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ARTICLE

An Efficient Heterogenized Palladium Catalyst for N-Alkylation of Amines and α -Alkylation of Ketones Using Alcohols

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Silica supported palladium NiXantphos complex is reported as an efficient and a high turnover heterogeneous catalyst for the N-alkylation of amines and the α -alkylation of ketones using readily available alcohols under neat conditions at 120 – 140 °C following hydrogen borrowing strategy. The catalyst is easily separable and offers negligible amount of palladium leaching (<0.01 ppm). A high turnover number of about 46000 for the N-alkylation of amines and 4400 for the α -alkylation of ketones were achieved in the respective single batch reactions. The catalyst is recyclable up to four times without appreciable change in catalytic performance.

Introduction

C–N and C–C bond forming reactions are two indispensable transformations in organic synthesis as well as pharmaceutical and fine chemical industries.¹ Conventional alkylation methods that utilizes reactive and toxic alkyl halides have been in practice for the past several decades as the most convenient method for the synthesis of alkylated amines and α -alkylated ketones.² This method often produces over-alkylated products causing selectivity issues that not only reduces the overall yield of the desired product but also poses separation issues apart from generating toxic halogenated waste, which needs further downstream processing. Under this context, utilization of readily available and less-toxic alcohols as alkylating agents following the recently developed catalytic hydrogen borrowing strategy³ offers a green and sustainable alternative method for the direct alkylation of amines and ketones.

Ru⁴ and Ir⁵ remain to be the preferred choice of metals for developing promising catalysts for the direct alkylation of amines using alcohols under homogeneous reaction conditions. Other metals such as Rh,⁶ Au,⁷ Cu,⁸ Fe,⁹ Pd¹⁰ and Os¹¹ were also reported as alternative catalysts. Although, these developments in homogeneous catalysts are remarkable achieving turn-over-numbers (TON) up to 1000,^{10a} several heterogeneous catalysts were also reported¹² to address the

catalyst-product separation and recycle issues. Apart from the requirement of stringent conditions, and limited substrate scope with most of these heterogeneous catalyst systems, the main drawback is the low turnover numbers, which limit their potential applications.

Supported metal nanoparticles, oxides and hydroxides of Ru,¹³ Ir,¹⁴ Au,¹⁵ Ag,¹⁶ Pd,¹⁷ Ni,¹⁸ Cu,¹⁹ Fe,²⁰ and Mn,²¹ as well as unmodified magnetite²² were reported to be promising heterogeneous catalysts for N-alkylation using various alcohols at temperatures of 100 – 180 °C to achieve 50 – 98% yields. An improved TON of about 11,800 was reported using Au/TiO₂ catalyst at 180 °C for 96 h.^{15e} Under similar condition, a TON of 570 was reported using Pd/MgO^{17e} as a solid catalyst for the mono-alkylation of aniline in trifluorotoluene. Bimetallic heterogeneous catalysts²³ were also reported for N-alkylation of amines using alcohols as well as diols. The metal leaching and the recyclability of many of these heterogeneous catalysts are not well reported.

Heterogenization of active homogeneous catalysts is another approach²⁴ to circumvent the separation and recyclability problems associated with efficient homogeneous catalysts. Accordingly, heterogenization of an active N-heterocyclic carbene (NHC) iridium complex on mesoporous silica (SBA-15)^{14b} was reported for the N-alkylation of amines and β -alkylation of secondary alcohols in the presence of 50 mol % a base. Though the catalyst gave high yields at 110 °C for 24 – 48 h and was recyclable, the catalyst loading was high (1.5 mol %) that limits the TON (<70). Recently, we have developed a reusable ruthenium catalyst^{13a} for the N-alkylation of amines at 120 °C under batch (5 h) and continuous flow conditions (30 min residence-time). In our continued effort to develop efficient heterogeneous catalyst systems, herein we report a

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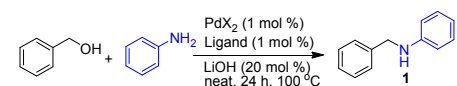
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silica supported palladium NiXantphos complex as an efficient and high turnover catalyst for the alcohol activation towards *N*- and *C*- alkylation reactions.

Results and discussion

In our previous work,^{10a} we have reported an *in situ* formed homogeneous palladium catalyst from PdCl₂ and a bidentate phosphine ligand such as dppe, Xantphos(*t*-Bu), etc., as an efficient catalyst for the *N*-alkylation of amines under relatively mild operating conditions. In order to select a suitable bidentate ligand for the facile anchoring on readily available and inexpensive solid supports, such as silica, to develop the corresponding heterogeneous analogue, we have further screened other promising bidentate ligands for the *N*-alkylation of aniline using benzyl alcohol and the representative results are given in Table 1. We have observed that XantPhos(*t*-Bu) is still one of the best bidentate ligands screened giving near quantitative yield of the *N*-alkylated product at 100 °C for 24 h (entry 3). The corresponding commercially available NiXantPhos, which is easy to anchor through the free N-H group, gave a promising yield of 86% (entry 6). To our delight, quantitative yield was achieved (entry 7) when the free N-H group of NiXantPhos was protected using alkyl groups such as *n*-Bu to mimic the tethering group for anchoring to the solid support. Under homogeneous conditions, PdCl₂ gave higher performance compared to that of Pd(OAc)₂ (entry 7 vs 8). Encouraged by these results, NiXantphos was selected as the potential ligand to anchor on to the readily available solid support such as silica to prepare the heterogenized palladium catalyst.

Table 1. Ligand screening for Pd-catalyzed *N*-alkylation of aniline using benzyl alcohol.^a

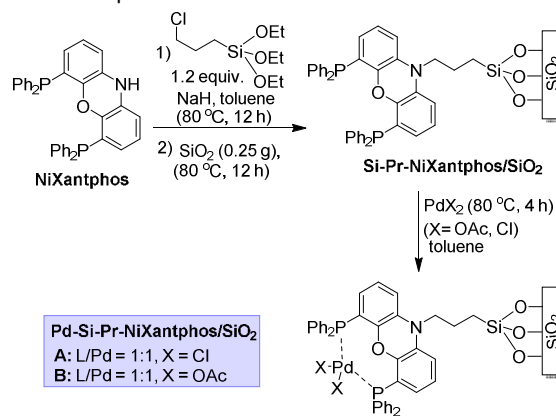


Entry	PdX ₂	Ligand	Product, 1 (%) ^b
1	PdCl ₂	dppe	96
2	PdCl ₂	XantPhos	34
3	PdCl ₂	XantPhos(<i>t</i> -Bu)	>99
4	PdCl ₂	dpePhos(Cy)	95
5	PdCl ₂	dppf(<i>t</i> -Bu)	89
6	PdCl ₂	NiXantPhos	86
7	PdCl ₂	BuNiXantPhos	>99
8	Pd(OAc) ₂	BuNiXantPhos	83

^a Reaction condition: aniline (2 mmol), benzyl alcohol (3 equiv.), catalyst (1 mol %, Pd/L=1:1), LiOH (20 mol %) 100 °C, 24 h. ^b NMR yield using mesitylene as the internal standard.

Immobilization of NiXantphos on solid supports was reported earlier for the rhodium catalyzed hydrofomylation²⁵ and for the palladium catalyzed allylic alkylation²⁶ of diethyl 2-

methylmalonate. Adopting a similar procedure, we have prepared silica supported Pd-NiXantphos catalysts in a modified one-pot protocol as depicted in Scheme 1. The alkylation of NiXantphos with 3-chloropropyl(trimethoxy)silane afforded the intermediate alkylated Si-Pr-NiXantphos, which was subsequently anchored on to silica to obtain Si-Pr-NiXantphos/SiO₂. Addition of palladium(II) precursor such as PdCl₂ or Pd(OAc)₂ in toluene at 80 °C resulted in the formation of the solid Pd-Si-Pr-NiXantphos/SiO₂ catalysts A and B, which were filtered under argon and washed with dry toluene to remove impurities.



Scheme 1. One-pot synthesis of Pd-Si-Pr-NiXantphos/SiO₂ catalyst.

The silica supported palladium catalysts were characterized by solid state NMR, XPS and ICP methods. For example, catalyst B gave ¹³C NMR signals in the region 10 – 50 ppm and 110 – 150 ppm in the solid state NMR spectrum (Figure 1) indicating the presence of aliphatic and aromatic carbons corresponding to that of the Si-Pr-NiXantphos ligand. The presence of 3d_{5/2} peak at 337.21 eV in XPS spectra corresponds to that of Pd(II)-phosphine complex. The amount of palladium present in the catalysts A and B were found to be 2.31 wt. % and 2.23 wt. % respectively by ICP analysis.

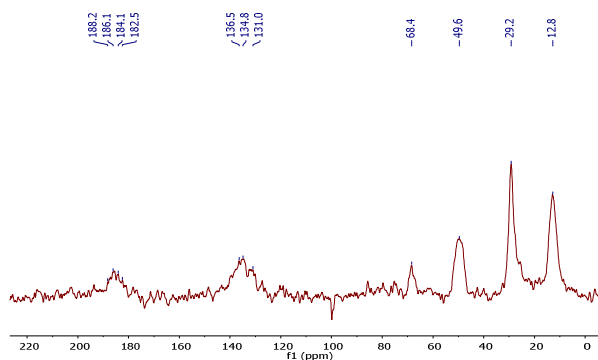
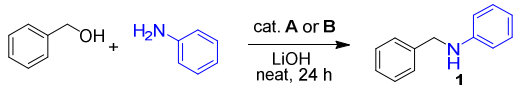


Figure 1. Solid-state ¹³C NMR spectra of catalyst B.

To our surprise, we observed that only very small amount of palladium is required to achieve good yield of the *N*-alkylated product when using the solid catalysts A or B. Accordingly, up to 65% yield was observed with 0.043 mol % of palladium at 100 °C for 24 h that provided a high TON of 1511 as shown in Table 2 (entry 1) for the *N*-alkylation of aniline using benzyl

alcohol with catalyst A. Under these conditions, catalyst B gave better results with a TON of 1928 (entry 2) and was selected for further optimization. Upon increasing the temperature to 120 °C, quantitative yield with an improved TON of 2381 was observed. Decreasing LiOH from 20 mol % to 10 mol % had only a marginal decrease in the catalytic performance. Decreasing the catalyst loading to 0.021 mol % and 0.0105 mol % of palladium gave further improved TON of 4666 and 7429 respectively (entries 5 and 6).

Table 2. Optimization of conditions for *N*-alkylation of aniline with benzyl alcohol.^a



Entry	Cat. (mg, Pd mol %)	LiOH (equiv.)	Temp. (°C)	Product, 1 (%) ^b	TON
1	A (4, 0.043)	0.2	100	65	1511
2	B (4, 0.042)	0.2	100	81	1928
3	B (4, 0.042)	0.2	120	>99	2381
4	B (4, 0.042)	0.1	120	95	2262
5	B (2, 0.021)	0.2	120	98	4666
6	B (1, 0.0105)	0.2	120	78	7429

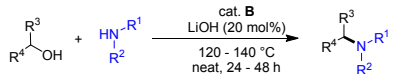
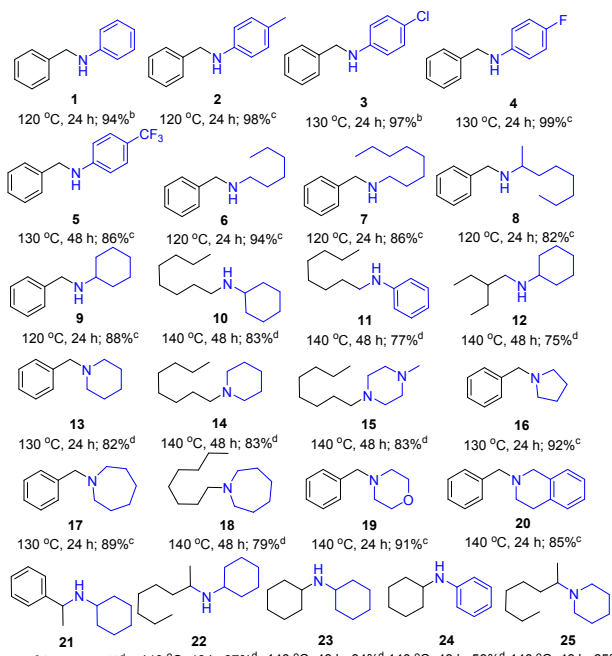
^aReaction condition: aniline (2 mmol), benzyl alcohol (3 equiv.), LiOH (20 mol %) 120 °C, 24 h. ^bNMR yield using mesitylene as an internal standard. No alkylation reaction was observed in the absence of catalyst A or B.

After achieving the high TON, we have evaluated the substrate scope and limitations using the catalyst B for the *N*-alkylation of various amines using primary and secondary alcohols. In most cases, the desired products were obtained in good to excellent isolated yields as given in Table 3. Aniline and 4-methylaniline were benzylated to the corresponding mono substituted anilines **1** and **2** in 94% and 98% isolated yields respectively at 120 °C. Less reactive and challenging substrates required slightly higher temperature or increased catalyst loading. Electron deficient anilines having substituents such as Cl, F and CF₃ were benzylated at 130 °C for 24 h to give the corresponding products **3**, **4** and **5** in excellent yields up to 99%. Electron rich linear aliphatic amines such as *n*-hexyl amine and *n*-octyl amine were also benzylated under similar conditions to afford the secondary amines **6** (94%) and **7** (86%) in excellent yields. α -Branched amines were also found to be good substrates and the corresponding alkylated products **8** and **9** were obtained in 82% and 88% yields respectively. Less reactive aliphatic alcohols such as *n*-octanol and 2-ethyl-1-butanol could also be used as electrophilic partner for obtaining the secondary amines **10** – **12** in 75 – 83% yields.

Involvement of unfavorable iminium intermediate makes the cyclic amines generally less reactive under hydrogen borrowing conditions. However, the current heterogeneous Pd catalyst promotes the alkylation of cyclic amines such as piperidine, pyrrolidine, azepane, morpholine, tetralin and *N*-methyl piperazine to the corresponding tertiary amines **13** – **20** in 75 – 92% isolated yields. The alkylation of amines with

challenging secondary alcohols such as 1-phenyl ethanol, 2-octanol and cyclohexanol also gave the corresponding alkylated products **21**, **22** and **23** in very good isolated yields (81 – 87%) in the case of cyclohexylamine as the substrate. With aromatic amines such as aniline, the alkylated product **24** was obtained in 53% isolated yield when cyclohexanol was used as the alkylating agent. The alkylation of piperidine with 2-octanol resulted in 65% isolated yield of the desired product **25**. In most cases, higher TON was observed compared to the literature reports.

Table 3. Substrates scope for *N*-alkylation of amines using heterogeneous Pd catalyst.^a

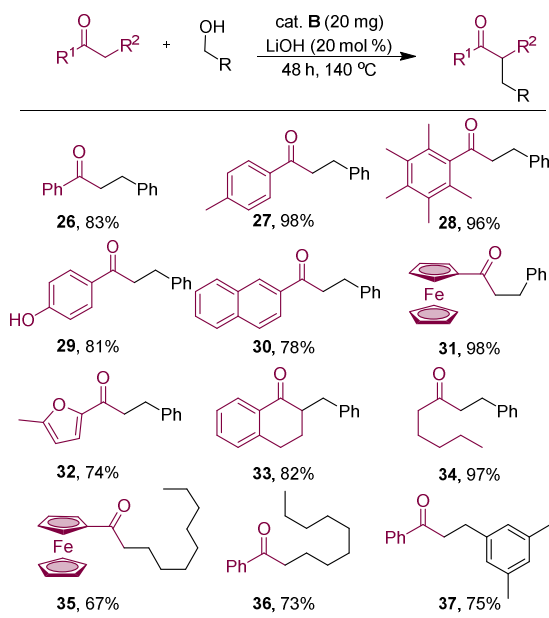



^aReaction condition: amine (2 mmol), alcohol (3 equiv.), LiOH (20 mol %), 24 h. ^b**B** (2 mg, 0.021 mol % of Pd; TON, 4476 – 4666); ^c**B** (8 mg, 0.084 mol % of Pd; TON, 976 – 1179); ^d**B** (20 mg, 0.21 mol % of Pd; TON, 252 – 400).

Transition metals catalyzed α -alkylation of ketones using alcohols following hydrogen borrowing strategy also attracted a greater attention in recent years as it provides an environmentally attractive protocol compared to the classical alkylation methods.²⁷ Most of the catalysts reported were based on Ru and Ir complexes and required stoichiometric amount of an inorganic base to achieve very good yields. Palladium was also explored as an alternative catalyst for α -alkylation using alcohols. For example, a homogeneous Pd-NHC catalyst²⁸ was reported for the α -alkylation of acetophenone using benzyl alcohol at 125 °C giving a mixture of alcohol and ketone products in 20% and 56%, respectively. A heterogeneous Pd catalyst (Pd/AIOOH)²⁹ was reported that gave a TON of up to 490 for the α -alkylation of ketones using a variety of alcohols in at 80 °C. Palladium nanoparticles supported on viologen³⁰ was reported under solvent free

condition, however the TON was found to be very low (<20). Recently, Pd/C was reported as a catalyst in water as the solvent at temperatures of 140 – 160 °C in the presence of 1 – 3 equivalents of base giving up to 93% yield with TON of 46.³¹

Table 4. Substrates scope for α -alkylation of ketones using primary alcohols.^a



^aReaction condition: ketone (2 mmol, 1 equiv.), alcohol (6 mmol, 3 equiv.), LiOH (20 mol %), catalyst **B** (20 mg, 0.21 mol % of Pd, TON, 319 – 467).

We have explored the potential use of the silica supported palladium Ni-Xantphos catalyst **B** for the α -alkylation of ketones in the presence of sub-stoichiometric amounts of base under solventless conditions. As given in Table 4, α -alkylation of methyl ketones were achieved at 140 °C in the presence of only 20 mol % of LiOH as a base providing excellent yields of the α -alkylated ketones **26** – **37** with a TON of up to 467. Under these pre-optimized conditions acetophenone gave 1,3-diphenylpropan-1-one (**26**) in 83% yield, while 98% and 96% yields were achieved with 4-methyl (**27**) and penta-methyl (**28**) substituted acetophenones respectively, when benzyl alcohol was used as the alkylating agent. Unprotected hydroxy group was tolerated and the corresponding alkylated product **29** was obtained in 81% yield. Other aromatic methyl ketones such as naphthyl, ferrocenyl and furanyl ketones were also excellent substrates and the corresponding benzylated products **30** – **32** were obtained in 74 – 98% yield. Excellent yields were achieved in the case of cyclic (**33**) and acyclic (**34**) ketones. Less reactive aliphatic alcohol such as 1-octanol was also found to be a very good alkylating agent and the alkylated products **35** and **36** were obtained in 67% and 73%, respectively. In addition, the alkylation of acetophenone with substituted benzyl alcohol such as 3,5-dimethylbenzyl alcohol afforded the ketone product **37** in 75% isolated yield.

Further, we have investigated the recyclability of the silica supported palladium Ni-Xantphos catalyst **B** by taking *N*-

alkylation of aniline using benzyl alcohol at 120 °C for 24 h as the representative reaction. 4 mg (0.042 mol%) of catalyst **B** was used for easy handling and the catalyst was recovered by simple filtration under argon and reused for subsequent reactions. Unfortunately, the yield of the mono-alkylated amine decreased to 59% for the first recycle and 22% in the second recycle compared to 99% in the first reaction (Figure 2). This may be due to the decomposition of the Pd(II) catalyst either in presence of water produced in the reaction or in contact with small amount of air during the recycling procedure.

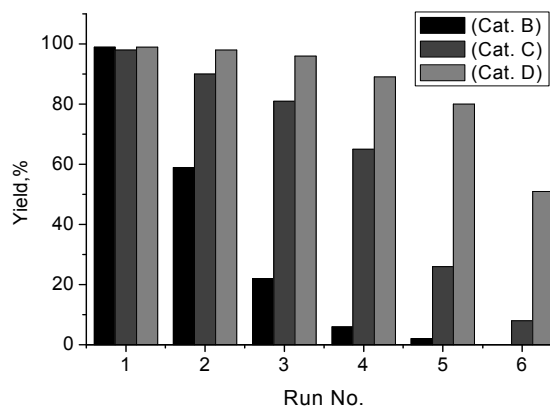


Figure 2. Recycle studies of silica supported Pd-NiXantphos catalysts B, C and D.

Improved recyclability was observed when the reaction was carried out in the presence of molecular sieves (50 mg) to partially absorb the water produced during the reaction, providing 99%, 98% and 45% yields respectively, in first, second and third runs.³² Though the addition of molecular sieves improved the recyclability, higher amount of solids in the reaction mixture may not be very much practicable. Hence, we decided to improve the stability of the catalyst by increasing the ligand to palladium ratio on the silica support and two new catalysts **C** (0.95 wt. % Pd) and **D** (0.52 wt. % Pd) with ligand/Pd ratios of 3:1 and 6:1 respectively were synthesized. Both the catalysts **C** and **D** were found to be active and not only gave near quantitative yields under the standard reaction conditions, but also provided higher recyclability compared to that of the catalyst **B** (Figure 2). The catalyst **D** with a ligand/Pd ratio of 6:1 was found to be more stable and could be recycled up to four times without significant loss in activity as shown in figure 2. A total TON of about 16000 was achieved after 6 runs using the Catalyst **D**. The palladium leaching in each run was found to be less than 0.01 ppm.³⁵ In order to further investigate the stability of the catalyst **D**, the representative *N*-alkylation of aniline with benzyl alcohol was carried out with very low catalyst loading (2 mg, 0.00196 mol %) for 5 mmol of substrate and a surprisingly high TON of about 46000 was achieved in 72 h of reaction with 91% yield.³² A high TON of about 4400 was also achieved in the case of α -alkylation of 4-methyl acetophenone with benzyl

alcohol using 0.0146 mol % catalyst **D** for 5 mmol of substrate, providing 65% yield in 96 h.³²

The catalytic cycle may be initiated by the formation of an *in situ* formed palladium alkoxide species on the silica support and proceeds through hydrogen borrowing mechanism similar to that reported for the homogeneous palladium catalyst.^{10a}

Conclusions

In conclusion, we have reported silica supported Pd-NiXantphos as an efficient and high turnover heterogeneous catalyst for the *N*-alkylation of amines and α -alkylation of ketones using a variety of alcohols including challenging aliphatic and secondary alcohols as alkylating agents under solvent free conditions. The catalyst can be readily recovered from the reaction mixture for subsequent runs and offers a very low palladium leaching of less than 0.01 ppm. The catalyst provided very high turnover numbers (TON) compared to most of the reported catalysts and a remarkably high TON of up to 46000 was achieved in a single batch reaction for the *N*-alkylation of amine using alcohols. The catalyst can be recycled up to four times without appreciable change in catalytic performance. A high TON of about 4400 was also achieved for the α -alkylation of ketone in the presence of only 20 mol % of base under solventless conditions. Though the supported palladium catalysts **B**, **C** and **D** provided similar catalytic performance in a single batch reaction, the catalyst **D** having higher ligand to Pd ratio is superior and is preferred in terms of stability and recyclability.

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Experimental

General procedure for one-pot preparation of solid catalysts: 10 mL of dry toluene, 55.2 mg of NiXantphos (0.1 mmol), NaH (0.3 mmol) were charged under argon-atmosphere in a Schlenk tube followed by additions of (3-chloropropyl)triethoxysilane (0.3 mmol). The reaction tube was closed with the Teflon stopper and was heated to 80 °C under stirring for 12h. 250 mg of dry SiO₂ was introduced in to the reaction mixture and stirring continued at 80 °C for another 12h. The reaction mixture was cooled to room temperature and the calculated amount of Pd precursor (Pd(OAc)₂) was introduced under argon and the reaction was stirring continued at 80 °C for another 4h. The reaction mixture was allowed to cool to RT and the brown solid catalyst was collected by filtration and washing with toluene (3 times, 20 mL) under argon atmosphere. The solid catalyst was dried in vacuum oven at 50 °C overnight, collected and stored under argon atmosphere.

General procedure for *N*-alkylation of amine with alcohol: Catalyst **B** (2-20 mg), LiOH (20.0 mol%), alcohol (6.0 mmol), and amine (2.0 mmol) were charged under argon-atmosphere in a Radleys carousel reaction tube. The reaction tube was closed with the Teflon stopper and was heated to the desired temperature under stirring. After the desired reaction time, the reaction mixture was allowed to cool to room temperature and diluted with toluene (10 mL). The SiO₂ (400mg) was added into the crude mixture. The organic solvent was removed under vacuum and then the product was purified by column chromatography.

General procedure for α -alkylation of ketones with alcohols: Catalyst **B** (20 mg), LiOH (20.0 mol%), alcohol (6.0 mmol), and ketone (2.0 mmol) were charged under argon-atmosphere in a Radleys carousel reaction tube. The reaction tube was closed with the Teflon stopper and was heated to the desired temperature under stirring. After the desired reaction time, the reaction mixture was allowed to cool to room temperature and diluted with toluene (10 mL). The SiO₂ (400mg) was added into the crude mixture. The organic solvent was removed under vacuum and then the product was purified by column chromatography.

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