ChemPubSoc Europe

DOI: 10.1002/cctc.201300971

Reusable Supported Ruthenium Catalysts for the Alkylation of Amines by using Primary Alcohols

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Efficient and recyclable ruthenium catalysts were synthesized from readily available polystyrene- or silica-supported phosphine ligands. Catalysts bound to the polymer support through an ether linkage showed good to excellent activity towards the *N*-alkylation of primary and secondary amines to afford the alkylated products in 62–99% yield at 120–140 °C. The supported phosphine ligand/ruthenium ratio was found to be crucial for higher catalytic activity and lower ruthenium leaching. The continuous flow *N*-alkylation of amines was demonstrated by using the supported catalyst in a column reactor. By adopting the hydrogen-borrowing strategy, the synthesis of the anti-Parkinson agent Piribedil was established in 98% yield at 140 °C.

Introduction

Substituted amines are widely used as building blocks in the agrochemical, dye, and detergent industries.[1] They also serve as pharmacophores in biologically important pharmaceutical products,[2] and *N*-alkylation has been frequently exploited by pharmaceutical industries for nitrogen-substitution reactions. Carey and co-workers[3] estimated that 64% of all nitrogen-substitution reactions performed at the process research and development stage at Astra Zeneca, GlaxoSmithKline, and Pfizer fall into the *N*-alkylation category, and 36% of them use genotoxic/mutagenic organic halides. Organic halides were traditionally obtained from nonhazardous alcohols and were used as electrophiles for further alkylation of primary and secondary amines. Alternatively, the alcohols could be utilized directly as electrophiles for *N*-alkylation reactions by using transition-metal catalysts adopting the "hydrogen-borrowing" strategy.[4] Under this methodology, the alcohols are activated to an active carbonyl compound by dehydrogenation. The in situ formed carbonyl compound reacts with an amine to form an imine intermediate, which undergoes hydrogenation to form the corresponding amine product by using the borrowed hydrogen. The overall process is redox neutral and water is the only byproduct. Adopting this strategy, Grigg[5] and Watanabe[6] independently reported the *N*-alkylation of amines by using $RhH(PPh_3)_4$ and $RuCl_2(PPh_3)_3$, respectively, for the first time. Subsequently, a number of Ru[7] and Ir[8] catalysts have been reported, and they were proven to be effective for the alkylation of both amines and carbonyl compounds under homogenous reaction conditions. Catalysts derived from other metals, such as Cu,[9] Fe,[10] Os,[11] and Rh,[12] have also been explored. Though progress made in the alkylation of alcohols by homogeneous catalysts is significantly remarkable, the recovery of the products from the reaction mixture often requires more effort and becomes increasingly tedious in large-scale processes.

The interest in developing recyclable heterogeneous catalysts is consistently increasing owing to their ease of handling and operational simplicity. Adopting the hydrogen-borrowing strategy, Shimizu and co-workers[13] reported alumina-supported Ni nanoparticles as a heterogeneous catalyst for the *N*-alkylation of amines at 144 °C. Under these conditions, the *N*-alkylation of primary and secondary amines was performed effectively to provide the alkylated products in 74–99% yield. Up to 96% yield was reported by Cao et al. for the formation of secondary amines from selected substituted anilines by using Au/TiO_2[14] at 120 °C in toluene. However, a higher reaction temperature (140 °C) and a long reaction time (50 h) were needed for the alkylation of cyclic amines such as pyrrolidine. A supported bimetallic Pt–Sn[15] catalyst was employed for the *N*-alkylation of diols at 145 °C to afford the substituted diamines in 20–94% yield. Other heterogeneous catalysts such as Pd/MgO, Cu–Ag/Al_2O_3, γ-Al_2O_3/Ag, NiCu–FeO_x, CuAl–hydrotalcite, and $Ru(OH)_x/Al_2O_3$ are also known[16] for the alkylation of aniline derivatives at temperatures >135 °C. In the presence of an excess amount of KOH (130 mol%), impregnated ruthenium on magnetite $[Ru(OH)_3–Fe_3O_4]$[17] catalyzed the *N*-alkylation of substituted anilines in 71–99% yield at 130 °C. Ag/Al_2O_3[18] catalysts were found to be active in the presence of Cs_2CO_3 (30 mol%) for the *N*-alkylation of anilines at 120 °C and gave up to 99% yield. An iridium catalyst derived from a mesoporous silica (SBA-15)-supported N-heterocyclic carbene[19] ligand gave good to excellent yields (58–99%) at 110 °C for both the *N*-alkylation of amines and the β-alkylation of secondary alcohols in the presence of

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201300971. It contains the experimental procedures for the α-alkylation of methyl ketones and continuous flow alkylation and the product characterization data.

KOH (100 mol%). The catalyst was recycled 12 times without any significant loss in catalytic activity, and no detectable level of metal leaching was reported. In the presence of *t*BuOK (200 mol%), Fe_2O_3 catalyzed[20] the alkylation of aromatic amines with benzylic alcohols to form the alkylated products in 33–99% yield at 90 °C with a reaction times of 7–10 days.

In general, the reported heterogeneous catalysts require either higher reaction temperatures (>140 °C) or the presence of a base to achieve higher yields of N-alkylated products. Major hurdles that still need to be overcome in hydrogen-borrowing methodology with the use of heterogeneous catalysts are:

1) The high reaction temperature,
2) The use of strong base,
3) The narrow substrate scope,[21]
4) The limited accessibility to reusable catalysts that are obtained from readily available supported ligands.

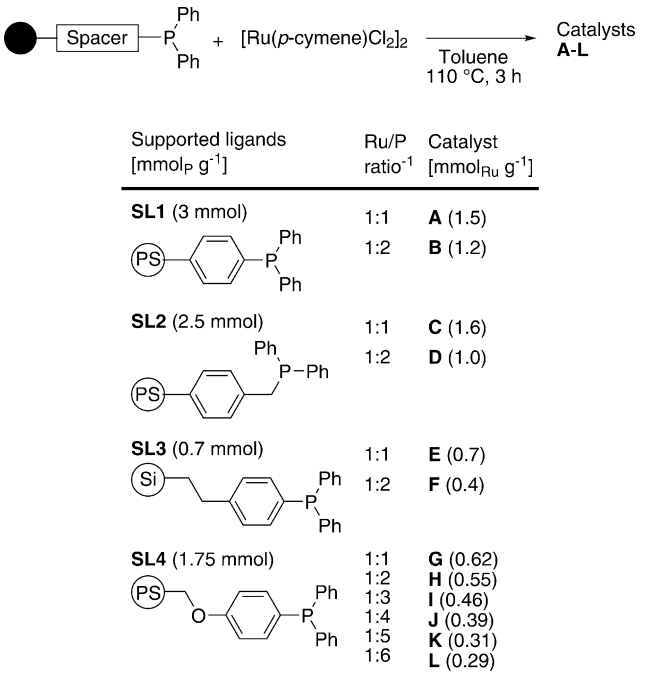
Here, we report a promising reusable catalyst for the *N*-alkylation of amines by using alcohols at moderate temperatures in the absence of an external base. Interestingly, the catalysts obtained from triphenylphosphine bound to the polymer support through an ether linkage showed superior activity towards the alkylation of both primary and secondary amines. The catalyst was easy to recover and was recycled over five runs; it also showed very low ruthenium leaching. The catalyst was used in a packed-bed reactor, and the *N*-alkylation of piperidine was demonstrated under continuous flow.

Results and Discussion

Catalyst synthesis and reaction optimization

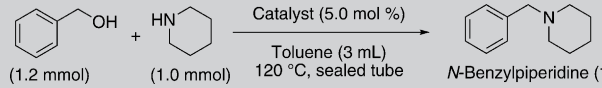
For the present study, supported catalysts **A**–**L** were obtained from commercially available supported phosphine ligands SL**1**–SL**4** and $[Ru(p\text{-cymene})_2Cl_2]_2$. As shown in Scheme 1, catalysts **A**, **C**, **E**, and **G** were prepared from an equimolar ratio of the supported ligand and ruthenium, whereas the phosphine ratio was doubled to obtain catalysts **B**, **D**, **F**, and **H**. Ruthenium incorporation was determined by inductively coupled plasma (ICP) analysis (see Table S1, Supporting Information). The following important points were observed from the initial screening of catalysts **A**–**H** (5 mol%) for the alkylation of piperidine by using benzyl alcohol at 120 °C in toluene (Table 1, entries 1–8):

1) Catalysts **G** and **H** obtained from SL**4** gave a better yield of 87 and 91% (Table 1, entries 7 and 8), respectively, than the other catalysts.
2) Catalysts obtained with Ru/P = 1:2, as in **B**, **D**, **F**, and **H**, gave better yields than the corresponding 1:1 analogues, that is, **A**, **C**, **E**, and **G** (Table 1, entries 2, 4, 6, 8 vs. 1, 3, 5, 7).
3) Ruthenium leaching for catalyst **G** (125 ppm; Table 1, entry 7) was higher than that for catalyst **H** (99 ppm; Table 1, entry 8); this suggests the benefit of having a higher number of equivalents of the phosphine in minimizing ruthenium leaching.



Scheme 1. Catalyst synthesis from commercially available supported phosphine ligands. PS = polystyrene, Si = silica.

Table 1. Initial catalyst screening and optimization of the reaction conditions.



Entry	Catalyst	Solvent	*t* [h]	Yield of **1** [%][a]	Ruthenium leaching [ppm][b]
1	**A**	toluene	12	55	–
2	**B**	toluene	12	60	–
3	**C**	toluene	12	26	–
4	**D**	toluene	12	40	–
5	**E**	toluene	12	57	–
6	**F**	toluene	12	65	–
7	**G**	toluene	12	87	125
8	**H**	toluene	12	91	99
9	**I**	toluene	12	>99 (82)[c]	12
10	**J**	toluene	5	>99 (21)[d]	5
11	**K**	toluene	5	>99 (27)[d]	2
12	**L**	toluene	5	>99 (36)[d]	2
13	**L**	diglyme	12	31	–
14	**L**	dioxane	12	40	–
15	**L**	water	12	n.r.[e]	–
16	**L**	toluene	5	24[f]	–
17	–	toluene	12	n.r.[e]	–

[a] Determined by gas chromatography by using hexadecane as an internal standard. [b] Calculated from ICP analysis. [c] Yield obtained after 5 h. [d] Yield obtained after 1 h. [e] No reaction; benzyl alcohol remained unreacted. [f] Reaction at 100 °C.

Accordingly, catalysts **I**–**L** (Scheme 1) were synthesized by using SL**4**, and their use in *N*-alkylation reactions was explored

further. To our delight, upon increasing the Ru/P ratio to 1:3 as in catalyst **I**, a quantitative yield of **1** was obtained (Table 1, entry 9) in 12 h. Additionally, ruthenium leaching was significantly reduced (Table 1, entry 8 vs. 9) from 99 to 12 ppm with the higher amount of phosphine. A further increase in the Ru/P ratio to 1:4 (for **J**), 1:5 (for **K**), and 1:6 (for **L**) had a clear influence on the catalytic activity and in minimizing ruthenium leaching (Table 1, entries 10 and 11). The catalytic reaction was complete in 5 h upon employing catalysts **J**–**L** (5 mol%; Table 1, entries 10–12). Although catalysts **J**–**L** showed similar catalytic activity, **L** gave a higher yield of the product (36%; Table 1, entry 12) than both **J** (21%; Table 1, entry 10) and **K** (27%; Table 1, entry 11) in 1 h. Hence, catalyst **L** was selected for further studies. Upon performing the catalytic reaction in ether solvents such as diglyme and dioxane at 120 °C, product **1** was obtained in only 31 (Table 1, entry 13) and 40% yield (Table 1, entry 14), respectively. No reaction was observed in water (Table 1, entry 15) as the solvent.

Reducing the reaction temperature to 100 °C (Table 1, entry 16) led to a poor yield of **1**. Among catalysts **G**–**L** that were derived from SL**4**, **L** showed the highest activity and **G** was the least active. The higher activity of **L** may be due to the greater stabilization of the ruthenium center in the presence of a higher percentage of phosphine. Scanning electron microscopy (SEM) analysis of catalyst beads **G** and **L** before and after the reaction[22] (Figures S1–S3, Supporting Information) indicated that the surface of **L** was largely unchanged after the reaction, whereas **G** suffered under the reaction conditions.[22]

Catalyst recycling studies

The recyclability of catalyst **L** was examined by its use (5 mol%) in the benzylation of piperidine under the optimized reaction conditions (Figure 1). After a reaction time of 4 h, the catalyst was recovered and reused over five runs without a significant loss in activity. Ruthenium leaching was determined by ICP analysis after each cycle and was found to be significantly low (< 2.5 ppm). To understand the heterogeneous nature of the catalyst, catalyst **L** was removed from the reaction mixture after 2 h, and the yield of product **1** was 37%. No further clear change in the product yield (39%) was observed upon continuing the reaction for an additional 12 h without catalyst **L** at 120 °C. Further, ICP analysis of the reaction mixture obtained by hot filtration showed only < 2 ppm ruthenium leaching. All these observations indicate that the catalytic reaction mainly proceeds in the presence of a heterogeneous catalyst and may not be due to a trace amount of ruthenium leached into the reaction mixture.

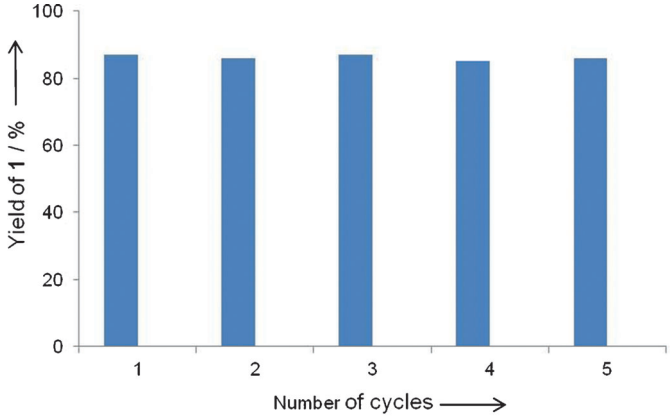
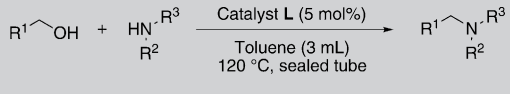


Figure 1. Recycling studies by using catalyst **L** (5 mol%). Reactions were performed with benzyl alcohol (1.2 mmol) and piperidine (1 mmol) in toluene (3 mL) at 120 °C for 4 h.

Alkylation of secondary amines

The alkylation of cyclic amines was performed by using different primary alcohols under the optimized reaction conditions in the presence of catalyst **L** (Table 2). We focused our attention on the alkylation of various secondary amines, as they are

Table 2. Substrate scope for the alkylation of secondary amines by using catalyst **L**.[a]



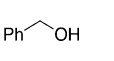
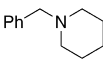
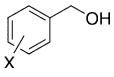
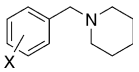
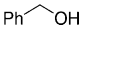
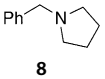
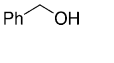
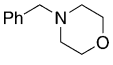
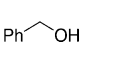
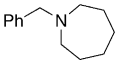
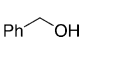
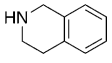
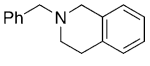
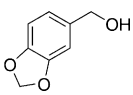
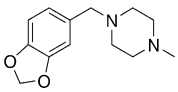
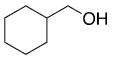
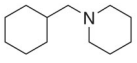
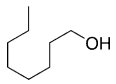
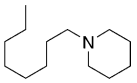
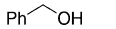
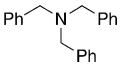
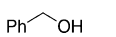
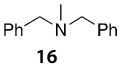
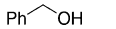
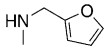
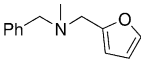
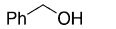
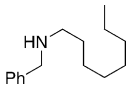
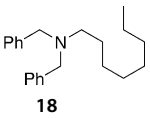
Entry	Alcohol	Amine	Product	Yield [%][b]
1			 **1**	94 (5 h)
2				
			X = *p*-Me (**2**)	86 (20 h)
3			*p*-OMe (**3**)	96 (20 h)
4			*p*-F (**4**)	98 (20 h)
5			*p*-Cl (**5**)	99 (20 h)
6			*p*-Br (**6**)	65 (20 h)
7			*o*-OMe (**7**)	90 (20 h)
8			 **8**	70 (24 h)
9			 **9**	87 (18 h)
10			 **10**	79 (24 h)
11			 **11**	89 (24 h)
12			 **12**	95 (24 h)
13			 **13**	94 (24 h)

Table 2. (Continued)

Entry	Alcohol	Amine	Product	Yield [%][b]
14			 **14**	78 (24 h)
15			 **15**	68 (30 h)
16			 **16**	95 (24 h)[c]
17			 **17**	68 (24 h)[c]
18			 **18**	64 (24 h)[c]

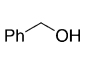
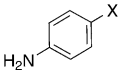
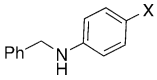
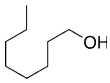
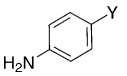
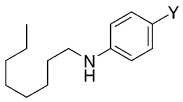
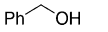
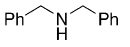
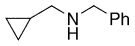
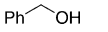
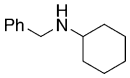
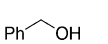
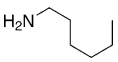
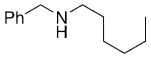
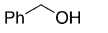
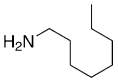
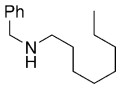
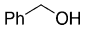
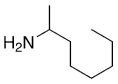
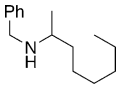
[a] Reactions were performed with the alcohol (1.2 mmol) and amine (1 mmol). [b] Yield of isolated product; the reaction time is given in parentheses. [c] Reactions were performed at 140 °C.

generally poorer substrates[21] under the hydrogen-borrowing strategy as a result of the involvement of an disfavored iminium intermediate. Substituted benzyl alcohols with electron-donating and electron-withdrawing groups reacted with piperidine to give products **2**–**6** in high yields (Table 2, entries 2–6). The presence of a OMe group at the *ortho* position did not affect the reactivity of the alcohols towards piperidine, and alkylated product **7** was obtained in 90% yield (Table 2, entry 7). Other cyclic amines such as pyrrolidine, morpholine, azepane, tetralin, and 1-methylpiperazine were benzylated to respective tertiary amines **8**–**12** in good to excellent yields (Table 2, entries 8–12). Importantly, alkylated products **13** and **14** were obtained in 94 (Table 2, entry 13) and 78% yield (Table 2, entry 14), respectively, from more challenging aliphatic alcohols such as cyclohexylmethanol and 1-octanol. Tertiary amines **15**–**18** were isolated in 64–95% yield from acyclic secondary amines (Table 2, entries 15–18).

Alkylation of primary amines

The catalyst also showed good activity towards the alkylation of primary amines. Aniline and substituted anilines were benzylated to secondary amines **19**–**21** (Table 3, entries 1–3) in good yields. Notably, more challenging 1-octanol was also used as an electrophilic partner for the alkylation of anilines and afforded alkylated products **22**–**24** in 67–88% yield (Table 3, entries 4–6). Benzylamine was alkylated by using benzyl alcohol and cyclopropylmethanol to give secondary amines **25** (Table 3, entry 7) and **26** (Table 3, entry 8), respectively. α-Branched cyclohexanamine was benzylated to product **27** in 87% yield at 140 °C (Table 3, entry 9). Linear aliphatic

Table 3. Substrate scope for the alkylation of primary amines by using catalyst **L**.[a]

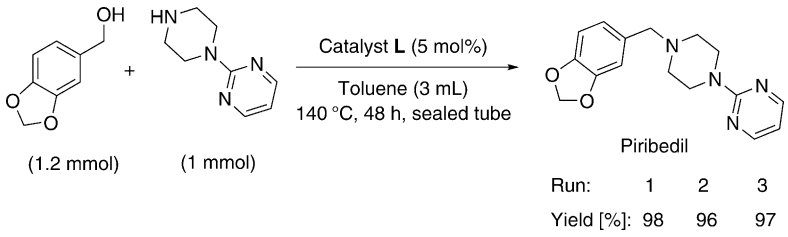
Entry	Alcohol	Amine	Product	Yield [%][b]
1			 X = H (**19**)	69
2			CH_3 (**20**)	86
3			Cl (**21**)	82
4			 Y = H (**22**)	88
5			CH_3 (**23**)	86
6			OCH_3 (**24**)	67
7			 **25**	63[c,d]
8			 **26**	90[c]
9			 **27**	87[c]
10			 **28**	77
11			 **29**	84
12			 **30**	73

[a] Reactions were performed with the alcohol (1.2 mmol) and amine (1 mmol) in toluene (3 mL) by using catalyst **L** (5 mol%). [b] Yield of isolated product after 24 h at 120 °C. [c] Reaction was performed at 140 °C. [d] Approximately 8% of tribenzylamine was identified together with **25** in the crude reaction mixture.

amines were alkylated to secondary amines **28**–**30** in 73–84% yield (Table 3, entries 10–12). Secondary alcohols such as 1-phenylethanol and 1-(naphthalen-2-yl)ethanol gave only <30% yield for the alkylation of piperidine in 48 h.

Piribedil synthesis

Further, the use of catalyst **L** was demonstrated in the synthesis[23] of piribedil, which is used for the treatment of Parkinson's disease. 1-(Pyrimidin-2-yl)piperazine was directly alkylated in nearly quantitative yield by using piperonyl alcohol (Scheme 2). After the initial run, the catalyst was recovered by simple filtration and reused in two subsequent runs effectively with comparable yields in each cycle.

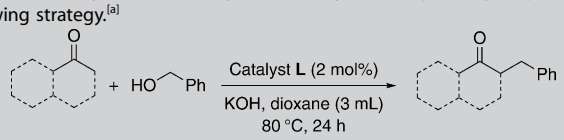


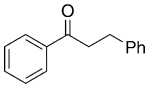
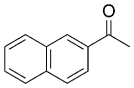
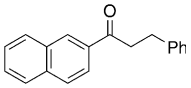
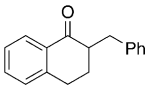
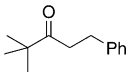
Scheme 2. Synthesis of piribedil by using catalyst **L**.

α-Alkylation of methyl ketones

The activity of catalyst **L** was also examined in C–C bond-forming reactions by adopting the hydrogen-borrowing strategy. The alkylation of methyl ketones was performed with benzyl alcohol under the conditions described in the literature for the homogeneous $RuCl_2(PPh_3)_3$ catalyst.[24] In the presence of catalyst **L** (2 mol%), alkylated products **31**–**34** were obtained in 60–78% yield (Table 4). The preliminary results obtained with the current catalyst system under the unoptimized conditions show the broad applicability of the catalyst for reactions in which alcohols can be used as alkylating agents.

Table 4. α-Alkylation of methyl ketones by adopting the hydrogen-borrowing strategy.[a]



Entry	Ketone	Product	Yield [%][b]
1		 **31**	65
2		 **32**	60
3		 **33**	78
4		 **34**	73

[a] Reactions were performed with the alcohol (1 mmol), amine (1.1 mmol), and KOH (1 mmol). [b] Yield of isolated product.

Continuous flow *N*-alkylation

Developing continuous flow methodology would be more practical if dealing with heterogeneous catalysts, and only a few reports are available for the alkylation of amines under continuous flow. Recently, Hii and co-workers[25] reported the alkylation of aromatic, aliphatic, and chiral amines in 59–99% yield by using a Au/TiO_2 catalyst under flow conditions at temperatures >180 °C. The *N*-alkylation of morpholine with benzyl alcohol by using supported ruthenium catalysts in a fixed-bed reactor was reported.[26] A high conversion (>98%) was achieved by using *p*-xylene as the solvent at 150 °C. The efficient recyclability and low ruthenium leaching of catalyst **L** encouraged us to use it in a packed-bed reactor for performing the *N*-alkylation reaction under continuous flow (Figure 2a). For the initial studies, supported catalyst **L**

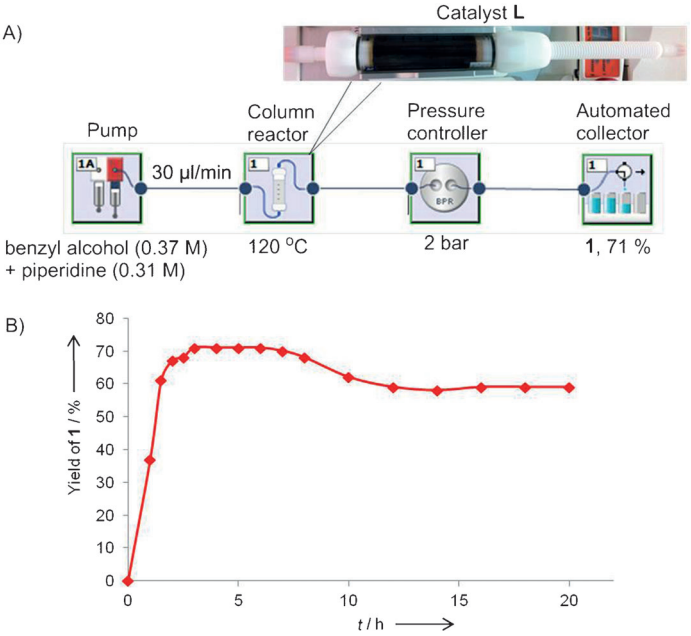


Figure 2. a) Fluidic setup for the continuous flow benzylation of piperidine. b) Reaction progress towards the formation of **1** with respect to time.

(1.20 g) was packed in a column reactor (6.6 mm diameter × 80 mm length); a mixture of benzyl alcohol (0.37 M) and piperidine (0.31 M) in toluene was then infused (20 µL min^{-1}) through the reactor at 120 °C with a back pressure of 2 bar (2 bar = 200 kPa). Fractions were collected at regular intervals for GC analysis. With a residence time of approximately 30 min, 30% of benzyl alcohol was converted into product **1**. To increase the residence time, catalyst **L** (5.8 g) was packed into a bigger reactor (16 mm diameter × 80 mm length), and the premixed reagents were infused at a flow rate of 30 µL min^{-1} (residence time ≈ 90 min). Notably, the reaction proceeded smoothly for approximately 6 h after reaching a steady state to form **1** in 71% yield (Figure 2b). We found that the yield slowly decreased to 59% over a period of 5 h and remained constant for an additional 10 h. The total turnover number was calculated to be 74 for 21 h of reaction. Interestingly, ruthenium leaching in the combined fractions was

found to be lower (<1 ppm) than that in the batch reaction. Currently, we are exploring the application of the catalyst bed for other pharmaceutically important drug intermediates.

Conclusions

In summary, a robust ruthenium-based catalyst was developed from readily available supported phosphine ligands. The *N*-alkylation of primary and secondary amines was performed at a moderate reaction temperature relative to that required for existing heterogeneous catalysts in the absence of any external base. The catalyst was shown to be effective for the α-alkylation of cyclic and acyclic methyl ketones. The supported catalyst was not only recyclable under batch, but it also offered a short residence time and low ruthenium leaching under flow conditions for the *N*-alkylation of piperidine. The current heterogeneous catalyst offers a highly atom efficient method for producing secondary and tertiary amines in a more sustainable manner.

Experimental Section

Synthesis of catalysts

Catalyst **A** was prepared by using an equimolar ratio of ruthenium and supported phosphine ligand SL**1**. A mixture of [Ru(*p*-cymene)Cl_2]$_2$ (306.2 mg, 0.5 mmol) and SL**1** 0.33 g, 1.0 mmol) was stirred in toluene (15 mL) at 110 °C for 3 h. After cooling, the supported catalyst was filtered and washed with toluene (3×10 mL) and pentane (3×10 mL). The catalyst obtained was dried overnight under vacuum at 100 °C and stored in a desiccator. The filtrate and washings were combined, and the volatiles were removed under reduced pressure. The residue was dissolved in concentrated nitric acid, and the ruthenium content was calculated by ICP analysis (Table S1). Accordingly, the amount of ruthenium incorporated into the polymer was calculated on the basis of the unreacted ruthenium present in the filtrate. Catalysts **B**–**L** were synthesized by varying the supported phosphine ligands (SL**1**–SL**4**) and their ratios by adopting the above procedure.

General procedure for the alkylation of amines

Dry toluene (3 mL) was added to a mixture of amine (1.00 mmol), alcohol (1.20 mmol), and catalyst **L** (0.19 g, 0.05 mmol) in a pressure tube (10 mL), which was then sealed. The reaction tube was heated to the required reaction temperature (120–140 °C) in an oil bath with constant stirring (500 rpm). The filtrate was concentrated, and the crude product was purified by column chromatography. For recycling studies, the catalyst was recovered by filtration and washed with toluene (2 mL) and pentane (5 mL) after the reaction mixture was cooled to room temperature.

Acknowledgements

*This work was funded by the GSK-EDB Singapore Partnership for Green and Sustainable Manufacturing and the Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology and Research (A*STAR), Singapore.*

Keywords: alcohol activation · alkylation · continuous flow · hydrogen borrowing · supported catalysts

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[22] To examine the change in catalyst morphology under identical conditions, benzylation of piperidine was performed by using catalysts **G** and **L** at 120 °C in 3 mL of toluene. After 12 h, the recovered catalysts were analyzed by SEM and compared with that of fresh catalysts.

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Received: November 12, 2013
Revised: December 10, 2013
Published online on January 27, 2014