NEW APPLICATIONS OF THE *BORROWING HYDROGEN* METHODOLOGY - SELECTIVE SYNTHESIS OF AMINES AND MECHANISTIC STUDIES

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Das Schönste am Leben
ist das Lachen seines Kindes.

Für Nadine und Tobias

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List of Publications

This thesis is based on the following papers, referred to in the captions by their Roman numerals **I**-**IX**.

I **A Novel Ruthenium-catalyzed Amination of Primary and Secondary Alcohols.** Annegret Tillack, Dirk Hollmann, Dirk Michalik, and Matthias Beller, *Tetrahedron Lett.* **2006**, *47*, 8881-8885.

II **An Improved Ruthenium Catalyst for the Environmentally Benign Amination of Primary and Secondary Alcohols.** Dirk Hollmann, Annegret Tillack, Dirk Michalik, Ralf Jackstell, and Matthias Beller, *Chem. Asian J.* **2007**, *3*, 403-410 (VIP paper with front cover).

III **Salt-free Synthesis of Tertiary Amines via Ruthenium-catalyzed Amination of Alcohols.** Annegret Tillack, Dirk Hollmann, Kathleen Mevius, Dirk Michalik, Sebastian Bähn, and Matthias Beller, *Eur. J. Org. Chem.* **2008**, 4745-4750.

IV **A General Ruthenium-catalyzed Synthesis of Aromatic Amines.** Dirk Hollmann, Sebastian Bähn, Annegret Tillack, and Matthias Beller, *Angew. Chem. Int. Ed.* **2007**, *46*, 8291-8294, *Angew. Chem.* **2007***, 119*, 8440-8444 (Hot Paper).

V ***N*-Dealkylation of Aliphatic Amines and Selective Synthesis of Monoalkylated Aryl Amines.** Dirk Hollmann, Sebastian Bähn, Annegret Tillack, and Matthias Beller, *Chem. Commun.* **2008**, 3199-3201.

VI **Ruthenium-catalyzed Synthesis of Secondary Alkylamines: Selective Alkylation with Aliphatic Amines.** Sebastian Bähn, Dirk Hollmann, Annegret Tillack, and Matthias Beller, *Adv. Synth. Cat.* **2008**, *350*, 2099-2103.

VII **A Novel Salt-free Ruthenium-catalyzed Alkylation of Aryl Amines.** Dirk Hollmann, Sebastian Bähn, Annegret Tillack, Rudy Parton, Rinke Altink, and Matthias Beller, *Tetrahedron Lett.* **2008**, *49*, 5742-5745.

VIII **Pyrrolidine Activation: C–N Bond Cleavage and Formation and New Mechanistic Aspects in the Activation of the Shvo Catalyst.** Dirk Hollmann, Rudy Parton, Rinke Altink, Annegret Tillack, Sebastian Bähn, Anke Spannenberg, Haijun Jiao, and Matthias Beller, *Organometallics* **2008**, submitted for publication.

IX **Deactivation of the Shvo Catalyst by Ammonia: Synthesis, Characterization and Modeling.** Dirk Hollmann, Haijun Jiao, Anke Spannenberg, Sebastian Bähn, Annegret Tillack, Rudy Parton, Rinke Altink, and Matthias Beller, *Organometallics* **2008**, accepted for publication.

Abstract

This cumulative thesis deals with the application of the *Borrowing Hydrogen* methodology in organic synthesis. This concept combines the dehydrogenation and hydrogenation with numerous of organic transformations. The introduction gives an overview of the current research in the area of *Borrowing Hydrogen*, which expands from activation of C-C bonds to C-O bonds and finally to C-N bonds. During my research, the *Borrowing Hydrogen* methodology was applied in the synthesis of secondary and tertiary amines starting from secondary alcohols by C-O activation. Furthermore, I was able to introduce the selective synthesis of monoalkylated aryl amines using primary, secondary, and tertiary amines by C-N activation. This new method was continuously applied in the alkylation of *t*-alkyl amines. Additionally, mechanistic studies in the activation and deactivation of the *Shvo* catalyst (**2**) were performed.

The results of my work, reported in the publications **I**-**IX** listed on the preceding page, are integrated and associated with state-of-the-art chemistry in this field.

My ambition is to help the reader to get interested in this field and to understand these transformations. I also want to emphasize the work I have been responsible for.

Zusammenfassung

Diese kumulative Dissertation befasst sich mit der Anwendung der *Borrowing Hydrogen* (Ausleihen von Wasserstoff) Methodik in der organischen Synthese. Dieses Konzept kombiniert die Schritte der Hydrierung und Dehydrierung mit einer Vielzahl von organischen Reaktionen. Die Einleitung gibt einen Überblick über die aktuelle Forschung auf dem Gebiet der *Borrowing Hydrogen* Methodik. Diese umfasst die Aktivierung von C-C Bindungen, C-O Bindungen sowie von C-N Bindungen. In meiner Forschung wurde diese Methodik in der Synthese von sekundären sowie tertiären Aminen mittels sekundärer Alkohole angewandt. Weiterhin befasste ich mich mit der selektiven Synthese von monoalkylierten Aryl aminen. Dabei konnten primäre, sekundäre sowie tertiäre Alkyl amine eingesetzt werden. Diese neue Methode wurde ebenfalls in der Alkylierung von *t*-Alkyl aminen angewandt. Zusätzlich zur organischen Synthese befasste ich mich mit mechanistischen Studien zur Aktivierung sowie Deaktivierung des eingesetzten *Shvo* Katalysators (**2**).

Die Ergebnisse meiner Forschung, welche in den Publikationen **I**-**IX** auf den vorherigen Seiten aufgelistet sind, wurden in diese Übersicht integriert und mit der aktuellen Forschung auf diesem Gebiet verknüpft.

Mein Bestreben mit dieser Arbeit ist es, das Interesse für dieses sehr interessante Gebiet sowie ein Verständnis für die damit möglichen Reaktionen in der organischen Chemie zu wecken.

Abbreviations

BINAP	2,2'-Binaphtyldiphenyldiphosphine
Bn	Benzyl
Bu	Butyl
CO	Carbonyl
cod	Cyclooctadien
Cp*	Pentamethylcyclopentadienyl
DME	Dimethoxyethane
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
ee	enantiomeric excess
E-factor	Environmental Factor
Et	Ethyl
et al.	et alia
ip-foxap	(S,S)-[2-(4'-Isopropyloxazolin-2'-yl)ferrocenyl]diphenylphosphine
i-	*iso-*
Me	Methyl
MPV	Meerwein-Pondorf-Verley reduction
Ph	Phenyl
Pr	Propyl
Py	Pyridinium
R	Alkyl-, Aryl moiety
t-	*tert-*
THF	Tetrahydrofurane
TsDPEN	Tosyldiphenylethylendiamine
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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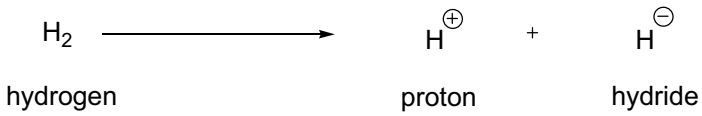
1. Introduction

1.1. Transfer Hydrogenation

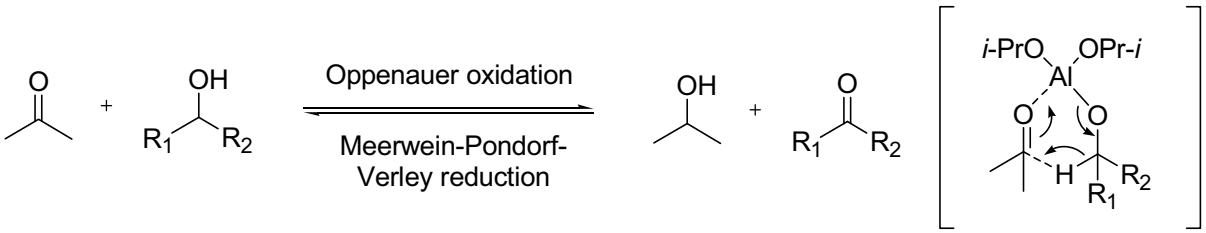
Hydrogen is the smallest atom in the periodic table and exists as the tiniest known molecule (H_2). By losing a proton, a hydride can be formed (Scheme 1). Hydrogen is used in a magnitude of catalytic reactions as reducing agent. The E-factor,[1] defined by the mass of the waste divided by the mass of the product, is very low since the reactions generally go to completion and no waste is generated. As hydrogen is explosive, the handling requires expensive and specialized equipment. Due to the high reactivity of hydrogen gas, another drawback is the low chemoselectivity towards other functional groups.[2]



Scheme 1: Separation of hydrogen into a proton and a hydride

One of the most popular procedures, the use of different borohydrides, has the disadvantage that stoichiometric amounts of reduction agent are required. Consequently, a lot of waste is produced, giving a high E-factor. Moreover, the workup requires tedious acid/base extractions that lower the yield and further increase the E-factor.

An attractive way to circumvent the hazard use of hydrogen and the stoichiometric use of metal hydrides is to employ alternative hydrogen sources such as 2-propanol or formic acid. 2-Propanol is cheap, liquid, non-toxic, and volatile. During the process, 2-propanol is oxidized to acetone. This makes the reduction of ketones a reversible process where the equilibrium is regulated by the excess of starting material or the removement of products.

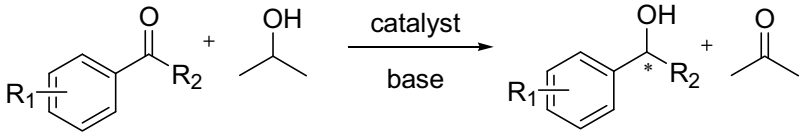


Scheme 2: Oppenauer oxidation of alcohols and Meerwein-Pondorf-Verley reduction of ketons

(1) (a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273 - 1283. (b) R. A. Sheldon, *Pure Appl. Chem.* **2000,** *72*, 1233-1246.

(2) S. Gladiali, E. Alberico, in *Transition Metals for Organic Synthesis*, (Eds.: M. Beller and C. Bolm) Wiley-VCH, Weinheim, **2004**, Vol. 2, p. 145.

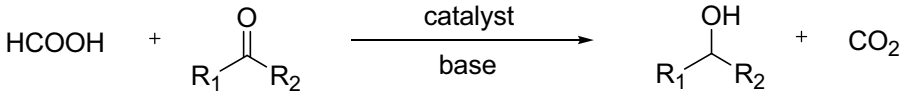
Acetone is unreactive and can easily be removed from the reaction mixture by distillation. Since the introduction of classical aluminium-based reagents used in the *Meerwein-Pondorf-Verley* reduction of ketones by 2-propanol in 1925[3] and the reverse reaction, the *Oppenauer* oxidation of alcohols by acetone in 1937[4] (Scheme 2), many other metals have been shown to be catalytically active for the transfer hydrogenation of carbonyls into alcohols. In particular, late transition metal catalysts combined with asymmetric ligands have widely been investigated for asymmetric hydrogenation reactions (Scheme 3).[5] Here, *Noyori's* ruthenium-based catalysts comprising the combination of BINAP and a chiral diamine constitute state-of-the-art transfer hydrogenations systems.[6]



Scheme 3: Transfer hydrogenation of ketones using 2-propanol

Unfortunately, the reversibility of the reaction remains a major drawback in asymmetric hydrogen transfer. As the conversion increases, the rate of the reverse reaction becomes higher and thus thermodynamic control of the enantiomers can occur, which is shown in a decrease of the enantiomeric purity of the product. This limitation can be overcome by continuously distilling off acetone as soon as it is formed.

Compared to 2-propanol, formic acid and its salts are better hydrogen donors and constitute a cheap and nontoxic hydrogen source. Pure formic acid can be stored as solid or as liquid in a mixture of formic acid/triethylamine 5:2. This mixture is miscible with many solvents at 20-60 °C. Under thermal conditions it can decay into hydrogen and carbon dioxide, which is released as gas and can be reused for further applications (Scheme 4).



Scheme 4: Transfer hydrogenation of ketones using formic acid

(3) a) H. Meerwein, R. Schmidt, *Liebigs Ann. Chem.* **1925**, *44*, 221-238. b) K. Nishide, M. Node, *Chirality* **2002**, *14*, 759-767.

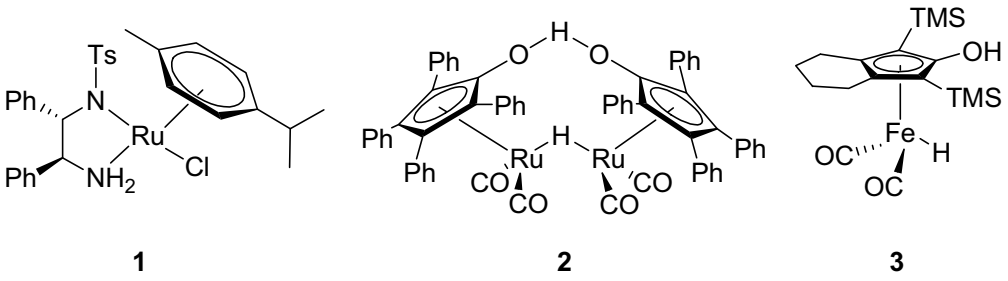
(4) a) R.V. Oppenauer, *Rec. Trav. Chim.* 1**937**, *56*, 137-144. b) M. L. S. Almeida, P. Kocovsky, J.-E. Bäckvall, *J. Org. Chem.* **1996**, *61*, 6587-6590.

(5) Review of asymmetric transfer hydrogenation, see: a) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226-236. b) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237-248.

(6) X. Wu, X. Li, F. King, J. Xiao, *Angew. Chem. Int. Ed.* **2005**, *44*, 3407-3411; *Angew. Chem.* **2005**, *117*, 3473-3477.

However, the use of formic acid is restricted. Several complexes undergo fast decomposition on attempted dissolution. Formic acid can also inhibit one of the steps of the activation process promoted by a base, which leads to the complete loss of the catalytic activity. In addition, the catalyst usually has to activate by a base. However, organic synthesis needs economically and technically more beneficial methods.

The hydride transfer takes place according to two mechanisms: Direct H-transfer (metal-templated concerted process) and hydridic H-transfer (metal hydride mediated multi-step process). The direct H-transfer proceeds via a complex, in which both the donor and the acceptor are bound to the metal. A cyclic transition state like in the *Meerwein-Pondorf-Verley* reaction is involved (see Scheme 2). The hydridic H-transfer involves the intermediate formation of metal hydrides by interacting with hydrogen donors followed by hydride transfer to the substrates. Depending on a ligand coordinated to the metal, either mono- or dihydride species are involved. In contrast to this, ligand metal bifunctional catalysts involve proton transfer from N-H or O-H bonds and hydride transfer from Ru-H species. Many remarkably reactive ruthenium hydrogenation catalysts are known, based on the chiral diamine ligands discovered by *Noyori* and co-workers[7] (catalyst **1**) or the cyclopentadienone ligands discovered by *Shvo*[8] (catalyst **2**).[5] Recently, *Casey* applied the iron catalyst **3**, developed by *Knölker et al.*,[9] in transfer hydrogenation.[10]



1 **2** **3**

Scheme 5: Ligand metal bifunctional catalysts

(7) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97 -102.

(8) a) R. Karvembu, R. Prabhakaran, N. Natarajan, *Coord. Chem. Rev.* **2005**, *249*, 911-918. b) Y. Shvo, D. Czarkie, Y. Rahamim, *J. Am. Chem. Soc.* **1986**, *108*, 7400-7402. c) Y. Blum, D. Czarkie, Y. Rahamim, Y. Shvo, *Organometallics* **1985**, *4*, 1459-1461. d) Y. Shvo, R. M. Laine, *J. Chem. Soc., Chem. Comm.* **1980**, 753-754.

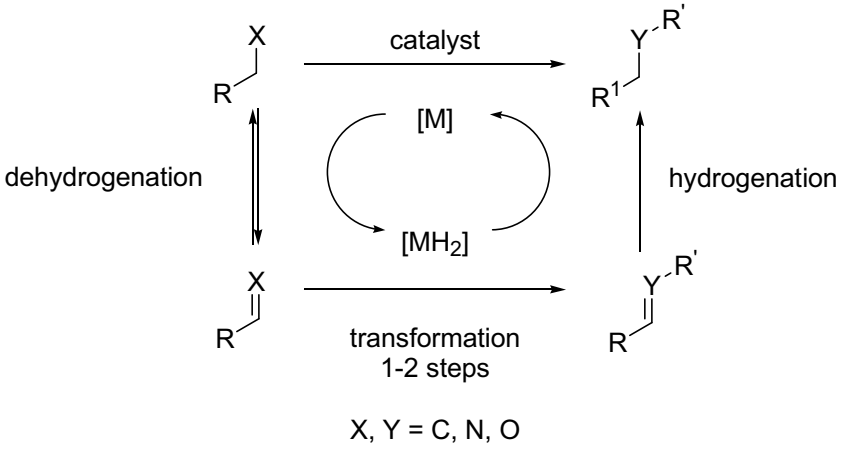
(9) H.-J. Knölker, E. Baum, H. Goesmann, R. Klauss, *Angew. Chem. Int. Ed.* **1999**, *38*, 2064-2066; *Angew. Chem.* **1999**, *111*, 2196-2199.

(10) a) C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2007**, *129*, 5816-5817. b) R. M. Bullock, *Angew. Chem. Int. Ed.* **2007**, *46*, 7360-7363; *Angew. Chem.* **2007**, *119*, 7504-7507.

2. *Borrowing Hydrogen* Methodology

2.1. Principles of the Borrowing Hydrogen Methodology

The *Borrowing Hydrogen* methodology also called *Hydrogen Auto Transfer Process* combines the advantages of transfer hydrogenation with additional transformations (Scheme 6). The hydrogen donor compound is not a waste compound such as 2-propanol. After dehydrogenation by a metal catalyst, the corresponding unsaturated compound can undergo further reactions and transformations such as condensation reactions with amines or *Wittig* reactions in order to form new unsaturated compounds. The corresponding compound can be hydrogenated by the metal hydride complex, which was generated in the dehydrogenation of the unsaturated starting material. The development of catalytic systems is therefore likely to involve metal complexes, in which H_2 dissociation and re-coordination is facile, preferably without the requirement of forcing conditions. Due to the stability of metal hydride complexes, most metal catalysts are inactive in the *Borrowing Hydrogen* methodology. Ideally, the hydrogenation step is irreversible, resulting in the complete shift of the equilibrium to the product. Under consideration of no hydrogen loss, even by side reaction or by gas evolution, the *Borrowing Hydrogen* methodology can refrain from using additional hydrogen sources, resulting in a very low E-factor. Thus, the *Borrowing Hydrogen* methodology is probably one of the best possibilities not only from a chemical point of view but also from an economical and environmental point of view. Based on these aspects, the *Borrowing Hydrogen* methodology received high attention in the last years. This atom efficient attractive method was applied in various reactions, which are discussed on the following pages.



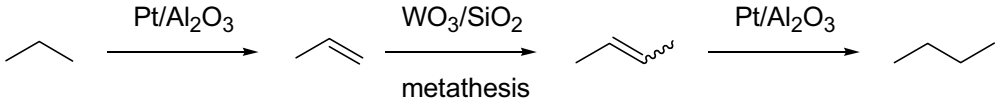
Scheme 6: Basic scheme of the Borrowing Hydrogen methodology

2.2. Activation of C-C Bonds

The carbon-carbon single bond represents one of the most stable single bond ever. Thus, it is of high interest to activate these bonds. One method to cleave carbon-carbon single bonds is the activation by dehydrogenation. The olefin can undergo transformations such as metathesis to cleave the unsaturated carbon-carbon double bond.

2.2.1. Alkane Metathesis[11]

Alkane conversion has been a major focus of petrochemical research in the last century.[12] The olefin metathesis received high attention which led to the development of important industrial processes such as the *Lummus ABB* process (conversion of ethylene to propylene).[13] The combination of heterogeneous hydrogenation/dehydrogenation and olefin metathesis catalysts led to the first alkane metathesis process, the so called *Chevron* process,[14] which allows a specific alkane to be converted into its lower and higher homologues (Scheme 7). As catalysts a combination of Pt/Al_2O_3 (dehydrogenation/hydrogenation) and WO_3 on silica (metathesis) was developed. Unfortunately, the dehydrogenation is highly disfavoured. Therefore, high temperatures of 400 °C is required for high concentration of olefins.



Scheme 7: Chevron process

Basset et al. reported heterogeneous catalysts based on tantalum (catalysts **4** and **5**, 1997)[15] and tungsten (catalysts **6** and **7**, 2005).[16] Some examples of these catalysts are displayed in Scheme 8. Notably, in contrast to the *Chevron* process, alkane metathesis is carried out on a dual catalyst

(11) J.-M. Basset, C. Coperet, D. Soulivong, M. Taoufik, J. Thivolle-Cazat, *Angew. Chem. Int. Ed.* **2006**, *45*, 6082-6085; *Angew. Chem.* **2006**, *118*, 6228-6231.

(12) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507-514.

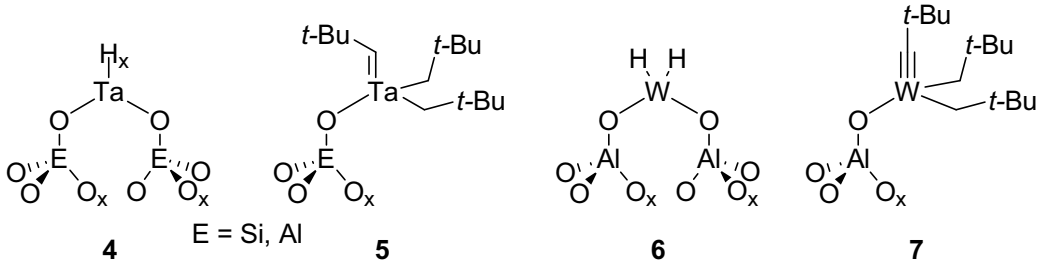
(13) J. C. Mol, *J. Mol. Catal.* **2004**, *213*, 39-45.

(14) a) L. F. Heckelsberg, R. L. Banks (Phillips Petroleum Co.), US3445541, **1969**. b) T. R. Hughes (Chevron Research Co.), US3773845, **1971**.

(15) V. Vidal, A. Theolier, J. Thivolle-Cazat, J.-M. Basset, *Science* **1997**, *276*, 99-102.

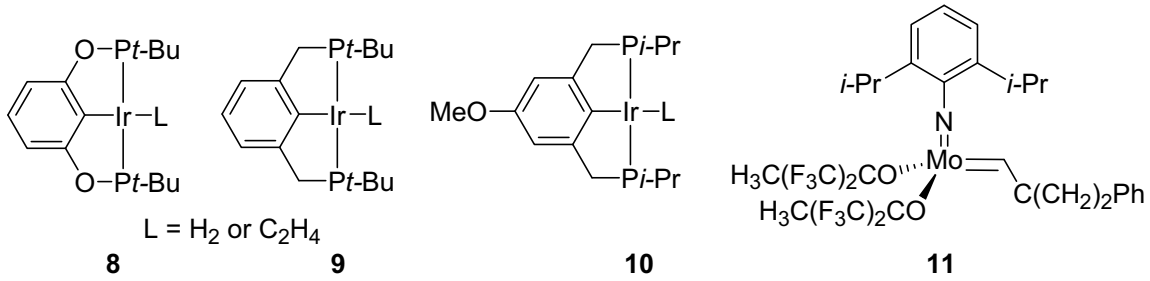
(16) E. Le Roux, M. Taoufik, C. Copéret, A. de Mallmann, J. Thivolle-Cazat, J.-M. Basset, B. M. Maunders, G. J. Sunley, *Angew. Chem. Int. Ed.* **2005**, *44*, 6755-6758; *Angew. Chem.* **2005**, *117*, 6913-6916.

based on a single metal having all the required properties such as C-H activation, dehydrogenation, hydrogenation, and metathesis.



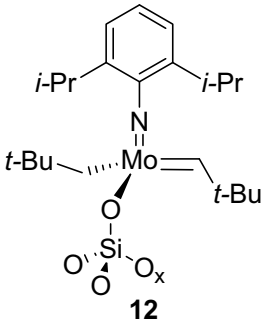
Scheme 8: Catalysts for alkane metathesis developed by Basset et al.

The first homogenous catalyst system based on a combination of the iridium complexes **8**-**10**, [17] as dehydrogenation and hydrogenation catalyst, and *Schrocks* molybdenium imido olefin catalyst **11** was reported in 2006 (Scheme 9) by *Goldman et al.*.[18] This process converted *n*-hexane to a range of C_2 to C_{15} *n*-alkanes.



Scheme 9: Catalysts for alkane metathesis developed by Brookhart, Goldman, and Chevron

Recently, *Basset et al.* described a very efficient molybdenium alkyl alkylidene imido complex **12** as precursor for alkane metathesis (Scheme 10).[19]



Scheme 10: Molybdenium alkyl alkylidene imido complex for alkane metathesis developed by Basset et al.

(17) M. Gupta, C. Hagen, R. J. Flesher, W. C. Kaska, C. M. Jensen, *Chem. Commun.* **1996**, 2083-2084.

(18) A. S. Goldman, A. H. Roy, Z. Huang, R. Ahuja, W. Schinski, M. Brookhart, *Science* **2006**, *312*, 257-261.

(19) F. Blanc, C. Coperet, J. Thivolle-Cazat, J.-M. Basset, *Angew. Chem. Int. Ed.* **2006**, *45*, 6201-6203; *Angew. Chem.* **2006**, *118*, 6347-6349.

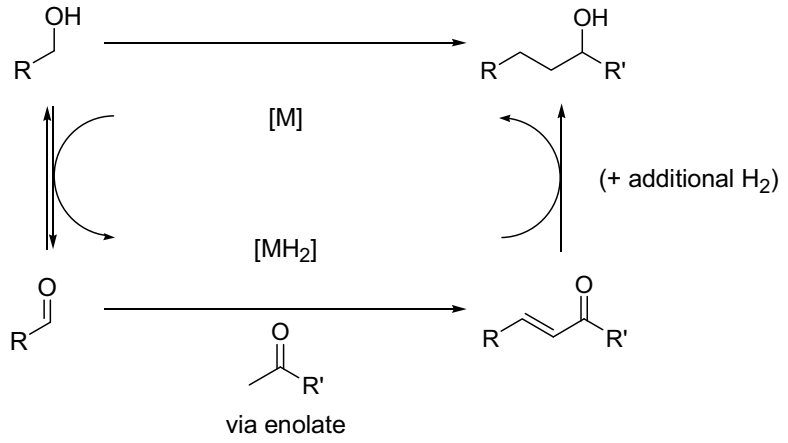
2.3. Activation of C-O Bonds

Alcohols have a limited reactivity without any type of activation such as addition of base in order to form nucleophilic alkoxides, or addition of acid to form electrophilic species. The temporary conversion of alcohols into carbonyl compounds provides more active carbonyl compounds than alcohols. They can react as electrophilic compounds in addition reactions such as condensation reactions or *Wittig* reactions but also as nucleophilic enol or enolate substrates in aldol reactions.

The activation of alcohols by the *Borrowing Hydrogen* methodology through a temporarily oxidized alcohol into a ketone has extensively been reviewed by *Williams et al.*[20] and *Yus et al.*[21] in 2007. Selected examples and new publications since these reviews are displayed in the following.

2.3.1. Aldol Condensation

The aldol condensation, the reaction of enolates derived from aldehydes or ketones with aldehydes or ketones into α,β-unsaturated carbonyl compounds via elimination of water, is one of the most common and famous C-C bond forming reactions in organic chemistry. Using the *Borrowing Hydrogen* methodology, the activation of primary or secondary alcohols to the corresponding aldehydes or ketones provides an access to this kind of C-C formation. The temporarily produced hydrogen can be used for hydrogenation of the α,β-unsaturated compounds to form alkylated alcohols (Scheme 11).



Scheme 11: Borrowing Hydrogen methodology combined with aldol reaction

(20) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams *Adv. Synth. Catal.* **2007**, *349*, 1555-1575.

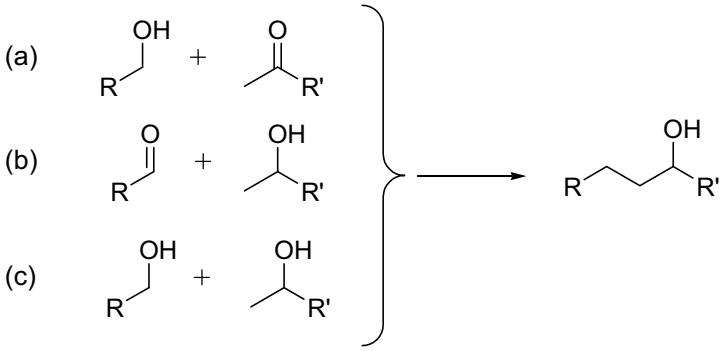
(21) G. Guillena, D. J. Ramon, M. Yus, *Angew. Chem. Int. Ed.* **2007**, *46*, 2358-2364; *Angew. Chem.* **2007**, *119*, 2410-2416.

Depending on the starting material, three different concepts are possible (Scheme 12):

(a) α-alkylation of ketones using alcohols

(b) β-alkylation of secondary alcohols with aldehydes

(c) β-alkylation of secondary alcohols with primary alcohols



Scheme 12: Starting concepts for the indirect aldol reaction

All of these concepts lead to saturated alcohols. Several catalysts are described for these reactions, which are included in the reviews of *Williams* [20]and *Yus*.[21] Concerning the atom economical point of view, it is preferable to avoid additives such as hydrogen acceptor (e.g. dodecene) or hydrogen donor (e.g. dioxane as solvent). Thus, the catalyst $RuCl_2(DMSO)_4$ (*Yus et al.*)[22] as well as the iridium catalyst $[Cp^*IrCl_2]_2$ (*Fujita et al.*)[23] can be highlighted, which are very active in the α-alkylation of ketones[24] as well as β-alkylation of secondary alcohols with primary alcohols. A new homogenous high efficient catalyst has recently been introduced by *Peris* and co-workers[25] for the β-alkylation of secondary alcohols with primary alcohols.

Interestingly, only two heterogeneous catalysts are described for β-alkylation of secondary alcohols. In 2005, *Park et al.* reported the first heterogeneous catalyst consisting of Pd/AlO(OH), which is composed of palladium nanoparticles entrapped in aluminium hydroxide.[26] This highly active catalyst was recovered by filtration or decantation. Furthermore, *Uozumi* described the palladium nanocatalyst nano-Pd-V, which is a mixture of palladium

(22) R. Martinez, D. J. Ramon, M. Yus, *Tetrahedron* **2006**, *62*, 8982-8987.

(23) K.-i. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka, R. Yamaguchi, *Org. Lett.* **2005**, *7*, 4017-4019.

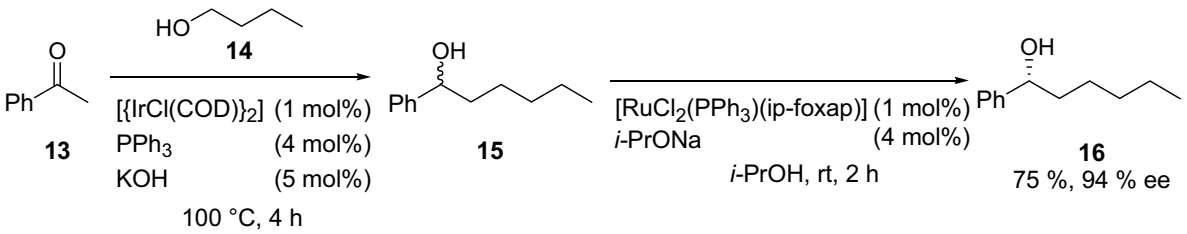
(24) a) R. Martinez, D. J. Ramon, M. Yus, *Tetrahedron* **2006**, *62*, 8988-9001. b) R. Martinez, G. J. Brand, D. J. Ramon, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 3683-3686.

(25) M. Viciano, M. Sanau, E. Peris, *Organometallics* **2007**, *26*, 6050-6054.

(26) M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala, J. Park, *Angew. Chem. Int. Ed.* **2005**, *44*, 6913-6915; *Angew. Chem.* **2005**, *117*, 7073-7075.

nanoparticles in viologen polymer.[27,28] As base for the aldol condensation barium hydroxide ($Ba(OH)_2$) was applied. In addition, this catalyst was used in the ring opening alkylation of diketones.[28]

Theoretically, using combinations of iridium and ruthenium precursors with chiral ligands, it should be possible to obtain the reduced alcohol with high enantioselectivity. Until to date, this has not been reported before. *Nishibayashi* and co-workers circumvent this problem by applying a sequential reaction of iridium-catalyzed α-alkylation of ketones using alcohols, to obtain the racemic alcohol and ruthenium-catalyzed enantioselective transfer hydrogenation, to convert the racemic alcohols into optically pure alcohols (Scheme 13).[29]



Scheme 13: One-pot combination of α-alkylation of ketones and transfer hydrogenation

A mixture of acetophenone (**13**) and 1-butanol (**14**) was converted in the presence of catalytic amounts of $[\{IrCl(COD)\}_2]$ and PPh_3, followed by an addition of $[RuCl_2(PPh_3)(ip\text{-}foxap)]$ to (*R*)-1-phenyl-1-hexanol (**16**) in 75 % yield and 94 % ee. Compared to this one-pot sequence, the direct enantioselective reaction catalyzed by using only $[RuCl_2(PPh_3)(ip\text{-}foxap)]$, provided low–to-moderate enantioselectivity.

2.3.2. β-Bromination of Alcohols

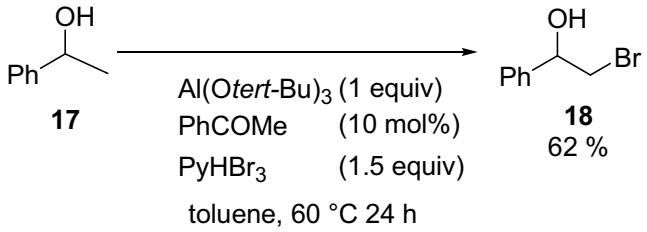
Activation of alcohols by reversible oxidation to ketones allows an access to enol and enolate chemistry. In 2003, *Hamid* and *Williams* described the indirect β-bromination of alcohols using the *Borrowing Hydrogen* methodology (Scheme 14).[30] The bromination of ketones was easily achieved with pyridinium tribromide. For the reversible oxidation, one equivalent of aluminium *t*-butoxide from the *Oppenauer/Meerwein-Pondorf-Verley* transfer hydrogenation was chosen.

(27) Y. M. A. Yamada, Y. Uozumi, *Org. Lett.* **2006**, *8*, 1375-1378.

(28) Y. M. A. Yamada, Y. Uozumi, *Tetrahedron* **2007**, *63*, 8492-8498.

(29) G. Onodera, Y. Nishibayashi, S. Uemura, *Angew. Chem. Int. Ed.* **2006**, *45*, 3819-3822; *Angew. Chem.* **2006**, *118*, 3903-3906.

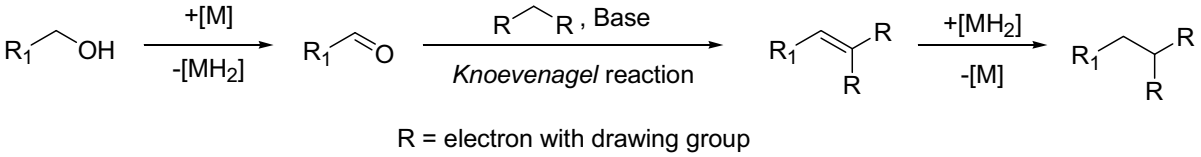
(30) M. H. S. A. Hamid, J. M. J. Williams, *Synlett* **2003**, 124-126.



Scheme 14: Indirect β-bromination of alcohols introduced by Williams et al.

2.3.3. *Knoevenagel* Reaction

In combination with the B*orrowing Hydrogen* methodology, a modified aldol reaction, the *Knoevenagel* reaction, can be used for monoalkylation of C-H acid methylene compounds (Scheme 15).

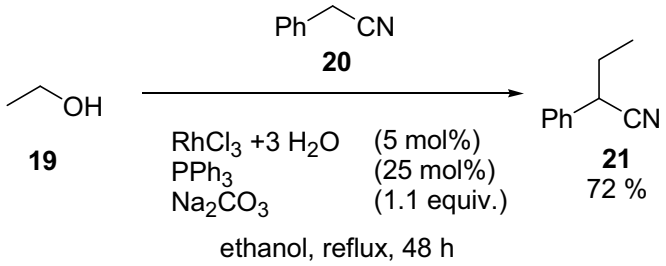


Scheme 15: Borrowing Hydrogen methodology combined with Knoevenagel reaction

The first transition metal-catalyzed alkylation using the *Knoevenagel* reaction was described by *Grigg* and co-workers in 1981.[31] By means of an *in situ* rhodium catalyst consisting of $RhCl_3$ and PPh_3, a small variety of arylacetonitriles derivatives such as **20** were converted to the monoalkylated arylacetonitrile **21**[32] which have a high potential as building blocks for the construction of amides, carboxylic acids, heterocyclic, and biologically active compounds. As alcohol substrates, primary alcohols such as methanol or ethanol (**19**) were chosen. Bulkier alcohols e.g. benzyl alcohol (**34**) seems to be problematic, long reaction times (132 h) were necessary and moderate yields were achieved. Compared to the rhodium *in situ* catalyst, the ruthenium catalyst $[RuH_2(PPh_3)_4]$ showed higher reactivity.

(31) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *Tetrahedron Lett.* **1981**, *22*, 4107-4110.

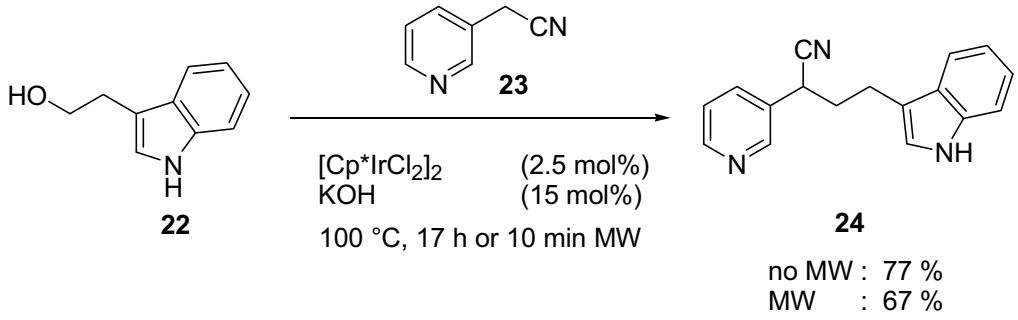
(32) Alkylated nitriles are traditionally synthesized using stoichiometric amounts of inorganic bases and alkyl halides. Major drawbacks with these methods are the toxicity of the alkylating agent, the concurrent formation of undesirable waste salts, and the potential for dialkylated by-products.



Scheme 16: First example of an indirect Knoevenagel reaction introduced by Grigg and co-workers

No more than three years ago, in 2004, *Kaneda* described the same reaction catalyzed by ruthenium-grafted hydrotalcide.[33] This heterogeneous catalyst was applicable with various substrates, however, only primary alcohols as reported by *Grigg et al.*[31] were converted. The ruthenium-grafted hydrotalcide possesses both active Ru^{4+} species for dehydrogenation and hydrogenation, as well as surface base sites for the *Knoevenagel* reaction, thus no additional base or additives were required.

In 2006, *Grigg et al.* described a highly efficient iridium-catalyzed alkylation of nitriles (Scheme 17).[34] A large diversity of alcohols and nitriles were converted in high yields selectively to the corresponding monoalkylated nitriles (e.g. **24**).



Scheme 17: Iridium-catalyzed indirect Knoevenagel reaction using conventional and microwave heating

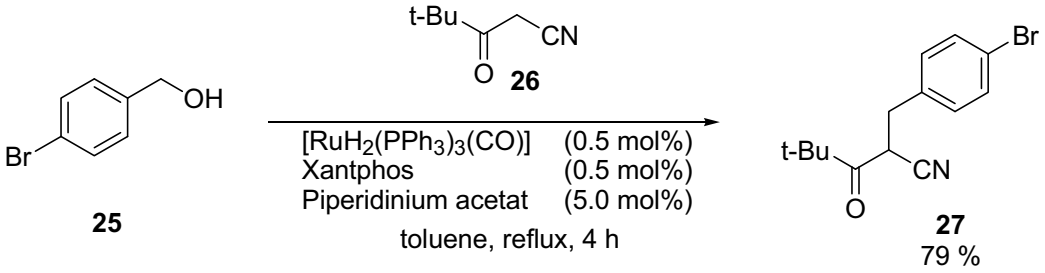
For example, pyridine and indoles were tolerated. In addition to conventional heating, the reactions were performed using microwave technique. Thereby, a shortening of the reaction time to 10 minutes was achieved. The same iridium catalyst was deployed in the alkylation of 1,3-dimethylbarbituric acid.[35]

(33) K. Motokura, D. Nishimura, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc.* **2004**, *126*, 5662-5663.

(34) C. Löfberg, R. Grigg, M. A. Whittaker, A. Keep, A. Derrick, *J. Org. Chem.* **2006**, *71*, 8023-8027.

(35) C. Löfberg, R. Grigg, A. Keep, A. Derrick, V. Sridharan, C. Kilner, *Chem. Commun.* **2006**, 5000-5002.

At the same time, *Williams* studied the iridium-catalyzed alkylation of alcohols using nitroalkanes (nitroaldole reaction), malonates, 1,3-diketones, and ketonitriles.[36] The reaction of dibenzylmalonate with benzyl alcohol provides an access to alkylated malonates although only moderate yields were achieved due to decarboxylation and transesterification. Recently, *Williams* reported a second generation ruthenium catalyst based on $[RuH_2(PPh_3)_3(CO)]$ and Xantphos for the alkylation of ketonitriles (Scheme 18).[37] It can be highlighted that with benzylic alcohols (**25**), unrivaled low catalyst loading of 0.5 mol% ruthenium catalyst was achieved. With aliphatic primary alcohols, complete conversion was achieved, too, although a higher catalyst loading of 5 mol% ruthenium catalyst was required.



Scheme 18: Ruthenium-catalyzed indirect Knoevenagel reaction introduced by Williams et al.

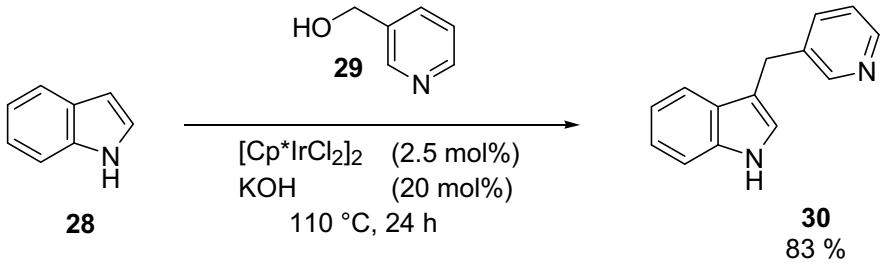
2.3.4. C-3 Alkylation of Indoles

Recently, *Grigg* and co-workers reported the first hydrogen transfer mediated alkylation of indoles with alcohols (Scheme 19).[38] Using the iridium complex $[Cp^*IrCl_2]_2$, with aromatic, heteroaromatic, and aliphatic alcohols such as **29**, indoles and substituted indoles were alkylated in the C-3 position. A proposed mechanism is displayed in Scheme 20. This mechanism was supported by the formation of minor bisindolylmethane side products resulting from *Michael* addition of indole **28** to intermediate **31**. In addition, it can be mentioned that this reaction was applied in an one-pot sequence of oxidative cyclization–alkylation starting from 2-aminophenethyl-alcohol (see chapter 2.3.7.) and benzyl alcohol.

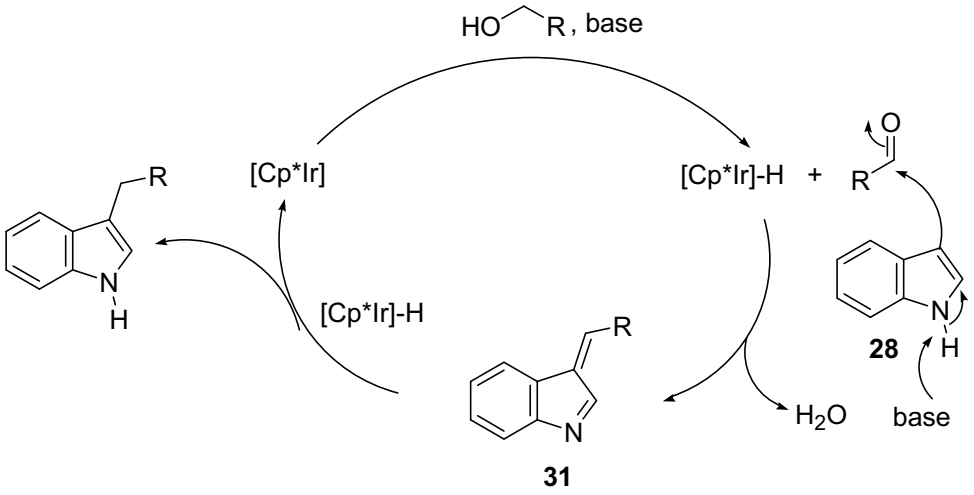
(36) P. J. Black, G. Cami-Kobeci, M. G. Edwards, P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Org. Biomol. Chem.* **2006**, *4*, 116-125.

(37) P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Tetrahedron Lett.* **2006**, *47*, 6787-6789.

(38) S. Whitney, R. Grigg, A. Derrick, A. Keep, *Org. Lett.* **2007**, *9*, 3299-3302.



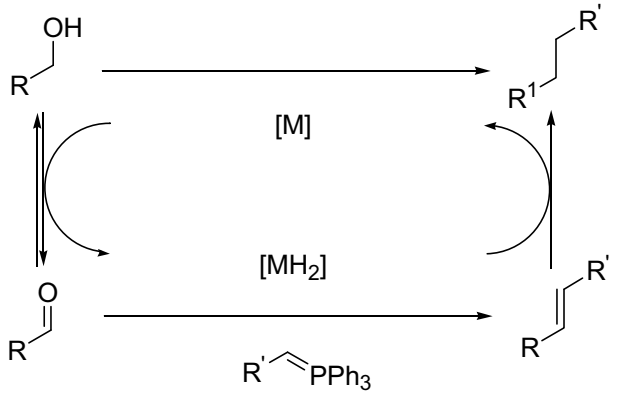
Scheme 19: C-3 Alkylation of indoles using alcohols



Scheme 20: Mechanism of the C-3 alkylation of indoles

2.3.5. *Wittig* Reaction

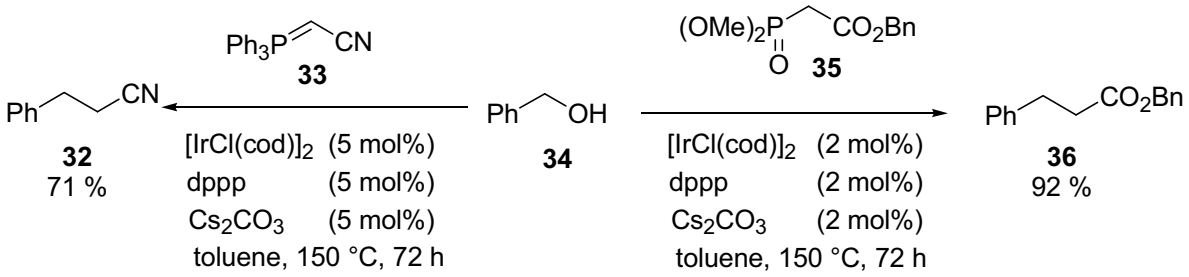
Ketones and aldehydes can undergo *Wittig* type reactions to form new C-C double bonds. Using the *Borrowing Hydrogen* methodology, alcohols can be used to generate an aldehyde, which undergoes *Wittig* type reactions to form alkenes (Scheme 21). The hydrogen is then returned in order to provide the corresponding alkane.



Scheme 21: Indirect Wittig reaction with alcohols

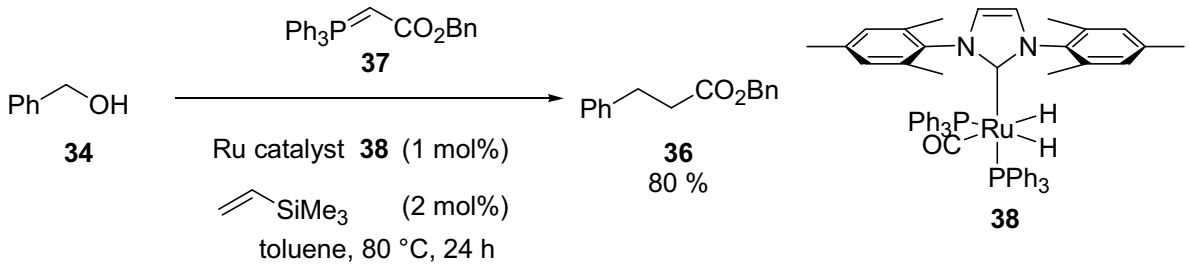
The group of *Williams* recently developed a variety of indirect *Wittig* type reactions[36] such as iridium-catalyzed indirect *Horner-Wadsworth-Emmons* reaction of benzyl alcohol (**34**) with

phosphonates (e.g. **35**)[39] or *Wittig* reactions with cyanoylides (e.g **33**) to obtain the corresponding propionitriles (Scheme 22).[40] High yields and a high tolerance towards functional groups were achieved.



Scheme 22: Indirect Wittig and Horner-Wadsworth-Emmons reaction of benzyl alcohol

In 2004, the ruthenium carbene complex **38** was described for the indirect *Wittig* reaction with phosphorane ester ylides, for example **37**. This second generation catalyst showed high reactivity at lower temperature. Unfortunately, an additional hydrosilyation additive (vinyltrimethylsilane) for the activation of the catalyst was necessary (Scheme 23).[41] In 2007, the active form of this ruthenium carbene complex was used in the transfer hydrogenation and *Wittig* reaction with cyanoylides.[42]



Scheme 23: Indirect Wittig reaction with alcohols with a ruthenium carbene complex

Notably, with an *in situ* catalyst based on $[Ir(cod)Cl_2]_2$ and dppf, an indirect Aza-*Wittig* reaction was reported (Scheme 24).[43] Starting from primary alcohols (**34**),

(39) M. G. Edwards, J. M. J. Williams, *Angew. Chem. Int. Ed.* **2002**, *41*, 4740-4743; *Angew. Chem.* **2002**, *114*, 4934-4937.

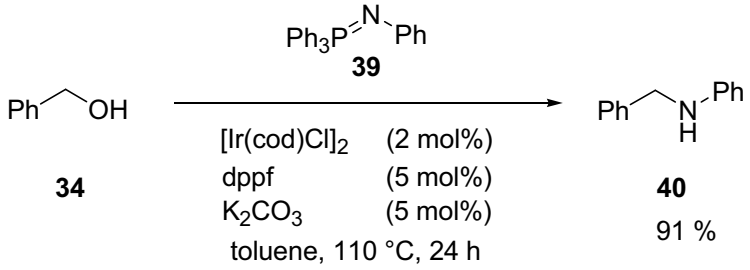
(40) P. J. Black, M. G. Edwards, J. M. J. Williams, *Eur. J. Org. Chem.* **2006**, 4367-4378.

(41) M. G. Edwards, R. F. R. Jazzar, B. M. Paine, D. J. Shermer, J. M. J. Williams, D. D. Edney, *Chem. Commun.* **2004**, 90-91.

(42) S. Burling, B. M. Paine, D. Nama, V. S. Brown, M. F. Mahon, T. J. Prior, P. S. Pregosin, M. K. Whittlesey, J. M. J. Williams, *J. Am. Chem. Soc.* **2007**, *129*, 1987-1995.

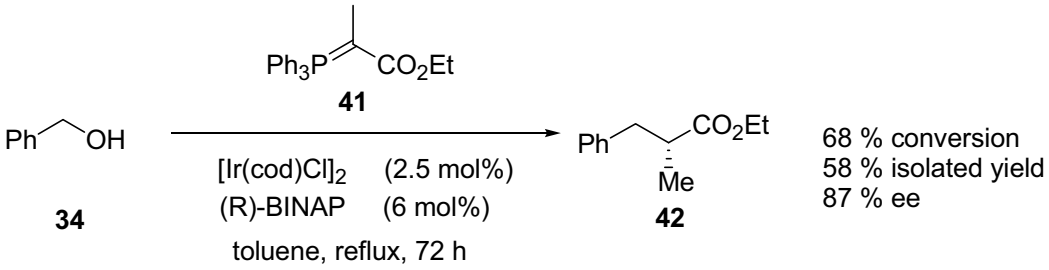
(43) H. Cami-Kobeci, J. M. J. Williams, *Chem. Commun.* **2004**, 1072-1073.

phenyliminphosphoranes (**39**) can be converted into the corresponding secondary amines (**40**) in high yields. The substrate scope was limited to primary alcohols as well as phenyliminophosphoranes.



Scheme 24: Indirect Aza-Wittig reaction with iminophosphoranes

Latest research on the field of *Wittig* type reactions, is highlighted by asymmetric variations. The iridium precursor $[Ir(cod)Cl_2]_2$ combined with different chiral ligands were screened. Highest enantiomeric excess (ee) and yields were achieved with *Noyori* BINAP ligands.[44]



Scheme 25: First indirect asymmetric Wittig reaction developed by Williams et al.

The shortening of the reaction time as well as the enhancement of the ee and the yield are considered desirable. It can be estimated that new and more efficient catalysts will be developed soon.

2.3.6. *N*-Alkylation of Amines using Alcohols[I, II, III]

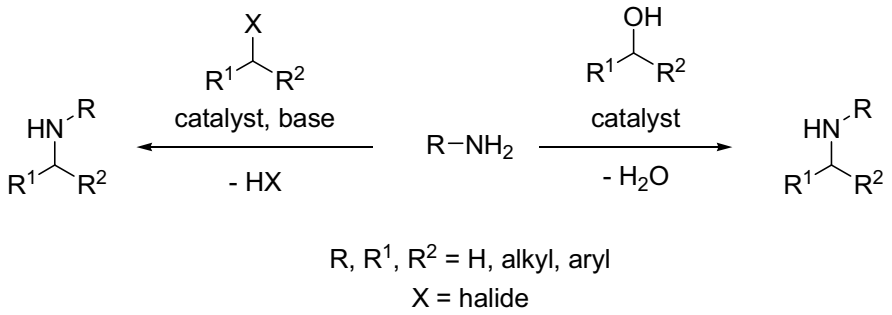
A variety of amines is of significant importance for the bulk and fine chemical industry as building blocks for polymers, dyes, but also for the synthesis of new pharmaceuticals and agrochemicals.[45] In addition, a plethora of naturally bio-active compounds such as alkaloids, amino acids, and nucleotides contain amino groups. Traditionally, alkylation of amines is

(44) D. J. Shermer, P. A. Slatford, D. E. Edney, J. M. J. Williams, *Tetrahedron Asymmetry* **2007**, *18*, 2845-2848.

(45) a) S. A. Lawrence in "Amines: Synthesis, properties, and applications", Cambridge University, Cambridge **2004**. b) J. F. Hartwig in "Handbook of Organo-palladium Chemistry for Organic Synthesis", Vol. 1 (Ed.: Negishi, E.-I.), Wiley-Interscience, New York, **2002**, p. 1051.

achieved by using conventional alkylation reagents, such as alkyl halides.[46] Despite numerous known non-catalytic procedures, the development of improved catalytic methods for the synthesis of amines continues to be a highly challenging and active area of research. During last decade, various catalytic aminations, like palladium- and copper-catalyzed aminations of aryl halides,[47] hydroaminations,[48] and hydroaminomethylations[49] of olefins or alkynes have received increased attention. Less interest was paid to the further development of catalytic alkylations of amines such as reductive aminations.[50]

Compared to the well-known classic *N*-alkylations of amines with alkyl halides and reductive alkylations, an atom economically[51] and environmentally attractive method is the *N*-alkylation of amines using primary and secondary alcohols (Scheme 26). Thus, alcohols can be used as alkylating reagent.



Scheme 26: Catalytic N-alkylation of amines with alcohols or alkyl halides

This domino reaction sequence is based on the *in situ* dehydrogenation of alcohols in order to give the corresponding aldehydes or ketones. Subsequent imine formation followed by

(46) R. N. Salvatore, C. H. Yoon, K. W. Jung, *Tetrahedron* **2001**, *57*, 7785-7811.

(47) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318-5365. b) M. Taillefer, N. Xia, N. Ouali, *Angew. Chem. Int. Ed.* **2007**, *46*, 934-936; *Angew. Chem.* **2007**, *119*, 952-954.

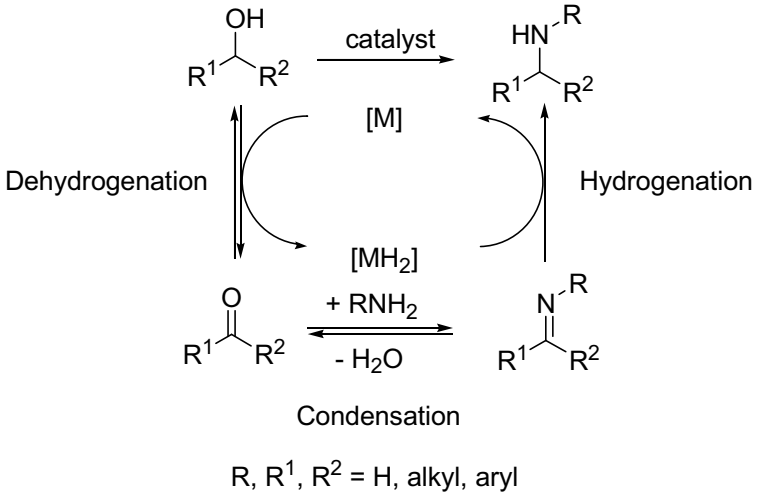
(48) a) K. Alex, A. Tillack, N. Schwarz, M. Beller, *ChemSusChem* **2008**, *1*, 333–338. b) J. J. Brunet, N. C. Chu, M. Rodriguez-Zubiri, *Eur. J. Inorg. Chem.* **2007**, 4711-4722;

(49) a) A. Moballigh, C. Buch, L. Routaboul, R. Jackstell, H. Klein, A. Spannenberg, M. Beller, *Chem. Eur. J.* **2007**, *13*, 1594 – 1601 and references therein.

(50) for Reductive Amination, see: a) A. V. Malkov, S. Stončius, P. Kočovsky, *Angew. Chem. Int. Ed.* **2007**, *46*, 3722-3724; *Angew. Chem.* **2007**, *119*, 3796-3798. b) G. Hughes, P. N. Devine, J. R. Naber, P. D. O'Shea, B. S. Foster, D. J. McKay, R. P. Volante, *Angew. Chem. Int. Ed.* **2007**, *46*, 1839-1842; *Angew. Chem.* **2007**, *119*, 1871-1874 and references therein.

(51) a) B. M. Trost, M. U. Frederiksen, T. M. Rudd, *Angew. Chem. Int. Ed.* **2005**, *44*, 6630-6666; *Angew. Chem.* **2005**, *117*, 6788-6825. b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259-281; *Angew. Chem.* **1995**, *107*, 285-307. c) B. M. Trost, *Science* **1991**, *254*, 1471-1477.

reduction with the initially produced hydrogen leads to the *N*-alkylated amine (Scheme 27). To obtain the desired amine, it is necessary, that the hydrogenation of the imine is an irreversible process.



Scheme 27: Catalytic hydrogen transfer in N-alkylation of amines with alcohols

So far, *N*-alkylation of amines has predominantly been performed with various heterogeneous catalysts at high temperature and pressure.[52] As an example, alkylations of aliphatic amines are catalyzed by Raney-Ni,[53] alumina, silica, and montmorillonite at temperatures >200 °C.[54,55] Industrial processes applying such amination reactions in the presence of heterogeneous catalysts involve the methylation of lower aliphatic amines with methanol.[56]

Although the alkylation of amines with alcohols has frequently been applied, there is no catalytic method available, which can be used for functionalized and sensitive substrates (alcohols and amines) under milder conditions (T<100 °C). In order to stimulate further

(52) Review of *N*-Alkylations before 1992, see: D. M. Roundhill, *Chem. Rev.* **1992**, *92*, 1-27.

(53) a) N. Botta, D. de Angelis, R. Nicoletti, *Synthesis* **1977**, 722-723. b) K. Kindler, D. Matthies, *Chem. Ber.* **1962**, *95*, 1992-1998. c) R. G. Rice, E. J. Kohn, L. W. Daasch, *J. Org. Chem.* **1958**, *23*, 1352-1354. d) R. G. Rice, E. J. Kohn, *J. Am. Chem. Soc.* **1955**, *77*, 4052-4054. e) C. F. Winans, H. Atkins, *J. Am. Chem. Soc.* **1932**, *54*, 306-312.

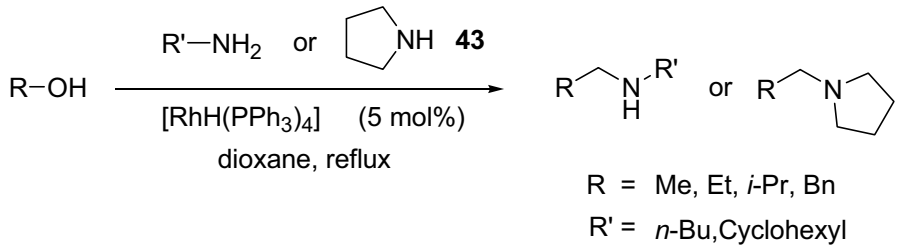
(54) Review of heterogeneous-catalyzed amination reaction, see: a) R. E. Vultier, A. Baiker, A. Wokaun, *Appl. Catal.* **1987**, *30*, 167-176. b) A. Baiker, J. Kijenski, *Catal. Rev.-Sci. Eng.* **1985**, *27*, 653-697. c) A. Baiker, W. Richarz, *Tetrahedron Lett.* **1977**, *22*, 1937-1938.

(55) Review of aniline alkylation over solid acid catalyst, see: A. Narayanan, K. Deshpande, *Appl. Catal. A: General* **2000**, *199*, 1-31.

(56) a) K. Weisermel, H. J. Arpe, "*Industrial Organic Chemistry*" Wiley-Interscience, New York, **2002**. b) M. Bosch, J. Eberhardt, R. Roettger, T. Krug, J.-P. Melder, *PCT Int. Appl.* WO 005123658, **2005**. c) T. Fujita, K. Ogura, K. Niwa, M. Fukatsu, *Eur. Pat. Appl.* EP 763519, **1997**.

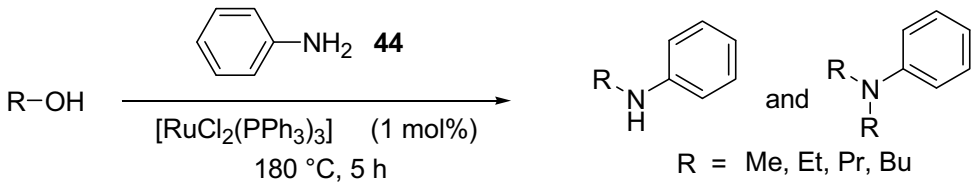
applications of this chemistry, the development of more active catalysts, which allow a broader substrate scope, is highly desired. A strategy to solve this problem might be the switch from heterogeneous to molecularly-defined organometallic catalysts. Here, a variety of transition metal complexes are known to have high activity for the dehydrogenation of alcohols to ketones and the hydrogenation of the resulting imines to amines by transfer hydrogenation, which are the basic requirements for the catalyst system.

The first homogeneous catalysts for *N*-alkylation of amines with alcohols were introduced by *Grigg et al.*[57] and *Watanabe et al.* [58] in 1981. *Grigg* and co-workers described the *N*-alkylation of primary and secondary alkyl amines with primary alcohols such as methanol or ethanol with the rhodium catalyst $[RhH(PPh_3)_4]$ being the most active catalyst (Scheme 28).



Scheme 28: First homogeneous N-alkylation of alkyl amines with alcohols by Grigg

Simultaneously to *Grigg*, *Watanabe* and co-workers reported the ruthenium-catalyzed *N*-alkylation and *N*-heterocyclization of aniline (**44**) using alcohols and aldehydes (Scheme 29). In both reactions, only basic primary alcohols were applied to the reaction.

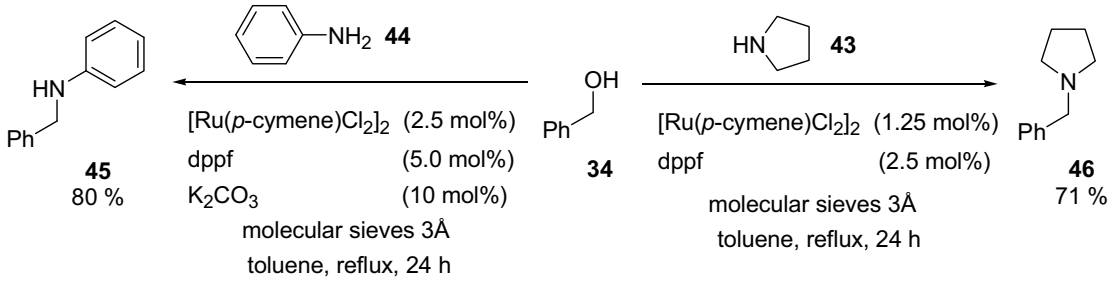


Scheme 29: First homogeneous N-alkylation of aryl amines with alcohols by Watanabe

(57) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *J. Chem. Soc., Chem. Commun.* **1981**, 611-612 (Ru/Ir).

(58) Y. Watanabe, Y. Tsuji, Y. Ohsugi, *Tetrahedron Lett.* **1981**, *22*, 2667-2670 (Ru).

Since these reports, *N*-alkylations forming secondary amines[59,67,72] as well as tertiary amines by reacting secondary amines with alcohols[60,61] or by reacting diols[60,62,68] or aminoalcohols[60] with primary amines have been reported. These reactions provide an access to important pharmaceutical *N*-substituted piperidines, morpholines, and piperazines. Recently, *Williams et al.* have reported a high efficient *in situ* ruthenium catalyst consisting of $[Ru(p\text{-cymene})Cl_2]_2$ and dppf for the *N*-alkylation of amines with primary alcohols. The reaction conditions are relatively mild and applicable to the alkylation of aryl amines[63] as well as cyclic aliphatic amines such as pyrrolidine (**43**)(Scheme 30).[64]



Scheme 30: Ruthenium-catalyzed N-alkylation of amines with primary alcohols by Williams et al.

(59) a) A. Arcelli, B.-T. Khai, G. Porzi, *J. Organomet. Chem.* **1982**, *235*, 93-96 (Ru). b) Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi, T. Ohta, *J. Org. Chem.* **1984**, *49*, 3359-3363 (Ru). c) Y. Tsuji, R. Takeuchi, H. Ogawa, Y. Watanabe, *Chem. Lett.* **1986**, 293-294 (Pt/Sn). d) K.-T. Huh, Y. Tsuji, M. Kobayashi, F. Okuda, Y. Watanabe, *Chem. Lett.* **1988**, 449-452 (Ru). e) Y. Watanabe, Y. Morisaki, T. Kondo, T. Mitsudo, *J. Org. Chem.* **1996**, *61*, 4214-4218 (Ru). f) A. D. Zotto, W. Baratta, M. Sandri, G. Verardo, P. Rigo, *Eur. J. Inorg. Chem.* **2004**, 524-529 (Ru). g) G. Cami-Kobeci, P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535-537 (Ir). h) S. Naskar, M. Bhattacharjee, *Tetrahedron Lett.* **2007**, *48*, 3367-3370 (Ru). i) D. Balcells, A. Nova, E. Clot, D. Gnanamgari, R. H. Crabtree, O. Eisenstein, *Organometallics* **2008**, *27*, 2529-2539 (Ir). j) A. Pontes da Costa, M. Viciano, M. Sanaú, S. Merino, J. Tejeda, E. Peris, B. Royo, *Organometallics* **2008**, *27*, 1305-1309 (Ir). k) B. Blank, M. Madalska, R. Kempe, *Adv. Synth. Catal.* **2008**, *350*, 749-758.

(60) First homogeneous catalyst reported for preparation of tertiary amines from amines and alcohols, see: S.-I. Murahashi, K. Kondo, T. Hakata, *Tetrahedron Lett.* **1982**, *23*, 229-232 (Ru).

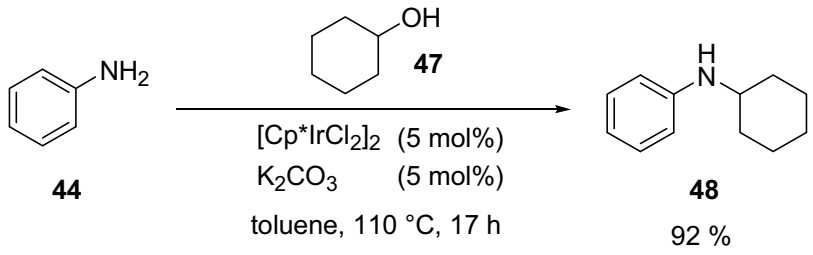
(61) a) G. Bitsi, E. Schleiffer, F. Antoni, G. Jenner, *J. Organomet. Chem.* **1989**, *373*, 343-352 (Ru). b) S. Ganguly, F. L. Joslin, D. M. Roundhill, *Inorg. Chem.* **1989**, *28*, 4562-4564 (Ru). c) S. Ganguly, D. M. Roundhill, *Polyhedron* **1990**, *9*, 2517-2526 (Ru). e) N. Tanaka, M. Hatanka, Y. Watanabe, *Chem. Lett.* **1992**, 575-578 (Ru).

(62) a) Y. Tsuji, K.-T. Huh, Y. Watanabe, *J. Org. Chem.* **1987**, *52*, 1673-1680 (Ru). b) J. A. Marsella, *J. Org. Chem.* **1987**, *52*, 467-468 (Ru). c) G. Jenner, G. Bitsi, *J. Mol. Catal.* **1988**, *45*, 165-168 (Ru). d) R. A. T. M. Abbenhuis, J. Boersma, G. van Koten, *J. Org. Chem.* **1998**, *63*, 4282-4290 (Ru). e) K.-i. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett.* **2004**, *6*, 3525-3528 (Ir). f) L. U. Nordstrøm, R. Madsen, *Chem. Commun.* **2007**, 5034-5036 (Ir).

(63) M. H. S. A. Hamid, J. M. J. Williams, *Chem. Commun.* **2007**, 725-727 (Ru).

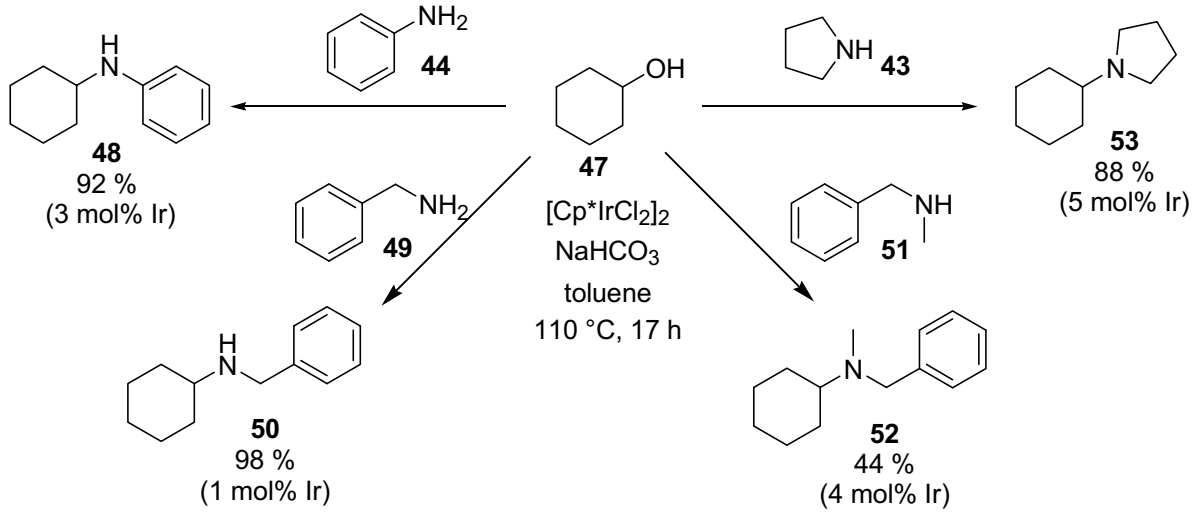
(64) M. H. S. A. Hamid, J. M. J. Williams, *Tetrahedron Lett.* **2007**, *48*, 8263-8265 (Ru).

Unfortunately, in the presence of most known homogeneous catalysts, high reaction temperatures (up to 215 °C) and long reaction times are required to obtain sufficient yields of the alkylated amine, too. Additionally, selectivity problems such as dialkylation and the restricted use of primary alcohols limited these reactions. Thus, with regard to the substrates, mainly primary alcohols were used in the past, because they are more reactive compared to secondary alcohols. Before 2003, no efficient catalyst was known for the *N*-alkylation with secondary alcohols. In 2003, *Fujita et al.* introduced the iridium dimeric catalyst $[Cp^*IrCl_2]_2$ for the *N*-alkylation with primary and secondary alcohols (Scheme 31).[65]



Scheme 31: Iridium-catalyzed N-alkylation with secondary alcohols introduced by Fujita et al.

In the course of these studies, *Fujita et al.* was able to apply this novel catalyst to aryl amines (e.g. **44**), primary alkyl amines (e.g. **49**), secondary alkyl amines (e.g. **51**), and cyclic alkyl amines (e.g. **43**), respectively (Scheme 32).[66]

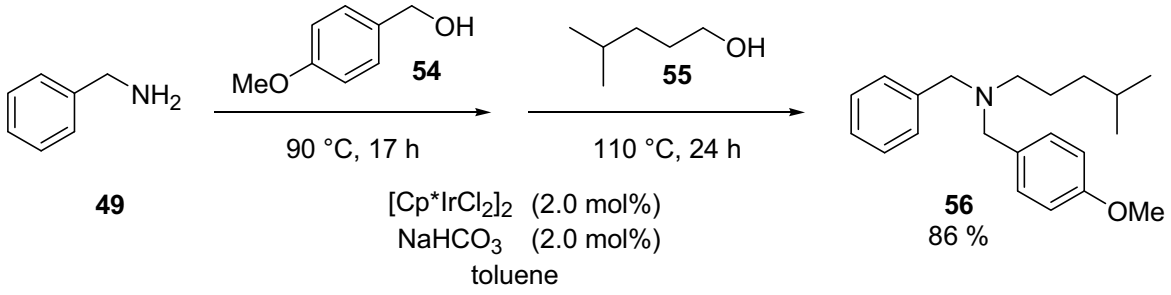


*Scheme 32: Compendium of the [Cp*IrCl2]2-catalyzed N-alkylation introduced by Fujita et al.*

(65) K.-i. Fujita, Z. Li, N. Ozeki, R. Yamaguchi, *Tetrahedron Lett.* **2003**, *44*, 2687-2690 (Ir).

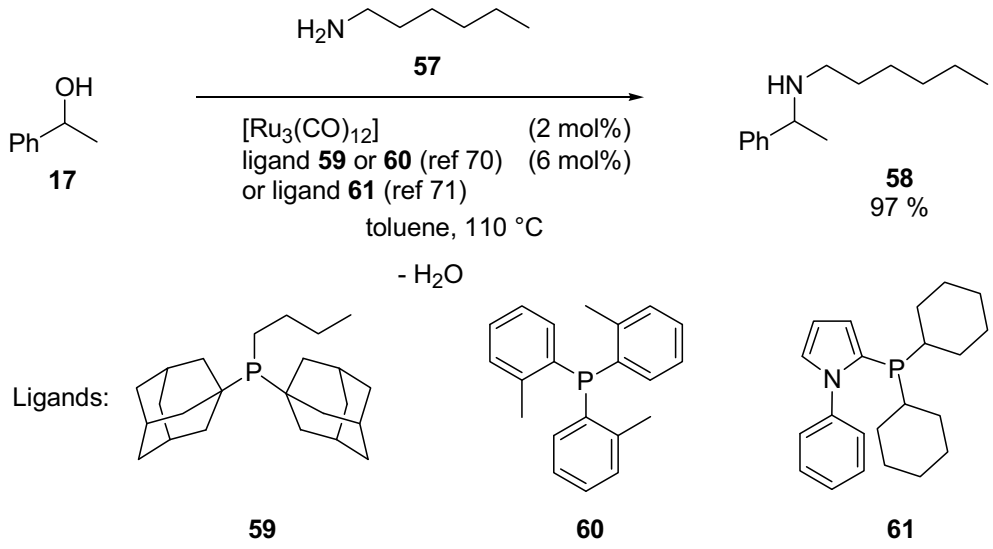
(66) K.-i. Fujita, Y. Enoki, R. Yamaguchi, *Tetrahedron* **2008**, *64,* 560-571.

Furthermore, *Fujita et al.* described an one-pot sequential *N*-alkylation of benzylamine (Scheme 33). The sequential addition of two different alcohols to the reaction system, lead up to the selective formation of tertiary amines, having three different substituents.



Scheme 33: $[Cp^*IrCl_2]_2$-catalyzed one-pot sequential N-alkylation leading to tertiary amines

Moreover, this catalyst was applied in *N*-heterocyclization,[62,67,68,69] and transfer hydrogenation.[70] The first ruthenium-catalyzed *N*-alkylation of primary amines with secondary alcohols was reported by our group in 2005 (Scheme 34).[71] In the presence of the *in situ* ruthenium catalysts $[Ru_3(CO)_{12}]$/tri-*o*-tolylphosphine (ligand **59**) or *n*-butyl-di-1-adamantyl-



Scheme 34: Ruthenium-catalyzed N-Alkylation of primary amines with secondary alcohols by Beller et al.

(67) K.-i. Fujita, K. Yamamoto, R. Yamaguchi, *Org. Lett.* **2002**, *4*, 2691-2964.

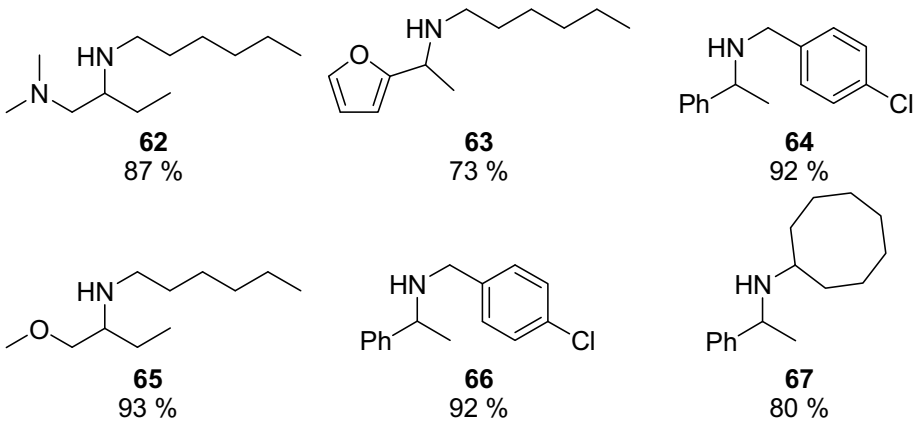
(68) K.-i. Fujita, Y. Enoki, R. Yamaguchi, in "*Organic Syntheses*", Wiley and Sons, New Jersey, **2006**, Vol. 83, pp. 217-221.

(69) C. T. Eary, D. Clausen, *Tetrahedron Lett.* **2006**, *47*, 6899-6902.

(70) For review of $[Cp^*IrCl_2]_2$ -catalyzed reactions, see: a) K.-i. Fujita, R. Yamaguchi, *Synlett* **2005**, 560-571.

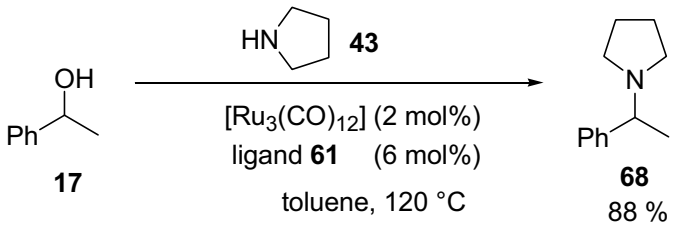
(71) A. Tillack, D. Hollmann, D. Michalik, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8881-8885.

phosphine (ligand **60**) (both first generation catalysts)[71] and the combination of $Ru_3(CO)_{12}$ and *N*-phenyl-2-(dicyclohexylphoshino)pyrrole (ligand **61**, cataCXium®PCy, second generation catalyst)[72] showed highest activity and selectivity. The alkylation reactions were performed under significantly milder conditions compared to most known amination reactions of alcohols. The catalyst systems showed their general applicability in the reaction of a variety of functionalized alcohols and amines, to give the corresponding secondary amines in high to excellent yields. A selection is displayed in Scheme 35.



Scheme 35: Selection of products in the ruthenium-catalyzed N-alkylation with secondary alcohols

Furthermore, different achiral but also chiral monodentate as well as bidentate ligands were tested to optimize and lower the reaction conditions.[73] Monodentate amine ligands showed no influence on the reactivity. Compared to these ligands, a strong dependency on the basicity of phosphine ligands was observed. Bidentate ligands showed a strong decrease of the reactivity. However, with all chiral ligands (e.g. TsDPEN, BINAP) tested, only racemic product mixtures were determined.



Scheme 36: Ruthenium-catalyzed N-alkylation of secondary amines with secondary alcohols by Beller et al.

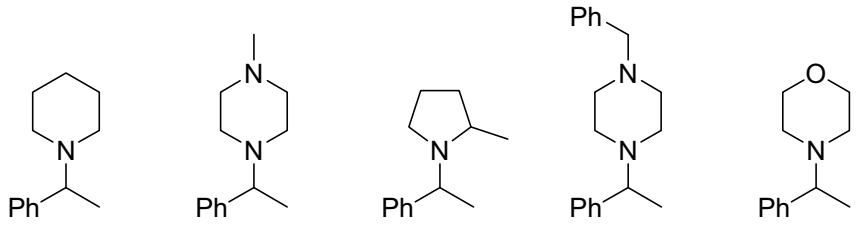
Furthermore, applying the same procedure secondary amines can be converted to the corresponding tertiary amines in high yield (Scheme 36).[74] In the presence of the *in situ*

(72) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chem. Asian J.* **2007**, *3*, 403-410.

(73) D. Hollmann, unpublished results.

(74) A. Tillack, D. Hollmann, K. Mevius, D. Michalik, S. Bähn, M. Beller, *Eur. J. Org. Chem.* **2008**, 4745-4750.

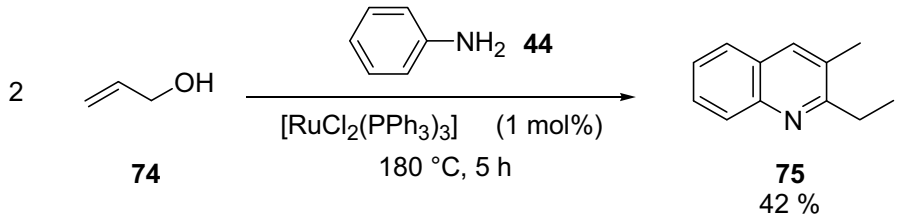
generated ruthenium catalyst of $Ru_3(CO)_{12}$ and *N*-phenyl-2-(dicyclohexylphoshino)pyrrole (ligand **61**, cataCXium®PCy, second generation catalyst), selective amination takes place in high yield and selectivity with cyclic amines such as piperidine, pyrrolidine (**43**), and piperazine. The reaction is atom efficient leaving only water as side product and can conveniently be carried out without additional pressure. A selection of substrates is given in Scheme 37.



Scheme 37: Selection of products in the ruthenium-catalyzed N-alkylation of secondary amines

2.3.7. *N*-Heterocyclization

Alcohols and thus the intermediate aldehydes can be used for the *N*-heterocyclization to alkaloids such as indoles (**28**) or quinolines. These *N*-heterocyclic compounds have attracted considerable attention going to their functionality in pharmaceutical chemistry, material chemistry, synthetic organic chemistry, and dyes. The first *N*-heterocyclization was described by *Watanabe* in 1981. Simultaneously with the *N*-alkylation of aniline (**44**), *Watanabe* described the synthesis of 2,3-alkylquinolines starting from 2,3-unsaturated alcohols such as allylalcohol (**74**) and crotylalcohol (Scheme 38).[58,75]



Scheme 38: Synthesis of quinolines using 2,3-unsaturated alcohols by Watanabe

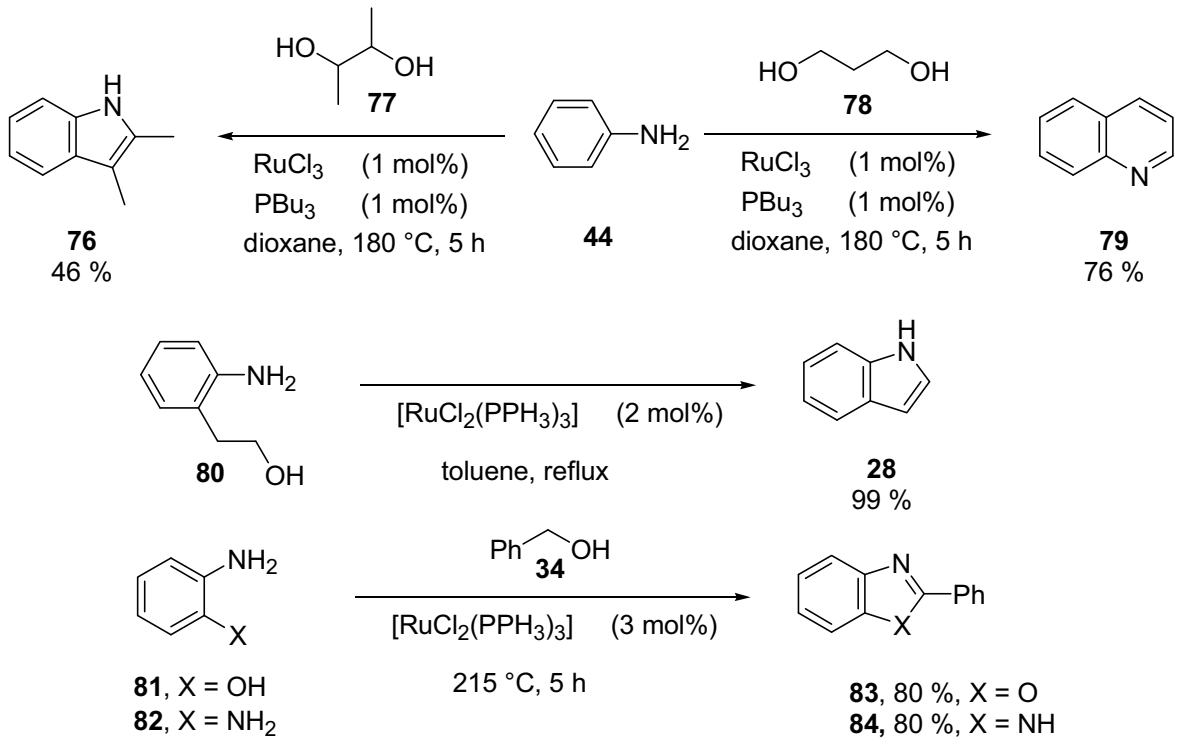
Modifying this methodology, *Watanabe* reported the synthesis of indoles (e.g. **76**) as well as quinolines such as **79** by reaction of dioles with aniline (**44**)[76] or cyclization of 2-aminophenethylalcohol (**80**) to indoles (**28**)[77] as well as the synthesis of benzoxazoles (e.g. **83**)

(75) Y. Watanabe, Y. Tsuji, Y. Ohsugi, J. Shida, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2452-2457.

(76) Y. Tsuji, K.-T. Huh, Y. Watanabe, *J. Org. Chem.* **1987**, *52*, 1673-1680.

(77) Y. Tsuji, S. Kotachi, K.-T. Huh, Y. Watanabe, *J. Org. Chem.* **1990**, *55*, 580-584.

and benzimidazoles (e.g. **84**) from aniline derivatives and primary alcohols,[78] the synthesis of 1,3-disubstituted 2,3-dihydroimidazol-2-ones (e.g. **87**) from *N*,*N*'-disubstituted ureas (e.g. **86**),[79] and finally imidazol[1,2-a]pyridines (e.g. **89**) starting from aminopyridines (e.g. **88**) and dioles (e.g. **77**).[80] An overview of these reactions is shown in Scheme 39 and Scheme 40.

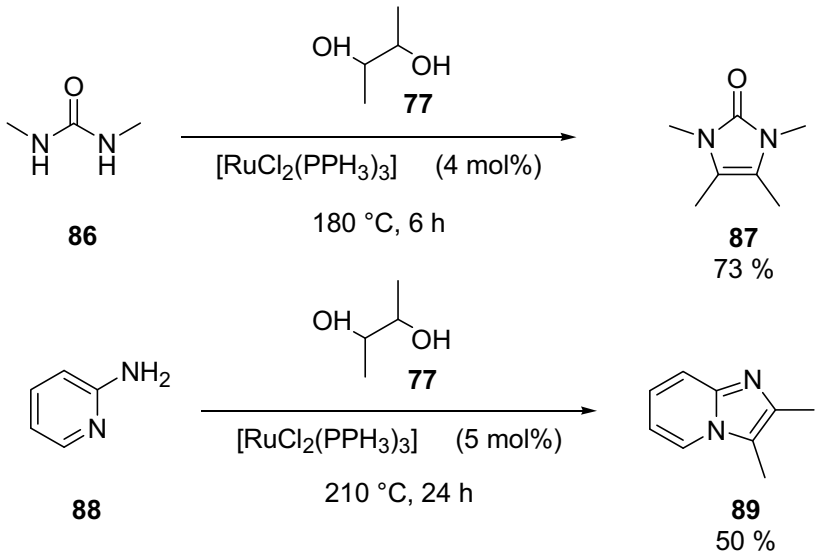


Scheme 39: Synthesis of indoles, quinolines, benzoxazoles, and benzimidazoles introduced by Watanabe und co-workers

(78) T. Kondo, S. Yang, K.-T. Huh, M. Kobayashi, S. Kotachi, Y. Watanabe, *Chem. Lett.* **1991**, 1275-1278.

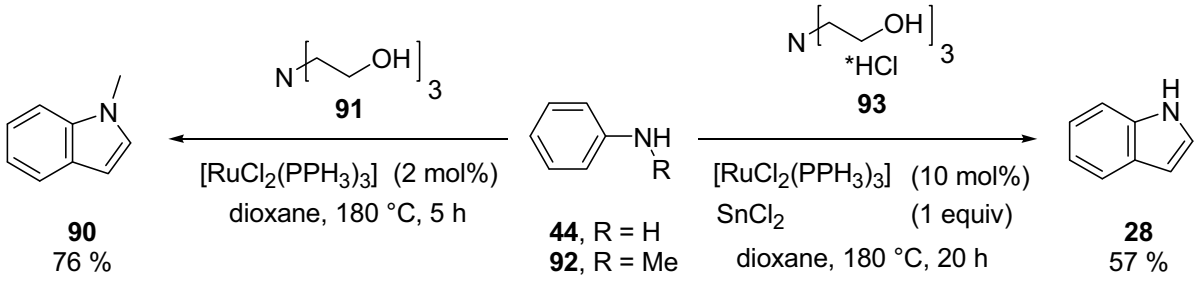
(79) T. Kondo, S. Kotachi, Y. Watanabe, *J. Chem. Soc., Chem. Commun.* **1992**, 1318-1319.

(80) T. Kondo, S. Kotachi, S.-I. Ogina, Y. Watanabe, *Chem. Lett.* **1993**, 1317-1320.



Scheme 40: Synthesis of 1,3-disubstituted 2,3-dihydroimidazol-2-ones and imidazol[1,2-a]pyridines introduced by Watanabe and co-workers

Based on this excellent research, *Cho* and co-workers reported the ruthenium-catalyzed cyclization of aniline (**44**) with trialkanolamines[81] and trialkanolammonium chlorides[82] to indoles (e.g. **90** and **28**) (Scheme 41) and allylammonium chlorides to quinolines (see chapter 2.4.2).



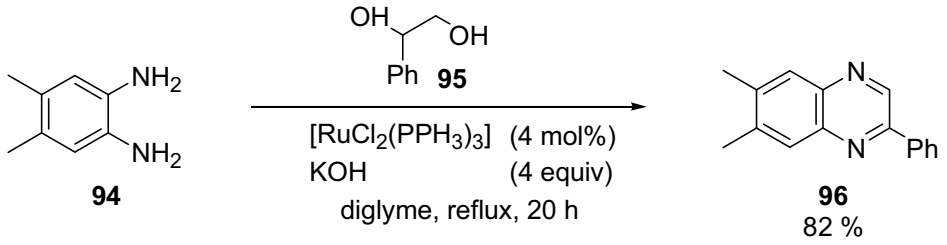
Scheme 41: Synthesis of indoles using trialkanolamines and trialkanolammonium chlorides

Furthermore, *Cho* was able to introduce a new method for the synthesis of quinoxalines (e.g. **96**) using *o*-phenylenediamines such as (**94**) and vicinals diols such as (**95**) (Scheme 42).[83] Unfortunately, four equivalents of KOH as base and promoter and high temperature are necessary for the reaction which makes this reaction unattractive.

(81) a) D. Y. Lee, C. S. Cho, J. H. Kim, Y. Z. Youn, S. C. Shim, H. Song, *Bull. Korean Chem. Soc.* **1996**, *17*, 1132-1135. b) C. S. Cho, H. K. Lim, S. C. Shim, T. J. Kim, H.-J. Choin, *Chem. Commun.* **1998**, 995-996. c) C. S. Cho, B. H. Oh, S. C. Shim, *J. Heterocycl. Chem.* **1999**, *36*, 1175-1178. d) C. S. Cho, D. T. Kim, T.-J. Kim, S. C. Shim, *Bull. Korean Chem. Soc.* **2003**, *24*, 1026-1028.

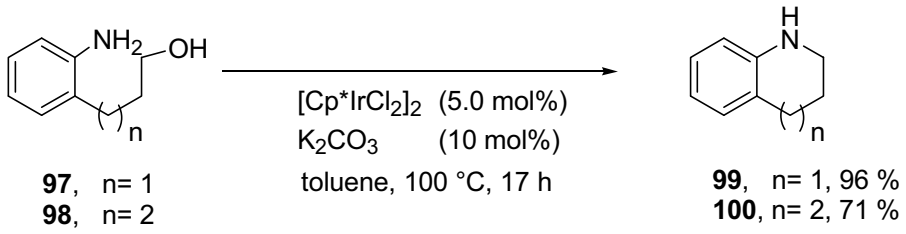
(82) a) C. S. Cho, J. H. Kim, S. C. Shim, *Tetrahedron Lett.* **2000**, *41*, 1811-1814. b) C. S. Cho, J. H. Kim, T.-J. Kim, S. C. Shim, *Tetrahedron* **2001**, *57*, 3321-3329.

(83) a) C. S. Cho, S. G. Oh, *Tetrahedron Lett.* **2006**, *47*, 5633-5636.

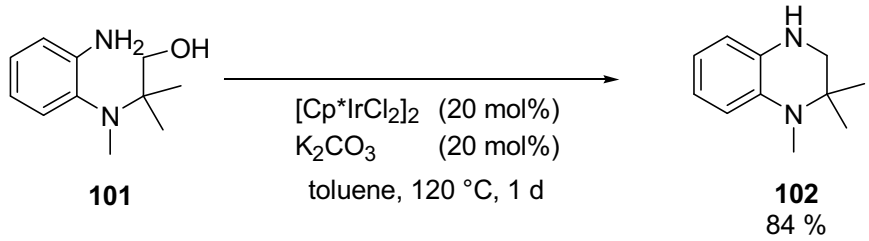


Scheme 42: Synthesis of quinoxalines using o-phenylendiamines and diols

In 2002, *Fujita et al.* described the iridium-catalyzed cyclization of 2-aminophenethyl alcohols to indoles.[67] Using $[Cp^*IrCl_2]_2$, a high variety of indoles were synthesized. No indoline products were observed. With longer alkyl groups (C_3-C_4) between the aromatic ring system and the alcohol functionality, *Fujita* did not observe oxidative products such as quinoline or dihydroquinoline, surprisingly the 1,2,3,4-tetrahydroquinoline (**99**) and 2,3,4,5-tetrahydro-1-benzazepine (**100**) were determined in moderate to high yields (Scheme 43). Thus, hydrogen transfers proceed during the reaction.



Scheme 43: $[Cp^*IrCl_2]_2$-catalyzed synthesis of 1,2,3,4-tetrahydroquinoline and 2,3,4,5-tetrahydro-1-benzazepines

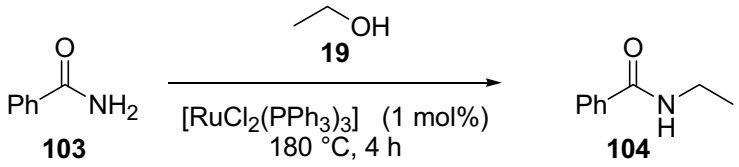


Scheme 44: $[Cp^*IrCl_2]_2$-catalyzed synthesis of 1,2,3,4-tetrahydroquinoxalines

Adapted from *Fujita*, *Eary* and *Clausen* recently reported a procedure for the synthesis of 1,2,3,4-tetrahydroquinoxalines (e.g. **102**) and 2,3,4,5-tetra-1-*H*-benzo[b][1,4]diazepines (Scheme 44).[69] Compared to *Fujita*, higher catalyst loading of 20 mol% $[Cp^*IrCl_2]_2$ as well as longer reaction times (2-5 d) are reported. Furthermore, *Madsen et al.* described the synthesis of piperazine with diols using the same iridium complex.[62f]

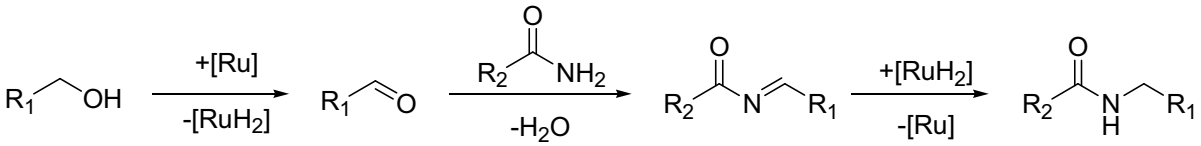
2.3.8. *N*-Alkylation of Amides using Alcohols

N-Alkylation is important for selective synthesis of amines but also of amides. Thus, various methods have been developed using conventional alkylating reagents such as alkyl halides. On the other hand alcohols as the alkylation reagents were reported (see chapter 2.3.6). In 1983, Watanabe described the first ruthenium-catalyzed *N*-alkylation of amides using alcohols (Scheme 45).[84] Different alkyl-, benz-, and acetamides were achieved in high yields with alcohols. Nevertheless, only primary alcohols were converted.



Scheme 45: N-Alkylation of amides

The reaction pathway proceeds through an oxidation of alcohol to an aldehyde catalyzed by a ruthenium complex. Next, the aldehyde can react with amides to give *N*-acylamino alcohols, which undergo dehydration. The dehydrated product is hydrogenated by the ruthenium hydride to give the corresponding alkylated amides.



Scheme 46: Mechanism of the N-alkylation of amides

(84) Y. Watanabe, T. Ohta, Y. Tsuji, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2647-2651.

2.4. Activation of C-N Bonds

Imines play an important role as intermediates including reductions, additions, condensations, or cycloadditions. Typically, imines are prepared by condensation between aldehydes or ketones with amines. However, the very electrophilic nature of the aldimine/ketimine can cause problems during workup and purification. Hydrolysis often occurrs. Beside these problems, the aldehydes and ketones used are very reactive intermediates, so substrates often have to be protected by multistep synthesis. Therefore, it would be of interest to generate imines from a more stable precursor.

As describe above in the amination of alcohols (see chapter 2.3.6), imines can be prepared by *in situ* oxidation of alcohols followed by condensation with amines. Beside alcohol substrates, alkyl amines constitute very attractive alkyl as well as hydrogen sources. Compared to alcohols, amines can directly be oxidized to the corresponding imines by abstracting hydrogen.[85] Thus, amines are excellent starting material for the transformations using the *Borrowing Hydrogen* methodology. Although this transformation - alkylation of amines with amines - seems to be unusual at first sight, there is significant industrial interest in analogous transalkylations.[86]

Due to the challenging oxidation of amines to imines by a transition metal catalyst, only a few reactions involving hydrogen transfer reactions such as transfer hydrogenation of amines[87] or racemization of amines[88] are known. Latest research of our group point out that alkyl amines

(85) For oxidation of amines, see: S.-I. Murahashi, *Angew. Chem. Int. Ed.* **1995**, *34*, 2443-2465; *Angew. Chem.* **1995**, *107*, 2670-2693.

(86) a) T. Gerlach, H. Evers, J.-P. Melder (BASF Aktiengesellschaft, Germany) WO 2007036499, **2007**. b) J.-P. Melder, T. Krug (BASF Aktiengesellschaft, Germany), WO 2006082203, WO 2006082202, **2006**. c) H. Evers, J.-P. Melder, C. Benisch, M. Frauenkron, T. Gerlach, A. Alba Perez, J. Nouwen (BASF Aktiengesellschaft, Germany), WO 2005061430, **2005**. d) M. Frauenkron, T. Krug, H. Evers, J.-P. Melder, R. Roettger, M. Siegert, T. Gerlach, J. Nouwen, E. Dahlhoff, C. Miller (BASF Aktiengesellschaft, Germany), WO 2005012223, **2005**. e) X. Qiao, J. Zhang, M. Cui, J. Tang (Nanjing University of Technology, Peop. Rep. China), CN 1629132, **2005**. f) S. Oikawa, H. Ando (Sumitomo Chemical Co., Ltd., Japan), JP 2003171353, **2003**.

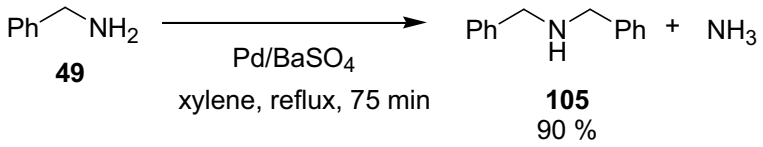
(87) a) J. S. M. Samec, A. H. Éll, J.-E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327-2337. b) J. S. M. Samec, A. H. Éll, J.-E. Bäckvall, *Chem. Commun.* **2004**, 2748-2749. b) A. H. Éll, J. B. Johnson, J.-E. Bäckvall, *Chem. Commun.* **2003**, 1652-1653. d) A. H. Éll, J. S. M. Samec, C. Brasse, J.-E. Bäckvall, *Chem. Commun.* **2002**, 1144-1145.

(88) O. Pamies, A. H. Éll, J. S. M. Samec, N. Hermanns, J.-E. Bäckvall, *Tetrahedron Lett.* **2002**, *43*, 4699-4702.

can be used in the *Borrowing Hydrogen* methodology with different nucleophiles. These results are reviewed in the following.

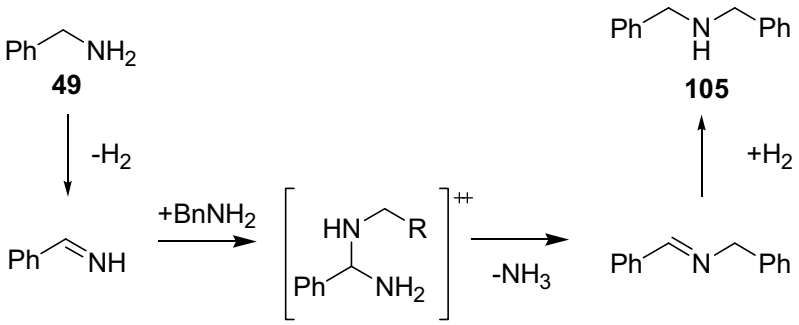
2.4.1. Condensation of Amines[VIII]

The condensation of amines is a well known reaction. The first condensation of primary amines to secondary amines was reported by *Rosenmund* and *Jordan* in 1925 using a heterogeneous Pd catalyst.[89] This reaction is displayed in Scheme 47, with benzylamine (**49**) as example.



Scheme 47: Condensation to symmetrical amines by Rosenmund and Jordan

In addition to *Rosenmund* and *Jordan*, different heterogeneous catalysts are described.[90] The reaction mechanism proceeds by dehydration of an amine to the corresponding imine, which can be attacked by a nuclephile, e.g. a second amine, to form an aminal as intermediate. After elimination of ammonia and hydrogenation, the desired secondary amine can be produced (Scheme 48).



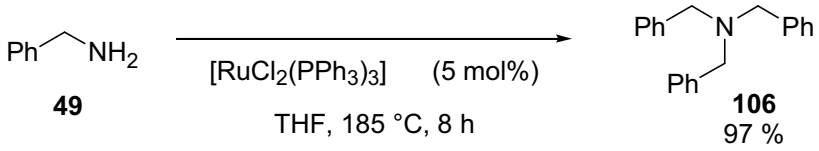
Scheme 48: Mechanism of the condensation of amines

(89) K. W. Rosenmund, G. Jordan, *Ber. Dtsch. Chem. Ges.* **1925**, *58*, 51-53 (Pd).

(90) a) K. Kindler, *Liebigs Ann. Chem.* **1931**, *485*, 113-126 (Pd). b) C. F. Winans, H. Atkins, *J. Am. Chem. Soc.* **1932**, *54*, 306-312 (Ni). c) E. T. Borrows, B. M. C. Hargreaves, J. E. Page, J. C. L. Resuggan, F. A. Robinson, *J. Chem. Soc., Chem. Commun.* **1947**, 197-202. d) K. Kindler, G. Melamed, D. Matthies, *Liebigs Ann. Chem.* **1961**, *644*, 23-30 (Raney-Ni). e) N. Yoshimura, I. Moritani, T. Shimamura, S.-I. Murahashi, *J. Am. Chem. Soc.* **1973**, *94*, 3038-3039 (Pd). f) F. de Angelis, I. Grhurina, R. Nicoletti, *Synthesis* **1979**, 70-71 (Raney-Ni).

Recently, *Miyazawa* has employed the Pt/C catalyst for the synthesis of secondary amines using microwave irradiation.[91] The reactions were performed in water as solvent. Unfortunately, the reaction mechanism involved hydrolysis of the imine with water to a ketone. Thus, tertiary amines can easily be generated, which is shown in a lower selectivity.

The first homogeneous catalyst was reported by *Porzi et al.*.[92] The ruthenium catalyst $[RuCl_2(PPh_3)_3]$ converted primary amines to the symmetrical tertiary amines (**106**). High temperature of 185 °C was deployed. With short chains or benzylamines (**49**), high yields were observed. Moreover, with steric hindered amines (dodecylamine or cyclohexylamine) a mixture of secondary and tertiary amines was determined.



Scheme 49: First homogeneous catalyzed condensation of amines

Further catalysts were developed by *Garrou et al.*[93] and *Watanabe et al.*,[94] but showed no enhancements of the reaction conditions. Between tertiary amines alkyl exchanges were often observed. Heterogeneous[95] as well as homogeneous[96] catalysts are known.

If cyclic secondary amines are used, trimerisation can occur.[97] However, previous catalysts included only heterogeneous palladium or silicates catalysts. Our group has recently found that

(91) A. Miyazawa, K. Saitou, K. Tanaka, T. M. Gädda, M. Tashiro, G. K. S. Prakash, G. L. Olah, *Tetrahedron Lett.* **2006**, *47*, 1437- 1439 (Pt/C).

(92) a) B.-T. Khai, C. Concilio, G. Porzi, *J. Organomet. Chem.* **1981**, *208*, 249-251. b) B.-T. Khai, C. Concilio, G. Porzi, *J. Org. Chem.* **1981**, *46*, 1759-1760. c) A. Arcelli, B.-T. Khai, G. Porzi, *J. Organomet. Chem.* **1982**, *231*, C31-C34.

(93) C. W. Jung, J. D. Fellmann, P. E. Garrou, *Organometallics* **1983**, *2*, 1042-1044.

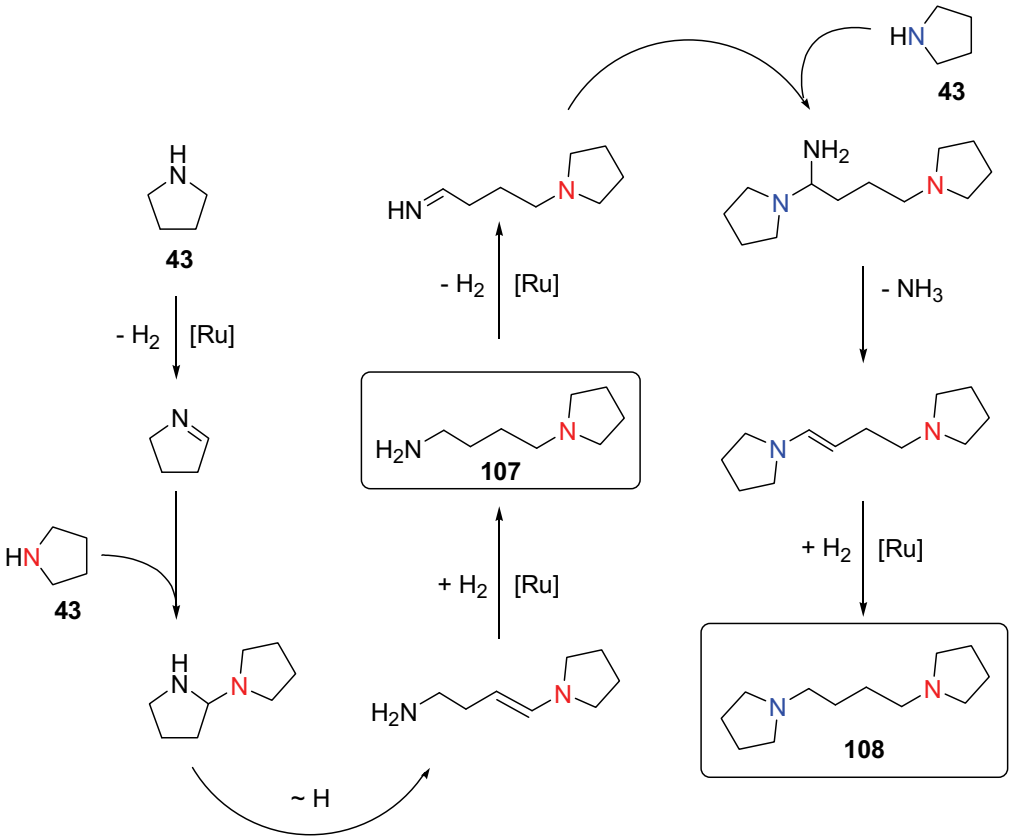
(94) Y. Tsuji, J. Shida, R. Takeuchi, Y. Watanabe, *Chem. Lett.* **1984**, 889-890.

(95) a) S.-I. Murahashi, T. Hirano, T. Yano, *J. Am. Chem. Soc.* **1978**, *100*, 348-350. b) R. M. Laine, D. W. Thomas, L. W. Cary, *J. Am. Chem. Soc.* **1982**, *104*, 1763-1765. c) S.-I. Murahashi, N. Yoshimura, T. Tsumiyama, T. Kojima, *J. Am. Chem. Soc.* **1983**, *105*, 5002-5011.

(96) a) Y. Shvo, R. M. Laine, *J. Chem. Soc., Chem. Commun.* **1980**, 753-754. b) Y. Shvo, D. W. Thomas, R. M. Laine, *J. Am. Chem. Soc.* **1981**, *103*, 2461-2463. c) R. D. Adams, H.-S. Kim, S. Wang, *J. Am. Chem. Soc.* **1985**, *107*, 6107-6108. d) R. B. Wilson, R. M. Laine, *J. Am. Chem. Soc.* **1985**, *107*, 361-369. e) Y. Shvo, M. Abed, Y. Blum, R. M. Laine, *Isr. J. Chem.* **1986**, *27*, 267-275.

(97) N. Yoshimura, I. Moritani, T. Shimamura, S.-I. Murahashi, *J. Chem. Soc., Chem. Commun.* **1973**, 307-308. b) J. A. Ballantine, H. Purnell, M. Rayanakorn, J. M. Thomas, K. J. Williams, *J. Chem. Soc., Chem. Commun.* **1981**, 9-10.

the homogeneous *Shvo* catalyst **2** is highly active for the dehydrogenation of cyclic aliphatic amines and for the hydrogenation of the corresponding imines or enamines under comparably mild conditions (100-150 °C).[98] Pyrrolidine was completely converted at 150 °C to the trimer **108**. Lowering the temperature results in the formation of dimeric intermediates. Kinetic observations support a mechanism involving **107** as an intermediate and **108** as the thermodynamically stable final product.



Scheme 50: Mechanism of the trimerization of pyrrolidine

As illustrated in Scheme 50, the first step is the dehydrogenation of pyrrolidine (**43**) to 1-pyrroline followed by a nucleophilic attack of a second pyrrolidine molecule. The second step is the ring opening (C–N cleavage) along with hydrogen shift resulting in the formation of enamine, which is hydrogenated to **107**. Due to the higher reactivity of primary amines in dehydrogenation compared to secondary amines, the primary amine group of **107** will preferably

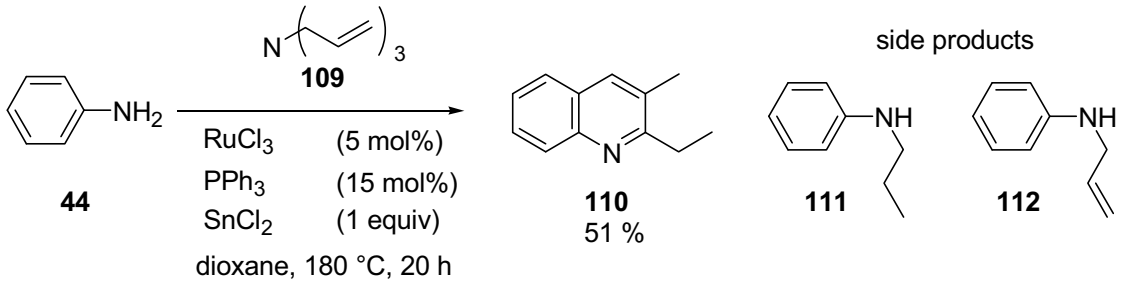
(98) D. Hollmann, R. Parton, R. Altink, A. Tillack, S. Bähn, A. Spannenberg, H. Jiao, M. Beller, *Organometallics* **2008**, submitted for publication.

be dehydrogenated. After an intermolecular attack of a third pyrrolidine molecule, loss of ammonia and hydrogenation of the corresponding enamine, **108** could be formed.

In addition to the ring opening of secondary cyclic amines by condensation, the ring opening was observed with benzeneselenolates to obtain aminoselenides, which was reported by Murahashi and Yano.[99]

2.4.2. Alkylation of Aryl amines with Noncyclic Aliphatic Amines[IV,V,IX]

Based on the formation of indoles (**28**) from aniline (**44**) and trialkanolamines (see chapter 2.3.7.),[81,100] *Shim* and co-workers were encouraged to study the reaction of aniline (**44**) by alkyl transfer reaction with triallylamine (**109**)[101] and allylammonium chlorides[102] to obtain quinolines (**112**) (Scheme 51). During these reactions, *N*-propylaniline (**111**) and *N*-allylaniline (**112**) were obtained as side products in 21 % yield. The formation of monoalkylated aryl amines was proposed by an amine exchange reaction between aniline (**44**) and triallylamine (**109**). The addition of one equivalent of tin(II)chloride was essential for effective heteroannulation. Instead of the trialkyl amines, allylammonium chlorides and 1-hexene as hydrogen acceptor can be used for the formation of quinolines.[103]



Scheme 51: Formation of quinolines with triallylamine

Using this information, *Cho* introduced the selective *N*-monoalkylation of anilines (**44**) with tetraalkylammonium halides (Scheme 52).[104] The *in situ* ruthenium catalyst consisting of $RuCl_3$ and PPh_3 as well as the ruthenium carbonyl catalyst $[Ru_3(CO)_{12}]$ showed reactivity in the

(99) S.-I. Murahashi, T. Yano, *J. Am. Chem. Soc.* **1980**, *102*, 2456-2458.

(100) C. S. Cho, H. K. Lim, S. C. Shim, T.-J. Kim, H.-J. Choi, *Chem. Commun.* **1998**, 995-996.

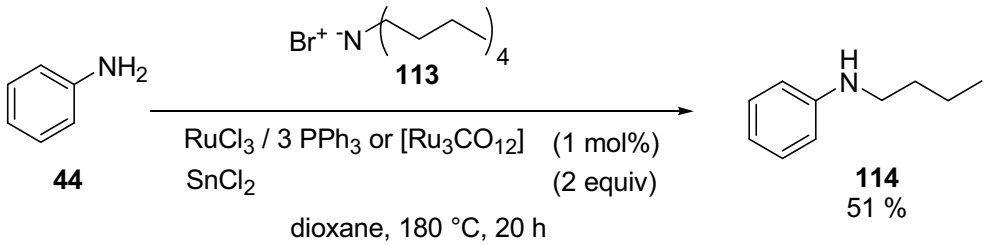
(101) a) C. S. Cho, B. H. Oh, S. C. Shim, *Tetrahedron Lett.* **1999**, *40*, 1499-1500. b) C. S. Cho, T. L. Kim, N. T. Kim, T.-J. Kim, S. C. Shim, *J. Organomet. Chem.* **2002**, *650*, 65-68.

(102) C. S. Cho, J. S. Kim, B. H. Oh, T.-J. Kim, S. C. Shim, N. S. Yoon,*Tetrahedron* **2000**, *56*, 7747-7750.

(103) a) C. S. Cho, B. H. Oh, J. S. Kim, T.-J. Kim, S. C. Shim, *Chem. Commun.* **2000**, 1885-1886. b) C. S. Cho, T. K. Kim, H.-J. Choi, T.-J. Kim, S. C. Shim, *Bull. Korean Chem. Soc.* **2002**, *23*, 541-542.

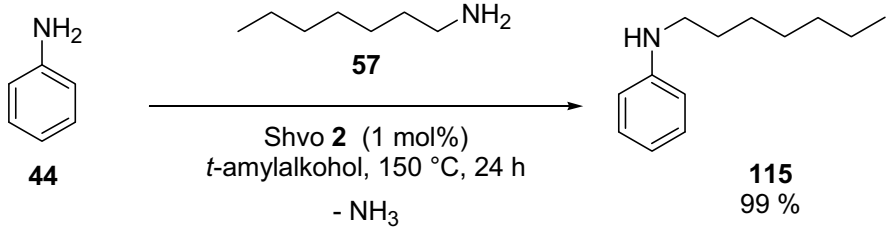
(104) C. S. Cho, J. S. Lim, H. S. Kim, T.-J. Kim, S. C. Shim, *Synth. Commun.* **2001**, *31*, 3791-3797.

amination reaction. The addition of tin(II)chloride was found to be increasing the selectivity of monoalkylated product. But unfortunately, by adding tin(II)chloride, the reactivity decreased. Only a small variation of aniline derivatives or tetraalkylammonium halides was converted in moderate yields.



Scheme 52: N-Monoalkylation of aniline with tetraalkylammonium halides

Recently, we have described the first arylation of primary aliphatic amines with anilines leaving ammonia as the only side product (Scheme 53).[105] In the presence of **2**, a variety of functionalized anilines and primary amines react smoothly to give the corresponding aryl amines in excellent yields.



Scheme 53: N-Alkylation of aryl amines using the Shvo catalyst

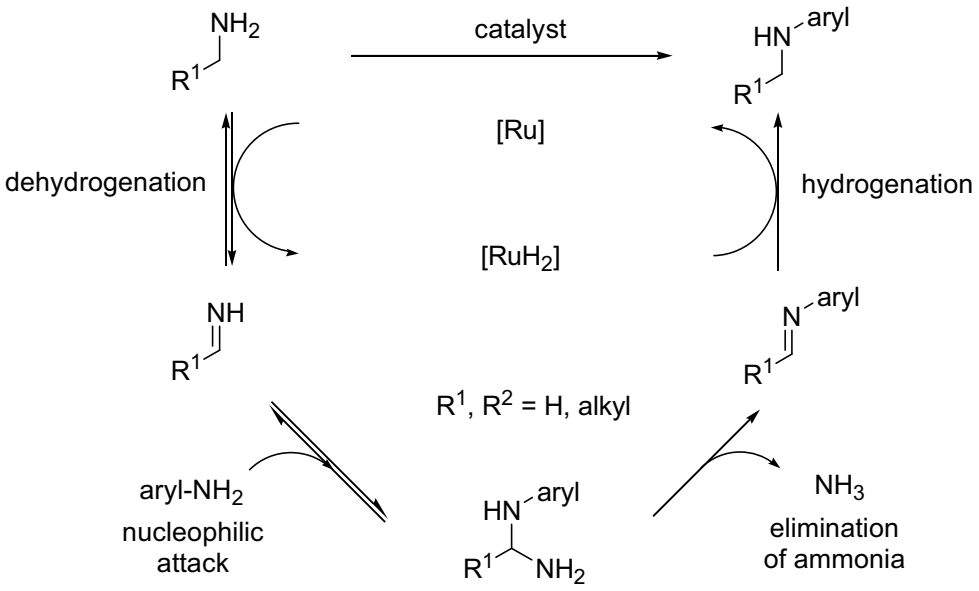
Furthermore, we were able to combine the selective synthesis of monoalkylated aniline derivates with the dealkylation of aliphatic amines. It was shown that starting from primary, secondary, and tertiary amines, a complete and selective transfer of all alkyl groups takes place highly selective. [106]

In analogy to the amination of alcohols, the reaction occurs through a *Borrowing Hydrogen* mechanism (Scheme 54). Initially, ruthenium-catalyzed dehydrogenation of the alkyl amine occurs via coordination and β-hydride elimination. Then, nucleophilic attack of the aryl amine on the resulting imine and elimination of ammonia yields the corresponding secondary imine. Subsequent catalytic hydrogenation leads to the alkylated aryl amine.

(105) D. Hollmann, S. Bähn, A. Tillack, M. Beller, *Angew. Chem. Int. Ed.* **2007**, *46*, 8291-8294; *Angew. Chem.* **2007**, *119*, 8440-8444.

(106) D. Hollmann, S. Bähn, A. Tillack, M. Beller, *Chem. Commun.* **2008**, 3199-3201.

In the first step, dehydrogenation of the alkyl amine occurs. After nucleophilic attack of the aniline (**44**) and elimination of ammonia, the corresponding secondary imine is hydrogenated to the alkylated aniline. The reaction was confirmed by using ^{15}N-labeled aniline- and dibenzylamine. The resulting *N*-benzylaniline is obtained in 96 % isolated yield and showed >99 % of ^{15}N-labelling.[106]

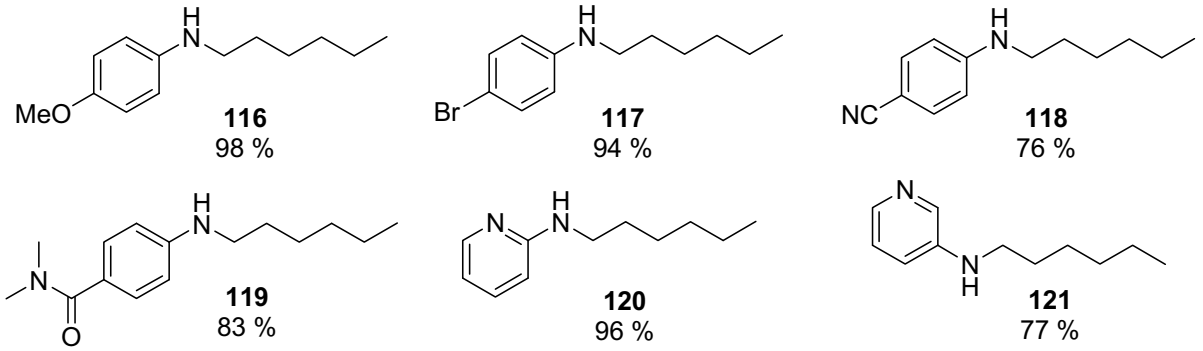


Scheme 54: Mechanism of the arylation of aliphatic amines

Noteworthy, in these alkyl transfer reactions, the hydrogen donors for the final hydrogenation step are the primary, secondary, and tertiary amines. Hence, no additional hydrogen or hydrogen transfer reagents are required during the process. Advantageously, there is no need for high pressure equipment, which is often used in hydrogenation reactions such as reductive amination.

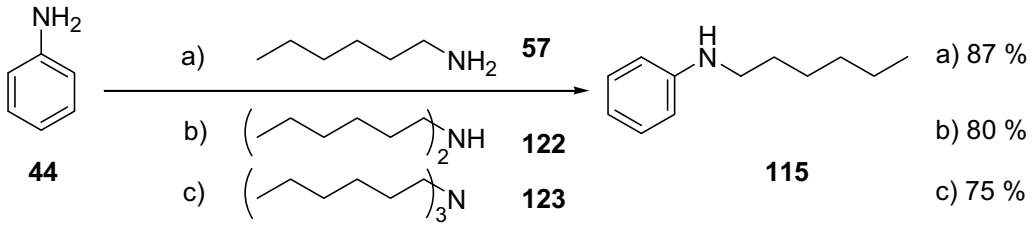
No additives such as acids, bases or ligands are necessary, which makes this reaction economically attractive. High tolerance towards solvents was determined, unpolar but also protic polar solvents are tolerated.

In order to demonstrate the general applicability of **2** for this reaction and the scope of the process, various aryl amines and alkyl amines were investigated. In general, catalytic experiments were done with 1 mol% of the *Shvo* catalyst (**2**) in the presence of two equivalents of aryl amine in *t*-amylalcohol at 150 °C. The *Shvo* catalyst (**2**) shows a high tolerance towards functional groups. Ether- **116**, halogen- **117**, nitril- **118**, and amide **119** functional groups are tolerated and thus the corresponding anilines and aliphatic amines react smoothly to give the corresponding aryl amines in excellent yields. It is important to emphasize that halogenated anilines and heterocyclic amino pyridine derivates **120** and **121** can easily be synthesized.



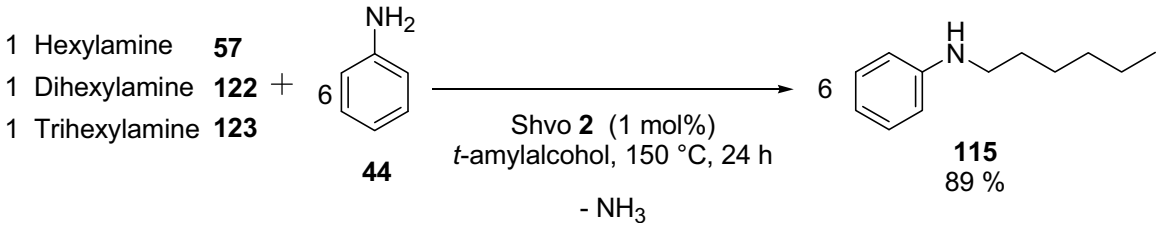
Scheme 55: Selection of products in the ruthenium-catalyzed N-alkylation with alkyl amines

As mentioned before, primary, secondary as well as tertiary amines can be used for alkylation. This is shown in the application of the amination of aniline (**44**) with *n*-hexylamine (**57**), di-*n*-hexylamine (**122**), and tri-*n*-hexylamine (**123**). All different hexylamines are converted in high yields (75-87 %) to the same *N*-hexylaniline (**115**) (Scheme 56).



Scheme 56: Amination of aniline with different alkyl amines (isolated yields are based on hexyl groups)

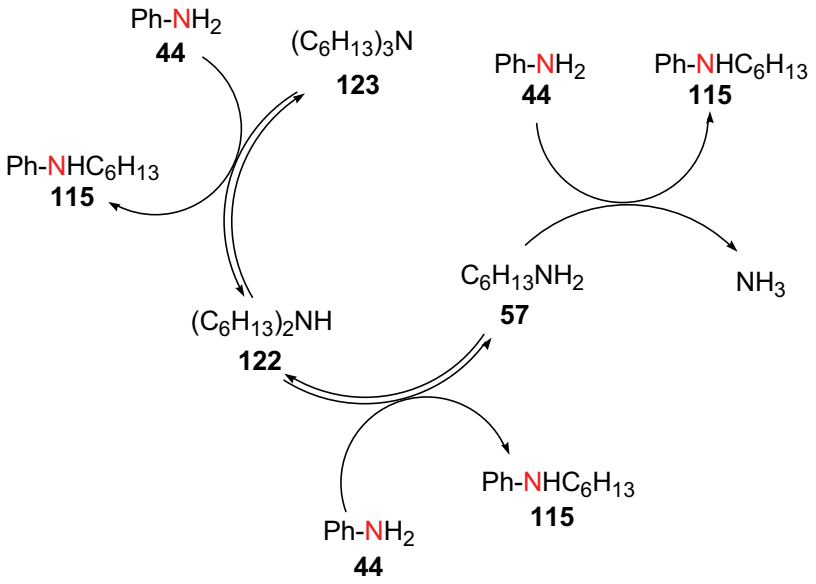
Upon optimization we found that two equivalents of aniline per hexyl group in the presence of 1 mol% of **2** in *t*-amylalcohol gave the best results. Notably, a mixture of mono-, di-, and tri-*n*-hexylamine can be converted highly selective to give **115** (Scheme 57).



Scheme 57: Amination of aniline with a mixture of hexylamines (isolated yields are based on hexyl group).

As shown in chapter 2.4.1., equilibrium between the mono-, di-, and trialkyl amines is observed under these reaction conditions. All alkyl amines are converted into each other and can be monitored until the reaction is finished (reversible steps). However, by reaction of the respective imines or iminium species with aniline (**44**), *N*-hexylaniline (**115**) is formed in an irreversible step. Thus, reaction of tri-*n*-hexylamine (**123**) with **44** yields exclusively **115** and di-*n*-

hexylamine (**122**). Then, the next alkyl group is transferred. Finally, the reaction of *n*-hexylamine (**57**) with aniline (**44**) results in the formation of ammonia (irreversible step) (Scheme 58).



Scheme 58: Mechanism of the alkyl transfer with aniline

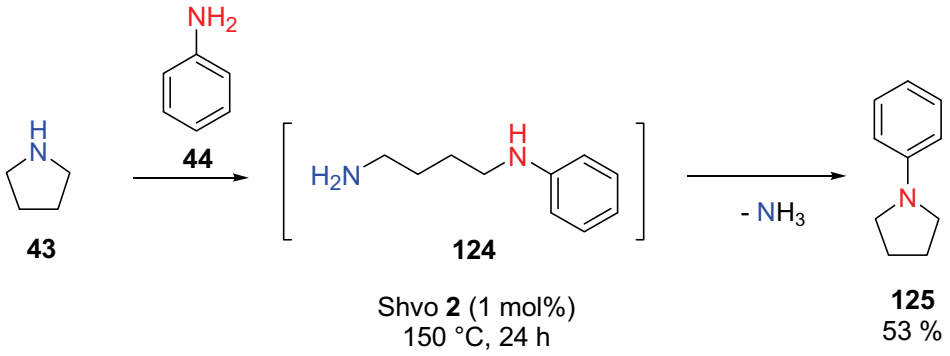
In addition, the substrate scope was extended to secondary and tertiary amines. Thus, different alkyl amines and aminoalkoxyethers were converted in excellent selectivity and high yields.

So far, conversion of steric hindered amines (tribenzylamine) and aryl amines (2,6-substituted aryl amines) and nitro groups possess a challenge.

2.4.3. Alkylation of Aryl amines with Cyclic Aliphatic Amines[VII]

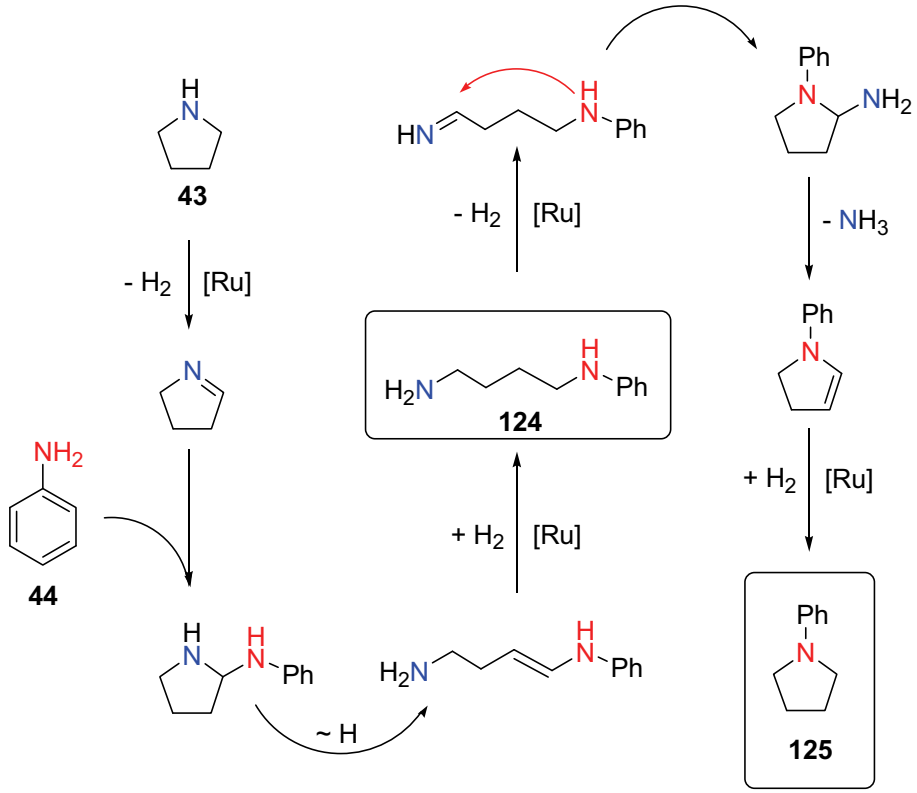
In addition to noncyclic aliphatic amines, alkylation of aryl amines using cyclic amines such as pyrrolidine (**43**) and piperidine proceeds via B*orrowing Hydrogen* methodology in the presence of 1 mol% *Shvo* catalyst (**2**) (Scheme 59). Remarkably, in this catalytic transformation three carbon-nitrogen bond cleaving and forming steps take place. This novel reaction sequence leads to *N*-aryl-pyrrolidines and -piperidines.[107]

(107) D. Hollmann, S. Bähn, A. Tillack, R. Parton, R, Altink, M. Beller, *Tetrahedron Lett.* **2008**, *49*, 5742-5745.



Scheme 59: N-Alkylation of aniline with pyrrolidine

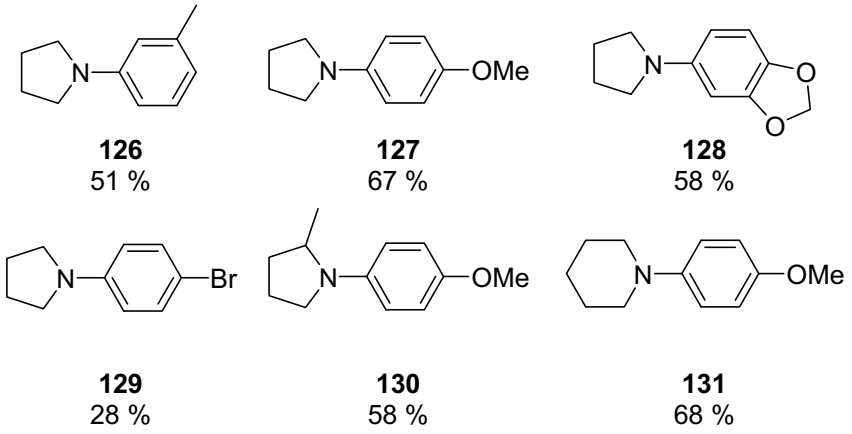
In analogy to the monoalkylation of aryl amines (Chapter 2.4.2.), the supposed reaction mechanism is illustrated in Scheme 60. Initially, ruthenium-catalyzed dehydrogenation of pyrrolidine (**43**) occurs via coordination and β-hydride elimination. Then, nucleophilic attack of the aryl amine on the resulting imine gives a diaminal. Ring opening and hydrogenation yields the corresponding 1,4-diamine **124**. Here, dehydrogenation of the primary amino group is fast compared to the secondary amine. Subsequent nucleophilic attack on the imine, elimination of ammonia, and catalytic hydrogenation leads to the arylated pyrrolidine **125**.



Scheme 60: Proposed mechanism for the reaction of pyrrolidine with aniline

In order to demonstrate the general applicability of **2** and the scope of the process, the reaction of various aryl amines and cyclic alkyl amines was investigated (Scheme 61). Moderate to good yields were achieved. Noteworthy, the product yield depends on the electron density of

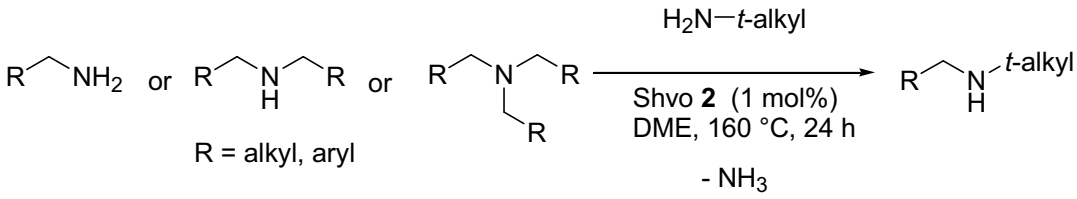
the aromatic ring and thus the nucleophilicity of the amino group.[108] Apparently, the nuclephilic attack of the aryl amine is involved in the rate-determined step. Electron deficient aryl amines are problematic. No reaction was observed with 4-trifluoromethylaniline.



Scheme 61: Selection of products in the N-alkylation with cyclic aliphatic amines

2.4.4. Alkylation of *t*-Alkyl amines[VI]

Based on the alkylation of aryl amines (Chapter 2.4.2.), we got interested in the selective alkylation of tertiary aliphatic amines (Scheme 62).[109] The resulting *t*-alkyl amines are of interest as intermediates. For example, this structural element is found in pharmaceuticals[110] such as vildagliptin.[111]



Scheme 62: Selective N-alkylation of t-alkyl amines

Further nucleophiles such as aryl amines, are *t*-alkyl amines without having a α-carbon-hydrogen group. Clearly, dehydrogenation of the *t*-alkyl group is not feasible since β-hydride elimination is not possible. Hence, a selective alkyl transfer takes place. This atom efficient alkyl transfer proceeds with primary as well as secondary, and tertiary aliphatic amines leaving ammonia as the only side product.

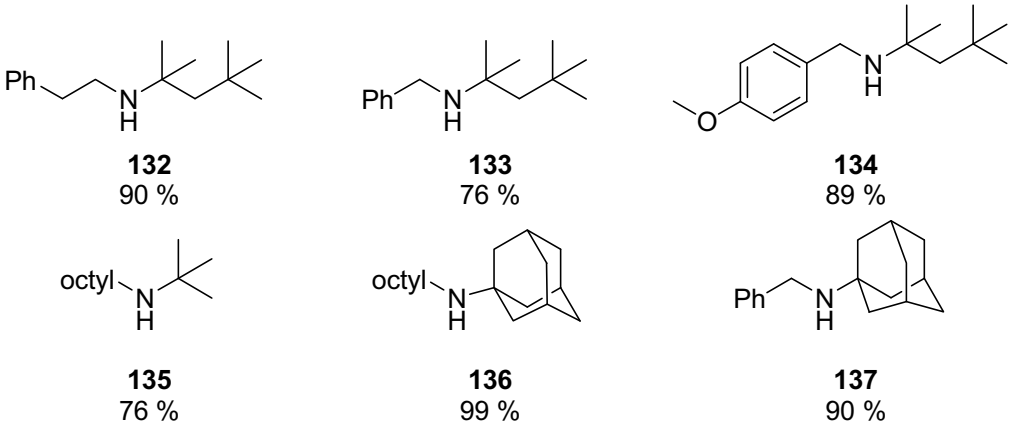
(108) F. Brotzel, Y. C. Chi, H. Mayr, *J. Org. Chem.* **2007**, *72*, 3679-3688.

(109) S. Bähn, D. Hollmann, A. Tillack, M. Beller, *Adv. Synth. Cat.* **2008**, *350*, 2099-2103.

(110) R. R. Ruffolo, Jr., W. Bondinell, J. P. Hieble, *J. Med. Chem.* **1995**, *38*, 3681-3716.

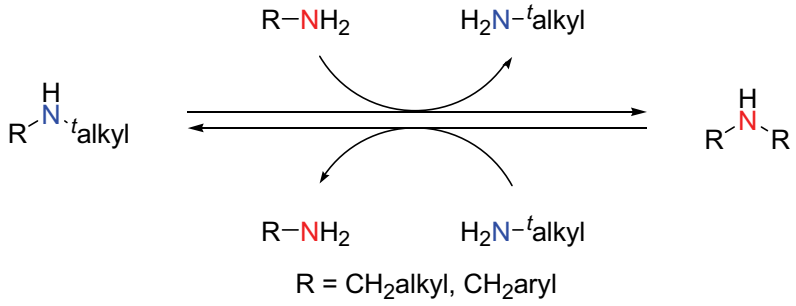
(111) B. Boerk, H. D. Grenville, H. T. Edward, V. E. Bernard (Novartis A.G., Switz.), WO 2008057337, **2008**.

In order to demonstrate the generality of the alkyl transfer, different amines were investigated in the reaction with *t*-octylamine (**141**), 1-adamantylamine, and *t*-butylamine. Primary amines as well as secondary gave the desired products in good to excellent yield. A selection of products is shown in Scheme 63. Remarkably, even tertiary amines such as trioctylamine can be used as alkylating agents, although activation of these substrates is known to be difficult. Problematic seems to be the reaction of steric hindered tribenzylamine and cyclic amines such as cyclohexylamine or cyclooctylamine. Thus, no reactions with *t*-octylamine or 1-adamantylamine were observed.



Scheme 63: Selection of products in the N-alkylation of tertiary alkyl amines from secondary alkyl amines

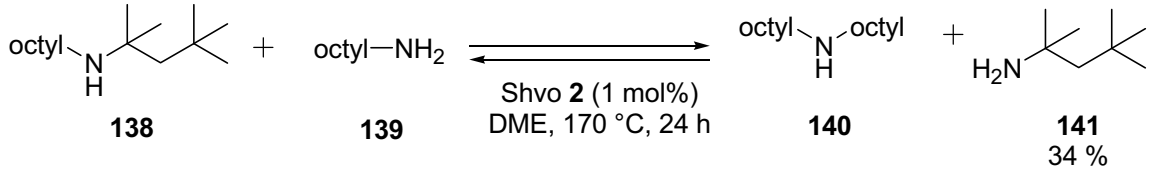
During our research we found that the formation of alkyl-*t*-alkyl amine is a reversible process.[112] The corresponding alkyl-*t*-alkylimine can be attacked by primary and secondary amines to form the free *t*-alkyl amine and secondary as well as tertiary alkyl amines. This equilibrium with primary alkyl amines is shown in Scheme 64.



Scheme 64: Equilibrium in the N-alkylation of tertiary alkyl amines with primary alkyl amines

During the reaction of octyl-(1,1,3,3-tetramethyl-butyl)-amine (**138**) with octylamine (**139**), 34 % of the free *t*-octylamine (**141**) was observed (Scheme 65). Based on these results, it became clear that an excess of *t*-alkyl amine (**141**) is necessary to shift the equilibrium to the products.

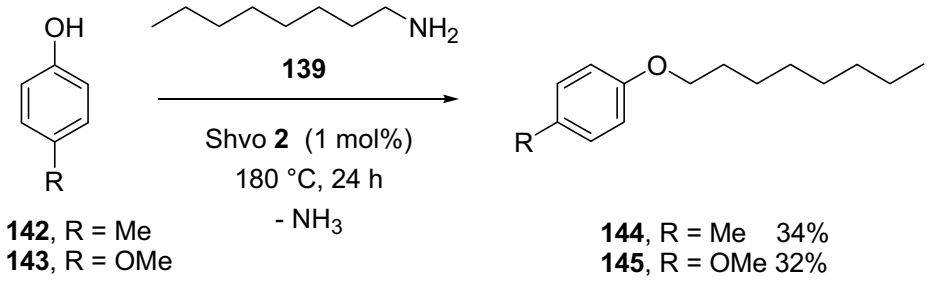
(112) S. Bähn, diploma thesis, unpublished results.



Scheme 65: Reaction of octyl-t-octylamine with octylamine and adjustment of the equilibrium

2.4.5. Alkylation of Phenols

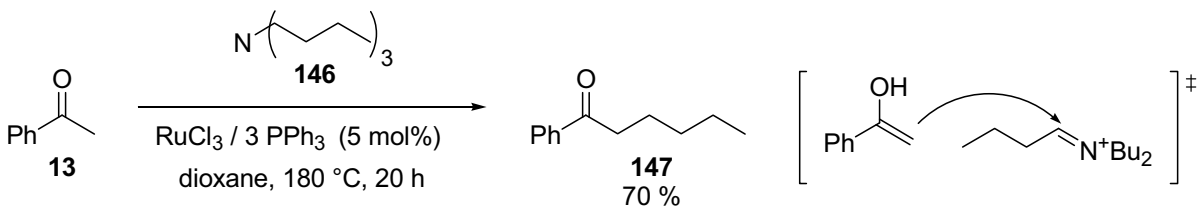
The synthetic procedure for alkylation using alkyl amines was attempted to phenols.[113] Unfortunately, optimization showed that high temperatures of 180 °C are necessary (Scheme 66). In addition, strong solvent influence was observed, which makes the reaction unattractive for chemists. Only moderate yields of 34 % for *O*-octyl-*p*-cresol (**144**) and *O*-octyl-*p*-hydroxy-anisol (**145**) were achieved.



Scheme 66: Phenols as nucleophiles

2.4.6. α-Alkylation of Ketones by Amines

Based on the report of the alkylation of aryl amines with trialkyl amines (see Chapter 2.4.2.) in 2001,[104] *Cho et al.* reported an α-alkylation of ketones with trialkyl amines (Scheme 67).[114] This alkyl group transfer was carried out with an *in situ* catalyst of $RuCl_3$ and PPh_3.



Scheme 67: α-Alkylation of ketones with trialkyl amines

(113) D. Hollmann, unpublished results.

(114) C. S. Cho, B. T. Kim, M. J. Lee, T.-J. Kim, S. C. Shim, *Angew. Chem. Int. Ed.* **2001**, *40*, 958-960; *Angew. Chem.* **2001**, *113*, 984-986.

Given these results, several ketones and amines were tested with this catalyst system. As side products, reductive amination products of the aldehydes with the excess amine were observed. The reaction proceeds via dehydrogenation of the tertiary amine to iminium cation, followed by nucleophilic attack of the enolate derivates formed from the ketones. Liberation of a secondary amine and dehydrogenation lead to the alkylated ketone.

2.5. Concluding Remarks

The *Borrowing Hydrogen* methodology combined well-known organic reactions with transfer hydrogenation. But until now, this method is in the fledging stages, thus improved catalysts and reaction conditions will be developed soon. So far, best catalysts are the iridium catalyst $[Cp^*IrCl_2]_2$ developed by *Fujita* and co-workers, as well as the ruthenium *in situ* catalyst [Ru(*p*-cymene)$Cl_2]_2$ and dppf developed by *Williams et. al.*, and $[Ru_3(CO)_{12}]$ combined with ligand **63** developed in our group. Recently, we introduced the ligand metal bifunctional *Shvo* catalysts (**2**), which showed significantly higher reactivity. But unfortunately, high temperatures are necessary for the activation of the *Shvo* catalyst.

Until to date, no chiral transformation and dehydrogenation were performed. The reaction conditions are too harsh to obtain enantioselectivity. Thus, it will be of continuous interest to develop catalysts, which work under milder conditions (<50 °C).

Furthermore, only a limited area of organic chemistry was combined with the *Borrowing Hydrogen* methodology. In future, more transformations will be explored.

3. Objectives of the Work

The *Borrowing Hydrogen* methodology, also called *Hydrogen Auto Transfer Process*, provides an alternative way for avoiding of use of hydrogen or other hydrogen donor compounds. After dehydrogenation by a metal catalyst, the corresponding unsaturated compound can undergo further reactions and transformations to form new unsaturated compounds, which are finally hydrogenate. Under consideration of no hydrogen loss, even by side reaction or by gas evolution, the *Borrowing Hydrogen* methodology can refrain from using additional hydrogen sources. Thus, the *Borrowing Hydrogen* methodology is an economically and environmetally attractive strategy in organic synthesis. During my research, the *Borrowing Hydrogen* methodology was first applied in the synthesis of secondary amines starting from secondary alcohols (*Tetrahedron Lett.* **2006** (**I**, see chapter **4.1**) and *Chem. Asian J.* **2007** (**II**, see chapter **4.2**)). Furthermore, tertiary amines can be prepared by applying secondary cyclic amines and secondary alcohols (*Eur. J. Org Chem.* **2008** (**III**, see chapter **4.3**)). Next, we were able to introduce the selective synthesis of monoalkylated aryl amines with primary amines using the *Shvo* catalyst (**2**) (*Angew. Chem. Int. Ed.* **2007** (**IV**, see chapter **4.4**)). In an expansion of this concept we showed that primary, secondary, and tertiary amines can be converted selectively to the monoalkylated aryl amines (*Chem. Commun.* **2008** (**V**, see chapter **4.5**)). This new method was continuously applied in the alkylation of *t*-alkyl amines (*Adv. Synth. Cat.* **2008** (**VI**, see chapter **4.6**)). Finally, to round out this method, *N*-alkylation of aryl amines with cyclic alkyl amines was performed (*Tetrahedron Lett.* **2008** (**VII**, see chapter **4.7**)). Additionally, mechanistic studies in the activation (*Organometallics* **2008** (**VIII**, see chapter **4.8**)) and deactivation (*Organometallics* **2008** (**IX**, see chapter **4.9**)) of the *Shvo* catalyst (**2**) were performed.

4. Publications

4.1. A Novel Ruthenium-catalyzed Amination of Primary and Secondary Alcohols

Annegret Tillack, Dirk Hollmann, Dirk Michalik, and Matthias Beller, *Tetrahedron Lett.* **2006**, *47*, 8881-8885.

Contributions

In this paper, I was involved in the investigation of different metal precursor and ligand screening (Table 1 and 2) as well as substrate screening (Table 3). My contribution as co-author of this paper is approximately 40 %.

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A novel ruthenium-catalyzed amination of primary and secondary alcohols

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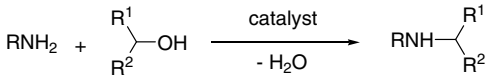
Abstract—An improved method for the N-alkylation of primary amines with primary and secondary alcohols has been developed. Novel, effective catalyst systems, for example, $Ru_3(CO)_{12}$ combined with tri-*o*-tolylphosphine or *n*-butyl-di-1-adamantylphosphine, allow for aminations in a good yield under comparatively mild conditions.

The catalytic formation of carbon–nitrogen bonds is of a broad interest to synthetic organic chemists since a large number of nitrogen-containing molecules are of importance for both the bulk and fine chemical industries, for example, for the production of solvents and emulsifiers. In addition, a variety of naturally occurring bio-active compounds such as alkaloids, amino acids and nucleotides contain amino groups, which are particularly useful for the development of new pharmaceuticals and agrochemicals.[1] Thus, the development of improved methods for the synthesis of amines continues to be a challenging and active area of research.[2]

Among the various catalytic amination methods, palladium-catalyzed amination of aryl halides,[3] hydroamination,[4] and hydroaminomethylation[5] of olefins or alkynes has received special attention in the last decade. Less interest has been paid to the further development of catalytic alkylations of amines.[6] Compared to the frequently applied N-alkylations with alkyl halides and reductive aminations, an economically and environmentally attractive method is the N-alkylation of amines using primary and secondary alcohols (Scheme 1).



Scheme 1. Catalytic N-alkylation of amines with alcohols.

This consecutive domino reaction consists of an initial dehydrogenation of the alcohol, subsequent imine formation followed by reduction with the initially produced hydrogen. The advantages of this method are the ubiquitous availability of alcohols and high atom efficiency, for example, no salt formation, water as the only by-product. Moreover, compared to reductive aminations, it is possible to run these reactions in the absence of hydrogen pressure.

The general principle of alkylation of amines with alcohols is well known.[7] The methylation of lower aliphatic amines with methanol is even performed on an industrial scale.[8] Until now mainly heterogeneous catalysts are used for N-alkylation at a high temperature and pressure. For example, alkylations of aryl amines are catalyzed by Raney-Ni,[9] alumina,[10] silica and montmorillonite at temperatures >200 °C.[11]

The first homogeneous catalysts were introduced by Grigg et al.[12] and Watanabe et al.[13] in 1981. Thereafter, ruthenium,[14] rhodium,[15] platinum,[16] and iridium complexes[15,17] have been introduced as molecular-defined transition metal catalysts for such reactions. Similar to heterogeneous systems the drawbacks of the known homogeneous catalysts are the high reaction temperatures (up to 215 °C) and long reaction times, which are required to obtain sufficient yields. In addition, the scope of these reactions is limited. With regard to the alcohol, mainly primary alcohols have been used as substrates. These are more reactive compared to secondary alcohols. With the exception of $[IrCp^*Cl_2]$, which was introduced by Fujita et al.[18] no efficient catalyst is known for the N-alkylation with secondary alcohols.

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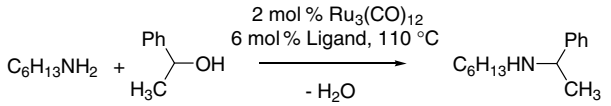
Thus, a major challenge in this area is the development of more active catalysts that work under milder conditions and allow a broader substrate scope. Clearly, the demands on improved catalysts for the N-alkylation of amines with alcohols are: (1) High activity for the dehydrogenation of alcohols to ketones and the hydrogenation of the resulting imines to amines via a transfer hydrogenation process, and (2) low sensitivity to water and functional groups on the substrate. From an environmental point of view the use of additional base for the activation of the catalyst should be avoided.

Based on our previous research in intermolecular hydroaminations of olefins and alkynes,[19] we recently became interested in the development of novel ruthenium complexes for the amination of alcohols, especially secondary alcohols. Herein, we report our results from this study and present $Ru_3(CO)_{12}$/ligand-systems which are active for the N-alkylation of amines with different alcohols at 100–110 °C.

Initial studies were performed using *n*-hexylamine and 1-phenylethanol as the substrates in the presence of different ruthenium sources. As a result of these reactions the ruthenium cluster $Ru_3(CO)_{12}$ was tested in the presence of different phosphine ligands. Typically, the catalytic reactions were run without a solvent using 2 mol % $Ru_3(CO)_{12}$ and 6 (3) mol % of monodentate (bidentate) ligands at 110 °C. The selected results and the ligands used are shown in Table 1 and Scheme 2.

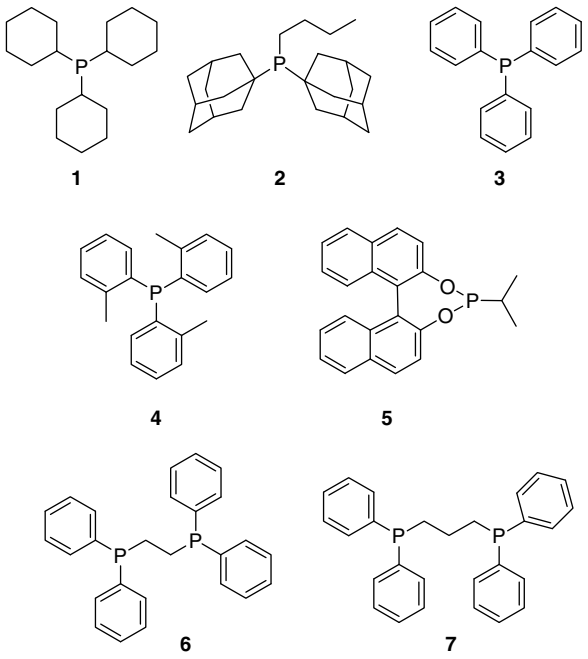
Notably, the reaction proceeds in a good yield (74%) in the presence of the ruthenium carbonyl cluster (Table 1, entry 1). With respect to the used ligands, there was no clear trend observed. For example electron-rich bulky phosphines such as tricyclohexylphosphine **1** and *n*-butyl-di-1-adamantyl-phosphine[20] **2** behaved quite differently (Table 1, entries 2 and 3). Similar divergent behaviour was observed with aryl phosphines **3** and **4** (Table 1, entries 4 and 5). The best results were obtained with **2** and **4** (>90% of *N*-(1-phenyl-ethyl)hexylamine).

Table 1. N-Alkylation of *n*-hexylamine with 1-phenyl-ethanol in the presence of $Ru_3(CO)_{12}$ and different ligands[a]



Entry	Ligand	Conversion (%)	Yield (%)
1	None	100	74
2	**1**	100	59
3	**2**	**100**	**90**
4	**3**	81	47
5	**4**	**100**	**97**
6	**5**	56	33
7	**6**	85	30
8	**7**	82	34

[a] Reaction conditions: 2 mmol *n*-hexylamine, 10 mmol 1-phenylethanol, 0.04 mmol $Ru_3(CO)_{12}$, 0.12 mmol monodentate ligand (or 0.06 mmol bidentate ligand), 110 °C, 24 h, conversion and yield were determined by GC analysis with hexadecane as the internal standard.



Scheme 2. Ligands for N-alkylation of amines with alcohols.

For all other tested ligands the conversion of substrate was significantly higher than the yield of the desired product. In these cases the corresponding imine was observed as the major side product. Thus, the hydrogenation of the imine appears problematic.

Next, critical reaction parameters of the model reaction were studied in more detail (Table 2). The $Ru_3(CO)_{12}$/tri(*o*-tolyl)-phosphine catalyst system **4** was chosen for its high yield, robustness and favourable price.

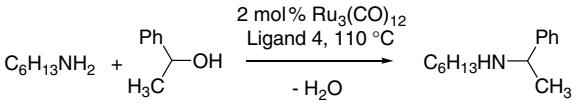
Reducing the catalyst loading from 2 to 1 mol %, the conversion decreased from 100% to 79%, and the yield of secondary amine dropped to 37%. Variation of the alcohol/amine ratio demonstrated the importance of the alcohol concentration for the hydrogenation step (Table 2, entries 2–5). Although the conversion decreased only slightly to around 80%, the product yield decreased steadily to only 29%. Reducing the reaction time to 7 h showed that almost 24 h are necessary for a full conversion (Table 2, entry 8).

The two best catalysts identified from these studies were applied to the alkylation of various amines under the optimized conditions (Table 3).

In addition to the model reaction described above, the N-alkylation of *n*-octylamine and benzylamine with 1-phenylethanol proceeded in moderate yield (64% and 49%, respectively) (Table 3, entries 4 and 8). Cyclooctylamine gave 29% of the corresponding alkylated amine (Table 3, entry 6). In all cases ligand **4** gave better product yields than **2**.

Finally, different alcohols were examined in the N-alkylation of *n*-hexylamine (Table 4). Again, all substrates were tested in the presence of ligands **2** and **4**. Notably,

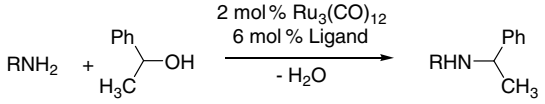
Table 2. N-Alkylation of *n*-hexylamine with 1-phenylethanol in the presence of $Ru_3(CO)_{12}$ and tri(*o*-tolyl)phosphine (**4**)[a]



Entry	Catalyst (mol %)	Amine/alcohol	Temperature (°C)	Time (h)	Conversion (%)	Yield (%)
1	1	1:5	110	24	79	37
2	2	1:5	110	24	100	97
3	2	1:4	110	24	88	58
4	2	1:3	110	24	80	38
5	2	1:2	110	24	82	29
6	2	1:5	100	24	90	52
7	2	1:5	90	24	38	10
8	2	1:5	110	7	58	22

[a] Reaction conditions: 2 mmol *n*-hexylamine, 10 mmol 1-phenylethanol, 0.04 mmol $Ru_3(CO)_{12}$, 0.12 mmol **4**, conversion and yield were determined by GC analysis with hexadecane as the internal standard.

Table 3. N-Alkylation of different amines with 1-phenyl-ethanol in the presence of $Ru_3(CO)_{12}$/**2** or **4**[a]



Entry	Amine	Ligand	Conversion (%)	Yield (%)
1	Hexylamine	**2**	100	90
2	Hexylamine	**4**	100	97
3	Octylamine	**2**	100	35
4	Octylamine	**4**	100	64
5	Cyclooctylamine	**2**	56	21
6	Cyclooctylamine	**4**	44	29
7	Benzylamine	**2**	81	19
8	Benzylamine	**4**	72	49

[a] Reaction conditions: 1 mmol amine, 5 mmol 1-phenylethanol, 0.02 mmol $Ru_3(CO)_{12}$, 0.06 mmol ligand, 110 °C, 24 h, conversion and yield were determined by GC analysis with hexadecane as

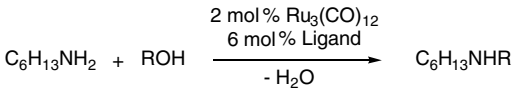
secondary aliphatic alcohols such as 2-octanol and cyclohexanol gave *N*-hexyl-2-octylamine and *N*-hexyl-cyclohexylamine in excellent yields (90–94%) (Table 4, entries 1–4). We were also pleased to find that hetero-aromatic alcohols, for example, 1-(2-furyl)-ethanol (Table 4, entries 5 and 6), furan-2-yl-methanol (Table 4, entries 7 and 8), and thiophen-2-yl-methanol (Table 4, entries 9 and 10) were converted to the corresponding secondary *N*-hexylamines in moderate to good yields. Ligand **4** was again superior to **2** in all cases studied.

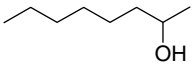
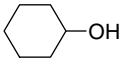
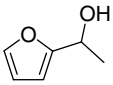
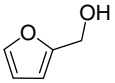
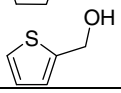
In conclusion, we present a novel ruthenium-catalyzed N-alkylation of amines with alcohols in the presence of different sterically hindered phosphine ligands. The reactions can be performed under significantly milder conditions (110 °C) compared to the known ruthenium catalysts and proceed with good yields.

Acknowledgements

This work has been supported by the State of Mecklenburg-Western Pommerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Leibniz-price), and the Fonds

Table 4. N-Alkylation of *n*-hexylamine with different alcohols in the presence of $Ru_3(CO)_{12}$/**2** or **4**[a 21]



Entry	Alcohol	Ligand	Temperature (°C)	Conversion (°C)	Yield (%)
1		**2**	110	100	92
2		**4**	110	100	90
3		**2**	120	100	94
4		**4**	120	100	93
5		**2**	110	100	17
6		**4**	110	100	49
7		**2**	110	100	33
8		**4**	110	100	60
9		**2**	110	66	7
10		**4**	110	100	70

[a] Reaction conditions: 2 mol % catalyst, 24 h, conversion and yield were determined by GC analysis with hexadecane as internal standard.

der Chemischen Industrie (FCI). We thank Mrs. C. Mewes, Mrs. A. Lehmann and Mrs. S. Buchholz for the excellent technical and analytical support as well as Dr. D. Nielsen for the improvement of the manuscript.

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20. (a) Klaus, S.; Neumann, H.; Zapf, A.; Struebing, D.; Huebner, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154; (b) Köllhofer, A.; Plenio, H. *Adv. Synth. Catal.* **2005**, *347*, 1295; (c) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron* **2005**, *61*, 9705; (d) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056; (e) Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 515.
21. Preparative procedure for the amination reaction: In an Ace-pressure tube under an argon atmosphere $Ru_3(CO)_{12}$ (0.1 mmol) and ligand **4** (0.3 mmol) were dissolved in thiophen-2-yl-methanol (25 mmol) and hexylamine (5 mmol). The pressure tube was fitted with a Teflon cap and heated at 110 °C for 48 h in an oil bath. The excess alcohol was distilled (40 °C, 0.88 mbar). The residue was extracted with 1 N HCl (3×5 mL). The combined HCl-phases were spiked with 15 N NaOH solution, extracted with dichloromethane (5×5 mL), dried over magnesium sulfate and reduced in vacuo to yield *N*-(thiophen-2-ylmethyl)hexan-1-amine hydrochloride as a brown powder. Isolated yield: 317 mg (32%). ^{1}H NMR (500.13, $CDCl_3$, δ): 0.84 (t, 3H, $^3J = 6.9$ Hz, H-6); 1.21–1.35 (m, 6H, H-3,4,5); 1.84 (m, 2H, H-2); 2.81 (m, 2H, H-1); 4.26 (m, 2H, H-7); 7.03 (dd, 1H, $^3J_{10,11} = 5.2$ Hz, $^3J_{9,10} = 3.6$ Hz, H-10); 7.34 (dd, 1H, $^3J_{10,11} = 5.2$ Hz, $^4J_{9,11} = 1.0$ Hz, H-11); 7.42 (dd, 1H, $^3J_{9,10} = 3.6$ Hz, $^4J_{9,11} = 1.0$ Hz, H-9); 9.80 (br, 2H, NH_2). ^{13}C NMR ($CDCl_3$, 125.8 MHz, δ): 13.9 (C-6); 22.4 (C-5);

25.8 (C-2); 26.4 (C-3); 31.1 (C-4); 44.3 (C-7); 45.6 (C-1); 127.9 (2) (C-10, C-11); 130.9 (C-8); 131.3 (C-9). MS (EI, 70 eV) *m/z* (rel. intensity): 197 (1) [M^+], 126 (24) [M^+–C_5H_{11}], 112 (9) [M^+–C_4H_3S], 97 (100) [M^+–$C_6H_{14}N$]. FT IR (KBr, cm^{-1}): 3070 (w, C-H_{ar}), 2932 (s), 2862 (s), 2794 (s), 2740 (s), 2550 (m), 2421 (m), 1581 (m), 1472 (s), 853 (m), 717 (m), 696 (s). Anal. Calcd for $C_{11}H_{19}NS$·HCl: C, 56.51; H, 8.62; N, 5.99; S, 13.71; Cl, 15.16. Found: C, 56.30; H, 9.08; N, 5.75; S, 13.42; Cl, 14.37. HRMS calcd for $C_{11}H_{19}NS$: 197.12327. Found: 197.12334.

4.2. An Improved Ruthenium Catalyst for the Environmentally Benign Amination of Primary and Secondary Alcohols

Dirk Hollmann, Annegret Tillack, Dirk Michalik, Ralf Jackstell, and Matthias Beller, *Chem. Asian J.* **2007**, *3*, 403-410.

Contributions

In this paper, I was involved in the investigation of different metal precursor and ligand screening (Table 1 and 2) as well as substrate screening (Table 3 and 4). My contribution as co-author of this paper is approximately 50 %.

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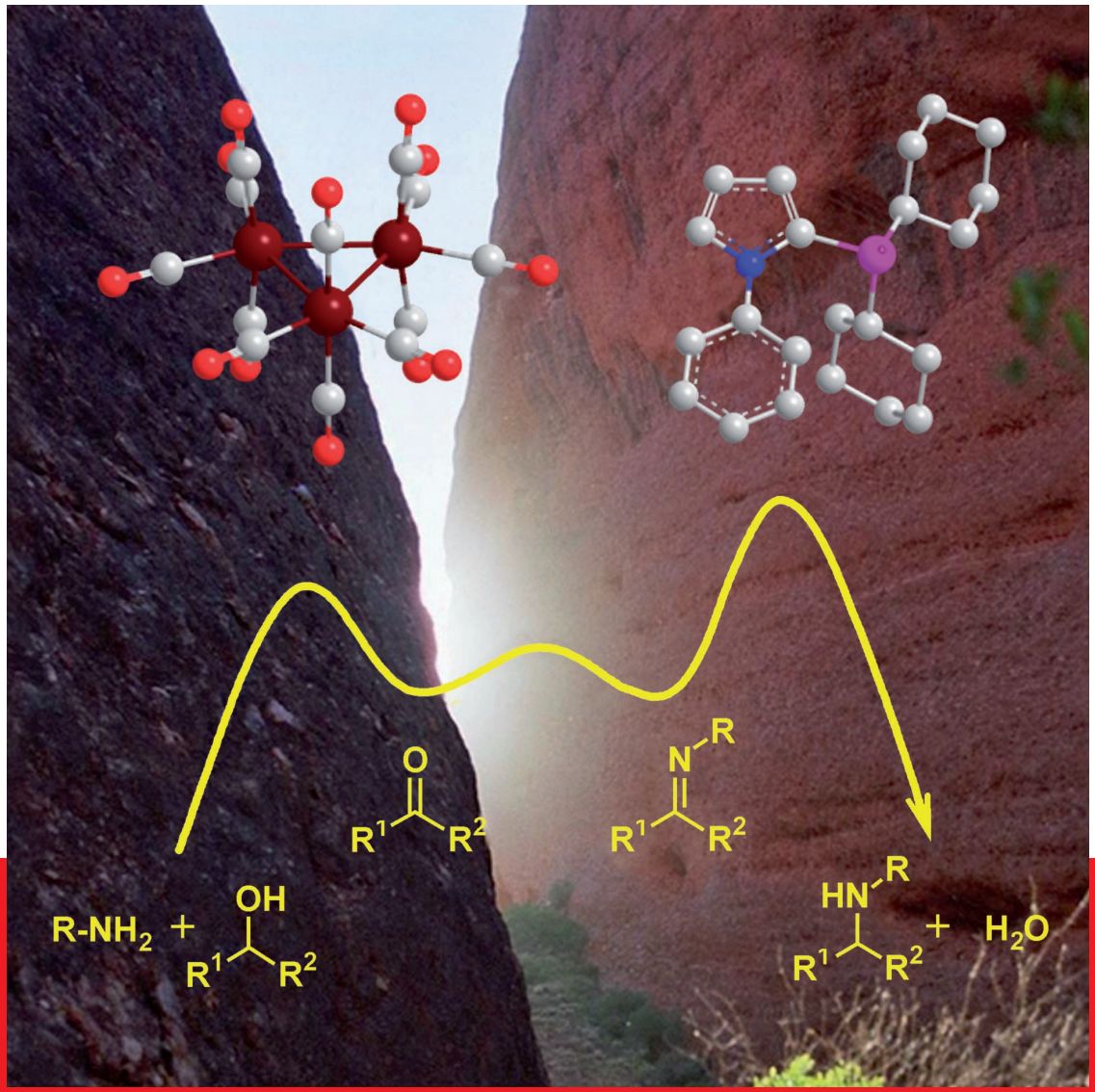

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An Improved Ruthenium Catalyst for the Environmentally Benign Amination of Primary and Secondary Alcohols

Dirk Hollmann, Annegret Tillack, Dirk Michalik, Ralf Jackstell, and Matthias Beller*[a]

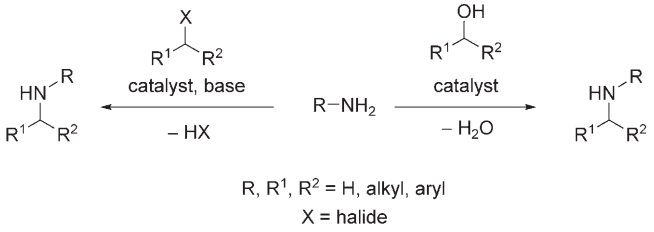
Abstract: The N-alkylation of amines in the presence of different ruthenium catalysts generated in situ was investigated. Among the various catalysts tested, the combination of $[Ru_3(CO)_{12}]$ and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole showed the best performance. By applying this novel catalyst, a variety of functionalized alcohols and amines were converted into the corresponding secondary amines in high yield.

Keywords: alcohols · amination · amines · ruthenium · transfer hydrogenation

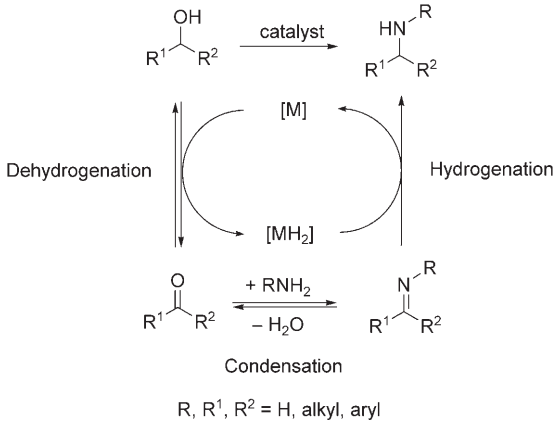
Introduction

A variety of amines is of significant importance for the bulk- and fine-chemical industries not only as building blocks for polymers and dyes, but also for the synthesis of new pharmaceuticals and agrochemicals.[1] Furthermore, a plethora of naturally bioactive compounds such as alkaloids, amino acids, and nucleotides contain amine groups. Despite numerous known procedures, the development of improved methods for the synthesis of amines continues to be a highly challenging and active area of research.[2] In the last decade, various catalytic aminations, such as palladium- and copper-catalyzed amination of aryl halides,[3] hydroamination,[4] and hydroaminomethylation[5] of olefins or alkynes, have received increased attention. However, less interest has been paid to the further development of catalytic alkylations of amines, such as reductive amination.[6]

As opposed to the well-known classic N-alkylations of amines with alkyl halides and reductive alkylations, an atom-economical[7] and environmentally attractive method is the N-alkylation of amines by using primary and secondary alcohols (Scheme 1). This domino reaction sequence is based on the dehydrogenation of the alcohol in situ to give the corresponding aldehyde or ketone. Subsequent imine formation followed by reduction with the hydrogen initially produced leads to the N-alkylated amine (Scheme 2). To obtain the desired amine, it is necessary that the hydrogenation of the imine is irreversible.



Scheme 1. Catalytic N-alkylation of amines with alcohols or alkyl halides.



Scheme 2. Catalytic hydrogen transfer in N-alkylation of amines with alcohols.

Interestingly, the same principle of the dehydrogenation–functionalization–hydrogenation sequence was recently used in alkane metathesis,[8] β alkylation of alcohols,[9] and C–C

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bond formation by the Knoevenagel reaction.[10] The advantages of this type of amination are the ubiquitous availability of alcohols and the high atom efficiency of the reaction sequence, which forms water as the only by-product. Moreover, as opposed to typical reductive aminations, it is possible to run these reactions in the absence of additional hydrogen. Hence, the reaction can be performed at ambient pressure.

Until now, N-alkylation of amines has been predominantly performed with various heterogeneous catalysts at high temperature and pressure. As an example, alkylation of aliphatic amines can be catalyzed by Raney Ni,[11] alumina, silica, or montmorillonite at temperatures greater than 200 °C.[12] Industrial processes that apply such amination reactions in the presence of heterogeneous catalysts involve the methylation of lower aliphatic amines with methanol.[13]

Although the alkylation of amines with alcohols has been frequently applied, there is no catalytic method available for functionalized and sensitive substrates (alcohols and amines) under milder conditions (< 100 °C). To stimulate further applications of this chemistry, the development of more-active catalysts, which allow for a broader substrate scope, is highly desirable. A strategy to solve this problem might be the switch from heterogeneous to molecularly defined organometallic catalysts. Here, a variety of transition-metal complexes are known to have high activity for the dehydrogenation of alcohols to ketones and the hydrogenation of the resulting imines to amines via transfer hydrogenation, which are the basic requirements for the catalyst system.

The first homogeneous catalysts for N-alkylation of amines with alcohols were introduced by Grigg et al.[14] and Watanabe et al.[15] in 1981. Thereafter, ruthenium,[16] rhodium,[17] platinum,[18] and iridium complexes[17,19] have been described as homogeneous transition-metal catalysts for such reactions. Unfortunately, for most known homogeneous catalysts, high reaction temperatures (up to 215 °C) and long reaction times are required to obtain sufficient yields of the alkylated amine. With regard to the substrates, mainly primary alcohols have been used in the past because they are more reactive than secondary alcohols. With the exception of $[IrCp^*Cl_2]_2$ ($Cp^* = 1,2,3,4,5$-pentamethylcyclopentadienyl), which was introduced by Fujita et al.,[20] and our recently developed ruthenium catalyst system,[21] no efficient catalyst is known for N-alkylation with secondary alcohols.

Abstract in German: Die Synthese von sekundären Aminen aus primären Aminen und Alkoholen ist eine salzfreie und damit umweltfreundliche Alternative zu den bisherigen Alkylierungsverfahren. Durch die in situ Dehydrierung–Kondensation–Hydrierung Reaktionsequenz, welche die Vorteile der Transferhydrierung nutzt, wurden die Produkte atomeffizient hergestellt. Ermöglicht wird dies durch die einen neuartigen Ruthenium Katalysator bestehend aus $[Ru_3(CO)_{12}]$ und *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrol. Der robuste und wasserstabile Katalysator ermöglicht die Synthese von funktionalisierten Aminen in guten bis sehr guten Ausbeuten.

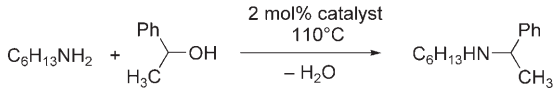
Results and Discussion

On the basis of our interest in intermolecular hydroaminations of olefins and alkynes,[22] we started a program to develop novel catalysts for the amination of alcohols, especially secondary alcohols. In an initial communication, we reported the use of ruthenium/*n*-butyldi-1-adamantylphosphine and ruthenium/tri-*o*-tolylphosphine as catalysts.[21] Herein, we summarize our results from this study and present a significantly improved in situ Ru catalyst that is highly active for the N-alkylation of various amines with different alcohols under comparably mild conditions (100–120 °C).

Initially, the reaction of *n*-hexylamine with 1-phenylethanol was studied as a model reaction. In general, the amination reaction was run without solvent at 110 °C for 24 h in the presence of 2 mol % $[Ru_3(CO)_{12}]$ and 6 mol % of the corresponding phosphine ligand. To obtain complete hydrogenation of the corresponding imine *n*-hexyl-(1-phenylethylidene)amine, an excess of alcohol with respect to amine (typically a 5:1 ratio was employed) was necessary.

At the beginning of our investigation, we focused our attention on the influence of different ruthenium precatalysts (Table 1). Basically, all ruthenium sources tested showed some activity for the conversion of the alcohol. However, only the ruthenium carbonyl cluster $[Ru_3(CO)_{12}]$ catalyzed the N-alkylation of *n*-hexylamine to a significant extent (Table 1, entry 1). Interestingly, the Shvo catalyst,[23] which is known to be highly active in transfer hydrogenations, showed high activity too, but mainly di-*n*-hexylamine was obtained as product (Table 1, entry 7). In the presence of all the other ruthenium complexes tested, the corresponding imine was formed as product. Apparently, the hydrogenation of imines seems to be problematic. These imines were the only observed "by-products" formed with our described catalyst system.

Table 1. Amination of 1-phenylethanol with hexylamine in the presence of different ruthenium precatalysts.[a]



Entry	Catalyst	Conv. [%][b]	Yield [%][b]
1	$[Ru_3(CO)_{12}]$	100	74
2	$[RuCl_2(bpy)_2]\cdot 2H_2O$	22	< 1
3	$[Ru(CO)(H)_2(PPh_3)_3]$	65	2
4	$[RuCp_2]$	18	2
5	$[RuCp^*Cl_2]_n$	52	0
6	[RuCp*(cod)Cl]	48	0
7	Shvo catalyst	92	39

[a] Reaction conditions: 2 mol % catalyst, amine/alcohol = 1:5, 110 °C, 24 h. [b] Conversion and yield determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on the conversion of hexylamine and the corresponding secondary amine. bpy = 2,2′-bipyridine, cod = 1,5-cyclooctadiene, Cp = cyclopentadienyl.

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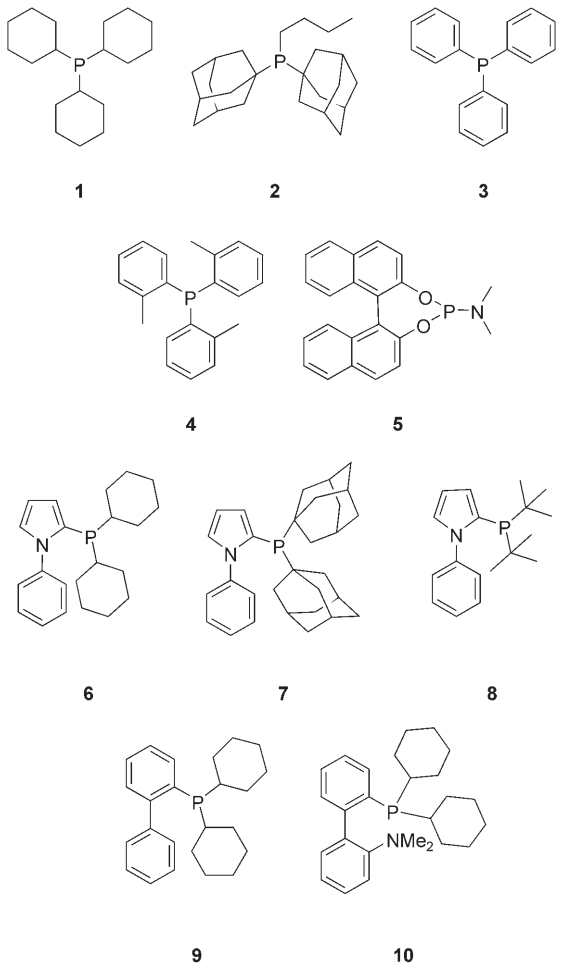
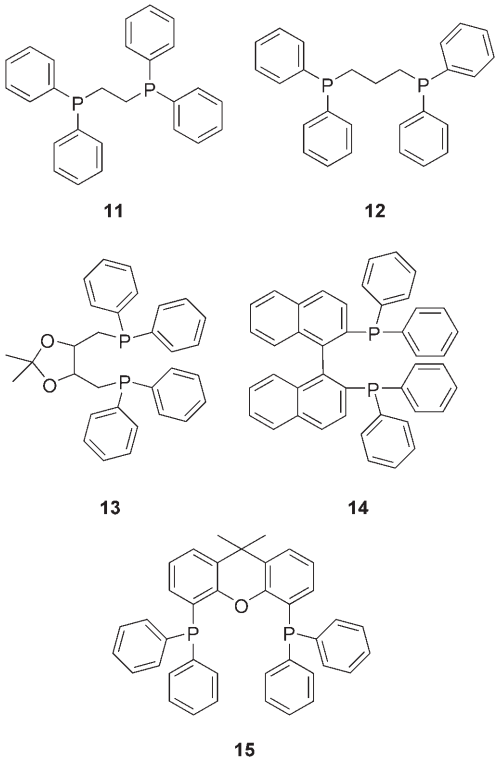
Next, we investigated the influence of monodentate and bidentate phosphine ligands in detail. For the sake of simplicity and practicability, instead of using defined phosphine–ruthenium complexes, we formed the corresponding ruthenium catalysts in situ from commercially available $[Ru_3(CO)_{12}]$ and phosphines **1**–**15** (Schemes 3 and 4) .

We employed the alkyl phosphines **1** and **2** (Table 2, entries 2 and 3), the aryl phosphines **3** and **4** (Table 2, entries 4 and 5), the monophos ligand **5**[24] (Table 2, entry 6), the pyrrole phosphines **6**, **7**, and **8** developed inhouse[25] (Table 2, entries 7–9), as well as the Buchwald ligands **9** and **10**[26] (Table 2, entries 10 and 11) as monodentate ligands. The reactivity of the $[Ru_3(CO)_{12}]$ complex is strongly dependent on the ligand. Notably, the reaction proceeded in 74% yield without ligand. With respect to the electronic and steric properties of the ligands, no clear trend was observed. For example, electron-rich bulky phosphines such as tricyclohexylphosphine (**1**) and *n*-butyl-di-1-adamantyl-phosphine[27] (**2**) behaved quite differently (Table 2, entries 2 and 3). Similar divergent results were observed for aryl phosphines **3** and **4** (Table 2, entries 4 and 5) and the pyrrole ligands **6**–**8**. In the presence of racemic monophos ligand **5**, only low conversion

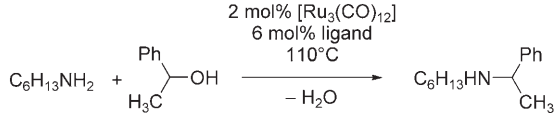


Scheme 3. Monodentate ligands for N-alkylation of *n*-hexylamine with 1-phenylethanol.



Scheme 4. Bidentate ligands for N-alkylation of *n*-hexylamine with 1-phenylethanol.

Table 2. N-alkylation of *n*-hexylamine with 1-phenylethanol in the presence of $[Ru_3(CO)_{12}]$ and different ligands.[a]



Entry	Ligand	Conv. [%][b]	Yield [%][b]
1	none	100	74
2	**1**	100	59
3	**2**	100	90
4	**3**	81	47
5	**4**	100	97
6	**5**	56	33
7	**6**	100	98
8	**7**	100	74
9	**8**	100	84
10	**9**	100	84
11	**10**	88	42
12	**11**	85	30
13	**12**	82	34
14	**13**	80	40
15	**14**	90	50
16	**15**	82	34

[a] Reaction conditions: 2 mmol *n*-hexylamine, 10 mmol 1-phenylethanol, 0.04 mmol $[Ru_3(CO)_{12}]$, 0.12 mmol monodentate ligand (or 0.06 mmol bidentate ligand), 110 °C, 24 h. [b] Conversion and yield determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on the conversion of hexylamine and the corresponding secondary amine.

and yield were obtained. With regard to *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole, the Buchwald ligands **9** and **10** showed lower activity. Among the different ligands, **2**, **4**, and **6** showed the best performance (100% conversion, ≥90% yield) in the model reaction.

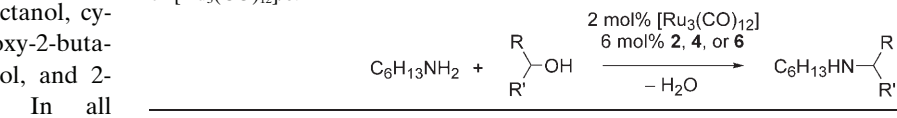
We were also interested in the effect of bidentate ligands. 1,2-Bis(diphenylphosphanyl)ethane (dppe) and 1,3-bis(diphenylphosphanyl)propane (dppp), *rac*-2,2-dimethyl-4,5-bis(diphenylphosphanylmethyl)-1,3-dioxolane (*rac*-diop; **13**), *rac*-2,2′-bis-(diphenylphosphanyl)-1,1′-binaphthyl (*rac*-binap; **14**), and xantphos (**15**) (Table 2, entries 12–16, respectively) showed low reactivity. In general, these ligands inhibit the dehydrogenation of the alcohol and the hydrogenation of the imine. This effect is explained by the fact that the coordination sites on the ruthenium are blocked by the bidentate ligand.

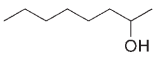
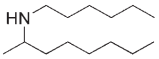
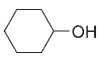
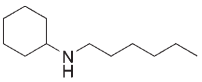
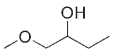
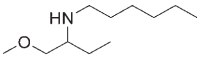
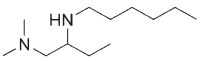
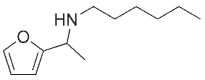
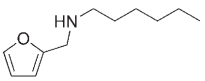
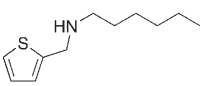
Owing to the superior performance, we compared the in situ system consisting of $[Ru_3(CO)_{12}]$/**2**, $[Ru_3(CO)_{12}]$/**4**, and $[Ru_3(CO)_{12}]$/**6** for the more-difficult reaction of *n*-hexylamine with 2-octanol, cyclohexanol, 1-methoxy-2-butanol, 1-(2-furyl)ethanol, and 2-thiophenylmethanol. In all cases the new catalyst with **6** gave significantly higher product yields compared to **2** and **4** (Table 3, entry 1 vs. 2 and 3, entry 10 vs. 7–9, entry 14 vs. 15, entry 18 vs. 19, entry 22 vs. 23). The reactions of eight different alcohols with *n*-hexylamine in the presence of the best catalyst system are shown in Table 3. At 110 °C, 2-octanol was converted into *N*-hexyl-2-octylamine in the presence of **6** in excellent yield (98%) and selectivity (Table 3, entry 1). In this case, the alcohol/amine ratio could be reduced without much problem to 1:2, whereas the catalyst system containing ligand **4** needed a larger excess of alcohol for the yield to reach 90%.

On the other hand, by decreasing the temperature to 100 °C, a higher alcohol/amine ratio of 1:5 was necessary for excellent yield (Table 3, entries 4 and 5). However, by lowering the temperature to 90 °C, the conversion and yield dropped to 64% and 23%, respectively (Table 3, entry 6). Apparently, the hydrogen-transfer step requires higher reaction temperatures. Below 100 °C, considerable amounts of the corresponding Schiff base were formed. In the presence of $[Ru_3(CO)_{12}]$/**6**, the less-reactive substrate cyclohexanol was converted into *N*-hexylcyclohexylamine in nearly quantitative yield (99%) at 100 °C (Table 3, entry 10). As opposed to ligand **6**, full conversion and yield were achieved with ligand **2** or **4** at 120 °C (Table 3, entries 7 and 8). Notably, functionalized alcohols such as 1-methoxy-2-butanol and 1-(*N*,*N*-dimethylamino)-2-propanol also gave the corresponding secondary amines in 87–93% yield (Table 3, entries 15 and 16). With ligand **4**, only decomposition of 1-methoxy-2-butanol was observed (Table 3, entry 14). Hence, synthetically interesting 1,2-aminoether derivatives as well as 1,2-diamines can be prepared by this route.

Apart from linear and cyclic aliphatic alcohols, we also tested different heterocyclic alcohols. We were pleased to find that 1-(2-furyl)ethanol, 2-furylmethanol, and 2-thio-

Table 3. N-alkylation of *n*-hexylamine with different alcohols in the presence of $[Ru_3(CO)_{12}]$/**2**, $[Ru_3(CO)_{12}]$/**4**, or $[Ru_3(CO)_{12}]$/**6**.[a]



Entry	Alcohol	Product	Ligand	Amine/alcohol	*T* [°C]	Conv. [%][b]	Yield [%][b]
1			**6**	1:2	110	100	98
2			**2**	1:5	110	100	92
3			**4**	1:5	110	100	90
4			**6**	1:5	100	100	98
5			**6**	1:2	100	90	63
6			**6**	1:5	90	64	23
7			**2**	1:5	120	100	94
8			**4**	1:5	120	100	93
9			**4**	1:5	110	50	38
10			**6**	1:5	100	100	99
11[c]			**6**	1:5	100	84	65
12			**6**	1:2	100	100	78
13			**6**	1:5	90	50	29
14			**4**	1:5	110	80	<6
15			**6**	1:5	110	100	93
16			**6**	1:5	140	100	87 (78)[e]
17			**6**	1:5	120	100	73
18			**4**	1:5	110	100	49
19[d]			**6**	1:5	110	100	74
20			**6**	1:5	110	100	66
21[d]			**6**	1:5	110	100	49
22			**4**	1:5	110	100	70
23			**6**	1:5	110	96	84

[a] Reaction conditions: 2 mol% $[Ru_3(CO)_{12}]$, 6 mol% ligand, 24 h. [b] Conversion and yield determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on the conversion of primary amines and the corresponding secondary amines. [c] 8 h reaction time. [d] 4 mol% $[Ru_3(CO)_{12}]$, 12 mol% ligand. [e] Yield of isolated product.

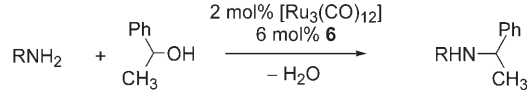
phenylmethanol (Table 3, entries 17, 20, and 23) gave the corresponding secondary *N*-hexylamines in moderate to good yields (66–84%). Interestingly, at 110°C the primary furyl alcohol led to more side reactions. Even at a higher catalyst loading of 4 mol%, the yield dropped to 49% (Table 3, entry 21) owing to the formation of difuryl side products. This demonstrates the importance of the development of new catalysts for this transformation under milder conditions.

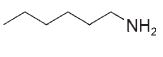
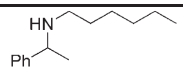
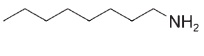
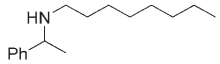
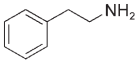
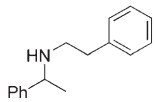
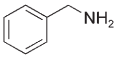
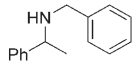
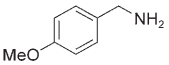
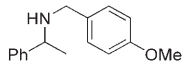
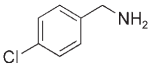
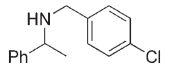
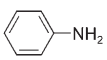
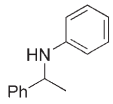
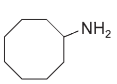
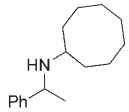
To demonstrate the usefulness of this novel amination catalyst, we explored the alkylation of various amines (Table 4). All catalytic reactions were run at the same reaction temperature to observe the effect of steric and electronic parameters. In some cases no full conversion was observed (Table 4, entries 5, 7, 9, and 13). However, the yield of the corresponding amination product could be optimized by increasing the reaction temperature. As expected, the reactivity and yield of the alkylated amine decreased in the order *n*-hexylamine > *n*-octylamine = 2-phenylethylamine > benzylamine > cyclooctylamine (Table 4, entries 1–3, 5, and 13). These observations can be explained by steric effects of the aliphatic amines, and in the case of aniline by the reduced nucleophilicity. With aniline, no conversion was observed (Table 4, entries 11 and 12). Electron-rich anilines (3,5-dimethoxyaniline and 2,4,6-trimethylaniline) also gave no reaction at all. By comparing the reaction of benzylamine, *p*-methoxybenzylamine, and *p*-chlorobenzylamine, it became clear that there is no strong electronic influence on the reaction (Table 4, entries 5, 7, 9). Notably, at 110°C the sterically more hindered cyclooctylamine was converted into the desired amine in good yield (80%) and selectivity (Table 4, entries 13 and 14).

Conclusions

In summary, we have presented a study on the ruthenium-catalyzed N-alkylation of amines with alcohols. We tested 22 different ruthenium complexes as amination catalysts. Among these, the novel in situ catalyst $[Ru_3(CO)_{12}]$/*N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole showed the highest activity and selectivity. The alkylation reactions were performed under significantly milder conditions than those of most known aminations of alcohols and proceeded in good to excellent yield. The catalyst system showed its general applicability in the reaction of 16 different functionalized amines and alcohols.

Table 4. N-alkylation of different amines with 1-phenylethanol in the presence of $[Ru_3(CO)_{12}]$ and ligand **6**.[a]



Entry	Amine	Product	*T* [°C]	Conv. [%][b]	Yield [%][b]
1			110	100	98
2			110	100	92
3			110	98	90
4			120	100	96
5			110	88	68
6			120	100	87
7			110	86	66
8			120	100	84
9			110	89	68
10			120	100	92
11			110	0	0
12			150	5	trace
13			110	80	58
14			120	98	80

[a] Reaction conditions: 1 mmol amine, 5 mmol 1-phenylethanol, 0.02 mmol $[Ru_3(CO)_{12}]$, 0.06 mmol ligand **6**, 110°C, 24 h. [b] Conversion and yield determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on the conversion of primary amines and the corresponding secondary amines.

Experimental Section

General Remarks

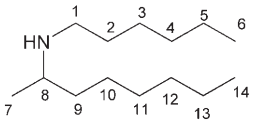
All reactions were carried out under argon atmosphere. Chemicals were purchased from Aldrich, Fluka, Acros, and Strem and, unless otherwise noted, were used without further purification. Amines and alcohols were distilled under argon. All compounds were characterized by ^1H and ^{13}C NMR and IR spectroscopy as well as MS and HRMS. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 300, AV 400, and AV 500 spectrometers. For new substances, complete assignment of the ^1H and ^{13}C signals is given. ^1H and ^{13}C NMR chemical shifts are reported relative to the center of the solvent resonance ($CDCl_3$: 7.25 (^1H), 77.0 ppm (^{13}C)). EI mass spectra were recorded on an AMD 402 spectrometer (70 eV, AMD Intectra GmbH). IR spectra were recorded on a Nicolet Magna 550 spectrometer. Elemental analysis was performed on a C/H/N/S Analysator 932 instrument (Leco). GC was performed on a Hewlett Packard HP 6890 chromatograph with an Optima 5 amine column (Machery-Nagel, 30 m × 0.25 μm, 0.5 μm film thickness, 50–8–200/5–8–260/5–8–280/5–8–300/20). All yields reported in Tables 1–4 were determined by GC with hexadecane as an

internal standard. To verify the reproducibility, all reactions were carried out at least twice. In general, large-scale reactions were carried out with tri-*ortho*-tolylphoshine as ligand at 110–140 °C. Here the products were isolated in yields of up to 80%. The synthesis and experimental data of *N*-(2-thiophenylmethyl)-*n*-hexyl-1-amine hydrochloride has been described previously.[21]

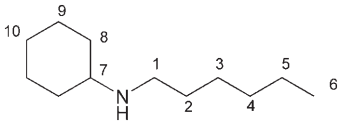
Syntheses

General procedure for the amination reaction: In a pressure tube (ACE) under argon atmosphere, $[Ru_3(CO)_{12}]$ (0.02 mmol) and **6** (0.06 mmol) were dissolved in the alcohol (5 mmol) and amine (1 mmol). The pressure tube was fitted with a teflon cap and heated at 110 °C for 24 h in an oil bath. The yield and conversion was determined by GC. In preparative reactions the excess alcohol was distilled. The residue was purified by column chromatography with hexane/ethyl acetate or chloroform/ethyl acetate to give the corresponding amine as an oil.

n-Hexyl(1-methylheptyl)amine: FTIR (neat): $\tilde{\nu}$ = 3290 (br, NH), 2958 (s), 2926 (vs), 2856 (s), 1684 (m), 1467 (s), 1377 (m), 725 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.87 (m, 6H, 6-H, 14-H), 0.99 (d, ^3J = 6.2 Hz, 3H, 7-H), 1.12–1.31 (m, 16H, 3-H–5-H,9-H–13-H), 1.32–1.48 (m, 3H, 2-H, NH), 2.45–2.63 ppm (m, 3H, 1-H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.0 (2×CH_3, C6, C14), 20.3 (CH_3, C7), 22.6 (2×CH_2), 26.0 (CH_2), 27.1 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 37.2 (CH_2), 47.4 (CH_2), 53.2 ppm (CH, C8); MS (EI, 70 eV): *m/z* (%) = 214 (2) $[M+H]^+$, 213 (2) $[M]^+$, 212 (3) $[M-H]^+$, 198 (41) $[M-CH_3]^+$, 142 (26) $[M-C_5H_{11}]^+$, 129 (40), 128 (100) $[M-C_6H_{13}]^+$, 58 (17), 57 (13), 44 (24), 43 (23), 41 (15), 30 (11); HRMS: *m/z* calcd for $C_{14}H_{30}N$: 212.2373 $[M-H]^+$; found: 212.2363.

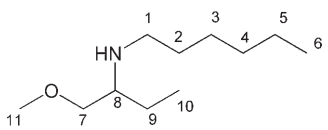


Cyclohexyl-*n*-hexylamine: FTIR (neat): $\tilde{\nu}$ = 3281 (br, NH), 2958 (s), 2926 (vs), 2854 (s), 1684 (m), 1450 (s), 1379 (m), 1133 (m), 726 cm^{-1} (m); ^1H NMR (500, $CDCl_3$): δ = 0.86 (t, $^3J_{5\text{-H},6\text{-H}}$ = 7.0 Hz, 3H, 6-H), 1.03 (m, 2H, 8-H_{ax}), 1.13 (m, 1H, 10-H_{ax}), 1.19–1.31 (m, 7H, 3-H–5-H, 9-H_{ax}),

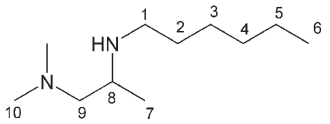


1.41–1.47 (m, 2H, 2-H), 1.59 (m, $^2J_{10\text{-Heq},10\text{-Hax}}$ = 12.3 Hz, 1H, 10-H_{eq}), 1.70 (m, $^2J_{9\text{-Heq},9\text{-Hax}}$ = 13.2 Hz, 2H, 9-H_{eq}), 1.85 (m, $^2J_{8\text{-Heq},8\text{-Hax}}$ = 12.5 Hz, 2H, 8-H_{eq}), 2.38 (tt, $^3J_{7\text{-H},8\text{-Hax}}$ = 10.5 Hz, $^3J_{7\text{-H},8\text{-Heq}}$ = 3.8 Hz, 1H, 7-H), 2.58 (t, $^3J_{1\text{-H},2\text{-H}}$ = 7.3 Hz, 2H, 1-H), 2.58 ppm (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_3, C6), 22.6 (CH_2, C5), 25.1 (CH_2, C9), 26.2 (CH_2, C10), 27.1 (CH_2, C3), 30.5 (CH_2, C2), 31.8 (CH_2, C4), 33.6 (CH_2, C8), 47.1 (CH_2, C1), 56.9 ppm (CH, C7); MS (EI, 70 eV): *m/z* (%) = 183 (8) $[M^+]$, 140 (94) $[M-C_3H_7]^+$, 112 (100) $[M-C_5H_{11}]^+$, 56 (24), 55 (19), 43 (14), 41 (20), 30 (37), 29 (10); HRMS: *m/z* calcd for $C_{12}H_{25}N$: 183.1982; found: 183.1979.

N-(1-methoxy-2-butyl)-*n*-hexylamine: FTIR (neat): $\tilde{\nu}$ = 3328 (w, NH), 2958 (s), 2926 (s), 2873 (s), 2840 (s), 1463 (s), 1378 (s), 1198 (s, CO), 1112 cm^{-1} (s, CO); ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 7.0 Hz, 3H, 6-H), 0.89 (t, ^3J = 7.6 Hz, 3H, 10-H), 1.24–1.33 (m, 6H, 3-H–5-H), 1.36–1.54 (m, 4H, 2-H, 9-H), 1.82 (br, 1H, NH), 2.51–2.65 (m, 3H, 1-H, 8-H), 3.25 (dd, $^3J_{7a\text{-H},8\text{-H}}$ = 7.1 Hz, $^2J_{7a\text{-H},7b\text{-H}}$ = 9.5 Hz, 1H, 7a-H), 3.33 (s, 3H, 11-H), 3.37 ppm (dd, $^3J_{7b\text{-H},8\text{-H}}$ = 4.3 Hz, $^2J_{7a\text{-H},7b\text{-H}}$ = 9.5 Hz, 1H, 7b-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.3 (CH_3, C10), 14.1 (CH_3, C6), 22.7 (CH_2, C5), 24.2 (CH_2, C9), 27.1 (CH_2, C3), 30.4 (CH_2, C2), 31.8 (CH_2, C4), 47.5 (CH_2, C1), 58.9 (CH, C8), 59.0 (CH_3, C11), 74.8 ppm (CH_2, C7); MS (EI, 70 eV) *m/z* (%): 187 (1) $[M]^+$, 186 (1) $[M-H]^+$, 158 (12) $[M-C_2H_5]^+$, 143 (21), 142 (100) $[M-CH_2OCH_3]^+$, 116 (9) $[M-C_5H_{11}]^+$, 84 (7), 72 (12), 58 (38), 45 (13), 43 (16), 11 (52).

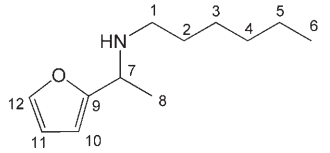


N^2-hexyl-N^1,N^1-dimethylpropyl-1,2-diamine: FTIR (neat): 3303 (w, NH), 2958 (s), 2927 (s), 2854 (s), 2817 (s), 2792 (s), 2768 (s), 1458 (s), 1376 (m), 1337 (m), 1264 (m), 1143 (m), 1037 (m), 840 cm^{-1} (m); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, ^3J = 6.8 Hz, 3H, 6-H), 0.91 (d, ^3J = 6.2 Hz,



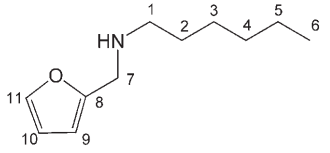
3H, 7-H), 1.18–1.30 (m, 6H, 3-H–5-H), 1.38–1.48 (m, 2H, 2-H), 1.84 (s, 1H, NH), 1.94 (dd, $^3J_{8a\text{-H},9a\text{-H}}$ = 4.2 Hz, $^3J_{8b\text{-H},9a\text{-H}}$ = 12.1 Hz, 1H, 9a-H), 2.12 (s, 6H, 10-H), 2.22 (dd, $^3J_{8a\text{-H},9b\text{-H}}$ = 10.0 Hz, $^3J_{8b\text{-H},9b\text{-H}}$ = 12.1 Hz, 1H, 9b-H), 2.35–2.43 (m, 1H, 8-H), 2.57–2.67 ppm (m, 2H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3, C6), 18.6 (CH_3, C7), 22.7 (CH_2, C5), 27.2 (CH_2, C3), 30.3 (CH_2, C2), 31.8 (CH_2, C4), 45.8 (2×CH_3, C10), 47.8 (CH_2, C1), 50.6 (CH, C8), 66.4 ppm (CH_2, C9); MS (EI, 70 eV): *m/z* (%) = 128 (100) $[M-C_2H_6NCH_2]^+$, 58 (30) $[C_2H_6NCH_2]^+$.

N-(1-(2-furyl)ethyl-*n*-hexylamine: FTIR (neat): $\tilde{\nu}$ = 3316 (br, NH), 3115 (w), 2957 (s), 2927 (s), 2856 (s), 2023 (w), 1938 (w), 1741 (m), 1505 (m), 1466 (m), 1372 (m), 1239 (m), 1150 (m), 1008 (m), 923 (m), 803 (m), 731 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 7.0 Hz, 3H, 6-



H), 1.23–1.31 (m, 8H, 2-H–5-H), 1.39 (d, $^3J_{7\text{-H},8\text{-H}}$ = 6.8 Hz, 3H, 8-H), 2.50 (t, ^3J = 6.8 Hz, 2H, 1-H), 3.83 (q, $^3J_{7\text{-H},8\text{-H}}$ = 6.8 Hz, 1H, 7-H), 6.11 (dd, $^3J_{9\text{-H},10\text{-H}}$ = 3.2 Hz, $^4J_{9\text{-H},11\text{-H}}$ = 0.8 Hz, 1H, 10-H), 6.29 (dd, $^3J_{9\text{-H},10\text{-H}}$ = 3.2 Hz, $^3J_{10\text{-H},11\text{-H}}$ = 1.9 Hz, 1H, 11-H), 7.33 ppm (dd, $^3J_{10\text{-H},11\text{-H}}$ = 1.9 Hz, $^4J_{9\text{-H},11\text{-H}}$ = 0.8 Hz, 1H, 12-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3, C6), 20.4 (CH_3, C8), 22.6 (CH_2, C5), 27.1 (CH_2, C3), 30.2 (CH_2, C2), 31.8 (CH_2, C4), 47.3 (CH_2, C1), 51.3 (CH, C7), 105.1 (CH, C10), 109.8 (CH, C11), 141.3 (CH, C12), 158.1 ppm (C_q, C9); MS (EI, 70 eV): *m/z* (%) = 195 (1) $[M]^+$, 180 (34) $[M-CH_3]^+$, 124 (6), 110 (6), 96 (18), 95 (100), 41 (15); HRMS: *m/z* calcd for $C_{12}H_{21}ON$: 195.16177; found: 195.19127.

N-(2-furylmethyl)-*n*-hexylamine: FTIR (neat): $\tilde{\nu}$ = 3319 (br, NH), 3119 (w), 2955 (s), 2927 (s), 2856 (s), 1505 (m), 1457 (m), 1148 (m), 1111 (m), 1010 (m), 919 (m), 803 (m), 729 (m), 599 cm^{-1} (m); ^1H NMR (500 $CDCl_3$): δ = 0.86 (t, ^3J = 7.0 Hz, 3H, 6-H), 1.23–1.32 (m, 6H, 3-H–5-H), 1.47 (m, 2H, 2-H), 1.83 (br, 1H, NH), 2.62 (t, $^3J_{1,2}$ = 7.2 Hz, 2H, 1-H), 3.76 (s, 2H, 7-H), 6.15 (dd, $^3J_{9\text{-H},10\text{-H}}$ = 3.2 Hz, $^4J_{9\text{-H},11\text{-H}}$ = 0.7 Hz, 1H, 9-H), 6.29 (dd, $^3J_{9\text{-H},10\text{-H}}$ = 3.2 Hz, $^3J_{10,11}$ = 1.8 Hz, 1H, 10-H), 7.34 ppm (dd, $^3J_{10\text{-H},11\text{-H}}$ = 1.8 Hz, $^4J_{9\text{-H},11\text{-H}}$ = 0.7 Hz, 1H, 11-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_3, C6), 22.6 (CH_2, C5), 27.0 (CH_2, C3), 29.9 (CH_2, C2), 31.7 (CH_2, C4), 46.2 (CH_2, C7), 49.2 (CH, C1), 106.8 (CH, C9), 110.0 (CH, C10), 141.7 (CH, C11), 154.0 ppm (C_q, C8); MS (EI, 70 eV): *m/z* (%) = 181 (1) $[M]^+$, 110 (26), 96 (8), 81 (100); HRMS: *m/z* calcd for $C_{11}H_{19}ON$: 181.14612; found: 181.14622.



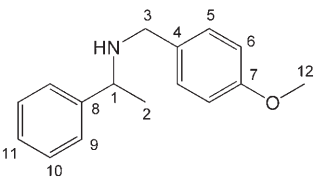
n-Hexyl(1-phenylethyl)amine:[28] FTIR (neat): $\tilde{\nu}$ = 3334 (br, NH), 3083, 3062, 3026 (w), 2958 (s), 2926 (vs), 2856 (s), 1492 (m), 1452 (vs), 1261 (m), 1130 (m), 1079 (m), 1027 (m), 804 (m), 761 (m), 700 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.18–1.32 (m, 6H, CH_2), 1.34 (d, ^3J = 6.5 Hz, 3H, CH_3), 1.38–1.51 (m, 2H, CH_2), 2.44 (m, 2H, CH_2), 3.72 (q, ^3J = 6.5 Hz, 1H, CH), 7.20–7.35 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6 (CH_2), 24.3 (CH_3), 27.0 (CH_2), 30.2 (CH_2), 31.7 (CH_2), 47.9 (CH_2), 58.4 (CH), 126.5 (CH, C_{Ar}), 126.8 (CH, C_{Ar}), 128.3 (CH, C_{Ar}), 145.9 ppm (C_q, C_{Ar}); MS (EI, 70 eV): *m/z* (%) = 205 (4) $[M]^+$, 190 (47) $[M-CH_3]^+$, 134 (25) $[M-C_5H_{11}]^+$, 106 (25), 105 (100) $[PhCHCH_3]^+$, 79 (11), 77 (11), 43 (13), 30 (45), 28 (22), 27 (11); HRMS: *m/z* calcd for $C_{14}H_{23}N$: 205.18304; found: 205.18278.

n-Octyl(1-phenylethyl)amine:[29] FTIR (neat): 3333 (br, NH), 3083, 3062, 3025 (w), 2958 (s), 2925 (vs), 2854 (s), 1492 (m), 1452 (s), 1132 (m), 761 (m), 700 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.5 Hz, 3H, CH_3), 1.17–1.28 (m, 10H, CH_2), 1.34 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.38–1.51 (m, 2H, CH_2), 2.44 (m, 2H, CH_2), 3.74 (q, ^3J = 6.6 Hz, 1H, CH), 7.19–7.35 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6 (CH_2), 24.4 (CH_3), 27.3 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 30.3 (CH_2), 31.8 (CH_2), 47.9 (CH_2), 58.4 (CH), 126.5 (CH, C_{Ar}), 126.7 (CH, C_{Ar}), 128.3 (CH, C_{Ar}), 145.9 ppm (C_q, C_{Ar}); MS (EI, 70 eV): *m/z* (%) = 233 (3) $[M]^+$, 218 (71) $[M-CH_3]^+$, 134 (35) $[M-C_7H_{15}]^+$, 106 (24), 105 (100) $[PhCHCH_3]^+$, 85 (12), 71 (20), 58 (36), 56 (13), 43 (18), 41 (15), 30 (31), 29 (12); HRMS: *m/z* calcd for $C_{16}H_{27}N$: 233.21436; found: 233.21345.

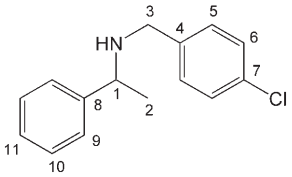
2-Phenylethyl(1-phenylethyl)amine:[30] FTIR (neat): 3318 (br, NH), 3083, 3061, 3026 (w), 2960 (m), 2924 (m), 2835 (m), 1494 (m), 1452 (m), 1130 (m), 1079 (m), 1027 (m), 751 (m), 699 cm^{-1} (s); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.40 (s, 1H, NH), 2.59–2.72 (m, 4H, CH_2), 3.69 (q, ^3J = 6.6 Hz, 1H, CH), 7.06–7.24 ppm (m, 10H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (CH_3), 36.4 (CH_2), 49.0 (CH_2), 58.2 (CH), 126.0 (CH, C_{Ar}), 126.5 (CH, C_{Ar}), 126.8 (CH, C_{Ar}), 128.4 (2× CH, C_{Ar}), 128.6 (CH, C_{Ar}), 140.0 (C_q), 145.5 (C_q); MS (EI, 70 eV): *m/z* (%) = 225 (1) $[M]^+$, 224 (1) $[M-H]^+$, 210 (8) $[M-CH_3]^+$, 134 (100) $[M-C_7H_7]^+$, 105 (100) $[PhCHCH_3]^+$, 91 (23) $[PhCH_2]^+$, 77 (35) $[Ph]^+$; HRMS: *m/z* calcd for $C_{16}H_{18}N_1$: 224.14338 $[M-H]^+$; found: 224.14310.

Benzyl(1-phenylethyl)amine:[31] FTIR (neat): $\tilde{\nu}$ = 3316 (br, NH), 3084 (w), 3062 (m), 3036 (m), 2969 (m), 2925 (w), 2864 (w), 1686 (m), 1602 (m), 1493 (s), 1493 (s), 1377 (m), 761 (s), 738 (m), 700 cm^{-1} (vs); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, J = 6.5 Hz, 3H), 1.58 (s, 1H, NH), 3.62 and 3.68 (ABX system, J = 13.1 Hz, 2H), 3.83 (q, J = 6.5 Hz, 1H), 7.21–7.40 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (CH_3), 51.6 (CH_2), 57.7 (CH), 126.7 (CH, C_{Ar}), 126.8 (CH, C_{Ar}), 126.9 (CH, C_{Ar}), 128.1 (CH, C_{Ar}), 128.3 (CH, C_{Ar}), 128.4 (CH, C_{Ar}), 140.6 (C_q, C_{Ar}), 145.6 ppm (C_q, C_{Ar}); MS (EI, 70 eV): *m/z* (%) = 211 (2), $[M]^+$, 197 (11), 196 (67) $[M-CH_3]^+$, 105 (15) $[PhCHCH_3]^+$, 91 (100) $[PhCH_2]^+$, 77 (10); HRMS: *m/z* calcd for $C_{15}H_{17}N$: 211.13609; found: 211.136024.

(4-Methoxybenzyl)(1-phenylethyl)amine:[32] FTIR (neat): $\tilde{\nu}$ = 3328 (br, NH), 3061 (m), 3026 (m), 2995 (m), 2959 (m), 2930 (m), 2833 (m), 1611 (m), 1512 (s), 1451 (m), 1301 (m), 1247 (s), 1036 (m), 822 (m), 761 (m), 702 cm^{-1} (m); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, ^3J = 6.6 Hz, 3H, 2-H), 1.59 (s, 1H, NH), 3.51 and 3.59 (ABX system, ^2J = 12.9 Hz, 2H, 3-H), 3.78 (s, 3H, 12-H), 3.80 (q, J = 6.6 Hz, 1H, 1-H), 6.81–6.86 (m, 2H, 5-H), 7.17–7.22 (m, 2H, 6-H), 7.23–7.28 (m, 1H, 11-H), 7.32–7.37 (m, 4H, 9-H, 10-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6 (CH_3, C2), 51.1 (CH_2, C3), 55.3 (CH_3, C12), 57.5 (CH, C1), 113.8 (CH, C6), 128.5 (CH, C10), 126.8 (CH, C9), 127.0 (CH, C11), 129.4 (CH, C5), 132.9 (C_q, C4), 145.7 (C_q, C8), 158.6 ppm (C_q, C7); MS (EI, 70 eV): *m/z* (%) = 241 (11) $[M]^+$, 226 (99) $[M-CH_3]^+$, 136 (33), 121 (100) $[CH_2C_6H_4OMe]^+$, 105 (35), 91 (16), 77 (31); HRMS: *m/z* calcd for $C_{16}H_{19}N_1O_1$: 241.14612; found: 241.146301.

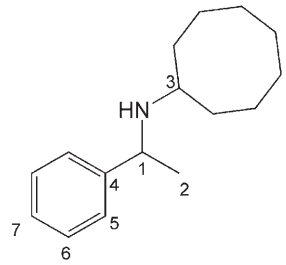


(4-Chlorobenzyl)(1-phenylethyl)amine: FTIR (neat): $\tilde{\nu}$ = 3331 (br, NH), 3082 (s), 3061 (s), 3025 (m), 2962 (m), 2924 (m), 2832 (m), 1490 (s), 1451 (m), 1125 (m), 1088 (s), 1015 (m), 761 (m), 701 cm^{-1} (m); ^1H NMR



(300 MHz, $CDCl_3$): δ = 1.38 (d, ^3J = 6.6 Hz, 3H, CH_3), 3.55 and 3.63 (ABX system, ^2J = 12.9 Hz, 2H, CH_2), 3.79 (q, ^3J = 6.6 Hz, 1H, 1-H), 7.20–7.35 (m, 9H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5 (CH_3, C2), 50.9 (CH_2, C3), 57.5 (CH, C1), 126.7 (CH, C9), 128.5 (CH, C10), 127.1 (CH, C11), 128.5 (CH), 129.5 (CH) (C5, C6), 132.5 (C_q, C7), 139.1 (C_q, C4), 145.4 ppm (C_q, C8); MS (EI, 70 eV): *m/z* (%): 230 (100) $[M-CH_3]^+$, 125 (100) $[ClC_6H_4CH_2]^+$, 105 (27) $[C_6H_5CH_2CH_3]^+$; HRMS: *m/z* calcd for $C_{14}H_{13}N_1Cl_1$: 230.07310 $[M-CH_3]^+$; found: 230.072815.

Cyclooctyl(1-phenylethyl)amine: FTIR (neat): $\tilde{\nu}$ = 3308 (br, NH), 3061 (w), 3024 (w), 2920 (vs), 2852 (s), 1668 (m), 1492 (w), 1481 (m), 1471 (m), 1367 (m), 1123 (m), 760 (s), 738 (m), 700 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, ^3J = 6.6 Hz, 3H, 2-H), 1.35–1.80 (m, 15H, CH_2, NH), 2.49 (m, 1H, 3-H), 3.86 (q, ^3J = 6.6 Hz, 1H, 1-H), 7.19–7.33 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6 (CH_2), 24.2 (CH_2), 24.9 (CH_3, C2), 25.6 (CH_2), 27.1 (CH_2), 27.6 (CH_2), 31.0 (CH_2), 33.9 (CH_2), 54.3 (CH, C3), 54.9 (CH, C1), 126.5 (CH, C5), 126.7 (CH, C7), 128.3 (CH, C6), 146.3 ppm (C_q, C4); MS (EI, 70 eV): *m/z* (%) = 231 (17) $[M]^+$, 216 (32) $[M-CH_3]^+$, 188 (11), 160 (33) $[M-C_5H_{11}]^+$, 147 (19), 126 (15), 106 (32), 105 (100) $[PhCHCH_3]^+$, 104 (11), 84 (12), 79 (11), 77 (10), 56 (39), 43 (12), 41 (10); HRMS: *m/z* calcd for $C_{16}H_{25}N$: 231.19870; found: 231.19847.



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4.3. Salt-free Synthesis of Tertiary Amines via Ruthenium-catalyzed Amination of Alcohols

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Contributions

In this paper, I was involved in the planning of experiments, discussion, and argumentation of the results. My contribution as co-author of this paper is approximately 20 %.

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Salt-Free Synthesis of Tertiary Amines by Ruthenium-Catalyzed Amination of Alcohols

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Keywords: Ruthenium / Amination / Alcohols

The amination of secondary alcohols to give tertiary amines in the presence of different in situ generated ruthenium catalysts has been investigated in detail. By applying a combination of $[Ru_3(CO)_{12}]$ and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole as the catalyst, cyclic amines can be alkylated with different alcohols in high yield, whereas aliphatic amines gave transalkylation side products.

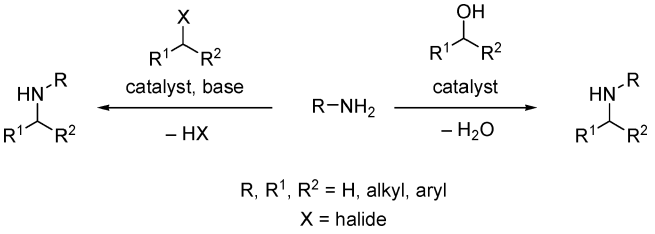
Introduction

A variety of amines is of significant importance for the bulk- and fine-chemical industry as building blocks for polymers and dyes, but also for the synthesis of pharmaceuticals and agrochemicals.[1] In addition, a plethora of naturally bioactive compounds such as alkaloids, amino acids, and nucleotides contain amino groups. Despite numerous known procedures, the development of improved methods for the synthesis of amines continues to be a challenging and actual area of research.[2] In the last decade especially catalytic aminations, such as palladium-, copper-, and nickel-catalyzed aminations of aryl halides,[3] hydroaminations,[4,5] as well as hydroaminomethylations[6] of olefins or alkynes have received significant attention. Compared to the well-known classic *N*-alkylations of amines by using alkyl halides as starting materials[7] and reductive aminations with carbonyl compounds,[8] an atom economical[9] and environmentally attractive method is the amination of primary and secondary alcohols (Scheme 1).

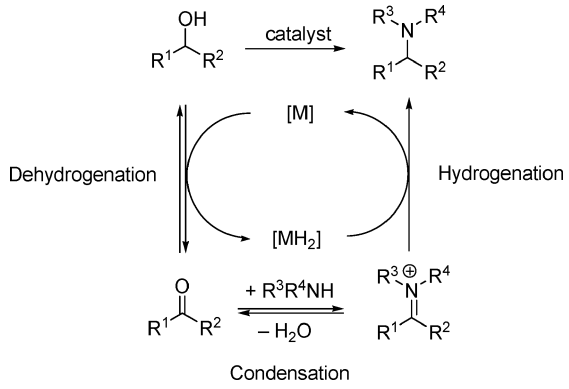
Although formally a nucleophilic substitution takes place, this reaction is based on the in situ dehydrogenation of the alcohol to give the corresponding aldehyde or ketone. Then, the carbonyl intermediate reacts with an amine to give the corresponding imine or iminium species. Depending on the substituents, an enamine intermediate might also be involved, for example, $R^1 = RCH_2$ (R = H, alkyl, aryl). Finally, reduction with the initially produced hydrogen produces the *N*-alkylated amine (Scheme 2).

As no additional hydrogen is needed, this reaction sequence has been coined by Williams and coworkers as the "borrowing hydrogen" mechanism.[10] Notably, the same type of dehydrogenation–functionalization–hydrogenation sequence has recently been used in alkane metathesis,[11] β-alkylation of alcohols,[12] and C–C bond-formation processes such as the Wittig or Knoevenagel reactions.[13–15]

Advantages of the catalytic amination of alcohols are the availability of substrates and the high atom efficiency of the reaction sequence, which forms water as the only sideprod-



Scheme 1. Catalytic *N*-alkylation of amines with alcohols or alkyl halides.



Scheme 2. Catalytic hydrogen transfer in the *N*-alkylation of secondary amines with secondary alcohols.

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uct. Moreover, compared to typical reductive aminations, it is possible to run these reactions in the absence of additional hydrogen. Hence, the reaction can be performed at ambient pressure in typical glassware.

The first homogeneous catalysts for *N*-alkylation of amines with alcohols were introduced by Grigg et al.[16] and Watanabe et al.[17] in 1981. Thereafter, ruthenium,[18,19] rhodium,[19] platinum,[20] and iridium complexes[19,21] have been described as homogeneous transition-metal catalysts for such reactions. Recently, we developed a general protocol for the synthesis of secondary aliphatic amines starting from primary amines and secondary alcohols in the presence of ruthenium carbonyl {$[Ru_3(CO)_{12}]$} and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole (cataCXium® PCy) (**I**) as catalyst system.[22] Moreover, we discovered a related synthesis of secondary aromatic amines starting from aliphatic amines and anilines by using the so-called Shvo catalyst.[23]

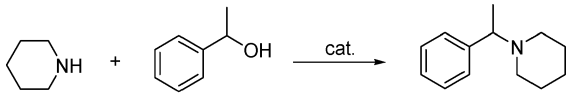
On the basis of this work, we became interested in the synthesis of tertiary amines by *N*-alkylation of secondary amines. Clearly, a variety of tertiary amines are of pharmaceutical interest,[24] especially piperazine derivatives.[25] However, so far only few examples are known for catalytic *N*-alkylations of secondary amines.[16,18g,19] For example, Williams et al. reported recently the Ru-catalyzed synthesis of tertiary amines from primary alcohols and secondary amines.[18a] Earlier, Fujita et al.[21c] reported the *N*-alkylation of secondary amines, for example, *N*-methylaniline, *N*-(1-phenethyl)aniline, and pyrrolidine, with cyclohexanol as the secondary alcohol in the presence of $[Cp^*IrCl_2]_2$. However, to the best of our knowledge, there is no general ruthenium-catalyzed synthesis of tertiary amines from secondary alcohols known.

Results and Discussion

Recently, we reported the advantageous use of ruthenium carbonyl $[Ru_3(CO)_{12}]$ and *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole[22] for the synthesis of secondary amines. Hence, we started our investigations with this in situ generated catalyst system. Initially, the reaction of 1-phenylethanol with piperidine was investigated as a model system. Preliminary results are shown in Table 1. By using an excess amount of alcohol, only moderate yields and no complete conversions were observed (Table 1, Entries 1–4).

Increasing the reaction temperature to 140 °C led to an improved product yield of 71% (Table 1, Entries 2–4). Surprisingly, in the presence of *tert*-amyl alcohol (2-methylbutan-2-ol) as solvent, full conversion and excellent yield (98%) of the desired product were obtained (Table 1, Entry 6). Notably, under the same conditions without ligand only 41% yield was observed (Table 1, Entry 5). Upon further optimization (Table 1, Entries 7–20), the ratio of amine to alcohol could be reduced without decreasing the yield (Table 1, Entry 11).

Table 1. Catalytic *N*-alkylation of piperidine with 1-phenylethanol.[a]



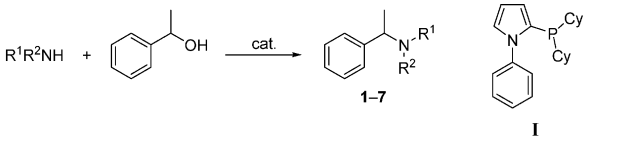
1

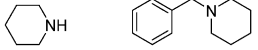
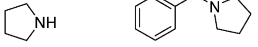
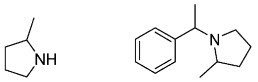
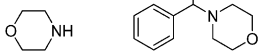
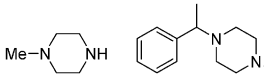
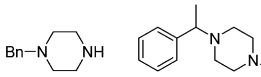
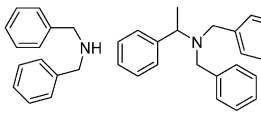
Entry	Ligand	Solvent (mL)	*T* [°C]	Amine/Alcohol	Conv.[b] [%]	Yield[b] [%]
1	–	–	130	1:5	72	32
2	cataCXium® PCy[c]	–	130	1:5	80	50
3	cataCXium® PCy[c]	–	140	1:5	87	71
4	cataCXium® PCy[c]	–	150	1:5	84	70
5	–	*tert*-amyl alcohol (0.5)	140	1:3	51	41
6	cataCXium® PCy[c]	*tert*-amyl alcohol (0.5)	140	1:3	100	98
7	cataCXium® PCy[c]	*tert*-amyl alcohol (0.5)	140	1:2	100	88
8	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:2	100	94
9	cataCXium® PCy[c]	*tert*-amyl alcohol (0.5)	140	1:1.1	87	78
10	cataCXium® PCy[c]	*tert*-amyl alcohol (0.2)	140	1:1.1	94	88
11	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:1.5	100	97 (92)
12	cataCXium® PCy[c]	*tert*-amyl alcohol (0.4)	140	1:1.5	100	93
13	cataCXium® PCy[c]	*tert*-amyl alcohol (0.2)	140	1:1.5	100	84
14	cataCXium® PCy[c]	toluene (0.3)	140	1:1.5	99	86
15	cataCXium® PCy[c]	dioxane (0.3)	140	1:1.5	97	84
16[d]	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:1.5	83	64
17[e]	cataCXium® PCy[c]	*tert*-amyl alcohol (0.3)	140	1:1.5	88	77
18	2-(dicyclohexylphosphanyl)biphenyl	*tert*-amyl alcohol (0.3)	140	1:1.5	80	68
19	(*o*-tolyl)$_3$P[f]	*tert*-amyl alcohol (0.3)	140	1:1.5	69	49
20	cataCXium® A[g]	*tert*-amyl alcohol (0.3)	140	1:1.5	78	74

[a] Reaction conditions: pyridine (1.0 mmol), 1-phenylethanol (1.1–5.0 mmol), $[Ru_3(CO)_{12}]$ (2.0 mol-%), ligand (6.0 mol-%), without or with solvent (0.20–0.50 mL), 130–150 °C, 8–24 h. [b] Conversions and yields were determined by GC analysis with hexadecane as internal standard, isolated yields are given in parenthesis. [c] CataCXium® PCy = *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole. [d] Catalyst (1.0 mol-%). [e] Reaction time: 8 h. [f] Tri-*o*-tolylphosphane. [g] CataCXium® A = *n*-butyldi-1-adamantylphosphane.[26]

Next, the amination of 1-phenylethanol with different secondary amines was explored. Unfortunately, it turned out that all of the substrates performed in their own way. Hence, each reaction needed its own set of optimized conditions, which are shown in Table 2. Pyrrolidine gave the best results (88% yield) without any stabilizing phosphane ligand present (Table 2, Entry 2).

Table 2. Catalytic *N*-alkylation of different secondary amines with 1-phenylethanol in the presence of $[Ru_3(CO)_{12}]$ and cataCXium® PCy (**I**).[a]

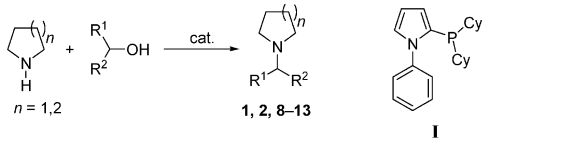


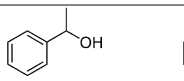
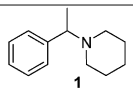
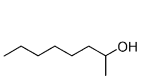
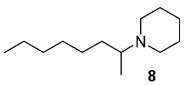
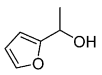
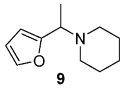
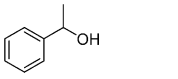
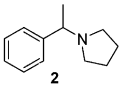
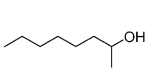
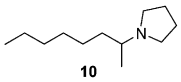
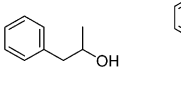
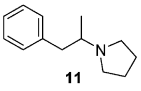
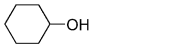
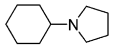
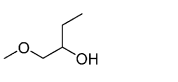
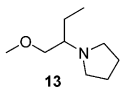
Entry	Amine	Product	Solvent (mL)	Amine/ Alcohol	Yield[b] [%]
1		**1**	*tert*-amyl alcohol (0.3)	1:1.5	97 (92)
2[c,d]		**2**	*tert*-amyl alcohol (0.2)	1:1.5	88 (83)
3[e]		**3**	*tert*-amyl alcohol (0.25)	1:1.5	81 (69)
4[f]		**4**	*tert*-amyl alcohol (0.5)	1:3	47 (37)
5[g]					34
6[c]		**5**	–	1:5	90 (69)
7[c]		**6**	–	1:5	97 (79)
8[c,h]		**7**	–	1:5	<5

[a] Reaction conditions: amine (1.0 mmol), 1-phenylethanol (1.5–5.0 mmol), $[Ru_3(CO)_{12}]$ (2.0 mol-%), cataCXium® PCy (6.0 mol-%), without or with *tert*-amyl alcohol (0.20–0.50 mL), 140 °C, 24 h. [b] Yields were determined by GC analysis with hexadecane as internal standard; isolated yields are given in parenthesis. [c] Reaction without ligand. [d] 120 °C. [e] 130 °C. [f] 62% conversion. [g] Without ligand, 49% conversion. [h] 90% conversion; main reaction is the transalkylation to tribenzylamine and benzyl(1-phenylethyl)-amine. In the presence of ligand, the conversion was <10%.

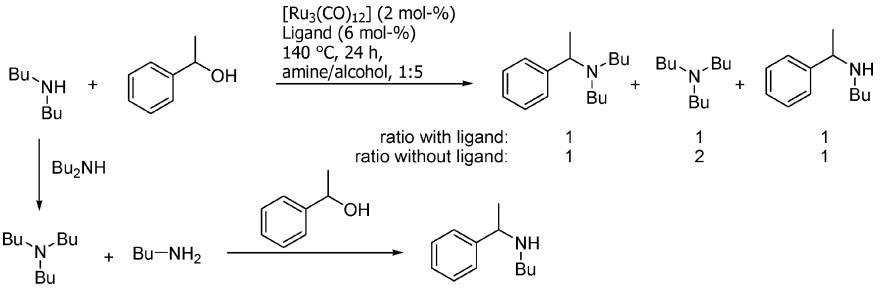
N-Methylpiperazine and *N*-benzylpiperazine led to the corresponding tertiary amines in high yield (90–97%) without any solvent (Table 2, Entries 6 and 7). By using morpholine only moderate conversion and yield (47%) were obtained (Table 2, Entries 4 and 5). In addition to *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole, 11 different ligands were tested for this reaction. However, no improved yield was obtained [e.g., tri-*o*-tolylphosphane: 42% conv., 28% yield; tricyclohexylphosphane: 19% conv., 18% yield; *n*-butyldi-1-adamantylphosphane: 55% conv., 42% yield; 2-(dicyclohexylphosphanyl)biphenyl: 48% conv., 34% yield; and *N*-(2-trimethylsilylphenyl)-2-(dicyclohexylphosphanyl)pyrrole: 52% conv., 45% yield]. Because 2-methylpyrrolidine was used as a racemic mixture, the corresponding tertiary amine was obtained as a mixture of diastereomers in a ratio of 1:1

Table 3. Catalytic *N*-alkylation of piperidine and pyrrolidine with different alcohols in presence of $[Ru_3(CO)_{12}]$ and cataCXium® PCy (**I**).[a]



Entry	Alcohol	Product	Solvent (mL)	Amine/ Alcohol	Yield[b] [%]
1		 **1**	*tert*-amyl alcohol (0.3)	1:1.5	97 (92)
2		 **8**	*tert*-amyl alcohol (0.25)	1:1.5	91 (79)
3[c]		 **9**	–	1:5	75 (52)
4[d]		 **2**	*tert*-amyl alcohol (0.2)	1:1.5	88 (83)
5		 **10**	*tert*-amyl alcohol (0.4)	1:3	89 (54)
6		 **11**	*tert*-amyl alcohol (0.4)	1:3	85 (72)
7		 **12**	*tert*-amyl alcohol (0.3)	1:1.5	92 (76)
8[e]		 **13**	–	1:5	85 (63)

[a] Reaction conditions: amine (1.0 mmol), alcohol (1.5–5.0 mmol), $[Ru_3(CO)_{12}]$ (2.0 mol-%), cataCXium® PCy (6.0 mol-%), without or with *tert*-amyl alcohol (0.20–0.40 mL), 140 °C with piperidine and 120 °C with pyrrolidine, 24 h. [b] Yields were determined by GC analysis with hexadecane as internal standard, isolated yields are given in parenthesis. [c] 91% conversion. [d] Reaction without ligand. [e] 130 °C.



Scheme 3. *N*-Alkylation of di-*n*-butylamine with 1-phenylethanol and transalkylation of di-*n*-butylamine.

(Table 2, Entry 3). However, by column chromatography the two diastereomers could be separated.

Apart from cyclic amines, we also tested acyclic substrates such as di-*n*-butylamine, *N*-methyl-*N*-octylamine, *N*-cyclohexyl-*N*-methylamine, and dibenzylamine (Table 2, Entry 8). Here, in general transalkylation of the different alkyl groups to the aliphatic amine was observed as a side reaction.[23,27] For example, in the case of the reaction of di-*n*-butylamine with 1-phenylethanol, three *n*-butyl-substituted products were observed. Unexpectedly, dehydrogenation of the aliphatic amine occurred to a considerable amount and led to tri-*n*-butylamine and *n*-butylamine. The latter product also reacts with 1-phenylethanol. Noteworthy, the product ratio can be influenced by the reaction conditions (Scheme 3). By applying mixed acyclic amines, a variety of alkylated products was observed by GC as a result of the various transalkylation reactions.

Finally, piperidine and pyrrolidine were treated with arylalkyl alcohols as well as with linear and cyclic aliphatic alcohols to give the corresponding tertiary amines in high yields (85–97%; Table 3). To our delight also some functionalized and heterocyclic derivatives such as 1-methoxy-2-butanol and 1-(2-furyl)ethanol provided the desired products in 85 and 75% yield, respectively (Table 3, Entries 3 and 8). With respect to the mechanism, it is interesting to note that only small amounts (<5%) of the respective ketones were found in the reaction mixtures.

Conclusions

In summary, we present a salt-free amination of secondary alcohols to give various tertiary amines. In the presence of an in situ generated ruthenium catalyst selective amination takes place in high yield and selectivity with secondary cyclic amines such as piperidine, pyrrolidine, and piperazine. The reaction is atom efficient leaving only water as a side product and can be conveniently carried out without additional pressure. In the case of secondary alkylamines, transalkylations occur as side reactions.

Experimental Section

General Procedure for *N*-Alkylation Reaction with Solvent: In a pressure tube (ACE) under an argon atmosphere $[Ru_3(CO)_{12}]$ (0.02 mmol) and ligand (0.06 mmol) were dissolved in *tert*-amyl alcohol (0.2–0.5 mL). Then, the corresponding alcohol (1.5 or 3 mmol) and secondary amine (1 mmol) were added. The pressure tube was fitted with a Teflon cap and stirred at 120–140 °C for 24 h. The solvent was removed in vacuo, and the crude product was purified by column chromatography.

General Procedure for *N*-Alkylation Reaction without Solvent: In a pressure tube (ACE) under an argon atmosphere $[Ru_3(CO)_{12}]$ (0.2 mmol) and ligand (0.6 mmol) were dissolved in the corresponding alcohol (50 mmol) and secondary amine (10 mmol). The pressure tube was fitted with a Teflon cap and stirred at 130–140 °C for 24 h. The excess alcohol was distilled, and the crude product was purified by column chromatography.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for compounds **1**–**6** and **8**–**13**.

Acknowledgments

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4.4. A General Ruthenium-catalyzed Synthesis of Aromatic Amines

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Contributions

My contribution as co-author of this paper is approximately 85 %. I was responsible for the complete work. Mr. Sebastian Bähn worked under my supervision as a student trainee.

Aminierungen

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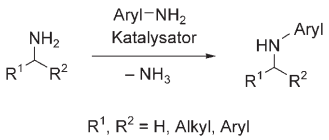
Eine allgemeine rutheniumkatalysierte Synthese von aromatischen Aminen**

*Dirk Hollmann, Sebastian Bähn, Annegret Tillack und Matthias Beller**

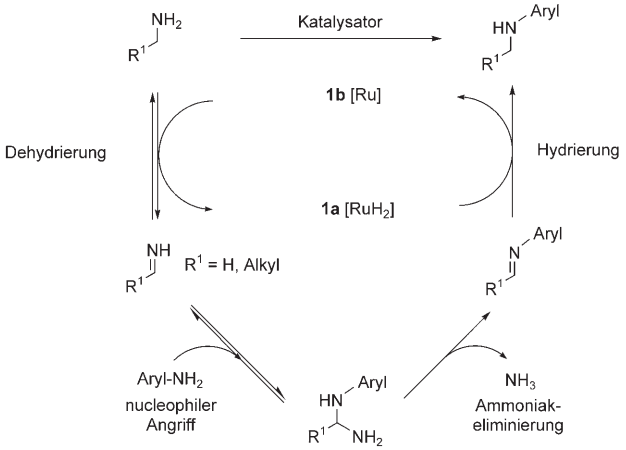
Aromatische und heteroaromatische Amine haben eine herausragende Bedeutung als biologisch aktive Substanzen. Zudem sind Arylamine wichtige Ausgangsprodukte für Groß- und Feinchemikalien sowie Agrarprodukte.[1] Dementsprechend ist die Entwicklung effizienter Methoden zur Synthese von Anilinen von großem Interesse. Atomökonomische Methoden wie die Lewis-Säure-katalysierte Aminierung,[2] die intermolekulare Hydroaminierung[3] und die Hydroaminomethylierung[4] bieten einen guten Zugang zu substituierten Anilinen. Besonders bedeutend ist die palladium- und kupferkatalysierte Aminierung von Arenen mit Halogen-, Tosyl- und Triflatsubstituenten.[5,6] Aniline sind besser verfügbar und preiswerter als diese Substrate. Theoretisch ist es möglich, Aniline direkt und unter Abgabe von Ammoniak als einzigem Nebenprodukt mit aliphatischen Aminen umzusetzen (Schema 1).



Schema 1. Synthese von aromatischen Aminen.

Wir entwickelten kürzlich ein Verfahren zur Herstellung von sekundären Aminen aus primären und sekundären Alkoholen.[7] Das Katalysatorsystem bestand dabei aus Rutheniumcarbonyl ($[Ru_3(CO)_{12}]$) und *N*-Phenyl-2-(dicyclohexylphosphanyl)pyrrol. Nach dieser Methode konnten wir zwar aliphatische Amine, nicht jedoch Arylamine umsetzen. Williams und Hamid beschrieben einen alternativen Ruthenium-dppf-Komplex, der die Umsetzung primärer Alkohole mit aliphatischen Aminen und Anilinderivaten katalysiert.[8]

Hier präsentieren wir eine neue Methode zur Synthese substituierter aromatischer Amine, die die Vorteile des Systems von Williams und unseres Katalysatorsystems kombiniert; dabei werden aliphatische Amine direkt mit Arylaminen umgesetzt. Analog zur Aminierung von Alkoholen läuft diese Reaktion nach einem Hydrogen-borrowing-Mechanismus ab (Schema 2).[9] In der ersten Stufe entsteht durch Dehydrierung des aliphatischen Amins ein Imin, das anschließend nucleophil von einem Arylamin angegriffen wird, wobei sich ein instabiles Aminoaminal bildet. Nach Eliminierung von Ammoniak wird das Imin zum Amin hydriert.[10] Der Wasserstoff für die Hydrierung wird aus der Dehydrierung des Amins gewonnen, weshalb kein zusätzlicher Wasserstoff oder eine weitere Wasserstoffquelle benötigt werden. Anders als bei der reduktiven Aminierung kann daher auf Hochdruckausrüstung verzichtet werden. Das Prinzip der Dehydrierung/Hydrierung in Kombination mit einer bestimmten Reaktion fand auch bei der Alkanmethathese,[11] der β-Alkylierung[12] und der Wittig- oder Knoevenagel-Reaktion[13–15] Anwendung.



Schema 2. Katalytischer Wasserstofftransfer bei der N-Alkylierung von Anilinen mit aliphatischen Aminen.

Zu Beginn unserer Studien setzten wir Anilin mit *n*-Hexylamin um. Zunächst testeten wir verschiedene Rutheniumkatalysatoren (Tabelle 1). Unter Standardbedingungen (150 °C, kein Lösungsmittel) wurden 1 Mol-% Katalysator und ein Überschuss an Anilin (2 Äquiv.) eingesetzt. Dabei zeigte sich, dass nur der Shvo-Komplex (**1**)[16,17] sowie der (Shvo–H_2)-Komplex (**2**) die Reaktion katalysieren (Tabelle 1, Nr. 15 und 16). **1** zeigte schon bei der Transferhydrierung eine herausragende Aktivität. Studien zum Mechanismus wurden von Bäckvall[18] und Casey et al.[19] durchgeführt. Dabei wurde nachgewiesen, dass **1** in zwei Spezies dissoziiert: Der 18-Elektronen-Komplex **1a** ist aktiv in der Hydrierung und der 16-Elektronen-Komplex **1b** in der Dehydrierung (Schema 3). Alle anderen getesteten Katalysatoren, darunter

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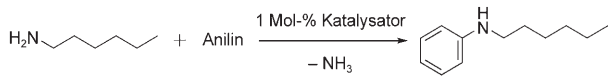
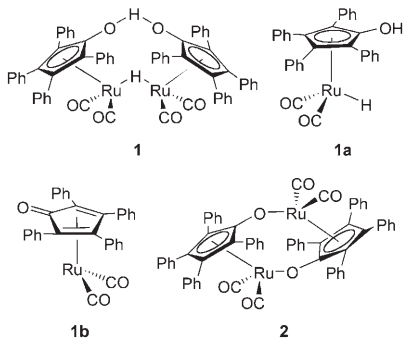
Tabelle 1: Screening von Katalysatoren für die Arylierung von *n*-Hexylamin.[a]



Nr.	Katalysator	Ausb. [%][b]
1	–	–
2	[{Ru[(+)-binap](Cl)}$_2$]	–
3	[Ru(Cl)$_2$(bipy)$_2$]·2 H$_2$O	–
4	[RuCO(H)$_2$(PPh$_3$)$_3$]	2
5	[Ru(Cl)$_2$(PPh$_3$)$_3$]	5
6	[{Ru(Cl)(cod)}$_2$]	–
7	[RuCp$_2$]	–
8	[{RuCp*(Cl)$_2$}$_x$]	–
9	[RuCp*(cod)(Cl)]	–
10	[{Ru(*p*-Cymol)(Cl)$_2$}$_2$][c]	14
11	[{Ru(*p*-Cymol)(Cl)$_2$}$_2$]/TsDPEN[d]	–
12	[{Ru(*p*-Cymol)(Cl)$_2$}$_2$]/dppf[d]	9
13	[Ru$_3$(CO)$_{12}$]	–
14	[Ru$_3$(CO)$_{12}$]/cataCXium PCy	–
15	Shvo (**1**)	94
16	Shvo–H$_2$ (**2**)	70

[a] Reaktionsbedingungen: 1 Mol-% Katalysator in Bezug auf *n*-Hexylamin, 2 mmol *n*-Hexylamin, 4 mmol Anilin, 150 °C, 24 h. [b] Umsätze und Ausbeuten wurden mit Hexadecan als internem Standard mittels GC-Analyse bestimmt. Umsätze und Ausbeuten basieren auf der Umsetzung von *n*-Hexylamin und *N*-Hexylanilin. [c] 4 Mol-% K_2CO_3. [d] 2 Mol-% Ligand, 4 Mol-% K_2CO_3, 4-Å-MS. Binap = 2,2′-Bis(diphenylphosphanyl)-1,1′-binaphthyl, Bipy = Bipyridin, cod = Cycloocta-1,5-dienyl, Cp = Cyclopentadienyl, Cp* = Pentamethylcyclopentadienyl, TsDPEN = *N*-(4-Toluolsulfonyl)-1,2-diphenylethylendiamin, dppf = 1,1′-Bis(diphenylphosphanyl)ferrocen, cataCXium PCy = *N*-Phenyl-2-(dicyclohexylphosphanyl)pyrrol.

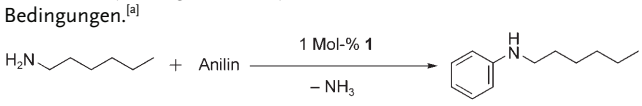


Schema 3. Shvo-Komplex (**1**), aktive Spezies **1a**, **1b** und (Shvo–H$_2$)-Komplex (**2**).

das Ruthenium-dppf-System von Hamid und Williams[8] (Tabelle 1, Nr. 12), das TsDPEN-System von Noyori[20] (Tabelle 1, Nr. 11) und unser Rutheniumcarbonyl-Phosphan-System[7] (Tabelle 1, Nr. 14), zeigten wenig oder keine Aktivität.

Da die Reaktion noch vergleichsweise hohe Temperaturen erforderte, wollten wir als nächstes die Temperaturbedingungen optimieren (Tabelle 2, Nr. 1–4). Dabei zeigte sich, dass Temperaturen über 140 °C wesentlich für die Reaktion sind. Unter 140 °C war fand kaum eine Reaktion mit Anilin statt, und Diamine entstanden als Nebenprodukte; dies

Tabelle 2: Arylierung of *n*-Hexylamin mit Anilin unter verschiedenen Bedingungen.[a]



Nr.	*T* [°C]	Lösungsmittel	Ausb. [%][b]
1	150	–	95
2	140	–	95
3	130	–	60
4	120	–	12
5	140	Heptan	>99
6	140	Cyclohexan	>99
7	140	Toluol	>99
8	140	Acetonitril	96
9	140	DMF	90[c]
10	140	DMSO	>99
11	140	2-Methylbutan-2-ol	>99

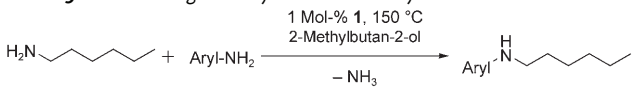
[a] Reaktionsbedingungen: 1 Mol-% Shvo-Komplex in Bezug auf *n*-Hexylamin, 2 mmol *n*-Hexylamin, 4 mmol Anilin, 24 h. [b] Umsätze und Ausbeuten wurden mit Hexadecan als internem Standard mittels GC-Analyse bestimmt. Umsätze und Ausbeuten basieren auf der Umsetzung von *n*-Hexylamin und *N*-Hexylanilin. [c] Nebenprodukt war Formylanilin.

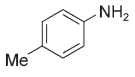
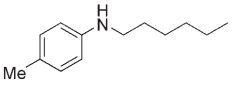
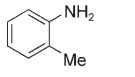
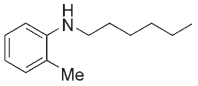
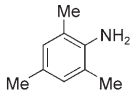
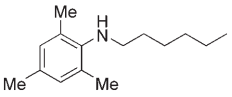
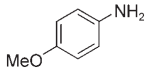
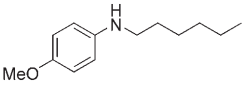
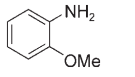
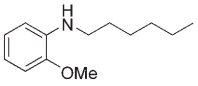
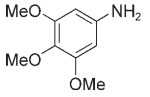
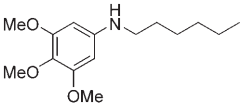
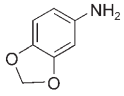
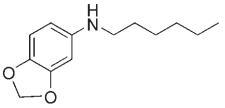
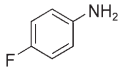
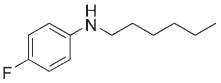
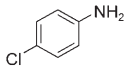
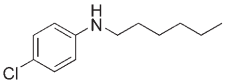
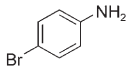
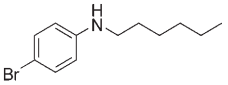
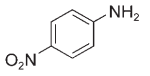
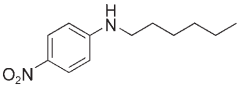
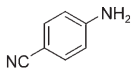
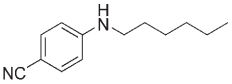
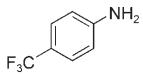
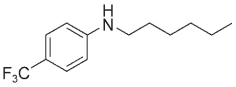
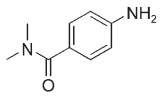
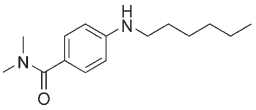
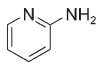
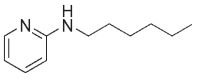
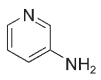
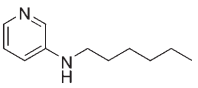
spiegelt sich auch in den niedrigen Ausbeuten wider. Weiterhin prüften wir, ob Lösungsmittel für die Reaktion genutzt werden können (Tabelle 2, Nr. 5–11), was besonders wichtig ist, da einige Arylamine nicht in flüssiger Form vorliegen. Tatsächlich lassen sich unpolare (Heptan, Cyclohexan, Toluol, Tabelle 2, Nr. 5–7), polare aprotische (Acetonitril, DMSO, Tabelle 2, Nr. 8 und 10) und polare protische Lösungsmittel (2-Methylbutan-2-ol, Tabelle 2, Nr. 11) für die Reaktion verwenden. In allen Lösungsmitteln wurden vollständige Umsätze und sehr hohe Ausbeuten erreicht.

Um die Anwendungsbreite von **1** zu demonstrieren, wurden verschiedene Aryl- und Alkylamine untersucht. Die Reaktionen wurden mit 1 Mol-% **1** und mit zwei Äquivalenten Anilin bei 150 °C[21] durchgeführt. Als Lösungsmittel wurde 2-Methylbutan-2-ol eingesetzt, da es sich nach der Reaktion sehr leicht durch Destillation abtrennen lässt. Die Ergebnisse der Umsetzung mit Arylaminen sind in Tabelle 3 zusammengefasst. Mit aktivierten und elektronenreichen Anilinen wie *o*/*p*-Toluidin und *o*/*p*-Anisidin (Tabelle 3, Nr. 1, 2, 4 und 5) wurden hohe Ausbeuten von 93 % und mehr erzielt. Schwierig war die Umsetzung von *n*-Hexylamin mit sterisch gehinderten 2,6-dimethyl-substituierten Anilinen. Dabei wurde eine niedrige Ausbeute von 34 % erhalten (Tabelle 3, Nr. 3). Darüber hinaus konnten pharmazeutisch interessante Aniline – 3,4,5-Trimethoxyanilin und 3,4-(Methylendioxy)anilin – in hohen Ausbeuten von 97 bzw. 86 % umgesetzt werden (Tabelle 3, Nr. 6 und 7).

Des Weiteren wurden halogenierte Aniline als selektive Arylierungsmittel verwendet. Mit 4-Fluor-, 4-Chlor-, und 4-Bromanilin entstanden die entsprechenden alkylierten Aniline in sehr guten Ausbeuten (Tabelle 3, Nr. 8–10). Diese Umsetzungen sind besonders interessant, da sie einen Zugang zu alkylierten Halogenanilinen eröffnen, die mithilfe der palladiumkatalysierten Buchwald-Hartwig-Aminierung schwierig herzustellen sind. Im Anschluss wurde die Toleranz gegenüber funktionellen Gruppen untersucht, wobei wir feststellten, dass der Katalysator Nitro-, Nitril- und Amid-

Tabelle 3: Aminierung von Aryl- und Heteroarylaminen.[a]



Nr.	Anilin	Produkt	Ausb. [%][b]
1			98
2			93
3			34
4			98
5			97
6			97
7			86
8			99
9			97
10			94
11			20
12			76
13			95
14			83
15			96
16			77

[a] Reaktionsbedingungen: 1 Mol-% Shvo-Komplex **1** in Bezug auf *n*-Hexylamin, 2 mmol *n*-Hexylamin, 4 mmol Arylamin, 2-Methylbutan-2-ol, 150 °C, 24 h. [b] Ausbeute an isoliertem Produkt basierend auf *n*-Hexylamin.

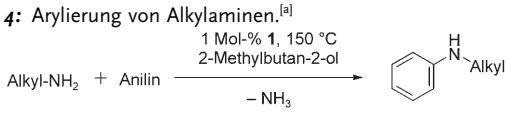
gruppen toleriert (Tabelle 3, Nr. 11–14). Bei der Reaktion mit 4-Nitroanilin bildeten sich mehrere Zersetzungsprodukte, was die geringe Ausbeute von nur 20 % erklärt (Tabelle 3, Nr. 11). Außer Anilinen konnten auch heterocyclische Aminopyridine eingesetzt werden. 2- und 3-Aminopyridin wurden vollständig mit *n*-Hexylamin umgesetzt (Tabelle 3, Nr. 15 und 16).

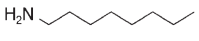
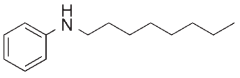
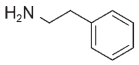
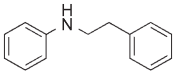
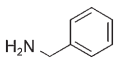
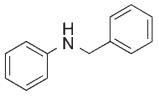
Fazit: Die Ausbeuten hängen offenbar nicht stark von der Donor- oder Akzeptorsubstitution des Arylamins ab. Des Weiteren wird eine Vielzahl von funktionellen Gruppen toleriert. Lediglich die schlechte Umsetzung mit sterisch stark gehinderten 2,6-dimethyl-substituierten Anilinen sowie die Zersetzung von Nitroanilinen bleiben Probleme, die noch zu lösen sind (Tabelle 3, Nr. 3 und 11).

Zum Abschluss untersuchten wir das Substratspektrum der Alkylamine (Tabelle 4). Unverzweigte Alkylamine wie *n*-Octyl-, Phenethyl- und Benzylamin ergaben sehr gute Ausbeuten (Tabelle 4, Nr. 1–3). Verzweigte Amine, wie 2-Octylamin, Cyclohexylamin oder Cyclooctylamin, wurden ebenfalls in sehr guten Ausbeuten von 99 % isoliert (Tabelle 4, Nr. 4–6). Darüber hinaus wurden Furan-, Thiophen- und Indol-substituierte Amine umgesetzt (Tabelle 4, Nr. 7–9).

Wir haben ein Verfahren entwickelt, das erstmals die Synthese von alkylierten aromatischen Aminen aus einfachen

Tabelle 4: Arylierung von Alkylaminen.[a]



Nr.	Amin	Produkt	Ausb. [%][b]
1			99
2			99
3			94
4			99
5			99
6			99
7			89
8			97
9			93

[a] Reaktionsbedingungen: 1 Mol-% **1** in Bezug auf Alkylamin, 2 mmol Alkylamin, 4 mmol Anilin, 2-Methylbutan-2-ol, 150 °C, 24 h. [b] Ausbeute an isoliertem Produkt basierend auf Alkylamin.

Anilinen über eine Transferhydrierung ermöglicht. Eine Reihe von funktionalisierten Arylaminen und aliphatischen Aminen wurde mithilfe des Shvo-Komplexes in hohen Ausbeuten zu Alkylarylaminen umgesetzt. Es ist zu betonen, dass halogenierte Aniline ebenso wie heterocyclische Aminopyridine hergestellt werden können. Diese basen- und damit salzfreie Methode kann eine vorteilhafte Alternative zu den herkömmlichen Methoden für die Synthese substituierter Aniline bilden.

Experimentelles

Allgemeine Vorschrift am Beispiel der Synthese von *N*-(2-(Thiophen-2-yl)ethyl)anilin (Tabelle 4, Nr. 8): In einem ACE-Druckrohr wurden unter Argon der Shvo-Komplex (**1**; 0.02 mmol) und 2-(Thiophen-2-yl)ethanamin (2 mmol) in 2-Methylbutan-2-ol (0.5 mL) und Anilin (4 mmol) gelöst. Das Druckrohr wurde verschlossen und 24 h bei 150 °C in einem Ölbad erhitzt. Nach Entfernen des Lösungsmittels im Vakuum wurde der Rückstand säulenchromatographisch (Pentan/Ethylacetat 20:1) gereinigt. *N*-(2-(Thiophen-2-yl)ethyl)anilin (393.5 mg, 97 %) wurde als schwach rötliches Öl erhalten.

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Stichwörter: Aminierungen · Anilin · Homogene Katalyse · Ruthenium · Shvo-Katalysator

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[21] Damit die Reaktion für alle Substrate vollständig abläuft, wurden die Reaktionen bei 150 °C durchgeführt.

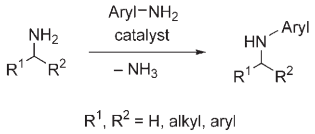
Aminations

DOI: 10.1002/anie.200703119

A General Ruthenium-Catalyzed Synthesis of Aromatic Amines**

*Dirk Hollmann, Sebastian Bähn, Annegret Tillack, and Matthias Beller**

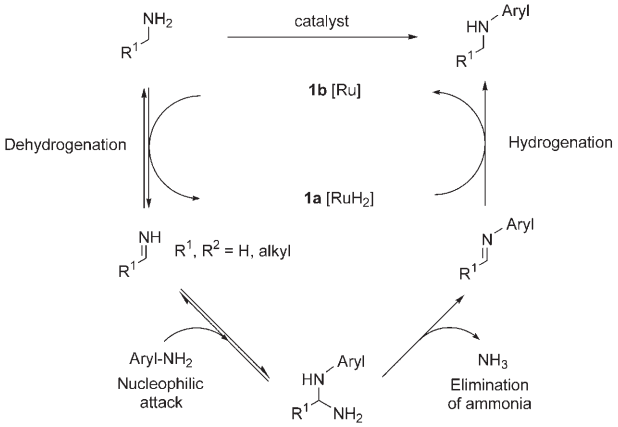
Aromatic amines play a prominent role as biologically active compounds and as industrial chemicals.[1] Hence, the development of new efficient syntheses is of enormous interest. Atom-economical methods such as Lewis acid catalyzed amination,[2] intermolecular hydroaminations,[3] and hydroaminomethylations[4] represent attractive approaches for the synthesis of substituted anilines. Among the various methods, the widely used palladium- and copper-catalyzed aminations of aryl halides, tosylates, and triflates are probably most important.[5,6] In comparison to these substrates, anilines are readily available and inexpensive. In principle, aryl amines could be aminated, leaving ammonia as the only by-product (Scheme 1).



Scheme 1. Synthesis of aromatic amines.

Recently, we developed a procedure for the synthesis of secondary amines starting from the corresponding alcohols using ruthenium carbonyl ($[Ru_3(CO)_{12}]$) and *N*-phenyl-2-(dicyclohexylphosphino)pyrrole.[7] Using this method, we were able to convert only aliphatic amines but no aryl amines. Hamid and Williams described an alternative ruthenium–dppf complex that is able to catalyze the amination of primary alcohols with primary aliphatic and aryl amines.[8]

Herein, we present a new methodology for the synthesis of substituted aniline derivatives, which combines the advantages of our and of Williams's catalyst systems. In analogy to the amination of alcohols, the reaction occurs through a hydrogen-borrowing mechanism (Scheme 2).[9] In the first step, dehydrogenation of the alkyl amine to an imine occurs. After nucleophilic attack of the aniline to form an unstable aminoaminal and subsequent elimination of ammonia, the corresponding secondary imine is hydrogenated to the alkylated aniline.[10] In this reaction, the hydrogen donor for the transfer hydrogenation is the primary amine. Hence, no additional hydrogen or hydrogen transfer reagent is required. An advantage of this method compared to most reductive aminations is that there is no need for high-pressure equipment. Interestingly, the same type of dehydrogenation–reaction–hydrogenation sequence has recently been used in alkane metathesis,[11] β-alkylation of alcohols,[12] and C–C bond formation by means of a Wittig or Knoevenagel reaction.[13–15]



Scheme 2. Catalytic hydrogen transfer in N alkylation of anilines with aliphatic amines.

To start our investigations, we examined the amination of aniline with *n*-hexylamine. Different ruthenium complexes were tested using 1 mol% catalyst and two equivalents of aniline at 150°C without solvent in a sealed tube (Table 1). Several precatalysts and catalyst systems were investigated, including the ruthenium–dppf system of Hamid and Williams[8] (Table 1, entry 12), the TsDPEN system reported by Noyori and co-workers[16] (Table 1, entry 11), and our ruthenium carbonyl–phosphine system[7] (Table 1, entry 14). Of all ruthenium catalysts tested, the Shvo complex **1**[17,18] and the analogous Shvo–H_2 complex **2** showed the highest reactivity (Table 1, entries 15 and 16). These catalysts are known to be highly active in transfer hydrogenations. Studies of the mechanism with **1** were performed by Bäckvall and co-workers[19] and Casey et al.[20] It was demonstrated that **1** dissociates into two species. The 18-electron complex **1a** is active in the hydrogenation, and the 16-electron complex **1b** is active in the dehydrogenation reaction (Scheme 3). All other tested catalysts showed low or no reactivity.

Next, we investigated the influence of the temperature and the solvent in more detail (Table 2). Below 140°C the reaction rate and yield dropped dramatically (Table 2, entries 1–4), and diamines were observed as by-products. Surprisingly, variation of the solvent had no significant effect on the amination reaction. In nonpolar solvents (heptane,

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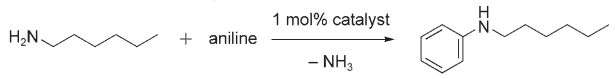
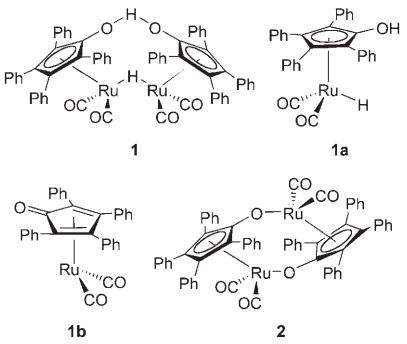
Table 1: Arylation of *n*-hexylamine with aniline in the presence of different ruthenium catalysts.[a]



Entry	Catalyst	Yield [%][b]
1	–	–
2	[{Ru[(+)-binap](Cl)}$_2$]	–
3	[Ru(Cl)$_2$(bipy$_2$)·2 H$_2$O	–
4	[RuCO(H)$_2$(PPh$_3$)$_3$]	2
5	[Ru(Cl)$_2$(PPh$_3$)$_3$]	5
6	[{Ru(Cl)(cod)}$_2$]	–
7	[RuCp$_2$]	–
8	[{RuCp*Cl$_2$}$_x$]	–
9	[RuCp*(cod)Cl]	–
10	[{Ru(p-cymene)(Cl)$_2$}$_2$][c]	14
11	[{Ru(p-cymene)(Cl)$_2$}$_2$]/TsDPEN[d]	–
12	[{Ru(p-cymene)(Cl)$_2$}$_2$]/dppf[d]	9
13	[Ru$_3$(CO)$_{12}$]	–
14	[Ru$_3$(CO)$_{12}$]/cataCXium PCy	–
15	Shvo (**1**)	94
16	Shvo–H$_2$ (**2**)	70

[a] Reaction conditions: 1 mol% catalyst relative to *n*-hexylamine, 2 mmol *n*-hexylamine, 4 mmol aniline, 150°C, 24 h. [b] Conversion and yield were determined by GC with hexadecane as internal standard. Conversions and yields are based on the conversion of *n*-hexylamine and *N*-hexylaniline. [c] 4 mol% K_2CO_3. [d] 2 mol% ligand, 4 mol% K_2CO_3, 4-Å M.S. Binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, bipy = bipyridine, cod = cycloocta-1,5-diene, Cp = cyclopentadienyl, Cp* = pentamethylcyclopentadienyl, TsDPEN = *N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, cataCXium PCy = *N*-phenyl-2-(dicyclohexylphosphino)pyrrole.

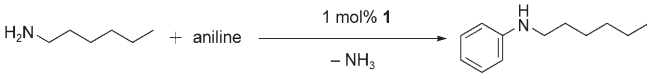


Scheme 3. Shvo complex (**1**), dissociated species **1a**, **1b**, and the analogous Shvo–H$_2$ complex **2**.

cyclohexane, and toluene, Table 2, entries 5–7) as well as polar solvents (acetonitril and DMSO, Table 2 entries 8 and 10) and polar protic solvents (2-methylbutan-2-ol, Table 2 entry 11), complete conversion and excellent yield (over 99%) is observed. Considering the different solubilities and melting points of the aryl or aliphatic amine substrates, this finding seems important.

To demonstrate the general applicability of the Shvo catalyst for this reaction and the scope of the process, various aryl and alkyl amines were investigated (Table 3). In general,

Table 2: Arylation of *n*-hexylamine with aniline under different conditions.[a]



Entry	*T*	Solvent	Yield [%][b]
1	150	–	95
2	140	–	95
3	130	–	60
4	120	–	12
5	140	heptane	>99
6	140	cyclohexane	>99
7	140	toluene	>99
8	140	acetonitrile	96
9	140	DMF	90[c]
10	140	DMSO	>99
11	140	2-methylbutan-2-ol	>99

[a] Reaction conditions: 1 mol% Shvo catalyst **1** relative to *n*-hexylamine, 2 mmol *n*-hexylamine, 4 mmol aniline, 24 h. [b] Conversion and yield were determined by GC with hexadecane as internal standard. Conversions and yields are based on the conversion of *n*-hexylamine and *N*-hexylaniline. [c] Formylaniline was formed as by-product.

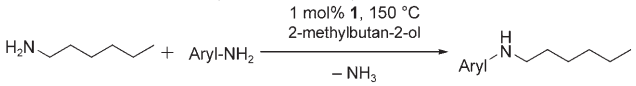
catalytic experiments were performed with 1 mol% of **1** in the presence of two equivalents of aryl amine in 2-methylbutan-2-ol at 150°C.[21] Various aryl amines react with *n*-hexylamine to give the desired products in excellent yields. High yields over 93% were observed with activated and electron-rich anilines such as *o*/*p*-toluidine and *o*/*p*-anisidine (Table 3, entries 1, 2, 4 and 5). The amination of sterically hindered 2,6-dimethyl-substituted aniline was more problematic and gave only a low yield of 34% (Table 3, entry 3). However, reactions with pharmaceutically important aniline derivatives such as 3,4,5-trimethoxyaniline and 3,4-(methylenedioxy)-aniline occurred in high yields of 97 and 86% (Table 3, entries 6 and 7).

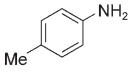
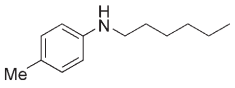
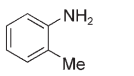
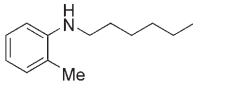
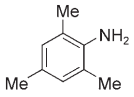
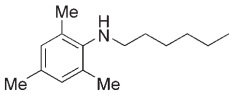
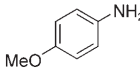
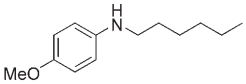
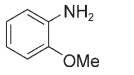
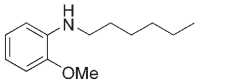
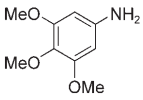
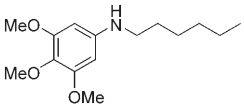
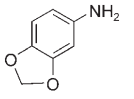
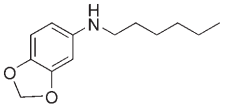
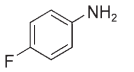
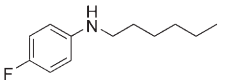
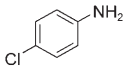
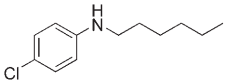
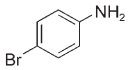
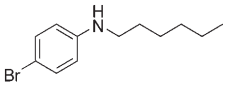
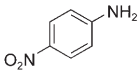
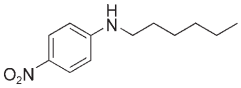
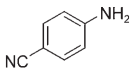
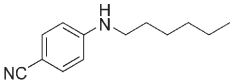
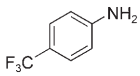
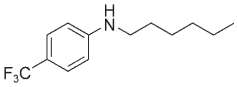
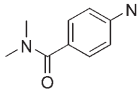
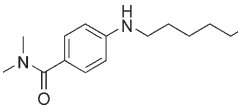
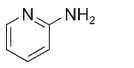
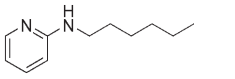
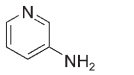
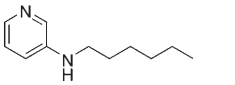
Furthermore, halogenated anilines can be employed as selective arylation reagents. 4-Fluoro-, 4-chloro-, and 4-bromoaniline gave excellent yields of the corresponding alkylated aniline (Table 3, entries 8–10). In general, such products cannot be easily prepared by the palladium-catalyzed Buchwald–Hartwig reaction. The catalyst also tolerates nitro, nitrile, and amide groups (Table 3, entries 11–14). However, the reaction of 4-nitroaniline with *n*-hexylamine gave a poor yield of 20%, as a number of decomposition products formed (Table 3, entry 11). In addition to aniline derivatives, heterocyclic aminopyridines such as 2-aminopyridine and 3-aminopyridine also react smoothly with *n*-hexylamine (Table 3, entries 15 and 16).

In general, we did not observe a strong dependence of the product yield on donor or acceptor substitution of the aryl amine. Merely the amination of very sterically hindered 2,6-dimethyl-substituted aniline and the decomposition of nitroanilines seem to be challenges for the future (Table 3, entries 3 and 11).

Finally, our protocol was applied to different alkyl amines (Table 4). *n*-Octyl-, phenethyl- and benzylamine are converted in excellent yields to the corresponding aniline derivatives (Table 4, entries 1–3). Branched amines such as

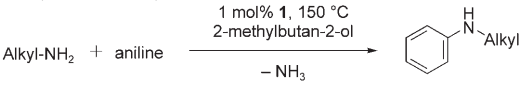
Table 3: Amination of aryl and heteroaryl amines.[a]

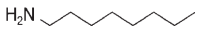
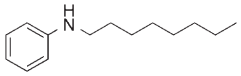
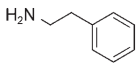
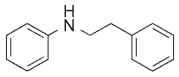
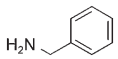
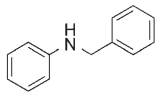


Entry	Aniline	Product	Yield [%][b]
1			98
2			93
3			34
4			98
5			97
6			97
7			86
8			99
9			97
10			94
11			20
12			76
13			95
14			83
15			96
16			77

[a] Reaction conditions: 1 mol% Shvo catalyst **1** relative to *n*-hexylamine, 2 mmol *n*-hexylamine, 4 mmol aryl amine, 2-methylbutan-2-ol, 24 h, 150°C. [b] Yields of isolated product are based on *n*-hexylamine.

Table 4: Arylation of alkyl amines.[a]



Entry	Amine	Product	Yield [%][b]
1			99
2			99
3			94
4			99
5			99
6			99
7			89
8			97
9			93

[a] Reaction conditions: 1 mol% **1** relative to alkyl amine, 2 mmol alkyl amine, 4 mmol aniline, 24 h, 2-methylbutan-2-ol, 150°C. [b] Yields of isolated product are based on alkyl amine.

2-octylamine, cyclohexylamine, and cyclooctylamine gave yields of isolated product of 99% (Table 4, entries 4–6). Moreover, furane-, thiophene-, and indole-substituted amines gave yields up to 97% (Table 4, entries 7–9).

In summary, we described the first arylation of aliphatic amines with anilines that proceeds under transfer hydrogenation conditions. In the presence of the Shvo catalyst **1**, a variety of functionalized anilines and aliphatic amines react smoothly to give the corresponding aryl amines in excellent yields. It is important to emphasize that halogenated anilines and heterocyclic aminopyridine derivates can be easily synthesized. This base- and salt-free method can be a useful alternative to the known methods for the synthesis of aniline derivatives.

Experimental Section

General amination procedure: In an ACE-pressure tube under an argon atmosphere, Shvo catalyst (**1**; 0.02 mmol) and 2-(thiophen-2-yl)ethanamine (2 mmol) were dissolved in 2-methylbutan-2-ol (0.5 mL) and aniline (4 mmol). The pressure tube was fitted with a teflon cap and heated at 150°C for 24 h in an oil bath. The solvent was removed in vacuo, and the crude product was easily purified by

column chromatography with pentane/ethyl acetate (20:1) to afford *N*-(2-(thiophen-2-yl)ethyl)aniline (393.5 mg, 97%) as a pale red oil.

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[21] To ensure full conversion of all substrates, reactions were carried out at 150 °C.

4.5. **N-*Dealkylation of Aliphatic Amines and Selective Synthesis of Monoalkylated Aryl Amines***

Dirk Hollmann, Sebastian Bähn, Annegret Tillack, and Matthias Beller, *Chem. Commun.* **2008**, 3199-3201.

Contributions

My contribution as co-author of this paper is approximately 85 %. I was responsible for the complete work. Mr. Sebastian Bähn worked under my supervision as a student trainee.

N-Dealkylation of aliphatic amines and selective synthesis of monoalkylated aryl amines†

Dirk Hollmann, Sebastian Bähn, Annegret Tillack and Matthias Beller*

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Highly selective alkyl transfer processes of mono-, di- and trialkyl amines in the presence of the Shvo catalyst have been realized; in addition, a general method for *N*-alkylation of aniline with di- and trialkyl amines is presented.

Metabolic *N*-dealkylation is an important biotransformation in nature. Such processes are catalyzed by monooxygenases such as Cytochrome P 450,[1] although these enzymes are mainly known for oxidation reactions such as hydrocarbon hydroxylation and alkene epoxidation.[2] Ever since the identification of the first dealkylation catalyst,[3] the understanding and the development of new systems is of significant interest, albeit only a few methods are known.[4]

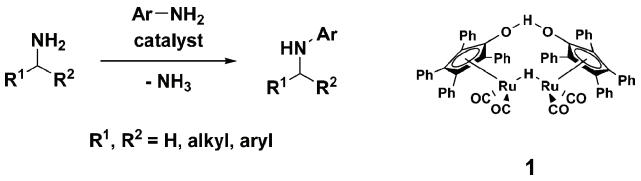
In recent years, the synthesis of aniline derivatives has received high attention. Aromatic amines play an outstanding role as biologically active compounds.[5] In addition, for industry the development of improved syntheses is of enormous interest. Among the various methods, the widely used palladium- and copper-catalyzed aminations of aryl halides (Buchwald–Hartwig aminations) became the most general method to form C–N bonds of aromatic amines.[6,7] Apart from well established aryl halides, tosylates and triflates, simple anilines constitute available and cheap substrates.

Recently, we have described the first arylation of aliphatic amines with anilines leaving ammonia as the only side-product (Scheme 1).[8] In the presence of the so-called Shvo catalyst **1**[9,10] a variety of functionalized anilines and primary amines react smoothly to give the corresponding aryl amines in excellent yields.[11]

In this communication we present our new studies of the dealkylation of aliphatic amines combined with the selective synthesis of monoalkylated aniline derivates. For the first time it is shown that starting from primary, secondary and tertiary amines, a complete and selective transfer of all alkyl groups takes place highly selectively.

As a starting point of our investigations we compared the amination of aniline with *n*-hexylamine, di-*n*-hexylamine and tri-*n*-hexylamine. To our surprise, all the different hexylamines are converted in high yields (75–87%) to the same *N*-hexylaniline (Scheme 2)! Especially remarkable is the activation and alkyl transfer of the tertiary amine.

Upon optimization we found that two equivalents of aniline per hexyl group in the presence of 1 mol% of the Shvo catalyst



Scheme 1 Arylation of aliphatic amines using the Shvo catalyst **1**.

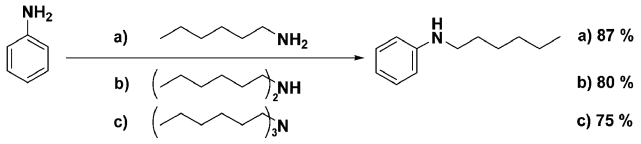
in *tert*-amyl alcohol gave the best results. Notably, a mixture of mono-, di- and tri-*n*-hexylamine is also converted highly selectively to give *N*-hexylaniline (Scheme 3).

We believe that the reaction proceeds through a hydrogen borrowing mechanism as proposed by Williams,[12] which involves dehydrogenation of the amine, imine formation, nucleophilic attack by the aniline, elimination of ammonia, and final hydrogenation. To confirm this mechanism, a reaction was carried out with labeled aniline-^{15}N and dibenzylamine. The resulting *N*-benzylaniline was obtained in 96% isolated yield and showed >99% of ^{15}N-labelling (Table 1, entry 5).[13]

Of note, in this alkyl transfer reactions the hydrogen donors for the final hydrogenation step are the primary, secondary and tertiary amines. Hence, no additional hydrogen or hydrogen transfer reagent is required in the process. Advantageously there is no need for high-pressure equipment which is used often in hydrogenation reactions such as reductive amination.

As shown in Scheme 4 under the reaction conditions, equilibrium between the mono-, di- and trialkyl amines is observed. All alkyl amines are converted into each other and can be monitored until the reaction is finished (reversible steps).[14,15] However, by reaction of the respective imines or iminium species with aniline, the corresponding *N*-hexylaniline is formed in an irreversible step. Thus, reaction of tri-*n*-hexylamine with aniline yields exclusively *N*-hexylaniline and di-*n*-hexylamine. Then, the next alkyl group is transferred. Finally, the reaction of *n*-hexylamine with aniline, results in the formation of ammonia (irreversible step).

Next, we were interested in the generality of the dealkylation process and their application in the *N*-alkylation of aniline with various di- and trialkyl amines. Using polyalkylated short-chain amines, this method provides a convenient access



Scheme 2 Amination of aniline with different alkyl amines (isolated yields are based on hexyl groups).

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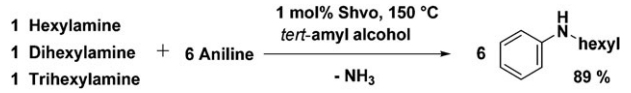
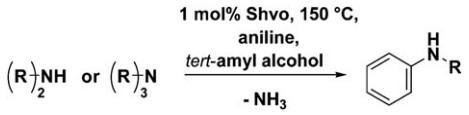
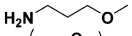
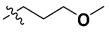
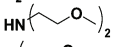
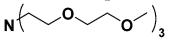
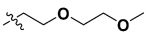


Scheme 3 Amination of aniline with a mixture of hexylamines (isolated yields are based on hexyl groups).

Table 1 Amination of aniline with di- and trialkyl amines



Entry	Amine	Product	Yield (%)
1	Triethylamine	R = 	95
2	Dipropylamine	R = 	96
3	Diisopropylamine	R = 	92
4	Dibenzylamine	R = 	98
5	Dibenzylamine	R = 	92[b]
6	Tribenzylamine	R = 	21[c]
7	Dicyclohexylamine	R = 	99
8		R = 	92
9		R = 	91
10		R = 	74

[a] *Reaction conditions*: 1 mol% Shvo catalyst per alkyl group, 1 mmol mono-, di- or trialkyl amine, 2 mmol aniline per alkyl group, 24 h, *tert*-amyl alcohol, 150 °C. Isolated yields are based on alkyl groups. [b] Aniline-^{15}N; product content of ^{15}N > 99%. [c] 78% recovered tribenzylamine.

to monoalkylated anilines with short-chain alkyl groups. For comparison, in the Buchwald–Hartwig reaction, these compounds have to be synthesized from the corresponding volatile amines using a sealed tube technique,[16] benzylmethylamine or methylammonium chloride.[17]

Instead of ethylamine (bp, 16.6 °C), propylamine (bp, 48 °C), isopropylamine (bp, 33.5 °C), we are able to use the convenient non-volatile triethylamine, dipropylamine and diisopropylamine (Table 1, entries 1–3). Excellent yields of 92–98% are observed. In addition, different alkyl amines and aminoalkoxyethers are converted in excellent selectivity and high yields (Table 1, entries 4, 5, 7–10). So far, only the full conversion of tertiary benzylic amine poses a challenge (Table 1, entry 6).

In summary, we have presented the first selective *N*-alkylation with mono-, di- and trialkyl amines. This tool provides a general access to the synthesis of monoalkylated aryl amines *via* alkyl transfer and acts as a model for metabolic *N*-dealkylations. This novel reaction is highly atom efficient leaving only ammonia as side-product and can be conveniently carried out. Further applications with functionalized anilines as well as other alkyl amines can be easily envisioned.

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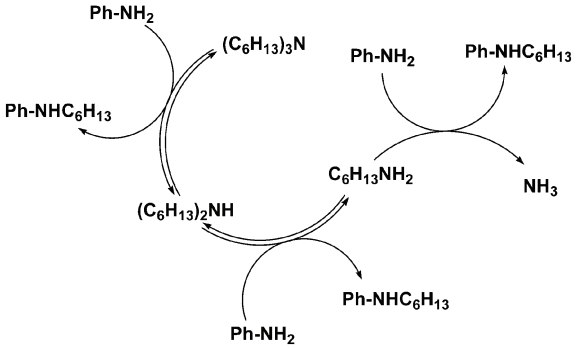

Scheme 4 Equilibrium and selective transfer of alkyl groups.

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11. In an ACE-pressure tube under an argon atmosphere the Shvo catalyst (0.02 mmol) and the corresponding alkyl amine (2 mmol

of alkyl groups) were dissolved in *tert*-amyl alcohol (0.5 ml) and aniline (4 mmol). The pressure tube was fitted with a Teflon cap and heated at 150 °C for 24 h. The solvent was removed *in vacuo*, and the crude alkyl aryl amine product was easily purified by column chromatography with pentane–ethyl acetate (20 : 1).
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4.6. Ruthenium-catalyzed Synthesis of Secondary Alkylamines: Selective Alkylation with Aliphatic Amines

Sebastian Bähn, Dirk Hollmann, Annegret Tillack, and Matthias Beller, *Adv. Synth. Cat.* **2008**, *350*, 2099-2103.

Contributions

My contribution as co-author of this paper is approximately 40 %. Mr. Sebastian Bähn worked under my supervision as a diploma student. I was involved in the planning of experiments, discussion, and argumentation of the results.

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Ruthenium-Catalyzed Synthesis of Secondary Alkylamines: Selective Alkylation with Aliphatic Amines

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Abstract: The chemoselective *N*-alkylation of *tert*-alkylamines applying aliphatic amines is described for the first time. In the presence of the Shvo catalyst **1**, *tert*-octylamine **4** and 1-adamantylamine **5** are alkylated using primary, secondary, and even tertiary amines to give the corresponding monoalkylated *tert*-alkylamine in moderate to very good yields and excellent selectivity. This novel reaction proceeds without an additional hydrogen source and ammonia is formed as the only by-product.

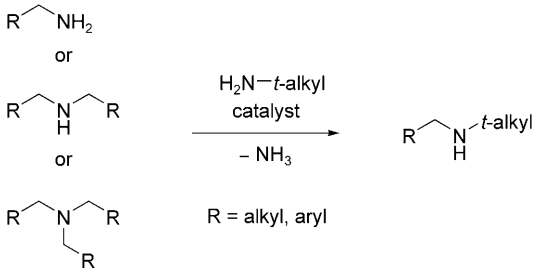
Keywords: alkylation; amines; homogeneous catalysis; hydrogen transfer; ruthenium

Amines are of significant importance for the bulk and fine chemical industry. Due to their numerous applications in polymers, dyes, agrochemicals, and pharmaceuticals,[1] there is an ongoing interest for improved and new synthetic preparations.[2] Besides the well known *N*-alkylations of amines with alkyl halides,[2,3] catalytic methodologies such as reductive amination,[2,4] hydroaminations,[5] and hydroaminomethylations[6] of olefins or alkynes have been developed for the synthesis of aliphatic amines within the last decade. In addition, the environmentally friendly *N*-alkylation of amines using primary[7] and secondary alcohols[8,9] has attracted considerable interest.

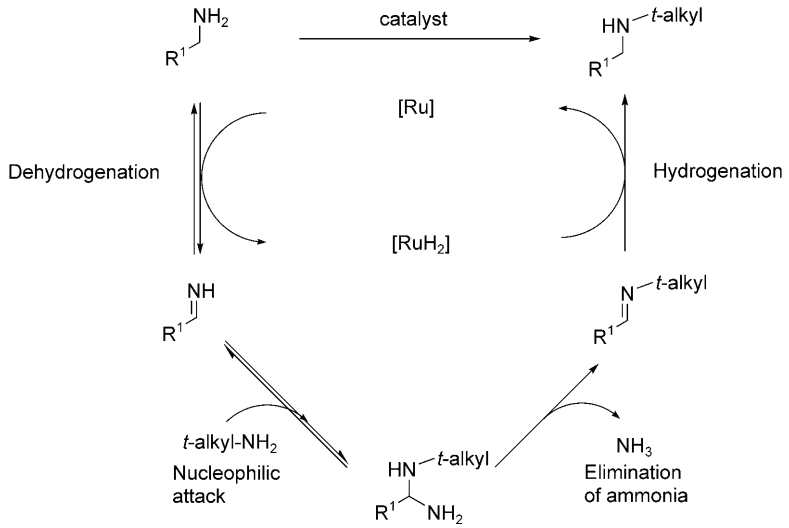
Recently, we demonstrated that aliphatic amines can be used as alkylating agents instead of the corresponding alcohol. Although this transformation – alkylation of amines with amines – seems to be unusual at first sight, there is significant industrial interest in analogous transalkylations.[10] More specifically, we discovered that anilines are converted in high yield to *N*-alkylanilines.[11] This atom-efficient alkyl transfer proceeds with primary as well as secondary and tertiary aliphatic amines leaving ammonia as the only by-product.[12] Based on these reactions, we also became interested in the selective alkylation of aliphatic amines (Scheme 1). The resulting *tert*-alkylamines are of interest as intermediates; for example, this structural element is found in pharmaceuticals[13] like vildagliptin.[14]

From a mechanistic viewpoint the alkylation of amines proceeds *via* a so-called borrowing hydrogen sequence which is shown in Scheme 2.[15] Initially, the ruthenium-catalyzed dehydrogenation of the alkylamine should occur *via* coordination and ß-hydride elimination. Then, nucleophilic attack of the *tert*-alkylamine on the resulting imine and elimination of ammonia yields the corresponding secondary imine. Subsequent catalytic hydrogenation leads to the alkylated *tert*-alkylamine. Notably, applying secondary or even tertiary amines, in the first reaction cycle a primary or secondary amine is eliminated instead of ammonia.

In the case of tertiary amines, we assume that initially an iminium ion is generated by ß-hydride elimination. Another possible reaction mechanism involving hydrolysis of the amines to form ketones[16] could be excluded. For this purpose, reactions under strict water-free conditions and in the presence of small amount of water (5 mol%) were performed, however the results do not indicate any influence of water.



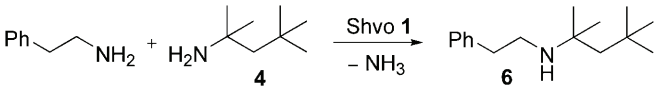
Scheme 1. Selective *N*-alkylation of *tert*-alkylamines.



Scheme 2. Catalytic hydrogen transfer in *N*-alkylation of *tert*-alkylamines with aliphatic amines.

The formed alkylamine reacts further until all alkyl chains are transferred to the *tert*-alkylamine. Clearly, dehydrogenation of the *tert*-alkyl group is not feasible because ß-hydride elimination is not possible. Hence, a selective alkyl transfer takes place.

Table 1. Influence of the catalyst on the reaction of *tert*-octylamine **4** and phenethylamine.[a]



Entry	Catalyst	Yield [%][b]
1	Shvo **1**	49
2	Shvo-H_2 **2**	19
3	Shvo PPh_3	14
4	Shvo cataCXium®PCy[e]	12
5	[Ru[(+)-BINAP](Cl)$_2$][e]	<1
6	[{Ru(*p*-cymene)(Cl)$_2$}$_2$][c]	–
7	[{Ru(*p*-cymene)(Cl)$_2$}$_2$]/TsDPEN[e] **3**[d]	–
8	[{Ru(*p*-cymene)(Cl)$_2$}$_2$]/dppf[d,e]	–
9	[$Ru_3(CO)_{12}$]/cataCXium®PCy[e]	<1

[a] *Reaction conditions*: 1 mmol phenethylamine, 2 mmol *tert*-octylamine **4**, 1 mol% ruthenium catalyst relative to phenethylamine, 24 h, 160 °C.

[b] Yields were determined by GC with hexadecane as internal standard and are based on phenethyl-(1,1,3,3-tetramethylbutyl)-amine **6**.

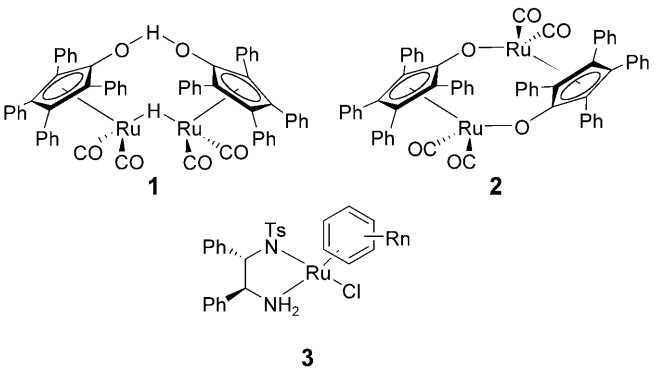
[c] 4 mol% K_2CO_3.

[d] 2 mol% ligand, 4 mol% K_2CO_3.

[e] BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, TsDPEN = *N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine, dppf = 1,1′-bis(diphenyl-phosphanyl)ferrocene, cataCXium®PCy = *N*-phenyl-2-(dicyclohexylphosphino)-pyrrole.

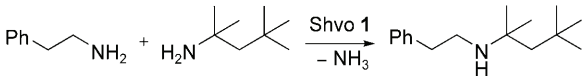
As model system the alkylation of *tert*-octylamine **4** (1,1,3,3-tetramethylbutlamine) was performed with phenethylamine. Different ruthenium complexes were tested by applying 1 mol% ruthenium catalyst and 2 equivalents of *tert*-octylamine **4** at 160 °C in a pressure tube without additional solvent (Table 1). The different pre-catalysts investigated included the ruthenium/TsDPEN system **3** reported by Noyori and co-workers[17] (Table 1, entry 7), the ruthenium/dppf system of Hamid and Williams[7c] (Table 1, entry 8), and our ruthenium carbonyl/phosphine system (Table 1, entry 9).[9a] However, similar to the alkylation of anilines[11] the Shvo catalyst {[2,3,4,5-$Ph_4(\eta^5$-$C_4CO)]_2H$}$Ru_2(CO)_4(\mu$-H) **1**, shown in Scheme 3, provided the best result (Table 1, entry 1). Surprisingly, catalyst **2** was less reactive. So far, we cannot explain this observation.

Next, we investigated the influence of different reaction conditions (Table 2). Without solvent, the opti-



Scheme 3. Different ruthenium catalysts for the alkylation of *tert*-alkylamines.

Table 2. Optimization of the reaction conditions.[a]



Entry	T [°C]	Solvent	Shvo **1** [mol%]	*tert*-Octylamine **4** [equiv.]	Yield [%][b]
1	140	–	1	2	16
2	150	–	1	2	35
3	160	–	1	2	49
4	170	–	1	2	34
5	160	Heptane	1	2	38
6	160	DME	1	2	48
7	160	NMP	1	2	44
8	170	Heptane	1	2	60
9	170	DME	1	2	69
10	170	NMP	1	2	35
11	160	–	1	1	23
12	160	–	1	3	55
13	160	–	0.5	2	41
14	160	–	2	2	48
15[c]	170	DME	1	2	44
16[d]	170	DME	1	2	70
17[e]	170	DME	1	2	60
18[f]	170	DME	1	2	51
19	170	DME	1	3	75

[a] *Reaction conditions*: 2 mmol phenethylamine, 24 h, 0.5 mL solvent.
[b] Yields were determined by GC with hexadecane as internal standard and are based on phenethyl-(1,1,3,3-tetramethylbutyl)-amine **6**.
[c] 12 h.
[d] 48 h.
[e] 0.25 mL solvent.
[f] 1 mL solvent.

mal yield is obtained at 160 °C (Table 2, entry 3). At lower temperature more diphenethylamine is formed, while a higher temperature gave triphenethylamine as by-product. Applying 1-methyl-pyrrolidin-2-one (NMP) as solvent decreased the chemoselectivity and significantly more triphenethylamine is obtained (Table 2, entries 7 and 10). In heptane as non-polar solvent the catalyst is less reactive but more selective and a moderate yield of 60% at 170 °C is achieved (Table 2, entry 8). An improved yield of 69% is observed in dimethoxyethane (DME) (Table 2, entry 9) and the best yield (75%) is achieved using an excess of 3 equiv. *tert*-octylamine **4** in DME (Table 2, entry 19).

Reactions in DMSO, 2-methylbutan-2-ol, dioxane, and toluene are comparable. Variation of the catalyst loading (Table 2, entries 13 and 14), reaction time (Table 2, entries 15 and 16), and solvent concentration (Table 2, entries 17 and 18) did not lead to any further improvement.

In order to demonstrate the generality of the alkyl transfer, different amines were investigated in the reaction with *tert*-octylamine **4**. The results are summarized in Table 3. Primary amines as well as secondary ones gave the desired products in good to excellent yield. Remarkably, even tertiary amines such as trioctylamine can be used as alkylating agents, although activation of these substrates is known to be difficult. However, tribenzylamine is less reactive and no reaction with *tert*-octylamine **4** or 1-adamantylamine **5** is observed (Table 3, entries 6 and 17). The more electron-rich 4-methoxybenzylamine showed increased reactivity compared to benzylamine (Table 3, entries 4 and 11). Moreover, aliphatic amino ethers are converted selectively to the secondary amines (Table 3, entry 10). We were pleased to find that 1-adamantylamine reacted with primary, secondary, and tertiary amines providing excellent yields of the corresponding *N*-alkyl-1-adamantylamines (Table 2, entries 12–14). In all cases, the reaction was highly selective towards monoalkylation. Neither the formation of dialkylated *tert*-alkylamines nor of the alkyl-di-*tert*-alkylamines was observed.

In conclusion, we present the first selective alkylation of aliphatic amines using amines. Proceeding under transfer hydrogenation conditions, no additional hydrogen is needed for the alkylation. In the presence of the Shvo catalyst **1**, selective alkyl transfer, using primary as well as secondary and tertiary aliphatic amines to *tert*-alkylamines proceeds selectively in high yield.

Experimental Section

General Procedure for the Selective Monoalkylation of *tert*-Alkylamines

In an ACE-pressure tube under an argon atmosphere alkylamine (2 mmol mono-, 1 mmol di-, or 0.67 mmol trialkylamine) and Shvo catalyst (21.7 mg, 0.02 mmol, 1 mol% per alkyl group) were dissolved in DME (0.5 mL) and *tert*-alkylamine (6 mmol, 3 equiv. per alkyl group). The pressure tube was fitted with a Teflon cap and stirred at 170 °C for 24 h. The solvent was removed under vacuum, and the crude product was purified by column chromatography.

Supporting Information

Experimental details and characterization data for compounds **6**–**12** are given in the Supporting Information.

Acknowledgements

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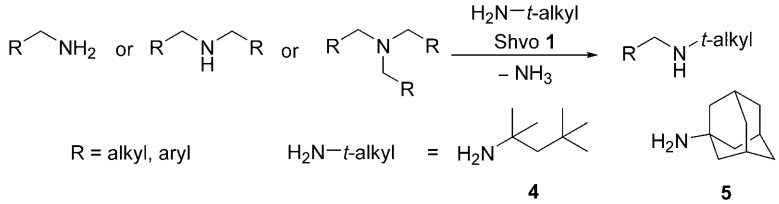
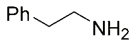
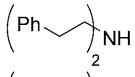
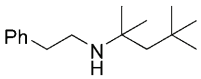
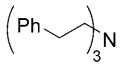
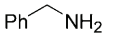
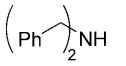
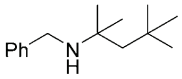
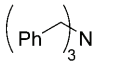
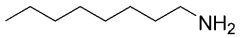
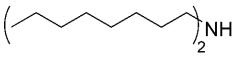
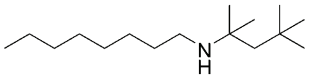
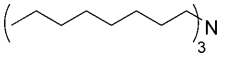
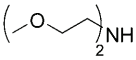
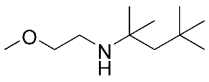
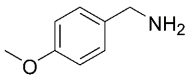
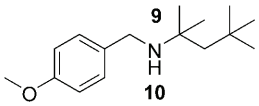
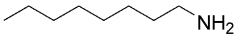
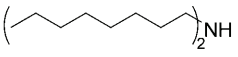
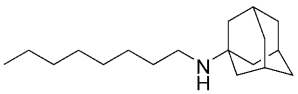
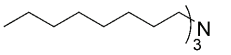
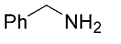
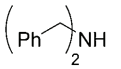
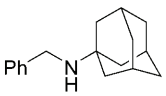
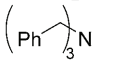
Table 3. Catalytic *N*-alkylation of *tert*-alkylamines.[a]



Entry	Substrate	*tert*-Alkylamine	Product	Yield [%][b]
1		**4**		75 (68)
2		**4**	 **6**	90
3		**4**		87 (75)
4		**4**		58 (49)
5		**4**	 **7**	76 (58)
6		**4**		<1
7		**4**		90 (61)
8		**4**	 **8**	89 (78)
9		**4**		85
10		**4**	 **9**	60 (43)
11		**4**	 **10**	89 (63)
12[c]		**5**		99 (94)
13[c]		**5**	 **11**	99
14[c]		**5**		99
15[c]		**5**		81 (67)
16[c]		**5**	 **12**	90
17[c]		**5**		<1

[a] *Reaction conditions*: 2 mmol mono-, 1 mmol di-, or 0.67 mmol trialkylamine, 6 mmol *tert*-alkylamine, 1 mol% Shvo catalyst **1** per alkyl group, 24 h, 0.5 mL DME.

[b] Yields were determined by GC with hexadecane as internal standard and are based on alkyl groups. Isolated yields in brackets.

[c] 1 mL DME.

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4.7. A Novel Salt-free Ruthenium-catalyzed Alkylation of Aryl Amines

Dirk Hollmann, Sebastian Bähn, Annegret Tillack, Rudy Parton, Rinke Altink, and Matthias Beller, *Tetrahedron Lett.* **2008**, *49*, 5742-5745.

Contributions

My contribution as co-author of this paper is approximately 80 %. I was responsible for the complete work. Mr. Sebastian Bähn worked under my supervision as a student trainee. Dr. Rudy Parton and Dr. Rinke Altink are industrial cooperation partner.

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A novel salt-free ruthenium-catalyzed alkylation of aryl amines

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ABSTRACT

The alkylation of aryl amines using cyclic amines such as pyrrolidine proceeds via borrowing hydrogen methodology in the presence of 1 mol % Shvo catalyst. During the reaction multiple carbon–nitrogen cleavage and formation occurred. This novel reaction sequence leads to *N*-aryl-pyrrolidines and -piperidines.

Aromatic amines are important intermediates in the bulk and fine chemical industry.[1] In addition, the presence of carbon–nitrogen bonds is essential for the function of most biologically active molecules.[2] Apart from amino acids, DNA and RNA bases, especially alkaloids constitute privileged naturally occurring amines. One of the simplest alkaloid structures represents the pyrrolidine skeleton. Based on this structure many important natural products, for example, proline, as well as pharmaceuticals like retronecine and opiod receptor agonists (CJ-15,161) are known (Fig. 1).[3]

Clearly, a number of practical methods have been developed for the synthesis of amines in the past decades. Besides the well-known non-catalytic N-alkylations of amines with alkyl halides and reductive alkylations, various catalytic reactions, like reductive amination,[4] palladium-[5] and copper-catalyzed[6] aminations of aryl halides,[7] hydroaminations,[8] and hydroaminomethylations[9] of olefins or alkynes have been developed within the last decade. Nevertheless, the diversity of amines as well as their biological and pharmaceutical relevance is still motivating academic and industrial researchers to look for new and improved syntheses for all kinds of amine derivatives. In this respect, the N-alkylation of amines using primary[10] and secondary alcohols[11,12] is an environmentally attractive method, which is not fully exploited yet.

Based on our interest in new synthetic methods for salt-free alkylation of amines via borrowing hydrogen methodology,[13] we recently discovered that aryl amines react with alkyl amines to furnish the corresponding *N*-alkyl-aryl amines in high yields (Scheme 1).[14] Although this transformation—alkylation of amines

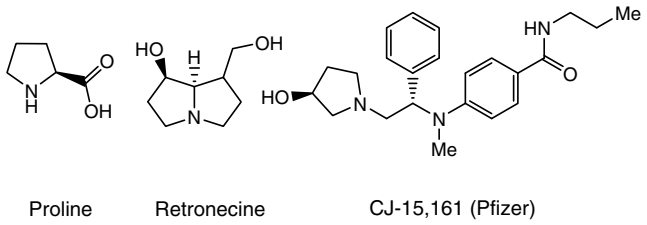

Figure 1. Selected examples of alkaloids and pharmaceuticals with pyrrolidine motif.

with amines—seems to be unusual at first sight, there is significant industrial interest in analogous transalkylations.[15] Clearly, this atom efficient alkyl transfer proceeds with primary as well as secondary and tertiary aliphatic amines leaving ammonia as the only side product.[16]

Here, we report for the first time the selective N-alkylation of aryl amines using cyclic alkyl amines such as pyrrolidine (Scheme 1; right arrow). Remarkably, in this novel catalytic transformation three C–N bond cleaving and forming steps take place.

As a starting point of our investigations we examined the reaction of aniline with pyrrolidine in the presence of catalytic amounts of the so-called Shvo catalyst **I**[17] (Table 1). After the reaction *N*-phenylpyrrolidine **1**, 1,4-diphenyl-aminobutane **2** and *N*-(4-phenylaminobutyl)-pyrrolidine **3** were isolated and identified. Upon variation of the concentrations of aniline and pyrrolidine the ring opening products were observed in diverse amounts. Applying an excess of pyrrolidine, mainly **1** and self-condensation products of pyrrolidine as by-products were obtained (Table 1, entry 1). In the presence of excess or stoichiometric amounts of

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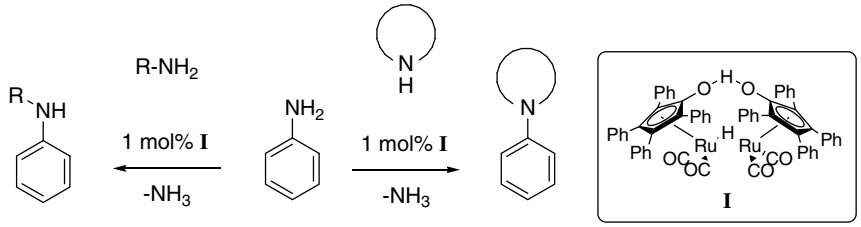
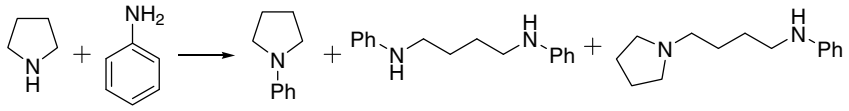


Scheme 1. Amination of aniline using non-cyclic and cyclic alkylamines.

Table 1
N-Alkylation of aniline with pyrrolidine in the presence of the Shvo catalyst **I** under different conditions[a]

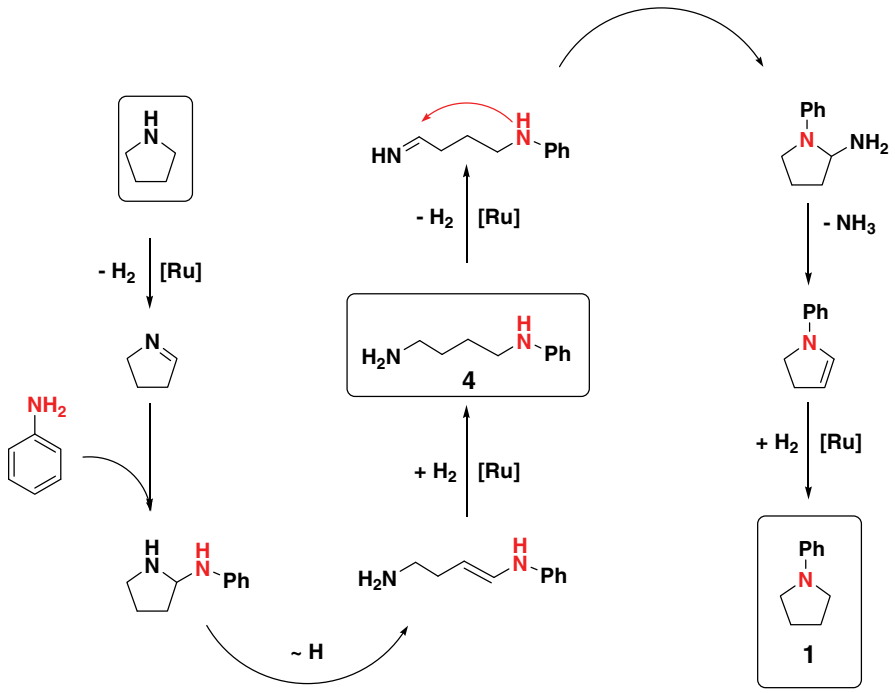


Entry	Solvent	*T* (°C)	Ratio py:an	**1** (%)	**2** (%)	**3** (%)
1	–	150	2:1	22 (21)	4 (2)	8 (7)
2	–	150	1:1	47 (32)	<1	3
3	–	150	1:2	53 (32)	5	2
4	–	140	1:2	22	–	–
5	–	130	1:2	3	–	–
6	–	110	1:2	–	–	–
7	Toluene	130	1:2	–	–	–

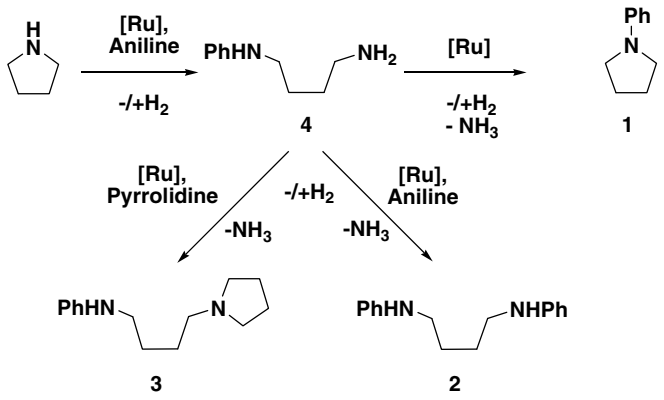
[a] Reaction conditions: 1 mol % Shvo catalyst, 24 h. Yields were determined by GC analysis with hexadecane as internal standard. Isolated yields in brackets.

aniline, *N*-phenylpyrrolidine **1** was observed as the major product in up to 53% yield (Table 1, entries 2 and 3). Here, no self-condensation products of pyrrolidine have been detected. The arylated 1,4-diamine derivates **2** and **3** were determined as minor products. Lowering of the reaction temperature provided a higher selectivity towards **1** but decreased the reactivity. Interestingly, in the presence of a solvent, for example, toluene, no reaction with aniline was observed (Table 1, entry 7).

In analogy to the monoalkylation of aryl amines,[16] the supposed reaction mechanism is illustrated in Scheme 2. Initially, ruthenium-catalyzed dehydrogenation of pyrrolidine should occur via coordination and β-hydride elimination. Then, nucleophilic attack of the aryl amine on the resulting imine to give the aminal, ring opening and hydrogenation yields the corresponding 1,4-diamine. Here, dehydrogenation of the primary amino group is fast compared to that of the secondary amine. Subsequent nucleophilic



Scheme 2. Proposed mechanism for the reaction of pyrrolidine with aniline.



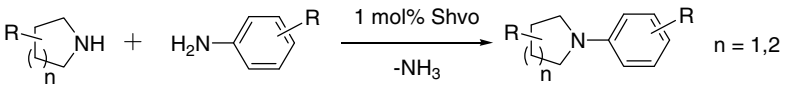
Scheme 3. Synthesis of the side products **2** and **3**.

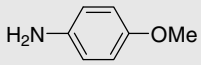
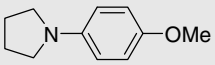
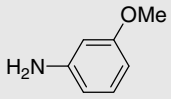
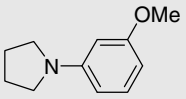
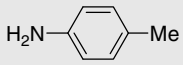
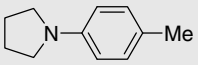
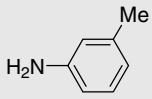
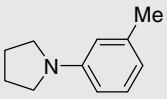
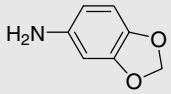
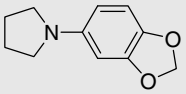
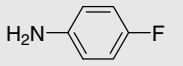
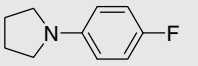
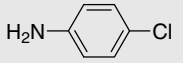
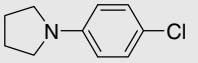
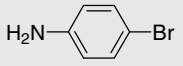
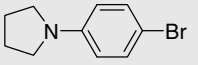
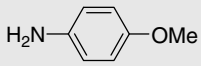
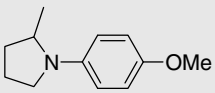
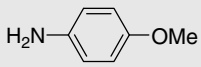
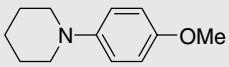
attack on the imine, elimination of ammonia and catalytic hydrogenation lead to the arylated pyrrolidine. Notably, *N*-phenylbutan-1,4-diamine **4** might react intermolecular with a second molecule of aniline to give **2**. Moreover, the primary amine group of **4** reacts with dehydrogenated pyrrolidine to yield **3** after a similar sequence of reaction steps (Scheme 3).

In order to demonstrate the general applicability of the Shvo catalyst and the scope of the process, the reaction of various aryl amines and three cyclic alkyl amines were investigated. These results are summarized in Table 2.

In general, catalytic experiments were run with 1 mol % of Shvo **I** in the presence of 2 equiv of aryl amine (Table 2). Noteworthy, the product yield depends on the electron density of the aromatic ring and thus the nucleophilicity of the amino group. Apparently, the nucleophilic attack of the aryl amine is involved in the rate-determined step. We were pleased to find that electron-rich aryl amines

Table 2
N-Alkylation of aryl amines with cyclic secondary alkylamines in the presence of Shvo **I**[a,18]



Entry	Arylamine	Product	Yield[b] (%)
1			67
2			48
3			31
4			51
5			58
6			31
7			25
8			28
9			58
10			68

[a] Reaction conditions: 1 mol % Shvo catalyst, 24 h, 150 °C.
[b] Isolated yields, Yields in brackets were determined by GC analysis with hexadecane as internal standard.

such as *m*/*p*-toluidine and *m*/*p*-anisidine gave the *N*-arylpyrrolidines in 39–67% yield (Table 2, entries 1–4). The pharmaceutically important 3,4-(methylenedioxy)-aniline gave 58% of the corresponding product (Table 2, entry 5). More problematic is the alkylation of halogenated anilines. Hence, 4-fluoro-, 4-chloro-, and 4-bromoaniline yielded the alkylated anilines in low to moderate yield (Table 2, entries 6–8). In accordance with this observation 4-trifluoromethylaniline showed no reaction even at higher temperature (Table 2, entry 9). Finally, other cyclic amines like piperidine and 2-methylpyrrolidine do also react with electron-rich anilines in good yield (Table 2, entry 11).

In conclusion, we have discovered a novel catalytic reaction of anilines and cyclic amines. In the presence of the Shvo catalyst selective activation of the secondary amine takes place and the aliphatic nitrogen atom is replaced by the aromatic one. Thus, electron-rich anilines furnish the corresponding *N*-aryl heterocycles in moderate to good yields. Notably, these reactions do not require any special handling, and do not need exclusion of air or water.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.107.

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18. General procedure for the amination reaction: In an ACE-pressure tube under an argon atmosphere the Shvo catalyst (0.02 mmol) and pyrrolidine (2 mmol) were dissolved in *tert*-amylalcohol (0.5 ml) and 4-methoxyaniline (4 mmol). The pressure tube was fitted with a Teflon cap and heated at 150 °C for 24 h. The solvent was removed in vacuo, and the crude alkyl aryl amine product is easily purified by column chromatography with pentane/ethyl acetate (20:1) to give *N*-(4-methoxyphenyl)pyrrolidine in 67% yield (238 mg) as red pale crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.98–2.03 (m, 4H), 3.22–3.28 (m, 4H), 3.76 (s, 3H), 6.55–6.62 (m, 2H), 6.83–6.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 25.4 (CH_2), 48.6 (CH_2), 56.0 (CH_3), 113.0 (CH), 115.1 (CH), 142.9 (C_q), 151.1 (C_q). IR (ATR): ν (cm^{-1}) = 3045w, 2977m, 2958m, 2947m, 2905w, 2863m, 2825m, 1616m, 1510m, 1487m, 1465m, 1439m, 1369m, 1337m, 1282m, 1234m, 1178m, 1155m, 1043m, 1034m, 964m, 869m, 812s, 799m, 743m. MS (EI): *m*/*z* (rel. int.) 177 (69), 176 (30), 162 (100), 134 (11), 121 (13), 120 (16). HRMS (EI): calcd for $C_{11}H_{15}O_1N_1$ (M^+) 177.11482, found 177.114495. For characterization of the other products see Supplementary data.

4.8. Pyrrolidine Activation: C–N Bond Cleavage and Formation and New Mechanistic Aspects in the Activation of the Shvo Catalyst

Dirk Hollmann, Rudy Parton, Rinke Altink, Annegret Tillack, Sebastian Bähn, Anke Spannenberg, Haijun Jiao, and Matthias Beller, *Organometallics* **2008**, submitted for publication.

Contributions

My contribution as co-author of this paper is approximately 80 %. I was responsible for the complete work. Dr. Anke Spannenberg was involved in the measurement of the X-ray-crystal structures of **IIIa**, **IIIb**, and **Vc**. Dr. Haijun Jiao performed calculation on the mechanism. Dr. Rudy Parton and Dr. Rinke Altink are industrial cooperation partner.

Pyrrolidine Activation: C–N Bond Cleavage and Formation and New Mechanistic Aspects in the Activation of the Shvo Catalyst

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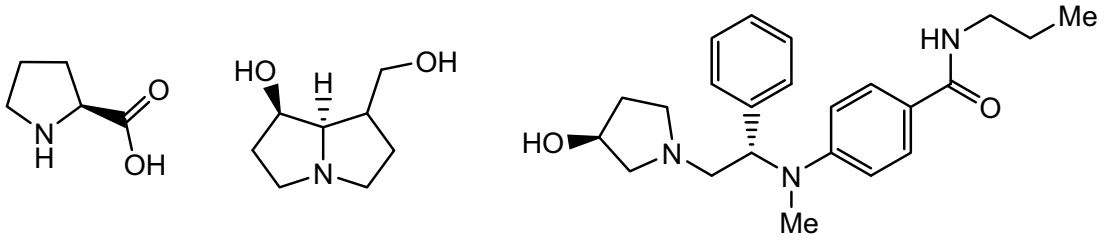
Abstract:

The ruthenium ligand metal bifunctional Shvo catalyst (**1**) is highly active for the dehydrogenation of cyclic aliphatic amines and for the hydrogenation of the corresponding imines or enamines under comparably mild conditions (100-150 °C). Pyrrolidine was completely converted at 150 °C to the thermodynamic stable N,N'-dipyrrolidyldiaminobutane. At lower temperature, the formation of kinetic stable dimeric intermediates results was observed. During the borrowing hydrogen transformation, carbon-nitrogen cleavage and formation occur. During these studies we were able to isolate new ammonium Shvo complexes with pyrrolidine, benzylamine and hexylamine. Crystals suitable for X-ray structure analysis were obtained for $[Ru_2(CO)_4(\eta^4\text{-}Ph_4C_4CO)_2(H)]^-[C_4H_8NH_2]^+$ (**IIIa**) and the

corresponding benzylamine complex (**IIIb**). In addition, **IIIa** was computed at the level of B3LYP density functional theory for comparison. Reasonable agreements between values obtained by X-ray crystallography and computation were found. These stable complexes indicate a different activation to the known thermic cleavage of the Shvo catalyst to generate both active species **A** and **B**. With these complexes, we were able to study the activation of the Shvo complex by kinetic NMR measurements in DMSO-d_6. Indeed a new activation pathway (Pathway II) was determined, which involves formation of B and an ammonium ruthenium hydride complex **C**.

Introduction

In organic molecules, fundamental structural components are functional groups containing hetero-atoms, such as nitrogen, oxygen or sulfur. Especially the presence of carbon-nitrogen (C–N) bonds is found to be essential for the function of many biologically active molecules.[1] Due to the basic character of the nitrogen lone pair and the hydrogen donating capacity of the NH group, alkaloid skeletons constitute privileged structures. One of the highest ranked alkaloids is found in DNA. In comparison, the pyrrolidine skeleton represents one of the simplest alkaloid structures. Based on this structure many important natural and pharmaceutical products like proline, retronecine[2] and CJ-15,161 (opiod receptor agonist) are known (Figure 1).

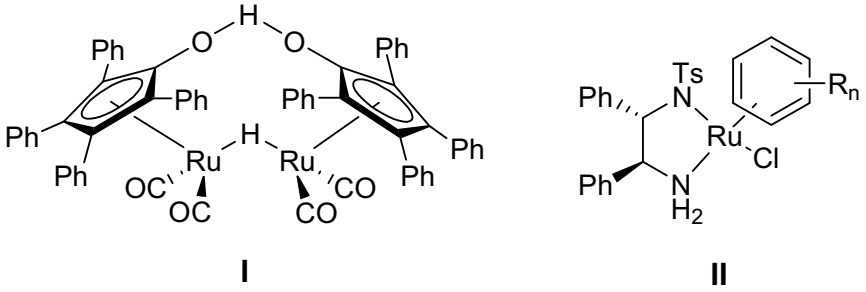


Proline Retronecine CJ-15,161 (Pfizer)

Figure 1. Examples of natural and pharmaceutical alkaloids containing a pyrrolidine moiety

For the metabolism of humans and animals, the formation of C–N bonds is of high interest. However, the cleavage of C–N bonds is also of paramount interest, and *N*-dealkylation is a commonly observed biotransformation. For example, monooxygenases such as Cytochrome P450[3] metabolize a wide range of endogenous compounds and xenobiotics, such as pollutants, environmental compounds, and drug molecules. P450 catalyzes a multitude of reactions, such as hydrocarbon hydroxylation and alkene epoxidation, as well as *N*-, *O*-, and *S*-dealkylation.[4] Despite the identification of these enzymes in 1964,[5] the development of new dealkylation methods is of great interest, but only few reactions are known.[6]

Further important transformations are oxidation and reduction of organic compounds. In nature the nicotinamide adenine dinucleotide NAD^+ and NADH are responsible for hydrogen and electron transfer.[7] In chemical synthesis, biomimetic catalysts, such as the Shvo catalyst **I**[8,9] or Noyori TsDPEN catalyst **II**[10] were used in a multitude of reductions, transfer hydrogenation or dynamic kinetic resolution sequences[11] (Figure 2).



I **II**

Figure 2. Shvo **I** and Noyori **II** catalysts for transfer hydrogenation

On the basis of our ongoing interest in the synthesis of aliphatic and aryl amines,[12] our group has recently developed a very efficient method of transfer hydrogenation and dealkylation using the Shvo catalyst.[13,14] During these studies we were able to synthesize monoalkylated anilines using mono-, di-, and trialkyl amines selectively.[13]

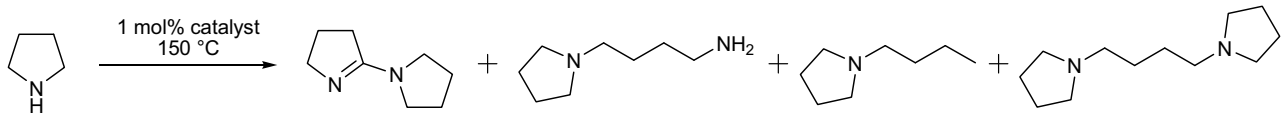
Additionally, we are interested in the conversion of cyclic alkyl amines with aryl amines.[15] Due to the high basicity of the nitrogen in cyclic amines and thus the high reactivity of the nitrogen in these substrates, these rings bear a great challenge. If cyclic secondary amines are used, trimerisation can

occur.[16] However, previous catalysts included only heterogeneous palladium or silicates catalysts. In order to stimulate further applications of this chemistry, the development of more active catalysts for amines is highly desired. A strategy to overcome this problem might be the switch from heterogeneous to molecularly-defined organometallic catalysts. However, no homogeneous catalysts are known for the ring opening of cyclic amines yet.

Results and Discussion

On the basis of our interest in the synthesis of aryl amines with aliphatic amines[13,14] we started a comprehensive study on the ring opening of secondary cyclic aliphatic amines, especially pyrrolidine. In the following we report our results of a ruthenium catalyst, which is highly active for the dehydrogenation of cyclic aliphatic amines and the hydrogenation of the corresponding imines or enamines under comparably mild conditions (100-150 °C). During the hydrogen borrowing transformation,[17] carbon-nitrogen cleavage and formation occur.

(a) Catalyst screening and Optimization: At the beginning of our investigation we focused our attention on the influence of different ruthenium and rhodium catalysts (see Table 1, Supporting Information). The reaction with pyrrolidine was run without solvent at 150 °C for 24 h in the presence of 1 mol% ruthenium or rhodium catalysts.



	1	**2**	**3**	**4**
$[RhCp^*Cl_2]_2$	7 %	5 %	3 %	4 %
Shvo **I**	-	-	-	82 %

Scheme 1. Reaction of pyrrolidine with Shvo **I** and $[RhCp^*Cl_2]_2$

Among all catalysts tested, only Shvo **I** and $[RhCp^*Cl_2]_2$ were active (Scheme 1), and Shvo **I** showed reactivity to a significant extent. For example, Shvo **I** has the highest yield of **4** (82 %), and $[RhCp^*Cl_2]_2$ resulted in the formation of products **1**, **2**, **3,** and **4** in rather small amounts. **1** and **4** were

purified by aluminium oxide column chromatography and characterized by ^{1}H-, ^{13}C-, Dept, COSY, HMQC-NMR, IR, and GC-MS, while **2** and **3** were identified by GC-MS and could not be isolated.

As a next step we paid our attention to the optimization of the reaction conditions by using Shvo **I**. First, the temperature and solvent influences were investigated (Table 1). With undiluted pyrrolidine high yields of **4** (82 %) were observed (Table 1, entries 1 and 2), while toluene as solvent lowered the reactivity and the yield (up to 60 %, Table 1, entries 3 and 4). On the one hand the reactivity dropped significantly at 110 °C and on the other hand products **2** and **4** were determined (Table 1, entry 5). At 90 °C the conversion was poor but the ratio switched in favour of **2**.

Table 1: Temperature and solvent influence on the selectivity of **2** and **4**[a]

Entry	Solvent	Temperature	**1**[c] [%]	**2**[c] [%]	**3**[c] [%]	**4**[d] [%]
1	-	150 °C	-	-	-	82
2	-	130 °C	-	-	-	77
3	toluene	150 °C	-	-	-	60
4	toluene	130 °C	3	-	-	59
5	toluene	110 °C	-	13	-	17
6	toluene	90 °C	-	5	-	2
7[b]	-	110 °C	-	22	-	28
8[b]	heptane	110 °C	-	2	-	<1
9[b]	toluene	110 °C	-	8	-	12
10[b]	nitromethane	110 °C	-	-	-	-
11[b]	acetonitril	110 °C	-	-	-	-
12[b]	dimethoxyethane (DME)	110 °C	-	8	-	3
13[b]	N-methylpyrrolidinone (NMP)	110 °C	2	-	10	51
14[b]	dimethylformamid (DMF)	110 °C	-	4	-	20[e]
15[b]	dimethylsulfoxide (DMSO)	110 °C	-	2	-	53
16[b]	^{t}amylalcohol	110 °C	-	8	-	10

[a] Reaction condition: 1 mol% Shvo **I**, 24 h, solvent/pyrrolidine = 1/1, pressure tube. [b] Zinsser carousel. [c] Yields are estimated by GC analysis with hexadecane as internal standard. [d]Yields are determined by GC analysis with hexadecane as internal standard. [e] Side product: formylpyrrolidine.

Surprisingly, significant solvent effect was observed in the amination reaction in contrast to the alkylation of aryl amines,[13]. For example, only toluene showed a moderate reactivity compared to other nonpolar solvents (heptane and toluene, Table 1, entries 8 and 9), while no clear trend was noticed in polar solvents (acetonitril, DME, NMP, DMF and DMSO, Table 1, entries 12-15) and polar protic solvents (^{t}amylalcohol, Table 1, entry 16). Highest reactivity was achieved with DMSO and NMP, followed by toluene and ^{t}amylalcohol.

Finally, we investigated different additives (Table 2). First we thought about an inhibition of the catalyst by chelatization of product **4** (Table 2, entries 2 and 3). Surprisingly after addition of 2 mol% of **4**, the yields and thus the reactivity slightly increased, but more than 80 mol% of **4** (meaning a second addition of pyrrolidine after full conversion) inhibited the reaction and the yields dropped dramatically. Moreover, the effect of hydrogen excess was examined. By adding one equivalent formic acid, which forms carbon dioxide and hydrogen at elevated temperatures, no effect was observed. The addition of water to the reaction mixture inhibited the reactivity (Table 2, entries 5 and 6) and consequently low or no yields of **2** and **4** were achieved. The addition of tetrafluoroboric acid as Lewis acid decreased the reactivity (Table 2, entry 8). On the basis of these tests the best reaction conditions should be 1 mol% Shvo **I** at 150 to 140 °C in DMSO (or without solvent) and without additives.

Table 2: Screening of the conditions and effects on the selectivity of **2** and **4**[a]

Entry	Solvent	Additives	**2**[b] [%] (8 h)	**4**[c] [%] (8 h)	**2**[b] [%] (24 h)	**4**[c] [%] (24 h)
1	-	-	3	2	21	23
2	-	2 mol% **4**	8[f]	5[f]	23[f]	30[f]
3[e]	-	1. 100 % conv. 2. 1 equiv Pyrrolidine	-[f]	1.5[f]	13[f]	5[f]

4	-	1 eq H_2 (HCOOH)	7	3	21	21
5	-	3 mol% H_2O	-	1	13	5
6	-	1 equiv H_2O	-	-	1	1
7	DMSO	-	<1	<1	2	46
8	DMSO	5 mol% HBF_4	<1	<1	9	27

[a] Reaction condition: 1 mol% Shvo **I**, 24 h, solvent/pyrrolidine = 1/1, Zinsser carousel. [b] Yields are estimated by GC analysis with hexadecane as internal standard. [c]Yields are determined by GC analysis with hexadecane as internal standard. [e] First: 150 °C, 48 h, then determination of the GC-yields, next addition of one equivalent of pyrrolidine. [f] Yields are corrected by deduction of **4**.

(b) Mechanistic Aspect: By applying a Zinsser 12-fold carousel, we were able to record the kinetics of the reaction (online sampling and offline analysis). Figure 3 shows the comparison of the reactivity of Shvo **I** with and without toluene. In undiluted reaction solution, both **2** and **4** were found at the beginning of the reaction (up to 15 h), while **4** was the only product at the end of the reaction. In toluene, however, the solvent effects were dramatical. At the beginning of the reaction, the formation of **2** was faster than that of **4**, and **2** reached the maximum yield (30 %) after 20 hours. At the end of the reaction, **4** reached the maximum yield, while the yield of **2** decreased to 15 %. These observations support a mechanism involving **2** as an intermediate and **4** as the thermodynamically stable final product.

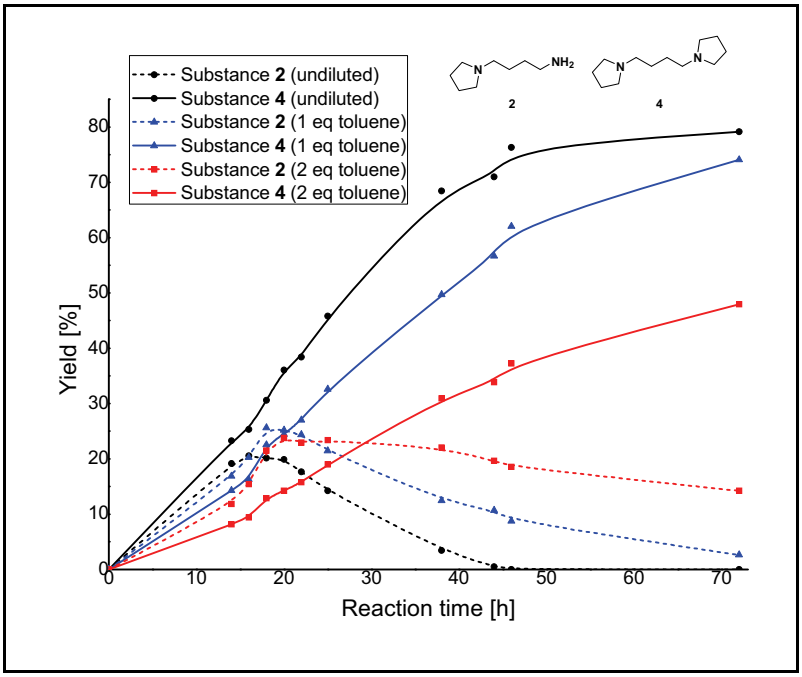
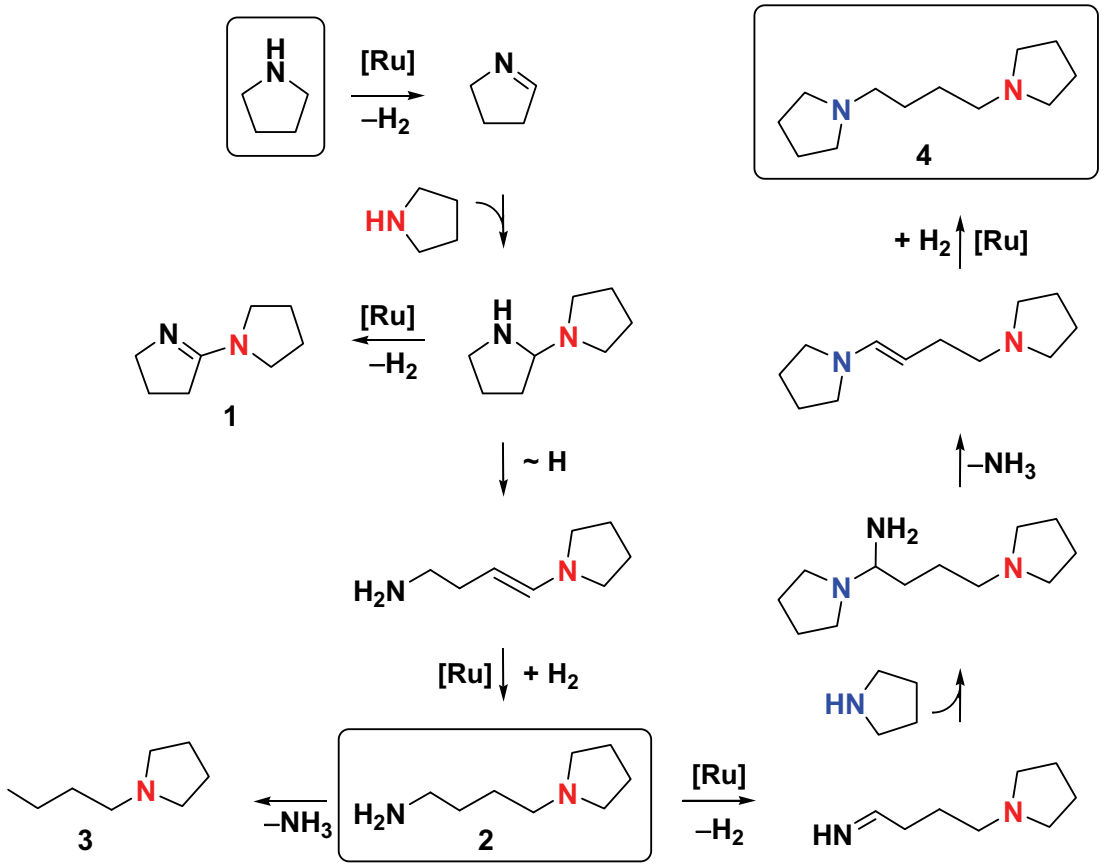


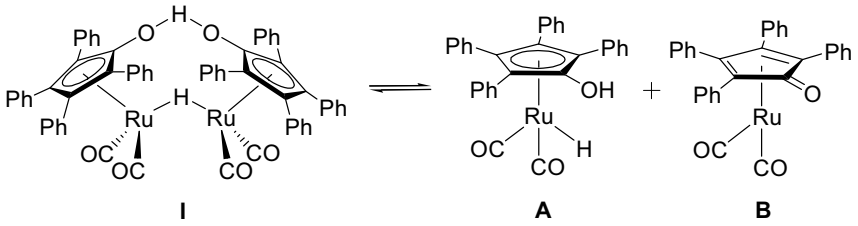
Figure 3: Kinetics of **2** and **4** at different toluene concentrations with 1 mol% Shvo **I** at 100 °C

As illustrated in Scheme 2, the first step is the dehydrogenation of pyrrolidine to 1-pyrroline followed by a nucleophilic attack of a second pyrrolidine molecule. The second step is the ring opening (C–N cleavage) along with hydrogen shift resulting in the formation of enamine, which is hydrogenated to **2**. Due to the higher reactivity of primary amines in dehydrogenation compared to secondary amines, the primary amine group of **2** will preferably be dehydrogenated. After an intermolecular attack of a third pyrrolidine molecule, loss of ammonia and hydrogenation of the corresponding enamine, **4** could be formed. This mechanism is also the basis for the understanding of the reactivity and formation of the observed side products **1** and **3**. For example, **1** can be generated by dehydrogenating 1,2'-bipyrrolidine, while **3** could be formed by ammonia elimination.



Scheme 2: Proposed mechanism for the reaction of pyrrolidine

(c) Mechanism with Shvo I: Shvo **I** has been the subject of detailed mechanistic investigations by Bäckvall,[18] Casey[19], and others.[20] Shvo **I** can dissociate into two active species **A** and **B** (Scheme 3), which are able to hydrogenate unsaturated compounds, such as alcohols or amines and dehydrogenate the corresponding saturated compounds, respectively. The reaction takes places by transferring a hydride (bonded to a metal center) and a proton (bonded to a ligand). However, the reaction mechanism for the hydrogen transfer process, whether concerted without substrate coordination or concerted with substrate coordination and ring slippage of the aromatic ring, is a matter of controversy.



Scheme 3: Equilibrium between **I** and the active species **A** and **B**

Compared to this, only a few studies were performed on the formation of **A** and **B** starting from Shvo **I** and this is very important for the initial activation and production of the active species. So far, it has been estimated that Shvo **I** can be cleaved by rising temperature in order to generate **A** and **B**. In the reaction of Shvo **I** with 1-(4-methoxyphenyl)-*N*-methylethanamine Bäckvall et al.[9] observed a new amine Shvo complex using NMR measurements, but no other analysis was performed. In our study we found that Shvo **I** can protonate secondary and primary amines and forms new ammonium complexes (Table 3).

One example is the complex of Shvo **I** with pyrrolidine $[Ru_2(CO)_4(\eta^4\text{-}Ph_4C_4CO)_2(H)]^-[C_4H_8NH_2]^+$ (**IIIa**). Treatment of **I** in dichloromethane with pyrrolidine at room temperature for five minutes gave **IIIa** in 92 % yield as yellow powder. Crystals suitable for X-ray structure analysis (Figure 4) were obtained by recrystallization from pentane-diethylether. In addition, we were able to isolate the corresponding benzylamine complex (**IIIb**), which crystallizes as a dimeric complex, whereas one unit is stabilized by a diethyl ether molecule and another one by a further benzylamine molecule (see Supporting Information). One unit of **IIIb** is shown in Figure 5. The crystallographic data of **IIIa** and **IIIb** are summarized in Table 4. Selected bond lengths and angles are given in Tables 5 and 6, and general agreements in structural parameters were found between the two complexes. In addition, **IIIa** was computed at the level of B3LYP density functional theory for comparison. As shown in Table 5, reasonable agreements between values obtained by X-ray crystallography and computation were found.

The characteristics of these new complexes **III** are the formation of the ammonium ion, which bridges the two carbonyl oxygen atoms of the cyclopentadienone (CPD) rings by hydrogen bonds. This confirms the observation that the second bridged hydrogen has a strong acidic character. In **IIIa** strong

hydrogen bonds between the ammonium ion and the carbonyl groups of the cyclopentadienone ring (N-H···O: N1-H1 0.89(4), H1-O1 1.72(4) Å) were observed.

In complex **IIIa** the long distance Ru1-C1 (2.514(3) Å) compared to the distances of the other four carbon atoms to Ru1 (2.193(3)-2.283(3) Å) and the short C-O bond length of 1.246(3) Å give evidence for η^4 coordination of the CPD ligand to the ruthenium centre. Additionally, the cyclopentadienone rings have an envelope conformation with an angle between the plane defined by C2, C3, C4, C5 and the plane defined by C1, C2, C5 of 16.9(4)°. The same bonding situation (Ru-C_{CPD}: 2.471(3)/2.503(3) versus 2.179(3)-2.264(3), C1-O1/C63-O7 1.261(3)/1.246(3) Å) and an analogous envelope angle of the CPD (15.1(3)-17.9(4)°) were found for **IIIb**. As in **IIIa** two strong hydrogen bonds between the ammonium ion and the carbonyl groups of the cyclopentadienone rings (N-H···O: N1-H3 0.97(4), H3-O1 1.69(4); N1-H4 1.05(4), H4-O4 1.80(4) / N2-H6 0.93(4), H6-O7 1.82(4); N2-H7 0.89(3), H7-O10 1.93(4) Å) were observed. A further hydrogen bond exists between the third hydrogen atom of the ammonium ion and a diethyl ether (N-H···O: N1-H5 0.98(4), H5-O13 1.87(4) Å) and a benzyl amine molecule (N-H···N: N2-H8 0.90(3), H8-N3 2.05(3) Å), respectively.

Table 3: Spectral data of Shvo ammonium complexes[a]

compound	amine	δ(H) Hydride, ppm	ν(CO), cm^{-1}
I	-	-9.73	1959, 1972, 2004, 2029
IIIa	pyrrolidine	-13.71	1934, 1953, 1982, 2015
IIIb	benzylamine	-13.69	1947, 1993, 2019
IIIc	hexylamine	-13.69	1942, 1990, 2017
Va	pyrrolidine	-	1944, 2003
Vb	benzylamine	-	1955, 2011
Vc	hexylamine	-	1947, 2006

[a] ^{1}H NMR spectra were measured in DMSO-d_6, FTIR spectra were measured using ATR technique.

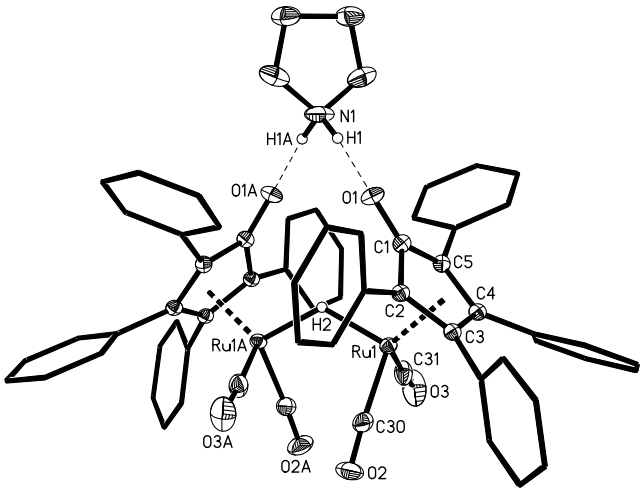


Figure 4. Molecular structure of **IIIa**. Thermal ellipsoids are set at the 30 % probability level. H atoms (except H1, H1A, and H2) are omitted and the phenyl rings are simplified.

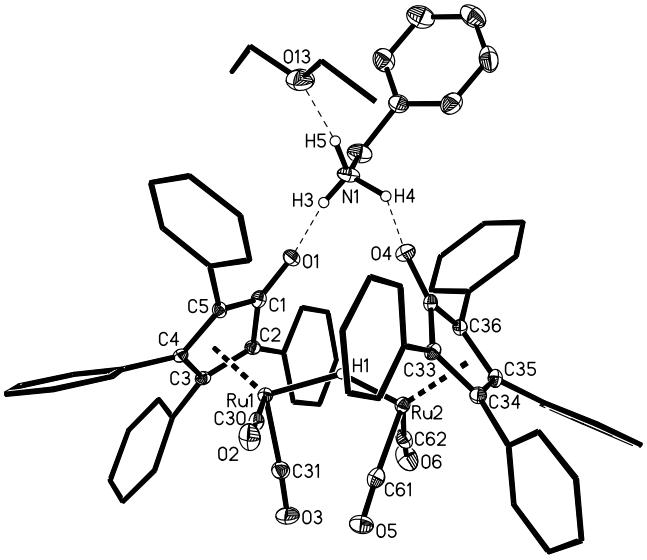


Figure 5. Molecular structure of one part of the asymmetric unit of **IIIb**. Thermal ellipsoids are set at the 30 % probability level. For clarity H Atoms (except H1, H3 - H5) are omitted and the phenyl rings and ether molecule are simplified.

Table 4. Crystallographic Data of **IIIa**, **IIIb** and **Vc**

	IIIa	**IIIb**	**Vc**
chemical formula	$C_{66}H_{51}NO_6Ru_2$	$C_{76.5}H_{65.5}N_{1.5}O_7Ru_2$	$C_{37}H_{35}NO_3Ru$
formula weight	1156.22	1319.94	642.73
cryst syst	monoclinic	triclinic	monoclinic
space group	*C*2/*c*	*P*-1	$P2_1/c$
a [Å]	20.891(4)	15.597(3)	10.6912(3)
b [Å]	12.983(3)	17.173(3)	11.5346(3)
c [Å]	19.940(4)	25.181(5)	25.2807(7)
α [deg]	90	106.71(3)	90
β [deg]	102.89(3)	92.11(3)	102.180(2)
γ [deg]	90	100.49(3)	90
V [$Å^3$]	5272(2)	6324(2)	3047.4(1)
Z	4	4	4
density [$g \cdot cm^{-3}$]	1.457	1.386	1.401
μ(Mo Kα) [mm^{-1}]	0.629	0.535	0.552
T [K]	293(2)	200(2)	200(2)
no. of rflns (measd)	9406	85379	44534
no. of rflns (indep)	4858	23565	6451
no. of rflns (obsd)	3144	13483	4735
no of params	316	1595	385
R1 (I>2σ(I))	0.0364	0.0296	0.0278
wR^2 (all data)	0.0621	0.0471	0.0613

Table 5. Selected bond distances [Å] and angles [°] for compound **IIIa**

parameters	X-ray analysis	Theory
Ru1-C1	2.514(3)	2.569
Ru1-C2	2.283(3)	2.280
Ru1-C3	2.195(3)	2.230
Ru1-C4	2.193(3)	2.244
Ru1-C5	2.234(3)	2.331
C1-O1	1.246(3)	1.256
O1-H1	1.72(4)	1.631
Ru1-C30	1.888(4)	1.902
C30-O2	1.161(4)	1.159
Ru1-C31	1.876(4)	1.908
C31-O3	1.152(5)	1.159
Ru1-H2	1.84(2)	1.800
Ru1-H2-Ru1A	126(2)	142.18
Hydrogen bonds [Å]		
O1···H1	1.72(4)	1.631
N1-H1	0.89(4)	1.055
N1···O1	2.607(4)	2.672

Table 6. Selected bond distances [Å] and angles [°] or compound **IIIb**

IIIb (unit 1)		**IIIb** (unit 2)	
C1-O1	1.261(3)	C63-O7	1.246(3)
C32-O4	1.249(4)	C94-O10	1.249(3)
Ru1-C30	1.872(3)	Ru3-C92	1.884(4)
C30-O2	1.164(3)	C92-O8	1.155(4)
Ru1-C31	1.880(4)	Ru3-C93	1.875(4)
C31-O3	1.156(4)	C93-O9	1.153(4)
Ru1-H1	1.83(4)	Ru3-H2	1.91(3)
Ru2-H1	1.60(4)	Ru4-H2	1.55(3)
Ru1-H1-Ru2	138(2)	Ru3-H1-Ru4	140(2)
Hydrogen bonds [Å]			
O1···H3	1.69(4)	O7···H6	1.82(4)
N1-H3	0.97(4)	N2-H6	0.93(4)
N1···O1	2.604(4)	N2···O7	2.680(4)
O4···H4	1.80(4)	O10···H7	1.93(4)
N1-H4	1.05(4)	N2-H7	0.89(3)
N1···O4	2.710(4)	N2···O10	2.727(4)
O13···H5	1.87(4)	N3···H8	2.05(3)
N1-H5	0.98(4)	N2-H8	0.90(3)
N1···O13	2.844(4)	N2···N3	2.904(5)

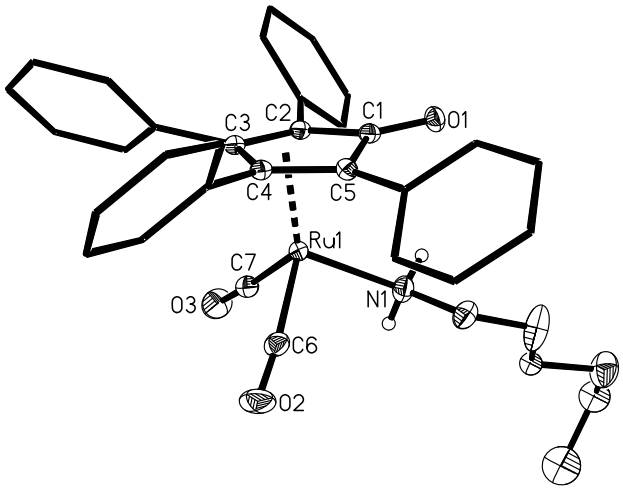
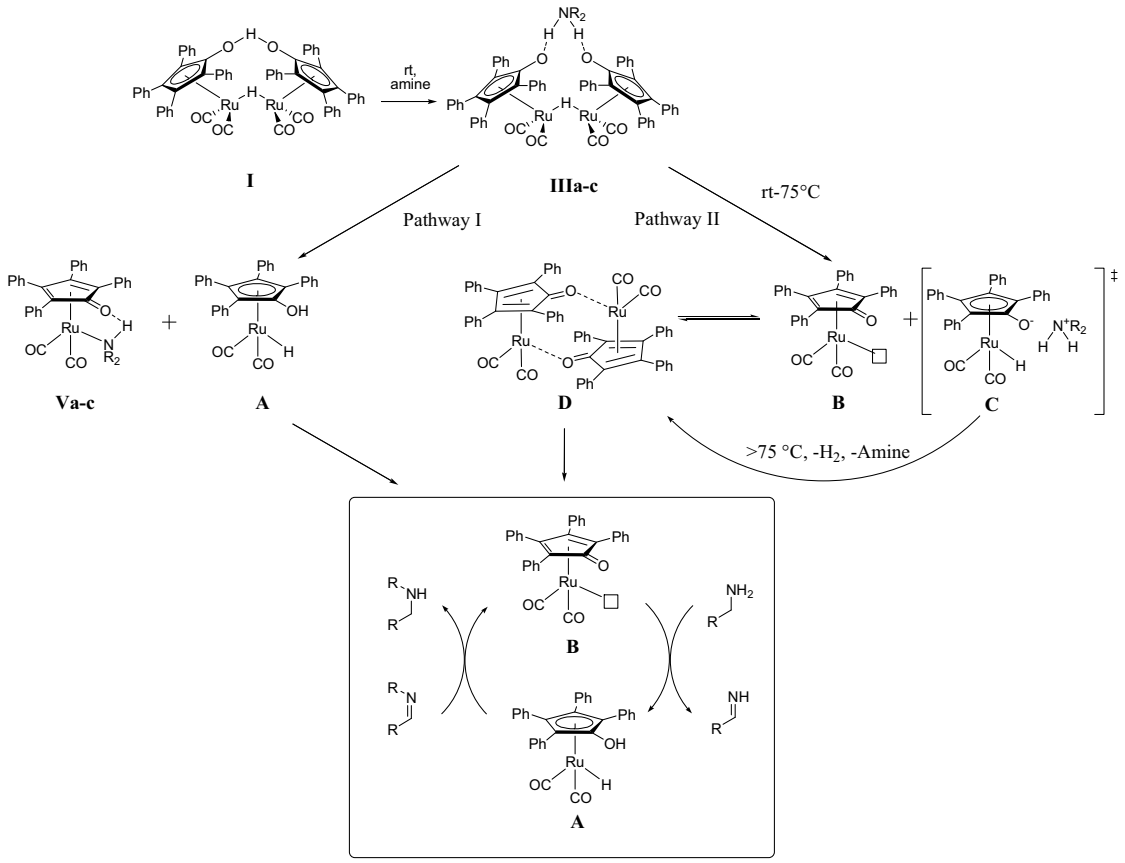


Figure 6. Molecular structure of **Vc**. Thermal ellipsoids are set at the 30 % probability level. H atoms are omitted and phenyl rings are simplified for clarity. Selected bond lengths [Å]**:** Ru1-C1 2.429(2); Ru1-C2 2.225(2); Ru1-C3 2.1922; Ru1-C4 2.200(2); Ru1-C5 2.245(2); C1-O1 1.251(3); Ru1-N1 2.169(2); Ru1-C6 1.887(3); Ru1-C7 1.894(3).

With these complexes we were able to study the activation of the Shvo complex to form the active species A and B.

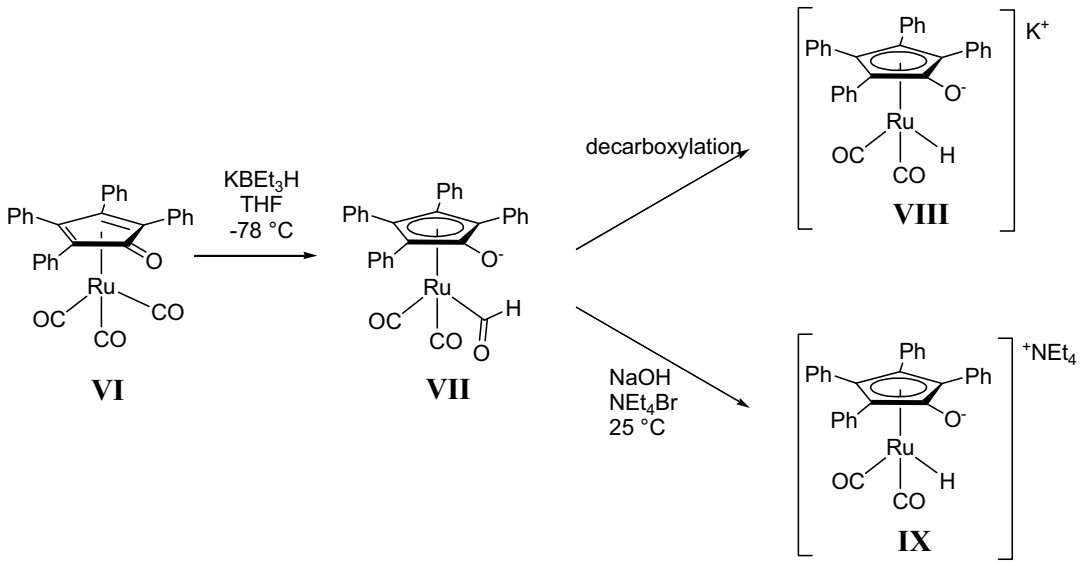
The formation of the two active species is possible via two different pathways (Scheme 4). On the one hand (Pathway I) it is possible that complex **III** is dissociated to the intermediate **A** and **B**. The free coordination site of **B** could be stabilized by the corresponding amines to form stable ruthenium-amine complexes **Va-c**. Some analogous kinetic stable amine complexes were isolated and characterized by other groups.[19g,21,22] On the other hand (Pathway II) the ammonium complexes **III** are dissociated to form intermediate **B** and ammonium hydride compound **C**. Due to missing amine compounds, the intermediate **B** is stabilized through a dimerisation to form compound **D**. At elevated temperature compound **C** is decomposed to **B** and the corresponding amine and hydrogen.



Scheme 4: Proposed activation of the Shvo catalyst

In order to study this activation starting from the ammonium ruthenium complexes, we monitored dynamic ^{1}H NMR in DMSO-d_6 of **IIIa** and **IIIb**. Starting from 24 °C, the temperature was increased to 140 °C in steps of 10 °C. At 24 °C the hydride signal for complex **IIIa** appeared at –13.70 ppm. During heating to 65 °C, this hydride signal shifted to lower ppm (–13.95 ppm), and the broad NH signal (8.48 ppm) disappeared. At this temperature, the intensity of the hydride signal of **IIIa** decreased and a new hydride signal at –9.95 ppm was observed. At 75 °C complete conversion of **IIIa** was determined, and only the new hydride signal was found. Changes were also found for the aromatic signals of **IIIa** (6.90-7.03 and 7.39-7.44 at 24 °C vs. 6.93-7.37, 7.50-7.53, and 7.55-7.58 ppm at 75 °C) and the two pyrrolidine CH_2-groups (1.81-1.85 and 3.07-3.10 at 24 °C vs. 1.68-1.75 and 2.88-2.94 ppm at 75 °C). Starting from **IIIa** two new complexes (minor complex: –9.95 ppm and 7.50-7.53 ppm, major complex: 7.55-7.58) were formed in a ratio of 1:3.5. Finally, by increasing the temperature from 75 °C to 110 °C the hydride and the aromatic signals of the minor complex decreased and disappeared at 110 °C. The minor complex was completely converted into the major complex. Cooling down the reaction mixtures at 75 °C and 130 °C to room temperature, comparison with known complexes was possible. For comparison of the two pathways we prepared the complexes **Va-c** and **A**. Instead of complex **B,** the dimeric complex $[Ru(CO)_2(\eta^4\text{-}Ph_4C_4CO)]_2$ (**D**) was synthesized.[23] Crystals suitable for X-ray crystal structure analysis were obtained for **Vc** but not for **Va** and **Vb** (Figure 6).

First the major complex formed at 140 °C was investigated (Comparison and overview of the spectra see supporting information). The major complex corresponded exactly with complex **D**. Next the minor compound was examined. The NMR spectra of the minor compound did not correspond with any prepared complexes. Due to the absence of a hydroxyl signal and the presence of a hydride signal, which is in the same range as compound **A**, we assume that under these conditions complex **C** was formed. This assumption is confirmed by the isolation of the analogues potassium and tetraethylammonium complexes (Scheme 5).[23g] The hydride signal was observed at -9.68 ppm for the tetraethylammonium complex.



Scheme 5: Synthesis of cationic Shvo analogues by Casey et al.

Similar observations were also found for the benzyl amine complex (**IIIb**). For example, the transformation temperature from **IIIb** to **C** was 65 °C and a new hydride signal of **C** appeared at –9.93 ppm. At 75 °C, these hydride signals appeared at the same shift and thus the same intermediate **C** is formed. Finally, only compound **D** was observed.

With these results in hand we were able to confirm but also to modify the mechanism of Bäckvall et al. (Scheme 4).[9a] Instead of thermal dissociation of **I**, the cycle starts with the protonation of the amine and the formation of the ammonium complex **IIIa-c**. In the next step the ruthenium-hydride-ruthenium bond is cleaved. Passing through the intermediates **C**, compound **B** is formed which exists as dimeric complex **D**. This complex could now dehydrogenate amines to imines in order to start the catalytic circle.

In addition to our experimental studies, we also have computed the thermodynamic properties of the formation of **IIIa**. As shown in Scheme 4, the formation of Shvo **I** is kinetically favored by **A** and **B** and the computed reaction enthalpy (ΔH_1) is –24.30 kcal/mol and the reaction free energy (ΔG_1) is –9.47 kcal/mol, indicating that this reaction is both exothermic and exogonic. Most importantly, these data reveal that this reaction is not reversible and the dissociation is thermodynamically not possible.

The reaction of Shvo **I** with pyrrolidine with the formation of **IIIa** is thermodynamically favored, as indicated by its exothermic reaction enthalpy (ΔH_2 = –16.32 kcal/mol) and exogonic reaction free energy (ΔG_2= –4.2 kcal/mol). This corresponds with the experimental observations that the reaction takes place at room temperature and **IIIa** is found as stable intermediate.

Summary

The Shvo catalyst (**1**) was shown to be highly active in the dehydrogenation of pyrrolidine and for the hydrogenation of the corresponding imines or enamines under comparably mild conditions (100-150 °C). At 150 °C, trimerisation of pyrrolidine was observed. Kinetic measurements revealed that trimer **4** is the thermodynamic stable product and dimer **2** is a kinetically stable intermediate. During the borrowing hydrogen transformation, carbon-nitrogen cleavage and formation occur. Additionally the activation of the Shvo catalyst in the reaction of pyrrolidine does not proceed by thermal cleavage. During our studies we were able to isolate new ammonium Shvo complexes with pyrrolidine, benzylamine and hexylamine. Crystals suitable for X-ray structure analysis were obtained for $[Ru_2(CO)_4(\eta^4\text{-}Ph_4C_4CO)_2(H)]^-[C_4H_8NH_2]^+$ (**IIIa**) and the corresponding benzylamine complex (**IIIb**). The crystal structure was supported by B3LYP density functional theory calculations. Kinetic NMR measurements in DMSO-d_6 of these complexes indicate a new activation pathway (Pathway II), which involves formation of B and an ammonium ruthenium hydride complex **C**. These results were supported by previous reported complexes of Casey.

Experimental section

Computational details: All structures were optimized at the B3LYP[24] level of density functional theory along with the LANL2DZ basis set by adding a set of polarization functions (LANL2DZ(d)).[25] All optimized structures were characterized by frequency calculation as energy minima without imaginary frequencies (NImag = 0) or transition states with only one imaginary frequency (NImag = 1) at the same level of theory (B3LYP/LANL2DZ(d)).[26] The thermal corrections to enthalpy and Gibbs free energies at 298 K from the frequency calculations were added to the total electronic energies for

analyzing the relative reaction energies. All calculations were carried out by using the Gaussian 03 program package.[27]

General Remarks: All reactions were carried out under an inert atmosphere of argon gas by standard Schlenk technique. Chemicals were purchased from Aldrich, Fluka, Acros, and Strem and unless otherwise noted were used without further purification. Amines were distilled and stored under argon. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, HRMS, and FTIR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 300 and AV 400 spectrometer. The ^{1}H and ^{13}C NMR chemical shifts were reported relative to the center of solvent resonance ($CDCl_3$: 7.25 (^{1}H), 77.0 (^{13}C)). For complexes **I-IV** ^{1}H and ^{13}C NMR chemical shifts were recorded in DMSO-d_6 and the chemical shifts δ were relative to $SiMe_4$. EI mass spectra were recorded on an MAT 95XP spectrometer (70 eV, Thermo ELECTRON CORPORATION). ESI high resolution mass spectra were recorded on an Agilent Technologies 6210 TOF LC/MS. For complexes **IIIa-IIIc,** the measurement of EI, CI, FAB and ESI mass spectra were not possible. FTIR spectra were recorded on a Nicolet 6700 spectrometer and a ATR SMART ENDURANCE (Thermo ELECTRON CORPORATION) equipment. Elemental analyses were determined by C/H/N/S-Analysator 932 (Leco). GC was performed on a Hewlett Packard HP 6890 chromatograph with an Optima 5 - amine column (Company: Machery-Nagel, 30m x 0.25µm, 0.5µm film thickness, 50-8-200/5-8-260/5-8-280/5-8-300/20). All yields reported in Tables 1-4 refer to GC yields using hexadecane as an internal standard. In order to verify the reproducibility, all reactions were carried out at least twice.

Synthesis of $[Ru_2(CO)_4(\eta^4\text{- }Ph_4C_4CO)_2(H)][C_4H_8NH_2]$ (IIIa). Shvo catalyst **I** (100 mg, 0.092 mmol) was dissolved in CH_2Cl_2 (1 ml). To this solution pyrrolidine (0.25 mL) was added and the mixture was stirred at room temperature for 5 min. During this time a yellow substance dropped out of the solution. To complete the precipitation pentane (1 mL) was added. The yellow precipitate was filtered and washed with pentane (1 mL) to yield 99.2 mg (92 %) of **IIIa** (yellow powder). Crystals suitable for X-ray crystal structure analysis were obtained by recrystallisation from pentane-diethylether. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = -13.70 (s, 1H, Ru-H-Ru), 1.81-1.85 (m, 4H, $NCH_2C\underline{H}_2$), 3.07-3.10 (m, 4H, $NC\underline{H}_2CH_2$), 6.90-7.03 (m, 32H, Ar_{Shvo}), 7.41-7.43 (m, 8H, Ar_{Shvo}), 8.49 (s, 2H, $N\underline{H}_2$). ^{13}C NMR (DMSO-d_6, 100 MHz)): δ = 23.6 (CH_2 of Pyrr), 44.9 (CH_2 of Pyrr), 78.1(q, $C_{3,4}$ of Cp), 100.8 (q, $C_{2,5}$ of Cp), 124.7(CH, Ph), 126.5 (CH, Ph), 126.7 (CH, Ph), 127.1 (CH, Ph), 130.5 (CH, Ph), 131.9 (CH, Ph), 133.1(q, Ph), 135.0 (q, Ph), 172.1 (q, C_1 of Cp), 202.0 (q, CO). FTIR (ATR): ν (cm^{-1}) = 3057m, 3035w,

2982w, 2015s, 1982s, 1953s, 1934s, 1601m, 1577m, 1499m, 1442m, 1072m, 1027m, 844m, 807m, 748s, 725m, 714m, 694s.

Synthesis of $[Ru_2(CO)_4(\eta^4\text{- }Ph_4C_4CO)_2(H)][C_7H_7NH_3]_4$ (IIIb). Shvo catalyst **I** (100 mg, 0.092 mmol) was dissolved in CH_2Cl_2 (1 ml). To this solution benzylamine (0.25 mL) was added and the mixture was stirred at room temperature for 5 min. During this time a yellow substance dropped out of the solution. To complete the precipitation pentane (1 mL) was added. The yellow precipitate was filtered and washed with pentane (1 mL) to yield 135.9 mg (98 %) of **IIIb** (yellow powder). Crystals suitable for X-ray crystal structure analysis were obtained by recrystallisation from pentane-diethylether. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = -13.70 (s, 1H, Ru-H-Ru), 3.82 (s, 6H, 3xCH_2), 4.69 (s, br, 6H), 6.90-7.04 (m, 32H, Ar_{Shvo}), 7.23-7.28 (m, 3H, Ar_{Benzyl}), 7.32-7.38 (m, 12 H, Ar_{Benzyl}), 7.40-7.44 (m, 8H, Ar_{Shvo}). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 44.5 (CH_2 of Benzylamine), 78.2(q, $C_{3,4}$ of Cp), 100.9 (q, $C_{2,5}$ of Cp), 124.8 (CH, Ph), 126.6 (CH, Ph), 126.8 (CH, Ph), 126.9 (CH, Ph_{Benzyl}), 127.2 (CH, Ph), 127.6(CH, Ph_{Benzyl}), 128.2(CH, Ph_{Benzyl}), 130.6 (CH, Ph), 132.0 (CH, Ph), 133.2(q, Ph), 135.1 (q, Ph), 140.8 (q, Ph_{Benzyl}), 172.2 (q, C_1 of Cp), 202.1 (q, CO). FTIR (ATR): ν (cm^{-1}) = 3372w, 3057m, 3025m, 2925w, 2019s, 1993s, 1947s, 1599m, 1557m, 1498m, 1444m, 1382m, 916m, 844m, 748m, 693s.

Synthesis of $[Ru_2(CO)_4(\eta^4\text{- }Ph_4C_4CO)_2(H)][C_6H_{13}NH_3]_2$ (IIIc). Shvo catalyst **I** (100 mg, 0.092 mmol) was dissolved in CH_2Cl_2 (1 mL). To this solution hexylamine (0.25 mL) was added and the mixture was stirred at room temperature for 5 min. During this time a yellow substance dropped out of the solution. To complete the precipitation pentane (1 mL) was added. The yellow precipitate was filtered and washed with pentane (1 mL) to yield 101.1 mg (93 %) of **IIIc** (yellow powder). Crystals were obtained by recrystallisation from pentane-diethylether but due to high flexibility of the long hexyl chain, these crystals were not suitable for X-ray crystal structure analysis.^{1}H NMR (DMSO-d_6, 400 MHz): δ = -13.69 (s, 1H, Ru-H-Ru), 0.84-0.89 (m, 6H, CH_3), 1.21-1.32 (m, 12H), 1.36-1.48 (m, 4H), 2.61 (t, 4H. J = 7.3 Hz), 5.40 (s, 3H, NH), 6.90-7.05 (m, 32H, Ar_{Shvo}), 7.39-7.45 (m, 8H, Ar_{Shvo}). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.9 (CH_3), 22.0, 25.7, 29.9, 30.9, 40.1 (5xCH_2), 78.2 (q, $C_{3,4}$ of Cp), 100.9 (q, $C_{2,5}$ of Cp), 124.8 (CH, Ph), 126.6 (CH, Ph), 126.8 (CH, Ph), 127.2 (CH, Ph), 130.6 (CH, Ph), 132.0 (CH, Ph), 133.2 (q, Ph), 135.0 (q, Ph), 172.2 (q, C_1 of Cp), 202.0 (q, CO). FTIR (ATR): ν (cm^{-1}) = 3369w, 3057w, 2955m, 2929m, 2856m, 2017s, 1990s, 1942s, 1600m, 1563m, 1498m, 1442m, 1388m, 843m, 747m, 728m, 696s.

^{1}H NMR Temperature experiments in DMSO-d_6. A solution of **IIIa** was heated in an Bruker AV 400 spectrometer. Starting from 297 K (24 °C), the temperature was increased to 413 K (140 °C) in steps of 10 K. At 75 °C the spectra showed the following resonances: ^{1}H NMR (DMSO-d_6, 400 MHz, 75 °C): δ = -9.94 (s, 1H, Ru-H, complex **C**), 1.68-1.75 (m, 4H, CH_2, **C**), 2.88-2.94 (m, 4H, CH_2, **C**), 3.74-3.75 (d, 0.5H), 4.78-4.79 (d, 0.5H), 6.93-7.37 (m, ~42H, complex **D**/**C**), 7.50-7.53 (m, 1H, **C**), 7.55-7.58 (m, 3H, **D**). At 130 °C the spectra showed the following resonances: ^{1}H NMR (DMSO-d_6, 400 MHz, 130 °C): δ = 1.74-1.79 (m, 4H, CH_2), 2.96-3.00 (m, 4H, CH_2), 3.73-3.75 (d, 1H), 4.70-4.71 (d, 1H), 6.93-7.37 (m, ~120H, **D**), 7.55-7.62 (m, 16H, **D**). Cooling to rt showed the following resonances: ^{1}H NMR (DMSO-d_6, 400 MHz, 24 °C): δ = 1.67-1.70 (m, 8H, **4**), 1.75-1.79 (m, 4H, **4**), 2.86-2.89 (m, 8H, **4**), 3.19-3.22 (m, 4H, **4**), 3.76 (d, 2H), 4.91 (d, 2H), 7.11-7.39 (m, Ar, **D**), 7.52-7.52 (m, Ar, **D**).

Va: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.37-1.50 (4H, m), 2.27-2.37 (2H, m), 2.48-2.57 (2H, m), 4.27-4.36 (1H, m), 7.06-7.18 (16H, m), 7.52-7.55 (4H, m). ^{13}C NMR (DMSO-d_6, 100 MHz)): δ = 24.5 (CH_2), 53.9 (CH_2), 80.9 (q, $C_{3,4}$ of Cp), 102.4 (q, $C_{2,5}$ of Cp), 125.7 (CH, Ph), 127.2 (CH, Ph), 127.4 (CH, Ph), 127.5 (CH, Ph), 129.5 (CH, Ph), 131.6 (CH, Ph), 131.7 (q, Ph), 133.6 (q, Ph), 165.4 (q, C_1 of Cp), 201.4 (q, CO). FT IR (neat, cm^{-1}): 3144w, 3060w, 2946w, 2870w, 2033s, 1944s, 1600m, 1543m, 1498m, 1443m, 1072m, 1028m, 907m, 842m, 803m, 746m, 734m, 695s. HRMS (ESI) Calcd. for $C_{35}H_{29}NO_3Ru$ $[M+H]^+$: 614.12637. Found: 614.12560.

Vb:^{1}H NMR (DMSO-d_6, 400 MHz): δ = 3.78-3.85 (2H, m, CH_2), 7.00-7.04 (2H, m), 7.09-7.28 (19H, m), 7.45-7.50 (4H, m). ^{13}C NMR (DMSO-d_6, 100 MHz)): δ = 54.3 (CH_2, Benzyl), 81.9 (q, $C_{3,4}$ of Cp), 102.7 (q, $C_{2,5}$ of Cp), 126.0 (CH, Ph), 127.4 (CH, Ph), 127.6 (CH, Ph), 127.9 (CH, Ph), 128.4 (CH, Ph), 129.7 (CH, Ph), 131.7 (CH, Ph), 132.9 (q, Ph), 140.2 (q, C_1 of Cp), 200.7 (q, CO), 210.7 (q, Ph). FT IR (neat, cm^{-1}): 3288w, 3052w, 2950w, 2851w, 2011s, 1955s, 1599m, 1577m, 1530m, 1498m, 1443m, 1208m, 1072m, 1027m, 1002m, 842m, 802m, 749m, 711m, 696s. HRMS (ESI) Calcd. for $C_{38}H_{29}NO_3Ru$ $[M+H]^+$: 650.12637. Found: 650.12693.

Vc:^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.77 (3H, t, J = 7.3 Hz), 0.87-0.95 (2H, m), 1.05-1.18 (6H, m), 2.24-2.31 (2H, m), 2.36-3.40 (2H, m), 7.07-7.17 (16H, m), 7.42-7.45 (4H, m). ^{13}C NMR (DMSO-d_6, 100 MHz)): δ = 13.6, 21.7, 25.2, 30.2, 31.7, 50.6 (6xCH_2, Hexyl), 81.6 (q, $C_{3,4}$ of Cp), 102.6 (q, $C_{2,5}$ of Cp), 125.8 (CH, Ph), 127.2 (CH, Ph), 127.4 (CH, Ph), 127.5 (CH, Ph), 129.6 (CH, Ph), 131.5 (CH, Ph), 131.7 (q, Ph), 132.9 (q, Ph), 163.3 (q, C_1 of Cp), 200.9 (q, CO). FT IR (neat, cm^{-1}): 3087w, 3052w, 2950w, 2916w, 2847w, 2006s, 1947s, 1598m, 1576m, 1556m, 1524m, 1497m, 1443m, 1177m, 1071m, 1028m, 841m, 801m, 749m, 729m, 709m, 694s. HRMS (ESI) Calcd. for $C_{37}H_{35}NO_3Ru$ $[M+H]^+$: 644.17332 Found: 644.17366.

General procedure for the amination reaction with pyrrolidine: In an carousel tube under an argon atmosphere the Shvo catalyst (0.12 mmol, 130 mg, 1 mol%) was dissolved in pyrrolidine (12 mmol, 1ml), hexadecane (250 µL), and additional substances. The reaction mixture was heated at 110 °C for 24 h under reflux. The allocation of samples was done via septum. The yield and conversion was determined by GC. The products **1** and **4** were purified by aluminium oxide column chromatography and characterized by ^{1}H, ^{13}C, Dept, COSY, HMQC-NMR, FTIR, and GC-MS. Products **2** and **3** were identified by GC-MS.

5-(pyrrolidine-1yl)-3,4-dihydro-2*H*-pyrrole (**1**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98-2.07 (m, 4H), 2.20 (dt, 2H, ^{3}J = 7.9 Hz, ^{3}J = 7.3 Hz), 2.85 (t, 2H, ^{3}J = 7.9 Hz), 3.55 (t, 2H, ^{3}J = 6.3 Hz), 3.76 (t, 2H, ^{3}J = 7.3 Hz), 3.80-3.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.9 (CH_2), 25.3, 25.4 (2xCH_2), 31.5 (CH_2), 47.9 (CH_2), 50.6 (CH_2), 50.8 (CH_2), 165.2 (C_q). FT IR (neat, cm^{-1}): 3394br, 3115br, 2957s, 2887s, 2810m, 2741m, 1678s, 1456m, 1299m, 927s, 728s. MS (EI, 70 eV) *m/z* (rel. intensity): 138 (66) $[M^+]$, 110 (100) $[M^+-C_2H_4]$, 95 (12), 82 (25), 69 (24), 55 (25), 41 (30). HR-MS could not be measured.

N'-1-(pyrrolidin-1-yl)butandiamine (**2**): MS (EI, 70 eV) *m/z* (rel. intensity): 142 (3) $[M^+]$, 84 (100) $[CH_2=N^+C_4H_8]$, 70 (15), 42 (11) $[CH_2=N^+=CH_2]$.

1-Butylpyrrolidine (**3**): MS (EI, 70 eV) *m/z* (rel. intensity): 127 (8) $[M^+]$, 98 (3) $[M^+-C_2H_5]$, 84 (100) $[CH_2=N^+C_4H_8]$, 42 (24) $[CH_2=N^+=CH_2]$.

1,4-di(pyrrolidine-1-yl)butane (**4**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57-1.64 (m, 4H), 1.78-1.97 (m, 8H), 2.52-2.57 (m, 4H), 2.60-2.64 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.4 (CH_2), 27.3 (CH_2), 54.2 (CH_2), 56.6 (CH_2). FT IR (ATR, cm^{-1}): 3383br, 2938m, 2878m, 2783m, 1675m, 1458m, 1349m, 1145m, 875m, 696s. MS (EI, 70 eV) *m/z* (rel. intensity): 196 (1) $[M^+]$, 97 (15), 84 (100) $[CH_2=N^+C_4H_8]$, 72 (21), 42 (20). HRMS Calcd. for $C_{12}H_{24}N_2$: 196.19340. Found: 196.19341.

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Supporting Information:

Experimental procedures, spectroscopic data as well as ^{1}H and ^{13}C NMR spectra for all compounds reported. Crystallographic information for **IIIa**, **IIIb**, and **Vc** (cif files). This material is available free of charge via the Internet at http://pubs.acs.org.

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4.9. Deactivation of the Shvo Catalyst by Ammonia: Synthesis, Characterization and Modeling

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Contributions

My contribution as co-author of this paper is approximately 80 %. I was responsible for the complete work. Dr. Anke Spannenberg was involved in the measurement of the X-ray-crystal structures of **I**. Dr. Haijun Jiao performed calculation on the stability of *Shvo*-amine complexes. Dr. Rudy Parton and Dr. Rinke Altink are industrial cooperation partner.

Deactivation of the Shvo Catalyst by Ammonia: Synthesis, Characterization and Modeling

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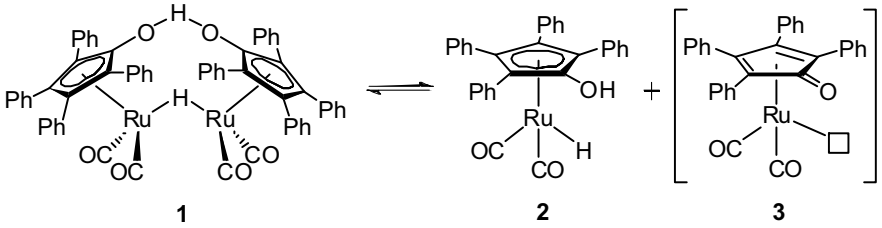
Abstract.

The novel stable ruthenium ammonia complex [2,3,4,5-Ph_4(η^4-C_4CO)]$Ru(CO)_2(NH_3)$ (**6**) has been isolated in high yield in the catalytic alkylation of aniline with hexylamine. It has been characterized by X-ray analysis and density functional theory computation. The thermodynamic stability of Shvo-like ruthenium complexes with primary, secondary and tertiary amines has been computed and compared. Calculations confirmed the high stability of this ruthenium ammonia complex.

Introduction

Shvo complex {[2,3,4,5-Ph$_4$(η^5-C$_4$CO)]$_2$H}Ru$_2$(CO)$_4$(μ-H) (**1**) constitutes an efficient catalyst for numerous hydrogen transfer processes.[1] More specifically, it has been applied successfully in the hydrogenation reactions of alkynes[2], carbonyl compounds, and imines,[3,4] and in the oxidation reactions of alcohols[5,6] and amines,[7,8] as well as in the dynamic kinetic resolution of secondary alcohols and primary amines in combination with lipases.[9–15] In addition, tandem catalysis processes are known.[16] On the basis of our ongoing interests in the development of amination methodologies[17,18] and the synthesis of aliphatic and aromatic amines,[19] recently we have developed novel alkylation reactions of amines applying Shvo catalyst (**1**) with mono-, di-, and trialkylamines as selective alkylation reagents.[20]

Due to its significant catalytic potential, **1** has been the subject of detailed mechanistic investigations by Bäckvall,[21–26] Casey,[27–33] and others.[34] It is well known that the Shvo complex dissociates into two active species **2** and **3** (Scheme 1) by transferring a hydride (bonded to a metal center) and a proton (bonded to a ligand). Despite the known studies on the mechanism of hydrogen transfer process, it is still speculated whether the respective reaction proceeds concerted without substrate coordination in a solvent cage (Casey) or concerted with substrate coordination and ring slippage of the aromatic ring (Bäckvall). Until to date few investigations were performed on the deactivation of the Shvo catalyst **1**.



Scheme 1: Equilibrium between **1** and active species **2** and **3**

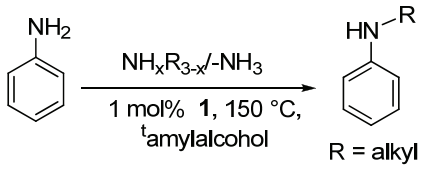
Previous amine Shvo complexes: In 1988, Shvo et al. isolated the crystals of [2,3,4,5-Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_2$(NHEt$_2$) (**4**) during transalkylation of amines.[35] Later, in a joint cooperation Casey, Bäckvall and Park reinvestigated the structure of the isopropyl alcohol complex [2,3,4,5-Ph$_4$(η^4-C$_4$CO)]-Ru(CO)$_2$(HOCHMe$_2$)[36] which turned out to be the stable [2,3,4,5-Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_2$(H$_2$NCHMe$_2$) complex (**5**).[37] During their mechanistic investigations on the reduction of imines, Casey[27-32] and

Bäckvall[4,7,8,23] identified and characterised different ruthenium amine complexes [2,3,4,5-Ph_4(η^4-C_4CO)]Ru$(CO)_2$(R_2CHNHR).

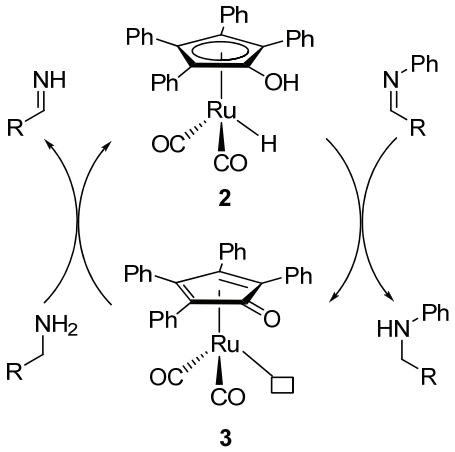
Herein, we report for the first time the deactivation of the active species **3** by ammonia. The resulting Shvo-ammonia complex **6** is structurally characterized by X-ray analysis. Calculations on the thermodynamic stability of amine-substituted cyclopentadienone ruthenium complexes and on the exchange of amines demonstrate that complex **6** is one of the most stable amine complexes known.[38,39]

Results and Discussion

During our studies on the selective synthesis of monoalkylated arylamines we performed the reaction of alkylamines with arylamines in *t*-amylalcohol in the presence of 1 mol% of **1** (Scheme 2). The observed alkyl transfer proceeds by a coupled reaction of hydrogenation and dehydrogenation of the alkylamine (Scheme 3).



Scheme 2: Alkylation of aniline with alkylamines



Scheme 3: Coupled catalytic system for hydrogenation of imines and dehydrogenation of amines

After complete conversion, we were able to isolate the desired product along with an unknown white powder. Due to the insolubility of the side-product in methanol, ether, acetone, and water identification

and characterization was initially difficult. However, it was soluble in boiling DMSO. After cooling to room temperature crystals suitable for X-ray analysis were obtained. Surprisingly, the side-product was identified by single-crystal X-ray diffraction analysis as the Shvo ammonia complex [2,3,4,5-Ph_4(η^4-C_4CO)]Ru$(CO)_2(NH_3)$ (**6**) (Figure 1). The detailed crystallographic data and selected bond lengths of **6** are given in Tables 1 and 2, respectively. Apparently, ammonia is stabilized by a weak intramolecular hydrogen bond between H(1) and O(1) of the cyclopentadienone ring (2.28(2) Å) and by a strong intermolecular hydrogen bond between H(2A) and O(1B) of the second cyclopentadienone ring (1.97(2) Å), which is shown in Figure 2 and in the Supporting information. Such an intermolecular hydrogen bond is not known for any ruthenium Shvo-like complexes with primary or secondary amines. In comparison to **1** with an η^5-coordination mode, **6** exhibits a C(1)-O(1) bond length of 1.250(2) Å and a Ru(1)-C(1) distance of 2.425(1) Å, which is distinctly elongated compared to the other four ruthenium ring carbon atom distances (2.196(1) – 2.236(1) Å). This suggests that the cyclopentadienone ring is bonded to the Ru in an η^4-coordination mode.

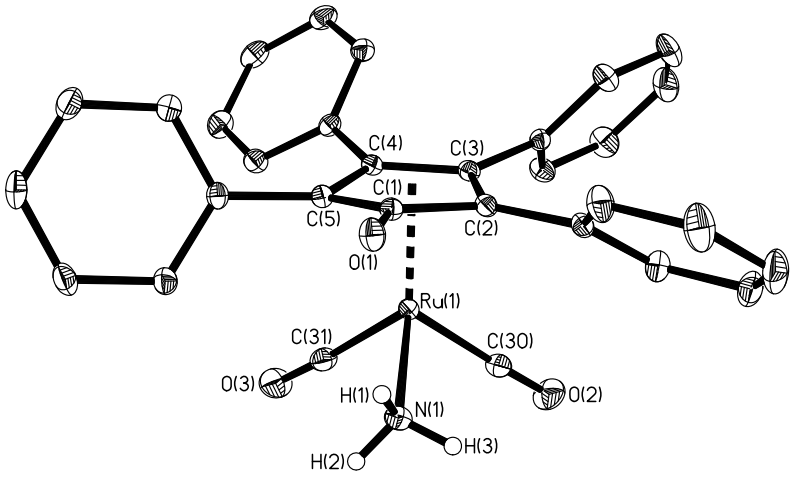


Figure 1. ORTEP diagram of **6**. Thermal ellipsoids are set at the 30% probability level. For clarity H atoms are omitted except H(1), H(2) and H(3).

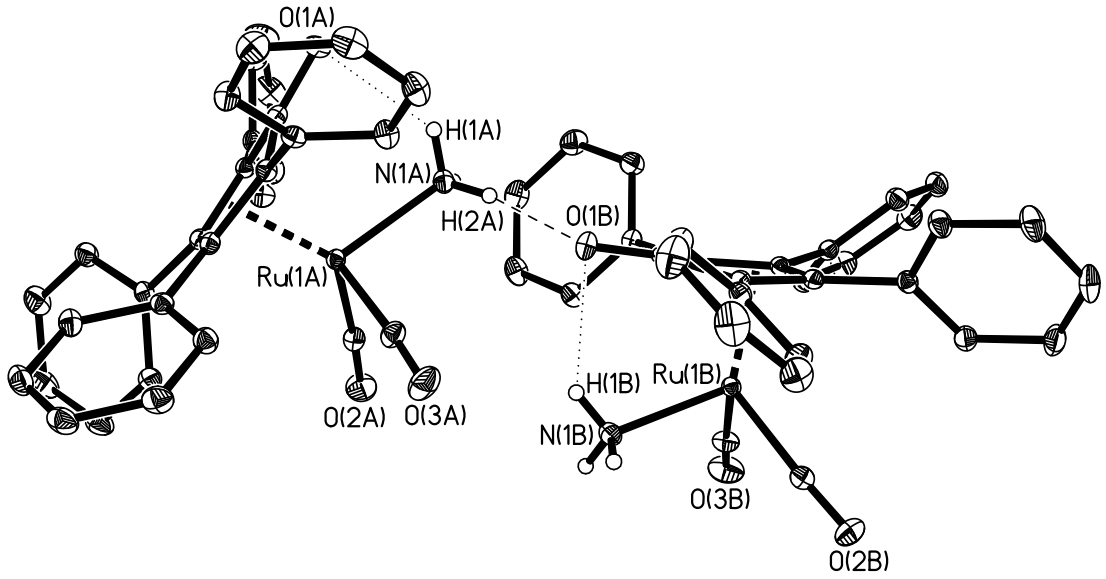


Figure 2. ORTEP diagram of **6** showing intra- and intermolecular hydrogen bond interactions. Thermal ellipsoids are set at the 30% probability level. For clarity H atoms are omitted except hydrogen atoms attached to nitrogen.

Table 1. Crystallographic data of **6**

	[2,3,4,5-Ph_4(η^4-C_4CO)]Ru$(CO)_2(NH_3)$ (**6**)
chemical formula	$C_{31}H_{23}NO_3Ru$
formula weight	558.57
cryst syst	monoclinic
space group	$P2_1/c$
a [Å]	12.656(3)
b [Å]	8.767(2)
c [Å]	22.359(5)
β [deg]	101.79(3)
V [$Å^3$]	2428.6(8)
Z	4

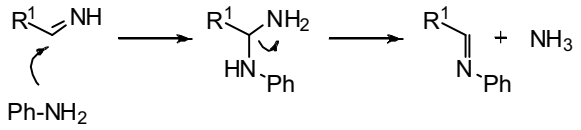
ρ_{calc} [g·cm^{-3}]	1.528
μ(Mo Kα) [mm^{-1}]	0.680
T [K]	200(2)
no. of rflns (measd)	38827
no. of rflns (indep)	5572
no. of rflns (obsd)	4907
no of params	337
R_1 (I>2σ(I))	0.0182
wR_2 (all data)	0.0479

Table 2. Selected bond distances [Å] for compound [2,3,4,5-Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_2$(NH$_3$) **6**.

	X-ray (**6**)	Theory (**6**)	Theory (**6'**)
Ru1-C1	2.425(1)	2.4668	2.4825
Ru(1)-C(2)	2.236(1)	2.2892	2.2951
Ru(1)-C(3)	2.197(1)	2.2645	2.2435
Ru(1)-C(4)	2.196(1)	2.2485	2.2435
Ru(1)-C(5)	2.214(1)	2.2907	2.2951
Ru(1)-C(30)	1.891(2)	1.9090	1.9077
Ru(1)-C(31)	1.895(2)	1.9052	1.9077
C(1)-O(1)	1.250(2)	1.2483	1.2506
C(30)-O(2)	1.139(2)	1.1600	1.1600
C(31)-O(3)	1.135(2)	1.1604	1.1600
Ru(1)-N(1)	2.155(1)	2.2443	2.2387
intramolecular hydrogen bonds N(1)-H(1)···O(1) (Figure 1)			
N(1)-H(1)	0.85(2)	1.0345	1.0345
O(1)-H(1)	2.28(2)	1.9944	1.9868

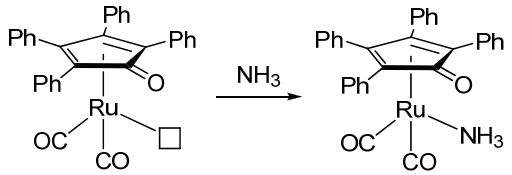
N(1)-O(1)	2.960(2)	2.8884	2.8883
intermolecular hydrogen bonds N(1A)-H(2A)···O(1B)			
N(1)-H(2)	0.86(2)	1.0210	1.0206
H(2)-O(1b)	1.97(2)		
N(1)-O(1b)	2.828(2)		

The formation of **6** is explained by the reaction of ammonia (produced from dealkylation of alkyl-amines, Scheme 4) with the unsaturated 16-electron compound **3** (Scheme 5).



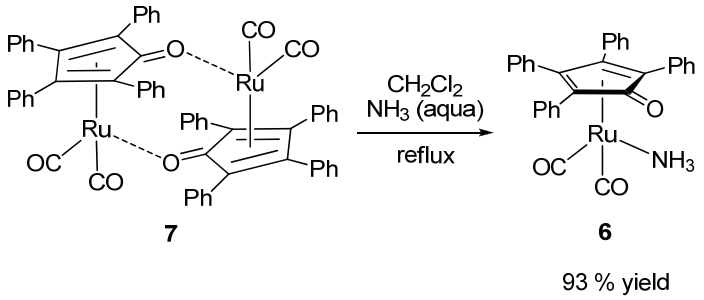
Scheme 4: Formation of ammonia during the dealkylation of alkylamines

We assume that under the reaction conditions, complex **3** is in equilibrium with the cyclopentadienone dimer **7**.[40] Indeed, **6** is generated in 93% yield by treating a dichloromethane solution of **7** with an ammonium hydroxide solution (28% NH_3) under reflux conditions (Scheme 6). Upon heating, a grey precipitate dropped out of the solution. The ATR FTIR spectra of this grey powder exactly correspond with the ATR FTIR spectra of **6**. As stated above, this complex is insoluble in any solvent with the exception of boiling DMSO.



3 **6**

Scheme 5: Proposed formation of **6** during the amination reaction with alkylamines



Scheme 6: Synthesis of **6** from **7**

Next, we were interested in the stability of the Ru-N bond and the potential exchange of amines on the ruthenium centre. Hence, the thermodynamic properties of the reactions of complex **7** with different amines were calculated at the B3LYP level of density functional theory (Table 3).

As shown in Figure 3, we have computed two ammonia complexes; one has the propelled orientation of the four phenyl groups as found in **6** (Figure 1) and one has C_s symmetry with the phenyl groups in symmetrical orientations (**6'**). The computed structural parameters are compared with the X-ray data in Table 2; and reasonable agreement has been found between two methods. In **6** (or **6'**), one N–H bond directs to the ketone group and the other two N–H bonds are eclipsed to the two CO groups, the N–H···O=C distance is 1.9944 Å (or 1.9868 Å), which is in the range of hydrogen bonding. As discussed below, this hydrogen bonding is responsible for the enhanced stability of the ammonia complex and complexes with primary and secondary ammines. We have also calculated the conformation with NH_3 staggered to the metal fragment, but free optimization resulted in **6** (or **6'**) in eclipsed conformation.

Figure 3 shows that the symmetrical one (**6'**) is computed to be more stable than the propelled one (**6**) by 2.07 kcal/mol. This small energy difference indicates equilibrium of two conformations in gas phase or solution. The observed propelled conformation of **6** in solid state is attributed to packing effects.

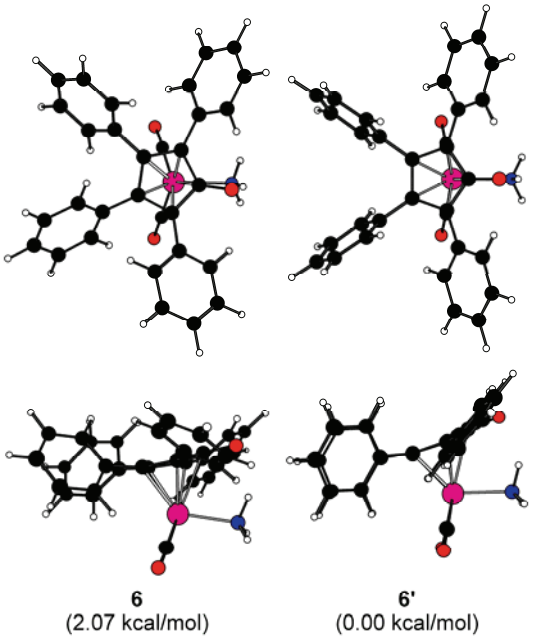


Figure 3. Conformations of the ruthenium ammonia complex

In addition, we have also computed the complexes of primary, secondary amines and tertiary amines. As shown in Figure 4, the complexes **8**, **9**, **10**, **13** and **14** of primary and secondary amines have the eclipsed conformation of the amine groups with one N-H bond towards to the C=O group as found in **6**. They also contain comparable N–H···O=C distances. However, the complexes **11** and **12** with tertiary amines have staggered conformation of the amine group to the metal fragment, and most importantly complexes **11** and **12** do not show hydrogen bonding between the amine and carbonyl group.

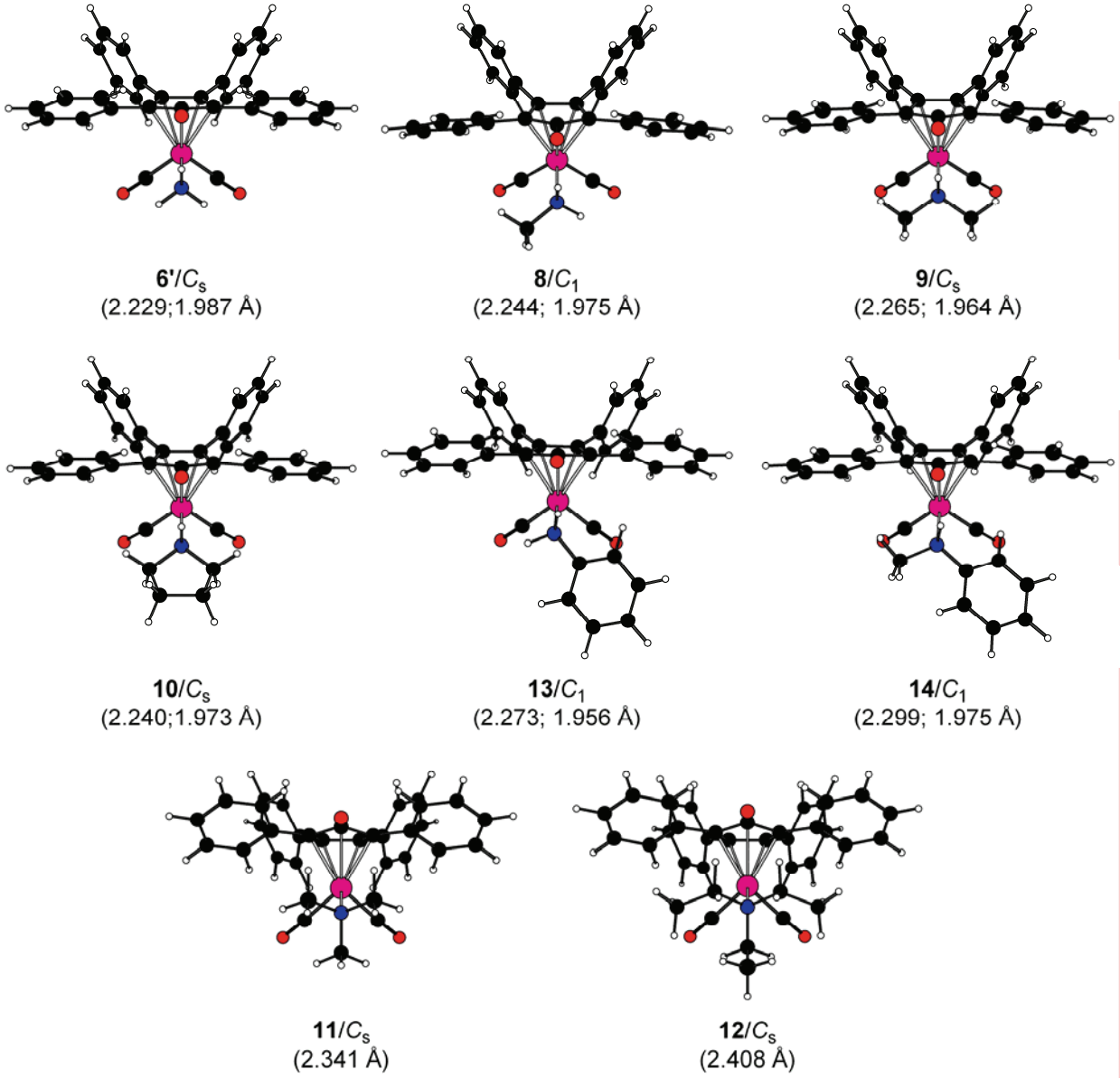
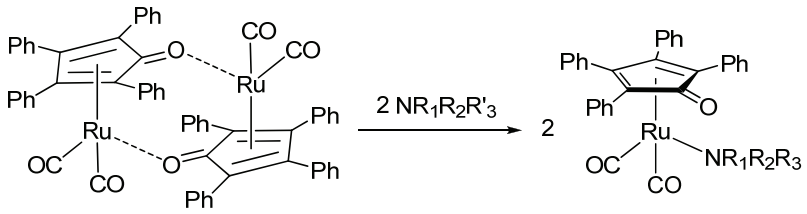


Figure 4. Ruthenium complexes with different amines and the respective Ru–N and N–H···O=C distances

Figure 4 demonstrates also clearly the change of the Ru-N distance upon amines. From NH_3 and methylamine to trimethylamine, the Ru-N distance increases gradually from 2.229 and 2.244 Å to 2.341 Å, indicating the increased steric effects between amine and metal fragment. Stronger steric effects have been found for the complex with triethylamine (**12**) with Ru-N distance of 2.408 Å. The changes are associated directly with the relative stability of the respective complex as discussed below.

Table 3: Free energy for the formation of Shvo ruthenium - amine complexes

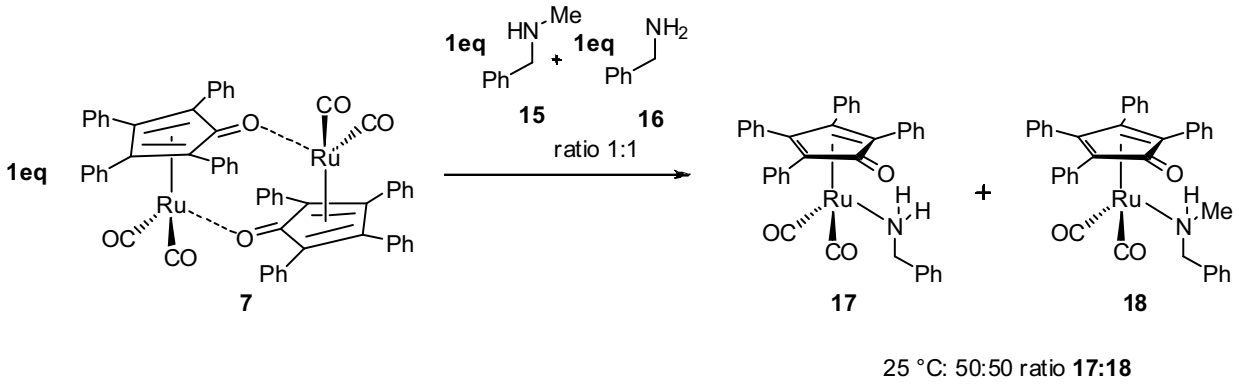


7

Entry	Amine	formed complex	ΔG [kcal/mol]
1	-	**3**	+10.55
2	NH_3	**6**	–22.66
3	NH_2Me	**8**	–22.82
4	$NHMe_2$	**9**	–19.28
5	c-$HN(C_4H_8)$	**10**	–22.78
6	NMe_3	**11**	–4.98
7	NEt_3	**12**	+9.56
8	$PhNH_2$	**13**	–11.72
9	PhNHMe	**14**	–7.46

As shown in Table 3, the direct dissociation of **7** into **3** is computed to be endogonic by 10.55 kcal/mol and disfavoured thermodynamically (Table 3, entry 1). However, the formation of most ruthenium amine complexes is exogonic, and the theoretical data correspond well with the experimental observations of Casey and Bäckvall. For example, the reaction of **7** with ammonia to form **6** is thermodynamically favoured (ΔG_2= –22.66 kcal/mol, Table 3, entry 2). In addition, reactions of primary, secondary as well as secondary cyclic aliphatic amines with **7** are also strongly exogonic (Table 3, entries 3-5), revealing the high thermodynamic stability of these compounds, and the driving force of such stability is the formation of the intramolecular hydrogen bonding between NH_3 and the C=O group.

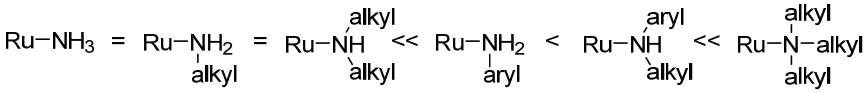
The small difference between the free energy of primary and secondary amine complexes is in agreement with a competition experiment of benzylamine with *N*-methylbenzylamine reported by Casey (Scheme 7).[30] During equilibrium a 1:1 ratio of 17 and 18 was observed.



Scheme 7: Competition experiments of alkylamines

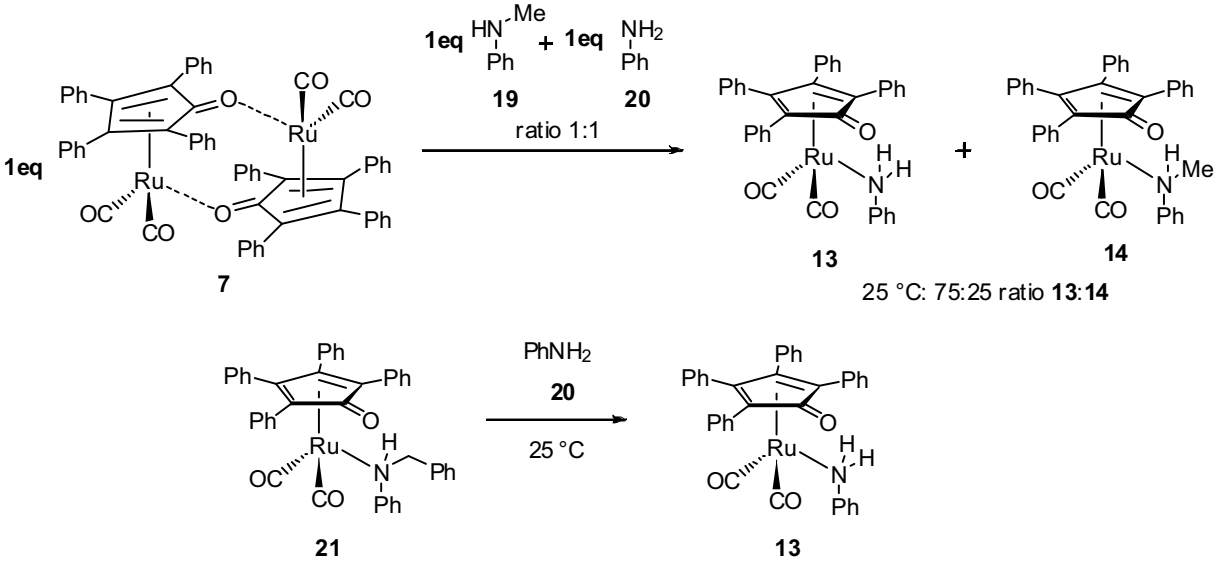
In contrast to ammonia and primary as well as secondary aliphatic amines, tertiary aliphatic amines showed only a low exogonic free energy of -4.98 kcal/mol (trimethylamine, Table 3, entry 6) or even energonic free energy of +9.56 kcal/mol (triethylamine, Table 3, entry 7). Clearly, tertiary amines can't form stabilizing intramolecular hydrogen bonding between the amine hydrogen and the carbonyl oxygen of the cyclopentadienone ring on one hand, and on the other hand they have increased steric interaction with the metal fragment.

Next, the formation of ruthenium amine complexes with primary as well as secondary arylamines was calculated. Again reactions are exogonic, but less pronounced with respect to aliphatic amines. The energy difference between primary and secondary arylamines is larger compared with aliphatic amines. Thus, primary arylamine complexes are more stable ($\Delta\Delta G$= +4.26 (arylamines) vs. +3.54 kcal/mol (alkylamines)). The general stability order of Shvo ruthenium amine complexes is shown in Scheme 8.

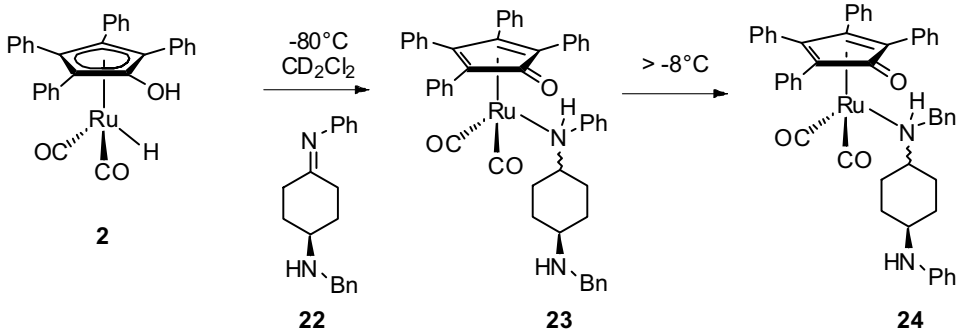


Scheme 8: Stability order of Shvo ruthenium amine complexes

Our computed thermodynamic data explains nicely known experimental findings. For example, the rapid displacement of *N*-phenylbenzylamine (**21**) by aniline (**20**), observed by Casey et al.[30] as well as competition experiments during equilibrium of aniline (**20**) and *N*-methylaniline (**19**) shown in Scheme 9 are in good agreement with the calculated free energies. The higher stability of ruthenium alkylamine complexes corresponds also with the trapping experiments of Bäckvall (Scheme 10).[30] Under equilibrium conditions the kinetic product **23** is converted to the thermodynamically more stable secondary alkylamine **24**.



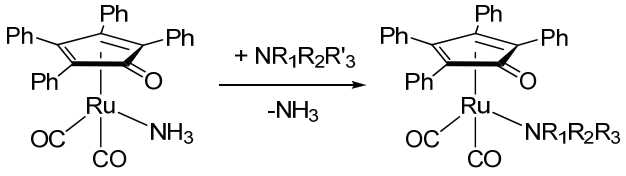
Scheme 9: Exchange and competition experiments of arylamines



Scheme 10: Trapping experiments of Bäckvall.

The relatively small difference of the free energy between the ammonia complex **6** and primary and secondary alkylamine complexes **8-10** seemed surprising. Thus, we calculated the exchange reaction of ammonia by other amines. In Table 4 the free energies[41] and the ratios of **3** in % during equilibrium at 25 °C with different amines are displayed.

Table 4: Free energy of the exchange of ammonia with different amines

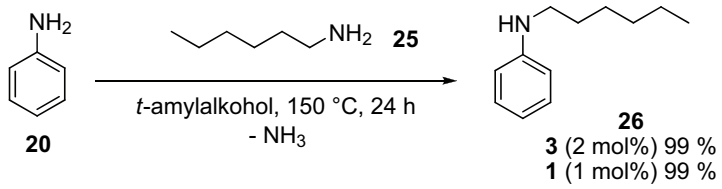


3

Entry	Amine	formed complex	ΔG [kcal/mol]	ratio of **3** [%]
1	NH_2Me	**8**	+0.42	67
2	$NHMe_2$	**9**	+2.20	97
3	c-$HN(C_4H_8)$	**10**	+0.44	68
4	NMe_3	**11**	+9.34	100
5	NEt_3	**12**	+16.61	100
6	$PhNH_2$	**13**	+5.97	100
7	PhNHMe	**14**	+8.10	100

These results point out that the reaction of **6** with all amines is thermodynamically disfavoured, as indicated by positive reaction free energies. Only sterically non-hindered aliphatic amines are in equilibrium with **6**. Clearly, if ammonia is present or formed in the reaction of amines, then arylamines and tertiary alkylamines will be completely replaced at the metal centre. Notably, in reactions of primary or secondary cyclic amines, a significant amount of the Shvo catalyst will be blocked by ammonia, which is important to understand the catalytic behaviour of the Shvo catalysts in amination reactions.

Finally, we were interested in the reactivity of the Shvo ammonia complex **6** in the alkylation of aniline with *n*-hexylamine.[18] To compare complex **6** with the Shvo catalyst **1**, the reactions were performed in the presence of 2 mol% **6** or 1 mol% **1**, *t*-amylalcohol as solvent, and two equivalents of aniline (Scheme 11). Interestingly, with both catalysts *N*-hexylaniline is obtained in excellent yield of 99 %!



Scheme 11: Reactivity of the Shvo ammonia complex **3**

Apparently, under the reaction conditions complex **6** is in equilibrium with the corresponding alkylamine complex. However, in agreement with the theoretical calculations complex **6** precipitated after the reaction in 85 % yield and can be re-used for catalysis. Hence, the addition of ammonia offers a convenient way to recycle the Shvo catalyst for catalytic aminations and probably other reactions, too.

Summary

In summary, we have synthesized and isolated a new neutral ammonia ruthenium complex **6**. The stabilities of different Shvo amine complexes were calculated and compared. The high stability of the ammonia complex **6** is to be noted. The driving forces of the enhanced stability of 6 are inter- and intramolecular hydrogen bonding interactions between the N-H of the amine and the carbonyl group of the cyclopentadienone ring. Calculation on the exchange of ammonia with other amines demonstrates that **6** is in equilibrium with primary and secondary cyclic amines but not tertriary amines. The novel complex **6** is shown to be active in the alkylation reaction of aniline with hexylamine. The final precipitation of **6** allows for convenient recycling of Shvo-like ruthenium complexes.

Experimental section

Computational details: All structures have been optimized at the B3LYP [42] level of density functional theory along with the LANL2DZ basis set by adding a set of polarization functions (LANL2DZ(d)).[43] Optimized structures were characterized by frequency calculation as energy minima without imaginary frequencies (NImag = 0) or transition states with only one imaginary frequency (NImag = 1) at the same level of theory (B3LYP/LANL2DZ(d)).[44] The thermal corrections to enthalpy and Gibbs free energies at 298 K from the frequency calculations were added to the total electronic energies for analyzing the relative reaction free energies. All calculations were carried out by using the Gaussian 03 program package.[45]

General Remarks: All reactions were carried out under an inert atmosphere of argon gas by standard Schlenk technique. Chemicals were purchased from Aldrich, Fluka, Acros and Strem and unless otherwise noted were used without further purification. Amines were distilled and stored under argon. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, HRMS and IR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 spectrometer. The ^{1}H and ^{13}C NMR chemical shifts δ reported are relative to $SiMe_4$. . EI mass spectra were recorded on an MAT 95XP spectrometer (70 eV, Thermo ELECTRON CORPORATION). ESI high resolution mass spectra were recorded on an Agilent Technologies 6210 TOF LC/MS. FTIR spectra were recorded on a Nicolet 6700 spectrometer and a ATR SMART ENDURANCE (Thermo ELECTRON CORPORATION) equipment. Elemental analyses were determined by C/H/N/S-Analysator 932 (Leco). X-ray Crystallographic Study of Complex **6:** Data were collected with a STOE-IPDS diffractometer using graphite-monochromated Mo-Kα radiation. The structure was solved by direct methods [SHELXS-97: Sheldrick, G. M., SHELXS-97, University of Göttingen, Germany, **1997**.] and refined by full-matrix least-squares techniques against F^2 [SHELXL-97: Sheldrick, G. M., SHELXL-97, University of Göttingen, Germany, **1997**.] XP (BRUKER AXS) was used for structural representations.

Synthesis of [Ru(CO)$_2$(η^4- Ph$_4$C$_4$CO)(NH$_3$)] (6). Shvo-H$_2$ complex **7** (520 mg, 0.481 mmol) was suspended in dichloromethane (5 mL) and ammonia-water solution (25 % NH_3, 5 mL). The reaction

mixture was heated for 10 min under reflux. The color of the precipitate changed from brown to grey. After filtration and washing with acetone (2x 5 mL), the grey precipitate was filtered and washed with acetone (2x 5 mL) and dichloromethane (5 mL) to yield 499.2 mg (93 %) of **6** (grey powder). Crystals were obtained by recrystallisation of **6** from dimethylsulfoxide.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 3.06 (s, 3H, NH_3), 7.06-7.16 (m, 16H, Ar), 7.37-7.40 (m, 4H, Ar). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 82.0 (q, $C_{3,4}$ of Cp), 102.9 (q, $C_{2,5}$ of Cp), 126.0 (CH, Ph), 127.4 (CH, Ph), 127.5 (CH, Ph), 127.6 (CH, Ph), 129.7 (CH, Ph), 130.2 (CH, Ph), 131.8 (CH, Ph), 131.9 (q, Ph), 133.2 (q, Ph), 163.7 (q, C_1 of Cp), 201.2 (q, CO). FTIR (ATR): ν (cm^{-1}) = 3349m (N-H), 3229w, 3053m, 1996s, 1942s, 1598m, 1541s, 1498m, 1442m, 1264m (C-N), 1071m, 1029m, 837, 767, 760m, 745m, 730m, 708s, 696s. HRMS(ESI) Calcd. for $C_{31}H_{23}O_3NRu$: 560.07942. Found: 560.08012. Anal. Calcd for $C_{31}H_{23}NO_3Ru$ (%)*1/2 DCM: C, 62.95; H, 4.02; Cl 5.90; Found: C, 62.75; H, 4.45; Cl, 6.00.

General amination procedure. In an ACE-pressure tube under an argon atmosphere Shvo ammonia catalyst (**6**, 0.04 mmol) and hexylamine (**25**, 2 mmol) were dissolved in ^{t}amylalcohol (0.5 ml) and aniline (**20**, 4 mmol). The pressure tube was fitted with a Teflon cap and heated at 150 °C for 24 h in an oil bath. The solvent was removed in vacuo, and the crude product was easily purified by column chromatography with pentane/ethyl acetate (20:1). To recycle the catalyst, the reaction mixture was filtered. The precipitate was washed with ethyl acetate, transferred with ethyl acetate and dried in vacuo to give 38.5 mg (85 %) catalyst **6** (for two reactions).

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Supporting Information:

Crystallographic information for **6** in cif format, energetic data for calculations, NMR data of **6**, and complete reference 45. This material is available free of charge via the Internet at http://pubs.acs.org.

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5. Appendix

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10/2003 - 07/2005	Technical University Berlin, Berlin/Germany Undergraduate Studies in Chemistry **Diplom**, Advisor: **Prof. Dr. Siegfried Blechert** „Zinc-catalyzed Hydroamination of Alkynes and Olefines“
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01/2002 - 07/2002	Technical University Berlin, Berlin/Germany Organic Chemistry/ Projectmanagment „Clever Project for Pupil”
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Fellowships

10/2001	Robert - Koch - Scholarship (Technical University Berlin)
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11/2000 – 07/2005	Chemistry Students Group (Studenteninitative der Chemie)
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03/2007 – 05/2008	Organising Comitee Conference „10. JCF-Frühjahrssymposium"

Journal Contributions

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"Intramolekulare Hydroaminierung funktionalisierter Alkene und Alkine mit einem Zink-Homogenkatalysator"

3. Annegret Tillack, Dirk Hollmann, Dirk Michalik, and Matthias Beller, *Tetrahedron Lett.* **2006***, 47,* 8881-8885.
"A novel ruthenium-catalyzed amination of primary and secondary alcohols"

4. Dirk Hollmann, Annegret Tillack, Dirk Michalik, Ralf Jackstell, and Matthias Beller, *Chem. Asian J.* **2007, *3,*** 403-410.
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5. Dirk Hollmann, Sebastian Bähn, Annegret Tillack, and Matthias Beller, *Angew. Chem. Int. Ed.* **2007**, *46*, 8291-8294. (Hot Paper)
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12. Dirk Hollmann, Haijun Jiao, Anke Spannenberg, Sebastian Bähn, Annegret Tillack, Rudy Parton, Rinke Altink, and Matthias Beller, *Organometallics* **2008**, accepted for publication.
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Oral Presentations

1. Dirk Hollmann**,** Sebastian Bähn, Annegret Tillack, and Matthias Beller. 41. Jahrestreffen Deutscher Katalytiker, 27 - 29 February 2008, Weimar, Germany.
"**A general and selective synthesis of monoalkylated aryl amines from primary, secondary, and tertiary alkyl amines**"

2. Dirk Hollmann*,* Annegret Tillack, and Matthias Beller. IXth Netherlands' Catalysis and Chemistry Conference, 3 - 5 March 2007, Noordwijkerhout, Netherlands.
"A general and selective synthesis of monoalkylated aryl amines from primary, secondary, and tertiary alkyl amines"

3. Dirk Hollmann, Sebastian Bähn, Annegret Tillack, and Matthias Beller. 13th Nordic Symposium on Catalysis, 5 - 7 October 2008, Göteborg, Sweden.
"New Application of the Borrowing Hydrogen Methodology - Selective Synthetic Approach to Amines"

Poster Contributions

1. Dirk Hollmann**,** Annegret Tillack and Matthias Beller. VIIIth Netherlands' Catalysis and Chemistry Conference, 5 - 7 March 2007, Noordwijkerhout, Netherlands.
"Ruthenium-catalyzed Amination of Secondary Alcohols"

2. Dirk Hollmann, Annegret Tillack and Matthias Beller. 40. Jahrestreffen Deutscher Katalytiker, 14 - 16 March 2007, Weimar, Germany.
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3. Dirk Hollmann, Annegret Tillack and Matthias Beller. Eighth Tetrahedron Symposium, 27 - 29 June 2007, Berlin, Germany.
"Novel Ruthenium Catalyst System for the Environmentally Benign Amination of Secondary Alcohols

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"A General Selective Synthesis of Monoalkylated Aryl Amines using Alkyl Amines"

5. Sebastian Bähn, Dirk Hollmann*,* Annegret Tillack and Matthias Beller. 10. Frühjahrssymposium, 27 - 30 March 2008, Rostock, Germany.
"A General Selective Synthesis of Monoalkylated Aryl Amines using Alkyl Amines"

6. Annegret Tillack, Dirk Hollmann, Kathleen Mevius, Sebastian Bähn, Dirk Michalik, Matthias Beller. 16th International Symposium on Homogeneous Catalysis (ISHC XVI), 6 - 11 July 2008, Florence, Italy.
"Ruthenium-catalyzed Synthesis of Secondary and Tertiary Amines from Alcohols"

7. Dirk Hollmann, Sebastian Bähn, Annegret Tillack, and Matthias Beller. 13th Nordic Symposium on Catalysis, 5 - 7 October 2008, Göteborg, Sweden.
"Studies to Activation and Deactivation of the Shvo Catalyst"

Eidesstattliche Erklärung

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe angefertigt habe, keine außer mir den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, den

Dirk Hollmann