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Letter

Palladium-Catalyzed Cascade Reactions of δ-Ketonitriles with Arylboronic Acids: Synthesis of Pyridines

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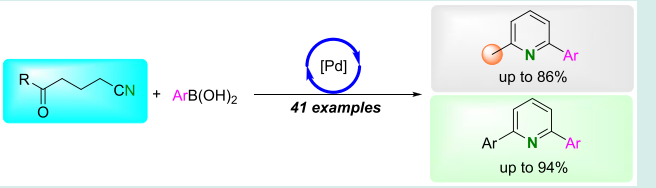
ABSTRACT: This study presents the first example of the Pd-catalyzed cascade reactions of 5-oxohexanenitrile with arylboronic acids, affording important synthon 2-methylpyridines that can be further translated through C(sp^3)-H functionalization to construct pyridine derivatives. Furthermore, this chemistry allows 5-oxo-5-arylpentanenitrile to react with arylboronic acids to provide unsymmetrical 2,6-diarylpyridines. This protocol paves the way for the practical and atom economical syntheses of valuable pyridines with broad functional groups in moderate to excellent yields under mild conditions.



KEYWORDS: *carbopalladation, cascade coupling, ketonitrile, arylboronic acids, pyridine*

The nitrile is a relatively stable functional group that is usually used as a ligand or in a solvent in organometallic reactions. However, nitriles can be flexibly transformed by transition metal catalysis in organic syntheses.[1−3] The nitrile group can react in addition reactions with organoboron reagents or other analogues[4] to synthesize ketones and derivatives. On the basis of this strategy, several groups have disclosed the Pd-catalyzed C−C coupling to nitriles as the initial step to afford five-membered heterocycles (Figure 1). For example, the Shao group reported the carbopalladation of arylboronic acids to nitriles, followed by intramolecular cyclization to construct imidazoles.[5] The Adhikari group reported Pd(II)-catalyzed coupling substituted aliphatic nitriles with arylboronic acids to synthesize 3-substituted 2-aryl-1*H*-pyrroles.[6] The Liao group described Pd-catalyzed addition of arylboronic acids to carbonic ester substituted nitriles to synthesize spirooxindolyl oxazol-2(5*H*)-ones.[7] Our group developed a one-step syntheses of 2-arylbenzo[*b*]furans and 2-aryl-1*H*-indoles via sequential addition and intramolecular annulation reactions with hydroxy- or amino-substituted 2-phenylacetonitriles.[8,9]

Our group's study of novel Pd-catalyzed nitrile coordination and subsequent cascade-coupling reactions with easily available nitriles for the preparation of a wide variety of six-[10,11] and seven-[12]membered heterocycles, such as quinazolines, isoquinolines, and isoquinolones, has been reported. Despite the notable advancement obtained to the synthesis of six-membered heterocycles, the need for benzonitrile or 2-phenylacetonitrile as substrates to construct fused six-member ring compounds is a severe restriction. However, the synthesis of six-membered heterocycles, such as pyridine, by carbopalladation of alkyl nitrile is not known.

The 2,6-disubstituted pyridine constitutes privileged scaffolds of compounds with activities of relevance in a wide range of natural products, pharmaceuticals, and functional materials.[13] The heteroarenes introduction into alkyl groups, especially methyl groups, influences their drug metabolism and pharmacokinetic profiles.[14] On the other hand, the interconversion of 2-methylpyridines with enamine tautomers is a particular concern and plays an important role in the C(sp^3)-H functionalization of 2-methylpyridine to construct pyridine derivates.[15−18] In this context, potential bioactive compounds, 2-methyl-6-arylpyridines, could serve as key units in the syntheses of various pyridine derivates. 2-Methyl-6-arylpyridines were prepared from various strategies,[19−24] including methylation of 2-arylpyridine,[19] coupling 2-halogen-6-arylpyridine with organoborons or other surrogates,[20] dehydrogenative condensation of amino alcohols,[21] or intramolecular cyclizations with imine derivates.[22] However, the synthesis of 2-methyl-6-arylpyridines via cascade carbopalladation/cyclization of alkylnitriles has not been reported. Inspired by our recent findings, we present the Pd-catalyzed cascade carbopalladation/cyclization/aromatization of arylboronic acids with 5-oxohexanenitrile (commercial product, CAS 10412-98-3), leading to 2-methyl-6-arylpyridines. As an extension, this strategy was also applied for 2,6-diarylpyridine synthesis.

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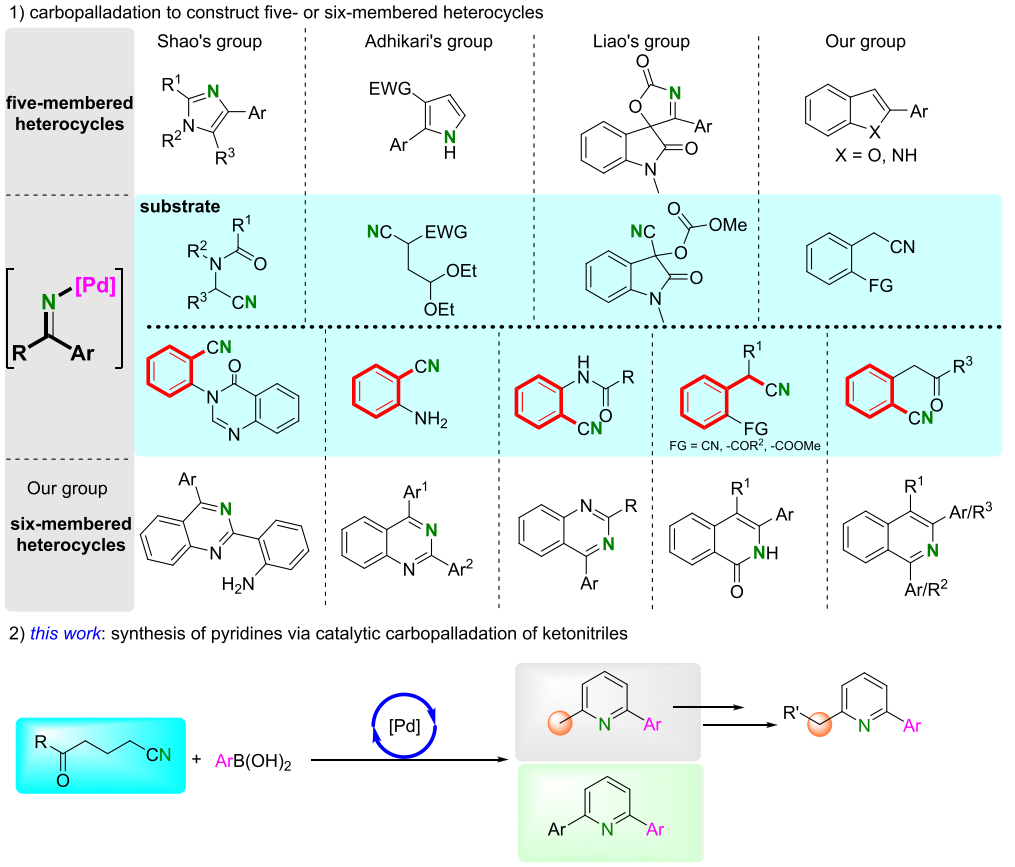

Figure 1. Carbopalladation cascade cyclization with nitriles.

We commenced our studies with 5-oxohexanenitrile **1a** and phenylboronic acid **2a** as the model substrates using a combination of $Pd(OAc)_2$, 2,2′-bipyridine (**L1**), and CF_3COOH in MeOH (Table 1, entry 1). In a preliminary experiment, the desired product 2-methyl-6-phenylpyridine (**3a**) was observed in 67% yield, determined from NMR data. Encouraged by this result, we then surveyed various Pd-salts as catalysts (entries 2−6), and the best outcome in terms of efficiency was obtained in case of $Pd_2(dba)_3$. The reaction conditions were evaluated with respect to various ligands to improve the yield. However, the examination of **L2**−**L9** (Table 1, entries 7−14) failed to show any improvement in the yield of **3a**. Next, solvent screening was undertaken (entries 15−26) and demonstrated that other solvents were less effective. Compared with MeOH, other alcohols, such as ethanol, propanol, butanol, and pentanol, exhibited obviously different performances by having low reaction activity, if any at all. Finally, attempts to enhance the efficiency of product formation further by elevated reaction temperature and shorter reaction time were successful to obtain **3a** in 90% yield (Table 1, entries 27−28). Hence, the optimum conditions involved conducting the reaction in MeOH with $Pd_2(dba)_3$ as catalyst, 2,2′-bipyridine (**L1**) as ligand, CF_3COOH as additive and a temperature of 90 °C in air.

With the established procedure, the scope of arylboronic acids in this tandem reaction was investigated (Scheme 1). The methyl groups on the phenyl ring of boronic acid provided the corresponding products **3b**−**d** in good yields. The yield reduced from **33** to **3c** and **3b**, which showed that the reaction seemed sensitive to steric hindrance of the arylboronic acid. The catalyst was compatible with phenylboronic acids bearing various functional groups, including tertiary butyl (**3e**), phenyl (**3f**), methoxyl (**3g-h**), phenoxy (**3i**), and trifluoromethoxy (**3j**). The selective synthesis of halide-substituted *N*-heterocycles has received increasing attention because they could be amenable to diverse functionalization. Fluoro-, chloro-, and bromo-substituted products as useful handles for further cross-coupling reactions, were obtained successfully in acceptable yields (**3k**−**n**). Fused rings, such as 2-naphthyl and 1-naphthyl, were also transformed smoothly (**3o**−**p**).

Unsymmetrical pyridines represent an important and abundant class of heterocyclic receiving significant attention as basic constituents of many biologically active pharmaceuticals, natural products, and functional materials. Thus, developing versatile and flexible methodologies to construct unsymmetrical pyridines using modularized building blocks are still needed. Excitingly, unsymmetrical 2,6-diarylpyridines are also obtained by carbopalladation cascade cyclization of 5-oxo-5-arylpentanenitrile with organoboronic reagents.

Next, the substrate scope of the cyclization was subsequently explored by employing various arylboronic acids with 5-oxo-5-phenyl-pentanenitrile (Scheme 1). First, the compatibility of different alkyl or aryl substituted arylboronic acids in the present transformation was examined. To our delight, a wide range of alkyl and aryl groups, including methyl, tertiary butyl, isopropyl, naphthyl, and phenyl, were well compatible in this transformation, giving access to the unsymmetrical pyridines in good to excellent yields (**4b**−**j**). It should be mentioned that the halogenated arylboronic acids were also suitable for the transformation, the products (**4k**−**n**) were obtained in good

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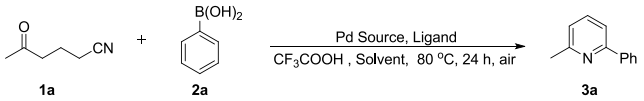
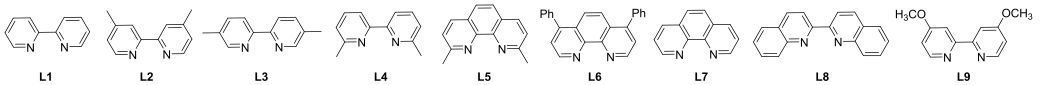
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	cat.	ligand	solvent	Yield (%)[b]
1	$Pd(OAc)_2$	L1	CH_3OH	67
2	$Pd(CH_3CN)_2Cl_2$	L1	CH_3OH	NR[c]
3	$Pd(CF_3CO_2)_2$	L1	CH_3OH	61
4	$Pd_2(dba)_3$	L1	CH_3OH	70
5	$PdCl_2$	L1	CH_3OH	NR
6	$Pd(PPh_3)_2Cl_2$	L1	CH_3OH	NR
7	$Pd_2(dba)_3$	L2	CH_3OH	63
8	$Pd_2(dba)_3$	L3	CH_3OH	56
9	$Pd_2(dba)_3$	L4	CH_3OH	trace
10	$Pd_2(dba)_3$	L5	CH_3OH	trace
11	$Pd_2(dba)_3$	L6	CH_3OH	50
12	$Pd_2(dba)_3$	L7	CH_3OH	51
13	$Pd_2(dba)_3$	L8	CH_3OH	trace
14	$Pd_2(dba)_3$	L9	CH_3OH	69
15	$Pd_2(dba)_3$	L1	THF	NR
16	$Pd_2(dba)_3$	L1	DMSO	NR
17	$Pd_2(dba)_3$	L1	DMF	32
18	$Pd_2(dba)_3$	L1	toluene	7
19	$Pd_2(dba)_3$	L1	1,4-dioxane	NR
20	$Pd_2(dba)_3$	L1	acetone	39
21	$Pd_2(dba)_3$	L1	EtOH	26
22	$Pd_2(dba)_3$	L1	*n*-propanol	trace
23	$Pd_2(dba)_3$	L1	*i*-propyl alcohol	NR
24	$Pd_2(dba)_3$	L1	*t*-butanol	12
25	$Pd_2(dba)_3$	L1	1-pentanol	NR
26	$Pd_2(dba)_3$	L1	H_2O	9
27[d]	$Pd_2(dba)_3$	L1	CH_3OH	83
28[d,e]	$Pd_2(dba)_3$	L1	CH_3OH	90



L1 L2 L3 L4 L5 L6 L7 L8 L9

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), cat. (5 mol %), ligand (10 mol %), CF_3COOH (0.15 mL), solvent (2.0 mL), 80 °C, 24 h, air. [b]Determined by ^1H NMR. [c]NR = No reaction. [d]At 90 °C. [e]For 12 h.

yields. Substrates with various electron-donating groups (−OMe, −OPh) and electron-drawing groups (−CHO, $-NO_2$, $-CF_3$) were also tolerated in this reaction, as demonstrated with **4o−t**.

We performed the cyclization of other *δ*-ketonitriles to display the synthetic utility of the transformation (Scheme 2). The *δ*-ketonitriles bearing a variety of functional groups, including electron-drawing groups or electron-donating groups were well tolerated and the desired products were obtained in moderate to good yields (**4b−e**, **4k−n**, **4t**). The 5-oxo-5-(*p*-tolyl)-pentanenitrile, as substrate, also produced unsymmetrical pyridines smoothly (**4u−y**).

A plausible mechanism for the reaction is proposed in Scheme 3. First, the Pd(II) catalyst underwent transmetalation with arylboronic acid to provide arylpalladium(II) intermediate **A**. The ketonitriles coordination with palladium then gave intermediate **B**. Next, the intermediate **C** was acquired, following 1,2-addition of the coordinated aryl group to the cyano group. Once the Paal−Knorr intermediate **C** was generated, it spontaneously underwent in situ cyclization, followed by dehydration/aromatization to give the desired products of unsymmetrical 2,6-diarylpyridines.

In summary, we have demonstrated the first example of palladium complexes as effective catalyst for the C−C, N−C cascade coupling of alkylketonitrile with arylboronic acids, affording important synthon 2-methylpyridines that can further be translated through C(sp^3)-H functionalization to construct pyridine derivatives. Furthermore, unsymmetrical 2,6-diarylpyridines were also obtained through the cascade carbopalladation/cyclization of 5-oxo-5-arylpentanenitrile with organoboronic reagents. This protocol paves the way for the practical and atom economical syntheses of valuable pyridines in moderate to excellent yields with a broad range of substituents under mild condition.

EXPERIMENTAL PROCEDURES

General Procedures for the Synthesis of 5-Oxo-5-penylpentanenitrile. Penylboronic acid (0.4 mmol, 0.5 equiv), $Pd(acac)_2$ (5 mmol %), bpy (10 mol %), $TsOH{\cdot}H_2O$ (2 equiv), toluene (2.5 mL), H_2O (0.5 mL), and glutaronitrile (38 μL, 0.8 mmol, 1 equiv) were successively added to a 25 mL sealing tube. The reaction mixture was stirred vigorously at 80 °C for 24 h. After the reaction mixture was cooled to room temperature, washed with saturated $NaHCO_3$, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatog-

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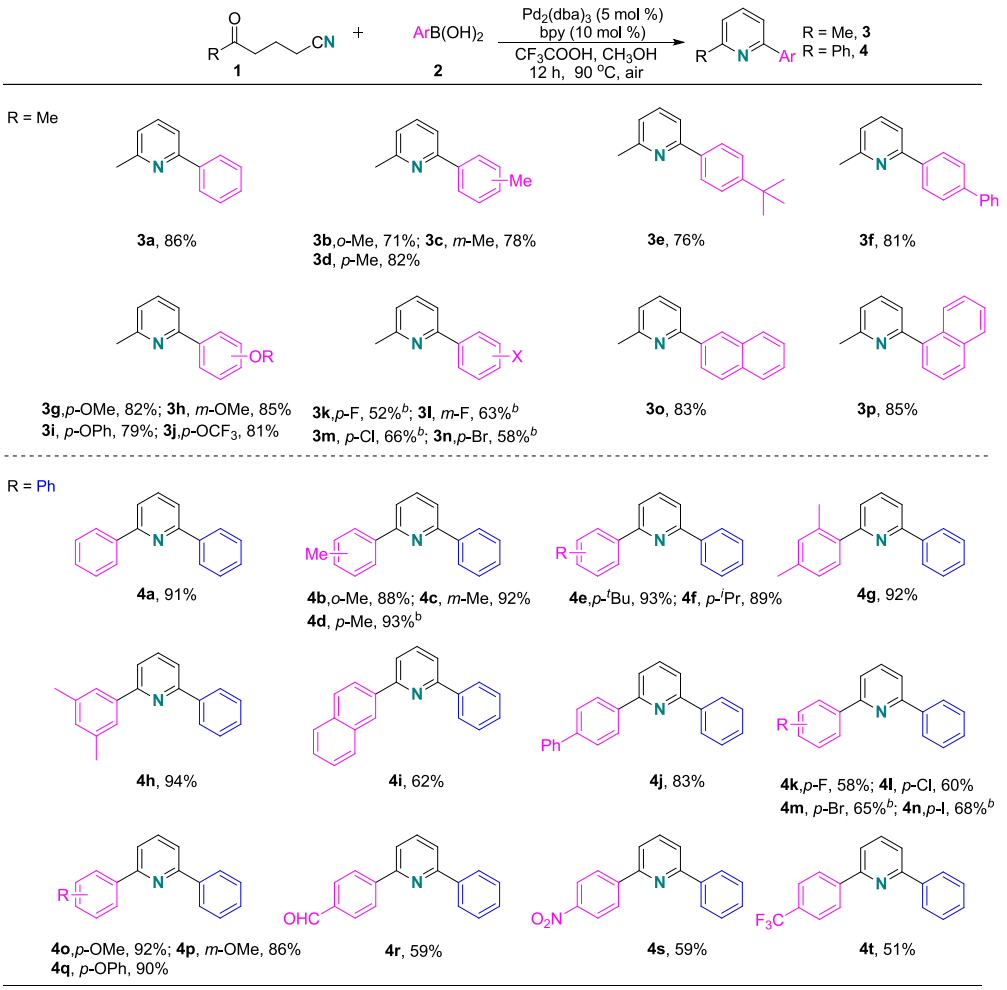
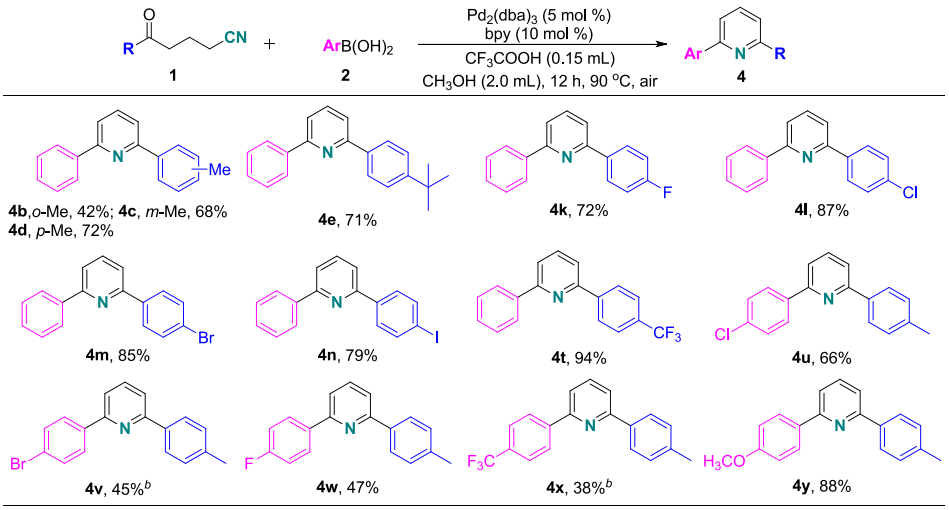
Scheme 1. Synthesis of 2-Methyl-6-arylpyridines and 2-Phenyl-6-arylpyridines[a]



[a]Reaction Conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd_2(dba)_3$ (5 mol %), bpy (10 mol %), CF_3COOH (0.15 mL), CH_3OH (2.0 mL), 90 °C, 12 h, air. Isolated yield. [b]For 24 h.

Scheme 2. Synthesis of Unsymmetrical Pyridines[a]



[a]Reaction Conditions: 1 (0.2 mmol), 2 (0.4 mmol), $Pd_2(dba)_3$ (5 mol %), bpy (10 mol %), CF_3COOH (0.15 mL), CH_3OH (2.0 mL), 90 °C, 12 h, air. Isolated yield. [b]For 24 h.

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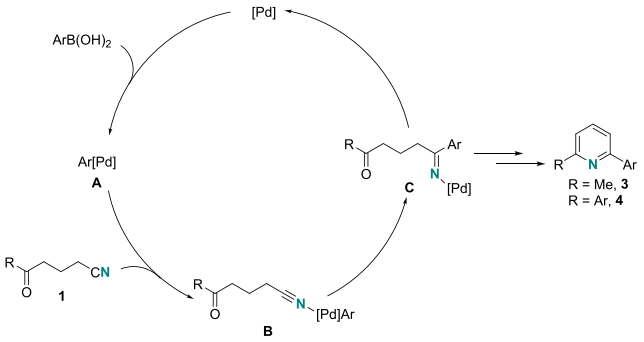
Scheme 3. Proposed Mechanism



raphy with petroleum ether/ethyl acetate (10:1) to afford 5-oxo-5-penylpentanenitrile.

General Procedures for the Synthesis of 2-Methyl-6-phenylpyridine. In air atmosphere, penylboronic acid (0.4 mmol, 2 equiv), $Pd_2(dba)_3$ (5 mmol %), bpy (10 mol %), CH_3OH (2 mL), 5-oxohexanenitrile (0.2 mmol, 1 equiv), and CF_3COOH (0.15 mL) were successively added to a 25 mL sealing tube. The reaction mixture was stirred vigorously at 90 °C and observed by TLC point plate until the end of the reaction. After the reaction mixture was cooled to room temperature, washed with saturated $NaHCO_3$, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10:1) to afford 2-methyl-6-phenylpyridine.

General Procedures for the Synthesis of 2,6-Diphenylpyridine. In air atmosphere, penylboronic acid (0.4 mmol, 2 equiv), $Pd_2(dba)_3$ (5 mmol %), bpy (10 mol %), CH_3OH (2 mL), 5−5-oxo-5-penylpentanenitrile (0.2 mmol, 1 equiv), and CF_3COOH (0.15 mL) were successively added to a 25 mL sealing tube. The reaction mixture was stirred vigorously at 90 °C and observed by TLC point plate until the end of the reaction. After the reaction mixture was cooled to room temperature, washed with saturated $NaHCO_3$, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10:1) to afford 2,6-diphenylpyridine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscombsci.9b00198.

Details of experimental and analytical procedures, along with spectroscopic data for synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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