Hydrogen Autotransfer in the *N*-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles

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1. Introduction and Definitions

The chemistry of amines, amides, and other nitrogen-containing compounds plays a central role in the organic synthesis. In fact, the first synthesized organic compound was urea.[1] The great importance of this type of nitrogen-containing compound takes its roots from several factors. The first one is that Nature has chosen different nitrogen derivatives as their typical building blocks in the construction of Life, such as amino acids and nucleotides.[2] But not only the main constituents of Nature are included in this category; other important minor compounds such as neurotransmissors, natural toxics, alkaloids, and other active biomolecules should be included in this group.[3]

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Gabriela Guillena was born in Alicante (Spain) in 1970 and received her B.Sc. degree (1993) from the University of Alicante. After spending one year as postgraduate student in the group of Prof. D. Seebach (ETH, Zürich), she returned to the University of Alicante and received her M.Sc. (1995) and Ph.D. (2000) degrees. After two years as a postdoctoral fellow in the research group of Prof. G. van Koten (University of Utrecht, Netherlands), she returned to the University of Alicante where she became assistant professor (2003) and associate professor (2007) through the National Habilitation process. Her current research interest is focused on new organic methodologies and asymmetric organocatalysis.

The unquestionable interaction between nitrogen-containing compounds with living organisms has impulsed the pharmaceutical and agrochemical industries into the development of many different molecules containing this atom.[4] In fact, the vast majority of compounds used in pharmaceutical companies contain at least one nitrogen atom. Moreover, nitrogen-containing compounds are of great importance in other aspects of the chemical industry, such as in the cases of preparation of dyes, detergents, surfactants, fabric softeners, emulsion and pigment stabilizers, epoxy hardeners, vulcanizing agents, and additives in the petroleum industry.[5]

Among nitrogen-containing compounds, amines are the main and most important ones, and therefore, there are a plethora of different methods and variants to prepare them,[6] including electrophilic alkylation processes,[7] reductive alkylation processes,[8] and amination of aryl halides.[9]

All of the above protocols have reached excellent levels of yield. However, since the beginning of the 1990s,[10] the attention of chemists has been drawn to the necessity to develop methods with increasing environmental awareness and integrated in sustainable processes.[11] A re-examination of the established strategy of synthesis, utilization of hazardous chemicals, and utility of solvents, as well as their environmental impact, has to be taken into account. Thus, following these environmental aspects, it is necessary not

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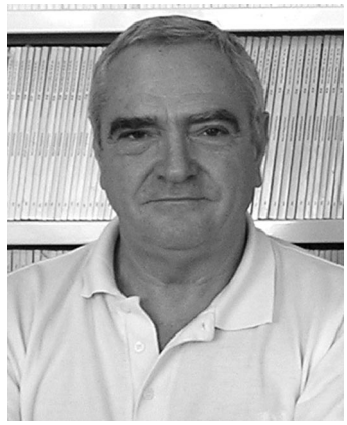
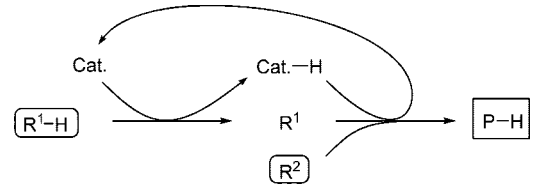
Diego J. Ramón was born in Alicante (Spain) in 1965 and received his B.Sc. (1988), M.Sc. (1989), and Ph.D. (1993) degrees from the University of Alicante. After spending two years as a postdoctoral fellow at the Eidgenössische Technische Hochschule in Zürich (ETH-Zentrum), he returned to the University of Alicante and, after a short stay at Miguel Hernández University, became associate professor (2000) in the former university. Dr. Ramón has been visiting professor at Debye Institute (University of Utrecht, Netherlands, 2001). In 1994, he was awarded the National Prize for Young Scientists of the Spanish Royal Society of Chemistry. His current research interest is focused on organometallic chemistry and asymmetric synthesis.



Miguel Yus (left) was born in Zaragoza (Spain) in 1947 and received his B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to Spain to the University of Oviedo where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in Organic Chemistry at the University of Alicante where he is currently the head of the Organic Synthesis Institute. Professor Yus has been visiting professor at different institutions and universities such as ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, and Strasbourg. He is co-author of more than 450 papers (among them 7 review articles in this journal) mainly in the field of the development of new methodologies involving organometallic intermediates. His current research interest is focused on the preparation of very reactive functionalized organometallic compounds and their use in synthetic organic chemistry, arene-catalyzed activation of different metals, and preparation of new metal-based catalysts for homogeneous and heterogeneous selective reactions. Among others, he has received the Spanish−French Prize (1999), twice the Japan Society for the Promotion of Science Prize (2000, 2007), and the Stiefvater Memorial Lectureship Award (2001). Professor Yus has belonged, among others, to the advisory board of the journals Tetrahedron, Tetrahedron Letters, European Journal of Organic Chemistry, Chemistry Letters, Current Organic Chemistry, and Trends in Organic Chemistry. Professor Yus, Dr. Ramón, and other members of the ISO founded the new chemical company MEDALCHEMY S.L. to commercialize fine chemicals.

only to maximize the chemical yields but also to minimize the waste production and ideally to eliminate it.

Scheme 1. General Scheme for a Hydrogen Autotransfer Process



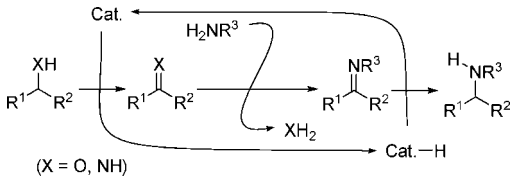
There are different parameters and ratios to evaluate the environmental impact of a reaction.[12] Perhaps the most simple and easy-to-calculate parameter is the atom efficiency, which gives a rapid idea of the percentage of the material incorporated to the product, as well as its waste (see eq a). According to this equation, the aforementioned methodology for the preparation of amines has a very low incorporation of reagents into the final product and a very high amount of waste. The presence of leaving groups with high molecular weights in the reagents, as well as the use of stoichiometric amount of reagents that only transfer small portions of them to the final product, decreases enormously the atom efficiency of the process.

$$\text{atom efficiency (\%)} = \text{yield (\%)} \times \frac{M_w \text{ of final product}}{\sum_{i=\text{reagents}} (\text{equiv} \times M_w)_i + \sum_{j=\text{catalysts and additives}} (\text{equiv} \times M_w)_j} \quad \text{(a)}$$

There are only few general and attractive methodologies for the synthesis of amines that take into account the atom efficiency factor. One of them is the hydroamination of olefins and alkynes,[13] which is limited due to the electrophilic character of the nitrogen reagent, as well as the existence of the corresponding olefin. Using this approach, it is impossible to perform the methylation, benzylation, and related processes. Moreover, the regioselectivity of the addition is an important aspect that never should be underestimated. Another interesting protocol is the hydrogen autotransfer process,[14] known also as either borrowing hydrogen[15] or self-supplying system for active hydrogen.[16] This type of reaction is included in the general hydrogen transfer reaction field[17] and always starts with the abstraction of a hydrogen atom from the starting reagent (R^1−H) by the corresponding catalyst to generate a new reagent (R^1). The abstracted hydrogen is further returned and incorporated to the final product, hence the reaction name (see Scheme 1). In the case of carbon−carbon bond-formation reactions, two subtypes of pathways have been found, depending on the sequence of reaction of the three formed reagents (R^1, R^2, and Cat.−H). One of them is the so-called activation of the intermediate,[18] in which the second step is the condensation reaction between both reagents R^1 and R^2, and finishes with the reduction of the formed double bond by a hydride catalyst. Another one is the so-called activation of reagent,[19] in which the second step is the hydrometalation of the initial reagent R^2 by the hydride catalyst, and finishes with the addition reaction of the above organometallic to the in situ generated reagent R^1.

Among all different protocols for the syntheses of amines, the hydroamination and hydrogen autotransfer processes are clearly superior and their superiority is illustrated, for instance, by the fact that industries synthesizing amine intermediates for foam booster in household detergents and other applications only use these two strategies. So, whereas P&G−Chemicals, Albermarle, and Huntsman use the hy-

Scheme 2. General Scheme for the *N*-Alkylation of Amines through a Hydrogen Autotransfer Process



droamination processes, Lonza (U.S.A.), Clariant (Germany), Kao (Japan), and Feixiang Chem. (China) use the hydrogen autotransfer protocols.

The alkylation of amines through a hydrogen autotransfer process should be classified into the intermediate activation set (Scheme 2), in which either an alcohol or an amine is the source of the electrophilic agent, changing the usual typical nucleophilic behavior of these compounds. This strategy has obvious advantages toward hydroamination processes such as the simplicity of protocol, the availability of starting reagents, and the important number of catalysts able to perform this reaction.

Although some previous reviews have covered partially the use of hydrogen autotransfer process for the preparation of amines,[20] there is not so far a general article showing the great potential of this strategy for these thrifty times. The review is assorted by the type of general source of the used electrophile, with the initial morphology of the reaction media, and taking into consideration the type of metal used.

2. Alcohols as Source of Electrophiles

The alkylation of amines by alcohols with loss of water is a thermodynamically favored process where the loss of a carbon−oxygen bond for forming a carbon−nitrogen bond is compensated by the gain of an oxygen−hydrogen bond from a nitrogen−hydrogen bond.[21] In fact, the suitability of this reaction was already proven in 1901, when the alkylation of aniline was successfully performed using different sodium alkoxides.[22]

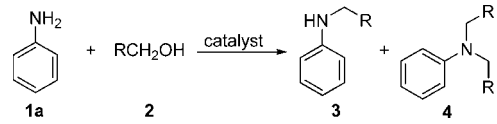
2.1. Heterogeneous Catalysts

Along this section, different examples of catalysts which were initially in a different phase (solid, liquid, gas) from the reagents will appear. The heterogeneous catalysts[23] have some advantages over the homogeneous one, with the possible easy recovery being the most important one.[24]

2.1.1. Derived from Silicon and Aluminum

Silicon and aluminum oxides are collected in the same section because of their similar behavior. In fact, different metal oxides can drive the *N*-alkylation of amines through an acid-catalyzed mechanism. However, there are several facts that could show us that, in the below reported cases, the reaction pathway goes through a hydrogen autotransfer process. One of them, favoring the hydrogen autotransfer process, is the presence of the corresponding aldehyde or alkane in the reaction media, which came from the oxidation of the alcohol and a decarbonylation process. Other arguments are the absence of reaction with tertiary alcohols, as well as the total regioselectivity for secondary alcohols, or the no-relationship between accessible acid sites and kinetics.[25] All these facts may indicate that the process goes through a hydrogen autotransfer mechanism and not through an acid-catalyzed process.

Table 1. *N*-Alkylation of Aniline with Primary Alcohols using Silicon or Aluminum Oxides



entry	catalyst	R	*T* (°C)	no.	yield (%)	no.	yield (%)
1	SiO_2	H	362	**3a**	20	**4a**	25
2	SiO_2	Me	385	**3b**	47	**4b**	13
3	SiO_2	Et	385	**3c**	37	**4c**	12
4	SiO_2	Pr	400	**3d**	27	**4d**	9
5	SiO_2	Me	400	**3b**	28	**4b**	5
6	$V_2O_5-SiO_2$	Me	400	**3b**	66	**4b**	15
7	Al_2O_3[a]	H	400	**3a**	32	**4a**	50
8	γ-Al_2O_3	H	400	**3a**	15	**4a**	2
9	γ-Al_2O_3	H	375	**3a**	24	**4a**	18
10	γ-Al_2O_3	H	200	**3a**	41	**4a**	5

[a] Prepared from $Al(OPr^i)_3$.

One of the oldest examples of *N*-alkylation by a hydrogen autotransfer process was performed by using silica gel as catalyst.[26] In this early work, simple aniline (**1a**) was alkylated with different aliphatic primary alcohols (**2**, 100−200 mol %) at very high temperatures to give a mixture of substituted anilines **3** and **4** with, in general, moderated yields (Table 1, entries 1−4). The detection of the corresponding aldehydes and hydrogen as byproduct showed that the reaction pathway was the hydrogen autotransfer process, with the silica gel being a modest catalyst to promote this reaction.

The aforementioned efficiency could be enhanced by mixing another metal oxide on the silica gel support.[27] Thus, when vanadia (V_2O_5), prepared by calcinations of NH_4VO_3, was used as the catalyst for the ethylation of aniline under flow reaction conditions, only 21% of compound **3b** was obtained, together with 6% of **4b**. However, when vanadia was supported on silica gel (2−20 wt %) by wet impregnation of silica with the appropriate amount of NH_4VO_3 and oxalic acid, the results were better. So, the conversion reached up to 93%, showing that the support enhanced the results (Table 1, entry 6) compared with the use of either the vanadia or the silica alone (Table 1, entry 5).

Conversely to typical acid metal oxides, basic metal oxides clearly catalyzed the *N*-alkylation of amines. Thus, different types of alumina (Al_2O_3) have been used as catalysts in this process. When alumina, prepared from aluminum isopropoxide, was used as heterogeneous catalyst in a conventional flow reactor and using a vaporized mixture of aniline (**1a**) and methanol (**2a**, 15 000 mol %) at 400 °C, the main product was the double alkylated compound **4a**. However, when the catalyst used was commercially available γ-Al_2O_3 under the same reaction conditions, the main product was compound **3a** with lower yield (compare entries 7 and 8 in Table 1). These facts highlighted the crucial role of the preparation of the catalyst.[28a] A systematic study using a fixed bed of γ-Al_2O_3 was carried with an integral-flow reactor,[28b] showing that the yield increased with the reaction temperature, with compound **4a** being the main one. Also, the increase of methanol/aniline molar ratio enhanced the selectivity toward the amine **4a**. The maximum amount of *N*-methylaniline (**3a**) was achieved at 375 °C and with an alcohol/aniline ratio of 2 (Table 1, entry 10). The kinetic measurements showed that the first methylation was a pseudofirst-order reaction with respect to the aniline concentration, with the apparent activation energies for the first and second methylation being 62.7 and 48.3 kJ mol^{-1}, respectively.

Better selectivity was obtained using gas-phase conditions and γ-Al_2O_3 at atmospheric pressure and lower temperature (Table 1, entry 10). Under similar conditions, other different alcohols such as 1- and 2-propanol (30 000 mol %) could be used as the initial source of the electrophile. Whereas for the primary alcohol yields up to 72% for **3c** and 8% for **4c** were reached, only 10% of the monomethylated aniline derived from the secondary one was obtained, probably due to steric effects.[29] Other amines such as octylamine, benzylamine, and chiral α-methylbenzylamine could be alkylated under similar reaction conditions using methanol, 1-propanol, or benzylic alcohol, with high conversions and selectivities for the monoalkylated products. Even ammonia (**5**) could be alkylated using benzylic alcohol, although in this case the reaction was performed at 170 °C under ammonia atmosphere, giving only 48% of benzylamine as well as 23% of di- and trialkylated amines.[30]

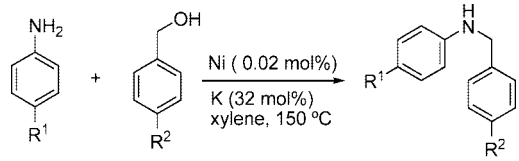
The selectivity of this process could also be changed to the dialkylated product just by changing the reaction conditions. Thus, the alkylation of 1-butylamine with methanol (alcohol/amine ratio = 3) at 320 °C and 4 atm gave *N,N*-dimethyl-1-butylamine as the main product, with this compound being an important component for the preparation of different polymers.[31]

2.1.2. Derived from Nickel

Different nickel catalysts have been historically used in the *N*-alkylation of amines using alcohols as electrophilic source. Thus, particles of nickel obtained by reduction of NiO at 300 °C were effective catalysts in the alkylation of different aromatic amines, such as aniline (**1a**) or *para*-toluidine, with aliphatic alcohols, such as methanol, ethanol, or cyclohexanol. For instance, the corresponding *N*-ethylaniline (**3b**) was obtained in 30% yield, by using 10% weight of nickel catalyst, 2/1 ratio of ethanol/aniline, at 180 °C in an autoclave for 12 h. In a similar way, it was possible to obtain cyclohexylamine or dicyclohexylamine from cyclohexanol and ammonia (**5**) by just varying the reaction temperature from 150 °C for the primary amine to 190 °C for the secondary one.[32]

Better results were achieved by using nickel particles (100 mesh) as catalyst and potassium as base in the alkylation of aniline (**1a**) with benzyl alcohol (**6a**, 200 mol %), as well as the corresponding 4-substituted derivatives, in xylene at 150 °C (see Table 2).[33] The reaction was performed in a Dean−Stark apparatus until water evolution was completed. Interestingly, whereas the presence of electron-withdrawing groups in the benzyl alcohol derivative **6** decreased the reaction rate, the opposite effect was observed for anilines **1**. Under these conditions, the reaction could also be performed using simple aliphatic primary alcohols **2**, such as hexanol or decanol.

Table 2. *N*-Alkylation of Aromatic Amines with Benzylic Alcohols Using Nickel Particles



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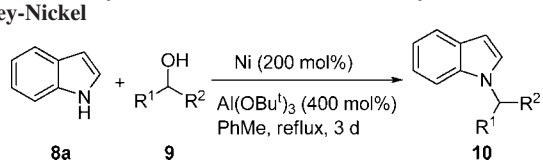
entry	R^1	R^2	no.	yield (%)
1	H	H	**7a**	89
2	H	Cl	**7b**	78
3	H	Me	**7c**	89
4	H	MeO	**7d**	84
5	Cl	H	**7e**	87
6	Me	H	**7f**	93
7	MeO	H	**7g**	88

Other catalysts such as nickel supported in SiO_2 or mixtures of SiO_2/Al_2O_3 were able to catalyze the reaction of 2-aminoethanol with ammonia (**5**) to give ethylenediamine,[34] with the second supported catalyst being more effective than the first one. However, yields never surpassed 25% of the product.

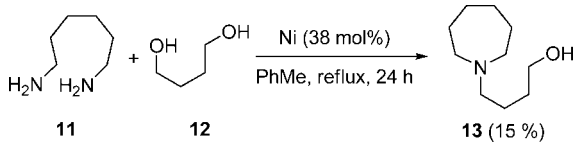
Without doubt, the so-called Raney-nickel or nickel sponge catalyst has been the most used catalyst in this context. These catalysts are produced when a block of nickel−aluminum alloy is treated with concentrated sodium hydroxide. This treatment, called activation, dissolves most of the aluminum out of the alloy. The resulting porous structure has a large surface area, which gives high catalytic activity, obtaining different types of Raney-nickel depending on the basic treatment, in all cases with a high amount of nickel (>85%), with the remaining aluminum helping to preserve the porous structure of the catalyst.[35] Thus, *N*-alkyl substituted anilines of type **3** were prepared using Raney-nickel (ca. 60% weight) in a refluxing mixture of aniline and an excess of alcohol (500 mol %) for 16 h. For straight-chain primary alcohols different from methanol, yields ranked 78−83%, while those derived from branched primary alcohols gave the corresponding *N*-alkyl anilines in only 41−49% yields.[36] Shorter reaction times (ca. 2 h) were sufficient if a large amount of catalyst was employed in similar reaction conditions. Following a similar protocol, not only aniline (**1**) but also 2,5-dimethoxyaniline and 2-naphthlyamine could be alkylated selectively using primary and secondary alcohols, such as ethanol, 2-propanol, 1-butanol, cyclohexanol, and benzyl alcohol, with yields ranging from 22 to 82%.[37] When 1 equiv of aluminum *tert*-butoxide was added into the reaction mixture, only 30% of Raney-nickel was necessary, with the amount of alcohol being decreased to 3−1 equiv with respect to the aniline. Under these conditions, the corresponding alkylated aniline derivatives could be obtained with excellent results (96−98%). This procedure could also be applied to other amines, such as cyclohexylamine, with similar results.[38] A kinetic study of the process was carried out, finding a reaction-rate law that depended on first order for aniline and aluminum *tert*-butoxide concentrations.[39] Also the influence of the substitution of the aniline in the reaction rate was studied. The data showed that the presence of electron-donating groups in the aromatic ring increased the reaction rate, whereas electron-withdrawing groups decreased it, with the exception of 4-methoxyaniline (**1d**) and the related 3-methoxyaniline, which reacted slower than aniline (**1a**). A plausible explanation for this behavior came from the possible complexation of the methoxy group and the aluminum atom, exerting the possible electron-donating effect of the methoxy group. According to the observed rate law, a mechanism scheme was postulated, in which, after the oxidation of alcohol to the corresponding carbonyl compound catalyzed by the Raney-nickel, the obtained carbonyl compound coordinates to the aluminum alkoxide, giving an activated carbonyl species that, in turn, reacts with aniline to yield the corresponding imine, which is reduced finally by the alcohol in a Meerwein−Ponndorf−Verley type process.

Table 3. *N*-Alkylation of Indole with Secondary Alcohols using Raney-Nickel



entry	R^1	R^2	no.	yield (%)
1	Me	Me	**10a**	90
2	Me	Et	**10b**	94
3	$(CH_2)_5$		**10c**	70

Scheme 3. Double *N*-Alkylation of a Primary Amine by an Alcohol and Another Amine Using Raney-Nickel

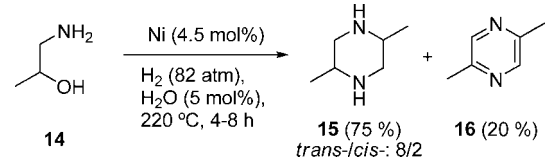


Following the former protocol, indole (**8a**) could be successfully alkylated using an excess of a secondary alcohol (**9**, 4 000 mol %) in the presence of an excess of aluminum *tert*-butoxide, and catalyzed by Raney-nickel W-2, after three days at toluene reflux (Table 3).[40]

Raney-nickel was effective not only in the monoalkylation of amines but also in their double alkylation, as is depicted in Scheme 3.[41] In this case, the alkylation of 1,6-hexanediamine (**11**) using equimolecular amounts of 1,4-butanediol (**12**) and a Dean−Stark apparatus surprisingly gave the azepine derivative **13**, with a hydroxy and an amine group, being the source of the successive electrophiles (for the use of amines as the source of electrophiles, see section 3). The considerable amount of ammonia evolved from the reaction media showed that the hydrogen autotransfer pathway was involved in both alkylation processes. The first step might be the oxidation of an amine group to the corresponding imine, followed by condensation of an amine group with the in situ formed imine, to give the expected cyclic imine and ammonia, and the final reduction gives the corresponding hexahydroazepine. Finally, the second alkylation takes place with the alcohol **12**.

Several secondary and tertiary amines were prepared in 34−80% yield using nickel catalyst (12 mol %) under a hydrogen atmosphere (100 atm pressure) at 200 °C in a few hours, using different aliphatic and cyclic amines as nucleophiles, and ethanol, 1-butanol, and cyclohexanol (200 mol %) as electrophiles.[42] The involved pathway is similar to the aforementioned one, with the nickel catalyst favoring the oxidation of the alcohol to the corresponding aldehyde or ketone and generating nickel hydride intermediates. Then, after formation of the corresponding imine, by condensation of the amine and the in situ formed carbonyl compound, the final reduction took place by the nickel hydride intermediate. Although the last reduction could be performed partially by the hydrogen present in the reaction media, the hydrogen autotransfer process was also acting. In fact further studies on similar processes showed that the presence or absence of hydrogen in different hydrogen autotransfer processes neither altered the kinetics nor the results of the processes, only affecting the deactivation of the nickel catalyst. In fact, the presence of hydrogen prevented the formation of an inactive nitride layer on the metal surface, as well as the formation of different nickel−carbonyl derivatives, permitting a decrease of the amount of the catalyst.[43]

Scheme 4. Double *N*-Alkylation of 1-Aminopropan-2-ol Using Raney-Nickel



Different nitrogen-containing heterocyclic compounds were prepared using amino alcohol derivatives as starting materials and Raney-nickel as catalyst under a hydrogen atmosphere. For instance, 1-aminopropan-2-ol (**14**) underwent a double hydrogen autotransfer process to form a mixture of *cis*/*trans*-piperazine **15** and the related aromatic pyrazine **16**.[44] The careful study of the reaction conditions permitted the authors to obtain the aliphatic heterocycle **15** as the main product (Scheme 4).

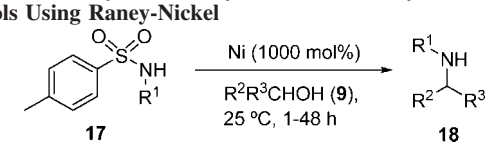
The same reaction using Raney-nickel (ca. 40 mol %) with different 4-aminobutan-1-ol derivatives under a hydrogen atmosphere (80−90 atm) at 195 °C gave the corresponding pyrrolidines with, in general, moderate yields (50−92%).[45]

Raney-nickel is a typical catalyst for the hydrogenation of different functionalities containing nitrogen atoms. Interestingly, *N*-alkylated amines could be formed also during the hydrogenation of nitriles. Thus, in the hydrogenation of different arylalkylnitriles using nickel at 115−125 °C under hydrogen atmosphere and using cyclohexanol as solvent, two compounds were isolated; one of them was the expected arylalkylamine, and the other one was the corresponding *N*-cyclohexyl arylalkylamine with yields ranging from 5 to 45% for the last compound.[46] Although the authors did not give any clear explanation for the formation of the second product, it looks probable that, after the standard hydrogenation to the primary amine, the alcoholic solvent suffered an oxidation process to give a nickel hydride intermediate. Then, the condensation of the formed primary amine with cyclohexanone gave the corresponding imine, which was finally reduced by the formed nickel hydride to the secondary amine byproduct. Although the last reduction could be performed partially by the hydrogen present in the reaction media, the hydrogen autotransfer process was also acting, as was mentioned previously. The use of a primary alcohol as solvent gave similar results.

Using a similar strategy for the alkylation of the in situ formed amines, different thioamides could be transformed into the corresponding *N*-ethyl amines derivatives by using a large excess of Raney-nickel as catalyst under a hydrogen atmosphere at reflux of ethanol after a long period of time.[47] In a similar way, hydrazobenzene and azoxybenzene could be converted into the corresponding *N*-ethylaniline (**3b**) by using Raney-nickel (500% in weight with respect to the starting reagent) under hydrogen atmosphere in refluxing ethanol with 43% and 36% yield, respectively.[48]

With this idea in mind, recently different *N*-sulfinylamides **17** have been transformed into the corresponding *N*-alkylated amines **18** using a large excess of Raney-nickel, through a tandem process involving initially a desulfinylation step to liberate the primary amine followed by the hydrogen autotransfer process with the alcohols, which are at the same time the solvent and the source of electrophile (Table 4). Yields were in general good, although the reaction times for primary alcohols were in the range of hours whereas those for the secondary ones were days. The reaction gave similar results for aromatic or aliphatic derivatives, with the presence

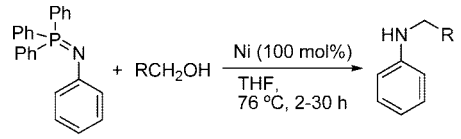
Table 4. Desulfinylation−Alkylation of *N*-Sulfinylamides with Alcohols Using Raney-Nickel



entry	R^1	R^2	R^3	no.	yield (%)
1	Ph	Me	H	**18a**	81
2	4-$MeOC_4H_4$	Me	H	**18b**	83
3	$PhCH_2$	Me	H	**18c**	0[a]
4	$Ph(CH_2)_2$	Me	H	**18d**	89
5	$Ph(CH_2)_2$	Me	Me	**18e**	76
6	PhCHMe	Me	H	**18f**	78
7	PhCHMe	Me	Me	**18g**	80

[a] Decomposition products.

Scheme 5. *N*-Alkylation Process by an Indirect aza-Wittig Reaction of *N*-(Triphenylphosphoranylidine)aniline with Primary Alcohols Using Nickel Nanoparticles



of substituents on the aromatic ones not seeming to have a detrimental effect.[49] The same protocol has been carried out with the related simple primary amines, obtaining similar results. The main drawback of the reaction was the large amount of catalyst required, although it could be recovered by filtration without losing its efficiency, at least after four cycles, but with longer reaction times being needed.

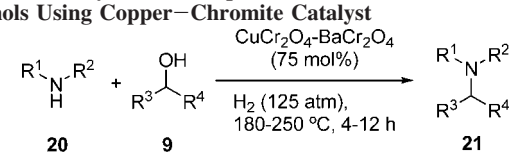
The nanoparticles of nickel obtained in the reduction of nickel(II) chloride with a large excess of lithium powder and a substoichiometric amount of 4,4′-di-*tert*-butylbiphenyl were used as catalyst for the *N*-alkylation process through an indirect aza-Wittig reaction between *N*-(triphenylphosphoranylidine)aniline (**19**) and different primary alcohols, producing moderate yields (Scheme 5). The obtained results seemed to be constant and independent of the primary alcohol used. So, benzyl alcohol, linear alkyl alcohols, and the related branched ones reached practically the same chemical yield.[50]

2.1.3. Derived from Copper

Simple copper or its oxide have been used as catalysts in the preparation of pyrazine from 2-aminoethanol, similar to that depicted in Scheme 4, by a hydrogen autotransfer process in a continuous flow reactor. However, the achieved yield for the aromatic compound was very low (6%), even at temperatures as high as 300 °C. After a few hours, the copper catalyst lost its activity, attributable, probably, to its reduction.[51]

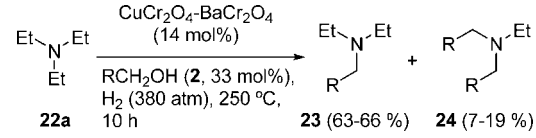
In order to stabilize copper catalysts, other complexes have been tested. Thus, one of them is the so-called copper−chromite catalyst ($CuCr_2O_4$−$BaCr_2O_4$), in which the association of copper and chromium increases the metal surface area, the hydrogen adsorption and storage, and the acidity sites. This catalyst can be easily prepared by mixing barium nitrate, copper nitrate, and ammonium chromate, which gives a complex mixture of different chromates. The ignition of this mixture at 350−450 °C yields the copper−chromite catalyst, in which the initial amount of reagents could be modified in order to obtain the desired aspect.[52] So, using $CuCr_2O_4$–$BaCr_2O_4$ as catalyst, several aliphatic amines **20** have been converted to the corresponding secondary or tertiary amines **21** with modest yields using an equimolecular amount of a primary or secondary alcohol **9** by heating under a hydrogen atmosphere (Table 5).[53]

Table 5. *N*-Alkylation of Aliphatic Amines with Secondary Alcohols Using Copper−Chromite Catalyst



entry	R^1	R^2	R^3	R^4	no.	yield (%)
1	$CH_3(CH_2)_4$	H	Me	H	**21a**	39
2	$CH_3(CH_2)_4$	H	Me	Me	**21b**	43
3	$CH_3(CH_2)_4$	H	Et	H	**21c**	15
4	$(CH_2)_5$		Me	H	**21d**	31
5	$(CH_2)_5$		Me	Me	**21e**	46
6	$(CH_2)_5$		$(CH_2)_5$		**21f**	59
7	PhCHMe	Me	Me	H	**21g**	67
8	Bu^iCHMe	H	Et	H	**21h**	61

Scheme 6. Transalkylation of Triethylamine with Primary Alcohols Using Copper−Chromite Catalyst

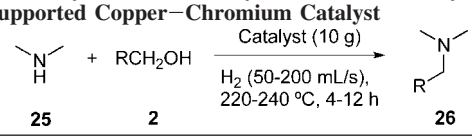


The aforementioned catalyst has been used in the transalkylation of triethylamine (**22a**) with a low amount of a primary alcohol **2**, such as octanol and dodecanol (Scheme 6). The reaction was performed under a high hydrogen pressure and only took place at 250 °C. At lower temperatures, the reaction did not take place. In all cases tested, the reaction gave the amine **23** as the main product with a small amount of the double transalkylated amine **24**.[54] Although the whole mechanism is not clear, the reaction might start with the dehydrogenation of starting amine **22a** to give the corresponding iminium derivative, which liberates diethylamine (and acetaldehyde); the same process will be discussed in section 3. Then, the reaction pathway goes probably through the known hydrogen autotransfer process, yielding the amine **23**. A second similar sequence, but starting from the tertiary amine **23**, might explain the presence of the byproduct **24**. This protocol has been used in the transalkylation of triethylamine (**22a**) with mixtures of commercially available long-chain surfactant alcohols at 250−300 °C and under 19 atm of hydrogen, obtaining the corresponding amines **23** with good yields (74−89%).[55] It should be pointed out that these amines could be used as efficient surfactants.

The $CuCr_2O_4$−$BaCr_2O_4$ catalyst has also been successfully used in the preparation of cyclohexylamine or aniline by reaction of a 9:1 mixture of cyclohexanol/cyclohexanone with ammonia (**5**) in the presence of hydrogen.[56] Cyclohexylamine was obtained in 88% yield when the reaction temperature was below 240 °C. However, the main product was aniline (**1a**, 85%) at 250 °C.

Supported copper and chromium catalysts have also been used in a tandem process[57] involving first the reduction of dodecanonitrile in methanol and second the double methylation of dodecylamine to give *N,N*-dimethyldodecylamine.[58] The reaction was performed in a stainless steel tubular flow reactor at 250 °C and 50 atm of hydrogen. Whereas the reaction using copper supported on alumina gave only the

Table 6. *N*-Alkylation of Dimethylamine with Primary Alcohols Using Supported Copper−Chromium Catalyst



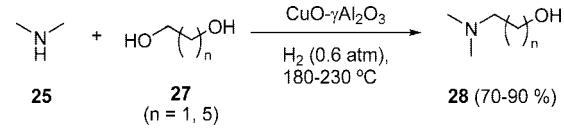
25 **2** **26**

entry	catalyst	R	feed **25/2**/H_2	no.	yield (%)
1	Cu−Cr on SiO_2	$CH_3(CH_2)_6$	8.3:6:6	**26a**	97
2	Cu−Cr on SiO_2	$CH_3(CH_2)_{10}$	5.6:6:6	**26b**	97
3	Cu−Cr on SiO_2	$CH_3(CH_2)_{14}$	4.5:6:6	**26c**	96
4	CuO on γ-Al_2O_3	Ph	43:26:12	**26d**	86
5	CuO on γ-Al_2O_3	$PhCH_2$	38:26:12	**26e**	87
6	CuO on γ-Al_2O_3	$Ph(CH_2)_2$	33:25:12	**26f**	90

initial process of reduction (78% of dodecylamine), and using only chromium on alumina gave a complicated mixture (the main product was tridodecylamine in 32%), the reaction using a mixture of copper−chromium gave the desired *N,N*-dimethyldodecylamine in good yield (77%). Significant variations on the activity and selectivity were observed, and they were attributed to the relative amount of copper used. Although the mixed catalyst was more stable than the monometallic one, the modification of the catalyst during the reaction affected the final results. Thus, the formation of water seemed to inhibit the catalyst. Therefore, the presence of hydrogen was necessary in the hydrogen autotransfer step since it reduced the strong adsorption of water and avoided the formation of other reaction products. The presence of ammonia and amines enhanced the modification of the catalyst surface by the formation of Cu_3N, the irreversible adsorption of amines, and the deposition of carbonaceous or nitrogenous compounds, which restricted the accessibility of reagents to the active centers. The exceptional good behavior of the 4:5 mixture of copper/chromium was attributed to the increase of both, the hydrogen activation, and the acidity resulting from the selective adsorption of water on Cr(III) species.

Supported catalysts bearing copper and chromium have been found to be effective and highly selective for the synthesis of long-chain aliphatic amines, which are widely used in many fields, such as corrosion inhibitors, epoxy hardeners, textile additives, etc. Thus, in a continuous fixed-bed reactor, a heterogeneous catalyst formed with CuO (25%), Cr_2O_3 (1%), Na_2O (0.1%), SiO_2 (70%), and water (4%) was able to catalyze the alkylation of dimethylamine (**25**) with dodecanol with practically quantitative yields (Table 6, entry 1).[59] A further careful study of this process showed that the optimal parameters depended on the apparatus used, so the temperature was 300 °C and the optimal ratio of amine **25** and dodecanol ranged from 1.0 to about 1.5 for a stirred autoclave.[60] Meanwhile, for a fixed-bed reactor, the range of temperature was lower (225−235 °C) and the feed ratio was higher (**25/2** = 5.5). One of the most important factors studied was the effect of the hydrogen pressure. Whereas in a fixed-bed reactor a considerable decrease in the activity and selectivity was observed in a short period of time in the absence of hydrogen, in the batch process the presence of hydrogen had a very small influence, since the hydrogen needed for the hydrogenation of the imine intermediate was furnished by the dehydrogenation of the alcohol (hydrogen autotransfer). Although initial studies seemed to conclude that the main reason for the catalyst deactivation was the irreversible adsorption of byproduct coming from the dimerization of alcohol **2**, as well as formation of large aggregates of copper by thermal diffusive fusion,[61] more conscientious kinetic studies showed that the catalyst deactivation was due to the formation of a bulk or surface copper nitride.[43,62] This nitride could be formed by reaction of the ammonia, originated from a disproportion reaction of initial amine (see section 3), with copper at temperatures as low as 197 °C. The in situ formed aldehyde could also inhibit the reaction by adsorption. These studies also showed that the dehydrogenation of the alcohol **2** was the only rate-determining step, with copper catalyzing this step as well as the hydrogenation of imine intermediate. Therefore, hydrogen did not have any influence on the overall reaction rate and only prevented the catalyst deactivation. It should be pointed out that, although the disproportion of dimethylamine (**25**) is thermodynamically favored, it only occurred in a small extent due to the inhibition by the alcohol.

Scheme 7. *N*-Alkylation of Dimethylamine with Diols Using Supported Copper Catalyst



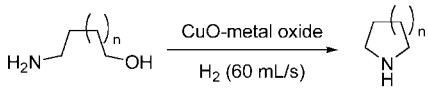
25 **27** (n = 1, 5) **28** (70-90 %)

Also CuO supported in γ-Al_2O_3 (60 wt %) could be used as catalyst to prepare different *N,N*-dimethylphenylalkylamines **26** with high yields following a similar procedure to that previously described for long-chain amines (Table 6, entries 4−6).[63]

A similar catalyst derived from CuO on γ-Al_2O_3 (63 wt %) has been used in the preparation of 2-methylaminoalkanols **28** by reaction of dimethylamine (**25**) with the corresponding aliphatic diol **27** (Scheme 7). The reaction of ethyleneglycol (**27a**: $n = 1$) with the amine **25** in 1:1 ratio in a fixed-bed reactor exhibited a maximum at 230 °C.[64] The hydrogen partial pressure did not have any influence on the conversion, but it was necessary to prevent the catalyst deactivation. The same reaction was performed with 1,6-hexanodiol (**27b**: $n = 5$) using a lower loaded catalyst of CuO on γ-Al_2O_3 (54 wt %), giving the expected amine **28** with 90% yield at 180 °C.[65] As in the previous case, the conversion of the amine **25** showed no dependence on the hydrogen partial pressure nor on the partial pressure ratio of reagent, which indicated that amine **25** is not involved in the rate-determining step.

Several cyclic amines, most of which are very important intermediates for some pharmaceuticals, detergents, and additives, have been synthesized starting from the corresponding aminoalcohol **29** by using copper supported either on γ-Al_2O_3 or on MgO in a continuous-flow, fixed-bed reactor (Table 7).[66] Although the same results were obtained when the reaction was performed under hydrogen or nitrogen, a deactivation of the catalyst was observed in the absence of hydrogen. In all cases and using CuO on γ-Al_2O_3 (63 wt %), cyclic amines **30** were obtained with high yields and selectivities (Table 7, entries 1, 4, and 7). Yields were slightly lower when methanol was used as solvent (Table 7, entries 2, 3, 5, 6, and 8), with the corresponding *N*-methyl cyclic amine being obtained as byproduct. This byproduct came from the *N*-methylation of cyclic amines **30** through a new hydrogen autotransfer process with methanol, similar to the process shown in Scheme 3. The amount of these byproducts was increased when the reaction was performed on MgO as support. Whereas this protocol could not be applied to the synthesis of four-membered ring amines, the reaction using 2-(2-aminobenzyl)ethanol gave the corresponding indoline with an excellent 94% yield.

Table 7. Cyclization of Aminoalcohols Using Supported Copper Catalyst

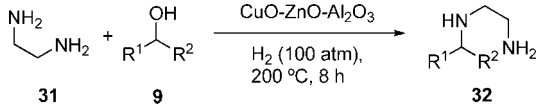


29 30

entry	metal oxide (solvent)	*n*	*T* (°C)	no.	yield (%)[a]
1	γ-Al_2O_3	1	200	**30a**	90
2	γ-Al_2O_3(MeOH)	1	225	**30a**	45 (13)
3	MgO (MeOH)	1	225	**30a**	62 (38)
4	γ-Al_2O_3	2	210	**30b**	75
5	γ-Al_2O_3(MeOH)	2	225	**30b**	89 (10)
6	MgO (MeOH)	2	225	**30b**	62 (37)
7	γ-Al_2O_3	3	225	**30c**	95
8	MgO (MeOH)	3	225	**30c**	84 (13)

[a] In parentheses are the isolated yields of the corresponding *N*-methyl cyclic amine.

Table 8. *N*-Alkylation of Ethylenediamine with Secondary Alcohols Using Supported Copper Catalyst



31 9 32

entry	R^1	R^2	no	yield (%)
1	H	H	**32a**	21
2	Me	H	**32b**	50
3	Ph	H	**32c**	45
4	$(CH_2)_5$		**32d**	73

It should be pointed out that copper supported on γ-Al_2O_3 was known to be effective in the synthesis of nitriles from alcohols by reaction with ammonia at 325 °C and atmospheric pressure with yields ranging from 87 to 96%.[67]

Commercially available CuO−ZrO−γ-Al_2O_3 has been used as catalyst for the methylation of *n*-butylamine (amine/methanol = 10/39) in a hydrogen atmosphere at 185 °C, rendering the corresponding *N*-methyl-1-butylamine with a 54% yield.[68] This study evidenced the correlation between the catalytic activity of the reduced catalyst and its ionic copper content. The obtained results confirmed that the rate-determining step of the alkylation of primary amines with alcohols was the dehydrogenation of the alcohol on ionic copper active sites of the catalysts.

A catalyst prepared by coprecipitation of Na_2CO_3, $Cu(NO_3)_2$, $Zn(NO_3)_2$, and $Al(NO_3)_2$ and subsequent calcination has been used in the alkylation of ethylenediamine (**31**) with different alcohols **9** (Table 8). The reaction was performed in a stainless-steel autoclave with an alcohol/amine ratio of 5. The results in the selective monoalkylation of the amine **31** were accountably lower for methanol than for other alcohols, suggesting that the methanol dehydrogenation step is the rate-determining step. The use of ZnO−Al_2O_3 as catalyst did not render the alkylated amine under these reaction conditions (for the use of alumina as catalyst, see section 2.1.1), showing that the activity was due to copper species. Nevertheless, the synergy effect between different copper and zinc species was observed since the activity of CuO−ZnO−Al_2O_3 catalyst was much higher than the related CuO−Al_2O_3 one.[69]

As was pointed out previously, tertiary long-chain aliphatic amines are very important industrial intermediates, and for that reason, different catalysts have been tested in their preparation. So, a colloidal catalyst bearing copper, nickel, and barium was initially developed for this purpose.[16] The initial copper reagent showed to be very important. For instance, copper stearate showed a higher activity than copper acetylacetonate or even CuO−$CuCr_2O_4$ in the *N*-alkylation of dimethylamine (**25**) with dodecylalcohol to give the corresponding amine **26b** with 40, 0, and 7% yield, respectively.[70] However, the equimolecular mixture of $Cu(C_{17}H_{35}CO_2)_2$ and $Ni(C_{17}H_{35}CO_2)_2$ gave even higher activity than the copper stearate alone (**26b**, 72%), with nickel stearate not being active. The Cu/Ni ratio had a great impact on the results, with the best results being obtained with ratios from 5:1 to 8:1. It should be pointed out that, under these conditions, small metal particles were observed during the reaction. The role of the stearic acid moiety was carefully studied, finding that it was an indispensable catalyst component, since its function seemed to be to prevent the copper sinterization or the coagulation of the Cu−Ni two-component nanoparticles. A maximum catalytic activity was obtained at 37 mol %. The stearic acid had to be added as a salt of an alkaline or an alkaline-earth metal ion, since they were not reduced under the reducing amination conditions (standard electrode potential of about −2.8 V). Beside the role of the fatty acid residue, the second catalyst component was optimized, finding that nickel stearate showed higher activity than other derivatives, from metals such as Mn, Fe, Co, or Zn. The addition of alkaline or alkaline-earth metal stearates stabilized the catalyst, with $Ba(C_{17}H_{35}CO_2)_2$ giving the best activity and selectivity. Amine **26b** could be obtained with an excellent 96% yield when the stearic salt of Cu/Ni/Ba was used in a 5:1:1 ratio. The X-ray diffraction analysis of the reduced catalyst indicated that Cu metal, CuO, and Ni metal were colloidally dispersed in the system. A further addition of calcium stearate to the initial catalytic mixture increased the yield up to 99% for the amine **26b** (5:1:1:1 ratio of Cu/Ni/Ba/Ca).[71] The incorporation of calcium in the Cu−Ni core resulted in the possible formation of Ca−Ni-based alloys such as $CaNi_5$ and their hydrides, always in a colloidal state, which increased the hydrogenolysis activity and prevented the transalkylation of dimethylamine, which occurred with the simple Cu−Ni-based colloidal catalyst. The transmission electron microscope (TEM) images of the catalysts showed the presence of Cu−Ni nanoparticules with a diameter of 125 nm.[72] The excellent results of this catalyst were demonstrated in a commercial plant using 5 763 kg (1 equiv) of dodecyl alcohol, 1.36 equiv of amine **25**, 0.29 equiv of hydrogen, and only 1 000 ppm of the catalyst (5:1:1 ratio of copper, nickel, and barium stearates) at 210 °C during 4 h, obtaining the tertiary amine **26b** in 90%.

The generation of small amounts of carbon monoxide by the decarbonylation of the in situ generated dodecanal was a side reaction in this process, which deactivated the Cu−Ni catalyst.[73] The generation of CO was a serious problem when the amine supply was insufficient during the catalytic activation. Therefore, a closed system using a CO absorber, which was composed of $CuCl_2$, CuCl, ethyleneglycol, a 50% aqueous solution of amine **25**, and liquid amine **25**, was designed to prevent the aforementioned catalyst deactivation. However, the use of the CO absorber is not economical, and therefore, a CO-resistant catalyst was prepared by the simple addition of $P(OPh)_3$ (0.16 equiv) to the standard Cu−Ni−Ba stearate catalyst.

Although the catalyst is a colloidal system, it could not be separated by simple filtration after the amination reaction because of its small particle size (1.5 nm), but its recovery

could be performed by distillation.[74] The distillation residue could be reused four times with only a slight decrease on both the yield and the initial reaction rate after the third use. The activity of the recovered catalyst decreased drastically when the used catalyst did not have barium stearate, and this fact was attributed to the coagulation of the Cu−Ni based colloid.

When the catalytic activity of colloidal Cu−Ni−Ba catalyst was compared with others such as $CuO-NiO-SiO_2$ and Raney-nickel, the colloidal system showed seven times higher catalytic activity than the solid one and more selectivity than Raney-nickel.[75] This effect was even higher when it was compared to the related Cu−Ni−Ba−Ca catalyst.

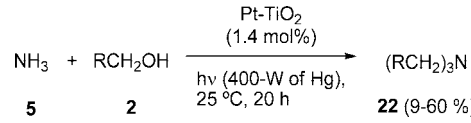
The aforementioned three-component colloidal catalyst has also been used in the alkylation of dimethylamine (**25**) with different diols **27**. For instance, the reaction with 1,6-hexanodiol gave the corresponding *N,N,N′,N′*-tetramethylhexanediamine with 85% yield. Other different alcohols such as mixtures of commercial long-chain oxoalcohols were also used as the source of the electrophile, giving the corresponding *N,N*-dimethylamines with good results (78−89%).[76]

2.1.4. Derived from Platinum

Platinum derived catalysts have been shown to be effective to promote the *N*-alkylation of amines by a hydrogen autotransfer process. Thus, a vapor phase containing cyclohexanol and ammonia (**5**) over platinum supported on silica (ca. 5% wt loading) was transformed into cyclohexylamine and aniline in a continuous-flow reactor at atmospheric pressure with yields of 30 and 58% at 267 °C, respectively (compare these results with those presented in section 2.1.3 using a copper−chromite catalyst, which is more selective).[77] Other platinum group metals also catalyzed the reaction, with the difference between platinum and rhodium being that the activity of the least active metal rhodium is within 1 order of magnitude lower. The yields of the reaction were dependent on the temperature as well as the contact time, increasing as those parameters increased. However, the selectivity changed for aniline (**1a**) at higher temperatures. It was found in this process that the catalytic activity per surface metal atom and product selectivity did not change so much with the platinum size. A deactivation of the catalyst was detected as the yield of each product decreased with the time, and it seems to occur at the surface, so it was found that the weight of the catalyst was increased by 10% after performing the reaction. It seems to be clear that the process started with the dehydrogenation of cyclohexanol to give cyclohexanone, which is the rate-determining step, although alternative mechanisms have also been suggested.[78]

Benzylic amine derivatives have been alkylated by electrolysis in alcoholic solutions using a platinum black-coated anode and a coiled platinum anode.[79] In this process, ethanol or methanol, which contained $LiClO_4$ or $LiNO_3$ as electrolyte, were used as solvents. After adding the corresponding amine, the galvanostatically or potentiostatically electrolysis at room temperature gave the expected alkylated amines with yields ranging from 27 to 91%. The electrolysis of alcohols in the absence of amines gave directly the corresponding aldehydes and hydrogen via an anodic oxidation of the alcohols and cathodic reduction of protons. In the presence of an amine, the condensation proceeded feasibly to give the corresponding imine,[80] which is hydrogenated in the platinum black surface of the anode under an open circuit.

Scheme 8. Triple *N*-Alkylation of Ammonia with Primary Alcohols Using Platinum Supported Catalyst



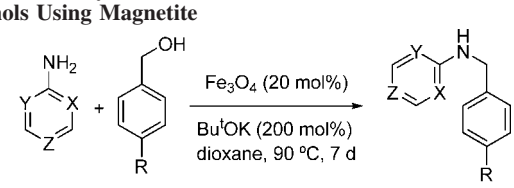
Ammonia (**5**) could also be converted into the corresponding tertiary amines **22** at room temperature by means of a photoirradiation procedure by a 400 W high-pressure mercury lamp, under catalysis with $Pt-TiO_2$, prepared in turn by simply mixing Pt black with anatase powder. The reaction of ammonia with an extraordinary high excess of a primary alcohol (**2**, 41 000 mol %) such as methanol, ethanol, or 1-butanol gave the corresponding amines **22** with moderate yields (Scheme 8). The photoirradiation in the absence of ammonia rendered the corresponding alcohol, which indicated that the whole process seemed to go through a hydrogen autotransfer process. When this reaction was performed in the presence of a small amount of water (4−8 mol %), the yield of the tertiary amine **22** decreased at the same extent as the increase of the yield of the secondary amine.[81] This protocol could also be extended to the use of simple primary or secondary amines instead of ammonia (**5**), giving in these cases the corresponding nonsymmetrical tertiary amines with slightly better results (28−93%).[82]

2.1.5. Others

Besides the already presented catalysts, other transition-metal derivatives have been used in the *N*-alkylation of amines and related compounds. For instance very recently, unmodified commercial magnetite has been shown as an excellent catalyst for the *N*-alkylation of different aromatic amines using benzylic alcohols (**6**) as the source of the electrophile.[83] The surface of Fe_3O_4 (111) is terminated by a hexagonal oxygen layer covered by one-quarter monolayer of iron atoms, with these metallic centers being responsible for the catalysis action.[84] After optimizing the reaction conditions for aniline (**1a**) with benzyl alcohol (**6a**, 4 equiv), the expected *N*-benzylaniline (**7a**) was obtained with a good 88% yield by using Fe_3O_4 (20 mol %) in the presence of potassium *tert*-butoxide (2 equiv) at 90 °C in dioxane after seven days. The results were independent of the electron-withdrawing or -donor character of the substituents at the four position of alcohols **6**, with results ranging from 80 to 83%. However, when different substituted anilines were used as nucleophiles, the results were dependent on the substitution, with the lowest nucleophilic 3-chloroaniline giving a surprisingly better result (99% yield) than the highest nucleophilic 4-methoxyaniline (42%). Therefore, this protocol was applied to different electron-poor heteroaromatic amine derivatives **33** with unbeatable results (Table 9). As was expected, the use of an electron-rich heteroaromatic amine such as 2-methylthiazol-2-ylamine gave a modest 33% yield in its reaction with benzyl alcohol. The selectivity was notable since the competitive reactions between a high nucleophilic aliphatic amine and a low nucleophilic amine such as aniline with benzyl alcohol only rendered *N*-benzylaniline (**7a**), with the selectivity between aliphatic and benzylic alcohols being exclusively favored to the benzylic derivatives.

The magnetite catalyst could be simply and easily recovered by using an external magnet and reused for at least eight cycles of reaction without a detrimental effect on the initial

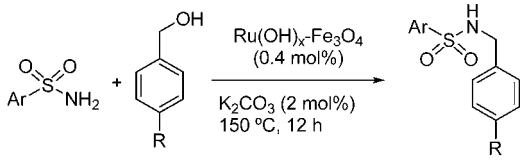
Table 9. *N*-Alkylation of Heteroamoatic Amines with Benzylic Alcohols Using Magnetite



33 6 34

entry	Z	Y	X	R	no.	yield (%)
1	CH	CH	N	H	**34a**	96
2	CH	CH	N	Cl	**34b**	>99
3	CH	CH	N	Me	**34c**	>99
4	CH	CH	N	MeO	**34d**	>99
5	N	CH	CH	H	**34e**	>99
6	CH	N	N	H	**34f**	>99

Scheme 9. *N*-Alkylation of Sulfonamides with Benzylic Alcohols Using Ruthenium-Impregnated Magnetite As Catalyst



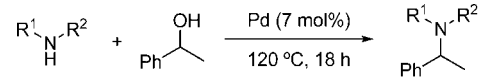
35 6 **36** (49-96 %)

results. In order to study the possible degradation of the catalysts, the Brunauer−Emmett−Teller (BET) surface and TEM images have been determined before and after eight reaction cycles, with the results being almost similar and showing that there was not a significant sinterization process.

Magnetite impregnated[85] with ruthenium hydroxide [$Ru(OH)_x-Fe_3O_4$] has been used in the alkylation of sulfonamides **35**. The reaction using an excess of benzylic alcohol (**6**, 400 mol %) and substoichiometric amounts of $Ru(OH)_x-Fe_3O_4$ (0.4 mol %) and K_2CO_3 (2 mol %) at 150 °C without solvent gave the expected derivatives **36** in general with excellent results (Scheme 9). From the obtained results, it could be concluded that the reaction worked well not only for aromatic and heteroaromatic sulfonamides but also for aliphatic sulfonamide derivatives. Other benzylic derivatives different from 4-substituted ones could be successfully used, as well as the related heteroarylmethanol derivatives. As in the previous case, the catalyst could be separated from the reaction media by using an external magnetic bar and directly reused five times.[86] The catalyst was characterized by different techniques including X-ray, X-ray photoelectron spectroscopy (XPS), BET area, and TEM images. The ruthenium particles were of a small size (1.5−5 nm), whereas the magnetite support showed particles of around 100 nm. The BET area measures showed no changes before and after the reaction cycles. The XPS studies showed equal binding energies of 461.7 and 461.9 eV for the Ru $3p_{3/2}$ peaks in the new and reused catalyst, respectively. All these results suggested that the catalyst contained Ru(0) nanoparticles immobilized on the surface of the crystalline magnetite, which remain stable and highly dispersed during the hydrogen autotransfer process. The labeling experiments, together with other competitive ones, showed a primary kinetic isotope effect for the dehydrogenation step, indicating that the benzylic C−H bond breaking was the rate-determining step.

The use of palladium metal (22 mol %) was less effective for the reaction of 2-phenylethylamine with benzyl alcohol (**6a**; alcohol/amine ratio = 1.2) to give the expected alkylated amine (25% yield).[87] However, a similar reaction but using a small excess of amine **20** (1.1 equiv) and 1-phenylethanol (**37**) gave the expected amines **38** with good results (Scheme 10).[88] When the reaction was performed using other alcohols such as benzyl or allyl alcohol, the results were accountably lower (12−34% yields).

Scheme 10. *N*-Alkylation of Amines with Secondary Alcohols Using Palladium Catalyst



20 37 **38** (77-79%)

Other metal oxides, such as tungsten oxide[89] or thorium oxide,[90] have also been used as catalysts for the alkylation of ammonia (**5**) with benzylic, aliphatic, or cyclic alcohols at 330 °C to give the corresponding primary amines, although the corresponding secondary and tertiary amines could be detected as byproducts. A similar protocol, but using aliphatic primary amines, gave the expected unsymmetrical secondary amines. Finally, it should be pointed out that the reaction of ammonia with alcohols at higher temperatures gave the corresponding symmetrical secondary amine as the main product.

2.2. Homogeneous Catalysts

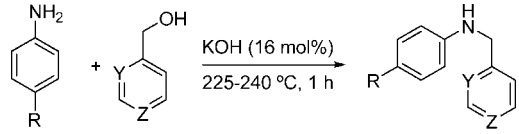
An argument often made in favor of the homogeneous catalysts is that these types of catalysts frequently allow reactions to occur at a lower temperature, with higher selectivity, and more easily than heterogeneous catalysts. In fact, as was previously mentioned, the first example of *N*-alkylation of aniline by alcohols was made in a homogeneous solution in the absence of transition-metal catalyst in 1901.[22] However, the homogeneous version using transition-metal catalysts was established in 1981, with the simultaneous introduction of different rhenium[91] and ruthenium[92a] catalysts, as will be presented in the corresponding sections.

2.2.1. Without Transition-Metal Catalysts

Reactions that are always performed under catalytic conditions can often be also performed in the absence of a catalyst, by just varying the reaction conditions, usually using a higher temperature, pressure, amount of reagents, reaction times, or using solvent-free conditions. This is also the case of the *N*-alkylation of amines using alcohols as the source of the electrophiles that could be made in the absence of a catalyst using just a strong base at higher temperature. For instance, when aniline (**1a**, 1.2 equiv) was heated at 250−300 °C with sodium 1-pentoxide for several hours, it gave the expected *N*-pentylaniline (**3e**, 40%).[22] Instead of sodium alkoxides, the reaction could also be performed using aluminum alkoxides giving the corresponding alkylated anilines **3** with good results.[93] For instance, the reaction with aniline (**1a**) at 275 °C using stoichiometric amounts of aluminum triethoxide gave after 4 h the expected amine **3b** with a 94% yield.

In a similar way, several aniline derivatives **1** could be alkylated with benzyl alcohol (**6a**, 140 mol %) to give the corresponding derivatives **7** with high yields (82−99%), using only potassium hydroxide (40 mol %) as base and heating the mixture at 250 °C during several hours (14−110 h), with continuous distilling of in situ formed water.[94] For instance, this protocol has been extended to the synthesis of

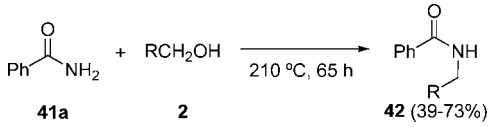
Table 10. *N*-Alkylation of Aromatic Amines with Pyridylmethanol Derivatives Using Potassium Hydroxyde as Catalyst



1 **39** **40**

entry	R	Y	Z	no.	yield (%)
1	H	N	CH	**40a**	63
2	Me	N	CH	**40b**	50
3	MeO	N	CH	**40c**	71
4	EtO	N	CH	**40d**	68
5	H_2N	N	CH	**40e**	73
6	EtO	CH	N	**40f**	60

Scheme 11. *N*-Alkylation of Benzamide with Primary Alcohols without Catalyst



41a **2** **42** (39-73%)

2-benzylamino pyridine (**34a**) with an excellent 99% yield.[95] It should be pointed out that the reaction could be accelerated by the addition of a small amount of benzaldehyde or by the use of a higher base concentration. Other amino heterocyclic compounds, such as 2-aminobenzimidazol derivatives, could be successfully benzylated using this protocol with nearly quantitative yields.[96] Alternatively, the reaction of compounds **1a** and **6a** could be performed in the presence of potassium *tert*-butoxide at only 90 °C but increasing the reaction time to 10 days (**7a**, 67%).[83]

Pyridylmethanol compounds **39** could also be used as the source of the electrophile in the alkylation of different aniline derivatives **1** (Table 10). The reaction of equimolecular amounts of these compounds in the presence of substoichiometric amounts of a base gave the expected amines **40** with moderated yields.[97] A further modified protocol using 200 mol % of amine, nitrobenzene (100 mol %) as the initial oxidant, and xylene as solvent did not change the previous results.[98]

The selective monoalkylation of aniline derivatives **1** could also be carried out by using aliphatic alcohols,[99] although, in this case, the amount of alcohol had to be increased up to 200 mol % and metallic sodium (68 mol %) was used to generate the corresponding base. The reaction performed in an autoclave at 270−300 °C during 4−6 h gave the expected compounds **3** generally with modest results (20−72%).

More recently, supercritical methanol conditions (239.4 °C, 79.9 atm) have been used in the methylation of aniline **1a** to give after 2 h a mixture of compounds **3a** (49%) and **4a** (1%).[100] About 70% of hydrogen bonds among methanol molecules are broken down under these conditions, producing dimers and monomers and, therefore, increasing the reactivity of the alcohol.

Finally, it should be pointed out that the reaction of benzamide (**41a**) with primary alcohols **2** in a sealed tube gave the corresponding *N*-alkylated benzamides **42** in general with moderate yields (Scheme 11), together with other byproducts such as benzoic acid, and the corresponding alkyl benzoate.[101]

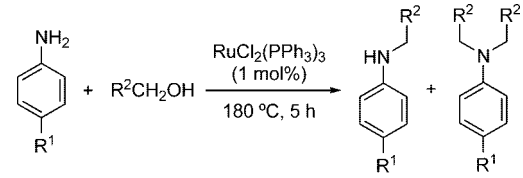
2.2.2. Derived from Ruthenium

Ruthenium complexes have been extensively used in organic synthesis as the prototype for the transition-metal catalysis.[102] Therefore, several ruthenium derived species have been reported as excellent catalysts in the homogeneous hydrogen autotransfer process for the *N*-alkylation of amines, with $RuCl_2(PPh_3)_3$ being probably the most widely used. This ruthenium complex was initially used in the alkylation of aniline derivatives **1** with primary alcohols **2** (Table 11) in a 1:5−12 amine/alcohol ratio, as well as with secondary ones, to yield the corresponding *N*,*N*-dialkylated amines as the main products in the absence of solvent.[92] Whereas very good yields were obtained for the dialkylated products **44**, the related reaction with secondary alcohols failed, giving only the corresponding monoalkylated amine with low yields (25−28%).

The introduction of electron-donating groups at the four position of the aromatic aniline derivative **1** enhanced both the reaction rate and the yields. Meanwhile, when the substitution was located at the two position, the monoalkylated product was the main isolated compound. Importantly, the control on the ratio of aniline/alcohol regulated the proportion of the obtained compounds **43** and **44**. So, when the above ratio was reduced to one, the monoalkylated compound **43** was predominantly formed in good yields (see, for instance, entries 6 and 7 in Table 11). A zero-order dependence on the aniline concentration was obtained from kinetic studies, as well as a first-order dependence on the alcohol and a first-order dependence on the catalyst. The activation energy from the Arrhenius plot was 73.6 kJ mol^{-1}, with the enthalpy and entropy being 70.2 kJ mol^{-1} and −123 J mol^{-1} K^{-1}, respectively.

The use of the same catalyst was further extended to the alkylation of more nucleophilic aliphatic primary amines with methanol (**2a**). Thus, the reaction of primary amines **45** with a large excess of methanol (**2a**, 3 000 mol %) at 180 °C catalyzed by 3 mol % of $RuCl_2(PPh_3)_3$ gave the corresponding dimethylamine derivative **26** with good yields (26−94%). However, when the amount of methanol was decreased to 500 mol %, the main product was the monomethyl tertiary amine **46** (Scheme 12), with a small amount of the corresponding amine **26** as byproduct (1−19%).[103] The formation of compounds **46** could be easily explained by taking into account that the initial amine **45** could be the source of the electrophile in a transalkylation amine process. The oxidation

Table 11. Dialkylation of Aniline with Primary Alcohols Using $RuCl_2(PPh_3)_3$

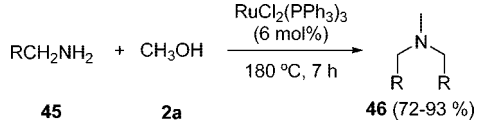


1 **2** **43** **44**

entry	R^1	R^2	no.	yield (%)	no.	yield (%)
1	H	Me	**43a**	13	**44a**	74
2	H	Et	**43b**	10	**44b**	88
3	H	Pr^n	**43c**	15	**44c**	79
4	MeO	Pr^n	**43d**	7	**44d**	91
5	Me	Pr^n	**43e**	15	**44e**	85
6[a]	H	Pr^n	**43c**	79	**44c**	6
7[a]	MeO	Pr^n	**43d**	99	**44d**	

[a] 1:1 ratio of compounds **1/2**.

Scheme 12. Autoalkylation and *N*-Methylation of Aliphatic Amines Using $RuCl_2(PPh_3)_3$ Catalyst



Scheme 13. *N*-Alkylation of Symmetrical Secondary Amines with Long-Chain Alcohols Using $RuCl_2(PPh_3)_3$ Catalyst

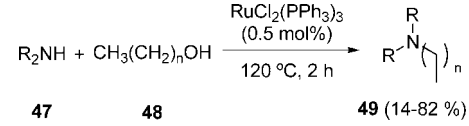
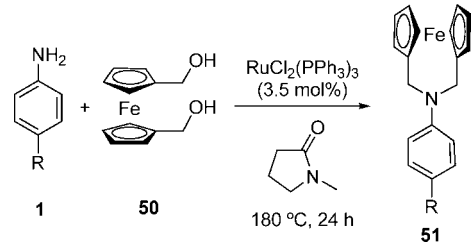


Table 12. *N*-Dialkylation of Aniline with Primary Alcohols Using $RuCl_2(PPh_3)$



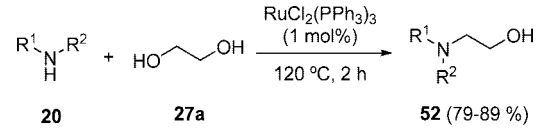
entry	R	no.	yield (%)
1	Bu^n	**51a**	63
2	Bu^t	**51b**	58
3	HO	**51c**	56

of the amine **45** catalyzed by ruthenium species gave the corresponding imine, which suffered the addition of the initial amine **45** to form a new *N*-alkyl imine derivative, with liberation of ammonia, and the final hydrogenation of this *N*-alkyl imine derivative by the ruthenium hydride species gave the corresponding symmetrical dialkylamine (see section 3.2.1). The final step was the expected methylation through a hydrogen autotransfer process.

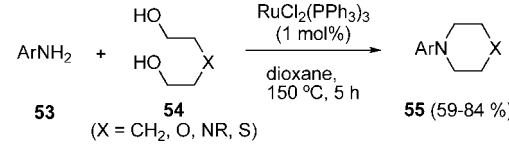
Symmetrical secondary amines **47** could also be alkylated with aliphatic long-chain primary alcohols **48** ($n = 9$, 13, 15, 17) to give the corresponding amines **49** with moderate to good results in the absence of solvent (Scheme 13). It should be pointed out that, whereas aromatic amines gave modest results, aliphatic amines gave poor results (yields lower than 28%), with dimethylamine reaching the highest yields.[104] This catalytic reaction showed an induction period of about 30 min before significant amounts of amine **49** were formed. This induction period could be reduced by the addition of 4 (mol of PPh_3)/(mol of $RuCl_2(PPh_3)_3$). This acceleration effect was attributed to the displacement of the formed aldehydes by the phosphine from the ruthenium catalytic species, thus facilitating the condensation with the amine and accelerating the hydrogenation of the in situ formed iminium derivative to the tertiary amine **49**. When the same reaction procedure was applied to secondary alcohols **9**, the reaction failed.

The double alkylation of primary amines can be also performed by using the corresponding diol. For instance, 1,1-ferrocenedimethanol (**50**) was reacted with different anilines **1** using *N*-methylpyrrolidin-2-one as solvent to give the corresponding ferrocenylamine derivatives **51** (Table 12). The results seemed to be independent of the aniline substitution, keeping the same level of yields when aliphatic or benzylic amines were used instead of compounds **1**.[105]

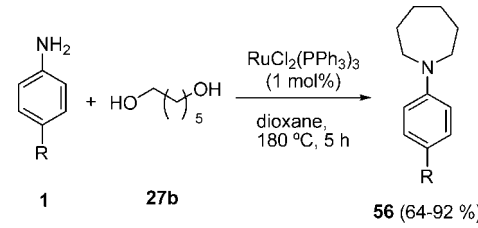
Scheme 14. *N*-Alkylation of Amines with Ethanediol Using $RuCl_2(PPh_3)_3$ Catalyst



Scheme 15. Cyclization of Aromatic Amines with Diols Using $RuCl_2(PPh_3)_3$ Catalyst



Scheme 16. Cyclization of Diols with Anilines Using $RuCl_2(PPh_3)_3$ Catalyst: Synthesis of *N*-Substituted Perhydroazepines



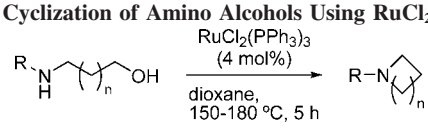
On the contrary, the reaction of secondary amines **20** with an excess of ethanediol **27a** (740 mol %) in the absence of solvent gave selectively the aminoethanol derivatives **52** with good yields (Scheme 14). However, when the catalyst was changed by $RuCl_3 \cdot nH_2O$, the main product was the corresponding ethylenediamine. Surprisingly, the same reaction catalyzed by $RuCl_2(PPh_3)_3$ using primary amines ($R^2 = H$ in Scheme 2) gave a mixture of three products including the aminoethanol **52**, the related ethylenediamine, and *N,N′*-dialkylpiperazine, with the ratio being strongly influenced by the alkyl moiety and the presence of an extra amount of PPh_3.[106]

When 1,5-diol derivatives **54** (150 mol %) were reacted with aromatic amines **53** in dioxane, the corresponding *N*-substituted piperidines **55** were obtained in moderate to good yields (Scheme 15), with the results being independent of the electron character of the substituents on the aromatic ring. It should be pointed out that the yields were lower when aliphatic amines were used instead of aromatic ones. However, in this case, the use of $RuCl_3 \cdot nH_2O$ combined with tributylphosphine increased the results to the initial level.[107] This strategy has been applied to the synthesis of biologically active substances such as 4-[2-(benzhydryloxy)ethyl]morpholine (from diethyleneglycol X = O in Scheme 15, 47%), which is an antihistaminic agent, or *N*-methyl-*N′*-benzhydrylpiperazine (from diethanolamine X = NH in Scheme 15, 19%), which is a drug preventing travel sickness.

Perhydroazepines **56** could be prepared by reaction between aniline derivatives **1** and 1,6-hexanodiol (**27b**, 150 mol %) in dioxane at 180 °C (Scheme 16). The $RuCl_2(PPh_3)_3$ complex was used as catalyst, although it could be prepared in situ by adding $RuCl_3 \cdot nH_2O$ and PPh_3. Yields were generally good, although for 2-substituted aniline derivatives, benzyl amine or lauryamine, the corresponding heterocyclic compound was obtained with lower results (12−29%).[108]

Some of the aforementioned heterocyclic compounds could also be obtained by using the corresponding *N*-substituted amino alcohols **57** as the appropriate starting material.[109]

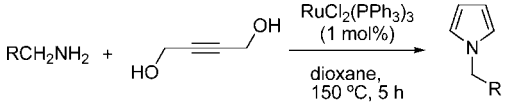
Table 13. Cyclization of Amino Alcohols Using $RuCl_2(PPh_3)_3$



57 **58**

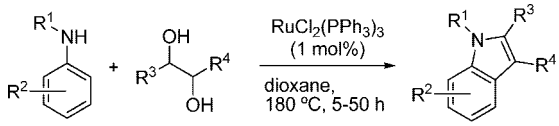
entry	R	*n*	no.	yield (%)
1	Pr^i	2	**58a**	70
2	Ph	2	**58b**	88
3	Bu^n	3	**58c**	71
4	Ph	3	**58d**	90
5	Bu^n	4	**58e**	71

Scheme 17. Cyclization of Alkynildiols with Primary Amines Using $RuCl_2(PPh_3)_3$ Catalyst: Synthesis of *N*-Substituted Pyrroles



45 **59** **60** (27-59 %)

Table 14. Cyclization of 1,2-Diols with Aniline Derivatives Catalyzed by $RuCl_2(PPh_3)_3$: Synthesis of *N*-Substituted Indoles



61 **62** **10**

entry	R^1	R^2	R^3	R^4	no.	yield (%)
1	Me	H	H	H	**10d**	51
2	Et	H	H	H	**10e**	34
3	Me	H	Me	Me	**10f**	58
4	H	H	Me	Me	**10g**	46
5	H	2-Cl	Me	Me	**10h**	72
6	H	4-Cl	Me	Me	**10i**	89
7	H	2-Me	Me	Me	**10j**	50
8	H	4-Me	Me	Me	**10k**	80
9	Me	H	H	Me	**10l**	50[a]
10	H	H	Ph	H	**10m**	43
11	H	4-Cl	$(CH_2)_4$		**10n**	65

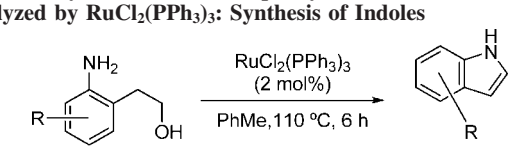
[a] 1:1 mixture of possible regioisomers.

Their reactions in dioxane gave the corresponding azacycloalkanes **58** with in general good yields (Table 13).

Heteroaromatic compounds could also be prepared following the former strategy using $RuCl_2(PPh_3)_3$ as catalyst. Thus, the reaction of aliphatic primary amines **45** with 4-butyne-1,4-diol (**59**, 150 mol %) in dioxane at 150 °C gave the corresponding pyrroles **60** with moderate yields (Scheme 17). The catalytic activity was slightly affected by the addition of a phosphorus ligand, with the addition of bis(diphenylphosphinoethane) as a bidentate ligand or tricyclohexylphosphine as a bulky ligand suppressing the catalytic activity. However, better results were obtained when butane-1,4-diol (**12**) was used, obtaining in this case the corresponding pyrrolidine derivative (45−91%).[110]

The reaction of substituted anilines **61** (250 mol %) with 1,2-diols **62** catalyzed by the $RuCl_2(PPh_3)_3$ complex gave the indoles **10** with moderate to good yields (Table 14). The results seemed not to be related with the position of substitution as well as its electronic character. Only the presence of a substituent on position two of aniline **61** had a small detrimental impact on the yield. This protocol could also be applied to cyclic diols with similar results.[111] A mechanistic study showed that the reaction goes through (a) the formation of the corresponding *N*,*N*′-diamino ethane derivative by a double autotransfer hydrogen alkylation process, (b) monodehydrogenation to give the corresponding imine (iminium) derivative, (c) *ortho*-metalation of amine moiety, (d) intramolecular addition to the imine (iminium) group, and (e) β-elimination of starting amine **61**. When the reaction was performed using 1,3-propanodiol derivatives, the corresponding substituted quinolines were obtained, with this approach being an alternative to the classical Friedländer synthesis.[112]

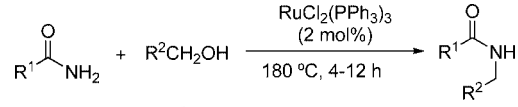
Table 15. Cyclization of Aminophenylethanol Derivatives Catalyzed by $RuCl_2(PPh_3)_3$: Synthesis of Indoles



63 **8**

entry	no.	R	yield (%)
1	**8a**	H	>99
2	**8b**	2-Ph	99
3	**8c**	3-Me	79
4	**8d**	4-Cl	92
5	**8e**	5-MeO	94
6	**8f**	6-Cl	82
7	**8g**	6-Me	80

Table 16. *N*-Alkylation of Carboxamides with Primary Alcohols Using $RuCl_2(PPh_3)_3$



41 **2** **64**

entry	R^1	R^2	no.	yield (%)
1	Me	Me	**64a**	43
2	Me	$CH_3(CH_2)_6$	**64b**	24
3	Ph	$CH_3(CH_2)_6$	**64c**	74
4	$PhCH_2$	Me	**64d**	15
5	Pr^n	$CH_3(CH_2)_6$	**64e**	28

Substituted indoles **8** were easily prepared by reaction of the corresponding substituted aminophenylethanol derivatives **63** with excellent results (Table 15). Yields seemed to be independent of the nature of substitution, the electronic character of the group, or the position in the indol.[113] The whole transformation implied first an intramolecular alkylation process through a hydrogen autotransfer process to give the corresponding indoline, which suffered a further final dehydrogenation process to yield the aromatic compound. Alternatively, the related nitroaromatic derivative could also be used as starting material, with an initial hydrogenation step being necessary in these cases.

The $RuCl_2(PPh_3)_3$ complex has also been used in the preparation of other heterocyclic compounds, such as benzoxazoles and benzimidazoles, using alcohols as electrophiles in the reaction,[114] as well as quinoxalines.[115] Alternatively, $RuH_2(PPh_3)_3(CO)$ and xantphos have been recently proposed for the same transformation.[116] Imidazo[1,2-*a*]pyridines were obtained in the reaction of 2-aminopyridines and 1,2-ethanediols.[117] However, it should be pointed out that these reactions are not standard hydrogen autotransfer processes, although they are closely related.

Finally, it should be highlighted that $RuCl_2(PPh_3)_3$ has been used as catalyst in the *N*-alkylation of simple carboxamides (Table 16). The reaction of amides **41** with different primary alcohols (320−850 mol %) gave the corresponding amides **64**, in general with modest yields. The obtained results were

Scheme 18. *N*-Alkylation of Aliphatic Primary Amines with Primary Alcohols Using $RuH_2(PPh_3)_4$ Catalyst

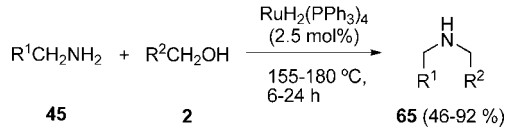
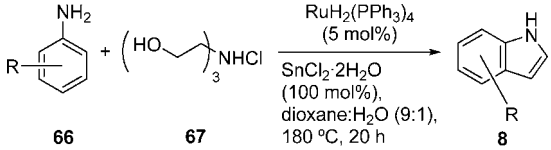


Table 17. Cyclization of Triisopropanolammonium Chloride with Aniline Derivatives Catalyzed by $RuH_2(PPh_3)_4$: Synthesis of Indoles



entry	no.	R	yield (%)
1	**8a**	H	85
2	**8h**	5-Cl	31
3	**8i**	5-Me	68
4	**8e**	5-MeO	80
5	**8j**	4,7-$(MeO)_2$	21

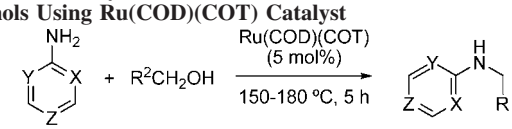
slightly better when benzamide derivatives were used as nucleophiles, where even benzyl alcohol could be used as electrophile and yields were about 50% in all cases. When different lactams or 3-pyridinecarboxamide were employed in the aforementioned protocol, the reactions failed. The protocol could not be extended to α,β-unsaturated carboxamides, since, besides the formation of the alkylation product, a hydrogenation of the double carbon−carbon bond also took place.[118]

Other well-defined ruthenium complexes have also been used in different hydrogen autotransfer reactions. For instance, $RuH_2(PPh_3)_4$ is a highly selective catalyst able to perform the reaction between high nucleophilic aliphatic primary amines **45** and primary alcohols **2** to render the corresponding secondary amines **65** with moderate to high yields (Scheme 18). The reaction was carried out using equimolecular amounts of reagents in a stainless steel autoclave and in the absence of solvent.[119] The intramolecular version of this reaction provides an excellent method for the preparation of cyclic amines. The process was performed starting from amino alcohols **29**, which were transformed into the cyclic compounds **30** ($n = 0-2$) with yields ranging from 41 to 79%. This protocol has also been used in the preparation of *N*-substituted cyclic amines of type **58** by reaction of either amino alcohols with primary alcohols or primary amines with diols, with the last approach being the most convenient since the yields were better. This approach has been successfully used in the preparation of tetrahydroisoquinolines starting from 2-(2-hydroxymethylphenyl)-ethanol.

The $RuH_2(PPh_3)_4$ catalyst has proven to be efficient for the preparation of amides by condensation of amines with nitriles[120] and esters by oxidative condensation with primary alcohols.[121] Very recently, $RuH_2(PPh_3)_3(CO)$ and xantphos have been proposed as an alternative for the last tansformation.[122]

$RuH_2(PPh_3)_4$ has been used, together with $SnCl_2 \cdot 2H_2O$, in the heteroannulation between an excess of aniline derivatives **66** (1 000 mol %) and triethanolammonium chloride (**67**) to give the corresponding 6-substituted indoles **8** (Table 17). The results were affected by the electron character of the substituent, with electron-withdrawing groups giving

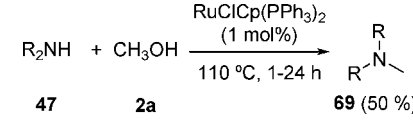
Table 18. *N*-Alkylation of Heteroaromatic Amines with Primary Alcohols Using Ru(COD)(COT) Catalyst



entry	Z	Y	X	R	no.	yield (%)
1	CH	CH	CH	Me	**68a**	3
2	CH	CH	CH	Me	**68a**	27[a]
3	CH	N	CH	Me	**68b**	79
4	N	CH	CH	Me	**68c**	70
5	CH	N	N	Me	**68d**	37
6	N	CH	CH	H	**68e**	67
7	N	CH	CH	Et	**68f**	82
8	N	CH	CH	Ph	**68g**	45

[a] Reaction performed in the presence of 12.5 mol % of pyridine.

Scheme 19. Methylation of Symmetrical Secondary Amines Using $RuClCp(PPh_3)_2$



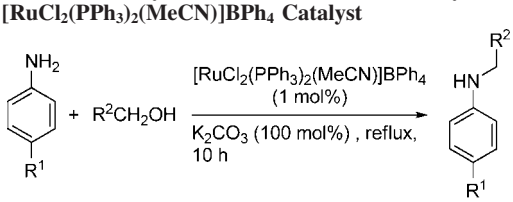
lower yields. Moreover, related 2- and 3-substituted aniline derivatives provided similar or better results than the corresponding 4-substituted ones.[123] When the reaction was performed using substituted triisopropanolammonium chloride as the initial source of nucleophile (secondary alcohol), 3-methylindoles were selectively formed. Other catalysts, such as $RuCl_3 \cdot nH_2O$ with either PPh_3 or bis(diphenylphosphino)methane, gave lower yields. Although the reaction mechanism is not fully understood, the reaction seemed to proceed through (a) a *N*-alkylation of aniline by a hydrogen autotransfer process, (b) oxidation of the trialkylamine moiety to the corresponding iminium, (c) *ortho*-metalation of the aniline ring, (d) intramolecular addition to the iminium group, and (e) β-elimination of diethanolamine (similar mechanism to that mentioned in Table 14).

The $RuH_2(PPh_3)_4$ complex has been used in the transformation of amino alcohols into the corresponding lactams with moderated yields.[124]

The well-defined catalyst (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene)ruthenium [Ru(COD)(COT)] was able to catalyze the *N*-alkylation of poor electrophilic heteroaromatic amines with a large excess of primary alcohols **2** (2 100 mol %).[125] This catalyst displayed a high activity in the selective alkylation of aminopyridine derivatives (Table 18), although it was ineffective in the alkylation of simple aniline, and the ethylation took place with a modest yield and only when pyridine was added as coligand. This fact suggested that the coordination of the nitrogen atom of the pyridine ring with the ruthenium atom is essential for the formation of the true catalytic species, with the possible chelation being intra- or intermolecular when using aminopyridine derivatives. Different primary alcohols were used with similar results, even when benzyl alcohol was used as electrophile.

The half-sandwich ruthenium complex $RuCl(\eta^5\text{-}C_5H_5)(PPh)_2$ has been used as catalyst in kinetic studies of the reaction of high nucleophilic aliphatic secondary amines **47** (as well as primary ones) with a large excess of methanol (**2a**, 10 000 mol %) to give the corresponding *N*-methyl (or *N,N*-dimethyl) tertiary amines (Scheme 19). The reaction rates depended strongly on the nature of the amine substituents, with the reaction rate increasing as the basicity (nucleophi-

Table 19. *N*-Monoalkylation of Aniline with Primary Alcohols Using $[RuCl_2(PPh_3)_2(MeCN)]BPh_4$ Catalyst



1 **2** **43**

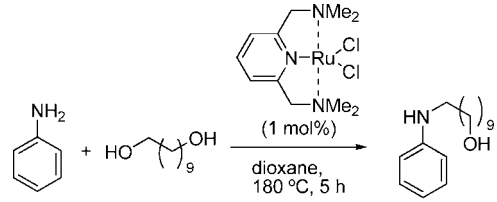
entry	R^1	R^2	no.	yield (%)
1	H	H	**43f**	60
2	H	Me	**43a**	40
3	H	Et	**43b**	28
4	H	Pr^n	**43c**	19
5	Me	Pr^n	**43e**	20

licity) of the starting amine increased. For instance, the reaction rate decreased along the series piperidine > *N*-methylpiperazine > morpholine. For primary amines, the highest basic amine, benzyl amine (with a pK_b of 4.67), gave the highest reaction rate. Furthermore, poor nucleophilic amines such as aniline (**1a**) did not react under these reaction conditions.[126] The mechanistic studies indicated apparently that the reaction proceeded stepwise, with the starting amine being transformed into the *N,N*-dialkyl formyl imine derivative whose concentration remained very low (ca. 5%) and almost constant throughout the reaction. The further hydrogenation of this imine gave the product **69**. The process was zero order for the amine, with the presence of free PPh_3 or chloride anions inhibiting the reaction. Measurements of $^{31}P\{^1H\}$-RMN showed that the dissolution of the catalyst in CD_3OD occurred with chloride dissociation and formation of the corresponding cationic solvent complex. Free PPh_3 appeared into the solution when this complex was heated at 80 °C together with the corresponding imine. The Ru–H–formaldehyde complex intermediate, which is probable the key species in the catalytic cycle, might be formed from the initial cationic complex via PPh_3 dissociation, which provides a vacant coordination site in the ruthenium metal center. This hypothesis was in agreement with the inhibition observed by the addition of PPh_3 or chloride anions to the reaction media.

Different aniline derivatives **1** were monoalkylated with a large excess of refluxing primary alcohols (**2**, > 24 500 mol %) in the presence of a base and substoichiometric amounts of the cationic ruthenium complex $[RuCl_2(PPh_3)_2(MeCN)]BPh_4$ (Table 19). Yields were dependent on the chain length of the alkyl group of the alcohol, with the methanol (**2a**) giving the best results.[127] When benzyl alcohol was used as electrophile, a mixture of mono- and dialkylated products were obtained, along with the corresponding imine, with similar yields.

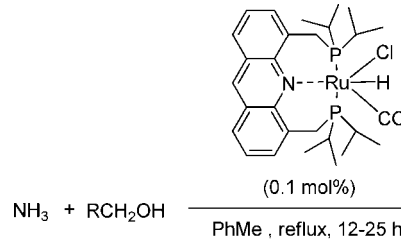
Ruthenium pincer type complexes have been used as promoter for the reaction reviewed here. For instance, the *N,N′,N*-ruthenium complex depicted in Scheme 20 was able to catalyze the selective reaction of aniline (**1a**) with different terminal diols [**12** (1,4), **54a** (1,5), **27b** (1,6), and **70** (1,10)] to give, in all cases, the corresponding amino alcohols with moderate to good yields (42−70%).[128] The analysis of reaction mixture with the time showed that the possible imine intermediates were not produced during the reaction. Therefore, it was concluded that the first condensation between the in situ formed aldehydes and the amine to give the expected imine must be the rate-limiting step, taking place in the coordination sphere of the ruthenium cationic center.

Scheme 20. *N*-Alkylation of Aniline with 1,10-Decanodiol Catalyzed by a Pincer Ruthenium Complex



1a **70** **71** (70 %)

Table 20. *N*-Alkylation of Ammonia with Primary Alcohols Catalyzed by a Ruthenium Pincer Complex: Synthesis of Primary Amines



5 **2** **45**

entry	no.	R	yield (%)
1	**45a**	Ph	87
2	**45b**	4-FC_6H_4	91
3	**45c**	4-MeC_6H_4	83
4	**45d**	4-$MeOC_6H_4$	78
5	**45e**	Bu^n	61
6	**45f**	$MeOCH_2$	95
7	**45g**	$(CH_2)_5CH$	82

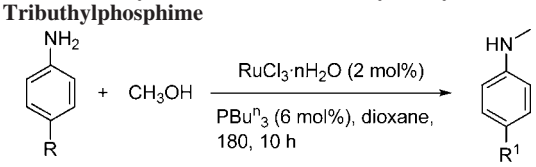
The no-formation of the cyclic amines as major products was explained as a function of the difficulty for the iminium intermediate formation in the cationic ruthenium species, with the formation of these byproducts proceeding most probably by a enamine intermediate on the coordination sphere of the complex. Ruthenium carbonyl complexes, formed by decomposition of aldehyde−ruthenium intermediates, were detected in some reactions, with these carbonyl complexes being inactive for the hydrogen autotransfer reactions.

A ruthenium acridine-based pincer complex has shown its efficiency in the selective monoalkylation of ammonia (**5**) with primary alcohols (**2**) at toluene reflux to give the corresponding primary amines (**45**) in high yields (Table 20). Benzyl alcohol derivatives bearing electron-donating groups reacted faster than those containing electron-withdrawing groups. Heteroaromatic and aliphatic alcohols could also be used as initial source of electrophiles under these conditions. Furthermore, the reaction also proceeded on water, with its presence enhancing the selectivity toward the formation of the primary amine. Probably, the hydrogenation of the imine intermediate is favored in the presence of water. Surprisingly, the reaction gave good results even with nonsoluble primary alcohols; meanwhile water-soluble alcohols, such as pyridine-2-methanol, gave a complex mixture of products in water in sharp contrast to the excellent result obtained in toluene (96%).[129]

Other ruthenium pincer-type complexes have been successfully used as catalysts for the formation of either amides from the reaction of alcohols with amines[130] or acetals by trimerization of alcohols.[131]

Besides the use of well-defined ruthenium-complex catalysts, other catalysts generated in situ could be employed for the hydrogen autotransfer processes. The first ones were

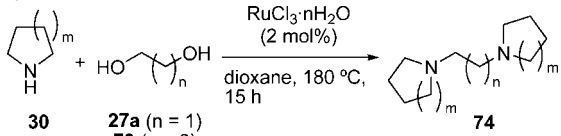
Table 21. *N*-Methylation of Anilines Catalyzed by a Ruthenium and Tributhylphosphime



1 2a 72

entry	R	no.	yield (%)
1	H	**72a**	80
2	Cl	**72b**	86
3	Me	**72c**	76
4	MeO	**72d**	71

Table 22. *N*-Alkylation of Cyclic Amines with Diols Using $RuCl_3 \cdot nH_2O$



30 27a (n = 1), 73 (n = 2), 12 (n = 3), 54a (n = 4) 74

entry	*m*	*n*	no.	yield (%)
1	1	1	**74a**	79
2	2	1	**74b**	79
3	2	2	**74c**	59
4	2	3	**74d**	81[a]
5	2	4	**74e**	77[a,b]

[a] Reaction performed using 6 mol % of PBu^n_3. [b] At 100 °C.

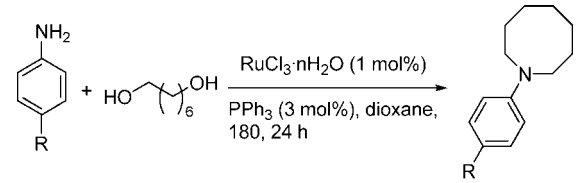
obtained by combination of $RuCl_3 \cdot nH_2O$ with phosphines. Hence, $RuCl_3 \cdot nH_2O$ and PBu^n_3 have shown their efficiency as catalyst in the *N*-methylation of anilines **1** using methanol (**2a**, 400 mol %) as source of the electrophile in dioxane (Table 21). Although the yields were very high, the obtained results were lower when the protocol was extended to the methylation of *N*-alkylanilines of type **43**.[132]

Piperidine (**30b**, $m = 2$) could be alkylated with primary alcohols (**2**, 300 mol %), such as methanol, ethanol, and 1-butanol, in good yields (70−92%) using $RuCl_3 \cdot nH_2O$ (1 mol %) at 220 °C.[133] The reaction with the secondary alcohol 2-butanol gave, however, a lower yield (8%). When a similar reaction was performed using cyclic aliphatic amines (**30**, 300 mol %) and different diols (Table 22) in dioxane at 180 °C, the expected tertiary diamines **74** were obtained with good results.[133] The use of tributylphosphine was compulsory to obtain good yields in the case of using longer-chain diols (**12** and **54a**).[134] However, if the reaction was carried out using $Ru_3(CO)_{12}$ as the source of ruthenium species, triphenylphosphine was the ligand of choice, and the temperature had to be raised up to 220 °C in THF.[133]

The ruthenium source $RuCl_3 \cdot nH_2O$ has been used in the formation of perhydroazocines **76** by reaction of the corresponding aniline derivative **1** with 1,7-heptanediol (**75**, 200 mol %) in the presence of triphenylphosphine (Scheme 21). Yields were very modest, with the substitution on the aromatic ring not affecting the results.[135]

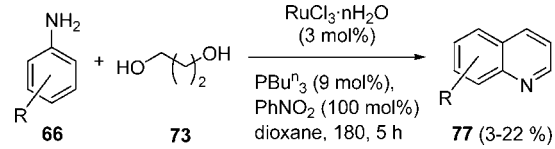
Slightly better results were obtained in the preparation of quinolines **77** by reaction of anilines **66** with 1,3-propanediol (**73**, 150 mol %) in the presence of a hydrogen scavenger (nitroarene) in dioxane at 180 °C (Scheme 22). The mechanism of the reaction showed that the pathway started with the *N*-alkylation of the amine **66** to give the corresponding 3-arylaminopropan-1-ol through a hydrogen autotransfer

Scheme 21. *N*-Alkylation of Aniline with 1,7-Heptanediol Using $RuCl_3 \cdot nH_2O$ Catalyst



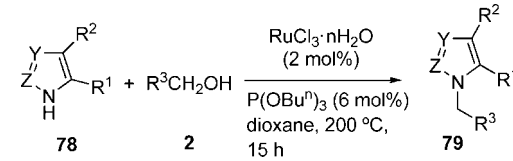
1 75 76 (3-22 %)

Scheme 22. Cyclization of 1,3-Propanodiol with Aniline Derivatives Using $RuCl_3 \cdot nH_2O$ Catalyst: Synthesis of Quinolines



66 73 77 (3-22 %)

Table 23. *N*-Alkylation of Azoles with Primary Alcohols Using $RuCl_3 \cdot nH_2O$



78 2 79

entry	Z	Y	R^1	R^2	R^3	no.	yield (%)
1	CH	N	H	H	H	**79a**	97
2	N	CH	H	H	H	**79b**	67
3	N	CH	H	Me	H	**79c**	85
4	N	CMe	Me	H	H	**79d**	94
5	N	CMe	Me	H	Me	**79e**	32
6	N	CMe	Me	H	Ph	**79f**	>99
7	N	N	H	H	H	**79g**	47

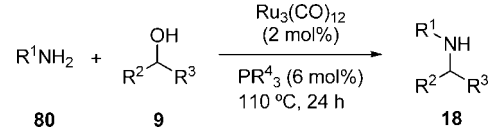
process. The oxidation of primary alcohol, followed by an intramolecular Friedel−Crafts and final dehydrogenation, gave quinolines **77**.[136]

Indoles **8** were synthesized in a similar way to that presented in Table 17 by reaction of the corresponding anilines **66** with triethanolamine (instead of the ammonium chloride used in Table 17) using $RuCl_3 \cdot nH_2O$ (7 mol %), PPh_3 (2 mol %), and $SnCl_2 \cdot 2H_2O$ (100 mol %) in dioxane at 180 °C for 20 h.[137] Yields depended on the electronic character of the substituent, with electron-withdrawing groups giving poor results (9−21%), one electron-donating group giving moderate results (33−66%), and two electron-donating groups giving good results (86−99%). When tri(propan-2-ol)amine was used as the source of the electrophile, the two possible regioisomers were isolated, with the corresponding 2-methylindole being the major one.

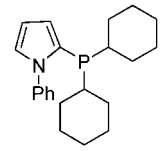
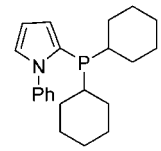
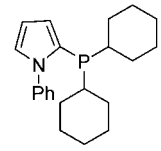
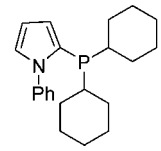
Azoles **78** could be alkylated with primary alcohols (400 mol %) to give the corresponding heterocycles **79** with good results (Table 23) independently of the substitution of the starting azole. It should be pointed out that the reaction with ethanol gave moderate yields.[138]

Different carboxamides **41** could be alkylated in a similar way to that presented in Table 16 by using an excess of a primary alcohol **2** (300 mol %) and catalyzed by the mixture of $RuCl_3 \cdot nH_2O$ (0.6 mol %) and tributylphosphine (8 mol %) in the absence of solvent at 210 °C for 10 h. Yields were good for the acetamide alkylation (88−99% for **64**) but moderate for both the specific case of ethylation and the use of other aliphatic amides (55−71%).[139] This protocol could

Table 24. *N*-Alkylation of Primary Aliphatic Amines with Secondary Alcohols Using $Ru_3(CO)_{12}$ and Phosphines



80 **9** **18**

entry	R^1	R^2	R^3	PR^4_3	no	yield (%)
1	$CH_3(CH_2)_5$	Ph	Me	$P(2\text{-}MeC_6H_4)_3$	**18h**	97
2	$CH_3(CH_2)_5$	Ph	Me		**18h**	98
3	$CH_3(CH_2)_5$	$(CH_2)_5$		$P(2\text{-}MeC_6H_4)_3$	**18i**	93
4	$CH_3(CH_2)_5$	$(CH_2)_5$			**18i**	>99
5	$PhCH_2$	Ph	Me	$P(2\text{-}MeC_6H_4)_3$	**18j**	64
6	$PhCH_2$	Ph	Me		**18j**	87[a]
7	$(CH_2)_7CH$	Ph	Me	$P(2\text{-}MeC_6H_4)_3$	**18k**	13
8	$(CH_2)_7CH$	Ph	Me		**18k**	78[a]

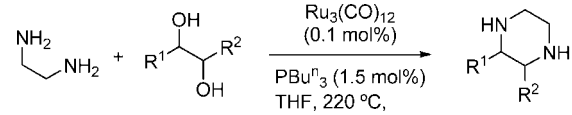
[a] At 120 °C.

be successfully expanded to different lactams, and $Ru_3(CO)_{12}$ could alternatively be used with slightly lower results.

Another source of ruthenium used in the former processes of hydrogen autotransfer was $Ru_3(CO)_{12}$, which was an effective catalyst for the reaction of different amines **20** with ethanediol (**27a**, 300 mol %) to give, after 24 h, the corresponding 2-aminoethanol derivatives **52**, as was depicted in Scheme 14, with moderate yields (9−42%).[106b]

The obtained results using other more hindered phosphines were much more successful. The reaction of primary amines **80** with different alcohols **9** (500 mol %), using $Ru_3(CO)_{12}$ and the phosphines depicted in Table 24, gave the expected secondary amines **18** in general with good results in the absence of solvent.[140] It should be pointed out that *ortho*-tolylphosphine[140a] gave always worse results than the related *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole.[140b] These differences were the highest when α-substituted primary amines were used as nucleophiles (compare entries 7 and 8 in Table 24). The reaction rendered similar yields for either aliphatic or benzylic primary and secondary alcohols, and even acid-sensitive alcohols (such as furanyl and thienylmethanol) could be used with similar results. The presence of a substituent at the four position of benzylamine did not have any appreciable effect on the final result. However, the reaction failed for poor nucleophilic anilines under these conditions, even using electron-donating substituted ones.

Scheme 23. Cyclization of 1,2-Ethanodiamine with 1,2-Diols Using $Ru_3(CO)_{12}$: Synthesis of Substituted Piperazines



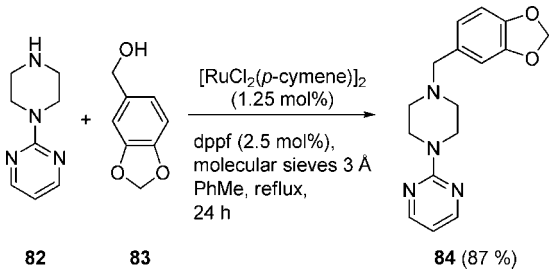
31 **62** **81** (63-99 %)

The aforementioned protocol using the *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole ligand has been expanded to secondary amines **20**, using in this case *tert*-amyl alcohol as solvent. The obtained yields for amines **21** were generally very good, with the best results being obtained with cyclic aliphatic derivatives (47−97%).[141]

Piperazines **81** were prepared by the reaction of equimolecular amounts of the diamine **31** with 1,2-diols **62** in THF (Scheme 23).[142] Other phosphanes, sources of ruthenium species, and solvents were tested, giving in all cases lower results.

The combination of the dimeric (*para*-cymene)ruthenium dichloride $[RuCl_2(p\text{-cymene})]_2$ with different phosphanes seemed to be a more versatile protocol, having been used with very different nitrogen-containing compounds. Initially,

Scheme 24. *N*-Alkylation of 2-(Piperazin-1-yl)pyrimidine with Benzo[*d*][1,3]dioxol-5-ylmethanol Using [RuCl$_2$(*p*-cymene)]$_2$: Synthesis of Piribedil



82 **83** **84** (87 %)

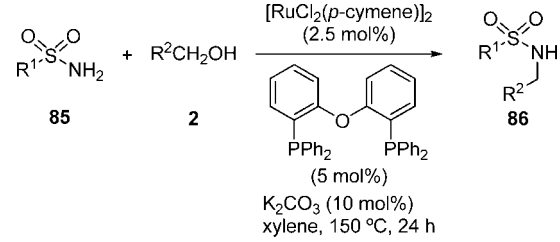
[RuCl$_2$(*p*-cymene)]$_2$ was used in combination with 1,1′-bis(diphenylphosphanoferrocene) (dppf) as the catalytic system for the alkylation of equimolecular amounts of secondary amines **20** with primary alcohols **2** in the presence of molecular sieves, with good yields (62−97%).[143] For illustrating the possibilities of this protocol, it was used in the synthesis of piribedil (Scheme 24), which is a piperazine dopamine agonist used in the treatment of Parkinson's disease. Even ammonium acetate could be used as the source of the nucleophile to give, in this case, tribenzylamine by reaction with 5 equiv of benzyl alcohol, in the absence of solvent.

The above protocol was also used with either very crowded primary aliphatic amines, such as *tert*-butylamine, or poor nucleophilic aniline (**1a**) and 2-aminopyridine (**33a**) to give the corresponding secondary amine derivatives with good yields (69−99%).[144] It should be pointed out that, in these cases, the amount of the catalyst has to be double, and the presence of K_2CO_3 (10 mol %) was necessary in order to achieve good yields.

A further modification of the protocol, essentially by changing the ferrocene diphosphane derivative for bis(2-diphenylphosphanophenyl)ether, improved the previous results using [RuCl$_2$(*p*-cymene)]$_2$ and permitted the synthesis of anti-inflammatory agents such as antergan, tripelennamine, pheniramine, and chlorpheniramine. The new protocol permitted the use of secondary alcohols **9** as the source of the electrophile in the alkylation of secondary amines **20** to give the expected tertiary amines **21** with good results (36−99%). This combination was also able to catalyze the reaction of anilines **66** with different diols (**12**, **54a**, and **27b**) to give the corresponding *N*-aryl substituted pyrrolidines, piperidines, and perhydroazepines, respectively, in the presence of triethylamine (10 mol %) as base. Mechanistic studies showed that the in situ formed aldehydes could dissociate from the ruthenium coordination sphere, and therefore, the imine formation did not necessarily take place while it was coordinated. Moreover, it should be highlighted that this combination of ruthenium source and phosphane was able to alkylate simple sulfonamides **85** with primary alcohols **2** (100 mol %) to give the expected compounds **86** with good yields for the first time (Table 25). The results seemed to be independent of the nature of the sulfonamide or alcohol used.[145] A similar catalytic combination has been successfully used in the conversion of 1,4-alkynediols into pyrroles.[146]

Finally, it should be pointed out that a modification of the above protocol using triphenylphosphane has been used for the alkylation of trimethylsilylethanesulfonamide to give the corresponding *N*-alkyl sulfonamide, which by treatment with cesium fluoride gave directly the related amine **45** with yields from 53 to 74% for both steps. This strategy is an

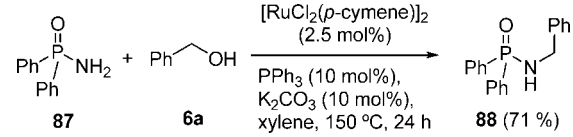
Table 25. *N*-Alkylation of Sulfonamides with Primary Alcohols Using [RuCl$_2$(*p*-cymene)]$_2$



85 **2** **86**

entry	R^1	R^2	no.	yield (%)
1	Me	Ph	**86a**	91
2	Ph	Ph	**86b**	92
3	4-$O_2NC_6H_4$	Ph	**86c**	72
4	4-ClC_6H_4	Ph	**86d**	89
5	4-MeC_6H_4	Ph	**86e**	95
6	4-$MeOC_6H_4$	Ph	**86f**	99
7	4-MeC_6H_4	$(CH_2)_2CH$	**86g**	>99
8	4-MeC_6H_4	$(CH_2)_5CH$	**86h**	91

Scheme 25. *N*-Benzylation of Diphenylphosphinic Amide Using [RuCl$_2$(*p*-cymene)]$_2$



87 **6a** **88** (71 %)

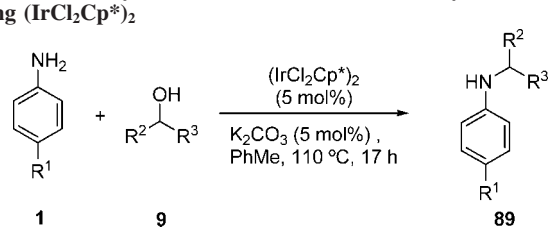
indirect alternative to the *N*-alkylation of ammonia (**5**). In this context, the first alkylation of a phosphinic amide was described with a good yield (Scheme 25).[147] This catalytic system has also been used in the preparation of amides from amines and alcohols.[148]

2.2.3. Derived from Iridium

Iridium complexes have catalyzed different reactions such as carbon−carbon forming reactions, as well as isomerization and hydrogen autotransfer reactions.[149] One of these iridium complexes, which has shown its efficiency in the reaction reviewed here, was the dimeric η^5-pentamethylcyclopentadienyliridium(III) dichloride [(IrCl$_2$Cp*)$_2$]. This complex has been used as catalyst in the *N*-alkylation of different amine and nitrogen-containing derivatives. Hence, this catalyst was able to promote the reaction between aniline derivatives **1** with primary and secondary alcohols (**9**, 100 mol %) in the presence of substoichiometric amounts of K_2CO_3 to give compounds **89** with excellent yields (Table 26). The electronic nature of the substituent in aniline did not have any influence on the obtained results. Lower yields were obtained when either other primary aliphatic amines (such as benzylamine, pentylamine, or octylamine) or secondary alcohols were used (61−88%).[150] Under similar reaction conditions, *N*-methylaniline and *N*-methylbenzylamine could be benzylated with 75 and 93% yield, respectively.

Slightly better results were obtained when $NaHCO_3$ (1−3 mol %) was used as base, achieving products **89** with yields ranging from 71 to 98%. Other substituents such as methyl, bromo, nitro, cyano, and ester moieties in the aniline derivative **1** were well-tolerated.[151] This improved protocol was applied to the alkylation of secondary amines **20** with secondary alcohols **9** to give the expected tertiary amines **21** with, in general, good results (Table 27). The reaction required a slightly higher amount of catalyst loading with less basic amines such as *N*-methylaniline. The reaction of an imine in the presence of a hydrogen donor was performed

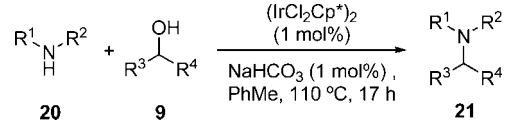
Table 26. *N*-Alkylation of Anilines with Secondary Alcohols Using $(IrCl_2Cp^*)_2$



1 **9** **89**

entry	R^1	R^2	R^3	no.	yield (%)
1	H	H	Ph	**89a**	88
2	H	H	4-ClC_6H_4	**89b**	83
3	H	H	4-$MeOC_6H_4$	**89c**	95
4	H	H	2-$MeOC_6H_4$	**89d**	95
5	H	H	$CH_3(CH_2)_6$	**89e**	79
6	Cl	H	Ph	**89f**	93
7	MeO	H	Ph	**89g**	95
8	H	Me	$(CH_2)_5$	**89h**	69

Table 27. Alkylation of Secondary Amines with Secondary Alcohols Using $(IrCl_2Cp^*)_2$



20 **9** **21**

entry	R^1	R^2	R^3	R^4	no.	yield (%)
1	Me	Ph	H	Ph	**21i**	91
2	Me	Ph	$(CH_2)_5$		**21j**	83
3	$(CH_2)_4$		H	Ph	**21k**	92
4	$(CH_2)_4$		$(CH_2)_5$		**21l**	88
5	$PhCH_2$	$PhCH_2$	H	Ph	**21m**	75
6	$PhCH_2$	Me	$(CH_2)_5$		**21n**	44

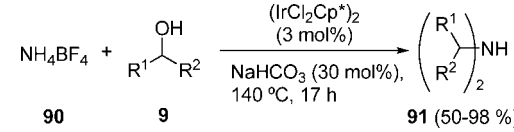
under catalytic conditions to understand the possible reaction mechanism, finding only traces of the expected amine. This result seemed to indicate that the imine formation must occur in the coordination sphere of the iridium complex. Finally, it should be pointed out that this protocol has been successfully used for the sequential double alkylation of benzylamine first with a benzylic alcohol and second with an aliphatic one, obtaining the corresponding tertiary amine with good yields (42−88%).

The above protocol has been recently used in the preparation of *N*,*N*′-disubstituted piperazines from the corresponding *N*-substituted 2-aminoethanol derivatives of type **57** ($n = 0$).[152]

Tertiary amines **22** could also be obtained by reaction of ammonium acetate with a slight excess of a great variety of primary alcohols **2** (360 mol %) using the former protocol but increasing the amount of base ($NaHCO_3$ 5−30 mol %) and the temperature (130 °C).[153] Although yields were very high for benzylic alcohols **6** (71−92%), in the case of aliphatic alcohols, a higher amount of catalyst should be loaded [$(IrCl_2Cp^*)_2$ 5 mol %; $NaHCO_3$ 30 mol %]. Surprisingly, when ammonium tetrafluoroborate (**90**) was used instead of acetate, a high selectivity toward the formation of the corresponding symmetrical secondary amine **91** was observed using only a little excess of the corresponding alcohol in the absence of solvent (Scheme 26; 220 mol % for primary alcohols $R^1 = H$, and 300 mol % for secondary ones). The reaction procedure could be extended to the formation of heterocyclic amines such as 2-phenylpyrrolidine and 2-phenylpiperidine with 62 and 85% yield, respectively, just by starting from the corresponding diol **92**.

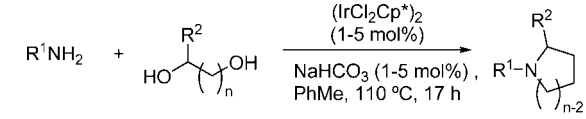
The reaction of diols **92** with different amines **80** (150 mol %), instead of ammonium trifluoroborate, gave the

Scheme 26. Double *N*-Alkylation of Ammonium Tetrafluoroborate with Secondary Alcohols Using $(IrCl_2Cp^*)_2$



90 **9** **91** (50-98 %)

Table 28. Cyclization of Primary Amines with Diols Using $(IrCl_2Cp^*)_2$



80 **92** **93**

entry	R^1	R^2	*n*	no.	yield (%)
1	Ph	H	3	**93a**	70
2	4-$MeOC_6H_4$	H	3	**93b**	90
3	$CH_3(CH_2)_7$	H	3	**93c**	81
4	$PhCH_2$	H	3	**93d**	72
5	$PhCH_2$	H	4	**93e**	91
6	$PhCH_2$	H	5	**93f**	73
7	$PhCH_2$	Ph	4	**93g**	78
8	(*R*)-PhCHMe	Ph	4	**93h**	76[a]

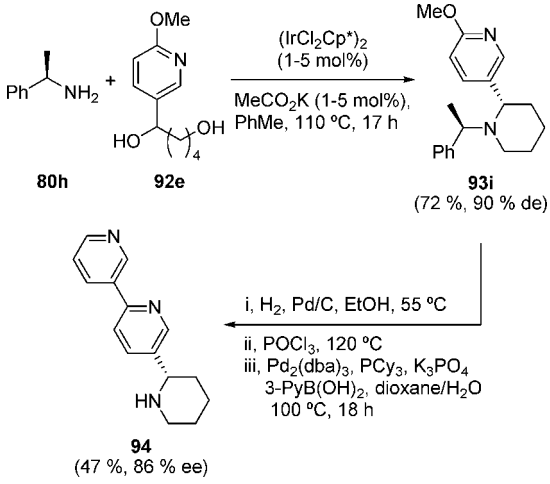
[a] Reaction performed using 6 mol % potassium acetate as base, with the (*R*,*S*)-diasteroisomer being the major product (92% diastereomeric excess (de)).

corresponding cyclic tertiary amines **93** with good yields (Table 28), with the presence of electron-donating groups on the aromatic ring of aniline derivatives enhancing the results.[154] This heterocyclization reaction has been scaled up in the case of compound **93e** (0.1 mol) with practically the same yield.[154b] The diastereoisomeric version of the reaction could be performed by using the corresponding chiral (*R*)-phenethylamine. In this case, the reaction was carried out using sodium acetate as base to give the expected *N*-phenethylpiperidine **93h**. Although the diastereoisomeric excess was good, the enantiomeric excesses of the isolated diastereoisomers were 86 and 93% for the major (*R*,*S*)-**93h** and minor (*R*,*R*)-**93h**, respectively. This racemization could be explained by isomerization of the initial imine or the iminium intermediate.

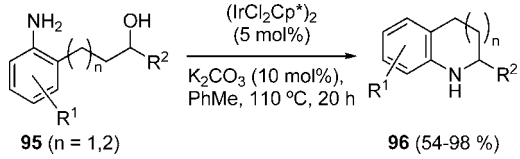
This strategy has been used in the diastereoselective synthesis of noranabasamine (**94**), which is an amphibian alkaloid isolated from the Columbian poison dart frog *Phyllobates terribilis*.[155] For this purpose, diol **92e** was reacted with chiral (*R*)-phenethylamine (**80h**) to give the expected piperidine **93i** with good yield (Scheme 27). The final debenzylation of the chiral auxiliary, followed by chlorination of the pyridine ring and a final Suzuki reaction, gave the expected alkaloid **94**. The enantiomeric compound was also prepared with similar results just by changing the absolute configuration of the initial amine.

Other heterocyclic compounds have been prepared by means of a *N*-alkylation process catalyzed by $(IrCl_2Cp^*)_2$. For instance, indoles **8** were synthesized by reacting amino alcohols **63** with 5 mol % of $(IrCl_2Cp^*)_2$ and 10 mol % of K_2CO_3 in toluene at 110 °C for 20 h, with good yields (68−99%).[156] 2-Nitrophenylethanol could be used, instead of the corresponding amino derivative, as the starting material, rendering the expected indole **8a** in 68%. In a similar process, other heterocyclic compounds **96** could be obtained from the aminophenyl alcohols **95** (Scheme 28).

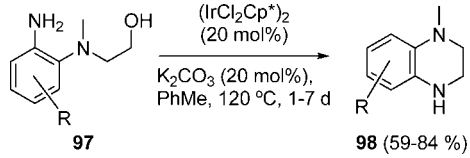
Scheme 27. Cyclization of 1-(6-Methoxypyridin-3-yl)butane-1,4-diol with (*R*)-1-Phenylethylamine: Synthesis of Noranabasamine



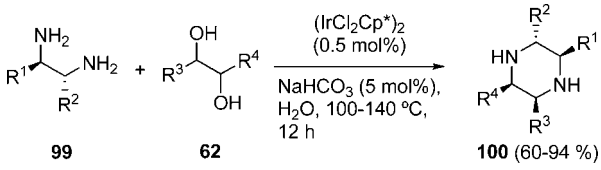
Scheme 28. Cyclization of 2-Aminophenylalkyl Alcohol Derivatives Using ($IrCl_2Cp^*)_2$



Scheme 29. Cyclization of 2-Aminophenylaminoethanol Derivatives Using ($IrCl_2Cp^*)_2$



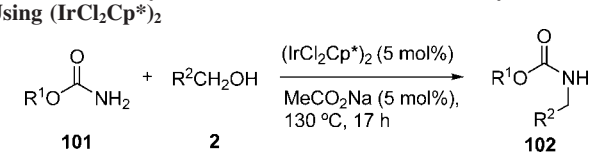
Scheme 30. Cyclization of 1,2-Diamine Derivatives with 1,2-Diols Catalyzed by ($IrCl_2Cp^*)_2$: Synthesis of Substituted Piperazines



The presence of a nitrogen atom in the aliphatic chain did not change the previous results. Thus, different 2-aminoethanol derivatives **97** could be converted into the corresponding 1,2,3,4-tetrahydroquinooxalines **98** (Scheme 29). The reaction needed a higher catalyst loading, as well as longer reaction times, and the yields were slightly lower than previously presented in Scheme 28. Moreover, the presence of the *N*-methyl moiety in the tertiary amine **97** was of great importance, since the reaction with the corresponding secondary amine failed, probably due to the coordination of iridium atom at this position.[157]

The cyclization of diols **62** with different 1,2-diamines **99** catalyzed by $(IrCl_2Cp^*)_2$ was accomplished in water as solvent to give the corresponding piperazines **100** (Scheme 30). It should be pointed out that the diastereoselectivities on the newly formed sterogenic centers were from good [in the case of the formation of two new sterogenic centers (75% de)] to excellent [in the case of the formation of only one stereogenic center (>95% de, $R^4 = H$)].[158]

Table 29. *N*-Alkylation of Carbamates with Primary Alcohols Using ($IrCl_2Cp^*)_2$



entry	R^1	R^2	no.	yield (%)
1	Me	Ph	**102a**	46
2	Bu^n	Ph	**102b**	87
3	Bu^n	4-ClC_6H_4	**102c**	55
4	Bu^n	4-MeC_6H_4	**102d**	92
5	Bu^n	$CH_3(CH_2)_2$	**102e**	65

Mechanistic studies on the homogeneous iridium-catalyzed alkylation of amines with alcohols have been performed using density functional theory (DFT) calculations.[159] This study showed that the found reaction energetic barriers were consistent with the experimental requirements of elevated temperatures. The reaction was composed of three multistep processes: the first one was the iridium-catalyzed oxidation of the alcohol, the second one was the nucleophilic addition of the amine to the formed aldehydes, and the third one was the iridium-catalyzed reduction of the imine to the final amine, requiring the coordination of the alcohol and/or the imine to the metal coordination sphere. Because the amine dissociation from the metal center was a high energetic step, although it is required to regenerate the catalytic species, high temperature must be used to overcome this energetic barrier. The presence of a carbonate as ancillary ligand has been found to decrease the energetic barrier in many different steps. It participates in the dehydrogenation of the alcohol by hosting the proton, while the hydride coordinates to the metal, and in the final step it has the reverse effect as proton reservoir for the reduction of the imine. The dehydrogenation of the alcohol via proton transfer, followed by β-elimination of a hydride, has a lower energetic barrier than the related one with the amine. This is connected with the iridium−oxygen bond in the alkoxy intermediate compared with the iridium−nitrogen bond in the possible amido intermediate. These facts contribute to the production of the required aldehyde by oxidation of the initial alcohol rather than the generation of the imine intermediate by oxidation of the initial amine. Moreover, the imine formed by condensation of the initial amine and the aldehyde is more easily hydrogenated that the aldehyde, favoring the overall reaction pathway.

The former catalyst has been used not only in the alkylation of amines but also in the alkylation of amides. The reaction of different carbamates **101** with primary alcohols **2** (400 mol %) at 130 °C without solvent gave the expected carbamic derivatives **102** (Table 29). The presence of a base accelerated the reaction, with sodium acetate being the most effective one. The temperature was also an important aspect, since temperatures higher or lower than 130 °C gave lower yields. The best results were obtained with the benzyl alcohol derivative bearing electron-donating groups at the four position, with the yields using aliphatic alcohols being moderated. However, the reaction failed when secondary alcohols were used as electrophilic partners.[160] Owing to the facile deprotection of carbamates under basic methanol/water conditions, these carbamates could be regarded as an ammonia equivalent. In fact, the reaction of compound **102b** with NaOH in $MeOH/H_2O$ gave the corresponding benzyl amine in 92% yield. The same protocol

Scheme 31. *N*-Alkylation of Primary Amines with 2-(1*H*-indol-3-yl)ethanol Using [IrCl(COD)]$_2$: Synthesis of *N*-Alkylated Tryptamine Derivatives

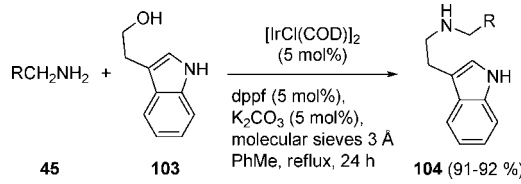
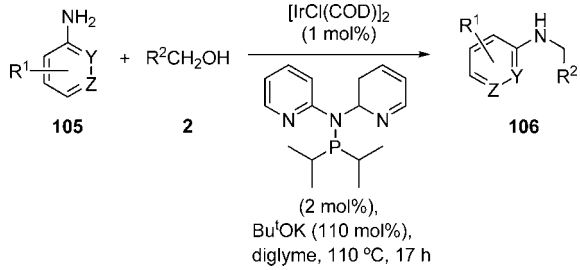


Table 30. *N*-Alkylation of Heteroaromatic Amines with Primary Alcohols Using [IrCl(COD)]$_2$



entry	R^1	Z	Y	R^2	no.	yield (%)
1	H	CH	CH	Ph	**106a**	92
2	4-CF_3	CH	CH	Ph	**106b**	67
3	4-MeO	CH	CH	Ph	**106c**	92
4	H	CH	N	Ph	**106d**	93
5	H	N	CH	Ph	**106e**	97
6	H	CH	N	4-ClC_6H_4	**106f**	82
7	H	CH	N	4-$MeOC_6H_4$	**106g**	97

could also be applied to simple amides **41** to give the corresponding *N*-alkylated amides **64** with good yields (59−91%).

Another iridium complex widely used in this type of reaction was the dimer of (η^4-1,5-cyclooctadiene)iridium chloride {[IrCl(COD)]$_2$}. Initially, it was used in the preparation of *N*-alkylated tryptamine **104** (Scheme 31). Tryptamine is a substance presented in various naturally occurring products, as well as in synthetic ones, that exhibit an important pharmacological activity. Its derivatives were prepared by reaction of tryptophol (**103**) with different primary amines **45** in the presence of 1,1-bis(diphenylphosphanoferrocene) (dppf) with excellent yields.[161] The same structures **104** could be obtained by reaction of primary tryptamine with the corresponding primary alcohols **2**, although with lower yields (64−86%). This protocol has been applied to the reaction of tryptamine with diols, such as 1,4-butanediol (**12**), 1,5-pentanediol (**54a**), and 1,6-hexanediol (**27b**), rendering the corresponding pyrrolidine, piperidine, and azepine derivative, respectively, with moderate to good yields.

The combination of the aforementioned iridium source with ligands of type *N*-phosphanopyridin-2-amine has shown its potential in the alkylation of different substituted (hetero)aromatic amino derivatives **105** with primary alcohols **2** (110 mol %). The reaction gave good yields independently of the substitution position on the amine derivative **105**. However, lower yields were obtained when electron-withdrawing group were placed in the four position of both the amine derivative **105** or the benzylic alcohol (Table 30). It should be pointed out that the presence of strong bases diminished the tolerance of the process toward the use of basic sensitive compounds. Surprisingly, the reaction using high nucleophilic aliphatic amines failed.[162]

Scheme 32. Double *N*-Alkylation of 2,6-Diaminopyridine with Primary Alcohols Using [IrCl(COD)]$_2$

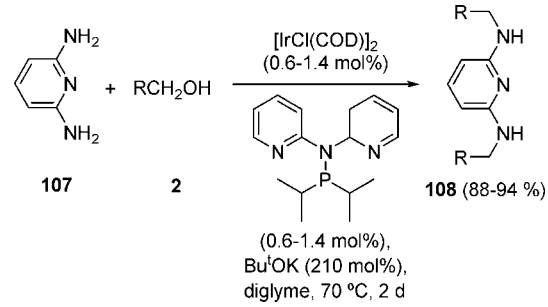
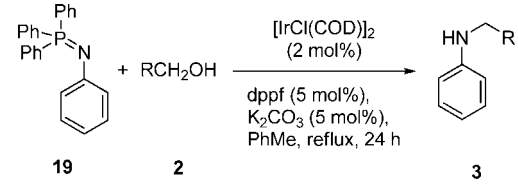


Table 31. *N*-Alkylation Process through an Indirect aza-Wittig Process of *N*-(Triphenylphosphoranylidine)aniline with Primary Alcohols Using [IrCl(COD)]$_2$



entry	R	no.	yield (%)
1	Ph	**3e**	91
2	4-$NO_2C_6H_4$	**3f**	38
3	4-$MeOC_6H_4$	**3g**	81
4	2-furyl	**3h**	71
5	$PhCH_2$	**3i**	85

A further optimization of the reaction conditions showed that the process could be performed at 70 °C, with a lower iridium loading (0.1−0.6 mol %) but longer reaction times (24 h), affording the expected products **106** with similar yields. Under these new conditions, the double alkylation of 2,6-diaminopyridine (**107**) was attempted using primary alcohols **2** (210 mol %), yielding the corresponding amine **108** after 2 days with excellent results (Scheme 32). In the case of using benzylic alcohols, the presence of electron-donating groups was well-tolerated, but in the case of electron-withdrawing groups, yields were slightly lower.[163] The related unsymmetrical alkylated diaminopyridine derivates could be obtained in a two-step procedure with similar results to those for symmetrical amine ones.

The first alkylation of amines through an indirect aza-Wittig process was performed using the former iridium source (Table 31). The reaction using a slight excess of the starting compound **19** (110 mol %) gave the expected compound **3** in general with good yields.[164]

A similar iridium complex has been successfully used in the oxidative dimerization of alcohols to give the corresponding esters.[165]

N-Heterocyclic carbenes have attracted much attention because of their behavior as stable ligands for homogeneous catalysis. The first example of their application to the alkylation of aniline (**1a**) with primary alcohols **2** (100 mol %) is depicted in Scheme 33. The reaction gave better results for benzyl alcohol than for 1-butanol, with the presence of a strong base being mandatory to get good results.[166]

A similar complex has been used in the alkylation of primary amines with primary and secondary alcohols **9** (500−1000 mol %) to give a mixture of products, with the selectivity being highly dependent on the combination of amines and alcohol used without any apparent trend (Table 32). The presence of silver trifluoromethanosulfonate (Ag-

Scheme 33. *N*-Alkylation of Aniline with Primary Alcohols Using a Simple Carbine−Iridium Complex

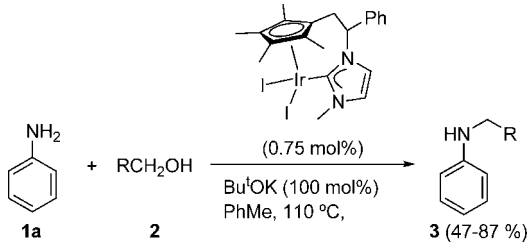
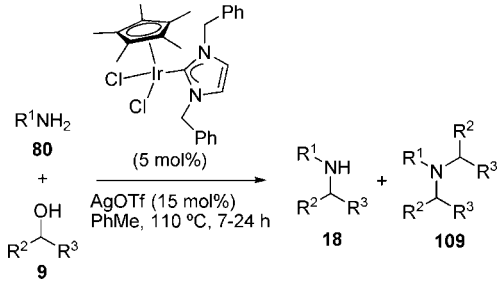
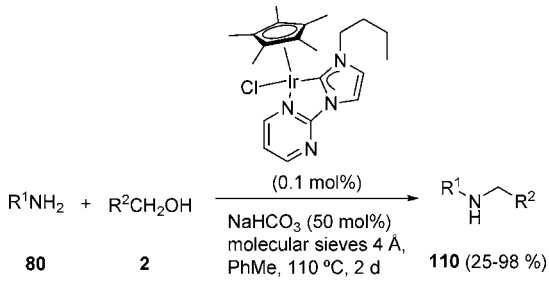


Table 32. *N*-Alkylation of Primary Amines with Secondary Alcohols Using a Simple Carbene−Iridium Complex



entry	R^1	R^2	R^3	no.	yield (%)	no.	yield (%)
1	Ph	Ph	H	**18l**	90	**109a**	0
2	$PhCH_2$	Ph	H	**18m**	0	**109b**	90
3	$PhCH_2$	Pr^n	H	**18n**	33	**109c**	62
4	$CH_3(CH_2)_5$	Ph	Me	**18h**	67	**109d**	33
5	$PhCH_2$	Ph	Me	**18j**	90	**109e**	0

Scheme 34. *N*-Alkylation of Primary Amines with Primary Alcohols Using a Carbene−Iridium Complex

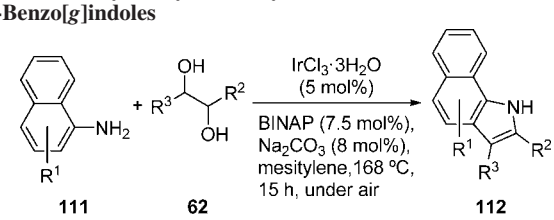


OTf) is compulsory in order to perform the reaction successfully. The reaction of highly nucleophilic *tert*-butylamine with benzyl alcohol (**6a**) gave the corresponding benzylated amine in 95% yield. Following the same procedure, a secondary amine, such as *N*-methylaniline, could also be alkylated with benzyl alcohol to give the corresponding tertiary amine in a excellent 95% yield. However, the reaction failed with other secondary amines.[167]

Very recently, the aforementioned iridium catalyst has been used in the conversion of waste glycerol into the aniline derivative **3c** in a poor yield (10%).[168] Glycerol was converted into 1,3-propanediol (**73**) by fermentation using *Clostridium butyricum*, and this aqueous culture supernatant was directly transformed into *N*-propylaniline by reaction with an excess of aniline (**1a**, 200 mol %) in a two-phase media using an ionic liquid.

An iridium complex bearing a chelating pyrimidine-functionalized *N*-heterocyclic carbene has been used as the catalyst in the *N*-alkylation of aliphatic and aromatic primary amines **80** with an equimolecular amount of primary alcohols **2** (Scheme 34). The reaction was active in the presence of weak bases, such as $NaHCO_3$, and molecular sieves, yielding

Table 33. Cyclization of Naphthylamine Derivatives with 1,2-Diols Catalyzed by $IrCl_3$: Synthesis of Substituted 1H-Benzo[*g*]indoles



entry	R^1	R^2	R^3	no.	yield (%)
1	H	H	H	**112a**	47
2	H	Me	Me	**112b**	96
3	H	$(CH_2)_3$		**112c**	90
4	H	$(CH_2)_3$		**113d**	98[a]
5	4-Me	H	H	**112e**	90
6	4-Me	Me	Me	**112f**	88
7	5-MeO	H	H	**112g**	72
8	7-MeO	H	H	**112h**	72
9	$5\text{-}Me_2N$	H	H	**112i**	59

[a] The same result was obtained using either *cis*- or *trans*-diol.

the corresponding alkylated amines, in general, with moderate results.[169]

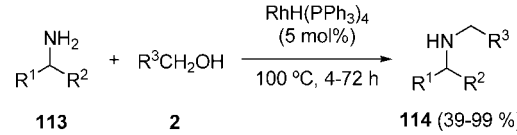
An in situ generated iridium complex was also active catalyst in the hydrogen autotransfer process. Thus, the combination of nearly equimolecular amounts of iridium trichloride and 2,2′-bis(diphenylphosphano)-1,1′-binaphthyl (BINAP) was an efficient catalyst for the *N*-heterocyclization of different substituted naphthylamines **111** with 1,2-diols (**62**) to give the corresponding 1*H*-benzo[*g*]indoles **112** (Table 33). The reaction was faster in the presence of air and did not show any effect due to the presence of substitution on the starting amine **111**.[170] The protocol was further expanded to the use of 1,3-propanediol **73**, rendering the corresponding benzoquinolines with good to excellent results (66−95%). The mechanism seemed to go through the alkylation of 2 equiv of the starting amine with the diol to give the corresponding diamine, which suffers an intramolecular Friedel−Crafts reaction, liberating the starting amine **111**. The final dehydrogenation by the oxygen in the air gave the corresponding heterocyclic compound.

2.2.4. Others

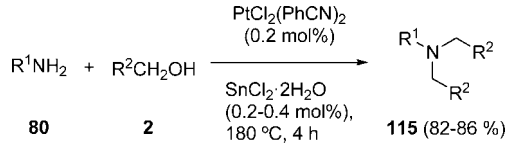
Other different complexes were active in the hydrogen autotransfer process. Hence, simple copper(II) acetate has been very recently proposed as a catalytic alternative in the alkylation of sulfonamides **85** with different alcohols of type **2**.[171]

The $RhH(PPh_3)_4$ complex was effective in the alkylation of primary amines **113** with a large excess of primary alcohols **2** (such as methanol, ethanol, or benzyl alcohol) used both as source of the electrophile and solvent at the same time, to give the expected *N*-alkylated amines **114** (Scheme 35). The results were in general excellent, as the yields and time were concerned. Only when the secondary amine pyrrolidine was used as nucleophilic partner was the yield decreased to 74%.[91]

Scheme 35. *N*-Alkylation of Primary Amines with Primary Alcohols Using $RhH(PPh_3)_4$ Catalyst



Scheme 36. Double *N*-Alkylation of Primary Amines with Primary Alcohols Using $PtCl_2(PhCN)$ Complex



The last example of this section is depicted in Scheme 36. The reaction of different primary amines **80** using an excess of a primary alcohol **2** (1200 mol %) catalyzed by $PtCl_2(PhCN)_2$ in the presence of tin(II) chloride, gave the double alkylation process, rendering the corresponding amines **115**. Allylic alcohols, instead of aliphatic ones, could also be used, yielding in these cases the corresponding monoalkylated products.[172]

3. Amines as Source of Electrophiles

Surprisingly, the alkylation of amines using other amines as initial source of the electrophile has been performed using many different heterogeneous and homogeneous catalysts, although it should be highlighted that this process is less developed than the one using alcohols as electrophiles. The hydrogen autotransfer process of amine alkylation does not have to be confused with an alkylation using in situ formed ammonium derivatives through a typical S_N2.[173] The process reviewed here always begins with the oxidation[174] of an alkylamine to the corresponding imine (iminium), followed by addition of a second nucleophilic amine to the in situ formed imine, generating an aminal intermediate, elimination of the initial dealkylated amine and formation of a new imine (iminium), with a final hydrogenation of this imine. The thermodynamics of the whole process is in some cases highly favorable, above all when ammonia is one of the products of the reaction.[175]

3.1. Heterogeneous Catalysts

Initially, heterogeneous catalysts were used in a different reduction process, with the *N*-alkylation of amines by other amines being an unwanted side reaction. However, later on these processes have gained the attention of the scientific community.

3.1.1. Derived from Nickel

Historically, nickel was the first metal catalyst used to perform the *N*-alkylation of amines with other amines being the source of the electrophile. This catalytic ability was found when Raney-nickel was used as catalyst to carry out the reduction of nitrile derivatives. When this process was performed at 20 atm of hydrogen and 110−130 °C, in tetralin or decalin, symmetrical secondary amines were formed in low yields (2−47%), together with the expected primary amine.[46] The presence of the main side product was explained by reaction of the intermediate imine formed, either in the first step of the reduction of the starting nitrile or by dehydrogenation of final primary amine product, with the final primary amine to give an aminal intermediate, which in its turn liberated ammonia and gave a *N*-substituted imine. The final hydrogenation of this imine led to the formation of the secondary amine. The yield of this side product could be minimized by carrying out the reaction in the presence of ammonia.[53] Surprisingly, moderate yields of the corresponding secondary amines (45 and 66%, respectively) were obtained when the reduction of octanenitrile or nonanenitrile with hydrogen (75 atm) was performed at lower temperatures (65−80 °C) in ethanol using Raney-nickel as catalyst (15 mol %).[176]

Scheme 37. Auto *N*-Alkylation of Amylamine Using Raney-Nickel

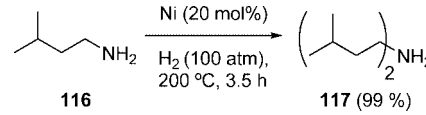
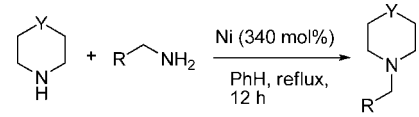
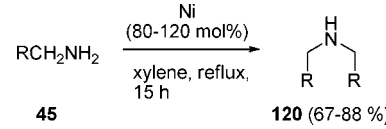


Table 34. *N*-Alkylation of Cyclic Amines with Primary Amines by Raney-Nickel



entry	Y	R	no.	yield (%)
1	CH_2	$CH_3(CH_2)_4$	**119a**	40
2	CHMe	$CH_3(CH_2)_4$	**119b**	72
3	O	$CH_3(CH_2)_4$	**119c**	52
4	CH_2	$PhCH_2$	**119d**	58
5	CHMe	$Ph(CH_2)_3$	**119e**	72

Scheme 38. Auto *N*-Alkylation of Primary Amines Using Raney-Nickel



The former alkylation process was also observed in the reduction of other nitrogen-containing derivatives, such as amides and oximes. Thus, in the reduction of benzaldoxime, benzamide, and other compounds, in the absence of solvent, and using Raney-nickel (8−15 mol %) at 200 °C under 100 atm of hydrogen, the corresponding symmetrical secondary amine was obtained in low yields (6−23%). Better results were obtained in the direct alkylation of cyclohexylamine and 3-methylbutan-1-amine (**116**) under similar reaction conditions (Scheme 37), affording the corresponding dialkylamine with 36 and 99% yield, respectively, and liberating ammonia.[42]

The shown auto *N*-alkylation process of amines (Scheme 37) was also observed as a side reaction when thioamides were reduced in the presence of Raney-nickel (1 150−1 600 mol %) at reflux of ethanol or dioxane, yielding the corresponding symmetrical secondary amines in moderate yields (40−45%).[47]

The auto *N*-alkylation of primary amines, under benzene, toluene, or xylene reflux to give the corresponding symmetrical secondary amines, has been accomplished by the use of Raney-nickel in the absence of hydrogen with good yields (70−86%). This protocol was also extended to the alkylation of cyclic secondary amines **118** (400 mol %) using primary alkyl amines **45** as the source of the electrophile (Table 34), to give the corresponding tertiary amines **119** in moderate yields, with concomitant liberation of ammonia.[177]

The large excess of Raney-nickel required above could be reduced in the auto *N*-alkylation of primary amines **45** to give the corresponding symmetrical secondary ones **120** when the reaction was performed under xylene reflux conditions, retaining the good yields (Scheme 38).[178]

3.1.2. Derived from Copper

Several copper species have been used as catalysts either in the transalkylation or in the autoalkylation of amines. For instance, diethylamine could be obtained from ethylamine by using porous copper in a closed recycling system at 256 °C after 2.5 h under a hydrogen atmosphere (1 atm), with only 14% yield.[179] The kinetic data obtained from this transformation showed a zero-order equation rate, with the desorption of ammonia and absorption of ethylamine being the possible controlling mechanism pathway. Both, the amount of ammonia and hydrogen presented on and over the catalysts surface influenced strongly the reactivity and the product distribution of the reaction.

Alumina-supported copper (56 wt %) has been used in a continuous bead reactor at an atmospheric hydrogen pressure and 227−257 °C to perform the autoalkylation and transalkylation of benzylamine (**45a**) and benzylmethylamine, respectively. When benzylamine was the starting material, the main reaction product was dibenzylamine (42−50% yield), with the corresponding imine (*N*-benzylidene-1-phenylmethanamine) being also detected. However, when benzylmethylamine was the initial reagent, the main product was dibenzylmethylamine and methylamine, albeit in lower yields (14−17%).[180] In these processes catalyzed by copper and other metals, the presence of hydrogen was necessary in order to prevent the formation of bulk copper nitride, which deactivated the catalyst. Temperature-programmed desorption (TPD) and surface reaction (TPSR) studies indicated that three different deactivation processes had to be considered, namely, the formation of metal nitride, the formation of metal carbide, and carbonaceous species,[181] independently of the metal used (copper, nickel, or cobalt). While only copper nitride formation was observed with copper, all of the other three deactivation processes occurred with nickel and cobalt.

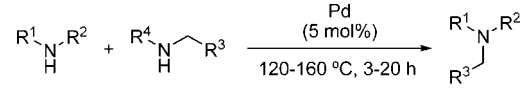
The copper−chromite catalyst ($CuCr_2O_4$−$BaCr_2O_4$, 93 mol %) has been used in the synthesis of the symmetrical secondary amine dilaurylamine by hydrogenation of lauramide at 220 °C and under 340−365 atm of hydrogen pressure. The corresponding didodecylamine was obtained with a moderate 52% yield.[54] Also, the reduction of dodecylnitrile in a stainless steel tubular flow reactor at 150 °C and under 30 atm of hydrogen pressure, using in this case a copper−chromium catalyst supported in alumina, gave the aforementioned didodecylamine in a modest 34% yield.[58]

3.1.3. Derived from Palladium

Heterogeneous palladium catalysts have been extensively used in the *N*-alkylation of amines using another (or the same) amine as the source of the electrophile. At the beginning of the previous century, the optimal conditions to obtain secondary amines from primary ones by using palladium as catalyst were discovered. So, when palladium on Ba_2SO_4 (2.5 wt %, 2.5 mol %) was used as catalyst in the presence of hydrogen, benzylamine (**45a**) was transformed into the corresponding dibenzylamine with 90% yield under xylene reflux conditions and after 2 h.[182]

When the aforementioned reaction was performed using palladium black (18 mol %) in ethanol at reflux, dibenzylamine was also quantitatively obtained after 3 h. However, when the same protocol was applied to 2-phenylethylamine, only a modest 10% yield of the corresponding symmetrical secondary amine was obtained.[87]

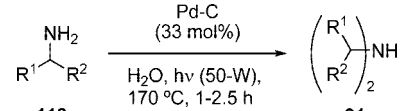
Table 35. *N*-Alkylation of Secondary Amines with Secondary Amines by Palladium Black



20 **110** **121**

entry	R^1	R^2	R^3	R^4	no.	yield (%)
1	H	$CH_3(CH_2)_5$	H	Ph	**121a**	5
2	H	$CH_3(CH_2)_4$	Pr^n	Me	**121b**	34
3	H	$CH_3(CH_2)_4$	Ph	Me	**121c**	20
4	H	Ph	Ph	Me	**121d**	19
5		$(CH_2)_4$	Ph	Me	**121e**	56
6		$(CH_2)_5$	Pr^n	Me	**121f**	83
7		$(CH_2)_5$	Ph	Me	**121g**	87

Table 36. Auto *N*-Alkylation of Primary Amines using Palladium on Carbon



113 **91**

entry	R^1	R^2	no.	yield (%)
1	H	Pr^n	**91a**	47
2	H	Pr^i	**91b**	50
3	Me	Et	**91c**	41

Following the above ideas, different evaporated metal films (Pt, Pd, Ni, W, and Co) were incorporated in carbon to prepare the corresponding catalysts. These catalysts were tested in the reaction of methylamine and dimethylamine (**25**) at 227 °C under a hydrogen atmosphere: only palladium on carbon showed activity but rendered mixtures of dimethylamine and trimethylamine as main products.[183]

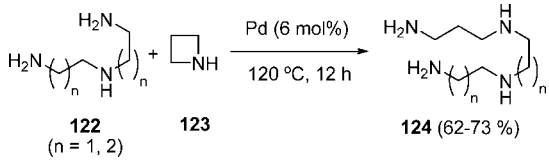
After these preliminary studies on the activity of palladium, the studies were revisited. Hence, when benzylamine (**45a**) was treated with palladium black (5 mol %) at 80 °C, 41% of dibenzylamine was formed after a few hours, together with 41% of the corresponding imine *N*-benzylideneaniline. However, allylamine was converted into *N*-propylideneallylamine (95%). By heating the reaction at higher temperatures, secondary amines were converted into the corresponding tertiary ones, albeit in general with low yields (3−60%). The interesting results obtained when amines **20** were alkylated by other secondary amines **110** to give the corresponding tertiary amines **121** are depicted in Table 35.[184]

Following a similar protocol, pyrrolidine (**30**: $m = 1$) was transformed into 1,4-di(pyrrolidin-1-yl)butane (**74f**: $m = 1$; $n = 3$) in 75% yield, after being heated at 200 °C during 5 h.[185]

The aforementioned protocol using palladium black was extended to the transalkylation of two different tertiary amines **22**, affording a mixture of all statistically possible tertiary amines. For instance, when equimolecular amounts of tributylamine and trihexylamine were reacted, a mixture of tributylamine (16% yield), trihexylamine (16% yield), dibutylhexylamine (31% yield), and butyldihexylamine (31% yield) was obtained.[186]

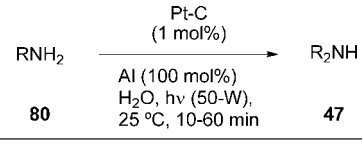
The above alkylation process was used in the selective synthesis of different 1,1- or 1,2-diamino compounds, which are interesting molecules because of their potential ability as metal cation and anion receptor molecules, as well as biologically active substances. Thus, the treatment of an excess of triamines **122** (333 mol %) with azetidine **123** gave the polyamines **124** in moderate to good yields (Scheme 39).[187] Studies on the mechanism of this exchange reaction

Scheme 39. Selective *N*-Alkylation of Primary Amines with Azetidine Using Palladium Black



122 (n = 1, 2) **123** **124** (62-73 %)

Table 37. Auto *N*-Alkylation of Primary Amines using Platinum on Carbon



80 **47**

entry	R	no.	yield (%)
1	Bu^i	**47a**	97
2	Bu^s	**47b**	37
3	$CH_3(CH_2)_4$	**47c**	73
4	$(CH_3)_3CCH_2$	**47d**	75
5	$(CH_3CH_2)_2CH$	**47e**	21
6	$(CH_2)_4CH$	**47f**	37
7	$CH_3(CH_2)_5$	**47g**	51
8	$(CH_2)_5CH$	**47h**	26

showed that the first step was a rapid equilibrium between the starting electrophilic amine and its planar imine intermediate. The formed imine underwent a rapid equilibrium toward the enamine−palladium complex, which suffered the addition of the nucleophilic amine to give an aminal, which after a reductive cleavage gave the final amine. In addition, palladium black (40 mol %) was also able to catalyze the hydrolysis of tertiary amines, such as tributylamine, to afford the corresponding secondary ones in moderate yields (22−60%) at 200 °C in water and HCl (35 mol %).[188]

The auto alkylation of amines **113** could be performed either by continuous microwave irradiation (2.45 GHz, 50 W) or by heating at 170 °C in water in the presence of palladium on carbon (Table 36). It should be pointed out that, besides the amine **91**, the corresponding imine and its carbonyl compound derivative were also observed as byproducts.[189]

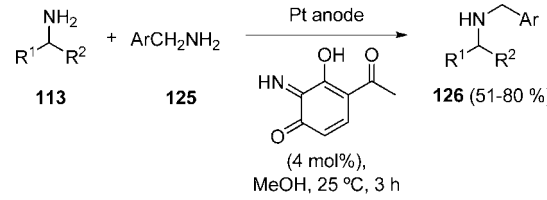
Recently, palladium on carbon has been successfully used in the alkylation of different substituted anilines **66** using nitriles under hydrogen atmosphere.[190] Similar compounds could be obtained when nitroarenes were used instead of anilines.

3.1.4. Derived from Platinum

The use of platinum catalysts has been reported more recently for the *N*-alkylation of amines using other amines as source of the electrophile. Thus, platinum black supported in titanium dioxide (5 wt %, 22 mol %) was used as catalyst to convert primary alkylamines **45** into the corresponding symmetrical secondary ones **120** by means of a photoirradiation (300 nm with a 500 W high-pressure mercury arc) at room temperature in low yields (24−33%). When the same protocol was followed for terminal diamines, the corresponding cyclic aliphatic amines **30** were obtained (20−67% yield).[191]

Primary amines **80** suffered an autoalkylation process upon microwave irradiation using platinum on carbon to give the corresponding secondary ones **47**, in general, with moderate results (Table 37). It should be pointed out that microwave heating gave better results than conventional heating at 156 °C and that the yields for α-substituted primary amines were quite lower, with the corresponding ketone being the main isolated compound.[192]

Scheme 40. *N*-Alkylation of α-Substituted Primary Amines with Arylmethylamine Derivatives Using Pt Electrodes



113 **125** **126** (51-80 %)

Secondary amines could also be obtained electrolytically starting from primary ones. However, the presence of highly unstable cationic radicals, which are rapidly deprotonated and attached to the electrode surface, makes the overall process very difficult. A biomimetic pathway has been used in order to overcome this difficulty. Thus, the alkylation of α-substituted primary amines **113** was carried out using arylmethyl amines **125** (150 mol %) as initial source of the electrophile, giving the expected amines **126** with moderate results (Scheme 40). From a mechanistic point of view, the process started with the condensation of 4-acetyl-5-hydroxy-6-iminocyclohexa-2,4-dienone with the arylmethylamine to give the corresponding imine and liberating ammonia. Then, isomerization of the above imine gave the corresponding *N*-arylidene imine derivative, which reacted with the nucleophilic amine **113**, rendering a new iminic arylidene alkylamine and 3-amino-2,4-dihydroxyacetophenone. The ketone was oxidized on the anode to the starting 4-acetyl-5-hydroxy-6-iminocyclohexa-2,4-dienone, while the arylidene alkylamine was reduced on the cathode to the corresponding arylmethyl alkylamine **126**. The presence of different functional groups on the nucleophilic amine **113**, as well as on the aromatic ring of the alkylating amine **125** (such as hydroxy, alkoxy, or fluoro moieties), was well-tolerated.[193]

3.1.5. Others

The auto *N*-alkylation reaction of amines has also been carried out using ion-exchange montmorillonites as catalyst (20 wt %) at 220 °C. Primary amines **80** gave the corresponding secondary ones **47**, liberating ammonia. Cyclic amines, such as pyrrolidine (**30**: $m = 1$), were transformed into a mixture of products including 1,4-di(pyrrolidin-1-yl)butane (**74f**: $m = 1$; $n = 3$) in 5% yield and 4-(pyrrolidin-1-yl)butaneamine in 21% yield after 74 h.[194]

Other pure metals, such as rhodium and ruthenium, were used as catalysts in some alkylation processes. The best results were obtained in the hydrogenation of aniline (**1a**) with rhodium (0.05 mol %) at 145 °C under 54−68 atm of hydrogen. This reaction gave not only the hydrogenation of aniline but also its alkylation to form dicyclohexylamine (**47h**, 25% yield).[195]

Rhodium on carbon (5 mol %) has also been used in the alkylation of different aliphatic primary amines **45**, using nitriles under hydrogen atmosphere, in good yields (71−96%).[190] Different amines have been used as source of electrophiles in the alkylation of lithium areneselenolates catalyzed by ruthenium, with good yields for the alkylareneselenides formed.[196]

3.2. Homogeneous Catalysts

In the *N*-alkylation of amines using other amines as electrophiles, the use of homogeneous catalysts has been more successful than the heterogeneous ones, with better results and a wider scope being achieved.

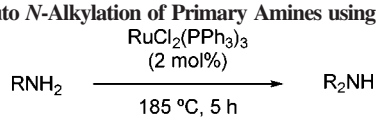
3.2.1. Derived from Ruthenium

As in the previous case of *N*-alkylation of amines using alcohols as electrophiles, ruthenium complexes have been the most successful and widely used catalysts to perform a similar transformation but using amines as electrophiles. $RuCl_2(PPh_3)_3$ has been used in a substoichiometric amount to promote the auto *N*-alkylation process of primary amines **80** to give the corresponding symmetrical secondary amines with excellent yields in the absence of solvent (Table 38). When α-substituted amines were used, the results were slightly worse but they could be improved either by increasing the amount of catalyst or by using tetrahydrofuran (THF) as solvent.[197]

Following a similar procedure, the aforementioned catalyst was able to convert *N,N*-dimethylalkylamines **26** into the corresponding *N*-methyldialkylkamines **46** in good yields (Table 39). The process formally involved the dehydrogenation of the initial amine, on one hand to the methylene derivative, followed by hydrolysis to give the corresponding *N*-methylalkylamine (nucleophilic partner of the reaction), and on the other hand to the alkylene derivative (electrophilic partner of the reaction). The nucleophilic addition to give the corresponding aminal, followed by methylamine elimination, formation of iminium intermediate, and final hydrogenation, rendered the amine **46**. In fact, the same products were obtained when the corresponding *N*-methylalkylamines were used as initial reagents.[198]

Different terminal primary diamines **127** have been cyclized using the former approach as depicted in Scheme 41.

Table 38. Auto *N*-Alkylation of Primary Amines using $RuCl_2(PPh_3)_3$

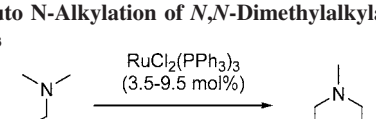


80 **47**

entry	R	no.	yield (%)
1	Pr^i	**47i**	72[a]
2	Bu^n	**47j**	96
3	$CH_3(CH_2)_5$	**47g**	98
4	$CH_3(CH_2)_{11}$	**47k**	99
5	$PhCH_2$	**47l**	99
6	$(CH_2)_5CH$	**47h**	90

[a] THF used as solvent.

Table 39. Auto N-Alkylation of *N,N*-Dimethylalkylamines using $RuCl_2(PPh_3)_3$

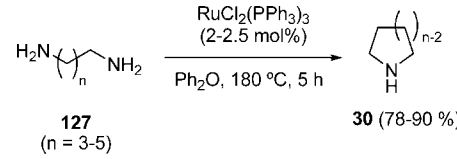


26 **46**

entry	R	no.	yield (%)
1	Pr^n	**46a**	68[a]
2	$CH_3(CH_2)_4$	**46b**	80[a]
3	$CH_3(CH_2)_7$	**46c**	78
4	Ph	**46d**	90

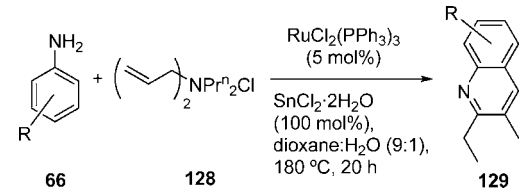
[a] Reaction performed using THF as solvent.

Scheme 41. Cyclization of α-Substituted Primary Amines Using $RuCl_2(PPh_3)_3$



127 (n = 3-5) **30** (78-90 %)

Table 40. Cyclization of Aniline Derivatives with Diallylammonium Derivatives Catalyzed by $RuCl_2(PPh_3)_3$: Synthesis of Quinolines



66 **128** **129**

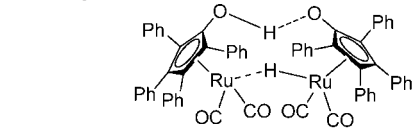
entry	no.	R	yield (%)
1	**129a**	H	57
2	**129b**	6-Cl	34
3	**129c**	6-MeCO	63
4	**129d**	6-Me	64
5	**129e**	6-MeO	58
6	**129f**	7-MeO	50
7	**129g**	8-Me	45

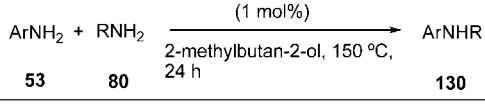
The results were good independent of the ring size, although in these cases the use of diphenyl ether as solvent showed a beneficial effect on the yields.[199] It should be pointed out that the same reaction could also be performed by using $RuCl_3 \cdot nH_2O$ and an adequate amount of PPh_3 with similar results. Moreover, this in situ preparation of the ruthenium catalyst was used in the auto alkylation of primary amines **45** to give the corresponding tertiary amines **22** with good yields (51−98%).

Mechanistic studies performed in the reaction of auto *N*-alkyaltion of primary amines **45** to give the corresponding symmetrical secondary derivatives **120** catalyzed by $RuCl_2(PPh_3)_3$ revealed a first-order dependence on both the catalyst and the amine concentration, with the rate-determining step being the amine dehydrogenation. During the reaction, the free secondary amine **120** was observed, indicating that the dissociation of this nitrogen-containing ligand from the ruthenium intermediate complex was possible. The imine initially formed from the starting amine must react quickly either with the starting amine or with the liberated ammonia, since it was not observed in the reaction media.[200]

As in previous examples, different quinolines could be prepared by reaction of the diallylammonium derivative **128** with different anilines **66** (Table 40). The reaction gave, in all cases, moderate yields, independent of either the electronic character of the substituent or its position. The reaction seems to proceed via the initial dehydrogenation of the amine included in **128** to render the corresponding iminium derivative, which suffers a nucleophilic condensation with the aniline **66** to give the corresponding imine. This aniline derivative is hydrogenated to the corresponding *N*-allylaniline, closing the hydrogen autotransfer cycle. The final steps involved the isomerization of this allylamine to the corresponding enamine−imine, auto Mannich-type reaction, followed by an intramolecular Friedel−Crafts cyclation; the final dehydrogenation and dehydroamination processes gave the corresponding 2-ethyl-3-methylquinoline **129**.[201] The same quinolines **129** could be prepared starting from the corre-

Table 41. N-Alkylation of Aromatic Amines with Primary Amines using [(η^4-Ph_4C_4CO)$Ru(CO)_3$]$_2$ Complex





entry	Ar	R	no.	yield (%)
1	Ph	$CH_3(CH_2)_7$	**130a**	99
2	4-$O_2NC_6H_4$	$CH_3(CH_2)_5$	**130b**	20
3	4-FC_6H_4	$CH_3(CH_2)_5$	**130c**	99
4	2-MeC_6H_4	$CH_3(CH_2)_5$	**130d**	93
5	4-$MeOC_6H_4$	$CH_3(CH_2)_5$	**130e**	98
6	2,4,6-$Me_3C_6H_2$	$CH_3(CH_2)_5$	**130f**	34
7	2-pyridyl	$CH_3(CH_2)_5$	**130g**	96
8	Ph	$(CH_2)_5CH$	**130h**	99

sponding nitrobenzene derivatives and tripropylamine, instead of anilines derivatives **66** and the ammonium salt **128**, respectively. In these cases, yields were similar (22−85%), with the two- and four-position substituted nitroarenes giving the best results.[202]

In situ generated ruthenium complexes, obtained by reaction of $RuCl_3 \cdot nH_2O$ (5 mol %) and PPh_3 (15 mol %) in the presence of $SnCl_2 \cdot 2H_2O$ (100 mol %), promoted the reaction of aninile derivatives **66** with triallylamine in dioxane at 180 °C after 20 h to give the corresponding quinolines **129** with moderate yields (24−61%), with the worst results being obtained with anilines bearing electron-withdrawing groups.[203] When bis(diphenylphosphane)methane was used as a phosphane, in a similar protocol, the obtained results for the synthesis of quinolines **129** were slightly better (21−86%), with the presence of hex-1-ene, acting as an hydrogen scavenger, being mandatory.[204]

Other simple catalysts showed to be very effective in the *N*-alkylation of amines using different amines as the source electrophile. For instance, $Ru_3(CO)_{12}$ (0.42 mol %) catalyzed the transalkyaltion reaction between triethylamine (**22a**) and tripropylamine at 100 °C under a nitrogen atmosphere (7 atm) to give diethylpropylamine and ethyldipropylamine in 25 and 27% yield, respectively.[205] Mechanistic and kinetic studies for this reaction showed a very complex rate dependence.[206] This catalyst was also able to catalyze the hydrogen−deuterium exchange in tertiary amines from deuterium oxide, showing a very high selectivity toward α versus β position.[207]

Perhaps, the bisruthenium complex depicted in Table 41 is the most useful catalyst for the reaction described along this section. Different aromatic amines **53** (200 mol %) could be alkylated with primary amines **80** to afford the corresponding secondary amines **130** with excellent yields. The electronic nature of the substituent and its position at the aromatic ring did not have any impact on the results. Only in the case of nitroaniline derivatives was the yield lower, and this fact could be attributed to the possible reduction of the nitro group to give different compounds. A very broad scope of alkyl amines **80**, including aliphatic primary and secondary amines, benzylic amine derivatives, and the corresponding heterocyclic methylamines, could be used as source of the electrophile, affording in all cases the corresponding amines **130** with excellent yields.[208]

The above-cited protocol was further extended to the reaction of aniline (**1a**, 200 mol %) with different symmetrical secondary amines **120** to give the expected *N*-alkylated anilines **3** with excellent yields. Not only secondary amines but also tertiary amines **22** could be used successfully. Moreover, the use of aliphatic α-substituted primary amines **113** did not have any detrimental effect on the previous excellent results.[209]

Scheme 42. Double *N*-Alkylation of Aniline Derivatives with Cyclic Amines Using a Bisruthenium Complex

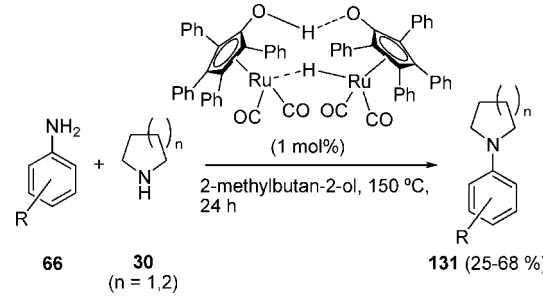
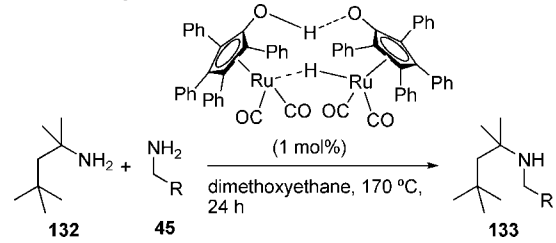


Table 42. N-Alkylation of *tert*-Octylamine Amines with Primary Amines using [(η^4-Ph_4CCO)$Ru(CO)_3$]$_2$ Complex



entry	R	no.	yield (%)
1	Ph	**133a**	58
2	4-$MeOC_6H_4$	**133b**	89
3	$PhCH_2$	**133c**	75
4	$CH_3(CH_2)_6$	**133d**	90

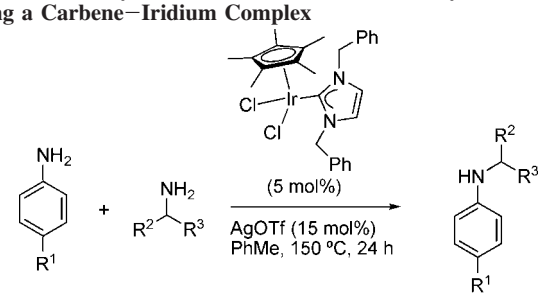
The use of cyclic amines of type **30** as source of the electrophile permitted to perform the double alkylation of aniline derivatives **66** to give the corresponding *N*-phenyl substituted cyclic amines **131**, but it was less successful (Scheme 42), with the lowest yields (around 25%) being obtained for anilines bearing an electron-withdrawing group at the four-position, such as a halogen atom. Notwithstanding these yields, the use of cyclic amines as dialkylating agents was proved.[210]

Finally, it should be pointed out that the aforementioned protocol has also been extended to the alkylation of aliphatic amines by other amines. So, *tert*-butyl amine derivatives such as the amine **132** (300 mol %), which could not suffer a dehydrogenation process to form imines, was alkylated with different primary amines **45** to give selectively the corresponding secondary amines **133** (Table 42). Instead of primary amines **45**, symmetrical secondary amines **120** (even the related tertiary ones **22** as well as alkoxy functionalized ones) could be used as electrophiles with similar results. Another nucleophilic amine such as adamantylamine, could be used, with its alkylation being achieved with slightly better chemical yields.[211]

3.2.2. Others

Other transition-metal complexes were able to catalyze the alkylation of amines with other amines. Thus, $Os_3(CO)_{12}$ (0.42 mol %) was effective in the standard transalkylation reaction between triethylamine (**22a**) and tripropylamine at 150 °C under 7 atm of nitrogen pressure during 3 h, affording

Table 43. *N*-Alkylation of Anilines with Secondary Amines Using a Carbene−Iridium Complex



1 113 89

entry	R^1	R^2	R^3	no.	yield (%)
1	H	H	Ph	**89a**	94
2	H	H	$CH_3(CH_2)_5$	**89i**	>95
3	H	H	$CH_3(CH_2)_{10}$	**89j**	>95
4	H		$(CH_2)_5$	**89k**	>95
5	Me	H	$CH_3(CH_2)_5$	**89l**	63
6	Cl	H	$CH_3(CH_2)_5$	**89m**	>95
7	MeO	H	$CH_3(CH_2)_5$	**89n**	25

a mixture of diethylpropylamine and ethyldipropylamine in 27 and 28% yield, respectively.[212] This transformation was also catalyzed by $Rh_6(CO)_{16}$ but rendering the same mixture with lower yields,[213] with this catalyst being able to perform the hydrogen−deuterium exchange in amines from deuterium oxide.[214]

Very recently, the carbene−iridium complex shown in Table 43 has been able to catalyze very successfully the alkylation of anilines **1** (200 mol %) with different α-substituted primary amines **113**, in general, with excellent results.[167] Only in the cases of using anilines having an electron-donating group were the yields accountably lower.

The $PtCl_2(PPh_3)_2$ complex (0.5 mol %) in the presence of $SnCl_2 \cdot 2H_2O$ (25 mol %) promoted the auto alkylation process of primary amines **80** in benzene at 180 °C after 5 h to give the corresponding secondary ones **47** with moderate to good yields (27−81%), independently of the substitution on the starting amine. The protocol has also been used in the cyclization of 1,4-butanediamine **127a** ($n = 3$) to give the expected pyrrolidine in low yields.[215]

4. Conclusions and Outlook

With this review, we have tried to show the versatility and usefulness of heterogeneous and homogeneous catalysts in the alkylation of amines through the so-called hydrogen autotransfer process. The use of alcohols and amines, which are normally considered as nucleophiles in organic textbooks, acting in these transformations as electrophiles is highly convenient owing to the easy handling, stability, wide availability, and low cost of such compounds. Furthermore, the use of this strategy of alkylation substitutes the classical ones employing hazardous and expensive alkyl halides, sulfonates, or sulfates and allows a greener process, since the only generated waste is water or ammonia. Moreover, the low molecular weight of wastes makes this synthetic strategy unbeatable as far as the atom efficiency numbers are concerned.

These facts, together with the plethora of new and useful homogeneous and heterogeneous catalysts, make it possible to perform these reactions with excellent selectivities and also make this synthetic strategy very attractive not only for academia but also for industrial purposes. In the near future, these processes might be applied to a wide range of nitrogen-containing compounds, which are interesting because of their application in several chemical industries (such as pharmaceutical, agrochemical, detergent, dye, or textile industries), with the whole synthetic protocol being cleaner, greener, safer, and more economical and meeting the sustainability, all goals highly demanded by our present day society.

In the near future, the development of recoverable, more effective or chiral catalysts, as well as the application of this type of transformation to other new substrates will improve the scope of this protocol, with the information review here serving to envisage the new possibilities and the new niches unoccupied nowadays.

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6. References

(1) (a) Wöhler, F. *Ann. Phys. Chem.* **1828**, *12*, 253. (b) Kauffman, G. B.; Chooljian, S. H. *Chem. Educ.* **2001**, *6*, 121.
(2) (a) *Chemical Biology*; Waldmann, H., Janning, P., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Chemical Biology: From Small Molecules to Systems Biology and Drug Design*; Schreiber, S. L., Kapoor, T., Wess, G., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vols. 1−3.
(3) (a) Hesse, M. *Alkaloids: Nature's Curse or Blessing?*; VHCA: Zürich, 2002. (b) Bhat, S. V.; Nagasampagi, B. A.; Sivakumar, M. *Chemistry of Natural Products*; Springer: Berlin, 2005.
(4) (a) *Pesticide Chemistry and Bioscience*; Brooks, G. T., Roberts, T. R., Eds.; Royal Society of Chemistry: Cambridge, U.K., 1999. (b) *Pharmaceuticals: Classes, Therapeutic Agents, Areas of Application*; McGuire, J. L., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vols. 1−4.
(5) (a) Egan, R. R. *J. Am. Oil Chem. Soc.* **1968**, *45*, 581. (b) Arif, S. In *Surfactant Science Series: Detergency of Specialty Surfactants*; Friedli, F., Ed.; Marcel Dekker: New York, 2001; Vol. 98; pp 71−115. (c) Hayes, K. S. *Appl. Catal., A* **2001**, *221*, 187. (d) Wittcoff, H. A.; Reuben, B. G.; Plotkin, J. S. *Industrial Organic Chemicals*; Wiley-Interscience: Hoboken, NJ, 2004.
(6) (a) Malpass, J. R. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, U.K., 1979; Vol. 2, pp 3−59. (b) Gladych, J. M. Z.; Hartley, D. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, U.K., 1979; Vol. 2, pp 61−130. (c) Lindsay, R. J. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, U.K., 1979; Vol. 2, pp 131−184. (d) Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 6, pp 65−101. (e) Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 8, pp 381−402. (f) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785.
(7) Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*; Wiley-Interscience: New York, 2001; pp 499−501 and literature quoted therein.
(8) (a) Emerson, W. S. In *Organic Reactions*; Adams, E., Ed.; Wiley: New York, 1948; Vol. 4, pp 175−255. (b) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395. (c) Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Synthesis* **2005**, 2631.
(9) For recent reviews, see: (a) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (b) Hartwig, J. F. H. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Surry, D. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.
(10) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) *Green Chemistry: Designing Chemistry for the Environment*; Anastas, P. T., Williamson, T. C., Eds.; ACS: Washington, DC, 1996. (c) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233. (d) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (e) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007.
(11) (a) Metzger, J. O.; Eissen, M. *C. R. Chim.* **2004**, *7*, 569. (b) Jenck, J. F.; Agterberg, F.; Droescher, M. J. *Green Chem.* **2004**, *6*, 544. (c)

Thomas, J. M.; Raja, R. *Annu. Rev. Mater. Res.* **2005**, *35*, 315. (d) Parthasarathy, G.; Hart, R.; Jamro, E.; Miner, L. *Clean Technol. Environ. Policy* **2005**, *7*, 219. (e) Noyori, R. *Chem. Commun.* **2005**, 1807. (f) Ranke, J.; Stolte, S.; Störmann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183. (g) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629. (h) Murzin, D. Y.; Leino, R. *Chem. Eng. Res. Des.* **2008**, *86*, 1002. (i) Clark, J. H.; Deswarte, F. E. I.; Farmer, T. J. *Biofuels, Bioprod. Biorefin.* **2009**, *3*, 72.

(12) (a) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273. (b) Sheldon, R. A. *Chem. Commun.* **2008**, 3352.

(13) For recent reviews, see: (a) Beller, M.; Tillack, A.; Seayad, J. In *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Beller, M., Bolm, C., Eds.; Viley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 403−414. (b) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (c) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407. (d) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (e) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(14) (a) Martínez, R.; Brand, G. J.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 3683. (b) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8982. (c) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988.

(15) Edwards, M. G.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4740.

(16) Hoshino, F.; Kimura, H.; Matsutani, K. *Chem. Abstr.* **1980**, *92*, 41325c Ger. Offen. Patent DE2907869, 1979.

(17) (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (c) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (d) *Hydrogen-Transfer Reactions*; Hynes, J. T., Klinman, J. P., Limbach, H.-H., Schowen, R. L., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vols. 1−4.

(18) (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753.

(19) (a) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (b) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34.

(20) (a) Klyuev, M. V.; Khidekel′, M. L. *Russ. Chem. Rev. Engl. Transl.* **1980**, *49*, 14. (b) Baiker, A.; Kijenski, J. *Catal. Rev. Sci. Eng.* **1985**, *27*, 653. (c) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1.

(21) Pašek, J.; Kondelik, P.; Richter, P. *Ind. Eng. Chem., Prod. Res. Dev.* **1972**, *11*, 333.

(22) Nef, J. U. *Liebigs Ann. Chem.* **1901**, *318*, 137.

(23) For recent reviews, see: (a) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215. thematic issue on recoverable catalysts and reagents. (b) Corma, A.; García, H. *Chem. Rev.* **2003**, *103*, 4307. (c) Dai, L.-X. *Angew. Chem., Int. Ed.* **2004**, *43*, 5726. (d) Itsuno, S.; Haraguchi, N.; Arakawa, Y. *Recent Res. Dev. Org. Chem.* **2005**, *9*, 27. (e) Ding, K.; Wang, Z.; Shi, L. *Pure Appl. Chem.* **2007**, *79*, 1531. (f) Matsumoto, T.; Ueno, M.; Wang, N.; Kobayashi, S. *Chem. Asian J.* **2008**, *3*, 196. (g) Felpin, F.-X.; Fouquet, E. *ChemSusChem* **2008**, *1*, 718.

(24) For recent examples from our laboratory, see: (a) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2054. (b) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2009**, *20*, 65.

(25) Takita, Y.; Nishida, Y.; Seiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3699.

(26) Brown, A. B.; Reid, E. E. *J. Am. Chem. Soc.* **1924**, *46*, 1836.

(27) Narayanan, S.; Prasad, B. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1204.

(28) (a) Matshuhashi, H.; Arata, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2605. (b) Ko, A.-N.; Yang, C.-L.; Zhu, W.-d.; Lin, H.-e. *Appl. Catal., A* **1996**, *134*, 53.

(29) Valot, F.; Fache, F.; Jacquot, R.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* **1999**, *40*, 3689.

(30) Rosenmund, K. W.; Joithe, A. *Ber. Dtsch. Chem. Ges.* **1925**, *58B*, 2054.

(31) Li, K.-T.; Peng, Y.-C. *Appl. Catal., A* **1994**, *109*, 225.

(32) Guyot, A.; Fournier, M. *Bull. Soc. Chim. Fr.* **1930**, *47*, 203.

(33) Pratt, E. F.; Frazza, E. J. *J. Am. Chem. Soc.* **1954**, *76*, 6174.

(34) Barnes, C. M.; Rase, H. F. *Ind. Eng. Chem., Prod. Res. Dev.* **1981**, *20*, 399.

(35) (a) Billica, H. R.; Adkins, H. In *Organic Synthesis, Collective Volume 3*; Horning, E. C., Ed.; John Wiley & Sons: New York, 1955; Vol. 3, pp 176−180. (b) Mozingo, R. In *Organic Synthesis, Collective Volume 3*; Horning, E. C., Ed.; John Wiley & Sons: New York, 1955; Vol. 3, pp 181−183 and literature quoted therein.

(36) Rice, R. G.; Kohn, E. J. *J. Am. Chem. Soc.* **1955**, *77*, 4052.

(37) Ainsworth, C. *J. Am. Chem. Soc.* **1956**, *78*, 1635.

(38) Botta, M.; De Angelis, F.; Nicoletti, R. *Synthesis* **1977**, 722.

(39) De Angelis, F.; Ferretti, G.; Botta, M.; Grgurina, I.; Nicoletti, R. *Gazz. Chim. Ital.* **1982**, *112*, 267.

(40) De Angelis, F.; Crasso, M.; Nicoletti, R. *Synthesis* **1977**, 335.

(41) Rice, R. G.; Kohn, E. J.; Daasch, L. W. *J. Org. Chem.* **1958**, *23*, 1352.

(42) Winans, C. F.; Adkins, H. *J. Am. Chem. Soc.* **1932**, *54*, 306.

(43) Baiker, A. *Ind. Eng. Chem., Prod. Res. Dev.* **1981**, *20*, 615.

(44) Langdon, W. K.; Levis, W. W.; Jackson, D. R. *Ind. Eng. Chem., Process. Des. Dev.* **1962**, *1*, 153.

(45) (a) Venot, A.; Glacet, C. *C. R. Chim.* **1971**, *273*, 718. (b) Venot, A.; Glacet, C. *C. R. Chim.* **1971**, *273*, 1266. (c) Venot, A. *Bull. Soc. Chim. Fr.* **1972**, 4732. (d) Venot, A. *Bull. Soc. Chim. Fr.* **1972**, 4736. (e) Venot, A. *Bull. Soc. Chim. Fr.* **1972**, 4744.

(46) von Braun, J.; Blessing, G.; Zobel, F. *Ber. Dtsch. Chem. Ges.* **1923**, *56B*, 1988.

(47) Kornfeld, E. C. *J. Org. Chem.* **1951**, *16*, 131.

(48) Mozingo, R.; Spencer, C.; Folkers, K. *J. Am. Chem. Soc.* **1944**, *66*, 1859.

(49) García Ruano, J. L.; Parra, A.; Alemán, J.; Yuste, F.; Mastranzo, V. M. *Chem. Commun.* **2009**, 404.

(50) Alonso, F.; Riente, P.; Yus, M. *Eur. J. Org. Chem.* **2008**, 4908.

(51) Aston, J. G.; Peterson, T. E.; Holowchak, J. *J. Am. Chem. Soc.* **1934**, *56*, 153.

(52) Laizer, W. A.; Arnold, H. R. In *Organic Synthesis, Collective Volume 2*; Horning, E. C., Ed.; John Wiley & Sons: New York, 1943; Vol. 2, pp 142−145.

(53) Schwoegler, E. J.; Adkins, H. *J. Am. Chem. Soc.* **1939**, *61*, 3499.

(54) Schneider, H.; Adkins, H.; McElvain, S. M. *J. Am. Chem. Soc.* **1952**, *74*, 4287.

(55) Takehara, K.; Okajima, S.; Agawa, T.; Komori, S. *J. Am. Oil Chem. Soc.* **1971**, *48*, 748.

(56) Becker, J.; Niederer, J. P. M.; Keller, M.; Hölderich, W. F. *Appl. Catal., A* **2000**, *197*, 229.

(57) For reviews, see: (a) Ho, T.-L. *Tandem Organic Reaction*; John Wiley & Sons: New York, 1992. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (e) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (f) Wessjohann, L. A.; Ruijter, E. *Mol. Diversity* **2005**, *9*, 159. (g) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (h) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (i) Dondoni, A.; Massi, A. *Acc. Chem. Res.* **2006**, *39*, 451. (j) Lieby-Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR Comb. Sci.* **2006**, *25*, 432. (k) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (l) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2008**, 5474. (m) Ismabery, N.; Lavilla, R. *Chem.—Eur. J.* **2008**, *14*, 8444.

(58) Barrault, J.; Essayem, N.; Guimon, C. *Appl. Catal., A* **1993**, *102*, 151.

(59) Baiker, A.; Richarz, W. *Tetrahedron Lett.* **1977**, 1937.

(60) Baiker, A.; Richarz, W. *Ind. Eng. Chem., Prod. Res. Dev.* **1977**, *16*, 261.

(61) Baiker, A.; Richarz, W. *Helv. Chim. Acta* **1978**, *61*, 1169.

(62) (a) Baiker, A.; Richarz, W. *Stud. Surf. Sci. Catal.* **1981**, *7B*, 1428. (b) Baiker, A.; Caprez, W.; Holstein, W. L. *Ind. Eng. Chem., Prod. Res. Dev.* **1983**, *22*, 217.

(63) Baiker, A.; Richarz, W. *Synth. Commun.* **1978**, *8*, 27.

(64) Runeberg, J.; Baiker, A.; Kijenski, J. *Appl. Catal.* **1985**, *17*, 309.

(65) Vultier, R.; Baiker, A.; Wokaun, A. *Appl. Catal.* **1987**, *30*, 167.

(66) (a) Hammerschmidt, W.; Baiker, A.; Wokaun, A.; Fluhr, W. *Appl. Catal.* **1986**, *20*, 305. (b) Kijeński, J.; Niedzielski, P. J.; Baiker, A. *Appl. Catal.* **1989**, *53*, 107.

(67) Card, R. J.; Schmitt, J. L. *J. Org. Chem.* **1981**, *46*, 754.

(68) Göbölös, S.; Hegedüs, M.; Kolosova, I.; Maciejewski, M.; Margitfalvi, J. L. *Appl. Catal., A* **1988**, *169*, 201.

(69) Yamakawa, T.; Tsuchiya, I.; Mitsuzuka, D.; Ogawa, T. *Catal. Commun.* **2004**, *5*, 291.

(70) Abe, H.; Yokota, Y.; Okabe, K. *Appl. Catal.* **1989**, *52*, 171.

(71) Kimura, H.; Taniguchi, H. *Appl. Catal., A* **2005**, *287*, 191.

(72) Kimura, H.; Matsutani, K.; Tsutsumi, S.-i.; Nomura, S.; Ishikawa, K.; Hattori, Y.; Itahashi, M.; Hoshino, H. *Catal. Lett.* **2005**, *99*, 119.

(73) Kimura, H.; Ishikawa, K.; Nishino, K.; Nomura, S. *Appl. Catal., A* **2005**, *286*, 120.

(74) Kimura, H.; Tsutsumi, S.-i.; Tsukada, K. *Appl. Catal., A* **2005**, *292*, 281.

(75) Kimura, H.; Yokota, Y.; Sawamoto, Y. *Catal. Lett.* **2005**, *99*, 133.

(76) Kimura, H.; Taniguchi, H. *Catal. Lett.* **1996**, *40*, 123.

(77) Hamada, H.; Kuwahara, Y.; Sato, T.; Wakabayashi, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 55.

(78) Richardson, J. T.; Lu, W.-C. *J. Catal.* **1976**, *42*, 275.

(79) Ohtani, B.; Nakagawa, K.; Nishimoto, S.-i.; Kagiya, T. *Chem. Lett.* **1986**, 1917.

(80) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 8471.
(81) Ohtani, B.; Osaki, H.; Nishimoto, S.-i.; Kagiya, T. *Tetrahedron Lett.* **1986**, *27*, 2019.
(82) Ohtani, B.; Osaki, H.; Nishimoto, S.-i.; Kagiya, T. *J. Am. Chem. Soc.* **1986**, *108*, 308.
(83) Martínez, R.; Ramón, D. J.; Yus, M. *Org. Biomol. Chem.* **2009**, *7*, 2176.
(84) For the recent use of commercial magnetite as soft Lewis acid catalyst, see: (a) Martínez, R.; Ramón, D. J.; Yus, M. *Adv. Synth. Catal.* **2008**, *350*, 1235. (b) Mojtahedi, M. M.; Abaee, M. S.; Alishiri, T. *Tetrahedron Lett.* **2009**, *50*, 2322.
(85) For other examples of metal-impregnated magnetite derivatives; see: (a) Basińska, A.; Jóźwiak, W. K.; Gŏralski, J.; Domka, F. *Appl. Catal., A* **2000**, *190*, 107. (b) Basińska, A.; Klimkiewicz, R.; Domka, F. *Appl. Catal., A* **2001**, *207*, 287. (c) Wang, Z.; Shen, B.; Aihua, Z.; he, N. *Chem. Eng. J.* **2005**, *113*, 27. (d) Uheida, A.; Iglesias, M.; Fontàs, C.; Hidalgo, M.; Salvadó, V.; Zhang, Y.; Muhammed, M. *J. Colloid Interface Sci.* **2006**, *301*, 402. (e) Kotani, M.; Koike, T.; Yamaguchi, K.; Mizuno, N. *Green Chem.* **2006**, *8*, 735.
(86) Shi, F.; Tse, M. K.; Zhou, S.; Pohl, M.-M.; Radnik, J.; Hübner, S.; Jähnisch, K.; Brückner, A.; Beller, M. *J. Am. Chem. Soc.* **2009**, *131*, 1775.
(87) Kindler, K. *Liebigs Ann. Chem.* **1931**, *485*, 113.
(88) Murahashi, S.-I.; Shimamura, T.; Moritani, I. *J. Chem. Soc., Chem. Commun.* **1974**, 931.
(89) Sabatier, P.; Mailhe, A. *C. R. Chim.* **1909**, *148*, 898.
(90) (a) Sabatier, P.; Mailhe, A. *C. R. Chim.* **1911**, *153*, 160. (b) Sabatier, P.; Mailhe, A. *C. R. Chim.* **1912**, *153*, 1204.
(91) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611.
(92) (a) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, *22*, 2667. (b) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.
(93) Lazier, W. A.; Adkins, H. *J. Am. Chem. Soc.* **1924**, *46*, 741.
(94) Sprinzak, Y. *J. Am. Chem. Soc.* **1956**, *78*, 3207.
(95) Sprinzak, Y. In *Organic Synthesis, Collective Volume 4*; Rabjohn, N., Ed.; John Wiley & Sons: New York, 1963; Vol. 4, pp 91−92.
(96) Zvezdina, E. A.; Pozharskii, A. F.; Sokolov, V. I. *Chem. Heterocycl. Compd.* **1970**, *6*, 389.
(97) (a) Miyano, S. *Chem. Pharm. Bull.* **1965**, *13*, 1135. (b) Miyano, S.; Uno, A.; Abe, N. *Chem. Pharm. Bull.* **1967**, *15*, 515.
(98) Miyano, S.; Abe, N.; Abe, A. *Chem. Pharm. Bull.* **1967**, *15*, 511.
(99) Miyano, S.; Nakao, M. *Chem. Pharm. Bull.* **1972**, *20*, 1328.
(100) Horikawa, Y.; Uchino, Y.; Sako, T. *Chem. Lett.* **2003**, *32*, 232.
(101) Reid, E. E. *Am. Chem. J.* **1911**, *45*, 38.
(102) For reviews on ruthenium in organic chemistry, see: (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Grubbs, R. H. *Chem. Eng. News* **2003**, *81* (36), 112. (e) *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (f) *Ruthenium Catalysts and Fine Chemistry in Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer: Berlin, 2004; Vol. 11. (g) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490.
(103) Arcelli, A.; Khai, B.-T.; Porzi, G. *J. Organomet. Chem.* **1982**, *235*, 93.
(104) (a) Ganguly, S.; Joslin, F. L.; Roundhill, D. M. *Inorg. Chem.* **1989**, *28*, 4562. (b) Ganguly, S.; Roundhill, D. M. *Polyhedron* **1990**, *9*, 2517.
(105) Yamaguchi, I.; Sakano, T.; Ishii, H.; Osakada, K.; Yamamoto, T. *J. Organomet. Chem.* **1999**, *584*, 213.
(106) (a) Marsella, J. A. *J. Org. Chem.* **1987**, *52*, 467. (b) Marsella, J. A. *J. Organomet. Chem.* **1991**, *407*, 97.
(107) Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365.
(108) Shim, S. G.; Doh, C. H.; Woo, B. W.; Kim, H. S.; Huh, K. T.; Park, W. H.; Lee, H. *J. Mol. Catal.* **1990**, *62*, L11.
(109) Felföldi, K.; Klyavlin, M. S.; Bartók, M. *J. Organomet. Chem.* **1989**, *362*, 193.
(110) Tsuji, Y.; Yokoyama, Y.; Huh, K.-T.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3456.
(111) (a) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *Tetrahedron Lett.* **1986**, *27*, 377. (b) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1673.
(112) For examples of the indirect Friedländer synthesis of quinolines using an usual hydrogen transfer process, see: (a) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576. (b) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 7997. (c) Motokura, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2004**, *45*, 6029. (d) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539. (e) Cho, C. S.; Ren, W. X.; Shim, S. C. *Bull. Korean Chem. Soc.* **2005**, *26*, 1286. (f) Cho, C. S.; Ren, W. X.; Shim, S. C. *Bull. Korean Chem. Soc.* **2005**, *26*, 2038. (g) Cho, C. S.; Seok, H. J.; Shim, S. C. *J. Heterocycl. Chem.* **2005**, *42*, 1219. (h) Cho, C. S.; Ren, W. X.; Shim, S. C. *Tetrahedron Lett.* **2006**, *47*, 6781. (i) Martínez, R.; Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, 1599. (j) Vander Mierde, H.; Ledoux, N.; Allaert, B.; Van Der Voort, P.; Drozdzak, R.; De Vos, D.; Verpoort, F. *New. J. Chem.* **2007**, *31*, 1572. (k) Cho, C. S.; Ren, W. X. *J. Organomet. Chem.* **2007**, *629*, 4182. (l) Vander Mierde, H.; Van Der Voort, P.; De Vos, D.; Verpoort, F. *Eur. J. Org. Chem.* **2008**, 1625. (m) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778. (n) Vander Mierde, H.; Van Der Voort, P.; De Vos, D.; Verpoort, F. *Tetrahedron Lett.* **2008**, *49*, 6893. (o) Vander Mierde, H.; Van Der Voort, P.; De Vos, D.; Verpoort, F. *Tetrahedron Lett.* **2009**, *50*, 201. For a recent review on general Friedländer synthesis, see: (p) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2653.
(113) (a) Tsuji, Y.; Huh, K.-T.; Yokoyama, Y.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1575. (b) Tsuji, Y.; Kotachi, S.; Huh, K.-T.; Yokoyama, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580.
(114) Kondo, T.; Yang, S.; Huh, K.-T.; Kobayashi, M.; Kotachi, S.; Watanabe, Y. *Chem. Lett.* **1991**, 1275.
(115) Cho, C. S.; Oh, S. G. *Tetrahedron Lett.* **2006**, *47*, 5633.
(116) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039.
(117) Kondo, T.; Kotachi, S.; Ogino, S.-i.; Watanabe, Y. *Chem. Lett.* **1993**, 1317.
(118) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2647.
(119) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229.
(120) Murahashi, S.-I.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* **1986**, *108*, 7846.
(121) Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319.
(122) Owston, N. A.; Nixon, T. D.; Parker, A. J.; Whittlesey, M. K.; Williams, J. M. J. *Synthesis* **2009**, 1578.
(123) Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2001**, *57*, 3321.
(124) Naota, T.; Murahashi, S.-i. *Synlett* **1991**, 693.
(125) Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T.-a. *J. Org. Chem.* **1996**, *61*, 4214.
(126) Del Zotto, A.; Baratta, W.; Sandri, M.; Verardo, G.; Rigo, P. *Eur. J. Inorg. Chem.* **2004**, 524.
(127) Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* **2007**, *48*, 3367.
(128) Abbenhuis, R. A. T. M.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, *63*, 4282.
(129) Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661.
(130) (a) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790. (b) Ulrik, L.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. (c) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559.
(131) Gunanathan, C.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2009**, *131*, 3146.
(132) Huh, K.-T.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* **1988**, 449.
(133) Bitsi, G.; Schleiffer, E.; Antoni, F.; Jenner, G. *J. Organomet. Chem.* **1989**, *373*, 343.
(134) Huh, K.-T.; Shim, S. C.; Doh, C. H. *Bull. Korean Chem. Soc.* **1990**, *11*, 45.
(135) Shim, S. C.; Doh, C. H.; Yoon, J. H.; Lee, D. Y.; Youn, Y. Z. *Bull. Korean Chem. Soc.* **1991**, *12*, 649.
(136) Tsuji, T.; Nishimura, H.; Huh, K.-T.; Watanabe, Y. *J. Organomet. Chem.* **1985**, *286*, C44.
(137) Cho, C. S.; Lim, H. Y.; Shim, S. C.; Kim, T. J.; Choi, H.-J. *Chem. Commun.* **1998**, 995.
(138) Tanaka, N.; Hatanaka, M.; Watanabe, Y. *Chem. Lett.* **1992**, 575.
(139) Jenner, G. *J. Mol. Catal.* **1989**, *55*, 241.
(140) (a) Tillack, A.; Hollman, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881. (b) Hollman, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian J.* **2007**, *2*, 403.
(141) Tillack, A.; Hollman, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745.
(142) Jenner, G.; Bitsi, G. *J. Mol. Catal.* **1988**, *45*, 165.
(143) Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263.
(144) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725.
(145) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766.
(146) Pridmore, S. J.; Slatford, P. A.; Daniel, A.; Whittlesey, M. K.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 5115.

(147) Lamb, G. W.; Watson, A. J. A.; Jolley, K. E.; Maxwell, A. C.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 3374.
(148) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667.
(149) For reviews on iridium complexes in different hydrogen autotransfer reactions, see: (a) Ishii, Y.; Sakaguchi, S. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 909. (b) Fujita, K.-i.; Yamaguchi, R. *Synlett* **2005**, 560.
(150) Fujita, K.-i.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687.
(151) Fujita, K.-i.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943.
(152) Fujita, K.-i.; Kida, Y.; Yamaguchi, R. *Heterocycles* **2009**, *77*, 1371.
(153) Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K.-i. *Org. Lett.* **2008**, *10*, 181.
(154) (a) Fujita, K.-i.; Fuji, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525. (b) Fujita, K.-i.; Enoki, Y.; Yamaguchi, R. In *Organic Synthesis*; Curran, D. P., Ed.; John Wiley & Sons: Hoboken, NJ, 2006; Vol. 83, pp 217−221.
(155) Miao, L.; DiMaggio, S. C.; Shu, H.; Trudell, M. L. *Org. Lett.* **2009**, *11*, 1579.
(156) Fujita, K.-i.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, *4*, 2691.
(157) Eary, C. T.; Clausen, D. *Tetrahedron Lett.* **2006**, *47*, 6899.
(158) Nordstrøm, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034.
(159) Balcells, D.; Nova, A.; Clot, E.; Gnanamgari, D.; Crabtree, R. H.; Eisenstein, O. *Organometallics* **2008**, *27*, 2529.
(160) Fujita, K.-i.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* **2009**, *65*, 3624.
(161) Cami-Kobei, G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535.
(162) Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth. Catal.* **2008**, *350*, 749.
(163) Blank, B.; Michlik, S.; Kempe, R. *Chem.—Eur. J.* **2009**, *15*, 3790.
(164) Cami-Kobeci, G.; Williams, J. M. J. *Chem. Commun.* **2004**, 1072.
(165) Izumi, A.; Obara, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2006**, *47*, 9199.
(166) Pontes da Costa, A.; Viciano, M.; Sanaú, M.; Merino, S.; Tejeda, J.; Peris, E.; Royo, B. *Organometallics* **2008**, *27*, 1305.
(167) Prades, A.; Corbeŕan, R.; Poyatos, M.; Peris, E. *Chem.—Eur. J.* **2008**, *14*, 11474.
(168) Liu, S.; Rebros, M.; Stephens, G.; Marr, A. C. *Chem. Commun.* **2009**, 2308.
(169) Gnanamgari, D.; Sauer, E. L.; Schley, N. D.; Butler, C.; Incarvito, C. D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 321.
(170) Aramoto, H.; Obara, Y.; Ishii, Y. *J. Org. Chem.* **2009**, *74*, 628.
(171) Shi, F.; Tse, M. K.; Cui, X.; Gördes, D.; Michalik, D.; Thurow, K.; Deng, Y.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5912.
(172) Tsuji, Y.; Takeuchi, R.; Ogawa, H.; Watanabe, Y. *Chem. Lett.* **1986**, 293.
(173) Snyder, H. R.; Carnahan, R. E.; Lovejoy, E. R. *J. Am. Chem. Soc.* **1954**, *76*, 1301.
(174) For a review on oxidation of amines, see: Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443.
(175) Issoire, J.; van Long, C. *Bull. Soc. Chim. Fr.* **1960**, 2004.
(176) Borrows, E. T.; Hargreaves, B. M. C.; Page, J. E.; Resuggan, J. C. L.; Robinson, F. A. *J. Chem. Soc.* **1947**, 197.
(177) Klindler, K.; Melamed, G.; Matthies, D. *Liebigs Ann. Chem.* **1961**, *644*, 23.
(178) De Angelis, F.; Grgurina, I.; Nicoletti, R. *Synthesis* **1979**, 70.
(179) Pommersheim, J. M.; Coull, J. *AIChE J.* **1971**, *17*, 1075.
(180) Kijeński, J.; Burger, J.; Baiker, A. *Appl. Catal.* **1984**, *11*, 295.
(181) Baiker, A.; Monti, D.; Fan, Y. S. *J. Catal.* **1984**, *88*, 81.
(182) Rosenmund, K. W.; Jordan, G. *Ber. Dtsch. Chem. Ges.* **1925**, *58B*, 51.
(183) Anderson, J. R.; Clark, N. J. *J. Catal.* **1966**, *5*, 250.
(184) Yoshimura, N.; Moritani, I.; Shimamura, T.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1973**, *95*, 3038.
(185) Yoshimura, N.; Moritani, I.; Shimamura, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1973**, 307.
(186) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348.
(187) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.
(188) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429.
(189) Miyazawa, A.; Tanaka, K.; Sakakura, T.; Tashiro, M.; Tashiro, H.; Prakash, G. K. S.; Olah, G. A. *Chem. Commun.* **2005**, 2104.
(190) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977.
(191) Nishimoto, S.-i.; Ohtani, B.; Yoshikawa, T.; Kagiya, T. *J. Am. Chem. Soc.* **1983**, *105*, 7180.
(192) Miyazawa, A.; Saitou, K.; Tanaka, K.; Gädda, T. M.; Tashiro, M.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron Lett.* **2006**, *47*, 1437.
(193) Largeron, M.; Fleury, M.-B. *Org. Lett.* **2009**, *11*, 883.
(194) Ballantine, J. A.; Purnell, H.; Rayanakorn, M.; Thomas, J. M.; Williams, K. J. *J. Chem. Soc., Chem. Commun.* **1981**, 9.
(195) Greenfield, H. *J. Org. Chem.* **1964**, *29*, 3082.
(196) Murahashi, S.-I.; Yano, T. *J. Am. Chem. Soc.* **1980**, *102*, 2456.
(197) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249.
(198) Arcelli, A.; Khai, B.-T.; Porzi, G. *J. Organomet. Chem.* **1982**, *231*, C31.
(199) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Org. Chem.* **1981**, *46*, 1759.
(200) Jung, C. W.; Fellmann, J. D.; Garrou, P. E. *Organometallics* **1983**, *2*, 1042.
(201) Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C.; Yoon, N. S. *Tetrahedron* **2000**, *56*, 7747.
(202) Cho, C. S.; Kim, T. K.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Organomet. Chem.* **2002**, *650*, 65.
(203) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499.
(204) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885.
(205) Laine, R. M. *J. Mol. Catal.* **1983**, *21*, 119.
(206) Wilson, R. B.; Laine, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 361.
(207) Shvo, Y.; Thomas, D. W.; Laine, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 2461.
(208) Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8291.
(209) Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Chem. Commun.* **2008**, 3199.
(210) Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink, R.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 5742.
(211) Bähn, S.; Hollmann, D.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2099.
(212) Shvo, Y.; Laine, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 753.
(213) Laine, R. M.; Thomas, D. W.; Cary, L. W. *J. Am. Chem. Soc.* **1982**, *104*, 1763.
(214) Laine, R. M.; Thomas, D. W.; Cary, L. W.; Buttrill, S. E. *J. Am. Chem. Soc.* **1978**, *100*, 6527.
(215) Tsuji, Y.; Shida, J.; Takeuchi, R.; Watanabe, Y. *Chem. Lett.* **1984**, 889.

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