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Selective Ruthenium-Catalyzed Alkylation of Indoles by Using Amines

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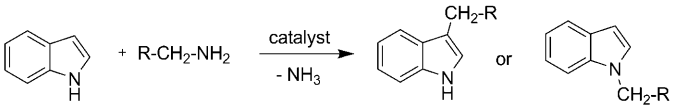
Indoles belong to the important heterocyclic ring systems in nature. Based on their significant structural diversity and potent biological activity they have become key building blocks for several pharmaceutical agents.[1] In the past, the development of novel synthetic methodologies for the generation of the basic heterocyclic core, as well as functionalization reactions on the aromatic ring system, have stimulated widespread utilization of indoles in life sciences.[2]

Among the numerous known bioactive indoles, C-3-alkylated derivatives, for example, naturally occurring serotonin and melatonin, are of major importance. More recently developed efficient approaches for catalytic C-3-functionalization of indoles are based on different types of Friedel–Crafts reactions, which proceed, for example, in the presence of Lewis and Brønsted acids as well as organocatalysts.[3] In contrast to these alkylations, transition-metal-catalyzed methodologies have been rarely exploited. In this respect, the recent work of Grigg et al.[4] is noteworthy, they achieved good yields by applying mainly benzylic alcohols as alkylation reagents. This reaction is based on the so-called "borrowing hydrogen methodology".[5] Thereby, the alcohol is initially dehydrogenated, then undergoes a functionalization reaction, and finally, re-hydrogenated. Elegant applications of this general methodology came from the groups of Williams,[6] Yus,[7] Fujita,[8] Grigg,[9] and us.[10]

Based on our continuing interest in the activation of amines[11] and the synthesis of novel indoles,[12] we had the idea to apply the former methodology for the derivatization of this important class of natural products. As a result, the reaction of indoles with amines was studied. In principle, such alkylations might result in N- and C-alkylated products (Scheme 1).



Scheme 1. Possible alkylations of indole using amines. R = alkyl, aryl.

Notably, such an alkylation process would lead to ammonia as the only side product and proceed under basic conditions, which is quite different from the more general Lewis acid catalyzed reactions.

As a starting point of our investigations, we examined the alkylation of indole with di-*n*-hexylamine (DHA) as a model system. At first, several catalysts, including the ruthenium *p*-cymene/1,1′-bis(diphenylphosphano)ferrocene (dppf) system of Williams and Hamid,[13] ruthenium *p*-cymene/*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) system developed by Noyori et al.,[14] the iridium/η^5-C_5Me_5 (Cp*) catalyst of Fujita[8] and our ruthenium carbonyl–phosphane system,[15] which are known to be highly active in transfer hydrogenation reactions were tested at 140 °C without solvent in a sealed tube. Unfortunately, we obtained only low to moderate conversions. Thus, the catalyst screening was repeated at 160 °C by applying the five most active catalysts of the initial screening (Table 1). From all catalysts tested, the Shvo complex (**1**)[16,17] (Scheme 2) showed the highest reactivity, giving 41 % of 3-hexylindole (Table 1, entry 4). To our delight, C-alkylation in the 3-position occurred selectively and no formation of the N-alkylated product took place. To the best of our knowledge, these reactions represent the first examples of borrowing-hydrogen-catalyzed alkylation of arenes with amines.[18]

Intensive mechanistic studies on transfer hydrogenation processes in the presence of **1** were performed by the groups of Bäckvall[19] and Casey.[20] It was shown that **1** is dissociated into two active species when exposed to higher temperatures. The 16 electron complex **1a** catalyzes the dehydrogenation reaction, while the 18 electron complex **1b** is active in the hydrogenation step. Based on the known reac-

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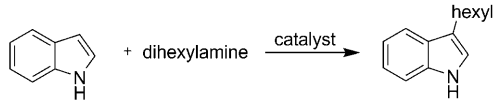
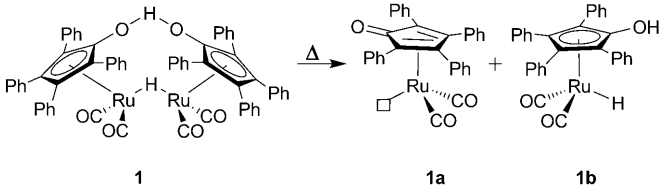
Table 1. Alkylation of indole with di-*n*-hexylamine in the presence of different catalysts.[a]



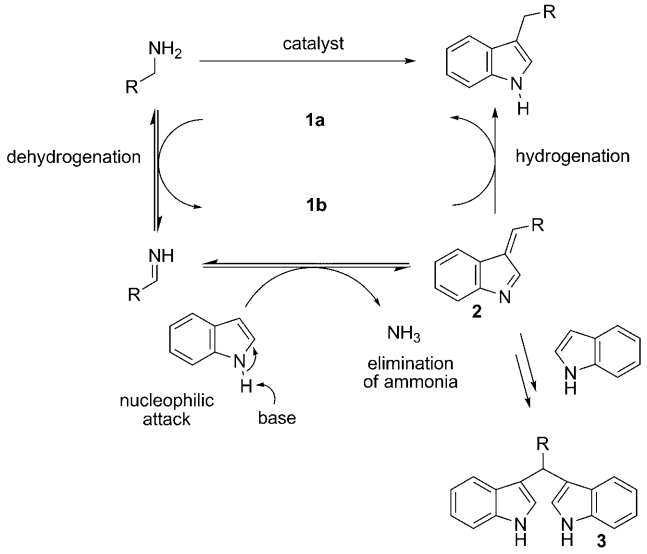
Entry	Catalyst[b]	Conv.[c] [%]	Yield[c] [%]
1	–	–	–
2	[Ru{(+)-binap}Cl_2]	55	15
3	[$Ru_3(CO)_{12}$]/CataCXium®PCy	33	14
4	Shvo (**1**)	78	41
5	[{Rh(Cp*)Cl_2}$_2$]	63	30
6	[{Ir(Cp*)Cl_2}$_2$], $NaHCO_3$	53	22

[a] Reaction conditions: di-*n*-hexylamine (0.5 mmol), indole (1 mmol), catalyst (2 mol% metal with respect to indole), 160°C, 24 h. [b] BINAP = 2,2′-bis(diphosphano)-1-1′-binaphthyl, CataCXium®PCy = *N*-phenyl-2-(dicyclohexylphosphanyl)pyrrole. [c] Conversion and yield are determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on indole.



Scheme 2. Dissociation of **1**.

tivity of **1**, we propose the typical borrowing hydrogen mechanism for this novel reaction (Scheme 3).

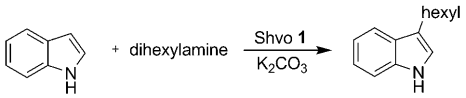


Scheme 3. Borrowing hydrogen mechanism for the alkylation of indoles with amines.

In situ dehydrogenation of the amine gives the corresponding imine, which reacts with indole to form the aminoalkylated product. Subsequent elimination of ammonia results in the formation of intermediate **2**, which is finally hydrogenated to give the desired product. Clearly, the hydrogen required for the final hydrogenation step is generated completely by dehydrogenation of the amine in the first reaction step. Hence, there is no need for additional hydrogen. The discrepancy between conversion and yield (Table 1, entry 4) is mainly explained by the formation of two side products. On the one hand, reaction of intermediate 2 with a second molecule of indole leads to the bis(3-indolyl)methane species **3**,[21] also reported by the group of Grigg.[4] On the other hand, the formation of small amounts of 2,3′-biindole are observed.

Next, we investigated the influence of various reaction parameters on the model reaction (Table 2). Most importantly, we discovered that the addition of catalytic amounts of potassium carbonate increased the yield and selectivity for the main product to a synthetically useful level. As shown in Table 2 the product yield is increased to 87 and 96% in the presence of potassium carbonate at 130 or 150°C, respectively (Table 2, entries 2 and 3). Best results are obtained by applying two equivalents of di-*n*-hexylamine (Table 2, entry 2, 5, and 6). The excess of secondary amine undergoes transalkylation side reactions to give also the corresponding primary and tertiary amines. Interestingly, the amount of potassium carbonate can be reduced to 2.5 mol% without any decrease in the yield of the main product (Table 2, entry 8).

Table 2. Alkylation of indole with di-*n*-hexylamine under different reaction conditions.[a]



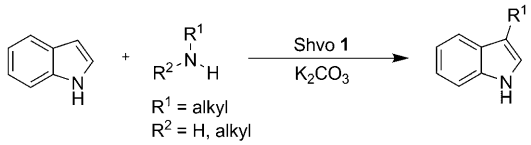
Entry	DHA/indole	K_2CO_3 [mol%]	*T* [°C]	Conv.[b] [%]	Yield[b] [%]
1	2	10	110	37	31
2	2	10	130	93	87
3	2	10	150	99	96
4	2	10	170	99	96
5	1	10	130	75	70
6	0.5	10	130	52	44
7	2	5	130	92	88
8	2	2.5	130	94	89

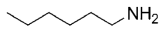
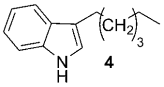
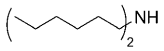
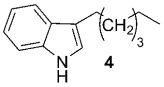
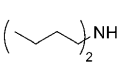
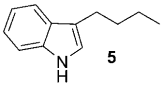
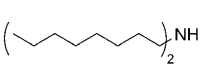
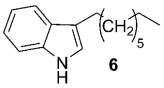
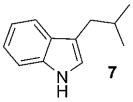
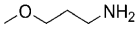
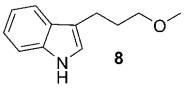
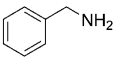
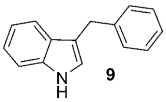
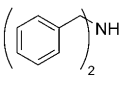
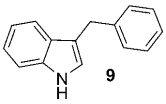
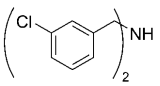
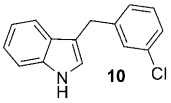
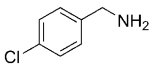
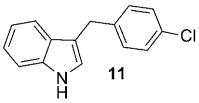
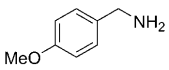
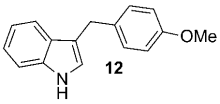
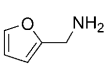
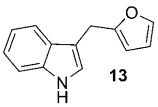
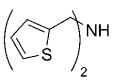
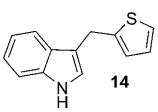
[a] Reaction conditions: indole (1 mmol), Shvo catalyst **1** (1 mol%), 24 h. [b] Conversion and yield are determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on indole.

Finally, we were interested in the general applicability of **1** for this reaction. To demonstrate the scope of the process, both various alkyl amines and indoles were investigated (Tables 3 and 4).

In general, catalytic experiments were performed with 1 mol% of **1** in the presence of 4 equiv of the alkyl chain of the amine. To achieve high yields even with less reactive substrates, a reaction temperature of 140°C and an amount of 5 mol% of potassium carbonate were chosen. The variation of the amines is summarized in Table 3. We were pleased to find that different amines, including those with

Table 3. Alkylation of indole with different amines.[a]

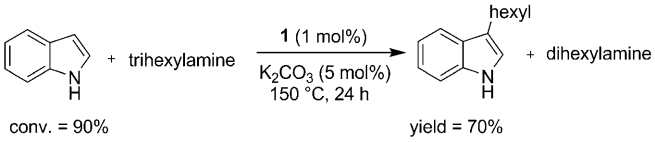


Entry	Amine	Product	Conv.[b] [%]	Yield[b] [%]
1[c]		 **4**	97	85
2		 **4**	97	89 (83)
3		 **5**	98	96 (78)
4		 **6**	96	90 (61)
5[c]		 **7**	94	85 (78)
6[d]		 **8**	95	77 (56)
7[d]		 **9**	88	86
8		 **9**	95	91 (84)
9[c]		 **10**	96	94 (83)
10[d]		 **11**	94	92 (90)
11[d]		 **12**	89	87 (85)
12[d]		 **13**	82	74
13		 **14**	90	89 (80)

[a] Reaction conditions: indole (1 mmol), alkyl chain of the amine (4 equiv), Shvo catalyst **1** (1 mol%), K_2CO_3 (5 mol% with respect to indole), 140°C, 24 h. [b] Conversion and yield are determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on indole. Isolated yields in brackets. [c] 150°C. [d] 160°C.

nonactivated alkyl chains are converted to the C-3-alkylated indoles in good yields (85–96%). High yields were observed by applying secondary amines like di-*n*-hexylamine or dibenzylamine (Table 3, entries 2 and 8), but also with primary amines at slightly higher temperature (Table 3, entries 1 and 7), which is in line with previous investigations in our group.[22] These results constitute a significant improvement compared with the work of Grigg and co-workers, who achieved a maximum yield of 35% using non-benzylic alcohols.[4]

When considering the stability of tertiary amines, it is noteworthy that the reaction of tri-*n*-hexylamine with indole proceeded smoothly and resulted in a good yield of the alkylated indole (Scheme 4).



Scheme 4. Alkylation of indole using tri-*n*-hexylamine.

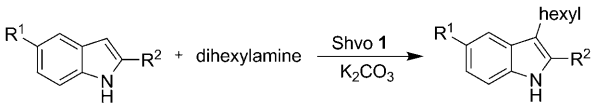
Apparently, this process proceeds through the generation of an iminium cation in the dehydrogenation step of the borrowing hydrogen mechanism. After variation of the amines, different indoles were tested in the reaction with di-*n*-hexylamine. Here, we focused on commercially available 5-substituted indoles. Electron-rich and -deficient indoles are converted in very good yields and selectivities to the desired products (Table 4, entries 1–4). Due to the steric hindrance of the methyl group, 2-methylindole showed somewhat lower reactivity and a higher reaction temperature was required to give the corresponding product in 89% yield (Table 4, entry 5).

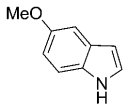
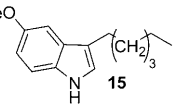
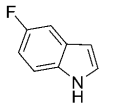
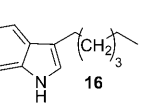
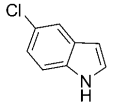
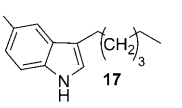
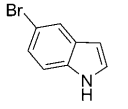
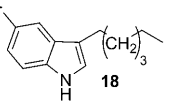
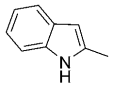
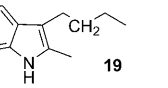
In summary, we have demonstrated for the first time that transition-metal-catalyzed C-alkylation of indoles with easily available aliphatic amines is possible. This novel atom efficient and selective method for indole alkylation proceeds in the presence of **1** under basic conditions. It constitutes a complementary and valuable method for alkylations and benzylations. Hence, various substrates, including primary, secondary, and even tertiary amines, react in good to excellent yield with the C-alkylated indoles.

Experimental Section

General procedure for the Shvo-catalyzed alkylation of indoles: In an ACE pressure tube under an argon atmosphere, catalyst **1** (10.8 mg, 0.01 mmol), indole (117.2 mg, 1 mmol), potassium carbonate (6.9 mg, 0.05 mmol), and dibenzylamine (394.6 mg, 2 mmol) were stirred at 140°C for 24 h. Then, the volatile compounds were removed under vacuum and the residue was purified in the first step by column chromatography (heptane/ethyl acetate = 4:1). In the second step the pre-cleaned product was dissolved in methanol and purified by using an Isolute SCX-2 column (2 g/15 mL, Biotage) to remove remaining amines, which were

Table 4. Alkylation of different indoles with di-*n*-hexylamine.[a]



Entry	Indole	Product	Conv.[b] [%]	Yield[b] [%]
1		 **15**	100	95 (89)
2		 **16**	100	90 (56)
3		 **17**	100	92 (78)
4		 **18**	100	85 (58)
5[c]		 **19**	95	89 (68)

[a] Reaction conditions: indole (1 mmol), di-*n*-hexylamine (2 mmol), Shvo catalyst **1** (1 mol%), K_2CO_3 (5 mol% with respect to indoles), 140 °C, 24 h. [b] Conversion and yield are determined by GC analysis with hexadecane as internal standard. Conversions and yields are based on the indole. Isolated yields in brackets. [c] 160 °C.

kept back by the SPE column and the product passed through. Afterwards methanol was removed under vacuum to afford 3-benzyl-1*H*-indole (174.8 mg, 84%) as a white solid (m.p. = 108 °C).

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