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A Ruthenium-Based Catalytic System for a Mild Borrowing-Hydrogen Process

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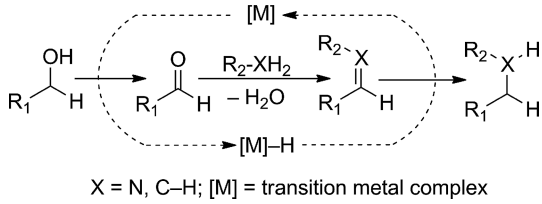
The alkylation of arylamines using stoichiometric amounts of aliphatic and benzylic alcohols in the presence of *t*BuOK was carried out at 55 °C using a low catalyst loading of [Ru(cod)-$Cl_2]_n$/PTA (1,3,5-triaza-7-phosphaadamantane). The overall borrowing-hydrogen process does not require a controlled nitrogen atmosphere, and it could also be carried out at room temperature using higher loading of base. A wide range of substrates can be used in this transformation, and it has a good tolerance of different substituents. This catalytic system proved also to be efficient for other hydrogen-transfer reactions such as a tandem oxidation/C–C coupling between 1-phenylethanol and primary alcohols.

Introduction

The catalytic hydrogen-transfer reaction is a powerful method that allows stable, more readily available, and less harmful alcohols to be used instead of aryl halides, aldehydes, or ketones in many of the typical reactions of carbonyl compounds, such as C–C- and C–N-bond-forming reactions.[1] As shown in Scheme 1, the general feature of borrowing-hydrogen reactions is the metal-mediated in situ oxidation of the alcohol to the corresponding carbonyl compound, which then reacts with a nucleophile. Reduction of the condensation product occurs by hydride transfer from the metal complex to give the final product in a highly atom- and redox-economic process.[2]



Scheme 1. General borrowing-hydrogen strategy.

Several noble metals have been used for this task, and excellent protocols for the preparation of amines, alcohols, ketones, aldehydes, and heterocycles have been described.[3–5] The majority of the reported procedures require high temperatures (>100 °C) and long reaction times,[4] which makes this catalytic protocol unsuitable for thermally unstable molecules. However, some examples of the alkylation of amines with alcohols have been reported to proceed at 50–80 °C or even at room temperature using expensive iridium catalysts.[6,7] Following our interest in borrowing-hydrogen and hydrogen-autotransfer reactions,[8] we have investigated the possibility of carrying out the Ru-catalysed alkylation of amines with alcohols under mild conditions. Recently, the first example of a Ru-catalysed *N*-alkylation of amines at 65 °C (and even at room temperature) using the alcohol itself as the reaction solvent was published by Enyong and Moasser.[9]

In this paper, we report our results relating to the efficient alkylation of arylamines using stoichiometric amounts of aliphatic and benzylic alcohols in the presence of *t*BuOK. The reaction takes place under mild reaction conditions in terms of reagent amounts, Ru catalyst loading, reaction time, and temperature.

Results and Discussion

For the optimization of the reaction conditions, the *N*-alkylation of aniline with benzyl alcohol was chosen as a test reaction (Scheme 1, Table 1). Based on our previous experience, different Ru complexes were tested in toluene at 55 °C in the presence of base (Table 1, entries 1–4; see also Supporting Information, Table SI-1).[10] Among the various precatalysts used, the most active one, [Ru(η^6-benzene)-$Cl_2]_2$/**6**, gave a conversion of 55% with a good selectivity for secondary amine formation (Table 1, entry 4). An in depth study of this transformation has revealed the importance of the base. In fact, it was reported that alcohols and amines react in the presence of a base to give imines in a metal-free auto-catalysed oxidation.[11] The NaOH-cata-

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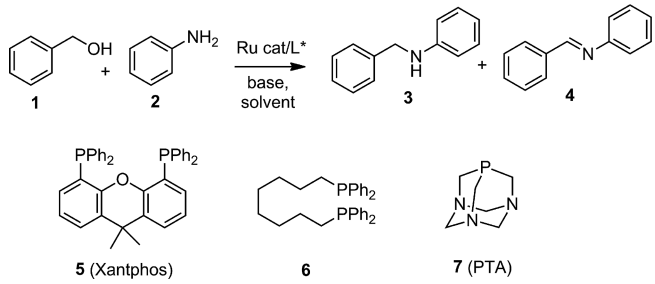
Table 1. Optimization and screening of the reaction conditions.[a]



Entry	Ru-catalyst (mol-%)	Ligand (mol-%)	Base (equiv.)	*t* [h]	Solvent	Conv. [%][b]	**3**/**4**[c]
1	$[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ (5)	**5** (5)	–	15	toluene	n.r.	
2	$[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ (2.5)	**5** (5)	*t*BuOK (0.5)	15	toluene	10	1:99
3	$Ru_3(CO)_{12}$ (2.5)	**6** (2.5)	*t*BuOK (0.5)	15	toluene	11	1:99
4	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**6** (2.5)	*t*BuOK (0.5)	15	toluene	55	80:20
5	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**6** (2.5)	*t*BuONa (0.5)	18	toluene	37	75:25
6	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**6** (2.5)	KOH (0.5)	15	toluene	19	45:55
7	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**6** (2.5)	NaOH (0.5)	15	toluene	19	49:51
8	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**6** (2.5)	K_3PO_4 (0.5)	36	toluene	56	0:100
9	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (5)	*t*BuOK (0.5)	15	toluene	64	88:12
10	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (5)	*t*BuOK (0.5)	15	THF	53	75:25
11	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (5)	*t*BuOK (0.5)	15	dioxane	48	65:35
12	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (5)	*t*BuOK (0.5)	15	dimethoxyethane	67	24:76
13	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (5)	*t*BuOK (1)	15	–	78	94:6
14	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (5)	*t*BuOK (1)	15	toluene	82 (89)[d]	93:7 (99:1)
15	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (10)	*t*BuOK (1)	15	toluene	86	97:3
16	$[Ru(\eta^6\text{-benzene})Cl_2]_2$ (2.5)	**7** (5)	*t*BuOK (1)	40	toluene (r.t.)	66	51:49
17	$Ru_3(CO)_{12}$ (2.5)	**7** (8)	*t*BuOK (1)	40	toluene	68	20:80
18	$[Ru(cod)Cl_2]_n$ (2.5)	**7** (5)	*t*BuOK (1)	15	toluene	97 (90)[e]	99:1 (94:6)
19	$[Ru(cod)Cl_2]_n$ (1.25)	**7** (2.5)	*t*BuOK (1)	20	toluene	91	94:6
20	$[Ru(cod)Cl_2]_n$ (5)	**7** (10)	*t*BuOK (1)	15	toluene	92	91:9
21	$[Ru(cod)Cl_2]_n$ (2.5)	**7** (5)	*t*BuOK (2)	24	toluene (25 °C)	92	77:23
22	$[Ru(cod)Cl_2]_n$ (2.5)	**7** (5)	*t*BuOK (2)	15	toluene (40 °C)	96	92:8
23	$[Ru(cod)Cl_2]_n$ (2.5)	**7** (5)	*t*BuOK (0.3)	15	toluene (85 °C)	72	84:16

[a] Reaction conditions: benzyl alcohol (0.5 mmol), aniline (0.5 mmol), base (as stated), catalyst (as stated), solvent (0.5 mL), at 55 °C unless otherwise stated, in air. [b] Determined by GC–MS analysis; n.r.: no reaction. [c] Relative proportion determined by GC–MS. [d] Conversion and amine/imine ratio after 40 h given in parentheses. [e] Experiment run with distilled solvent under a nitrogen atmosphere.

lysed *N*-alkylation of benzyl alcohols with amines and amides has also been reported.[12] These results inspired us to investigate the influence of different bases on the formation of *N*-benzylaniline (Table 1, entries 4–8). All bases except Et_3N and K_2CO_3 promoted the first oxidative step of the hydrogen autotransfer (i.e., the formation of **4** from **1**; Scheme 1; see also Supporting Information, Table SI-2), whereas only in the presence of KOH, NaOH, *t*BuOK, or *t*BuONa did the reductive step take place to form amine **3** (Table 1, entries 4–7). Used together with $[Ru(\eta^6\text{-benzene})Cl_2]_2$, 1,3,5-triaza-7-phosphaadamantane (PTA; **7**)[13] gave a higher conversion than **6** (Table 1, entries 4 and 9).

Under the specified reaction conditions, *t*BuOK emerged as the best base, giving a higher conversion and selectivity for the formation of **3** (Table 1, entry 9). The effect of solvent under these reaction conditions was then evaluated, and we found that toluene was the best medium, although a solvent-free procedure was also possible (Table 1, entries 9–13; see also Supporting Information, Table SI-3).[14]

When the amount of *t*BuOK was increased, the selectivity for *N*-benzylamine **3** increased, and a conversion of 82% was obtained after 15 h with 2.5 mol-% of Ru and a Ru/P ratio of 1:1. When the reaction time was increased from 15 to 40 h, the conversion and the selectivity for product **3** both increased further (Table 1, entry 14). However, the optimum conversion and selectivity for **3** were obtained with a Ru/P ratio of 1:2 after a reaction time of 15 h using toluene as solvent (Table 1, entry 15). Used in combination with PTA, $[Ru(cod)Cl_2]_n$ (cod = η^4-1,5-cyclooctadiene) was superior to all the other Ru sources tested, giving a conversion of 97% after 15 h at 55 °C, with the formation of pure *N*-benzylaniline (**3**) (Table 1, entries 16–18). The lower limit for the catalyst loading was investigated: with 1.25 mol-% of the catalyst, a good yield of compound **3** was obtained if a longer reaction time was used (Table 1, entry 19). On the other hand, even at double the catalyst loading, no significant difference in activity was observed (Table 1, entry 20), which suggests that a catalyst loading of 2.5 mol-% could be the best choice for the reaction.

It was also possible to reduce the reaction temperature from 55 to 40 °C while maintaining a good yield and selectivity for *N*-benzylaniline when the reaction was carried out

in the presence of 2 equiv. of *t*BuOK (Table 1, entry 22). Room temperature experiments carried out with 2 equiv. of base gave acceptable conversions after 24 h, but with lower selectivities (Table 1, entry 21).[15] An important feature of this catalytic protocol is that the reagents and the solvent can be mixed in air, and the reaction vial can be heated without the need for an inert atmosphere or degassed solvents. No significant difference was observed in the activity of the reaction when it was carried out under nitrogen using degassed toluene (Table 1, entry 18).

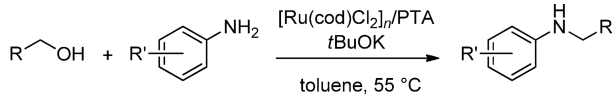
As the use of stoichiometric amounts of *t*BuOK could be a limitation for this method in terms of its use with sensitive substrates, we examined the effect of the concentration of base on the reaction products. When less than 0.4 equiv. of *t*BuOK was used, at 55 °C the reaction was too slow, so the temperature must be increased to 85 °C in order to reach acceptable conversions in a reasonable time. The best compromise was to use either 0.3 equiv. of *t*BuOK at 85 °C for 48 h, or 0.5 equiv. of *t*BuOK at 55 °C for 46 h (see Supporting Information, Table SI-4).

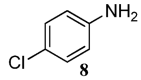
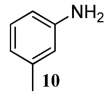
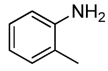
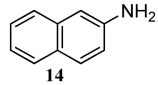
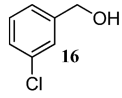
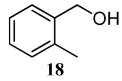
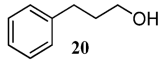
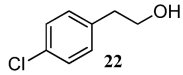
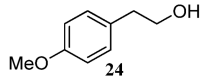
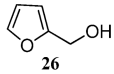
Although the mechanism has not been studied in detail so far, experimental observations revealed that most suitable precatalyst for the reaction is $[Ru(cod)Cl_2]_n$/**7**, and that the presence of *t*BuOK is important for the activation of the alcohol (as no reaction occured at all in the absence of the base). The Ru catalyst takes part in the reaction by capturing the hydrogen after the benzaldehyde has been formed, and then transferring it to the imine (formed by the condensation of benzaldehyde and aniline) in the last step to form the amine. Apparently, the reaction works by a "Ru-catalyst–base" cooperative mechanism to give the desired *N*-benzylamine with good selectivity and in good yield.[16] It is important to have the appropriate amount of Ru catalyst along with a stoichiometric amount of base to achieve a faster reaction and a high selectivity for the amine. The base also seems to play a role in the reduction step, as when the base loading was decreased, the benzyl alcohol was converted into imine **4**, which remained unreacted in a high ratio with respect to amine **3** at the end of the reaction.

The high concentration of the reaction mixture led to an apparently heterogeneous system. In order to verify the homogeneous nature of the catalysis, a standard Hg^0 poisoning test was carried out,[17] which revealed a very low decrease of activity under these conditions (see Supporting Information). The developed reaction conditions represent a significant improvement compared to results described in a recently published paper that require the use of the alcohol as solvent, 6–7% of the Ru catalyst, and heating to 65 °C for 22–48 h.[9]

The scope of the reaction was further explored by allowing different (primary) alcohols and amines to react under the optimized reaction conditions (Table 2). Diverse substituents on both alcohol and amine substrates did not significantly influence the reactivity or the selectivity for the amine. Substituents at the *meta* and *para* positions of the amine did not affect the reactivity, and gave higher yields (Table 2, entries 2 and 3), whereas an *ortho* substituent reduced the reactivity, and gave the imine as the major product (Table 2, entry 4). The use of 2-naphthylamine was well

Table 2. Alkylation of different anilines.[a]



Entry	Alcohol	Amine	Product	*t* [h]	Conv. [%][b][c] (% yield)[d]
1	**1**	**2**	**3**	15	99 (97)
2	**1**	 **8**	**9**	12	95 (83)
3	**1**	 **10**	**11**	12	86 (79)
4	**1**	 **12**	**13**	48	75 (30)[e]
5	**1**	 **14**	**15**	15	99 (90)
6	 **16**	**2**	**17**	15	92 (85)
7	 **18**	**2**	**19**	16	91 (84)[f]
8	 **20**	**2**	**21**	12	99 (87)
9	 **22**	**2**	**23**	24	81 (77)
10	 **24**	**2**	**25**	24	90 (85)
11	 **26**	**2**	**27**	36	89 (82)
12	CH_3CH_2OH **(28)**	**2**	**29**	15	99(89)
13	$CH_3(CH_2)_3OH$ **(30)**	**2**	**31**	15	91(80)
14	$CH_3(CH_2)_5OH$ (**32**)	**2**	**33**	18	98 (85)
15	**16**	**8**	**34**	15	91 (82)

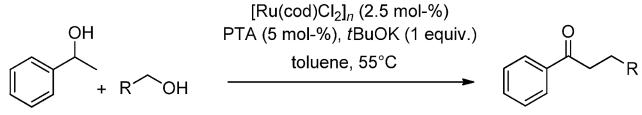
[a] Reaction conditions: alcohol (1.06 mmol), amine (1 mmol), *t*BuOK (1 equiv.), $[Ru(cod)Cl_2]_n$ (2.5 mol-%), PTA (5 mol-%), toluene (1 mL), 55 °C. [b] Amine/imine ratios >99:1 as determined by GC. [c] Conversion determined by GC–MS. [d] Isolated yields based on amine substrates. [e] Amine/imine ratio: 40:60. [f] Amine/imine ratio: 90:10.

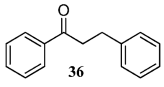
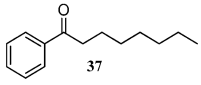
tolerated, and a quantitative yield was achieved in 15 h (Table 2, entry 5). In contrast, aliphatic amines did not give the desired *N*-alkylated products under these reaction conditions.[18]

Substituents at the *ortho*, *meta*, and *para* positions of the aryl ring of the alcohols were well tolerated, and the expected products were obtained in good to excellent yields. In the alkylation of *p*-chloroaniline with *m*-chlorobenzyl alcohol, a 91% conversion was obtained with >99% selectivity for the amine (Table 2, entry 15). Aliphatic and heteroaromatic alcohols like furan-2-ylmethanol (**26**) were also used, and gave high yields of the isolated products and high selectivities for the amine (Table 2, entries 11–14). Compound **26** required a longer reaction time than other alcohols to obtain a good yield of the amine.

To explore the versatility of our catalytic system in other mild hydrogen-transfer processes, we briefly investigated the borrowing-hydrogen reaction between phenethyl alcohol (acetophenone precursor) and benzyl alcohol (benzaldehyde precursor).[19] The oxidation step took place at 55 °C, the presence of *t*BuOK induced an aldol condensation followed by elimination, and finally the double bond was reduced (Table 3). Our system was able to mediate a domino oxidation–alkylation process using primary and secondary alcohols with the formation of negligible amounts of homocoupled products.

Table 3. Ru-catalysed coupling of primary and secondary alcohols.[a]



Entry	Primary alcohol	Secondary alcohol	Product	*t* [h]	Conv. [%][b] (% yield)[c]
1	**1**	 **35**	 **36**	46	98 (76)
2	**32**	 **35**	 **37**	46	90 (78)

[a] Reaction conditions: 1-phenylethanol (1 mmol), primary alcohol (1.1 mmol), *t*BuOK (1 mmol), $[Ru(cod)Cl_2]_n$ (2.5 mol-%), PTA (5 mol-%), toluene (1 mL), 55 °C. [b] GC conversion. [c] Yield determined by GC–MS using 2,4-dimethylbenzophenone as internal standard.

Conclusions

In conclusion, we have shown that aniline can be alkylated with stoichiometric amounts of benzyl alcohol to selectively give the corresponding amine. The reaction uses 2.5 mol-% of commercially available $[Ru(cod)Cl_2]_n$ together with PTA as catalyst, and an equimolar amount of base. We have succeeded in developing a catalytic protocol that brings about the *N*-alkylation of anilines, and also a domino oxidation/C–C bond formation between a secondary and a primary alcohol, at 55 °C in 12–46 h. This $[Ru(cod)Cl_2]_n$/PTA system is a potent catalyst, comparable to the best catalysts reported to date for hydrogen-transfer processes.

Experimental Section

***N*-Benzylaniline (3). General Procedure:** Aniline (92 μL, 1 mmol) and benzyl alcohol (110 μL, 1.06 mmol) were added to a screw-capped glass vial containing $[Ru(cod)Cl_2]_n$ (0.025 mmol, 8 mg), PTA (0.05 mmol, 9 mg), and *t*BuOK (112 mg, 1 mmol) at room temperature open to the air, and then toluene (1 mL) was added. The glass vial was closed, and the mixture was stirred at 55 °C. The reaction progress was monitored by TLC [petroleum ether (40–60)/CH_2Cl_2] or GC–MS (an aliquot of the crude material was passed through a small silica pad using $CHCl_3$ with an equimolar amount of an internal standard). After 15 h, the reaction mixture was cooled to room temp. and filtered. The filtrate was concentrated under vacuum. The crude product mixture was directly loaded onto a silica gel column for flash chromatographic purification (petroleum ether/CH_2Cl_2) to give **3** (177 mg, 97%).

The identities of known compounds **9**, **11**, **13**, **15**, **17**, **19**, **21**, **25**, **27**, **29**, **31**, and **33** were determined by comparison of their spectroscopic properties with reported data (see Supporting Information).

***N*-(4-Chlorophenethyl)aniline (23):**[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.3 Hz, 2 H), 7.21–7.14 (m, 4 H), 6.73 (t, J = 7.3 Hz, 1 H), 6.61 (d, J = 8.3 Hz, 2 H), 4.07–3.47 (br. s, 1 H), 3.38 (t, J = 7.0 Hz, 2 H), 2.88 (t, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 137.4, 131.8, 129.7, 128.9, 128.3, 117.2, 112.6, 44.5, 34.4 ppm. MS (ES): 232.08 $[M + H]^+$. $C_{14}H_{14}ClN$ (231.72): calcd. C 72.57, H 6.09, N 6.04; found C 72.53, H 6.11, N 6.03.

4-Chloro-*N*-(3-chlorobenzyl)aniline (34): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 1 H), 7.28–7.16 (m, 3 H), 7.10 (d, J = 8.8 Hz, 2 H), 6.51 (d, J = 8.8 Hz, 2 H), 4.27 (s, 2 H), 4.09 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 140.8, 134.2, 129.6, 128.7, 127.1, 126.9, 124.9, 122.0, 113.6, 47.3 ppm. MS (ES): 253.02 $[M + H]^+$. $C_{13}H_{11}Cl_2N$ (252.14): calcd. C 61.93, H 4.40, N 5.56; found C 61.88, H 4.41, N 5.54.

1,3-Diphenyl-1-propanone (36). General Procedure: 1-Phenylethanol (121 μL, 1 mmol) and benzyl alcohol (114 μL, 1.1 mmol) were added to a screw-capped glass vial containing $[Ru(cod)Cl_2]_n$ (0.025 mmol, 8 mg), PTA (0.05 mmol, 9 mg), and *t*BuOK (1 mmol) at room temperature open to the air, and then toluene (1 mL) was added. The glass vial was closed, and the mixture was stirred at 55 °C. The reaction progress was monitored by TLC (petroleum ether/CH_2Cl_2) and GC–MS (an aliquot of the crude material was passed through a small silica pad using $CHCl_3$ with an equimolar amount of an internal standard). The reaction was stopped after conversion of the substrate was complete. The resulting reaction mixture was subsequently cooled to room temp., and filtered, and the filter residue was washed very well with dichloromethane. The filtrate was concentrated under vacuum. The resulting crude residue was directly loaded onto a column for flash chromatography (petroleum ether/CH_2Cl_2) to give pure **36** (160 mg, 76%).

The identity of compounds **36** and **37** was determined by comparison of their spectroscopic properties with reported data (see Supporting Information).

Supporting Information (see footnote on the first page of this article): Details of: (1) screening of various Ru precursors with/without

ligand; (2) effect of base in the *N*-alkylation reaction; (3) effect of solvents in the *N*-alkylation reaction; (4) effect of *t*BuOK in the *N*-alkylation reaction at different temperatures. General reaction conditions; References for known compounds; ^{1}H and ^{13}C NMR spectra of isolated products.

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[14] When the reaction was carried out with the alcohol itself as the solvent (6 equiv.), the secondary amine was obtained in good yield, and no further alkylation was observed.

[15] In the absence of the Ru catalyst system, a partial conversion of **1** and **2** into imine **4** was observed. With $[Ru(cod)Cl_2]_n$ alone, a lower yield of amine **3** was obtained.

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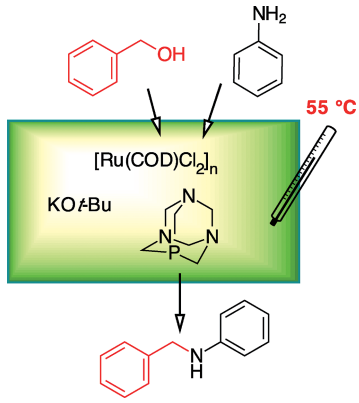
Low-Temperature Alkylation

The alkylation of anilines with alcohols is possible at 55 °C using a Ru catalyst (2.5 mol-%) and a ligand that does not require an inert atmosphere.



Keywords: Homogeneous catalysis / Hydrogen transfer / Alkylation / Ruthenium / Amines / Alcohols

