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酰胺功能化吡啶/嘧啶螯合氮杂环卡宾钯化合物的合成、结构及其催化的咪唑 C-5 芳基化反应

孟祥辉 杨亮茹* 刘琪琳 董振华 袁金伟*
肖咏梅 毛 璞*
(河南工业大学化学化工学院 郑州 450001)

摘要 以氨基酸为原料，合成了一系列 *N*-烷基酰胺-*N*′-吡啶/嘧啶双官能团化的咪唑鎓盐，室温下与 $Pd(OAc)_2$ 在 CH_2Cl_2 溶液中经直接金属化反应生成吡啶/嘧啶螯合的氮杂环卡宾钯化合物. 所得化合物的结构经核磁共振(NMR)、质谱(MS)或元素分析(EA)鉴定，其中吡啶螯合氮杂环卡宾钯化合物**5c**的结构进一步经X射线单晶衍射确证. 催化活性研究表明，使用二甲基乙酰胺(DMAc)为溶剂、KOAc 为碱时，这些化合物对咪唑衍生物的 C-5 芳基化反应表现出很高的催化活性.
关键词 氮杂环卡宾；螯合；钯化合物；咪唑芳基化反应

Amide Functionalized Pyridine/Pyrimidine Chelating *N*-Heterocyclic Carbene Palladium Complexes: Synthesis, Structure, and Catalysis for C-5 Arylation of Imidazoles

Meng, Xianghui Yang, Liangru* Liu, Qilin Dong, Zhenhua
Yuan, Jinwei* Xiao, Yongmei Mao, Pu*
(*School of Chemistry & Chemical Engineering*, *Henan University of Technology*, *Zhengzhou 450001*)

Abstract A series of *N*-alkylamide-*N*′-pyridine/pyrimidine di-functionalized imidazolium salts were synthesized using amino acids as starting material. The following direction metallation with $Pd(OAc)_2$ in CH_2Cl_2 at room temperature produced chelating *N*-heterocyclic carbene (NHC) palladium complexes with pyridine/pyrimidine coordinated. The structures have been characterized by nuclear magnetic resonance (NMR), mass spectrum (MS) or elemental analysis (EA). The molecular strucuture of pyridine chelating NHC palladium complex **5c** has been further characterized unambiguously by X-ray single crystal analysis. Catalytic activity exploration of the complexes demonstrated their high efficiency towards the C-5 arylation of imidazole derivatives in dimethylacetamide (DMAc) with KOAc as base.
Keywords *N*-heterocyclic carbene; chelating; palladium complex; arylation of imidazoles

1 Introduction

N-Heterocyclic carbenes (NHCs) have evolved into one of the most powerful tools in organic chemistry since the successful isolation and characterization of the first stable one by Arduengo and co-workers[1] in 1991. Duo to their strong *σ*-donor and comparatively weak *π*-acceptor abilities, facilely modifiable steric and electronic properties, and easy accessibility, NHCs have received intensive attention as ligands and contributed extensively to organometallic chemistry and homogeneous catalysis.[2] Various stable NHC metal complexes have been synthesized and utilized successfully to catalyze a number of organic transformations.[3] NHCs with *N*-arm containing heteroatom donor (P, N, S, O, *etc.*) become chelating (sometimes pincer) type ligands, which have interesting properties and form metal complexes showing increased stability that are

* Corresponding authors. E-mail: lryang@haut.edu.cn; yuanjinweigs@126.com; maopu@haut.edu.cn
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advantageous in catalysis.[4] Chelating NHC metal (Pd, Ni, Ir, Rh, and Ru) complexes containing $C_{NHC}P$, $C_{NHC}S$, $C_{NHC}N$ or $C_{NHC}O$ *etc.* ligands have demonstrated outstanding performance in the catalytic C—C, C—hetero bond formation, hydrogenation, or C—H activation.[5] Chelating NHC-Pd catalyzed Mizoroki-Heck reaction has been investigated through different mechanistic pathways, and density functional theory (DFT) studies have been performed to better understand and improve the catalyst.[6] Palladium(II) complexes supported by *bis*-NHC pincer ligands have been applied to the electrochemical activation of CO_2.[7] Palladium(II) ligated with selenated NHC based ($SeC_{NHC}N^-$) type pincer has been reported to be efficient catalyst for Mizoroki-Heck and Suzuki-Miyaura coupling in water.[8] Thioether-functionalized magnetically retrievable NHC Pd complexes have been developed for Suzuki-Miyaura coupling in Water.[9]

Arylated imidazoles constitute an important class of compounds due to their diverse applications in pharmaceuticals, drug candidates, and functional materials.[10] Palladium salts associated with sterically demanding and electron-rich phosphines, such as PPh_3,[11] PCy_3,[12] P(2-furyl)$_3$,[13] P(*n*-Bu)Ad$_2$,[14] dppb,[15] X-phos,[16] and Xant-phos,[17] have been the most extensively studied systems to obtain arylated imidazoles via direct arylations. However, in most cases, high palladium loadings (usually 5～10 mol%) or sophisticated phosphine ligands (usually expensive and unstable) are required. During the searching of more effective protocol for the synthesis of arylated imidazoles by direct arylation, several types of NHC-palladium complexes showing prominent application prospect have been established. Lee and co-workers[18] reported palladium complexes with phosphines and NHC ligands for the direct C5-arylation reaction between imidazoles and aryl chlorides. Liu's group[19] synthesized a series of bulky Pd-PEPPSI complexes highly efficiently for the direct C5-arylation of imidazoles with aryl bromides under aerobic conditions with low catalyst loading (＜1 mol%). NHC palladium complexes featuring tridentate $C_{NHC}NO$[20] $C_{NHC}NS$[21], $C_{NHC}NSe$[21], or $SeC_{NHC}S$[22] ligands have been synthesized and showed promising research and application value for the direct C5-arylation reaction between imidazoles and aryl bromides.

NHC ligand precursors bearing amido-, amide-, hydroxyl-, or carboxylate-functionalized *N*-substituents have been reported to form NHC metal complexes featuring diverse tunable structure and demonstrate excellent catalytic activity in C—C coupling reactions.[5b,23] Our group[24] have synthesized a series of *N*-hydroxylalkyl functionalized heteroaryl coordinated chelating NHC palladium complexes featuring different *N*-arms, chelating rings or NHC backbones from commercially available amino alcohols conveniently (Figure 1, **C1**～**C8**). Catalytic exploration demonstrated their high activity towards C—H activation, C—C and C—P bond formation and the relationship between the structure and the activity. To further investigate the effect of the *N*-arm on the structure and catalytic activity, *N*-amides functionalized hetero aryl chelating NHC palladium complexes were synthesized and their catalytic activity towards arylation of imidazoles was studied.

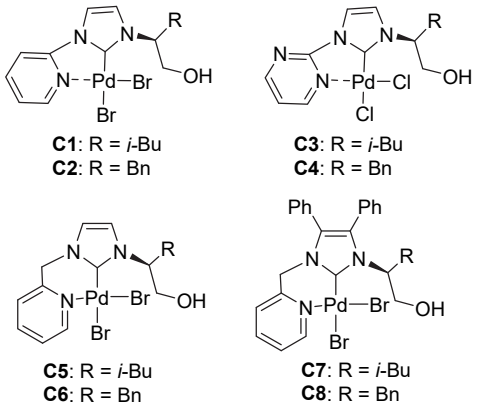


Figure 1 *N*-Hydroxylalkyl functionalized chelating NHC palladium complexes we have synthesized

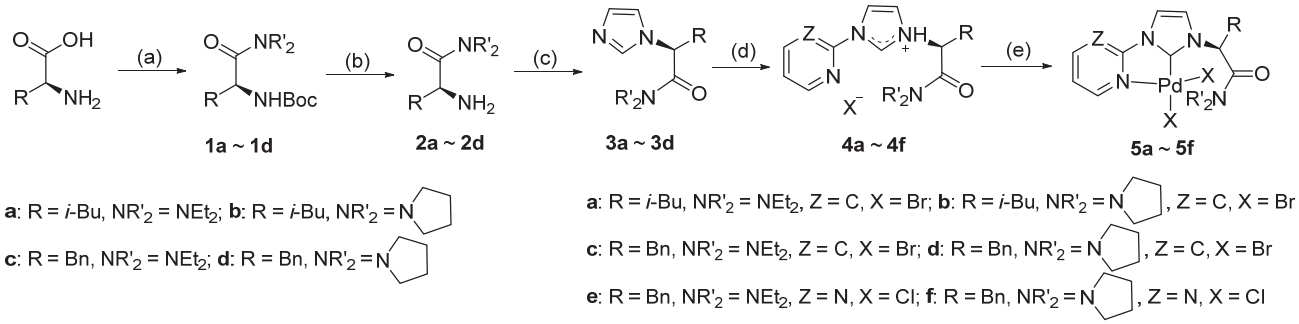
2 Results and discussion

2.1 Synthesis of *N*-amide-*N*′-pyridine/pyrimidine di-functionalized imidazolium salts

Through the continuous reaction of *L*-phenylalanine or *L*-leucine with di-*tert*-butyl dicarbonate ($(Boc)_2O$), amidation by diethylamine or pyrrolidine, and deprotection by methanesulfonic acid, *N*,*N*-disubstituted *L*-phenylalanine amides and *L*-leucine amides (**2a**～**2d**) were obtained. The following reaction of **2a**～**2d** with formaldehyde, glyoxal, and ammonia chlorides in MeOH afforded imidazole amides (**3a**～**3d**) in moderate yields (Scheme 1). The structures were characterized by NMR and MS analysis. Compared to the starting amino acids, the additional aliphatic proton signals appeared in the NMR spectra of **2a**～**2d** confirmed the successful amidation. The formation of imidazole amides **3a**～**3d** was confirmed by NMR and MS analysis.

N-Amide-*N*′-pyridine di-functionalized imidazolium salts (**4a**～**4d**) were obtained by heating a mixture of imidazole amides (**3a**～**3d**) and excessive 2-bromopyridine at 150 ℃ for 48 h. *N*-Amide-*N*′-pyrimidine di-functionalized imidazolium salts (**4e**～**4f**) were obtained by heating the mixture of imidazole amides (**3c**～**3d**) and 2-chloropyrimidine in toluene at 110 ℃ overnight (Scheme 1). Purification by column chromatography produced the pure products in moderate to high yields, which were characterized by NMR and MS analysis.

In the NMR spectra of **3a**～**3d**, the resonances of N*C*HN protons appeared at δ 7.46, 7.58, 7.30 and 7.44, respectively. While in compounds **4a**～**4f**, the NCHN protons shifted significantly to δ 10.50, 10.49, 10.43, 11.57, 10.50 and 10.50, respectively, indicating the successful formation of the imidazolium salts. Additional signals appeared in the aromatic region, which can be attributed to pyridine or pyrimidine substituents confirmed the formation of *N*-amide-*N*′-pyridine/pyrimidine di-functionalized imidazolium salts. The structures of the imidazolium



Reaction conditions: (a) i) $(Boc)_2O$, ii) CDI, R'$_2$NH; (b) CH_3SO_3H; (c) HCHO, CHOCHO, NH_4Cl, MeOH; (d) 2-bromopyridine or 2-chloro-pyrimidine, 150 or 110 ℃; (e) $Pd(OAc)_2$, CH_2Cl_2, r.t.

Scheme 1 Synthesis of the imidazolium salts and chelating NHC palladium complexes

salts were further confirmed by MS analysis.

2.2 Synthesis of chelating NHC palladium complexes

Direct metallation of imidazolium salts (**4a**～**4f**) by $Pd(OAc)_2$ in dichloromethane at room temperature produced the chelating NHC-Pd complexes (**5a**～**5f**) (Scheme 1). The structures of which were characterized unambiguously by NMR and single-crystal X-ray diffraction studies.

Comparison of the ^{1}H NMR spectra of **5a**～**5f** with **4a**～**4f** showed the conspicuous disappearance of the N*C*HN signals of imidazolium salts **4a**～**4f** indicating the formation of NHC metal complexes. In addition, the signals of the pyridine proton adjacent to the nitrogen atom in **4a**～**4d** appeared at δ 8.66, 8.66, 8.63, 8.52, respectively, while in complexes **5a**～**5d**, the corresponding protons down fielded obviously to δ 9.64, 9.63, 9.72, 9.67, supporting the coordination of pyridine to the palladium. In compounds **4e**～**4f**, the two pyrimidine protons adjacent to the nitrogen atom appeared as one doublets at δ 9.06 (**4e**～**4f**), while in complexes **5e**～**5f**, the adjacent protons appeared magnetic unequally, with one shifted significantly to δ 9.85 (**5e**) and 9.77 (**5f**), confirming the coordination of pyrimidine to the palladium. In the ^{13}C NMR spectra, appearance of additional signals in the aromatic region, which should be attributed to the new $C_{carbene}$-Pd resonance, showed the formation of the NHC palladium complexes. The structure of complexes **5c** has been further characterized unambiguously by the single-crystal X-ray diffraction studies.

Single crystals of **5c** suitable for X-ray diffraction analysis were obtained from slow evaporation of a dichloromethane/hexane (V∶V=1∶1) solution of complex **5c**. The molecular structure was shown in Figure 2, with selected bond lengths, bond angles and torsion angles listed in the caption. The palladium atom adopts a slightly distorted square-planar coordination bonded to NHC, pyridine and two bromides, with the five membered chelating ring exist as a nearly planar conformation. Similar to the *N*-alkylhydroxyl substituted analogous, the *N*-amide substituent hangs freely.[24a]

The substitution pattern on the nitrogen atom has large effect on the electronic and steric properties, and coordination mode of the NHCs, hence leading to the formation of different catalytic active species.[23c] Using DMAc as solvent and KOAc as base, the catalytic activity of complexes **5a**～**5f** and **C1**～**C4** towards the reaction of 1,2-dimethylimidazole and *p*-bromoacetophenone was tested (Table 1). All the chelating NHC complexes tested showed moderate to high efficiency, with the *N*-amides functionalized chelating NHC palladium complexes **5a**～**5f** showed relatively high yields than the corresponding *N*-alkylhydroxyl functionalized analogous **C1**～**C4** (Table 1, Entries 1～6, 8～11). Complex **5f** was proved to be the best one.

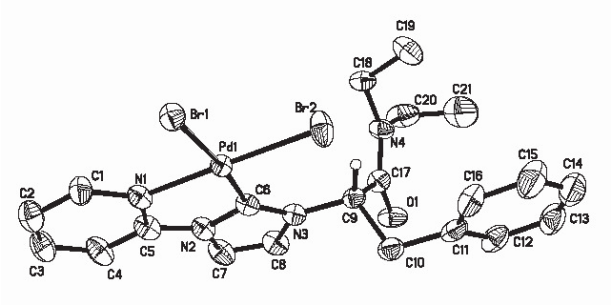


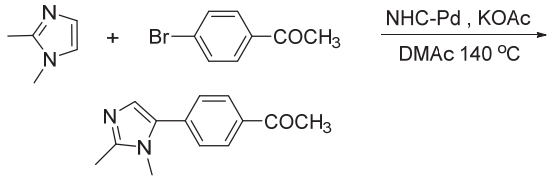
Figure 2 Molecular structure of complex **5c** (50% displacement ellipsoids)

Selected bond lengths (nm), angles (deg) and torsion angles: Pd(1)—C(6) 0.1986(9), Pd(1)—N(1) 0.2052(5), Pd(1)—Br(1) 0.24678(12), Pd(1)—Br(2) 0.23849(12), N(2)—C(6) 0.1347(13), N(3)—C(6) 0.1357(14), N(2)—C(7) 0.1387(14), N(3)—C(8) 0.1429(14), C(7)—C(8) 0.1323(19); C(6)—Pd(1)—Br(1) 173.4(3), C(6)—Pd(1)—Br(2) 98.4(34), C(6)—Pd(1)—N(1) 79.9(4), N(1)—Pd(1)—Br(1) 93.58(18), N(1)—Pd(1)—Br(2) 178.31(18), Br(1)—Pd(1)—Br(2) 88.10(4); Pd(1)-C(6)-N(2)-C(5) 0.3(13), Pd(1)-C(6)-N(2)-C(7) 180.0(9), Pd(1)-C(6)-N(3)-C(8) 178.9(10), Pd(1)-C(6)-N(3)-C(9) 1.4(18), N(1)-C(5)-N(2)-C(6) 1.3(13)

In general, the pyrimidine chelating complexes (**5e**～**5f**) (Table 1, Entries 5～6) displayed higher activities than the pyridine chelating complexes (**5a**～**5d**) (Table 1, Entries 1～4). This maybe tentatively attributed to the comparatively weak coordination ability of pyrimidine, which favors the formation of the catalytic active species. For complexes having the same chelating structure, the *N*-amides substituent showed some effect on the catalytic activity. The complexes containing benzyl substituent (**5c**～**5d**) (Table 1, Entries 3～4) showed slightly higher activity than the *iso*-butyl substituted counterparts (**5a**～**5b**) (Table

1, Entries 1～2). Pyrrolidine amides functionalized complexes (**5b**, **5d**, **5f**) (Table 1, Entries 2, 4, 6) showed higher activity than the diethyl amide counterparts (**5a**, **5c** **5e**) (Table 1, Entries 1, 3, 5). This could be attributed to the favorable steric effects of the pyrrolidine and benzyl groups. Nearly full conversion was obtained when 2.0 mol% **5f** was used and loading of 1.0 mol% **5f** resulted in a slightly decrease in the yield (Table 1, Entries 6～7).

Table 1 Catalytic activities comparison of complexes **5a**～**5f** and **C1**～**C4**



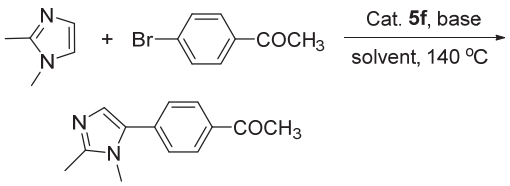
Entry[a]	NHC-Pd (mol%)	Yield[b]/%
1	**5a** (2.0)	65
2	**5b** (2.0)	79
3	**5c** (2.0)	74
4	**5d** (2.0)	81
5	**5e** (2.0)	76
6	**5f** (2.0)	99
7	**5f** (1.0)	87
8	**C1** (2.0)	55
9	**C2** (2.0)	67
10	**C3** (2.0)	57
11	**C4** (2.0)	89

[a] Reaction conditions: *p*-bromoacetophenone (1.0 mmol), 1,2-dimethylimidazole (1.7 mmol), KOAc (2.0 equiv.), DMAc (5.0 mL), 140 ℃, 18 h, nitrogen atmosphere. [b] Isolated yield.

Running the reaction of 1,2-dimethylimidazole and *p*-bromoacetophenone as a model, the effect of solvent and base on the reaction was screened briefly (Table 2). DMAc was proved to be the proper solvent (Table 2, Entry 1). Reaction in dimethyl sulfoxide (DMSO) or *N*,*N*-dimethylformamide (DMF) produced a bit lower yields (Table 2, Entries 2～3). Moderate yield was obtained in toluene, and no reaction occurred in 1,4-dioxane or tetrahydrofuran (THF) (Table 2, Entries 4～6). Among the bases used, KOAc was proved to be the best (Table 2, Entry 1). K_2CO_3, K_3PO_4•$3H_2O$, K_3PO_4 produced moderate yields (Table 2, Entries 8～10). NaOAc afforded a low yield (Table 2, Entries 7). No reaction occurred when Cs_2CO_3 or NaH was used (Table 2, Entry 11～12).

Using KOAc as base, DMAc as solvent, complex **5f** catalyzed direct arylation of imidazoles by different aryl bromides were explored (Table 3). Generally, a wide range of 5-arylated imidazole derivatives were obtained successfully. Aryl bromides bearing electron-rich, electron-neutral, or electron-poor substituents are tolerated in such transformations, but the substituents showed obvious electronic and steric effect on the reaction. Electron-withdrawing substituents ($COCH_3$, CHO, CN, CH_2CN, CF_3, F) in aryl

Table 2 Screening of the solvent and base effect



Entry[a]	Solvent	Base	Temp./℃	Yield[b]/%
1	DMAc	KOAc	140	99
2	DMF	KOAc	140	84
3	DMSO	KOAc	140	90
4	Toluene	KOAc	110	65
5	1,4-Dioxane	KOAc	110	0
6	THF	KOAc	60	0
7	DMAc	NaOAc	140	34
8	DMAc	K_2CO_3	140	61
9	DMAc	K_3PO_4•$3H_2O$	140	55
10	DMAc	K_3PO_4	140	68
11	DMAc	Cs_2CO_3	140	0
12	DMAc	NaH	140	0

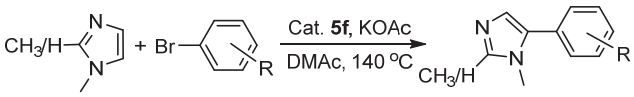
[a] Reaction conditions: *p*-bromoacetophenone (1.0 mmol), 1,2-dimethylimidazole (1.7 mmol), **5f** (2.0 mol%), base (2.0 equiv.), solvent (5.0 mL), 18 h, nitrogen atmosphere. [b] Isolated yield.

bromides were favorable for the reaction (Table 3, Entries 1～2, 4～10), and electron-donating substituents (CH_3, OCH_3) resulted in lower yields (Table 3, Entries 12～16). Similar reactions of 1-methylimidazole produced a bit lower yields than reactions using 1,2-dimethylimidazole (Table 3, Entries 1, 4～6, 18～21), indicating that electron-donating substituent in imidazole is favorable for the reaction. *o*- or *m*-substituted aryl bromides gave inferior results than their *p*-substituted counterparts (Table 3, Entries 1～2, 4～6, 12～13, 19～21), and no reaction occurred when *o*-$COCH_3$, *o*-CH_3, or *o*-OCH_3 substituted aryl bromides were used (Table 3, Entries 3, 14, 17). This might be attributed to the high steric hindrance.

3 Conclusions

Using amino acids as starting material, a series of *N*-alkylamide-*N*′-pyridine/pyrimidine di-functionalized imidazolium salts were synthesized. Direction metallation of the imidazolium salts with $Pd(OAc)_2$ in CH_2Cl_2 produced pyridine/pyrimidine coordinating chelating NHC palladium complexes, with the *N*-alkylamide group hanging freely. The structure has been characterized unambiguously by NMR and X-ray single crystal analysis. Catalytic activity exploration showed that the complexes catalyze the C-5 arylation of imidazole derivatives effectively when using KOAc as base and DMAc as solvent. Further modification of the structure and properties of the chelating NHC palladium complexes and their catalytic activity towards other organic transformations are currently in progress in our laboratory.

Table 3 Direct arylation of imidazoles by different aryl bromides



Entry [a]	Imidazole	Bromide	Yield[b]/%
1	1,2-Dimethylimidazole	*p*-$BrC_6H_4COCH_3$	99
2	1,2-Dimethylimidazole	*m*-$BrC_6H_4COCH_3$	83
3	1,2-Dimethylimidazole	*o*-$BrC_6H_4COCH_3$	0
4	1,2-Dimethylimidazole	*p*-BrC_6H_4CHO	99
5	1,2-Dimethylimidazole	*m*-BrC_6H_4CHO	84
6	1,2-Dimethylimidazole	*o*-BrC_6H_4CHO	70
7	1,2-Dimethylimidazole	*p*-BrC_6H_4CN	96
8	1,2-Dimethylimidazole	*p*-$BrC_6H_4CH_2CN$	74
9	1,2-Dimethylimidazole	*p*-$BrC_6H_4CF_3$	91
10	1,2-Dimethylimidazole	*p*-BrC_6H_4F	90
11	1,2-Dimethylimidazole	C_6H_5Br	66
12	1,2-Dimethylimidazole	*p*-$BrC_6H_4CH_3$	54
13	1,2-Dimethylimidazole	*m*-$BrC_6H_4CH_3$	51
14	1,2-Dimethylimidazole	*o*-$BrC_6H_4CH_3$	0
15	1,2-Dimethylimidazole	*p*-$BrC_6H_4OCH_3$	49
16	1,2-Dimethylimidazole	*m*-$BrC_6H_4OCH_3$	56
17	1,2-Dimethylimidazole	*o*-$BrC_6H_4OCH_3$	0
18	1-Methylimidazole	*p*-$BrC_6H_4COCH_3$	92
19	1-Methylimidazole	*p*-BrC_6H_4CHO	81
21	1-Methylimidazole	*m*-BrC_6H_4CHO	70
22	1-Methylimidazole	*o*-BrC_6H_4CHO	46

[a] Reaction conditions: aryl bromides (1.0 mmol), imidazole (1.7 mmol), KOAc (2.0 equiv.), DMAc (5.0 mL), 140 ℃, 18 h, nitrogen atmosphere. [b] Isolated yield.

4 Experimental section

4.1 Instruments and reagents

NMR spectra were recorded at 25 ℃ on a 400 MHz Bruker spectrometer. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific LTQ Orbitrap XL instrument using the ESI technique. All reagents and solvents were purchased from commercial sources and used as received unless otherwise stated.

4.2 Synthesis of *N*,*N*-disubstituted *L*-phenylalanine/*L*-peucine *tert*-butyl ester amide (**1a**～**1d**)

$NaHCO_3$ (0.84 g, 10 mmol) and Boc_2O (2.62 g, 12 mmol) were added to a solution of *L*-phenylalanine/*L*-leucine (10 mmol) in a mixture of THF (10 mL) and H_2O (30 mL) in an ice-bath. The mixture was then kept in an ultrasonic cleaner at room temperature for 1.5 h before ethyl acetate (40 mL) was added. The mixture was then separated and the pH of the aqueous phase was adjusted to 2～3, before being extracted with CH_2Cl_2 (20 mL×3). The CH_2Cl_2 extracts were combined, dried and evaporated, producing *L*-phenylalanine/*L*-leucine *tert*-butyl ester as light yellow liquids.

A CH_2Cl_2 (30 mL) solution of *L*-phenylalanine/ *L*-peucine *tert*-butyl ester (10 mmol)) was cooled to 0 ℃, then CDI (1.62 g, 10 mmol) was added. The mixture was stirred for 0.5 h before diethyl amine or pyrrolidine (20 mmol) was added. The mixture was then stirred at room temperature for 12 h before all the volatiles were evaporated. Purification of the residue by flash chromatography (silica, *V*(pentane) ∶ *V*(CH_3COOEt) = 5 ∶ 1～3 ∶ 1) produced compounds **1a**～**1d**.

(*S*)-2-NHBoc-*N*,*N*-diethyl-4-methylpentanamide (**1a**): Light yellow oil (2.23 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.52 (d, *J*=9.3 Hz, 1H, NHBoc), 4.62 (td, *J*=9.8, 3.7 Hz, 1H, COCH), 3.56～3.51 (m, 1H, NCH_2), 3.42～3.37 (m, 2H, NCH_2), 3.26～3.23 (m, 1H, NCH_2), 1.74～1.73 (m, 1H, $CH(CH_3)_2$), 1.60～1.53 (m, 1H, $CH_2CH(CH_3)_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.38～1.34 (m, 1H, $CH_2CH(CH_3)_2$), 1.26 (t, *J*=7.1 Hz, 3H, $NCH_2C\mathbf{H}_3$), 1.12 (t, *J*=7.1 Hz, 3H, $NCH_2C\mathbf{H}_3$), 0.99 (d, *J*=6.6 Hz, 3H, $CH(CH_3)_2$), 0.94 (d, *J*=6.7 Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.0, 155.4, 78.8, 48.3, 42.9, 41.5, 40.1, 24.38, 23.29, 21.58, 14.36, 12.70; HRMS (ESI) calcd for $C_{15}H_{31}N_2O_3$ $(M+H)^+$ 287.2329, found 287.2331.

(*S*)-2-NHBoc-4-methyl-1-(pyrrolidin-1-yl)pentan-1-one (**1b**): Light yellow oil (2.30 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.26 (d, *J*=8.96, 1H, NHBoc), 4.44 (td, *J*=3.94, 9.57 Hz, 1H, COCH), 3.69～3.63 (m, 1H, NCH_2), 3.53～3.46 (m, 1H, NCH_2), 3.42～3.36 (m, 2H, NCH_2), 1.97～1.92 (m, 2H, $NCH_2C\mathbf{H}_2$), 1.88～1.82 (m, 2H, $NCH_2C\mathbf{H}_2$), 1.74～1.65 (m, 1H, $CH(CH_3)_2$), 1.52～1.31 (m, 11H, $CH_2CH(CH_3)_2$ and $C(CH_3)_3$), 0.96 (d, *J*=6.52 Hz, 3H, $CH(CH_3)_2$), 0.91 (d, *J*=6.68 Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 171.5, 155.7, 79.4, 50.4, 46.3, 45.9, 42.6, 26.1, 24.6, 24.2, 23.5, 21.9; HRMS (ESI)

calcd for $C_{15}H_{29}N_2O_3$ $(M+H)^+$ 285.2173, found 285.2175.

(*S*)-2-NHBoc-*N*,*N*-diethyl-3-phenylpropanamide (**1c**): Colourless oil (3.04 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20～7.14 (m, 5H, PhH), 5.51 (d, J=8.92 Hz, 1H, NHBoc), 4.71～4.65 (m, 1H, COCH), 3.50～3.41 (m, 1H, $PhCH_2$), 3.06～2.87 (m, 5H, $PhCH_2$ and NCH_2), 1.35 (s, 9H, $(CH_3)_3O$), 0.97 (t, J=7.1 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.89 (t, J=7.1 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 155.0, 136.7, 129.5, 128.2, 126.6, 79.2, 51.3, 41.5, 40.3, 28.2, 14.0, 12.7; HRMS (ESI) calcd for $C_{18}H_{29}N_2O_3$ $(M+H)^+$ 321.2173, found 321.2171.

(*S*)-2-NHBoc-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**1d**): Colourless oil (2.87 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28～7.19 (m, 5H, PhH), 5.54～5.52 (d, J=8.0 Hz, 1H, NHBoc), 4.62～4.56 (m, 1H, COCH), 3.45～3.30 (m, 3H, NCH_2), 3.0～2.92 (m, 2H, $PhCH_2$), 2.60～2.43 (m, 1H, NCH_2), 1.76～1.68 (m, 2H, NCH_2CH_2), 1.66～1.60 (m, 1H, NCH_2CH_2), 1.57～1.51 (m, 1H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 155.1, 136.6, 129.4, 128.3, 126.8, 79.4, 53.6, 46.2, 45.6, 40.1, 28.3, 25.7, 24.0; HRMS (ESI) calcd for $C_{18}H_{27}N_2O_3$ $(M+H)^+$ 319.2016, found 319.2017.

4.3 Synthesis of *N*,*N*-disubstituted *L*-phenylalanine/*L*-leucine amides (**2a**～**2d**)

At room temperature, methanesulfonic acid (2 mL, 30 mmol) was added to a CH_2Cl_2 (30 mL) solution of compounds **1a**～**1d** (10 mmol), and the mixture was kept stirring for 0.5 h. NaOH aqueous solution (10%) was then added until the pH of the mixture reached 11～12. The mixture was separated and the aqueous phase was extracted by CH_2Cl_2 (20 mL×3). The combined organic phase was washed by brine, dried over Na_2SO_4, and evaporated. Purification of the residue by flash chromatography [silica, $V(CH_3COOEt)$∶$V(EtOH)$=4∶1～2∶1] produced compounds **2a**～**2d**.

(*S*)-2-amino-*N*,*N*-diethyl-4-methylpentanamide (**2a**): Colourless oil (1.75 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.64～3.61 (m, 1H, COCH), 3.55～3.50 (m, 1H, NCH_2), 3.41～3.34 (m, 1H, NCH_2), 3.29～3.22 (m, 2H, NCH_2), 1.87～1.84 (m, 1H, $CH(CH_3)_2$), 1.67 (s, 2H, NH_2), 1.42～1.38 (m, 1H, $CH_2CH(CH_3)_2$), 1.35 ～ 1.32 (m, 1H, $CH_2CH(CH_3)_2$), 1.21 (t, J=7.1 Hz, 3H, $NCH_2C\mathbf{H}_3$), 1.12 (t, J=7.1 Hz, 3H, $NCH_2C\mathbf{H}_3$), 0.95 (d, J=6.7 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.3, 49.4, 45.0, 41.3, 40.3, 24.7, 23.7, 21.5, 14.7, 13.0; HRMS (ESI) calcd for $C_{10}H_{23}N_2O$ $(M+H)^+$ 187.1805, found 187.1807.

(*S*)-2-amino-4-methyl-1-(pyrrolidin-1-yl)pentan-1-one (**2b**): Colourless oil (1.68 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.42～3.34 (m, 3H, COCH and NCH_2), 3.33～3.23 (m, 2H, NCH_2), 1.87～1.81 (m, 2H, NCH_2CH_2), 1.76～1.68 (m, 3H, NCH_2CH_2 and $CH(CH_3)_2$), 1.56 (s, 2H, NH_2), 1.26～1.21 (m, 2H, $CH_2CH(CH_3)_2$), 0.81 (d, J=6.60 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.4, 51.2, 45.9, 45.8, 44.4, 26.0, 24.5, 24.0, 23.5, 21.5; HRMS (ESI) calcd for $C_{10}H_{21}N_2O$ $(M+H)^+$ 185.1648, found 185.1649.

(*S*)-2-amino-*N*,*N*-diethyl-3-phenylpropanamide (**2c**): Colourless oil (2.09 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31～7.19 (m, 5H, PhH), 3.76 (t, J=7.04 Hz, COCH), 3.51～3.42 (m, 1H, $PhCH_2$), 3.14～3.03 (m, 2H, $PhCH_2$ and NCH_2), 2.98～2.90 (m, 2H, NCH_2), 2.75～2.70 (m, 1H, NCH_2), 2.23 (s, 2H, NH_2), 1.02 (t, J=7.12 Hz, 3H, CH_2CH_3), 0.98 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 137.8, 129.3, 128.4, 126.6, 52.8, 43.1, 41.3, 40.5, 14.5, 12.8; HRMS (ESI) calcd for $C_{13}H_{21}N_2O$ $(M+H)^+$ 221.1648, found 221.1650.

(*S*)-2-amino-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**2d**): Colourless oil (2.01 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15～7.13 (m, 5H, PhH), 3.59 (t, J=7.24 Hz, COCH), 3.30～3.17 (m, 3H, NCH_2), 2.82～2.77 (m, 1H, $PhCH_2$), 2.69～2.60 (m, 2H, $PhCH_2$ and NCH_2), 2.29 (s, 2H, NH_2), 1.64～1.45 (m, 4H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 137.7, 129.2, 128.3, 126.6, 55.0, 46.0, 45.7, 42.8, 25.8, 24.0; HRMS (ESI) calcd for $C_{13}H_{19}N_2O$ $(M+H)^+$ 219.1492, found 219.1493.

4.4 Synthesis of imidazole amides (**3a**～**3d**)

A mixture of *N*,*N*-disubstituted *L*-phenylalanine/*L*-leucine amides (**2a**～**2d**) (60 mmol), ammonium chloride (3.21 g, 60 mmol) and MeOH (120 mL) was cooled in an ice-bath. Aqueous HCHO solution (36%, 60 mmol) and CHOCHO solution (40%, 60 mmol) were then added dropwise. The mixture was then heated to 60 ℃ for 5 h and cooled to room temperature. The solvent was removed by evaporation and the residue was dissolved in NaOH solution (150 mL, 2 mol/L), and then extracted by CH_2Cl_2 (20 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the residue by flash chromatography [silica, $V(CH_3COOEt)$∶$V(EtOH)$=20∶1～10∶1] afforded the pure products.

(*S*)-*N*,*N*-diethyl-2-(1*H*-imidazol-1-yl)-4-methylpentanamide (**3a**): Colourless oil (8.40 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (s, 1H, Imidazole-H), 6.97 (s, 1H, Imidazole-H), 6.86 (s, 1H, Imidazole-H), 4.86～4.82 (m, 1H, COCH), 3.28～3.12 (m, 4H, NCH_2), 1.85～1.78 (m, 1H, $CH_2CH(CH_3)_2$), 1.67～1.60 (m, 1H, $CH_2CH(CH_3)_2$), 1.22～1.16 (m, 1H, $CH(CH_3)_2$), 0.95 (dt, J=12.3, 7.1 Hz, 6H, CH_2CH_3), 0.75 (dd, J = 24.0 Hz, 6.60 Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.4, 129.0, 118.2, 54.5, 42.7, 42.0, 40.9, 24.2, 22.8, 21.6, 14.5, 12.6; HRMS (ESI) calcd for $C_{13}H_{24}N_3O$ $(M+H)^+$ 238.1914, found 238.1915.

(*S*)-2-(1*H*-imidazol-1-yl)-4-methyl-1-(pyrrolidin-1-yl)-pentan-1-one (**3b**): Colourless oil (8.19 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (s, 1H, Imidazole-H), 7.12 (t, J=1.3 Hz, 1H, Imidazole-H), 7.04 (s, 1H, Imidazole-H), 4.84 (dd, J=9.5, 5.6 Hz, 1H, COCH), 3.56～3.42 (m, 3H, NCH_2), 3.40～3.34 (m, 1H, NCH_2), 2.05～1.91 (m, 3H, $CH_2CH(CH_3)_2$ and NCH_2CH_2), 1.91 ～ 1.77 (m, 3H, $CH_2CH(CH_3)_2$ and NCH_2CH_2), 1.40 ～ 1.31 (m, 1H, $CH(CH_3)_2$), 0.91 (dd, J=19.9, 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ: 167.2, 136.6, 129.4, 118.2, 56.7,

46.4, 46.3, 42.1, 26.1, 24.3, 24.0, 22.9, 21.7; HRMS (ESI) calcd for $C_{13}H_{22}N_3O$ $(M+H)^+$ 236.1757, found 236.1759.

(*S*)-*N*,*N*-diethyl-2-(1*H*-imidazol-1-yl)-3-phenylpropanamide (**3c**): Colourless oil (11.07 g, 68%). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.30 (s, 1H, Imidazole-H), 7.00～6.96 (m, 3H, Ph-H), 6.95 (s, 1H, Imidazole-H), 6.84～6.82 (m, 2H, Ph-H), 6.77 (s, 1H, Imidazole-H), 4.94 (t, J=7.42 Hz, 1H, COCH), 3.21～3.12 (m, 2H, Ph-CH_2 and NCH_2), 3.05～2.90 (m, 4H, Ph-CH_2 and NCH_2), 0.81 (t, J=7.10 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.63 (t, J=7.12 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 136.3, 135.9, 128.9, 128.8, 128.4, 126.9, 118.0, 77.9, 77.5, 77.2, 57.7, 41.9, 40.9, 40.5, 14.1, 12.5; HRMS (ESI) calcd for $C_{16}H_{22}N_3O$ $(M+H)^+$ 272.1757, found 272.1759.

(*S*)-2-(1*H*-imidazol-1-yl)-3-phenyl-1-(pyrrolidin-1-yl)-propan-1-one (**3d**): Colourless oil (10.34 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (s, 1H, Imidazole-H), 7.29～7.26 (m, 3H, Ph-H), 7.16 (t, J=1.16 Hz, 1H, Imidazole-H), 7.08 (s, 1H, Imidazole-H), 7.06～7.03 (m, 2H, Ph-H), 4.90 (t, J=7.96 Hz, 1H, COCH), 3.49～3.42 (m, 3H, Ph-CH_2 and NCH_2), 3.23～3.16 (m, 3H, Ph-CH_2 and NCH_2), 1.87～1.78 (m, 4H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 136.7, 136.1, 129.5, 129.0, 128.7, 127.2, 118.1, 60.3, 46.4, 46.3, 40.3, 26.0, 24.0; HRMS (ESI) calcd for $C_{16}H_{20}N_3O$ $(M+H)^+$ 270.1601, found 270.1602.

4.5 Synthesis of amides pyridine di-functionalized imidazolium bromides (**4a**～**4d**)

A mixture of imidazole amides **3a**～**3d** (5 mmol) and 2-bromopyridine (3 mL) was heated at 150 ℃ for 48 h. It was then cooled to room temperature and added to diethyl ether (30 mL) dropwise. The resulting deep yellow precipitate was collected and purified by flash chromatography [silica, $V(CH_2Cl_2)$∶V(EtOH)=15∶1～8∶1] to produce the pure products **4a**～**4d**.

(*S*)-1-(1-diethylamino-4-methyl-1-oxopentan-2-yl)-3-(pyridin-2-yl) imidazolium bromide (**4a**): Brown viscous oil (1.40 g, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.50 (s, 1H, Imidazole-H), 8.66 (dd, J=5.2, 1.7 Hz, 1H, Pyridine-H), 8.62 (t, J=2.0 Hz, 1H, Imidazole-H), 8.35 (t, J=1.9 Hz, 1H, Imidazole-H), 8.23 (td, J=7.8, 7.4, 1.8 Hz, 1H, Pyridine-H), 8.17 (d, J=8.1 Hz, 1H, Pyridine-H), 7.68～7.65 (m, 1H, Pyridine-H), 5.93 (dd, J=11.3, 3.6 Hz, 1H, COCH), 3.63 (dq, J=14.3, 7.0 Hz, 1H, NCH_2), 3.44～3.41 (m, 2H, NCH_2), 3.24 (dq, J=13.9, 7.0 Hz, 1H, NCH_2), 2.39～2.25 (m, 1H, $CH_2CH(CH_3)_2$), 1.83～1.65 (m, 1H, $CH_2CH(CH_3)_2$), 1.40～1.38 (m, 1H, $CH(CH_3)_2$), 1.24 (t, J=7.0 Hz, 3H, $NCH_2C\mathbf{H}_3$), 1.10～0.95 (m, 6H, NCH_2CH_3 and $CH(CH_3)_2$), 0.90 (d, J=6.6 Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.9, 149.6, 146.8, 141.0, 136.0, 125.8, 124.1, 119.3, 115.03, 58.2, 42.2, 41.1, 40.7, 24.7, 23.1, 21.5, 14.9, 13.1; HRMS (ESI) calcd for $C_{18}H_{27}N_4O$ $[M-Br]^+$ 315.2179, found 315.2181.

(*S*)-1-(4-methyl-1-oxo-1-(pyrrolidin-1-yl)pentan-2-yl)-3-(pyridin-2-yl) imidazolium bromide (**4b**): Brown viscous oil (1.32 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.49 (s, 1H, Imidazole-H), 8.66～8.62 (m, 2H, Imidazole-H and Pyridine-H), 8.39 (s, 1H, Imidazole-H), 8.23～8.17 (m, 1H, Pyridine-H), 7.68～7.64 (m, 1H, Pyridine-H), 5.88 (dd, J=2.90, 11.50 Hz, 1H, COCH), 4.03～3.97 (m, 1H, NCH_2), 3.52～3.41 (m, 1H, NCH_2), 3.34～3.30 (m, 2H, NCH_2), 2.33～2.26 (m, 1H, $CH_2CH(CH_3)_2$), 2.00～1.79 (m, 5H, $CH_2CH(CH_3)_2$ and NCH_2CH_2), 1.41～1.37 (m, 1H, $CH(CH_3)_2$), 0.99(d, J=6.52, 3H, $CH(CH_3)_2$), 0.90 (d, J=6.60 Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.8, 149.6, 146.8, 141.0, 135.9, 125.8, 124.2, 119.1, 115.0, 60.0, 46.8, 46.5, 39.7, 26.1, 24.7, 24.1, 23.2, 21.3; HRMS (ESI) calcd for $C_{18}H_{25}N_4O$ $[M-Br]^+$ 313.2023, found 313.2025.

(*S*)-1-(1-diethylamino-1-oxo-3-phenylpropan-2-yl)-3-(pyridin-2-yl) imidazolium bromide (**4c**): Brown viscous oil (1.52 g, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.43 (s, 1H, Imidazole-H), 8.63 (dd, J=5.0, 1.8 Hz, 1H, Pyridine-H), 8.56 (t, J=1.9 Hz, 1H, Imidazole-H), 8.30 (t, J=1.9 Hz, 1H, Imidazole-H), 8.22～8.19 (m, 1H, Pyridine-H), 8.14 (d, J=8.1 Hz, 1H, Pyridine-H), 7.64 (ddd, J=7.5, 4.9, 1.0 Hz, 1H, Pyridine-H), 7.40～7.31 (m, 2H, Ph-H), 7.32～7.23 (m, 3H, Ph-H), 6.23 (t, J=7.8 Hz, 1H, COCH), 3.51 (d, J=7.7 Hz, 2H, $PhCH_2$), 3.45～3.31 (m, 3H, NCH_2), 3.23～3.14 (m, 1H, NCH_2), 1.02 (t, J=7.32 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.98 (t, J=7.32 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.1, 149.7, 146.6, 141.1, 135.7, 135.2, 129.8, 129.0, 127.8, 125.8, 123.9, 119.2, 114.9, 59.7, 42.3, 40.9, 39.0, 14.8, 13.0; HRMS (ESI) calcd for $C_{21}H_{25}N_4O$ $[M-Br]^+$349.2023, found 349.2021.

(*S*)-1-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-3-(pyridin-2-yl) imidazolium bromide (**4d**): Brown viscous oil (1.41 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.57 (s, 1H, Imidazole-H), 8.52 (dd, J=4.9, 1.8 Hz, 1H, Pyridine-H), 8.32 (t, J=1.9 Hz, 1H, Imidazole-H), 8.27～8.24 (m, 2H, Pyridine-H and Imidazole-H), 8.01 (td, J=7.8, 1.8 Hz, 1H, Pyridine-H), 7.48～7.43 (m, 3H, Pyridine-H and Ph-H), 7.32～7.23 (m, 3H, Ph-H), 6.64 (t, J=7.84 Hz, 1H, COCH), 4.20～4.14 (m, 1H, NCH_2), 3.54～3.35 (m, 4H, NCH_2 and $PhCH_2$), 2.92～2.86 (m, 1H, $PhCH_2$), 1.88～1.75 (m, 2H, NCH_2CH_2), 1.70～1.60 (m, 2H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 149.1, 145.8, 140.5, 135.1, 133.3, 129.6, 128.8, 127.9, 125.1, 122.7, 117.9, 114.4, 60.6, 47.5, 46.4, 40.2, 25.8, 23.9; HRMS (ESI) calcd for $C_{21}H_{23}N_4O$ $[M-Br]^+$ 347.1866, found 347.1865.

4.6 Synthesis of amides pyrimidine di-functionalized imidazolium chlorides (**4e**～**4f**)

A mixture of imidazole amides **3c**～**3d** (5 mmol), 2-chloropyrimidine (0.69 g, 6 mmol,) and toluene (15 mL) was heated at 110 ℃ overnight. It was then cooled to room temperature and the deep brown precipitate formed was collected and purified by flash chromatography [silica, $V(CH_2Cl_2)$∶V(EtOH)=15∶1～8∶1] to produce the pure products **4e**～**4f**.

(*S*)-1-(1-diethylamino-1-oxo-3-phenylpropan-2-yl)-3-

(pyrimidin-2-yl) imidazolium chloride (**4e**): Brown viscous oil (1.25 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.50 (s, 1H, Imidazole-H), 9.06 (d, J=4.48 Hz, 2H, Pyrimidine-H), 8.44 (s, 1H, Imidazole-H), 8.33 (s, 1H, Imidazole-H), 7.79 (t, J=4.32 Hz, Pyrimidine-H), 7.35～7.21 (m, 5H, Ph-H), 6.45 (t, J=7.44 Hz, 1H, COCH), 3.50～3.48 (m, 3H, Ph-CH_2 and NCH_2), 3.40～3.36 (m, 2H, NCH_2), 3.23～3.15 (m, 1H, NCH_2), 1.09～0.96 (m, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.1, 160.5, 152.5, 136.7, 135.2, 127.8, 124.1, 123.0, 119.0, 59.5, 42.3, 40.8, 39.0, 14.8, 13.0; HRMS (ESI) calcd for $C_{20}H_{24}N_5O$ $[M-Cl]^+$ 350.1975, found 350.1977.

(*S*)-1-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-3-(pyrimidin-2-yl) imidazolium chloride (**4f**): Brown viscous oil (1.13 g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.50 (s, 1H, Imidazole-H), 9.06 (d, J=4.76 Hz, 2H, Pyrimidine-H), 8.44 (s, 1H, Imidazole-H), 8.37 (s, 1H, Imidazole-H), 7.78 (t, J=4.72 Hz, Pyrimidine-H), 7.34～7.20 (m, 5H, Ph-H), 6.30 (t, J=8.24 Hz, 1H, COCH), 3.98～3.92 (m, 1H, NCH_2), 3.54～3.52 (m, 2H, $PhCH_2$), 3.33～3.30 (m, 2H, NCH_2), 3.21～3.17 (m, 1H, NCH_2), 1.84～1.70 (m, 4H, NCH_2CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.0, 160.6, 152.5, 136.7, 135.5, 129.7, 129.0, 127.7, 124.5, 123.0, 118.8, 61.9, 46.3, 37.7, 25.9, 24.1; HRMS (ESI) calcd for $C_{20}H_{22}N_5O$ $[M-Cl]^+$ 348.1819, found 348.1818.

4.7 Synthesis of chelating NHC palladium complexes (**5a**～**5f**)

A suspension mixture of imidazolium salt (**4a**～**4f**, 1.0 mmol) and $Pd(OAc)_2$ (0.22 g, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 12 h. The solvent was evaporated and purification of the residue by column chromatography [silica, gradient elution, $V(CH_2Cl_2)$∶V(acetone)=15∶1～4∶1] produced the pure NHC palladium complexes **5a**～**5f**.

5a: Yellow solids (0.18 g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (dd, J=5.9, 1.6 Hz, 1H, Pyridine-H), 8.23 (m, 1H, Pyridine-H), 7.95 (d, J=2.4 Hz, 1H, Imidazole-H), 7.89 (d, J=8.1 Hz, 1H, Pyridine-H), 7.60 (d, J=2.3 Hz, 1H, Imidazole-H), 7.49～7.36 (m, 2H, Pyridine-H and COCH), 3.76～3.67 (m, 1H, NCH_2), 3.61～3.52 (m, 1H, NCH_2), 3.47～3.33 (m, 2H, NCH_2), 1.89 (t, J=7.2 Hz, 2H, $(CH_3)_2CHCH_2$), 1.62～1.52 (m, 1H, $(CH_3)_2CH$), 1.30 (t, J=7.0 Hz, 3H, $CH_2C\mathbf{H}_3$), 1.14 (t, J=7.1 Hz, 3H, $CH_2C\mathbf{H}_3$), 1.04 (d, J=6.5 Hz, 3H, $(CH_3)_2CH$), 0.95 (d, J=6.6 Hz, 3H, $(CH_3)_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 157.1, 151.8, 151.0, 142.8, 123.3, 123.0, 115.8, 112.1, 58.6, 42.5, 42.3, 40.4, 25.2, 23.2, 22.6, 14.8, 12.7. Anal. calcd for $C_{18}H_{26}Br_2N_4OPd+0.25\ C_6H_{14}$ (602.21): C 38.89, H 4.94, N 9.30; found C 38.76, H 4.71, N 9.58.

5b: Yellow solids (0.19 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.63(dd, J=1.02, 5.78 Hz, 1H, Pyridine-H), 8.23～8.19 (m, 1H, Pyridine-H), 7.83 (d, J=2.28 Hz, 1H, Imidazole-H), 7.75 (d, J=8.08 Hz, 1H, Pyridine-H), 7.57 (d, J=2.32 Hz, 1H, Imidazole-H), 7.43～7.39 (m,1H, Pyridine-H), 7.31～7.27 (m, 1H, COCH), 4.26～4.21 (m, 1H, NCH_2), 3.54～3.44 (m, 3H, NCH_2), 2.05～1.80 (m, 6H, $(CH_3)_2CHCH_2$ and NCH_2CH_2), 1.55～1.43 (m, 1H, $(CH_3)_2CH$), 1.07 (d, J=6.52 Hz, 3H, CH_3), 0.94 (d, J=6.64 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.7, 157.5, 152.0, 150.9, 142.8, 123.4, 123.0, 115.4, 111.8, 60.2, 47.3, 46.7, 41.4, 26.2, 25.1, 23.9, 23.3, 22.3. Anal. calcd for $C_{18}H_{24}Br_2N_4OPd+0.25\ C_6H_{14}$ (600.18): C 39.02, H 4.62, N 9.33; found C 39.28, H 4.41, N 9.47.

5c: Yellow solids (0.21 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.74 (dd, J=5.9, 1.6 Hz, 1H, Pyridine-H), 8.18 (td, J=7.8, 1.7 Hz, 1H, Pyridine-H), 8.06 (d, J=2.4 Hz, 1H, Imidazole-H), 7.76～7.73 (m, 2H, Pyridine-H and Imidazole-H), 7.68～7.64 (m, 1H, COCH), 7.46～7.44 (m, 2H, Ph-H), 7.42～7.38 (m, 1H, Pyridine-H), 7.30～7.21 (m, 3H, Ph-H), 3.44～3.14 (m, 6H, $PhCH_2$ and NCH_2), 0.96 (t, J=7.04 Hz, CH_3), 0.95 (t, J=7.04 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 157.0, 152.1, 151.2, 142.5, 134.5, 130.2, 128.5, 127.4, 123.2, 122.8, 115.8, 112.0, 42.7, 41.1, 40.9, 15.0, 12.6. Anal. calcd for $C_{21}H_{24}Br_2N_4OPd$ (614.67): C 41.03, H 3.94, N 9.11; found C 41.42, H 4.17, N 9.01.

5d: Yellow solids (0.20 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.67 (dd, J=5.9, 1.7 Hz, 1H, Pyridine-H), 8.17 (m, 1H, Pyridine-H), 8.05 (d, J=2.5 Hz, 1H, Imidazole-H), 7.73～7.69 (m, 2H, Pyridine-H and Imidazole-H), 7.66～7.62 (m, 1H, COCH), 7.42～7.40 (m, 2H, Ph-H), 7.37～7.34 (m, 1H, Pyridine-H), 7.30～7.23 (m, 3H, Ph-H), 3.87～3.82 (m, 1H, NCH_2), 3.40～3.23 (m, 4H, NCH_2 and $PhCH_2$), 2.97～2.94 (m, 1H, NCH_2), 1.78～1.74 (m, 2H, NCH_2CH_2), 1.66～1.58 (m, 2H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 157.7, 152.3, 151.1, 142.3, 134.3, 129.8, 128.6, 127.5, 123.2, 123.1, 115.1, 111.5, 60.4, 47.6, 46.3, 40.5, 26.0, 23.8. Anal. calcd for $C_{21}H_{22}Br_2N_4OPd$ (612.66): C 41.17, H 3.62, N 9.15; found C 41.53, H 3.67, N 9.52.

5e: Yellow solids (0.23 g, 43 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (dd, J=5.7, 2.2 Hz, 1H, Pyrimidine-H), 8.89 (dd, J=4.9, 2.2 Hz, 1H, Pyrimidine-H), 8.06 (d, J=2.3 Hz, 1H, Imidazole-H), 7.77 (d, J=2.4 Hz, 1H, Imidazole-H), 7.59～7.52 (m, 2H, Pyrimidine-H and COCH), 7.45～7.43 (m, 2H, Ph-H), 7.32～7.22 (m, 3H, Ph-H), 3.48～3.18 (m, 6H, $PhCH_2$ and NCH_2), 1.00 (t, J=7.16 Hz, 3H, CH_3), 0.98 (t, J=7.16 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 160.6, 159.5, 156.6, 154.2, 134.4, 130.1, 128.5, 127.4, 122.9, 120.0, 116.2, 57.7, 42.7, 41.2, 41.1, 14.8, 12.6. Anal. calcd for $C_{20}H_{23}Cl_2N_5OPd$ (526.76): C 45.60, H 4.40, N 13.30; found C 45.98, H 4.56, N 13.15.

5f: Yellow solids (0.22 g, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.77 (dd, J=5.7, 2.2 Hz, 1H, Pyrimidine-H), 8.88 (dd, J=4.8, 2.2 Hz, 1H, Pyrimidine-H), 8.04 (d, J=2.4 Hz, 1H, Imidazole-H), 7.75 (d, J=2.4 Hz, 1H, Imidazole-H), 7.57～7.48 (m, 2H, Pyrimidine-H and COCH), 7.39～7.37 (m, 2H, Ph-H), 7.30～7.20 (m, 3H, Ph-H), 3.90～3.85 (m, 1H, NCH_2), 3.42～3.22 (m, 4H, $PhCH_2$ and NCH_2), 3.00～2.94 (m, 1H, NCH_2), 1.81～1.62 (m, 4H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5,

160.7, 159.4, 156.5, 154.0, 134.2, 129.7, 128.6, 127.5, 123.2, 120.0, 116.0, 59.6, 47.3, 46.3, 40.5, 25.9, 23.9. Anal. calcd for $C_{20}H_{21}Cl_2N_5OPd$ (524.74): C 45.78, H 4.03, N 13.35; found C 46.10, H 4.09, N 13.25.

4.8 General procedure for the C5-arylation of imidazole

A Schlenk tube containing aryl bromides (1.0 mmol), imidazoles (1.7 mmol), base (2.0 mmol), NHC-Pd complex as indicated in the text, and solvent (5 mL) was stirred at set temperature for 18 h under Ar. After cooling, the volatiles were evaporated. Purification of the residue by flash chromatography on silica gel [V(CH_3COOEt) ∶ V(EtOH)＝10 ∶ 1) afforded the pure products, which were characterized by ^{1}H NMR and ^{13}C NMR.

4.9 X-Ray diffraction studies

Crystals of **5c** (CCDC 2104040) were obtained by recrystallization from CH_2Cl_2/hexane (V ∶ V＝1 ∶ 1) at ambient temperature. The data were collected on a Xcalibur, Eos, Gemini diffractometer with graphite monochromated Cu Kα radiation (λ＝0.154184 nm). Using Olex2,[25] the structure was solved with the Superflip[26] structure solution program using Charge Flipping and refined with the ShelXL[27] refinement package using Least Squares minimisation.

Supporting Information The characterization data of C-5 arylated imidazoles, NMR spectra of compounds **1**～**5** and C-5 arylated imidazoles. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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