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Research paper

Tandem α/β -alkylation and transfer hydrogenation by heterodimetallic ruthenium-iridium complex



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Keywords: Phenanthroline-pyrazine Iridium-ruthenium heterodinuclear complex α-alkylation β-alkylation Tandem catalysis Transfer hydrogenation Herein, we present a new and air-stable polypyridyl based heterodimetallic complex $[cp^*Ir^{III}(\mu-L)Ru^{II}(p-cym)]$ (PF₆)₂ (**5**) exhibiting facile tandem α/β -alkylation/transfer hydrogenation of ketones/alcohol under mild reaction conditions. The heterodimetallic **5** is found to show better reactivity and selectivity as compared to their homodimetallic analogues (**3** and **4**), monometallic (**1** and **2**) and dimeric precursors $[cp^*IrCl(\mu-Cl)]_2$ and $[(p-cym)RuCl(\mu-Cl)]_2$. In addition, the present catalytic system **5** demonstrates a good flexibility and selective formation of α -alkylated ketones (**C**) or β -alkylated alcohol (**D**) by simple variation of reagents and reaction condition which may be envisioned to play a pivotal role in organic and organometallic chemistry as it lead to the development of pharmaceutically relevant intermediates for the synthesis of different types of heterocycles.

1. Introduction

The design and development of embellished heterodimetallic complexes with suitable bridging ligands is a fascinating area of contemporary research [1–5]. The presence of two different metal unit into a single molecular framework can potentially combine the properties of individual metals which often display properties superior to their corresponding mono- and dimetallic analogues due to synergistic interaction [2–12]. As a results, the heterodimetallic systems find wide applications in biological and chemical sciences [13–22].

Assembling multiple metals into a single molecular framework is a challenging task. For that, a well-defined ligand framework to hold two different metals is essential. In addition, the ligand framework can control the interaction between the metal centers which then reflects in their reactivity [3,23,24]. In this context, several polypyridyl-based ligands have been used considering their easy preparation, excellent metal binding ability and high stability. Most of the cases, the bridging ligands used are either rigid or flexible. The use of bridging ligand having semi-flexible nature have rarely been documented in literature although they can offer advantages over flexible and rigid analogues [15,25–28]. Thus, development of heterodimetallic complexes using semi-flexible polypyridine based ligands would be interesting with exciting property and reactivity.

Parallelly, construction of C–C bond catalyzed by transition metal is one of the important reactions in organic synthesis. In this direction, direct α/β -alkylation of ketones/alcohols has attracted a serious interest in recent years as this route provides a greener way over conventional multistep transformations which generates stoichiometric amount of toxic salt waste. This process involves dehydrogenation of ketone/aldehyde followed by aldol condensation, generating enone intermediate which subsequently hydrogenated to yield α -alkylated ketones (C) or β -alkylated alcohol (D) (known as hydrogen autotransfer/hydrogen borrowing process) (Scheme 1). The only side product obtained in this process is H₂O [29–34]. A major problem in this process is the possibility of formation of mixture of alkylated products C and D. Achieving either of these compounds selectively is, thus, desirable and challenging.

Literature reports demonstrate that α -alkylation of ketones generally results in the formation **C** whereas β -alkylation secondary alcohols yields **D** as major products. Several research groups utilize the aforementioned strategies to achieve the synthetically important intermediates (**C** or **D**). The research group of Cho has reported for the first time the α -alkylation of ketone catalyzed by Ru in presence of excess hydrogen acceptor [35–37]. After that, several other metals (Ir, Rh, Pd) have also been employed for conducting the aforementioned conversion. Different ligands frameworks have also been used to enhance the reactivity [38–45]. Similarly, α -alkylation of ketones with alcohols have also been explored extensively. The metals like Ir, Ru, Rh have been used to achieve α -alkylated ketones [29,46–59]. Although, a large number of mononuclear metal complexes have been studied for α/β -alkylation process, the use of homo- or heterodimetallic complexes are rare [60–69]. The homo- or heterodimetallic complexes are known

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Chart 1. Heterodimetallic complex using semi-flexible ligand L.

to exhibit improved property and reactivity as compared to their monometallic counterparts and have potential to conduct mechanistically different reactions in one pot.[6] Thus, considering the aforementioned, the present work would like to highlight the development heterodimetallic Ru-Ir system using semi-flexible N,*N*-donating pyrazine based bridging ligand 2,3-di(pyridin-2-yl)pyrazino[2,3-f] [1,10] phenanthroline (**L**) to study the α/β -alkylation processes. The ligand **L** is semi-flexible and capable to hold two different metal centers via rigid coordination through phenanthroline nitrogen and flexible coordination through pyridine nitrogen of pyrazine end (Chart 1).

Herein, we report the synthesis and characterization of air stable heterodimetallic complex (5) based on polypyridyl ligand L (L = 2,3-di (pyridin-2-yl)pyrazino[2,3-f] [1,10] phenanthroline) (Fig. 1) and tandem α/β -alkylation-transfer hydrogenation reaction of aromatic ketones using the heterodimetallic complex (5). The tandem reactivity of **5** is studied using aryl ketone and primary alcohol. Further,

mononuclear $[cp^*Ir^{III}(L)(Cl)](PF_6)$ (1) and $[(p-cym)Ru^{II}(L)(Cl)](PF_6)$ (2), and homodimetallic $[cp^*Ir^{III}(\mu-L)Ir^{III}(cp^*)](PF_6)_2$ (3) and [(p-cym)(Cl)Ru^{II}(μ -L)Ru^{II}(Cl)(p-cym)](PF₆)₂ (4) have also been developed to examine the influence of second metal on the tandem process (Fig. 1).

2. Results and discussion

2.1. Synthesis and characterization of polypyridyl-pyrazine based complexes

The semi-flexible polypyridine-pyrazine based ligand L was synthesized by following the reported procedure [15,70,71]. The preparation of complexes (1-5) are outline in Scheme S1. The mononuclear complexes of iridium (1) and ruthenium (2) and their corresponding dinuclear analogues (3 and 4) were prepared by reacting L and dimeric precursors $[(cp^*)IrCl(\mu-Cl)]_2/[(p-cym)RuCl(\mu-Cl)]_2$ in 1:0.5 and 1: 1 ratio, respectively, in methanol at reflux under aerial environment. The heterodinuclear polypyridyl-pyrazine ligand based 5 was synthesized by reacting the isolated mononuclear 1 with [(p-cym) $RuCl(\mu-Cl)]_2$ precursor under identical reaction condition (Scheme S1). The complexes 1 & 2 and 3-5 behaved as 1:1 and 1:2 electrolyte, respectively, in acetonitrile. The solution identities of the complexes were confirmed by ¹H NMR and ¹³C NMR spectroscopy. All the complexes displayed expected numbers of proton resonances in the chemical shift range 0-11 ppm (Figures S1a and b). The molecular composition of the complexes were further confirmed by positive ion electrospray ionization mass spectrometry (Figure S2). The complexes showed molecular ion peaks centered at 656.3 for $[2 - PF_6]^+$ (calcd. 657.1), 1258.9 for [3– PF₆]⁺ (calcd. 1257.19) and 1165.8 for [5 – PF₆]⁺ (calcd. 1165.01) in CH₃OH and confirmed the existence of entire molecular framework of the complexes in solution.

2.2. X-ray crystallography

The formation of **5** was further authenticated by single crystal X-ray crystallography (Fig. 2). The crystal of **5** was grown in DMSO at room



Fig. 1. Mono-, di- and heterodimetallic complexes of iridium and ruthenium with L.



Fig. 2. ORTEP diagram of complex 5. Ellipsoids are drawn at 20% probability level. Hydrogen atoms and counter ions are eliminated for clarity.

temperature. The complex 5 was crystallized out in orthorhombic crystal system with space group Pbca. Important crystallographic parameters and selected bond lengths and bond angles are presented in Tables TS1 and TS2 (SI). From the crystal structure it is observed that both iridium and ruthenium centers display expected piano-stool geometry. The iridium center is coordinated through phenanthroline end whereas the ruthenium center is bonded with the pyridine nitrogen of pyrazine end. It is observed that the pyridine rings are twisted out of plane of ligand L during coordination with ruthenium center. The Ru-C, and Ir-C distances are varying in the range of 2.163 Å – 2. 224 Å and 2.128 Å – 2.180 Å, respectively, which are well agreement with the reported complexes. The Ir-Cl (2.400 Å), Ir-N (2.126 Å - 2.093 Å), Ru-Cl (2.396 Å) and Ru-N (2.144 Å -2.147 Å) bond distances are also matching well with the reported complexes. The observed N1-Ir1-N2 (77.1°) and N5-Ru1-N6 (85.8°) bite angles are also similar to the previously reported complexes. The Ir-C(Cp*), Ru-C(p-cym) and Ru-Ir distances are found to be 1.793 Å, 1.685 Å and 9.901 Å, respectively.

2.3. Evaluation of catalytic performances of polypyridyl-pyrazine based complexes

Both ruthenium and iridium complexes are known to exhibit catalytic activity towards various organic transformations [72,73]. To explore the catalytic performance of the complexes first we studied acceptorless dehydrogenation using benzyl alcohol (**B**). The reaction was carried out at 100 °C in toluene using KOH as base. It was observed that homodinuclear iridium complex (**3**) displayed good reactivity (entry 3, Table 1), whereas, the dinuclear ruthenium complex (**4**) and mononuclear **1** and **2** performed poorly (entry 1, 2 and Table 1). Interestingly, the heterodimetallic **5** (with one iridium center) displayed reactivity similar to **3** (having two iridium centers). This suggests the importance of second hetero-metal in the framework and both metal centers are acting as catalyst. Similar reactivity was also observed while 1-phenyl ethanol(A) was used (entry 6, Table 1).

We next studied tandem α -alkylation (through borrowing hydrogen

 Table 1

 Acceptorless alcohol dehydrogenation of primary and secondary alcohol.^{a.}

| С ОН | Catalyst toluene, KOH,100 °C | | |
|-------|------------------------------------|--------|------------------------|
| Entry | Catalyst(mol%) | R | Yield (%) ^b |
| 1 | 1 (0.2) | Н | 39 |
| 2 | 2 (0.2) | Н | 33 |
| 3 | 3 (0.1) | Н | 83 |
| 4 | 4 (0.1) | Н | 31 |
| 5 | 5 (0.1) | Н | 82 |
| 6 | 5 (0.1) | CH_3 | 76 |

^aReaction conditions: Alcohol (0.5 mmol), KOH (0.5 mmol), toluene (1 mL), 100 °C, reaction time = 12 h. ^bIsolated yields after column chromatography.

Table 2

Comparison of reactivity towards the tandem α/β -alkylation/transfer hydrogenation reaction of acetophenone and 1-phenylethanol using complexes.^{a.}



^aReaction conditions: Acetophenone (0.5 mmol), base (0.5 mmol), PhCH₂OH (1 mL), 100 °C, reaction time = 16 h. ^bIsolated yields after column chromatography. ^c1-phenylethanol (A') was taken instead of acetophenone (A). ^dReaction carried out in presence of ligand L (10 times of metal precursors). ^eReaction temperature 130 °C at 8 h. ^fCatalysts loading 0.01 mol% at 130 °C.

mechanism) and transfer hydrogenation reactions using our synthesized complexes. To test the catalytic behavior of the complexes, the α alkylation reaction of acetophenone (**A**) in presence of excess benzyl alcohol (**B**) was conducted. It was observed that both mono- and dinuclear ruthenium complexes (**2** and **4**) yielded only α -alkylated product (**C**) (Table 2, entry 2 and 5). On the other hand, mononuclear iridium complex **1** resulted only hydrogenated product **E** (Table 2, entry 1), whereas diiridium **3** yielded hydrogenated product **E** along with a small amount α -alkylated product **D** under similar reaction conditions (Table 2, entry 3).[3] These results suggest that (although low yields) ruthenium and iridium centers conduct two mechanistically distinct reactions, independently.

The complex 5 possesses both ruthenium and iridium centers in the same molecular framework. The same α -alkylation reaction was conducted using heterodinuclear 5. It was observed that the heterodinuclear 5 selectively yielded α -alkylated product (D) (the hydrogenated product of C) (entry 7, Table 2). Thus, incorporation of second metal ruthenium in the same molecular framework significantly improve yield and selectivity of specific product (95% **D**) (via tandem α -alkylation/transfer hydrogenation process) which is remarkable (entry 7, Table 2). Interestingly, an equimolar mixture of dimeric 3 and 4 displayed much lower yield (61%) (entry 9, Table 2) suggesting the importance of different metal present into a single molecular framework. As expected, the reaction did not proceed at all in presence of dimeric precursors $[cp*IrCl(\mu-Cl)]_2$ and $[(p-cym)RuCl(\mu-Cl)]_2$ (entry 10 and 11, Table 2), however, 40% formation of C was registered when an equimolar mixture of both precursors ([cp*IrCl(µ-Cl)]₂ and [(p-cym)RuCl(µ-Cl)]2) were used (entry 12, Table 2) in presence 10 mol % of L. This again emphasis the importance of well-define ligand framework for better catalytic activity. While raising reaction temperature to 130 °C an improved yield of formation of D was observed (entry 13, Table 2). Similarly, a generous yield of D also registered at reduced amount of catalyst loading (0.01 mol %) at higher temperature (entry 14, Table 2).

Next, we conducted β -alkylation of 1-phenylethanol (**A**') in excess benzyl alcohol (**B**). It was observed that β -alkylation of 1-phenylethanol

Table 3

| ОН А' В | Catalyst toluene, KOH,100°C | | | |
|-----------------------|-----------------------------------|---------------|----|--|
| Entry | Catalyst (mol %) | Yields $\%^b$ | | |
| | | С | D | |
| 1 | 1 (0.2) | 19 | 12 | |
| 2 | 2 (0.2) | - | 57 | |
| 3 | 3 (0.1) | 44 | 29 | |
| 4 | 4 (0.1) | - | 96 | |
| 5 | 5 (0.1) | 92 | - | |
| 6 ^{<i>c</i>} | 5 (0.1) | 72 | 20 | |

Comparison of reactivity towards the tandem α/β -alkylation dehydrogenation reaction of 1-phenylethanol and acetophenone using complexes in toluene.^{a.}

^aReaction conditions: 1-phenylethanol (0.5 mmol), benzyl alcohol (0.5 mmol), base (0.5 mmol), toluene (1 mL), 100 °C, reaction time = 16 h. ^bIsolated yields after column chromatography. ^cAcetophenone (**A**) instead of 1-phenylethanol (**A**') was taken.

(A') in excess benzyl alcohol (B) in presence of heterodimetallic 5 yielded D (83%) (entry 8, Table 2), whereas, it was 23% and 71% for homodinuclear 3 and 4, respectively (entry 4 and 6, Table 2). This results further confirms the improved reactivity of heterodimetallic 5 over homodimetallic 3 and 4.

We then studied β -alkylation of 1-phenylethanol and benzyl alcohol (**B**) in toluene. The diruthenium **4** displayed excellent yield of β -alkylated product **D** with high selectivity (entry 4, Table 3) whereas both yield and selectivity were dropped for diiridium **3** (entry 3, Table 3). On the other hand, β -alkylation by heterodimetallic **5** in toluene demonstrated high yield and selectivity towards the formation of **C** (entry 5, Table 3), however, the β -alkylation was much inferior both in terms of yield and selectivity (entry 6, Table 3). Both yield and selectivity were much inferior for monometallic **1** and **2** (entry 1 and 2, Table 3).

Combining, the results suggest that heterodimetallic **5** is potentially a good catalyst for both α/β -alkylation. The complex offers the selective formation of alkylated ketone (**C**) or alcohol (**D**) by mere variation of solvent and reagent which is very important for getting desired alkylated products as useful synthetic intermediates.

We next studied the reaction profile of tandem α -alkylation/transfer hydrogenation reaction with time (Fig. 3). In the case of α -alkylation/ transfer hydrogenation reaction the tandem reaction sequence was as follows: first there was α -alkylation and formed α -alkylated ketone (C) and in the subsequent step this converted to hydrogenated product (D). Hence, the reaction profile diagram was drawn by monitoring the



Fig. 3. Time-dependent reaction profile diagram of acetophenone towards tandem α -alkylation/transfer hydrogenation reaction by 5. Reaction conditions: Catalyst/acetophenone/Base = 1/1000/1000 (molar ratio), catalyst (0.1 mol %), acetophenone (0.5 mmol), base (0.5 mmol), PhCH₂OH (1 mL), 100 °C.

consumption of **A** along with the formation of **C** and **D**. It was observed that formation of α -alkylated **C** started immediately after the initiation of the reaction whereas the formation of **D** took an induction time 3 h. This suggests the consecutive nature of the reactions and α -alkylation process leads the tandem process in step I and successive hydrogenation process initiated in step II.

Based on the literature reports and present reaction profile study we may draw a plausible mechanism of tandem α/β -alkylation and transfer hydrogenation reaction as shown in Scheme S2.

3. Conclusion

In conclusion, we have developed monometallic (1 and 2), homodimetallic (3 and 4) and heterodimetallic (5) complexes of iridium and ruthenium. The complexes have been characterized by various analytical techniques. The single crystal X-ray crystallography study indicates that the iridium unit is coordinated at phenanthroline end and ruthenium unit is coordinated with pyridine unit of pyrazine end. The heterodimetallic 5 displays excellent α/β -alkylation of ketone/alcohol with better selectivity and yield as compared to mono- and homodimetallic analogues. In addition, the selectivity of alkylated ketone (C) or alcohol (D) can easily controlled by changing solvent system and reagents. Metal catalyzed construction of C-C bond using fairly available alcohol/ketone is exciting and improving selectivity of formation of products by simple variation of solvent is added advantage. The present heterodimetallic system (5) offers both facile C-C bond construction and controls formation of selective α/β -alkylated products. We, thus, envision that the present work would be an important addition to the area who are engaged in the area of coordination, organometallic and organic chemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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