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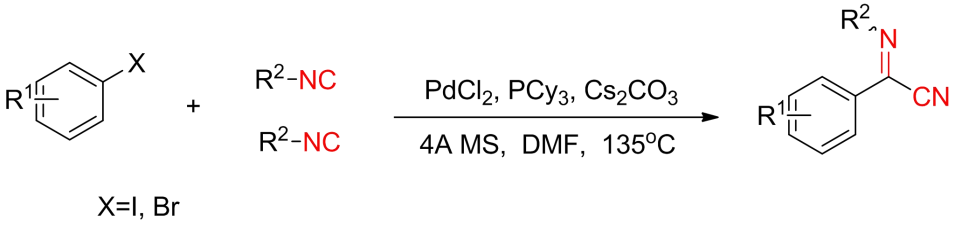
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b02777 • Publication Date (Web): 27 Jan 2016

Palladium-Catalyzed Synthesis of *α*-Iminonitriles from Aryl Halides *via* Isocyanide Double Insertion Reaction

Zhen-Bang Chen,[†] Ying Zhang,[†] Qing Yuan,[†] Fang-Ling Zhang,[†] Yong-Ming Zhu,*[,†] and Jing-Kang Shen*[,‡]

[†]College of Pharmaceutical Sciences, Soochow University, Suzhou, 215123, China

[‡]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 201203, China



ABSTRACT

An efficient one-pot synthesis of *α*-iminonitriles from readily available aryl halides *via* palladium-catalyzed double isocyanide insertion and elimination has been developed, without using various hypertoxic cyanides and excess oxidants. Furthermore, the utility of this reaction was demonstrated by the rapid total synthesis of quinoxalin and the reaction of functional groups exchange with aryl halides.

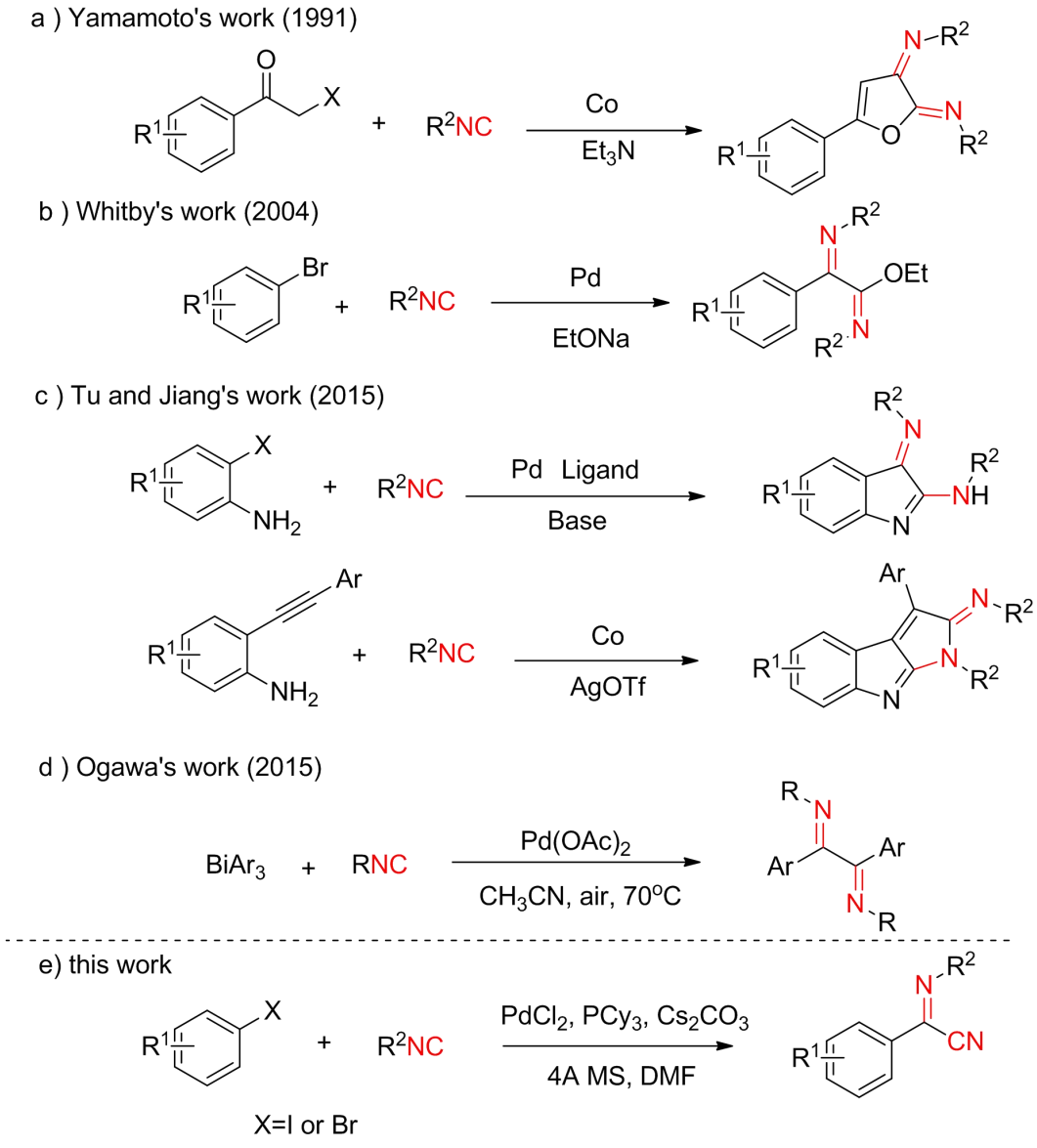
INTRODUCTION

Isocyanides are an important class of organic molecules which have been widely applied in organic, medicinal and combinatorial chemistry since the Passerini and Ugi reactions were discovered.[1] In the past decade, isocyanides have emerged as versatile C_1 building blocks to build C-C,[2] C-N,[3,4] and C-O[5] bonds in palladium-catalyzed two-component

reaction and evolutionary multicomponent reactions (MCRs). Recently, *tert*-butyl isocyanide as a cyanide alternative have been reported,[6] which further broadened the application of isocyanides in organic synthesis. During the last few years, our group have synthesized many kinds of organic compounds including isocoumarins, phthalides,[5c] quinazolinones,[3e] diazoles,[4c] indenoindolones,[2h] alkynones,[2c] indane-*1,3*-dione,[2f] diarylketones,[2g] and aryl aldehydes[7] *via* palladium-catalyzed isocyanide insertion into C−X bonds (X=Br, I). Nevertheless, the most reported achievements mainly focus on the utility of isocyanides single insertion for the synthesis of nitrogen-containing compounds. Readily polymerized in the presence of transition metal,[8] isocyanides were seldomly used for multiple insertion reaction, especially for the reaction of isocyanides multiple insertion at the same site. Only a few examples of metal-catalyzed double isocyanides insertion have been reported. For instance, in 1991, Yamamoto and co-workers[9] reported double insertion of isocyanides into a metal-carbon bond through cobalt-catalyzed (**scheme 1**, a). In 2004, Whitby *et al.*[10] reported palladium-catalyzed double isocyanides insertion into aryl bromides for the synthesis of *α*-iminoimidates (**scheme 1**, b). Recently, Tu and Jiang developed a palladium-catalyzed[3c] or cobalt(II)/silver relay catalyzed[11] isocyanides double insertion intramolecular cyclization for the formation of indole derivatives (**scheme 1**, c). Subsequently, Ogawa and co-workers[12] achieved isocyanides double insertion into Pd-C bond for the synthesis of *α*-diimines (**scheme 1**, d). Obviously, with the powerful development space and potential application, transition-metal-catalyzed isocyanides

multiple insertion reactions have increasingly attracted the attention of more and more chemists.

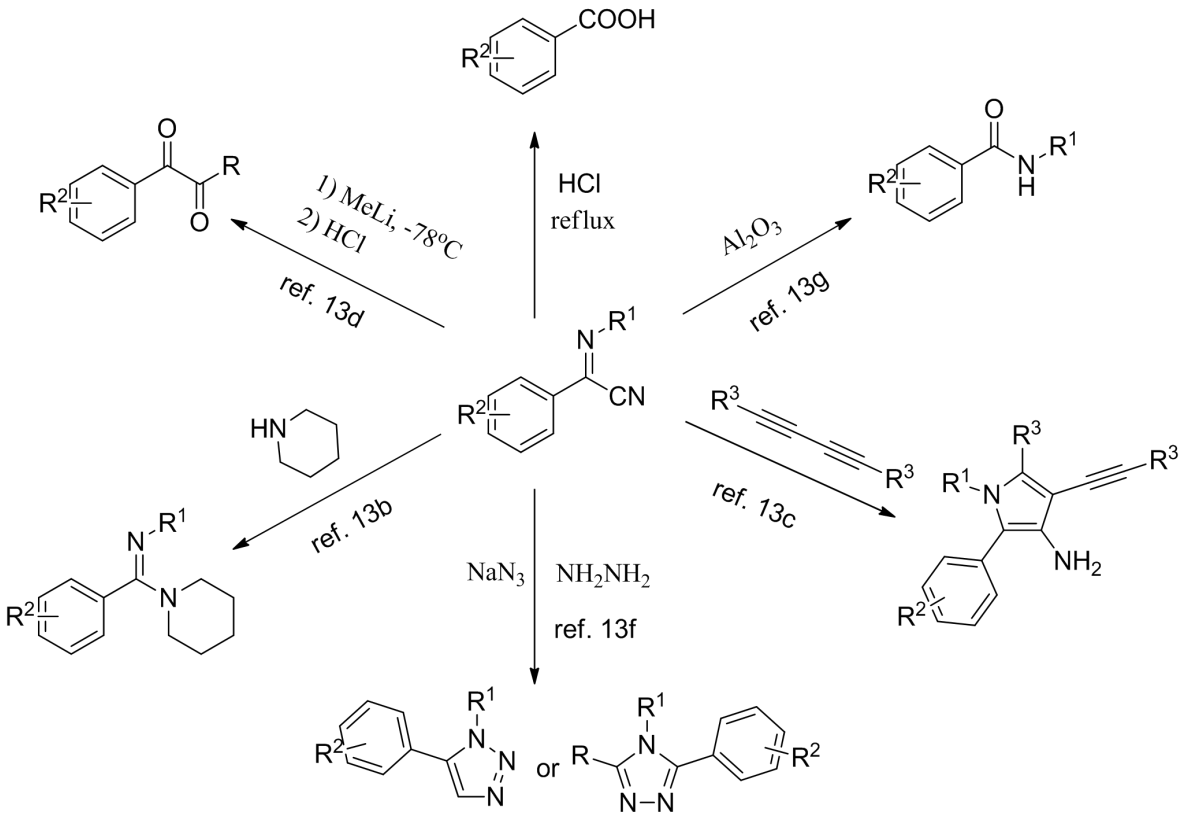
Scheme 1. Metal-Catalyzed Isocyanide Double Insertion Reaction



The α-iminonitriles (imidoyl cyanides) are an valuable class of synthetic intermediates,[13] which could not only serve as precursors for α-ketoacids, amides, *N*-alkylketene-imines, triazoles, aminopyrroles, diimines and dicarbonyl (**scheme 2**), but also provide a rapid and

valid access to build the construction of nitrogen heterocycles in cycloadditions.[14] Moreover, the α-iminonitriles are quite stable to high temperature (greater than 100^{o}C) and water, which make them as an effective substitute for acylnitriles to participate in metal-catalyzed C–CN activation.[15] In addition to its widespread use in organic transformation, α-iminonitriles also exhibit diverse biological activities, such as inhibit the function of histamine-induced or acetylcholine-induced contraction in rat ileum.[16] As a result, many methodologies have been reported for the synthesis of α-iminonitriles.[7a,13a,17] However, most of them are multistep reactions, use complex substrates, excess oxidants and various toxic cyanides such as Bu_3SnCN, $Hg(CN)_2$, NaCN, CuCN and so on. Herein, we provide a new protocol for the synthesis of α-iminonitrile *via* palladium-catalyzed double isocyanide insertion in one pot (**scheme 1**, e), of note is that the protocol employs no hypertoxic cyanides.

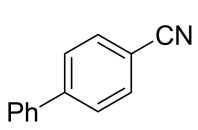
Scheme 2. Application of α-Iminonitrile



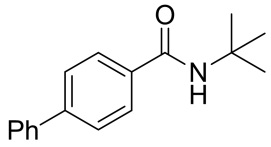
RESULTS AND DISCUSSION

Initiated investigation was performed by using *4*-iodobiphenyl **1a** and *tert*-butyl isocyanide in the presence of $Pd(OAc)_2$ and PCy_3 with K_2CO_3 as base, when the reaction was carried out in the solvent of dimethyl sulfoxide (DMSO) under nitrogen at 120°C for 12 h, the desired product **2a** was found in 31% yield (**Table 1**, entry 1), along with minor amounts of **2aa** and **2ab** (**scheme 3**), however, almost half of **1a** were remained. Prolonged reaction time increased the yield to 44% (**Table 1**, entry 2).

Scheme 3. Byproducts in the Synthetic Reaction of 2a.



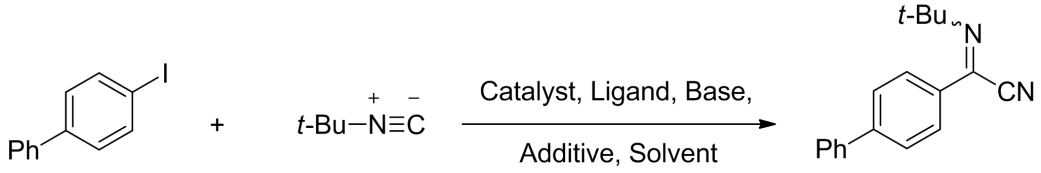
2aa



2ab

Considering that water resulted in the formation of **2ab**, we used molecular sieves (4A MS) as additive under argon, the yield was up to 57% (**Table 1**, entry 3). Raising the temperature led to an increase in the yield (**Table 1**, entry 3-5). Solvent screening showed that *N,N*-dimethylformamide (DMF) was optimal (**Table 1**, entry 5-8). Then, several bases were tested, as the base weaken, the yield of byproduct **2aa** increased, when the base was switched to Cs_2CO_3, to our surprise, the yield was improved to 79% (**Table 1**, entry 11). Subsequently, other palladium sources also were investigated, however, none of them were superior to $PdCl_2$ (**Table 1**, entry 15-16). Phosphines played a pivotal role in the reaction. We conducted the reaction with using other mono- or diphosphines, the yield of using monophosphines was superior to diphosphines and higher yield was obtained when using PCy_3 (**Table 1**, entry 17-21). Eventually, the optimized reaction conditions were $PdCl_2$ (10 mol %) and PCy_3 (20 mol %) as catalyst system, with Cs_2CO_3 (2 equiv) as base and DMF as solvent and 4A MS as additive under argon at 135°C.

Table 1. **Optimization of Reaction Conditions**[a]



1a **2a**

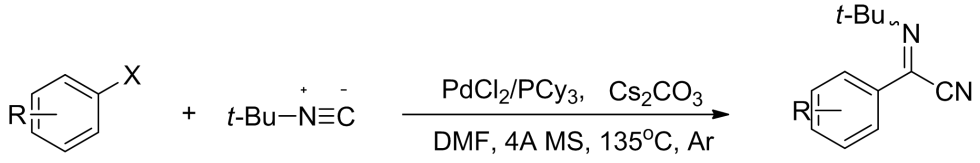
Entry	Catalyst	Ligand	Base	Additive	Solvent	Yield[%][b]

1	$Pd(OAc)_2$	PCy_3	K_2CO_3	---	DMSO	31[c]
2	$Pd(OAc)_2$	PCy_3	K_2CO_3	---	DMSO	44[d]
3	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMSO	57[e]
4	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMSO	41[f]
5	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMSO	65
6	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	dioxane	19
7	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	toluene	22
8	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMF	61
9	$Pd(OAc)_2$	PCy_3	NaOAc	4A MS	DMF	trace
10	$Pd(OAc)_2$	PCy_3	Na_2CO_3	4A MS	DMF	31
11	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	4A MS	DMF	79
12	$Pd(OAc)_2$	PCy_3	K_3PO_4	4A MS	DMF	60
13	$Pd(OAc)_2$	PCy_3	Na_2O*t*Bu	4A MS	DMF	44
14	$Pd(OAc)_2$	PCy_3	DBU	4A MS	DMF	trace
15	**$PdCl_2$**	**PCy_3**	**Cs_2CO_3**	**4A MS**	**DMF**	**87**
16	$Pd_2(dba)_3$	PCy_3	Cs_2CO_3	4A MS	DMF	52
17	$PdCl_2$	PPh3	Cs_2CO_3	4A MS	DMF	79
18	$PdCl_2$	(*R*)-BINAP	Cs_2CO_3	4A MS	DMF	22
19	$PdCl_2$	$BuPAd_2$	Cs_2CO_3	4A MS	DMF	53
20	$PdCl_2$	DPPP	Cs_2CO_3	4A MS	DMF	17
21	$PdCl_2$	DPEphos	Cs_2CO_3	4A MS	DMF	39

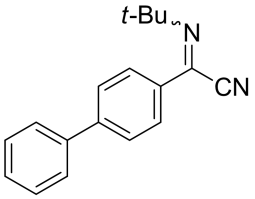
[a] Reaction conditions: All reactions were performed under argon with **1a** (0.5 mmol), *tert*-butyl isocyanide (1.5 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1 mmol) and additive (100 mg) in 2 mL of solvent at 135 °C for 18 h in a sealed tube. [b] Isolated yield. [c] Under N_2 at 120°C for 12 h. [d] Under N_2 at 120°C for 18 h. [e] 120°C. [f] 100°C.

With the optimized conditions in hand, then, the substrate scope and limitations of this methodology was explored. As illustrated in Table 2, aryl iodides with electron -rich, -poor substituents (**2d**-**2f**, **2k**, **2o**-**2q**, **2g**-**2j**, **2l**), aryl bromides (**2x**-**2y**) as well as *α, β*-unsaturated aryl bromide (**2z**) were all compatible with the method, affording the respective products in moderate to excellent yields, and also, electron-poor phenyl halides afforded higher yields than their electron-rich counterparts. *2*-Methyliodobenzene gave product only in 33% yield (**2c**), which resulted from the steric hindrance in the *ortho*-position. In addition, the method tolerates a variety of functional groups, such as halogen, ketone (**2m**), ester (**2n**), ether (**2o**, **2q**), also leading to the corresponding products in good yields. Unfortunately, several sensitive groups such as phenolic hydroxy and aromatic amino were incompatible. Interestingly, *4*-iodophenylmethanol (**2r**) could be converted into the corresponding *α*-iminonitrile in 86% yield. In addition, heteroaryl halides (**2s**-**2u**, **2y**) also gave good results in the standard conditions. Meanwhile, the *1,3*-diiodobenzene was converted into *N,N′*-di-*tert*-butylisophthalimidoyl cyanide in 31% yield (**2w**).

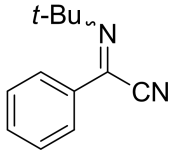
Table 2. **Palladium-Catalyzed Synthesis of *α*-Iminonitriles** [a]



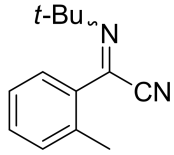
1 **2**



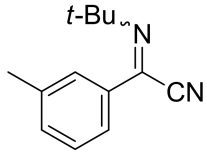
2a, 87%(65%[b])



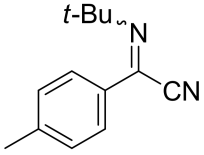
2b, 77%



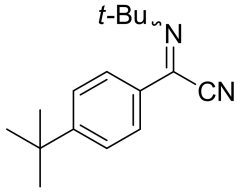
2c, 32%



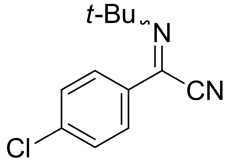
2d, 80%



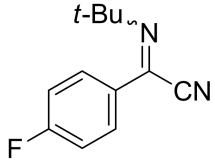
2e, 70%



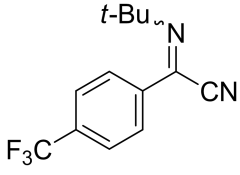
2f, 69%



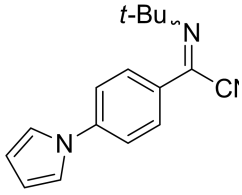
2g, 86%



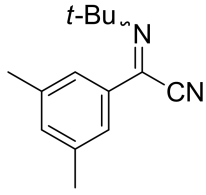
2h, 87%



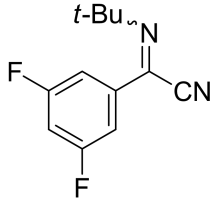
2i, 83%



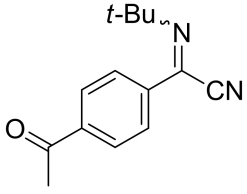
2j, 92%



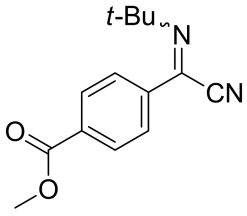
2k, 71%



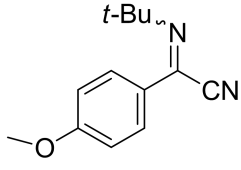
2l, 55%



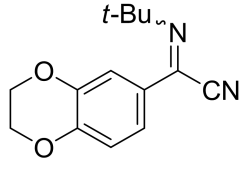
2m, 57%



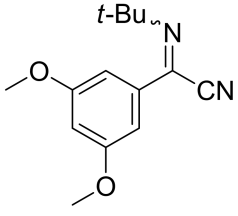
2n, 65%



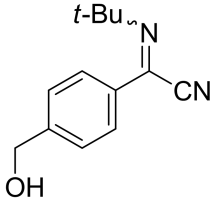
2o, 65%



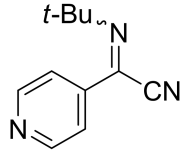
2p, 50%



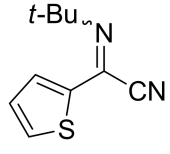
2q, 78%



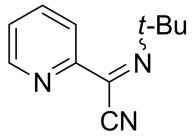
2r, 86%



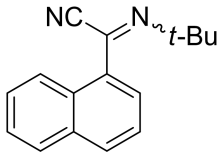
2s, 88%



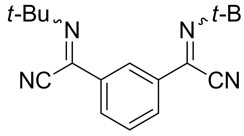
2t, 67%



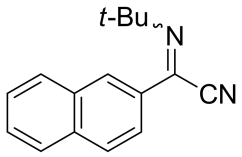
2u, 92%



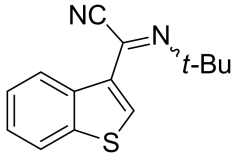
2v, 49%



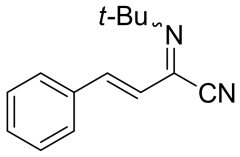
2w[c], 30%



2x[d], 65%



2y[d], 62%



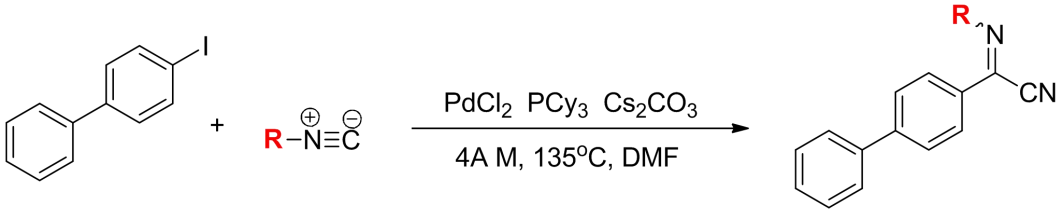
2z[d], 44%

[a] All reactions were performed under argon with aryl iodides (0.5 mmol), *tert*-butyl isocyanide (1.5 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1 mmol) and additive (100 mg) in 2 mL of solvent at 135 °C for 18 h in a sealed tube; isolated yields. [b] Using *4*-bromobiphenyl instead of *4*-iodobiphenyl. [c] Aryl halides (0.5 mmol), *tert*-butyl isocyanide (3 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol) and additive (100 mg) in 2 mL of solvent. [d] Aryl bromides.

To extend the application of this reaction, various substituted isocyanides such as cyclohexyl (**3a**), phenylethyl (**3b**), *1*-adamantyl (**3c**) *1,1,3,3*-tetramethylbutyl (**3d**) isocyanides were investigated. Unfortunately, only the *1,1,3,3*-tetramethylbutyl isocyanide could smoothly be transformed, giving *N*-(*2,4,4*-trimethylpentan-*2*-yl)-[*1,1'*-biphenyl]-*4*-carbimidoyl cyanide (**3d**) in 71% yield (**Scheme 4).** The results suggested the importance of the quaternary carbon. In addition, the steric hindrance of isocyanides with different substituent has large influence on this kind of

reaction, and we consider that **3d** and *tert*-butyl isocyanide are more prone to eliminate to transformation into cyano.

Scheme 4. Scope of Isocyanide Double Insertion



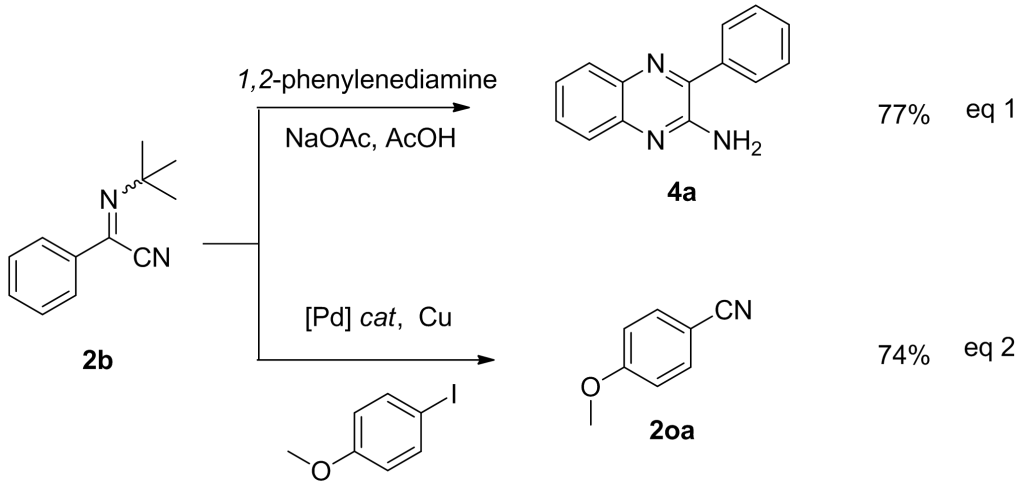
1a **3a-d**

R = Cy (**3a**), $PhCH_2CH_2$ (**3b**), Ad (**3c**) no product

R = $C(CH_3)_3CH_2C(CH_2)_2$ (**3d**) 71%

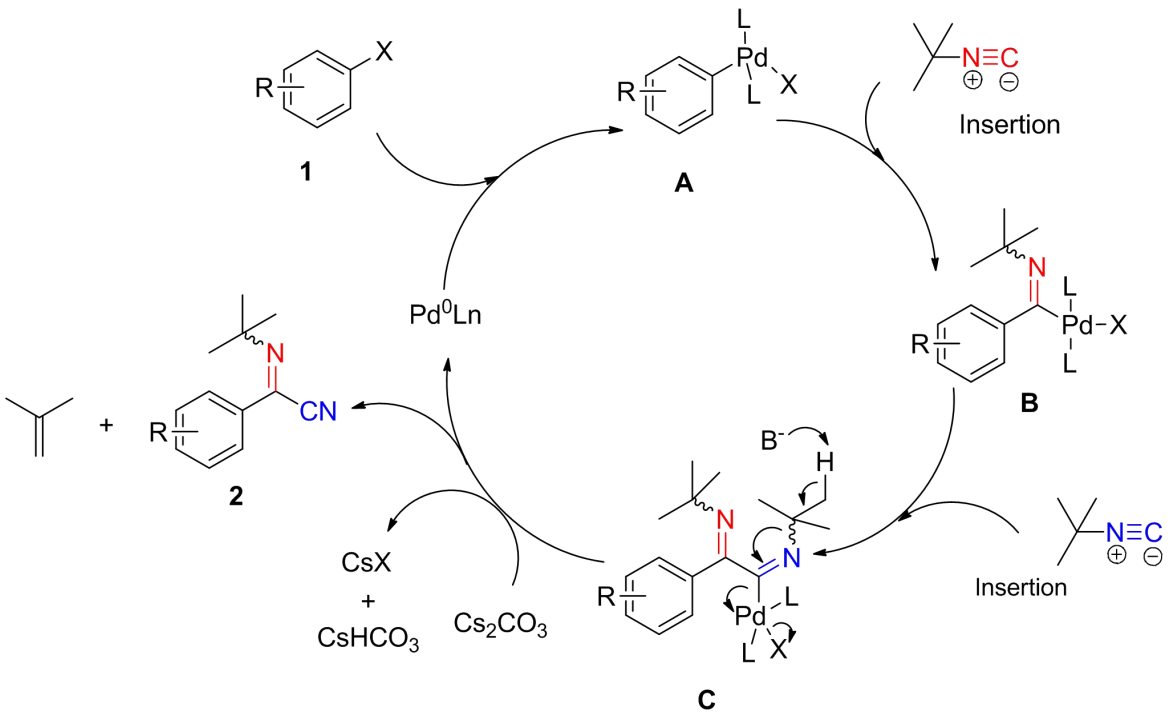
Next, to further explore the synthetic utility of our methodology, we performed a number of preliminary experiments as depicted in **scheme 5**. When **2** was refluxed under acetic acid with *1,2*-phenylenediamine in the presence of NaOAc, *3*-phenylquinoxalin-*2*-amine (**4a**) was formed in 77% yield (**scheme 5**, eq 1). And also, benzonitrilic compound (**2oa**) was formed in 74% yield (**scheme 5**, eq 2) with dissolving iodobenzene and **2** in DMSO in the presence of $Pd(OAc)_2$ and $Cu(TFA)_2$ at 120°C, which showed that **2** could be used as cyano source, and the further studies are underway in our laboratory. The compounds of **4a** are common building blocks found in many biologically and pharmaceutically compounds,[18] and the compounds of **2oa** are important intermediates in organic synthesis.[19]

Scheme 5. Transformation of 2



Based on the basis of literature reports,[3c,6,10] a plausible mechanism for this reaction is depicted in **Scheme 6**. First, oxidative addition of **1** to the Pd(0) catalyst lead to the palladium complex **A**, followed by *tert*-butyl isocyanide insertion to form intermediate **B.** Subsequently, the second isocyanide insertion takes place to form intermediate **C**. With the assistance of Cs_2CO_3, intermediate **C** undergoes *tert*-butyl elimination and Pd expulsion to form the product **2**.

Scheme 6. Plausible Reaction Mechanism



CONCLUSION

In summary, we have illustrated a simple and efficient approach for palladium-catalyzed synthesis of *α*-iminonitrile *via tert*-butyl isocyanide double insertion and elimination in one pot. In this reaction, we overcame the challenge of isocyanides polymerization in the presence of transition metal in double isocyanides insertion, and achieved isocyanides as cyano source without any oxidants. Compared to others methods, the reaction is tolerant of a wide range of substrates and is more efficient, convenient, low-toxic for the synthesis of *α*-iminonitrile.

EXPERIMENTAL SECTION

General Information. Reactants and reagents were purchased from commercial suppliers. All solvents were dried and freshly distilled. TLC was performed on silica

HSGF254 plates. Melting points were determined with a digital melting-point apparatus. NMR spectra were run in a solution of deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard and were reported in parts per million (ppm). ^1H and ^{13}C NMR spectra were obtained at 400/101 MHz ($^1H/^{13}C$), respectively. High-resolution mass spectra (HRMS) analyses were carried out on a chemical ionization (CI) apparatus using time-of-flight (TOF) mass spectrometry. Infrared (IR) obtained using KBr tablets and wavenumbers in cm^{-1}.

General procedure for the synthesis of *α*-Iminonitrile. 1 (0.5 mmol), *tert*-butyl isocyanide (1.5 mmol), $PdCl_2$ (0.05 mmol), PCy_3 (0.1 mmol), Cs_2CO_3 (1.0 mmol) and 4A MS (100 mg) were added into a 15 ml sealed tube equipped with a magnetic stirring bar. The mixture was stirred in DMF (2 mL) under argon at 135 °C for 18 h. After completion of the reaction as indicated by TLC, poured in to water (30 mL) and extracted by ethyl acetate (3×30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

Preparation of *3*-Phenylquinoxalin-*2*-amine (4a). To a solution of **2** (0.4 mmol), *1,2*-phenylenediamine (0.6 mmol) and NaOAc (1 mmol) in AcOH (4 mL) in a round bottom flask. The reaction mixture was refluxed for 2 h. After cooling to room temperature, concentrated in vacuo, then washed with brine and extracted with DCM (10 mL × 3). The combined organic phases dried over anhydrous Na_2SO_4 and evaporated. The residue was

purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

Preparation of *4*-Methoxybenzonitrile (2oa). *1*-Iodo-*4*-methoxybenzene (0.3 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (0.05 mmol), $Cu(TFA)_2$ (0.6 mmol) were added into a 15 ml sealed tube equipped with a magnetic stirring bar. The mixture was stirred in DMSO (1.5 mL) at 120 °C for 10 h. After completion of the reaction as indicated by TLC, poured in to water (30 mL) and extracted by ethyl acetate (3×30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

*N-(tert-Butyl)-[1,1'-biphenyl]-4-carbimidoyl cyanide (**2a**).* White solid (114 mg, 87% yield). Mp: 91-93 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.4 Hz, 2H), 7.45 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 7.1 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (s), 140.0 (s), 134.3 (s), 129.1 (s), 128.2 (s), 127.7 (s), 127.4 (s), 127.3 (s), 111.9 (s), 58.6 (s), 29.5 (s). IR (KBr): v 2971, 2918, 2213, 1669, 1592, 1475, 1363, 1205, 1181, 999, 843 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{18}H_{19}N_2$ $[M+H]^+$, 263.1548 ; found, 263.1555.

*N-(tert-Butyl)-benzimidoyl cyanide (**2b**).*[17a] Yellow oil (72mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.4 Hz, 2H), 7.53 – 7.41 (m, 3H), 1.54 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (s), 131.8 (s), 128.8 (s), 127.3 (s), 111.8 (s), 58.5 (s), 29.5 (s). HRMS (CI): *m/z* calcd for $C_{12}H_{14}N_2$ $[M+H]^+$, 186.1157 ; found, 186.1154.

*N-(tert-Butyl)-2-methylbenzimidoyl cyanide (**2c**).* Colorless oil (32 mg, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 2.49 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (s), 137.2 (s), 135.4 (s), 131.9(s), 130.5 (s), 129.3 (s), 126.4 (s), 112.6(s), 59.2 (s), 29.5 (s), 21.0 (s). IR (KBr): v 2970, 2926, 2856, 2212, 1676, 1615, 1457, 1363, 1202, 990, 878, 756, 722 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{13}H_{17}N_2$ $[M+H]^+$, 201.1392 ; found, 201.1385.

*N-(tert-Butyl)-3-methylbenzimidoyl cyanide (**2d**).* Yellow oil (80mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 6.8 Hz, 2H), 7.34 (q, J = 7.7 Hz, 2H), 2.42 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7 (s), 137.0 (s), 135.3 (s), 132.6 (s), 128.7 (s), 127.6 (s), 124.6 (s), 111.9 (s), 58.4 (s), 29.4 (s), 21.5 (s). IR (KBr): v 2972, 2929, 2872, 2216, 1603, 1585, 1460, 1304, 1206, 1020, 790, 700 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{13}H_{17}N_2$ $[M+H]^+$, 201.1392 ; found, 201.1395.

*N-(tert-Butyl)-4-methylbenzimidoyl cyanide (**2e**).*[17a] Colorless oil (70mg 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 2.40 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (s), 136.7 (s), 132.9 (s), 129.5 (s), 127.2 (s), 112.0 (s), 58.3 (s), 29.5 (s), 21.6 (s). HRMS (CI): *m/z* calcd for $C_{13}H_{17}N_2$ $[M+H]^+$, 201.1392 ; found, 201.1389.

*N,4-Di-tert-butylbenzimidoyl cyanide (**2f**).* White solid (83mg, 69% yield) Mp: 47-48^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 1.54 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (s), 136.6 (s), 132.8 (s), 127.1 (s), 125.8 (s), 111.9 (s), 58.3 (s), 35.1 (s), 31.2 (s), 29.5 (s). IR (KBr): v 2965, 2926, 2869, 2211,

1612, 1595, 1462, 1362, 1266, 1204, 999, 837, 657 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{16}H_{23}N_2$ $[M+H]^+$, 243.1861 ; found, 243.1835.

*N-(tert-Butyl)-4-chlorobenzimidoyl cyanide (**2g**)*[17c]. Yellow oil (95mg, 86% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (s), 135.7 (s), 133.8 (s), 129.1 (s), 128.5 (s), 111.5 (s), 58.7 (s), 29.4 (s). HRMS (CI): *m/z* calcd for $C_{12}H_{14}N_2Cl$ $[M+H]^+$, 221.0846 ; found, 221.0851.

*N-(tert-Butyl)-4-fluorobenzimidoyl cyanide (**2h**).* Yellow oil (90mg, 87% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (ddd, J = 8.8, 5.3, 1.6 Hz, 2H), 7.17 – 7.10 (m, 2H), 1.52 (d, J = 1.6 Hz, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (s), 163.9 (s), 135.5 (s), 131.7 (d, J = 3.1 Hz), 129.5 (d, J = 8.9 Hz), 116.1 (s), 115.9 (s), 111.7 (s), 58.6 (s), 29.5 (s). IR (KBr): *v* 2972, 2927, 2855, 2215, 1614, 1601, 1588, 1507, 1230, 1156, 842 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{12}H_{14}N_2F$ $[M+H]^+$, 205.1141 ; found, 205.1133.

*N-(tert-Butyl)-4-(trifluoromethyl)benzimidoyl cyanide (**2i**).* White solid (105mg, 83% yield). Mp: 59-61^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.28 (s), 135.64 (s), 133.98 (s), 133.65 (s), 133.33 (s), 133.00 (s), 127.69 (s), 125.85 (t, J = 5.7 Hz), 125.18 (s), 122.47 (s), 119.77 (s), 111.43 (s), 59.22 (s), 29.42 (s). IR (KBr): *v* 2972, 2927, 2855, 2216, 1639, 1618, 1460, 1324, 1164, 1126, 1013 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{13}H_{14}N_2F_3$ $[M+H]^+$, 255.1109 ; found, 255.1120.

*N-(tert-Butyl)-4-(1H-pyrrol-1-yl)benzimidoyl cyanide (**2j**).* White solid (115mg, 92% yield).Mp: 77-79°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.19 – 7.16 (m, 2H), 6.42 – 6.39 (m, 2H), 1.56 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (s), 135.8 (s), 132.4 (s), 128.8 (s), 119.8 (s), 119.1 (s), 111.7 (s), 111.5 (s), 58.6 (s), 29.5 (s). IR (KBr): v 2967, 2919, 2850, 2226, 1669, 1604, 1519, 1477, 1334, 1183, 1066, 842, 723 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{16}H_{18}N_3$ $[M+H]^+$, 252.1501 ; found, 252.1497.

*N-(tert-Butyl)-3,5-dimethylbenzimidoyl cyanide (**2k**).* Yellow oil (76mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 2H), 7.13 (s, 1H), 2.37 (s, 6H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (s), 137.2 (s), 135.4 (s), 133.6 (s), 125.0 (s), 112.0 (s), 58.4 (s), 29.5 (s), 21.3 (s). IR (KBr): v 2996, 2970, 2922, 2869, 2214, 1601, 1588, 1457, 1363, 1183, 1160, 856, 704 cm-1.HRMS (CI): *m/z* calcd for $C_{14}H_{19}N_2$ $[M+H]^+$, 215.1548 ; found, 215.1542.

*N-(tert-Butyl)-3,5-difluorobenzimidoyl cyanide (**2l**).* Yellow oil (61mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.4 Hz, 2H), 6.96 (d, J = 7.3 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47 (d, J = 12.3 Hz), 161.99 (d, J = 12.3 Hz), 138.51 (t, J = 9.2 Hz), 134.66 (t, J = 4.0 Hz), 111.16 (s), 110.63 – 110.15 (m), 107.44 (s), 107.19 (s), 106.93 (s), 59.24 (s), 29.39 (s). IR (KBr): v 2955, 2921, 2852, 2215, 1620, 1594, 1460, 1329, 1123, 992 cm^{-1}.HRMS (CI): *m/z* calcd for $C_{12}H_{13}N_2F_2$ $[M+H]^+$, 223.1047 ; found, 223.1035.

*4-Acetyl-N-(tert-butyl)benzimidoyl cyanide (**2m**).* Yellow solid (65mg, 57% yield). Mp: 87-88°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 2.63 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5 (s), 139.3 (s), 138.9 (s), 136.0 (s), 128.7 (s), 127.5 (s), 111.5 (s), 59.1 (s), 29.4 (s), 27.0 (s). IR (KBr): v 2972, 2917, 2850, 2600, 2218, 1685, 1607, 1592, 1420, 1366, 1260, 1204, 1005, 954, 851, 835, 671 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$, 229.1341 ; found, 229.1335.

*Methyl 4-((tert-butylimino)(cyano)methyl)benzoate (**2n**).* Yellow solid (79mg, 65% yield). Mp: 79-80°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H), 3.94 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (s), 138.9 (s), 136.1 (s), 132.9 (s), 130.0 (s), 127.3 (s), 111.5 (s), 59.1 (s), 52.5 (s), 29.4 (s). IR (KBr): v 3067, 2994, 2971, 2949, 2219, 1719, 1613, 1593, 1265, 1204, 1106, 871, 776, 700 cm^{-1}.HRMS (CI): *m/z* calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$, 245.1290 ; found, 245.1287.

*N-(tert-Butyl)-4-methoxybenzimidoyl cyanide (**2o**)*[17a]. Yellow oil (70mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 1.52 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (s), 136.1 (s), 128.9 (s), 128.4 (s), 114.1 (s), 111.9 (s), 58.0 (s), 55.5 (s), 29.5 (s). HRMS (CI): *m/z* calcd for $C_{13}H_{17}N_2O$ $[M+H]^+$, 217.1341 ; found, 217.1338.

*N-(tert-Butyl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carbimidoyl cyanide (**2p**).* Yellow oil (61mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.5, 2.1 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.29 (d, J = 5.1 Hz, 2H), 4.27 (d, J = 5.1 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (s), 143.8 (s), 135.8 (s), 129.2 (s), 121.0

(s), 117.5 (s), 116.1 (s), 111.8 (s), 64.7 (s), 64.3 (s), 58.1 (s), 29.5 (s). IR (KBr): *v* 2969, 2932, 2877, 2216, 1666, 1579, 1504, 1291, 1065, 889 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$, 245.1290 ; found, 245.1293..

*N-(tert-Butyl)-3,5-dimethoxybenzimidoyl cyanide (**2q**)*. White solid (96mg,78% yield). Mp: 99-101°C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 2.0 Hz, 2H), 6.59 (s, 1H), 3.84 (s, 6H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (s), 137.4 (s), 136.7 (s), 111.8 (s), 105.2 (s), 104.3 (s), 58.6 (s), 55.7 (s), 29.5 (s). IR (KBr): *v* 2976, 2939, 2833, 2212, 1606, 1586, 1458, 1308, 1207, 1154, 1066, 1021 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$, 247.1447 ; found, 247.1452.

*N-(tert-Butyl)-4-(hydroxymethyl)benzimidoyl cyanide (**2r**)*. Yellow oil (93mg, 86% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.75 (s, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (s), 136.5 (s), 134.7 (s), 127.5 (s), 127.0 (s), 111.9 (s), 64.8 (s), 58.6 (s), 29.5 (s). IR (KBr): *v* 3348, 2971, 2932, 2858, 2214, 1721, 1594, 1572, 1364, 1264, 1203, 1004, 825, 676 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{13}H_{17}N_2O$ $[M+H]^+$, 217.1341; found, 217.1342.

*N-(tert-Butyl)isonicotinimidoyl cyanide (**2s**)*. Yellow oil (82mg, 88% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 4.5 Hz, 2H), 7.82 (d, J = 4.5 Hz, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (s), 142.0(s), 135.4 (s), 120.8 (s), 111.0 (s), 59.6 (s), 29.4 (s). IR (KBr): *v* 2966, 2928, 2853, 2215, 1703, 1614, 1593, 1408, 1364, 1278, 1218, 1188, 1008, 988 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{11}H_{14}N_3$ $[M+H]^+$, 188.1188 ; found,188.1184.

*N-(tert-Butyl)thiophene-2-carbimidoyl cyanide (**2t**).* Yellow oil (64mg, 67% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 1H), 7.45 (d, J = 5.6 Hz, 1H), 7.12 – 7.09 (m, 1H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (s), 130.9 (d, J = 11.3 Hz), 127.9 (s), 111.3 (s), 58.5 (s), 29.6 (s). IR (KBr): v 2971, 2925, 2854, 2218, 1654, 1597, 1580, 1425, 1364, 1203, 955, 850, 711 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{10}H_{13}N_2S$ $[M+H]^+$, 193.0799 ; found, 193.0787.

*N-(tert-Butyl)picolinimidoyl cyanide (**2u**).* Yellow solid (99mg, 92%yield). Mp: 35-37^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 5.6 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.3 Hz, 1H), 7.41 – 7.36 (m, 1H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (s), 149.4 (s), 138.4 (s), 136.9 (s), 125.8 (s), 121.0 (s), 111.8 (s), 58.9 (s), 29.3 (s). IR (KBr): v 2971, 2924, 2853, 2220, 1620, 1604, 1583, 1464, 1364, 1207, 1012, 793, 742 cm-1. HRMS (CI): *m/z* calcd for $C_{11}H_{14}N_3$ $[M+H]^+$, 188.1188 ; found, 188.1176.

*N-(tert-Butyl)-1-naphthimidoyl cyanide (**2v**).* Yellow oil (58mg, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.4 Hz, 1H), 7.98 – 7.89 (m, 3H), 7.62 – 7.53 (m, 3H), 1.66 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (s), 134.2 (s), 132.6 (s), 132.0 (s), 130.2 (s), 128.9 (d, J = 8.5 Hz), 127.9 (s), 126.7 (s), 124.9 (d, J = 2.7 Hz), 112.9 (s), 59.5 (s), 29.6 (s). IR (KBr): v 2970, 2927, 2854, 2222, 1611, 1590, 1510, 1364, 1202, 954, 801, 772 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{16}H_{17}N_2$ $[M+H]^+$, 237.1392 ; found, 237.1388.

*N,N'-Di-tert-butylisophthalimidoyl cyanide (**2w**).* Colorless oil (43mg,30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.39 (dd, J = 7.8, 1.7 Hz, 2H), 7.83 (t, J = 7.8 Hz, 1H), 1.83 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (d, J = 4.7 Hz), 130.3 (s), 129.3

(s), 125.8 (s), 111.5 (s), 59.0 (s), 29.4 (s). IR (KBr): *v* 2972, 2926, 2854, 2217, 1607, 1582, 1462, 1365, 1190, 1031, 806, 690 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{18}H_{23}N_4$ $[M+H]^+$, 295.1923 ; found, 295.1919.

*N-(tert-Butyl)-2-naphthimidoyl cyanide (**2x**)*. White solid (77mg,65% yield). Mp: 50-53°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.60 – 7.54 (m, 2H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (s), 135.1 (s), 133.0 (s), 132.9 (s), 129.3 (s), 129.2 (s), 128.7 (s), 128.1 (s), 127.9 (s), 127.0 (s), 122.8 (s), 111.9 (s), 58.6 (s), 29.6 (s). IR (KBr): *v* 2972, 2921, 2851, 2215, 1596, 1459, 1361, 1277, 1187, 1124, 862, 820, 751 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{16}H_{17}N_2$ $[M+H]^+$, 237.1392 ; found, 237.1386.

*N-(tert-Butyl)-3a,7a-dihydrobenzo[b]thiophene-3-carbimidoyl cyanide (**2y**)*. White solid (75mg, 62% yield). Mp:76-78°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 8.1 Hz, 1H), 8.23 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.50 – 7.42 (m, 2H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (s), 135.7 (s), 134.8 (s), 132.9 (s), 132.7 (s), 126.0 (s), 125.9 (s), 125.7 (s), 122.6 (s), 111.9 (s), 58.6 (s), 29.6 (s). IR (KBr): *v* 2984, 2971, 2919, 2845, 2219, 1614, 1587, 1460, 1361, 1189, 892, 769 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{14}H_{15}N_2S$ $[M+H]^+$, 243.0956 ; found, 243.0961.

*N-(tert-Butyl)cinnamimidoyl cyanide (**2z**)*. Yellow oil (47mg,44% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.5, 1.6 Hz, 2H), 7.40 (t, J = 11.9 Hz, 4H), 6.93 (d, J = 16.4 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (s), 138.2 (s), 134.9 (s), 130.1 (s), 129.1 (s), 128.5 (s), 127.9 (s), 111.2 (s), 58.6 (s), 29.6 (s). IR (KBr): *v* 2970, 2927, 2855,

2218, 1704, 1626, 1580, 1449, 1364, 1192, 966, 753, 691 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{14}H_{17}N_2$ $[M+H]^+$, 213.1392 ; found, 213.1396.

*N-(2,4,4-Trimethylpentan-2-yl)-[1,1'-biphenyl]-4-carbimidoyl cyanide (**3d**).* Colorless oil (113mg,71%yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 2H), 7.67 (dd, J = 23.1, 8.1 Hz, 4H), 7.45 (dt, J = 14.6, 7.8 Hz, 3H), 1.94 (s, 2H), 1.62 (s, 6H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (s), 140.1 (s), 135.2 (s), 134.6 (s), 129.1 (s), 128.2 (s), 127.8 (s), 127.4 (d, J = 19.7 Hz), 112.2 (s), 62.5 (s), 56.6 (s), 32.0 (s), 29.6 (s). IR (KBr): *v* 2952, 2869, 2212, 1596, 1485, 1365, 1214, 1003, 846, 766, 729, 695 cm^{-1}. HRMS (CI): *m/z* calcd for $C_{22}H_{27}N_2$ $[M+H]^+$, 319.2174 ; found, 319.2169.

*3-Phenylquinoxalin-2-amine (**4a**).*[18e] Yellow solid(68 mg, 77%yield). Mp: 181-183^oC .^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 6.8 Hz, 2H), 7.70 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 7.4 Hz, 2H), 7.45 (t, J = 7.0 Hz, 2H), 5.17 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (s), 146.0 (s), 141.3 (s), 138.2 (s), 137.1 (s), 130.2 (s), 129.9 (s), 129.4 (s), 129.2 (s), 128.5 (s), 125.7 (s), 125.5 (s). HRMS (CI): *m/z* calcd for $C_{14}H_{12}N_3$ $[M+H]^+$, 222.1031 ; found, 222.1035.

*4-Methoxy-benzonitrile (**2oa**).*[6d] White solid(29 mg, 74%yield). Mp: 62-63^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 5.1 Hz, 1H), 6.93 (d, J = 5.2 Hz, 1H), 3.83 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (s), 134.0 (s), 119.2 (s), 114.8 (s), 103.9 (s), 55.6 (s). HRMS (CI): *m/z* calcd for C_8H_8NO $[M+H]^+$, 134.0606; found, 134.0604.

ASSOCIATED CONTENT

Supporting Information Figures giving ^1H and ^{13}C NMR spectra. This material is available

free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01758.

AUTHOR INFORMATION

Corresponding Authors

*(Yong-Ming Zhu) E-mail: zhuyongming@suda.edu.cn; fax: (+86)-512-67166591.

*(Jing-Kang Shen) E-mail: jkshen@mail.shcnc.ac.cn .

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge the financial support by PAPD (A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions).

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