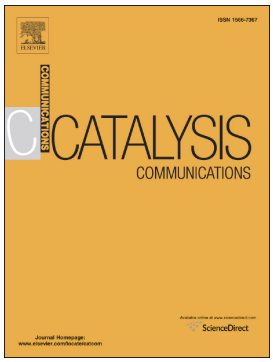

Methoxylation on the C5 and C6 positions of quinolines with methanol

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Methoxylation on the C5 and C6 Positions of Quinolines with Methanol

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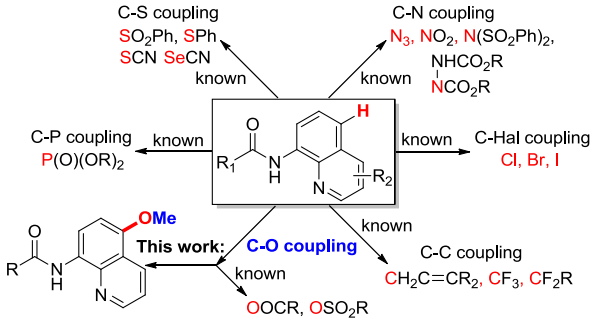
Abstract

The C(5)−H and C(6)−H methoxylation of quinoline amides with methanol was presented by using $PtCl_2$ or triethylamine as an additive. The reaction when conducted under mild conditions provides expedient access to quinoline derivatives, which are frequently found in many drug candidates.

Keywords: 8-Aminoquinoline amides; Methoxylation; Trimethoxylation

Introduction

Etherification as an important reaction can be traced back to 1852[1]. Since then, more attention has been paid to explore many new methods for the formation of C–O bonds. In the past decades, C–H activation/C–O bond formation was used as a facile and robust method for the synthesis of ethers or esters. For example, the radical addition of a C(sp^2) atom to halides[2], phenols[3], the carbonyl oxygen of amides[4], ketones[5], phenylacetic acids[6], or esters[7] was reported as a novel strategy to construct C–O bonds. Moreover, an unactivated C(sp^3)–H bond can also be reacted with hydroxyl[8], phosphonic, or phosphinic acids[9] to synthesize *N*-arylindolines and benzoxaphosphole 1- or 2-oxides. The 8-aminoquinoline scaffold is an important motif, which is widely found in bioactive compounds, natural products, and pharmaceuticals[10]. Thus, methods for their expeditious functionalization are highly desirable. For example, it can work as the directing group in C-H activation[11], and the functionalization of quinolines at the C5 position has received considerable attention. Many approaches for C(5)–H fluoroalkylation[12], halogenation[13], sulfonylation[14], selenylation[15], thio/selenocyanation[16], nitration[17], amination[18], azidation[19], amidation[20], and phosphonation[21] have been developed (**Scheme** 1). Moreover, many methods for the C5 selective formation of C–O bonds by C-H activation have also been developed. For example, Vinayak[22] and coworkers demonstrated the C5 benzoylation of quinolines in the presence of an iron catalyst. The Volla[23] group developed a direct C(sp^2)-H acetoxylation of quinolines using $PhI(OAc)_2$. More recently, the Shen[24] group reported an iodobenzene-catalyzed synthesis of aryl sulfonate esters from aminoquinolines by remote radical C–O cross-coupling. However, the methodology for the C-5 selective etherification remains underdeveloped. In view of our recent success in the copper-catalyzed selective remote esterification of 8-aminoquinoline amides[25], herein we disclose an efficient protocol for the C(5)–H and C(6)–H methoxylation of 8-aminoquinoline amides with methanol.

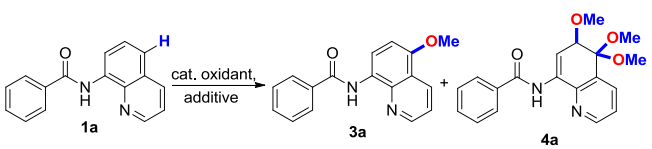


Scheme 1. Functionalization on the C5 position of quinoline amides.

Results and Discussion

Initially, the methoxylation of N-(quinolin-8-yl)benzamide (**1a**) with methanol was selected as a model reaction (Table 1). We explored the effectiveness of different catalysts in the presence of $PhI(OAc)_2$ (1.5 eq.) and Na_2CO_3 (2.0 eq.) under air for 2 h (Table 1, entries 1-8). In comparison with the other catalysts, including $Cu(OAc)_2$, CuI, $Ni(OTf)_2$, $[Ru(p\text{-cymene}Cl_2)]_2$, $LaCl_3$, $CoCl_2$, and $PdCl_2$, $PtCl_2$ gave the best yield of the desired product **3a** (86%) with trace amounts of **4a**. Subsequently, when the catalyst loading was increased from 1 to 5 mol%, the yield was decreased to 70% (Table 1, entry 8). Next, various additives including Na_2CO_3, Cs_2CO_3, and CsF were evaluated. Among them, the yield of **3a** was increased to 87% when Cs_2CO_3 was replaced with Na_2CO_3. Moreover, the yield was significantly improved to 89% while the reaction was conducted under additive-free conditions (Table 1, entries 8-11). Various oxidants involving $PhI(OAc)_2$, [bis(trifluoroacetoxy)iodo]benzene ($PhI(OTFA)_2$), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (DMP), and di-tert-butyl peroxide (DTBP) were tested, and $PhI(OAc)_2$ gave the best result. When the molar ratio of $PhI(OAc)_2$ was reduced to 1.5 eq., the yield was lowered to 88% (Table 1, entries 11-14). It was surprising that the desired products **3a** and **4a** were both observed with the ratio of 10/30 in the absence of $PtCl_2$ (Table 1, entry 15). Encouraged by this result, more additives were screened. The use of triethylamine (TEA) gave a better result, providing **4a** in a good yield with good selectivity (Table 1, entries 16-18). Finally, from the results shown above, the optimized reaction conditions were as follows: $PtCl_2$ (1 mol%), $PhI(OAc)_2$ (2.0 eq.) in CH_3OH for 2 h at room temperature for **3a**, and TEA (2.0 eq.), $PhI(OAc)_2$ (2.0 eq.) in CH_3OH for 5 h at 60 °C for **4a**. Unfortunately, the related products were not obtained when EtOH, propanol, isopropyl alcohol, or tertiary butyl alcohol was used as the solvent in the trimethoxylation reaction, and only a trace amount of the product was observed in EtOH.

Table 1. Reaction optimization[a]



Entry	Catalyst [mol%]	Additive	Oxidant [eq.]	Yield [%][b]
1	$Cu(OAc)_2$	Na_2CO_3	$PhI(OAc)_2$	27/15
2	CuI	Na_2CO_3	$PhI(OAc)_2$	36/21
3	$Ni(OTf)_2$	Na_2CO_3	$PhI(OAc)_2$	N.R.
4	*p*-Cymeneruthenium(II) Dichloride Dimer	Na_2CO_3	$PhI(OAc)_2$	N.R.
5	$LaCl_3$	Na_2CO_3	$PhI(OAc)_2$	N.R.

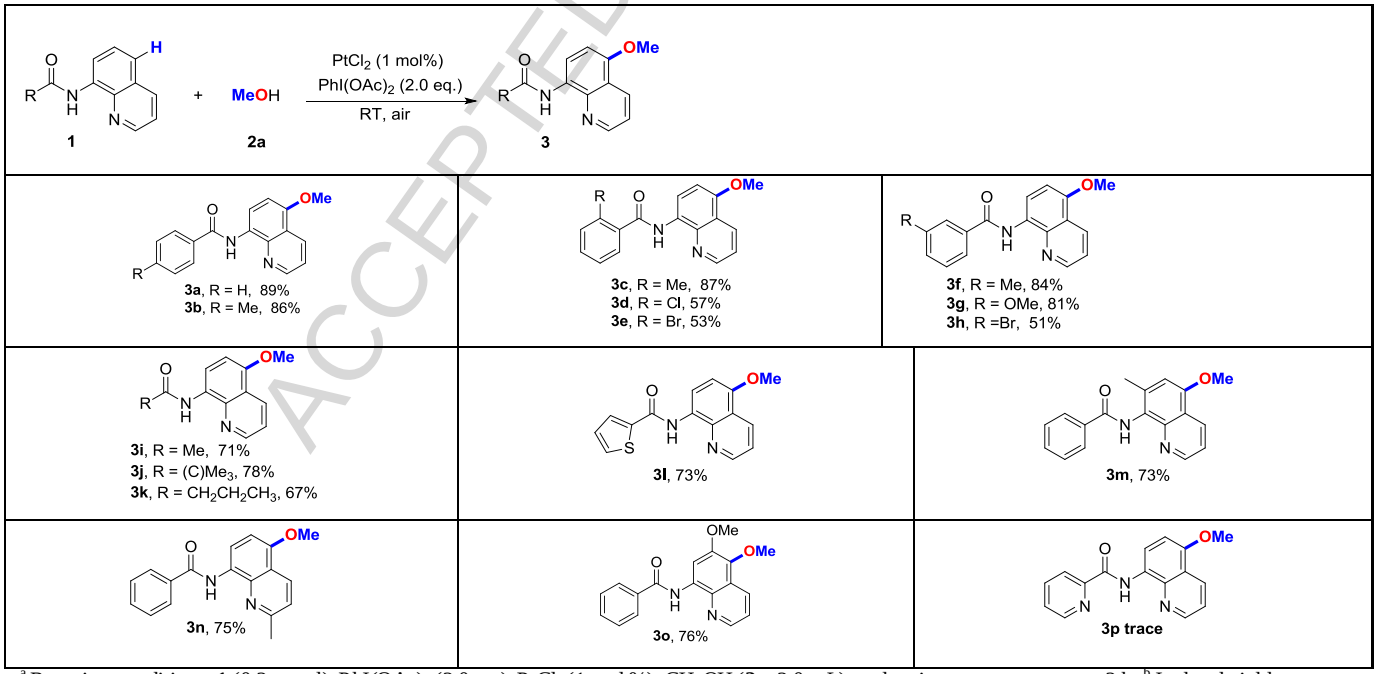
6	$CoCl_2$	Na_2CO_3	$PhI(OAc)_2$	N.R.
7	$PdCl_2$	Na_2CO_3	$PhI(OAc)_2$	30/10
8	$PtCl_2$	Na_2CO_3	$PhI(OAc)_2$	86(70)[c]/7(9)
9	$PtCl_2$	Cs_2CO_3	$PhI(OAc)_2$	87/trace
10	$PtCl_2$	CsF	$PhI(OAc)_2$	76/trace
11	$PtCl_2$	-	$PhI(OAc)_2$	**89**(88)[d]/**8**(10)
12	$PtCl_2$	-	$PhI(OTFA)_2$	61/trace
13	$PtCl_2$	-	DMP	35/trace
14	$PtCl_2$	-	DTBP	trace/trace
15	-	Cs_2CO_3	$PhI(OAc)_2$	10/30
16	-	CsF	$PhI(OAc)_2$	5/23
17	-	PivOH	$PhI(OAc)_2$	trace/trace
18	-	TEA	$PhI(OAc)_2$	7(**10**)/21(**72**)[e]

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (1 mol%), oxidant (2.0 eq.), additive (2.0 eq.), CH_3OH (2.0 mL), under air, room temperature, 2 h, unless otherwise noted. [b] Isolated yields. [c] $PtCl_2$(5 mol %). [d] $PhI(OAc)_2$ (1.5 eq.). [e]Stirred at 60 °C for 5 h.

With the optimized reaction conditions in hand, we then investigated the substrate scope of this monomethoxylation, and the results are presented in Table 2. Various 8-aminoquinoline amides were tested for the C–H activation/etherification, affording the desired products in moderate-to-good yields. In general, quinolines bearing an aryl amide could be converted to the corresponding ethers **3a**-**3h** in good yields (51-89%). However, aliphatic or heterocyclic substituents **3i**-**3l** showed a slightly lower activity with moderate yields. Notably, different substitutions on aryl amide, including methoxy, methyl, and halogen groups **3b**-**3h**, had negligible effect on the reaction giving the corresponding products in good yields. Next, 8-aminoquinoline scaffolds were examined under these optimized methoxylation conditions. *N*-(7-methylquinolin-8-yl)benzamide, *N*-(2-methylquinolin-8-yl)benzamide, and *N*-(6-methoxyquinolin-8-yl)benzamide could perform well, affording the corresponding products **3m**-**3o** in good yields, *N*-(quinolin-8-yl)picolinamide, which gave a low yield of **3p**.

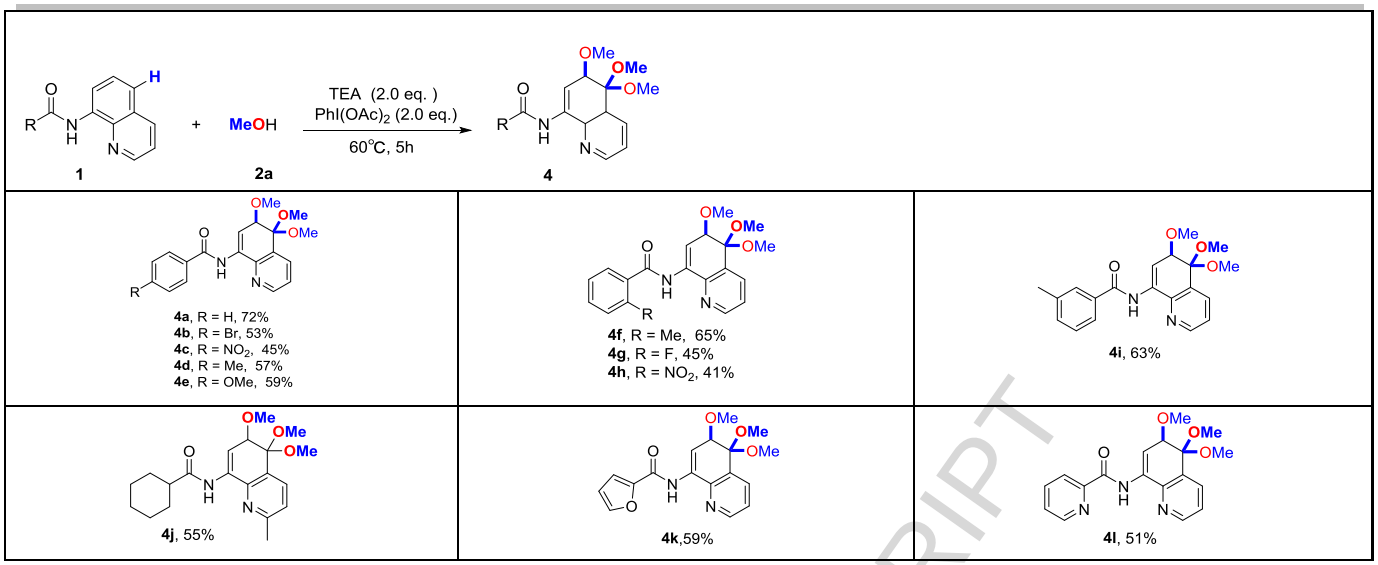
Subsequently, we examined the substrate scope of the trimethoxylation reaction to synthesize product **4**. As shown in Table 3, various groups such as methyl, methoxy, nitro, and halogen groups on aryl amide were well tolerated in this reaction, and the desired products were obtained in moderate yields **4a**-**4j**. The structure of compound **4a** was further confirmed unambiguously by X-ray crystal analysis (Figure 1). In general, the substrates with electron-donating groups (**4a**, **4d**, **4e**, **4f**, and **4i**) rather than electron-withdrawing groups (**4b**, **4c**, **4g**, and **3h**) gave slightly higher yields. The substituted quinoline at the C2 position, 2-methyl-8-aminoquinoline amide, underwent the reaction smoothly, affording the corresponding product **4j** with 55% yield. Because of the effect of chelation, *N*-(quinolin-8-yl)furan-2-carboxamide and *N*-(quinolin-8-yl)picolinamide were transformed to products **4k** and **4l** with slightly lower yields.

Table 2. Scope of monomethoxylation [a,b]



[a] Reaction conditions: **1** (0.2 mmol), $PhI(OAc)_2$ (2.0 eq.), $PtCl_2$ (1 mol %), CH_3OH (**2a**, 2.0 mL), under air, room temperature, 2 h. [b] Isolated yields.

Table 3. Scope of the trimethoxylationg reaction[a,b]



[a] Reaction conditions: **1** (0.2 mmol), $PhI(OAc)_2$ (2.0 eq.), TEA (2.0 eq.), CH_3OH (**2a**, 2.0 mL), 60 °C, under air, 5h. [b] Isolated yields.

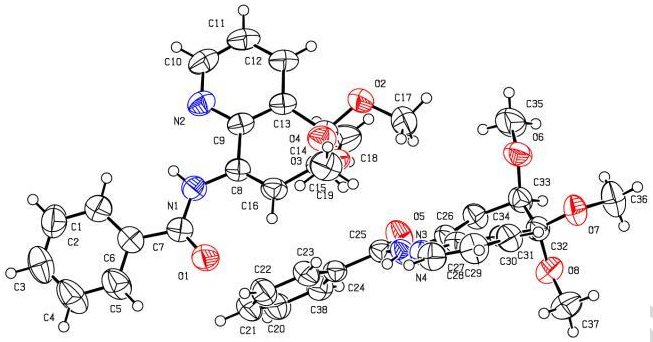
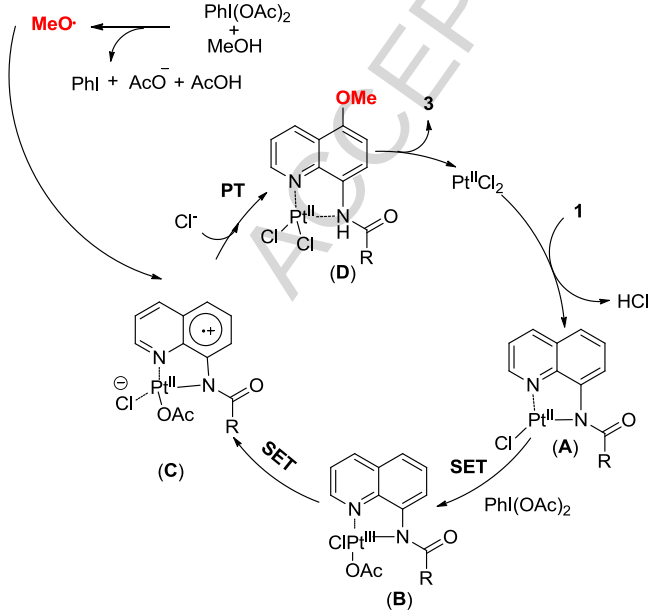


Figure 1. Single-crystal X-ray structure of **4a.** Ellipsoids are represented at 30% probability.

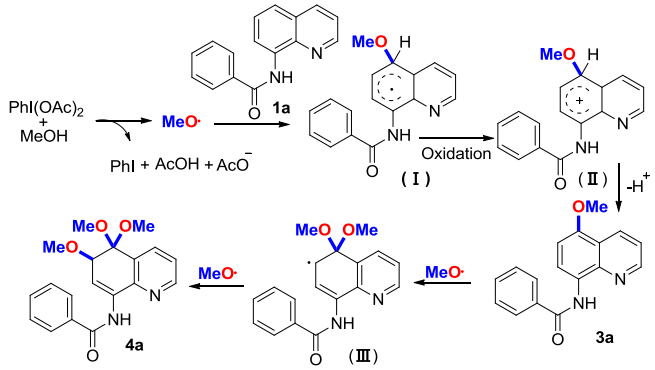
Additionally, many analogous substrates of quinolines were investigated, such as *N*-phenylbenzamide, *N*-(pyridin-2-ylmethyl)benzamide, and quinolin-8-amine. However, no desired products were observed. Moreover, the same result was obtained for substrates such as *N*-methyl-*N*-(quinolin-8-yl)benzamide and quinolin-8-yl benzoate. All these results indicate that *N,N'*-bidentate 8-aminoquinoline structure and the proton on the amido scaffold play very important roles in ensuring the methoxylation to be carried out effectively. The control experiments were conducted to gain an insight into the C–H methoxylation mechanism. Only a trace amount of **3a** was detected after an addition of 2,4-di-tert-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the catalytic system. However, (2-methoxyethene-1,1-diyl)dibenzene ($[M+H]^+$ 211.1218. Found 279.1215.) was detected under the standard conditions.



Scheme 2. Proposed mechanism for the remote methoxylation of the quinolines.

On the basis of our experimental results and previous reports[17a], an SET mechanism was proposed to be involved in the methoxylation of quinolines (Scheme 2). Step (i): the aminoquinoline amide **1** produces a chelated complex **A** in the presence of $PtCl_2$. Step (ii): Pt (II) intermediate **A** would then be oxidized to Pt (Ⅲ) species **B** by $PhI(OAc)_2$(**2**). Step (iii): complex **C** was produced by an SET. Step (ⅳ): the methoxy radical,

which was produced from the oxidation of methanol by $PhI(OAc)_2$, attacked complex **C** to deliver intermediate **D** through a proton transfer process. Step (v): product **3** was obtained, and $PtCl_2$ was released, which can be used for the next catalytic.



Scheme 3. Proposed mechanism for the remote trimethoxylation of the quinolines

A plausible reaction mechanism of the trimethoxylation of the quinolines is shown in Scheme 3. Step (i): the methoxy radical formed by $PhI(OAc)_2$ made methanol to attack **1a** to produce intermediate (I). In step (ii), intermediate (II) was obtained by the oxidation of intermediate (I). In step (iii), **3a** was produced by the reduction a hydrogen proton of intermediate (II). Step (iv): the methoxy radical attacked **3a** to produce intermediate (Ⅲ). Finally, the final product **4a** was obtained by the reaction of intermediate (Ⅲ) with methoxy radical.

Conclusions

In conclusion, we established an efficient and convenient method for the methoxylation of quinoline amides on the C5 and C6 positions by using $PtCl_2$ or TEA as an additive. The experimental results confirmed that a SET-based C−H functionalization pathway was involved in the monomethoxylation on the C5 position.

Experimental Section

General information

All reactions were carried out under air in Schlenk tubes. All the chemicals were obtained commercially and used without any prior purification. ^1H NMR and ^{13}C NMR spectra were recorded using a 500-MHz spectrometer in $CDCl_3$ with shifts referenced to $SiMe_4$ ($\delta = 0$). IR spectra were recorded on a FTIR spectrophotometer. Melting points were determined using a local hot-stage melting point apparatus and were uncorrected. Mass spectra were recorded using LC-MS and HRMS (ESI-TOF analyzer) equipment.

General procedure for the synthesis of *N*-(5-methoyquinolin-8-yl) benzamide (3a)

A mixture of **1a** (0.2 mmol), $PhI(OAc)_2$ (128.8 mg, 2.0 eq.), and $PtCl_2$ (2.6 mg, 1 mol%) in CH_3OH (2.0 mL) was stirred at room temperature under air for 2.0 h. After the reaction was completed, the catalyst was filtered and washed with ethyl acetate and water. The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel using PE/AcOEt (20: 1) as the eluent to give the product **3a**.

General procedure for the synthesis of *N*-(5,5,6-trimethoxy-5,6-dihydroquinolin-8-yl)benzamide (4a)

A mixture of **1a** (0.2 mmol), $PhI(OAc)_2$ (128.8 mg, 2.0 eq), and TEA (2.0 eq.) in CH_3OH (2.0 mL) was stirred at 60 °C under atmosphere for 5.0 h. After the reaction was completed, water (10 mL) was added to the mixture. The mixture was extracted with EtOAc (6 mL x 3), and the combined organic layer was washed with brine (10 mL), dried with Na_2SO_4, and removed under reduced pressure. The product **4a** was purified by flash column chromatography using PE/AcOEt (10 : 1) as an eluent.

Acknowledgments

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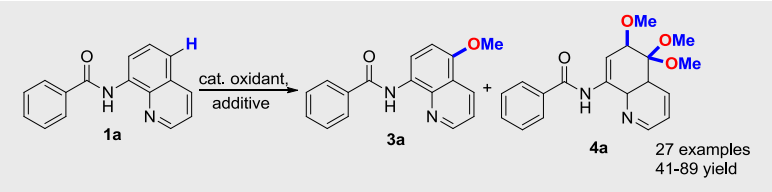
Graphical abstract



Text for Table of Contents: *Many various C5- and C6- methoxylated quinoline amides were obtained in moderate to high yields by employing $PtCl_2$ or TEA as additive.*

Guodong Wang,[a] Junfen Han,[a] Kai Wang, [a] Hongshaung Li, [a] Guiyun Duan,[a] Chengcai Xia[a,b] and Furong Li*[a]*

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Title

Methoxylation on the C5- and C6-Positions of Quinolines with Methanol

Highlights

- The C(5)-H methoxylation of quinoline catalyzed by $PtCl_2$ with methanol.
- Trimethoxylation of quinoline with methanol at C6-position promote by triethylamine.
- Report the plausible mechanisms of methoxylation and trimethoxylation of quinoline