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Facile synthesis of aryl(het)cyclopropane catalyzed by palladacycle

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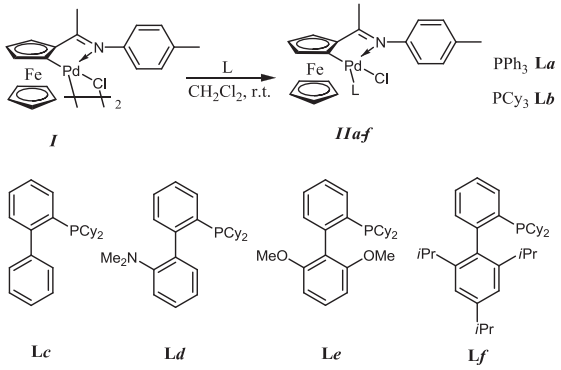
ABSTRACT

Sphos (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl) adduct of cyclopalladated ferrocenylimine (**IIe**) exhibited highly catalytic activity for the Suzuki cross-coupling reaction of cyclopropylboronic acid with aryl(het) halides with 1 mol % catalyst loading. This process was applied to both of aryl and heteroaryl halides (Br and Cl), and made the various arylcyclopropane and heteroarylcyclopropane to be easily synthesized. A variety of substituents on the aryl halides, such as alkyl, acetyl, benzoyl, ether, formyl, carboxylate, methoxy, nitro and cyano were tolerated.

1. Introduction

The cyclopropyl group is an increasingly common structural motif in pharmaceutically active molecules due to its unique steric, electronic, conformational properties and its microsomal metabolic stability.[1] It is also the smallest cyclic alkyl group to be frequently included as a substituent in medicinal chemistry for the structure–activity relationship studies.[2] Arylcyclopropane have been attractive for medicinal chemists particularly because its motif allows the exploration of lipophilic binding pockets and the optimization of hydrophobic interactions with a biological target.[3] An impressive number of synthetic methodologies for such structures have been developed recently.[4] Among, which, palladium catalyzed Suzuki cross-coupling reaction between aryl halides or pseudohalides and cyclopropylboronic acid or boronate has emerged particularly as an effective tool.[5] Such methodology overcomes the limitation of Negishi reaction, Stille reaction and Kumada reaction, such as inferior tolerance of functional groups, toxicity of the inorganic waste and being of sensitive to the moisture. Pd catalysts derived from electron-rich, bulky di, tri, or tetra-alkylphosphanes have led to considerable progress in this area. However, high catalyst loading, complicate and large excessive phosphine ligand, strong base and harsh reaction condition are often required to attain satisfactory results. There is still a need for more efficient catalystic system, which can significantly lower the catalyst loading and improve the reactivity with a broad scope of substrates.

In our laboratory, we synthesized easily series of phosphine adducts of cyclopalladated ferrocenylimines in large scale. They were stable under air and could serve as efficient catalysts for several cross coupling reactions, such as Heck reaction, borylation reaction, Suzuki reaction, amination reaction, Sonogashra reaction.[6] Herein, we would like to disclose our work on screening a series of phosphine adducts of cyclopalladated ferrocenylimine **IIa–f** (shown in Scheme 1) for the Suzuki cross-coupling of cyclopropylboronic acid with aryl(het) halides under mild conditions to synthesize arylcyclopropane and heteroarylcyclopropane easily.



Scheme 1. Synthesis of phosphine adducts of cyclopalladated ferrocenylimine.

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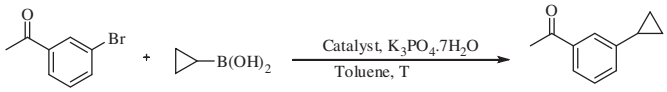
2. Results and discussion

2.1. Screening of catalysts

To evaluate the activity of the cyclopalladated ferrocenylimines **IIa–f** (Scheme 1), the coupling of cyclopropylboronic acid with 3-bromoacetophenone was initially chosen as a model reaction in toluene at 100 °C in the presence of 1 mol % catalyst and $K_3PO_4·7H_2O$ as base. As shown in Table 1, palladacycles **IIa**, **IIb**, **IIc**, **IId** and **IIf** gave 75%, 90%, 45%, 40% and 72% yields, respectively (Table 1, entries 1–5), and compound **IIe** gave 94% yield (Table 1, entry 6). To compare the catalytic activity, the palladium catalysts derived from $Pd(OAc)_2$ and $Pd_2(dba)_3·CHCl_3$ with phosphine ligand **Le** was used as a catalyst instead of **IIe** under the same reaction conditions. $Pd(OAc)_2$·**Le** and $Pd_2(dba)_3·CHCl_3$·**Le** gave 60% and 62% yields, respectively (Table 1, entries 7 and 8). Therefore, palladacycle **IIe** was chosen as a catalyst for the following study. The yield was decreased when the catalyst loading was reduced from 1 mol % to 0.5 mol % (Table 1, entry 6 vs 9), while the reaction was not significantly improved when temperature increased from 100 °C to 110 °C (Table 1, entry 6 vs 10). No desired product was obtained when reaction temperature was 50 °C and 25 °C even after the reaction time was prolonged from 3 h to 24 h (Table 1, entries 11 and 12).

Table 1
Screening of catalysts for the Suzuki cross-coupling of cyclopropylboronic acid with 3-bromoacetophenone[a]



Entry	Catalyst	Ligand	Temp (°C)	Time (h)	Yield[c] (%)
1	**IIa**	—	100	3	75
2	**IIb**	—	100	3	90
3	**IIc**	—	100	3	45
4	**IId**	—	100	3	40
5	**IIf**	—	100	3	72
6	**IIe**	—	100	3	94
7[b]	$Pd(OAc)_2$	**Le**	100	3	75
8[b]	$Pd_2(dba)_3·CHCl_3$	**Le**	100	3	60
9	**IIe**	—	100	3	62[d]
10	**IIe**	—	110	3	93
11	**IIe**	—	25	24	—
12	**IIe**	—	50	24	—

[a] Reaction conditions: 0.25 mmol 3-bromoacetophenone, 1 mol % [Pd], 2.0 equiv cyclopropylboronic acid, 3 equiv $K_3PO_4·7H_2O$, toluene/H_2O=2 mL/100 μL, 3 h, 100 °C.
[b] [Pd]/**Le**=1:1.
[c] Isolated yield.
[d] [Pd] (0.5 mol %).

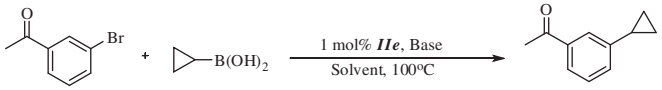
2.2. Screening of reaction parameters

The coupling of cyclopropylboronic acid with 3-bromoacetophenone was also chosen as a model reaction to screen different reaction parameters including bases, solvents by fixing 1 mol % loading of catalyst **IIe**. It was found that both of base and solvent played critical role on the catalytic efficiency. Na_2CO_3 only gave 43% yield (Table 2, entry 1). 70%, 86%, 81%, 84% and 76% yields were obtained when K_2CO_3, $CsCO_3$, NaH, KOH and ^{t}BuONa was used as a base, respectively (Table 2, entries 2–6). $K_3PO_4·7H_2O$ was found to be the best base and provided the isolated yield of 94% (Table 2, entry 7). Mixture of toluene with water (20/1, v/v) was proved to be superior to DMF and dioxane (Table 2, entries 8 and 9).

2.3. Scope of substrates

Under the optimized reaction conditions (1 equiv of aryl (het) bromides, 2.0 equiv cyclopropylboronic acid, 3.0 equiv $K_3PO_4·7H_2O$, 1 mol % complex **IIe**, toluene/H_2O (20/1) as solvent, 100 °C, under nitrogen), the scope of the substrates for the Suzuki cross-coupling reaction of cyclopropylboronic acid was investigated. As shown in Table 3, the catalyst **IIe** exhibited highly efficient in the Suzuki cross-coupling of cyclopropylboronic acid with aryl bromides substituted by electron-withdrawing groups, such as acetyl, benzoyl, formyl, carboxylate, nitro and nitrile, affording the desired product in good to excellent yields (Table 3, entries 1–9). 1-Bromonaphthalene and electron-rich aryl bromide, such as 1-bromo-3-methoxybenzene, gave 57% and 46% yields, respectively (Table 3, entries 10 and 11). The cross-coupling of the cyclopropylboronic acid with heteroaromatic bromides including pyridines and thiophene was also tested. The desired products were obtained up to 86% yield (Table 3, entries 12–17), among which, 5-bromo-*N*,*N*-dimethyl-2-pyridinamine, 5-bromo-2-pyridinamine and 5-bromo-2-phenylpyridine were smoothly transformed to the desired products in 80%, 83% and 86% yields, respectively (Table 3, entries 14–16). Methylboronic and allyl boronate also could be suitable coupling partner with aryl bromide to provide desired products in 85 and 76% yields, respectively (entry 18 and 19).

Table 2
Screening of bases and solvents for Suzuki cross-coupling of cyclopropylboronic acid with 3-bromoacetophenone[a]



Entry	Base	Solvent	Temp (°C)	Yield[b] (%)
1	Na_2CO_3	Toluene/water	100	43
2	K_2CO_3	Toluene/water	100	70
3	$CsCO_3$	Toluene/water	100	86
4	NaOH	Toluene/water	100	81
5	KOH	Toluene/water	100	84
6	^{t}BuONa	Toluene/water	100	76
7	$K_3PO_4·7H_2O$	Toluene/water	100	94
8	$K_3PO_4·7H_2O$	DMF/water	140	57
9	$K_3PO_4·7H_2O$	Dioxane/water	100	44

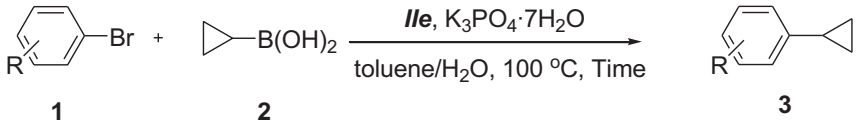
[a] Reaction conditions: 0.25 mmol 3-bromoacetophenone, 1 mol % **IIe**, 2.0 equiv cyclopropylboronic acid, 3 equiv base, solvent 2 mL, 3 h.
[b] Isolated yield.

Aryl chloride is one kind of interesting substrates due to being cheaper and commercially available. However, to the best of our knowledge, there are only two reports of the cross-coupling of cyclopropylboronic acid with aryl(het) chlorides,[5c,7] and complicate phosphine was required. Thus, we turned our attention to the aryl(het) chlorides **4** for the palladacycle-catalyzed Suzuki reaction with cyclopropylboronic acid (shown in Table 4). Under the optimized reaction conditions, aryl chlorides with electron-withdrawing group, such as acetyl, formyl, nitro and cyano, could converted smoothly into the desired products (Table 4, entries 1–6). 2-Chloronitrobenzene only gave 45% yield (Table 4, entry 4 vs 5). Perhaps large bulk in aryl chloride affected the yields. Two Cl atoms in 2,4-dichlorobenzaldehyde could be replaced by cyclopropyl at the same time and 2,4-dicyclopropylbenzaldehyde was obtained in 68% yield (Table 4, entry 6). 2-Chloro-6-phenylpyrazine was also a suitable substrate and gave 87% yield (Table 4, entry 7).

3. Conclusion

In summary, we have developed SPhos adduct of cyclopalladated ferrocenylimine (**IIe**) as an efficient catalyst for Suzuki cross-coupling reaction of cyclopropylboronic acid with a wide range of aryl, heteroaryl halides to synthesize the arylcyclopropane and heteroarylcyclopropane. This reaction system could tolerate various functional groups, and was applied to both of bromides and activated chlorides.

Table 3
Palladium-catalyzed coupling reactions of cyclopropylboronic acid with aryl bromides[a]



1 2 3

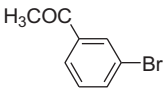
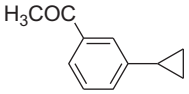
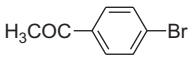
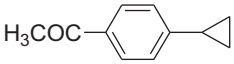
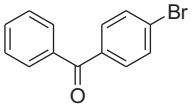
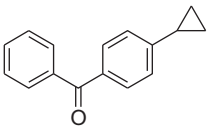
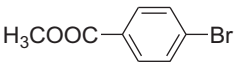
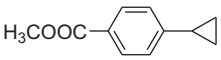
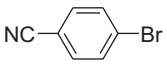
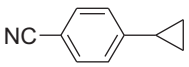
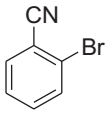
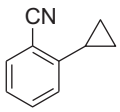
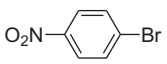
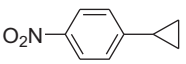
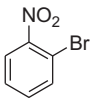
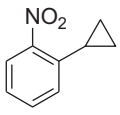
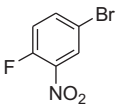
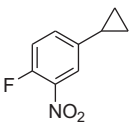
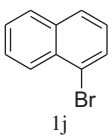
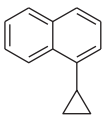
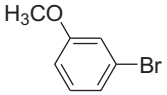
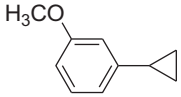
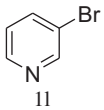
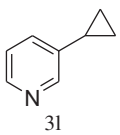
Entry	Aryl bromide	Product	Time (h)	Yield[b] (%)
1	 1a	 3a	3	94
2	 1b	 3b	8	95
3	 1c	 3c	3	90
4	 1d	 3d	8	92
5	 1e	 3e	6	91
6	 1f	 3f	6	73
7	 1g	 3g	8	96
8	 1h	 3h	8	65
9	 1i	 3i	10	88
10	 1j	 3j	5	57
11	 1k	 3k	4.5	46
12	 1l	 3l	8	57

Table 3 (*continued*)

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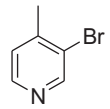
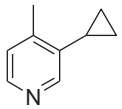
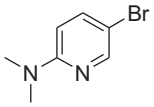
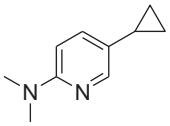
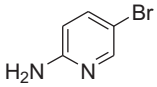
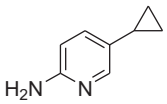
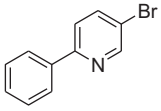
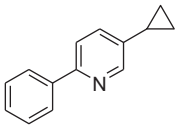
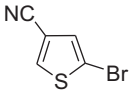
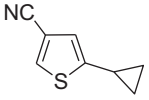
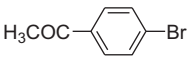
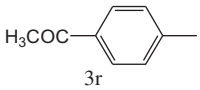
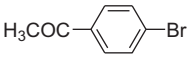
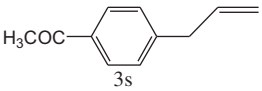
13	 1m	 3m	8	52
14	 1n	 3n	6	80
15	 1o	 3o	6	83
16	 1p	 3p	4.5	86
17	 1q	 3q	10	62
18	 1r	 3r	8	85
19	 1s	 3s	8	76

[a] Conditions: (hetero)aryl halides: 0.25 mmol, 1 mol % **IIe**, cyclopropylboronic acid: 0.5 mmol, $K_3PO_4 \cdot 7H_2O$: 0.75 mmol, toluene/H_2O=2 mL/100 μL, 100 °C, nitrogen.
[b] Isolated yield.

4. Experimental section

4.1. General conditions

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard. High-resolution mass spectra were measured on a Waters Q-Tof Micro™ spectrometer. Aryl(het) halides and ligands were used as received. Palladacycle **IIa**–**IIe**[6c] and cyclopropylboronic acid[8] were prepared according to literature.

4.2. General experimental procedure

Potassium phosphate (0.75 mmol) and **IIe** (1 mol %) was added to the solution of aryl halides (0.25 mmol) and cyclopropylboronic acid (0.5 mmol) in toluene (2.0 mL) and water (100 μL). The mixture was heated to 100 °C for a proper time under nitrogen atmosphere and cooled to room temperature. Water (10 mL) was added and the mixture was extracted with EtOAc (3×15 mL), evaporated and purified by chromatography on silica gel.

4.3. Characterization

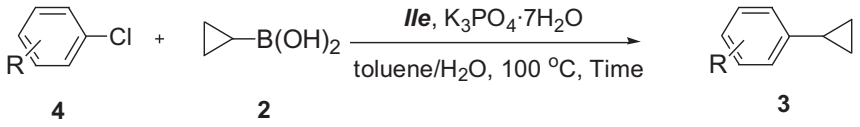
*4.3.1. 1-Acetyl-3-cyclopropylbenzene(**3a**)*[9]. ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.71 (d, *J*=7.45 Hz, 1H), 7.66 (s, 1H), 7.33 (t, *J*=7.56 Hz, 1H), 7.25 (d, *J*=7.80 Hz, 1H), 2.58 (s, 3H), 1.94 (m, 1H), 0.99 (m, 2H), 0.71 (m, 2H). GC–MS, (EI): [M^+]: 160.0.

*4.3.2. 1-Acetyl-4-cyclopropylbenzene (**3b**)*[10]. ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.84 (d, *J*=8.06 Hz, 2H), 7.12 (d, *J*=8.06 Hz, 2H), 2.56 (s, 3H), 1.94 (m, 1H), 1.06 (m, 2H), 0.78 (m, 2H). GC–MS, (EI): [M^+]: 160.4.

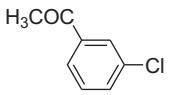
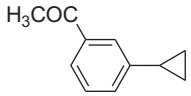
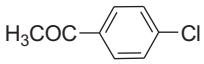
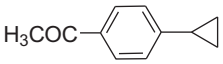
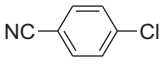
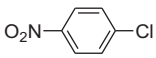
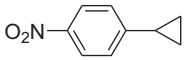
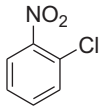
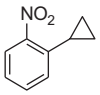
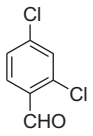
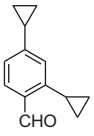
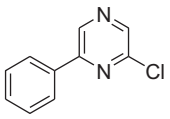
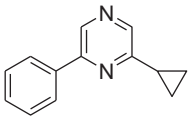
*4.3.3. 1-Benzoyl-4-cyclopyropylbenzene (**3c**)*[11]. ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.77 (d, *J*=7.38 Hz, 2H), 7.72 (d, *J*=8.2 Hz, 2H), 7.57 (t, *J*=7.38 Hz, 1H), 7.47 (d, *J*=7.57 Hz, 2H), 7.14 (d, *J*=8.2 Hz, 2H), 1.97 (m, 1H), 1.08 (m, 2H), 0.80 (m, 2H). GC–MS, (EI): [M^+]: 222.6.

*4.3.4. 4-Cyclopropylbenzoic acid methyl ester (**3d**)*[12]. ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.91 (d, *J*=8.2 Hz, 2H), 7.09 (d, *J*=8.2 Hz,

Table 4
Palladium-catalyzed coupling reactions of cyclopropylboronic acid with aryl chlorides[a]



4 2 3

Entry	Aryl chloride	Product	Time (h)	Yield[b] (%)
1	 4a	 3a	8	72
2	 4b	 3b	4	81
3	 4c	 3e	4	63
4	 4d	 3g	8	78
5	 4e	 3h	8	45
6	 4f	 3t	5.5	68
7	 4g	 3u	4	87

[a] Conditions: aryl chloride: 0.25 mmol, 1 mol % **IIe**, cyclopropylboronic acid: 0.5 mmol, $K_3PO_4·7H_2O$: 0.75 mmol, toluene/H_2O=2 mL/100 μL, 100 °C, nitrogen.
[b] Isolated yield.

2H), 3.89 (s, 3H), 1.93 (m, 1H), 1.05 (m, 2H), 0.76 (m, 2H). GC–MS, (EI): [M^+]: 176.6.

*4.3.5. 4-Cyclopropylbenzonitrile (**3e**)*[13]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.52 (d, *J*=7.72 Hz, 2H), 7.11 (d, *J*=7.72 Hz, 2H), 1.92 (m, 1H), 1.08 (m, 2H), 0.76 (m, 2H). GC–MS, (EI): [M^+]: 143.0.

*4.3.6. 2-Cyclopropylbenzonitrile (**3f**)*[14]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.58 (d, *J*=8.46 Hz, 1H), 7.46 (m, 1H), 7.22 (m, 1H), 6.94 (d, *J*=7.98 Hz, 1H), 2.28 (m, 1H), 1.14 (m, 2H), 0.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.7, 132.7, 132.5, 125.7, 125.4, 118.3, 112.9, 14.0, 9.5. HRMS (ESI) calcd for $C_{10}H_9N$ ([M+H]$^+$): 143.0735, found: 144.0812.

*4.3.7. 1-Cyclopropyl-4-nitrobenzene (**3g**)*[15]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.10 (d, *J*=8.72 Hz, 2H), 7.16 (d, *J*=8.72 Hz, 2H), 2.01 (m, 1H), 1.04 (m, 2H), 0.82 (m, 2H). GC–MS, (EI): [M^+]: 163.1.

*4.3.8. 1-Cyclopropyl-2-nitrobenzene (**3h**)*[16]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.80 (d, *J*=7.52 Hz, 1H), 7.47 (m, 1H), 7.28 (m, 1H), 7.15 (d, *J*=7.84 Hz, 1H), 2.39 (m, 1H), 1.05 (m, 2H), 0.71 (m, 2H). GC–MS, (EI): [M^+]: 163.0.

*4.3.9. 4-Cyclopropyl-1-fluoro-2-nitrobenzene (**3i**)*[17]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.71 (s, 1H), 7.32 (m, 1H), 7.15 (t, 1H), 1.94 (m, 1H), 1.05 (m, 2H), 0.71 (m, 2H). GC–MS, (EI): [M^+]: 181.0.

*4.3.10. 1-Cyclopropylnaphthalene (**3j**)*[18]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.45 (d, *J*=8.44 Hz, 1H), 7.89 (d, *J*=8.30 Hz, 1H), 7.74 (d, *J*=8.10 Hz, 1H), 7.58 (m, 1H), 7.54 (m, 1H), 7.42 (m, 1H), 7.31 (d, *J*=7.01 Hz, 1H), 2.38 (m, 1H), 1.10 (m, 2H), 0.81 (m, 2H). GC–MS, (EI): [M^+]: 168.0.

*4.3.11. 1-Cyclopropyl-3-methoxybenzene (**3k**)*[19]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.04 (s, 1H), 7.02 (s, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 3.79 (s, 1H), 1.86 (m, 1H), 0.91 (m, 2H), 0.63 (m, 2H). GC–MS, (EI): [M^+]: 148.0.

*4.3.12. 3-Cyclopropylpyridine (**3l**)*[20]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.42 (s, 1H), 8.39 (d, *J*=3.68 Hz, 1H), 7.28 (m, 1H), 7.16 (m,

1H), 1.88 (m, 1H), 1.04 (m, 2H), 0.72 (m, 2H). GC–MS, (EI): [M^+]: 119.0.

*4.3.13. 3-Cyclopropyl-4-methylpyridine (**3m**)*[21]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.27 (d, J=4.83 Hz, 1H), 8.20 (s, 1H), 7.03 (d, J=4.82 Hz, 1H), 2.40 (s, 3H), 1.80 (m, 1H), 0.96 (m, 2H), 0.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.4, 147.1, 147.0, 136.7, 124.2, 18.8, 11.1, 5.9. HRMS (ESI) calcd for $C_9H_{11}N$ ([M+H]$^+$): 133.0891, found: 134.0969.

*4.3.14. 5-Cyclopropyl-N,N-dimethylpyridin-2-amine (**3n**)*[22]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.02 (s, 1H), 7.17 (d, J=8.59 Hz, 1H), 6.45 (d, J=8.72 Hz, 1H), 3.05 (s, 6H), 1.78 (m, 1H), 0.86 (m, 2H), 0.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0, 146.0, 135.1, 126.1, 105.6, 38.3, 29.6, 12.0, 7.3. HRMS (ESI) calcd for $C_{10}H_{14}N_2$ ([M+H]$^+$): 162.1157, found: 163.1235.

*4.3.15. 5-Cyclopropylpyridin-2-amine (**3o**)*[23]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.60 (s, 1H), 7.14 (d, J=7.94 Hz, 1H), 6.59 (d, J=8.72 Hz, 1H), 5.56 (s, 2H), 1.66 (m, 1H), 0.81 (m, 2H), 0.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.1, 140.1, 138.3, 128.5, 110.6, 11.9, 7.4. HRMS (ESI) calcd for $C_8H_{10}N_2$ ([M+H]$^+$): 134.0844, found: 135.0921.

*4.3.16. 5-Cyclopropyl-2-phenylpyridine (**3p**)*[24]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.41 (s, 1H), 7.87–7.85 (dd, J=7.85 Hz, 2H), 7.50 (dd, J=8.2 Hz, 1H), 7.37–7.34 (dd, J=11.3 Hz, 2H), 7.29 (dd, J=6.87 Hz, 1H), 7.23 (dd, J=8.24 Hz, 1H), 1.82 (m, 1H), 0.94 (m, 2H), 0.65 (m, 2H). GC–MS, (EI): [M^+]: 195.1.

*4.3.17. 5-Cyclopropylthiophene-3-carbonitrile (**3q**)*[25]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.65 (s, 1H), 6.92 (s, 1H), 2.07 (m, 1H), 1.07 (m, 2H), 0.76 (m, 2H). GC–MS, (EI): [M^+]: 149.0.

*4.3.18. 1-Acetyl-4-methylbenzene (**3r**)*[26]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.85 (d, J=8.00 Hz, 2H), 7.25 (d, J=8.00 Hz, 2H), 2.57 (s, 3H), 2.41 (s, 3H).

*4.3.19. 1-Acetyl-4-allylbenzene (**3s**)*[27]. H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.81 (d, J=8.00 Hz, 2H), 7.60 (J=8.00 Hz, 2H), 5.96 (m, 1H), 5.10 (d, 2H), 3.44 (d, 2H), 2.58 (s, 3H).

*4.3.20. 2,4-Dicyclopropylbenzaldehyde (**3t**)*[28]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 10.51 (s, 1H), 7.7 (d, J=8.0 Hz, 1H), 6.92 (d, J=7.96 Hz, 1H), 6.81 (s, 1H), 2.60 (m, 1H), 1.88 (m, 1H), 1.04 (m, 4H), 0.76 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.9, 151.2, 145.9, 131.3, 126.5, 123.7, 122.5, 15.8, 10.9, 8.4. HRMS (Positive ESI) [M+H]$^+$: 187.1124 (186.1045).

*4.3.21. 2-Cyclopropyl-6-phenylpyrazine (**3u**)*[29]. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.66 (s, 1H), 8.31 (s, 1H), 7.91 (d, J=1.64 Hz, 1H), 7.90 (d, J=3.58 Hz, 1H), 7.40–7.34 (m, 3H), 2.01 (m, 1H), 1.09 (m, 2H), 0.98 (m, 2H). GC–MS, (EI): [M^+]: 196.1.

Acknowledgements

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