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Zinc-Catalyzed Direct Cyanation of Indoles and Pyrroles: Nitromethane as a Source of a Cyano Group

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Abstract: With nitromethane and diphenylsilane (Ph_2SiH_2), zinc triflate behaves as a Lewis acid catalyst for the cyanation of nitrogen-containing heteroarenes such as indoles and pyrroles. This is the first realization of the Lewis acid-catalyzed direct cyanation of a C(aryl)−H bond with no CN group-containing cyanating agent.

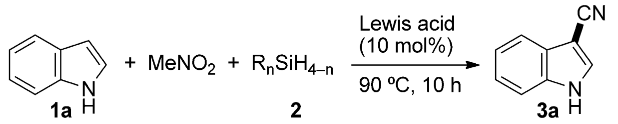
Keywords: heteroarenes; heterocycles; Lewis acids; nitriles; zinc

Aryl and heteroaryl nitriles represent an important class of core structures found in natural products, pharmaceuticals, agrochemicals, and functional materials.[1] The CN group has also been recognized as a versatile scaffold for elaboration of functional groups, for instance, CHO, CO_2H, CO_2R, $CONH_2$, CH_2NH_2, and others.[2] The most common way to construct (hetero)aryl−CN linkages is likely to be treatment of pre-activated (hetero)arenes with metal cyanides under transition metal catalysis,[3,4,5] which has developed since the advent of Sandmeyer[6] and Rosenmund–von Braun[7] reactions. However, due to recent trends towards reducing our dependence on pre-activation and toxic metal reagents,[8] a major interest has been rapidly shifting to direct (hetero)aryl C−H cyanation[9] with inexpensive, harmless and readily available non-metallic reagents.[10] Of particular interest is the use of cyanating agents that have no CN group but act as CN sources. In this regard, the pioneering research by Yu and colleagues has disclosed that nitromethane is able to cyanate 2-phenylpyridine with the aid of a stoichiometric amount of $Cu(OAc)_2$, based on a chelation-assisted strategy.[11] Approaches with DMF,[12] DMF–$NH_3(NH_4I)$,[13] DMSO–NH_4HCO_3[14] and *t*-BuNC[15] as CN suppliers have emerged also in succession recently, but, here again, as transition metal-based systems: Pd catalysts–Cu cooxidants or a stoichiometric amount of Cu salts.[5j,16] In sharp contrast, we have found for the first time that a Lewis acid can participate as a catalyst in this reaction category.[17] We disclose herein a conceptually new cyanation reaction using a nitromethane–hydrosilane system under zinc catalysis.

We first examined suitable reaction conditions for the cyanation of indole (**1a**) (Table 1). Treating **1a** with 10 mol% of $Zn(OTf)_2$ ($Tf = SO_2CF_3$) at 90 °C for 10 h in $MeNO_2$, which was used not only as a reagent but also as a reaction medium, resulted in no cyanation of **1a** (entry 1). Although the addition of monohydrosilanes **2a**–**2c** provided no improvement, 3-cyanoindole (**3a**) was formed by using di- and trihydrosilanes **2d**–**2f** (entries 2–7). Among them, Ph_2SiH_2 (**2e**) is the most preferable, giving **3a** in 76% yield (entry 6). Reducing the amount of **2e** from 3 to 2.5 molar equiv. lowered the yield, and its higher loading was unnecessary (entries 8 and 9). Investigating the effect of other Lewis acids clearly showed that only zinc salts are valid as catalysts, and $Zn(OTf)_2$ is the most promising for the cyanation (entries 6 and 10–20). No cyanation occurred without a catalyst (entry 21). The use of a co-solvent had no positive effect, and the simple reduction of the quantity of $MeNO_2$ resulted in a poor yield (entries 22–26).

With the suitable reaction conditions in hand, we explored the scope of the indole substrate (Table 2). Besides *N*-unsubstituted indole **1a**, *N*-methyl- and *N*-benzylindoles participated in the cyanation reaction (see **3a**–**3c**). Indoles **1** with alkyl, alkoxy and bromo groups on the carbon atom were also cyanated to afford **3d**–**3j** in moderate to good yields. The acid-labile benzyloxy moiety was retained here (see **3h**).[18] In contrast to the preceding copper-based systems,[4,11–15] the aryl−boron bond that is useful for further transformations also remained intact (see **3k**).

Table 1. Lewis acid-catalyzed cyanation of indole.[a]



Entry	Lewis acid	R_nSiH_{4-n} (equiv.)	Co-solvent	Yield [%][b]
1	$Zn(OTf)_2$	none	none	<1
2	$Zn(OTf)_2$	Et_3SiH **2a** (6)	none	1
3	$Zn(OTf)_2$	Me_2PhSiH **2b** (6)	none	<1
4	$Zn(OTf)_2$	$MePh_2SiH$ **2c** (6)	none	<1
5	$Zn(OTf)_2$	$MePhSiH_2$ **2d** (3)	none	35
6	$Zn(OTf)_2$	Ph_2SiH_2 **2e** (3)	none	76
7	$Zn(OTf)_2$	$PhSiH_3$ **2f** (2)	none	40
8	$Zn(OTf)_2$	**2e** (2.5)	none	66
9	$Zn(OTf)_2$	**2e** (3.5)	none	63
10	$Cu(OTf)_2$	**2e** (3)	none	<1
11	AgOTf	**2e** (3)	none	<1
12	$In(OTf)_3$	**2e** (3)	none	<1
13	$Bi(OTf)_3$	**2e** (3)	none	<1
14	$Fe(OTf)_3$	**2e** (3)	none	<1
15	$Sc(OTf)_3$	**2e** (3)	none	<1
16	$Zn(ONf)_2$[c]	**2e** (3)	none	51
17	$Zn(NTf_2)_2$	**2e** (3)	none	10
18	ZnI_2	**2e** (3)	none	2
19	$ZnBr_2$	**2e** (3)	none	25
20	$ZnCl_2$	**2e** (3)	none	20
21	none	**2e** (3)	none	<1
22[d]	$Zn(OTf)_2$	**2e** (3)	toluene	72
23[d]	$Zn(OTf)_2$	**2e** (3)	Bu_2O	47
24[d]	$Zn(OTf)_2$	**2e** (3)	dioxane[e]	6
25[d]	$Zn(OTf)_2$	**2e** (3)	EtCN	40
26[f]	$Zn(OTf)_2$	**2e** (3)	none	11

[a] *Reagents:* **1a** (0.80 mmol), $MeNO_2$ (7.4 mmol, 0.40 mL), **2** (1.6–4.8 mmol), Lewis acid (80 μmol).

[b] Determined by GC.

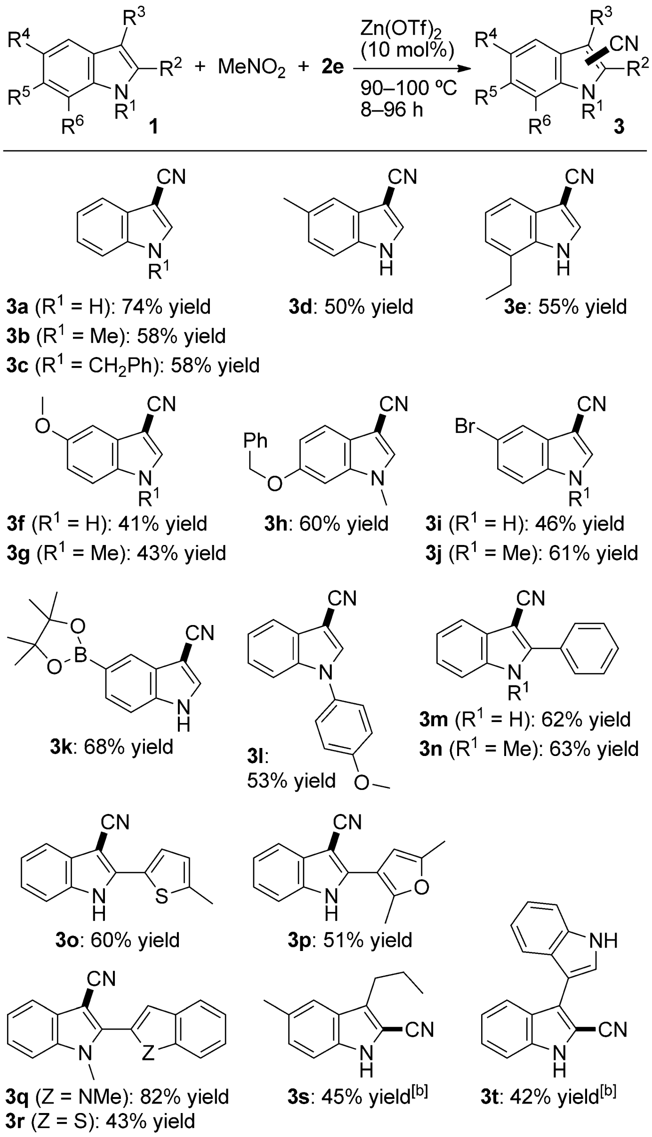
[c] $Nf = SO_2C_4F_9$.

[d] Performed in $MeNO_2$ (0.30 mL) and the co-solvent (0.10 mL).

[e] Dioxane = 1,4-dioxane.

[f] Performed in $MeNO_2$ (0.20 mL).

Table 2. Zinc-catalyzed cyanation of indoles with $MeNO_2$ and Ph_2SiH_2.[a]



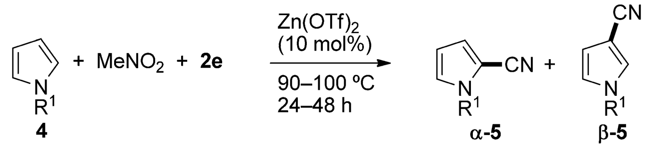
[a] Yields of isolated **3** based on **1** are shown here. Further details on the reaction conditions for each reaction are given in the Supporting Information.

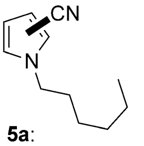
[b] $Zn(OTf)_2$ (15 mol%) was used.

This is an advantage of the present zinc catalysis.[19] Despite the fact that a series of 1- and 2-(hetero)aryl-indoles have multiple possible reaction sites, only mono-cyanation at the indolyl C-3 atom occurred to provide **3l**–**3r**, thus showing remarkable chemo- and regioselectivity. This should be because the indolyl C-3 site is the most nucleophilic among the aromatic carbons,[20] and the electron-withdrawing character of the CN group decreases the nucleophilicity of the products so as to retard extra cyanation. The less nucleophilic C-2, compared to a C-3, also worked as a reaction site (see **3s** and **3t**).

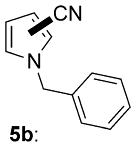
This zinc process is also applicable to the cyanation of pyrroles (Table 3). Thus, 1-hexylpyrrole was cyanated with $MeNO_2$ and **2e** under zinc catalysis to afford **5a** as a separable mixture of α- and β-isomers. Pyrroles with other alkyl and aryl groups on the nitrogen atom also participated in this protocol (see **5b**–**5d**), whereas the size of the substituent did not affect significantly the α/β ratio. Here again, no extra cyanation on and except on the pyrrole ring was observed. In contrast, other aromatic substrates such as 3,4-ethylenedioxythiophene and $PhNMe_2$ were not cyanated successfully (≤5%), due probably to their low nucleophilicity. However, such a reactivity would have contributed to the selective mono-cyanation.

Table 3. Zinc-catalyzed cyanation of pyrroles with $MeNO_2$ and Ph_2SiH_2.[a]

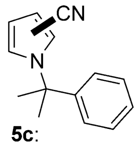




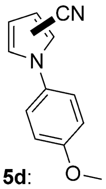
5a:
43% yield
α/β = 51:49



5b:
51% yield
α/β = 52:48



5c:
69% yield
α/β = 41:59



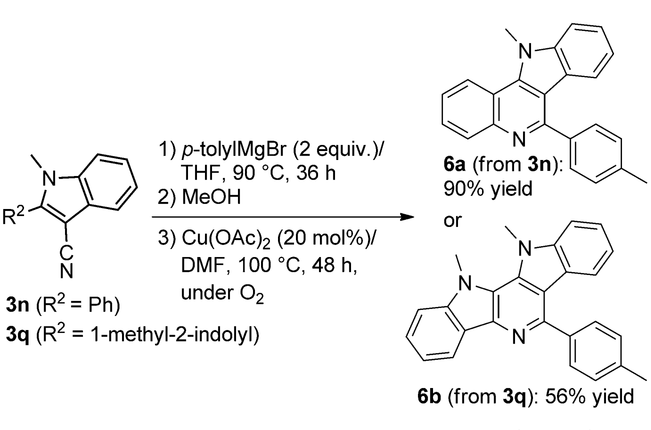
5d:
55% yield
α/β = 59:41

[a] Yields of isolated **5** based on **4** are shown here. Further details on the reaction conditions for each reaction are provided in the Supporting Information.

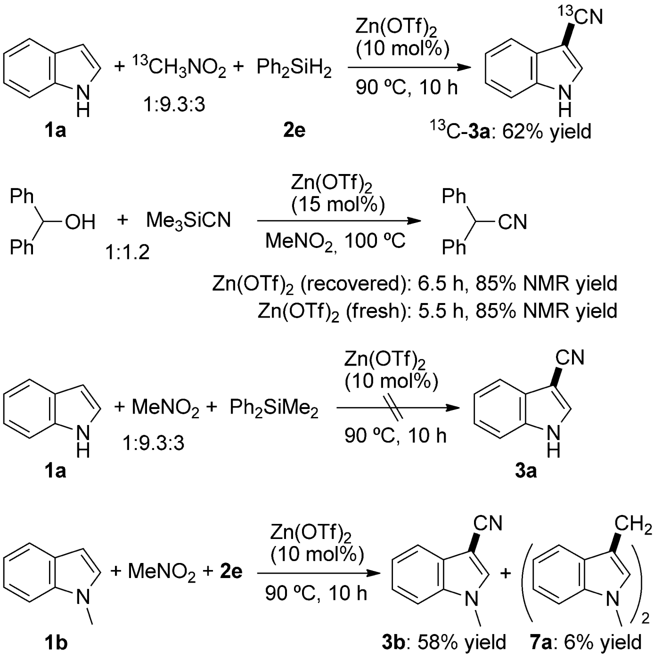
Importantly, a practical application is accomplished by the synthesis on a preparative scale. For example, cyanation of **1a** on a 10-mmol scale provided us with 1.03 g (72% yield) of **3a**.

The utility of the present reaction can be demonstrated by transforming the product into a biologically important structure, an indolo[3,2-*c*]quinoline,[21] which is found, for instance, in natural isocryptolepine[22] showing antimalarial activity (Scheme 1). Thus, nucleophilic attack of *p*-tolylMgBr to the CN group of **3n** followed by protonation with MeOH and Cu-catalyzed oxidative N–C bond-forming annulation gave **6a** in 90% yield.[23] This one-pot reaction is also effective for **3q**, thus indicating its good flexibility.

Some experimental observations might be useful for the mechanistic studies (Scheme 2). We first addressed the role of $MeNO_2$. When ^{13}C-labeled nitromethane was used, the ^{13}C atom was incorporated exclusively into the CN group of the product (^{13}C-**3a**), thus showing that the CN group comes from $MeNO_2$. In order to clarify the role of $Zn(OTf)_2$, we next tried its recovery after the cyanation reaction and then used the recovered solid for other reaction in which $Zn(OTf)_2$ has been found to act as a Lewis acid catalyst.[24] Thus, a solid recovered with 97% efficiency after the cyanation of **1a** nicely catalyzed the transformation of benzhydrol to diphenylacetonitrile in 85% NMR yield, which is fully comparable to that obtained with fresh $Zn(OTf)_2$. Accordingly, $Zn(OTf)_2$ would exist without changing its form during the cyanation process, and its role in the cyanation would be that of a Lewis acid catalyst. We successively examined the role of silicon reagent **2e** and carried out the reaction of **1a** with Ph_2SiMe_2 having no hydrogen atom, instead of **2e**, which, however, led to no cyanation. This result clearly shows that the Si–H moiety is essential for the cyanation reaction. The hydride character of Si–H might thus play an important role in this reaction. A final observation is that the reaction of *N*-methylindole (**1b**) (Table 2, **3b**) provided a non-negligible amount of 3,3′-diindolylmethane **7a** as a by-product in addition to **3b**.[25] Based on the literature, where $MeNO_2$ activated by a Lewis acid reacts with 1,3-dicarbonyl compounds as nucleophiles to be incorporated as a methylene unit into products,[26] **7a** might be formed *via* a similar type of process triggered by activation of $MeNO_2$ by $Zn(OTf)_2$.[27]

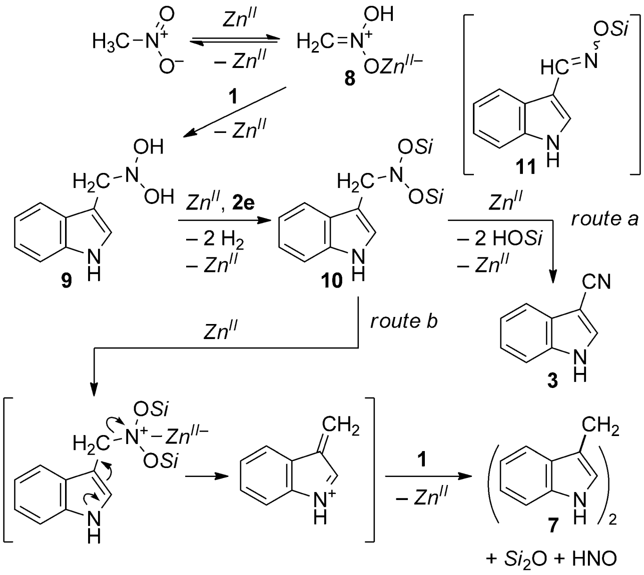


Scheme 1. One-pot annulation of 3-cyano-2-(hetero)aryl-indoles.



Scheme 2. Mechanistic studies.

Although further studies are required to verify the reaction mechanism, its tentative interpretation is



Scheme 3. A proposed reaction mechanism. Zn^{II} = Zn(OTf)$_2$. *Si* = SiR$_3$.

proposed in Scheme 3, where substituents of **1** are omitted for clarity. The first should be nucleophilic attack of **1** to *aci*-nitromethane **8** activated by Zn^{II}, just like the attack of water occurring in the Nef reaction.[28] In the present reaction, generation of **12** and **13** as non-polymeric siloxanes, which would be derived from self-dehydration of the corresponding silanol, is always observed (Figure 1). Accordingly, **9** might be converted to silylated form **10** rapidly *via* zinc-catalyzed dehydrogenative silylation.[29] The sequential elimination of two molecules of HO*Si* from **10** by way of the formation of silyl oxime **11** should lead to **3** (*route a*).[30] On the other hand, the C–N bond cleavage followed by nucleophilic attack of **1** should give **7** and also release Si_2O and HNO, similarly as in the Nef reaction (*route b*).[31]

In summary, we have developed the zinc-catalyzed cyanation of indoles and pyrroles with nitromethane and Ph$_2$SiH$_2$. This is the first demonstration of the Lewis acid-catalyzed direct cyanation of C(aryl)–H bonds with no CN group-containing cyanating agent. In terms of the promotion of sustainable chemistry, the use of a common metal, such as zinc, as the catalyst is an advantage of this approach. Further studies on the mechanism and synthetic applications are currently underway in our laboratory.

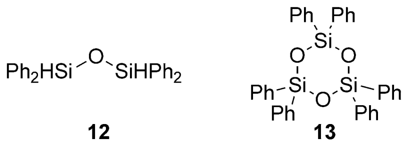


Figure 1. Non-polymeric Si-containing by-products.

Experimental Section

General Procedure Exemplified by the Synthesis of 3a on a 10-mmol Scale

Zn(OTf)$_2$ (364 mg, 1.00 mmol) was placed in a 100-mL Schlenk tube, which was heated at 150 °C under vacuum for 2 h. The tube was cooled down to room temperature and filled with argon. Nitromethane (5.0 mL) was added to the tube, and the mixture was stirred at room temperature for 3 min. To this were added indole (1.17 g, 10.0 mmol) and Ph$_2$SiH$_2$ (5.53 g, 30.0 mmol) successively. After stirring at 90 °C for 10 h, a saturated aqueous NaHCO$_3$ solution (3 mL) was added and the resulting mixture was stirred and filtered through a cotton plug, which was then flushed with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (30 mL × 2), and the combined organic layer was washed with brine and dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation of the solvent followed by column chromatography on silica gel (*n*-hexane/EtOAc = 2/1) gave 3-cyanoindole (**3a**); yield: 1.03 g (72%).

Acknowledgements

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