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Pd-catalyzed amination of 6-halo-2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one

Ramesh Garlapati [a,b], Narender Pottabathini [a,*], Venkateshwarlu Gurram [a], Avinash B. Chaudhary [a], Venkata Rao Chunduri [b,*], Balaram Patro [a,*]

[a] Medicinal Chemistry Division, GVK Biosciences Pvt. Ltd., 28A, IDA Nacharam, Hyderabad 500076, AP, India
[b] Organic Chemistry Division, Department of Chemistry, Sri Venkateshwara University, Tirupathi 517 502, AP, India

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ABSTRACT

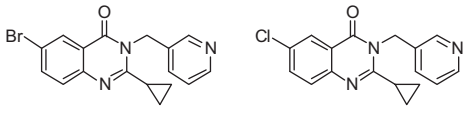
6-Halo-2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one derivatives have been synthesized and utilized for amination reactions with aryl, heteroaryl and alkyl amines. Optimization of reaction conditions with different catalysts, ligands, bases, and solvents was conducted. The combination of $Pd_2(dba)_3$ with DavePhos (L3) proved to be best for these conversions in the presence of NaO^{t}Bu in 1,4-dioxane at 100 °C. The relative reactivities of 6-bromo and 6-chloro-2,3-disubstitued quinazolinones with *p*-toluidine were conducted and as anticipated the 6-bromo analogue was totally consumed and 6-chloro derivative was completely unreactive.

The quinazoline moiety has proven to be a versatile building block for development of a variety of pharmaceutical entities. For example, many of the quinazolines show a broad spectrum of chemotherapeutic activities.[1–7] 2,3-Disubstituted 3*H*-quinazolin-4-ones are useful for the treatment for diabetes, obesity, and related disorders, as well as regulation of food intake. Certain quinazolinone derivatives are also useful for the treatment of wasting (e.g., cahexia) associated with cancer, AIDS, chronic liver diseases, chronic obstructive pulmonary disease (COPD), or respiratory insufficiency.[8]

The cyclopropyl group is an increasingly common structural motif in pharmaceutically active molecules due to its unique steric, electronic, conformational properties, and its microsomal metabolic stability.[9] Cyclopropyl is also smallest cyclic alkyl group to be generally included as substituent in medicinal chemistry for the structure–activity relationship studies.[10] Although there are many reports describing the synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones class of compounds, most of these approaches are limited in that only phenyl groups at N-3 are tolerated.[11] There are only a few specific reports on the preparation of the simple N-3 aliphatic, benzyl, and other heterocyclic functional groups of 2,3-disubstituted 3*H*-quinazolin-4-ones.[12] We have synthesized quinazoline-4-one with a pyridyl-3-ylmethyl group at N–3 position and have also introduced a cyclopropyl group at C-2 position.

Palladium-catalyzed amination reactions have become an important type of transformation to construct C–N bonds among a wide range of substrates.[13] Currently there is no literature evidence for introduction of amino groups into the C-6 position of 2-cyclopropyl-quinazoline-4-one derivatives. Sui Xiong Cai et al. synthesized 6-*N*,*N*-dimethylamino-2-methyl-*N*-methyl-4-(4-methoxyanilino) quinazoline and it was prepared by hydrogenation of the 6-nitro analogue, followed by the reductive amination with formaldehyde in the presence of sodium cyanoborohydride.[14] Herein we report a novel Pd-catalyzed amination reaction at C-6 of 2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one in excellent yields. Another highlight of this report is the stability of the cyclopropyl moiety toward the amination conditions.

For the present work, 6-bromo and 6-chloro-2-cyclopropyl-3-(pyridyl-3-ylmethyl)quinazolin-4(3*H*)-ones were chosen for study.



3a 3b

Figure 1. 6-Halo-2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-ones selected for analysis.

* Corresponding authors. Tel.: +91 40 66281666; fax: +91 40 66281515 (B.P.); tel.: +91 40 66281275; fax: +91 40 66281515 (N.P.).
E-mail addresses: narender.pottabathini@gvkbio.com (N. Pottabathini), cvrsvu@gmail.com (V.R. Chunduri), balaram.patro@gvkbio.com (B. Patro).

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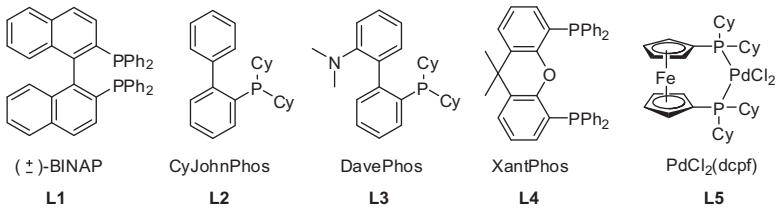
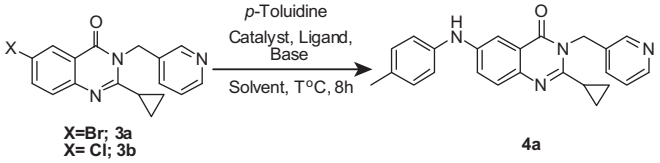


Figure 2. Four ligands and one pre-catalyst selected for the analysis.

Table 1
Optimization of C–N bond forming reactions[a,b]



Entry	Catalyst system, conditions, t = 8 h	Yield[c] (%)
1	25 mol % $Pd(PPh_3)_4$/NaO^{t}Bu, 1,4-dioxane, 100 °C	48
2	10 mol % $Pd(OAc)_2$/15 mol % **L1**/Cs_2CO_3, 1,2-DME, 90 °C	45
3	10 mol % $Pd(OAc)_2$/15 mol % **L2**/Cs_2CO_3, 1,2-DME, 90 °C	66(48)[d]
4	10 mol % $Pd(OAc)_2$/15 mol % **L2**/Cs_2CO_3, toluene, 110 °C	25
5	10 mol % $Pd(OAc)_2$/15 mol % **L2**/K_3PO_4, toluene, 110 °C	35
6	10 mol % $Pd(OAc)_2$/15 mol % **L3**/NaO^{t}Bu, 1,4-dioxane, 100 °C	81 (58)[d]
7	10 mol % $Pd(OAc)_2$/15 mol % **L4**/Cs_2CO_3, 1,2-DME, 90 °C	54
8	10 mol % $Pd(OAc)_2$/15 mol % **L4**/K_3PO_4, 1,2-DME, 90 °C	66 (41)[d]
9	10 mol % $Pd(OAc)_2$/15 mol % **L4**/NaO^{t}Bu, 1,4-dioxane, 100 °C	87
10	10 mol % $Pd_2(dba)_3$/15 mol % **L1**/K_3PO_4, 1,4-dioxane, 100 °C	74 (62)[d]
11	10 mol % $Pd_2(dba)_3$/15 mol % **L3**/NaO^{t}Bu, 1,4-dioxane, 100 °C	93 (78)[d]
12	10 mol % $Pd_2(dba)_3$/15 mol % **L4**/K_3PO_4, 1,2-DME, 90 °C	55
13	10 mol % $Pd_2(dba)_3$/15 mol % **L4**/K_3PO_4, toluene, 110 °C	34
14	20 mol % $PdCl_2$(dcpf), Cs_2CO_3, 1,4-dioxane, 100 °C	29

[a] Reaction conditions (entries 1–14) 6-bromo, **3a** precursor 0.0711 mM in anhydrous solvent, 3.0 mol. equi. *p*-toluidine, 1.5 mol equi. of base.
[b] Reactions were conducted in closed vial sparged with argon.
[c] % Yields refer to isolated and purified products.
[d] Yield obtained with chloro substrate **3b**.

The overall aim was to determine the best conditions for amination of both the precursors and to find the optimal conditions that can be applied for the synthesis of a broad range of 6-aryl, heteroaryl, and alkyl, 2,3-disubstituted quinazolinones.

Both halo quinazoline-4-one precursors **3a** and **3b** (Fig. 1) are conveniently synthesized by known procedures (See the Supplementary data for details).[15] With **3a** and **3b** in hand, conditions for Pd-catalyzed amination reactions were evaluated. $Pd(OAc)_2$ and $Pd_2(dba)_3$ served as metal sources, further more ligands **L1**–**4** (Fig. 2) and a ferrocenyl Pd(II) precatalyst (**L5**, Fig. 2) were also selected for the investigation.

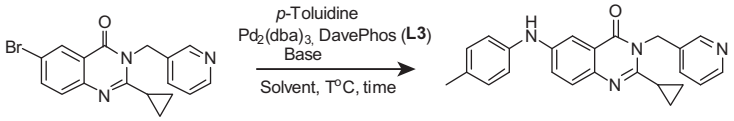
The optimization experiments were performed with *p*-toluidine. Results from our initial investigations are shown in Table 1.

The initial attempts with $Pd(PPh_3)_4$ (25 mol %), NaO^{t}Bu, 1,4-dioxane resulted in low yield (entry 1). The combination of $Pd(OAc)_2$, with **L1** (entry 2), **L2** (entries 3, 4 and 5), **L3** (entry 6), or **L4** (entries 7, 8 and 9) ligands, in the presence of Cs_2CO_3(entry 2, 3, 4 and 7), K_3PO_4 (entries 5 and 8), and NaO^{t}Bu (entries 6 and 9) as base, 1,4-dioxane (entries 6 and 9, at 100 °C), toluene (entries 4 and 5 at 110 °C) and 1,2-DME (entries 2, 3, 7 and 8, at 90 °C) as solvents lead to good to moderate product formation from 25 to 87% yields in 8 h with *p*-toluidine. The combination of $Pd_2(dba)_3$ with **L1** (entry 10), **L3** (entry 11), and **L4** (entries 12 and 13) with different bases and solvents also resulted in moderate to excellent yields (34–93%). The reaction with the precatalyst, $PdCl_2$(dcpf) also ended up with low yield (entry 14, 29%). Among these initial screening reactions, 10 mol % $Pd_2(dba)_3$/15 mol % **L3**/1.5molar eq. NaO^{t}Bu in 1,4-dioxane at 100 °C was proved to be the best (93%, entry 11) and 10 mol % $Pd(OAc)_2$/15 mol % **L4**/NaO^{t}Bu in 1,4-dioxane was proved to be the next best catalyst/ligand system (87%, entry 9) for Pd-catalyzed amination. The total reaction time for all reactions was 8 h. These yields did not change appreciably when the reactions were conducted over 8 h.

After identifying proper catalyst/ligand system, we further investigated the catalyst/ligand loading, influence of base, solvent, and temperature. These results are tabulated in Table 2. The initial reactions were conducted with 10 mol % $Pd_2(dba)_3$/15 mol % **L3**/ 1.5 mol. equi. NaO^{t}Bu in 1,4-dioxane at 100 °C (93%, entry 1). The reduction of catalyst/ligand loading to 5 mol % $Pd_2(dba)_3$/7.5 mol % **L3** resulted in 81% yield (entry 2) and on further reduction to 5 mol % $Pd_2(dba)_3$/5 mol % **L3** resulted in a drastical drop of yield to 53% (entry 3). It was also observed that increasing the catalytic loading to 15 mol % $Pd_2(dba)_3$/15 mol % **L3** (entry 4), 20 mol % $Pd_2(dba)_3$/20 mol % **L3** (entry 5), and 20 mol % $Pd_2(dba)_3$/30 mol % **L3** (entry 6) did not change the yields.

The influence of base and solvent was also evaluated. We initially examined the influence of the nature of base on the conversion for the reactions using 1,4-dioxane as solvent and 10 mol % $Pd_2(dba)_3$/15 mol % **L3** as the catalyst/ligand system. NaO^{t}Bu was superior to K_3PO_4, Cs_2CO_3, and K_2CO_3, whereas CsF was ineffective.

Table 2
Screening of catalyst loading, base, solvent, and temp for the C–N coupling of **3a** with *p*-toluidine[a]



3a **4a**

Entry	Variable conditions	Time (h), Temp (°C)	% of **4a** formed
1	10 mol % $Pd_2(dba)_3$, 15 mol % **L3**	8, 100	93[b]
2	5 mol % $Pd_2(dba)_3$, 7.5 mol % **L3**	8, 100	81[b]
3	5 mol % $Pd_2(dba)_3$, 5 mol % **L3**	8, 100	55[b]
4	15 mol % $Pd_2(dba)_3$,15 mol % **L3**	8, 100	89[b]
5	20 mol % $Pd_2(dba)_3$, 20 mol % **L3**	8, 100	90[b]
6	20 mol % $Pd_2(dba)_3$, 30 mol % **L3**	8, 100	93[b]
7	K_3PO_4	8, 100	63[c]
8	NaO^tBu	8, 100	93[c]
9	Cs_2CO_3	8, 100	71[c]
10	K_2CO_3	8, 100	66[c]
11	CsF	8, 100	10[c]
12	1,4-Dioxane	8, 100	93[d]
13	1,2-DME	8, 90	62[d]
14	Toluene	8, 100	27[d]
15	*tert*-BuOH	8, 100	43[d]
16	Conventional	8, 100	90[b]
17	Sample vial	8, 100	93[b]
18	Microwave	0.5, 100	93[b]

[a] Reaction conditions (entries 1–18) bromoquinazolinone (**3a**) 0.0711 mM in anhydrous solvent, 3.0 mol. equi. *p*-toluidine, 1.5 mol. equi. of base and% yields refer to isolated and purified products.
[b] 1.5 Mol. equi. of NaO^tBu, 1,4-dioxane as solvent.
[c] Only change in base, 1,4-dioxane as solvent
[d] Change in solvent only, other conditions were unaltered, 1.5 mol. equi. of NaO^tBu.

We have observed that the nature of the solvent often modifies the catalyst activity in cross-coupling reactions. Among the solvents 1,4-dioxane was much superior to 1,2-DME, toluene, and *tert*-BuOH. Majority of these reactions were conducted in closed vials, only one reaction was performed in a round bottomed flask fitted with reflux condenser. This reaction was also complete in 8 h with 90% product. Under the microwave irradiation there was significant rate acceleration (reaction time 30 min at 100 °C) but yield remained the same as the reaction in sample vial (compound **4a** with 93% yield).

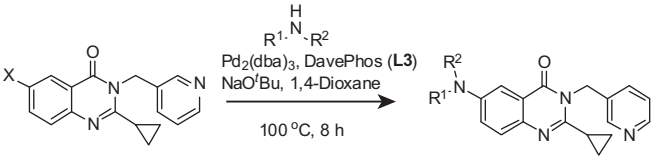
With the optimal conditions ascertained, in the next stage we evaluated the generality of the methodology with variety of amines shown in Table 3. A wide assortment of aryl, heteroaryl, and alkyl amines participated in the Pd-catalyzed amination reactions.

The amines with electron donating groups like *p*-toludine (entry 1), *o*-methoxyaniline (entry 6), and substituted morpholine with oxygen atom are flanked by two methyl groups (entry 15) resulted in excellent yields. The naphthalene system resulted in good yield (entry 11). We were extremely gratified to observe that reactions of amines with electron-with drawing groups like 4-cyanoaniline (entry 4), fluorinated substituents like 2-fluoro and 2-trifluoromethyl benzyl amines (entries 13 and 14) also resulted in good yields. The reactions were also efficient with aliphatic amines (entries 17, 18 and 19). Reactions with heteroaryl amines resulted in moderate yields from 44% to 55% (entries 8, 9 and 10).

Relative reactivity studies of bromo quinazolinone **(3a)** and chloro quinazolinone **(3b)**[17]

It is evident that **3a** is superior to **3b** in terms of product yield under the C–N bond forming conditions (Table 3). We decided to determine their relative reactivities in a competitive experiment. For this we conducted a reaction of an equimolar amount of **3a** and **3b** (1.5 mol. equi. each) with 1 mol. equi of *p*-toluidine, under the optimized conditions. After the complete consumption of

Table 3
Evaluation of the scope of amination reaction of 6-bromo (**3a**) and 6-chloro -3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one (**3b**)[ab] using various amines[16]



X= Br; 3a
X= Cl; 3b

4a - 4q

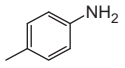
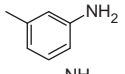
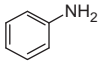
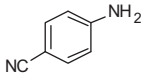
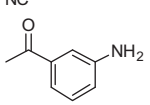
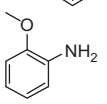
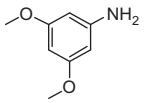
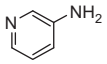
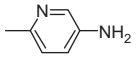
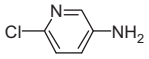
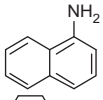
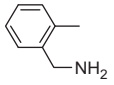
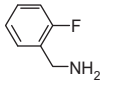
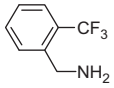
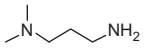
Entry	Amine	Product	Yield, %[c]
1		**4a**	93 (82)[d]
2		**4b**	91 (71)[d]
3		**4c**	91
4		**4d**	76
5		**4e**	91 (83)[d]
6		**4f**	91

Table 3 (*continued*)

Entry	Amine	Product	Yield, %[c]
7		**4g**	92
8		**4h**	44
9		**4i**	56
10		**4j**	45
11		**4k**	87
12		**4l**	78
13		**4m**	88
14		**4n**	83 (71)[d]
15		**4o**	91
16		**4p**	87
17		**4q**	87
18		**4r**	81
19		**4s**	55 (51) [d]

[a] Reaction conditions (entries 1–19) bromo (**3a**) and chloro (**3b**) precursors 0.0711 mM in anhydrous, 3 mol. equi. amine, 1.5 equiv NaO^tBu, 10 mol % of $Pd_2(dba)_3$, 15 mol % L3, 100 °C.
[b] Reactions were conducted in closed vial sparged with argon.
[c] % Yields refer to isolated and purified products.
[d] Yield obtained with chloro substrate **3b**.

p-toluidine the experiment was stopped, product **4a** as well as reactants **3a**, **3b** were collected together by column chromatography, and subjected to LC/MS analysis. In the mixture, bromo quinazolinone **3a** was completely consumed and 43.9% of the chloro quinazolinone **3b** was observed. Compound **3b** was completely unreactive and it was completely recovered at the end of the reaction. In addition, LC/MS analysis indicated formation of the dehalogenated quinazolinone in *ca* 4.1% yield (Fig. 3).

This experiment shows two important factors. First, that C-6 bromo quinazolinone precursor **3a** is more rapidly consumed than chloro analogue **3b**, and second, reductive dehalogenation does not appear to be significant. Figure 3 shows the LC trace of the reaction mixture from the competition experiment. The LC/MS analysis data can be found in the Supplementary data.

In conclusion, Pd-catalyzed C–N bond formation is effective for the introduction of substituted amino groups at the C-6 position of 2-cyclopropyl-3-(pyridyl-3-ylmethyl)quinazolin-4(3*H*)-ones. The combination of 10 mol % $Pd_2(dba)_3$, 15 mol % DavePhos (**L3**)/NaO^t-Bu in 1,4-dioxane gave good to excellent yields with 6-bromo and 6-chloro-2-cyclopropyl-3-(pyridyl-3-ylmethyl) quinazolin-4(3*H*)-one using a variety of aryl, heteroaryl, and alkyl amines. The methodology for the amination appears to be broad in scope for 2,3-disubstituted quinazoline-4-ones. To our knowledge, this

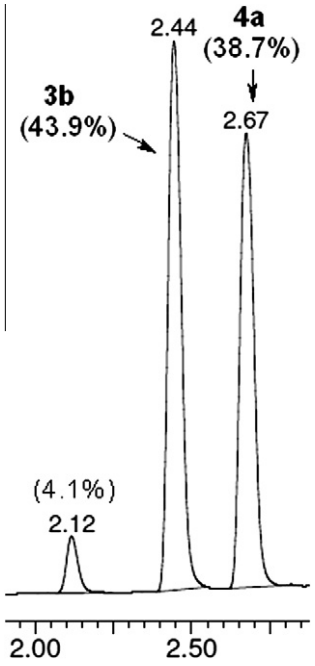


Figure 3. LC analysis of the reaction mixture from a competitive reaction of compound **3a** and compound **3b** with *p*-toluidine (showing the integrated percentages).

is the first report on successful C–N bond forming reactions at the C-6 position of 2, 3-disubstituted quinazoline-4-ones, particularly with a cyclopropyl substituent that is stable under the amination conditions. Finally, we have studied the relative reactivities of the bromo and chloro quinazolinone precursors toward amination and it was clear that former is superior.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

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16. Typical experimental procedure for the preparation of compound **4a**: In an oven dried, screw-cap vial equipped with a stirring bar were placed 6-bromo-2-cyclopropyl-3-(pyridin-3-ylmethyl) quinazolin-4(3*H*)-one (**3a**) (100 mg, 0.28 mmol) dissolved in anhydrous 1, 4-dioxane (2 mL), *p*-toluidine (90 mg, 0.85 mmol), and NaO^{t}Bu (53 mg, 0.56 mmol). The vial was flushed with argon for 10 min, $Pd_2(dba)_3$ (2.5 mg, 0.028 mmole) and DavePhos (**L3**) (1.7 mg, 0.042 mmol) were added. The vial was sealed with a Teflon-lined cap, and placed in a sand bath that was maintained at 100 °C. The reaction was monitored by TLC. Upon completion at 8 h, the mixture was cooled and diluted with CH_2Cl_2. The mixture was washed with water and the organic layer was separated and dried over anhydrous Na_2SO_4. The mixture was evaporated under reduced pressure. The crude product was purified by column chromatography, compound was loaded onto a silica column packed in CH_2Cl_2. Sequential elution with pet-ether, followed by 20% EtOAc in pet-ether afforded compound **4a** (100 mg, 93% yield) as white solid.
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