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Note

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Transition-Metal-Free Conversion of Trifluoropropanamides into Cyanoformamides through C-CF_3 Bond Cleavage and Nitrogenation

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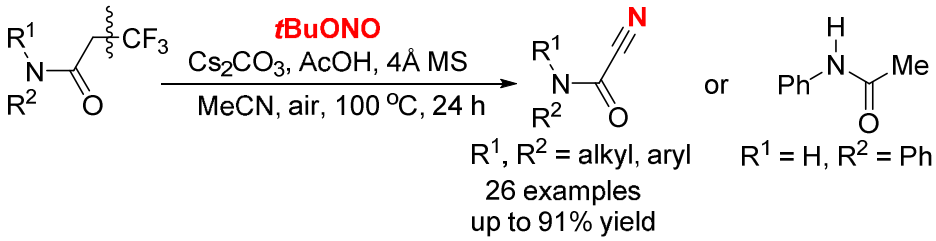
Abstract



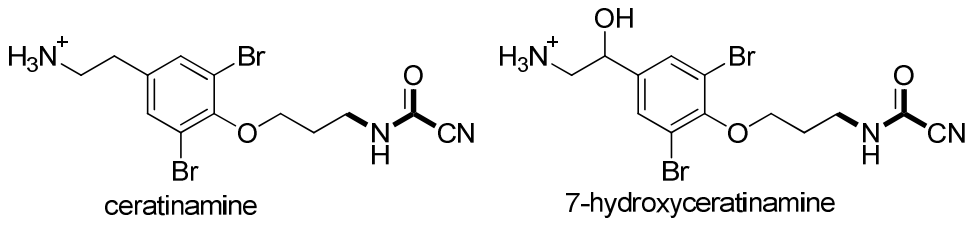
A new transition-metal-free transformation of trifluoropropanamides into cyanoformamides through a sequence of C-CF_3 bond cleavage and nitrogenation using *tert*-butyl nitrite (TBN) as the nitrogen source is described. The method features direct detrifluoromethylation, broad substrate scopes and excellent selectivity control, representing a new shortcut for constructing the nitrile group involving C-CF_3 σ-bond cleavage.

With the increased awareness of degrading the environmentally persistent nature of fluorinated molecules and improvement of fluorine-containing compounds in synthesis,[1] development of fluorocarbon disposal methods for such purposes is of increasing importance.[2] In the field, common and attractive strategies include the defluorination reaction, which has received much attention in the past decades. Typically, the elimination of fluorine atoms from fluorinated molecules, particularly trifluoromethylated compounds, is achieved *via* hydrodefluorination; however, these transformations are restricted to the requirement of strong reductive reagent and/or transition-metal catalysts because the

fluorocarbon group is one of the most chemically and thermally stable functional groups.[3] Although approaches *via* direct cleavage of C-CF_3 bond are especially fascinating for fluorocarbon degradation, such available examples are much less abundant.[4] Thus, the establishment of new efficient and practical methods for achieving the detrifluoromethylation, especially avoiding the use of strong reducing agents and transition-metal catalysts, is worthy of investigation.

Nitriles, including cyanoformamides (Scheme 1),[5] are prevalent as key structures in numerous pharmaceuticals, agricultural chemicals and materials, as well as versatile building blocks in chemical synthesis.[6] Accordingly, considerable efforts have been devoted to development of new efficient and reliable synthetic processes that allow the preparation of diverse functionalized nitriles. Classical methods focus on transition-metal-catalyzed cyanation of aryl halides[7] and transition-metal-catalyzed C-H cyanation;[8] however, both suffer from the use of highly toxic metal cyanide as the nitrile group resources. Alternatively, attractive access to nitriles has been developed by direct transformations of functional groups into the nitrile group in recent years. Generally, the nitrile group is formed by the dehydration of the corresponding amides, oximes or their precursors.[9] Recently, Jiao and co-workers reported a conceptually-new C-C unsaturated bond cleavage and nitrogenation cascade for assembling the nitrile group using $TMSN_3$ as the nitrogen source (Scheme 2a).[10] Maiti and co-workers have subsequently developed a metal-free nitrogenation of terminal arylalkynes with TBN (the nitrogen source) in the presence of 2-picoline-*N*-oxide, which delivered aryl nitriles *via* C-C triple bond cleavage.[11] Despite recent advances in direct transformations of functional groups into the nitrile group, similar versions for the preparation of cyanoformamides are quite rare.[12] We envisioned that a combination of detrifluoromethylation and nitrogenation might be applicable to the construction of the nitrile group. Herein, we report a new design cascade strategy for producing a wide range of cyanoformamides in moderate to high yields *via* transition-metal-free conversion of trifluoropropanamides into cyanoformamides using *tert*-butyl nitrite as the nitrogen source, which represents the first example of direct construction of the nitrile group *via* the C-CF_3 single bond cleavage and nitrogenation cascades.

Scheme 1. Examples of Cyanoformamide-Containing Natural Products.



Scheme 2. Construction of the Nitrile Group by C-C Bond Cleavage.

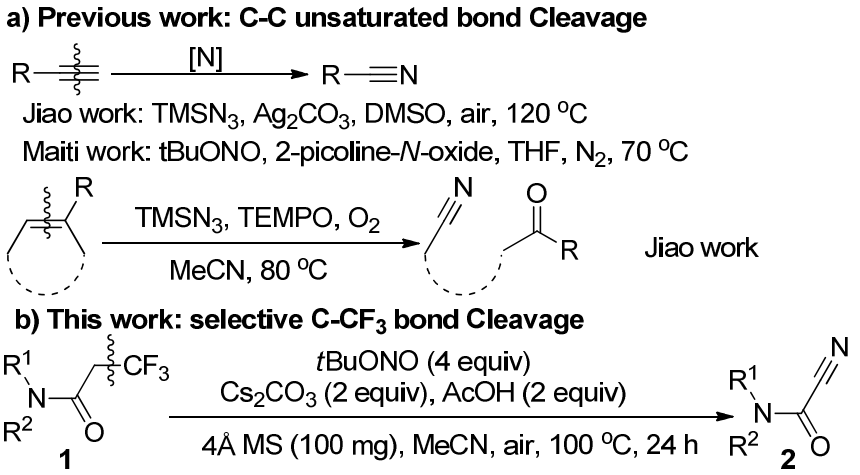
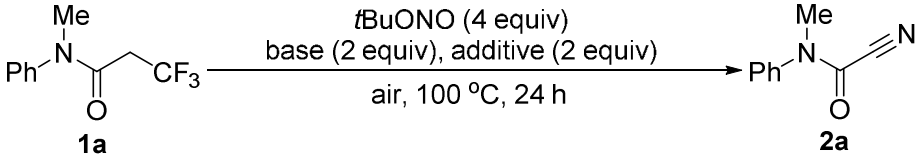


Table 1. Screening of Optimal Reaction Conditions[a]



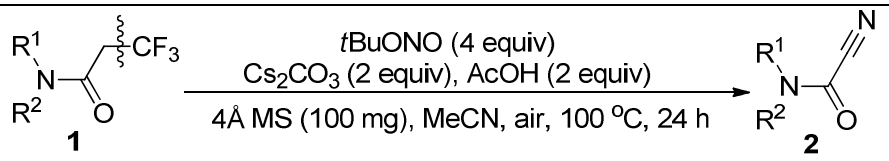
Entry	Base	Additive	Solvent	Yield (%)
1	Cs_2CO_3	-	MeCN	55
2	Cs_2CO_3	-	dioxane	29
3	Cs_2CO_3	-	DMF	47
4	Cs_2CO_3	-	toluene	38
5	CsOAc	-	MeCN	34
6	K_2CO_3	-	MeCN	27
7	K_3PO_4	-	MeCN	11
8	*t*-BuOK	-	MeCN	27
9	Cs_2CO_3	HOAc	MeCN	78
10	Cs_2CO_3	CF_3CO_2H	MeCN	trace
11	-	HOAc	MeCN	0
12	Cs_2CO_3	HOAc and 4Å MS	MeCN	91
13[b]	Cs_2CO_3	HOAc and 4Å MS	MeCN	39

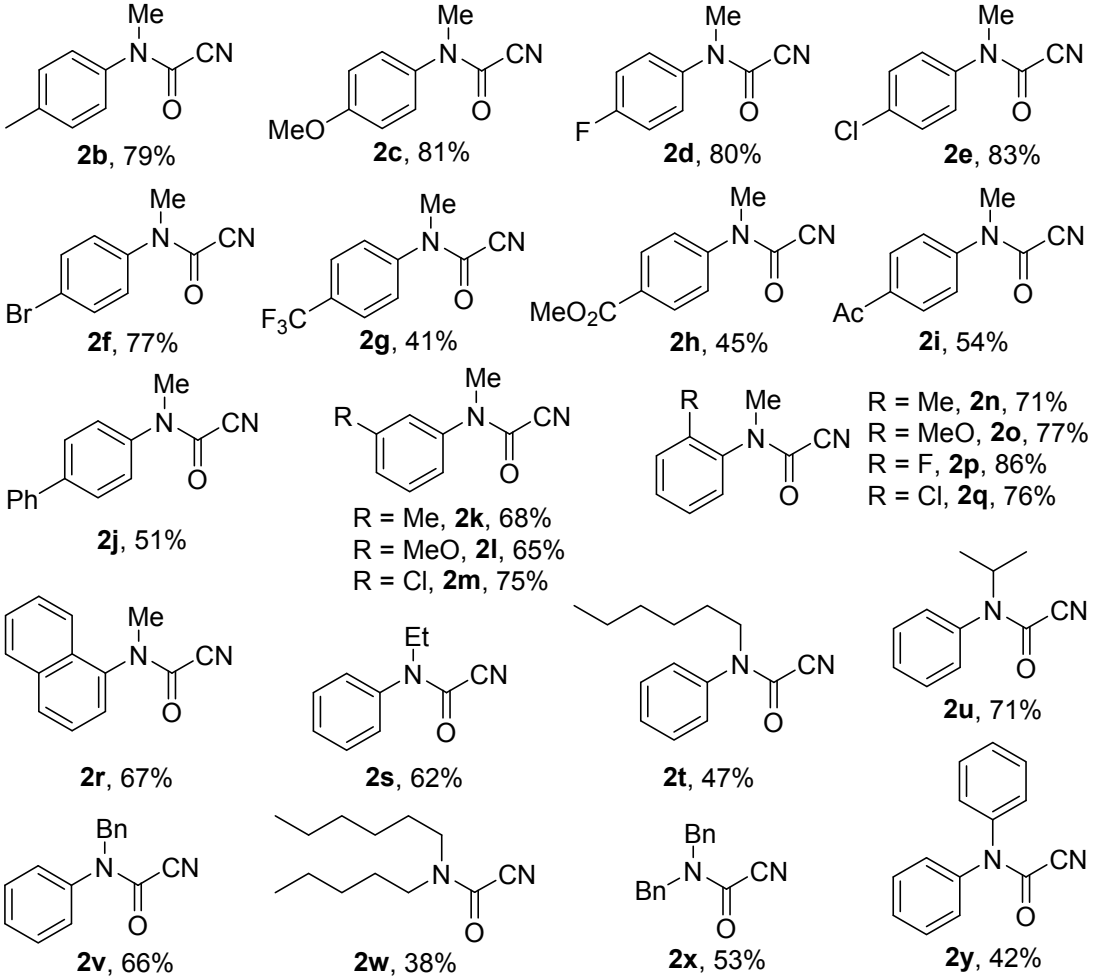
[a] Reaction conditions: **1a** (0.2 mmol), *t*BuONO (0.8 mmol), base (2 equiv), acid (2 equiv), 4Å MS (100 mg), dry solvent (2 mL), 100 °C, air and 24 h. [b] At 80 °C.

We began our studies by evaluating the reaction between 3,3,3-trifluoro-*N*-methyl-*N*-phenylpropanamide (**1a**) and *tert*-butyl nitrite to optimize the reaction condition (Table 1). Initially, substrate **1a** was reacted with TBN and Cs_2CO_3 in MeCN at 100 ^oC for 24 h, giving the target product **2a** in 55% yield (entry 1). A rotamerization of amide **2a** was observed in NMR spectra (see SI). Encouraged by the results, three other solvents, including dioxane, DMF and toluene, were examined to enhance the yield, (entries 2-4), which supported MeCN as the preferred solvent. A screen of the base effect revealed that other bases, such as CsOAc, K_2CO_3, K_3PO_4 and *t*-BuOK, were less effective than Cs_2CO_3 (entries 5-8). Gratifyingly, the yield increased from 55% (entry 1) to 78% when using 2 equiv of HOAc (entry 9). However, the reaction could not take place using CF_3CO_2H instead of HOAc (entry 10) or in the absence of Cs_2CO_3 (entry 11). We were pleased to find that molecular sieves (MS) improved the reaction: in the presence of 100 mg 4Å MS, a 91% yield of **2a** was obtained (entry 12). Notably, a lower reaction temperature (80 ^oC) had a negative effect on the reaction by comparison with the result at 100 ^oC (entry 13).

With the optimal reaction conditions in hand, we set out to investigate the substrate scope (Schemes 3 and 4). First, the substitution effect on the aromatic ring of the *N*-aryl moiety was examined: an array of substituents, including Me, MeO, F, Cl, Br, CF_3, CO_2Me, CH_3CO and Ph, were well tolerated, and the electronic nature of the substrates had a fundamental influence on the reactivity (**2b-j**). While trifluoropropanamides **1b-c**, bearing an electron-donating group (Me or MeO) on the *N*-aryl ring, afforded **2b-c** in good yields, substrates **1g-i** with a strong electron-withdrawing group, namely CF_3, CO_2Me and CH_3CO, furnished **2g-i** with lower yields. Importantly, halide substituents (F, Cl and Br) were consistent with the optimal conditions (**2d-f**), thus providing potential handles for further modification, and the structure of product **2f** was confirmed by X-ray single-crystal diffraction analysis (see SI). Using 4-Ph-substituted amide **1j**, the reaction gave *N*-(4-biphenyl)-cyanoformamide (**2j**) in 51% yield. The results showed that the steric hindrance effect slightly affected the reaction. Both *melta*-substituted and *ortho*-substituted trifluoropropanamides **1k-q** delivered **2k-q** in 65-86% yields. Moreover, *N*-methyl-*N*-(naphthalen-1-yl)trifluoropropanamide **1r** was compatible with the optimal conditions, affording **2r** in 67% yield. Subsequently, the substitution effect on the nitrogen atom was examined. Gratifyingly, symmetrical and unsymmetrical disubstituted amines **1s-y**, either *N,N*-diaryl, *N,N*-dialkyl or *N*-aryl-*N*-alkyl variations, were viable for the assembly of **2s-y** in moderate to good yields. For example, *N,N*-dihexyltrifluoropropanamide **1w** was successfully converted into **2w**, albeit giving a lower yield. For *N,N*-dibenzyltrifluoropropanamide **1x** and *N,N*-diphenyltrifluoropropanamide **1y**, the corresponding products **2x-y** were obtained in 53% and 42% yields, respectively.

Scheme 3. Variation of the Trifluoropropanamides **1**[a]

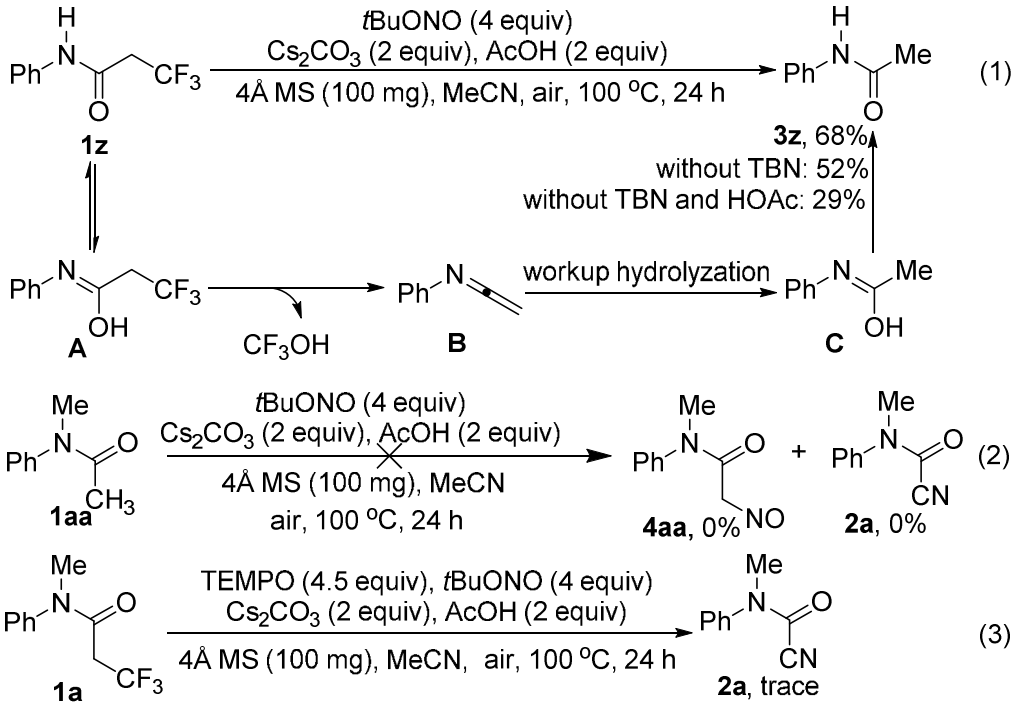




[a] Reaction conditions: **1** (0.2 mmol) and TBN (0.8 mmol), Cs_2CO_3 (2 equiv), AcOH (2 equiv), 100 mg 4Å MS and MeCN (dry 2 mL) under air atmosphere at 100 °C for 24 h.

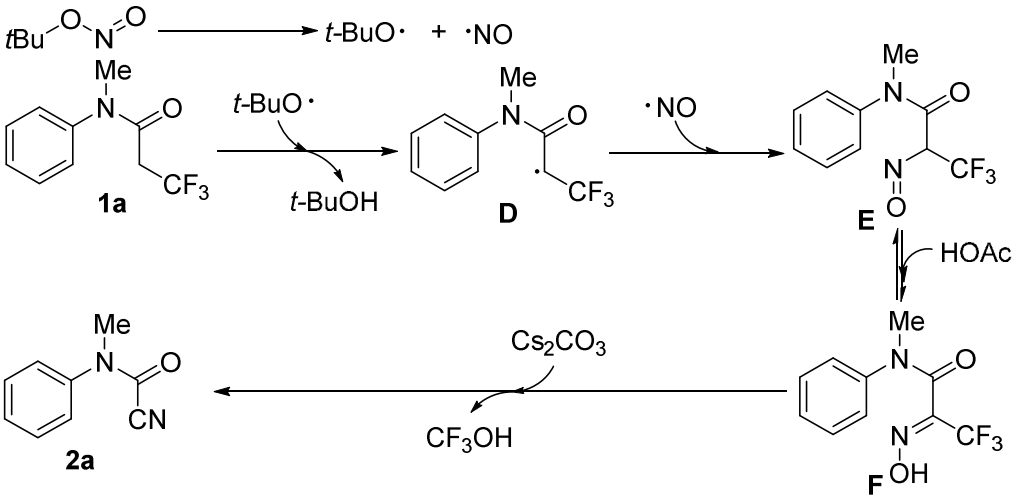
However, using *N*-mono-substituted trifluoropropanamide (**1z**) resulted in no occurrence of the cyanation reaction under the optimal conditions, and furnished the *N*-acetylaniline **3z** in 68% yield [Scheme 4, eq (1)]. The reaction could be performed in the absence of TBN and/or HOAc, albeit with diminished yields (52%). These results suggest that product **3z** is formed from a sequence of detrifluoromethylation and workup hydrolyzation. The experiment was also confirmed by ^{19}F NMR experiments of the reaction mixture of **1z** under the standard conditions after 24 h, in which the generation of the volatile trifluoromethanol resulted in observation of no signal.[13]

Scheme 4. Reaction with Other Propanamides **1** and Control Experiments.



To probe the mechanism of this detrifluoromethylative cyanation, some control experiments were conducted (Scheme 4). The reaction of *N*-methyl-*N*-phenylacetamide **1aa** with TBN was carried out under the optimal conditions. However, neither nitrosative product nor the target product **2a** could be observed [eq (2)], suggesting that the elimination of trifluoromethyl group occurred after the nitrosation. Furthermore, the reaction of substrate **1a** with TBN was completely inhibited by adding 4.5 equiv of 2,2,6,6-tetramethylpiperidine oxide (TEMPO), a radical scavenger [eq (3)]. These results indicated that the reaction might involve a radical process.

Scheme 5. Possible mechanism.



A plausible mechanism for this cascade reaction is proposed (Scheme 5).[14] Decomposition of *tert*-butyl nitrite readily takes place and gives the *tert*-butoxy radical and NO radical.[9d, 14] Hydrogen abstraction of substrate **1a** by the *tert*-butoxy radical generates the alkyl radical intermediate **D**,[14a, 14e] which sequentially reacts with the NO radical to afford the intermediate **E**. The tautomerization of intermediate **E** delivers the corresponding oxime **F**. Finally, *β*-elimination of intermediate **F** with the aid of Cs_2CO_3 furnishes the desired detrifluoromethylative product **2a**.[4a]

In summary, we have developed a new convenient and efficient method for conversion of trifluoropropanamides into cyanoformamides *via* C-CF_3 bond cleavage and nitrogenation cascades, which exhibits a broad scope with regard to a wide range of trifluoropropanamides and excellent tolerance of functional groups. Most importantly, new C-C single bond cleavage and nitrogenation cascades to construct the nitrile group are established.

Experimental Section

General Information:

Chemicals were either purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in *δ* relative to TMS, the coupling constants *J* are given in Hz. High resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometry. All reactions under air atmosphere were conducted using standard Schlenk techniques. Melting points were measured on X4 melting point apparatus and uncorrected. Column chromatography was performed using EM Silica gel 60 (300-400 mesh).

General Procedure for the Synthesis of Trifiuoromethylacetanilides 1:

To a stirred suspension of 3,3,3-trifluoropropionic acid (0.58 mL, 6.5 mmol) in dichloromethane (20 mL) was added oxalyl chloride (0.52 mL, 6 mmol) followed by three drops of DMF at 0 °C. The reaction mixture was stirred at rt for 3 h. To this solution was added a solution of anilines (5 mmol) in dichloromethane (10 mL) followed by triethylamine (1.74 mL, 12.5 mmol) at 0 °C. The reaction mixture was stirred for 12–24 hours and then washed with water (15 mL) and 1N HCl (15 mL). The

organic layer was dried over Na_2SO_4 and evaporated to afford residue, which was purified by flash column chromatography (hexane/ethyl acetate) to afford trifiuoromethylacetanilides **1**.[15]

General Procedure for the Synthesis of Cyanoformamides 2:

To a flame-dried Schlenk tube with a magnetic stirring bar was charged with **1** (0.2 mmol), TBN (0.8 mmol), Cs_2CO_3 (130.4 mg, 0.4 mmol), HOAc (24 mg, 0.4 mmol), 4Å MS (100 mg) in dry MeCN (2 mL) under air atmosphere. The reaction mixture was stirred at 100 °C until complete consumption of the starting material as detected by TLC or GC-MS analysis. After the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 x 10 mL) and then brine (1 x 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired products. A rotamerization of amide **2** was observed in NMR spectra.

methyl(phenyl)carbamoyl cyanide (**2a, 1:14**)[12c]: White solid (29.1 mg, 91% yield), mp 61-62 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.40 (m, 3H), 7.25-7.23 (m, 2H), 3.57 (s, 0.2H), 3.29 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 139.8, 130.1, 129.8, 127.0, 110.6, 36.8; LRMS (EI, 70 eV) m/z (%): 160 (M^+, 100), 132 (38), 106 (16), 91 (48).

methyl(p-tolyl)carbamoyl cyanide (**2b, 1:14**)[12c]: Yellow solid (27.5 mg, 79% yield), mp 80-82 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 3.63 (s, 0.2H), 3.34 (s, 2.8H), 2.41 (s, 2.8H), 2.37 (s, 0.2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 140.0, 137.3, 130.7, 126.8, 110.7, 36.8, 21.2; LRMS (EI, 70 eV) m/z (%): 174 (M^+, 100), 146 (17), 105 (58).

(4-methoxyphenyl)(methyl)carbamoyl cyanide (**2c, 1:14**)[12c]: Brown oil (30.8 mg, 81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 3.84 (s, 2.8H), 3.82 (s, 0.2H), 3.61 (s, 0.2H), 3.32 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 144.8, 132.4, 128.3, 115.2, 110.7, 55.5, 36.9; LRMS (EI, 70 eV) m/z (%): 190 (M^+, 100), 159 (8), 120 (25).

(4-fluorophenyl)(methyl)carbamoyl cyanide (**2d, 1:14**): Yellow solid (28.5 mg, 80% yield), mp 85-87 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2H), 7.22-7.18 (m, 2H), 3.63 (s, 0.2H),

3.34 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (d, J = 254.0 Hz), 144.6, 135.9, 129.2, 117.3 (d, J = 23.0 Hz), 110.4, 36.8; LRMS (EI, 70 eV) m/z (%): 178 (M^+, 100), 150 (11), 124 (39), 109 (27); HRMS (ESI) calcd for $C_9H_7FN_2ONa^+$ ([M + Na]$^+$) 201.0435, found 201.0431.

(4-chlorophenyl)(methyl)carbamoyl cyanide (**2e, 1:14**)[12c]: Yellow oil (32.2 mg, 83% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 3.65 (s, 0.2H), 3.35 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 138.3, 135.9, 130.4, 128.4, 110.4, 36.8; LRMS (EI, 70 eV) m/z (%): 194 (M^+, 100), 166 (12), 131 (23), 125 (21).

(4-bromophenyl)(methyl)carbamoyl cyanide (**2f, 1:14**)[12c]: Yellow solid (36.7 mg, 77% yield), mp 105-107 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 9.0 Hz, 2H), 7.21 (d, J = 9.0 Hz, 2H), 3.64 (s, 0.2H), 3.35 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 138.9, 133.5, 128.6, 123.9, 110.4, 36.7; LRMS (EI, 70 eV) m/z (%): 240/238 (M^+, 48), 184 (13), 131 (14), 105 (28), 67(100).

methyl(4-(trifluoromethyl)phenyl)carbamoyl cyanide (**2g, 1:14**): Yellow solid (18.7 mg, 41% yield), mp 81-83 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 3.60 (s, 0.2H), 3.30 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 142.9, 131.7 (q, J_{C-F} = 33.0 Hz), 127.5, 127.4, 123.4 (q, J_{C-F} = 270.1 Hz), 110.4, 36.6; LRMS (EI, 70 eV) m/z (%): 228 (M^+, 100), 200 (28), 174 (15), 159 (24), 145 (44); HRMS (ESI) calcd for $C_{10}H_8F_3N_2O^+$ ([M + H]$^+$) 229.0583, found 229.0580.

(4-(methoxycarbonyl)phenyl)(methyl)carbamoyl cyanide (**2h, 1:14**): White solid (19.6 mg, 45% yield), mp 75-76 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 3.96 (s, 2.8H), 3.93 (s, 0.2H), 3.70 (s, 0.2H), 3.40 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 144.2, 143.5, 131.5, 126.9, 124.5, 110.4, 52.5, 36.6; LRMS (EI, 70 eV) m/z (%): 218 (M^+, 100), 187 (94), 121 (56); HRMS (ESI) calcd for $C_{11}H_{11}N_2O_3^+$ ([M + H]$^+$) 219.0764, found 219.0772.

(4-acetylphenyl)(methyl)carbamoyl cyanide (**2i, 1:14**): Yellow solid (21.8 mg, 54% yield), mp 121-123 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 3.70 (s, 0.2H), 3.40 (s, 2.8H), 2.65(s, 2.8H), 2.61(s, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 144.1, 143.6, 137.8, 130.1, 127.0, 110.4, 36.6, 26.7; LRMS (EI, 70 eV) m/z (%): 202 (M^+, 48), 187 (100), 121 (33); HRMS (ESI) calcd for $C_{11}H_{10}N_2O_2Na^+$ ([M + Na]$^+$) 225.0634, found 225.0638.

[1,1'-biphenyl]-4-yl(methyl)carbamoyl cyanide (**2j, 1:14**)[12c]: White solid (24.1 mg, 51% yield), mp 151-153 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.41-7.38 (m, 2H), 7.32-7.29(m, 3H), 3.62 (s, 0.2H) 3.32 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

144.6, 142.8, 139.5, 138.9, 129.0, 128.8, 128.1, 127.3, 127.2 110.7, 36.8; LRMS (EI, 70 eV) m/z (%): 236 (M^+, 100), 207 (20), 182 (21), 170 (29), 167 (29), 154 (21), 152(48), 67(60).

methyl(m-tolyl)carbamoyl cyanide (**2k, 1:14**)[12c]: Yellow oil (23.7 mg, 68% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (m, 1H), 7.28-7.26(m, 1H), 7.11-7.10 (m, 2H), 3.63 (s, 0.2H), 3.34 (s, 2.8H), 2.41 (s, 2.8H), 2.37 (s, 0.2H),. ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 140.4, 139.8, 130.5, 129.8, 127.5, 124.0, 110.7, 36.7, 21.2; LRMS (EI, 70 eV) m/z (%): 174 (M^+, 100), 146 (36), 105 (96).

(3-methoxyphenyl)(methyl)carbamoyl cyanide (**2l, 1:14**): Yellow solid (24.7 mg, 65% yield), mp 77-78 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.38 (m, 1H), 7.01-7.00 (m, 1H), 6.91-6.89 (m, 1H), 6.83 (s, 1H), 3.84 (s, 2.8H), 3.80 (s, 0.2H), 3.63 (s, 0.2H), 3.35 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 144.5, 140.8, 130.9, 119.1, 115.3, 112.9, 110.7, 55.6, 36.7; LRMS (EI, 70 eV) m/z (%): 190 (M^+, 100), 159 (72), 120 (56); HRMS (ESI) calcd for $C_{10}H_{11}N_2O_2^+$ ($[M + H]^+$) 191.0815, found 191.0814.

(3-chlorophenyl)(methyl)carbamoyl cyanide (**2m, 1:14**)[12c]: Yellow oil (29.1 mg, 75% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.34 (s, 1H), 7.25-7.23 (m, 1H), 3.65 (s, 0.2H), 3.36 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 140.9, 135.7, 131.2, 130.1, 127.4, 125.5, 110.4, 36.8; LRMS (EI, 70 eV) m/z (%): 194 (M^+, 100), 166 (46), 131 (32), 125 (50).

methyl(o-tolyl)carbamoyl cyanide (**2n, 1:14**)[12c]: Yellow solid (24.7 mg, 71% yield), mp 75-76 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.32 (m, 3H), 7.22 (d, J = 7.0 Hz, 1H), 3.55 (s, 0.2H), 3.28 (s, 2.8H), 2.30 (s, 2.8H), 2.20 (s, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 138.6, 136.1, 131.9, 130.4, 128.4, 127.9, 110.6, 35.8, 17.2; LRMS (EI, 70 eV) m/z (%): 174 (M^+, 100), 157 (88), 146 (33), 118 (50).

(2-methoxyphenyl)(methyl)carbamoyl cyanide (**2o, 1:29**): Yellow solid (29.3 mg, 77% yield), mp 74-76 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.43 (m, 1H), 7.26-7.24 (m, 1H), 7.06-7.03 (m, 2H), 3.89 (s, 2.9H), 3.85 (s, 0.1H), 3.53 (s, 0.1H), 3.26 (s, 2.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 145.8, 131.4, 129.0, 128.4, 121.3, 112.4, 110.9, 55.7, 35.7; LRMS (EI, 70 eV) m/z (%): 190 (M^+, 100), 159 (90), 120 (88); HRMS (ESI) calcd for $C_{10}H_{11}N_2O_2^+$ ($[M + H]^+$) 191.0815, found 191.0810.

(2-fluorophenyl)(methyl)carbamoyl cyanide (**2p, 1:14**): Yellow solid (30.6 mg, 86% yield), mp 81-83 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.47 (m, 1H), 7.38-7.35 (m, 1H), 7.30-7.26 (m, 2H), 3.61 (s, 0.2H), 3.34 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2 (d, J = 250.6 Hz), 144.9, 131.9, 129.6, 127.5 (d, J = 12.8 Hz), 125.1, 117.4 (d, J = 19.5 Hz), 110.3, 36.2; LRMS (EI, 70 eV) m/z

(%): 178 (M^+, 100), 159 (24), 124 (25), 109 (30); HRMS (ESI) calcd for $C_9H_7FN_2ONa^+$ ([M + Na]$^+$) 201.0435, found 201.0443.

(2-chlorophenyl)(methyl)carbamoyl cyanide (**2q, 1:14**): Yellow oil (29.5 mg, 76% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 1H), 7.40-7.30 (m, 3H), 3.48 (s, 0.2H), 3.21 (s, 2.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 137.2, 133.3, 131.6, 131.1, 130.1, 128.7, 110.3, 36.6; LRMS (EI, 70 eV) m/z (%): 194 (M^+, 100), 166 (68), 131 (43), 125 (63); HRMS (ESI) calcd for $C_9H_7ClN_2ONa^+$ ([M + Na]$^+$) 217.0139, found 217.0131.

methyl(naphthalen-1-yl)carbamoyl cyanide (**2r, 1:29**): Yellow oil (28.1 mg, 67% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.89 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.60-7.52 (m, 2H), 7.50-7.47 (m, 1H), 7.42 (d, J = 7.5 Hz, 1H), 3.65 (s, 0.1H), 3.39 (s, 2.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 136.0, 134.8, 130.8, 130.0, 129.0, 128.3, 127.3, 126.6, 125.6, 121.3, 110.6, 36.8; LRMS (EI, 70 eV) m/z (%): 210 (M^+, 97), 182 (20), 154 (38), 141 (21), 128 (54), 115 (37), 67 (100); HRMS (ESI) calcd for $C_{13}H_{10}N_2ONa^+$ ([M + Na]$^+$) 233.0685, found 233.0692.

ethyl(phenyl)carbamoyl cyanide (**2s, 1:9**)[12c]: Yellow solid (21.6 mg, 62% yield) , mp 94-95 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.45 (m, 3H), 7.31-7.26 (m, 2H), 4.04 (q, J = 7.0 Hz, 0.2H), 3.83 (q, J = 7.0 Hz, 1.8H), 1.29 (t, J = 7.0 Hz, 0.3H), 1.18 (t, J = 7.0 Hz, 2.7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 138.3, 130.1, 129.9, 128.2, 110.6, 44.4, 12.4; LRMS (EI, 70 eV) m/z (%): 174 (M^+, 100), 159 (71), 146 (28), 118 (55), 105 (69).

hexyl(phenyl)carbamoyl cyanide (**2t, 1:9**): Yellow oil (21.6 mg, 47% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.39 (m, 3H), 7.21 (d, J = 7.5 Hz, 2H), 3.90 (t, J = 7.5 Hz, 0.2H) 3.69 (t, J = 7.5 Hz, 1.8H), 1.49-1.43 (m, 2H), 1.24-1.19 (m, 6H), 0.80-0.78 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 138.6, 130.1, 129.8, 128.1, 110.7, 49.4, 31.3, 27.1, 26.2, 22.4, 13.9; LRMS (EI, 70 eV) m/z (%): 230 (M^+, 26), 188 (20), 159 (100), 146 (51), 132 (33), 119 (28), 105 (66); HRMS (ESI) calcd for $C_{14}H_{18}N_2ONa^+$ ([M + Na]$^+$) 253.1311, found 253.1311.

isopropyl(phenyl)carbamoyl cyanide (**2u**): Yellow solid (26.7 mg, 71% yield), mp 92-94 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.40 (m, 3H), 7.20-7.16 (m, 2H), 4.73 (hept, J = 7.0 Hz, 1H), 1.09 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 135.3, 130.3, 130.2, 129.8, 110.7, 48.6, 20.4; LRMS (EI, 70 eV) m/z (%): 188 (M^+, 100), 173 (52), 146 (59), 119 (67); HRMS (ESI) calcd for $C_{11}H_{13}N_2O^+$ ([M + H]$^+$) 189.1022, found 189.1029.

benzyl(phenyl)carbamoyl cyanide(**2v, 1:19**): Yellow solid (31.2 mg, 66% yield), mp 119-121 °C(uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.39 (m, 3H), 7.30-7.29 (m, 3H), 7.17-7.15 (m,

2H), 7.10-7.08 (m, 2H), 5.14 (s, 0.1H), 4.91 (s, 1.9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 138.3, 134.6, 130.0, 129.98, 129.1, 128.8, 128.43, 128.35, 110.6, 53.1; LRMS (EI, 70 eV) m/z (%): 236 (M^+, 91), 119 (100), 91 (97); HRMS (ESI) calcd for $C_{15}H_{13}N_2O^+$ ($[M + H]^+$) 237.1022, found 237.1025.

dihexylcarbamoyl cyanide (**2w**): Colourless oil (18.1 mg, 38% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (t, *J* = 7.0 Hz, 2H), 3.29 (t, *J* = 7.0 Hz, 2H), 1.58-1.48 (m, 4H), 1.26-1.19 (m, 12H), 0.83-0.81 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 110.9, 49.1, 45.4, 31.3, 31.2, 28.8, 27.0, 26.4, 26.1, 22.44, 22.43, 13.89, 13.86; LRMS (EI, 70 eV) m/z (%): 238 (M^+, 1), 166 (51), 96 (100), 83 (50), 55 (28); HRMS (ESI) calcd for $C_{14}H_{27}N_2O^+$ ($[M +H]^+$) 239.2118, found 239.2125.

dibenzylcarbamoyl cyanide (**2x**)[12c]: Yellow oil (26.5 mg, 53% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.20 (m, 6H), 7.13-7.07 (m, 4H), 4.52 (s, 2H), 4.36 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 134.4, 133.8, 129.3, 129.1, 128.9, 128.7, 128.5, 127.9, 110.9, 51.4, 47.1; LRMS (EI, 70 eV) m/z (%): 250 (M^+, 10), 159 (52), 109 (38), 92 (89), 91 (100), 79 (34), 65 (27).

diphenylcarbamoyl cyanide(**2y**): Yellow oil (18.7 mg, 42% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.41 (m, 3H), 7.33-7.29 (m, 4H), 7.22-7.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 139.4, 139.1, 130.3, 130.0, 129.4, 128.7, 127.8, 125.1, 110.9; LRMS (EI, 70 eV) m/z (%): 222 (M^+,95), 193 (28), 167 (45), 128 (100), 77 (47); HRMS (ESI) calcd for $C_{14}H_{11}N_2O^+$ ($[M + H]^+$) 223.0866, found 223.0856.

dibenzylcarbamoyl cyanide (**3z**)[16]: Yellow solid (18.5 mg, 68% yield), mp 161-164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.20 (m, 2H), 7.00 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 138.0, 128.9, 124.3, 120.1, 24.4; LRMS (EI, 70 eV) m/z (%): 135 (M^+, 58), 93 (100), 77 (7), 65 (5).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for product **2a-2y** and **3z**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

References

(1) For selected reviews, see: (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 237-432. (b) Hagmann, W. K. *J. Med. Chem*. **2008**, *51*, 4359-4369. (c) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Pozo, C. del.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2012**, *114*, 2432-2506.

(2) (a) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev*. **2015**, *115*, 931-972. (b) Torrens, H. *Coord. Chem. Rev*. **2005**, *249*, 1957-1985. (c) Amii, H.; Uneyama, K. *Chem. Rev*. **2009**, *109*, 2119-2183. (d) Chen, Z.; He, C.-Y.; Yin, Z.; He, L.; He, Y.; Zhang, X. *Angew. Chem., Int. Ed*. **2013**, *52*, 5813-5817.

(3) For selected examples: (a) Yoshida, S.; Shimomori, K.; Kim, Y.; Hosoya, T. *Angew. Chem., Int. Ed*. **2016**, *55*, 10406-10409. (b) Scott, V. J.; Çelenligil-Çetin, R.; Ozerov, O. V. *J. Am. Chem. Soc*. **2005**, *127*, 2852-2853. (c) Douvris, C.; Ozerov, O. V. *Science*. **2008**, *321*, 1188-1190. (d) Stahl, T.; Klare, H. F. T.; Oestreich, M. *J. Am. Chem. Soc*. **2013**, *135*, 1248-1251. (e) Amii, H.; Hatamoto, Y.; Seo, M.; Uneyama, K. *J. Org. Chem*. **2001**, *66*, 7216-7218. (f) Doi, R.; Ohashi, M.; Ogoshi, S. *Angew. Chem., Int. Ed*. **2016**, *55,* 341-344.

(4) (a) Li, H.-Y.; Delucca, I.; Drummond, S.; Boswell, G. A. *J. Org. Chem*. **1997**, *62,* 2550-2554. (b) Schwarz, M. C.; Dastbaravardeh, N.; Kirchner, K.; Schnürch, M.; Mihovilovic, M. D. *Monatsh. Chem*. **2013**, *144*, 539-552. (c) Kobayashi, Y.; Kumadaki, I.; Taguchi, S.; Hanzawa, Y. *Chem. Pharm. Bull*. **1972**, *20*, 1047-1049.

(5) (a) Tsukamoto, S.; Kato, H.; Hiroshi, H.; Fusetani, N. *J. Org. Chem*. **1996**, *61*, 2936-2937. (b) Fu, X.; Schmitz, F. J. *J. Nat. Prod*. **1999**, *62*, 1072-1073. (c) Lacy, C.; Scheuer, P. *J. Nat. Prod*. **2000**, *63*, 119-121. (d) Jr, J. H.; Han, J. C.-Y.; Reiser, R. W. *J. Agric. Food. Chem*. **1978**, *26*, 529-536.

(6) (a) Patai, S.; Rappaport, Z. *Preparation and synthetic applications of cyano compounds*. *Wiley*. New York, 1983. (b) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications, 4th ed.* Thieme: Stuttgart. 2008.

(7) For selected examples: (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev*. **2011**, *40*, 5049-5067. (b) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 2890-2891. (c) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem*. **1998**, *63*, 8224-8228. (d) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem*. **2005**, *70*, 1508-1510.

(8) For selected examples: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc*. **2006**, *128*, 6790-6791. (b) Kim, J.; Chang, S. *J. Am. Chem. Soc*. **2010**, *132*, 10272-10274. (c) Ding, S.; Jiao, N. *J. Am. Chem. Soc*. **2011**, *133*, 12374-12377. (d) Yu, D.-G.; Gensch, T.; Azambuja, F. D.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722-17725. (e) Yang, Y.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2014**, *53*, 8677-8681. (f) Shu, Z.; Ji, W.; Wang, X.; Zhou, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed*. **2014**, *53,* 2186-2189.

(9) (a) Ishihara, K., Furuya, Y.; Yamamoto, H. *Angew. Chem., Int. Ed*. **2002**, *41*, 2983-2986. (b) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem., Int. Ed*. **2007**, *46*, 3922-3925. (c) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed*. **2013**, *52*, 10573-10576. (d) Guo, S.; Wan, G.; Sun, S.; Jiang, Y.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 5085-

5088. (e) Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed*. **2009**, *48,* 7094-7097. (f) Wu, D.; Zhang, J.; Cui, J.; Zhang, W.; Liu, Y. *Chem. Commun*. **2014**, *50*, 10857-10860.

(10) (a) Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 6677-6680. (b) Wang, T.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 11692-11695.

(11) Dutta, U.; Lupton, D. W.; Maiti, D. *Org. Lett.* **2016**, *18*, 860-863.

(12) (a) García-Egido, E.; Paz, J.; Iglesias, B.; Muñoz, Luis. *Org. Biomol. Chem.* **2009**, *7*, 3991-3999. (b) Yang, J.; Xiang, D.; Zhang, R.; Zhang, N.; Liang, Y.; Dong, D. *Org. Lett.* **2015**, *17*, 809-811. (c) Zhan, Z.; Cheng, X.; Zheng, Y.; Ma, X.; Wang, X.; Hai, L.; Wu, Y. *RSC Adv.* **2015**, *5*, 82800-82803.

(13) Christe, K. O.; Hegge, J.; Hoge, B.; Haiges, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6155-6158.

(14) (a) Chen, F.; Huang, X.; Li, X.; Shen, T.; Zou, M.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 10495-10499. (b) Yang, Z.-J.; Liu, C.-Z.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. *Chem. Commun.* **2014**, *50*, 14554-14557. (c) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1120-1123. (d) Prateeptongkum, S.; Jovel, I.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Chem. Commun.* **2009**, *40*, 1990-1992. (e) Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1991**, *56*, 4772-4778.

(15) Kobayashi, Y.; Kuroda, M.; Toba, N.; Okada, M.; Tanaka, R.; Kimachi, T. *Org. Lett*. **2011**, *13*, 6280-6283.

(16) Tsukamoto, H.; Suzuki, R.; Kondo, Y. *J. Comb. Chem.* **2006**, *8*, 289-292.