyridyl, Boc, ester, and amide. Unfortunately, some secondary aliphatic amines such as **1r** provided poor results. Next, the effects of reaction time on yield were examined, however, 12 h led to similar results.

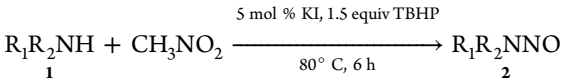
To further explore the potential of the methodology, selected secondary aromatic amines have also been tested. Unfortunately, low yields were obtained under the optimized conditions. Considering catalytic and phase-transfer activity of TBAI, it was chosen as the catalyst. To our delight, good yields could be achieved when 30 mol % of TBAI and 2.3 equiv of TBHP were used. Table 3 showed that aromatic amines bearing electron-donating groups afforded better yields in comparison to those with electron-withdrawing groups.

The N-dealkylation of tertiary amines under oxidative conditions is an important P-450 specific reaction.[14] The transition-metal-catalyzed dealkylation of tertiary amines[15] has become a well-established procedure since the pioneering work of Murahashi et al.[15a] During the current study, it was envisaged that secondary amines could be generated in situ via the dealkylation of tertiary amines and subsequently reacted with $MeNO_2$ to form the desired *N*-nitrosamines. After screening of reaction conditions, we found tertiary amines reacted smoothly under slightly modified conditions, leading to the corresponding products in moderate to good yields as shown in Table 4 (more oxidants were required for C–N cleavage of tertiary amines).

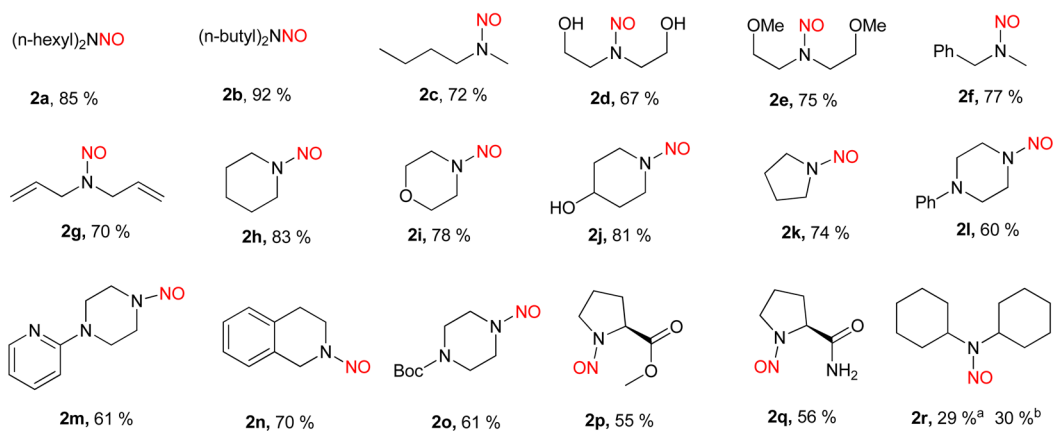
Further control experiments were conducted to gain insight into the reaction mechanism. The in situ generation of hypoiodite[13g] results in the desired product **2a** in 52% yield (Scheme 1a). The reaction did not proceed smoothly in the presence of iodine or KOH alone (Scheme 1b,c). When $PhI(OAc)_2$ or IBX was used as catalyst, no **2a** was detected (Scheme 1d,e). Consequently, we have deduced that hypoiodite is the active oxidant in this reaction. As shown in Scheme 1f, the formation of compound **4** suggests that tertiary amines can be converted to secondary amines under the oxidative conditions. Notably, compounds **5** could also be detected, indicating that NO^+ is likely to be the key nitrating reagent (Scheme 1f). However, we failed to trap NO^+ by pentane-1-thiol due to its lability under the oxidative conditions. When we uses 4-bromo-*N*,*N*-dimethylaniline as substrate, a trace amount of the corresponding byproducts, bearing both ^{79}Br and ^{81}Br, could be detected by LC-MS.

On the basis of these observations and the literature, a plausible mechanism has been proposed as shown in Scheme 2. First, iodide is oxidized to hypoiodite **B**[13g] by TBHP (Scheme 2a), followed by the formation of iodo(nitro)methane **C** (Scheme 2b).[16,17] This rearranges to form 2-oxo-1,2-oxaziridin-2-ium **D** and then decomposes into formaldehyde and NO^+ (Scheme 2c).[18] Finally, nucleophilic attack of the amine on NO^+ generates the

Table 2. KI-Catalyzed *N*-Nitrosation of Secondary Aliphatic Amines[a]



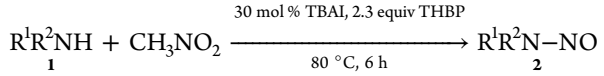
1 2

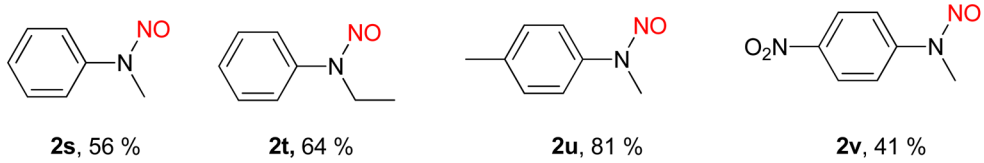


[a]Reaction conditions: 0.5 mmol of amines **1**, 5 mol % of KI, 1.5 equiv of TBHP (70% aqueous solution) in 2.0 mL of nitromethane at 80 °C for 6 h. [b]12 h.

dx.doi.org/10.1021/jo401915t | J. Org. Chem. 2013, 78, 11366–11372

Table 3. TBAI-Catalyzed *N*-Nitrosation of Secondary Aromatic Amines[a]

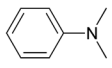
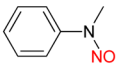
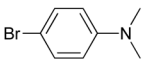
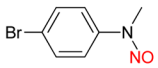
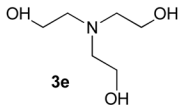
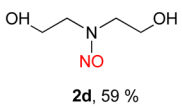




2s, 56 % **2t**, 64 % **2u**, 81 % **2v**, 41 %

[a]Reaction conditions: 0.5 mmol of amines **1**, 30 mol % of TBAI, 2.3 equiv of TBHP (70% aqueous solution) in 2.0 mL of nitromethane at 80 °C for 6 h.

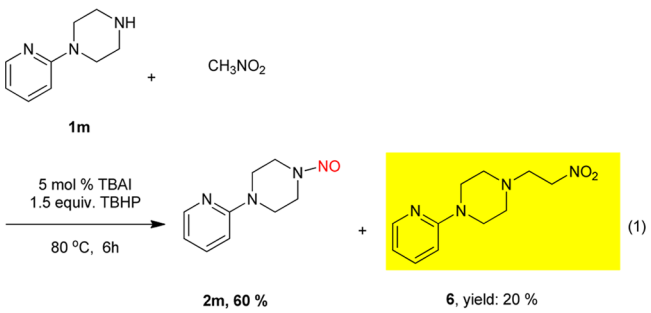
Table 4. TBAI -Catalyzed *N*-Nitrosation of Tertiary Amines

entry	substrates	products
1[a]	 **3a**	 **2s**, 61 %
2[a]	 **3b**	 **2w**, 64 %
3[b]	$(n\text{-butyl})_3N$ **3c**	$(n\text{-butyl})_2NNO$ **2b**, 63 %
4[b]	$(n\text{-octyl})_3N$ **3d**	$(n\text{-octyl})_2NNO$ **2x**, 76 %
5[b]	 **3e**	 **2d**, 59 %

[a]Reaction conditions: 0.5 mmol of amines **3**, 20 mol % of TBAI, 3.0 equiv of TBHP (70% aqueous solution) in 2.0 mL of nitromethane at 80 °C for 6 h. [b]Reaction conditions: 0.5 mmol of amines **3**, 30 mol % of TBAI, 3.7 equiv of TBHP (70% aqueous solution) in 2.0 mL of nitromethane at 80 °C for 6 h.

desired product (Scheme 2d). At present, another mechanism, proposed by Challis, could not be excluded.[16]

As shown in Scheme 2c, formaldehyde is generated as a byproduct in the proposed mechanism, which was verified by treatment with 1-(pyridin-2-yl)piperazine (**1m**) leading to the Mannich product **6** (eq 1). When the reaction was completed, the



2m, 60 % **6**, yield: 20 %

mixture was brown due to the formation of iodine. Therefore, we could not detect HCHO by the Nash test on the basis of a change in color. Fortunately, a trace amount of the adduct from HCHO and Nash reagent could be observed by LC-MS.

CONCLUSIONS

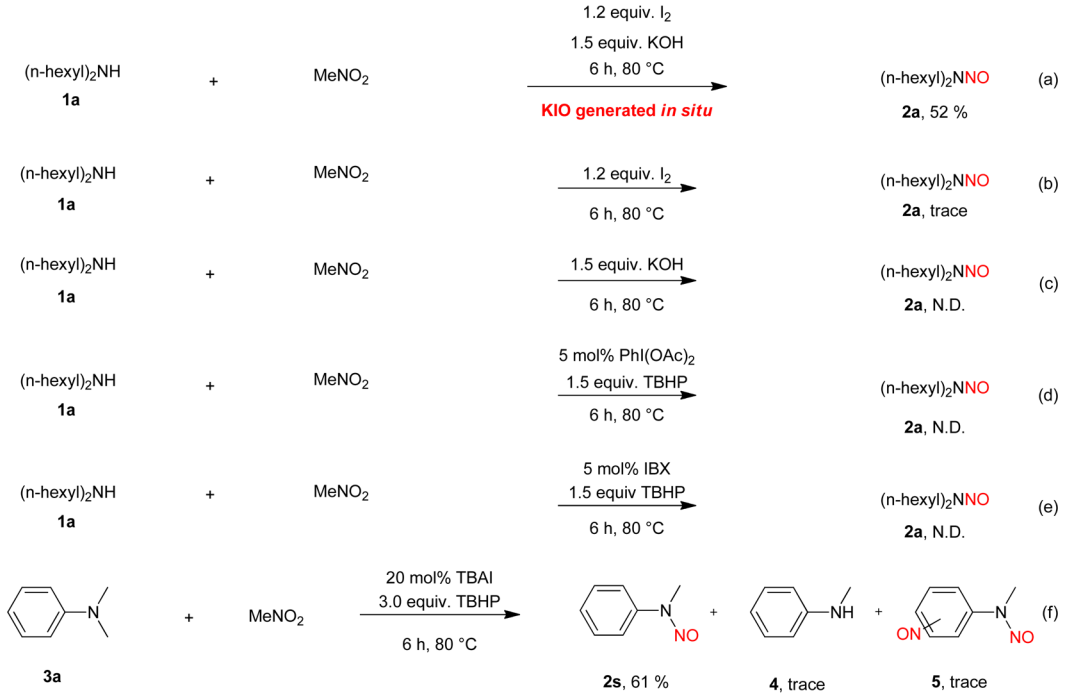
To summarize, we have successfully developed the synthesis of *N*-nitrosamines using nitromethane as the source of the nitroso group under catalytic conditions via C–N cleavage. No expensive oxidant was involved in this transformation. The advantages of this mild catalytic system include a wide range of substrates, high practical convenience, and commercially available materials. We believe that this method provides a promising alternative to previous methodologies.

EXPERIMENTAL SECTION

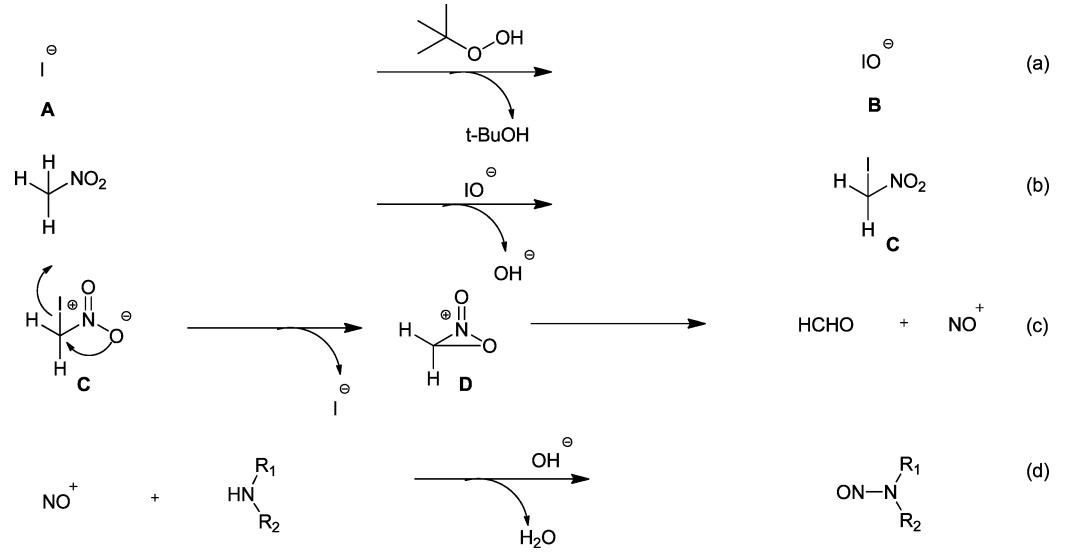
General Procedures for Amines 1a–r. KI (0.025 mmol) and amine (0.5 mmol) were placed in a test tube. CH_3NO_2 (2.0 mL) and

dx.doi.org/10.1021/jo401915t | J. Org. Chem. 2013, 78, 11366–11372

Scheme 1. Investigation into the Reaction Mechanism



Scheme 2. Proposed Catalytic Cycle



TBHP (0.75 mmol, 0.1 mL, 70% solution in water) were added via syringe. The reaction mixture was stirred at 80 °C for 6 h. It was then quenched (consumption of residual TBHP) with saturated Na_2SO_3 solution and extracted with ethyl acetate. The organic layer was combined and dried with Na_2SO_4. Removal of solvent followed by flash column chromatography using a mixture of petroleum ether and ethyl acetate afforded the desired product.

General Procedures for Amines 1s–v. TBAI (0.15 mmol) and amine (0.5 mmol) were placed in a test tube. CH_3NO_2 (2.0 mL) and TBHP (1.15 mmol, 0.15 mL, 70% solution in water) were added via syringe. The reaction mixture was stirred at 80 °C for 6 h. It was then quenched (consumption of residual TBHP) with saturated Na_2SO_3 solution and extracted with ethyl acetate. The organic layer was combined and dried with Na_2SO_4. Removal of solvent followed by flash column chromatography using a mixture of petroleum ether and ethyl acetate afforded the desired product.

General Procedures for Amines 3a,b. TBAI (0.1 mmol) and amine (0.5 mmol) were placed in a test tube. CH_3NO_2 (2.0 mL) and TBHP (1.5 mmol, 0.2 mL, 70% solution in water) were added via syringe. The reaction mixture was stirred at 80 °C for 6 h. It was then quenched (consumption of residual TBHP) with saturated Na_2SO_3 solution and extracted with ethyl acetate. The organic layer was combined and dried with Na_2SO_4. Removal of solvent followed by flash column chromatography using a mixture of petroleum ether and ethyl acetate afforded the desired product.

General Procedures for Amines 3c–e. TBAI (0.15 mmol) and amine (0.5 mmol) were placed in a test tube. CH_3NO_2 (2.0 mL) and TBHP (1.85 mmol, 0.25 mL, 70% solution in water) were added via syringe. The reaction mixture was stirred at 80 °C for 6 h. It was then quenched (consumption of residual TBHP) with saturated Na_2SO_3 solution and extracted with ethyl acetate. The organic layer was combined and dried with Na_2SO_4. Removal of solvent followed by

dx.doi.org/10.1021/jo401915t | J. Org. Chem. 2013, 78, 11366–11372

flash column chromatography using a mixture of petroleum ether and ethyl acetate afforded the desired product.

*N,N-Dihexylnitrous amide (**2a**):* pale yellow liquid (91 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (t, J = 8.0 Hz, 2H), 3.53 (t, J = 8.0 Hz, 2H), 1.82−1.65 (m, 2H), 1.54−1.42 (m, 2H), 1.30−1.24 (m, 12H), 0.95−0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 43.6, 31.21, 31.17, 28.2, 26.7, 26.1, 25.9, 22.4, 13.9; MS (ESI-quadrupole) calcd for $C_{12}H_{27}N_2O$ 215, found 215 (M + H$^+$); IR (KBr, cm^{-1}) ν 1627, 1575, 1458.

*N,N-Dibutylnitrous amide (**2b**):* pale yellow liquid (73 mg, 92% yield for **1b**; 49 mg, 63% for **3c**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (t, J = 8.0 Hz, 2H), 3.54 (t, J = 8.0 Hz, 2H), 1.80−1.67 (m, 2H), 1.53−1.23 (m, 6H), 1.02−0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.7, 43.2, 30.1, 27.9, 20.2, 19.5, 13.3; MS (EI-ion trap) calcd for $C_8H_{18}N_2O$ 158, found 158 (M$^+$); IR (KBr, cm^{-1}) ν 1640, 1571, 1458.

*N-Butyl-N-methylnitrous amide (**2c**):* pale yellow liquid (42 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (t, J = 8.0 Hz, 1.62H), 3.75 (s, 0.57H), 3.59 (t, J = 8.0 Hz, 0.38H), 3.05 (s, 2.43H), 1.76−1.69 (m, 1.62H), 1.53−1.44 (m, 0.38H), 1.42−1.34 (m, 1.62H), 1.32−1.25 (m, 0.38H), 0.97 (t, J = 8.0 Hz, 2.43H), 0.92 (t, J = 8.0 Hz, 0.57H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 44.5, 38.9, 31.2, 29.8, 27.6, 20.1, 19.4, 13.5, 13.4; MS (ESI-quadrupole) calcd for $C_5H_{13}N_2O$ 117, found 117 (M + H$^+$); IR (KBr, cm^{-1}) ν 1648, 1571, 1414.

*N,N-Bis(2-hydroxyethyl)nitrous amide (**2d**):* pale yellow liquid (45 mg, 67% yield for **1d**; 40 mg, 59% for **3e**); ^{1}H NMR (400 MHz, d_6-DMSO) δ 4.01−3.96 (m, 1H), 3.95−3.89 (m, 1H), 3.27−3.19 (m, 2H), 2.82−2.74 (m, 2H), 2.74−2.68 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 58.8, 56.9, 55.2, 46.6; MS (ESI-quadrupole) calcd for $C_4H_{11}N_2O_3$ 135, found 135 (M + H$^+$); IR (KBr, cm^{-1}) ν 3442, 1638, 1571, 1419.

*N,N-Bis(2-methoxyethyl)nitrous amide (**2e**):* pale yellow liquid (61 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (t, J = 6.0 Hz, 2H), 3.86 (t, J = 6.0 Hz, 2H), 3.73 (t, J = 6.0 Hz, 2H), 3.45 (t, J = 6.0 Hz, 2H), 3.37 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.4, 68.5, 58.5, 52.6, 44.2; MS (ESI-quadrupole) calcd for $C_6H_{15}N_2O_3$ 163, found 163 (M + H$^+$); IR (KBr, cm^{-1}) ν 1638, 1571, 1452.

*N-Benzyl-N-methylnitrous amide (**2f**):* pale yellow liquid (58 mg, 77% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.10 (m, 5H), 5.29 (s, 1.55H), 4.79 (s, 0.45H), 3.67 (s, 0.68H), 2.92 (s, 2.32H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 133.6, 128.8, 128.6, 128.3, 128.0, 127.8, 127.7, 57.2, 47.4, 38.2, 30.7; HRMS (EI-TOF) calcd for $C_8H_{10}N_2O$ 150.0793, found 150.0772 (M$^+$); IR (KBr, cm^{-1}) ν 1620, 1572, 1449.

*N,N-Diallylnitrous amide (**2g**):* pale yellow liquid (44 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96−5.86 (m, 1H), 5.67−5.58 (m, 1H), 5.39−5.27 (m, 2H), 5.21−5.18 (m, 1H), 5.13−5.08 (m, 1H), 4.74−4.69 (m, 2H), 4.22−4.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 129.1, 120.1, 119.1, 54.1, 45.1; MS (ESI-quadrupole) calcd for $C_6H_{11}N_2O$ 127, found 127 (M + H$^+$); IR (KBr, cm^{-1}) ν 1637, 1572, 1420.

*1-Nitrosopiperidine (**2h**):* pale yellow liquid (47 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (t, J = 6.0 Hz, 2H), 3.78 (t, J = 6.0 Hz, 2H), 1.87−1.70 (m, 4H), 1.59−1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.6, 39.5, 26.2, 24.5, 23.9; MS (ESI-quadrupole) calcd for $C_5H_{11}N_2O$ 115, found 115 (M + H$^+$); IR (KBr, cm^{-1}) ν 1638, 1571, 1419.

*4-Nitrosomorpholine (**2i**):* pale yellow liquid (45 mg, 78% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35−4.26 (t, J = 4.5 Hz, 2H), 3.95−3.82 (m, 4H), 3.66 (t, J = 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.2, 65.8, 49.9, 40.3; MS (ESI-quadrupole) calcd for $C_4H_9N_2O_2$ 117, found 117 (M + H$^+$); IR (KBr, cm^{-1}) ν 1672, 1561, 1431.

*1-Nitrosopiperidin-4-ol (**2j**):* pale yellow liquid (53 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48−4.38 (m, 1H), 4.20−4.08 (m, 2H), 4.03−3.92 (m, 1H), 3.86−3.74 (m, 1H), 3.45 (s, 1H), 2.10−2.00 (m, 1H), 1.91−1.74 (m, 2H), 1.68−1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.1, 46.6, 35.7, 33.6, 32.0; MS (ESI-quadrupole) calcd for $C_5H_{11}N_2O_2$ 131, found 131 (M + H$^+$); IR (KBr, cm^{-1}) ν 3411, 1638, 1560, 1421.

*1-Nitrosopyrrolidine (**2k**):* pale yellow liquid (37 mg, 74% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, J = 6.0 Hz, 2H), 3.59 (t, J = 8.0 Hz, 2H), 2.12−1.98 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.8, 45.2, 23.9, 22.6; MS (ESI-quadrupole) calcd for $C_4H_9N_2O$ 101, found 101 (M + H$^+$); IR (KBr, cm^{-1}) ν 1638, 1559, 1408.

*1-Nitroso-4-phenylpiperazine (**2l**):* yellow solid (57 mg, 60% yield); mp 65−66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (m, 2H), 6.99−6.90 (m, 3H), 4.40 (t, J = 6.0 Hz, 2H), 3.96 (t, J = 6.0 Hz, 2H), 3.39 (t, J = 6.0 Hz, 2H), 3.17 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 129.3, 121.0, 117.1, 50.2, 49.3, 48.6, 39.5; MS (ESI-quadrupole) calcd for $C_{10}H_{14}N_3O$ 192, found 192 (M + H$^+$); IR (KBr, cm^{-1}) ν 1647, 1570, 1409.

*1-Nitroso-4-(pyridin-2-yl)piperazine (**2m**):* yellow solid (58 mg, 61% yield); mp 85−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 4.0 Hz, 1H), 7.59−7.48 (m, 1H), 6.76−6.66 (m, 2H), 4.36 (t, J = 6.0 Hz, 2H), 3.89 (t, J = 6.0 Hz, 2H), 3.82 (t, J = 6.0 Hz, 2H), 3.62 (t, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 147.8, 137.6, 114.0, 107.2, 48.7, 45.6, 43.5, 39.6; MS (EI-ion trap) calcd for $C_9H_{12}N_4O$ 192, found 192 (M$^+$); IR (KBr, cm^{-1}) ν 1637, 1566, 1409.

*2-Nitroso-1,2,3,4-tetrahydroisoquinoline (**2n**):* pale yellow liquid (57 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.09 (m, 4H), 5.40 (s, 0.60H), 4.84 (s, 1.40H), 4.55 (t, J = 6.0 Hz, 1.40H), 3.89 (t, J = 8.0 Hz, 0.60H), 3.11 (t, J = 6.0 Hz, 1.40H), 2.97 (t, J = 8.0 Hz, 0.60H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 129.8, 128.5, 127.9, 127.8, 127.1, 127.0, 126.0, 51.1, 47.5, 44.3, 40.6, 29.6, 27.2; MS (ESI-quadrupole) calcd for $C_9H_{11}N_2O$ 163, found 163 (M + H$^+$); IR (KBr, cm^{-1}) ν 1627, 1575, 1428.

*tert-Butyl 4-nitrosopiperazine-1-carboxylate (**2o**):* pale yellow liquid (66 mg, 61% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (t, J = 4.0 Hz, 2H), 3.81 (t, J = 4.0 Hz, 2H), 3.68 (t, J = 4.0 Hz, 2H), 3.46 (t, J = 4.0 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 80.4, 49.0, 43.7, 42.0, 39.4, 28.0; MS (ESI-quadrupole) calcd for $C_9H_{18}N_3O_3$ 216, found 216 (M + H$^+$); IR (KBr, cm^{-1}) ν 1697, 1570, 1418.

*(S)-Methyl 1-nitrosopyrrolidine-2-carboxylate (**2p**):* pale yellow liquid (43 mg, 55% yield);^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33−5.28 (m, 1H), 4.58−4.35 (m, 5.12H), 3.81 (s, 3.22H), 3.73 (s, 3.64H), 3.72−3.61 (m, 1.83H), 2.45−2.18 (m, 3.89H),2.28−2.18 (m, 1.70H), 2.15−1.99 (m, 5.72H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.9, 61.7, 57.7, 52.6, 52.3, 49.7, 45.4, 28.7, 27.5, 23.0, 20.9; MS (EI-ion trap) calcd for $C_6H_{10}N_2O_3$ 158, found 158 (M$^+$); IR (KBr, cm^{-1}) ν 1648, 1560, 1409.

*(S)-1-Nitrosopyrrolidine-2-carboxamide (**2q**):* yellow solid (40 mg, 56% yield); mp 165−166 °C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.75 (s, 1H), 7.48 (s, 1.20H), 7.33 (s, 1H), 7.03 (s, 1.20H), 5.07 (t, J = 3.0 Hz, 1H), 4.41−4.33 (m, 2.40H), 4.22 (t, J = 3.0 Hz, 1.20H), 3.53−3.38 (m, 2H), 2.38−1.73 (m, 8.80H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 172.0, 170.2, 62.4, 59.2, 50.1, 46.0, 29.1, 28.2, 22.7, 20.9; MS (ESI-quadrupole) calcd for $C_5H_{10}N_3O_2$ 144, found 144 (M + H$^+$); IR (KBr, cm^{-1}) ν 1681, 1613, 1403.

*N,N-Dicyclohexylnitrous amide (**2r**):* yellow solid (30 mg, 29% yield); mp 104−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93−4.82 (m, 1H), 3.79−3.66 (m, 1H), 2.01−1.09 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.3, 52.0, 34.2, 29.2, 25.9, 25.3, 25.2; MS (EI-ion trap) calcd for $C_{12}H_{22}N_2O$ 210, found 210 (M$^+$); IR (KBr, cm^{-1}) ν 1638, 1561, 1446.

*N-Methyl-N-phenylnitrous amide (**2s**):* pale yellow liquid (38 mg, 56% yield for **1s**; 41 mg, 61% for **3a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.31(m, 5H), 3.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 129.4, 127.3, 119.1, 31.4; MS (ESI-quadrupole) calcd for $C_7H_9N_2O$ 137, found 137 (M + H$^+$); IR (KBr, cm^{-1}) ν 1631, 1515, 1468.

*N-Ethyl-N-phenylnitrous amide (**2t**):* pale yellow liquid (48 mg, 64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.50 (m, 2H), 7.50−7.45 (m, 2H), 7.35 (t, J = 6.0 Hz, 1H), 4.07 (q, J = 8.0 Hz, 2H), 1.16 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 129.3, 127.2, 119.4, 39.0, 11.6. MS (ESI-quadrupole) calcd for $C_8H_{11}N_2O$ 151, found 151 (M + H$^+$); IR (KBr, cm^{-1}) ν 1598, 1496, 1473.

*N-Methyl-N-(p-tolyl)nitrous amide (**2u**):* yellow solid (61 mg, 81% yield); mp 50−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 3.45 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 137.1, 129.8, 119.1, 31.5, 20.8;

MS (ESI-quadrupole) calcd for $C_8H_{11}N_2O$ 151, found 151 (M + H^+); IR (KBr, cm^{-1}) ν 1630, 1514, 1454.

*N-Methyl-N-(4-nitrophenyl)nitrous amide (**2v**):* yellow solid (37 mg, 41% yield); mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 2H), 3.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 145.7, 125.1, 117.8, 30.0; MS (ESI-quadrupole) calcd for $C_7H_8N_3O_3$ 182, found 182 (M + H^+); IR (KBr, cm^{-1}) ν 1630, 1492, 1459.

*N-(4-Bromophenyl)-N-methylnitrous amide (**2w**):* yellow solid (68 mg, 64% yield); mp 69−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 132.08, 120.1, 120.0, 30.7; MS (ESI-quadrupole) calcd for $C_7H_8{}^{79}BrN_2O$ 215, found 215 (M + H^+); IR (KBr, cm^{-1}) ν 1631, 1492, 1460.

*N,N-Dioctylnitrous amide (**2x**):* pale yellow liquid (103 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (t, J = 8.0 Hz, 2H), 3.52 (t, J = 8.0 Hz, 2H), 1.78−1.69 (m, 2H), 1.53−1.43 (m, 2H), 1.39−1.19 (m, 20H), 0.93−0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 43.5, 31.6, 29.0, 28.2, 27.1, 26.4, 25.9, 22.4, 13.9. HRMS (ESI-TOF) calcd for $C_{16}H_{34}N_2NaO$ 293.2569, found 293.2569 (M + Na^+); IR (KBr, cm^{-1}) ν 1610, 1552, 1462.

*1-(2-Nitroethyl)-4-(pyridin-2-yl)piperazine (**6**):* yellow solid (24 mg, 20% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.17 (m, 1H), 7.51−7.45 (m, 1H), 6.70−6.55 (m, 2H), 4.53 (t, J = 8.0 Hz, 2H), 3.53 (t, J = 4.0 Hz, 4H), 3.05 (t, J = 8.0 Hz, 2H), 2.63 (t, J = 4.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 147.9, 137.5, 113.4, 107.0, 73.1, 54.7, 52.7, 45.0; HRMS (ESI-TOF) calcd for $C_{11}H_{17}N_4O_2$ 237.1352, found 237.1355 (M + H^+); IR (KBr, cm^{-1}) ν 1625, 1451, 1400.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and NSFC (21072142, 21272165). Y.L. is grateful to the National Natural Science Foundation of China (No. 21104064) and Natural Science Foundation of Jiangsu Normal University (10XLR03).

■ REFERENCES

(1) For selected examples, see: (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622. (b) Golisz, S. R.; Hazari, N.; Labinger, J. A.; Bercaw, J. E. *J. Org. Chem.* **2009**, *74*, 8441. (c) Wang, A.; Jiang, H.; Li, X. *J. Org. Chem.* **2011**, *76*, 6958. (d) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354. (e) Li, M.-B.; Wang, Y.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2968. (f) Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8291. (g) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098. (h) Koreeda, T.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 7238. (i) Wu, W.; Su, W. *J. Am. Chem. Soc.* **2011**, *133*, 11924. (j) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 519. (k) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522. (l) Zhang, L.; Peng, C.; Zhao, D.; Wang, Y.; Fu, H.-J.; Shen, Q.; Li, J.-X. *Chem. Commun.* **2012**, *48*, 5928. (m) Zhang, J.; Chen, J.; Liu, M.; Zheng, X.; Ding, J.; Wu, H. *Green Chem.* **2012**, *14*, 912. (n) Kuninobu, Y.; Nishi, M.; Takai, K. *Chem. Commun.* **2010**, *46*, 8860. (o) Liu, C.-R.; Yang, F.-L.; Jin, Y.-Z.; Ma, X.-T.; Cheng, D.-J.; Li, N.; Tian, S.-K. *Org. Lett.* **2010**, *12*, 3832. (p) Hu, C.; Chin, R. M.; Nguyen, T. D.; Nguyen, K. T.; Wagenknecht, P. S. *Inorg. Chem.* **2003**, *42*, 7602. (q) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046. (r) Liu, J.; Robins, M. J. *Org. Lett.* **2004**, *6*, 3421. (s) Kleckley, T. S.; Bennett, J. L.; Wolczanski, P. T.; Lobkovsky, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 247. (t) Bonanno, J. B.; Henry, T. P.; Neithamer, D. R.; Wolczanski, P. T.; Lobkovsky, E. B. *J. Am. Chem. Soc.* **1996**, *118*, 5132. (u) Shen, H.; Chan, H.-S.; Xie, Z. *J. Am. Chem. Soc.* **2007**, *129*, 12934. (v) Cameron, T. M.; Abboud, K. A.; Boncella, J. M. *Chem. Commun.* **2001**, 1224.

(2) (a) Lao, K. Q.; Jensen, E.; Kash, P. W.; Butler, L. J. *J. Chem. Phys.* **1990**, *93*, 3958. (b) Inui, H.; Murata, S. *J. Am. Chem. Soc.* **2005**, *127*, 2628. (c) Klima, R. F.; Jadhav, A. V.; Singh, P. N. D.; Chang, M.; Vanos, C.; Sankaranarayanan, J.; Vu, M.; Ibrahim, N.; Ross, E.; McCloskey, S.; Murthy, R. S.; Krause, J. A.; Ault, B. S.; Gudmundsdóttir, A. D. *J. Org. Chem.* **2007**, *72*, 6372. (d) Wu, X.-S.; Tian, S.-K. *Chem. Commun.* **2012**, *48*, 898. (e) Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.* **2010**, *132*, 5018. (f) Dong, D.-J.; Li, Y.; Wang, J.-Q.; Tian, S.-K. *Chem. Commun.* **2011**, *47*, 2158. (g) Wang, Y.; Chi, Y.; Zhang, W.-X.; Xi, Z. *J. Am. Chem. Soc.* **2012**, *134*, 2926. (h) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Tetrahedron Lett.* **1983**, *24*, 5227. (i) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017. (j) Potturi, H. K.; Gurung, R. K.; Hou, Y. *J. Org. Chem.* **2012**, *77*, 626. (k) Burés, J.; Vilarrasa, J. *Tetrahedron Lett.* **2008**, *49*, 441. (l) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112.

(3) Williams, D. L. H. *Nitrosation Reactions and the Chemistry of Nitric Oxide*; Elsevier: Amsterdam, 2004.

(4) (a) Bumgardner, C. L.; McCallum, K. S.; Freeman, J. P. *J. Am. Chem. Soc.* **1961**, *83*, 4417. (b) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed.* **1975**, *14*, 15. (c) Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Maluszynska, H.; Polonski, T. *J. Org. Chem.* **2001**, *66*, 501.

(5) (a) Neurath, G.; Dünger, M. *Chem. Ber.* **1964**, *97*, 2713. (b) Sahu, J.; Dehuri, S. N.; Naik, S. K.; Nayak, A. *J. Indian Chem. Soc.* **1984**, *61*, 982. (c) Zolfigol, M. A.; Bamoniri, A. *Synlett* **2002**, 1621. (d) Montazerozohori, M.; Karami, B. *Helv. Chim. Acta* **2006**, *89*, 2922. (e) Célariès, B.; Párkányi, C. *Synthesis* **2006**, 2371. (f) Borikar, S. P.; Paul, V. *Synth. Commun.* **2010**, *40*, 654.

(6) (a) Verardo, G.; Giumanini, A. G.; Strazzolini, P. *Tetrahedron* **1990**, *46*, 4303. (b) Roche, D.; Lardy, C.; Tournier, L.; Prunier, M.; Valeur, E. *Tetrahedron Lett.* **2010**, *51*, 2277.

(7) (a) Challis, B. C.; Outram, J. R. *J. Chem. Soc., Chem. Commun.* **1978**, 707. (b) Goldstein, S.; Czapski, G. *J. Am. Chem. Soc.* **1996**, *118*, 3419. (c) Itoh, T.; Matsuya, Y.; Maeta, H.; Miyazaki, M.; Nagata, K.; Ohsawa, A. *Chem. Pharm. Bull.* **1999**, *47*, 819. (d) Nudelman, N. S.; Bonatti, A. E. *Synlett* **2000**, 1825. (e) Iranpoor, N.; Firouzabadi, H.; Pourali, A.-R. *Synthesis* **2003**, 1591. (f) Iranpoor, N.; Firouzabadi, H.; Pourali, A. R. *Synth. Commun.* **2005**, *35*, 1517.

(8) Castedo, L.; Riguera, R.; Vázquez, M. P. *J. Chem. Soc., Chem. Commun.* **1983**, 301.

(9) Demir, A. S.; Mahasneh, A. S.; Aksoy, H.; Gercek, Z. *Synth. Commun.* **1992**, *22*, 2607.

(10) (a) Oláh, G.; Noszkó, L.; Kuhn, S.; Szelke, M. *Chem. Ber.* **1956**, *89*, 2374. (b) Zolfigol, M. A.; Zebarjadian, M. H.; Chehardoli, G.; Keypour, H.; Salehzadeh, S.; Shamsipur, M. *J. Org. Chem.* **2001**, *66*, 3619.

(11) Chang, S.-K.; Harrington, G. W.; Rothstein, M.; Shergalis, W. A.; Swern, D.; Vohra, S. K. *Cancer Res.* **1979**, *39*, 3871.

(12) Fanning, J. C.; Keefer, L. K. *J. Chem. Soc., Chem. Commun.* **1987**, 955.

(13) (a) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J.* **2011**, *17*, 4085. (b) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, *47*, 10827. (c) Chen, S.; Xu, Y.; Wan, X. *Org. Lett.* **2011**, *13*, 6152. (d) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (e) Shi, E.; Shao, Y.; Chen, S.; Hu, H.; Liu, Z.; Zhang, J.; Wan, X. *Org. Lett.* **2012**, *14*, 3384. (f) Zhang, J.; Jiang, J.; Li, Y.; Zhao, Y.; Wan, X. *Org. Lett.* **2013**, *15*, 3222. (g) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (h) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, *12*, 2841. (i) He, T.; Li, H.; Li, P.; Wang, L. *Chem. Commun.* **2011**, *47*, 8946. (j) Ma, L.; Wang, X.; Yu,

W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333. (k) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (l) Zhu, C.; Wei, Y. *ChemSusChem* **2011**, *4*, 1082. (m) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979. (n) Zhu, Y.-P.; Lian, M.; Jia, F.-C.; Liu, M.-C.; Yuan, J.-J.; Gao, Q.-H.; Wu, A.-X. *Chem. Commun.* **2012**, *48*, 9086. (o) Huang, J.; Li, L.-T.; Li, H.-Y.; Husan, E.; Wang, P.; Wang, B. *Chem. Commun.* **2012**, *48*, 10204. (p) Yan, Y.; Zhang, Y.; Feng, C.; Zha, Z.; Wang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8077. (q) Tan, B.; Toda, N.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2012**, *51*, 12538. (r) Feng, J.; Liang, S.; Chen, S.-Y.; Zhang, J.; Fu, S.-S.; Yu, X.-Q. *Adv. Synth. Catal.* **2012**, *354*, 1287. (s) Wu, X.-F.; Bheeter, C. B.; Neumann, H.; Dixneuf, P. H.; Beller, M. *Chem. Commun.* **2012**, *48*, 12237. (t) Li, X.; Xu, X.; Zhou, C. *Chem. Commun.* **2012**, *48*, 12240. (u) Li, Z.; Cui, Z.; Liu, Z.-Q. *Org. Lett.* **2013**, *15*, 406. (v) Wertz, S.; Leifert, D.; Studer, A. *Org. Lett.* **2013**, *15*, 928. (w) Li, X.; Xu, X.; Hu, P.; Xiao, X.; Zhou, C. *J. Org. Chem.* **2013**, *78*, 7343. (x) Li, X.; Xu, X.; Tang, Y. *Org. Biomol. Chem.* **2013**, *11*, 1739.

(14) Sato, R., Omura, T., Eds. *Cytochrome P-450*; Kodansha: Tokyo, 1978.

(15) For selected examples, see: (a) Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256. (b) Li, Y.; Jia, F.; Li, Z. *Chem. Eur. J.* **2013**, *19*, 82.

(16) Bromonitromethane readily converts secondary amines to *N*-nitrosamines; see: Challis, B. C.; Yousaf, T. I. *J. Chem. Soc., Chem. Commun.* **1990**, 1598.

(17) Nenitzescu, C. D.; Isaăcescu, D. A. *Ber. Dtsch. Chem. Ges. A/B* **1930**, *63*, 2484.

(18) (a) Polasek, M.; Turecek, F. *J. Phys. Chem. A* **2001**, *105*, 1371. (b) Najafpour, J. *J. Phys. Theor. Chem.* **2009**, *6*, 131.