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Research Paper

Palladium Catalyzed Aerobic Oxidative Cyclization of *ortho*-Vinylanilines with Isocyanides

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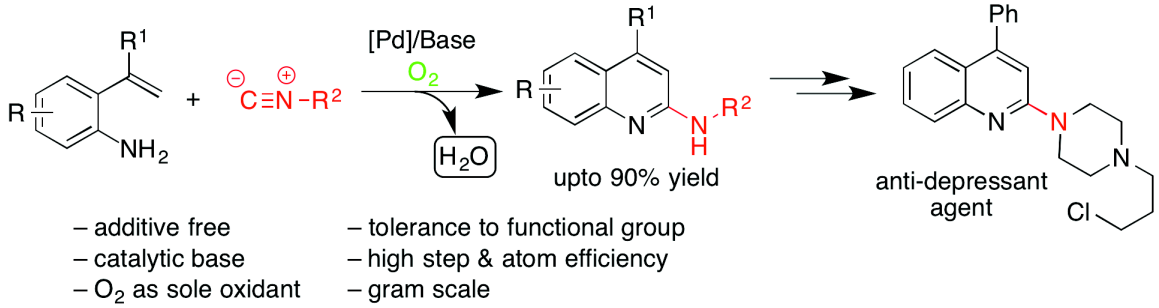

Efficient palladium catalyzed aerobic oxidative cyclization of *ortho*-vinylanilines with isocyanides have been achieved for the synthesis of 2-aminoquinolines in good to excellent yield. Characteristic features of the method are tolerance to various functional groups, use of catalytic amount of [Pd]/base and O_2, the most sustainable oxidant, gram scale synthesis and high step and atom efficiency. Control experiments suggested the formation of carbodiimide followed by electrocyclization and [1, 7]-H shift as possible pathway. Utility of the developed method was further demonstrated through synthesis of anti-depressant agent.

Keywords: Palladium; Oxidative Cyclization; Isocyanide; 2-Aminoquinoline; Aerobic Oxidation; Carbodiimide

Introduction

Isocyanides are a versatile building have found prevalent application in organic, medicinal and combinatorial chemistry (Nenajdenko, 2012). Traditional reactions that utilize isocyanides include multicomponent reactions such as Passerini and Ugi reactions, (Domling, 2006) synthesis of heterocycles (Lygin and de Meijere, 2010) and cycloadditions (Gulevich *et al.*, 2010). Recently, significant attention has been devoted to transition metals, (Boyarskiy *et al.*, 2015; Qiu *et al.*, 2013) specifically palladium (Lang, 2013; Vlaar *et al.*, 2013), catalyzed isocyanide insertion reactions for the synthesis of heterocycles, so called imidoylative reactions, (Jiang *et al.*, 2011; Jiang *et al.*, 2014; Jiang *et al.*, 2014; Liu *et al.*, 2013; Nanjo *et al.*, 2013; Odabachian *et al.*, 2013; Vlaar *et al.*, 2014; Vlaar *et al.*, 2012; Vlaar *et al.*, 2013; Wang *et al.*, 2014; Wolstenhulme *et al.*, 2014) in line with the reactivity of isoelectronic carbon monoxide with palladium catalysts [known as carbonylative reactions (Brennfuhrer *et al.*, 2009; Wu *et al.*, 2011; Wu *et al.*, 2013)]. Most of these reactions utilize prefunctionalized coupling partner and nucleophiles [amines and alcohols], but transformations involving functionalization of C-H bond in unactivated coupling partner *via* oxidative isocyanide insertion are rather limited.(Chen *et al.*, 2015; Liu *et al.*, 2014; Peng *et al.*, 2012; Sharma *et al.*, 2015; Wang *et al.*, 2011; Yang and Huang, 2015; Zheng *et al.*, 2015; Zhu *et al.*, 2014). Hence, development of a new method that incorporates C-H functionalization through oxidative isocyanide insertion, particularly employing molecular oxygen as sole oxidant, is highly desirable.

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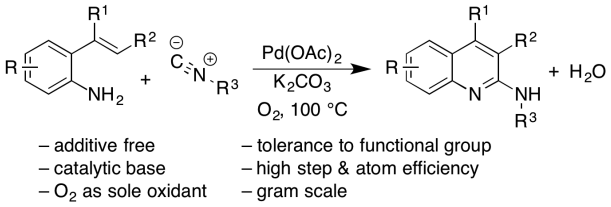
2-Aminoquinolines are privileged structures present in various natural products, pharmaceutically important synthetic molecules, which were known to exhibit diverse bioactivities such as anti-skin cancer, enzyme inhibitor, antagonist of hormone, etc. (Cheng *et al.*, 2011; Cinelli *et al.*, 2014; Clark *et al.*, 2004; Walter *et al.*, 2013) Particularly, the introduction of aryl substituent at 4-position of 2-aminoquinolines was shown to increase anti-depressant and anti-hypothermia activity. (Alhaider *et al.*, 1985; Hino *et al.*, 1980). Because of their potent bioactivity, number of methods for the synthesis of 2-aminoquinolines has been developed. Typical synthesis of 2-aminoquinolines that utilize *ortho*-amino- or nitro-benzaldehyde derivatives and quinoline derivatives requires either more than a one-step sequence or harsh reaction conditions. (Marco-Contelles *et al.*, 2009; Tomioka *et al.*, 2012; Wang *et al.*, 2012). Similarly, *ortho*-vinylanilines were also cyclized in multistep sequence *via* either generation of corresponding iminophosphoranes (Molina *et al.*, 1992) or urea derivatives (Wiggall and Richardson, 1995) at an elevated temperature.



Scheme 1: Palladium catalyzed aerobic oxidative cyclization

These methods were recently replaced with the transition metal catalyzed amination of prefunctionalized quinolines such as 2-haloquinolines and quinoline *N*-oxide. However, most of these methods suffer from limited availability and high cost of functionalized quinolines. Most recently, Feng *et al*. reported the palladium catalyzed synthesis of 2-aminoquinolines from isocyanides and 2-vinylanilines using 1.2-equivalents of an Ag_2CO_3, expensive oxidant.(Wang *et al.*, 2015) In continuation of our ongoing interest in the synthesis of *N*-heterocycles through functionalization of divalent carbon compounds and C-H bonds,(Ghorai and Anbarasan, 2015; Rajasekar and Anbarasan, 2014; Saravanan and Anbarasan, 2014; Yadagiri and Anbarasan, 2013; Yadagiri and Anbarasan, 2014; Yadagiri and Anbarasan, 2015) we herein disclose the palladium catalyzed oxidative isocyanide insertion reaction with *ortho*-vinylanilines for the elegant synthesis of 2-aminoquinoline derivatives employing molecular oxygen as the sole oxidant (Scheme 1).

Materials and Methods

General procedure for the synthesis of 2-aminoquinolines 3

Substituted 2-vinyl anilines **1** (0.3 mmol, 1 equiv), $Pd(OAc)_2$ (0.009 mmol, 3 mol%), K_2CO_3 (0.09 mmol, 30 mol%) and toluene (1.5 mL) were added under argon atmosphere to an oven dried 10 mL reaction tube equipped with stir bar. Successively, isocyanide **2** (0.6 mmol, 2 equiv) was introduced and the reaction tube was sealed with rubber septum and kept at 100 °C in pre-heated oil bath. Based on the TLC analysis, after the completion of reaction, the reaction mixture was cooled to room temperature. Evaporation of solvent followed by purified by column chromatography using hexane/ethyl acetate mixture as eluent afforded 2-aminoquinoline derivatives **3** in high yield and purity.

3a: (Wang *et al.*, 2015) 73 mg, 90% yield; light orange liquid; FT-IR (Neat): 3423, 2958, 2213, 1607, 1512, 761, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.69-7.65 (m, 1H), 7.50-7.39 (m, 5H), 7.24-7.16 (m, 1H), 7.02-6.96 (m, 1H), 6.51 (s, 1H), 4.52 (s, 1H), 3.70 (s, 3H), 1.53 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 155.1, 154.8, 148.0, 144.2, 139.0, 129.2, 128.5, 128.4, 128.1, 122.2, 120.2, 113.3, 105.4, 55.5, 51.4, 29.7; MS (*m*/*z*): 306.2 (M^+), 291.1, 250.1 (100%), 235.1, 190.0, 57.1.

3b: (Wang *et al.*, 2015) 70 mg, 83% yield; orange solid; Mp: 118-110°C; FTIR (KBr): 3433, 3055, 2922, 1606, 1445, 865, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.73 (d, 1H, *J* = 8.2 Hz), 7.58 (d, 1H, *J* = 8.1 Hz), 7.52-7.39 (m, 6H), 7.14-7.08 (m, 1H), 6.51 (s, 1H), 4.61 (s, 1H), 1.55 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 156.2, 148.9, 148.8, 138.8, 129.4, 129.2, 128.5, 128.1, 127.1, 125.6, 122.0, 121.9, 113.0, 51.6, 29.6; MS (*m*/*z*): 276.1 (M^+), 261.2, 220.1 (100%), 207.1, 96.0.

3c: (Wang *et al.*, 2015) 74 mg, 89% yield; colorless liquid; FTIR (Neat): 3098, 2921, 2852, 2213, 1466,

797, 761, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.63 (d, 1H, *J* = 8.2 Hz), 7.51-7.40 (m, 5H), 7.35-7.31 (m, 2H), 6.49 (s, 1H), 4.57 (s, 1H), 2.33 (s, 3H), 1.53 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 155.8, 148.4, 147.0, 139.0, 131.3, 131.1, 129.4, 128.4, 128.0, 126.8, 124.6, 121.8, 112.9, 51.4, 29.7, 21.4; MS (*m*/*z*): 290.1 (M^+), 275.1, 234.1 (100%), 207.

3d: 65 mg, 82% yield; colorless solid; Mp: 108-109°C; FTIR (KBr): 3429, 3056, 2959, 1727, 1506, 1228, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.60 (dd, 1H, *J* = 8.1, 1.1 Hz), 7.55-7.46 (m, 2H), 7.55-7.30 (m, 5H), 6.42 (s, 1H), 4.49 (s, 1H), 1.44 (s, 9H), 1.18 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 156.0, 148.9, 147.0, 144.5, 139.0, 129.4, 128.4, 128.0, 127.7, 126.6, 121.3, 120.8, 113.0, 51.5, 34.6, 31.4, 29.6; MS (*m*/*z*): 332.2 (M^+), 317.1, 276.1, 261.1, 57.0 (100%).

3e: 53 mg, 65% yield; orange oil; FTIR (Neat): 3428, 3036, 2963, 2868, 1506, 1228, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.47-7.38 (m, 5H), 7.24-7.17 (m, 2H), 6.38 (s, 1H), 4.39 (s, 1H), 2.67 (s, 3H), 2.29 (s, 3H), 1.57 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 154.5, 148.6, 145.8, 139.4, 134.5, 131.5, 130.6, 129.4, 128.3, 127.8, 122.6, 121.5, 113.0, 51.5, 29.2, 21.4, 18.7; MS (*m*/*z*): 304.4 (M^+), 289.1, 248.1 (100%), 233.1, 57.0.

3f: 64 mg, 78% yield; colorless semi solid; FTIR (KBr): 3432, 3051, 2963, 2868, 1506, 1444, 1228, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.35 (s, 1H), 7.29-7.26 (m, 3H), 7.21-7.17 (m, 2H), 6.67 (s, 1H), 6.23 (s, 1H), 4.41 (s, 1H), 2.31 (s, 3H), 1.75 (s, 3H), 1.43 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 155.2, 150.0, 149.2, 143.3, 138.7, 135.0, 128.7, 127.8, 127.7, 127.4, 125.4, 119.2, 114.1, 51.4, 29.6, 24.2, 21.4; MS (*m*/*z*): 304.4(M^+), 289.1, 248.1 (100%), 233.0, 57.0.

3g: 61 mg, 76% yield; colorless liquid; FTIR (Neat): 3432, 3054, 2923, 1590, 1258, 1038, 862, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.47-7.38 (m, 5H), 7.10 (s, 1H), 6.91 (s, 1H), 6.42 (s, 1H), 5.94 (s, 2H), 4.53 (s, 1H), 1.51 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 155.6, 150.0, 148.3, 146.5, 144.5, 139.3, 129.2, 128.5, 128.0, 117.2, 110.4, 104.6, 101.9, 101.1, 51.3, 29.7; MS (*m*/*z*): 320.1(M^+), 305.1, 264.1, 205.0, 151.0, 57.0 (100%).

3h: 35 mg, 42% yield; grey solid; Mp: 194-195°C; FTIR (KBr): 3428, 3067, 2863, 2868, 1606, 1228, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.63 (d, 2H, *J* = 8.9 Hz), 7.47-7.41(m, 5H), 7.15 (dd, 1H, *J* = 2.7, 8.9 Hz), 6.99 (d, 1H, *J* = 2.7 Hz), 6.58 (s, 1H), 1.50 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 161.8, 154.9, 151.9, 138.6, 129.1, 128.4(6), 128.4(2), 128.0, 127.7, 122.4, 120.4, 112.9, 108.4, 51.3, 29.7.

3i: 73 mg, 88% yield; green liquid; FTIR (Neat): 3436, 2965, 1407, 1105, 908, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.69 (dd, 1H, *J* = 8.7, 5.4 Hz), 7.50-7.38 (m, 5H), 7.29-7.20 (m, 2H), 6.52 (s, 1H), 4.58 (s, 1H), 1.54 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 158.1 (*J* = 239.8 Hz), 155.7, 148.3, 145.6, 138.3, 129.2, 128.8 (*J* = 8.6 Hz), 128.6, 128.3, 122.2 (*J* = 9.1 Hz), 118.4 (*J* = 24.9 Hz), 113.8, 109.4 (*J* = 23.0 Hz), 51.6, 29.5; MS (*m*/*z*): 294.1(M^+), 279.1, 238.0 (100%), 237.0, 57.0.

3j: 51 mg, 65% yield; colorless solid; Mp: 147-149 °C; FTIR (KBr): 3429, 2972, 1407, 1705, 1024, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 8.29 (d, 1H, *J* = 1.72 Hz), 8.03 (dd, 1H, *J* = 8.7, 1.8 Hz), 7.63 (d, 1H, *J* = 8.8 Hz), 7.44-7.36 (m, 5H), 6.45 (s, 1H), 4.74 (s, 1H), 4.25 (q, 2H, *J* = 7.1 Hz), 1.49 (s, 9H), 1.27 (t, 3H, *J* = 7.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 167.0, 157.3, 151.6, 149.9, 138.1, 129.4, 129.3, 128.9, 128.7, 128.5, 126.9, 123.6, 121.2, 113.7, 60.8, 51.9, 29.5, 14.4; MS (*m*/*z*): 348.4 (M^+), 334.1, 214.1, 191.1, 91.1, 57.1 (100%).

3k: 56 mg, 68% yield; colorless solid; Mp: 106-107 °C; FTIR (KBr): 3408, 2927, 1407, 1705, 1204, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.56-7.36 (m, 5H), 7.21 (dd, 1H, *J* = 8.3, 1.2 Hz), 7.03 (t, 1H, *J* = 8.2 Hz), 6.94 (dd, 1H, *J* = 7.6, 1.1 Hz), 6.77 (s, 1H), 5.18 (s, 1H), 4.02 (s, 3H), 1.50 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 155.9, 153.6, 149.5, 140.5, 139.2, 129.4, 128.4, 128.0, 122.8, 121.2, 118.0, 111.6, 108.6, 56.3, 50.9, 29.9; MS (*m*/*z*): 306.1 (M^+), 291.1, 275.1, 249.1, 220.9, 152.0, 57.0 (100%).

3l: 59 mg, 74% yield; red semi solid; FTIR (KBr): 3430, 2968, 1595, 1705, 1371, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 9.11 (d, 1H, *J* = 7.9 Hz), 7.69 (d, 1H, *J* = 7.1 Hz), 7.55-7.45 (m, 3H), 7.41-7.30 (m, 6H), 6.43 (s, 1H), 4.53 (s, 1H), 1.56 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 155.9, 149.3, 146.4, 139.1, 134.1, 131.3, 129.5, 128.5, 128.0,

127.5, 127.4, 125.9, 125.2, 123.4, 122.2, 117.9, 112.2, 51.7, 29.4; MS (*m*/*z*): 324.5 (M^+), 291.4, 207.7 152.2, 133.8, 51.0 (100%).

3m: 65 mg, 81% yield; colorless liquid; FTIR (Neat): 3429, 3049, 2964, 1608, 1355, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.56 (d, 2H, *J* = 9.0 Hz), 7.24 (s, 1H), 7.17 (d, 2H, *J* = 7.52 Hz), 7.09 (dd, 1H, *J* = 8.8, 2.3 Hz), 6.93 (d, 1H, *J* = 2.19 Hz), 6.41 (s, 1H), 4.44 (s, 1H), 3.61 (s, 3H), 2.32 (s, 3H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 155.2, 154.7, 148.0, 144.2, 137.8, 136.0, 129.2, 129.1, 128.3, 122.3, 120.2, 113.2, 105.5, 55.5, 51.4, 29.7, 21.3; MS (*m*/*z*): 320.1 (M^+), 305.1, 264.1, 249.0, 57.0 (100%).

3n: 65 mg, 82% yield; colorless liquid; FTIR (Neat): 3433, 2961, 3049, 2964, 1677, 1355, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.77 (d, 2H, *J* = 9.0 Hz), 7.60 (dd, 1H, *J* = 8.4, 0.7 Hz), 7.53 (dd, 2H, *J* = 8.4, 1.3 Hz), 7.40-7.32 (m, 6H), 7.27 (d, 2H, *J* = 8.5 Hz), 6.99 (ddd, 1H, *J* = 8.1, 6.8, 1.2 Hz), 6.41 (s, 1H), 4.54 (s, 1H), 1.27 (s, 9H), 1.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 155.2, 154.7, 148.0, 144.2, 137.8, 136.0, 129.2, 129.1, 128.3, 122.3, 120.2, 113.2, 105.5, 55.5, 51.4, 29.7, 21.3; MS (*m*/*z*): 332.1 (M^+), 317.1, 276.1 (100 %), 261.1, 116.5, 57.0.

3o: 64 mg, 80% yield; orange liquid; FTIR (Neat): 3437, 2978, 1594, 1259, 1355, 1111, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.68 (d, 1H, *J* = 9.2 Hz), 7.50-7.37 (m, 2H), 7.25-7.10 (m, 3H), 6.93 (d, 1H, *J* = 2.8 Hz), 6.50 (s, 1H), 4.53 (s, 1H), 3.73 (s, 3H), 1.54 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 162.7 (*J* = 247.2 Hz), 155.0, 154.9, 146.9, 144.2, 134.9, 130.9 (*J* = 8.1 Hz), 128.5, 122.2, 120.3, 115.6 (*J* = 21.4 Hz), 113.4, 105.2, 55.6, 51.5, 29.6; MS (*m*/*z*): 324.3 (M^+), 309.1, 281.1, 268.1, 207.1 (100%).

3p: 71 mg, 88% yield; colorless solid; Mp: 85-86 °C; FTIR (KBr): 3440, 2935, 1600, 1457, 1114, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.64-7.61 (m, 1H), 7.20-7.16 (m, 1H), 7.13-7.12 (m, 1H), 6.40 (d, 1H, *J* = 1.7 Hz), 5.81-5.80 (m, 1H), 4.47 (s, 1H), 3.85 (s, 3H), 2.37-2.31 (m, 2H), 2.26-2.24 (m, 2H), 1.84-1.76 (m, 4H), 1.52 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 155.4, 154.4, 144.0, 136.3, 128.3, 127.6, 122.1, 119.5, 111.4, 105.6, 55.6, 51.3, 30.1, 29.7, 25.4, 23.1, 22.2; MS (*m*/*z*): 310.1 (M^+), 295.1, 254.1 (100%), 223.1, 57.0.

3r: 31 mg, 37% yield; colorless semi solid; FTIR (KBr): 3429, 2959, 1727, 1604, 1436, 1018, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.73 (d, 1H, *J* = 8.1 Hz), 7.61 (dd, 1H, *J* = 8.2, 1.0 Hz), 7.55-7.46 (m, 6H), 7.14 (td, 1H, *J* = 8.1, 1.0 Hz), 6.57 (s, 1H), 4.86 (s, 1H), 3.52-3.46 (m, 2H), 1.71-1.61 (m, 2H), 1.50-1.43 (m, 2H), 0.97 (t, 3H, *J* = 7.3 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 156.8, 149.9, 148.6, 138.7, 129.6, 129.4, 128.5, 128.2, 126.4, 125.8, 122.4, 122.0, 112.8, 110.9, 41.7, 32.0, 20.3, 14.0; MS (*m*/*z*): 276.1 (M^+), 247.1, 233.1, 220.0 (100%), 204.0, 116.1.

3s: 14 mg, 15% yield; orange liquid; FTIR (Neat): 3440, 2975, 2857, 1602, 1104, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.78 (dd, 1H, *J* = 8.3, 1.6 Hz), 7.64 (dd, 1H, *J* = 8.2, 1.2 Hz), 7.58-7.53 (m, 1H), 7.50-7.42 (m, 6H), 7.38-7.28 (m, 5H), 7.19-7.16 (m, 1H), 6.58 (s, 1H), 5.06 (s, 1H), 4.76 (d, 2H, *J* = 5.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 156.4, 149.9, 148.7, 139.5, 138.6, 129.6, 129.4, 128.7, 128.5, 128.3, 127.9, 127.4, 126.8, 125.8, 122.7, 122.3, 111.4, 46.0.

3x: 32 mg, 32% yield; red liquid; FTIR (Neat): 3432, 2857, 1599, 1502, 1263,1035, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.81-7.75 (m, 1H), 7.67 (dd, 1H, *J* = 8.3, 1.7 Hz), 7.61-7.55 (m, 1H), 7.48-7.39 (m, 6H), 7.24-7.18 (m, 1H), 7.08 (s, 1H), 7.03 (d, 1H, *J* = 8.01 Hz), 6.73 (s, 1H), 6.62 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 155.6, 150.4, 148.6, 138.5, 135.3, 135.1, 132.6, 131.9, 129.8, 129.4, 128.5, 128.3, 127.6, 126.6, 125.9, 124.7, 123.0, 122.8, 110.3, 21.0, 18.2.

4: 36 mg, 42% yield; light green solid; Mp: 80-82 °C; FTIR (KBr): 3036, 2863, 2021, 1506, 1228, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.64-7.60 (m, 1H), 7.60-7.51 (m, 3H), 7.38-7.30 (m, 2H), 7.28-7.20 (m, 1H), 7.20-7.14 (m, 2H), 7.12-7.03 (m, 2H), 1.40 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 138.8, 137.8, 135.5, 131.5, 129.6, 128.7, 128.4, 127.7, 126.8, 126.0, 124.8, 124.7, 124.2, 57.4, 31.8; MS (*m*/*z*): 276.1 (M^+), 219.1(100%), 207.1, 193.1, 165.0.

5: 58 mg, 56% yield; green semi solid; FTIR (KBr): 3444, 2959, 1727, 1604, 1436, 1018, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 8.08-8.02 (m, 2H), 7.51 (d, 1H, *J* = 8.7 Hz), 7.31 (d, 2H, *J* = 9.0 Hz), 7.25-7.22 (m, 4H), 6.93-6.87 (m, 2H), 6.62-6.59 (m, 1H), 6.32 (bs, 1H), 5.74 (s, 1H), 5.29 (s, 1H), 4.42 (bs, 1H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz,

$CDCl_3$, 24°C): δ 157.7, 152.7, 146.6, 145.0, 142.4, 139.5, 128.8, 128.4, 127.3, 126.5, 126.4, 125.1, 118.1, 117.0, 116.3, 114.2, 113.5, 55.7.

Synthesis of Substituted 4-phenylquinolin-2-amine (6 and 7)

N-(*tert*-Butyl)-4-phenylquinolin-2-amine derivatives (**3**) (60 mg/800 mg, 0.195 mmol/1.92 mmol) was heated at 70°C for 2 h in trifluoroacetic acid (0.5 mL/ 1.5 mL). The reaction mixture was cooled to room temperature, concentrated under reduced pressure. The resulting mixture was basified with aq. NaOH solution, and extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant crude was purified by column chromatography using mixture of ethyl acetate/hexane as eluent.

6: 33 mg, 72% yield; white semi solid; FTIR (KBr): 3412, 3050, 2985, 1674, 1122, 1030, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.84 (d, 1H, *J* = 9.2 Hz), 7.61-7.53 (m, 2H), 7.51-7.43 (m, 2H), 7.37-7.29 (m, 1H), 7.26 (s, 1H), 7.05 (s, 1H), 6.75 (s, 1H), 5.29 (s, 2H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 155.4, 153.5, 145.1, 135.9, 130.0, 129.2, 128.7, 127.7, 122.6, 120.3, 117.7, 113.2, 107.7, 55.7; MS (*m*/z): 250.0 (M^+, 100%), 235.0, 217.9.

7:(Samson and Daltrozzo, 2011) 427 mg, 67% yield; white solid; mp 192-193°C; FTIR (KBr): 3430, 2931, 1599, 1409, 1092, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.77-7.71 (m, 1H), 7.66 (dd, 1H, *J* = 8.2, 1.1 Hz), 7.61-7.54 (m, 1H), 7.53-7.44 (m, 5H), 7.24-7.19 (m, 1H), 6.67 (s, 1H), 5.00 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 156.3, 151.5, 146.4, 137.8, 130.3, 129.3, 128.6, 126.1, 125.1, 123.2, 122.4, 111.9; MS (*m*/z): 220.0 (M^+, 100%),180.0, 165.0, 95.5, 51.0.

Synthesis of N-*(4-phenylquinolin-2-yl) Piperazine 8*

(Alhaider *et al.*, 1985) In 10 mL reaction tube, bis-2-(chloroethyl) amine Hydrochloride (100 mg, 0.45 mmol,), 4-phenylquinolin-2-amine (80 mg, 0.45 mmol) and K_2CO_3 (313 mg) were refluxed in *n*-butanol (2 mL) for 28 h. After the completion of the reaction, the reaction mixture was cooled to room temperature and excess of K_2CO_3 was filtered off. Evaporation of solvent and followed by recrystallization in mixture of butanol/DCM to furnish the *N*-(4-phenylquinolin-2-yl) piperazine **8.** 84 mg, 64% yield; colorless liquid; FTIR (Neat): 3431, 2933, 1461, 1343, 1029, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.91 (d, 1H, *J* = 8.3 Hz), 7.76 (dd, 1H, *J* = 8.0, 0.7 Hz), 7.66-7.58 (m, 1H), 7.55-7.45 (m, 5H), 7.35-7.27 (m, 1H), 6.86 (s, 1H), 4.52 (t, 2H, *J* = 6.6 Hz), 1.90-1.79 (m, 2H), 1.60-1.49 (m, 2H), 1.05-0.98 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24°C): δ 162.1, 151.1, 147.4, 138.2, 129.4(9), 129.4(6), 128.5, 128.4, 127.7, 125.8, 124.1, 123.9, 113.2, 65.8, 31.3, 19.5, 14.0; MS (*m*/z): 289.4 (M^+), 159.0, 115.1, 141.1, 73.0 (100%).

Synthesis of 11

4-Methoxy-2-(1-phenylvinyl) aniline **1a** (100 mg, 0.44 mmol, 1 equiv), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol, 3 mol%), K_2CO_3 (18 mg, 0.133 mmol, 30 mol%) and toluene (2 mL) were added under argon atmosphere to an oven dried 10 mL reaction tube equipped with stir bar. Successively, isocyanide **2a** (0. 1 mL, 0.88 mmol, 2 equiv) was introduced and the reaction tube was sealed with rubber septum and kept at 80°C in pre-heated oil bath. After stirring for 2 h, the reaction mixture was cooled to room temperature. Evaporation of solvent followed by purified by column chromatography using hexane/ethyl acetate mixture (97:03) as eluent afforded **11** in 67 % yield along with 16% of **3a**. 91 mg, 67 % yield; light green liquid; FTIR (Neat): 3429, 3056, 2959, 2868, 1604, 1436, 1018, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24°C): δ 7.32-7.23 (m, 5H), 7.09 (d, 1H, *J* = 8.73 Hz), 6.83 (dd, 1H, *J* = 8.6, 2.9 Hz), 6.75 (d, 1H, *J* = 2.9 Hz), 5.81 (d, 1H, *J* = 1.1 Hz), 5.28 (d, 1H, *J* = 1.1 Hz), 3.77 (s, 3H), 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 156.6, 147.1, 145.3, 140.4, 137.4, 131.5, 128.3, 127.7, 126.7, 124.9, 116.1, 115.9, 114.4, 56.8, 55.7, 31.4; MS (*m*/z): 306.1 (M^+), 291.1, 250.0 (100%), 235.0, 57.1.

Results and Discussion

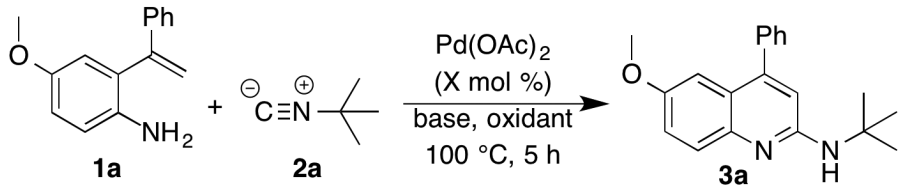
To begin with, optimization of palladium catalyzed oxidative isocyanide insertion reaction utilizing *ortho*-vinylaniline **1a** and *tert*-butylisocyanide **2a** as model substrate was envisioned, as shown in Table 1. Initially, 1 equivalent of **1a** and 2 equivalent of **2a** was treated with 5 mol % of $Pd(OAc)_2$ and 1.5 equivalent of K_3PO_4 in toluene at 100°C for 5 h. Formation of expected 2-aminoquinoline **3a** was observed in 13%

yield (Table 1, entry 1). To improve the yield of **3a** addition of external oxidant was envisaged to regenerate the active Pd-catalyst, because substrates are oxidatively coupled by Pd-catalyst whereby two protons are removed and palladium also reduced to Pd(0). Thus, the addition of 1 equivalent of CuI improved the yield of **3a** to 48% (Table 1, entry 2). Decreasing the equivalent of CuI to 5 mol % and use of molecular oxygen as co-oxidant at 1 atm, led to the formation of **3a** in 72% yield (Table 1, entry 3). Interestingly, increase in the yield (92%) of **3a** was observed when molecular oxygen was used as sole oxidant, without CuI (Table 1, entry 4). Next, importance of palladium and base in the present reaction was examined. Reaction in the absence of $Pd(OAc)_2$ did not afford the product **3a**, only **1a** was recovered (Table 1, entry 5). On the other hand, decrease in the yield (52%) was observed with removal of K_3PO_4 (Table 1, entry 6). This reveals that both $Pd(OAc)_2$ and K_3PO_4 are important and the reaction indeed catalyzed by palladium.

Subsequently, different bases like K_2CO_3, Na_2CO_3, KOAc were screened (Table 1, entries 7-9). Among them, only K_2CO_3 gave the comparable yield. Due to the ease of handling, K_2CO_3 was chosen as suitable base for the subsequent studies. Decreasing the catalyst loading from 5 mol% to 3 mol% also gave the product **3a** in similar yield (89%, Table 1, entry 10). Similarly, decreasing the equivalents of K_2CO_3 to 30 mol% with 3 mol% of $Pd(OAc)_2$ also gave the comparable yield (Table 1, entries 11-12). But, further decreasing the equivalents of K_2CO_3 decreased the yield of **3a**. Finally, these studies suggested that the best optimized conditions as 3 mol% of $Pd(OAc)_2$, 30 mol% of K_2CO_3, O_2, toluene, 100°C, 5 h.

With the optimized conditions in hand, we moved on to explore of substrates scope. Thus, various substituted *ortho*-vinylaniline derivatives **1** were examined with *tert*-butylisocyanide **2a** under the optimized conditions. As shown in Scheme 2, unsubstituted, methyl, and *tert*-butyl substituted aniline derivatives gave the corresponding 2-aminoquinolines **3b**, **3c** and **3d** in 83%, 89% and 82%, respectively.

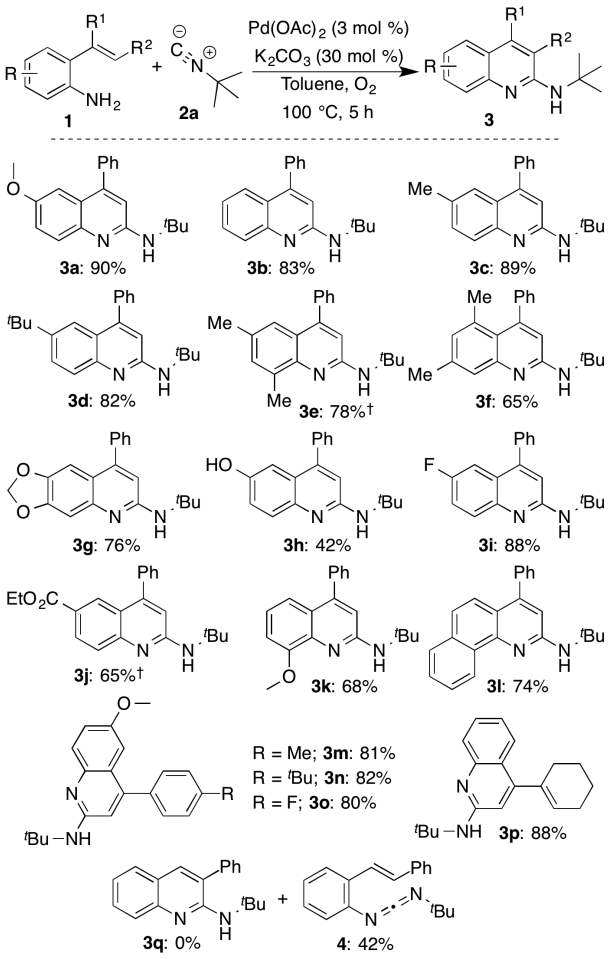
Table 1: Palladium catalyzed oxidative cyclization of *ortho*-vinylaniline 1a **and isocyanide** 2a**.**[a]



Entry	X mol%	Base (equiv)	Oxidant	Yield (%)[b]
1	5	K_3PO_4 (1.5)	-	13
2	5	K_3PO_4 (1.5)	CuI[c]	48
3	5	K_3PO_4 (1.5)	CuI[d]/O_2	72
4	5	K_3PO_4 (1.5)	O_2	92
5	-	K_3PO_4 (1.5)	O_2	0
6	5	-	O_2	52
7	5	K_2CO_3 (1.5)	O_2	88
8	5	Na_2CO_3 (1.5)	O_2	61
9	5	KOAc (1.5)	O_2	72
10	3	K_2CO_3 (1.5)	O_2	89
11	3	K_2CO_3 (1.0)	O_2	87
12	3	K_2CO_3 (0.3)	O_2	90 (67) [e]

[a] Reaction conditions: **1a** (1 equiv), **2a** (2 equiv), $Pd(OAc)_2$ (X mol%), base (equiv), oxidant, toluene, 100 °C, 5 h. [b] Isolated yield. [c] 1 equiv of CuI. [d] 5 mol% of CuI. [e] 10 mol% of K_2CO_3

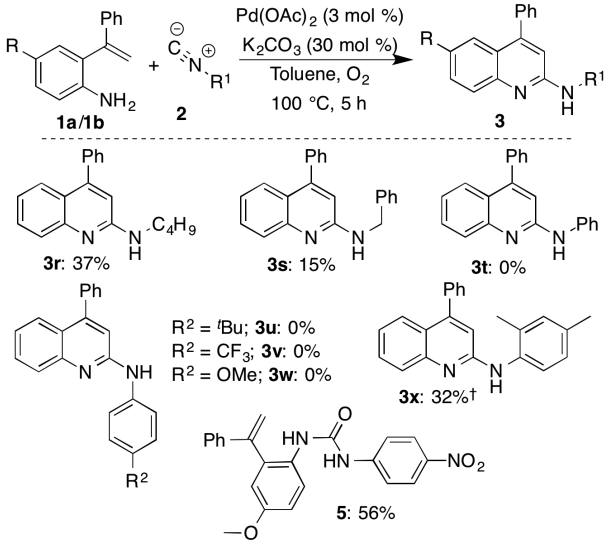
The optimized conditions are compatible with both electron rich and electron deficient aniline derivatives, which led to the synthesis of **3a**, **3i** and **3j** in good yield. Interestingly, the reaction tolerates free hydroxyl and sensitive functional group like acetal as part of aniline derivatives and corresponding products **3g** and **3h** were isolated in 76% and 42% yield. Sterically hindered 6-substituted aniline derivatives underwent smooth reaction to products **3e**, **3k** and **3l** in good yield. On the other hand, 3-substituted aniline derivatives gave the product **3f** in slightly lower yield. Furthermore, different aryl moiety on the alkene gave the corresponding 2-aminoquinolines **3m-o** in ~81% yield. Replacement of aryl with alkenyl substituent also furnished the product **3p** in 88% yield. Reaction of *â*-phenyl substituted *o*-vinylaniline did not furnish the expected cyclized product **3q**, instead formation of carbodiimide **4** was observed in 42%.



Scheme 2: Palladium catalyzed aerobic oxidative cyclization: Scope of substituted *ortho*-vinylaniline 1. † **8 h**

Unfortunately, possibly due the steric reason, further heating of **4** at higher temperature (140°C) also did not afford the **3q**.

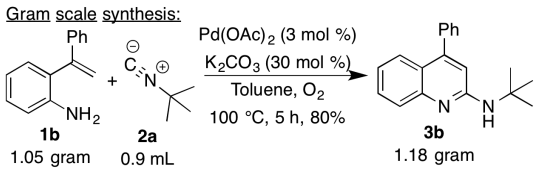
After successfully demonstrating the applicability of various substituted *o*-vinylaniline derivatives, we focused our attention on the scope of various isocyanides. Isocyanide derived from *n*-butylamine under the optimized conditions with **1b** gave the product **3r** in 37% yield. The present reaction also works well with benzylamine-derived isocyanide and the corresponding 2-aminoquinoline **3s** was isolated in 15% yield. Unfortunately, phenylisocyanide did not afford the cyclized product **3t**, instead decomposition of starting material was observed. Similar result was also observed with the synthesis of **3u-w** from corresponding *p*-substituted arylisocyanides. Interestingly, sterically hindered *ortho*-substituted arylisocyanide gave corresponding product **3x** in 32% yield. On the other hand, electron deficient *p*-nitro substituted arylisocyanide gave the urea derivative **5**, instead of expected cyclized product.



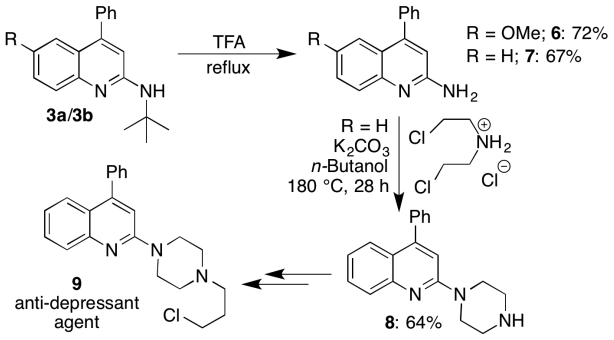
Scheme 3: Palladium catalyzed aerobic oxidative cyclization: Scope of isocyanides 2

For the wide synthetic utility, the developed transformation should also be successful in large-scale experiment. Hence, the reaction was performed in gram scale with **1b** and **2a** under the palladium-catalyzed conditions, which effectively gave the product **3b** in comparable yield (80%), proving that

the developed reaction is applicable in large scale (eq. 1).



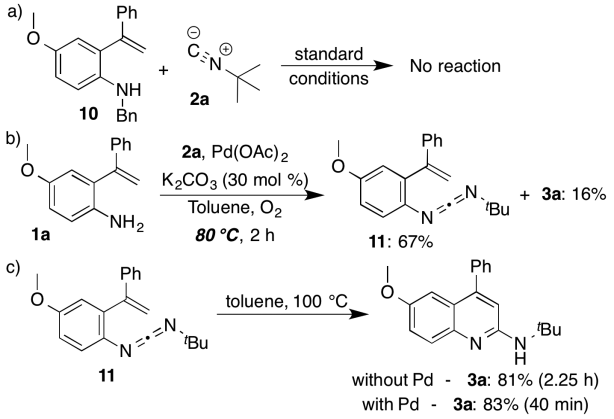
Further synthetic application of the developed methodology was demonstrated through the conversion of **3** to free amine and formal synthesis of anti-depressant agent **9** (Scheme 4). (Alhaider *et al.*, 1985; Hino *et al.*, 1980) Deprotection of *tert*-butyl group in **3a** to free amine **6** was achieved on treatment with TFA under reflux conditions in 72% yield. Similarly, **3b** was also successfully converted to the free amine **7** in 67% yield. Reaction of **7** with bis(2-chloroethyl)amine hydrochloride and K_2CO_3 gave the piperazine derivative **8**, a valuable intermediate for the synthesis of anti-depressant agent **9**.



Scheme 4: Formal synthesis of anti-depressant agent

Having demonstrated the new palladium catalyzed aerobic oxidative cyclization of *ortho*-vinylanilines with isocyanides, the preliminary mechanistic investigation was undertaken. Reaction of *N*-benzyl protected *ortho*-vinylaniline **10** with **2a** under the standard conditions did not afford any product, only starting material was recovered, suggesting that free 'NH_2' is important for the reaction (Scheme 5a).

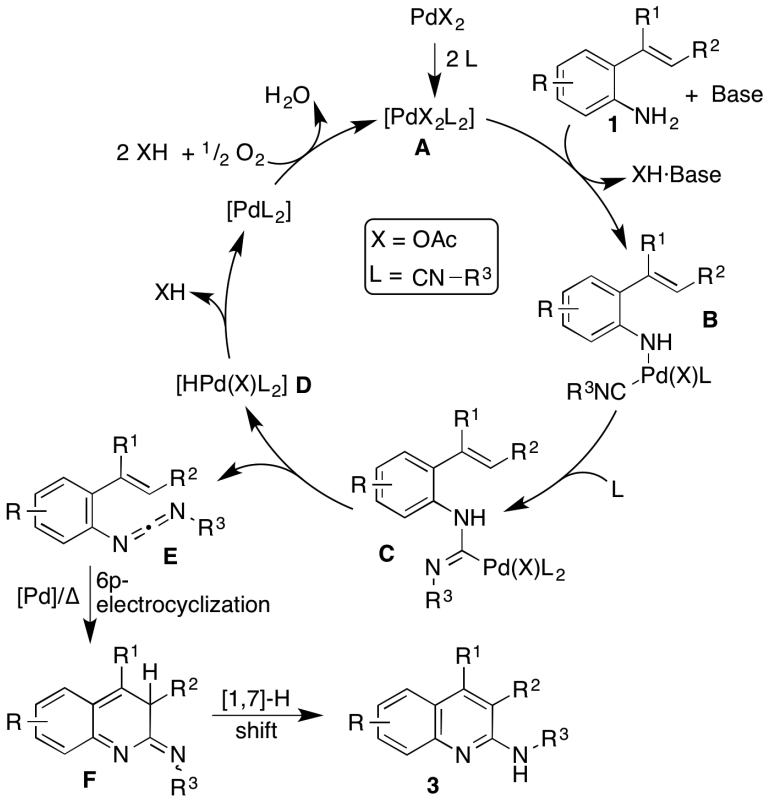
Based on the observation mentioned in Scheme 2, the standard reaction of **1a** with **2a** was stopped after 20 min and the crude reaction mixture was



Scheme 5: Isolation and conversion of intermediate 11

analyzed using NMR to understand the possible formation of carbodiimide **11** as intermediate. The analysis revealed generation of carbodiimide **11** and to further confirm, carbodiimide **11** was successfully isolated in 67% yield from the palladium catalyzed reaction of **1a** and **2a** at 80°C, along with 16% of **3a** (Scheme 5b). Thermal cyclization of **11**, in the absence of $Pd(OAc)_2$ and O_2, at 100°C for 2.25 h furnished the 2-aminoquinoline **3a** in 81% yield (Scheme 5c). In the presence of $Pd(OAc)_2$ similar result for the cyclization of **11** was observed in only 40 min. These results suggesting that the reaction going through carbodiimide and its cyclization to 2-aminoquinoline is promoted by both thermal and palladium.

Based on the preliminary mechanistic investigation, we propose the following mechanism for the palladium catalyzed aerobic oxidative cyclization (Scheme 6). Palladium complex **A**, formed from $Pd(OAc)_2$ and isocyanide, reacts with amine in the presence of base to form complex **B**. Formation of palladium species **C** from **B** can be explained through the insertion of isocyanide onto Pd-N bond. β-Hydride elimination from **C** would generate intermediate carbodiimide **E** and complex **D**. Reductive elimination of acid from **D** afford the Pd(0) species, which on oxidation with molecular oxygen and acid would regenerate the catalytically active species **A**. On the other hand, carbodiimide **E** undergoes Pd-assisted thermal 6π-electrocyclization to afford cyclized compound **F** followed by [1,7]-H shift would furnish the expected 2-aminoquinolines **3**.



Scheme 6: Plausible mechanism for the synthesis of 3

In conclusion, we have developed a new palladium catalyzed aerobic oxidative cyclization of *o*-vinylaniline and isocyanides for the synthesis of biologically important substituted 2-aminoquinolines in good to excellent yield. The method tolerates various functional groups and utilizes catalytic amount of palladium catalyst/base and molecular oxygen, the most sustainable oxidant, as sole oxidant. The protocol is operationally simple and environmentally benign owing to the low catalyst use and base loading and excellent atom and step efficiency. Preliminary mechanistic investigation revealed the formation of cabodiimide as possible intermediate and subsequent palladium assisted thermal electrocyclization and [1, 7]-H shift to cyclized product. Furthermore, the reaction is applicable to synthesis of pharmaceutically important heterocycles, as illustrated by a formal synthesis of anti-depressant agent.

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