New Synthons for the Preparation of Arylimidazolines and Tetrahydropyrimidine Analogues

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Abstract: An adaptation of the Fujioka method for the efficient synthesis of arylimidazolines from aryl aldehydes was used for the synthesis of aryltetrahydropyrimidines. *tert*-Butoxycarbonyl-protected bromo- or iodophenyl-substituted imidazolines and tetrahydropyrimidines both undergo Suzuki coupling reactions with arylboronic acids in good yields.

Key words: imidazolines, tetrahydropyrimidines, protecting groups, Suzuki coupling, amidine heterocycles

Imidazoline receptors are a heterogeneous group of proteins, divided into I_1, I_2, and I_3 sites on the basis of physiological functions and pharmacological tools available.[1] The I_1 site participates in blood pressure regulation.[2–7] While general agreement is lacking, it is thought that the I_2 receptors are associated with the inhibition of monoamine oxidase enzymes in the central nervous system.[3a,7–10,11] Recently it has been reported that I_1 and I_2 receptors play a role in cell proliferation, inflammation, regulation of body fat, and some psychiatric disorders.[3] The I_3 receptor regulates insulin secretion from pancreatic β-cells.[3] Imidazoline receptors in addition to recognizing bioactive endogenous ligands also recognize a variety of exogenous compounds containing the imidazoline (dihydroimidazole) moiety.[4,12–14] Consequently, aryl-substituted imidazolines (Im) and related analogues are receiving extensive attention as potential therapeutic agents in blood pressure control[3a] and the treatment of depressive illness,[11b] cancer, pain-killer and opioid addictions,[11c] stress, cell adhesion, epilepsy,[2] diabetes, cardiovascular diseases,[4,7,15,16] and food intake.[3,17]

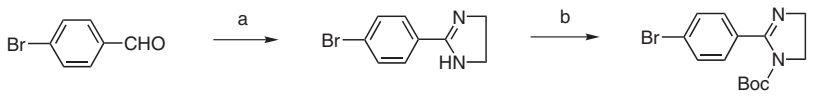
Tetrahydropyrimidines (THP) are a closely related class of important cyclic amidine analogues, which are reported to have promising activity against inflammatory diseases,[18,19] pain,[19,20] type II diabetes,[20] cancer,[21,22] and *Pneumocystis carinni*.[22,23] The THP-based drug Pyrantel is a commonly used anthelmintic in worm control for animals.[24]

Both bis-Im and related bis-THP compounds have shown promising antimicrobial[25–27] and antifungal[28] properties and activity against AIDS-related opportunistic pathogens.[29] In view of the important applications of both these cyclic amidine compounds, a convenient synthesis of these systems is highly desirable.

These cyclic amidines are often synthesized by classic methods starting with the appropriate nitrile by the Pinner process, which requires rigorous exclusion of water and frequently requires long reaction times, sometimes as much as a week.[30] Another similar process involves the reaction of thioacetamide with the appropriate nitrile to form an intermediate thioamide, which is further reacted with the desired amine to give the Im or THP analogues.[31] An alternative route to thioamides requires the use of the poisonous gas hydrogen sulphide.[32,33] All of these methods have significant drawbacks. More recently, more advantageous methods that start with aldehydes and involve oxidation of in situ generated 2-arylimidazolidinylidene have been reported.[34–36]

To provide synthetic flexibility for the introduction of aryl-substituted Im and THP groups into an array of structures, we have explored the use of nitrogen-protected haloaryl-substituted Im and THP analogues, which can be used in palladium(0) coupling reactions such as the Suzuki approach. Consequently, we have also examined some common protecting groups for use with this approach. This report describes approaches for the synthesis of Im and THP synthons, which are successfully used in Suzuki coupling reactions.

To prepare an Im synthon that can be used in palladium(0) coupling sequences, we have used the convenient and efficient procedure reported by Fujioka[35] for the formation of the imidazoline ring from the corresponding aldehyde



1 (73%)

Scheme 1 *Reagents and conditions*: (a) amine, NBS, CH_2Cl_2, 0 °C to r.t.;[33] (b) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to r.t.

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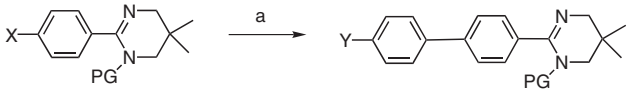
(Scheme 1). The reaction proceeds at room temperature and leads to near quantitative isolation of the desired product without the need for chromatography. The *tert*-butoxycarbonyl-protected analogue **1** was obtained in good yield by a standard protocol.

We found that the original Fujioka[35] procedure that worked quite well for the synthesis of imidazolines was not very efficient for the preparation of the analogous tetrahydropyrimidines. We modified the reaction conditions by allowing the aldehyde to react with the diamine for 24 hours at room temperature, followed by exposure to *N*-bromosuccinimide for 24 hours at room temperature (Scheme 2). This modified procedure for the synthesis of THP analogues from the corresponding benzaldehydes (Scheme 2, Y = CHO) gave the THP products **2**–**4** in good yields.

We also explored the synthesis of THP analogues starting with benzonitriles, using the method reported by Houlihan[37] et al. This methodology requires the reaction of the benzonitrile, an amine, and *p*-toluenesulfonic acid, followed by aqueous workup and basification (Scheme 2, Y = CN). We modified this procedure slightly by replacing the solvent ethylene glycol with diethylene glycol. We studied the effect of the reaction temperature, and concluded after a series of experiments that a temperature of 160 °C allows the isolation of the desired analogue **2** in optimal yields (ca. 60%). However, attempts to synthesize **4** from the corresponding benzonitrile failed. This procedure is less effective than the methodology described above starting from aldehydes.

We evaluated the utility of various common protecting groups (PGs), e.g., acetyl, pivaloyl, and *tert*-butoxycarbonyl (Scheme 2), for use in the Suzuki coupling process. First, we studied THP moieties **5**–**9** containing different protecting groups for their effectiveness as potential synthons (Scheme 3). The acetyl-protected THP **15** turned out to be very sensitive to acidic media; deacetylation was observed on silica gel, and only a small amount of the desired product **15** could be isolated (Scheme 3). Pivaloyl-protected THPs **10**–**13**, on the other hand, were quite stable. Even after stirring for 24 hours in ethanol at reflux in the presence of strong acid (HCl or H_2SO_4), deprotection was incomplete. Attempts to remove the pivaloyl group under strongly basic conditions (NaOH) at 70 °C after stirring for 24 hours were also unsuccessful. Because of stability on silica gel, the *tert*-butoxycarbonyl-protected THP analogues **8** and **9** turned out to be the most effective substrates for use in the Suzuki coupling reaction. After the coupling reaction was completed, the *tert*-butoxycarbonyl group was readily cleaved with hydrogen chloride. After cleavage of the protecting group, the yields of these coupling products ranged from 65% to 72%. The yields of the coupling reactions of **8** were improved by 15% when the corresponding *p*-iodophenyl analogue **9** of *tert*-butoxycarbonyl-protected THP was used. The yields of the coupling reactions of **6** with different boronic acids were also improved by about 15% when the corresponding *p*-iodophenyl-substituted pivaloyl-protected THP analogue **7** was used.

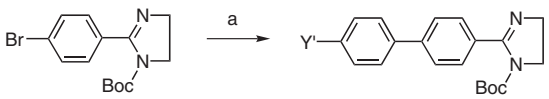


5–9

10 (Y = F, PG = Pv)
11 (Y = Me, PG = Pv)
12 (Y = Ph, PG = Pv)
13 (Y = CN, PG = Pv)
14 (Y = CN, PG = Boc)
15 (Y = CN, PG = Ac)
(18–72%)

Scheme 3 *Reagents and conditions*: (a) $Pd(PPh_3)_4$, 2 M K_2CO_3, arylboronic acid, DME, reflux.

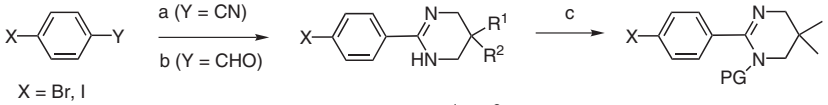
To further illustrate this approach, we explored the reactivity of the *tert*-butoxycarbonyl-protected Im moiety **1** as synthon in Suzuki coupling reactions with various *para*-substituted phenylboronic acids (Scheme 4). The yields, obtained after deprotection, of the biphenylylimidazolines **16**–**20** ranged from 58 to 71%.



16 (Y' = F)
17 (Y' = OMe)
18 (Y' = Ph)
19 (Y' = CN)
20 (Y' = CHO)
(58–71%)

Scheme 4 *Reagents and conditions*: (a) $Pd(PPh_3)_4$, 2 M K_2CO_3, arylboronic acid, DME, reflux.

In conclusion, we report modified Fujioka conditions that give high yields of THP analogues starting from aryl aldehydes. We show that *tert*-butoxycarbonyl-protected haloaryl-substituted imidazolines and tetrahydropyri-



X = Br, I
Y = CN, CHO

2 (X = Br, $R^1 = R^2$ = Me)
3 (X = I, $R^1 = R^2$ = Me)
4 (X = Br, $R^1 = R^2$ = H)
(52–90%)

5 (X = I, PG = Ac)
6 (X = Br, PG = Pv)
7 (X = I, PG = Pv)
8 (X = Br, PG = Boc)
9 (X = I, PG = Boc)
(78–87%)

Scheme 2 *Reagents and conditions*: (a) Y = CN: amine, TsOH, diethylene glycol, 100 °C; (b) Y = CHO: amine, NBS, CH_2Cl_2, 0 °C to r.t.; (c) acid anhydride, Et_3N, CH_2Cl_2, 0 °C to r.t.

midines are quite functional synthons, which undergo Suzuki coupling reactions with arylboronic acids in good yields. Iodoaryl synthons underwent more efficient coupling than the bromoaryl ones. Both can be used for the synthesis of imidazolines and tetrahydropyrimidines involving more complex scaffolds.

All commercial reagents were used without purification. THF was distilled from sodium benzophenone ketyl immediately before use. Chromatography was conducted on a chromatotron (Harrison Research) with silica gel coated rotors. Melting points were determined on a Mel-Temp 3.0 melting point apparatus, and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity 300 spectrometer (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR); the indicated solvents were used with TMS as an internal reference. Mass spectra were obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA. Elemental analysis was performed by Atlantic Microlab Inc., Norcross, GA. The data of 2-(4-bromophenyl)-4,5-dihydro-1*H*-imidazole were reported previously;[35] the physical and spectral data obtained here were comparable.

1-Protected 2-(4-Halophenyl)-Substituted Dihydroimidazole 1 and Tetrahydropyrimidines 5–9; General Procedure

A soln of **2**, **3**, or 2-(4-bromophenyl)-4,5-dihydro-1*H*-imidazole[33] (1.0 equiv) in anhyd CH_2Cl_2 was stirred with Et_3N (3.0 equiv) for 30 min. The appropriate acid anhydride (1.2 equiv) was then added dropwise (if solid, it was first dissolved in anhyd CH_2Cl_2 and then added to the mixture) at 0 °C. The resulting mixture was stirred overnight under N_2 at r.t., and then concentrated; the solid was recrystallized from hexanes.

2-(4-Bromophenyl)-1-(*tert*-butoxycarbonyl)-4,5-dihydro-1*H*-imidazole (1)[38]

By the above general procedure, the reaction between 2-(4-bromophenyl)-4,5-dihydro-1*H*-imidazole[35] (7.0 g, 22.9 mmol), Et_3N (9.6 mL, 68.6 mmol), and Boc_2O (6.0 g, 27.5 mmol) yielded white crystals.

Yield: 5.4 g (73%); mp 123.7–124.7 °C (hexanes).

^{1}H NMR ($CDCl_3$): δ = 7.50 (d, *J* = 7.8 Hz, 2 H), 7.39 (d, *J* = 7.8 Hz, 2 H), 3.95 (t, *J* = 4.9 Hz, 4 H), 1.29 (s, 9 H).

MS (EI, 70 eV): *m*/*z* (%) = 325.2 (100) [M$^+$].

1-Acetyl-2-(4-iodophenyl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (5)

By the above general procedure, the reaction between **3** (0.5 g, 1.6 mmol), Et_3N (0.7 mL, 4.8 mmol), and Ac_2O (180 μL, 1.9 mmol) yielded oily white crystals.

Yield: 0.5 g (86%); mp 105–106 °C (hexanes).

^{1}H NMR ($CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 3.54 (s, 2 H), 3.42 (s, 2 H), 1.82 (s, 3 H), 1.00 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 171.1, 153.8, 137.9, 137.6, 128.8, 96.5, 60.0, 53.5, 32.6, 25.6, 25.5.

ESI-MS: *m*/*z* (%) = 357.1 (100) [M + 1].

Anal. Calcd for $C_{14}H_{17}N_2O$: C, 47.21; H, 4.81; N, 7.86. Found: C, 47.27; H, 4.70; N, 7.74.

2-(4-Bromophenyl)-5,5-dimethyl-1-pivaloyl-1,4,5,6-tetrahydropyrimidine (6)

By the above general procedure, the reaction between **2** (5.0 g, 18.7 mmol), Et_3N (7.9 mL, 56.2 mmol), and Pv_2O (4.6 mL, 22.4 mmol) yielded a white solid.

Yield: 5.6 g (85%); mp 132.7–133.7 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.45 (d, *J* = 8.7 Hz, 2 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 3.44 (s, 4 H), 1.30 (s, 9 H), 1.01 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 182.2, 154.5, 137.4, 131.4, 128.1, 123.3, 59.6, 54.9, 40.9, 31.4, 28.9, 25.2.

MS (EI, 70 eV): *m*/*z* (%) = 351 (45) [M$^+$].

Anal. Calcd for $C_{17}H_{23}BrN_2O$: C, 58.12; H, 6.60; N, 7.97. Found: C, 57.94; H, 6.75; N, 7.90.

2-(4-Iodophenyl)-5,5-dimethyl-1-pivaloyl-1,4,5,6-tetrahydropyrimidine (7)

By the above general procedure, the reaction between **3** (0.5 g, 1.6 mmol), Et_3N (0.7 mL, 4.8 mmol) and Pv_2O (0.4 mL, 1.9 mmol) yielded white crystals.

Yield: 0.6 g (87%); mp 140–141 °C (hexanes).

^{1}H NMR ($CDCl_3$): δ = 7.65 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 3.44 (s, 4 H), 1.29 (s, 9 H), 1.00 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 182.1, 154.4, 137.9, 137.2, 128.1, 95.2, 59.5, 54.7, 40.8, 31.3, 28.8, 25.1.

ESI-MS: *m*/*z* (%) = 399 (100) [M + 1].

Anal. Calcd for $C_{17}H_{23}IN_2O$: C, 51.27; H, 5.82; N, 7.03. Found: C, 51.27; H, 5.89; N, 7.00.

2-(4-Bromophenyl)-1-(*tert*-butoxycarbonyl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (8)

By the above general procedure, the reaction between **2** (0.5 g, 1.9 mmol), Et_3N (0.8 mL, 5.7 mmol), and Boc_2O (0.5 g, 2.2 mmol) yielded white crystals.

Yield: 0.57 g (81%); mp 107.6–108.6 °C (hexanes).

^{1}H NMR ($CDCl_3$): δ = 7.47 (d, *J* = 8.5 Hz, 2 H), 7.36 (d, *J* = 8.5 Hz, 2 H), 3.44 (s, 2 H), 3.39 (s, 2 H), 1.15 (s, 9 H), 0.99 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 153.4, 152.6, 138.3, 130.9, 128.3, 122.9, 82.0, 59.7, 53.6, 31.0, 27.5, 24.7.

MS (EI, 70 eV): *m*/*z* (%) = 366 [M$^+$] (20), 311, [M$^+$ – $C(CH_3)_3$] (50), 267 [M$^+$ – $OC(CH_3)_3$ – $(CH_3)_2$] (65), 57 (100).

Anal. Calcd for $C_{17}H_{23}BrN_2O_2$: C, 55.59; H, 6.31; N, 7.63. Found: C, 55.61; H, 6.39; N, 7.43.

1-(*tert*-Butoxycarbonyl)-2-(4-iodophenyl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (9)

By the above general procedure, the reaction between **3** (3.0 g, 9.5 mmol), Et_3N (4.0 mL, 28.7 mmol), and Boc_2O (2.5 g, 11.4 mmol) yielded white crystals.

Yield: 3.1 g (78%); mp 92.5–93.5 °C (hexanes).

^{1}H NMR ($CDCl_3$): δ = 7.68 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 3.43 (s, 2 H), 3.39 (s, 2 H), 1.14 (s, 9 H), 0.99 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 153.4, 152.9, 139.0, 137.0, 128.5, 94.6, 82.1, 59.8, 53.8, 31.1, 27.6, 24.8.

ESI-MS: *m*/*z* (%) = 315.02 (100) [M + 1].

Anal. Calcd. for $C_{17}H_{23}IN_2O_2$: C, 49.29; H, 5.60; N, 6.76. Found: C, 49.69; H, 5.70; N, 6.62.

2-(4-Halophenyl)tetrahydropyrimidines 2–4

2-(4-Bromophenyl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (2); Typical Procedures

Compound **2** was synthesized by two independent procedures:

From nitrile: A mixture of 4-bromobenzonitrile (1.0 g, 5.4 mmol), 2,2-dimethylpropane-1,3-diamine (0.8 mL, 6.6 mmol), and $TsOH·H_2O$ (0.5 g, 2.7 mmol) was heated in diethylene glycol (10 mL) at 160–180 °C for 48 h under N_2. The mixture was slightly bas-

ified and the resulting crystals (tosyl salt) were stirred with aq NaOH for 1 d to give the free base.

Yield: 0.7 g (52%).

From aldehyde: A mixture of 4-bromobenzaldehyde (5.0 g, 27.0 mmol) and 2,2-dimethylpropane-1,3-diamine (3.9 mL, 24.4 mmol) in CH_2Cl_2 (50 mL) was stirred for 24 h, and then cooled to 0 °C before NBS (5.3 g, 29.7 mmol) was added. The resulting soln was stirred for 24 h in the dark, under N_2. The resulting solid (HBr salt) was filtered and basified with 10% NaOH to give the free base.

Yield: 6.5 g (90%); mp 200.8–202.8 °C (Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.51 (m, 4 H), 3.12 (s, 4 H), 1.00 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 151.3, 134.9, 130.6, 128.0, 122.6, 53.3, 25.4, 24.5.

MS (EI, 70 eV): *m*/*z* (%) = 267 (100) [M$^+$].

Anal. Calcd for $C_{12}H_{15}BrN_2 \cdot 0.55H_2O$: C, 52.02; H, 5.85; N, 10.11. Found: C, 51.70; H, 5.48; N, 9.92.

2-(4-Iodophenyl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (3)

By the procedure outlined for **2**, the reaction between 4-iodobenzonitrile (0.5 g, 2.7 mmol), 2,2-dimethylpropane-1,3-diamine (0.4 mL, 3.3 mmol), and $TsOH \cdot H_2O$ (0.3 g, 1.3 mmol) yielded an off-white solid.

Yield: 0.5 g (58%); mp 215.6–216.6 °C (Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.68 (d, *J* = 8.5 Hz, 2 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 3.10 (s, 4 H), 0.97 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 152.6, 137.4, 136.4, 127.8, 95.8, 54.4, 26.3, 24.9.

ESI-MS: *m*/*z* (%) = 315 (100) [M + 1].

Anal. Calcd for $C_{12}H_{15}N_2I \cdot 0.2H_2O$: C, 45.36; H, 4.88; N, 8.81. Found: C, 45.30; H, 4.79; N, 8.77.

2-(4-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (4)

By the procedure outlined for **2**, the reaction between 4-bromobenzaldehyde (1.0 g, 5.4 mmol), propane-1,3-diamine (0.5 mL, 6.5 mmol), and NBS (1.1 g, 5.9 mmol) yielded a white solid after basification and drying.

Yield: 1.1 g (89%); mp 155.5–156.5 °C (Et_2O).

^{1}H NMR (DMSO-d_6): δ = 7.68 (m, 2 H), 7.54 (m, 2 H), 3.30 (t, *J* = 5.7 Hz, 4 H), 1.67 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 152.4, 136.5, 131.2, 128.5, 123.1, 42.0, 21.0.

MS (EI, 70 eV): *m*/*z* (%) = 239 (100) [M$^+$].

Anal. Calcd for $C_{10}H_{11}N_2Br$: C, 50.23; H, 4.64; N, 11.71. Found: C, 50.15; H, 4.72; N, 11.25.

2-Biphenyl-4-yl-5,5-dimethyl-1,4,5,6-tetrahydro-1-pivaloylpyrimidines 10–15 and 2-Biphenyl-4-yl-4,5-dihydro-1*H*-imidazoles 16–20; General Procedure

To a soln of **1**, **5**, **6**, or **9** (1.0 equiv) in anhyd DME (10.0 mL) was added $Pd(PPh_3)_4$ (4 mol%), and the resulting mixture was thoroughly purged with N_2. The appropriate 4-substituted phenylboronic acid (1.1 equiv) and 2 M K_2CO_3 (2.2 equiv) were added to the mixture, and the resulting soln was heated at reflux overnight under N_2. The mixture was allowed to cool and was filtered through Celite, the filtrate was concentrated, and the resulting crystals were purified by chromatography (Et_2O–hexanes).

2-(4′-Fluorobiphenyl-4-yl)-5,5-dimethyl-1-pivaloyl-1,4,5,6-tetrahydropyrimidine (10)

By the above general procedure, the reaction between **6** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (15.1 mg, 0.01 mmol), (4-fluorophenyl)boronic acid (0.1 g, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 1:1).

Yield: 130 mg (65%); mp 169–170 °C (Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.53 (m, 6 H), 7.11 (t, *J* = 8.9 Hz, 2 H), 3.48 (s, 4 H), 1.31 (s, 9 H), 1.04 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 182.3, 164.9, 160.9, 155.3, 141.0, 137.2, 136.8, 128.8, 128.7, 127.0, 126.8, 115.7, 115.4, 59.6, 55.1, 41.1, 31.9, 28.9, 25.4.

MS (EI, 70 eV): *m*/*z* (%) = 366 (50) [M$^+$]

Anal. Calcd for $C_{23}H_{27}FN_2O \cdot 0.25\ H_2O$: C, 74.46; H, 7.47; N, 7.55. Found: C, 74.24; H, 7.33; N, 7.40.

5,5-Dimethyl-2-(4′-methylbiphenyl-4-yl)-1-pivaloyl-1,4,5,6-tetrahydropyrimidine (11)

By the above general procedure, the reaction between **6** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (15.1 mg, 0.01 mmol), 4-tolylboronic acid (90 mg, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 1:1).

Yield: 15 mg (72%); mp 186.5–187.5 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.46 (d, *J* = 1.8 Hz, 4 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 3.40 (d, *J* = 2.1 Hz, 4 H), 2.32 (s, 3 H), 1.22 (s, 9 H), 0.97 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 182.4, 155.6, 142.1, 137.7, 137.2, 136.8, 129.4, 127.0, 127.0, 126.8, 59.6, 55.2, 41.2, 32.2, 29.0, 25.5, 21.1.

ESI-MS: *m*/*z* (%) = 369.09 (100) [M + 1].

Anal. Calcd for $C_{24}H_{30}N_2O \cdot 0.5H_2O$: C, 77.59; H, 8.41; N, 7.54. Found: C, 77.33; H, 8.27; N, 7.14.

5,5-Dimethyl-1-pivaloyl-2-(1,1′:4′,1″-terphenyl-4-yl)-1,4,5,6-tetrahydropyrimidine (12)

By the above general procedure, the reaction between **6** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (15.1 mg, 0.01 mmol), biphenyl-4-ylboronic acid (130 mg, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 1:1).

Yield: 170 g (70%); mp 203.5–204.5 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.67–7.60 (br m, 8 H), 7.55 (m, 2 H), 7.47 (m, 2 H), 7.36 (m, 1 H), 3.48 (d, *J* = 2.7 Hz, 4 H), 1.31 (s, 9 H), 1.05 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 182.3, 155.4, 141.5, 140.7, 140.3, 139.5, 137.3, 128.8, 127.5, 127.5, 127.3, 127.0, 126.9, 59.6, 55.1, 41.1, 32.1, 29.0, 25.4.

ESI-MS: *m*/*z* (%) = 425.07 (100) [M + 1].

Anal. Calcd for $C_{29}H_{32}N_2O \cdot 1.3H_2O$: C, 77.47; H, 7.78; N, 6.25. Found: C, 77.52; H, 7.38; N, 6.23.

2-(4′-Cyanobiphenyl-4-yl)-5,5-dimethyl-1-pivaloyl-1,4,5,6-tetrahydropyrimidine (13)

By the above general procedure, the reaction between **6** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (15.1 mg, 0.01 mmol), (4-cyanophenyl)boronic acid (0.1 g, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 1:1).

Yield: 140 mg (66%); mp 198.7–199.7 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.69 (q, *J* = 12.6, 4.5 Hz, 4 H), 7.56 (s, 4 H), 3.48 (d, *J* = 2.4 Hz, 4 H), 1.33 (s, 9 H), 1.04 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 182.2, 154.6, 145.1, 139.7, 138.7, 132.5, 127.7, 127.8, 127.1, 118.9, 111.0, 59.6, 54.9, 40.9, 31.4, 28.9, 25.2.

ESI-MS: *m*/*z* (%) = 374 (100) [M + 1].

Anal. Calcd for $C_{24}H_{27}N_3O{\cdot}1.25H_2O$: C, 72.79; H, 7.51; N, 10.61. Found: C, 72.85; H, 7.14; N, 10.72.

1-(*tert*-Butoxycarbonyl)-2-(4′-cyanobiphenyl-4-yl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (14)

By the above general procedure, the reaction between **9** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (29.4 mg, 0.02 mmol), (4-cyanophenyl)boronic acid (0.1 g, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 2:1); yield: 0.2 g (85%). When **8** was used (0.2 g, 0.5 mmol) instead of **9**, **14** was isolated as white crystals; yield: 147 mg (70%).

Mp 181–182 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.75 (m, 4 H), 7.63 (s, 4 H), 3.49 (d, *J* = 10.8 Hz, 4 H), 1.18 (s, 9 H), 1.06 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 153.4, 152.9, 145.0, 139.6, 139.5, 132.5, 127.6, 127.4, 126.6, 118.8, 110.9, 81.8, 59.7, 53.7, 31.0, 27.4, 24.7.

ESI-MS: *m*/*z* (%) = 390.4 (100) [M + 1].

Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 73.76; H, 6.99; N, 10.66.

1-Acetyl-2-(4′-cyanobiphenyl-4-yl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (15)

By the above general procedure, the reaction between **5** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (29.4 mg, 0.02 mmol), (4-cyanophenyl)boronic acid (0.1 g, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded semi-crystals after chromatographic purification (Et_2O–hexanes, 2:1). (Deacetylation was detected by TLC.)

Yield: 30 mg (18%)

^{1}H NMR (DMSO-d_6): δ = 7.93 (m, 4 H), 7.77 (d, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.8 Hz, 2 H), 3.48 (s, 2 H), 3.38 (s, 2 H), 1.95 (s, 3 H), 0.95 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 170.8, 152.9, 143.9, 138.8, 138.2, 132.9, 127.6, 127.6, 126.8, 118.8, 110.7, 59.0, 53.3, 31.9, 24.8.

ESI-MS: *m*/*z* (%) = 332.3 (100) [M + 1].

1-(*tert*-Butoxycarbonyl)-2-(4′-fluorobiphenyl-4-yl)-4,5-dihydro-1*H*-imidazole (16)

By the above general procedure, the reaction between **1** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (28.2 mg, 0.02 mmol), (4-fluorophenyl)boronic acid (120 mg, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded white crystals.

Yield: 120 mg (58%); mp 134–135 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.61–7.53 (br m, 6 H), 7.13 (t, *J* = 8.7 Hz, 2 H), 3.99 (t, *J* = 3.9 Hz, 4 H), 1.30 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 159.7, 151.1, 141.5, 136.7, 131.3, 128.8, 128.7, 126.1, 115.8, 115.5, 81.8, 53.3, 47.8, 27.9.

ESI-MS: *m*/*z* (%) = 341.3 (100) [M + 1].

Anal. Calcd for $C_{21}H_{23}FN_2O_2$: C, 70.57; H, 6.22; N, 8.23. Found: C, 70.62; H, 6.15; N, 8.20.

1-(*tert*-Butoxycarbonyl)-2-(4′-methoxybiphenyl-4-yl)-4,5-dihydro-1*H*-imidazole (17)

By the above general procedure, the reaction between **1** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (28.2 mg, 0.02 mmol), (4-methoxyphenyl)boronic acid (110 mg, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 1:1).

Yield: 140 mg (65%); mp 135–136 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.56–7.53 (m, 6 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 3.98 (t, *J* = 4.8 Hz, 4 H), 3.85 (s, 3 H), 1.29 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 159.8, 159.4, 151.2, 142.1, 133.1, 130.7, 128.7, 128.1, 125.8, 114.2, 81.7, 55.3, 53.3, 47.8, 27.9.

ESI-MS: *m*/*z* (%) = 353.0 (70) [M + 1].

Anal. Calcd for $C_{21}H_{24}N_2O_3{\cdot}0.2H_2O$: C, 70.84; H, 6.91; N, 7.87. Found: C, 70.75; H, 6.89; N, 7.86.

1-(*tert*-Butoxycarbonyl)-2-(1,1′:4′,1″-terphenyl-4-yl)-4,5-dihydro-1*H*-imidazole (18)

By the above general procedure, the reaction between **1** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (28.2 mg, 0.02mmol), biphenyl-4-ylboronic acid (140 mg, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.5 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 2:1).

Yield: 150 mg (71%); mp 226.5–227.5 °C (hexanes–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 7.72–7.60 (br m, 10 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 4.00 (t, *J* = 4.2 Hz, 4 H), 1.30 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 159.8, 151.2, 141.9, 140.6, 140.5, 139.4, 131.4, 128.8, 128.8, 127.5, 127.5, 127.4, 127.0, 126.1, 81.8, 53.4, 47.8, 28.9.

ESI-MS: *m*/*z* (%) = 348.1 (100) [M + 1].

Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.40; H, 6.60; N, 6.91.

1-(*tert*-Butoxycarbonyl)-2-(4′-cyanobiphenyl-4-yl)-4,5-dihydro-1*H*-imidazole (19)

By the above general procedure, the reaction between **1** (1.0 g, 3.3 mmol), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol), (4-cyanophenyl)boronic acid (1.1 g, 3.6 mmol), and 2 M K_2CO_3 (3.6 mL, 7.8 mmol) yielded white crystals after chromatographic purification (Et_2O–hexanes, 3:1).

Yield: 830 mg (71%); mp 187–188 °C (hexanes–Et_2O).

^{1}H NMR (DMSO-d_6): δ = 7.96 (m, 4 H), 7.82 (d, *J* = 7.8 Hz, 2 H), 7.62 (d, *J* = 8.1 Hz, 2 H), 3.91 (t, *J* = 4.8 Hz, 4 H), 1.24 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 159.4, 151.0, 144.9, 140.3, 132.7, 132.6, 129.0, 127.7, 126.4, 118.8, 111.2, 81.9, 53.4, 47.7, 27.9.

ESI-MS: *m*/*z* (%) = 348.1 (100) [M + 1].

Anal. Calcd. for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.35; H, 6.09; N, 11.98.

1-(*tert*-Butoxycarbonyl)-2-(4′-formylbiphenyl-4-yl)-4,5-dihydro-1*H*-imidazole (20)

By the above general procedure, the reaction between **1** (0.2 g, 0.6 mmol), $Pd(PPh_3)_4$ (28.2 mg, 0.02 mmol), (4-formylphenyl)boronic acid (0.1 g, 0.7 mmol), and 2 M K_2CO_3 (0.7 mL, 1.4 mmol) yielded pale yellow crystals after chromatographic purification (Et_2O–hexanes, 1:1).

Yield: 130 g (62%); mp 172–174 °C (hexanes–Et_2O).

^{1}H NMR (DMSO-d_6): δ = 10.06 (s, 1 H), 8.00 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, 8.1 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 3.88 (t, *J* = 4.8, 4 H), 1.23 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 192.5, 158.0, 150.4, 145.0, 139.5, 135.2, 132.7, 130.0, 128.8, 127.2, 126.1, 80.8, 53.0, 47.3, 27.3.

ESI-MS: *m*/*z* (%) = 351.2 (100) [M + 1].

Anal. Calcd for $C_{21}H_{22}N_2O_3{\cdot}0.2H_2O$: C, 71.25; H, 6.38; N, 7.91. Found: C, 71.31; H, 6.30; N, 7.83.

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