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Palladium(0)-catalyzed Carbon–Hydrogen Bond Functionalization for Synthesis of Indoloquinazolinones

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Abstract. Indoloquinazolinone has attracted considerable attentions as a pharmacophore, because it shows various biological activities. The reported synthetic methods for the compound are simple and direct, but are not effective for direct synthesis of indoloquinazolinone with a methylene at the C6 position. A palladium(0)-catalyzed cyclization of chloroquinazolinone via C–H functionalization was developed for a concise synthesis of indoloquinazolinone derivatives. The presence of a substituent at the C6 position is important for obtaining the product in good yield. The conformation of the reaction intermediate, in particular the N-C-Pd bond angle, is important for regioselectivity of the reaction.

Keywords: C–H functionalization; Cyclization; Indoloquinazolinone; Palladium; Regioselectivity; Substituent effects

Indoloquinazolinone is a tetracyclic alkaloid skeleton consisting of a quinazolinone ring fused to an indole and is found in several natural products including tryptanthrin,[1a,b] phaitanthrins[1c] and ophiuroidine[1d] (Figure 1). These alkaloids show various biological activities, including antibiotic,[2] antiparasitic,[3] anticancer,[1c,4] and antitubercular[5] activities. As such, indoloquinazolinone has attracted considerable attentions as a pharmacophore.

To date, several synthetic methods have been developed to further the biological studies on these natural products and their congeners.[1b] Indoloquinazolinones are generally prepared by coupling of isatin and isatoic anhydride, under basic conditions, although the scope of this method is limited.[6] Recently, Argade and co-workers reported aryne insertion into quinazolinones as an effective synthesis for indoloquinazolinone, and achieved a concise total synthesis of phaitanthrins.[7] Reactions that generate indoloquinazolinone under mild conditions using Oxone-induced[8] and copper-catalyzed aerobic oxidation[9] were developed by Grundt, and Liu and Wang, respectively. These synthetic methods are simple and direct, but are not effective for direct synthesis of indoloquinazolinone with a methylene at the C6 position. For accessing the indoloquinazolinone, a two-step sequence consisting of a formation of indoloquinazolinedione and a reduction is often employed.[10] While there are three reports of direct construction of the reduced form, the scope of these methods is limited.[11] There remains a need for a direct method to construct the reduced form.

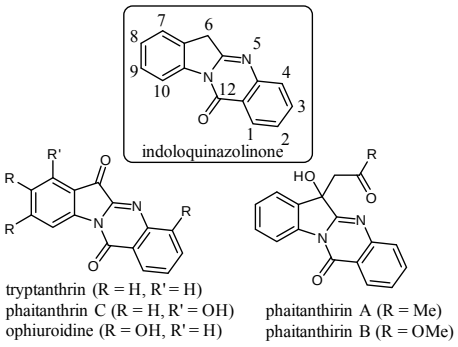
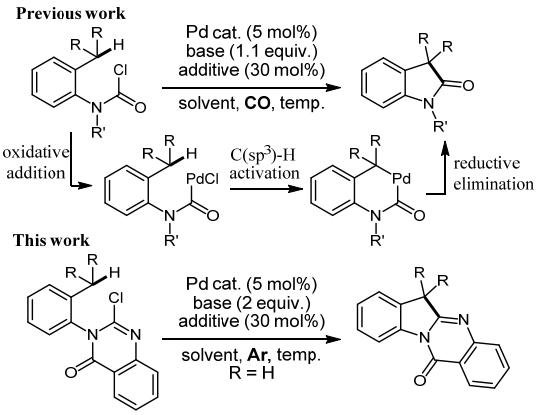


Figure 1. Indoloquinazolinone natural products.

Pd-catalyzed C(sp^3)–H bond activation has attracted attention for the development of more straightforward synthetic routes with better atom-economy.[12] To date, several examples of Pd-catalyzed C(sp^3)–H functionalization for synthesis of heterocycles have been reported, including indole-related compounds.[13-15] We previously reported the synthesis of oxindole and spirooxindole from carbamoyl chlorides with a methyl and cyclopropyl group at the ortho position, through oxidative addition, benzylic C(sp^3)–H activation and reductive elimination of the resultant palladacycle (Scheme 1).[15a,c] The synthesis of 3-acyl-2-arylindole derivatives was also performed through Pd(0)-catalyzed isocyanide insertion and oxypalladation of an alkyne.[15b] These results suggest that indoloquinazolinone could be accessed from chloroquinazolinone via Pd(0)-catalyzed C(sp^3)–H functionalization. In the synthesis of oxindole, the main side reaction was decarboxylation after oxidative addition, requiring the reaction to be performed under a CO atmosphere. In contrast, CO is not required in the synthesis of indoloquinazolinone

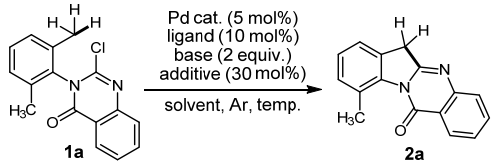
because the reaction intermediate is stabilized by attachment to another ring system. Additionally, this may allow the direct synthesis of indoloquinazolinones having a methylene group at the C6 position from simple starting materials. Thus, use of a Pd(0)-catalyzed C(sp^3)-H activation has good potential for this cyclization. In this paper, we report a short synthesis of indoloquinazolinone in its reduced form, via Pd(0)-catalyzed C(sp^3)–H functionalization.



Scheme 1. Pd(0)-catalyzed C(sp^3)–H functionalization for synthesis of heterocycles.

For initial investigations, chloroquinazolinone **1a** was first prepared from 2,6-dimethylaniline in four steps including isocyanate formation, condensation with anthranilic acid and chlorination using $POCl_3$. We first attempted the cyclization of chloroquinazolinone **1a** under the conditions used for the synthesis of oxindoles without a CO atmosphere, namely 5 mol % palladium acetate, 10 mol % Ad_2PBu, two equivalents of Cs_2CO_3 and 30 mol % *N*-hydroxypivalamide (PivNHOH) in mesitylene at 140 °C. The reaction proceeded to give indoloquinazolinone **2a** in 22% yield (entry 1). Use of Na_2CO_3 instead of Cs_2CO_3 improved the yield (entry 2). While the reaction with tBu$_3$P·HBF$_4$ gave the product **2a** in 17% yield, the addition of dialkylbiarylphosphine ligands including Sphos, Xantphos and DavePhos gave no reaction (entries 3–6). Interestingly, the reaction with 20 mol % PPh_3 proceeded to give **2a**, although at 10 mol % of ligand, the yield significantly decreased (entries 7 and 8). To improve the yields, several palladium catalysts were also examined. While [η^3-(C_3H_5)PdCl]$_2$ was not effective, it was found that $Pd_2(dba)_3$ and $Cy_3P{\cdot}HBF_4$, and $Pd(PPh_3)_4$ gave better yields (entries 9–11).

Table 1. Investigation of Pd(0)-catalyzed C(sp^3)-H functionalization for synthesis of indoloquinazolinone **2a**.



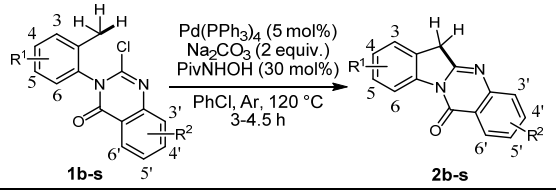
Entry	Pd cat.	Ligand	Base	Additive	Solvent	Temp.	Yield [a]
1	$Pd(OAc)_2$	Ad_2PBu	Cs_2CO_3	PivNHOH	mesitylene	140 °C	22%
2	$Pd(OAc)_2$	Ad_2PBu	Na_2CO_3	PivNHOH	mesitylene	140 °C	56%
3	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	Na_2CO_3	PivNHOH	mesitylene	140 °C	17%
4	$Pd(OAc)_2$	SPhos	Na_2CO_3	PivNHOH	mesitylene	140 °C	0%
5	$Pd(OAc)_2$	Xantphos	Na_2CO_3	PivNHOH	mesitylene	140 °C	0%
6	$Pd(OAc)_2$	DavePhos	Na_2CO_3	PivNHOH	mesitylene	140 °C	0%
7	$Pd(OAc)_2$	PPh_3	Na_2CO_3	PivNHOH	mesitylene	140 °C	trace
8	$Pd(OAc)_2$	PPh_3 [b]	Na_2CO_3	PivNHOH	mesitylene	140 °C	28%
9	[(η^3-C_3H_5)PdCl]$_2$	Ad_2PBu	Na_2CO_3	PivNHOH	mesitylene	140 °C	28%
10	$Pd_2(dba)_3$ [c]	$Cy_3P{\cdot}HBF_4$	Na_2CO_3	PivNHOH	mesitylene	140 °C	68%
11	$Pd(PPh_3)_4$	none	Na_2CO_3	PivNHOH	mesitylene	140 °C	68%
12	$Pd(PPh_3)_4$	none	Cs_2CO_3	PivNHOH	mesitylene	140 °C	26%
13	$Pd(PPh_3)_4$	none	K_2CO_3	PivNHOH	mesitylene	140 °C	33%
14	$Pd(PPh_3)_4$	none	NaOAc	PivNHOH	mesitylene	140 °C	42%
15	$Pd(PPh_3)_4$	none	Et_3N	PivNHOH	mesitylene	140 °C	0%
16	$Pd(PPh_3)_4$	none	Na_2CO_3	none	mesitylene	140 °C	0%
17	$Pd(PPh_3)_4$	none	Na_2CO_3	PivOH	mesitylene	140 °C	34%
18	$Pd(PPh_3)_4$	none	Na_2CO_3	PivNHOH	mesitylene	160 °C	18%
19	$Pd(PPh_3)_4$	none	Na_2CO_3	PivNHOH	mesitylene	120 °C	58%
20	$Pd(PPh_3)_4$	none	Na_2CO_3	PivNHOH	toluene	100 °C	46%
21	$Pd(PPh_3)_4$	none	Na_2CO_3	PivNHOH	PhCl	120 °C	76%
22	$Pd(PPh_3)_4$	none	Na_2CO_3	PivNHOH	DMA	120 °C	0%

[a] Isolated yield. [b] 20 mol % of PPh_3 was used. [c] 2.5 mol % of $Pd_2(dba)_3$ was used.

Using $Pd(PPh_3)_4$ as a catalyst, extensive screening of bases, additives, temperature and solvents was performed. Several bases were tested including K_2CO_3, Cs_2CO_3 and NaOAc, which gave the product **2a** in 26–42% yield (entries 12–14). No desired product was obtained in the case of triethylamine (entry 15). The use of an additive was essential for this reaction, and PivNHOH gave a higher yield than PivOH (entries 16 and 17).[15a] While higher reaction temperatures gave lower yields, at 100–120 °C the reaction proceeded to give a reasonable yield (entries 18 and 19). Aromatic hydrocarbons including mesitylene, toluene and PhCl were effective solvents, with the best yields for PhCl (entries 19–21). In contrast, the use of dimethylacetamide (entry 22) did not give any of the cyclized products. Therefore, we set the conditions as 5 mol % of $Pd(PPh_3)_4$, two equivalents of Na_2CO_3 and 30 mol % of PivNHOH in PhCl at 120 °C for further investigations (entry 21).

We next investigated the scope and limitations of the reaction (Table 2). Cyclization of chloroquinazolinones **1b**–**d**, containing ethyl, chloro- and methoxy groups, under the optimized conditions proceeded smoothly to give indoloquinazolinones **2b**–**d** in good to excellent yield (entries 1–3). The presence of substituents at the other ortho position (i.e., the C6 position) gave good results, while yields

Table 2. Synthesis of various indoloquinazolinones **2**.



1b-s **2b-s**

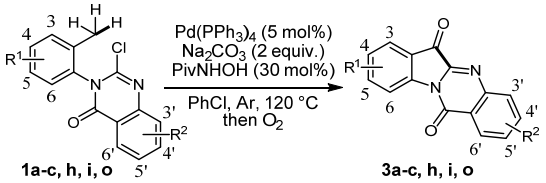
Entry	R^1	R^2	Product	Yield [a]
1	6-Et	H	**2b**	quant.
2	6-Cl	H	**2c**	68%
3	6-MeO	H	**2d**	70%
4	H	H	**2e**	58%
5 [b]	3-Me	H	**2f**	32% [c]
6 [d]	4-MeO	H	**2g**	16% [e]
7	6-Me	5′-F	**2h**	quant.
8	6-Me	5′-Cl	**2i**	93%
9	6-Me	5′-Br	**2j**	0%
10 [f]	6-Me	3′-Me	**2k**	63%
11	6-Me	5′-Ph	**2l**	74%
12	6-Me	5′-CH=CH_2	**2m**	52%
13	6-Me	4′-CO_2Me	**2n**	80%
14	6-Me	4′,5′-$(MeO)_2$	**2o**	99%
15	6-Me	4′-CO_2H	**2p**	0%
16	6-Me	5’-OH	**2q**	0%
17	6-Me	5’-OTBS	**2r**	43% [g]
18	6-Me, 4-NMe_2	H	**2s**	90%

[a] Isolated yield. [b] The reaction was performed for 6.5 h. [c] Starting material **1f** was recovered in 58% yield. [d] The reaction was performed for 5.5 h. [e] Starting material **1g** was recovered in 68% yield. [f] 10 mol % of $Pd(PPh_3)_4$ and 3 equiv. of Na_2CO_3 were used. [g] based on recovered starting material.

for substrates having no substituent at the C6 position were less favorable. For example, cyclization of **1e**–**g** gave indoloquinazolinones **2e**–**g** in yields of 16–58% with a significant amount of starting material recovered (entries 4–6). This may be attributed to the ortho effect proposed by Catellani et al.[16] Several substituents including fluoro-, chloro-, methoxy, phenyl, vinyl groups, ester and amine on the aromatic ring were tolerated under these conditions and the desired indoloquinazolinones **2h**, **i**, **k**–**o**, **s** were obtained in moderate to good yields (entries 7, 8, 10–14, 18). Interestingly, chloroquinazolinones **1c** and **1i** featuring a chloro- group on the aromatic ring could be used for this reaction and elimination of chloride was not observed (entries 2 and 8). In the case of a substrate having bromo group, the cyclization did not proceed probably due to deactivation of the palladium catalyst by competitive oxidative addition (entry 9). Although substrates **1p** and **1q** having alcohol and carboxylic acid were not suitable for this reaction, the reaction of **1r**, in which an hydroxyl group was protected as siloxy ether, gave the cyclized product **2r** (entries15-17). As described in previous reports,[10] the majority of the obtained indoloquinazolinones were unstable and readily oxidized to indoloquinazolinedione on exposure to atmosphere.

Thus we examined a one-pot reaction including cyclization and oxidation for the synthesis of indoloquinazolinedione (Table 3). Chloroquinazolinone **1a** was treated under the same conditions. The argon atmosphere was then replaced by oxygen and the reaction mixture was stirred at room temperature for several hours. As expected, indoloquinazolinedione **3a** was obtained in 57% yield (entry 1). Several substituents on the aromatic ring including fluoro-, chloro- and alkyl groups were tolerated under these conditions for the synthesis of indoloquinazolindione, although the yields were low compared with the corresponding indoloquinazolinone (entry 2–5). Interestingly, oxidation of the indoloquinazolinone **2o** possessing an electron-rich aromatic ring was slow, and the reaction for 1 h gave **3o** in 24% yield with a significant amount of **2o** (entry 6).

Table 3. Synthesis of various indoloquinazolinediones **3**.

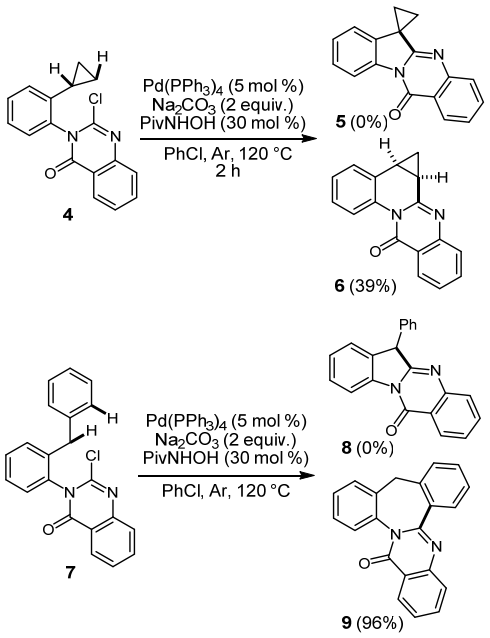


1a-c, h, i, o **3a-c, h, i, o**

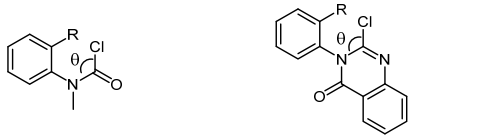
Entry	R^1 [a]	R^2 [b]	Product	yield [a]
1	6-Me	H	**3a**	57%
2	6-Et	H	**3b**	80%
3	6-Cl	H	**3c**	35%
4	6-Me	5′-F	**3h**	50%
5	6-Me	5′-Cl	**3i**	55%
6	6-Me	4′,5′-$(MeO)_2$	**3o**	24% [b]

[a] Isolated yield. b) Compound **2o** was also obtained in 70% yield.

We then turned our attention to the regioselectivity of the reaction of chloroquinazolinone having substituents other than a methyl group. Because we developed the cyclization of compound **10** for synthesis of spirooxindole based on methine C(sp^3)–H functionalization (Figure 2), the reaction of chloroquinazolinone **4** having a cyclopropyl group was attempted under the optimized conditions (Scheme 2). Interestingly, the reaction proceeded to give cyclized compound **6** in 39% yield via methylene C(sp^3)–H functionalization, and the indoloquinazolinone **5** was not observed. Additionally, the reaction of **7** with a benzyl instead of a methyl group resulted in formation of a seven-membered ring via C(sp^2)–H functionalization, without any five-membered ring formation leading to indoloquinazolinone **8**. For the carbamoyl chloride **11**, the cyclization did not occur at all. This selectivity was unexpected,[17] and stable conformations of the chloroquinazolinones **4**, **7** and carbamoyl chlorides **10**, **11** were evaluated using Gaussian 09[18] at the B3LYP/6-31G* level,[19] to explain this result (Figure 2).[20] Our preliminary calculations indicate a large difference in the N–C–Cl bond angles of the intermediates (115.86° vs 113.19°, for **4** and **10**; 116.29° vs 113.10°, for **7** and **11**, respectively). It is suggested that the palladium center of the reaction intermediates derived from carbamoyl chlorides **10** and **11** are closer to the benzylic C–H bond than the cyclopropyl methylene C(sp^3)–H and the aromatic C(sp^2)–H bonds. In sharp contrast, the methylene C(sp^3)–H of the cyclopropyl ring and the aromatic C(sp^2)–H bonds of the chloroquinazolinones **4** and **7** can readily approach the palladium center of the intermediated to form six- and seven-membered rings.



Scheme 2. Regioselective cyclization of chloroquinazolinones **4** and **7**.



10 (R = cyclopropyl): θ = 113.19° **4** (R = cyclopropyl): θ = 115.86°
11 (R = CH_2Ph): θ = 113.10° **7** (R = CH_2Ph): θ = 116.29°

Figure 2. Carbamoyl chlorides having cyclopropyl and benzyl groups and bond angles of the carbamoyl chloride **10**, **11** and chloroquinazolinone **4**, **7** calculated by Gaussian 09.

In summary, we have developed a reaction for the synthesis of indoloquinazolinone **2** and indoloquinazolinedione **3** via Pd(0)-catalyzed C-H functionalization. Several substituents were tolerated under the optimized conditions, although the presence of substituents at the C6 position is important for obtaining the product in good yield. It was found that for substrates containing benzyl and cyclopropyl groups, the reaction did not occur at the benzylic position probably because of the larger N–C–Pd angle of the reaction intermediate compared with that of the carbamoyl chloride substrate.

Experimental Section

Synthesis of 10-methylindolo[2,1-b]quinazolin-12(6*H*)-one (**2a**): 2-chloro-3-(2,6-dimethylphenyl)quinazolin-4(3*H*)one (**1a**) was mixed with $Pd(PPh_3)_4$ (5.0 mol%), sodium carbonate (2.0 equiv.) and PivNHOH (30 mol%). Under an argon atmosphere, chlorobenzene (0.1 M) was added to the mixture. The reaction mixture was stirred at 120 °C for 3 h until the starting material was completely consumed. The resulting mixture was filtered through celite and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to give 10-methylindolo[2,1-b]quinazolin-12(6*H*)-one (**2a**) in 76% yield as a solid: m.p. 208-210 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.67 (ddd, 1H, *J* = 8.5, 7.5, 1.5 Hz), 7.59 (d, 1H, *J* = 8.0 Hz), 7.41 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz), 7.21-7.12 (m, 3H), 4.13 (s, 2H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 158.1, 146.9, 139.7, 134.2, 132.4, 128.0, 127.6, 127.1, 126.6, 126.5, 126.2, 121.9, 121.7, 36.4, 23.7; IR (ATR, cm^{-1}): 3069, 2928, 1724, 1699, 1585, 1464, 1307, 1178, 753, 687; MS (FAB) *m/z* 249 $(M+H)^+$; HRMS calcd for $C_{16}H_{13}N_2O$ $(M+H)^+$ 249.1028; Found: *m/z* 249.1027.

Acknowledgements

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