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Design and synthesis of ruthenium bipyridine catalyst: An approach towards low-cost hydroxylation of arenes and heteroarenes

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ABSTRACT

Two new ruthenium bipyridine complexes were designed and synthesized for intermolecular Csp^2-H hydroxylation. An environmentally begin and inexpensive oxidant was employed as an oxygen source thereby enhancing its applicability and resulting in the remarkable increase of yield. In the catalytic process a ruthenium (IV) cationic complex is formed which enables the regioselective C—O bonds formation and also proves to be tolerant to a broad substrate scope. Activation of C—H bonds adjacent to removable and non-removable directing groups have been explored efficiently.

Introduction

Design and development of different homogeneous catalysts and utilising them for direct C—C/C—O/C—N/C—X bond formation has always been a challenge to the chemists worldwide. The direct hydroxylation of C(sp^2)—H bonds[1–3] is of immense importance as the phenol derivatives are omnipresent in the synthesis of a number of drugs and natural products.[4–6] In 1990, Fujiwara and co-workers reported a pioneering work on $Pd(OAc)_2$ catalyzed hydroxylation of benzene using molecular oxygen as the sole oxidant.[7] Later on Sun and co-workers reported $Pd(OAc)_2$ catalyzed hydroxylation using TBHP (tertiary butyl hydrogen peroxide) as oxidant.[8] Recently, Sanford[9] and co-workers as well as Yu[10] and co-workers have reported two efficient protocols towards *ortho*-acetoxylation and hydroxylation. C—O functionalization reactions have achieved considerable success using versatile ruthenium(II) catalysts (Scheme 1).[11–14] Reports have shown that ruthenium (II)-catalyzed hydroxylation of substrates bearing directing groups shows excellent site selectivity.[15]

The *ortho*-hydroxylation reactions with weakly coordinating groups, including amides,[16,17] carbamates,[18,19] esters,[20] amines,[21] anilides,[22] ketones,[23,24] and aldehydes,[25] are well studied in the literature compared to reactions with strongly coordinating groups. The presence of Lewis basic heterocyclic directing groups, in bioactive organic compounds[26] has enabled the study of C—H activation of these components such as pyridines or pyrimidine's.

Challenges have been accepted by researchers for the development of highly stable ruthenium catalysts that performs site selective activation even in less mole percent. In this context, several catalysts like ruthenium *p*-cymene, ruthenium mesitoate etc. have been extensively used.[27–29]

An excellent catalytic protocol was well established using ruthenium mesitoate as an efficient catalyst for hydroxylation.[20] The presence of mesitoate group enhances the activity of the catalyst as it helps to form a thermodynamically stable cyclic intermediate directing the coupling partner site selectively. However, we noticed that there are limited reports on the synthesis of new ruthenium (II) catalysts for oxidative coupling reactions.[30,31] Milstein et al. have developed several PNP and NNP type ruthenium pincer catalysts[31,32] using substituted bipyridine ligands for highly effective oxidative addition reactions. The use of tridentate ligands drew our attention to replace ruthenium (II) *p*-cymene dimer in a more effective manner by synthesizing new Ru-catalyst and utilizing them in the C—H activation chemistry. We have already accomplished the effective catalytic activity for C—H activation on conversion of ruthenium (II) *p*-cymene dimer to ruthenium (II) mesitoate.[33] Herein, we derivatized our catalyst replacing one COOH— group by bipyridine and substituted bipyridine ligands in ruthenium (II) mesitoate (Fig. 1).

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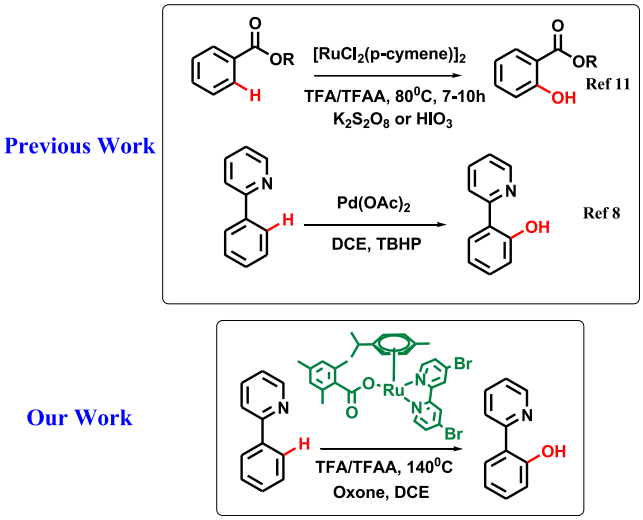


Scheme 1. Schematic representation for the *ortho*-hydroxylation of heteroarenes.

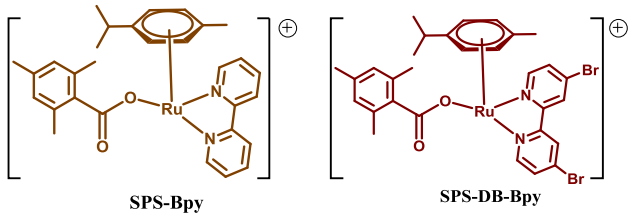


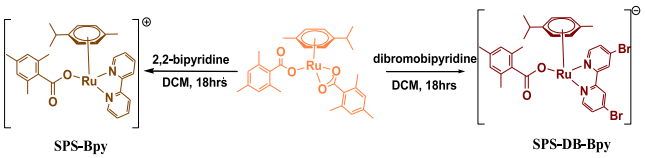
Fig. 1. Chemical structure of SPS-Bpy and SPS-DB-Bpy catalyst.

Results and discussion

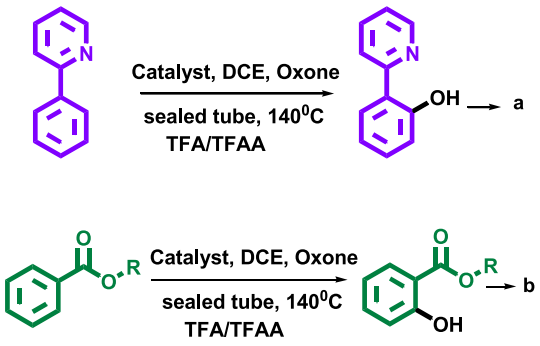
To study the effect of substitution of one of the mesitoate groups with bipyridine we have synthesized two catalysts SPS-Bpy and SPS-DB-Bpy using bipyridine and dibromobipyridine as the respective substituent (Scheme 2). In order to understand the efficiency and test its versatility we studied the catalytic behavior of the synthesized catalysts for one of the most challenging C—O coupling reactions. These catalysts were successfully characterized using ^{1}H NMR, ESI-MS, and HRMS (See ESI).

It was found that on substituting one of the mesitoate with bipyridine ligands the catalysts proved to be efficient in the C—O coupling reactions. Both SPS-Bpy and SPS-DB-Bpy (Fig. 1) showed moderate to high reactivity in various solvents. The mesitoate anion is expected to assist the deprotonation of the hydrogen from aryl derivatives thereby increasing the feasibility of the reaction.

However, it is still unknown whether the mesitoate anion in the counterpart of the cationic complex or the mesitoate anion directly attached to the catalyst, gets dissociated in due course of the reaction and is exactly responsible for the abstraction of proton. The C—O coupling reactions showed promising results in presence of chlorinated solvents. Here the reaction was performed both with strongly coordinating [Scheme 3a] as well as weakly coordinating



Scheme 2. Synthetic scheme of SPS-Bpy and SPS-DB-Bpy.



Scheme 3. (a) Hydroxylation of phenylpyridines. (b) Hydroxylation of aryl ester.

[Scheme 3b] directing groups and was found to be highly regioselective and exclusively resulted in mono-hydroxylated products with good efficiency.

These catalysts were highly stable and showed promising results for C—O bond formation reactions with both removable[24] and non-removable coordinating groups. Although there is not much difference in the yields with SPS-Bpy and SPS-DB-Bpy we observed better results with SPS-DB-BPy. This may be due to the presence of electron withdrawing bromine moiety that helps to stabilize the HOMO level[34] of the catalyst for the easy electron flow during the oxidative addition process. After rigorous screening, (7:3/v:v) ratio of TFA/TFAA (trifluoroacetic acid/trifluoroacetic anhydride) co-solvent was found to be best reaction condition leading to the improved yield up to 77%.[2] C—H bond cleavage via *ortho*-metallation process through chelation of the Ru-metal center with nitrogen of pyridine (Scheme 3a) or oxygen of carbonyl (Scheme 3b) is expected to take place under proper acidic conditions. This is followed by the reductive elimination leading to the formation of the desired C—O bonds.

The hydroxylation reactions were screened with a variety of solvents [Table 1] and major yield was obtained with chlorinated solvent compared to non-chlorinated ones even alcoholic solvents failed to show good results which prove that H-bonding do not facilitate the reaction.[35] The solvent screening was performed keeping the other parameters same. The reaction was also screened with a variety of oxidants like TBHP, PhI(OAc)$_2$ etc.

These oxidants were much stronger and yielded a large number of byproducts. PhI(OAc)$_2$ resulted in the formation of the acetyl derivative of the hydroxylated product and also some unwanted homocoupling products. TBHP was comparatively better but resulted in low yields under our catalytic conditions. We further

Table 1
Solvent screening for hydroxylation of phenylpyridine.[a]

Sl. No	Solvent	Yield (%) SPS-Bpy[b]	Yield (%) SPS-DB-Bpy[b]
1	Acetonitrile	32	40
2	Acetone	38	42
3	DCM	56	65
4	DMF	24	32
5	THF	16	28
6	Toluene	33	38
7	MeOH	1	3
8	EtOH	–	–
9	1,4-Dioxane	22	36
10	1,2-DCE	68	75
11	Chloroform	63	71
12	DMSO	32	28

[a] Reagents and conditions: phenylpyridine (0.3 mmol),catalyst (5 mol%), oxone (0.5 mmol), 8 h at 140 °C, TFA:TFAA = 0.6 ml:0.4 ml.
[b] Isolated yields.