

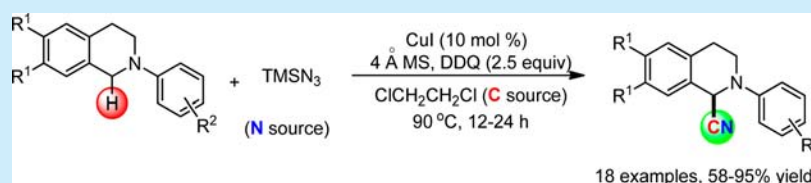
A Unique Combined Source of “CN” from 1,2-Dichloroethane and TMSN₃ in the Copper-Catalyzed Cyanation of a C(sp³)–H Bond Adjacent to a Nitrogen Atom

Gen Zhang,^{†,‡} Yunxia Ma,[‡] Guangbin Cheng,[†] Dabin Liu,[†] and Rui Wang^{*,‡}

[†]School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210000, China

[‡]Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China

S Supporting Information



ABSTRACT: A novel combined metal-free “CN” source from trimethylsilyl azide and 1,2-dichloroethane has been developed and successfully applied to copper-catalyzed oxidative cyanation of α -C–H tertiary amines for the synthesis of C1-cyanation tetrahydroisoquinoline derivatives with good to excellent yields for the first time.

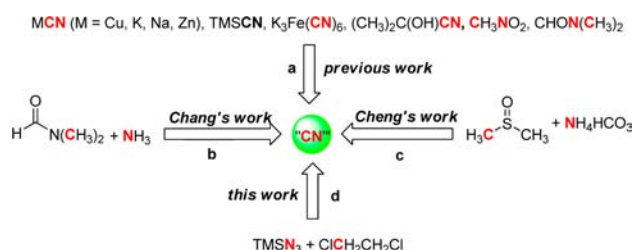
A metal-catalyzed cyanation reaction through direct C–H functionalization with cyanide-containing reagents provides an efficient route to various useful organonitriles.¹ Many metal cyanide salts (CuCN, KCN, NaCN, and ZnCN), TMSCN, and K₃Fe(CN)₆ have been used as the original “CN” source.^{2–4} In addition, the “CN” unit can be generated in situ from acetone cyanohydrins,⁵ nitromethane,⁶ or *N,N*-dimethylformamide (DMF).⁷ Generally, those are the signal sources of “CN”. The discovery of new sources of “CN” generated in situ from other simple and readily available reagents is still an extremely attractive yet challenging goal, especially from two different sources. In 2010, Chang and co-workers reported a combined –CN source in which the carbon originates from *N,N*-dimethylformamide (DMF) and the nitrogen from ammonia for the direct cyanation of aryl C–H bonds (Scheme 1b).⁸ Recently, Cheng and co-workers disclosed the

our knowledge, remained elusive, especially for the catalytic cyanation of a C_{sp}³–H bond adjacent to a nitrogen atom, even though it presents a powerful method for amine functionalization.

α -Aminonitriles are highly useful intermediates in organic synthesis for a wide range of natural products, pharmaceuticals, functional materials, and agricultural chemicals.¹⁰ In addition, the nitrile functional group could be easily transformed to other important groups such as aldehydes, amines, amides, amidines, tetrazoles, and their carboxyl derivatives.¹¹ Thus, it is reasonable that considerable efforts have been devoted to the development of novel methods for their preparation. The transition-metal-catalyzed oxidative α -cyanation of tertiary amines via direct C(sp³)–H bonds functionalization provides one of the most straightforward and convenient routes to α -aminonitriles.³

We recently demonstrated original examples on copper-catalyzed oxidative^{12,13} α -C–H alkylation and olefination of tertiary amine for the synthesis of C1-alkylation^{14a,c} C1-alkene,^{14b} and ring-fused^{14d} tetrahydroisoquinolines. Under the oxidizing conditions, a hydride at the α -position of tertiary amines could be abstracted, and then a cationic intermediate¹⁵ would be formed, which could react with a CN[–] to construct a new C_{sp}³–C_{sp} bond (Scheme 2). We report the first example of generating “CN” from two different, readily available precursors, azidotrimethylsilane (TMSN₃) and 1,2-dichloroethane (DCE), in the copper-catalyzed oxidative cyanation of tertiary amines for the synthesis of C1-cyanation tetrahydroisoquinoline (Scheme 1d).

Scheme 1. Sources of “CN” in Cyanation Reactions

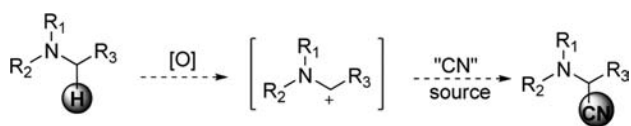


cyanation of the 3-position of indole sp² C–H bonds by the combination of DMSO and NH₄HCO₃ as the –CN source (Scheme 1c).⁹ However, the similar process at unactivated alkyl C–H sites using a combined –CN source, to the best of

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Scheme 2. Strategy for Cyanation of a C(sp³)–H Bond Adjacent to a Nitrogen Atom



Initially, we used *N*-PMP tetrahydroisoquinoline (**1a**) as tertiary amine to couple with the combined “CN” source from TMSN₃ and DCE catalyzed by copper salt under oxidative conditions. When the reaction was run with 0.2 equiv of CuI, 2.0 equiv of TMSN₃, and 1.5 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at 80 °C, we got the desired product, 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**3a**) with poor yield (Table 1, entry 1). The

Table 1. Optimization of the Reaction Conditions^a

entry	metal (mol %)	TMSN ₃ (equiv)	oxidative (equiv)	yield ^b (%)
1 ^c	CuI (20)	2.0	DDQ (1.5)	23
2 ^c	CuI (20)	4.0	DDQ (1.5)	61
3	CuI (20)	5.0	DDQ (1.5)	72
4	CuI (10)	5.0	DDQ (2.5)	77
5	CuI (10)	5.0	DDQ (2.5)	85 ^d
6	CuBr (10)	5.0	DDQ (2.5)	61
7	CuCl (10)	5.0	DDQ (2.5)	45
8	CuOTf (10)	5.0	DDQ (2.5)	42
9	Cu(OTf) ₂ (10)	5.0	DDQ (2.5)	trace
10	none	5.0	DDQ (2.5)	trace
11	CuI (10)	5.0	TBHP (2.5)	trace
12	CuI (10)	5.0	PhI(OAc) ₂ (2.5)	trace
13	CuI (10)	5.0	BQ (2.5)	30
14	CuI (10)	5.0	O ₂ (1 atm)	n.d. ^e

^aReaction conditions: **1a** (0.2 mmol), TMSN₃, catalyst, oxidant, molecular sieves (4 Å; 50 mg), DCE (2 mL), stirred at 80 °C under Ar. ^bYield of the isolated product. ^cThe reaction was carried out in the absence of molecular sieves (4 Å). ^dThe reaction was carried out at 90 °C. ^eNot determined. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBHP = *tert*-butyl hydroperoxide, BQ = benzoquinone, M.S. = molecular sieves, TMS = trimethylsilyl, DCE = 1,2-dichloroethane.

yield of **3a** could be improved to 61% when 4.0 equiv of TMSN₃ was used (Table 1, entry 2). To our delight, 72% yield of the coupling product could be obtained when the quantity of the TMSN₃ was improved to 5.0 equiv and 4 Å molecular sieves were used as additive (Table 1, entry 3). Furthermore, a small increase of the yield could be observed when 2.0 equiv of DDQ was used, although 10% of CuI was employed (Table 1, entry 4). On the other hand, temperature is also a key factor for this reaction because when the temperature was raised to 90 °C a better yield could be achieved (Table 1, entry 5). Then, a series of other copper salts (CuBr, CuCl, CuOTf, Cu(OTf)₂) were evaluated, wherein Cu(I) salts could promote the reaction with the moderate yield, while Cu(II) salt gives no desirable product (Table 1, entries 6–9). However, the reaction could not occur without the CuI (Table 1, entry 10). Other organic oxidants, including *tert*-butyl hydroperoxide (TBHP), PhI(OAc)₂, benzoquinone (BQ), and molecular oxygen (O₂), were

also used to improve the activity of this reaction. However, those organic oxidants could not give the desired product in good yield (Table 1, entries 11–14).

Having the optimized reaction conditions in hand, we then examined the scope and limitation of this novel oxidative α -cyanation of tertiary amines with combined “CN” source (Table 2). The combined –CN source of TMSN₃ and DCE could coupled with various aromatic-substituted tetrahydroisoquinolines **1a–q** giving good to excellent yields. The aromatic-substituted tetrahydroisoquinolines bearing electron-withdrawing groups on the *para* position of the phenyl ring led to slightly lower product yields than those with electron-donating groups on the *para* position (Table 2, entries 1–7). This might be due to the fact that the electron-withdrawing substituent in the *para* position of the phenyl ring reduces the activity of the tetrahydroisoquinoline to form an iminium cation. The same results were obtained when the electron-withdrawing and electron-donating groups were on the *meta* (Table 2, entries 8–10) and *ortho* position of the phenyl ring of **1**. However, when there was a substituent on the *ortho* position of the phenyl ring of **1**, neither the electron-withdrawing group nor the electron-donating group, the desired oxidative coupling products were worse than those with the substituents on the *para* or the *meta* position (Table 2, entries 11–13). This may be due to steric factors. With no substituent on the phenyl ring of **1**, the desired oxidative coupling product **3n** was obtained in satisfactory yields of 88% (Table 2, entry 14). The reaction worked well with good to excellent yields when there were double substituents on the *N*-aryl ring of aromatic-substituted tetrahydroisoquinolines **1** (76–93%, Table 2, entries 15–17). However, due to the weak activity, the coupling with the acyclic tertiary amine, *N*-benzylaniline **1r**, could not occur to yield the desired product. Other combined –CN sources were also tested, although worse results were obtained (see the Supporting Information). Some indirect proof suggested that the nitrogen of the combined “CN” source originates from TMSN₃ and the carbon from DCE, which was used as both reagent and solvent (see the Supporting Information). The possible mechanism of this novel oxidative copper-promoted cyanation of α -C–H tertiary amines was presumed to involve single-electron transfer (SET) (see the Supporting Information), and the structure of the α -cyanation product **3n** was determined by single-crystal X-ray crystallographic analysis (Figure 1).¹⁶

In conclusion, we have successfully developed a novel combined “CN” source from TMSN₃ and DCE, and applied it to copper-catalyzed oxidative cyanation of α -C–H tertiary amines for the synthesis of C1-cyanation tetrahydroisoquinoline derivatives with good to excellent yields (58–95%). Compared with the metal cyanide salts, this protocol is very environmentally friendly. The application of this new combined

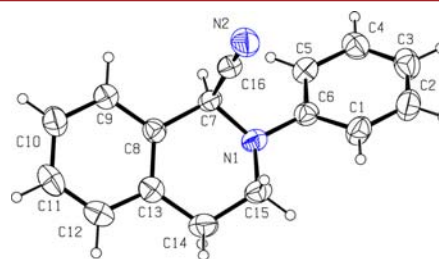


Figure 1. X-ray crystal data of compound **3n**.

Table 2. Investigation of the Scope of the Procedure^a

entry	substrate	time (h)	product	yield (%) ^b
1		12		85
2		12		83
3		18		77
4		18		62
5		12		81
6		18		76
7		12		82
8		18		84
9		24		71
10		18		95
11		24		66
12		24		78
13		24		58
14		12		88
15		12		93
16		18		92
17		18		76
18		24		n.d. ^c

^aReaction conditions: **1a** (0.2 mmol), TMSN₃ (1.0 mmol), CuI (0.02 mmol), DDQ (0.5 mmol), molecular sieves (4 Å; 50 mg), DCE (2 mL), stirred at 90 °C under Ar atmosphere. ^bYield of the isolated product. ^cNot determined.

"CN" source in other transformations is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **3n**. This material is available free of charge via the Internet at <http://pubs.acs.org>

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangrui@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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(16) CCDC 966884 (**3n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.