DOI: 10.1002/chem.201003095

Ruthenium-Catalyzed Nitro and Nitrile Compounds Coupling with Alcohols: Alternative Route for N-Substituted Amine Synthesis

Xinjiang Cui,[a, b, c] Yan Zhang,[a] Feng Shi,*[a] and Youquan Deng[a]

Amines and their derivatives play critical roles as building blocks, functional linkages, and key moieties in peptides, polymers, and many natural products and pharmaceuticals. In addition, a plenty of naturally and man-made bioactive compounds, such as amino acids, nucleic acids, and enzymes, contain N-substituted amines.[1] N-Substituted amines are usually prepared by the alkylation of amines with halides.[2] However, this method is problematic due to overalkyation, the toxic nature of halides and related alkylating reagents, and the generation of stoichiometric unwanted byproducts. In many cases, N-substituted amines could also be synthesized by hydroamination[3] and hydroaminomethylation[4] reactions. An environmental benign procedure to produce N-substituted amines is the catalytic alkylation of amines with alcohols.[5] Clearly, alcohols are readily available, nonexpensive, and nontoxic, and water is the only byproduct theoretically. Thus, the reaction is environmentally friendly intrinsically. However, employing alcohols as alkylation reagents is severely limited because of the poor electrophilicity of most alcohols. The borrowing-hydrogen technology makes the use of alcohol as alkylation reagent more facile. In this method, the poorly electrophilic alcohol was converted into aldehyde with the liberation of metal hydride. The aldehyde reacts with amine to form imine with water as byproduct. The imine was then reduced by the metal hydride to obtain the final product. This interesting transformation has been studied extensively since the reports by Grigg[6] and Watanabe,[7] and various transition-metal catalysts including ruthenium[8] and iridium[9] complexes were studied subsequently.

Despite the importance of the N-substituted amines, to date, the selective synthesis of N-substituted amines through borrowing hydrogen methods was restricted to the reaction of amines with alcohols. It is still a challenge to find other ways to achieve the amination of alcohols. It is known that primary amines are normally produced by the hydrogenation of nitrobenzenes and benzonitriles.[10] The transfer hydrogenation reaction of nitroarenes and nitriles[11] by alcohols has been long known in the literature, as has the condensation reaction of amines with alcohols .[5,8] However, these reactions have not previously been performed in one pot in the presence of a single catalytic system. It would be an ideal reaction if substituted amines could be synthesized in one step from nitro or nitrile compounds and alcohols. In this way, the specific equipment, rigorous reaction conditions, and complicated operations could be avoided. In one word, a multistep reaction would be realized in one-pot. Based on the continuous interest in the developing of simple and economic method for the synthesis of N-substituted secondary amine, we tried a new route to realize the amination of alcohols to secondary amine from nitro or nitrile compounds directly (Scheme 1).

Scheme 1. One-pot synthesis of N-substituted amines from nitro and nitrile compounds and alcohols.

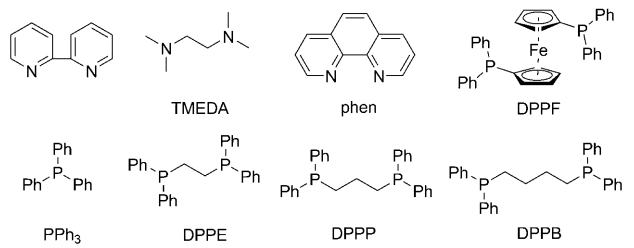
The reaction condition optimization was started with [{Ru(*p*-cymene)Cl_2}$_2$] as catalyst[12] with a variety of ligands at 130 °C (Scheme 2, Table 1). Clearly, under ligand-free conditions, the nitrobenzene is totally converted into imine and no alkylated amine was observed, entry 1. With the addition of typical nitrogen ligands, that is, bpy (bipyridine), TMEDA (tetramethylethylenediamine), and phen (phenanthroline), there is no evident improvement in the catalytic activity (entries 2–4). The selectivity to N-alkylated product was $<10\%$. The employment of phosphine ligand, however, promoted the reaction more efficiently. In the presence of PPh_3, 23% of amine could be obtained (entry 5). Interestingly, the selectivity to *N*-benzyl-*p*-tolueneamine could be promoted efficiently by using DPPE (1,2-bis(diphenylphosphino)ethane), DPPP (1,3-bis(diphenylphosphino)propane) and DPPB (1,2-bis(diphenylphosphanyl)benzene) (en-

[a] X. Cui, Dr. Y. Zhang, Dr. F. Shi, Prof. Y. Deng
Centre for Green Chemistry and Catalysis
Lanzhou Institute of Chemical Physics, CAS
Middle Tian Shui Road, 18, Lanzhou (P.R. China)
Fax: (+86) 931-8277088
E-mail: fshi@licp.cas.cn

[b] X. Cui
Graduate School of the Chinese Academy of Sciences
Beijing, 100049 (P.R. China)

[c] X. Cui
State Key Laboratory of Applied Organic Chemistry and
Department of Chemistry, Lanzhou University
Lanzhou, 730000 (P.R. China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003095.



Scheme 2. Ligands tested in this work.

Table 1. Results of 4-nitrotoluene reductive alkylation with benzylalcohol.[a]

Entry	Catalyst	Ligand	Base	Conv [%][b]	Sel [%][b]
1	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	—	K_2CO_3	100	0
2	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	bpy	K_2CO_3	100	0
3	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	TMEDA	K_2CO_3	100	6
4	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	phen	K_2CO_3	100	2
5	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	PPh_3	K_2CO_3	100	23
6	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPE	K_2CO_3	100	13
7	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPP	K_2CO_3	100	33
8	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPB	K_2CO_3	100	40
9	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPF	K_2CO_3	100	21
10	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPB	—	20	0
11	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPB	KO-*t*Bu	100	8
12	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPB	Na_2CO_3	100	12
13	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPB	KOH	100	13
14[c]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	DPPB	K_2CO_3	100	97
15[c]	$[\{Ru(benzene)Cl_2\}_2]$	DPPB	K_2CO_3	100	55
16[c]	$RuCl_3$	DPPB	K_2CO_3	100	14

[a] nitrobenzene (1.0 mmol), benzylalcohol (1.25 equiv, 5.0 mmol), $[\{Ru(p\text{-cymene})Cl_2\}_2]$ (2.5 mol%), ligand (5.0 mol%), K_2CO_3 (15 mol%), 130°C, Ar, 12 h. [b] Determined by GC-MS. The byproduct was imine. [c] Alcohol (2 equiv, 8.0 mmol).

tries 6–8). Especially when DPPB was employed, its selectivity reached to 40%.

As one of the most effective ligands in the alkylation of amines with alcohol,[8c] DPPF (diphenylphosphinoferrocene) does not work well for this reaction; the selectivity was only 23% (Table 1entry 9). The addition of base was also essential. The conversion was only 20% and there is no amine formation under base-free conditions (entry 10). If other bases such as KO-*t*Bu, Na_2CO_3, and KOH were applied, the selectivities were all lower than 20%, (entries 11–13). The selectivity to the desired product could reach to 97% with the addition of two equivalents of alcohol (entry 14). No improvement could be achieved if other ruthenium complexes such as $[\{Ru(benzene)Cl_2\}_2]$ and $RuCl_3$ were used as catalyst, (entries 15 and 16). In addition, it should be noted that the major product from alcohol is the corresponding ester.

The one-pot synthesis of N-alkylated amines was employed under the optimized reaction conditions with different nitrobenzenes and alcohols, Table 2. Firstly, the reductive alkylation of 4-nitrotoluene with various benzylic alcohols containing methyl, methoxyl, and chloro groups were performed. Clearly, all these reactions progressed well and 83–95% isolated yields were achieved (entries 1–5). Then, the alteration of nitrobenzenes was performed. Different ni-

Table 2. Results of the reductive alkylation of nitrobenzenes with alcohols.[a]

$$R^1NO_2 + R^2OH \xrightarrow[130\ ^\circ C,\ Ar]{[\{Ru(p\text{-cymene})Cl_2\}_2]/DPPB/K_2CO_3} R^1NHR^2$$

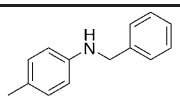
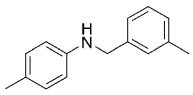
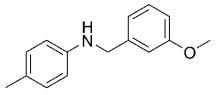
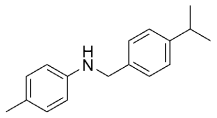
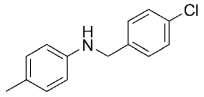
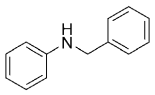
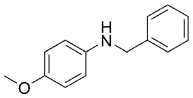
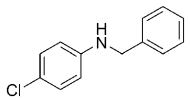
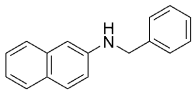
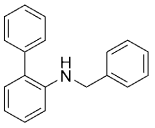
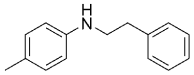
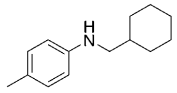
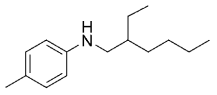
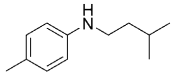
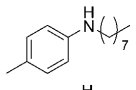
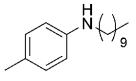
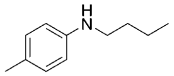
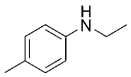
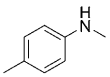
Entry	Products	*t* [h]	Yield [%][b]
1		12	94
2		12	95
3		12	83
4		12	84
5		12	87
6		12	93
7		12	89
8		16	92
9		24	86
10		24	83
11		24	85
12		18	82
13		24	75
14		24	73
15		12	93
16		12	83

Table 2. (Continued)

Entry	Products	*t* [h]	Yield [%][b]
17		24	83
18		12	70
19		24	81

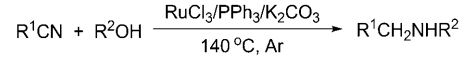
[a] 1.0 mmol nitrobenzenes, alcohols (2 equiv, 8.0 mmol), 2.5 mol% [{Ru(*p*-cymene)Cl_2}$_2$], 5 mol% DPPB, 15 mol% K_2CO_3, 130°C, Ar. [b] Isolated yields.

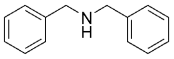
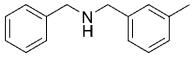
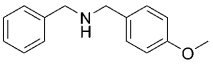
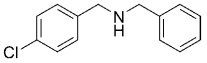
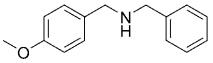
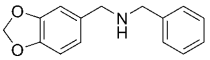
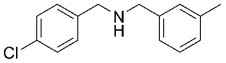
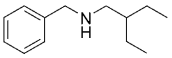
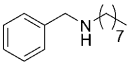
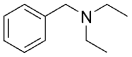
trobenzenes including nitrobenzene, *p*-methoxylnitrobenzene, *p*-chloronitrobenzene, 2-nitronaphthalene, and 2-nitrobiphenyl can react with benzyl alcohol to afford the corresponding N-benzyl amines with 83–93% yields (entries 6–10).

One of the major challenges in the C–N bond formation reaction is the alkylation with aliphatic alcohols due to the chemical inertness of aliphatic alcohols. Thus, the N-alkylated amine synthesis starting from various aliphatic alcohols were tested here. To our delight, 2-phenylethanol, cyclohexylmethanol, 2-ethylhexan-1-ol, 3-methylbutan-1-ol, *n*-decanol, *n*-octanol and *n*-butanol can react with *p*-nitrotoluene to give the N-alkylated amines with up to 93% yields (Table 2 entries 11–17). Importantly, for the industriously interesting compounds, that is, *N*-ethyl or *N*-methyl-*p*-toluidine, 70 and 81% yields, respectively, were also obtained (entries 18 and 19). These results suggest that our methodology covers the reductive alkylation of nitrobenzenes possess various structures.

Benzonitrile hydrogenation[10b] is also one of the important routes for the synthesis of amines, although it is not as extensive as the hydrogenation of nitrobenzene. Therefore, the synthesis of N-alkylated amines starting form some typical benzonitriles were also tried. However, we found this reaction needs different catalyst from those using nitrobenzenes as starting materials. After optimization, although the detailed screening results are not given here, we found that $RuCl_3/PPh_3/K_2CO_3$ is an ideal system (Table S1 in the Supporting Information). So the results for the synthesis of N-alkylated amines using this catalyst system are shown below (Table 3). The yields were 88–93% if using benzonitrile as starting reagents, and benzylalcohol, *m*-methylbenzylalcohol and *p*-methoxylbenzylalcohol as alkylation compounds (entries 1–3). Further, the reductive alkylation of benzonitriles with different functional groups, that is, *p*-chloro-benzonitrile, *p*-methoxylbenzonitrile, and piperonylnitrile were carried out and 87–95% yields were obtained (entries 4–7). Similarly to the N-alkylated amine synthesis with nitrobenzene as starting material, the employment of inert aliphatic alcohol as alkylation reagent was also performed. Here, several typical aliphatic alcohols, that is, 2-ethylbutan-1-ol and *n*-octanol, were tested and the corresponding yields were 80–90% (entries 8 and 9). Importantly, the reaction of benzonitrile and ethanol can afford *N*,*N*′-diethylbenzyl amine with good result. The conversion was 100% and the selectivity was ≈90% as determined by GC-MS (entry 10). Therefore, our catalyst proposes more choice for the synthesis of N-alkylated amines.

Table 3. Results of the reductive alkylation of benzonitriles with alcohols.[a]

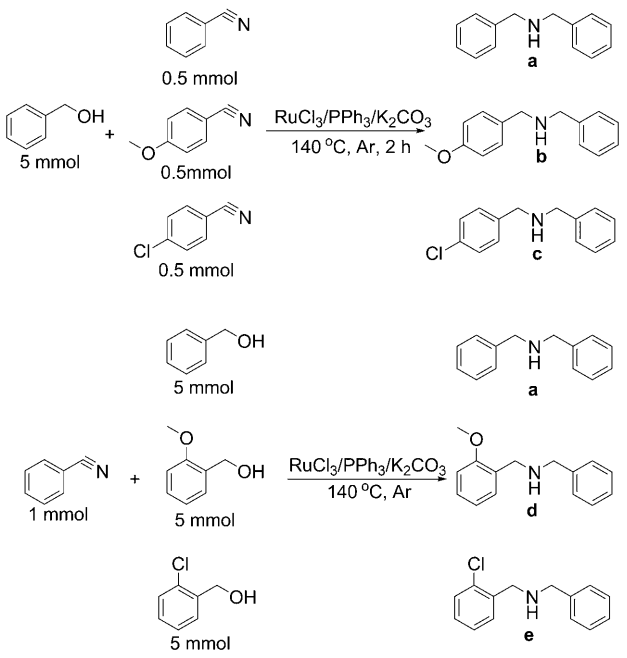


Entry	Products	*t* [h]	Yield [%][b]
1		9	93
2		9	88
3		9	92
4		9	90
5		9	95
6		9	94
7		9	87
8		24	90
9		24	81
10[c]		24	90[d]

[a] 1.0 mmol benzonitriles, alcohols (2.7 equiv, 8.0 mmol), 5 mol% $RuCl_3$, 5 mol% PPh_3, 15 mol% K_2CO_3, 140°C, Ar. [b] Isolated yields. [c] 125°C. [d] Determined by GC-MS.

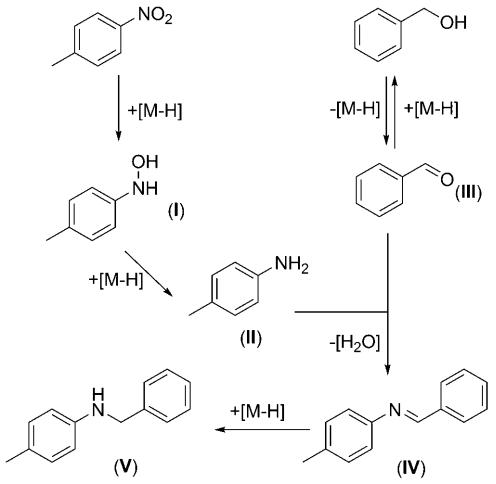
From the results shown in Table 3, it could be seen that the coupling of benzonitriles with benzylic alcohols only give different substituted dibenzylamines and it offers the possibility to check the substitution effect of different functional groups. Thus competitive reaction of benzonitrile, 4-methoxybenzonitrile, and 4-chlorobenzonitrile with benzyl alcohol were carried out (Scheme 3 and Table S2 in the Supporting Information). According to the GC-MS analysis, the ratio of products **a**/**b**/**c** was 1:1.4:14. This suggested the electron-withdrawing group favored the reduction of nitriles and the coupling reaction of nitriles and alcohols. In addition, the competitive reaction of benzonitrile with different benzylic alcohols was performed (Scheme 3 and Table S3 in the Supporting Information). According to the GC-MS analysis, full conversion of benzonitrile was observed and the ratio of **a**/**d**/**e** was 1:1.3:1.5. It is worth noting that compound **e** was generated selectively and all the imine intermediate was transferred into amine. These results indicated the existence of electron withdrawing group could promote the transfer hydrogenation of imine to produce the secondary amine.

The exploration of the reaction mechanism should be interesting. Here the reaction of *p*-nitrotoluene and benzyl



Scheme 3. Competitive reactions of benzonitriles with benzylic alcohols.

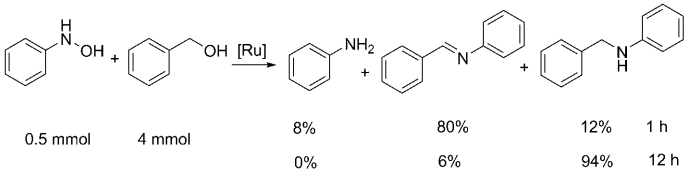
alcohol was studied. By tracing the reaction with GC-MS, the formation of *p*-*N*-tolylhydroxylamine, *p*-toluidine, benzaldehyde, *N*-benzylidene-4-methylaniline and *N*-benzyl-4-methylaniline could be clearly observed (Scheme 4).



Scheme 4. Possible mechanism.

So we can imagine that the reduction of nitro group in our reaction proceed with the same route as the hydrogenation reaction.[1b] Firstly, the nitro group was reduced into hydroxylamine and further on it is reduced into amine. In the next step, the amine reacts with the benzaldehyde to give imine and the desired product could be obtained after transfer hydrogenation. This process is a multistep, one-pot reaction.

To investigate the mechanism in detail, the reaction of *N*-phenylhydroxylamine and benzyl alcohol was employed. According to the results determined by GC-MS, 90% conversion of *N*-phenylhydroxylamine was obtained, and aniline, *N*-benzylaniline and (*E*)-*N*-benzylideneaniline were observed in 1 h (Scheme 5). The selectivity to *N*-benzyl aniline reached 94% in 12 h. These results verified that *N*-phenylhydroxylamine is a possible intermediate in the reaction.



Scheme 5. Reaction of N-phenylhydroxylamine with benzyl alcohol.

We found that the mechanism of the reaction with benzonitrile as the starting material is similar to that of nitrobenzene. However, the intermediate is phenylmethanimine for the formation of primary amine,[10b] but it is hydroxylamine when nitrobenzene is used.[1b] According to the mechanism discussed above, it could be concluded that 4 or 3 mol of alcohols for every mol of nitroarene or nitrile were needed in order to realize the whole reaction.

In conclusion, a new method has been developed for the synthesis of N-substituted secondary amines from nitrobenzenes or benzonitriles and alcohols under mild conditions. N-Alkylated amines with various structures could be synthesized with 73–95% isolated yields. In this process, multiple steps were realized in one-pot with high efficiency. It offers a clean and economic way for the synthesis of N-substituted amines.

Experimental Section

All solvents and chemicals were obtained commercially and were used as received. NMR spectra were measured using a Bruker ARX 400 or ARX 100 spectrometer at 400 MHz (1H) and 100 MHz (13C). All spectra were recorded in $CDCl_3$ and chemical shifts (δ) are reported in ppm relative to tetramethylsilane referenced to the residual solvent peaks. Mass spectra were in general recorded on an HP 6890/5973 GC-MS.

Representative procedure for the reaction of nitrobenzenes and alcohols: The representative nitrobenzene (1 mmol) and representative alcohol (8 mmol) were added to an oven-dried, argon-purged, reaction tube containing [{Ru(*p*-cymene)Cl_2}$_2$] (6.1 mg, 0.025 mmol), DPPB (22.6 mg, 0.05 mmol), and K_2CO_3 (20.8 mg, 0.15 mmol). Then, the tube was installed on the top-cooled carousel 12-reaction station, and the reaction mixture was stirred at 130 °C for 12 h. Then it was cooled to room temperature. ≈20 mL acetone was added to dissolve the reaction mixture and the resulting solution was filtered by celite. The crude reaction mixture was concentrated in vacuo. Then, 37% HCl (1 mL) and distilled water (10 mL) were added to the mixture. The solution was washed with diethyl ether (3×10 mL). The aqueous phase was neutralized by NaOH solution and extracted by diethyl ether (2×20 mL). Then, it was evaporated and purified by column chromatography (petroleum ether (b.p. 60–90 °C)/diethyl ether/triethylamine) to give the corresponding N-substituted amine

in good yield. The reactions using ethanol and methanol as starting materials were performed in 40 mL pressure tubes.

Representative procedure for the reaction of benzonitriles and alcohols: The representative benzonitrile (1 mmol) and representative alcohol (8 mmol) were added to an oven-dried, argon-purged, reaction tube containing $RuCl_3{\cdot}xH_2O$ (10.3 mg, 0.05 mmol), PPh_3 (13 mg, 0.05 mmol), PPh_3 (13.1 mg, 0.05 mmol), and K_2CO_3 (20.8 mg, 0.15 mmol). Then, the tube was installed on the top-cooled carousel 12-reaction station and the reaction mixture was stirred at 140 °C for 12 h. Then it was cooled to room temperature. ≈20 mL acetone was added to dissolve the reaction mixture. The crude reaction mixture was concentrated in vacuo and purified by column chromatography (petroleum ether (b.p. 60–90 °C)/diethyl ether/triethylamine) to give the corresponding N-substituted amine in good yield. The reaction using ethanol as starting material was performed in 40 mL pressure tubes.

Representative procedure for competitive reaction of functional nitriles with benzyl alcohol: The representative alcohol (10 mmol) and representative benzonitrile (0.5 mmol), 4-methoxybenzonitrile (0.5 mmol) and 4-chlorobenzonitrile (0.5 mmol) were added to an oven-dried, argon-purged reaction tube containing $RuCl_3{\cdot}xH_2O$ (10.3 mg, 0.05 mmol), PPh_3 (13 mg, 0.05 mmol), and K_2CO_3 (20.8 mg, 0.15 mmol). Then, the tube was installed on the top-cooled carousel 12-reaction station and the reaction mixture was stirred at 140 °C for 2 h. Then it was cooled to room temperature. ≈10 mL acetone was added to dissolve the reaction mixture and the nature of the products was determined by GC-MS.

Representative procedure for competitive reaction of functional benzylic alcohols with benzonitrile: The representative benzonitrile (1 mmol) and representative benzyl alcohol (5 mmol), 2-methoxybenzylalcohol (5 mmol) and 2-chlorobenzylalcohol (5 mmol) were added to an oven-dried, argon-purged, reaction tube containing $RuCl_3{\cdot}xH_2O$ (10.3 mg, 0.05 mmol), PPh_3 (13 mg, 0.05 mmol) and K_2CO_3 (20.8 mg, 0.15 mmol). Then, the tube was installed on the top-cooled carousel 12-reaction station and the reaction mixture was stirred at 140 °C for 2 h. Then it was cooled to room temperature. ≈10 mL acetone was added to dissolve the reaction mixture and the nature of the products was determined by GC-MS.

Representative procedure for the reaction of *N*-phenylhydroxylamine and benzyl alcohol: The representative nitrobenzene (0.5 mmol) and d7-benzyl alcohol (4.0 mmol) were added to an oven-dried, argon-purged, reaction tube containing $[\{Ru(p\text{-cymene})Cl_2\}_2]$ (3.0 mg, 0.013 mmol), DPPB (12 mg, 0.025 mmol) and K_2CO_3 (14 mg, 0.1 mmol). Then, the tube was installed on the top-cooled carousel 12-reaction station and the reaction mixture was stirred at 130 °C for 1 or 12 h. Then it was cooled to room temperature. ≈10 mL acetone was added to dissolve the reaction mixture and the nature of the products was determined by GC-MS.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (21073208) and "Hundred Talents Program" of the Chinese Academy of Sciences.

Keywords: alcohols · alkylation · amines · C–N coupling · nitro/nitrile compounds

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Received: September 29, 2010
Published online: January 26, 2011

