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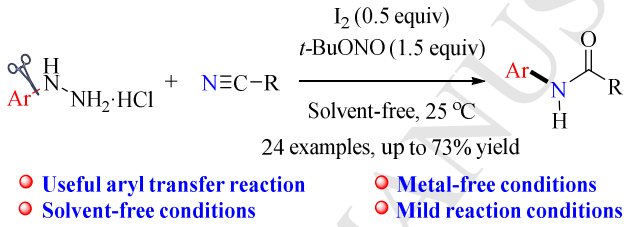
Iodine-Mediated Aryl Transfer Reaction from Arylhydrazine Hydrochlorides to Nitriles

Zhiguo Zhang,[a]* Xiang Li,[a] Yinghua Li,[a] Yan Guo,[a] Xunan Zhao,[a] Yan Yan,[a] Kai Sun,[b] Guisheng Zhang[a]*

[a] *Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Henan Key laboratory of Organic Functional Molecule and Drug Innovation, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China. E-mail: zhangzg@htu.edu.cn and zgs6668@yahoo.com, Fax: (+86)-373-332-5250.*

[b] *College of Chemistry and Chemical Engineering, Anyang Normal University, Anyang 455000, China*



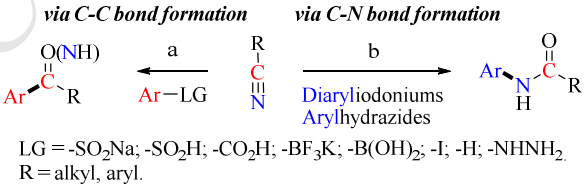
Abstract. An iodine-promoted, metal-, base-, and solvent-free cross-coupling reaction was developed for the synthesis of various useful secondary amides via an aryl *N*-addition reaction of aryl groups to cyano groups. This aryl transfer reaction proceeds with arylhydrazine hydrochlorides serving as the aryl donors. A labelling experiment shows that the *N* atom in the product comes from the cyano group of the nitriles, which are low in cost. A plausible radical-driven mechanism is also proposed.

Keywords: Arylhydrazine hydrochlorides; Nitrile N-addition; Aryl transfer reaction; Cross-coupling; Iodine; Secondary amides

1. Introduction

C-N triple bonds[1] are versatile functional groups in organic synthesis.[2] The cyano group of nitriles can undergo *C*-addition and *N*-addition reactions leading to C-C bond and C-N bond formation (Scheme 1). *C*-addition to the cyano group of nitriles has been widely observed in reactions with

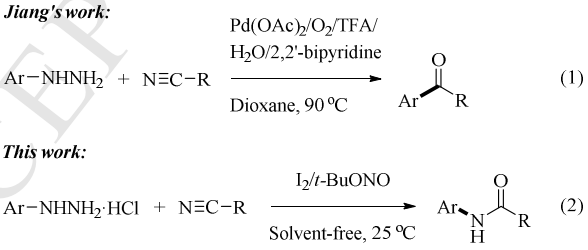
various aryl donors, such as arylsulfinic acids,[3] arylboronic acids,[4] aryl iodides,[5] benzoic acids,[6] arenes,[7] and hydrazines,[8] frequently in the presence of Ni, Pd, Rh, or Cu transition-metal catalysts (Scheme 1a). However, the *N*-addition reaction has rarely been achieved by cross-coupling of the aryl and nitrile portion to produce amides or their analogs via C-N bond formation (Scheme 1b). To the best of our knowledge, only two examples of this type of reaction have been described, both involving Cu catalysts. In 2013, Chen and co-workers[9] described, in two separate publications, the concise construction of polycyclic quinolines via intramolecular [2+2+2] annulation of diaryliodoniums, nitriles, and alkynes. The key intermediate *N*-phenyl nitrilium salt, which was produced by tethering the aryl and nitrile portion via a *N*-addition reaction, was involved in these regioselective processes. Furthermore, very recently, we developed a useful intermolecular phenyl transfer reaction for the synthesis of *N*-phenyl amides, which, for the first time, were synthesized starting from hydrazides and nitriles. The protocol proceeded via an oxidative cleavage reaction of sp^2 C-N bonds of phenylhydrazides to form a phenyl radical and the subsequent *N*-addition to the cyano group (Scheme 1b).[10] This metal-free *N*-phenylated reaction proceeded in the presence of [bis-(trifluoroacetoxy)iodo]benzene (PIFA) under mild and solvent-free conditions. Despite the considerable accomplishments achieved so far, the further development of practical, diverse, and flexible *N*-addition reactions of cyano groups, hence leading to more functional molecules, is highly desirable.



Scheme 1. The addition reactions of aryl donors to cyano groups.

Phenylhydrazine and its derivatives are an important moiety of various natural compounds with a rich diversity of structures and bioactivities.[11] In synthetic organic chemistry, these derivatives, such as nitrilimines, are useful in addition reactions to generate nitrogen-containing heterocycles because

of their high reactivity, low cost, and easy availability.[12] Additionally, they often serve as PhNH-group donors to access small organic molecules with desired functionality,[13] such as in the Fischer indole synthesis.[14] Furthermore, many studies have reported that phenylhydrazines can be decomposed into a phenyl group by expulsion of N_2 under mild conditions, thence participating in various coupling reactions to afford biaryls.[15] However, to date, the phenyl donor chemistry of phenylhydrazines toward the triple bonds of unsaturated compounds[8-10,16] has been far less explored than that toward other bond types.[17] A noteworthy example with arylhydrazines serving as the aryl donor was reported by Jiang's group in 2017.[8] They established a simple approach for the synthesis of aryl ketones in the presence of a palladium catalyst, 2,2'-bipyridine, trifluoroacetic acid, and using molecular oxygen as the sole oxidant starting from nitriles and arylhydrazines via a *C*-addition reaction to the cyano group (Eq 1). Here, we describe our successful cross-coupling of arylhydrazine hydrochlorides with nitriles in the presence of iodine and *tert*-butyl nitrite (*t*-BuONO) to produce secondary amides under metal-, base-, and solvent-free conditions with a broad substrate scope (Eq 2). Obviously, the advantage of the direct *N*-addition to the cyano group is to allow the introduction of an aryl directly to the nitrogen atom and facilitate various useful amides[18] without the need for pre-prepared carbonyl-containing starting materials and metal catalysts.



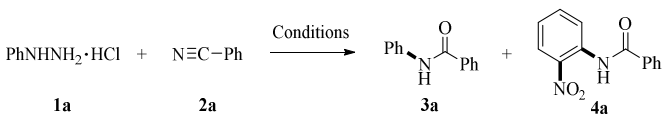
2. Results and discussion

We began our study with the selection of phenylhydrazine hydrochloride (**1a**) and benzonitrile (**2a**) as model substrates to optimize the reaction conditions (Table 1). Initially, we treated **1a** and **2a** (10 equiv) with 2 equiv of iodine and 2 equiv of *t*-BuONO at 25 °C (Table 1, entry 1). To our delight, *N*-phenylated product **3a** was isolated in 62% yield as a white solid, along with a trace amount of

by-product **4a** after 5 h. Further investigation indicated that the amount of iodine had little effect on the yield of product **3a** (Table 1, entries 2–5). It should be emphasized that the reaction showed a very low efficiency in the absence of iodine or *t*-BuONO (Table 1, entries 6 and 7). These observations show that both of those reagents are indispensable to this aryl transfer reaction. Experimentally, the reaction was found to be improved when we increased the amount of *t*-BuONO, and the reaction performance was optimized when 1.5 equiv of *t*-BuONO was employed (Table 1, entries 8–12). The amount of starting material **2a**, serving as both aryl acceptor and solvent, was also screened. It was found that using more than 5 equiv of compound **2a** allowed the reaction mixture to form a homogeneous solution and gave a higher yield of **3a** than when using a lower loading of **2a** (Table 1, entries 13 and 14). However, increasing the reaction temperature was unable to improve the yield of **3a** (Table 1, entries 15 and 16). Other commercially available nitrites, such as isopropyl nitrite (*i*-PrONO), isobutyl nitrite (*i*-BuONO), isopentyl nitrite (*i*-PenONO), *n*-butyl nitrite (*n*-BuONO), and *n*-hexyl nitrite (*n*-HexONO), were also tested in the reaction. All of them showed a lower efficiency than that of *t*-BuONO (Table 1, entries 17–21). Next, other phenylhydrazines were also investigated systematically. Under the optimized conditions, various phenylhydrazide derivatives phenylhydrazine (**1b**), *N*'-phenylacetohydrazide (**1c**), *N*'-phenylbenzenesulfonohydrazide (**1d**), and 4-methyl-*N*'-phenylbenzenesulfonohydrazide (**1e**) gave the amide **3a** in 39–48% yield, as well as 9–27% yield of by-product **4a** (Table 1, entries 22–25).

Table 1

Survey of the reaction conditions.[a]



Entry	**1**	I_2/equiv	RONO/equiv	t/h	**3a**/%	**4a**/%
1	**1a**	2	*t*-BuONO/2	5	62	Trace

2	**1a**	1.5	*t*-BuONO/2	5	63	Trace
3	**1a**	1	*t*-BuONO/2	8	65	6
4	**1a**	0.5	*t*-BuONO/2	5	64	4
5	**1a**	0.2	*t*-BuONO/2	5	57	10
6	**1a**	--	*t*-BuONO/1.5	5	7	0
7	**1a**	0.5	----	6	5	0
8	**1a**	0.5	*t*-BuONO/0.2	6	19	Trace
9	**1a**	0.5	*t*-BuONO/0.5	6	58	Trace
10	**1a**	0.5	*t*-BuONO/1	6	61	Trace
11	**1a**	0.5	*t*-BuONO/1.5	6	64	Trace
12	**1a**	0.5	*t*-BuONO/3	6	59	7
13[b]	**1a**	0.5	*t*-BuONO/1.5	5	40	Trace
14[c]	**1a**	0.5	*t*-BuONO/1.5	5	56	Trace
15[d]	**1a**	0.5	*t*-BuONO/1.5	5	43	0
16[e]	**1a**	0.5	*t*-BuONO/1.5	5	46	0
17	**1a**	0.5	*i*-PrONO/1.5	5	48	0
18	**1a**	0.5	*i*-BuONO/1.5	5	59	0
19	**1a**	0.5	*i*-PenONO/1.5	5	59	0
20	**1a**	0.5	*n*-BuONO/1.5	5	51	0
21	**1a**	0.5	*n*-HexONO/1.5	5	63	0
22	**1b**	0.5	*t*-BuONO/1.5	6	41	20
23	**1c**	0.5	*t*-BuONO/1.5	5	39	27
24	**1d**	0.5	*t*-BuONO/1.5	8	43	9
25	**1e**	0.5	*t*-BuONO/1.5	8	48	13

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.3 mmol), **2a**, I_2, and nitrites under solvent-free and open-air conditions.

[b] 3.0 equiv of **2a** was used.

[c] 5.0 equiv of **2a** was used.

[d] 50 ^{o}C was used.

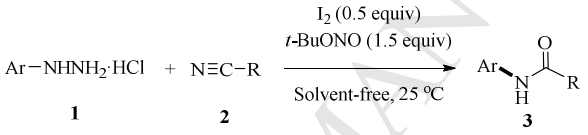
[e] 75 ^{o}C was used.

The optimized conditions were identified as 1 equiv of **1** and 10 equiv of **2** in the presence of 0.5 equiv of iodine and 1.5 equiv of *t*-BuONO under solvent-free conditions at 25 °C (Table 1, entry 11). The scope of this intermolecular cross-coupling reaction using various starting materials **2** was then investigated (Table 2). The phenyl group (**2a**) and a variety of substituted phenyls with an electron-donating group (EDG) (e.g., –OMe) (**2b**–**d**) or an electron-withdrawing group (EWG) (e.g., –CO_2Et) (**2e**–**f**) at the *ortho*-, *meta*-, or *para*-position could be well tolerated for the reaction, and gave the amide products **3a**–**f** in the yields of 34–73%. Except for the desired product **3f**, 15% of *N*-(2-nitrophenyl)-3-(methoxycarbonyl)benzamide (**4f**) was isolated simultaneously in the reaction between **1a** and **2f**. However, we found that the nitrification product **4f** could be suppressed completely if the reaction was carried out under N_2 atmosphere. It was deduced that the NO radicals derived from the *t*-BuONO were oxidized to nitro radicals (·NO) by air,[19] which served as the nitro group donor of the nitrification.[20] The reaction proceeded well for the starting materials 2-furonitrile (**2g**) and 2-thiophenecarbonitrile (**2h**) and afforded two commercialized products, **3g** and **3h**, in 47% and 57% yields, respectively. Interestingly, six other functionalized nitrile substrates **2i**–**n** smoothly afforded useful **3i**–**n** as the sole products in 45–66% yields, under the optimal conditions, without affecting the active cyclopropyl moiety, active methylene moiety, and C=C double bond functional groups of these substrates. These observations indicated the flexibility and controllability of this iodine-mediated aryl transfer reaction. To verify the convenience and flexibility of this approach and obtain structurally diverse amides, several random commercially available hydrazines (or their

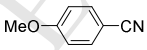
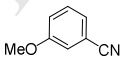
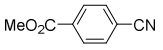
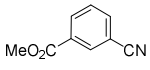
hydrochloride) **1**, including *tert*-butylhydrazine hydrochloride (**1f**), 4-hydrazinylpyridine hydrochloride (**1g**), 2-chloro-3-hydrazinylpyrazine hydrochloride (**1h**), and 3-chloro-6-hydrazinylpyridazine hydrochloride (**1i**), were employed in the reaction. All of them could react with **2a** and gave the corresponding amides **3o**–**r** in 46–68% yields. Despite the relatively low yields, this is a new and alternative approach to access these types of amides. In addition, other aryl donors including sodium benzenesulfinate, benzoic acid, phenylboronic acid, and iodobenzene were also employed to the reaction, but the reaction did not occur, and starting materials were recovered.

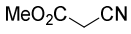
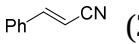
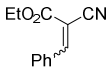
Table 2

Extension of the reaction scope.[a]



1 **2** **3**

Entry	**1**	**2**	t/h	**3**
1	**1a**	 (**2a**)	6	**3a**: 64%
2	**1a**	 (**2b**)	5	**3b**: 73%
3	**1a**	 (**2c**)	6	**3c**: 58%[b]
4	**1a**	 (**2d**)	5	**3d**: 45%
5	**1a**	 (**2e**)	6	**3e**: 35%
6	**1a**	 (**2f**)	6	**3f**: 34%[c]
7	**1a**	 (**2g**)	6	**3g**: 47%[d]
8	**1a**	 (**2h**)	6	**3h**: 57%
9	**1a**	 (**2i**)	6	**3i**: 65%

10	**1a**	 (**2j**)	5	**3j**: 66%
11	**1a**	 (**2k**)	5	**3k**: 65%
12	**1a**	 (**2l**)	5	**3l**: 64%
13	**1a**	 (**2m**)	5	**3m**: 50%
14	**1a**	 (**2n**)	9	**3n**: 45%
15	**1f**	**2a**	5.5	**3o**: 68%
16	**1g**	**2a**	6	**3p**: 46%
17	**1h**	**2a**	6	**3q**: 53%
18	**1i**	**2a**	6	**3r**: 51%

[a] Unless otherwise indicated, all reactions were carried out with **1** (0.3 mmol), **2** (3 mmol), *t*-BuONO (53 μL, 0.45 mmol), I_2 (38 mg, 0.15 mmol) under solvent-free conditions and air atmosphere at 25 °C.

[b] Along with 10% of *N*-(4-iodophenyl)-3-methoxybenzamide (**5c**).

[c] Along with 15% of *N*-(2-nitrophenyl)-3-(methoxycarbonyl)benzamide (**4f**).

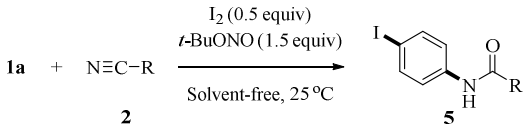
[d] Along with 18% of *N*-(4-iodophenyl)furan-2-carboxamide (**5g**).

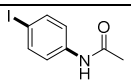
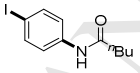
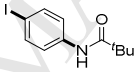
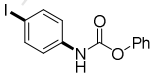
It was found that a mixture of *N*-phenylamides (**3s–u**) and *para*-iodine-substituted amides (**5s–u**) was generated when starting materials acetonitrile (**2s**), pentanenitrile (**2t**), and pivalonitrile (**2u**) reacted with **1a**, respectively,[21] and the products **3s–u** could be completely converted to the *N*-(4-iodophenyl)amides **5s–u** when the reaction time was prolonged to 12 h (Table 3). Advantageously, the strategy of prolonging the reaction time to obtain a single product avoided the need for isolation of the mixture of compounds **3s–u** and **5s–u**, which proved to have the same polarity in TLC. Furthermore, we found that the iodination reaction – unlike the nitrification reaction – could not be inhibited under N_2 atmosphere. Interestingly, a particular nitrile **2v** reacted with **1a** and smoothly afforded the useful **4v** as the sole product with the yield of 48% in 6 h. This

observation also discloses that the iodination occurs after the aryl transfer reaction. Moreover, the obtained iodine-substituted amides are suitable for further functionalization, such as by the Heck reaction, and the Suzuki and Stille cross-coupling reactions.

Table 3

Extension of the reaction scope.[a]

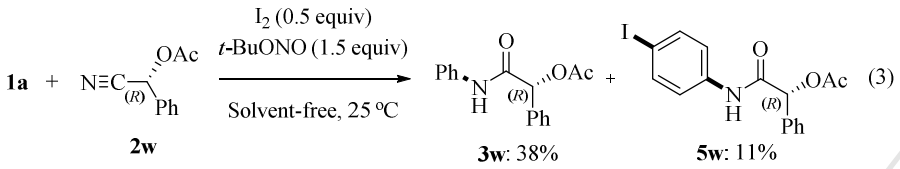


Entry	Substrate **2**	t/h	Product **5**
1	MeCN (**2s**)	12	 **5s**: 65%
2	^{n}BuCN (**2t**)	12	 **5t**: 57%
3	^{t}BuCN (**2u**)	12	 **5u**: 60%
4	PhOCN (**2v**)	6	 **5v**: 48%

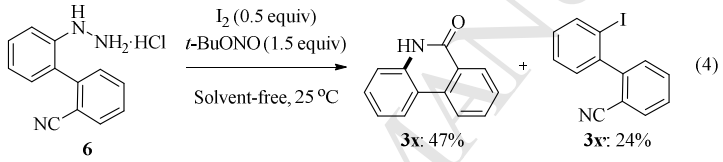
[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.3 mmol), **2** (3 mmol), *t*-BuONO (53 μL, 0.45 mmol), I_2 (38 mg, 0.15 mmol) under solvent-free conditions and air atmosphere at 25 °C.

The synthesis of chiral amides via the aryl transfer reaction was also investigated (Eq 1). It was found that the desired chiral amides (*R*)-2-oxo-1-phenyl-2-(phenylamino)ethyl acetate (**3w**) and (*R*)-2-((4-iodophenyl)amino)-2-oxo-1-phenylethyl acetate (**5w**) could be isolated in 38% and 11% yield, respectively, when **1a** and optically pure substrate (*R*)-cyano(phenyl)methyl acetate (**2w**) were employed in the reaction.[22] The α value of (*S*)-**3w** in the literature is $[\alpha]^{20} = +74.9°$ (c = 3.65, $CHCl_3$), while in our experiment, the $[\alpha]_D^{25.5}$ value of **3w** was observed as -64.5° (c = 0.2, CH_2Cl_2), revealing

that the (*R*)-configuration was mainly formed (Eq 3).[23] These observations also disclosed that the absolute configuration in the transformation remained essentially unchanged.



Finally, to demonstrate the synthetic potential of this reaction, an intramolecular generation of phenanthridin-6(5*H*)-one (**3x**) was conducted. Starting material 2'-hydrazinyl-[1,1'-biphenyl]-2-carbonitrile (**6**) was readily converted to phenanthridin-6(5*H*)-one (**3x**) in 47% yield under the optimal conditions, along with by-product 2'-iodo-[1,1'-biphenyl]-2-carbonitrile (**3x'**) (Eq 4).[24]



Radical trapping experiments were conducted to clarify whether a radical process was involved in the transformation. It was found that compound **3a** was not formed when 1 equiv of radical scavengers, including 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), *N*-*tert*-butyl-α-phenylnitrone (PBN), and galvinoxyl were added in the reaction mixture, in separate experiments, under the standard conditions. Under these conditions, the conversion was completely inhibited and none of the desired product **3** was formed. These results implied that radicals were involved in the transformation (Table 4). In addition, a separate reaction from *N*-phenylacetamide to **5s** was also inhibited by adding 1 equiv of TEMPO, which suggested a radical pathway maybe involved from *N*-phenylacetamide to **5s**. Moreover, in our recent work, we have demonstrated by a labelling experiment that the nitrogen source of the products **3** comes from the nitriles **2**, rather than the hydrazines.[10] In the present work, the labelling experiment showed that the N atom in the final products likewise came from the cyano group of the nitriles (**2**) (Eq 5). In addition, no target product

3a was generated in reactions performed in the absence of either I_2 or *t*-BuONO (Table 1, entries 6 and 7). These facts indicated that both I_2 and *t*-BuONO are indispensable to the transformation.

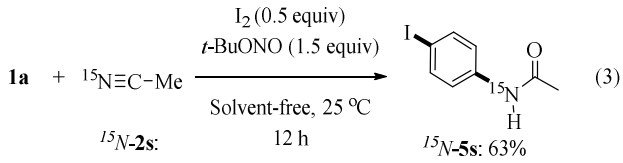
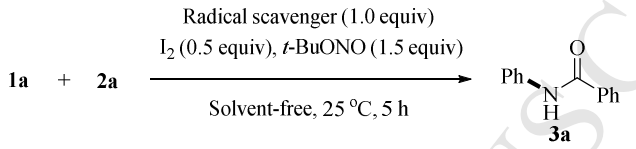


Table 4

Radical trapping experiments.[a]

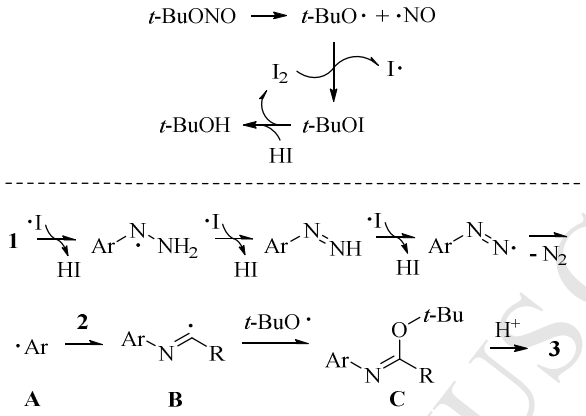


Radical scavenger (1 equiv)	Yield of **3a**/%
No Scavenger	64
TEMPO	0
PBN	0
Galvinoxyl	0

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.3 mmol), **2a** (3 mmol), *t*-BuONO (53 μL, 0.45 mmol), I_2 (38 mg, 0.15 mmol), and radical scavenger (0.3 mmol) under solvent-free conditions and air atmosphere at 25 °C.

Based on the results of these control experiments and information from previous works, a plausible mechanism is proposed in Scheme 2. It was envisioned that the homolysis of *t*-BuONO under the reaction conditions gave *tert*-butoxyl radicals and NO radicals.[19] Then, the *tert*-butoxyl radicals reacted with the initiator iodine to afford *tert*-butyl hypoiodite[25] and iodine radicals.[26] Next, the *in situ*-generated iodine radicals reacted with the phenylhydrazine hydrochlorides (**1**) to form the aryl radicals **A** with the release of N_2 and HI.[15b,27] Subsequently, the addition of the aryl radicals to **2** produced intermediate **B**.[28] We speculate that the steric hindrance of the N position is less than the C position in the nitrile group, which resulted in the *N*-addition of the transformation. Finally, this

intermediate was trapped by the *tert*-butoxyl radicals to generate the intermediate **C**, ultimately leading to the amide **3** in the presence of a proton.[9a,10] After this desired reaction, an iodination[29] or a nitrification[20] were possible, resulting in the production of *para*-iodinated product **5** or *ortho*-nitrogenated product **4** via a radical process.



Scheme 2. Proposed mechanism.

3. Conclusion

In summary, an iodine-promoted and *t*-BuONO-assisted intermolecular cross-coupling reaction was developed via relatively a rare *N*-addition reaction to the cyano group of nitriles. The protocol allows the introduction of an aryl, derived from arylhydrazine hydrochlorides, directly to the nitrogen atom of the nitriles, avoiding the pre-preparation of carbonyl-containing starting materials. In addition, this reaction proceeded under metal-, base-, and solvent-free conditions and produced structurally diverse *N*-aryl amides with a broad substrate scope.

4. Experimental section

4.1. General methods

All reactions were carried out under air atmosphere, unless otherwise indicated. Other all reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. The petroleum ether (PE) used refers to the fraction of petroleum with a boiling point of 60–90 °C. Ethyl acetate is abbreviated as EA. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance/600 (^{1}H: 600 MHz, ^{13}C: 150 MHz at 25 °C) or Bruker Avance/400 (^{1}H: 400 MHz, ^{13}C: 100

MHz at 25 °C) spectrometer using TMS as an internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer using electrospray ionization (ESI-oa-TOF), and the purity of all samples used for HRMS (>95%) were confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by thin layer chromatography with GF254 silica gel coated plates. Flash chromatography was carried out on silica gel (200–300 mesh).

4.2. Typical Experimental Procedure

*4.2.1. For **3** (**3a** as an example)*

To a round-bottom flask (25 mL) was added phenylhydrazine hydrochloride **1a** (43 mg, 0.3 mmol), benzonitrile **2a** (0.3 mL, 3 mmol), *t*-BuONO (53 μL, 0.45 mmol), I_2 (38 mg, 0.15 mmol), the mixture was well stirred for 6 h at 25 ^{o}C (the whole process was closely monitored by TLC). Then the reaction mixture was purified by a flash silica gel column chromatography (eluent: Petroleum ether (PE)/Ethyl acetate (EA) = 10:1) to give *N*-phenylbenzamide **3a** as a white solid (38 mg, 64%).

*4.2.2. For **2r***[30]

To a round-bottom flask (50 mL) was added acetic anhydride (188 μL, 2 mmol), DMAP (67 μL, 0.5 mmol), (R)-2-hydroxy-2-phenylacetonitrile (119 μL, 1 mmol) in tetrahydrofuran (5 mL), the mixture was stirred for 10 h at room temperature. (the whole process was closely monitored by TLC). The reaction was poured into water (5 mL), and the mixture was stirred vigorously for 30 min. The aqueous phase was extracted with EtOAc (3×15 mL). The combined organic phases were washed with 1 M aq HCl (15 mL), saturated aq $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the (R)-cyano(phenyl)methyl acetate **2r** as a colorless oil (149 mg, 85%).

*4.2.3. For **5***[31]

To a round-bottom flask (50 mL) was added 1-iodo-2-nitrobenzene (249 mg, 1 mmol), (2-cyanophenyl)boronic acid (220 mg, 1.5 mmol), $Pd(OAc)_2$ (1 mg, 0.5% mmol), K_3PO_4 (425 mg, 2 mmol) in ethylene glycol, the mixture was well stirred for 5 h at 80 ^oC (the whole process was closely monitored by TLC). After cooling, the mixture was added to brine. The mixture was extracted with diethyl ether. The organic phase was evaporated under reduced pressure, the reaction mixture was purified by a flash silica gel column chromatography to give 2'-nitro-(1,1'-biphenyl)-2-carbonitrile **7** as a gray solid (101 mg, 45%).

To a round-bottom flask (50 mL) was added 2'-nitro-(1,1'-biphenyl)-2-carbonitrile (224 mg, 1 mmol), Fe (336 mg, 6 mmol) in acetic acid, the mixture was well stirred for 13 h at 40 ^oC (the whole process was closely monitored by TLC). After cooling, the mixture was added to brine. The production of slag was filtered off and washed with CH_2Cl_2 and Et_2O. The organic phase was evaporated under reduced pressure to give 2'-amino-[1,1'-biphenyl]-2-carbonitrile **8** as a gray solid (126 mg, 85%).

To a round-bottom flask (50 mL) was added $NaNO_2$ (83 mg, 1.2 mmol) in water (0.5 mL), 2'-amino-[1,1'-biphenyl]-2-carbonitrile (118 mg, 1 mmol) in concentrated HCl (2 mL), the mixture was well stirred for 1 h at 0 ^oC. Then, solution of $SnCl_2$ (450 mg, 2 mmol) inconcentrated HCl (1.5 mL) was added at 0 °C and the resulting mixture was stirred for 2 h at room temperature. The formed precipitation was filtered off and washed with EtOH and Et_2O. The finalcompound was dried under the vacuum to give 2'-hydrazinyl-[1,1'-biphenyl]-2-carbonitrile **6** as a white solid (84mg, 45%).

4.3. Analytical Data

*4.3.1. (R)-cyano(phenyl)methyl acetate (**2w**)*

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a white solid (148 mg, 85%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.40 (m, 2H), 7.40-7.32 (m, 3H), 6.32 (s, 1H), 2.07 (s,

3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 131.8, 130.4, 129.3, 127.9, 116.1, 62.9, 20.5. HRMS (ESI), *m/z* calcd. for $C_{10}H_9NNaO_2$ ($[M+Na]^+$) 198.0525, found: 198.0529.

*4.3.2. N-phenylbenzamide (**3a**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (38 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.2 Hz, 2H), 7.80 (s, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H).

*4.3.3. 4-methoxy-N-phenylbenzamide (**3b**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (50 mg, 73%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.71 (s, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 3.88 (s, 3H).

*4.3.4. 3-methoxy-N-phenylbenzamide (**3c**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (39 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 1.5 Hz, 1H), 7.40 - 7.36 (m, 7.2 Hz, 4H), 7.16 (t, J = 7.4 Hz, 1H), 7.12-7.07 (m, 1H), 3.88 (s, 3H).

*4.3.5. 2-methoxy-N-phenylbenzamide (**3d**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 50/1) as a white solid (31 mg, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.30 (d, J = 8.0, 1H), 7.68 (d, J = 7.6 Hz, 2H), 7.54-7.46 (m, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.15-7.12 (m, 2H), 7.04 (d, J = 8.4 Hz, 1H), 4.07 (s, 3H).

*4.3.6. methyl 4-(phenylcarbamoyl)benzoate (**3e**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (27 mg, 35%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.82 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 3.96 (s, 3H).

*4.3.7. methyl 3-(phenylcarbamoyl)benzoate (**3f**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (26 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.22 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 7.67 (d, J = 7.9 Hz, 2H), 7.60 (t, J = 7.9 Hz, 1H), 7.40 (t, J = 7.9 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 3.97 (s, 3H).

*4.3.8. N-phenylfuran-2-carboxamide (**3g**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (26 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 0.8 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.25 (d, J = 3.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.57 (dd, J = 3.4, 1.8 Hz, 1H).

*4.3.9. N-phenylthiophene-2-carboxamide (**3h**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 30/1) as a white solid (34 mg, 57%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 2H), 7.62 (s, 2H), 7.56 (s, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.14 (s, 1H).

*4.3.10. N,2-diphenylacetamide (**3i**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (41 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.6 Hz, 4H), 7.34 (d, J = 7.6 Hz, 3H), 7.29 (d, J = 7.6 Hz, 2H), 7.08 (t, J = 7.4 Hz, 1H), 7.00 (s 1H), 3.75 (s, 2H).

*4.3.11. N,1-diphenylcyclopropane-1-carboxamide (**3j**)*[32]

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a white solid (47 mg, 66%); mp: 122-125 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 7.8 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.8 Hz, 2H), 7.04 (t, J = 7.2 Hz,

2H), 1.72-1.71 (m, 2H), 1.17-1.16 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 139.5, 138.0, 131.3, 129.5, 129.0, 128.5, 124.3, 119.7, 31.4, 16.3. HRMS (ESI), *m/z* calcd. for $C_{16}H_{15}NONa$ ($[M+Na]^+$) 260.1046, found: 260.1047.

*4.3.12. methyl 3-oxo-3-(phenylamino)propanoate (**3k**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a white solid (38 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.13 (t, J = 7.6 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 2H).

*4.3.13. 2-oxo-N,2-diphenylacetamide (**3l**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 40/1) as a white solid (43 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.46-8.40 (m, 2H), 7.70 (t, J = 6.2 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.41 (t, J = 8.0 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H).

*4.3.14. N-phenylcinnamamide (**3m**)*[10]

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a white solid (34 mg, 50%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J = 15.6 Hz, 1H), 7.63 (s, 2H), 7.54 (s, 2H), 7.43-7.33 (m, 6H), 7.14 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 15.6 Hz, 1H).

4.3.15. ethyl (Z)-3-phenyl-2-(phenylcarbamoyl)acrylate (3n)[33]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (40 mg, 45%); mp: 150-158 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.59 (d, J = 6.6 Hz, 2H), 7.57 (s, 1H), 7.52 (d, J = 7.8 Hz, 2H), 7.35 (m, 5H), 7.16 (t, J = 7.5 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H). HRMS (ESI), *m/z* calcd. for $C_{18}H_{17}NO_3Na$ ($[M+Na]^+$) 318.1101, found: 318.1103.

*4.3.16. N-(tert-butyl)-4-methoxybenzamide (**3o**)*[34]

The product was isolated by flash chromatography (eluent: PE/EA = 40/1) as a white solid (36 mg,

68%); mp: 112-113 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 77.71 (d, J = 7.8 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 5.95 (s, 1H), 1.47 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 136.1, 131.2, 128.6, 126.8, 51.7, 29.0. HRMS (ESI), *m/z* calcd. for $C_{11}H_{15}NONa$ ($[M+Na]^+$) 200.1042, found: 200.1046.

*4.3.17. N-(pyridin-4-yl)benzamide (**3p**)*[35]

The product was isolated by flash chromatography (eluent: PE/EA = 1/2) as a white solid (27 mg, 46%); mp: 208-210 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 2H), 8.03 (s, 1H), 7.88 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 4.2 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 150.8, 145.3, 134.2, 132.7, 129.1, 127.3, 114,0. HRMS (ESI), *m/z* calcd. for $C_{12}H_{11}N_2O$ ($[M+H]^+$) 199.0866, found: 199.0868.

*4.3.18. N-(3-chloropyrazin-2-yl)benzamide (**3q**)*

The product was isolated by flash chromatography (eluent: PE/EA = 5/1) as a white solid (37 mg, 53%); mp: 195-197 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.43 (s, 1H), 8.18 (s, 1H), 7.95 (d, J = 7.8 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 145.5, 141.5, 139.5, 139.3, 133.7, 133.1, 129.2, 127.7. HRMS (ESI), *m/z* calcd. for $C_{11}H_8ClN_3ONa$ ($[M+Na]^+$) 256.0244, found: 256.0248.

*4.3.19. N-(6-chloropyridazin-3-yl)benzamide (**3r**)*[35]

The product was isolated by flash chromatography (eluent: PE/EA = 3/1) as a white solid (36 mg, 51%); mp: 193-196 ^{o}C; 1H NMR (400 MHz, CDCl3) δ 9.06 (s, 1H), 8.67 (d, J = 9.6 Hz, 1H), 7.98-7.93 (m, 2H), 7.67-7.60 (m, 1H), 7.53-7.58 (m, 3H).13C NMR (150 MHz, CDCl3) δ 166.5, 159.5, 154.7, 152.6, 133.2, 130.1, 129.2, 127.5, 121.3. HRMS (ESI), m/z calcd. for C11H8ClN3ONa ([M+Na]+) 256.0249, found: 256.0248.

*4.3.20. (R)-2-oxo-1-phenyl-2-(phenylamino)ethyl acetate (**3w**) and (R)-2-((4-iodophenyl)amino)-2-oxo-1-phenylethyl acetate (**5w**)*

The product was isolated by flash chromatography (eluent: PE/EA = 7/1) as a white solid (31 mg, 49%) with a 3 : 1 of **3w** : **5w**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.64-7.60 (m, 1H), 7.55-7.46 (m, 5H), 7.43-7.35 (m, 5H), 7.35-7.29 (m, 3H), 7.13 (t, J = 7.4 Hz, 1H), 6.20 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 166.3, 138.0, 136.9, 135.2, 129.3, 129.1, 128.9, 127.5, 125.0, 121.8, 120.1, 75.7, 21.1. HRMS (ESI), *m/z* calcd. for $C_{16}H_{15}NO_3Na$ ($[M+Na]^+$) 292.0944, found: 292.0949.

*4.3.21. phenanthridin-6(5H)-one (**3x**)*[36]

The product was isolated by flash chromatography (eluent: PE/EA = 15/1) as a white solid (27 mg, 47%); mp: >300 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 8.4 Hz, 1H), 8.58-8.54 (m, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.13-8.09 (m, 1H), 7.96-7.90 (m, 1H), 7.81-7.67 (m, 3H). HRMS (ESI), *m/z* calcd. for $C_{13}H_9NONa$ ($[M+Na]^+$) 218.0576, found: 218.0576.

*4.3.22. 2'-iodo-[1,1'-biphenyl]-2-carbonitrile (**3x'**)*[37]

The product was isolated by flash chromatography (eluent: PE/EA = 25/1) as a white solid (22 mg, 24%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 8.4 Hz, 1H), 8.54 (dd, J = 8.0, 1.6 Hz, 1H), 8.49 (dd, J = 8.4, 0.8 Hz, 1H), 8.10 (dd, J = 8.2, 1.0 Hz, 1H), 7.92 (m, 1H), 7.74 (m 3H). HRMS (ESI), *m/z* calcd. for $C_{13}H_9IN$ ($[M+H]^+$) 305.9774, found: 305.9781.

*4.3.23. N-(2-nitrophenyl)benzamide (**4a**)*[38]

The product was isolated by flash chromatography (eluent: PE/EA = 25/1) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 9.02 (d, J = 8.4, 1H), 8.29 (d, J = 8.4, 1H), 8.01 (d, J = 7.2 Hz, 2H), 7.76-7.69 (m, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.55 (t, J = 7.4 Hz, 2H), 7.25-7.19 (m, 1H).

*4.3.24. methyl 3-((2-nitrophenyl)carbamoyl)benzoate (**4f**)*[39]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (14 mg, 15%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.41 (s, 1H), 8.99 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H), 8.32-8.27 (m, 2H), 8.18 (d, J = 7.2 Hz, 1H), 7.77-7.73 (m, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.54 (s, 1H), 3.99 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{15}H_{13}N_2O_5$ ($[M+H]^+$) 301.0819, found: 301.0815.

*4.3.25. N-(4-iodophenyl)-3-methoxybenzamide (**5c**)*[40]

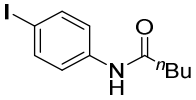
The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a white solid (11 mg, 10%); mp 92-93 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 9 Hz, 3H), 7.37 (dd, J = 9.7, 8.2 Hz, 2H), 7.09 (d, J = 7.2 Hz, 1H), 3.87 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{14}H_{12}INO_2Na$ ($[M+Na]^+$) 375.9805, found: 375.9805.

*4.3.26. N-(4-iodophenyl)furan-2-carboxamide (**5g**)*[41]

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a white solid (17 mg, 18%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.59 (t, J = 7.8 Hz, 2H), 7.45 (s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 6.50 (s, 1H)

*4.3.27. N-(4-iodophenyl)acetamide (**5s**)*[42]

The product was isolated by flash chromatography (eluent: PE/EA = 7/1) as a white solid (50 mg, 65%); mp: 184-186 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.21 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.3 (s), 137.9 (s), 137.6 (s), 121.6 (s), 87.5 (s), 24.7 (s). HRMS (ESI), *m/z* calcd. for C_8H_9INO ($[M+H]^+$) 261.9723, found: 261.9722.



*4.3.28. N-(4-iodophenyl)pentanamide (**5t**)*[43]

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a yellow solid (52 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.06 (s, 1H), 2.37-2.32 (m, 2H), 1.74-1.66 (m, 2H), 1.40 (dd, J = 15.0, 7.4 Hz, 2H), 0.95 (t, J = 7.0 Hz, 3H). HRMS (ESI), *m/z* calcd. for $C_{11}H_{14}INONa$ ($[M+Na]^+$) 326.0012, found: 326.0010.

*4.3.29. N-(4-iodophenyl)pivalamide (**5u**)*[44]

The product was isolated by flash chromatography (eluent: PE/EA = 20/1) as a yellow solid (55 mg, 60%); mp: 148-149 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.28 (s, 1H), 1.31 (s, 9H). HRMS (ESI), *m/z* calcd. for $C_{11}H_{14}INONa$ ($[M+Na]^+$) 326.0012, found: 326.0010.

*4.3.30. phenyl (4-iodophenyl)carbamate (**5v**)*[45]

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a white solid (49 mg, 48%); mp: 158-159 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 10.38 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.25 (dd, J = 19.6, 7.6 Hz, 3H). HRMS (ESI), *m/z* calcd. for $C_{13}H_{10}INO_2Na$ ($[M+Na]^+$) 361.9648, found: 361.9649.

*4.3.31. 2'-hydrazinyl-[1,1'-biphenyl]-2-carbonitrile (**6**)*

The product was isolated by flash chromatography (eluent: PE/EA = 1/1) as a white solid (84 mg, 45%); ^{1}H NMR (600 MHz, DMSO) δ 14.61 (s, 1H), 8.85 (d, J = 8.4 Hz, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.64 (d, J = 7.8 Hz, 1H), 8.09 (t, J = 7.5 Hz, 1H), 7.86 (t, J = 7.5 Hz, 1H), 7.71 (t, J = 6.9 Hz, 2H), 7.56-7.52 (m, 1H). ^{13}C NMR (150 MHz, DMSO) δ 154.9, 135.5, 134.1, 131.2, 129.5, 127.2, 125.6, 124.1, 119.4, 118.4, 118.0. HRMS (ESI), *m/z* calcd. for $C_{13}H_{12}N_3$ ($[M+H]^+$) 210.1026, found: 210.1028.

*4.3.32. 2'-nitro-(1,1'-biphenyl)-2-carbonitrile (**7**)*

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a gray solid (101 mg, 45%); ^{1}H NMR (400 MHz, DMSO) δ 8.23 (dd, J = 8.2, 1.1 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.92-7.87(m, 1H), 7.83-7.77 (m, 2H), 7.67-7.59 (m, 2H), 7.55 (d, J = 7.6 Hz, 1H). ^{13}C NMR (150 MHz, DMSO) δ 148.3, 141.9, 134.4, 133.9, 133.0, 132.9, 131.0, 129.9, 129.4, 125.3, 117.9, 111.5. HRMS (ESI), *m/z* calcd. for $C_{13}H_9N_3O_2$ ($[M+H]^+$) 225.0659, found: 225.0661.

*4.3.33. 2'-amino-[1,1'-biphenyl]-2-carbonitrile (**8**)*

The product was isolated by flash chromatography (eluent: PE/EA = 10/1) as a gray solid (126 mg, 85%); ^{1}H NMR (600 MHz, DMSO) δ 9.24 (d, J = 6.0 Hz, 1H), 9.11-8.90 (m, 2H), 8.43 (s, 1H), 8.27 (s, 1H), 8.14 (dd, J = 20.3, 6.1 Hz, 2H), 7.88 (s, 1H), 7.78 (s, 2H). ^{13}C NMR (150 MHz, DMSO) δ 172.6, 156.1, 145.4, 133.9, 131.0, 129.1, 127.5, 126.0, 125.0, 123.0, 122.8, 122.2, 120.7, 119.1. HRMS (ESI), *m/z* calcd. for $C_{13}H_{11}N_2$ ($[M+H]^+$) 195.0917, found: 195.0917.

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21. The reaction of **2i** and 1a as the example, under the optimal conditions after 4 h: The yield of **3i**: 31%, yield of **4i**: 48%.

22. Compounds **3w** and **3w'** were isolated in the ratio of Ca. 3:1. And complex mixture was formed if we prolonged the reaction times.

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