A ruthenium-based catalytic system for a mild borrowing-hydrogen process

A new ruthenium based catalytic system for a mild borrowing hydrogen process

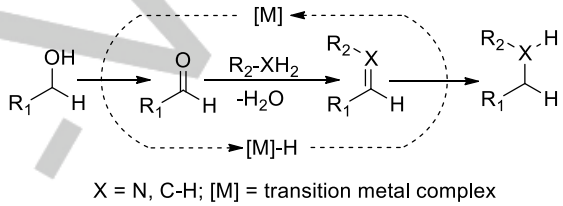
Varsha R. Jumde,[a] Luca Gonsalvi,[b] Antonella Guerriero,[b] Maurizio Peruzzini[b] and Maurizio Taddei[a]*

Abstract: The alkylation of aryl amines using stoichiometric amounts of aliphatic and benzyl alcohols in the presence of t-BuOK was carried out at 55 °C using low catalyst loading of [Ru(cod)Cl2]n/ PTA (1,3,5-triaza-7-phosphaadamantane). The overall borrowing hydrogen process does not demand a controlled nitrogen atmosphere and could also be carried out at room temperature using higher loading of base. A wide range of substrates can be employed in this transformation with good tolerance to different substituents. This catalytic system proved to be efficient also for the other hydrogen transfer reactions such as the tandem oxidation/C-C coupling between 1-phenylethanol and primary alcohols.

Introduction

The catalytic hydrogen transfer reaction is a powerful method that allows the use of stable, more readily available and less harmful alcohols instead of aryl halides, aldehydes or ketones in many of the typical reactions of carbonyl compounds such as in C-C and C-N bond forming reactions.[1] As shown in Scheme 1 the general strategy of borrowing hydrogen reactions is the metal mediated oxidation of the alcohol in situ to the corresponding carbonyl compound that 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 red-ox economic process.[2]

Several noble metals have been employed 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 procedures reported requires high temperatures (>100°C) and long reaction times,[4] making this catalytic protocol unsuitable for thermally unstable molecules. However, some examples of amine alkylation 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 investigated the possibility to perform the Ru-catalyzed amine alkylation with alcohols under mild conditions. Recently the first example of Ru-catalyzed N-alkylation of amines at 65°C (and even at room temperature) using alcohol itself as the reaction solvent was published by Enyong and Moasser.[9]



X = N, C-H; [M] = transition metal complex

Scheme 1. A general borrowing hydrogen strategy..

Herein we report our results related to the efficient alkylation of aryl amines using stoichiometric amounts of aliphatic and benzyl 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

The reaction conditions were optimized choosing a test reaction of N-alkylation of aniline with benzyl alcohol (Scheme 1, Table 1). Based on our previous experience, different Ru-complexes were tested in toluene at 55 °C in presence of base (entry 1-4 in Table 1, see also Table SI-1).[10] Among the various precatalysts used, the most active one, [Ru(η^6-benzene)Cl_2]$_2$/**6** gave 55% conversion with good selectivity in the secondary amine formation (entry 4). An in depth study on 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-catalyzed oxidation[11] and also the NaOH-catalyzed N-alkylation of benzyl alcohols with amines and amides has been reported.[12] These results inspired us to investigate the influence of different bases in the formation of N-benzylaniline (entries 4-8). All bases except Et_3N and K_2CO_3, promoted the first oxidative step of the hydrogen autotransfer (formation of **4** from **1** Scheme 1, see also Table SI-2), whereas only in the presence of KOH, NaOH, *t*-BuOK or *t*-BuONa the reductive step took place with formation of amine **3** (entries 4-7 Table 1). In the presence of [Ru(η^6-benzene)Cl_2]$_2$1,3,5-triaza-7-phospha-adamantane, PTA (**7**)[13] gave a higher conversion

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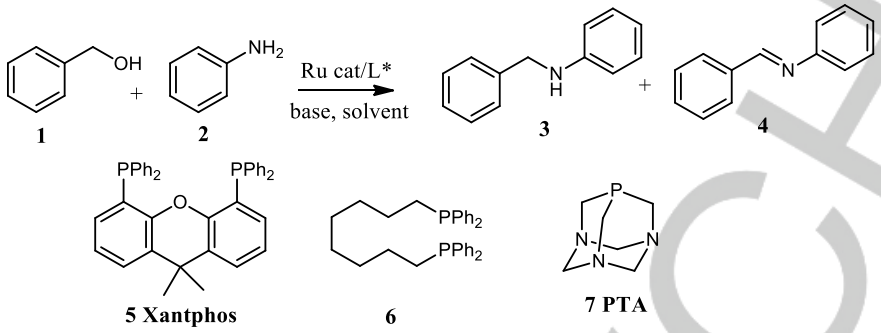
compared to **6** (entries 4 and 9).

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	nr	
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	DME	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 (rt)	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 mentioned) and the catalyst (as given) in 0.5 mL solvent at 55°C unless and until mentioned, in air. b) Determined by GCMS analysis, c) relative proportion determined by GCMS, d) in the parenthesis mentioned the conversion and A:I ratio after 40h, e) expt. run with distilled solvent and under nitrogen atmosphere.

Under the specified reaction conditions, *t*-BuOK emerged as the best base providing higher conversion and selectivity to **3** (entry 9). The effect of solvent under this reaction condition was further evaluated founding that toluene was the best medium, although a solvent free procedure was also possible (entries 9-13, see also Table SI-3).[14]

By increasing the amount of *t*-BuOK, the selectivity to N-benzylamine **3** was favoured, reaching 82% conversion after 15 h with 2.5 mol% of Ru and Ru:P, 1:1 ratio while increasing the reaction time from 15 to 40 h, product **3** was formed in higher conversion and selectivity (entry 14). However, the optimum conversion and selectivity to **3** were obtained with a Ru:P, 1:2 ratio after 15 h of reaction using toluene as solvent (entry 15). In combination with PTA, $[Ru(cod)Cl_2]_n$ (cod = η^4-1,5-cyclooctadiene) was superior to all the other Ru sources, giving 97% conversion after 15 h at 55 °C with formation of pure N-benzylaniline **3** (entries 16-18). The lower limit for catalyst load was investigated: by using 1.25 mol% of catalyst good yield of compound **3** was obtained if a longer reaction time was provided (entry 19). On the other hand, even at double catalyst loading no significant difference in the activity was observed (entry 20), suggesting 2.5 mol% of catalyst as the best choice for the reaction.

It was also possible to reduce the reaction temperature from 55 to 40 °C maintaining good yield and selectivity to N-benzylaniline when the reaction was carried out in the presence of 2 eq of *t*-BuOK (entry 22). Room temperature experiments carried out with 2 eq of base gave acceptable conversion after 24 h but with lower selectivity (entry 21).[15] An important feature of the proposed catalytic protocol is that the reactions can be carried out mixing reagents and solvent in open air and heating the reaction vial without need of an inert atmosphere or degassed solvents; in fact no major difference was observed in the activity of the reaction when it was carried out under nitrogen and using degassed toluene (entry 18).

As the use of stoichiometric amounts of *t*-BuOK could be a limit for application on sensitive substrates, we examined the effect of the base concentration on the reaction products. When less than 0.4 eq 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 eq of *t*-BuOK at 85 °C for 48 h or 0.5 eq of *t*-BuOK at 55 °C for 46 h (see Table SI-4).

Although the mechanism has not been studied in detail so far, it was evidenced by the experimental observations that most suitable precatalyst for the reaction is $[Ru(cod)Cl_2]_n$/**7** and that the presence of *t*-BuOK is important to activate the alcohol (as no reaction occurs 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 transferring then to the imine (formed by condensation of benzaldehyde and aniline) in the last step to form amine. Apparently, the reaction works with 'Ru-catalyst-base' co-operative mechanism to give desired N-benzyl amine with good selectivity and yields.[16] It is important to have the appropriate amount of Ru-catalyst along with stoichiometric amount of base to achieve faster reaction and high selectivity to amine. The base seems to play a role also in the reductive step as, when base loading was decreased, the conversion of benzyl alcohol proceeded to imine **4** that remain unreacted in high ratio respect to amine **3** at the end of the reaction.

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

The reaction scope was further explored by reacting different (primary) alcohols and amines under the optimized reaction conditions (Table 2). The diverse substituents both on alcohol and amine substrates do not influence significantly the reactivity and the selectivity to amine. The *meta* and *para* substituents at the amine do not affect the reactivity and provided higher yields (entries 2, 3), while *ortho* substituent reduced the reactivity giving imine as the major product (entry 4). Use of 2-naphthylamine is well tolerated as complete conversion and quantitative yield was achieved in 15 h (entry 5). On the contrary, aliphatic amines were unable to give the desired N-alkylated products under this reaction conditions.[18]

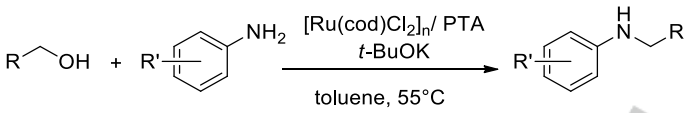
Substituents at *ortho, meta* and *para* positions at the aryl substituent of alcohols are well tolerated and the expected products obtained in good to excellent yields. In the alkylation of *p*-chloro aniline with *m*-chlorobenzyl alcohol 91% conversion was obtained with > 99% selectivity to amine (entry 15). Aliphatic and heteroaromatic alcohols like furan-2-ylmethanol **26** were also employed giving high yields of the isolated products and high selectivity to amine (entries 11-14). Compound **26** required longer reaction time compared to other alcohols to obtain good yield of the amine.

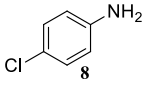
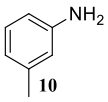
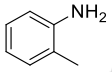
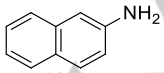
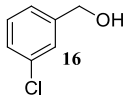
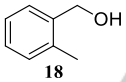
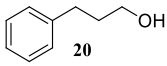
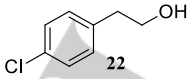
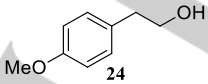
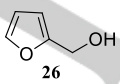
In order to explore the versatility of our catalytic system in other mild hydrogen transfer processes, we briefly investigated the borrowing hydrogen reaction between phenethyl alcohol (acetophenone precursor) and benzyl alcohol (benzaldehyde precursor).[19] The oxidation step took place at 55 °C and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

Conclusions

As conclusion we found that aniline can be alkylated with stoichiometric amount of benzyl alcohol with selective amine formation using 2.5 mol% of commercially available $[Ru(cod)Cl_2]_n$ and PTA as catalyst in presence of the equimolar amount of base. We have succeeded in developing the catalyst protocol that brings out N-alkylation of anilines and 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 proved to be the potent catalyst and can be comparable to the best catalysts reported for the hydrogen transfer processes until now.

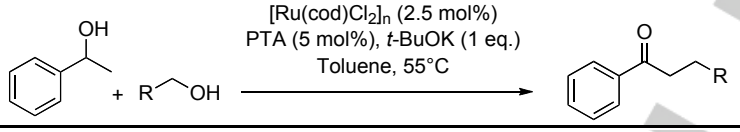
Table 2. Different anilines alkylation.[a]

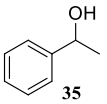
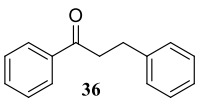
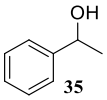
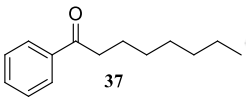


Entry	Alcohol	Amine	Product	*t* [h]	Conv. [%][b, c] (Yield %)[d]
1	**1**	**2**	**3**	15	99 (97)
2	**1**	 **8**	**9**	12	95 (83)
3	**1**	 **10**	**11**	12	86 (79)
4	**1**	 **12**	**13**	48	75 (30)[e]
5	**1**	 **14**	**15**	15	99 (90)
6	 **16**	**2**	**17**	15	92 (85)
7	 **18**	**2**	**19**	16	91 (84)[f]
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 eq), $[Ru(cod)Cl_2]_n$ (2.5 mol%) and 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)] A:I = 40:60 [f)] A:I = 90:10

Table 3: Ru-catalyzed coupling of primary and secondary alcohols[a]



Ent.	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%) and PTA (5 mol%), toluene (1 mL), 55 °C. [b)] GC conversion. [c)] Yield determined by GCMS using internal standard 2,4-dimethylbenzophenone.

Experimental Section

N-Benzyl aniline (3), general procedure. Aniline (92 μL mg, 1 mmol) and benzyl alcohol (110 μL, 1.06 mmol) were added in 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 in open atmosphere followed by the addition of toluene (1 mL). The glass vial was closed and stirred at 55 °C and the reaction progress was monitored by TLC (eluent: Pet. Eth (40-60):DCM) or GC-MS (an aliquot of the crude was passed through a small silica pad using $CHCl_3$ with equimolar amount of internal standard). After 15 h, the reaction mixture was cooled to rt and filtered. The organic solvent was concentrated under vacuum. The crude reaction mixture was directly loaded on silica gel column for flash chromatographic purification (eluent: Pet. Ether: DCM). Yield: 177 mg, 97 %. The identity 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 SI).

N-(4-Chlorophenethyl)aniline (23).[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.3 Hz, 2H), 7.21-7.14 (m, 4H), 6.73 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 8.3 Hz, 2H), 4.07 – 3.47 (br s, 1H), 3.38 (t, J = 7.0 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H). ^{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. [ES/MS]: 232.08 $[M+H]^+$ Anal. Calcd. for $C_{14}H_{14}ClN$ 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, 1H), 7.28 – 7.16 (m, 3H), 7.10 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 4.27 (s, 2H), 4.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 145.9, 140.8, 134.2, 129.6, 128.7, 127.1, 126.9, 124.9, 122.0, 113.6, 47.3. [ES/MS]: 253.02 $[M+H]^+$ Anal. Calcd. for $C_{13}H_{11}Cl_2N$ 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 (121μL, 1 mmol) and benzyl alcohol (114 μL, 1.1 mmol) were added in a screw capped glass vial containing $[Ru(cod)Cl_2]_n$ (0.025mmol, 8 mg), PTA (0.05 mmol, 9 mg) and *t*-BuOK (1 mmol) at room temperature in open atmosphere followed by the addition of toluene (1 mL). The glass vial was closed and stirred at 55°C. The reaction progress was monitored by TLC (eluent: PE:DCM) and GC-MS (an aliquot of the crude was passed through a small silica pad using $CHCl_3$ with equimolar amount of internal standard). The reaction was stopped after the complete substrate conversion. The obtained reaction mixture was subsequently cooled to rt, filtered and washed very well with dichloromethane. The filtrate was concentrated under vacuum to obtain the crude. This crude reaction mixture was directly loaded on a column for flash chromatography (eluent: Pet. Eth.: DCM) to afford the pure product (160 mg, 76 %). The identity of compounds **36** and **37** was determined by comparison of their spectroscopic properties with reported data (see S.

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Keywords: hydrogen transfer • alkylation • ruthenium homogeneous catalysis • amines

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

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

[16] The N-alkylation reactions might be proceeding via a similar mechanism to the one reported in: a) L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2014**, *53*, 761-765; b) C. Gonzalez-Arellano, K. Yoshida, R. Luque, P. L. Gai, *Green Chem.* **2010**, *12*, 1281-1287.

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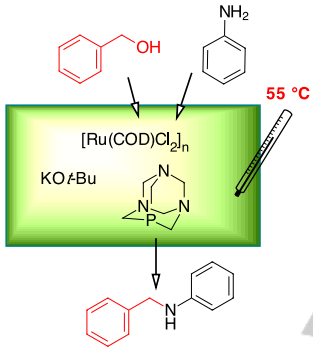
Layout 1:

FULL PAPER

Alkylation of anilines with alcohols is possible at 55 °C using Ru catalysis (2.5% mol) with a ligand that not requires controlled atmosphere.



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A new ruthenium based catalytic system for a mild borrowing hydrogen process

Key topic: Low-temperature alkylation