Palladium-Catalyzed Multicomponent Synthesis of 2-Aryl-2-imidazolines from Aryl Halides and Diamines

Joanna V. Geden, Alpa K. Pancholi, and Michael Shipman*

Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, United Kingdom

ABSTRACT: An efficient palladium-catalyzed three-component reaction that combines aryl halides, isocyanides, and diamines provides access to 2-aryl-2-imidazolines in yields up to 96%. Through variation of the diamine component, the reaction can be extended to the synthesis of 2-aryl-1H-benimidazoles and 2-aryl-1,4,5,6-tetrahydropyrimidines.

2-Imidazolines are an important class of heterocyclic compound which target numerous pharmaceutically relevant binding sites and receptors and which act as ligands in homogeneous catalysis.1 Of these, 2-aryl-2-imidazolines have demonstrated anticancer2 and appetite stimulant activity3 and have been used as ligands in polymer4 and asymmetric synthesis.5 A range of methods have been developed for the preparation of 2-aryl-2-imidazolines, but most commonly they have been made by coupling a 1,2-diamine with a carboxylic acid or its equivalent (usually an imidate or orthoester) or with an aldehyde in the presence of an oxidant.1

In the search for a general, catalytic route to 2-aryl-2-imidazolines, we were attracted to the report by Whitby et al. concerning the preparation of amidines by palladium-catalyzed coupling of an aryl halide, isocyanide, and amine.6 Since this initial report,6 palladium-catalyzed isocyanide insertion has been utilized in the preparation of various nitrogen heterocycles including cyclic amidines and imidates,7 oxazolines and benzoxazoles,8 quinazoline[3,2-c]quinazolines,9 4-aminooxazolines,10 quinazolin-4(3H)-imines,11 4-aminothiazolin-1(2H)-ones,12 2-substituted 1H-indole-3-carboxamides,13 6-aminoindolo[3,2-c]quinolines,14 4-amino-benzo[b][1,4]oxazepines,15 4-imino-3,4-dihydroquinazolin-2-ylphosphonates,16 and guanidine-containing heterocycles.17

By replacement of the amine component with a diamine, we imagined that this chemistry could provide a simple and general entry into imidazolines such as 2 through initial formation of amidine 1 and subsequent cyclization with loss of tert-butylamine (Scheme 1).

Reaction of iodobenzene, tert-butyl isocyanide and ethylenediamine in toluene using PdCl₂·dppf·CH₂Cl₂ as catalyst provided 2-phenyl-2-imidazoline (3) in a very encouraging 79% yield (Table 1, entry 1). Additional catalyst and ligand combinations were screened (entries 2–9), and PdCl₂ in combination with the dppp ligand led to further improvement to 94% yield (Table 1, entry 7). The reaction proceeds in excellent yield using 5 equiv of ethylenediamine, but lower yields are seen when the stoichiometry is reduced (Table 1, entries 10 and 11). The reaction proceeds well in toluene, 1,4-dioxane, and THF (entries 7, 12, and 13), but the yield is reduced when acetonitrile is used as the solvent (entry 14). Commercially available tert-butyl isocyanide proved to be the most convenient isocyanide source for this reaction. Alternative isocyanide sources (BnNC, 4-MeOC₆H₄NC, CyNC, PhMe₂CNC, and Ph₃CNC) all proved inferior. For example, when cumyl isocyanide (PhMe₂CNC) was used, 2-phenyl-2-imidazoline (3) was produced in just 43% yield under the conditions employed in Table 1, entry 7. When studying amidine synthesis, Whitby made similar observations.6 When the experiment detailed in entry 7 was performed without dppp, or separately without cesium carbonate, the yield of 3 reduced to 26% and 71%, respectively. These results indicate the importance of both the phosphine ligand and the inorganic base to achieving high yields.

Having optimized the reaction conditions, we then explored variation in the aryl halide component. A broad range of aryl halides and heteroaromatic halides, and an aryl triflate, were screened with our best two catalyst/ligand combinations (Table 2). Most substrates were found to give the desired imidazolines in good yield, with eight examples furnishing the product in greater than 90% yield (entries 1, 3, 6–7, 9, and 11–13). Initial

Note: Supporting Information

Scheme 1. Proposed Catalytic Cycle for the Preparation of 2-Aryl-2-imidazolines

Received: February 5, 2013
Published: March 8, 2013
Table 1. Optimization of Multicomponent Synthesis of 2-Phenyl-2-imidazoline (3)∗

| entry | catalyst | ligand | solvent | yield (%) |
|-------|----------|--------|---------|-----------|
| 1     | PdCl₂ | dppf⋅CH₂Cl₂ | toluene | 79 |
| 2     | Pd(OAc)₂ | dppf* | toluene | 76 |
| 3     | Pd₂(dba)₃ | dppf* | toluene | 74 |
| 4     | Pd(OAc)₂ | dpcy* | toluene | 45 |
| 5     | Pd(OAc)₂ | XantPhos* | toluene | 35 |
| 6     | PdCl₂ | dppf* | toluene | 77 |
| 7     | PdCl₂ | dppp* | toluene | 94 |
| 8     | Pd(PPh₃)₄ | toluene | 59 |
| 9     | Pd(P′Bu₂)₂ | toluene | 36 |
| 10    | PdCl₂, dppf⋅CH₂Cl₂ | toluene | 52 |
| 11    | PdCl₂, dppp⋅CH₂Cl₂ | toluene | 8* |
| 12    | PdCl₂ | dppp* | 1,4-dioxane | 90 |
| 13    | PdCl₂ | dppp* | THF | 91 |
| 14    | PdCl₂ | dppp* | MeCN | 48 |

∗Reaction conditions: tert-butyl isocyanide (1.5 equiv), Pd catalyst (5 mol %), ligand [(a) 10 mol % or (b) 20 mol %], ethylenediamine (5 equiv except (c) 3 equiv and (d) 1 equiv), Cs₂CO₃ (1.3 equiv), reflux.

†Yield of isolated product after column chromatography.

HRMS analyses were performed on a time-of-flight mass spectrometer equipped with an ESI source.

Synthesis of 3–20: General Procedure. Cesium carbonate (1.3 mmol, 1.3 equiv), anhydrous toluene (5 mL), aryl halide (1.0 mmol), isocyanide (1.5 mmol, 1.5 equiv), diamine (5.0 mmol, 5 equiv), palladium catalyst, and ligand (5 mol % PdCl₂⋅dppf⋅CH₂Cl₂, or 5 mol % PdCl₂ and 10 mol % 1,3-bis(diphenylphosphino)propane, dppp) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography to provide the nitrogen heterocycle.

2-Phenyl-4,5-dihydro-1H-imidazole (3). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), iodobenzene (112 μL, 1.0 mmol), tert-butyl isocyanide (170 μL, 1.5 mmol), ethylenediamine (334 μL, 5.0 mmol), palladium(II) chloride (8.9 mg, 0.05 mmol), and dppp (41.2 mg, 0.1 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO₂, 60:5:1, dichloromethane/methanol/triethylamine) to provide 3 as a beige solid (137 mg, 94%).19 R₁ (60:5:1, dichloromethane/methanol/triethylamine) 0.27; mp 100−101°C. [lit.19 mp 136−138°C] ν (cm⁻¹) 3183, 2923, 2835, 1603, 1570, 1512, 1474, 1174, 1025, 833; δ (CDCl₃) 7.74−7.88 (8H, m), 7.37 (2H, d, J = 8.8 Hz), 7.16−7.20 (3H, m), 3.83 (3H, s), 3.75 (4H, s); δC (CDCl₃) 164.5 (C), 161.8 (C), 157.3, 150.9, 147.8, 136.4, 130.7 (CH), 129.0 (CH), 121.2 (C), 113.8 (CH), 55.4 (CH₂), 49.7 (CH₃); m/z (ES⁺) 177 (MH⁺), found (MH⁺) 177.0919, C₁₁H₁₀N₂ requires (MH⁺) 177.0917.

2-(4-Methoxyphenyl)-4,5-dihydro-1H-imidazole (4). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 4-iodoanisole (234 mg, 1.0 mmol), tert-butyl isocyanide (170 μL, 1.5 mmol), ethylenediamine (334 μL, 5.0 mmol), palladium(II) chloride (8.9 mg, 0.05 mmol), and dppp (41.2 mg, 0.1 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO₂, 60:5:1, dichloromethane/methanol/triethylamine) to provide 4 as a beige solid (170 mg, 97%).20 R₁ (60:5:1, dichloromethane/methanol/triethylamine) 0.23; mp 138−139°C. [lit.20 mp 184−185°C] ν (cm⁻¹) 3183, 2923, 2835, 1603, 1570, 1512, 1474, 1174, 1025, 833; δ (CDCl₃) 7.74−7.88 (8H, m), 7.16−7.20 (3H, m), 3.83 (3H, s), 3.75 (4H, s); δC (CDCl₃) 164.5 (C), 161.8 (C), 128.8 (CH), 122.1 (C), 113.8 (CH), 55.4 (CH₂), 49.7 (CH₃); m/z (ES⁺) 177 (MH⁺), found (MH⁺) 177.0912, C₁₁H₁₀N₂O requires (MH⁺) 177.0912.
Table 2. Preparation of 2-Aryl-2-imidazolines (2)\textsuperscript{a}

| entry | ArX       | imidazoline | yield (%)\textsuperscript{a} | yield (%)\textsuperscript{b} |
|-------|-----------|-------------|-------------------------------|-------------------------------|
| 1     | \(\text{Ph}-\text{I}\) | ![Image] | 79                            | 94                            |
| 2     | \(\text{Ph}-\text{Br}\) | ![Image] | 21                            | 51                            |
| 3     | \(\text{MeO}-\text{Ph}-\text{I}\) | ![Image] | 88                            | 96                            |
| 4     | \(\text{Cl}-\text{Ph}-\text{I}\) | ![Image] | 69                            | 77                            |
| 5     | \(\text{Ph}-\text{I}\) | ![Image] | 32                            | 29                            |
| 6     | \(\text{Ph}-\text{C}_{6}\text{H}_{4}-\text{Br}\) | ![Image] | 86                            | 95                            |
| 7     | \(\text{MeO}-\text{Ph}-\text{Br}\) | ![Image] | 94                            | 62                            |
| 8     | \(\text{MeO}-\text{Ph}-\text{OTf}\) | ![Image] | 74                            | 31                            |
| 9     | \(\text{MeO}-\text{Ph}-\text{N}-\) | ![Image] | 93                            | 75                            |
| 10    | \(\text{Ph}-\text{N}-\text{Br}\) | ![Image] | 51                            | 8                             |
| 11    | \(\text{Ph}-\text{N}-\text{Br}\) | ![Image] | 44                            | 96                            |
| 12    | \(\text{Ph}-\text{Cl}\) | ![Image] | 18                            | 96                            |
| 13    | \(\text{Br}-\text{Ph}-\text{N}-\text{Br}\) | ![Image] | 74                            | 94                            |
| 14    | \(\text{S}-\text{I}\) | ![Image] | 51                            | 81                            |

\textsuperscript{a}Reaction conditions: \textit{tert}-butyl isocyanide (1.5 or 3 equiv for 11), ethylenediamine (5 or 10 equiv for 11), Cs\textsubscript{2}CO\textsubscript{3} (1.3 equiv), (a) PdCl\textsubscript{2\textsuperscript{dppf}}·CH\textsubscript{2}Cl\textsubscript{2} (5 mol %), (b) PdCl\textsubscript{2} (5 mol %) and dppp (10 mol %), toluene, reflux.
2-(4-Chlorophenyl)-4,5-dihydro-1H-imidazole (5). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 1-chloro-4-iodobenzene (238 mg, 1.0 mmol), tert-butyl isocyanide (170 µL, 1.5 mmol), ethylenediamine (334 µL, 5.0 mmol), palladium(II) chloride (8.9 mg, 0.05 mmol), and dppp (41.2 mg, 0.1 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:3:1, dichloromethane/methanol/triethylamine) to provide 5 as a cream solid (139 mg, 77%): Rf (60:3:1, dichloromethane/methanol/triethylamine) 0.63; mp 186–188°C (lit.19 mp 188°C); νmax (film)/cm−1 3105, 2969, 2920, 2862, 1605, 1593, 1559, 1515, 1467, 1270, 1090, 987, 837, 724; δH (400 MHz, CDCl3) 7.72 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 3.79 (4H, s); δC (100 MHz, CDCl3) 163.8 (C), 136.8 (C), 128.8 (C), 128.7 (CH), 128.4 (CH), 50.3 (CH2); m/z (ES+) 181 (MH+), found (MH)+ 181.0534, C9H9ClN2 requires (MH)+, 181.0527.

4,5-Dihydro-2-(2-methylphenyl)-1H-imidazole (6). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 2-iodotoluene (127 µL, 1.0 mmol), tert-butyl isocyanide (170 µL, 1.5 mmol), ethylenediamine (334 µL, 5.0 mmol), and PdCl2·dppf·CH2Cl2 (40.8 mg, 0.05 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:3:1, dichloromethane/methanol/triethylamine) to provide 6 as a solid.

| entry | diamine | product | yield (%) |
|-------|---------|---------|-----------|
| 1     |        |         | 95a       |
| 2     |        |         | 82a       |
| 3     |        |         | 60a       |
| 4     |        |         | 82b       |
| 5     |        |         | 50b       |
| 6     |        |         | 58b       |
| 7     |        |         | 39b       |

**Scheme 2. One-Pot Preparation of Chiral Pybim Ligand (20)**

2-(4-Chlorophenyl)-4,5-dihydro-1H-imidazole (5). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 1-chloro-4-iodobenzene (238 mg, 1.0 mmol), tert-butyl isocyanide (170 µL, 1.5 mmol), ethylenediamine (334 µL, 5.0 mmol), palladium(II) chloride (8.9 mg, 0.05 mmol), and dppp (41.2 mg, 0.1 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:3:1, dichloromethane/methanol/triethylamine) to provide 5 as a cream solid (139 mg, 77%): Rf (60:3:1, dichloromethane/methanol/triethylamine) 0.63; mp 186–188°C (lit.19 mp 188°C); νmax (film)/cm−1 3105, 2969, 2920, 2862, 1605, 1593, 1559, 1515, 1467, 1270, 1090, 987, 837, 724; δH (400 MHz, CDCl3) 7.72 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 3.79 (4H, s); δC (100 MHz, CDCl3) 163.8 (C), 136.8 (C), 128.8 (C), 128.7 (CH), 128.4 (CH), 50.3 (CH2); m/z (ES+) 181 (MH+), found (MH)+ 181.0534, C9H9ClN2 requires (MH)+, 181.0527.

4,5-Dihydro-2-(2-methylphenyl)-1H-imidazole (6). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 2-iodotoluene (127 µL, 1.0 mmol), tert-butyl isocyanide (170 µL, 1.5 mmol), ethylenediamine (334 µL, 5.0 mmol), and PdCl2·dppf·CH2Cl2 (40.8 mg, 0.05 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:3:1, dichloromethane/methanol/triethylamine) to provide 6 as a solid.

Table 3. Reaction of Other Diamines

| entry | diamine | product | yield (%) |
|-------|---------|---------|-----------|
| 1     |        |         | 95a       |
| 2     |        |         | 82a       |
| 3     |        |         | 60a       |
| 4     |        |         | 82b       |
| 5     |        |         | 50b       |
| 6     |        |         | 58b       |
| 7     |        |         | 39b       |

**Scheme 2. One-Pot Preparation of Chiral Pybim Ligand (20)**

2-(4-Chlorophenyl)-4,5-dihydro-1H-imidazole (5). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 1-chloro-4-iodobenzene (238 mg, 1.0 mmol), tert-butyl isocyanide (170 µL, 1.5 mmol), ethylenediamine (334 µL, 5.0 mmol), palladium(II) chloride (8.9 mg, 0.05 mmol), and dppp (41.2 mg, 0.1 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:3:1, dichloromethane/methanol/triethylamine) to provide 5 as a cream solid (139 mg, 77%): Rf (60:3:1, dichloromethane/methanol/triethylamine) 0.63; mp 186–188°C (lit.19 mp 188°C); νmax (film)/cm−1 3105, 2969, 2920, 2862, 1605, 1593, 1559, 1515, 1467, 1270, 1090, 987, 837, 724; δH (400 MHz, CDCl3) 7.72 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 3.79 (4H, s); δC (100 MHz, CDCl3) 163.8 (C), 136.8 (C), 128.8 (C), 128.7 (CH), 128.4 (CH), 50.3 (CH2); m/z (ES+) 181 (MH+), found (MH)+ 181.0534, C9H9ClN2 requires (MH)+, 181.0527.

4,5-Dihydro-2-(2-methylphenyl)-1H-imidazole (6). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 2-iodotoluene (127 µL, 1.0 mmol), tert-butyl isocyanide (170 µL, 1.5 mmol), ethylenediamine (334 µL, 5.0 mmol), and PdCl2·dppf·CH2Cl2 (40.8 mg, 0.05 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:3:1, dichloromethane/methanol/triethylamine) to provide 6 as a solid.
beige solid (51 mg, 32%):$^{22}$ Rf (60:3:1, dichloromethane/methanol/triethylamine) 0.45; mp 83–85°C (lit.$^{20}$ mp 88°C); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3149, 2922, 1611, 1588, 1498, 1262, 980, 767, 730; $\delta_1$ (400 MHz, CDCl$_3$) 7.44 (1H, d, $J = 7.5$ Hz), 7.28 (1H, t, $J = 7.5$ Hz), 7.22–7.14 (2H, m), 4.82–4.63 (1H, br s), 3.72 (4H, s), 2.46 (3H, s), $\delta_2$ (100 MHz, CDCl$_3$) 156.7, 136.9, 131.0 (C), 130.9 (CH), 129.6 (CH)$_2$, 128.4 (CH), 125.6 (CH), 50.5 (CH$_2$); m/z (ES$^+$) 161 (MH$^+$), found (MH$^+$) 161.1070, C$_8$H$_7$N$_2$S requires (MH$^+$) 161.1073.

4.5-Dihydro-2-(pyridin-2-yl)-1H-imidazole (10). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), 2-bromopyridine (95.4 μL, 1.0 mmol), tert-butyl isocyanide (170 μL, 1.5 mmol), ethylenediamine (334 μL, 5.0 mmol), palladium(II) chloride (8.9 mg, 0.05 mmol), and dppp (41.2 mg, 0.1 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO$_2$ 60:3:1, dichloromethane/methanol/triethylamine) to provide 10 as a cream solid (142 mg, 96%):$^{20}$ Rf (60:3:1, dichloromethane/methanol/triethylamine) 0.33; mp 100–102°C (lit.$^{20}$ mp 94°C); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3246, 3050, 2854, 1593, 1560, 1500, 1457, 1423, 1278, 976, 802, 752; $\delta_1$ (400 MHz, CDCl$_3$) 8.57 (1H, dd, $J = 4.8$, 1.7 Hz), 8.18 (1H, dd, $J = 7.8$, 1.7 Hz), 7.77 (1H, td, $J = 7.8$, 1.7 Hz), 7.38–7.33 (2H, m), 6.20–5.80 (1H, br s), 4.30–3.77 (2H, br s), 3.90–3.40 (2H, br s); $\delta_2$ (100 MHz, CDCl$_3$) 164.3 (C), 148.6 (CH), 148.2 (C), 136.6 (CH), 125.2 (CH), 122.4 (CH), 50.2 (CH$_2$); m/z (ES$^+$) 148 (MH$^+$), found (MH$^+$) 148.0869, C$_9$H$_{10}$N$_2$S requires (MH$^+$) 148.0869.
The Journal of Organic Chemistry

7.29 (3H, m), 5.26–5.15 (1H, br s), 3.44 (4H, t, J = 5.7 Hz), 1.79 (2H, quintet, J = 5.7 Hz); δ1 (100 MHz, CDCl3) 154.7 (C), 137.3 (C), 129.5 (CH), 128.2 (CH), 126.0 (CH), 42.2 (CH2), 20.7 (CH3); m/z (ES+) 161 (MH+)1 161.1073, C16H16N2 requires (MH)+, 161.1073.

4,5-Di-hy-dro-1-ethyl-2-phenyl-1H-imidazole (14). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), iodobenzene (112 μL, 1.0 mmol), tert-butyl isocyanide (170 μL, 1.5 mmol), N-methylthelyleneimine (436 mL, 5.0 mmol), and PdCl2-dppp(CH2)2Cl2 (40.8 mg, 0.05 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:5:1, dichloromethane/methanol/triethylamine) to provide 14 as a pale yellow oil (131 mg, 82%)27; Rf (60:5:1, dichloromethane/methanol/triethylamine) 0.14; νmax (film)/cm−1 3281, 3058, 2933, 1636, 1602, 1577, 1535, 1487, 1293, 693, δ13 (300 MHz, CDCl3) 7.56–7.51 (2H, m), 7.42–7.36 (3H, m), 3.85 (2H, t, J = 9.8 Hz), 3.43 (2H, t, J = 9.8 Hz), 2.78 (3H, s); δ1 (75 MHz, CDCl3) 167.4 (C), 130.5 (C), 129.1 (CH), 127.6 (CH), 127.5 (CH), 53.4 (CH2), 52.3 (CH), 35.8 (CH3); m/z (ES+) 161 (MH+)1 161.1074, C16H16N2 requires (MH)+, 161.1073.

4,5-Di-hy-dro-2-phenyl-1H-imidazole (15). Cesium carbonate (423 mg, 1.3 mmol), anhydrous toluene (5 mL), iodobenzene (112 μL, 1.0 mmol), tert-butyl isocyanide (170 μL, 1.5 mmol), N-methylthelyleneimine (751 μL, 5.0 mmol), and PdCl2-dppp(CH2)2Cl2 (40.8 mg, 0.05 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:5:1, ethyl acetate/triethylamine) to provide 15 as a pale yellow gum (142 mg, 60%):20 Rf (1:1, hexane/ethyl acetate) 0.67; mp 290–292 °C (lit. mp 290–292 °C); νmax (film)/cm−1 2627, 1621, 1590, 1443, 1409, 1275, 969, 737; δ13 (300 MHz, CDCl3) 8.05 (2H, d, J = 8.3 Hz), 7.70–7.55 (2H, br, s), 7.38–7.21 (4H, m), 7.06 (1H, m), 3.78 (2H, s), 3.50 (2H, t, J = 6.0 Hz), 2.84 (2H, t, J = 6.0 Hz); δ1 (75 MHz, CDCl3) 167.7 (C), 139.8 (C), 134.6 (C), 131.0 (CH), 128.5 (CH), 128.2 (CH), 127.2 (CH), 127.0 (CH), 126.7 (CH), 53.4 (CH3), 47.8 (CH3), 39.4 (CH3); m/z (ES+) 237 (MH+)1 237.1386, C16H12N2 requires (MH)+, 237.1385.

4,5-Di-hy-dro-2-phenyl-1H-imidazole (16). Cesium carbonate (212 mg, 0.65 mmol), anhydrous toluene (2.5 mL), iodobenzene (56 μL, 0.5 mmol), tert-butyl isocyanide (85 μL, 0.75 mmol), ciscyclohexylcarbenecobalt (300 μL, 2.5 mmol), and palladium(II) chloride (1.8 mg, 0.01 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 60:5:1, dichloromethane/methanol/triethylamine) then (SiO2, 98:2, ethyl acetate/triethylamine) to provide 16 as a beige solid (82 mg, 82%); Rf (98:2, ethyl acetate/triethylamine) 0.22; mp 139–141 °C; νmax (film)/cm−1 3105, 2930, 2849, 1610, 1594, 1563, 1506, 1471, 1353, 1000, 774; δ13 (400 MHz, CDCl3) 7.81 (2H, d, J = 6.8 Hz), 7.43–7.33 (3H, m), 5.82–5.60 (1H, br s), 3.88–3.81 (1H, m), 1.80–1.70 (2H, m), 1.69–1.60 (2H, m), 1.58–1.46 (2H, m), 1.38–1.24 (2H, m); δ1 (100 MHz, CDCl3) 164.2 (C), 130.6 (CH), 128.4 (CH3), 126.9 (CH3), 60.3 (CH), 28.5 (CH3), 21.0 (CH3); m/z (ES+) 237 (MH+)1 237.1386, C16H12N2 requires (MH)+, 237.1385. (4R,5R)-4,5-Di-hy-dro-2,4,5-triphenyl-1H-imidazole (17). Cesium carbonate (85 mg, 0.26 mmol), anhydrous toluene (1 mL), 2,6-dimorpholine (47.4 mg, 0.2 mmol), tert-butyl isocyanide (68 μL, 0.6 mmol), (1R,2R)-(−)-2,3-diphenylthelyleneamine (425 mg, 2.0 mmol), palladium(II) chloride (1.8 mg, 0.01 mmol), and dppf (8.2 mg, 0.02 mmol) were added to an oven-dried, three-necked flask under nitrogen. The mixture was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite which was washed well with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO2, 99:1, ethyl acetate/triethylamine) to provide 20 as a yellow solid (103 mg, >98% purity). Recrystallization from cyclohexane gave 20 as a cream solid (53 mg, 51%); Rf (99:1, ethyl acetate/triethylamine) 0.19; mp 122–124 °C (lit. mp 135–136 °C); νmax (film)/cm−1 3287, 3026, 1602, 1564, 1450, 1266, 1008, 830, 750, 697; δ13 (400 MHz, CDCl3)31 8.46 (2H, d, J = 7.8 Hz), 7.96 (1H, t, J = 7.8 Hz), 7.36–7.25 (2H, m), 6.47 (2H, br, s), 5.17 (2H, d, J = 8.7 Hz), 4.75 (2H, d, J = 8.7 Hz), 1.50 (100 MHz, CDCl3)161.8 (C), 147.6
ASSOCIATED CONTENT
2 Supporting Information
Copies of 1H and 13C NMR spectra for compounds 3–20 and the X-ray crystal structure of compound 11. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION
*Corresponding Author
E-mail: m.shipman@warwick.ac.uk.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS
We thank the EPSRC, the University of Warwick, and the Daphne Jackson Trust for financial support. We are grateful to Dr. Guy Clarkson for the X-ray crystallographic analysis of compound 11.

REFERENCES
(1) For a review, see: Liu, H.; Du, D.-M. Adv. Synth. Catal. 2009, 351, 489.
(2) (a) Hu, C.; Dou, X.; Wu, Y.; Zhang, L.; Hu, Y. Bioorg. Med. Chem. 2012, 20, 1417. (b) Hu, C.; Li, X.; Wang, W.; Zhang, L.; Tao, L.; Dong, X.; Sheng, R.; Yang, B.; Hu, Y. Bioorg. Med. Chem. 2011, 19, 5454. (c) Fischer, P. M.; Lane, D. P. Trends Pharmacol. Sci. 2004, 25, 343. (d) Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammottl, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. Science 2004, 303, 844.
(3) (a) Roeda, D.; Hinnen, F.; Dollé, F. J. Labelled Compd. Radiopharm. 2003, 46, 1141. (b) Polidori, C.; Gentili, F.; Pigini, M.; Quaglia, W.; Panocka, I.; Maurizio, M. Eur. J. Pharmacol. 2000, 392, 41. (c) Pigini, M.; Bousquet, P.; Carotti, A.; Dontenwill, M.; Giannella, M.; Moriconi, R.; Piergentili, A.; Quaglia, W.; Tayebati, S. K.; Brasili, L. Bioorg. Med. Chem. 1997, 5, 833.
(4) Battaro, A.; Claver, C.; Ruiz, A.; Castillón, S.; Daura, E.; Bo, C.; Zangrando, E. Chem.—Eur. J. 2004, 10, 3747.
(5) (a) Enthaler, S.; Hagemann, B.; Bhor, S.; Anilkumar, G.; Tse, M. K.; Bitterlich, B.; Junge, K.; Erre, G.; Beller, M. Adv. Synth. Catal. 2007, 349, 853. (b) Anilkumar, G.; Bhor, S.; Tse, M. K.; Klawonn, M.; Bitterlich, B.; Beller, M. Tetrahedron: Asymmetry 2005, 16, 3536.
(6) (a) Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. Org. Lett. 2005, 7, 3393.
(7) Gustaf Saluste, C.; Whitby, R. J.; Furber, M. Angew. Chem., Int. Ed. 2000, 39, 4156.
(8) Gustaf Saluste, C.; Crumpler, S.; Furber, M.; Whitby, R. J. Tetrahedron Lett. 2004, 45, 6995.
(9) Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammottl, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. Science 2004, 303, 844.
(10) (a) Eliseev, V.; Gusev, I.; Petrenko, M. Adv. Synth. Catal. 2007, 449, 853. (b) Bhor, S.; Tse, M. K.; Klawonn, M.; Bitterlich, B.; Beller, M. Tetrahedron: Asymmetry 2005, 16, 3536.
(11) (a) Eliseev, V.; Gusev, I.; Petrenko, M. Adv. Synth. Catal. 2007, 449, 853. (b) Bhor, S.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. Org. Lett. 2005, 7, 3393.
(12) Gustaf Saluste, C.; Whitby, R. J.; Furber, M. Angew. Chem., Int. Ed. 2000, 39, 4156.
(13) Gustaf Saluste, C.; Crumpler, S.; Furber, M.; Whitby, R. J. Tetrahedron Lett. 2004, 45, 6995.
(14) Boissarie, P.; Hamilton, Z. E.; Lang, S.; Murphy, J. A.; Suckling, C. J. Org. Lett. 2011, 13, 6256.
(15) Guanyinsheng, Q.; He, Y.; Wu, J. Chem. Commun. 2012, 48, 3836.
(16) (a) Van Baelen, G.; Kuijer, S.; Rychèk, L.; Sergeyev, S.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. Chem.—Eur. J. 2011, 17, 15039. (b) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. Org. Lett. 2011, 13, 4604.
(17) (a) Van Baelen, G.; Kuijer, S.; Rychèk, L.; Sergeyev, S.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. Org. Lett. 2011, 13, 6496.
(18) (a) Van Baelen, G.; Kuijer, S.; Rychèk, L.; Sergeyev, S.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. Org. Lett. 2011, 13, 6496.
(19) Hu, Z.; Liang, D.; Zhao, J.; Huang, J.; Zhu, Q. J. Org. Chem. 2012, 78, 4158–4164.