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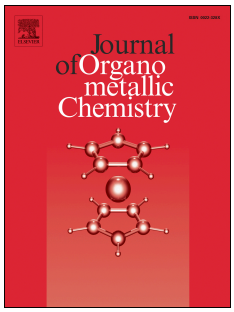

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Iridium(III)- Benzoxazolyl and Benzothiazolyl Phosphine Ligands Catalyzed Versatile Alkylation Reactions with Alcohols and the Synthesis of Quinolines and Indole

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Keywords: Iridium; Benzoxazolyl or benzothiazolyl phosphine ligands; Alkylation; Quinolines

Abstract: A series of benzoxazolyl and benzothiazolyl phosphine ligands **4a-4g** were synthesized and characterized, which prepared from commercially available 2-aminophenol / 2-aminobenzenethiol and 2-bromobenzaldehyde via cyclization and phosphination. The representative ligands **4c** and **4e** were determined by single-crystal X-ray diffraction. The corresponding iridium complexes could be generated *in situ* when $[Cp^*IrCl_2]_2$ (Cp* = pentamethylcyclopentadienyl) encountered ligands. The molecular structures of complexes **5c** and **5e** were crystallographically characterized. The dihedral angles of N(1)-C(1)-C(8)-C(9) showed an increasing twist compared with the corresponding ligand. The iridium(III) catalysts were screened, $[Cp^*IrCl_2]_2$ / **4a** proved to be the optimal catalyst, which exhibited efficient catalytic activity toward versatile alkylations including ketones, secondary alcohols and amines with primary alcohols. Additionally, the synthesis of quinolines from ketones with 2-aminobenzyl alcohol by intermolecular cyclization and indole from 2-(2-aminophenyl)ethanol by intramolecular cyclization were achieved

under the optimized conditions.

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1. Introduction

Alkylation is a fundamental method to construct C-C or C-N bond, and has been applied in organic synthesis for decades [1]. Transition-metal-catalyzed alkylation with alcohols by borrowing hydrogen strategy, compared to traditional methods, is green process with high atom efficiency, which has attracted significant attention in recent years [2].

Over the past decade, great progress has been witnessed in the alkylation reactions with primary alcohols. The *α*- or *β*-alkylation of ketones or secondary alcohols catalyzed by transition metals, such as Rh [3], Pd [4], Ir [5] Co [6], or Mn [7] has been paid much attention. The *N*-alkylation of amines using Ru [8], Pd [9], Ir [10], Co [11], Fe [12], Mn [13], or Ni [14] metals catalyst has also developed. Among them, iridium cooperated with *N*-heterocyclic carbene ligands [15], N^C^N-coordinating ligands [16] and several bidentate ligands have studies. Taking into account their easy access and diversity, bidentate ligands received more attentions. For example, N, C-ligands [17], N, O ligands [10s], N, N-ligands [10t] and P, N-ligands [5c, 10c, 10e] were reported. With respect to the established catalytic systems, ligands supported iridium complexes [18] catalyzed multi-alkylation reactions are rarely reported and highly desirable.

Based on our previous works on the hydrogen transfer reactions using [Cp*Ir(III)] complexes as catalyst [19], we made an attempt to design a series of new catalysts applying in versatile alkylations. The catalyst consists of $[Cp^*IrCl_2]_2$ and benzoxazolyl or benzothiazolyl phosphine ligands with

hemilable coordinating sites [20]. The steric and electronic properties of the catalysts can be easily tailored by the variation of the backbone of ligands as well as the substitution of benzoxazolyl and benzothiazolyl and phosphine group [21].

Herein, we describe *in situ* generated iridium(III)- benzoxazolyl and benzothiazolyl phosphine complexes catalyzed *α*-alkylation of ketones, *β*-alkylation of secondary alcohols and *N*-alkylation of amines with primary alcohols as well as its application in the synthesis of quinolines and indole.

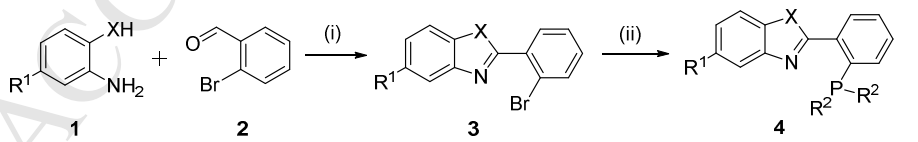
2. Results and discussion

2.1. Synthesis and characterization of benzoxazolyl and benzothiazolyl phosphine ligands

2-(2-Bromophenyl)-benzoxazoles or benzothiazoles **3** were prepared from 2-aminophenols / 2-aminobenzenethiols **1** and 2-bromobenzaldehyde **2** according to our previous report [22]. Starting from the brominated ligand precursors **3**, the benzoxazolyl and benzothiazolyl phosphine ligands **4a-4g** were afforded by lithiation with *n*-butyl lithium, then trapped with PR_2Cl (R = phenyl or cyclohexyl) [21, 23] (Scheme 1). All ligands (**4a-4g**) were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. It is worth noting that the substituents on the phosphorus atom and the type of benzoxazolyl and benzothiazolyl moiety had a significant effect on the ^{31}P NMR signal of **4a-4g**. The phosphorus signals of **4a** / **4c** (δ= -5.61 / -9.01 ppm) with phenyl group shifted to higher field in comparison with that of **4b** / **4d** (δ= -4.62/ -4.56 ppm) with cyclohexyl on the phosphorus atom. For

4e-**4g** with the same phosphine moiety, the ^{31}P NMR spectra of **4e** with electron-donating methyl, **4f** with electron-withdrawing fluoro group, and **4g** with large steric hindrance *t*-butyl group, appeared as singlets at -5.62, -5.37 and -6.14 ppm, respectively. These indicated that different substituents on the benzoxazolyl group had impact on the phosphorus signals. Therefore, phenyl or cyclohexyl on the phosphorus atom as well as electron-donating methyl, electron-withdrawing fluoro or steric hindrant *t*-butyl group on the benzoxazolyl moiety would probably affect the steric and electronic properties of benzoxazolyl and benzothiazolyl phosphine ligands.

Crystals of compounds **4c** and **4e** suitable for X-ray crystallography were obtained from slow evaporation of corresponding solution in *n*-hexane. The molecular structures of **4c** and **4e** (Fig. 1) show that PR_2 group is located in the N atom side of benzoxazolyl or benzothiazolyl group [24]. The torsion angle of benzothiazolyl with phenyl in **4c** (22.5 ^{o}) is slightly larger than the one of benzoxazolyl with phenyl in **4e** (9.8 ^{o}). Although there are torsion angles between benzoxazolyl or benzothiazolyl and phenyl ring, the distance between N(1) and P(1) are appropriate (2.88 Å in **4c**, 2.78 Å in **4e**), supporting the possibility of chelating coordination of N and P with one metal centre. The crystallographic data and the structure refinement details for **4c** and **4e** are summarized in Table 1.



3a X=O, R^1=H
3b X=S, R^1=H
3c X=O, R^1=CH_3
3d X=O, R^1=F
3e X=O, R^1=*t*-Bu

4a X=O, R^1=H, R^2=Ph
4b X=O, R^1=H, R^2=Cy
4c X=S, R^1=H, R^2=Ph
4d X=S, R^1=H, R^2=Cy
4e X=O, R^1=CH_3, R^2=Ph
4f X=O, R^1=F, R^2=Ph
4g X=O, R^1=*t*-Bu, R^2=Ph

Scheme 1. Synthetic pathway of the benzoxazolyl and benzothiazolyl phosphine ligands. (i) 3-Butyl-1-methyl-1*H*-imidazolium iodide, K_2CO_3, *m*-xylene, 120 ^{o}C; (ii) *n*-BuLi, THF, -78 ^{o}C; R_2PCl, -78 ^{o}C to r.t.

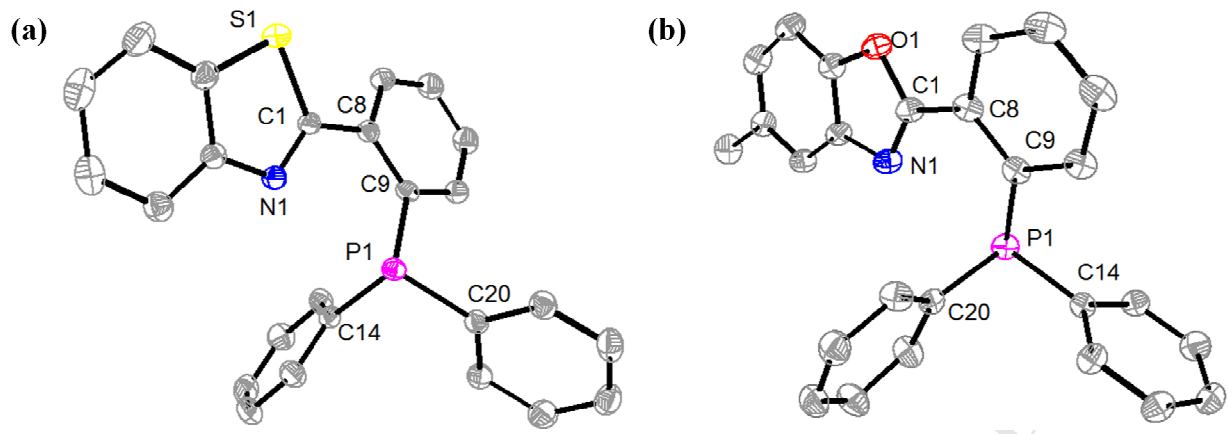


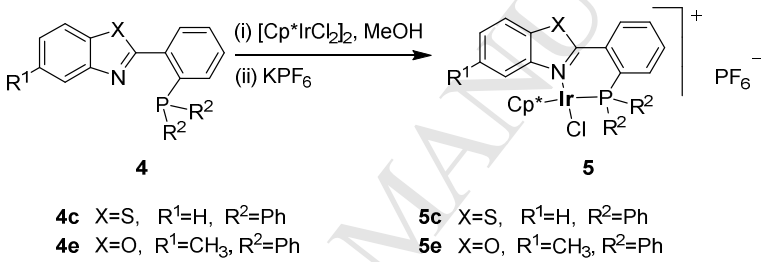
Fig. 1. Molecular structures of **4c** (a) and **4e** (b). Ellipsoids at the 20% probability level. Hydrogen atoms and solvent molecules have been omitted for clarity. Selected bond lengths (Å) and angles (deg) for molecule **4c** [molecule **4e**]: P(1)-C(9) 1.840(2) [1.847(3)], N(1)-C(1) 1.287(3) [1.277(3)], C(8)-C(9) 1.403(3) [1.414(3)]; N(1)-C(1)-C(8) 123.19(19) [128.7(2)], C(8)-C(9)-P(1) 120.66(16) [121.49(18)]; N(1)-C(1)-C(8)-C(9) 22.53(32) [9.808(424)].

2.2. Synthesis and characterization of Ir(III) complexes

Benzoxazolyl and benzothiazolyl phosphine Ir(III) complex **5** was prepared from $[Cp^*IrCl_2]_2$ with the corresponding ligand **4** in methanol at 55 ^oC [25]. Then through an anion-exchange process with KPF_6, the iridium complex **5** were isolated in quantitative yields (Scheme 2).

The representative complexes **5c** and **5e** were characterized by NMR spectroscopy and X-ray diffraction. In the ^1H NMR spectra, the singlets at 1.25 ppm for **5c** and 1.33 ppm for **5e** was assigned to CH_3 of Cp* group, indicating the formation of Cp*Ir complexes. The ^{31}P NMR spectra of **5c** and **5e**, the signals at -3.4, -3.3 ppm and around -144 ppm were attributed to PR_2 and PF_6^-, in which the signals of PR_2 shifted to lower field in comparison with the free ligands [10h]. X-ray crystal structures (Fig. 2) revealed that **5c** and **5e** are constituted by a cationic part and PF_6^- anion. A six-membered ring is observed between P, N atoms of ligand and metal centre. The iridium(III)

center is situated in a distorted octahedral environment with Cp* as a three-coordinated ligand, which is the classic piano stool conformation [2m, 19a,19c]. Other three coordination sites occupy by the N and P atoms of the ligand and a Cl atom. The lengths of Ir-N and Ir-P bond and bond angle N-Ir-P are in the range of the reported iridium complexes [10c, 10h, 10y]. It is noteworthy that the dihedral angles of N(1)-C(1)-C(8)-C(9) in **5c** is 33.9 °, and 26.5 ° for **5e**, both show an increasing twist compared with the corresponding ligand, which would benefit to match the coordination geometry of Ir(III) [21b]. The crystallographic and refinement data for **5c** and **5e** are shown in Table 1.



Scheme 2. Synthesis of iridium complexes **5**.

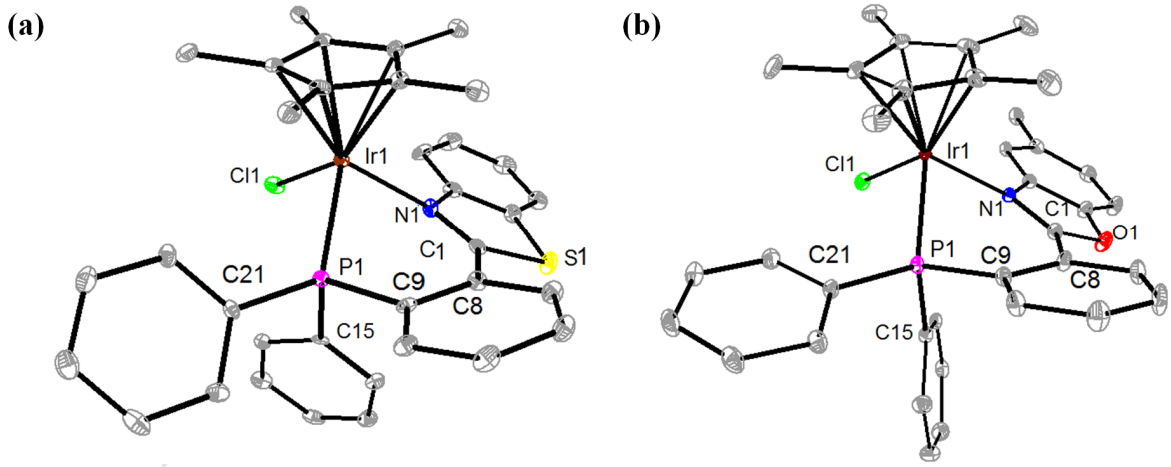


Fig. 2. Molecular structures of complexes (a) **5c** and (b) **5e**. Ellipsoids at the 20 % probability level. Hydrogen atoms and noncoordinated PF_6^- anions omitted for clarity. Selected bond lengths (Å) and angles (deg) for molecule **5c** [molecule **5e**]: Ir(1)-N(1) 2.131(7) [2.131(7)], Ir(1)-P(1) 2.309(3) [2.2932(11)], P(1)-C(9) 1.831(10)[1.841(4)], N(1)-C(1) 1.318(11) [1.306(6)], Ir(1)-Cl(1) 2.396(2)[2.4042(11)], P(1)-C(15) 1.820(8)[1.830(4)], P(1)-C(21) 1.819(9)[1.830(4)], S(1)-C(1)

1.731(9), O(1)-C(1) 1.359(5), C(1)-C(8) 1.482(12)[1.454(6)], C(8)-C(9) 1.400(13)[1.412(6)]; N(1)-Ir(1)-P(1) 81.7(2) [82.11(9)], P(1)-Ir(1)-Cl(1) 89.00(9) [93.41(4)], C(8)-C(9)-P(1) 118.6(7) [115.0(3)], C(1)-N(1)-Ir(1) 122.8(6)[123.6(3)], N(1)-C(1)-C(8) 127.7(8)[130.1(4)], C(1)-C(8)-C(9) 122.3(8)[123.3(4)] C(9)-P(1)-C(15) 106.2(4)[100.4(2)] C(15)-P(1)-C(21) 100.7(4)[103.2(2)]; N(1)-C(1)-C(8)-C(9) 33.973(23) [26.529(816)].

Table 1. Crystal data and structure refinement parameters for ligands **4c**, **4e** and complexes **5c**, **5e**.

	4c	**4e**	**5c**	**5e**
Empirical formula	$C_{25}H_{18}NPS$	$C_{26}H_{20}NOP$	$C_{35}H_{33}ClF_6IrNSP_2$	$C_{36}H_{35}ClF_6IrNOP_2$
Formula weight	395.43	393.40	903.27	901.24
Temperature, K	293(2)	293(2) K	173(2) K	173(2) K
Wavelength, Å	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$Pca2_1$	$P2_1/c$
a, Å	9.039(6)	11.059(4)	29.481(3)	10.5699(9)
b, Å	15.335(10)	9.699(4)	10.8787(10)	11.0799(10)
c, Å	15.174(10)	19.399(7)	21.0174(18)	29.220(3)
α, deg	90	90	90	90
β, deg	106.823(9)	96.049(6)	90	98.1930(10)
γ, deg	90	90	90	90
Volume, $Å^3$	2013(2)	2069.3(14)	6740.5(10)	3387.2(5)
Z	4	4	8	4
Density (calculated), Mg/m^3	1.305	1.263	1.780	1.767
Absorption coefficient, mm^{-1}	0.250	0.150	4.259	4.180
F(000)	824	824	3552	1776
Crystal size, mm^3	0.500 x 0.400 x 0.400	0.700 x 0.700 x 0.350	0.420 x 0.190 x 0.180	0.360 x 0.150 x 0.120
Theta range for data collection, deg	1.931 to 25.998	1.852 to 26.998	1.381 to 27.458	1.408 to 27.482
Index ranges	-11<=h<=11, -18<=k<=17, -15<=l<=18	-13<=h<=14, -11<=k<=12, -24<=l<=11	-38<=h<=35, -8<=k<=14, -27<=l<=27	-13<=h<=11, -14<=k<=14, -37<=l<=37
Reflections collected	9071	9922	41355	23994
Independent reflections	3936 [R(int) = 0.0348]	4453 [R(int) = 0.1023]	15286 [R(int) = 0.0588]	7699 [R(int) = 0.0393]
Completeness to theta = 25.242°	99.6 %	99.7 %	99.9 %	99.2 %
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.674	1.000 and 0.069	0.208 and 0.134	0.262 and 0.169

Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	3936 / 0 / 253	4453 / 0 / 263	15286 / 1 / 857	7699 / 12 / 439
Goodness-of-fit on F^2	1.003	0.788	0.925	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0444, wR2 = 0.1141	R1 = 0.0597, wR2 = 0.1286	R1 = 0.0373, wR2 = 0.0668	R1 = 0.0303, wR2 = 0.0765
R indices (all data)	R1 = 0.0632, wR2 = 0.1238	R1 = 0.1036, wR2 = 0.1356	R1 = 0.0570, wR2 = 0.0731	R1 = 0.0442, wR2 = 0.0839
Extinction coefficient	n/a	n/a	0.032(5)	n/a
Largest diff. peak and hole, e.$Å^{-3}$	0.409 and -0.185	0.386 and -0.355	1.391 and -0.922	1.212 and -0.852

2.3. Screening iridium catalysts by α-alkylation of acetophenone with benzyl alcohol

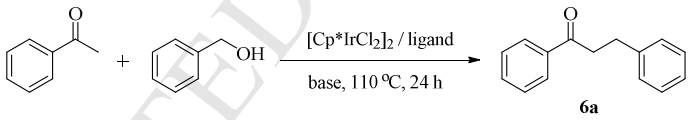
We initiated our work with the screen appropriate iridium(III) catalysts. *α*-Alkylation of acetophenone with benzyl alcohol to obtained 1,3-diphenylpropan-1-one (**6a**) was selected as a model reaction to optimize the reaction conditions (Table 2).

Without ligand, taking $[Cp^*IrCl_2]_2$ alone as precatalyst [10r], only moderate yield was observed (entry 1). When added ligand **4**, the reaction afforded up to 99 % yield (entries 2-8), indicating the ligand could enhance the catalytic activity. Then screening of ligands **4a**-**4g** was carried out. The ligands (**4a** and **4c**) with phenyl on the phosphorus atom (entries 2 and 4) gave better results than those containing cyclohexyl substituent (entries 3 and 5). The ligands with benzoxazolyl group (entries 2 and 3) also obtained higher yield than that of benzothiazolyl (entries 4 and 5). It was worthy to note that electron-donating methyl on the phenyl ring of benzoxazolyl (entry 6) was better than the electron-withdrawing fluoro and the large steric hindrance tert-butyl-substituent (entries 7 and 8). Therefore, ligand **4a** and $[Cp^*IrCl_2]_2$ were chosen as the optimal catalyst.

Subsequently, we adopted iridium(III) catalyst bearing ligand **4a** and $[Cp^*IrCl_2]_2$ to optimize

the reaction conditions. KOH (entries 2, and 9-12) and toluene (entries 2, and 13-16) were proved to be the best base and solvent, repectively. The polarity of solvent has no benefit for the reaction. Control experiments showed that desired product **6a** was barely detected without base (entry 17), further demonstrating the necessity of the base to the catalytic activity of precatalyst $[Cp^*IrCl_2]_2$/ **4a**. Increasing or reducing the amount of base had no positive effect on the yield of **6a** compared with 10 mol% KOH (entries 18-19 vs. entry 2). When the loading of catalyst decreased to 0.5 mol%, the yield of **6a** reduced (entry 20). Same yield could be achieved when well-defined complexes **5c** and **5e** from $[Cp^*IrCl_2]_2$ with **4c** and **4e** as precatalyst (entry 21 and entry 22), indicating that Ir complex generated *in situ* could be applied in the reaction of acetophenone with benzyl alcohol. Hence, the optimum reaction conditions were as follows: catalyst loading with 1 mol% of $[Cp^*IrCl_2]_2$/ **4a** (1/2), 10 mol% of KOH, and toluene (5 mL) at 110 °C for 24 h.

Table 2. Optimization study of α-alkylation of acetophenone with benzyl alcohol [a]



6a

Entry	Ligand	Base	Solvent	Yield (%) [b]
1 [c]	-	KOH	toluene	55
2	**4a**	KOH	toluene	99 (95) [d]
3	**4b**	KOH	toluene	97
4	**4c**	KOH	toluene	89
5	**4d**	KOH	toluene	72
6	**4e**	KOH	toluene	75
7	**4f**	KOH	toluene	66
8	**4g**	KOH	toluene	34
9	**4a**	KO^tBu	toluene	96
10	**4a**	K_2CO_3	toluene	65
11	**4a**	K_3PO_4	toluene	50
12	**4a**	$KHCO_3$	toluene	47
13	**4a**	KOH	1,4-dioxane	75
14	**4a**	KOH	THF	87
15	**4a**	KOH	DMF	< 2
16	**4a**	KOH	CH_3CN	< 2

17 [e]	**4a**	-	toluene	< 2
18 [f]	**4a**	KOH	toluene	61
19 [g]	**4a**	KOH	toluene	22
20 [h]	**4a**	KOH	toluene	87
21 [i]	-	KOH	toluene	90
22 [j]	-	KOH	toluene	76

[a] Reaction conditions: acetophenone (1.0 mmol), benzyl alcohol (1.1 mmol), [Ir] loading (1 mol %), $[Cp^*IrCl_2]_2$ / ligand = 1/2, base (10 mol %), solvent (5 mL), 110 ^oC, 24 h

[b] Yield determined by NMR analysis with 1,3,5-trimethoxybenzene as the internal standard

[c] $[Cp^*IrCl_2]_2$ as catalyst without ligand

[d] Isolated yield

[e] Without base

[f] KOH (100 mol %)

[g] KOH (5 mol %)

[h] [Ir] loading (0.5 mol %)

[i] **5c** as catalyst

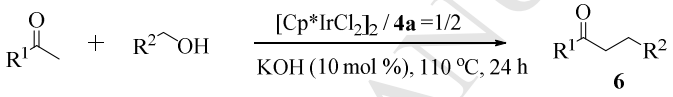
[j] **5e** as catalyst

2.4. α-Alkylation of ketones with primary alcohols

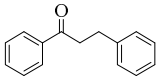
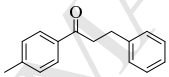
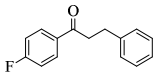
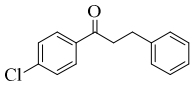
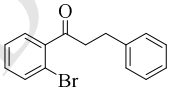
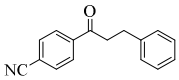
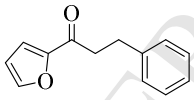
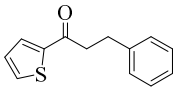
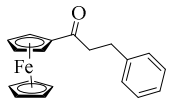
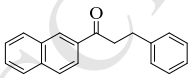
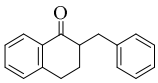
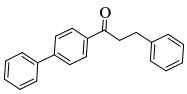
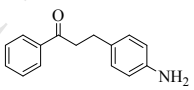
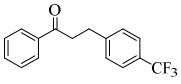
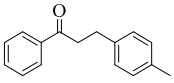
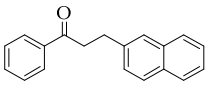
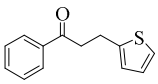
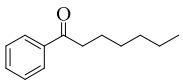
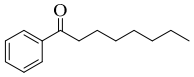
Under the optimized conditions, a wide range of substrates were screened (Table 3). The reactions of ketones with benzyl alcohol proceeded smoothly (**6a-6l**). 4-Methylacetophenone provided good yield (82 %). Acetophenones with halogen atoms such as fluoro, chloro and bromo on the phenyl ring afforded good to excellent yields (**6c-6e**). 4-Acetylbenzonitrile with cyano of strong electron-withdrawing group reacted smoothly with benzyl alcohol to afford **6f** in 87 % yield.

Heterocyclic ketones substituted with furyl and thienyl moieties could be alkylated in good yields (**6g, 6h**). Interestingly, acetylferrocene also forged the **6i** in 89 %. Other aromatic acetyl system, such as 2-acetylnaphthalene, 1-tetralone, and 4-acetylbiphenyl, were also examined (**6j-6l**). These reactions showed good tolerance for benzyl alcohols with amino (**6m**), trifluoromethyl (**6n**) or methyl (**6o**) groups. Reactions with 2-naphthalenemethanol and 2-thiophenemethanol gave 93 % and 75 % yields to produce alkylated products **6p** and **6q**. More importantly, the aliphatic substrates such as 1-pentanol and 1-hexanol also proceeded well with increasing the amount of alcohols and elongated time, led to **6r** and **6s** in 65 % and 69 % yields, respectively.

Table 3. α-Alkylation of ketones with alcohols [a,b]



6

 **6a,** 95%	 **6b**, 82 %	 **6c**, 84 %
 **6d,** 97 %	 **6e**, 91 %	 **6f**, 87 % [c]
 **6g,** 89 %	 **6h**, 96 %	 **6i**, 89 %
 **6j,** 87 %	 **6k**, 87 %	 **6l**, 72 %
 **6m,** 95 %	 **6n**, 73 % [c]	 **6o**, 89 %
 **6p,** 93 %	 **6q**, 75 %	 **6r**, 65 % [d]
		

6s, 69 % [d]	

[a] Reaction conditions: ketones (1.0 mmol), alcohols (1.1 mmol), [Ir] loading (1 mol %), $[Cp^*IrCl_2]_2$ / **4a**= 1/2, KOH (10 mol %), toluene (5 mL), 110 °C, 24 h

[b] Isolated yield

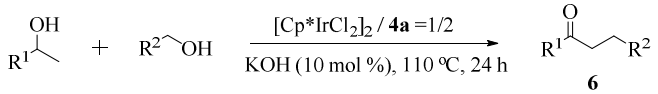
[c] 36 h

[d] Alcohol (2 mol), 36 h

2.5. β-Alkylation of secondary alcohols with primary alcohols

β-Alkylation of secondary alcohols with primary alcohols, due to dehydrogenation of secondary alcohols to carbonyl compounds, was more challenging than *α*-alkylation of ketones [26]. We attempted the reactions under the optimized conditions (Table 4). Delightedly, 3-phenylpropiophenone (**6a**) was obtained to yield 90 % from phenylethanol and benzyl alcohol. Phenylethanol bearing methyl group or chlorinated substituent, were also subjected to this reaction (**6b**, **6d)**. Benzyl alcohols containing amino, trifluoromethyl and methyl were compatible with this transformation (**6m**, **6n** and **6o**). Furthermore, 2-naphthalenemethanol reacted smoothly with phenylethanol to provide the desired product **6p** in 82 % yield. Satisfyingly, aliphatic alcohols such as 1-pentanol and 1-hexanol also furnished to this reaction in moderate yields (**6r**, **6s**).

Table 4. *β*-Alkylation of secondary alcohols with primary alcohols [a,b]



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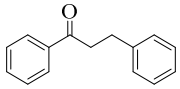
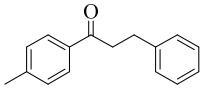
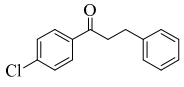
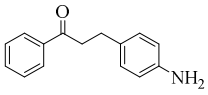
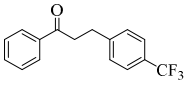
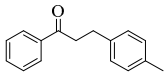
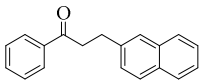
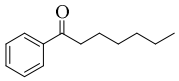
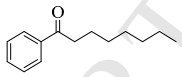
		
		6d, 92 %

6a, 90 % 	**6b**, 87 % 	
	6n, 81 % [c]	**6o**, 84 %
6m, 80 % 		
6p, 82 %	**6r**, 53 % [c]	**6s**, 45 % [c]

[a] Reaction conditions: secondary alcohols (1.0 mmol), primary alcohols (1.1 mmol), [Ir] loading (1 mol %), $[Cp^*IrCl_2]_2$ / **4a**= 1/2, KOH (10 mol %), toluene (5 mL), 110 ^oC, 24 h

[b] Isolated yield

[c] Alcohols (2 mol), 36 h

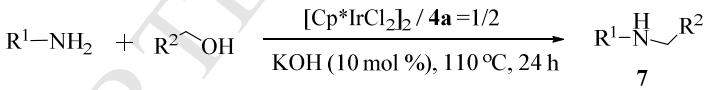
2.6. N-Alkylation of amines with primary alcohols

Encouraged by the above results, we checked the applicability to *N*-alkylation of amines with alcohols (Table 5). Initially, aniline was chosen to react with benzyl alcohol, 89 % isolated yield of **7a** was obtained. Either anilines with electron-donating methoxyl or electron-withdrawing substituents such as fluoro and chloro, could gave the desired compounds in good yields (**7b-7e**). The heterocyclic amines like 2-aminopyridine and 2-aminopyrimidine exhibited extremely high reactivity, affording products (**7f, 7g**), in 99 % and 98 % yields. Benzamide was also alkylated, giving **7h** as the only product (82 % yield). *p*-Toluenesulfonamide was proved to be suitable to react with benzyl alcohol, a moderate yield obtained (**7i**). Then we investigated the reactions of aniline with substituted benzyl alcohols. 2-Thiophenemethanol and 2-naphthalenemethanol were appropriate substrates for the reaction, smoothly delivering the products **7j-7k** in 84-85 % yields. While

electron-withdrawing substituent fluoro on the benzyl alcohol worked very well to provided the desired secondary amine product **7l**. More importantly, aliphatic alcohols such as 1-pentanol and 1-hexanol could still work as good coupling fragments (**7m-7n**), indicating the broad substrate compatibility of the *N*-alkylation reactions.

For the mechanism of *α*-, *β* and *N*-alkylation reactions with alcohols, based on previous reports [16, 17c, 17d, 18], it proceeded via the hydrogen-borrowing strategy. Initially, iridium(III) complex could be generated *in situ* when $[Cp^*IrCl_2]_2$ encountered ligand **4a**. Hydrogen autotransfer from primary alcohol to iridium would lead to the formation of aldehyde and the iridium-hydride intermediate. Subsequent base-mediated condensation of the producing aldehydes with ketones, alcohols, or amines to form *α*, *β*- unsaturated carbonyl compounds or imines, which would undergo a hydrogenation reaction in the presence of metal-hydride to give the *α*-, *β* and *N* -alkylated products and the catalyst Ir complex regenerated.

Table 5. *N*-Alkylation of amines with alcohols. [a,b]



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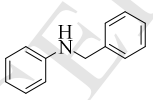
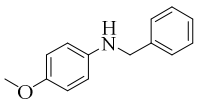
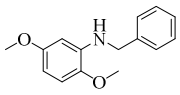


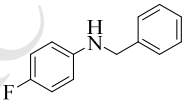
7a, 89 %



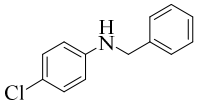
7b, 83 %



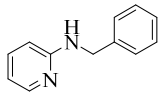
7c, 80 %



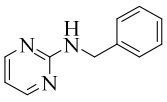
7d, 81 % [c]



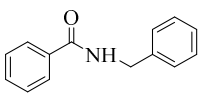
7e, 87 %



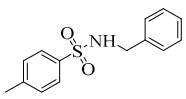
7f, 99 %



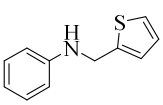
7g, 98 %

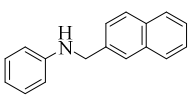


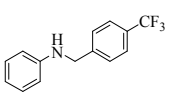
7h, 82 %

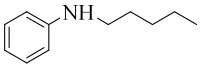
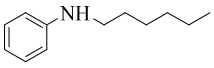


7i, 56 %







7j, 85 %	**7k**, 84 %	**7l**, 71 % [c]
		
7m, 64 % [d]	**7n**, 72 % [d]	

[a] Reaction conditions: amines (1.0 mmol), alcohols (1.1 mmol), [Ir] loading (1 mol %), $[Cp^*IrCl_2]_2$ / **4a**= 1/2, KOH (10 mol %), toluene (5 mL), 110 ^oC, 24 h

[b] Isolated yield

[c] 36 h

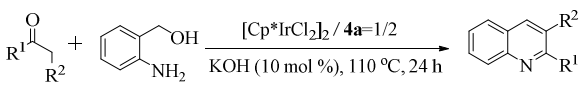
[d] Alcohol (3 mmol), 36 h

2.7. Synthesis of quinolines and indole

Quinolines exhibited a wide variety of biological and pharmacological activities [27] and applied in various polymers and nano materials [28]. The synthesis via hydrogen-borrowing concept is highly efficient and has less byproducts [6, 10y, 29].

With the optimal conditions, we were pleased to apply the catalytic system into the synthesis of quinolines from aromatic acetophenones and 2-aminobenzyl alcohol (Table 6). Substrates with *p*-Me, *p*-F, and *p*-OMe were amenable to this transformation, afforded the desired quinolines **8a-8c** in good yields. Furthermore, heterocyclic ketones such as thiophene acetone and 1-tetralone were extended to deliver **8d** (82 %) and **8e** (80 %). 3-Phenylpropiophenone was also compatible with the current system, leading to the formation of **8f** in 89 % yield.

Table 6. Formation of quinolines from ketones with 2-aminobenzyl alcohol [a,b]



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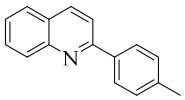
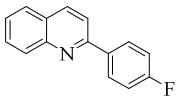
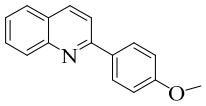
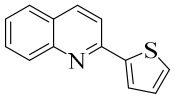
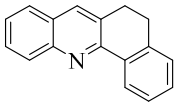
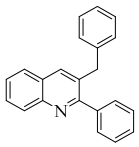
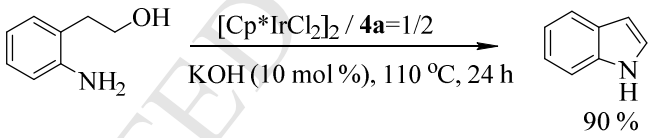
		
8a, 81 %	**8b**, 79 %	**8c**, 86 %
		
8d, 82 %	**8e**, 80 %	**8f**, 89 %

[a] Reaction conditions: ketones (1.0 mmol), 2-aminobenzyl alcohol (1.1 mmol), [Ir] loading (1 mol %), $[Cp^*IrCl_2]_2$ / **4a**= 1/2, KOH (10 mol %), toluene (5 mL), 110 °C, 24 h

[b] Isolated yield

Indole skeleton widely presents in natural products, raw organic materials, fine chemical products [30]. Our protocol also allowed for 2-(2-aminophenyl)ethanol by intramolecular cyclization leading to indole in 90% yield under the same conditions. The results further demonstrated the wide applicability of the catalytic system of iridium(III)-benzoxazolyl phosphine ligand. (Scheme 3)



Scheme 3. Alternative synthesis route for indole.

3. Conclusions

In summary, we have successfully prepared and characterized a series of new benzoxazolyl and benzothiazolyl phosphine ligands. The molecular structures of representative ligands **4c**, **4e** showed that the PR_2 group was located in the N atom side of benzoxazolyl or benzothiazolyl group. The corresponding iridium complexes could be generated *in situ* with $[Cp^*IrCl_2]_2$ and ligands. The representative complexes **5c**, **5e** were characterized by single-crystal X-ray study. The molecular

structures showed the typical piano-stool arrangement. The ligand was bound to the iridium(III) center via P, N atoms to form a six-membered ring. The dihedral angles of N(1)-C(1)-C(8)-C(9) in **5c** and **5e**, showed an increasing twist compared with the corresponding ligand. Subsequently, $[Cp^*IrCl_2]_2$ and **4a** were demonstrated as highly efficient catalysts for the alkylations of ketones, secondary alcohols and amines with primary alcohols. This catalytic protocol is advantageous for not only the effectiveness for versatile alkylation reactions from broad range of ketones, alcohols and amines, but also atom-economic syntheses of quinolines and indole. This catalytic system is of great interest for iridium(III) catalysts in synthetic chemistry regarding the formation of C-C and C-N bonds. Further studies towards more applications of the iridium(III) catalytic system are under way in our laboratory.

4. Experimental section

All alkylation reactions were carried out under standard Schlenk techniques. Reaction temperatures were the temperature of the bath surrounding the vessel. Chemical reagents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded by Bruker Avance III 400 MHz NMR Spectrometer. Spectra were collected at 295 K in $CDCl_3$ or DMSO-d_6. HRMS(ESI) analyses were proceeded by the EPSRC UK National Mass Spectrometry Facility (NMSF), Swansea. GC-MS analysis was reported at a HP 5973 GCD system using a HP5MS column (30 m × 0.25 mm). Fourier transform infrared (FT-IR) spectra were performed on a Nicolet AVATAR-360 IR using KBr discs in the range of 4000-400 cm^{-1}.

*4.1. Preparation of ligands **4a-4g***

Benzoxazolyl and benzothiazolyl phosphine ligands **4a-4g** were synthesized following by two steps:

Step 1, the brominated products (**3a-3e**) were prepared according to our published procedure [22]. The characterization data was listed in Supporting Information.

Step 2 [21]: **3a-3e** (5 mmol) was dissolved in dry THF (30 mL) under N_2. After the solution was cooled to -78 °C, *n*-butyl lithium (*n*-BuLi) 2.3 mL (5.5 mmol, 2.4 M, 1.1 equ.) was added dropwisely *via* syringe during 15 min. The reaction mixture was stirred at -78 °C for 0.5 h. Then diphenylphosphine / dicyclohexylphosphine chloride (5.5 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. Added water and ethyl acetate to the mixture. The organic phase was extracted and concentrated. Then dried over anhydrous Na_2SO_4. Finally, it was purified by silica gel column chromatography to obtain the corresponding products (**4a-4g**).

*2-(2-(Diphenylphosphanyl)phenyl)benzo[d]oxazole (**4a**)*

58% Isolated yield (light yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31- 8.20 (m, 1H, Ph), 7.74-7.67 (m, 1H, Ph), 7.50 (m, 1H, Ph), 7.47 - 7.23 (m, 15H, Ph), 7.08 (m, 1H, Ph) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.49, 150.37, 141.73, 139.22 (d, *J* = 26.9 Hz), 137.42, 134.48, 134.11 (d, *J* = 20.6 Hz), 131.20, 131.00, 130.64, 130.17(d, *J* = 3.3 Hz), 128.68, 128.44, 125.00, 124.25, 120.33, 110.43 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ -5.61 (s) ppm. HRMS(ESI) calcd for $C_{25}H_{19}NOP$ (380.1204) (M+H), found: 380.1199.

*2-(2-(Dicyclohexylphosphanyl)phenyl)benzo[d]oxazole (**4b**)*

62% Isolated yield (light yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 6.8 Hz, 1H, Ph), 7.83 (m, 1H, Ph), 7.69 (d, *J* = 7.3 Hz, 1H, Ph), 7.60 (m, 1H, Ph), 7.51 (m, 2H, Ph), 7.37 (m, 2H, Ph), 1.96 (d, *J* = 37.8 Hz, 4H, Cy-*H*), 1.72 (m, 8H, Cy-*H*), 1.38 - 1.10 (m, 10H, Cy-*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.06, 150.87, 141.89, 137.71 (d, *J* = 28.6 Hz), 135.06 (d, *J* = 27.6 Hz), 133.08 (d, *J* = 2.2 Hz), 130.84 (d, *J* = 5.7 Hz), 129.72, 128.37, 124.91, 124.23, 120.37, 110.68, 34.49 (d, *J* = 14.4 Hz), 29.84, 29.86(d, *J* = 27.8 Hz), 27.32 (d, *J* = 2.0 Hz), 27.22, 26.39 ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ -4.62 (s) ppm. HRMS (ESI) calcd for $C_{25}H_{31}NOP$ (392.2143) (M+H), found: 392.2138.

*2-(2-(Diphenylphosphanyl)phenyl)benzo[d]thiazole (**4c**)*

60 % Isolated yield (yellowish solid solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.89 (m, 2H), 7.84 (m, 1H), 7.48 (m, 1H), 7.42 (m, 1H), 7.39 - 7.29 (m, 12H), 7.12 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.61, 153.21, 134.87, 134.07, 133.87, 130.56 (d, *J* = 3.8 Hz), 129.80, 128.70, 128.49, 128.43, 128.36, 128.01, 127.88, 125.95, 125.14, 123.43, 121.31 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ -9.01 (s) ppm. HRMS(ESI) calcd for $C_{25}H_{19}NPS$ (396.0965) (M+H), found: 396.0964.

*2-(2-(Dicyclohexylphosphanyl)phenyl)benzo[d]thiazole (**4d**)*

54 % Isolated yield (yellow solid solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 - 7.88 (m, 1H, Ph), 7.72-7.56 (m, 2H, Ph), 7.55 - 7.42 (m, 4H, Ph), 7.16 (d, *J* = 8.0 Hz, 1H, Ph), 1.96 (m, 4H, Cy-*H*), 1.71 (m, 8H, Cy-*H*), 1.23 (m, 10H, Cy-*H*) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.06, 150.87, 141.89, 137.86, 137.57, 135.20, 134.92, 133.08 (d, *J* = 2.2 Hz), 130.84 (d, *J* = 5.7 Hz), 129.72, 128.37, 124.91, 124.23, 120.37, 110.68, 34.49 (d, *J* = 14.4 Hz), 29.86 (d, *J* = 27.9 Hz), 29.72, 27.32 (d, *J* = 2.0 Hz), 27.22, 26.39 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ -4.56 (s) ppm. HRMS (ESI) calcd for $C_{25}H_{31}NPS$ (408.1924) (M+H), found: 408.1928.

*2-(2-(Diphenylphosphanyl)phenyl)-5 methylbenzo[d]oxazole (**4e**)*

58 % Isolated yield (lightly yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (m, 1H, Ph), 7.49 (m, 2H, Ph), 7.39 (m, 5H, Ph), 7.33 (m, 7H, Ph), 7.13 - 7.04 (m, 2H, Ph), 2.45 (s, 3H, Ph-CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.55, 148.65, 141.94, 139.08 (d, *J* = 26.9 Hz), 137.56 (d, *J* = 10.6 Hz), 134.46, 134.19, 133.99, 131.31 (d, *J* = 21.1 Hz), 130.49, 130.06 (d, *J* = 2.9 Hz), 128.53(d, *J* = 21.5 Hz), 128.40(d, *J* = 6.9 Hz), 126.11, 120.21, 109.75, 21.42 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ -5.62 (s) ppm. HRMS (ESI) calcd for $C_{26}H_{21}NOP$ (394.1361) (M+H), found: 394.1350.

*2-(2-(Diphenylphosphanyl)phenyl)-5 fluorobenzo[d]oxazole (**4f**)*

61 % Isolated yield (lightly white solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (m, 1H, Ph), 7.49 (m, 1H, Ph), 7.45 - 7.28 (m, 13H, Ph), 7.09 - 6.97 (m, 2H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.11, 139.55, 137.22 (d, *J* = 10.1 Hz), 134.51, 134.18, 133.98, 130.90, 130.19 (d, *J* = 3.2 Hz), 128.75, 128.47, 128.46(d, *J* = 7.3 Hz), 112.80, 112.53, 110.72, 110.62, 106.73, 106.48 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.42 (td, *J* = 8.8, 4.3 Hz) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ -5.47 (s) ppm. HRMS (ESI) calcd for $C_{25}H_{18}FNOP$ (398.1110) (M+H), found: 398.1092.

*5-(tert-Butyl)-2-(2-(diphenylphosphanyl)phenyl)benzo[d]oxazole (**4g**)*

75 % Isolated yield (light green solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 1H, Ph), 7.71 (s, 1H, Ph), 7.49 (t, *J* = 7.5 Hz, 1H, Ph), 7.41 - 7.29 (m, 14H, Ph), 7.06 (m, 1H, Ph), 1.37 (s, 9H, Ph-C(CH_3)$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.56, 148.41, 147.70, 141.67, 139.06, 138.80, 137.57 (d, *J* = 10.5 Hz), 134.55, 134.07 (d, *J* = 20.5 Hz), 131.55, 131.34, 130.74, 130.47, 130.03 (d, *J* = 3.0 Hz), 128.48(d, *J* = 23.3.0 Hz), 128.43, 122.75, 116.86, 109.50, 34.85, 31.73 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ -6.14 (s) ppm. HRMS (ESI) calcd for $C_{29}H_{27}NOP$ (436.1830) (M+H), found: 436.1812.

*4.2 Preparation of Ir(III) complexes **5c** and **5e***

According to previous report [25], **4c** or **4e** (0.1 mmol) with $[Cp^*IrCl_2]_2$ (40 mg, 0.05 mmol) were added to a 25 mL Schlenk flask. Added into 2 mL of anhydrous methanol. The reaction mixture was warmed to 55 °C for 14 h. Then potassium hexafluorophosphate (KPF_6) (55 mg, 0.3 mmol) was added. By centrifugal separation, the corresponding product was obtained.

5c, light yellow solid (76.7mg, 85 %). $C_{35}H_{33}ClF_6IrNP_2S$ (903.1031): FT-IR (KBr) 3061 (w), 3000 (w), 2923 (w), 1509 (w), 1457(m), 1436 (w), 1411 (m), 1227 (w), 1090(w), 1028(w), 991(w), 842 (s), 756 (w), 713 (m), 556 (m), 535 (m), 508 (m) cm^{-1}. ^1H NMR (400 MHz, DMSO) δ 8.39 (m, 1H, Ph), 8.30 (m, 1H, Ph), 8.25 (m, 1H, Ph), 8.16 - 8.05 (m, 1H, Ph), 8.03 (m, 1H, Ph), 7.90 (m, 3H, Ph), 7.80 - 7.66 (m, 4H, Ph), 7.67 - 7.57 (m, 1H, Ph), 7.34 - 7.22 (m, 2H, Ph), 7.09 (m, 1H, Ph), 7.00 (m, 2H, Ph), 1.25 (s, 16H, Cp*-C*H*$_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.64, 174.58, 155.49, 140.30, 140.18, 139.86 (d, *J* = 7.3 Hz), 138.30, 138.22, 138.13, 137.97, 137.87, 137.76, 136.39, 135.83, 135.73, 134.77 (d, *J* = 11.6 Hz), 133.65, 133.48, 133.09 (d, *J* = 11.3 Hz), 132.71, 129.59, 128.98, 128.66, 128.41, 99.88, 13.09 ppm; ^{31}P NMR (162 MHz, DMSO) δ -3.43, -144.18 (hept, *J* = 711.4 Hz) ppm; ^{19}F NMR (376 MHz, DMSO) δ -70.12 (d, *J* = 711.4 Hz). HRMS (ESI) calcd for $C_{35}H_{34}ClF_6IrNP_2S$ (904.1109) (M+H), found: 904.1112.

5e, light yellow solid (80.2 mg, 89 %). $C_{36}H_{35}ClF_6IrNOP_2$ (901.1416): FT-IR (KBr) 3058 (w), 2994 (w), 2925 (w), 1530 (w), 1481(m), 1446 (w), 1434 (m), 1280 (w), 1191(w), 1108(w), 1031(w), 842 (s), 756 (w), 704 (m), 557 (m), 528 (m), 518 (m) cm^{-1}. ^1H NMR (400 MHz, DMSO) δ 8.48 (d, *J* = 3.3 Hz, 1H, Ph), 8.19 - 8.02 (m, 2H, Ph), 8.01- 7.93 (m, 1H, Ph), 7.87 (d, *J* = 7.9 Hz, 3H, Ph), 7.75

(s, 3H, Ph), 7.65 (s, 1H, Ph), 7.43 (d, *J* = 8.0 Hz, 1H, Ph), 7.25 - 6.87 (m, 5H, Ph), 2.47 (d, *J* = 14.1 Hz, 3H, Ph-C*H*$_3$), 1.33 (s, 15H, Cp*-C*H*$_3$) ppm; ^{13}C NMR (101 MHz, DMSO) δ 161.04, 160.97, 148.94, 137.95, 136.77, 135.49 (d, *J* = 12.7 Hz), 134.37, 133.63, 133.26 (d, *J* = 9.1 Hz), 133.10, 132.69, 131.62, 131.02, 130.09 (d, *J* = 11.6 Hz), 129.79, 129.55, 129.26, 129.05, 128.46 (d, *J* = 10.4 Hz), 128.05, 127.95, 124.41, 123.84, 119.75, 112.46, 95.26, 21.73, 8.49 ppm; ^{31}P NMR (162 MHz, DMSO) δ -3.34 (s, 1P, ligand **4e**), -144.19 (hept, *J* = 711.6 Hz, 1P, *P*F$_6$) ppm. ^{19}F NMR (376 MHz, DMSO) -70.14 (d, *J* = 711.4 Hz, P*F*$_6$) ppm. HRMS (ESI) calcd for $C_{36}H_{36}ClF_6IrNOP_2$ (902.1494) (M+H), found: 902.1488.

4.3 General procedure for alkylation reactions

[Cp*IrCl$_2$]$_2$ (1 mol %, 0.01mmol, 8.0 mg), **4a** (2 mol %, 0.02 mmol, 7.6 mg), KOH (10 mol %, 0.1 mmol, 5.6 mg), and toluene (5 mL) were added to a 25 mL Schlenk tube with stirring under N_2 at room temperature. Then ketones/ secondary alcohols/ amines (1 mmol), primary alcohols (1.1 mmol,) were added by syringe. The reaction mixture was heated to 110 °C under reflux in an oil bath for 24 h. It was cooled to ambient temperature. Then it was concentrated *in vacuo*, and purified by flash column chromatography with petroleum ether/ ethyl acetate to afford the corresponding alkylated product.

4.4 General procedure for preparation of quinolines and indole

In a 25 mL Schlenk tube, ketones (1 mmol) and 2-aminobenzyl alcohol (1.1 mmol) (for

quinolines), or 2-(2-aminophenyl)ethanol (1 mmol) (for indole), $[Cp^*IrCl_2]_2$ (1 mol %, 0.01mmol, 7.96 mg), **4a** (2 mol %, 0.02 mmol, 7.60 mg), KOH (10 mol %, 0.1 mmol, 5.6 mg), and toluene (5 mL) were placed under N_2. The reaction mixture was heated under reflux for 24 h. The reaction mixture was cooled to ambient temperature, concentrated *in vacuo*, and purified by flash column chromatography with petroleum ether/ ethyl acetate to afford the corresponding quinolines and indole.

4.5 X-ray crystallography

Suitable single crystals for X-ray diffraction analysis were obtained from slow evaporation of corresponding solution, **4c**,**4e** in *n*-hexane and **5c**, **5e** in MeOH. Intensity data for the compounds were collected on Bruke Smart APEX (at 293 K) and Bruker APEX DUO diffract meters (at 173 K). Both are equipped with 2.4 kW sealed tube X-ray source (Mo-Kα radiation, λ = 0.71073 Å) operating at 50 kV and 30 mA. A hemisphere of intensity data was collected at room temperature with a scan width of 0.60° in ω. Empirical absorption corrections were based on SADABS program [31]. The structures were solved by direct methods and refined by full-matrix least squares refinement using the SHELXTL-97 program [32]. The positions of all non-hydrogen atoms were refined with anisotropic displacement factors. The hydrogen atoms were generated theoretically onto the specific atoms and refined. Crystal structure and refinement data can be found in Table 1. CCDC 1821599 (**4c**), 1821600 (**4e**), 1821601(**5c**), and 1821602 (**5e**) contain the supplementary of crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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Highlights

- A series of new benzoxazolyl and benzothiazolyl phosphine ligands were prepared.
- Iridium(III) complexes could be generated *in situ* when $[Cp^*IrCl_2]_2$ encountered ligands.
- Versatile alkylation reactions were efficiently catalyzed by $[Cp^*IrCl_2]_2$/ligand.
- Quinolines and indole were synthesized using the same catalyst.