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Review Article

Ruthenium(II)-Catalyzed *ortho* C-O Bond formation of Substituted Aromatics with Oxygen Nucleophiles through C-H Bond Activation

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The present review describes a ruthenium-catalyzed *ortho* C-O bond formation such as hydroxylation, benzoxylation and acetoxylation of substituted aromatics with oxygen nucleophiles via C-H bond activation. Various oxygen sources such as trifluoroacetic anhydride, aromatic carboxylic acids and acetic acid are used as nucleophiles in the reaction. Most of the reactions shown in the review mechanistically proceeds via a concerted deprotonation *ortho* metalation pathway. A five-membered ruthenacycle intermediate was proposed in the reactions. These reactions provide an efficient route for the synthesis of *ortho*-hydroxy-, acetoxy- and benzoxy substituted aromatics in a highly regioselective manner in one pot.

Key Words: Ruthenium(II) Catalyst; Alkoxylation; Benzoxylation; Hydroxylation; C-H Activation; Oxygen Nucleophiles

Introduction

Metal-catalyzed chelation-assisted functionalization at the *ortho* C-H bond of aromatics with nucleophiles via C-H bond activation is an efficient method to construct the chemical bonds in organic synthesis (Pfeffer *et al*., 2002; Lautens *et al*., 2007; Lyons and Sanford, 2010; Ellman *et al*., 2010; Lei *et al.,* 2011; Ackermann, 2011; Cheng *et al.*, 2012; Dixneuf *et al*., 2012; Ackermann *et al*., 2014). By employing this method, various chemical bonds such as C-C, C-N, C-X (X = Halogens) and C-O are efficiently constructed in a highly atom economical and environmentally friendly manner. C-H Bond of aromatics can be activated by several ways in the presence of metal catalysts. However, the control of regioselectivity is key problem in most of cases. But, the regioselective issue can be controlled by activating the C-H bond via chelation-assisted metalation pathway (Scheme 1). Heteroatoms such as nitrogen or oxygen containing chelating groups are needed for this reaction. In the reaction, heteroatom of chelating group coordinates with metal and brings the *ortho* C-H bond of aromatics to close proximity to the reactive metal site. Thus, C-H bond activation takes place very selectively at the *ortho* position via either oxidative addition pathway or deprotonation metalation pathway, providing a five-membered metalacycle intermediate **A** or **B**. Generally, M(0) or M(I) active species favours oxidative addition pathway and $M(II)(OR)_2$ or $M(III)(OR)_2$ species favours deprotonation pathway. Based on the active catalyst, the reaction pathway can be altered selectively.

Palladium, rhodium and ruthenium complexes are widely used as catalysts for this reaction. In the presence of these catalysts, C-C, C-X (X = halogen) and C-N bond formation have been extensively studied in the literature. But, C-O bond formation has not been well explored. This is most probably due to the high electronegativity of the oxygen

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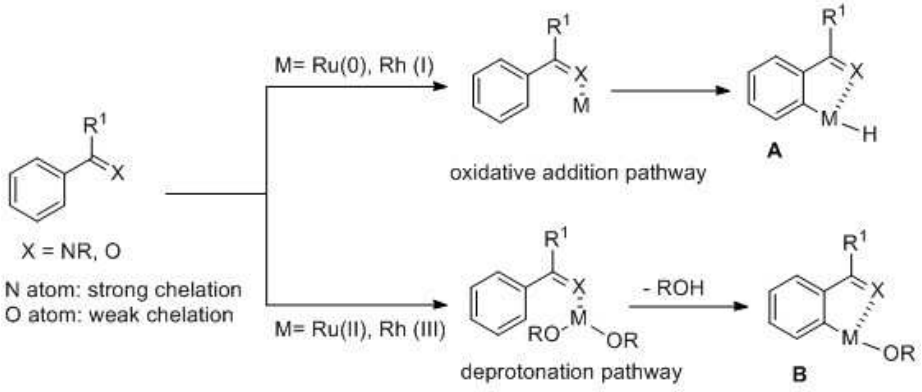
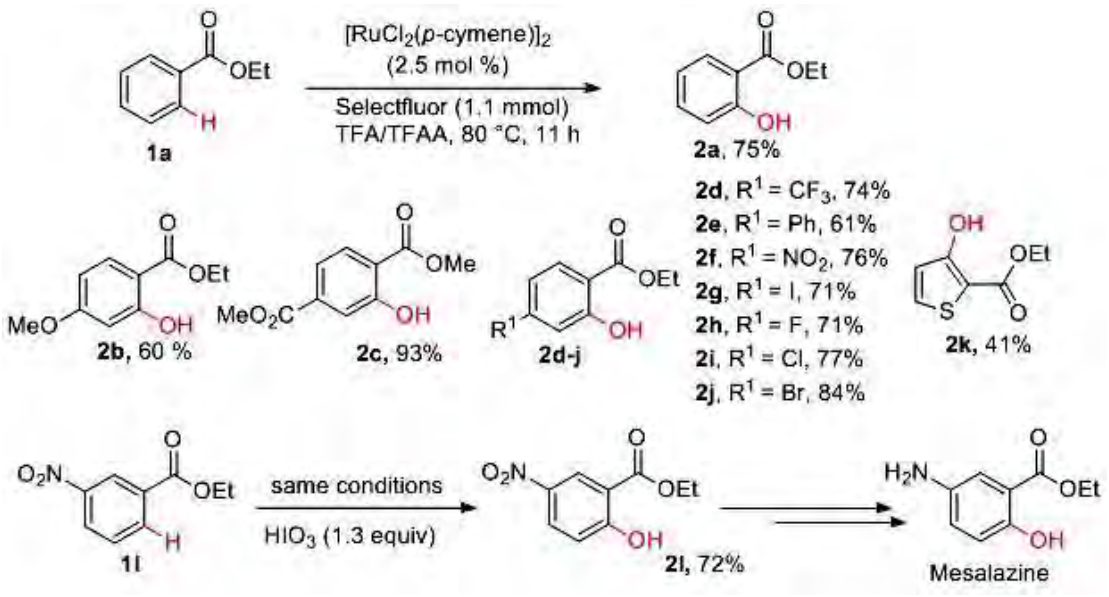
element and the strong metal-oxygen bond strength (Li and Sun, 2012). Various oxygen sources such as acetates, alkoxides, alcohols, aldehydes, anhydrides and carboxylic acids are used as nucleophiles in the reaction. Several directing groups such as 2-pyridyl, carbonyl, ester, nitrile, carboxylic acid, *N*-acetyl and amide can be efficiently used for the reaction. With the assistance of these directing groups, acetoxylation (Henry, 1971; Yoneyama and Crabtree, 1996; Sanford *et al*., 2004; Yu *et al*., 2005; Yu *et al*., 2006; Corey *et al*., 2006; Wu *et al*., 2008; Chen *et al*., 2009; Zhang *et al*., 2010; Cheng *et al*., 2010; Yu *et al*., 2010; Yu *et al*., 2011; Sanford *et al*., 2012; Kim *et al*., 2013), alkoxylation (Sanford *et al*., 2006; Wang and Yuan, 2010), hydroxylation (Yu *et al*., 2009; Rao *et al*., 2012; Dong *et al*., 2012) and benzoxylation (Sanford *et al*., 2005; Cheng *et al*., 2011) at the *ortho* C-H bond of directing group substituted aromatics with various oxygen nucleophiles have been studied. Palladium and copper complexes are efficient catalysts for this type of reaction. Recently, a less expensive ruthenium complex has gained tremendous attention in the heteroatom directed C-H bond activation of aromatics due to its remarkable reactivity and selectivity. In this review, we would like to highlight the recent observations of a ruthenium-catalyzed *ortho* C-O bond formation such as hydroxylation, acetoxylation and benzoxylation of substituted aromatics with oxygen nucleophiles such as trifluoroacetic anhydride/trifluoroacetic acid (TFAA/TFA), $PhI(TFA)_2$, acetic acid and aromatic carboxylic acids via a concerted deprotonation metalation pathway.

ortho-Hydroxylation of Substituted Benzoates

Rao's group (Rao *et al*., 2012) demonstrated a ruthenium-catalyzed *ortho*-hydroxylation of substituted benzoates (Scheme 2). Treatment of ethyl benzoate (**1a)** with trifluoroacetic anhydride (TFAA) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) and Selectfluor oxidant (1.1 mmol) in TFA at 80 °C for 11 h gave *ortho*-hydroxylated benzoate (**2a**) in 75% yield. Various oxidants such as $K_2S_2O_8$, KIO_4, $NaIO_4$, HIO_3, Selectfluor and $PhI(OAc)_2$ were tested. Among them, Selectfluor oxidant gave the better 75% yield of product **2a**. Under similar reaction conditions, electron-donating and halogen substituted benzoates **1** were smoothly converted into the corresponding *ortho*-hydroxylated benzoates **2** in moderate to excellent yields. When iodic acid was used as the oxidant instead of Selectfluor, satisfactory yields were observed with substrates containing electron-withdrawing groups such as $-CF_3$ and $-NO_2$ on the benzoate moiety. Notably, heteroaromatic ethyl-thiophene-2-carboxylate was also successfully employed in the reaction. By employing the present protocol, *ortho*-hydroxyl-3-nitobenzoate (**2l**) was prepared in 72% yield. Compound **2l** is a key starting material for the synthesis of a biologically active molecule Mesalazine. A possible reaction mechanism involving Ru(IV) intermediate having Ar-Ru-O bond followed by reductive elimination gives the final product was proposed.



Scheme 1: General Mechanism for Metal-Catalyzed Chelation-Assisted *ortho* C-H Bond Activation of Substituted Aromatics



Scheme 2: *ortho*-Hydroxylation of Substituted Benzoates

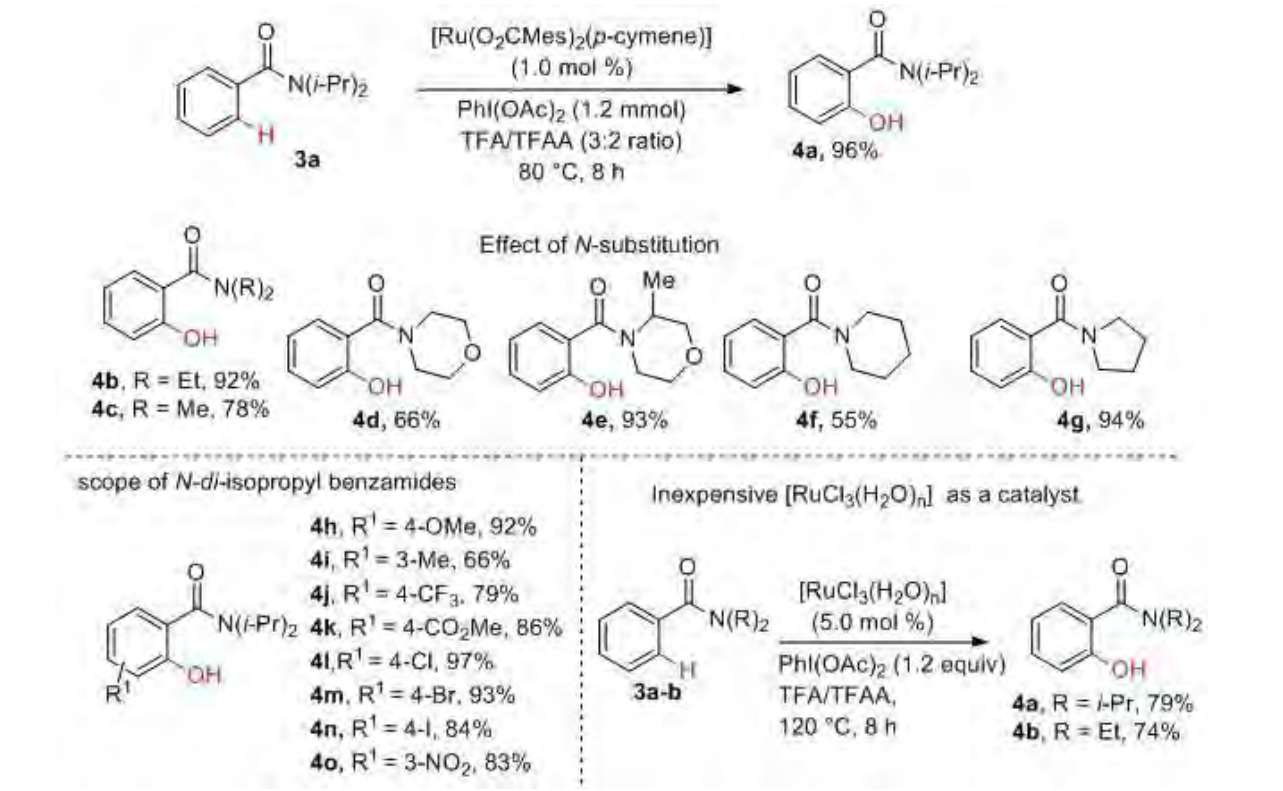
ortho-Hydroxylation of Substituted Benzamides

In the same year, Ackermann's group (Ackermann *et al*., 2012) showed a ruthenium-catalyzed site-selective *ortho*-hydroxylation of substituted benzamides (Scheme 3). Initially, the *ortho*-hydroxylation of *N*,*N*-di(*iso*-propyl)-benzamide (**3a**) was tested with a combination of TFAA/TFA in the presence of various Ru complexes such as $[RuCl_2(p\text{-cymene})]_2$, $[Ru(O_2CMes)_2(p\text{-cymene})]$, $[Ru_2(OAc)_4Cl]$ and $[Ru_2(hp)_4Cl]$ and oxidants such as $Cu(OAc)_2{\cdot}H_2O$, AgOAc, Oxone, $K_2S_2O_8$ and $PhI(OAc)_2$. The optimization studies revealed that $[Ru(O_2CMes)_2(p\text{-cymene})]$ was a best catalyst and $PhI(OAc)_2$ was a best oxidant for the reaction. In the reaction, *ortho*-hydroxylated benzamide **4a** was observed in 96% yield at 80°C for 8 h. The present methodology was also compatible with various *N*,*N*-di(*iso*-propyl)-substituted benzamides. Similarly, various electron-donating and electron-withdrawing group substituted benzamides gave the corresponding *ortho*-hydroxylated benzamides **4** in good to excellent yields. Also, an inexpensive $[RuCl_3(H_2O)n]$ complex served as an efficient catalyst for the reaction at 120°C.

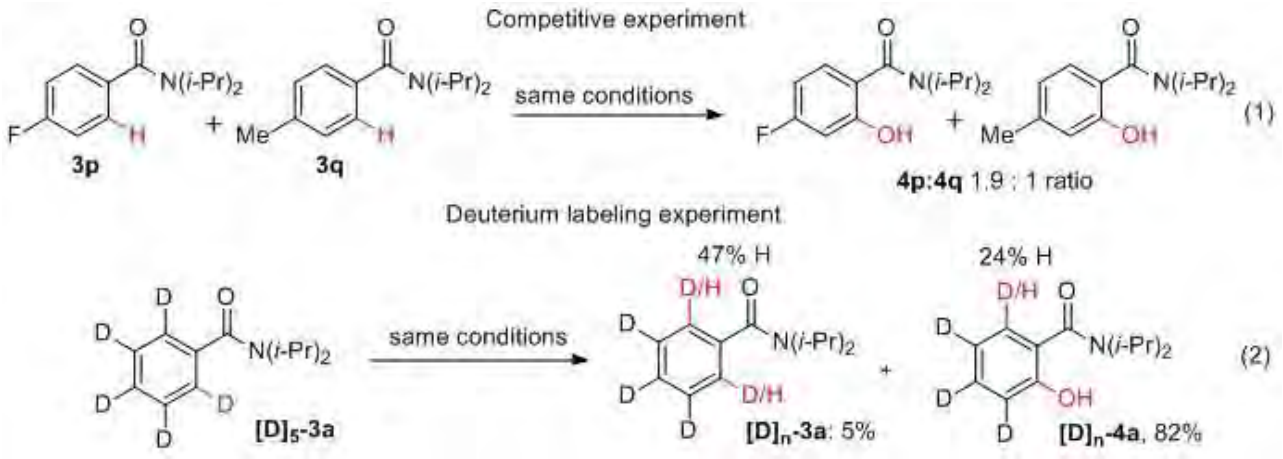
To understand the reactivity of the reaction, the competitive experiment between 4-fluoro **(3p)** and 4-methyl *N*,*N*-di(*iso*-propyl)-benzamide (**3q)** was carried out (eq. 1). In the reaction, *ortho*-hydroxylated 4-fluoro benzamide **4p** was observed in the better yield compared with *ortho*-hydroxylated 4-methyl benzamide **4q**. Moreover, the *ortho*-hydroxylation of deuterium labeled benzamide **$[D]_5$-3a** highlighted that a significant D/H exchange was observed at the *ortho* position of benzamide (eq. 2). Thus, this study indicated that the *ortho* C-H bond activation is a reversible process.

ortho-Hydroxylation of Substituted Acetophenones

Later, the same group reported a highly chemo- and site-selective *ortho*-hydroxylation of substituted aromatic ketones (Thirunavukkarasu and Ackermann, 2012) (Scheme 5). When *t*-butyl acetophenone (**5a**) was treated with TFAA in presence of $[Ru(O_2CMes)_2(p\text{-cymene})]$ (2.5 mol%) and $PhI(OAc)_2$ in TFA at 120 °C for 22 h, *ortho*-hydroxy-*t*-butylacetophenone (**6a**) was observed in 85% yield. The catalytic reaction was examined with various Ru catalysts such as $[Ru(O_2CMes)_2(p\text{-cymene})]$, $[RuCl_2(p\text{-cymene})]_2$, $[Ru_2(hp)_4Cl]$ and $[Ru_2(OAc)_4Cl]$ and oxidants such as oxone, $K_2S_2O_8$, $PhI(TFA)_2$ and $PhI(OPiv)_2$. Among them, $[Ru(O_2CMes)_2(p\text{-cymene})]$ catalyst and $PhI(OAc)_2$ oxidant was suitable conditions for the reaction. Next, the reaction was

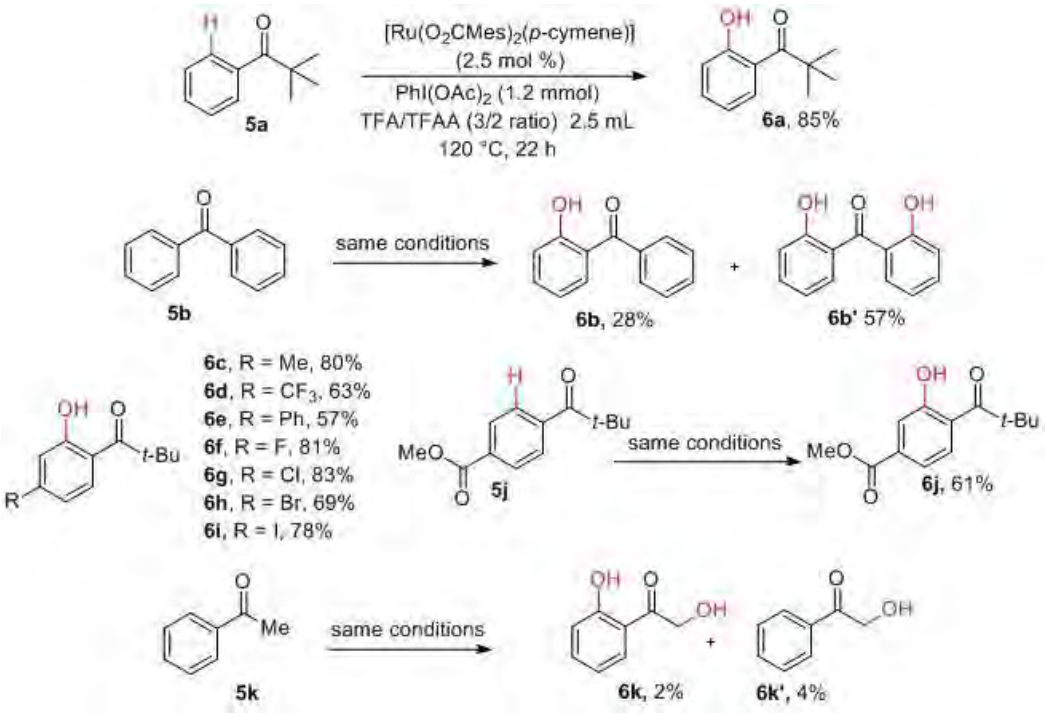


Scheme 3: *ortho*-Hydroxylation of Substituted *N,N*-di(*iso*-propyl)-benzamides



Scheme 4: Competitive and deuterium labeling experiment

tested with benzophenone (**5b**) under similar reaction conditions. In the reaction, a mixture of *mono*-hydroxylated **6b** and *bis*-hydroxylated **6b'** benzophenones were observed in 28% and 57% yields, respectively. Further, the versatility of reaction was tested with various *t*-butyl aromatic ketones having substituents such as F, Cl, Br, I, methyl and CF_3 at the *ortho*-, *para*- and *meta*-positions. In all these reactions, the corresponding *ortho*-hydroxylated aromatic ketones **6** were observed in good to excellent yields. The reaction was also tested with acetophenone (**5k**). In the reaction, *ortho*-



Scheme 5: *Ortho*-Hydroxylation of Substituted Acetophenones

hydroxy acetophenone (**6k**) was observed only in very low 2% yield. In addition, hydroxylation was also observed at methyl group of acetophenone **6k'** in 4% yield. Under the present reaction conditions, only *t*-butyl acetophenones and benzophenone worked very well compared with acetophenone.

ortho-Hydroxylation of Aromatic Ketones

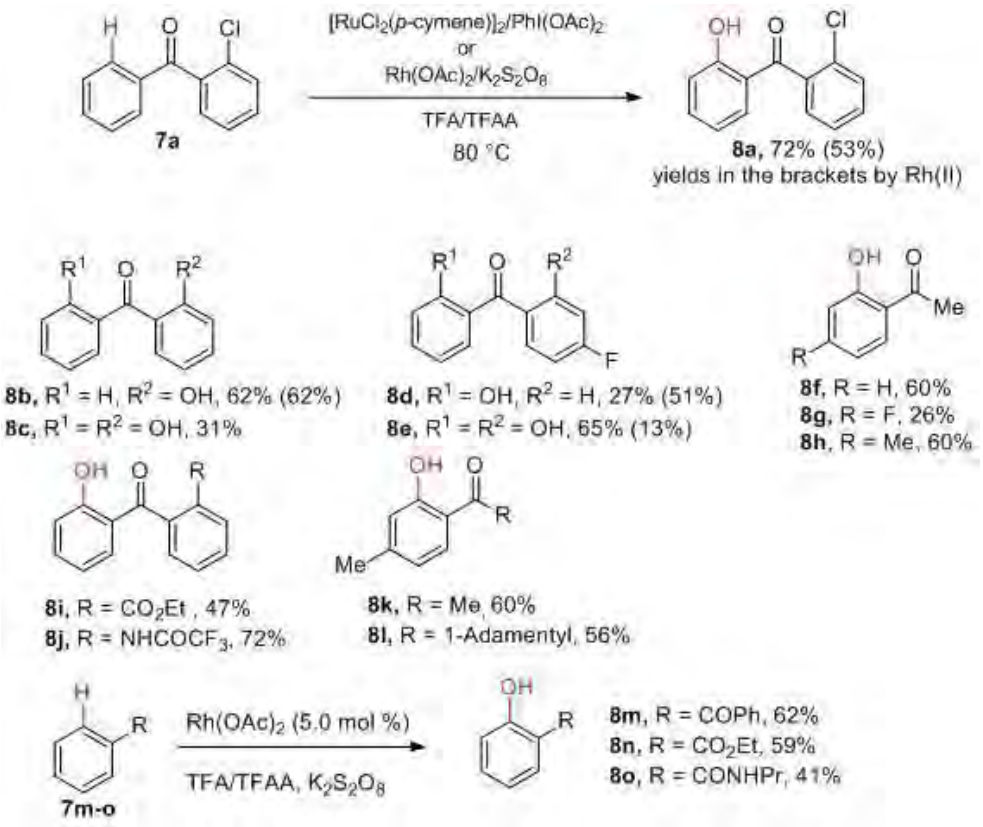
Recently, Rao's group (Rao *et al*., 2013) reported a regio- and chemoselective hydroxylation of aromatic ketones by using $Rh(OAc)_2$ or Ru(II) catalysts (Scheme 6). The practicality of this method was proved by a gram-scale synthesis of substituted 2-acylphenols from substituted acetophenones.

(2-Chlorophenyl) (phenyl) methanone (**7a**) was allowed to react with a mixture of TFAA/TFA in presence of Ru catalyst and $K_2S_2O_8$ or $PhI(OAc)_2$ to give *ortho*-hydroxylated benzophenone **8a** in 75% yield. The reaction was examined with various substituted benzophenones **7**. In these reactions, the corresponding hydroxylated benzophenones **8** were observed in good yields. The catalytic reaction also worked equally with the rhodium catalyst as like the ruthenium catalyst. It is important to note that the present methodology was also compatible with benzophenone, ethyl benzoate and benzamide in the presence of $Rh(OAc)_2$ catalyst.

The catalytic reaction involves coordination of the carbonyl oxygen atom of acetophenone to Ru(II) species followed by the *ortho* metalation affords a five-membered Ru(II) intermediate. Later, Ru(II) was oxidized into the possible Ru(IV) intermediate in the presence of TFAA and oxidant. The final step involves the carbon-oxygen bond forming reductive elimination at the *ortho* C-H bond of acetophenone providing the trifluoroacetated acetophenone and Ru(II) species for the next catalytic cycle. The trifluoroacetated product was further converted into the hydroxylated acetophenones after the aqueous workup.

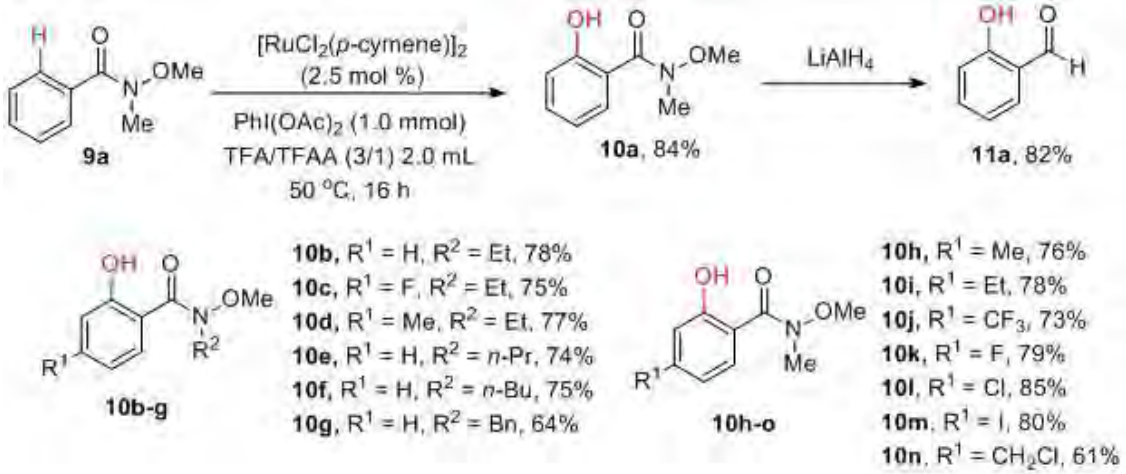
ortho-Hydroxylation of Weinreb Amides

Later, Ackermann's group (Ackermann *et al*., 2013) disclosed the *ortho*-hydroxylation of aryl Weinreb amides under the mild reaction conditions by using Ru(II) catalyst (Scheme 7). Treatment of *N*-Methoxy-



Scheme 6: *ortho*-Hydroxylation of Aromatic Ketones

N-methyl benzamide (**9a**) with TFAA in presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) and $PhI(OAc)_2$ (1.0 mmol) in TFA at 50 °C gave *ortho*-hydroxylated benzamide **10a** in 84% yield (Scheme 6). Initially, the hydroxylation reaction was examined with various oxidants such as $K_2S_2O_8$, $Cu(OAc)_2{\cdot}H_2O$, *m*-CPBA, AgOAc and $PhI(OAc)_2$. Among them, $PhI(OAc)_2$ was effective for the reaction. This methodology was compatible with various substituted benzamides. Also, the scope of the *ortho*-hydroxylation was also shown with halogen group such as Cl, F, I, and CF_3 substituted benzamides. Later, *ortho*-hydroxylated



Scheme 7: *ortho*-Hydroxylation of Weinreb Amides

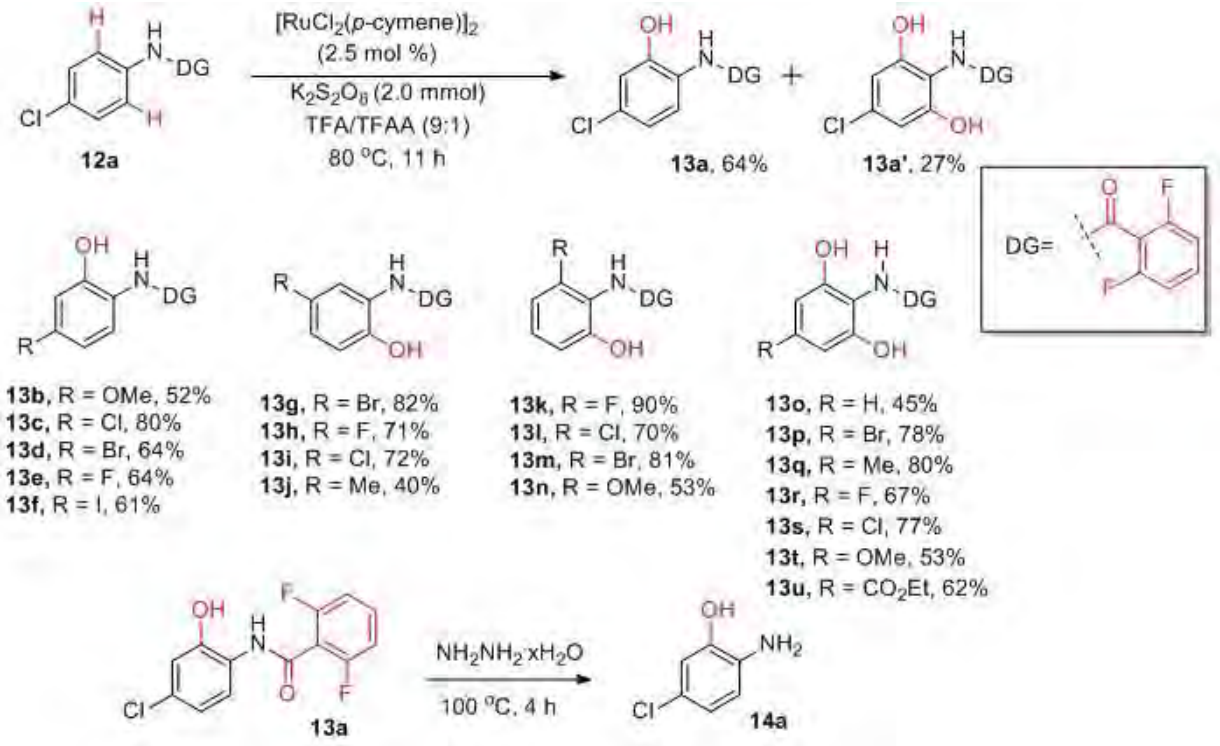
benzamides were converted into the corresponding *ortho*-hydroxylated aromatic aldehydes by $LiAlH_4$ reduction. But, a similar type of hydroxylation reaction was not compatible with aromatic aldehydes with a combination of TFAA/TFA in the presence of ruthenium catalyst and oxidant.

ortho-Hydroxylation of Substituted Anilines

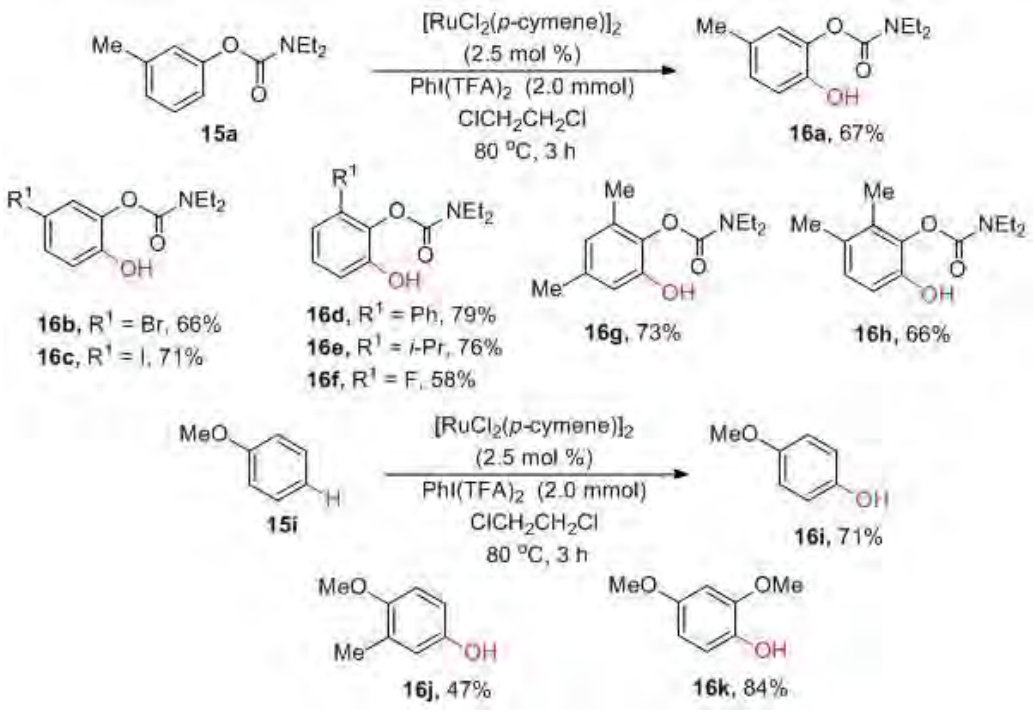
Rao's group (Rao *et al.*, 2013) reported a ruthenium-catalyzed *ortho*-hydroxylation of substituted anilines having a removable directing group (CO-Ar) on the nitrogen moiety (Scheme 8). The reaction of 2,6-difluorobenzoyl 4-chloro-acetanilide (**12a)** with TFAA in presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), oxidant $K_2S_2O_8$ (2.0 mmol) in TFA gave a mixture of mono-*ortho*-hydroxylated substituted aniline **13a** in 64% yield and bis-*ortho*-hydroxylated aniline derivative **13a'** in 27 % yield, respectively. In the reaction, $K_2S_2O_8$ was a suitable oxidant. The catalytic reaction worked very well with various *ortho*-, *meta*-, and *para*- substituted aniline derivatives having substituents such as halides, CF_3, ester, methyl and methoxy. Later, the directing group (CO-Ar) on the *ortho*-hydroxylated aniline **12a** was easily removed into 2-aminophenol (**14a**) in the presence of $NH_2NH_2{\cdot}H_2O$.

ortho-Hydroxylation of Aryl Carbamates

In the same year, Ackermann's group (Ackermann *et al.*, 2013) reported a highly regioselective Ru(II)-catalyzed *ortho*-hydroxylation of aryl carbamates (Scheme 9). This methodology provided an efficient method for the synthesis of *ortho*-hydroxylated aryl carbamates under the mild reaction conditions. To optimized the reaction, various Ru catalysts such as $[Ru_3(CO)_{12}]$, $[Ru(O_2CMes)_2(p\text{-cymene})]$, $[RuCl_2(PPh_3)_3]$, $[RuCl_3(H_2O)_n]$ and $[RuCl_2(p\text{-cymene})_2]$ were screened. Among them, $[RuCl_2(p\text{-cymene})_2]$ was very effective catalyst for the reaction. Among oxidants tested, $PhI(TFA)_2$ was very efficient for the reaction. When aryl carbamate **15a** was reacted with $PhI(TFA)_2$ in presence of $[RuCl_2(p\text{-cymene})]_2$ in 1,2-dichloroethane at 80°C for 3 h, the expected *ortho* hydroxyl aryl carbamate **16a** was observed in 67% yield (Scheme 8). The catalytic reaction was compatible with various substituted aryl carbamates. In the present reaction, substituted anisoles also **15i-k** also reacted with $PhI(TFA)_2$ under



Scheme 8: *ortho*-Hydroxylation of Aniline Derivatives



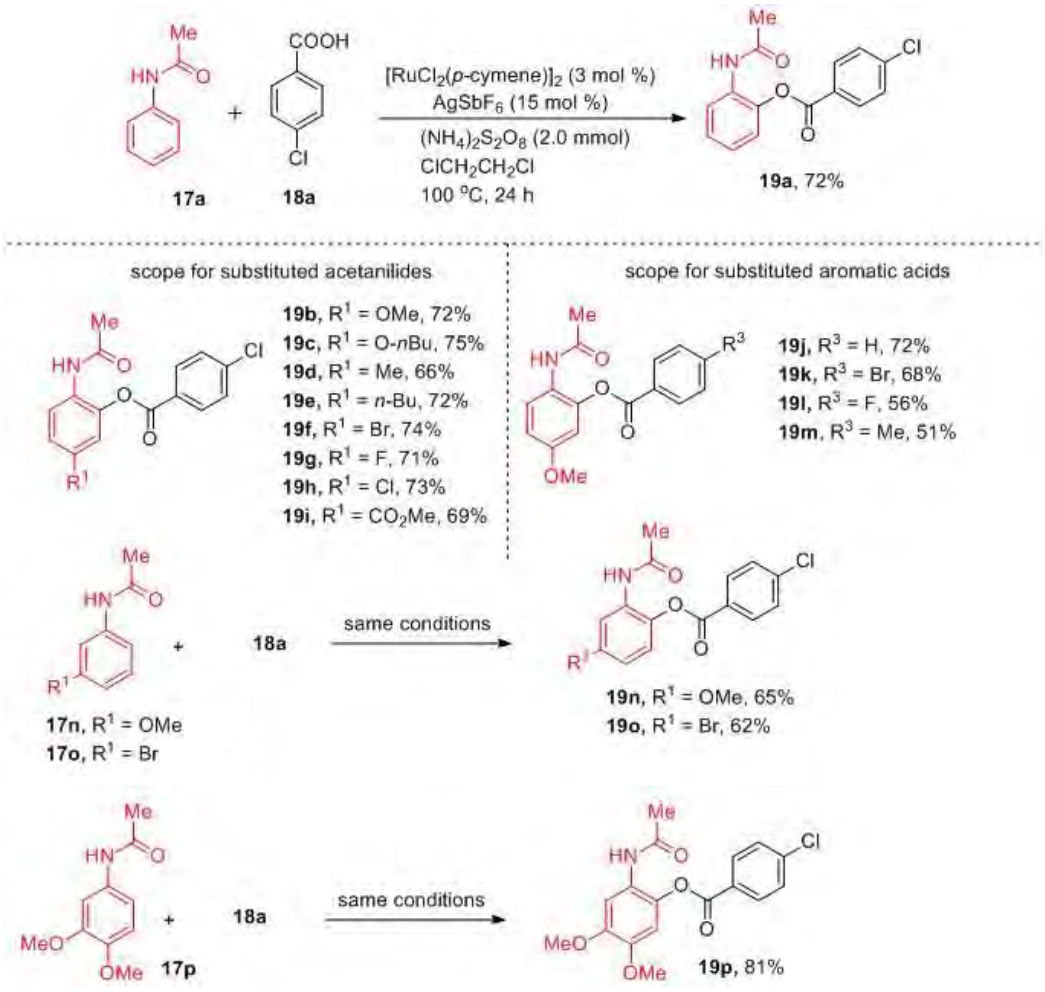
Scheme 9. ***ortho*-Hydroxylation of Aryl Carbamates**

similar reaction conditions yielding 4-hydroxy anisole derivatives **16i-k** in good to excellent yields.

ortho-Benzoxylation of Substituted Acetanilides

Several reports are disclosed for the *ortho* hydroxylation of substituted aromatics. But, the *ortho*-benzoxylation of substituted aromatics is less focused in the literature. This is mainly due to the rapid complex formation of the carboxylic acids with the metal complexes. To suppress the metal carboxylate complex formation, carboxylate sources such as benzoate iodonium salts, benzoyl chlorides, benzaldehydes and aromatic carboxylic anhydrides are used. Also, the known benzoxylation reaction is limited with 2-pyridyl, oxime and *NH*-acetyl directing group substituted aromatics.

Very recently our group (Padala and Jeganmohan, 2013) has reported a Ru(II)-catalyzed highly regioselective *ortho*-benzoxylation of acetanilides with aromatic acids (Scheme 10). The reaction of acetanilide (**17a**) with 4-chlorobenzoic acid (**18a**) in presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), $AgSbF_6$ (15.0 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in 1,2-dichloroethane at 100ºC for 24 h gave *ortho*-benzoxylated acetanilide **19a** in 72% yield (Scheme 10). Initially, the reaction was examined with various oxidants such as Ag_2CO_3, AgOAc, Ag_2O, $Cu(OAc)_2$, CsOAc, KOAc, $K_2S_2O_8$, $PhI(OAc)_2$ and $(NH_4)_2S_2O_8$. Among them, $(NH_4)_2S_2O_8$ oxidant was compatible for the reaction. The present methodology was widely applicable with electron donating as well as electron withdrawing group substituted aromatic acetanilides including OMe, Me, Cl, Br, F and CO_2Me. When study was carried out with the substituted aromatic acids, only halogen substituted aromatic acids such as Cl, Br and F worked very well for the reaction. Next, the regioselectivity of unsymmetrical acetanilides **17n-p** with 4-chlorobenzoic acid (**18a**) was studied. 3-Methoxy acetanilide (**17n**), 3-bromo acetanilide (**17o**) and 3,4-dimethoxy acetanilide (**17p**) underwent *ortho*-benzoxylation selectively at a less hindered C-H bond with 4-chlorobenzoic acid (**18a**) under similar reaction conditions affording *ortho*-benzoxylated anilides **19n-p** in good yields.

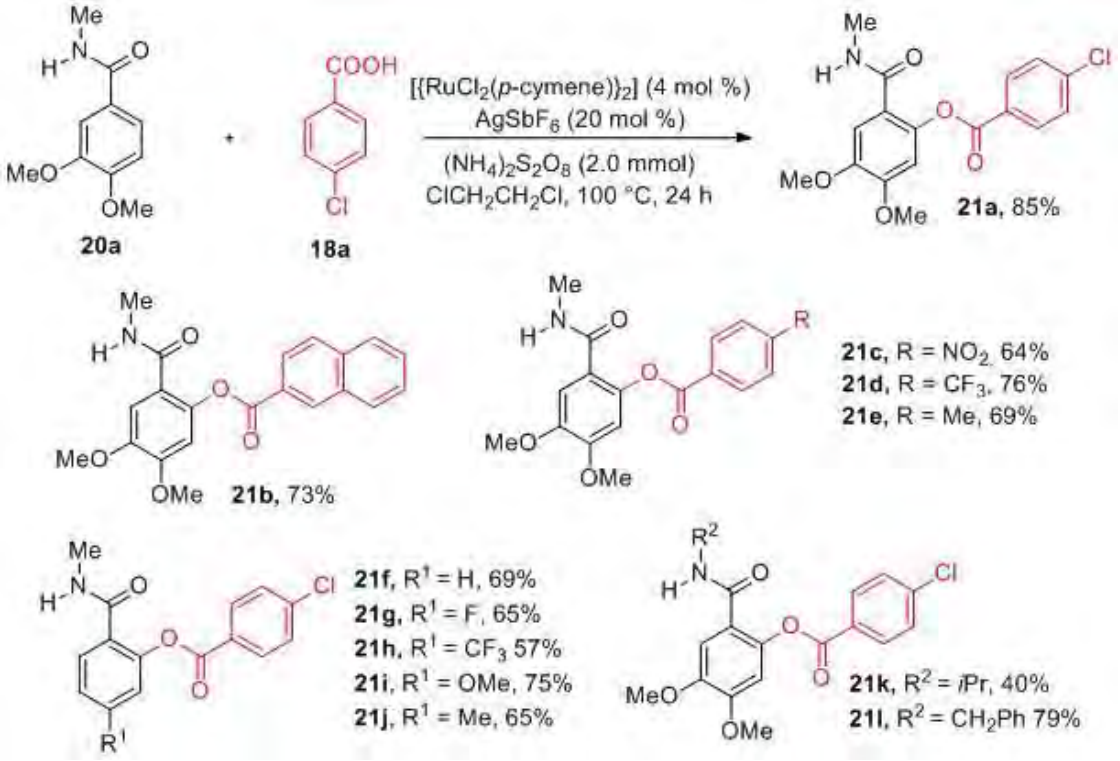


Scheme 10: *ortho*-Benzoxylation of Acetanilides

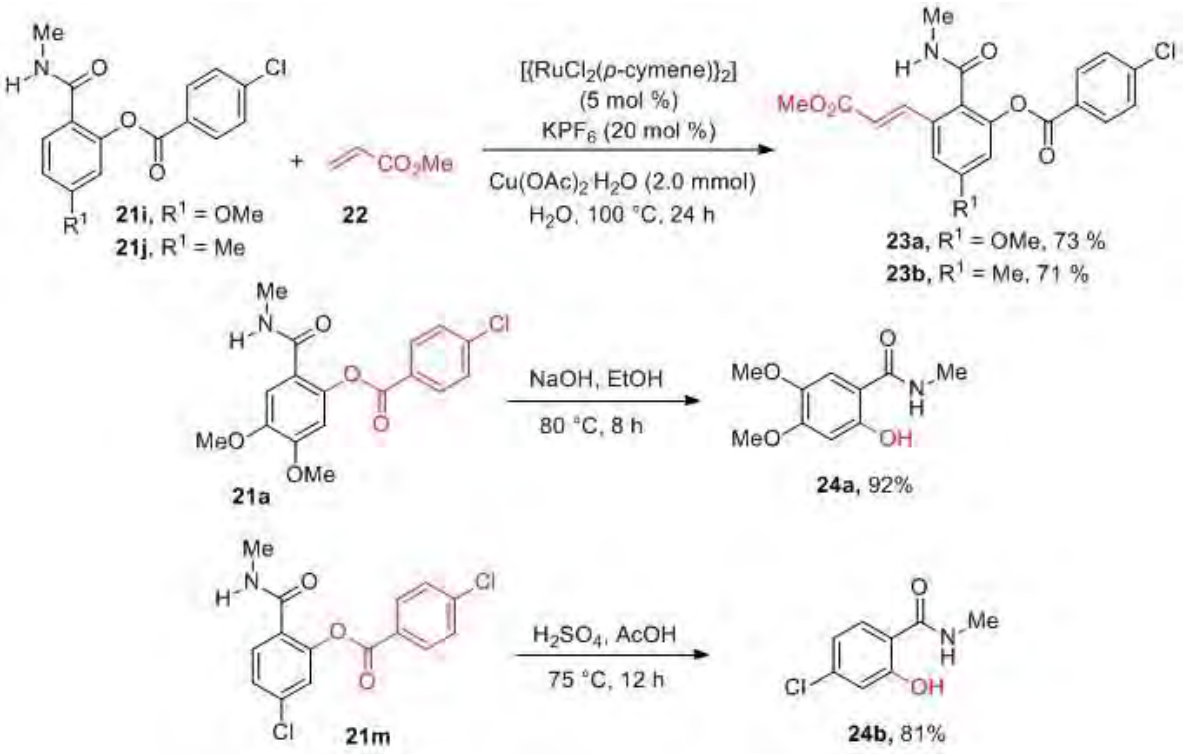
ortho-Benzoxylation of *N*-Alkyl Benzamides

Very recently, we have reported (Padala and Jeganmohan, 2014) a Ru(II)-catalyzed highly regioselective *ortho*-benzoxylation of *N*-alkyl benzamides with aromatic acids (Scheme 11). When *N*-methyl 3,4-dimethoxy benzamide (**20a)** was reacted with 4-chlorobenzoic acid (**18a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (4 mol%), $AgSbF_6$ (20 mol%) and $(NH_4)_2S_2O_8$ (2.0 mmol) in 1,2-dichloroethane (DCE) at 100 °C for 24 h, *ortho*-benzoxylated benzamide **21a** was observed in 85% yield (scheme 10). In this reaction also, $(NH_4)_2S_2O_8$ was a suitable oxidant for the reaction. The catalytic reaction was highly regioselective; C-H activation takes place selectively at a sterically less hindered C-H bond of **20a**. The coupling reaction was compatible with electron-donating, halogen and electron-withdrawing functional group substituted aromatic acids and substituted benzamides. The catalytic reaction was also examined with *N*-substituted benzamides such as *iso*-propyl and benzyl **20k-l** with 4-chloro benzoic acid (**18a**).

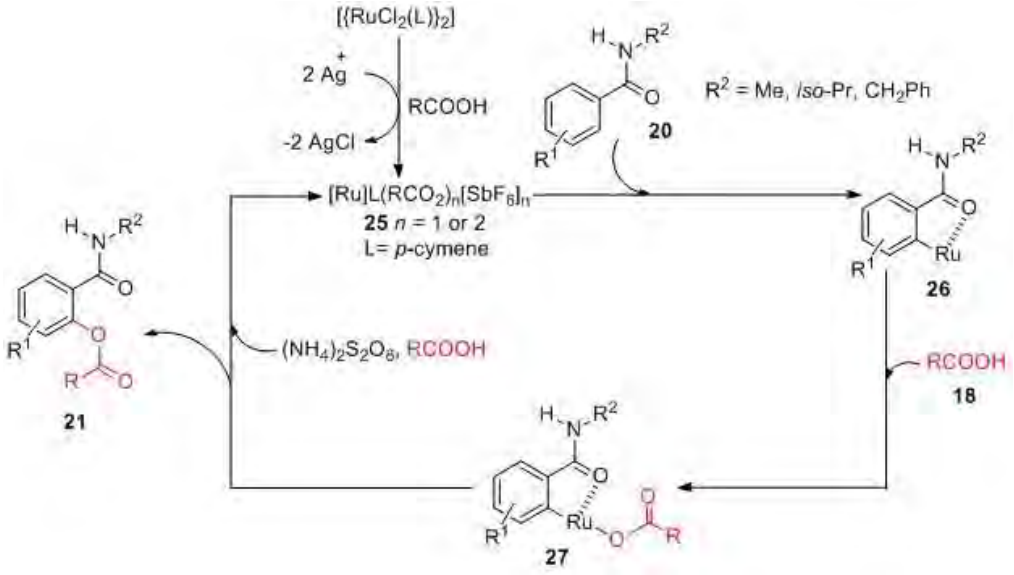
The *ortho* C-H bond of benzoxylated *N*-alkyl benzamides **21i-j** were efficiently alkenylated with methyl acrylate (**22**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), KPF_6 (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (2.0 mmol) in water solvent at 100 °C for 24 h, yielding products **23a-b** in 73% and 71% yields, respectively (Scheme 11). Subsequently, the benzoxyl moiety of benzamide **21a** was converted into the hydroxyl group, in which product 2-hydroxy-



Scheme 11: *ortho*-Benzoxylation of *N*-Substituted Benzamides



Scheme 12: *ortho* Alkenylation of *N*-Substituted Benzamides



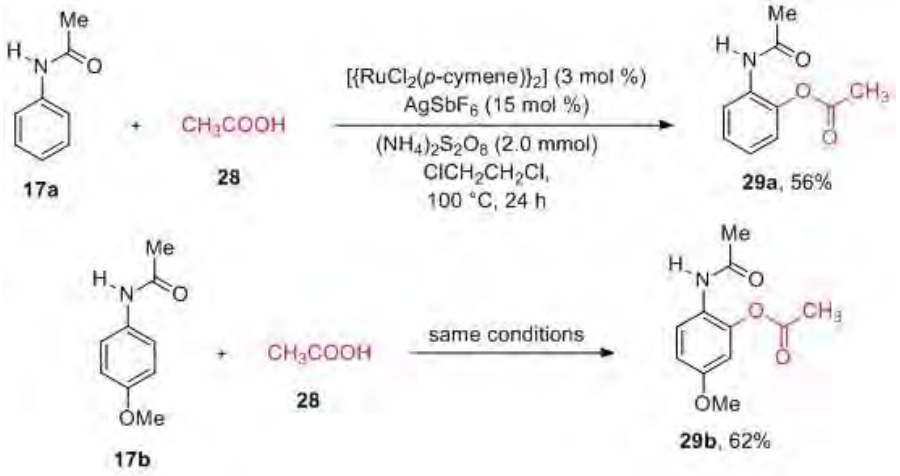
Scheme 13: Proposed mechanism

N-methyl benzamide (**24a)** was obtained in 92% yield in the presence of NaOH base (Scheme 12). Further, *ortho*-benzoxylated benzamide **21m** was converted into *ortho*-hydroxyl benzamide **24b** in 81% yield in the presence of H_2SO_4 solution.

A possible reaction mechanism was proposed for the present benzoxylation reaction in Scheme 13. $AgSbF_6$ likely removes the chloride ligand from the $[\{RuCl_2(p\text{-cymene})\}_2]$ complex, providing a cationic ruthenium carboxylate complex **25**. Coordination of the carbonyl oxygen of the benzamide **20** to the cationic species **25** followed by the *ortho*-metalation affords a five-membered metallacycle intermediate **26**. Coupling of benzoic acid **18** into the ruthenacycle **26** affords an intermediate **27**. Reductive elimination of intermediate **27** gives the final product **21** and Ru (0) species. Later, $(NH_4)_2S_2O_8$ oxidizes Ru(0) to active Ru(II) species **25** in the presence of carboxylic acid for the next catalytic cycle.

ortho-Acetoxylation of Acetanilides with Acetic Acid

In 2013, we have reported (Padala and Jeganmohan, 2013) a ruthenium-catalyzed *ortho* acetoxylation of acetanilides with acetic acid (Scheme 14). Treatment of acetanilide (**17a**) with acetic acid (**28**) in presence



Scheme 14: *ortho* Acetoxylation of Acetanilides

of [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), $AgSbF_6$ (15.0 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in 1,2-dichloroethane at 100 ºC for 24 h gave *ortho*-acetoxy acetanilide **29a** in 56% yield. Similarly, 4-methoxy acetanilide (**17b**) afforded *ortho*-acetoxy acetanilide **29b** in 62% yield.

Conclusions

In this review, we have discussed the recent observations of a ruthenium-catalyzed *ortho* C-O bond formation of substituted aromatics with oxygen nucleophiles via C-H bond activation. By employing the present method, *ortho* hydroxylated, benzoxylated and acetoxylated aromatics were prepared in a highly atom economical and environmentally friendly manner.

Acknowledgements

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