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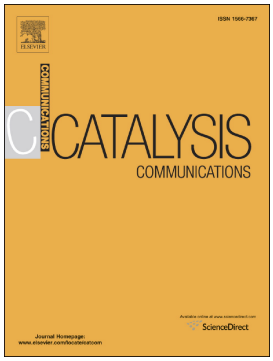

Hemilabile N-heterocyclic carbene (NHC)-nitrogen-phosphine mediated Ru (II)-catalyzed N-alkylation of aromatic amine with alcohol efficiently

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Hemilabile N-heterocyclic carbene (NHC)-nitrogen-phosphine mediated Ru (II)-catalyzed N-alkylation of aromatic amine with alcohol efficiently

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Abstract: Based on the hemilability, a novel N-heterocyclic carbene (NHC)-nitrogen-phosphine ligand (**1**) was synthesized, and the combination of it with $[Ru(COD)Cl_2]_n$ showed the high activity and selectivity with a low Ru loading of 0.1% for the N-alkylation of amine with alcohol. Especially, for these substrates with pyridine backbone, even if the catalyst loading was as low as 0.01%, good yields (81-95%) of the desired products were achieved.

Keywords: N-alkylation, N-heterocyclic carbene, phosphine, ruthenium

1. Introduction

Amine or N-containing compounds have versatile applications in the production of agrochemical, peptide, pharmaceutical and functional materials [1], so the construction of C-N bond has attracted wide attention and some effectively synthetic methods [2-4] have been developed. Among them, transition metal catalyzed N-alkylation of amine with alcohol are the most efficient and environment friendly protocol [5] to construct primary [6], secondary [7] and tertiary amine [8] without any waste except water according to "borrowing hydrogen" mechanism [9].

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Since the transition metal catalyzed N-alkylation was firstly established by Grigg and Watanabe in 1981 [10, 11], a great number of Ru [12-14], Ir [15-16], Pd [17], Co [18-19], Pt [20], and Fe [21] complexes with different ligands have been utilized in this system and significant progresses have been achieved. Unfortunately, the predominant combination of phosphine and inexpensive Ru usually required more than 5% catalyst loading to obtain a high conversion. Latest, some multidentate ligands [22-25] or functionalized carbene [26-30] were synthesized and applied for promoting the activity of the transition metals, so that the catalyst loadings could be decreased to *ca*. 1-0.5%. It is noteworthy that the anchoring effect and "hemilability" [31] of functionalized carbene is vital to improve the catalyst efficiency.

Besides, Kempe and Shafir found that the reactivity of transition metal catalyzed N-alkylation could be improved by the introduction of N atom in phosphine ligand [32-34] (Figure 1). Our previous works also proved that the application of N-containing *tetra*-phosphine ligand was highly efficient to Pd-catalyzed C-C coupling [35]. Inspired by these results, a new ligand including N-heterocyclic carbene, nitrogen and phosphine scaffold was designed (Figure 1) and synthesized (Scheme 1). As our expectation, this novel ligand (**1**) mediated Ru (II) catalyzed N-alkylation of amine with alcohol showed an excellent activity and the loading of ruthenium could be as low as 0.01%.

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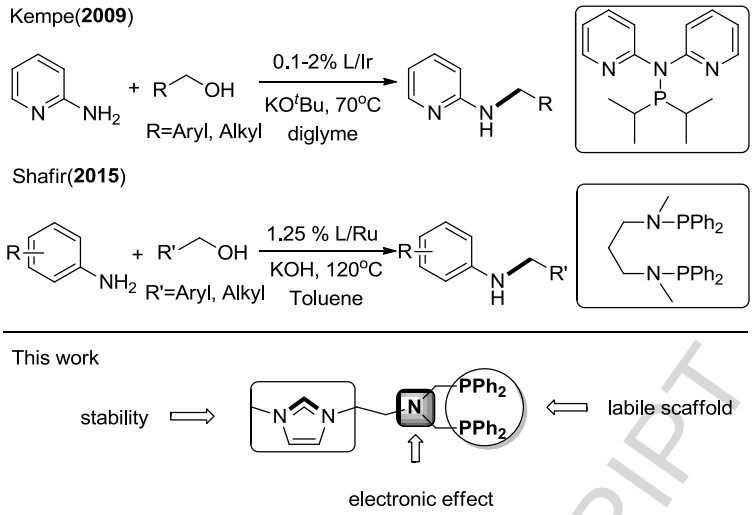
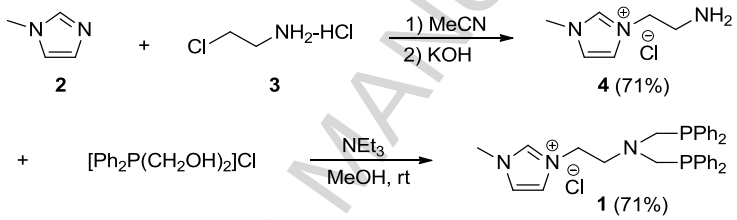


Figure 1. N-containing (non-coordinated) phosphines in N-alkylation and our design of hemilabile carbene-nitrogen-phosphine



Scheme 1. Synthesis of N-heterocyclic carbene-nitrogen-phosphine ligand

2. Results and discussions

The catalytic performance of combining Ru precursor with ligand (**1**) *in situ* was examined with N-alkylation of aniline with benzyl alcohol as model reaction. Initially, the effect of a series of bases on the reaction was tested, and it was found that KO^{t}Bu was the best (Table 1, entry 1, more results in supporting information). Further screening on Ru precursor showed that $[Ru(COD)Cl_2]_n$ was most effective (Table 1, entry 2-3). The effect of temperature and time on the reaction exhibited that the high conversion of 90% and selectivity of 95% were given at 100 °C for 6 hours (Table 1, entry 4-7). At room temperature, the catalyst system still gave a

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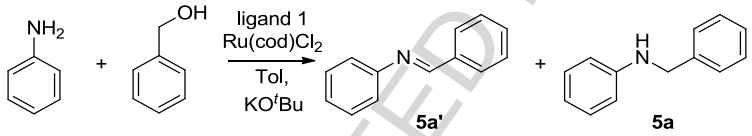
satisfying conversion of 83% when the time was extended to 120 hours. These results implied that the lifetime of the active species was long enough or the stability of this catalyst system was high enough. In order to shorten the reaction time, we chose the reaction temperature of 100 °C in the following reactions. Meanwhile, compared with this ligand (**1**), the introduction of common carbene and biphosphine ligands gave the low conversion and selectivity (Table 1, entry 8-11). Interestingly, even if catalyst loading of 0.1% was utilized, the system could result in a complete conversion when the reaction time was prolonged to 48 h (Table 1, entry 12-13). According to the previous results, the optimum conditions are 0.1% Ru loading, 2 *equiv* alcohol, 100 °C and 48 h.

Table 1. N-alkylation of aniline with benzyl alcohol [a]



Entry	Variable condition	Conv.(%)	Selec.(%)
1	$Ru(COD)Cl_2$	94	>99
2	$[Ru(C_6H_6)Cl_2]_2$	88	>99
3	$Ru(PPh_3)_3Cl_2$	64	99
4	25°C, 120h	83	91
5	6h	90	95
6	2 equiv. alcohol	>99(95)	>99
7 [b]	80°C	>99	>99
8 [b]	6h, dppe	71	36
9 [b]	6h, dppb	62	34

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10 [b]	6h, MI	44	29
11 [b]	6h	97	95
12 [b]	0.1% catalyst	93	81
13 [b]	0.1% catalyst, 48h	>99(96)	98

[a] Reaction condition: aniline (1 mmol), benzyl alcohol (1 mmol), KO^{t}Bu (1 mmol), $[Ru(COD)Cl_2]_n$ (1% mmol Ru), ligand **1** (1% mmol), toluene (4 ml) , 100^{o}C and 24h. Conversion and selectivity (amine **5a**) were determined by GC analysis. Conversion in parentheses was the isolated yield. dppe, 1,2-(diphenylphosphino)ethane; dppb, 1,4-(diphenylphosphino)butane; MI, 1,3-dimesityl-imidazolium chloride (0.02 mmol). [b] 2 *equiv*. alcohol.

On the basis of the optimum conditions, the scope of substrates was investigated. Firstly, the substituents toleration was explored (Table 2). It clearly showed that the electronic factor (**5a-d**) of substituents in *para*-position of amine group didn't affect the product yield. However, the methyl group in *ortho*-position greatly inhibited the formation rate of corresponding product (**5f**), but the yield of 80% could be still obtained when reaction time was extended to 72 h. Encouraged by these results, we tried to decrease the catalyst loading to 0.01% and got mediate yields (**5a**, **5d**) by extending reaction time to 120 h. However, for N-containing heterocyclic substrates, the high yields (**5g-m**) were obtained, especially, 2-aminopyridine derivatives could be almost completely converted into the desired products (**5g, 5i, 5j**) in the catalyst loading of 0.01% for 24 h. To the best of our knowledge, the high TON (up to 9500) in this case is unprecedented. The possible coordination of N-atom in pyridine skeleton with Ru center played a promotional role [32]. Compared with 2-aminopyridine, the reactivity of 3- and 4-aminopyridines decreased obviously and the reaction time had to be extended to 48h in order to get satisfactory yields (**5l**, **5m**). However, a mediate conversion of 59% (**5k**) was obtained with 0.02% catalyst for

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6-methoxy-2-amino-pyridine, and the inhibition role of the methyl group in *ortho*-position of amino group (**5h**) was in consistent with non-heterocyclic substrates due to steric hindrance. However, N-alkylation of alkyl amine gave imine as major products, such as benzyl amine gave only 15% yield of the desired product besides imine. The result was similar to other functionalized carbene system [26-30].

In addition, the reactivity of some diamines, which are difficult to react with alcohols to give N,N'-dialkylated products [26], was tested (Table 2, **5o-r**). Interestingly, a good yield of 84% was given with 2,6-diaminopyridine (**5o**) for 72 h. For phenylenediamines (**5p-r**), the satisfying yields could be gotten with a catalyst loading of 1.0%. To date, for the Ru-catalyzed N,N'-dialkylation of diamines with alcohols, our system was the most efficient and gave the highest TON among a few reported results [25, 26, 28, 30, 36-38].

Table 2. N-alkylation of amines with benzyl alcohol [a]

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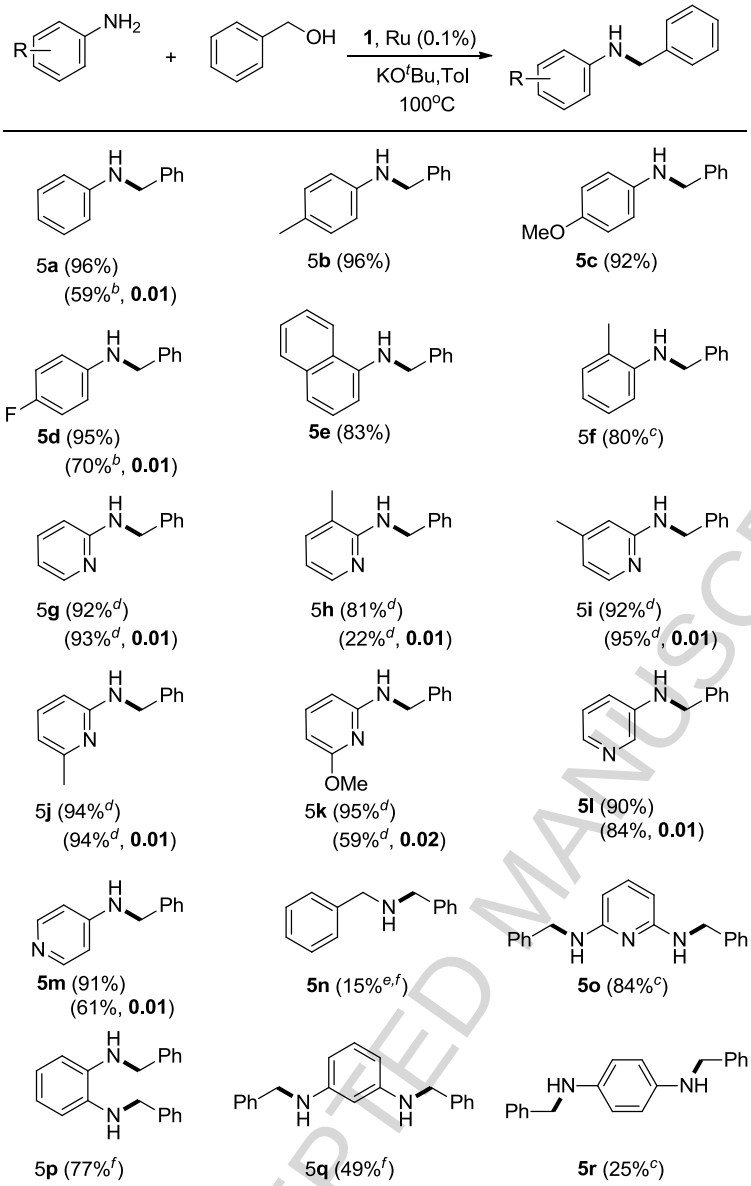

[a] Reaction condition: amine (1 mmol), benzyl alcohol (2 mmol), KO^{t}Bu (1 mmol), $[Ru(COD)Cl_2]_n$ (0.1% mmol Ru), ligand **1** (0.1% mmol), toluene (4 ml) , 100°C and 48h, isolated yield in parenthesis (followed bond figures is catalyst loading). [b] 120 h. [c] 72h. [d] 24 h. [e] 1% catalyst, 120°C and 24h. [f] Yield was determined by ^{1}H NMR and CH_2Br_2 as internal standard.

Also, the effect of alcohol structure on the N-alkylation was examined (Table 3). All primary alcohols (**6a**-**f**), whether they were aryl or alkyl alcohols, could react with aniline in the presence of 0.1% catalyst. However, using secondary alcohols (**6g**-**i**), aniline could be not converted completely into the desired products with the catalyst

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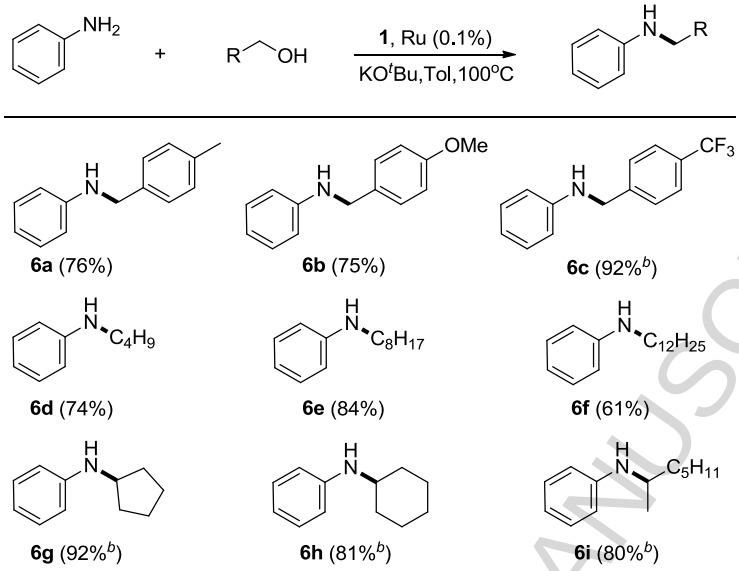
loading of 0.1% even in reaction temperature of 120 °C because of steric hindrance [24], but an appropriate increase of catalyst loading (1.0%) improved the yields.

Table 3. N-alkylation of aniline with alcohols [a]



[a] Reaction condition: aniline (1 mmol), alcohols (2 mmol), KO^{t}Bu (1 mmol), $[Ru(COD)Cl_2]_n$ (0.1% mmol Ru), ligand **1** (0.1% mmol), toluene (4 ml) , 100°C and 48h, isolated yield. [b] 1% mmol catalyst loading, 24 h. All reactions of *sec*-alcohol were conducted on 120°C, and yields were determined by GC (N-methylaniline as internal standard).

According to the reported mechanism, the transfer hydrogenation of imines was an important step [9] in this N-alkylation, so imine **7** (*N*-benzylideneaniline) was used in transfer hydrogenation and gave 99% GC conversion of corresponding amine product (**5a**) with 2 *equiv*. benzyl alcohol as hydrogen source. Thus, this result revealed the formation of imine-Ru intermediate was vital in the progress of N-alkylation. Interestingly, *N*-benzylidenebenzyl amine (**8**) finished transfer hydrogenation to provide amine (**5n**) with a conversion of 34%, but the transfer hydrogenation of *N*-benzylidene cyclohexylamine (**9**) was completely inhibited. Obviously, the high electron density on N atom of imine inhibited completely the

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transfer hydrogenation, which indicated the reason why alkyl amines did not give the desired products in this system.

Further mechanism exploration was performed with NMR *in situ* (see supporting information). The ^{1}H NMR spectra (Figure 2) evidenced clearly the formation of [MH_2] (2 dd signal, *J*=15.2 Hz and 2.8 Hz.) and aldehyde. Moreover, the splitting of ^{31}P NMR (Figure 2) at 73 ppm (dd, *J* = 30.0 Hz, 4.9 Hz) was attributed to the presence of Ru-OR complex (**I**). And total proton numbers of 6.32 ppm (coordinated **5a**) and 6.39 ppm (free **5a**) on ^{1}H NMR (see supporting information) was consistent with proton number of product **5a**. Interestingly, at different aniline levels (10 equiv. *vs* 2 equiv.), the integral area ratio of coordinated **5a** (6.32 ppm) to total product **5a** was approximately equal to the molar ratio of catalyst loading to aniline. The result revealed that product **5a** didn't intermediately leave form the Ru centre at the end of N-alkylation reaction and the coordination of benzyl alcohol promoted the elimination of product **5a** from ruthenium center. Furthermore, 2 doublets at 92 ppm and 73 ppm (*J* = 30.0 Hz) in ^{31}P NMR (Figure 2) suggested that ligand (**1**) in active catalytic species should chelate with ruthenium in κ^3-*C,P,P* model and N atom did not take part in coordination. The addition of substrate led to appearance of the broad signal in up-field of ^{31}P NMR, which implied that the coordinated phosphine scaffold dissociated from Ru centre to form free phosphine and provide available site for the activation of substrate. This phenomenon was not only consistent with "hemilability" as expectation, but also indicated the reason of high activity and long

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lifetime of this catalyst system. Hence, to combine the reported result and our evidence, the reaction mechanism was proposed as Figure 3.

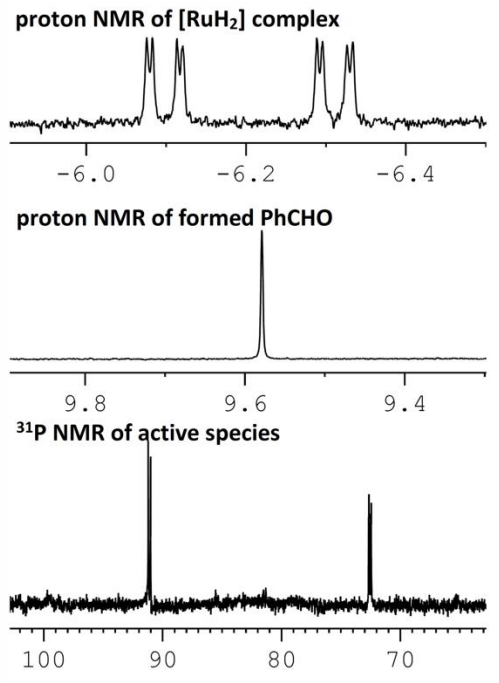

Figure 2. NMR spectra of N-alkylation reaction mixture

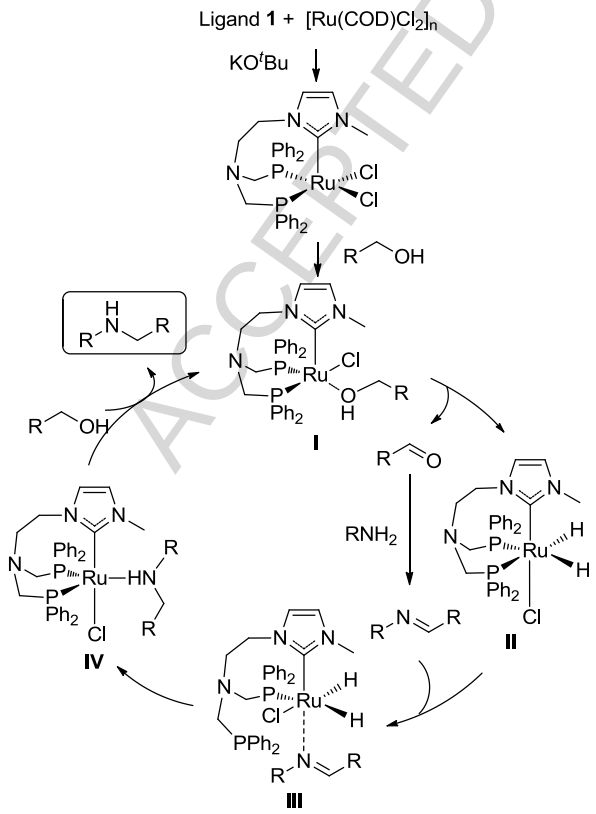

Figure 3. Proposed mechanism of N-alkylation

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3. Conclusion

In conclusion, a novel hemilabile N-heterocyclic carbene-nitrogen-phosphine (**1**) was synthesized conveniently. The combination of this ligand and $[Ru(COD)Cl_2]_n$ was used in the *N*-alkylation of aromatic amine with alcohol to give corresponding products in good to excellent yields with a low catalyst loading of 0.01-0.1%. NMR experimental proved the formation of aldehyde and $[MH_2]$, and the hemilability of present catalyst. All results indicated that the introduction of nitrogen atom between phosphine and carbene was a good strategy for the transition metal catalyzed *N*-alkylation.

Acknowledgement

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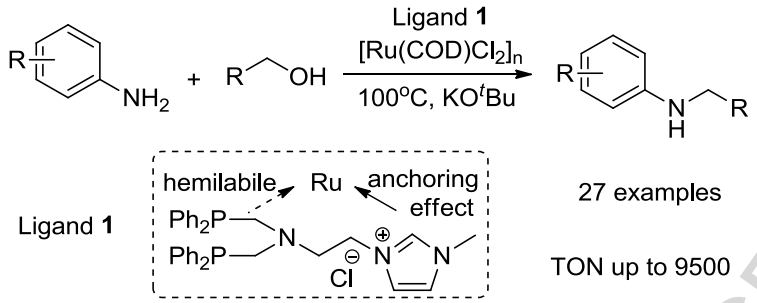
Graphical abstract and Highlights



Highlights

- A mixed tridentate carbene-nitrogen-phosphine was synthesized.
- The combination of this ligand with Ru(II) showed an unprecedented high activity in N-alkylation.
- Hemilability of this ligand played a key role for the high activity of this catalytic system.

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