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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

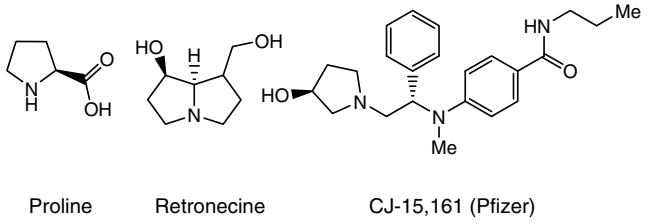

Figure 1. Selected examples of alkaloids and pharmaceuticals with pyrrolidine motif.

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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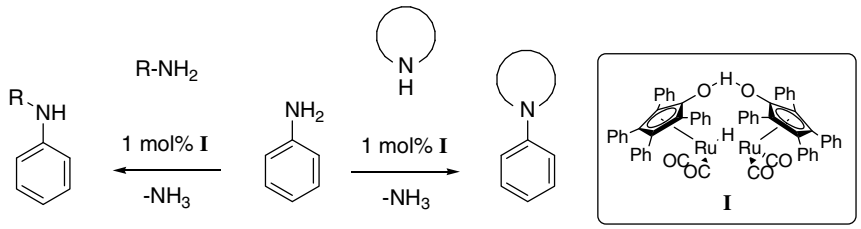
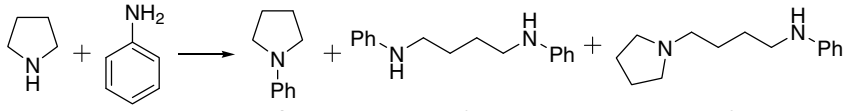


Scheme 1. Amination of aniline using non-cyclic and cyclic alkylamines.

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



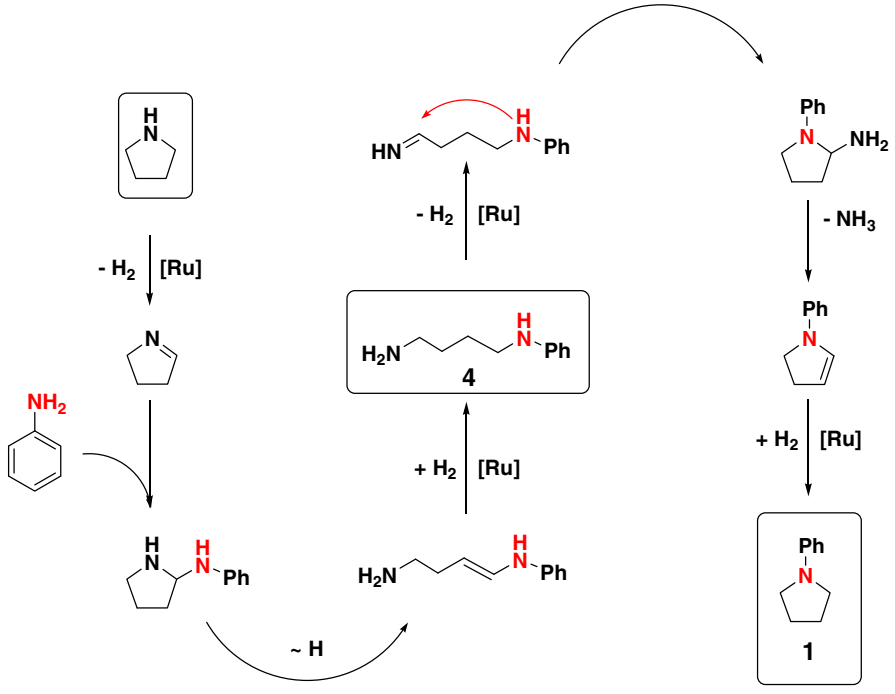
1 **2** **3**

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	–	–	–

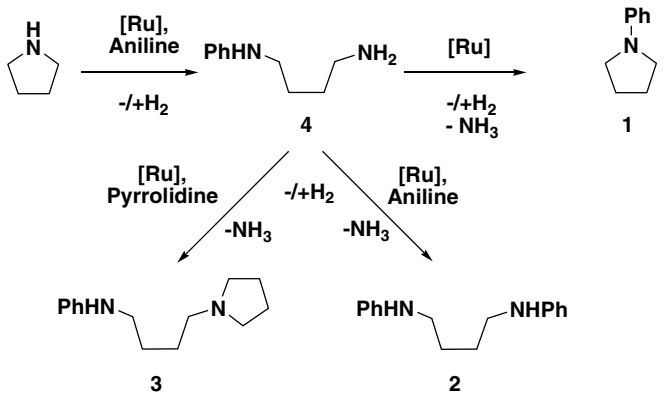
[a] Reaction conditions: 1 mol % Shvo catalyst, 24 h. Yields were determined by GC analysis with hexadecane as internal standard. Isolated yields in brackets.

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.



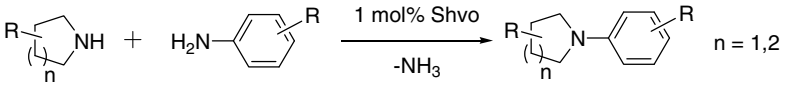
Scheme 3. Synthesis of the side products **2** and **3**.

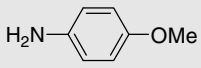
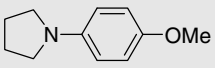
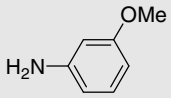
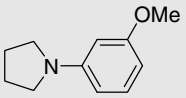
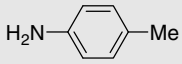
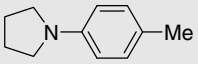
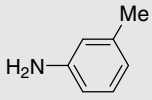
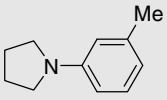
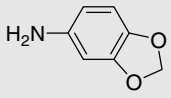
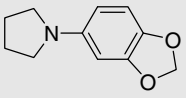
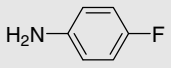
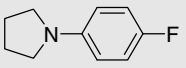
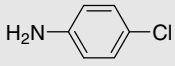
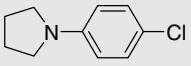
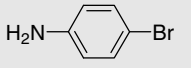
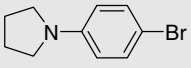
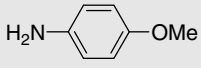
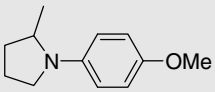
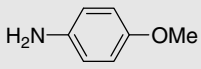
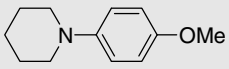
attack on the imine, elimination of ammonia and catalytic hydrogenation lead to the arylated pyrrolidine. Notably, *N*-phenylbutan-1,4-diamine **4** might react intermolecular with a second molecule of aniline to give **2**. Moreover, the primary amine group of **4** reacts with dehydrogenated pyrrolidine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

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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.