Tetrahedron Letters 52 (2011) 1783–1787

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of novel 3-bromo-1,2-dihydroquinolines via palladium mediated intramolecular cyclization of *N*-tosyl-*N*-propargyl anilines

Savitha Gurunathan, Paramasivam Thirumalai Perumal *

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India

ARTICLE INFO

Article history:
Received 12 October 2010
Revised 31 January 2011
Accepted 2 February 2011
Available online 25 February 2011

Keywords:
Quinolines
LiBr
$Pd(OAc)_2$
$CuBr_2$
Propargyl aniline

ABSTRACT

Facile synthesis of novel 3-bromo-1,2-dihydroquinolines by the intramolecular cyclization of *N*-tosyl-*N*-propargyl anilines catalyzed by $Pd(OAc)_2$ in conjunction with $CuBr_2$ and LiBr.

Quinolines and their derivatives occur in numerous natural products, and many of them display interesting biological activities.[1] In particular, one of the partially hydrogenated quinoline moieties namely dihydroquinoline is an important building block in various natural products and exhibits a broad range of biological activities and potential pharmaceutical applications.[2] Typical biological activities of such compounds include psychotropic,[3] anti-allergenic,[4] anti-inflammatory,[5] and estrogenic activities.[6] Compounds possessing this motif have also been shown to act as lipid peroxidation inhibitors,[7] HMG-CoA reductase inhibitors,[8] ileal bile acid transporter inhibitors[9] and progesterone agonists[10] and antagonists.[11] Owing to the biological and pharmaceutical importance of this class of heterocycles, there has been a constant research in the development of new methodologies for their synthesis .[12]

Among various quinoline systems, halogen containing quinolines are of significant interest because the halogen atom sometimes plays a pivotal role in the compound's bioactivity, and such compounds provide further avenue for structural elaboration.[13] Although simple 3-bromoquinolines can be obtained by the bromination of quinoline hydrochlorides,[14] the site selective aromatic halogenation of substituted quinolines remains a synthetic challenge.[15] 3-Haloquinolines have also been synthesized by a photochemical method,[16] a modified Skraup quinoline synthesis employing halo-substituted acroleins and anilines,[17] and the Friedlander quinoline synthesis.[13c] Some of these methods suffer from relatively low yields, poor regioselectivity, and/or rather lengthy synthetic sequences. Hence, efficient and general synthetic routes to these heterocyclic frameworks are of strong interest.

Taking these factors into consideration we were interested in developing a methodology that provides facile access to halogen substituted quinoline derivatives in good yields.

Recently, we described an efficient synthesis of 3-bromo-2*H*-chromene derivatives from the corresponding aryl propargyl ethers via an intramolecular cyclization catalyzed by $Pd(OAc)_2$ in the presence of LiBr and $CuBr_2$.[18]

Herein we wish to report the results of our investigations on the palladium mediated cyclization of *N*-tosyl-*N*-propargyl amines to novel 3-bromo-1,2-dihydroquinoline derivatives.

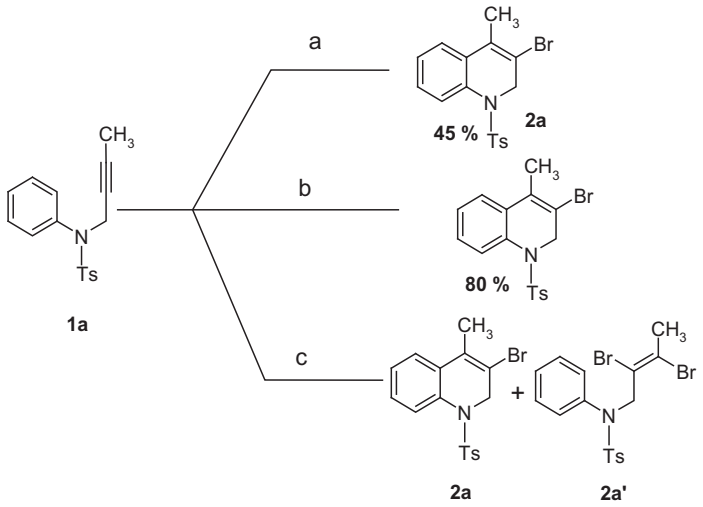
Our initial efforts focused on the cyclization of *N*-tosyl-*N*-propargyl aniline **1a** to the corresponding 3-bromo-1,2-dihydroquinoline derivative **2a** in the presence of $Pd(OAc)_2$ and $CuBr_2$. While screening a number of solvents to effect the cyclization it was found that solvents such as CH_3CN, CH_2Cl_2, DMSO, DMF, 1,4-dioxane were totally inefficient to effect the cyclization both at ambient and at reflux conditions. Whereas, acetic acid effected the cylization of **1a** in the presence of 5 mol % of $Pd(OAc)_2$ and $CuBr_2$ (2.5 equiv) at 80 °C in 3 h to the corresponding 3-bromo-1,2-dihydroquinoline derivative **2a** in 45% yield (Scheme 1., Condition a).

Further attempts to improve the yield by prolonging the reaction time and by increasing the mole ratio of $Pd(OAc)_2$ and $CuBr_2$ were futile.

Then we supposed that by increasing the bromide ion concentration in the reaction mixture we could arrive at the desired product. LiBr was our choice of bromide ion source.

* Corresponding author. Tel.: +91 44 24911386; fax: +91 44 24911589.
E-mail address: ptperumal@gmail.com (P.T. Perumal).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.02.004

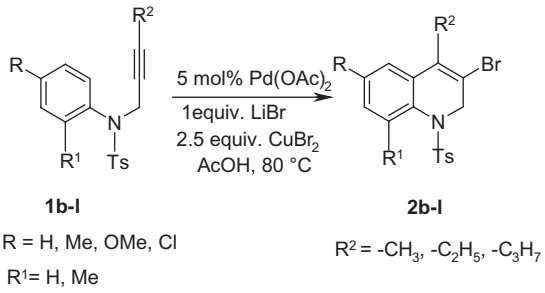


Scheme 1. Reagents and conditions: (a) 5 mol % $Pd(OAc)_2$, 2.5 equiv $CuBr_2$, AcOH, 80 °C; (b) 5 mol % $Pd(OAc)_2$, 2.5 equiv $CuBr_2$, 1 equiv LiBr, AcOH, 80 °C; (c) 5 mol % $Pd(OAc)_2$, 2.5 equiv $CuBr_2$, >1 equiv LiBr, AcOH, 80 °C.

Table 1
Optimization of the palladium catalyzed cyclization of *N*-tosyl, *N*-propargyl aniline **1a** to 3-bromo-1,2-dihydroquinoline derivative **2a** using LiBr

Entry	LiBr (equiv)	Time in mins	Yield (%)[a] of **2a**
1	0	180	45
2	0.2	120	52
3	0.5	90	64
4	0.8	60	73
5	1	50	80

[a] Isolated yield after column chromatography.



Scheme 2.

To our expectation, when 0.2 equiv of LiBr was used in addition to 5 mol % of $Pd(OAc)_2$ and 2.5 equiv $CuBr_2$ in the reaction, the yield of the cyclized product **2a** improved to 52%. Further we found that the time required for the completion of the reaction and the yield of the product **2a** was affected by increasing the quantity of LiBr (Table 1)

After a series of trials best result was obtained using 5 mol % $Pd(OAc)_2$ in conjunction with 2.5 equiv $CuBr_2$ and 1 equiv of LiBr in acetic acid at 80 °C. The reaction proceeded smoothly and the cyclization took place effectively furnishing the corresponding 3-bromo-1,2-dihydroquinoline **2a** in 50 min in 80% yield after purification through column chromatography (Scheme 1, Condition b).

It was found that, further increasing the amount of LiBr beyond 1 equiv resulted in the formation of a dibrominated product **2a′** in addition to the expected cyclized product **2a** (Scheme 1, Condition c). It is to be noted that when the amount of the LiBr was increased to 1.2 and 1.5 equiv the ratio of the product **2a′** to that of product **2a** increased and when the amount of LiBr was further increased to 2 equiv only the dibrominated product **2a′** was obtained as the product of the reaction.

The structure of the product **2a** was confirmed through spectroscopic studies. In the ^{1}H NMR spectrum of compound **2a**, the presence of only eight protons in the aromatic region confirmed the cyclization of **1a** to the corresponding 3-bromo-4-methyl-1,2-dihydroquinoline **2a**. Further the absence of the alkynyl carbon signals in the ^{13}C NMR spectrum confirmed the formation of the product **2a**. Finally mass spectral studies also supported the formation of **2a**.[19]

It was found that the reaction does not proceed in the absence of either $Pd(OAc)_2$ or $CuBr_2$ illustrating their significant roles in the reaction.

Having established the optimum condition for the reaction, a variety of *N*-tosyl-*N*-propargyl aniline derivatives (**1b–1l**) were cyclized following the optimized reaction conditions (Scheme 2).[20]

It was found that in all the cases the reaction proceeded smoothly furnishing the corresponding 3-bromo-1,2-dihydroquinoline derivatives in good yields. The results are summarized in Table 2.

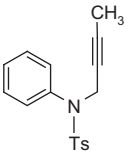
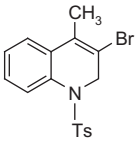
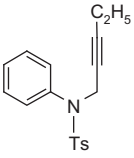
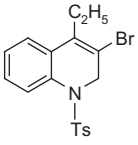
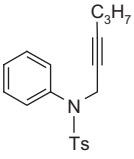
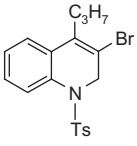
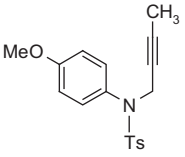
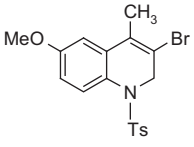
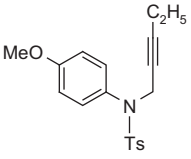
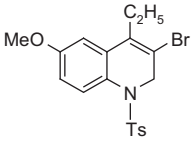
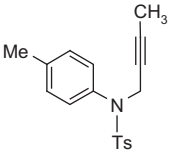
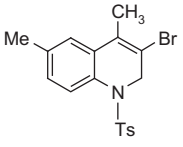
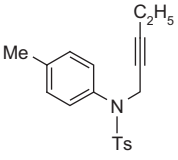
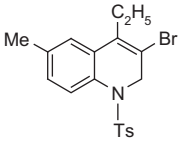
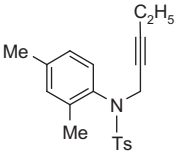
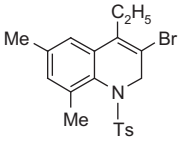
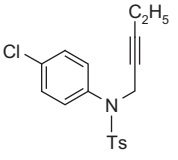
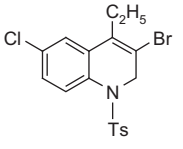
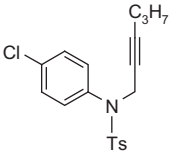
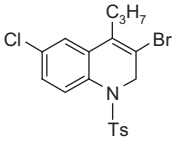
The structure of the compounds (**2b–2l**) was confirmed through ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques. X-ray diffraction studies were also performed to confirm the structure.[21] The ORTEP diagram of compound **2f** is given in Figure 1.

A plausible mechanism for the formation of 3-bromo-1,2-dihydroquinoline derivatives from the corresponding *N*-tosyl-*N*-propargyl aniline is given in Scheme 3.

The mechanism may involve co-ordination of palladium to the alkyne (step 1) which may lead to an intramolecular cyclization (step 2) to form the organointermediate (i). This intermediate may be converted to the palladium(IV) species (ii), which may decompose through reductive elimination to give the product **2**.[22]

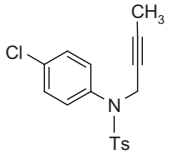
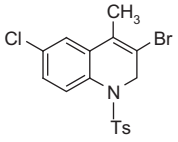
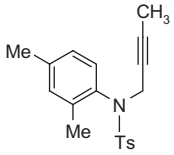
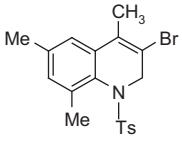
An alternate mechanism can also be explained for the formation of the product **2** from the intermediate (i) via intermediate (iii) in which copper(II) assists in ligand transfer while retaining palladium in its +2 oxidation state.[23]

Table 2
Synthesis of 3-bromo-1,2-dihydroquinoline derivatives

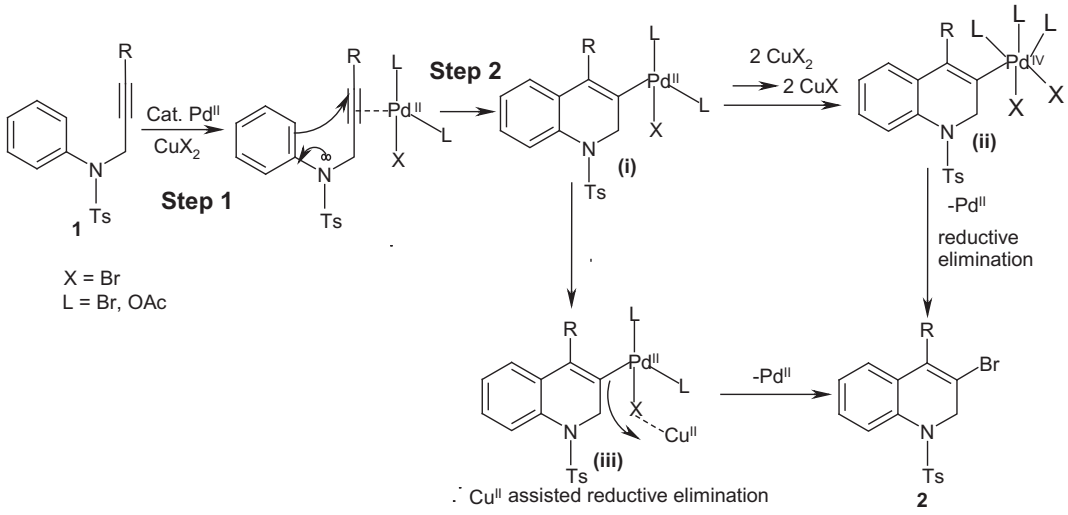
Entry	Aryl propargyl aniline (**1**)	3-Bromo-1,2-dihydroquinoline (**2**)	Time in mins	Yield[m] (%)
a			50	80
b			50	81
c			45	79
d			30	83
e			35	78
f			40	85
g			45	82
h			40	75
i			80	72
j			75	70

(*continued on next page*)

Table 2 (*continued*)

Entry	Aryl propargyl aniline (**1**)	3-Bromo-1,2-dihydroquinoline (**2**)	Time in mins	Yield[m] (%)
k			70	69
l			65	73

[m] Isolated yield after column chromatography.



Scheme 3.

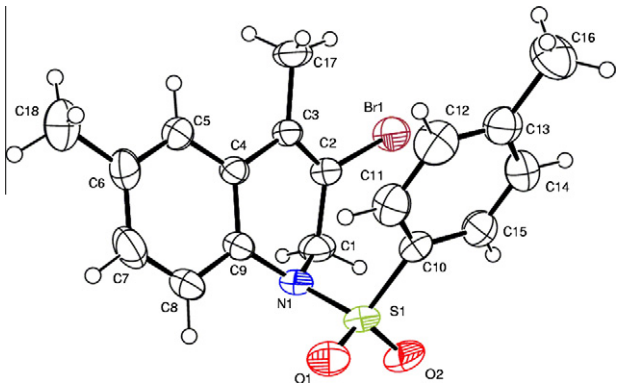
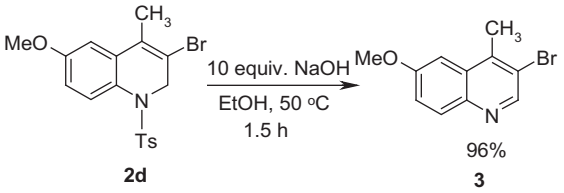


Figure 1. ORTEP diagram of compound **2f**.

The 3-bromo-1,2-dihydroquinolines synthesized can be easily converted to the corresponding 3-bromoquinolines by treating with NaOH in EtOH at 50 °C as shown in Scheme 4.[24]

In conclusion we have described a new approach for the facile synthesis of 3-bromo-1,2-dihydroquinolines in good yields from the easily accessible starting materials under mild reaction conditions.



Scheme 4.

Acknowledgment

One of the authors G.S. expresses her gratitude to the Council of Scientific and Industrial Research, New Delhi, for a research fellowship.

References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605; (b) Balasubramanian, M.; Keay, J. G. In II, Comprehensive Heterocyclic Chemistry, Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996.
2. (a) Witherup, K. M.; Ransom, R. W.; Varga, S. L.; Pitzenberger, S. M.; Lotti, V. J.; Lumma, W. J. U.S. Patent 5,288,725, **1994**; (b) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476; (c) Williamson, N. M.; March, P. R.; Ward, A. D. *Tetrahedron Lett* **1995**, *36*, 7721; (d) Johnson, J. V.; Rauckman, S.; Baccanari, P. D.; Roth, B. J. J. Med *Chem.* **1989**, *32*, 1942; (e) Biller,

S. A.; Misra, R. N. U.S. Patent 4,843,082, 1989; (f) Mohamed, E. A. *Chem. Pap.* **1994**, *48*, 261. Chem. Abstr. 1995, 123, 9315; (g) Caling, R. W.; Leeson, P. D.; Moseley, A. M.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R. *J. Med. Chem.* **1992**, *35*, 1942; (h) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Smith, J. D.; Saywell, K.; Trickelbank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65; i Cuny, G. D.; Hauske, J. D.; Hoemann, M. Z.; Rossi, R. F.; Xie, R. L. PCT Int. Appl. WO 9967238, 1999; *Chem. Abstr.* **1999**, *132*, 64182; j Hanada, K.; Furuya, K.; Inoguchi, K.; Miyakawa, M.; Nagata, N. PCT Int. Appl . WO 0127086, 2001; *Chem. Abstr.* 2001, *134*, 295752.

3. Nesterova, I. N.; Alekseeva, L. M.; Golovira, S. M.; Granik, V. G. *Khim.-Farm. Zh.* **1995**, *29*, 31. Chem. Abstr. 1996, 124, 117128t..
4. Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211.
5. Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177.
6. Akhmed, K. S.; Bessonova, I. A. *Dokl. Akad. Nauk Uzh. SSR* **1982**, 34. *Chem. Abstr.* 1983, *98*, 83727q..
7. Pearce, B. C.; Wright, J. J. **1995**, US 5411969.
8. Jones, T. K.; Winn, D. T.; Zhi, L.; Hamann, L. G.; Tegley, C. M.; Pooley, C. L. F. **1997**, US 5688808.
9. Kurata, H.; Kohama, T.; Kono, K.; Kitayama, K.; Hasegawa, T. 2001, WO 0134570 A1.
10. Jones, T. K.; Goldman, M. E.; Pooley, C. L. F.; Winn, D. T.; Edwards, J. E.; West, S. J.; Tegley, C. M.; Zhi, L.; Hamann, L. G. 1996, WO 9619458.
11. Coughlan, M. J.; Elmore, S. W.; Kort, M. E.; Kym, P. R.; Moore, J. L.; Pratt, J. K.; Wang, A. X.; Edwards, J. P.; Jones, T. K. 1999, WO 9941256.
12. (a) Yan, M.-C.; Tu, Z.; Lin, C.; Ko, S.; Hsu, J.; Yao, C.-F. J. *Org. Chem.* **2004**, *69*, 1565; (b) Lu, G.; Malinakova, H. C. J. *Org. Chem.* **2004**, *69*, 4701; (c) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2002**, *4*, 4265; (d) Luo, Y.; Li, Z.; Li, C. –J. *Org. Lett.* **2005**, *7*, 2675; (e) Waldmann, H.; Karunakar, G. V.; Kumar, K. *Org. Lett.* **2008**, *10*, 2159; (f) Yadav, J. S.; Reddy, B. V. S.; sreenivas, M.; Sathaiah, K. *Tetrahedron Lett.* **2005**, *46*, 8905; (g) Makino, K.; Hava, O.; Takiguchi, Y.; Katano, T.; Asakawa, Y.; Hatano, K.; Hamada, Y. *Tetrahedron Lett.* **2003**, *44*, 8925; (h) Theoclitou, M.-E.; Robinson, L. A. *Tetrahedron Lett.* **2002**, *43*, 3907; (i) Larock, R. C.; Pace, P.; Yang, H. *Tetrahedron Lett.* **1998**, *39*, 2515; (j) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763.
13. (a) Newhouse, B. J.; Bordner, J.; Augeri, D. J.; Litts, C. S.; Kleinman, E. F. J. *Org. Chem.* **1992**, *57*, 6991; (b) Torii, S.; Xu, L. H.; Sadakane, M.; Okumoto, H. *Synlett* **1992**, 513; (c) Nobuhide, M.; Yoshinobu, Y.; Hiroshi, I.; Yoshio, O.; Tamejiro, H. *Tetrahedron Lett.* **1993**, *24*, 8263; (d) Croisey-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629.
14. (a) Eisch, J. J. J. *Org. Chem.* **1961**, *27*, 1318; (b) Kress, T. J.; Costantino, S. M. J. *Heterocycl. Chem.* **1973**, *10*, 409.
15. Trecourt, F.; Mongin, F.; Mallet, M.; Queguiner, G. *Synth. Commun.* **1995**, *25*, 4011.
16. Campos, P. J.; Tan, C. Q.; Rodriguez, M. A.; Anon, E. J. *Org. Chem.* **1996**, *61*, 7195.
17. Baker, R. H.; Tinsley, S. W. *Jr.; Butler, D.; Riegel, B. J. Am. Chem. Soc.* **1950**, *72*, 393.
18. Savitha, G.; Felix, K.; Perumal, P. T. *Synlett* **2009**, 2079.
19. *3-Bromo-4-methyl-1-(4-methylphenylsulphonyl)-1,2-dihydroquinoline* (**2a**): Light brown solid. mp: 113–114 °C. ν_{max} (KBr): 2918, 2363, 1633, 1595, 1476 cm^{-1}.^{1}H NMR: (500 MHz, $CDCl_3$) δ 1.60 (s, 3H), 2.33 (s, 3H), 4.56 (s, 2H), 7.07–7.12 (m, 2H), 7.23–7.28 (m, 4H), 7.32–7.35 (m, 1H), 7.68 (d, 1H, J = 8.4 Hz).^{13}C NMR: (125 MHz, $CDCl_3$) δ 16.7, 21.4, 52.8, 115.3, 123.7, 127.2, 127.4, 127.8, 128.0, 128.9, 130.3, 131.5, 134.0, 135.0, 143.6. Mass (ESI): 378 (M^++1), 380 (M^++3). Anal. Calcd for $C_{17}H_{16}BrNO_2S$: C, 53.98; H, 4.26; N, 3.70. Found: C, 53.81; H, 4.31; N, 3.59.
20. *General procedure for the synthesis of 3-bromo-1, 2-dihydroquinoline derivatives* (**2a–2l**): To a stirred solution of *N*-tosyl-*N*-propargyl aniline (**1**) (1.0 mmol) in acetic acid, $Pd(OAc)_2$ (5 mol %), LiBr (1.0 mmol), and $CuBr_2$ (2.5 mmol) were added and refluxed at 80 °C. The reaction mixture was stirred until completion of the reaction as monitored by TLC. After the completion of the reaction saturated solution of $NaHCO_3$ was added and the product was extracted with ethyl acetate (3 × 10 mL). The organic layer was then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography on silica gel using ethyl acetate and hexane (2:8) as eluents to afford the pure product.
21. CCDC-729411 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
22. (a) Elsevier, C. J. *Coord. Chem. Rev.* **1999**, *185–186*, 809; (b) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83; (c) Canty, A. J.; Denney, M. C.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 1122.
23. (a) El-Qisairi, A.; Hamed, O.; Henry, P. M. J. *Org. Chem.* **1998**, *63*, 2790; (b) Hamed, O.; Henry, P. M. *Organometallics* **1998**, *17*, 5184; (c) El qisairi, A.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439. . L. J. Am. Chem. Soc. 1978, 100, 5800; (f) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. J. *Org. Chem.* **1996**, *61*, 3584; (e) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164.
24. *3-Bromo-6-methoxy-4-methylquinoline* (**3**): White crystalline solid. mp: 82–83 °C. ν_{max} (KBr): 2918, 1621, 1504, 1419 cm^{-1}.^{1}H NMR: (500 MHz, $CDCl_3$) δ 2.73 (s, 3H), 3.94 (s, 3H), 7.17 (d, 1H, J = 2.3 Hz), 7.34 (dd, 1H, J_1 = 9.2 Hz, J_2 = 3.1 Hz), 7.95 (d, 1H, J = 9.2 Hz), 8.74 (s, 1H). ^{13}C NMR: (125 MHz, $CDCl_3$) δ 18.5, 55.7, 102.3, 120.7, 121.5, 130.1, 131.6, 141.4, 142.5, 149.3, 158.5. Mass (ESI): 252 (M^++1), 254 (M^++3). Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56%. Found: C, 52.39; H, 3.97; N, 5.53.