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Triphenylphosphine-cyclometallated iridium(III) pyrimidine complexes: Synthesis, crystal structures and application in α -alkylation of ketones with alcohols

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1. Introduction

The α -alkylation of ketones with electrophiles such as alkyl halides is the conventional method to form C–C bonds [1]. In recent years, alcohols have emerged as alternative alkylating agents of carbonyl compounds by transition-metal catalysts [2–5]. This strategy can improve both the atom efficiency and the regioselectivity of the process producing only water as a side product. Several groups have reported the use of Ru [6–8], Pd [9–11] and Ni [12] catalysts for the α -alkylation of ketones with alcohols. In addition. Ir complexes serve as efficient cataltsts for hydrogen transfer from alcohols to aldehvdes [13.14], and they have been utilized in α -alkylation of ketones. Among them, $[Ir(cod)Cl]_2$ has been the most commonly employed Ir catalyst for this reaction [15-17]. For instance, the above reaction was successfully accomplished by Ishii et al. with [Ir(cod)Cl]₂/PPh₃ catalyst [15]. However, these reactions require highly catalytic loading and excessive ligand. Until now, other Ir(III) complexes-catalyzed α -alkylation of ketones have been less reported [18]. In this regard, convenience, along with efficacy, is of significance.

ABSTRACT

Two triphenylphosphine (PPh₃)-cyclometallated iridium(III) pyrimidine complexes Ir(NDMP)₂PPh₃Cl **1** and Ir(NDMP)(PPh₃)₂Cl₂ **2** (NDMP = 2-(2-naphthyl)-4,6- dimethyl-pyrimidine) were synthesized and characterized by NMR, IR, ESI-MS, and elemental analysis. Additionally, their detailed structures have been determined by X-ray single-crystal diffraction. The complex **1** was a PPh₃-biscyclometalated Ir(III) complex, while **2** was a PPh₃-monocyclometalated Ir(III) complex. These complexes were found to be efficient catalysts for α -alkylation of ketones with alcohols.

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Cyclometalated Ir(III) complexes have attracted considerable attention in molecular materials [19,20] and organic synthesis [13,14]. For example, bis(imino)aryl Ir(III) pincer complexes were used as the catalysts for the transfer hydrogenation of acetophenone and benzophenone [21]. To the best of our knowledge, there are no reports concerning cyclometalated Ir(III) complexes-catalyzed α alkylation of ketones. In recent years, part of our research effort has focused on the synthesis and application of cyclometalated complexes [22-24]. In a preliminary communication [25], we synthesized a new naphthalenylpyrimidine NDMP and its Ir(III) complexes. In view of these findings and our continuous interest in the synthesis and applications of other cyclometallated NDMP Ir(III) complexes, we prepared two PPh₃-cyclometallated NDMP Ir(III) complexes Ir(NDMP)₂PPh₃Cl 1 and Ir(NDMP)(PPh₃)₂Cl₂ 2 and examined their catalytic activity in the α-alkylation of ketones with alcohols. The results are presented below.

2. Results and discussion

2.1. Synthesis and structures of complexes 1-2

The synthetic routes to complexes 1-2 are depicted in Scheme 1.1 was prepared by reaction of Ir(III) Cl-bridged dimer [Ir(NDMP)₂Cl]₂



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Scheme 1. Synthesis of 1-2.

[25] with PPh₃ according to the literature procedure [26]. 2 was also accessed by cyclometalation reaction of NDMP with IrCl₃ and PPh₃ [27]. The two complexes are air and moisture stable both in the solid state and in solution. They were fully characterized by elemental analysis, IR, ¹H NMR, ¹³C NMR and ESI-MS. In order to further investigate the structures of these complexes, their detailed structures have been determined by X-ray single-crystal diffraction. Fig. 1 and Fig. 2 show that 1 · CH₃CH₂OH-2 are PPh₃-biscyclometalated and PPh₃-monocyclometalated Ir(III) complexes, respectively. The Ir atom in 1 · CH₃CH₂OH is located at a distorted octahedral environment composed of C₂N₂PCl donors. The two NDMP ligands are cisarranged with the two C donors in cis-position and the two N donors in trans-orientation. However, 2 contains only one NDMP ligand, the two phosphines occupy the axial site. Both Ir-N and Ir-C bond lengths of 1 · CH₃CH₂OH are similar to those of 2. Ir-P bond length of 1 · CH₃CH₂OH are similar to those of the related complexes [IrCl(arylpyridine)₂(PPh₃)] [28–30], while it is longer than those of **2** and the related PPh₃-monocyclometalated Ir(III) complexes [27,31]. In the crystal of 1.CH₃CH₂OH, chlorine atom forms O-H...Cl



Fig. 1. Molecular structure of complex $1 \cdot CH_3CH_2OH$. Displacement parameters are drawn at the 50% level. Non-hydrogen bonding H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ir(1)-C(1) 2.019(8), Ir(1)-C(17) 1.986(9), Ir(1)-N(2) 2.106(7), Ir(1)-N(3) 2.108(7), Ir(1)-C(11) 2.529(2), Ir(1)-P(1) 2.483(2), and C(17)-Ir(1)-C(11) 1.74.6(2), C(1)-Ir(1)-P(1) 169.4(2), N(2)-Ir(1)-N(3) 168.9(2), C(17)-Ir(1)-N(3) 80.4(3), N(3)-Ir(1)-P(1) 87.86(18), C(1)-Ir(1)-N(3) 89.9(3).



Fig. 2. Molecular structure of complex **2**. Displacement parameters are drawn at the 50% level. H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ir(1)–C(3) 2.029(3), Ir(1)–N(1) 2.127(3), Ir(1)–P(1) 2.3927(9), Ir(1)–P(2) 2.3672(9), Ir(1)–Cl(1) 2.3755(8), Ir(1)–Cl(2) 2.5045(9), and P(1)–Ir(1)–P(2) 176.46(3), Cl(1)–Ir(1)–P(1) 172.30(7), Cl(2)–Ir(1)–C(3) 175.77(9), N(1)–Ir(1)–C(3) 80.95(11), P(1)–Ir(1)–N(1) 91.25(7), P(2)–Ir(1)–N(1) 91.31(7).

hydrogen bond (the distance is 2.457 Å) with the adjacent O–H group of ethanol. In the crystal of **2** there exist two types of intermolecular C–H···Cl hydrogen bonds (the distances are 2.845 Å and 2.937 Å) (Fig. 3).

2.2. PPh₃-cyclometalated Ir(III) complexes-catalyzed α -alkylation of ketones with alcohols

Ishii reported direct α -alkylation of ketones and acetates with primary alcohols catalyzed by an [Ir(cod)Cl]₂/PPh₃/base system [15,17]. The reaction is thought to proceed via the following three key steps: oxidation of the primary alcohol, base-catalyzed aldol condensation and selective hydrogenation of α , β -unsaturated ketones and esters. Based on these results and in connection with our experience in the synthesis and application of cyclometalated Ir(III) complexes [22,25], we were interested to see whether the obtained PPh₃-cyclometalated Ir(III) complexes would be efficient catalysts for the α -alkylation of ketones with alcohols. Initially, the use of complex **2** as catalyst for the oxidation of benzyl alcohol was examined. Using 2 mol% of **2** in the presence of 0.5 equivalent of NaOH as base in dioxane at 110 °C provided benzaldehyde in an excellent yield (96%).

In the following experiments, the α -alkylation of acetophenone with benzyl alcohol was carried out with various bases and solvents in the presence of 2 mol% of **2**. The results from this study are summarized in Table 1. After screening a variety of bases (e.g., NaOH, KOH, Na₂CO₃, K₂CO₃ and *t*-BuOK) (entries 1–5), NaOH and KOH were found to give the good results (80 and 78% yield), Na₂CO₃, and K₂CO₃ displayed moderate efficiency, producing the products in 58 and 60% yield, respectively. Among the tested solvents, dioxane was much better than other solvents such as toluene and THF (entries 6–7). Furthermore, the activities of several related catalytic systems in the same model reaction were investigated. The Ir(III) Cl-bridged dimer [Ir(NDMP)₂Cl]₂ generated the product only in 42% yield under the same conditions (entry 8).



Fig. 3. Partial packing view of complex 2 showing the C-H···Cl hydrogen bonds. Non-hydrogen bonding H atoms are omitted for clarity.

Increasing catalyst loading to 2 mol% (Ir 4 mol%) gave 70% yield (entry 9). The yield was greatly improved by the addition of PPh₃ suggesting that PPh₃ participated in the catalytic cycles (entry 10). Additionally, **1** also showed comparable activity producing the product in 75% yield (entry 11). However, the activities of **1** and $[Ir(NDMP)_2Cl]_2/PPh_3$ system were still lower than that of **2**.

Under the optimized reaction conditions (**2**, NaOH, dioxane), various ketones were subjected to react with primary alcohols in order to investigate the reaction scope and several representative results are summarized in Table 2. The reaction also gave good results using acetophenone and 4-chlorophenylmethanol (entry 1). For 3-phenylpropanol and 1-butanol, the yields decreased in 62 and 53% yields (entries 2–3). The alkylations of 4-chlorophenylethanone and *p*-tolylethanone were not significant affected by the position and electronic nature of the substituent on the aromatic ring of ketones (entries 4–8). In the case of dialkyl ketone, the product yields were lower than those of the case of alkyl aryl ketones, the alkylation took place with complete regioselectivity at less-hindered position over methyl (entries 9–11). Finally, it was noteworthy that the reaction of acetylferrocene with benzyl alcohol also gave the expected product in a good yield (83%,

Table 1

Influence of base, solvent and catalyst on the $\alpha\text{-alkylation}$ of acetophenone with benzyl alcohol.^a



Entry	Catalyst (mol%)	Base	Solvent	Yield (%) ^b
1	2 (2)	NaOH	Dioxane	80
2	2 (2)	KOH	Dioxane	78
3	2 (2)	Na ₂ CO ₃	Dioxane	58
4	2 (2)	K ₂ CO ₃	Dioxane	60
5	2 (2)	t-BuOK	Dioxane	46
6	2 (2)	NaOH	Toluene	47
7	2 (2)	NaOH	THF	20
8	$[Ir(NDMP)_2Cl]_2(1)$	NaOH	Dioxane	42
9	$[Ir(NDMP)_2Cl]_2(2)$	NaOH	Dioxane	70
10	[Ir(NDMP) ₂ Cl] ₂ /PPh ₃ (1/2)	NaOH	Dioxane	72
11	1 (2)	NaOH	Dioxane	75

 $^a\,$ Reaction conditions: acetophenone (1.0 mmol), benzyl alcohol (2.0 mmol), base (1.0 mmol), solvent (3 mL), 110 $^\circ$ C, 12 h.

^b Isolated yields (average of two experiments).

entry 12), while the reaction with RuCl₂(DMSO)₄ gave the expected product with only a very low yield (17%) under the same reaction conditions [8].

3. Conclusions

In summary, we have prepared and characterized two PPh₃-cyclometallated iridium(III) pyrimidine complexes 1-2. Their detailed structures have been determined by X-ray single-crystal diffraction. These complexes were found to be efficient catalysts for α -alkylation of ketones with alcohols.

4. Experimental section

4.1. General procedures

Solvents were dried and freshly distilled prior to use. All other chemicals were commercially available expect for ligand NDMP and its cyclometalated Ir(III) Cl-bridged dimer [Ir(NDMP)₂Cl]₂ which were prepared according to the published procedure [25]. Melting points were measured using a WC-1 microscopic apparatus and were uncorrected. IR spectra were collected on a Bruker VECTOR22 spectrophotometer in KBr pellets. NMR spectra were recorded on a Bruker DPX-400 spectrometer in CDCl₃ with TMS as an internal standard. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. Elemental analyses were determined with a Carlo Erba 1160 Elemental Analyzer.

4.2. Synthesis of Ir(NDMP)₂PPh₃Cl 1

A solution of cyclometalated Ir(III) Cl-bridged dimer [Ir(NDMP)₂Cl]₂ (0.1 mmol) and PPh₃ (0.22 mmol) in dichloromethane (15 mL) was stirred at room temperature for 2 h. The product **1** was separated by passing through a short silica gel column with CH₂Cl₂/ethyl acetate (3:1) as eluent. Yellow solid, yield: 82%, m.p.>300 °C. IR (KBr, cm⁻¹): 2922, 2360, 1616, 1593, 1532, 1465, 1435, 1372, 1186, 1142, 1017, 959, 877, 794, 739, 721. The ¹H NMR (400 MHz, CDCl₃): δ 8.65 (s, 2H, Ar–H), 7.96 (d, 2H, Ar–H), 7.78 (m, 5H, Ar–H), 7.70 (s, 2H, Ar–H), 7.52 (t, 2H, Ar–H), 7.42 (t, 2H, Ar–H), 7.22 (m, 8H, Ar–H), 7.09 (s, 2H, Ar–H), 6.65 (s, 2H, Ar–H), 6.56 (s, 2H, Ar–H), 2.68 (s, 6H, –CH₃), 2.40 (s, 6H, –CH₃). ¹³C NMR (100 MHz, CDCl₃): 136.4, 135.8, 135.5, 134.8, 134.7, 134.6, 130.4, 130.2, 129.3, 128.9, 127.4, 127.3, 127.2, 127.1, 126.2, 126.0, 119.7, 29.4,

Table 2
$\alpha\text{-Alkylation}$ of ketones with alcohols catalysed by complex $2.^a$

Entry	Ketone	Alcohol	Product	Yield (%) ^b
1		СІ—	O CI	81
2	$\sqrt{2} - \sqrt{2}$	ОН		62
3		ⁿ C ₃ H ₇ OH	O nC3H7	53
4		ОН		82
5	$-\!$	CI		85
6	$-\!$	ОН		66
7	CI	ОН		76
8	CI-CI-CO	CI		78
9		ОН		72
10		СІОН		75
11 ^c		ОН		45
12 ^d	Fe Fe	ОН	Fe Fe	83

^a Reaction conditions: ketones (1.0 mmol), alcohols (2.0 mmol), **2** (2 mol%), NaOH (1.0 mmol), dioxane (3 mL), 110 °C, 12 h.

^b Isolated yields (average of two experiments).

^c Alcohol (4.0 mmol) was used.

^d KOH (1.0 mmol) was used.

24.2. MS-ESI⁺: *m/z* 921.3 [M – Cl]⁺. Anal. Calcd for C₅₀H₄₁ClIrN₄P: C, 62.78; H, 4.32; N, 5.86. Found: C, 62.97; H, 4.12; N, 5.99.

4.3. Synthesis of Ir(NDMP)(PPh₃)₂Cl₂ 2

Iridium trichloride (0.5 mmol), ligand NDMP (1.5 mmol), PPh₃(1.5 mmol), 2-ethoxyethanol (15 mL), and water (5 mL) were added into a three-neck flask. The mixture was refluxed under a nitrogen atmosphere for 12 h and then cooled to room temperature. A yellow precipitate was filtered and washed with water and ethanol several times. The resulted solid was purified by passing through a short silica gel column with CH₂Cl₂/ethyl acetate (5:1) as eluent to give yellow solid **2**. Yield: 70%, m.p.: 240–241 °C. IR (KBr, cm⁻¹): 3048, 2071, 1599, 1532, 1480, 1432, 1338, 1186, 1155, 1089, 1027, 999, 905, 827, 797, 745, 692. ¹H NMR (400 MHz, CDCl₃): δ 8.28 (s, 1H, Ar–H), 7.70 (d, 1H, Ar–H), 7.42(m, 12H, Ar–H), 7.19 (t, 3H,

Ar–H), 7.09 (m, 6H, Ar–H), 6.95 (m, 14H, Ar–H), 2.41 (s, 3H, –CH₃), 2.24 (s, 3H, –CH₃). ¹³C NMR (100 MHz, CDCl₃): 137.3, 135.9, 133.7, 132.5, 132.3, 132.2, 132.1, 130.6, 130.3, 129.4, 128.7, 128.6, 127.9, 127.1, 125.9, 123.3, 118.8, 29.8, 24.7. MS-ESI⁺: m/z 950.2 [M – 2Cl]²⁺. Anal. Calcd for C₅₂H₄₃Cl₂IrN₂P₂: C, 61.17; H, 4.25; N, 2.74. Found: C, 61.36; H, 4.01; N, 2.97.

4.4. General procedure for α -alkylation of ketones with alcohols

To a solution of Ir(III) complex (0.02 mmol) and base (1.0 mmol) in solution (3 mL) was added the corresponding ketone (1.0 mmol) and alcohol (2.0 mmol) under nitrogen. The reaction mixture was then placed in an oil bath and heated at 110 °C for 12 h, cooled and quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate, then the combined organic layers were washed with water, dried over MgSO₄, filtered,

and the solvent was removed on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel using suitable mixtures of hexane/ethyl acetate as eluent. The products were characterized by comparing their m.p., IR and ¹ H NMR spectra with those found in the literature [8.12.15.32.33].

4.5. X-ray diffraction studies

Crystallographic data for 1. CH₃CH₂OH-2 were collected on a Bruker SMART APEX-II CCD diffractometer with Mo-Ka radiation $(\lambda = 0.071073 \text{ Å})$. The data were corrected for Lorentz-polarization factors as well as for absorption. Structures were solved by direct methods and refined by full-matrix least-squares methods on F^2 with the SHELX-97 program [34]. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in geometrically calculated positions.

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Appendix A. Supplementary material

CCDC 844745-844746 contain the supplementary crystallographic data for 1 · CH₃CH₂OH-2. respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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