Research Paper



Investigations into the ligand steric and electronic effects of Ru-catalyzed C–H bond arylation directed by 8-aminoquinoline as a bidentate-directing group

### Hamad H. Al Mamari 🕩 and Yousuf Al Lawati

#### Abstract

In this study, we report an investigation into the steric (cone angle,  $\theta$ ) and electronic properties of ligands in Rucatalyzed C–H arylation of aromatic benzamides bearing 8-aminoquinoline as an *N*,*N*'-bidentate-directing group. The study employs [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> as a precatalyst, and a ligand, under study, as a cocatalyst. Various electronically and sterically different monodentate and bidentate phosphine ligands were examined. Other ligands such as phosphites and amines were also tested. The study reveals that while bidentate phosphines, phosphites, and aryl and alkyl amines were found to be ineffective, monodentate triarylphosphines represented by triphenylphosphine were found to be the most effective ligands in the Ru-catalyzed C–H arylation under the conditions specified. In addition, the study reveals that there is a correlation between the steric effects, cone angle ( $\theta$ ) and the reaction efficiency. Thus, for symmetrical phosphine ligands, as the cone angle increases, the yield of the CH arylation product gradually decreased. Moreover, the electronic properties of triarylphosphine ligands influenced the reaction as demonstrated by the decreased ability of electron-poor ligands to promote the reaction. The study also reveals a correlation between the electronic parameter,  $\upsilon$ CO, of the triarylphosphine ligand and the reaction efficiency. As the carbonyl stretching frequency increases, the reaction yield gradually decreased.

#### **Keywords**

8-aminoquinoline, bidentate-directing group, chelation-assistance, C–H functionalization, ligand effects, Ru-catalyzed C–H bond arylation

Date received: 5 February 2020; accepted: 27 March 2020



#### Introduction

C–H bond functionalization<sup>1–6</sup> has risen as a powerful atom economical strategy for formation of chemical bonds. Direct functionalization of C–H bonds provides rapid access to desired functionalized products from simple and readily available starting materials, thus manifesting atom- and step-economies. Controlling regiochemistry or site-selectivity is a major issue in the field of C–H activation/functionalization.<sup>7–18</sup> As a strategy to circumvent the issue, monodentate-<sup>7–18</sup> and bidentate-directing groups<sup>19–28</sup> have been developed. Directing groups have allowed, *via* chelation-assistance, a wide range of efficient C–H bond activation, acetoxylation, alkynylation, and alkenylation

reactions. The directed C–H bond fuctionalizations have been possible with the catalysis of second-row transition metals mainly represented by Pd, Rh, Ru, and less by the earth-abundant first-row transition metals such as Fe, Mn, Ni, and Co.

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Journal of Chemical Research 1–5 © The Author(s) 2020 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/1747519820920154 journals.sagepub.com/home/chl

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**Scheme I.** Original Ru-catalyzed C–H bond arylation of benzamides bearing 8-aminoquinoline as a directing group as reported by Aihara and Chatani *et al.*<sup>24</sup>

The use of 8-aminoquinoline as a bidentate-directing group is now well-established.<sup>19–28</sup> Recently, Aihara and Chatani<sup>24</sup> reported Ru-catalyzed C–H bond arylation of aromatic amides using 8-aminoquinoline as a directing group. Among other reaction conditions,  $[RuCl_2(p-cymene)]_2$  (5 mol%) and PPh<sub>3</sub> (40 mol%) were used as a catalyst system (Scheme 1). Hence, benzamide bearing 8-aminoquinoline (1) underwent efficient Ru-catalyzed C–H arylation with aryl bromides (2) to give the corresponding arylated products (3) in excellent yields.

Although it was reported that the use of PPh<sub>2</sub> as a ligand was essential for the reaction (no reaction in the absence of PPh<sub>3</sub>),<sup>24</sup> investigation of the effects of ligands in Ru-catalyzed C-H bond arylation using bidentatedirecting groups is not reported to date. The incentive would have been to seek insights into the reaction details such as the influence of the ligand steric and electronic effects on the reaction efficiency,29-35 for instance, whether substitution of the aryl group can cause any change in reactivity of the phosphine or even the active catalysts in the Ru-catalyzed C-H activation reaction. The modification of substitution could be altered by varying the position of the substituent on the aryl group and/ or by varying the electronic properties of the substituent whether it is an electron-donating group or an electronwithdrawing group. In addition, it was also proposed to replace the aryl groups on the phosphine with an alkyl group in order to see if this could result in any change in the reaction efficiency. It was an aim to seek knowledge of any correlation, at all, between the Tolman steric cone angles of phosphine ligands or bite angles of bidentate phosphines and the reaction outcome.<sup>29-35</sup> In particular, the quest was for information on the influence of the Tolman steric cone angle  $(\theta)$  parameter and electronic property parameter (carbonyl stretching frequency (UCO)) in Ni(CO)<sub>2</sub>L complexes of ligands in Ru-catalyzed C-H bond arylation.<sup>29</sup> The carbonyl stretching as coined by Tolman is the carbonyl frequency of Ni(CO)<sub>2</sub>L (L: phosphine ligand) in CH<sub>2</sub>Cl<sub>2</sub> and is a measure of electronic effects of the phosphine ligand.<sup>29</sup> Ultimately, any trends in reactivity or correlations obtained between steric and/or electronic properties of ligands and reaction efficiency could provide guidance toward judicial ligand design in catalytic C-H bond functionalization. To that end, we wish to report herein a study that we have conducted toward the ligand effects in Ru-catalyzed C-H bond arylation assisted by 8-aminoquinoline as an N,N'bidentate-directing group. The study involved various and electronically different monodentate and bidentate



**Scheme 2.** Ru-catalyzed C–H arylation of benzamides bearing 8-aminoquinoline as a bidentate-directing group.

phosphine ligands, and among others, aryl amines and carboxylic acids.

#### **Results and discussion**

At the outset of the study, established Ru-catalyzed arylation condition was employed.<sup>24</sup> Thus, 2-methylbenzamide bearing 8-aminoquinoline as a bidentate-directing group  $(4)^{28}$  was chosen as a representative substrate, ethyl 4-bromobenzoate (5) as an electrophile,  $[RuCl_2(p-cymene)]_2$  (5 mol%) as a precatalyst, and PPh<sub>3</sub> (40 mol%) as a ligand in *o*-xylene as a solvent at 140 °C for 24 h (Scheme 2). The desired arylation product (6) was obtained in 95% isolated yield.

In order to gain insights into the effect of ligands in the reaction, various monodentate and bidentate phosphine ligands were examined under the reaction conditions (Figure 1). The ligands differ in substitution and electronic properties of the aryl group in the case of aryl-based ligands such as triarylphosphines. Trialkylphosphines were also used in the study along with phosphines that have both alkyl and aryl groups or the sterically bulky electron-donating t-butyl groups. Some phosphines have electron-donating alkyl groups and dialkylamino groups, while others have heterocycles. The study employed bidentate phosphine ligands as well. The phosphines were sterically and electronically different as they differ in cone angles,  $\theta$ , for monodentate phosphines or different bite angles for bidentate phosphines.<sup>29–35</sup> The results are summarized in Table 1. The table lists the ligands used in the study with their respective literature-reported cone angles and carbonyl stretching frequencies, UCO, for monodentate phosphine ligands and bite angles for bidentate phosphine ligands.<sup>29-35</sup> The majority of phosphines used in the study have reported cone angles and stretching frequencies and are listed in the table as given by the studies<sup>29-35</sup> used. However, some cone angles were not available in the literature.<sup>29–35</sup>

While the standard PPh<sub>3</sub> (L1, Entry 1) gave 95% isolated yield of the C–H arylation product, the *para*-substituted more electron-rich P(*p*-tol)<sub>3</sub> (L2, Entry 3) gave the product in modest 58% yield. However, the use of the relatively electron-poor *para*-substituted tris(4-fluorophenyl)phosphine (L3, Entry 4) resulted in reduction of the yield to 26%. Performing the reaction in the absence of a ligand did not promote the reaction (Entry 2) at all. This confirms the result already reported by Aihara and Chatani<sup>24</sup> that the presence of a ligand was essential for the Ru-catalyzed C–H arylation of benzamides. The cone angles of the three phosphine ligands L1, L2, and L3 are the same, but their



Figure 1. Ligands used in the study.

 Table I. Results of ligand effect study in Ru-catalyzed C–H

 bond arylation.

Entry	Ligand	Cone angle, $\theta^{29}$ (steric)	υCO <sup>29</sup> , cm <sup>-1</sup> (electronic)	Bite angle	Yield (%)
I	LI	145°	2068.9		95
2	-	_			-
3	L2	145°	2066.7		58
4	L3	145°	2071.3		26
5	L4	184°	2090.9		-
6	L5	_			-
7	L6	170°	2056.4		51
8	L7	133°			15
9	L8	182°	2056. I		-
10	L9	-			-
11	LI0 <sup>a</sup>	_	2061.9		_
12	LII	_			25
13	LI2	128°	2085.3		-
14	LI3	107°	2079.5		8
15	LI4			72°	-
16	LI5			99°	-
17	LI6	-			-
18	LI7	-			-
19	LI8	_			-
20	LI9	-			-
21	L20	_			-
22	L2I	-			-

<sup>a</sup>80 °C was used as a reaction temperature.

respective yields are significantly different. Probably, the reaction is influenced by the electronic nature of the phosphine ligand rather than its sterics. Electron-rich phosphines promote the Ru-catalyzed C-H arylation more than their electron-poor counterparts.

The fully fluorinated triphenylphosphine, tri(pentafluorophenyl)phosphine,  $P(C_6F_5)_3$  (L4, Entry 5) failed to affect the C-H arylation reaction. The inability of L4 to promote the Ru-catalyzed C-H arylation reaction suggests that electron-withdrawing groups hinder the Ru-catalyzed C-H arylation reaction to the point when the reaction shuts down totally when triphenylphosphine is fully fluorinated. Trinaphthalene-1-ylphosphine (L5, Entry 6) also failed to deliver the C-H arylation product. Trialkylphosphines represented by tricyclohexylphosphine (PCy<sub>2</sub>) (L6, Entry 7) produced the product successfully in moderate 51% yield. The inability of L5 to participate in the reaction is probably due to the increased steric bulk around the lone pair on the phosphorous atom. This would subsequently hinder the coordination of the phosphine with the Ru metal. Tris(2furyl)phosphine (L7, Entry 8) gave the C-H arylation product in a low yield of 15%. L7 with a low cone angle of 133° did not greatly influence the arylation reaction as reflected in the low yield. Probably, this is attributed to electronic effects rather than steric. The inductively electron-withdrawing O in the furyl heterocyclic rings could decrease the availability of the P lone pair.

The sterically bulky and electron-rich alkyl phosphines such as tris-*t*-butylphosphine P(*t*-Bu)<sub>3</sub> (**L8**, Entry 9), JohnPhos (**L9**, Entry 10), and the electron-rich tris(dimethylamino)phosphine (**L10**, Entry 11) were unsuccessful in promoting the reaction. As the steric parameter, the cone angle,  $\theta$ , for symmetrical phosphine ligands increases in going from PPh<sub>3</sub>, **L1** ( $\theta$ =145°), PCy<sub>3</sub>, **L6** ( $\theta$ =170°), and P(*t*-Bu)<sub>3</sub>, **L8** ( $\theta$ =182°), the yield gradually dropped from 95% (L1, Entry 1) to 51% (L6, Entry 7) to 0% (L8, Entry 9), respectively. The decrease in the reaction yield, in that order, could be attributed to the gradual increase in the steric bulk around the lone pair on the phosphorous atom donor which in turn decreased its ability to bind and coordinate with the Ru metal center.

When one cyclohexyl group is replaced by a biphenyl group, the reactivity of the phosphine dropped to 25% (CyJohnPhos, L11, Entry 12). Phosphites (P(OR)<sub>3</sub>) were also examined. While triphenylphosphite (L12, Entry 13) did not give any C–H arylation product, trimethylphosphite (L13, Entry 14) was hardly successful (8%). This result indicates that phosphites are not suitable as ligands in the reaction.

Bidentate phosphines such as bis(diphenylphosphino) methane (L14, Entry 15) and 1,4-bis(diphenylphosphino) butane (L15, Entry 16) failed to deliver the desired product. The two diphosphines used in the study differ in the methylene chain between the two P atoms. Thus, both bis(diphenylphosphino)methane (L14, Entry 15) where there is one methylene group between the two P atoms and 1,4-bis(diphenylphosphino)butane (dppb, L15, Entry 16) with a methylene chain of four failed to promote the Ru-catalyzed C–H arylation. Diphosphine ligands are known to affect different reactions catalyzed by transition metals such as Ni, Pd, and Rh. However, in this study of Ru-catalyzed C–H bond arylation and under the specific reaction conditions outlined, diphosphines were found to be ineffective.

The *N*-counterpart to  $PPh_3$  and triphenylamine,  $NPh_3$ , was tested, but was found to be ineffective (**L16**, Entry 17). Other *N*-based ligands were also examined for possible reactivity. Thus, primary amines such as aryl and alkyl amines represented by aniline (**L17**, Entry 18), cyclohexy-lamine (**L18**, Entry 19), and *n*-butylamine (**L19**, Entry 20) were found unsuccessful. This result indicates that amines are not suitable as ligands in the reaction.

Pyridine (L20, Entry 21) and benzoic acid<sup>18</sup> (L21, Entry 22) were also tested, but they were found not to be successful in affecting the Ru-catalyzed C–H bond arylation reaction. From the results in Table 1, it can also be inferred that as the electronic parameter,  $\nu$ CO, increases in going from PPh<sub>3</sub> (L1, Entry 1) (no F group) to L3 (Entry 4) (one F group in each phenyl group) to L4 (Entry 5) (five F groups on the phenyl group), the yield gradually decreased from 95% to 26% to 0%. Thus, there is a correlation between this carbonyl stretching frequency parameter and the reaction efficiency. This in line with the observation made above that the presence of electron-withdrawing groups in the triarylphosphines hinders the reaction.

As a result, in this study, monodentate triarylphosphines, represented by triphenylphosphine, are the most effective in the reaction under the reaction conditions specified. The results suggest that a monodentate phosphine is required, as bidentate phosphines were found to be unsuccessful. The results obtained and observations made will hopefully contribute to the ligand design in metal-catalyzed C–H bond functionalization reactions. Work is currently underway to further investigate steric and electronic effects of ligands in metal-catalyzed C–H functionalization reactions.

## Conclusion

Effects of steric (represented by the Tolman cone angle,  $\theta$ ) and electronic properties of ligands have been investigated in Ru-catalyzed C-H bond arylation of aromatic amides bearing 8-aminoquinoline as an N,N'-bidentate-directing group under the reaction conditions specified. While bidentate phosphines, phosphites, and aryl and alkyl amines were found to be ineffective, monodentate triarylphosphines represented by triphenylphosphine are the most effective in Ru-catalyzed C-H arylation under the conditions specified. The study revealed a correlation between the steric parameter, the cone angle,  $\theta$ , of symmetrical phosphine ligands and their efficiency in the reaction. As the cone angle increases, the reaction yield gradually decreased. This trend was attributed to the increased steric bulk around the lone pair on the phosphorous atom, as the cone angle increases. Consequently, the ability of the phosphorous atom donor to bind and coordinate with the Ru metal center is gradually diminished. The study also reveals that electronic properties of ligands can influence the reaction. Specifically, the presence of electron-withdrawing groups in the triarylphosphine decreases the reaction efficiency to a total shut-down with electron-poor triarylphosphines fully substituted with such groups. It was also found that there is a correlation between the electronic parameter, UCO, and the reaction efficiency. As the carbonyl stretching frequency increases, the reaction yield gradually decreased. As a result, it can be concluded that steric and electronic properties of ligands influence the Ru-catalyzed C-H arylation. Based on the obtained correlations between the steric and electronic properties and the reaction efficiency, the role of the ligand is not purely steric or electronic, but probably both. The results obtained will hopefully provide directions and guidance toward judicial design of ligands not only of potential use in metal-catalyzed C-H bond functionalization reactions, but also in metal-catalyzed reaction as a whole. Work is currently underway to further investigate ligand effects of metal-catalyzed C-H bond functionalization.

#### **Experimental**

# Ru-catalyzed C–H arylation directed by 8-aminoquinoline; general procedure

2-Methyl-*N*-(quinolin-8-yl)benzamide<sup>28</sup> (4) (0.131 g, 0.499 mmol), ethyl-4-bromobenzoate (5) (100 μL, 0.612 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.160 g, 1.51 mmol), [RuCl<sub>2</sub> (p-cymene)]<sub>2</sub> (5 mol%), and a ligand (40 mol%) were added to o-xylene (2 mL) in an oven-dried Schlenk tube under Ar atmosphere. The reaction mixture was stirred for 24h at 140 °C. The reaction was quenched with saturated NH<sub>4</sub>Cl (3 mL). The mixture was extracted with  $CH_2Cl_2$  (3 × 5 mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub> and filtered. Concentration under reduced pressure gave a crude product which was analyzed by thin-layer chromatography (TLC), gas chromatography-mass spectrometry (GC-MS), and NMR spectroscopy.

3'-Methyl-2'-(quinolin-8-ylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester (6). 2-Methyl-N-(quinolin-8-yl)benzamide<sup>28</sup> (4) (0.131 g, 0.499 mmol), ethyl-4-bromobenzoate (5) (100  $\mu$ L, 0.612 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.160 g, 1.51 mmol), [RuCl<sub>2</sub>(p- $(5 \, mol\%),$ and  $PPh_3$  (52.5 mg, cymene)]<sub>2</sub> 0.200 mmol, 40 mol%) were added to o-xylene (2 mL) in an ovendried Schlenk tube under Ar atmosphere. The reaction mixture was stirred for 24 h at 140 °C. The reaction was quenched with saturated  $NH_4Cl$  (3 mL). The mixture was extracted with  $CH_2Cl_2$  (3×5mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub> and filtered. Concentration under reduced pressure gave a crude product which was purified by flash chromatography (SiO<sub>2</sub>) using hexane: EtOAc (4:1) to give the C-H arylation product (6) as a white solid;  $R_{f} = 0.4$  (hexane: EtOAc (1:1)); m.p. = 176-177 °C. <sub>1</sub>H NMR (CDCl3, 400 MHz) δ (ppm) δ 9.66 (s, 1H), 8.74 (dd, J = 7.2, 1.8 Hz, 1H), 8.60 (dd, J = 4.2, 1.6 Hz, 1H), 8.08 (dd, J = 8.3, 1.6 Hz, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.53 - 7.35 (m, 6H), 4.25 (q, J = 7.1 Hz, 2H), 2.53 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 168.0, 166.5, 148.2, 145.1, 138.7, 138.4, 136.8, 136.3, 136.1, 134.2, 132.1, 130.2, 129.6, 129.4, 128.7, 127.9, 127.6, 127.4, 122.0, 121.6, 116.8, 60.9, 19.9, 14.4 ppm. IR (neat) (cm<sup>-1</sup>): 3325, 2925, 2850, 1725, 1676, 1600, 1525, 1487, 1275. MS (ESI) m/z (relative intensity): 410 (50), 365 (10), 267 (15), 221 (7), 195 (100), 165 (47), 144 (15), 89 (6), 55 (3). Elemental anal. calcd: C, 76.08; H, 5.40; N, 6.82; found: C, 75.697; H, 5.713; N, 6.758.

#### **Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research work was supported by the Sultan Qaboos University Research Fund (grant no. RF/SCI/CHEM/19/01).

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#### Supplemental material

Supplemental material for this article is available online.

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