Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 3451

Ruthenium(II) complexes with N-heterocyclic carbene–phosphine ligands for the *N*-alkylation of amines with alcohols†

Ming Huang, *[a,b] Yinwu Li,[b] Xiao-Bing Lan, [b] Jiahao Liu, [b] Cunyuan Zhao,[b] Yan Liu *[c] and Zhuofeng Ke *[b]

Received 25th February 2021,
Accepted 19th March 2021

DOI: 10.1039/d1ob00362c

rsc.li/obc

Metal hydride complexes are key intermediates for *N*-alkylation of amines with alcohols by the borrowing hydrogen/hydrogen autotransfer (BH/HA) strategy. Reactivity tuning of metal hydride complexes could adjust the dehydrogenation of alcohols and the hydrogenation of imines. Herein we report ruthenium(II) complexes with hetero-bidentate N-heterocyclic carbene (NHC)-phosphine ligands, which realize smart pathway selection in the *N*-alkylated reaction *via* reactivity tuning of [Ru–H] species by hetero-bidentate ligands. In particular, complex **6cb** with a phenyl wingtip group and $BArF^-$ counter anion, is shown to be one of the most efficient pre-catalysts for this transformation (temperature is as low as 70 °C, neat conditions and catalyst loading is as low as 0.25 mol%). A large variety of (hetero)aromatic amines and primary alcohols were efficiently converted into mono-*N*-alkylated amines in good to excellent isolated yields. Notably, aliphatic amines, challenging methanol and diamines could also be transformed into the desired products. Detailed control experiments and density functional theory (DFT) calculations provide insights to understand the mechanism and the smart pathway selection *via* [Ru–H] species in this process.

Introduction

N-Alkylated amines are widely used compounds that have numerous applications in pharmaceuticals, agrochemicals, polymer materials, and synthetic industries.[1–4] One of the most appealing synthetic approaches for their preparation is the BH/HA methodology, in which the *N*-alkylated amines are furnished by using sustainable and abundant alcohols as coupling reagents.[5–7] Notably, these transformations are not only environmentally benign, allowing alcohols to replace the toxic alkyl halides as the alkylating agents, but also atom economical, eliminating only water as the byproduct.

More and more homogeneous transition metal (TM) complexes,[5–12] and even those based on non-noble metals (Co,[13–15] Fe,[16–18] Ni,[19–27] and Mn[28–31]), have been shown to be active for this transformation, since the seminal work of the groups of Grigg[32] and Watanabe[33] in the early 1980s. In particular, the Ru-based systems, mainly Ru(II) complexes, are among the most active catalysts in those fields.[9,10,34–39] The electronic and steric properties of the ancillary ligands are essential for the high performance of Ru(II) catalysts. For example, Williams *et al.* reported the use of $[Ru(p\text{-cymene})Cl_2]_2$ with either the bidentate phosphine ligand Dppf or DPEphos for the *N*-alkylation of amines with alcohols.[9] Those systems are tolerant to a large amount alcohols and amines and have been applied to the synthesis of some pharmaceutical drugs, as well as to the *N*-alkylation of sulfonamides and cyclization reactions. Recently, Takacs *et al.* developed a Ru(II) complex with a bidentate phosphine-dihydrooxazole ligand, which is capable of alkylating amines with primary and secondary alcohols and the regioselective mono- and sequential diamination of diols.[35] This system has also been applied to the synthesis of heterocyclic rings including indoles, piperazines, and pyrrolidines. Shortly afterward, Williams *et al.* reported a Ru(II) catalyst with a bidentate phosphine-pyridyl ligand, which could realize chemoselective benzylic *N*-alkylation of amines under mild conditions.[36] This system works without solvents and additives and is compatible with unprotected phenols and anilines. Despite numerous efforts, high temperatures (above 100 °C), or high catalyst loadings (above 1 mol%) are usually required to obtain satisfactory yields.[40,41]

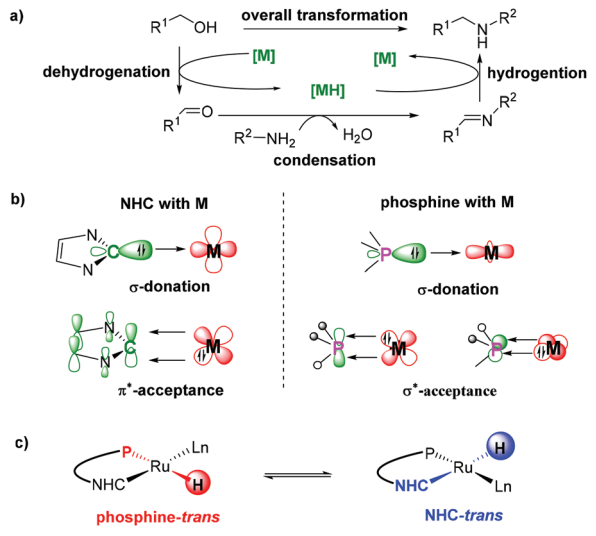
[a]*Clinical Pharmacy of The First Affiliated Hospital, School of clinical pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, P. R. China. E-mail: 1529236883@qq.com*
[b]*School of Materials Science & Engineering, PCFM Lab, School of Chemistry, Sun Yat-sen University, Guangzhou 510275, P. R. China. E-mail: kezhf3@mail.sysu.edu.cn*
[c]*School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, P. R. China. E-mail: yanliu@gdut.edu.cn*

†Electronic supplementary information (ESI) available. CCDC 1830666, 1911586 and 1912108. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob00362c

The BH/HA strategy for the TM-catalyzed *N*-alkylation reactions included three key steps: (i) the acceptorless dehydrogenation (AD) of alcohols to aldehydes, accompanied by the formation of the metal hydride ([M − H]) species; (ii) the *in situ* condensation of aldehydes with amines to imines; and (iii) the hydrogenation of imines by the [M − H] species (Scheme 1a). Thus, it is essential to tune the stability and the activity of the [M − H] species for the design of efficient BH/HA catalysts. If the [M − H] species are too active and less stable, the dehydrogenation of alcohols to [M − H] species may be suppressed. However, if the ligand makes the [M − H] species too stable, the successive hydrogenation of imines would be inhibited. We envisioned that hetero-bidentate ligands bearing different binding characters, enabling the [M − H] species to be adaptable to both stability and activity, which should be advantageous for the design of BH/HA catalysts. However, the specific role of hetero-bidentate ligands in tuning or accelerating chemical reactions has not been well elucidated for Ru-catalyzed *N*-alkylation. Therefore, we are focusing on the development of hetero-bidentate ligands towards smart pathway selection, which not only guarantees [M − H] stability, but also achieves high activity.

Recently, the combination of phosphine and N-heterocyclic carbene (NHC) ligands has resulted in the improvement of several important catalytic processes.[42–45] Both the phosphine and NHC ligands are strong σ-donating ligands, which are beneficial for the TM-catalyzed BH/HA reactions.[9,10,34,46–48] However, there are electronic and steric diversities between the phosphine and NHC ligands (Scheme 1b). NHC ligands have the sp^2 lone pair electrons on the central carbon atom that can coordinate to a TM, which confers strong σ-donation behavior. Meanwhile, the π* molecular orbital (MO) of the NHC ligands can accept electron density from the filled d orbitals of the TM *via* a classical d → π* back-donation.[49,50] Therefore, NHC is usually described as a class of strong σ-basic/weak π-acidic ligands. For the PR_3 ligands, the lone pair of the P atoms serves as an electron donator, while the σ* orbitals of the P–R bonds play the role of an acceptor. As compared with NHC, the phosphine ligand is a relatively weaker donor, and a stronger back-donation acceptor.[51] We assumed that the diversity of the hetero-bidentate NHC-phosphine ligands could stabilize or activate the hydride in [Ru–H] species *via* different coordination geometries, in which the hydride could locate *trans* to either the phosphine ligand or the NHC ligand (Scheme 1c). Inspired by this possible hetero-mixed ligand strategy, we are looking forward to developing a Ru(II) catalyst system with the hetero-bidentate NHC-phosphine ligands for realizing the smart pathway selection *via* the [M − H] species in the *N*-alkylation reaction.

Herein, we describe the development of a Ru(II)-catalyzed protocol enabling the smart pathway selection for the synthesis of *N*-alkylated amines from alcohols and amines. As a special highlight, this catalytic system is applicable even for the less active aliphatic alcohols including methanol. Moreover, experiments and DFT calculations were carried out to understand the mechanism and the smart pathway selection of the [Ru–H] species in this process. These results imply the potential of the smart pathway selection strategy using hetero-bidentate ligands in BA/HA or other tandem catalytic reactions.



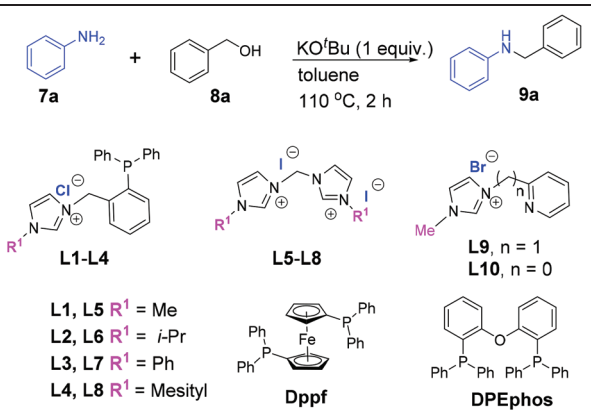
Scheme 1 (a) BH/HA strategy for the *N*-alkylation of amines with alcohols; (b) molecular orbitals of the NHC and phosphine ligands with the metal; (c) the isomerization of the hetero-bidentate NHC-phosphine Ru hydrides intermediates.

Results and discussion

Screening of the ligands

We initially prepared three types of bidentate NHC ligands including hetero-bidentate NHC-phosphine ligands (**L1–L4**),[52] bis-NHC ligands (**L5–L8**)[53] and hetero-bidentate NHC/pyridine ligand (**L9–L10**)[54,55] motifs (Table 1). All these ligands can be prepared in good yields in few steps starting from commercially available reagents (see the ESI† for more details). It should be noted that the steric environment of these hetero-bidentate ligands can be tuned modularly through the modification of the *N*-substituents of the imidazole. With these bidentate NHC ligands (**L1–L10**) and the bidentate phosphine ligands Dppf (**L11**) and DPEphos (**L12**), the *N*-alkylation of aniline with benzyl alcohol was performed *via* the catalytic systems formed *in situ*, which were derived from a mixture of ligands, different Ru resources, and KO^{t}Bu in toluene at 110 °C (Table 1). Trace amounts of products were observed in the absence of the Ru source (entry 1), whereas a control experiment in the absence of the ligand resulted in a poor yield (entry 2). The reactions were conducted with various Ru precursors and **L1**, in which good yields were obtained with all of the precursors $[Ru(p\text{-cymene})Cl_2]_2$, $RuCl_3{\cdot}3H_2O$, $Ru(COD)Cl_2$ and $RuCl_2(DMSO)_4$ (entries 3–6), demonstrating the great potential of the hetero-bidentate NHC-phosphine ligand in this transformation. Selecting $[Ru(p\text{-cymene})Cl_2]_2$ for further study, the effects of various ligands were evaluated (entries

Table 1 Effects of ligands on the *N*-alkylation of aniline with benzyl alcohol catalyzed by Ru[a,b]



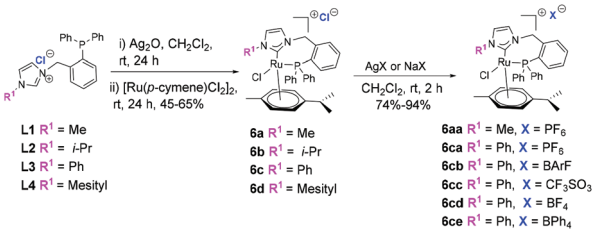
Entry[a]	Ligand (0.5 mol%)	Ru (0.5 mol% [Ru])	Yield[b] (%)
1	**L1**	—	—
2	—	$[Ru(p\text{-cymene})Cl_2]_2$	23
3	**L1**	$[Ru(p\text{-cymene})Cl_2]_2$	93
4	**L1**	$RuCl_3{\cdot}3H_2O$	90
5	**L1**	$Ru(COD)Cl_2$	83
6	**L1**	$RuCl_2(DMSO)_4$	85
7	**L2**	$[Ru(p\text{-cymene})Cl_2]_2$	91
8	**L3**	$[Ru(p\text{-cymene})Cl_2]_2$	77
9	**L4**	$[Ru(p\text{-cymene})Cl_2]_2$	49
10	**L5**	$[Ru(p\text{-cymene})Cl_2]_2$	58
11	**L6**	$[Ru(p\text{-cymene})Cl_2]_2$	27
12	**L7**	$[Ru(p\text{-cymene})Cl_2]_2$	33
13	**L8**	$[Ru(p\text{-cymene})Cl_2]_2$	28
14	**L9**	$[Ru(p\text{-cymene})Cl_2]_2$	30
15	**L10**	$[Ru(p\text{-cymene})Cl_2]_2$	22
16	Dppf	$[Ru(p\text{-cymene})Cl_2]_2$	27
17	DPEphos	$[Ru(p\text{-cymene})Cl_2]_2$	35

[a] *N*-Alkylation reaction conditions: 1.0 mmol **7a**, 1.0 mmol **8a**, 0.5 mol% **L**, 0.5 mol% [Ru], 1.0 mmol KO^{t}Bu, 2.0 mL toluene, 110 °C, 2 h. [b] GC yields.

7–15). The wingtip substituents at the hetero-bidentate NHC-phosphine ligands were found to have an impact on their performance. The best pre-catalysts were formed from methyl-substituted (**L1**, entry 3) and isopropyl-substituted (**L2**, entry 7) ligands, while the ligands with a phenyl group (**L3**, entry 8) or a mesityl-substituent (**L4**, entry 9) resulted in moderate activity. The use of bis-NHC ligands (**L5–L8**, entries 10–13), hetero-bidentate NHC/pyridine (**L9–L10**, entries 14 and 15) and bidentate phosphine ligands (entries 16 and 17) gave inferior results compared with hetero-bidentate NHC-phosphine ligands under identical conditions. Those results indicated that the hetero-bidentate NHC-phosphine ligands played a pivotal role in the Ru catalyzed the *N*-alkylation reactions.

Synthesis and characterization

Inspired by the promising performance of precatalysts formed from **L1–L4**/$[Ru(p\text{-cymene})Cl_2]_2$, we sought to isolate the corresponding well-defined Ru-complexes. Complexes **6a–d**, **6aa**,[56] and **6ca–6ce** were synthesized by following the reaction sequence depicted in Scheme 2. Treatment of **L1–L4** with Ag_2O



Scheme 2 Synthesis of complexes **6a–d**, **6aa**, and **6ba–be**.

and *trans*-metalation of the resulting silver carbene to $[Ru(p\text{-cymene})Cl_2]_2$, afforded the new complexes **6a–d** in high yields.[10] The analogues **6aa** and **6ca–ce** were prepared by the addition of AgX (X = PF_6, OTf, and BF_4 for complexes **6aa** or **6ca**, **6cc** and **6cd**, respectively) or NaX (X = BArF and BPh_4 for complexes **6cb** and **6ce**, respectively) to a solution of **6a** or **6c** in CH_2Cl_2.[35] The ruthenium complexes **6a–d**, **6aa** and **6ca–6ce** were all separated by column chromatography as air and moisture stable yellow solids. In their ^{1}H NMR spectra, the signals of the imidazole proton at the C-2 position, appearing for compounds **L1–L4**, completely disappeared. The characteristic signals of the carbene carbons in their ^{13}C NMR spectra [165.4 ppm (**6a**), 165.7 ppm (**6b**), 166.9 ppm (**6c**), and 171.5 ppm (**6d**)] are comparable to those of the previously reported ruthenium NHC complexes.[57,58]

Crystals suitable for X-ray diffraction of **6d**, **6aa**, and **6ca** were obtained by slow evaporation of their concentrated solutions in CH_2Cl_2/hexane at room temperature. ORTEP diagrams of **6d**, **6aa**, and **6ca** are displayed in Fig. 1. These complexes adopt a three-legged piano stool geometry with the facial planar *p*-cymene representing the "seat", and the chlorido and the hetero-bidentate NHC-phosphine ligands forming the three "legs". The Ru–$C_{carbene}$ distances in **6d** and **6aa** (2.076(2) and 2.079(3) Å, respectively) are slightly longer than that in **6ca**

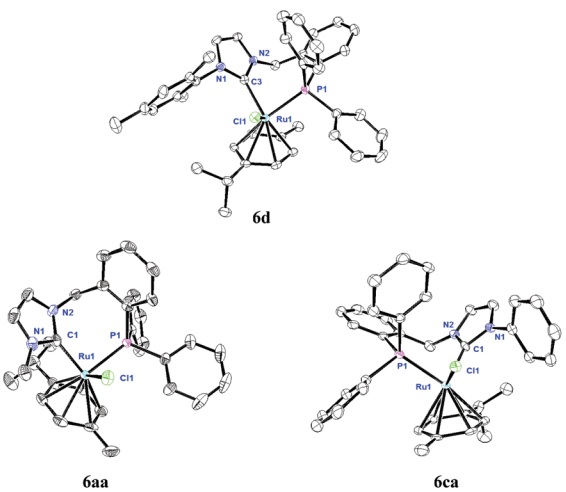


Fig. 1 ORTEP diagrams for complexes **6d**, **6aa** and **6ca** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms and counter anions are omitted for clarity.

(2.066(4) Å). The Ru–P distance in **6d** (2.3394 (6) Å) is slightly shorter than those in **6aa** and **6ca** (2.3528(7) and 2.3495(11) Å, respectively). These differences may result from the different steric environments of the *N*-substituents of the imidazole.

Optimization of the *N*-alkylation of amines with alcohols

A screening of the Ru complexes was carried out (Table 2). Interestingly, the ruthenium complex **6c** containing phenyl as the wingtip substituent (entry 4) led to a higher yield (92% yield) than those containing methyl, isopropyl, or mesityl groups (entries 2, 3 and 5). This behavior is in conformity with the performance of precatalysts *in situ* formed from **L1–L4**/[Ru(*p*-cymene)Cl_2]$_2$, which may result from the different coordination ability and stability of the free NHC. After these optimizations, we were interested in studying the analogs of **6c** in which one chloride ligand was replaced by a weaker coordinating counter-anion (entries 6–11). To our delight, complex **6cb** (entry 8) with the $BArF^-$ anion is more effective than the corresponding complex **6c**, which could improve the yield to 97%. In contrast, the other anions such as PF_6^- (**6ca**, entry 7), OTf^- (**6cc**, entry 9), BF_4^- (**6cd**, entry 10), and BPh_4^- (**6ce**, entry 11) led to a moderate decrease in the catalytic activity. Subsequently, complex **6cb** was chosen for further optimization studies including the base, catalyst loading, reaction time, and temperature. It was found that KO^{t}Bu is an effective base to obtain high yields. However, replacing KO^{t}Bu with other bases resulted in decreased yields, and even the weaker bases, such as K_2CO_3 and Na_2CO_3, were ineffective (Table S2,† entries 6–10). In addition, nearly 75 mol% KO^{t}Bu is needed to obtain sufficient yields (Table S2,† entries 1–5). Gratifyingly, the yield could reach 91% within 30 min (entry 12). An attempt to lower the catalyst loading to 0.25 mol% resulted in a slight decrease in the yield (entry 13). The temperature of the reaction was found to have a strong impact on the reaction rate (entries 14–16). The temperature could be lowered to 50 °C, but a longer reaction time was needed to obtain a high yield (24 h, 92% yield, entry 15). However, a lower yield was obtained when the reaction was performed at 30 °C or under an air atmosphere (entries 16 and 17). When the reaction was run in H_2O, the catalytic activity of **6cb** almost disappeared (entry 18). Gratifyingly, under neat conditions, the reaction could also successfully occur, and the yield was up to 97% (entry 19). Furthermore, a good yield was obtained, when the reaction was carried out without using the glovebox (entry 20).

Table 2 Optimization of the *N*-alkylation of aniline with benzyl alcohol

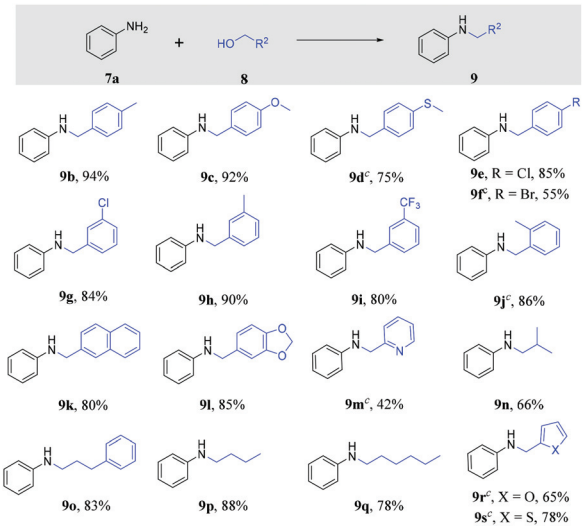
Entry[a]	Catalyst	R^1	X	Yield[b] (%)
1	None	—	—	6
2	**6a**	Me	Cl	76
3	**6b**	i-Pr	Cl	71
4	**6c**	Ph	Cl	92
5	**6d**	Mesityl	Cl	54
6	**6aa**	Me	PF_6	74
7	**6ca**	Ph	PF_6	90
8	**6cb**	Ph	BArF	97
9	**6cc**	Ph	CF_3SO_3	90
10	**6cd**	Ph	BF_4	92
11	**6ce**	Ph	BPh_4	87
12[c,d]	**6cb**	Ph	BArF	91
13[d,e]	**6cb**	Ph	BArF	91
14[d,e,f]	**6cb**	Ph	BArF	98
15[d,g]	**6cb**	Ph	BArF	92
16[d,h]	**6cb**	Ph	BArF	61
17[d,i]	**6cb**	Ph	BArF	25
18[d,j]	**6cb**	Ph	BArF	Trace
19[d,e,f,k]	**6cb**	Ph	BArF	97 (95)
20[d,e,f,k,l]	**6cb**	Ph	BArF	95

[a] *N*-Alkylation reaction conditions: 1.0 mmol **8a**, 1.0 mmol **7a**, 1.0 mmol KO^{t}Bu, 0.5 mol% **6**, 2.0 mL of toluene, 110 °C, 2 h. [b] GC yields, isolated yields in parentheses. [c] Time (0.5 h). [d] 0.75 mmol KO^{t}Bu. [e] Catalyst loading (0.25 mol%). [f] Temperature (70 °C), time (12 h). [g] Temperature (50 °C), time (24 h). [h] Temperature (30 °C), time (24 h). [i] Air atmosphere. [j] 2.0 mL H_2O instead of toluene. [k] Neat conditions. [l] Without using the glovebox.

N-Alkylation of aniline with alcohols

Encouraged by these results, we further investigated the substrate scopes of our catalyst system under neat conditions, which is more environmentally friendly. Firstly, we focused on the alkylation of aniline with various alcohol derivatives. As shown in Table 3, both electron-rich and electron-deficient benzylic alcohols could be employed efficiently in our process, and provided alkylated aniline derivatives **9b–l** in 55–94% yields. A series of functional groups, such as halide groups (**9e–g**), thioether group (**9d**), and trifluoromethyl group (**9i**), were compatible with the present catalytic system for alcohols. As for 4-bromobenzyl alcohol, the reaction suffered from debromination, and the product **9f** was isolated in moderate yield (55% at 90 °C). The sterically hindered *ortho*-methyl benzylic alcohol could provide the corresponding monoalkylated amine **9j** in 86% yield at 90 °C. When heterocylic alcohols, such as 2-pyridinemethanol, 2-furylmethanol, and 2-thiophenemetha-

Table 3 Alkylation of aniline with various primary alcohols[a,b]



[a] *N*-Alkylation reaction conditions: 0.5 mmol **7a**, 0.5 mmol **8**, 75 mol% KO^{t}Bu, 0.25 mol% **6cb**, 70 °C, 12 h. [b] Isolated yields. [c] 90 °C.

nol were used as the substrates, the corresponding products (**9m** and **9r–s**) were isolated in 42–78% yields at 90 °C. To our delight, aliphatic alcohols, such as isobutanol, phenylpropanol, and the chain-containing aliphatic alcohols, could efficiently convert to monosubstituted aniline derivatives **9n–q** in 66–88% isolated yields. However, attempts at the *N*-alkylation of aniline with secondary alcohols, such as 1-phenethyl alcohol, cyclohexanol, and isopropyl alcohol, were unsuccessful, yielding only trace amounts of products.

N-Alkylation of amines with benzyl alcohol

Next, the scope of the amines was investigated (Table 4). Substrates bearing either electron-donating or electron-withdrawing substituents on the aryl ring of aniline were selectively alkylated to afford the *N*-monoalkylated anilines **10a–h** in good yields (54–92%). In the cases of *ortho*-bromine aniline, debromination was also observed, and product **10g** was isolated in moderate yield (54%). Even sterically hindered, *ortho*-phenyl aniline could smoothly convert to the corresponding product **10h** with excellent selectivity (83%). Treatment of the bulky amines, such as 1,4-benzodioxan-6-amine and 2-naphthylamine, with benzyl alcohol resulted in desired products **10i–j** in very good yields (85–92%). Advantageously, heteroaromatic amines, such as 2-aminopyridine and 3-aminopyridine, were successfully transformed into the desired products **10k–l** in good yields (83–86%). Furthermore, aliphatic amines, such as benzylamine, *n*-hexylamine, and 4-methylphenethylamine could also be converted to the desired products **10m–o** in 43–51% yields. However, the secondary amine, such as morpholine (**10p**), was not tolerated. Furthermore, we have tested the more challenging reactions including the *N*-alkylation of diamine with dialcohols (Scheme S4a and b†), *N*-alkylation of *p*-toluenesulfonamide with benzyl alcohol (Scheme S4c†), *N*-alkylation of *p*-nitroaniline with benzyl alcohol (Scheme S4d†), *N*-alkylation of aniline with 4-nitrobenzyl alcohol (Scheme S4e†), and *N*-alkylation of aniline with methyl 4-(hydroxymethyl)benzoate (Scheme S4f†). However, these reactions were unsuccessful, even at a higher catalyst loading (1 mol%) and a higher temperature of 110 °C.

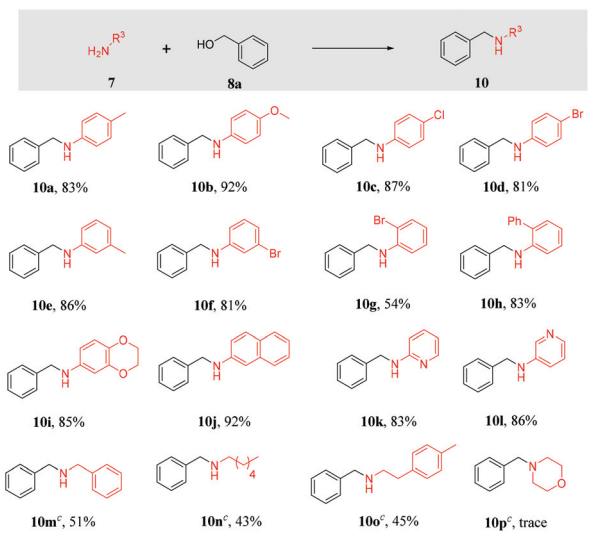
N-Methylation of anilines

N-Methylamines are also widely used as key intermediates and building blocks for the synthesis of bulk and fine chemicals as well as materials.[59,60] However, methanol is still a challenging substrate for the *N*-alkylation of amines, due to the higher activation barrier (ΔH = 21 kcal mol^{-1}) of the dehydrogenation step compared to that of higher alcohols, such as ethanol (ΔH = 16 kcal mol^{-1}).[61] To further expand the generality of the catalytic system, the *N*-methylation of amines with methanol was then investigated. To our delight, the *N*-methylation of anilines with methanol was successfully accomplished in the presence of 0.5 mol% **6cb** at 110 °C (Table S3†). As shown in Table 5, most of the catalytic reactions showed unprecedented efficiency, reaching at least 80% yields (**11a–o**: 40–94%). Again, a notable functional group tolerance was observed. Employing 2-iodoaniline led to **11i** in moderate isolated yields (40%), and the reaction also suffered from dehalogenation. Furthermore, important biologically relevant motifs, such as 3-trifluoromethylaniline and 1,3-benzodioxol-5-amine, were effectively transformed (**11m–n**). Remarkably, we did not observe dialkylation products in all the cases, although excess MeOH and high temperature were used. However, attempts at the *N*-methylation of aliphatic amines, such as benzylamine and *n*-hexylamine, were unsuccessful, yielding only traces of products.

N-Alkylation of diamines

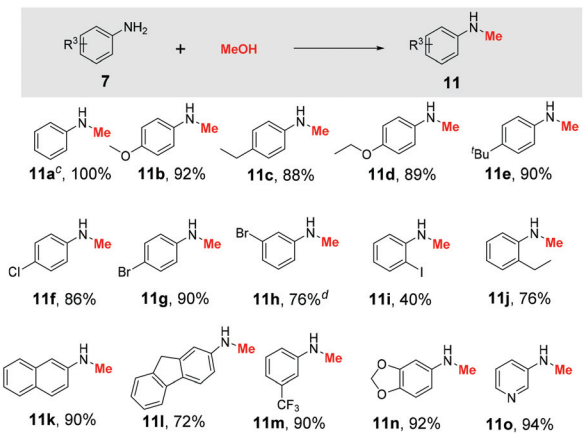
Encouraged by the promising results of *N*-alkylation of amines, we were interested in the sequential alkylation of di-

Table 4 *N*-Alkylation of amines using benzyl alcohol[a,b]



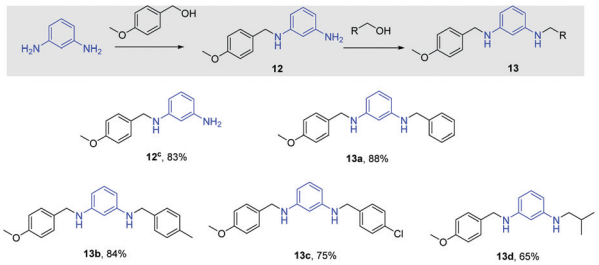
[a] *N*-Alkylation reaction conditions: 0.5 mmol **7**, 0.5 mmol **8a**, 75 mol% KO^{t}Bu, 0.25 mol% **6cb**, 70 °C, 12 h. [b] Isolated yields. [c] 100 mol% KO^{t}Bu, 0.5 mol% **6cb**, 110 °C, 24 h.

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



[a] General reaction conditions: **7** (0.5 mmol), MeOH (0.2 mL), **6cb** (0.5 mol%), KO^{t}Bu (75 mol%), 110 °C, 12 h. [b] Isolated yield. [c] GC yield. [d] MeOH (0.5 mL) and toluene (1.0 mL).

Table 6 *N*-Alkylation of diamines[a,b]



[a] *N*-Alkylation reaction conditions: 0.5 mmol **12**, 0.5 mmol **8**, 75 mol% KO^{t}Bu, 0.25 mol% **6cb**, 110 °C, 12 h. [b] Isolated yields. [c] Conditions: 0.5 mmol 4-methoxybenzyl alcohol, 2 mmol benzenediamine, 0.25 mol% **6cb**, 75 mol% KO^{t}Bu, 110 °C, 12 h.

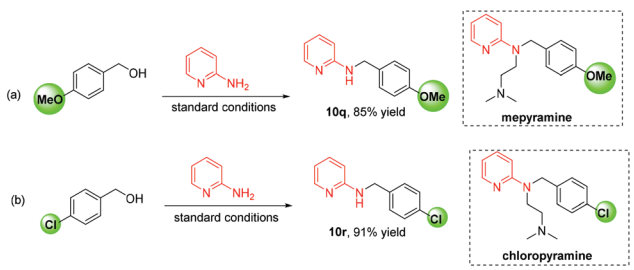
amines with two different alcohols (Table 6), which is undoubtedly a valuable synthetic tool to obtain compounds with desired diversity.[13,62] Firstly, the diamine was selectively monoalkylated to form compound **12** in 83% yield at 110 °C. Then, we were pleased to note that **12** can be alkylated with different alcohols to afford the corresponding unsymmetrically functionalized diamines (**13a–d**) in good yields (65–88%).

Gram-scale synthesis of bioactive intermediates

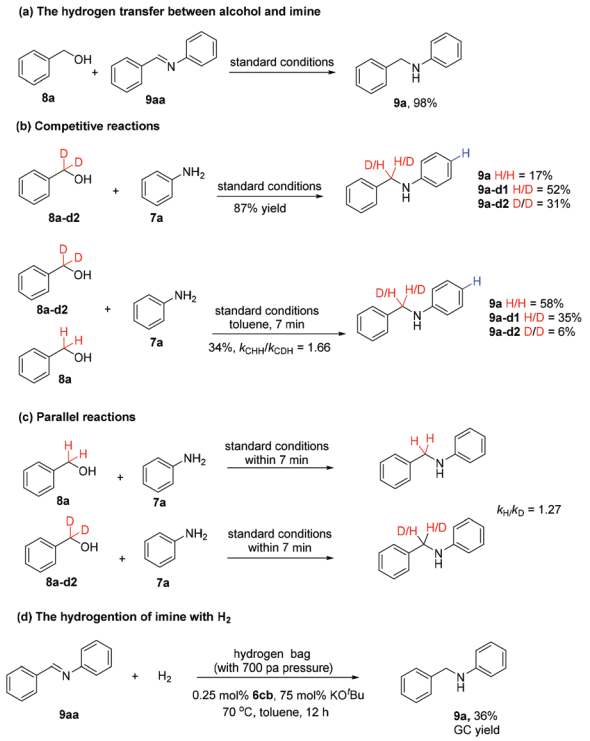
Next, the synthetic application was also demonstrated for the gram-scale transformation of 2-aminopyridine into the intermediates of bioactive drugs mepyramine (**10q**, Scheme 3a), and chloropyramine (**10r**, Scheme 3b), which are extensively used as antihistaminics.[19] Gratifyingly, with 2-aminopyridine as a substrate in 10 mmol scale reactions, *N*-alkylated derivatives **10q** and **10r** were obtained in 85% and 91% yields, respectively.

Mechanistic studies

To gain insight into the *N*-alkylation process, several control experiments were performed. Firstly, the dehydrogenation reaction of benzyl alcohol, and the *N*-alkylation of aniline with benzyl alcohol were monitored by ^{1}H NMR spectroscopy. However, the benzaldehyde was not observed, which indicated that the aldehyde should be a short-lived intermediate or it does not dissociate from the metal center in the *N*-alkylation reaction.[10] Additionally, the reaction of imine **9aa** with benzyl alcohol **8a** under the optimal conditions gave **9a** (98%) *via*



Scheme 3 Gram-scale synthesis of bioactive compounds.



Scheme 4 Preliminary mechanistic studies.

transfer hydrogenation of the C=N bond, supporting the BH/HA mechanism (Scheme 4a).[63] Moreover, the kinetic isotope effect (KIE) studies (Scheme 4b and c) were carried out to obtain more information concerning the reaction pathway.[19,64] The reaction of **8a-d2** (97% D) with **7a** under standard conditions gave a mixture of *N*-alkylated products **9a** (17%), **9a-d1** (52%) and **9a-d2** (31%) in 87% yield (Scheme 4b), which is indicative of the reversible alcohol dehydrogenation step and the existence of D/H exchange.[9] Both the intermolecular competition and the parallel reactions of **8a** and **8a-d2** with **7a** showed a low KIE value (KIE = 1.66 and 1.27, respectively), suggesting that the alcohol oxidation step should probably not be involved in the rate-determining step (rds.) of the reaction.[64] In addition, the production of hydrogen gas was detected from the head gas of the reaction of **7a** with **8a** under the standard conditions (Fig. S6†). We further evaluated the ability of **6cb** to hydrogenate the intermediate imine **9aa** (Scheme 4d).[65] Under the standard conditions, using toluene as the solvent, and the hydrogen bag with extra 700 pa pressure, product **9a** was obtained in 36% yield. This result indicated the potential of **6cb** to hydrogenate the imine with hydrogen gas.

To investigate the real catalytic species, the reaction between benzyl alcohol and aniline in toluene-d_8 with high catalyst loadings (20 mol% of **6cb**) was monitored by ^{1}H and ^{31}P NMR spectroscopy.[10,46,66] Immediately, hydrido signals were detected in the range from −3 to −11 ppm (Fig. 2a) after the addition of substrates and the base. This indicates a quick exchange of the chlorido ligand with the alkoxide, as an initial

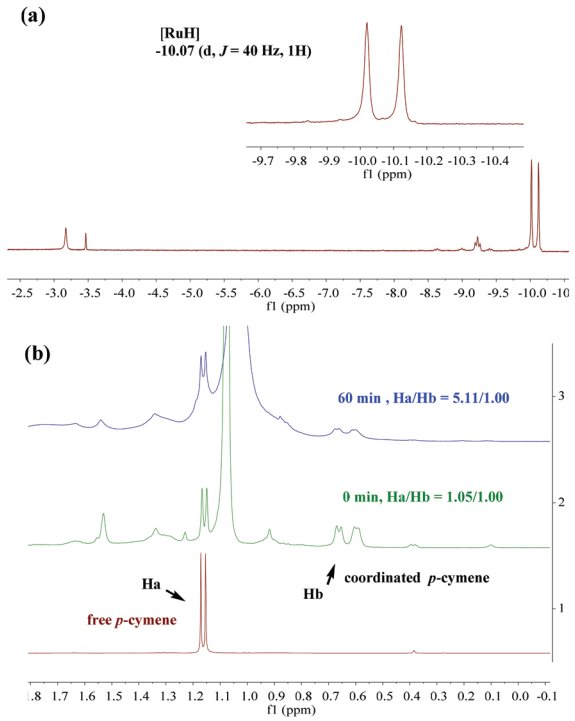


Fig. 2 (a) ^{1}H NMR (400 MHz, toluene-d_8) spectrum of reaction mixtures for amination at 0 min of the hydride region; (b) ^{1}H NMR (400 MHz, toluene-d_8) spectrum of the free *p*-cymene and reaction mixtures for amination (0 min and 60 min) in the range of 0–2 ppm.

step that does not require heating, in contrast to results reported by Valerga and co-workers.[10] In particular, a high-intensity doublet at −10.07 ppm with a coupling constant of ^{2}J(P, H) = 40 Hz, is indicative of the existence of a *cis* coordinated [RuH(PPh$_2$NHC)] species.[46,66] Furthermore, the proof for the existence of [RuH(PPh$_2$NHC)] species could also be found in the ^{31}P NMR spectrum (Fig. S8†), as the single signal of complex **6cb** at 23.95 ppm has been replaced by several new downfield signals ranging from 32 to 72 ppm.[46,66] In addition, the signal of dissociated *p*-cymene ligand (50% at 0 min and 80% at 60 min) could be found in the crude ^{1}H NMR spectra (Fig. 2b) at 110 °C, indicating that the *p*-cymene could be dissociated into the active species.[46,66]

Theoretical investigations

Density functional theory (DFT) calculations (see the ESI† for computational details) were used to investigate the unique role of the hetero-bidentate NHC-phosphine ligands in this process.[64,67] Herein, we are mainly focused on the dehydrogenation of alcohol and the insertion of imine steps involving the key intermediate, the metal hydride. In computational studies, the structure of the NHC ligand was simplified by replacing the phenyl group with a methyl substituent and the vacant site generated by the dissociation of *p*-cymene was occupied by the *tert*-butoxy groups. No further simplifications of the catalyst structure were introduced.

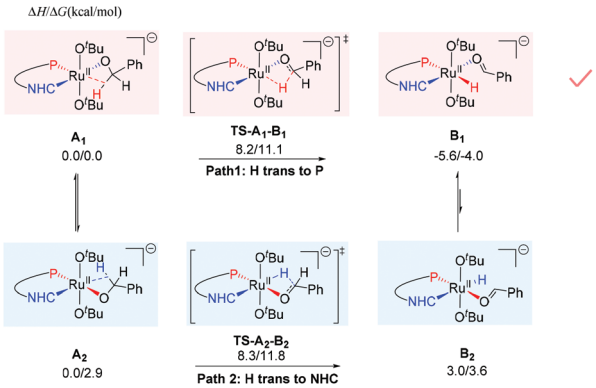


Fig. 3 The selection of the reaction pathways in the dehydrogenation of alcohol by the hetero-bidentate NHC-phosphine Ru catalyst (**A** → **B**).

The dehydrogenation of alcohol step occurs *via* the β-H elimination on the Ru center from complex $\mathbf{A_1}$ or $\mathbf{A_2}$ (Fig. 3). Because the hydride could be *trans* to either the phosphine or the NHC arm, the β-H elimination step diverges into two pathways ($\mathbf{A_1} \rightarrow \mathbf{B_1}$ and $\mathbf{A_2} \rightarrow \mathbf{B_2}$, respectively). The β-C–H agostic intermediate $\mathbf{A_1}$ with the hydride to be eliminated *trans* to the phosphine arm is 2.9 kcal mol^{-1} more stable than $\mathbf{A_2}$ with the hydride to be eliminated *trans* to the NHC ligand. With $\mathbf{A_1}$ as the reference point, the overall barriers for these two pathways are 11.1 kcal mol^{-1} and 11.8 kcal mol^{-1}, respectively, which are comparable. However, the intermediate $\mathbf{B_2}$ is more endergonic by 7.6 kcal mol^{-1} than $\mathbf{B_1}$, indicating that the P ligand is beneficial for stabilizing the Ru hydride.

Similarly, the insertion of imine step (Fig. 4, **C** → **D**) is also divided into two different pathways (Fig. 4, $\mathbf{C_1} \rightarrow \mathbf{D_1}$ and $\mathbf{C_2} \rightarrow \mathbf{D_2}$, respectively). Imine complex $\mathbf{C_1}$ with the hydride *trans* to the phosphine arm is 2.2 kcal mol^{-1} more stable than $\mathbf{C_2}$ with the hydride *trans* to the NHC arm. However, the overall free energy barrier from $\mathbf{C_1}$ to $\mathbf{D_1}$ (21.2 kcal mol^{-1}) is higher than that from $\mathbf{C_2}$ to $\mathbf{D_2}$ (9.5 kcal mol^{-1}). These results suggest that the NHC arm significantly favors the insertion of imine step over the phosphine arm. Therefore, these DFT calculations

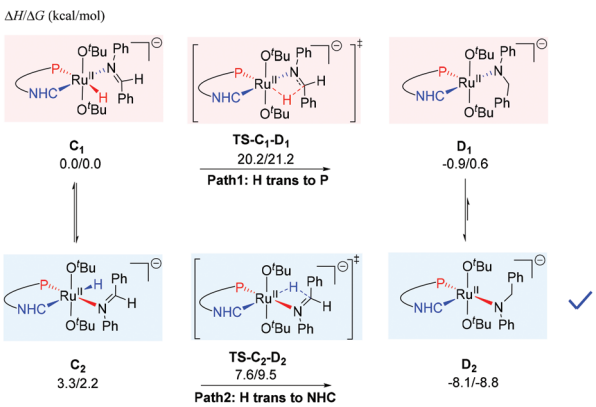
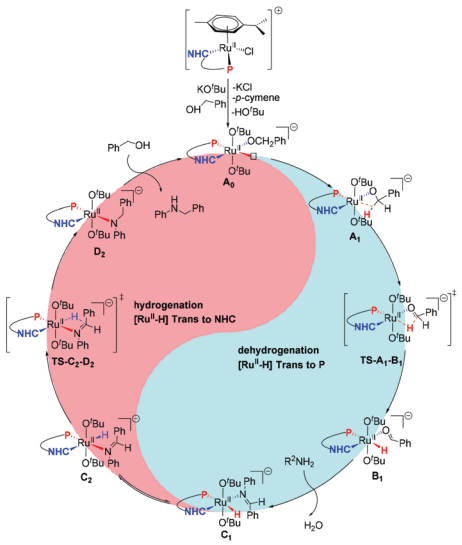


Fig. 4 The selection of reaction pathways in the insertion of imine by the hetero-bidentate NHC-phosphine Ru catalyst (**C** → **D**).



Scheme 5 Proposed catalytic cycle for the *N*-alkylation of amines with alcohols by the hetero-bidentate NHC-phosphine Ru catalyst.

provide clues to explain the importance of the hetero-bidentate NHC-phosphine ligands, which could realize the smart pathway selection for adjusting the dehydrogenation of alcohol and the insertion of imine steps *via* tuning the stability and activity of the [Ru–H] species.

On the basis of these observations and previous studies,[9,10] a possible mechanism for the *N*-alkylation reaction is suggested (Scheme 5). At the initial stage, the alkoxy ruthenium species $\mathbf{A_0}$ is generated by the dissociation of *p*-cymene and the coordination of the alcohol to the ruthenium center under the acceleration of the base. The phosphine arm is more prone to stabilize the Ru hydride. The dehydrogenation step would begin with the formation of an agostic intermediate $\mathbf{A_1}$ on the *trans* position to the phosphine arm. Accompanied by its β-hydride elimination ($\mathbf{TS\text{-}A_1\text{-}B_1}$), the ruthenium hydride species $\mathbf{B_1}$ coordinated with the aldehyde is generated. Subsequently, the condensation between the aldehyde and amine would occur on the metal center to give the imine complex $\mathbf{C_1}$. $\mathbf{C_1}$ would isomerize to $\mathbf{C_2}$ with the hydride *trans* to the NHC arm, which will promote the insertion of imine step. From $\mathbf{C_2}$, the hydride transfer ($\mathbf{TS\text{-}C_2\text{-}D_2}$) takes place to afford amido complex $\mathbf{D_2}$. Finally, the catalytically active alkoxy ruthenium species $\mathbf{A_0}$ will be regenerated by releasing the *N*-alkylated amine as the product by the reaction of species $\mathbf{D_2}$ with alcohol.

Conclusions

In summary, we have reported the synthesis and characterization of a series of air-stable ruthenium complexes (**6a–d**, **6aa**, and **6ca–6ce**) bearing a hetero-bidentate NHC-phosphine ligand, in which the substituents on the NHC wingtip and the coordinating counter-anions have been modified. These complexes were found to be highly effective catalysts for the selective monoalkylation of aromatic amines through a BH/HA mechanism. In particular, complex **6cb** is one of the most active ruthenium catalysts known to date; it can be used to catalyze the reaction at temperatures as low as 70 °C with a very low catalyst loading (0.25 mol%) under neat conditions. A large variety of (hetero)aromatic amines, aliphatic amines and primary alcohols including biologically relevant motifs and the challenging methanol, were efficiently converted into mono-*N*-alkylated amines in good to excellent isolated yields. Detailed control experiments and DFT calculations were carried out to understand the mechanism of this process and the smart pathway selection *via* tuning the stability and activity of the [Ru–H] species through the hetero-bidentate NHC-phosphine ligands. These results imply the potential of the pathway selection strategy by hetero-bidentate ligands in BA/HA or other tandem catalytic reactions.

Experimental section

General procedures and materials

Unless otherwise stated, all manipulations were carried out under dry argon using conventional Schlenk and glove box techniques. Non-halogenated solvents were dried over sodium benzophenone ketyl and halogenated solvents over CaH_2. All other commercial reagents were used without further purification. Detailed experimental procedures, characterization data, computational details and structures, copies of ^{1}H NMR and ^{13}C NMR spectra for all isolated compounds are available in the ESI.†

NMR spectra were recorded using a Bruker 400 MHz spectrometer, and chemical shifts are reported relative to TMS for ^{1}H and ^{13}C. ESI-MS spectra were recorded on a Shimadzu LCMS-2010 instrument. GC analyses were performed on a Shimadzu GC-2014C device equipped with a Wondacap 1 column. High resolution mass spectrometric (HRMS) data were obtained using an LTQ Orbitrap Elite instrument, using a sample concentration of approximately 1 ppm.

General method for the preparation of ruthenium complexes 6a–d

A suspension of appropriate imidazolium salts (**L1–L4**, 0.1 mmol) and silver oxide (0.5 equiv.) in CH_2Cl_2 was stirred at room temperature in the dark for 24 h. The mixture was then filtered through a pad of Celite into a solution of $[(p\text{-cymene})RuCl_2]_2$ (0.5 equiv.) in CH_2Cl_2 and stirred at room temperature for 24 h. Then the organic solvent was removed by evaporation and the crude product was purified by column chromatography (CH_2Cl_2 : MeOH = 20 : 1).

General method for the preparation of ruthenium complexes 6aa and 6ca–ce

To a solution of NaX (0.1 mmol; X = BArF, BPh_4; for complexes **6cb** and **6ce**, respectively) or appropriate AgX (0.20 mmol; X = PF_6, OTf and BF_4 for complexes **6ca**, **6cc** and **6cd**, respectively)

in CH_2Cl_2 (2 mL) was added complex **6a** or **6c** (0.1 mmol) and the resulting mixture was stirred at rt for 2 h. Then products **6aa** and **6ca–ce** were obtained directly by silica gel column chromatography (CH_2Cl_2 : MeOH = 100 : 1 for **6aa**; CH_2Cl_2 : *n*-hexane = 2 : 1 for **6cb**; CH_2Cl_2 : MeOH = 40 : 1 for **6ca**, **6cc** and **6cd**; CH_2Cl_2 : *n*-hexane = 5 : 1 for **6ce**).

General method for the *N*-alkylation of amines with alcohols

To a 15 mL reaction tube in a glovebox, was added complex **6cb** (0.25 mol%), KO^{t}Bu (75 mol%), alcohols (0.5 mmol), and amine (0.5 mmol) at room temperature. Then the tube was closed and removed from the glovebox. The reaction mixture was stirred at 70 °C for 12 h. After being cooled to rt, the reaction mixture was diluted with ethyl acetate, filtered and dried under vacuum. The product was purified by column chromatography over silica-gel (300–400 mesh) with an appropriate mixture of petroleum ether and ethyl acetate (80 : 1).

General method for the *N*-methylation of anilines with methanol

To a 15 mL sealing tube in a glovebox, was added amine (0.5 mmol), MeOH (200 μL), **6cb** (0.5 mol%), and KO^{t}Bu (75 mol%). Then the tube was closed with a screw-top cap and removed from the glovebox. The reaction mixture was stirred for 12 h at 110 °C. After being cooled to rt, the mixture was diluted with ethyl acetate and filtered through a short pad of silica (2 cm in a Pasteur pipette). Silica was washed with ethyl acetate. The filtrate was evaporated and the crude residue was purified by column chromatography (SiO_2, petroleum ether : ethyl acetate = 80 : 1).

General method for the *N*-alkylation of diamines

The general method for the *N*-alkylation of amines with alcohols was followed using 3-benzenediamine (216 mg, 2 mmol) and benzyl alcohol (52 μL, 0.5 mmol) for 12 h at 110 °C. After the reaction, the mixture was cooled to room temperature and the intermediate **12** was isolated by column chromatography. In the case of complexes **13a–d**, 0.5 mmol intermediate **12** and alcohols were used.

Gram-scale synthesis method

To a 25 mL round bottom flask in a glovebox, was added complex **6cb** (0.25 mol%), KO^{t}Bu (75 mol%), alcohols (10.0 mmol), and 2-aminopyridine (10.0 mmol) at room temperature. Then the tube was closed and removed from the glovebox. The reaction mixture was stirred at 70 °C for 12 h. After being cooled to rt, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried with Na_2SO_4. The product was purified by column chromatography over silica-gel (300–400 mesh) with an appropriate mixture of petroleum ether and ethyl acetate (4 : 1).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This study was supported by the 12th Five-Year Plan Key Discipline of Clinical Pharmacy, High Level Clinical Key Specialty in Guangdong Province, the NSFC (22002023, 21973113, and 21773312), the Guangdong Natural Science Funds (no. 2015A030306027 for Distinguished Young Scholar), the Tip-Top Youth Talents of Guangdong Special Support Program (no. 20153100042090537) and the Fundamental Research Funds for the Central Universities.

Notes and references

1 S. Kobayashi and H. Ishitani, Catalytic enantioselective addition to imines, *Chem. Rev.*, 1999, **99**, 1069–1094.
2 A. Seayad, M. Ahmed, H. Klein, R. Jackstell, T. Gross and M. Beller, Internal olefins to linear amines, *Science*, 2002, **297**, 1676–1678.
3 A. F. Abdel-Magid and S. J. Mehrman, A review on the use of sodium triacetoxyborohydride in the reductive amination of ketones and aldehydes, *Org. Process Res. Dev.*, 2006, **10**, 971–1031.
4 E. Vitaku, D. T. Smith and J. T. Njardarson, Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals, *J. Med. Chem.*, 2014, **57**, 10257–10274.
5 A. J. A. Watson and J. M. J. Williams, The Give and Take of Alcohol Activation, *Science*, 2010, **329**, 635–636.
6 A. Nandakumar, S. P. Midya, V. G. Landge and E. Balaraman, Transition-metal-catalyzed hydrogen-transfer annulations: access to heterocyclic scaffolds, *Angew. Chem., Int. Ed.*, 2015, **54**, 11022–11034.
7 X. Ma, C. Su and Q. Xu, in *Hydrogen Transfer Reactions: Reductions and Beyond*, ed. G. Guillena and D. J. Ramón, Springer International Publishing, Cham, 2016, pp. 291–364.
8 K.-i. Fujita, Z. Li, N. Ozeki and R. Yamaguchi, *N*-Alkylation of amines with alcohols catalyzed by a Cp*Ir complex, *Tetrahedron Lett.*, 2003, **44**, 2687–2690.
9 M. H. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. Watson and J. M. Williams, Ruthenium-catalyzed *N*-alkylation of amines and sulfonamides using borrowing hydrogen methodology, *J. Am. Chem. Soc.*, 2009, **131**, 1766–1774.
10 F. E. Fernandez, M. C. Puerta and P. Valerga, Ruthenium (II) Picolyl-NHC Complexes: Synthesis, Characterization, and Catalytic Activity in Amine *N*-alkylation and Transfer Hydrogenation Reactions, *Organometallics*, 2012, **31**, 6868–6879.
11 T. T. Dang, B. Ramalingam, S. P. Shan and A. M. Seayad, An Efficient Palladium-Catalyzed *N*-Alkylation of Amines Using Primary and Secondary Alcohols, *ACS Catal.*, 2013, **3**, 2536–2540.
12 M. Huang, Y. Li, J. Liu, X.-B. Lan, Y. Liu, C. Zhao and Z. Ke, A bifunctional strategy for N-heterocyclic carbene-stabilized

iridium complex-catalyzed N-alkylation of amines with alcohols in aqueous media, *Green Chem.*, 2019, **21**, 219–224.

13 S. Rosler, M. Ertl, T. Irrgang and R. Kempe, Cobalt-Catalyzed Alkylation of Aromatic Amines by Alcohols, *Angew. Chem., Int. Ed.*, 2015, **54**, 15046–15050.

14 M. Mastalir, G. Tomsu, E. Pittenauer, G. Allmaier and K. Kirchner, Co(II) PCP Pincer Complexes as Catalysts for the Alkylation of Aromatic Amines with Primary Alcohols, *Org. Lett.*, 2016, **18**, 3462–3465.

15 G. Zhang, Z. Yin and S. Zheng, Cobalt-Catalyzed *N*-Alkylation of Amines with Alcohols, *Org. Lett.*, 2016, **18**, 300–303.

16 M. Bala, P. K. Verma, U. Sharma, N. Kumar and B. Singh, Iron phthalocyanine as an efficient and versatile catalyst for *N*-alkylation of heterocyclic amines with alcohols: one-pot synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazoles, *Green Chem.*, 2013, **15**, 1687–1693.

17 T. Yan, B. L. Feringa and K. Barta, Iron catalysed direct alkylation of amines with alcohols, *Nat. Commun.*, 2014, **5**, 5602.

18 T. Yan, B. L. Feringa and K. Barta, Benzylamines via Iron-Catalyzed Direct Amination of Benzyl Alcohols, *ACS Catal.*, 2016, **6**, 381–388.

19 M. Vellakkaran, K. Singh and D. Banerjee, An Efficient and Selective Nickel-Catalyzed Direct *N*-Alkylation of Anilines with Alcohols, *ACS Catal.*, 2017, **7**, 8152–8158.

20 P. Yang, C. Zhang, Y. Ma, C. Zhang, A. Li, B. Tang and J. S. Zhou, Nickel-Catalyzed *N*-Alkylation of Acylhydrazines and Arylamines Using Alcohols and Enantioselective Examples, *Angew. Chem., Int. Ed.*, 2017, **56**, 14702–14706.

21 J. Das and D. Banerjee, Nickel-Catalyzed Phosphine Free Direct *N*-Alkylation of Amides with Alcohols, *J. Org. Chem.*, 2018, **83**, 3378–3384.

22 A. K. Bains, A. Kundu, S. Yadav and D. Adhikari, Borrowing Hydrogen-Mediated N-Alkylation Reactions by a Well-Defined Homogeneous Nickel Catalyst, *ACS Catal.*, 2019, **9**, 9051–9059.

23 S. Shee, D. Panja and S. Kundu, Nickel-Catalyzed Direct Synthesis of Quinoxalines from 2-Nitroanilines and Vicinal Diols: Identifying Nature of the Active Catalyst, *J. Org. Chem.*, 2020, **85**, 2775–2784.

24 M. Subaramanian, S. P. Midya, P. M. Ramar and E. Balaraman, General Synthesis of N-Alkylation of Amines with Secondary Alcohols via Hydrogen Autotransfer, *Org. Lett.*, 2019, **21**, 8899–8903.

25 G. E. Benitez-Medina and J. J. García, Hydrogenation and N-alkylation of anilines and imines via transfer hydrogenation with homogeneous nickel compounds, *Dalton Trans.*, 2019, **48**, 17579–17587.

26 G. Balamurugan, R. Ramesh and J. G. Malecki, Nickel(II)–NΛNΛO Pincer Type Complex-Catalyzed N-alkylation of Amines with Alcohols via the Hydrogen Autotransfer Reaction, *J. Org. Chem.*, 2020, **85**, 7125–7135.

27 V. Arora, M. Dutta, K. Das, B. Das, H. K. Srivastava and A. Kumar, Solvent-Free N-Alkylation and Dehydrogenative Coupling Catalyzed by a Highly Active Pincer-Nickel Complex, *Organometallics*, 2020, **39**, 2162–2176.

28 S. Elangovan, J. Neumann, J. B. Sortais, K. Junge, C. Darcel and M. Beller, Efficient and selective *N*-alkylation of amines with alcohols catalysed by manganese pincer complexes, *Nat. Commun.*, 2016, **7**, 12641.

29 A. Bruneau-Voisine, D. Wang, V. Dorcet, T. Roisnel, C. Darcel and J.-B. Sortais, Mono-*N*-methylation of anilines with methanol catalyzed by a manganese pincer-complex, *J. Catal.*, 2017, **347**, 57–62.

30 R. Fertig, T. Irrgang, F. Freitag, J. Zander and R. Kempe, Manganese-Catalyzed and Base-Switchable Synthesis of Amines or Imines via Borrowing Hydrogen or Dehydrogenative Condensation, *ACS Catal.*, 2018, **8**, 8525–8530.

31 M. Huang, Y. Li, Y. Li, J. Liu, S. Shu, Y. Liu and Z. Ke, Room temperature *N*-heterocyclic carbene manganese catalyzed selective *N*-alkylation of anilines with alcohols, *Chem. Commun.*, 2019, **55**, 6213–6216.

32 R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, Transition metal-catalysed *N*-alkylation of amines by alcohols, *J. Chem. Soc., Chem. Commun.*, 1981, 611–612.

33 Y. Watanabe, Y. Tsuji and Y. Ohsugi, The ruthenium catalyzed *N*-alkylation and *N*-heterocyclization of aniline using alcohols and aldehydes, *Tetrahedron Lett.*, 1981, **22**, 2667–2670.

34 L.-C. Yang, Y.-N. Wang, Y. Zhang and Y. Zhao, Acid-Assisted Ru-Catalyzed Enantioselective Amination of 1,2-Diols through Borrowing Hydrogen, *ACS Catal.*, 2017, **7**, 93–97.

35 K. O. Marichev and J. M. Takacs, Ruthenium-Catalyzed Amination of Secondary Alcohols using Borrowing Hydrogen Methodology, *ACS Catal.*, 2016, **6**, 2205–2210.

36 J. J. A. Celaje, X. Zhang, F. Zhang, L. Kam, J. R. Herron and T. J. Williams, A Base and Solvent-Free Ruthenium-Catalyzed Alkylation of Amines, *ACS Catal.*, 2017, **7**, 1136–1142.

37 B. C. Roy, S. Debnath, K. Chakrabarti, B. Paul, M. Maji and S. Kundu, ortho-Amino group functionalized 2,2′-bipyridine based Ru(ii) complex catalysed alkylation of secondary alcohols, nitriles and amines using alcohols, *Org. Chem. Front.*, 2018, **5**, 1008–1018.

38 K. Das, P. G. Nandi, K. Islam, H. K. Srivastava and A. Kumar, N–Alkylation of Amines Catalyzed by a Ruthenium–Pincer Complex in the Presence of in situ Generated Sodium Alkoxide, *Eur. J. Org. Chem.*, 2019, 6855–6866.

39 B. Yiğit, E. Ö. Karaca, M. Yiğit, N. Gürbüz, H. Arslan and İ. Özdemir, Active ruthenium(II)-NHC complexes for alkylation of amines with alcohols using solvent-free conditions, *Polyhedron*, 2020, **175**, 114234.

40 A. B. Enyong and B. Moasser, Ruthenium-Catalyzed *N*-Alkylation of Amines with Alcohols under Mild Conditions Using the Borrowing Hydrogen Methodology, *J. Org. Chem.*, 2014, **79**, 7553–7563.

41 V. R. Jumde, L. Gonsalvi, A. Guerriero, M. Peruzzini and M. Taddei, A Ruthenium-Based Catalytic System for a Mild Borrowing-Hydrogen Process, *Eur. J. Org. Chem.*, 2015, 1829–1833.

42 G. C. Vougioukalakis and R. H. Grubbs, Ruthenium-based heterocyclic carbene-coordinated olefin metathesis catalysts, *Chem. Rev.*, 2010, **110**, 1746–1787.

43 C. A. Wheaton, J. P. J. Bow and M. Stradiotto, New Phosphine-Functionalized NHC Ligands: Discovery of an Effective Catalyst for the Room-Temperature Amination of Aryl Chlorides with Primary and Secondary Amines, *Organometallics*, 2013, **32**, 6148–6161.

44 S. G. Rull, R. J. Rama, E. Alvarez, M. R. Fructos, T. R. Belderrain and M. C. Nicasio, Phosphine-functionalized NHC Ni(ii) and Ni(0) complexes: synthesis, characterization and catalytic properties, *Dalton Trans.*, 2017, **46**, 7603–7611.

45 S. H. Nazari, J. E. Bourdeau, M. R. Talley, G. A. Valdivia-Berroeta, S. J. Smith and D. J. Michaelis, Nickel-Catalyzed Suzuki Cross Couplings with Unprotected Allylic Alcohols Enabled by Bidentate *N*-Heterocyclic Carbene (NHC)/Phosphine Ligands, *ACS Catal.*, 2017, **8**, 86–89.

46 X. Xie and H. V. Huynh, Tunable Dehydrogenative Amidation versus Amination Using a Single Ruthenium-NHC Catalyst, *ACS Catal.*, 2015, **5**, 4143–4151.

47 J.-Q. Li and P. G. Andersson, Room temperature and solvent-free iridium-catalyzed selective alkylation of anilines with alcohols, *Chem. Commun.*, 2013, **49**, 6131–6133.

48 X.-B. Lan, Z. Ye, M. Huang, J. Liu, Y. Liu and Z. Ke, Nonbifunctional Outer-Sphere Strategy Achieved Highly Active α-Alkylation of Ketones with Alcohols by N-Heterocyclic Carbene Manganese (NHC-Mn), *Org. Lett.*, 2019, **21**, 8065–8070.

49 G. Frenking, M. Solà and S. F. Vyboishchikov, Chemical bonding in transition metal carbene complexes, *J. Organomet. Chem.*, 2005, **690**, 6178–6204.

50 L. Falivene and L. Cavallo, Theoretical NMR spectroscopy of *N*-heterocyclic carbenes and their metal complexes, *Coord. Chem. Rev.*, 2017, **344**, 101–114.

51 D. Setiawan, R. Kalescky, E. Kraka and D. Cremer, Direct Measure of Metal-Ligand Bonding Replacing the Tolman Electronic Parameter, *Inorg. Chem.*, 2016, **55**, 2332–2344.

52 A.-E. Wang, J.-H. Xie, L.-X. Wang and Q.-L. Zhou, Triaryl phosphine-functionalized *N*-heterocyclic carbene ligands for Heck reaction, *Tetrahedron*, 2005, **61**, 259–266.

53 S. Bai, C. Bu, Q. Tai, L. Liang, Y. Liu, S. You, Z. Yu, S. Guo and X. Zhao, Effects of Bis(imidazolium) Molten Salts with Different Substituents of Imidazolium Cations on the Performance of Efficient Dye-Sensitized Solar Cells, *ACS Appl. Mater. Interfaces*, 2013, **5**, 3356–3361.

54 L. Canovese, F. Visentin, C. Levi, C. Santo and V. Bertolasi, The interaction between heteroditopic pyridine–nitrogen NHC with novel sulfur NHC ligands in palladium(0) derivatives: Synthesis and structural characterization of a bis-carbene palladium(0) olefin complex and formation in solution of an alkene–alkyne mixed intermediate as a consequence of the ligands hemilability, *Inorg. Chim. Acta*, 2012, **390**, 105–118.

55 S. Gründemann, A. Kovacevic, M. Albrecht, J. W. Faller and R. H. Crabtree, Abnormal Ligand Binding and Reversible Ring Hydrogenation in the Reaction of Imidazolium Salts with $IrH_5(PPh_3)_2$, *J. Am. Chem. Soc.*, 2002, **124**, 10473–10481.

56 J. Trampert, Y. Sun and W. R. Thiel, The reactivity of [{2-(diphenylphosphino)phenyl}methyl]-3-imidazol-2-ylidenes towards group VIII element precursors, *J. Organomet. Chem.*, 2020, **915**, 121222.

57 J. H. Dam, G. Osztrovszky, L. U. Nordstrom and R. Madsen, Amide synthesis from alcohols and amines catalyzed by ruthenium *N*-heterocyclic carbene complexes, *Chem. – Eur. J.*, 2010, **16**, 6820–6827.

58 J. A. Cabeza, M. Damonte, P. García-Álvarez, M. G. Hernández-Cruz and A. R. Kennedy, Reactivity of Phosphine- and Thioether-Tethered N-Heterocyclic Carbenes with Ruthenium Carbonyl, *Organometallics*, 2012, **31**, 327–334.

59 T. T. Dang, B. Ramalingam and A. M. Seayad, Efficient Ruthenium-Catalyzed *N*-Methylation of Amines Using Methanol, *ACS Catal.*, 2015, **5**, 4082–4088.

60 Z. Liu, Z. Yang, X. Yu, H. Zhang, B. Yu, Y. Zhao and Z. Liu, Efficient Cobalt-Catalyzed Methylation of Amines Using Methanol, *Adv. Synth. Catal.*, 2017, **359**, 4278–4283.

61 W.-H. Lin and H.-F. Chang, A study of ethanol dehydrogenation reaction in a palladium membrane reactor, *Catal. Today*, 2004, **97**, 181–188.

62 S. Michlik, T. Hille and R. Kempe, The Iridium-Catalyzed Synthesis of Symmetrically and Unsymmetrically Alkylated Diamines under Mild Reaction Conditions, *Adv. Synth. Catal.*, 2012, **354**, 847–862.

63 H. Yang, R. Mao, C. Luo, C. Lu and G. Cheng, An efficient homogeneous gold(I) catalyst for *N*-alkylation of amines with alcohols by hydrogen autotransfer, *Tetrahedron*, 2014, **70**, 8829–8835.

64 A. Bartoszewicz, G. G. Miera, R. Marcos, P. O. Norrby and B. Martin-Matute, Mechanistic Studies on the Alkylation of Amines with Alcohols Catalyzed by a Bifunctional Iridium Complex, *ACS Catal.*, 2015, **5**, 3704–3716.

65 F. Kallmeier, R. Fertig, T. Irrgang and R. Kempe, Chromium-Catalyzed Alkylation of Amines by Alcohols, *Angew. Chem.*, 2020, **59**, 11789–11793.

66 S. P. Shan, X. Xiaoke, B. Gnanaprakasam, T. T. Dang, B. Ramalingam, H. V. Huynh and A. M. Seayad, Benzimidazolin-2-ylidene *N*-heterocyclic carbene complexes of ruthenium as a simple catalyst for the *N*-alkylation of amines using alcohols and diols, *RSC Adv.*, 2015, **5**, 4434–4442.

67 S. Shu, M. Huang, J. Jiang, L.-B. Qu, Y. Liu and Z. Ke, Catalyzed or non-catalyzed: chemoselectivity of Ru-catalyzed acceptorless dehydrogenative coupling of alcohols and amines via metal–ligand bond cooperation and (de) aromatization, *Catal. Sci. Technol.*, 2019, **9**, 2305–2314.