Aminations

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A General Ruthenium-Catalyzed Synthesis of Aromatic Amines**

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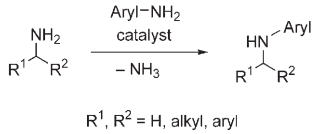
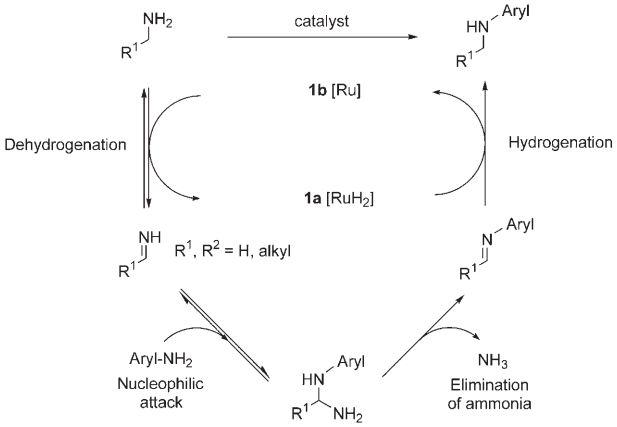
Aromatic amines play a prominent role as biologically active compounds and as industrial chemicals.[1] Hence, the development of new efficient syntheses is of enormous interest. Atom-economical methods such as Lewis acid catalyzed amination,[2] intermolecular hydroaminations,[3] and hydroaminomethylations[4] 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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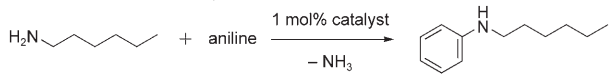
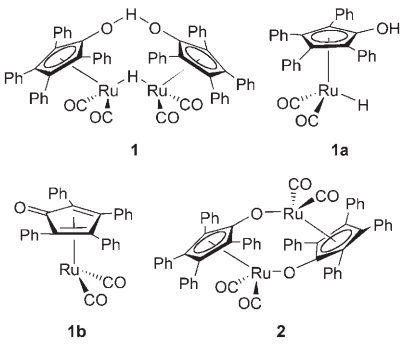
Table 1: Arylation of *n*-hexylamine with aniline in the presence of different ruthenium catalysts.[a]



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.

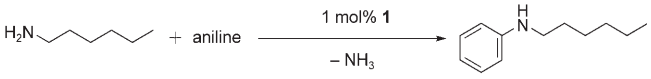


Scheme 3. Shvo complex (**1**), dissociated species **1a**, **1b**, and the analogous Shvo–H$_2$ complex **2**.

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.

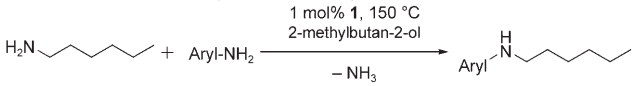
catalytic experiments were performed with 1 mol% of **1** in the presence of two equivalents of aryl amine in 2-methylbutan-2-ol at 150°C.[21] Various aryl amines react with *n*-hexylamine to give the desired products in excellent yields. High yields over 93% were observed with activated and electron-rich 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).

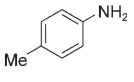
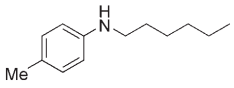
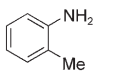
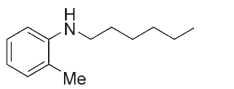
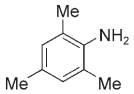
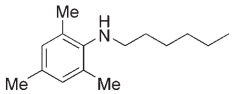
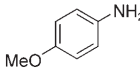
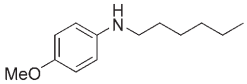
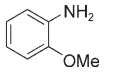
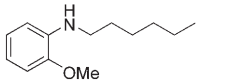
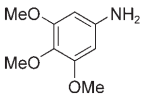
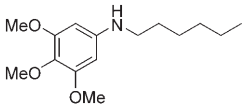
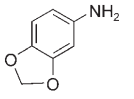
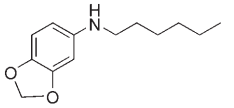
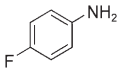
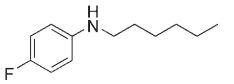
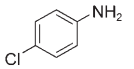
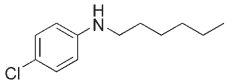
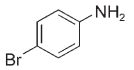
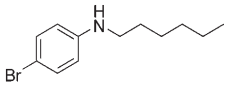
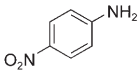
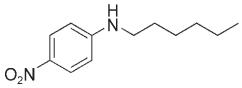
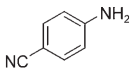
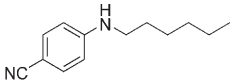
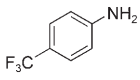
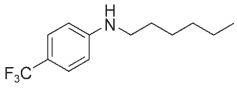
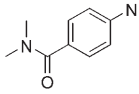
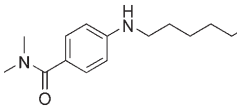
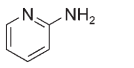
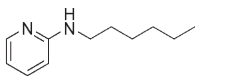
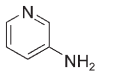
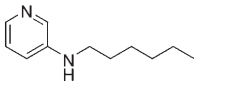
Furthermore, halogenated anilines can be employed as selective arylation reagents. 4-Fluoro-, 4-chloro-, and 4-bromoaniline gave excellent yields of the corresponding alkylated aniline (Table 3, entries 8–10). In general, such products cannot be easily prepared by the palladium-catalyzed Buchwald–Hartwig 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

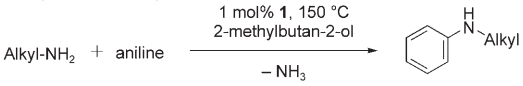
Table 3: Amination of aryl and heteroaryl amines.[a]

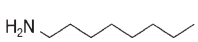
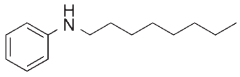
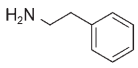
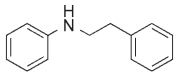
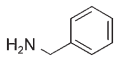
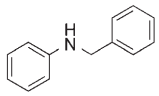


Entry	Aniline	Product	Yield [%][b]
1			98
2			93
3			34
4			98
5			97
6			97
7			86
8			99
9			97
10			94
11			20
12			76
13			95
14			83
15			96
16			77

[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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