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Synthesis of tetrahydropyrimidinium salts and their in situ catalytic activities towards the Buchwald–Hartwig amination reaction under microwave irradiation

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Abstract: A series of asymmetrical substituted tetrahydropyrimidinium salts and different kinds of bridged bis-tetrahydropyrimidinium salts were prepared through the quaterization of tetrahydropyrimidine or the dehydrogenation of hexahydropyrimidine. They were characterized and used as NHC precursors in the palladium catalyzed Buchwald–Hartwig amination reaction. The in situ formed catalytic system $Pd(OAc)_2$/tetrahydropyrimidinium and ^tBuOK catalyzed the amination of heteroaryl halides and heterocyclic amines effectively, producing the heterocyclic amine functionalized heteroaryl derivatives in high yields.

Key words: Tetrahydropyrimidinium salt, Buchwald–Hartwig amination, microwave irradiation, palladium catalysis, N-heterocyclic carbene

1. Introduction

The synthesis of N-containing molecules keeps attracting wide attention, as these structures are prevalent in compounds with biological, pharmaceutical, and materials interest.[1] Among the variety of useful methods to obtain these kinds of compounds, palladium-catalyzed Buchwald–Hartwig amination has become the most versatile strategy because of its high functional group tolerance, single-step procedure, commercially available starting materials, and mild reaction conditions.[2–5] Consequently, the development of new catalysts and ligands for the Buchwald–Hartwig amination reaction continues to be a research hotspot. N-heterocyclic carbenes (NHCs) have emerged as a very powerful class of ligands in organometallic chemistry and homogeneous catalysis, due to their stronger σ-donor character and higher thermal stability than phosphine-based ligands in most cases.[6,7] Probably due to the easy accessibility of the precursors of 5-membered NHCs, imidazolium or imidazolinium derivatives, the synthesis of 5-membered NHC metal complexes and their catalytic application have been investigated quite extensively. Due to the enhanced σ-donor ability and easy tunability of the electronic property and steric effect, 6-, 7-, etc. ring expanded NHCs began to attract extensive attention.[8,9] In recent years, tetrahydropyrimidinium salts have been reported to be highly efficient ligands for palladium catalyzed carbon-carbon bond formation, such as Suzuki coupling and the Heck reaction.[10–12] The catalytic activities of metal-NHC complexes are directly related to the unique properties of the supporting NHCs and sometimes chelating ligands exhibit special catalytic efficiency. Here we report the synthesis and characterization of pyridinyl functionalized tetrahydropyrimidinium salts, asymmetrical di-substituted tetrahydropyrimidinium salts, and bridged bis-tetrahydropyrimidinium salts. Their in situ catalytic performance in

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the palladium catalyzed Buchwald–Hartwig amination reaction of heteroaryl halides and heterocyclic amines was also investigated.

2. Results and discussion

Asymmetrical-substituted tetrahydropyrimidinium salts and different kinds of bridged di-tetrahydropyrimidinium salts LHXs **1a**–**1i** and **2a**–**2i** were synthesized by modification of literature reports.[13] The synthetic procedures are outlined in Figures 1–4. The pure products were obtained by crystallization and characterized by ESI-MS, EA, ^{1}H NMR, and ^{13}C NMR spectra.

As shown in Figure 1, asymmetrical-substituted tetrahydropyrimidinium halides LHX **1a** were obtained by the quaterization of N-methyl-1,4,5,6-tetrahydropyrimidine by 2-bromopyridine. Comparison of the proton spectra of N-methyl-1,4,5,6-tetrahydropyrimidine and LHX **1a** showed the appearance of additional signals attributed to pyridinyl and downfield shift of the proton signals of the tetrahydropyrimidine ring. The chemical shift of H-2 was downfielded from 6.82 to 9.33 ppm. Anion exchange reaction with NH_4PF_6 in ethanol produced the corresponding phosphate **2a**. Comparison of the proton spectra of **1a** and **2a** showed a slight shift of H-2 from 9.33 to 9.29 ppm. Anion exchange affected the mp significantly, and LHXs **1a** and **2a** had mps of 163–165 and 123–125 °C, respectively.

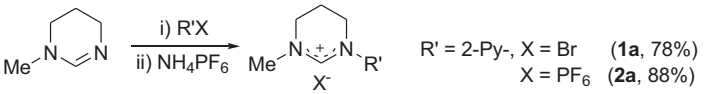


Figure 1. Synthesis of the asymmetrical di-substituted tetrahydropyrimidinium salts.

The synthesis of methylene bridged aryl-substituted tetrahydropyrimidinium salts **1b**, **1c**, **2b**, and **2c** are shown in Figure 2. Reaction of 1-aryl-propyl-1,3-diamines with aqueous formaldehyde in MeOH produced bis(3-aryl-hexahydropyrimidinyl)methanes, and the following dehydrogenation with NBS produced the methylene bridged tetrahydropyrimidinium salts **1b** and **1c**. Anion exchange reaction with NH_4PF_6 in ethanol produced the corresponding phosphates **2b** and **2c**. In the proton spectra of **1b** and **1c**, the signals of methylene linker appeared at 5.27 and 6.37 ppm, while the protons of H-2 appeared at 8.89 and 9.38 ppm respectively, indicating the formation of quaternary tetrahydropyrimidinium salts. ESI-MS peaks at 497.4 and 581.5 corresponding to $[M\text{-}Br]^+$ confirmed the successful dehydrogenation by NBS. Anion exchange reaction with NH_4PF_6 in ethanol produced the corresponding phosphates **2b** and **2c**. The conversion was confirmed by the change in the proton spectra and mps.

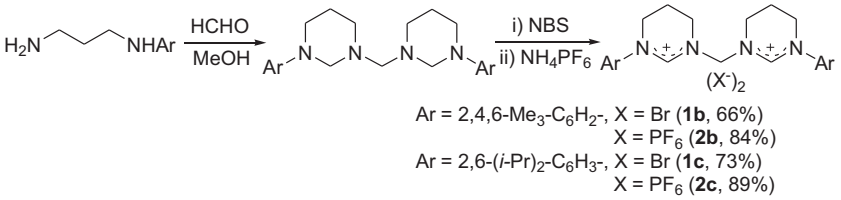


Figure 2. Synthesis of the methylene bridged aryl-substituted tetrahydropyrimidinium salts.

Figures 3 and 4 show 2 different strategies for the synthesis of alkylene bridged alkyl-substituted bis-tetrahydropyrimidinium salts. In Figure 3, using tetra-amine as starting material, the reaction with DMF-DMA afforded ethylene bridged 1,4,5,6-tetrahydropyrimidine first, and the following quaterization with different alkyl halides produced bridged bis-tetrahydropyrimidinium salts **1d** and **1e** carrying different substituents. In Figure

4, reaction of N-methyl-1,4,5,6-tetrahydropyrimidine with different alkylene dihalides afforded a series of bridged bis-tetrahydropyrimidinium salts carrying different linkages.

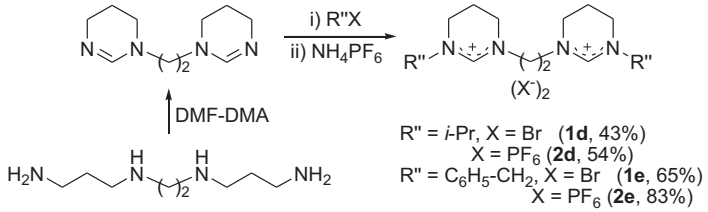


Figure 3. Synthesis of the ethylene bridged alkyl-substituted tetrahydropyrimidinium salts from tetra-amine.

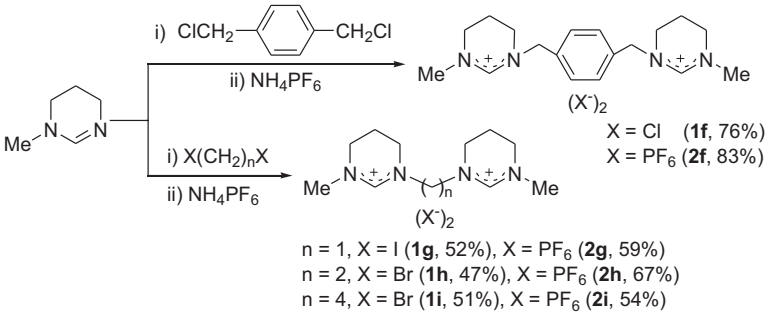
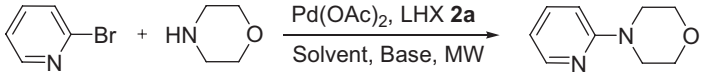


Figure 4. Synthesis of the alkylene bridged methyl-substituted tetrahydropyrimidinium salts from tetrahydropyrimidine.

MW irradiation has been successfully utilized in the formation of a variety of carbon–heteroatom and carbon–carbon bonds.[14] Having series of different tetrahydropyrimidinium salts in hand, their in situ catalytic activities towards MW assisted Buchwald–Hartwig amination was investigated. Initially, using ^{t}BuOK as base, DME as solvent, and the reaction of 2-bromopyridine with morpholine as a model, the potential of different tetrahydropyrimidinium salts in the MW assisted $Pd(OAc)_2$ catalyzed Buchwald–Hartwig amination was tested. The results showed that all the tetrahydropyrimidinium salts could accelerate the amination reaction effectively and pyridinyl functionalized hexaphosphate (**2a**) afforded the highest yield.

Using LHX **2a** as ligand precursor, a brief screening of solvents and bases was performed by running the reaction of 2-bromopyridine with morpholine as a model (Table 1). Among the bases tested, ^{t}BuOK proved to be the best. K_2CO_3 or Cs_2CO_3 improved the yields slightly, while KOH did not work here at all (Table 1, entries 1–4). Besides DME, solvents dioxane, DMF, and toluene were tested and the results showed that dioxane produced comparable yield, while DMF and toluene produced inferior yields (Table 1, entries 4–7). Choosing DME as solvent and ^{t}BuOK as base, the effect of catalyst loading and reaction time on the model reaction was then investigated. As listed in Table 1, the blank reaction produced the target product in 2% yield, and addition of LHX **2a** did not change the yield (Table 1, entries 8 and 9). Addition of $Pd(OAc)_2$ increased the yield to 27% (Table 1, entry 10), still obviously lower than the yield by addition of both $Pd(OAc)_2$ and LHX **2a** (Table 1, entry 4), indicating that the LHX **2a** could be effective ligand precursors for Pd catalyzed Buchwald–Hartwig amination. Results obtained under different reaction times proved that 40 min should be the appropriate MW irradiation time (Table 1, entries 4, 11, and 12). Compared to traditional oil bath heating, MW irradiation accelerated the reaction markedly (Table 1, entries 4 and 13). These results are consistent with the literature and the microwave irradiation gave the same results as conventional heating but in a very short time.[15]

Table 1. Screening of reaction conditions.[a]

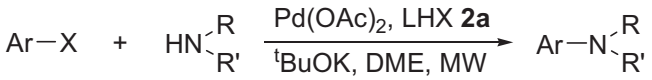


Entry	Solvent	Base	$Pd(OAc)_2$	LHX **2a**	Time	Yield (%)
			(mol%)	(mol%)	(min)	
1	DME	KOH	5	10	20	3
2	DME	K_2CO_3	5	10	20	15
3	DME	Cs_2CO_3	5	10	20	10
4	DME	^{t}BuOK	5	10	20	61
5	dioxane	^{t}BuOK	5	10	20	58
6	DMF	^{t}BuOK	5	10	20	6
7	toluene	^{t}BuOK	10	20	20	19
8	DME	^{t}BuOK	0	0	20	2
9	DME	^{t}BuOK	0	10	20	2
10	DME	^{t}BuOK	5	0	20	27
11	DME	^{t}BuOK	5	10	40	92
12	DME	^{t}BuOK	5	10	60	49
13	DME	^{t}BuOK	5	10	24 h	30[b]

[a] Reaction condition: 1.0 mmol 2-bromopyridine, 3.0 mmol morpholine, 2.0 mmol base, 2.0 mL solvent, 100 °C, MW 150 W. [b] Oil bath heating.

The feasibility of the catalytic application of LHX **2a** towards the Buchwald–Hartwig amination of heteroaryl halides and heterocyclic amines was further explored by expanding the substrates, and the results are listed in Table 2. Under the standard conditions, 2-bromopyridine coupled with morpholine, pyrrolidine, or 1H-benzo[d]imidazole smoothly, producing the target products in high yields (Table 2, entries 1–3). Exploration of the reaction of heteroaryl chlolides (2-chloropyridine and 2-chloropyrimidine) with heterocyclic amines also produced satisfactory results and the target coupling products were obtained in high yields (Table 2, entries 4–9). The experimental results indicated that LHX **2a** could accelerate the Buchwald–Hartwig amination of heteroaryl bromides or chlorides effectively.

Table 2. Buchwald–Hartwig amination of heteroaryl halides with heterocyclic amines.



Entry	Ar-X	RR'NH	Ar-NRR'	Yields (%)
1	2-bromopyridine	morpholine	**3a**	92
2	2-bromopyridine	pyrrolidine	**3b**	97
3	2-bromopyridine	1H-benzo[d]imidazole	**3c**	77
4	2-chloropyridine	morpholine	**3a**	88
5	2-chloropyridine	pyrrolidine	**3b**	84
6	2-chloropyridine	1H-benzo[d]imidazole	**3c**	74
7	2-chloropyrimidine	morpholine	**3d**	79
8	2-chloropyrimidine	pyrrolidine	**3e**	87
9	2-chloropyrimidine	1H-benzo[d]imidazole	**3f**	93

[a] Reaction condition: 1.0 mmol Ar-X, 3.0 mmol RR'NH, 2.0 mmol ^{t}BuOK, 0.05 mmol $Pd(OAc)_2$, 0.10 mmol LHX **2a**, 2.0 mL DME, MW 150 W, 40 min.

3. Conclusion

We have reported the efficient synthesis of asymmetrical substituted tetrahydropyrimidinium salts and different kinds of bridged bis-tetrahydropyrimidinium salts through different strategies and their catalytic application in MW assisted Buchwald–Hartwig amination. The results showed that under the standard conditions, using ^{t}BuOK as base, DME as solvent, $Pd(OAc)_2$ as catalyst, tetrahydropyrimidinium salt as ligand precursor, heteroaryl bromide or chloride coupled with heterocyclic amines under MW irradiation, producing the target compounds in high yields. The application of these tetrahydropyrimidinium salts in MW assisted Buchwald–Hartwig amination showed them to be efficient ligand precursors. Research on their metalation and catalytic activities towards other carbon–heteratom and carbon–carbon bond formation reactions is in progress in our lab.

4. Experimental

All experiments were performed in air unless indicated otherwise. All reagents and solvents were analytical grade materials purchased from commercial sources and used as received unless otherwise stated. Reactions were monitored by TLC (Qingdao Haiyang Chemical Co. Ltd. Silica gel 60 F254) and detected using a UV/Vis lamp (254 nm). Column chromatography was performed on Qingdao Haiyang Chemical Co. Ltd. Gel 60 (200–300 mesh).

NMR spectra were recorded at 25 °C on a 400 MHz Bruker spectrometer. Chemical shifts (δ in ppm, coupling constants J in Hz) were referenced to the internal solvent ($CDCl_3$, δ^1H = 7.24 ppm, ^{13}C = 77.0 ppm; DMSO-d_6, δ^1H = 2.50 ppm, ^{13}C = 40.0 ppm). EA were obtained from a Thermo Flash 2000. ESI-MS spectra were recorded on a Bruker Esquire 3000.

4.1. Synthesis of asymmetrical-substituted tetrahydropyrimidinium halides LHX 1a

A 25-mL flask containing N-methyl-1,4,5,6-tetrahydropyrimidine (1.47 g, 15 mmol) and 2-bromo-pyridine (2.84 g, 18 mmol) was heated in an oil bath at 100 °C for 48 h under Ar, after which time a red brown viscous oil formed. The oil was cooled to r.t. and then washed with ether 3 times. Crystallization of the residue in EtOH-Et_2O produced the pure product.

1-Methyl-3-(2-pyridinyl)-1,4,5,6-tetrahydropyrimidinium bromide (**1a**): Yield 78%, 3.00 g; brown solid; mp 163–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.50–8.49 (m, 1H), 8.06–8.01 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.42–7.39 (m, 1H), 3.93 (t, J = 5.8 Hz, 2H), 3.55 (t, J = 5.8 Hz, 2H), 3.43 (s, 3H,), 2.22–2.16 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.8, 151.6, 148.6, 140.2, 122.5, 113.0, 46.3, 43.1, 41.6, 18.8 ppm; ESI-MS m/z: 176.0 $[M\text{-}Br]^+$.

4.2. Synthesis of the methylene bridged diaryl-substituted tetrahydropyrimidinium dibromides LHXs 1b and 1c

Following a literature report,[16] reaction of 1-aryl-propyl-1,3-diamine with aqueous formaldehyde in methanol produced bis-(3-aryl-hexahydropyrimidinyl)methane. Bis(3-aryl-hexahydropyrimidinyl)methane (1.98 mmol) was dissolved in absolute 1,2-dimethoxy-ethane (50 mL) and treated with NBS (0.705 g, 3.96 mmol). The reaction mixture was stirred at room temperature for 2 h before the volatile compounds were removed in vacuo and a brown, oily residue remained. Crystallization of the residue in EtOH afforded the pure products.

3,3'-DiMes-1,1'-methylenedi(1,4,5,6-tetrahydropyrimidinium) dibromides (**1b**): Yield 66%, 0.76 g; white

solid; mp 186–188 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.89 (s, 2H), 7.08 (s, 4H), 5.27 (s, 2H), 3.75–3.68 (m, 8H), 2.57 (s, 6H), 2.29–2.28 (m, 16H) ppm; ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 156.3, 139.8, 137.2, 135.2, 129.8, 71.8, 46.0, 41.7, 29.9, 20.9, 17.6 ppm; ESI-MS m/z: 497.4 [M-Br]$^+$.

3,3'-Di(2,6-diisopropyl-phenyl)-1,1'-methylenedi(1,4,5,6-tetrahydropyrimidinium) dibromides (**1c**): Yield 73%, 0.96 g; white solid; mp 312–314 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.38 (s, 2H), 7.43 (t, J = 5.8 Hz, 2H), 7.27–7.22 (m, 4H), 6.37 (s, 2H), 4.41 (s, 4H), 3.85 (s, 4H), 3.09–3.03 (m, 4H), 2.30 (m, 4H), 1.24 (t, J = 6.5 Hz, 24 H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.7, 145.6, 135.9, 131.0, 125.0, 71.8, 48.2, 42.3, 28.5, 25.1, 24.1, 18.7 ppm; ESI-MS m/z: 581.5 [M-Br]$^+$.

4.3. Synthesis of the ethylene bridged dialkyl-substituted tetrahydropyrimidinium dibromides LHXs 1d and 1e

1,1'-Ethylenebis(l,4,5,6-tetrahydropyrimidine): Following a literature report,[17] a 25-mL flask containing N,N'-bis(3-aminopropyl)ethylenediamine (4.14 g, 23.95 mmol), DMF-DMA (6.3 g, 52.9 mmol), and toluene (10 mL) was heated in an oil bath at 100 °C for 3 h under Ar before all the volatiles were removed under vacuum. The residue was characterized as the crude product of 1,1'-ethylenebis(l,4,5,6-tetrahydropyrimidine) and used for the next reaction directly.

3,3'-Diisopropyl-1,1'-ethylenedi(1,4,5,6-tetrahydropyrimidinium) dibromides (**1d**): To a 25-mL flask containing a DMF (3 mL) solution of 1,1'-ethylenebis(l,4,5,6-tetrahydropyrimidine) (0.97 g, 5 mmol), 2-bromopropane (1.4 g, 11 mmol) was added slowly and the mixture was then stirred at room temperature for 8 h under Ar. The mixture was then washed with Et$_2$O 3 times. Crystallization of the residue in EtOH-Et$_2$O produced the pure product. Yield 43%, 0.92 g; white solid; mp 258–260 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.63 (s, 2H), 3.95–3.87 (m, 2H), 3.77 (s, 4H), 3.48 (t, J = 5.5 Hz, 4H), 3.36 (s, 4H), 1.98 (t, J = 5.4 Hz, 4H), 1.25 (d, J = 6.6 Hz, 12H) ppm; ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 152.6, 56.3, 51.6, 43.7, 39.2, 20.4, 19.1 ppm; ESI-MS m/z: 359.2 [M-Br]$^+$.

3,3'-Dibenzyl-1,1'-ethylenebis(1,4,5,6-tetrahydropyrimidinium) dibromides (**1e**): Compound **1e** was prepared by the same procedure as **1d** from 1,1'-ethylenebis(l,4,5,6-tetrahydropyrimidine) (0.97 g, 5 mmol) and benzyl bromide (1.88 g, 11 mmol). Yield 65%, 1.70 g; white solid; mp 234–236 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.99 (s, 2H), 7.45–7.40 (m, 10H), 4.70 (s, 4H), 3.84 (s, 4H), 3.51 (t, J = 5.4 Hz, 4H), 3.27 (t, J = 5.5 Hz, 4H), 1.97 (t, J = 5.2 Hz, 4H) ppm; ^{13}C NMR (400 MHz, DMSO-d$_6$) δ 154.1, 134.6, 129.3, 129.0, 128.8, 57.5, 51.8, 43.1, 42.6, 18.7 ppm; ESI-MS m/z: 455.4 [M-Br]$^+$.

4.4. Synthesis of the alkylene bridged dimethyl-substituted tetrahydropyrimidinium dihalides 1f–1i

3,3'-Dimethyl-1,1'-(1,2-phenylenebis(methylene))di(1,4,5,6-tetrahydropyrimidinium) dichlorides (**1f**): To a 25-mL flask containing a DMF (3 ML) solution of N-methyl-1,4,5,6-tetrahydropyrimidine (0.98 g, 10 mmol), 1,4-bis(chloromethyl)benzene (0.88 g, 5 mmol) was added slowly and the mixture was then stirred at room temperature for 12 h under Ar. The mixture was then washed with Et$_2$O 3 times. Crystallization of the residue in EtOH-Et$_2$O produced the pure product. Yield 76%, 1.41 g; white solid; mp 184–185 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.06 (s, 1H), 7.42 (m, 4H), 4.89 (s, 4H), 3.37 (t, J = 5.5 Hz, 4H), 3.22 (s, 6H), 3.16 (t, J = 5.4 Hz, 4H), 1.98 (t, J = 5.3 Hz, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 154.2, 133.5, 129.6, 129.1, 54.4, 44.7, 42.1, 41.9, 18.7 ppm; ESI-MS m/z: 335.3 [M-Cl]$^+$.

3,3'-Dimethyl-1,1'-methylenedi(1,4,5,6-tetrahydropyrimidinium) diiodides (**1g**): Compound **1g** was prepared by the same procedure as **1f** from N-methyl-1,4,5,6-tetrahydropyrimidine (0.98 g, 10 mmol) and diiodomethane (1.34 g, 5 mmol). Yield 52%, 1.21 g; white solid; mp 222–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 2H), 4.99 (s, 2H), 3.39–3.35 (m, 8H), 3.21 (s, 6H), 2.05–2.00 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 70.5, 45.1, 42.5, 41.0, 18.3 ppm; ESI-MS m/z: 337.2 $[M\text{-}I]^+$.

3,3'-Dimethyl-1,1'-ethylenedi(1,4,5,6-tetrahydropyrimidinium) dibromides (**1h**): Compound **1h** was prepared by the same procedure as **1f** from N-methyl-1,4,5,6-tetrahydropyrimidine (0.98 g, 10 mmol) and 1,2-dibromoethane (0.94 g, 5 mmol). Yield 47%, 0.90 g; white solid; mp 196–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 2H), 3.71 (s, 4H), 3.42 (d, J = 5.6 Hz, 4H), 3.34 (t, J = 5.7 Hz, 4H), 3.18 (s, 6H), 2.02–1.97 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.9, 51.5, 44.7, 42.6, 41.8, 18.7 ppm; ESI-MS m/z: 303.2 $[M\text{-}Br]^+$.

3,3'-Dimethyl-1,1'-butylenedi(1,4,5,6-tetrahydropyrimidinium) dibromides (**1i**): Compound **1i** was prepared by the same procedure as **1f** from N-methyl-1,4,5,6-tetrahydropyrimidine (0.98 g, 10 mmol) and 1,4-dibromobutane (1.08 g, 5 mmol). Yield 51%, 1.05 g; white solid; mp 162–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 2H), 3.45 (s, 4H), 3.36–3.30 (m, 8H), 3.16 (s, 6H), 2.01–1.96 (m, 4H), 1.58 (s, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6)$v\delta$ 153.2, 53.6, 44.6, 42.1, 41.6, 23.8, 18.7 ppm; ESI-MS m/z: 331.2 $[M\text{-}Br]^+$.

4.5. Synthesis of tetrahydropyrimidinium hexafluorophosphates 2a–2i

To a 50-mL flask containing an EtOH (25 mL) solution of tetrahydropyrimidinium halides (15 mmol), 10 mL aqueous solution of NH_4PF_6 (20 mmol for mono-tetrahydropyrimidinium halides and 40 mmol for di-tetrahydropyrimidinium halides) was added and the mixture was then stirred at room temperature for 15 h before all the volatiles were evaporated. The residue was dissolved in 20 mL of CH_2Cl_2, washed with H_2O, dried, and evaporated. Crystallization of the residue in EtOH produced the pure product.

1-Methyl-3-(2-pyridinyl)-1,4,5,6-tetrahydropyrimidinium hexafluorophosphate (**2a**): Yield 88%, 4.24 g; brown solid; mp 123–125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.51 (m, 1H), 8.06–8.02 (m, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.43–7.40 (m, 1H), 3.92 (t, J = 5.8 Hz, 2H), 3.54 (t, J = 5.8 Hz, 2H), 3.42 (s, 3H), 2.19 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.8, 151.6, 148.6, 140.2, 122.6, 112.7, 46.1, 43.0, 41.6, 18.7 ppm. Anal. Calcd for $C_{10}H_{14}F_6N_3P$ (321.2): C, 37.39; H, 4.39; N, 13.08; Found: C, 37.41; H, 4.40; N, 13.07.

3,3'-DiMes-1,1'-methylenedi(1,4,5,6-tetrahydropyrimidinium) di-hexafluorophosphate (**2b**): Yield 84%, 8.93 g; white solid; mp 237–238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78–8.68 (2s, 2H), 7.10–7.08 (2s, 4H), 5.11 (d, J = 8.0 Hz, 2H), 3.65–3.63 (m, 4H), 3.56–3.53 (m, 4H), 2.71 (s, 3H), 2.30–2.27 (m, 19H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 139.9, 137.2, 135.2, 129.9, 56.1, 45.7, 41.6, 28.7, 21.0, 17.5 ppm; Anal. Calcd for $C_{27}H_{38}F_{12}N_4P_2$ (708.55): C, 45.77; H, 5.41; N, 7.91. Found: C, 45.75; H, 5.39; N, 7.89.

3,3'-Di(2,6-diisopropyl-phenyl)-1,1'-methylenedi(1,4,5,6-tetrahydropyrimidinium) di-hexafluorophosphate (**2c**): Yield 89%, 10.54 g; white solid; mp 302–304 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 2H), 7.56 (t, J = 8.0 Hz, 2H), 7.45 (t, J = 7.6 Hz, 4H), 5.16 (s, 2H), 3.68 (t, J = 5.0 Hz, 4H), 3.58 (t, J = 5.6 Hz, 4H), 2.95–2.90 (m, 4H), 2.34 (t, J = 4.8 Hz, 4H), 1.29–1.23 (m, 24 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 145.9, 136.5, 131.3, 125.5, 72.4, 48.0, 41.3, 28.2, 25.0, 24.4, 18.4 ppm; Anal. Calcd for $C_{33}H_{50}F_{12}N_4P_2$ (792.71): C, 50.00; H, 6.36; N, 7.07. Found: C, 49.98; H, 6.35; N, 7.09.

3,3'-Diisopropyl-1,1'-ethylenedi(1,4,5,6-tetrahydropyrimidinium) di-hexafluorophosphate (**2d**): Yield 54%, 4.51 g; white solid; mp 237–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 2H), 3.84–3.81 (m, 2H), 3.68 (s, 4H), 3.41 (t, J = 5.6 Hz, 4H), 3.35 (t, J = 5.6 Hz, 4H), 2.00–1.94 (m, 4H), 1.24 (d, J = 6.7 Hz, 12H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.6, 56.6, 51.8, 43.5, 39.2, 20.3, 19.0 g ppm; Anal. Calcd for $C_{16}H_{32}F_{12}N_4P_2$ (570.38): C, 33.69; H, 5.65; N, 9.82. Found: C, 33.67; H, 5.63; N, 9.84.

3,3'-Dibenzyl-1,1'-ethylenebis(1,4,5,6-tetrahydropyrimidinium) di-hexafluorophosphate (**2e**): Yield 83%, 8.12 g; white solid; mp 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 2H), 7.47–7.38 (m, 10H), 4.64 (s, 4H), 3.78 (s, 4H), 3.44 (t, J = 5.4 Hz, 4H), 3.25 (t, J = 5.7 Hz, 4H), 1.99–1.95 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.3, 134.5, 129.4, 129.1, 129.0, 58.0, 52.0, 42.9, 42.7, 18.7 ppm; Anal. Calcd for $C_{24}H_{32}F_{12}N_4P_2$ (666.47): C, 43.25; H, 4.84; N, 8.41. Found: C, 43.27; H, 4.86; N, 8.39.

3,3'-Dimethyl-1,1'-(1,2-phenylenebis(methylene))di(1,4,5,6-tetrahydropyrimidinium) di-hexafluorophosphate (**2f**): Yield 83%, 7.35 g; white solid; mp 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 2H), 7.47–7.40 (m, 4H), 4.77 (s, 4H), 3.36 (t, J = 5.7 Hz, 4H), 3.21 (s, 6H), 3.16 (t, J = 5.6 Hz, 4H), 2.00–1.98 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 133.2, 129.2, 129.2, 54.4, 44.7, 42.3, 42.0, 18.7 ppm; Anal. Calcd for $C_{18}H_{28}F_{12}N_4P_2$ (590.37): C, 36.62; H, 4.78; N, 9.49. Found: C, 36.64; H, 4.76; N, 9.51.

3,3'-Dimethyl-1,1'-methylenedi(1,4,5,6-tetrahydropyrimidinium) di-hexafluorophosphate (**2g**): Yield 59%, 4.43 g; white solid; mp 199–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 2H), 4.93 (s, 2H), 3.36 (t, J = 5.8 Hz, 4H), 3.30 (t, J = 5.8 Hz, 4H), 3.20 (s, 6H), 2.02–2.00 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.6, 70.7, 45.1, 42.4, 40.8, 18.3 ppm; Anal. Calcd for $C_{11}H_{22}F_{12}N_4P_2$ (500.25): C, 26.41; H, 4.43; N, 11.20. Found: C, 26.44; H, 4.43; N, 11.19.

3,3'-Dimethyl-1,1'-ethylenedi(1,4,5,6-tetrahydropyrimidinium di-hexafluorophosphate (**2h**): Yield 67%, 5.17 g; white solid; mp 189-191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 2H), 3.64 (s, 4H), 3.37–3.30 (m, 8H), 3.16 (s, 6H), 2.00–1.97 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 51.7, 44.7, 42.4, 42.0, 18.6 ppm; Anal. Calcd for $C_{12}H_{24}F_{12}N_4P_2$ (514.27): C, 28.03; H, 4.70; N, 10.89. Found: C, 28.04; H, 4.73; N, 10.90.

3,3'-Dimethyl-1,1'-butylenedi(1,4,5,6-tetrahydropyrimidinium) di-hexafluorophosphate (**2i**): Yield 54%, 4.39 g; white solid; mp 153–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 2H), 3.44 (s, 4H), 3.40–3.32 (m, 8H), 3.16 (s, 6H), 2.01–1.97 (m, 4H), 1.58 (s, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.3, 53.9, 44.6, 42.0, 41.7, 23.9, 18.7 ppm; Anal. Calcd for $C_{14}H_{28}F_{12}N_4P_2$ (542.33): C, 31.01; H, 5.20; N, 10.33. Found: C, 31.00; H, 5.23; N, 10.35.

4.6. General procedure for the Buchwald–Hartwig amination reaction under microwave irradiation

The Buchwald–Hartwig amination reaction under microwave irradiation was conducted in a CEM Discover apparatus. A 10-mL Teflon vessel was charged with 1.0 mmol of hetero-aryl halide, 3.0 mmol of amine, 2.0 of mmol base, 0.05 mmol of $Pd(OAc)_2$, 0.10 mmol of LHX, and 2.0 mL of solvent. The mixture was irradiated at 150 W at 100 °C for the specified time and then allowed to cool. The reaction mixture was extracted 3 times with diethyl ether, and the combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness. Purification of the residue by flash chromatography on silica gel afforded the pure products.

3a: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.18 (m, 1H), 7.49–7.45 (m, 1H), 6.65–6.60 (m,

2H), 3.79 (t, J = 4.8 Hz, 4H), 3.47 (t, J = 4.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 147.9, 137.5, 113.8, 106.9, 66.7, 45.6 ppm.

3b: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.07 (m, 1H), 7.42–7.29 (m, 1H), 6.42–6.39 (m, 1H), 6.24–6.22 (d, J = 8.5 Hz, 1H), 3.34 (t, J = 6.7 Hz, 4H), 1.91–1.87 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 148.0, 136.8, 110.9, 106.4, 46.5, 25.4 ppm.

3c: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.35 (t, J = 2.4 Hz, 1H, HPy), 7.90–7.88 (m, 1H), 7.75–7.72 (m, 1H), 7.60–7.56 (m, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.22–7.17 (m, 2H), 7.02–7.00 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 149.9, 149.5, 144.6, 141.3, 139.0, 132.3, 132.1, 131.0, 128.8, 124.2, 123.3 ppm.

3d: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 4.7 Hz, 2H), 6.38 (t, J = 4.7 Hz, 1H), 3.67–3.62 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 157.6, 110.1, 66.6, 44.0 ppm.

3e: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 4.7 Hz, 2H, H-5, H-7), 6.13 (t, J = 4.7 Hz, 1H, H-6), 3.26 (t, J = 6.4 Hz, 4H, H-1, H-4), 1.67 (t, J = 6.4 Hz, 4H, H-2, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.3, 108.5, 46.2, 25.2 ppm.

3f: White solid; mp 138–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.94 (d, J = 4.8 Hz, 2H), 8.53 (d, J = 7.8 Hz, 1H), 7.80-7.78 (m, 1H), 7.49 (t, J = 4.8 Hz, 1H), 7.45–7.35 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 159.8, 155.9, 145.0, 142.3, 131.9, 124.9, 124.1, 120.5, 119.5, 115.8 ppm.

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