JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Rhodium(III)-Catalyzed Direct Cyanation of Aromatic C−H Bond to Form 2-(Alkylamino)benzonitriles Using *N*-Nitroso As Directing Group

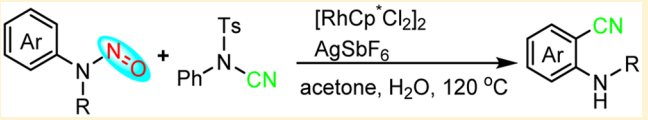
Jiawei Dong,[†] Zhongjie Wu,[†] Zhengyi Liu,[†] Ping Liu,[†,‡] and Peipei Sun*[,†,‡]

[†]College of Chemistry and Materials Science, Jiangsu Provincial Key Laboratory of Materials Cycling and Pollution Control, Nanjing Normal University, Nanjing 210097, China

[‡]Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Nanjing Normal University, Nanjing 210023, China

Supporting Information

ABSTRACT: 2-(Alkylamino)benzonitriles were synthesized via a rhodium-catalyzed cyanation on the aryl C−H bond and subsequent denitrosation of *N*-nitrosoarylamines using a removable nitroso as the directing group, in which *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) was used as the "CN" source. Various substituents on the aryl ring and amino group of *N*-nitrosoarylamines tolerated the reaction, and the corresponding products were achieved in moderate to good yields.



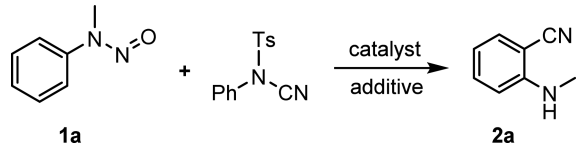
Benzonitriles are versatile and important structural motifs in organic synthesis as well as in agrochemicals, pharmaceuticals, and natural products.[1] For example, 2-aminobenzonitrile derivatives have favorable anti-inflammatory effects.[2] Cyano group can be converted into a variety of useful functional groups, such as carboxyl, carbamoyl, aminomethyl, carbonyl, and heterocycles.[3] The transition-metal-catalyzed cleavage of C−CN bond can also form various other important chemical bonds.[4] Thus, efficient and selective synthesis of benzonitriles is highly desirable in both organic and medicinal chemistry. There are numerous ways to be developed for the preparation of benzonitriles, e.g., by the Rosenmund−von Braun reaction from aryl halides[5] or by the diazotization of anilines and a subsequent Sandmeyer reaction.[6] In recent years, transition-metal-catalyzed cyanation of aryl halides provided an effective approach for the synthesis of these compounds.[3b,7] Significantly, in past decade, the direct C−CN bond formation via transition-metal-catalyzed C−H bond activation brought about a new insight, which provided a straightforward and economical sequences to prepare benzonitriles from nonprehalogenated arenes. By using nitromethane, $K_3[Fe(CN)_6]$, DMF, CuCN, AIBN, *N*-cyanosuccinimide, and *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as the "CN" source, a series of regioselective cyanation of aromatic or alkenyl C(sp^2)−H bond was developed, in which pyridyl,[8] carbamyl,[9] azo,[10] *O*-methyl oxime[11] were employed as the directing groups. Other reports referred to transition-metal-catalyzed cyanation of activated arenes and heteroarenes without coordinating directing groups.[12] Considering the importance of the benzonitrile derivatives in many fields, putting the direct cyanation strategy into more kinds of arene derivatives is still an urgent need and a challenge. Because of the moderate coordination effect of nitroso to transition metals,[13] the application of this group as a favorable directing group to carry out the functionalization of inert C−H bond has aroused much attention.[14] In our previous works, a palladium-catalyzed direct *ortho*-alkoxylation of *N*-alkyl-*N*-nitrosoarylamines was developed, and a series of *o*-alkoxy-*N*-alkylanilines were finally obtained.[15] In continuation of our longstanding interest in the directed C−H functionalization, herein we want to describe a Rh^{III}-catalyzed *ortho*-C(sp^2)−H bond cyanation of *N*-alkyl-*N*-nitrosoarylamines directed by nitroso group to form 2-(alkylamino)benzonitriles.

An easily accessible and user-friendly reagent NCTS was selected as the "CN" source in our investigations. We initially studied the cyanation conditions by employing *N*-methyl-*N*-phenylnitrous amide (**1a**) as the reactant (Table 1). Without catalyst, the reaction could not take place at all (entry 1). Thus, a series of transition-metal catalysts, such as palladium, ruthenium, and rhodium, were tested. Unfortunately, they did not show catalytic activity to this transformation (entries 2−4). However, to our delight, in the presence of $[RhCp^*Cl_2]_2$ combined with an additive $AgSbF_6$, the cyanation took place successfully. Surprisingly, the denitrosation occurred at the same time, and the product 2-(methylamino)benzonitrile (**2a**) was obtained in 54% yield (entry 5). Subsequently, we agreeably found out that the presence of 2 equiv water promoted the reaction efficiently and improved the yield to 77% (entry 6). Nevertheless, when 10 equiv water was added, a lower yield of 35% was obtained. Furthermore, some acids or bases could completely inhibit the reaction (entries 8−11). Solvent was then screened. In trifluorotoluene, the reaction also proceeded smoothly and gave a good yield as that in acetone (entries 6, 12). In toluene, however, only a lower yield of 22% was obtained (entry 13). If the reaction was carried out in DMF, acetonitrile, dioxane, or DCE, almost no desired product was found (entries 14−17). Considering economic reasons, in

Received: July 18, 2015
Published: November 5, 2015

DOI: 10.1021/acs.joc.5b01666
J. Org. Chem. 2015, 80, 12588−12593

Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	catalyst (mol %)	additive (equiv)	solvent	yield (%)
1	–	–	acetone	0
2	$Pd(OAc)_2$ (5)	–	acetone	0
3	$[RuCl_2(p\text{-cymene})]_2$ (2.5)	–	acetone	0
4	$[RhCp^*Cl_2]_2$ (2.5)	–	acetone	0
5	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)	acetone	54
6	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	acetone	77
7	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (10)	acetone	35
8	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ PivOH (2)	acetone	0
9	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ AcOH (2)	acetone	0
10	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ PivONa (2)	acetone	0
11	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ NaOAc (2)	acetone	0
12	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	trifluorotoluene	79
13	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	toluene	22
14	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	CH_3CN	trace
15	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	dioxane	0
16	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	DMF	0
17	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	DCE	0
18[b]	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (0.15)/ H_2O (2)	acetone	62

[a] **1a** (0.3 mmol), NCTS (1.5 equiv), catalyst, $AgSbF_6$ (15 mol %), additive, and solvent (2 mL) at 120 °C under N_2 atmosphere for 24 h. All yields are isolated ones. [b] At 100 °C.

our following research, acetone was used as the solvent. The appropriate reaction temperature was 120 °C. A lower temperature of 100 °C brought a measurable decrease of the yield (entry 18).

With the optimized reaction conditions in hand, we then explored the substrate scope of this cyanation and subsequent denitrosation reaction. The results are summarized in Table 2. *N*-Alkyl-*N*-nitrosophenylamines with several different alkyls substituted on amino group were first examined. For *N*-methyl, ethyl, propyl, and isopropyl-substituted derivatives, the reaction proceeded smoothly and afforded the cyanated products in good yields (**2a**–**2d**). Larger alkyl such as butyl, isobutyl, or cyclohexyl on amino group affected the reaction and led to the decrease of the yields (**2e**–**2g**), which was obviously due to the steric hindrance of these groups. Specially, N-aromatic group seemed unfavorable to this process. For these cases, the products with lower yields were obtained, and the cyanation strictly occurred on the electron-rich side (**2h**–**2j**).

N-Alkyl-*N*-nitrosoarylamines with a series of substituent groups on benzene ring were then employed for this cyanation/denitrosation reaction. The electron-donating groups seemed favorable for this transformation. For the substrates with alkyl, aryl, as well as alkoxy, the reaction gave the corresponding cyanated and denitrosated products in good yields (**2k**–**2r**). It is interesting that for most of the reactants with a *meta*-substituent, the cyanation selectively took place on the side with smaller steric hindrance (**2l**, **2p**, **2t**, **2y**). But when the *m*-methoxy-substituted substrate *N*-propyl-*N*-nitroso-3-methoxyaniline was used, a mixture of **2r** and **2r′** was obtained with a ratio of 2.3/1, and the exact reason was not clear. The electron-withdrawing groups such as chloro, bromo, and ester were also tolerated in this process, and the reaction afforded the desired products in moderate yields (**2t**–**2w**). However, the fluor-substituted substrate only gave a yield of 22% (**2s**). The presence of the strong electron-withdrawing group nitro restrained the reaction evidently, and only a trace product was found (**2x**). From the disubstituted arylamine derivative *N*,4-dimethyl-3-(trifluoromethyl)aniline, a yield of 38% was obtained (**2y**).

Dissolving the cyanated product 2-(methylamino)-benzonitrile (**2a**) in methol, in the presence of H_2SO_4, **2a** could be transformed into methyl 2-(methylamino)benzoate (**3a**) after heating the mixture for 24 h. And also, **2a** could be conveniently reduced to 2-(aminomethyl)-*N*-methylaniline (**4a**) by $LiAlH_4$ (Scheme 1). Both **3a** and **4a** are important compounds in pharmaceutical synthesis.[16]

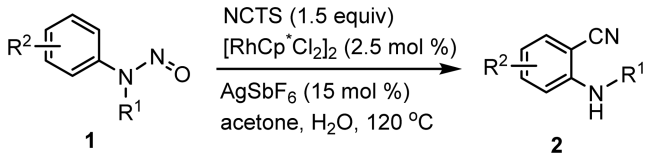
The isotope effect was investigated by using an equimolar mixture of *N*-methyl-*N*-phenylnitrous amide (**1a**) and *N*-methyl-*N*-(phenyl-d_5)nitrous amide (**1a**-d_5) to produce the reaction (Scheme 2, eq a). From this reaction system, a mixture of **2a** and **2a**-d_4 was obtained with a ratio of 3.1 after a reaction time of 3 h, which indicated that the rhodium-catalyzed C–H bond cleavage of benzene ring might occur in the rate-determining step. And also, when *N*-methyl-*N*-(phenyl-d_5)-nitrous amide (**1a**-d_5) was used as the reactant, in the absence of NCTS, about 16% of *ortho*-deuterium in **1a**-d_5 was substituted by hydrogen under the standard reaction conditions (Scheme 2, eq b). This result showed that the *ortho*-C(sp^2)–H bond activation was a reversible process.

Based on our present experimental results and the related reports,[8f,10,11,14a] we proposed a possible mechanism for this direct cyanation of the aryl C–H bond and denitrosation reaction (Scheme 3). First, treatment of $[RhCp^*Cl_2]_2$ with $AgSbF_6$ generated the active cationic rhodium(III) species **A**, which reacted with *N*-alkyl-*N*-phenylnitrous amide (**1**) to afford the cyclic rhodium species **B**. Then insertion of the CN group of NCTS into the C–Rh bond of **B** occurred and provided intermediate **C**. The electron-deficient nitrogen atom of nitroso in the intermediate **C** was attacked by a nucleophile H_2O, the N–N bond in the intermediate **C** was cleaved, a new intermediate **D** was formed, and the nitrous acid was released as well. Finally, the rearrangement of **D** led to the producing of cyanated product (**2**) along with the regeneration of active rhodium species **A** to carry on the next catalytic cycle. 4-Methyl-*N*-phenylbenzenesulfonamide was also separated from the reaction mixture.

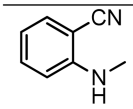
In summary, we have successfully developed an efficient and mild rhodium-catalyzed cyanation/denitrosation of *N*-nitrosoarylamines, using a removable nitroso as the directing group, to obtain 2-(alkylamino)benzonitriles. A range of corresponding products were synthesized by this strategy with moderate to good yields. Various active functional groups were compatible in this catalytic system. The result presented here should be of

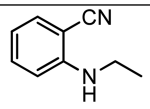
DOI: 10.1021/acs.joc.5b01666
J. Org. Chem. 2015, 80, 12588–12593

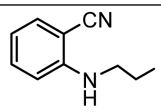
Table 2. Cyanation and Subsequent Denitrosation of *N*-Nitroso Arylamines[a]

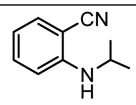


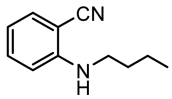
1 2

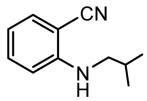

2a, 77%

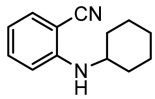

2b, 79%

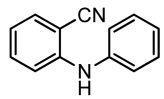

2c, 80%

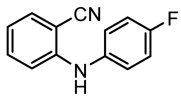

2d, 70%

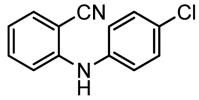

2e, 63%

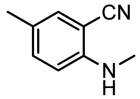

2f, 59%

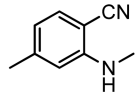

2g, 42%

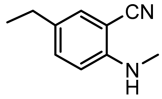

2h, 31%

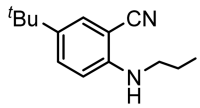

2i, 38%

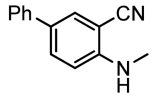

2j, 30%

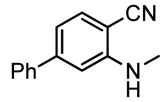

2k, 86%

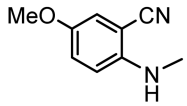

2l, 89%

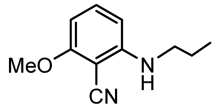
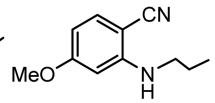

2m, 87%

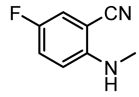

2n, 80%

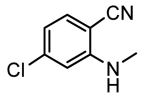

2o, 69%

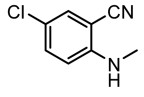

2p, 90%

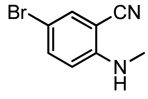

2q, 73%

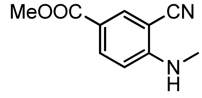


2r, **2r'**, 74% (2.3 : 1)

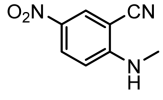

2s, 22%

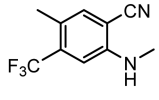

2t, 63%


2u, 41%


2v, 42%


2w, 57%


2x, trace


2y, 38%

[a]The reaction was carried out with **1** (0.3 mmol), NCTS (1.5 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (15 mol %), and H_2O (2.0 equiv) in acetone (2 mL) at 120 °C under N_2 atmosphere for 24 h. All yields are isolated ones.

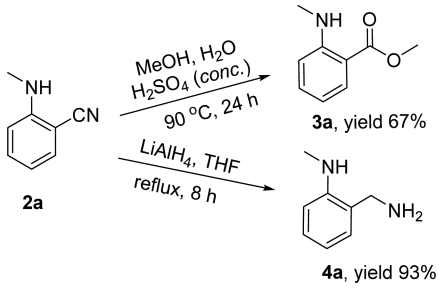
considerable interest for constructing valuable synthetic building blocks in organic synthesis.

EXPERIMENTAL SECTION

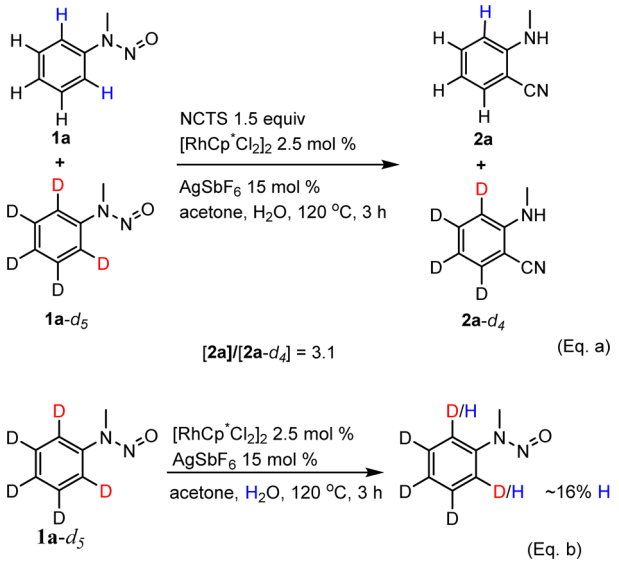
General. All reactions were run in a sealed tube with a Teflon-lined cap under nitrogen atmosphere. *N*-Alkyl-*N*-nitrosoarylamines were prepared according to the literature;[17] other reagents were commercially available and were used without purification. NMR spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C) using TMS as an internal standard. Chemical shifts are given relative to $CDCl_3$ (7.28 ppm for ^1H NMR, 77.16 ppm for ^{13}C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, brs = broad, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, dq = doublet of quartet, dhept = doublet of heptet, tdt = triplet of doublet of triplet, sepd =

DOI: 10.1021/acs.joc.5b01666
J. Org. Chem. 2015, 80, 12588−12593

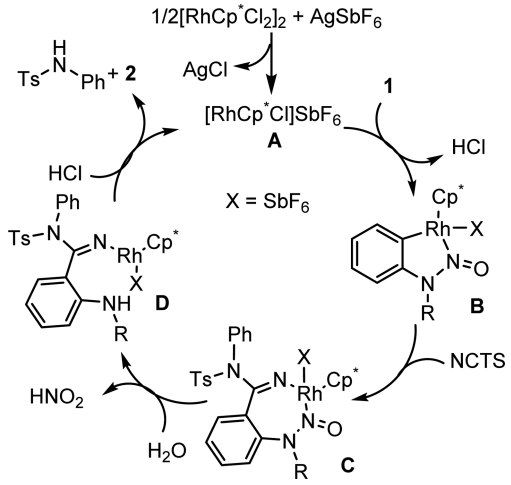
Scheme 1. Transformation of Cyanated Product



Scheme 2. Kinetic Isotope Effect



Scheme 3. Plausible Reaction Mechanism



septet of doublet, sept = septet of triplet. Melting points are uncorrected. For the HRMS measurements, Q-TOF was used.

General Procedures for the Rhodium-Catalyzed Cyanation and Subsequent Denitrosation of *N*-nitroso arylamines. *N*-Alkyl-*N*-nitrosoarylamine (0.3 mmol), NCTS (122 mg, 0.45 mmol), $[RhCp^*Cl_2]_2$ (4.6 mg, 2.5 mol %), $AgSbF_6$ (15.5 mg, 15 mol %), H_2O (0.01 mL, 2.0 equiv), and acetone (2 mL) were added in a 25 mL sealed tube with a Teflon-lined cap. The mixture was stirred at 120 °C (oil bath temperature) under N_2 for 24 h. After the reaction finished, the mixture was cooled to room temperature, diluted with dichloromethane, then washed with water, and dried. The solution was concentrated by vacuum and separated in a silica gel column using hexane/EtOAc (10:1, v/v) as eluent to give the corresponding pure 2-(alkylamino)benzonitrile products. For the solid products, the melting points were obtained after further recrystallization from hexane.

Preparation of Methyl 2-(methylamino)benzoate (3a). To a solution of 2-(methylamino)benzonitrile (**2a**, 66.1 mg, 0.5 mmol) in MeOH (4 mL) in a sealed tube was added H_2O (4 drops) and H_2SO_4 (conc., 1.5 mL). The reaction mixture was heated at 90 °C for 24 h. After cooling to room temperature, the reaction mixture was slowly quenched with saturated aqueous $NaHCO_3$ to pH 8 and extracted with DCM (10 mL × 3). The combined organic phases were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using hexane/ethyl acetate eluent (8:1) to afford the pure product **3a**.

Preparation of 2-(Aminomethyl)-*N*-methylaniline (4a). To a solution of 2-(methylamino)benzonitrile (**2a**, 66.1 mg, 0.5 mmol) in dry THF (2.5 mL) was added lithium aluminum hydride (56.9 mg, 1.5 mmol) under ice-cooling in an argon gas atmosphere. The solution was then heated and refluxed with stirring for 8 h. After cooling to room temperature, the reaction mixture was quenched with water until foaming ceased and diluted with DCM. Thereafter, the insolubles were filtered off, and the filtrate was concentrated to give 2-(aminomethyl)-*N*-methylaniline (**4a**).

*2-(Methylamino)benzonitrile (**2a**).*[18] Brown solid (30.5 mg, 77% yield). Mp: 69−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.36 (m, 2H), 6.72−6.63 (m, 2H), 4.68 (brs, 1H), 2.93 (d, J = 2.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 134.3, 132.6, 118.0, 116.3, 110.1, 95.5, 30.0.

*2-(Ethylamino)benzonitrile (**2b**).*[19] Brown oil (34.6 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 2H), 6.71−6.64 (m, 2H), 4.49 (brs, 1H), 3.26 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 134.3, 132.7, 118.0, 116.3, 110.5, 95.5, 37.9, 14.5.

*2-(Propylamino)benzonitrile (**2c**).*[20] Yellow oil (38.4 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 2H), 6.70−6.64 (m, 2H), 4.57 (brs, 1H), 3.19 (td, J = 10.8, 7.1 Hz, 2H), 1.76−1.65 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 134.2, 132.7, 118.0, 116.2, 110.6, 95.5, 45.1, 22.4, 11.5.

*2-(Isopropylamino)benzonitrile (**2d**).*[21] Yellow oil (33.6 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.35 (m, 2H), 6.71−6.62 (m, 2H), 4.38 (brs, 1H), 3.74 (sepd, J = 12.6, 6.4 Hz, 1H), 1.29 (d, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 134.2, 132.9, 118.1, 116.0, 111.0, 95.6, 44.1, 22.7.

*2-(Butylamino)benzonitrile (**2e**).* Yellow oil (32.9 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.35 (m, 2H), 6.75−6.61 (m, 2H), 4.54 (brs, 1H), 3.21 (t, J = 7.1 Hz, 2H), 1.75−1.58 (m, 2H), 1.47 (qt, J = 14.5, 7.3 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 134.2, 132.7, 118.0, 116.2, 110.5, 95.4, 43.0, 31.2, 20.2, 13.8; HRMS-ESI (m/z): calcd for $C_{11}H_{14}N_2Na$ $[M + Na]^+$ 197.1050, found 197.1055.

*2-(Isobutylamino)benzonitrile (**2f**).*[22] Yellow oil (30.8 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.34 (m, 2H), 6.71−6.61 (m, 2H), 4.64 (brs, 1H), 3.03 (d, J = 6.8 Hz, 2H), 1.95 (sept, J = 13.4, 6.7 Hz, 1H), 1.03 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 134.2, 132.7, 118.0, 116.2, 110.6, 95.5, 51.0, 28.0, 20.3.

*2-(Cyclohexylamino)benzonitrile (**2g**).*[23] Yellow oil (25.2 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 12.4, 4.6 Hz, 2H), 6.74−6.58 (m, 2H), 4.46 (br, 1H), 3.36 (tdt, J = 11.1, 7.6, 3.7 Hz, 1H), 2.04 (dd, J = 8.5, 4.2 Hz, 2H), 1.85−1.76 (m, 2H), 1.72−1.63 (m, 1H), 1.45−1.34 (m, 2H), 1.33−1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 134.1, 132.9, 118.1, 115.9, 111.0, 95.5, 51.4, 32.9, 25.6, 24.8.

*2-(Phenylamino)benzonitrile (**2h**).*[24] White solid (18.1 mg, 31% yield). Mp: 50−51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.8, 1.3 Hz, 1H), 7.43−7.35 (m, 3H), 7.27−7.19 (m, 3H), 7.19−7.12 (m, 1H), 6.86 (td, J = 7.8, 0.9 Hz, 1H), 6.42 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 139.9, 133.9, 133.1, 129.6, 124.2, 121.7, 119.2, 117.6, 114.2, 98.5.

*2-(4-Fluorophenylamino)benzonitrile (**2i**).*[24] White solid (24.2 mg, 38% yield). Mp: 104−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−

DOI: 10.1021/acs.joc.5b01666
J. Org. Chem. 2015, 80, 12588−12593

7.47 (m, 1H), 7.40−7.33 (m, 1H), 7.23−7.16 (m, 2H), 7.12−6.99 (m, 3H), 6.83 (td, J = 7.8, 0.9 Hz, 1H), 6.43 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (d, J = 244.9 Hz), 148.1, 135.8 (d, J = 2.8 Hz), 134.0, 133.1, 124.6 (d, J = 8.2 Hz), 119.0, 117.7, 116.4 (d, J = 22.7 Hz), 113.5, 97.9.

*2-(4-Chlorophenylamino)benzonitrile (**2j**).*[24] White solid (20.6 mg, 30% yield). Mp: 128−129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.50 (m, 1H), 7.41 (ddd, J = 8.8, 7.4, 1.6 Hz, 1H), 7.36−7.30 (m, 2H), 7.20−7.10 (m, 3H), 6.89 (td, J = 7.8, 1.0 Hz, 1H), 6.38 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 138.6, 134.0, 133.2, 129.7, 129.1, 122.8, 119.7, 117.4, 114.3, 98.9.

*5-Methyl-2-(methylamino)benzonitrile (**2k**).* Brown solid (37.7 mg, 86% yield). Mp: 121−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 8.5, 2.1 Hz, 1H), 7.20 (dd, J = 1.5, 0.6 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 4.49 (brs, 1H), 2.92 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 135.3, 132.4, 125.7, 118.1, 110.3, 95.4, 30.2, 19.9; HRMS-ESI (m/z): calcd for $C_9H_{10}N_2Na$ $[M + Na]^+$ 169.0736, found 169.0739.

*4-Methyl-2-(methylamino)benzonitrile (**2l**).* Brown solid (39.0 mg, 89% yield). Mp: 69−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 7.9 Hz, 1H), 6.54−6.49 (m, 1H), 6.47 (s, 1H), 4.59 (brs, 1H), 2.93 (d, J = 4.6 Hz, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 145.3, 132.4, 118.3, 117.7, 110.6, 92.8, 30.0, 22.4; HRMS-ESI (m/z): calcd for $C_9H_{10}N_2Na$ $[M + Na]^+$ 169.0736, found 169.0738.

*5-Ethyl-2-(methylamino)benzonitrile (**2m**).* Brown oil (41.8 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 8.2, 2.5 Hz, 1H), 7.23 (dd, J = 2.1, 0.4 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 4.51 (brs, 1H), 2.93 (d, J = 4.9 Hz, 3H), 2.55 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 134.2, 132.3, 131.3, 118.2, 110.3, 95.4, 30.2, 27.4, 15.6; HRMS-ESI (m/z): calcd for $C_{10}H_{12}N_2Na$ $[M + Na]^+$ 183.0893, found 183.0898.

*5-^{t}Butyl-2-(propylamino)benzonitrile (**2n**).* Yellow oil (51.9 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.9, 2.4 Hz, 1H), 7.39 (d, J = 2.3 Hz, 1H), 6.64 (d, J = 8.9 Hz, 1H), 4.45 (brs, 1H), 3.17 (td, J = 7.1, 5.6 Hz, 2H), 1.74−1.65 (m, 2H), 1.28 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 139.2, 131.8, 129.1, 118.5, 110.6, 95.0, 45.2, 33.8, 31.2, 22.5, 11.5; HRMS-ESI (m/z): calcd for $C_{14}H_{20}N_2Na$ $[M + Na]^+$ 239.1519, found 239.1516.

*4-(Methylamino)-[1,1′-biphenyl]-3-carbonitrile (**2o**).* Brown solid (43.1 mg, 69% yield). Mp: 155−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 8.7, 2.3 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.54−7.49 (m, 2H), 7.47−7.41 (m, 2H), 7.33 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 4.73 (brs, 1H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 139.3, 133.1, 130.8, 129.7, 128.9, 127.0, 126.2, 117.9, 110.6, 96.0, 30.2; HRMS-ESI (m/z): calcd for $C_{14}H_{12}N_2Na$ $[M + Na]^+$ 231.0893, found 231.0895.

*3-(Methylamino)-[1,1′-biphenyl]-4-carbonitrile (**2p**).* Yellow solid (56.2 mg, 90% yield). Mp: 115−116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 2H), 7.52−7.45 (m, 3H), 7.45−7.40 (m, 1H), 6.92 (dd, J = 8.0, 1.6 Hz, 1H), 6.84 (d, J = 1.5 Hz, 1H), 4.74 (brs, 1H), 3.01 (d, J = 1.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 147.4, 140.4, 133.0, 128.9, 128.4, 127.2, 115.7, 108.7, 94.4, 30.1; HRMS-ESI (m/z): calcd for $C_{14}H_{12}N_2Na$ $[M + Na]^+$ 231.0893, found 231.0891.

*5-Methoxy-2-(methylamino)benzonitrile (**2q**).*[25] Brown oil (35.5 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 9.1, 3.0 Hz, 1H), 6.93 (d, J = 3.0 Hz, 1H), 6.64 (d, J = 9.1 Hz, 1H), 4.35 (brs, 1H), 3.76 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 146.5, 122.5, 117.9, 115.8, 111.8, 95.4, 56.0, 30.6.

*2-Methoxy-6-(propylamino)benzonitrile (**2r**) and 4-methoxy-2-(propylamino)benzonitrile (**2r′**).* Yellow oil (42.2 mg, 74% yield, 2.3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 1H), 6.33−6.11 (m, 2H), 4.55 (brs, 1H), 3.88 (s, 3H × 0.7), 3.83 (s, 3H × 0.3), 3.16 (q, J = 7.0 Hz, 2H), 1.77−1.60 (m, 2H), 1.03 (dt, J = 13.3, 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.3, 152.1, 151.8, 134.7, 134.3, 118.5, 115.9, 103.2, 103.0, 98.3, 95.8, 88.3, 85.5, 55.8, 55.3, 45.2, 45.1, 22.4, 22.3, 11.5, 11.4; HRMS-ESI (m/z): calcd for $C_{11}H_{14}N_2ONa$ $[M + Na]^+$ 213.1009, found 213.1004.

*5-Fluoro-2-(methylamino)benzonitrile (**2s**).* Yellow solid (9.9 mg, 22% yield). Mp: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (ddd, J = 9.1, 8.1, 3.0 Hz, 1H), 7.13 (dd, J = 7.9, 3.0 Hz, 1H), 6.62 (dd, J = 9.2, 4.2 Hz, 1H), 4.54 (brs, 1H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (d, J = 238.0 Hz), 148.2, 139.3, 122.1 (d, J = 22.6 Hz), 118.2 (d, J = 25.1 Hz), 111.3 (d, J = 7.5 Hz), 95.4 (d, J = 3.9 Hz), 30.4; HRMS-ESI (m/z): calcd for $C_8H_7FN_2Na$ $[M + Na]^+$ 173.0486, found 173.0490.

*4-Chloro-2-(methylamino)benzonitrile (**2t**).* Brown solid (31.5 mg, 63% yield). Mp: 97−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.1 Hz, 1H), 6.71−6.62 (m, 2H), 4.77 (brs, 1H), 2.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 141.0, 133.6, 117.2, 116.8, 110.3, 94.1, 30.0; HRMS-ESI (m/z): calcd for $C_8H_7ClN_2Na$ $[M + Na]^+$ 189.0190, found 189.0195.

*5-Chloro-2-(methylamino)benzonitrile (**2u**).* Brown solid (20.4 mg, 41% yield). Mp: 97−99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.34 (m, 2H), 6.63−6.58 (m, 1H), 4.69 (s, 1H), 2.94 (d, J = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 134.5, 131.6, 120.8, 116.7, 111.4, 96.5, 30.1; HRMS-ESI (m/z): calcd for $C_8H_7ClN_2Na$ $[M + Na]^+$ 189.0190, found 189.0198.

*5-Bromo-2-(methylamino)benzonitrile (**2v**).* Brown solid (26.6 mg, 42% yield). Mp: 119−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 6.59−6.53 (m, 1H), 4.70 (brs, 1H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 137.2, 134.4, 116.6, 111.8, 107.1, 97.1, 30.1; HRMS-ESI (m/z): calcd for $C_8H_7BrN_2Na$ $[M + Na]^+$ 232.9685, found 232.9684.

*Methyl 3-cyano-4-(methylamino)benzoate (**2w**).* Orange solid (32.5 mg, 57% yield). Mp: 152−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.03 (m, 2H), 6.66 (d, J = 8.9 Hz, 1H), 5.17 (brs, 1H), 3.88 (s, 3H), 3.00 (d, J = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 153.6, 135.7, 135.1, 118.2, 117.0, 109.4, 95.3, 52.0, 30.0; HRMS-ESI (m/z): calcd for $C_{10}H_{10}N_2O_2Na$ $[M + Na]^+$ 213.0634, found 213.0637.

*5-Methyl-2-(methylamino)-4-(trifluoromethyl)benzonitrile (**2y**).* Orange solid (24.4 mg, 38% yield). Mp: 147−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.90 (s, 1H), 4.70 (br s, 1H), 2.97 (d, J = 5.0 Hz, 3H), 2.35 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 135.4, 134.2 (q, J = 30.0 Hz), 123.8 (q, J = 274.7 Hz), 123.6, 116.8, 107.8 (q, J = 6.0 Hz), 98.1, 30.1, 17.9 (d, J = 2.1 Hz); HRMS-ESI (m/z): calcd for $C_{10}H_9F_3N_2Na$ $[M + Na]^+$ 237.0611, found 237.0609.

*Methyl 2-(methylamino)benzoate (**3a**).*[18] Yellow oil (55.4 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 7.67 (brs, 1H), 7.40 (ddd, J = 8.6, 7.1, 1.7 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 6.61 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 3.87 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 152.0, 134.6, 131.6, 114.3, 110.7, 109.9, 51.4, 29.6.

*2-(Aminomethyl)-N-methylaniline (**4a**).*[16d] Light yellow oil (63.2 mg, 93% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.08 (td, J = 7.7, 1.6 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 6.54 (td, J = 7.3, 1.1 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.85 (brs, 1H), 3.66 (s, 2H), 2.72 (s, 3H), 1.96 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 128.8, 128.6, 125.6, 116.2, 109.8, 45.4, 30.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01666.

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products(PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sunpeipei@njnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Project 21272117, 21502097) and the

DOI: 10.1021/acs.joc.5b01666
J. Org. Chem. 2015, 80, 12588−12593

Priority Academic Program Development of Jiangsu Higher Education Institutions. The authors also thank Mr. Zilie Liu for the determination of HRMS.

REFERENCES

(1) (a) Rappoport, Z. *Chemistry of the Cyano Group*; John Wiley & Sons: London, 1970. (b) Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983.
(2) Heilman, W. P.; Battershell, R. D.; Pyne, W. J.; Goble, P. H.; Magee, T. A. *J. Med. Chem.* **1978**, *21*, 906.
(3) (a) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VCH: New York, 1989. (b) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049.
(4) (a) Wen, Q.; Lu, P.; Wang, Y. *RSC Adv.* **2014**, *4*, 47806. (b) Kou, X.; Fan, J.; Tong, X.; Shen, Z. *Youji Huaxue* **2013**, *33*, 1407.
(5) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
(6) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633.
(7) Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2014**, *55*, 1271.
(8) (a) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272. (c) Xu, H.; Liu, P. T.; Li, Y. H.; Han, F. S. *Org. Lett.* **2013**, *15*, 3354. (d) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660. (e) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. (f) Chaitanya, M.; Yadagiri, D.; Anbarasan, P. *Org. Lett.* **2013**, *15*, 4960. (g) Yu, D. G.; Gensch, T.; Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722. (h) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635. (i) Chaitanya, M.; Anbarasan, P. *J. Org. Chem.* **2015**, *80*, 3695. (j) Jia, X.; Yang, D.; Wang, W.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009**, *74*, 9470. (k) Chaitanya, M.; Anbarasan, P. *Org. Lett.* **2015**, *17*, 3766.
(9) (a) Liu, W.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 1878. (b) Su, W.; Gong, T. J.; Xiao, B.; Fu, Y. *Chem. Commun.* **2015**, *51*, 11848.
(10) Han, J.; Pan, C.; Jia, X.; Zhu, C. *Org. Biomol. Chem.* **2014**, *12*, 8603.
(11) Gong, T. J.; Xiao, B.; Cheng, W. M.; Su, W.; Xu, J.; Liu, Z. J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 10630.
(12) (a) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389. (b) Shu, Z.; Ji, W.; Wang, X.; Zhou, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2186. (c) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374. (d) Yang, Y.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 8677. (e) Zhu, Y.; Zhao, M.; Lu, W.; Li, L.; Shen, Z. *Org. Lett.* **2015**, *17*, 2602. (f) Yamaguchi, K.; Xu, N.; Jin, X.; Suzuki, K.; Mizuno, N. *Chem. Commun.* **2015**, *51*, 10034.
(13) Lee, J.; Chen, L.; West, A. H.; Richter-Addo, G. B. *Chem. Rev.* **2002**, *102*, 1019.
(14) (a) Liu, B. Q.; Fan, Y.; Gao, Y.; Sun, C.; Xu, C.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 468. (b) Liu, B. Q.; Song, C.; Sun, C.; Zhou, S. G.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625. (c) Wang, C. M.; Huang, Y. *Org. Lett.* **2013**, *15*, 5294. (d) Xie, F.; Qi, Z. S.; Yu, S. J.; Li, X. W. *J. Am. Chem. Soc.* **2014**, *136*, 4780. (e) Chen, J.; Chen, P.; Song, C.; Zhu, J. *Chem. - Eur. J.* **2014**, *20*, 14245. (f) Wu, Y.; Feng, L. J.; Lu, X.; Kwong, F. Y.; Luo, H. B. *Chem. Commun.* **2014**, *50*, 15352.
(15) Gao, T.; Sun, P. *J. Org. Chem.* **2014**, *79*, 9888.
(16) (a) Showell, G. A.; Bourrain, S.; Neduveli1, J. G.; Fletcher, S. R.; Baker, R.; Watt, A. P.; Fletcher, A. E.; Freedman, S. B.; Kemp, J. A.; Marshall, G. R.; Patel, S.; Smith, A. J.; Matassa, V. G. *J. Med. Chem.* **1994**, *37*, 719. (b) Ji, Q. G.; Yang, D.; Deng, Q.; Ge, Z. Q.; Yuan, L. J. *Med. Chem. Res.* **2014**, *23*, 2169. (c) Coyne, W. E.; Cusic, J. W. *J. Med. Chem.* **1968**, *11*, 1208. (d) Papot, S.; Rivault, F.; Tranoy, I.; Gesson, J. P. *Synlett* **2002**, *2002*, 164.
(17) Hartman, W. W.; Roll, L. J. *Org. Synth.* **1933**, *13*, 82.
(18) Gonzalez, I.; Mosquera, J.; Guerrero, C.; Rodriguez, R.; Cruces, J. *Org. Lett.* **2009**, *11*, 1677.
(19) Kamal, A.; Sattur, P. B. *J. Chem. Soc., Chem. Commun.* **1989**, 835.
(20) Ukrainets, I. V.; Sidorenko, L. V.; Gorokhova, O. V. *Chem. Heterocycl. Compd.* **2005**, *41*, 1151.
(21) Koreeda, T.; Kochi, T.; Kakiuchi, F. *J. Organomet. Chem.* **2013**, *741*−*742*, 148.
(22) Li, L. H.; Chua, W. K. S. *Tetrahedron Lett.* **2011**, *52*, 1574.
(23) Likhar, P. R.; Arundhathi, R.; Kantam, M. L. *Tetrahedron Lett.* **2007**, *48*, 3911.
(24) Rao, B.; Zeng, X. M. *Org. Lett.* **2014**, *16*, 314.
(25) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874.

DOI: 10.1021/acs.joc.5b01666
J. Org. Chem. 2015, 80, 12588−12593