Catalytic Alkylation of Aromatic Amines with Styrene in the Presence of Cationic Rhodium Complexes and Acid

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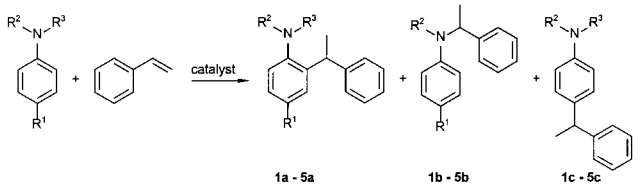
Abstract: The first transition metal-catalyzed Friedel-Crafts alkylation of aromatic amines with styrene is reported. *ortho*-Alkylation of anilines occurs using catalytic amounts of $[Rh(cod)_2]BF_4$ / 4 PPh_3 and HBF_4.

Key words: catalysis, alkylation, amination, rhodium, Friedel-Crafts alkylation

There has been much effort in recent years towards the development of catalytic electrophilic aromatic substitution reactions.[1] Of special importance are methods, e.g. Friedel-Crafts reactions, which enable the introduction of carbon substituents onto aromatic rings. Although these reactions work best for electron-rich aromatic compounds, frequently the observed selectivities (*ortho* vs. *para*) are low and the reactions proceed only in the presence of stoichiometric amounts of Lewis acids.



Scheme 1

Unlike typical Friedel-Crafts processes of substituted benzenes, electrophilic carbon-carbon bond forming reactions of aromatic amines are more problematic.[2] This is due to the coordination of the Lewis acid to the aromatic nitrogen atom which leads to a deactivation of the aromatic ring and side reactions. Hence, few examples of alkylations of anilines with olefins under Friedel-Crafts conditions have been described.[3] On the other hand, the alkylation of aniline with ethylene has been reported using basic aluminium anilide as catalyst under drastic conditions (40-60 bar; 330°C).[4,5] In addition, the reaction of aniline with styrene, leading to the formation of *ortho*-*C*- and *N*-alkylation products is possible when using aluminium phenoxide or zeolites as catalysts.[6] However, these catalysts always produce a mixture of regioisomers (*o*-, *p*-alkylated aniline). To the best of our knowledge the only known transition metal-catalyzed alkylation of anilines was previously observed by J. J. Brunet et al. for the conversion of norbornene with aniline.[7,8] Using $[(PEt_3)_2RhCl]_2$ / PhNHLi as catalyst the *ortho*-*C*-alkylation product (30 %) and the *N*-alkylation product (15 %) was obtained after 12 days at 70 °C. When applying the same catalyst to the reaction of styrene with aniline no *C*-alkylation product was detected.[9]

Based on our recent investigations on the regioselective amination of aromatic olefins with aliphatic amines,[10] we became interested in the reaction of styrene with various substituted anilines in the presence of cationic rhodium complexes. Herein, we demonstrate for the first time that anilines afford alkylated anilines in the presence of catalytic amounts of $HBF_4 \cdot OEt_2$ and a cationic rhodium species. Often high regioselectivities for the *ortho*-alkylated aniline **1a** – **5a** are obtained.

Recently, we described the first catalytic *anti*-Markovnikov hydroamination of styrene with aliphatic amines[11] using a catalyst system consisting of $HBF_4 \cdot OEt_2$ and a cationic rhodium complex. Now, we used this catalyst system for the reaction of substituted anilines with styrene. In general, the experiments were performed in Ace-pressure tubes at 140 °C in the presence of 2.5 mol% $[Rh(cod)_2]BF_4$ / 4 mol% PPh_3 and 20 mol% $HBF_4 \cdot OEt_2$ using toluene as solvent (Table 1).

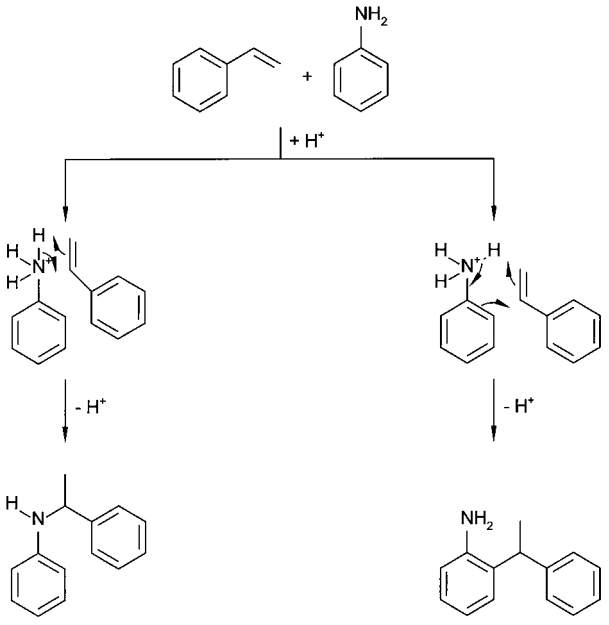
Table 1: *Ortho*-alkylation of aromatic amines with $[Rh(cod)_2]BF_4$ / 4 PPh_3 (2.5 mol%) and $HBF_4 \cdot OEt_2$ (20 mol%) as catalyst[a,b]

					Yield (%)		
Entry	Product	R^1	R^2	R^3	**a**	**b**	**c**
1	**1**	H	H	H	57 (51)	24 (20)	< 0.1
2[c]	**1**	H	H	H	64	24	< 0.1
3[d]	**1**	H	H	H	51	3	2
4[e]	**1**	H	H	H	32	16	14
5[f]	**1**	H	H	H	13	6	< 0.1
6	**2**	OMe	H	H	46 (39)	5	< 0.1
7[g]	**2**	OMe	H	H	61	2	< 0.1
8	**3**	F	H	H	31 (28)	23 (15)	< 0.1
9	**4**	H	Me	H	82 (73)	0	< 0.1
10	**5**	H	Me	Me	17 (16)	0	7 (6)

[a] styrene:amine = 5:1, 20 mol% $HBF_4 \cdot OEt_2$, $[Rh(cod)_2]BF_4$ / 4 PPh_3 (2.5 mol%), toluene, 140 °C, pressure tube, 20 h; [b] yields are determined by gas chromatography using hexadecane as internal standard, isolated yields are in brackets; [c] styrene:amine = 10:1; [d] reaction temperature 160 °C; [e] 20 mol% CF_3SO_3H instead of HBF_4; [f] styrene:amine = 1:1; [g] styrene:amine = 2:1.

After some initial screening studies of reaction conditions (vide supra) it turned out that aniline can be successfully *ortho*-alkylated with styrene in the presence of both acid *and* a cationic rhodium phosphine complex at temperatures of 140 – 160 °C. In addition to 2-(1-phenylethyl)aniline (**1a**), *N*-(1-phenylethyl)aniline (**1b**) is obtained in 24% yield. Without either $HBF_4{\cdot}OEt_2$ or $[Rh(cod)_2]BF_4$ / PPh_3 no reaction is observed. To verify the generality of the acid effect on this reaction other acids were used as co-catalysts (HCl; CF_3CO_2H; CF_3SO_3H; *p*-$CH_3C_6H_4SO_3H$). So far only triflic acid shows a similar effect compared to $HBF_4{\cdot}OEt_2$. A critical reaction parameter is the ratio of styrene to aniline. Best results are afforded applying an excess of styrene. Although the reaction takes place with a ratio of styrene to aniline of 1:1, the yields of **1a** (13%) and **1b** (6%) are significantly decreased (Table 1, entry 5). Also, using a large excess of styrene (> 10:1) decreased the yield in **1a** and **1b** due to the fact that mainly di-, tri- and tetra-alkylated products are afforded.

Apart from aniline we studied the reaction of *p*-anisidine and *p*-fluoroaniline.[12] In the latter case the yield of the corresponding products is slightly lower. Interestingly, the ratio of *C*- and *N*-alkylated products changes significantly with the electronic nature of the aryl amine. Next, we investigated the influence of substituents on the N-atom. *N*-Methylaniline gave the corresponding *ortho*-C-alkylated product in good yield (82%) with excellent selectivity (Table 1, entry 9). *N*,*N*-Dimethylaniline is much less reactive and leads to considerable amounts of the *para*-*C*-alkylation product **5c**. In addition α-methylstyrene reacts with aniline to afford 2-(1-methyl-1-phenylethyl)aniline (**6a**) in 20 % yield and *N*-(1-methyl-1-phenylethyl)aniline (**6b**) in 33 % yield.



Scheme 2

It is notable that the cationic rhodium catalyst system is approximately two orders of magnitude more active under acidic conditions (turnover frequency 1.8 h^{-1}, reaction of styrene with aniline vs 0.02 h^{-1}, reaction norbornene with aniline) compared to Brunet´s system under basic conditions.

As stated above the reaction of aniline with styrene does not proceed in the absence of a cationic rhodium complex. However, it was questionable whether this is also true for more electron-rich anilines. Indeed, when using 20 mol% of $HBF_4{\cdot}OEt_2$ as catalyst *p*-anisidine and *N*-methylaniline are *ortho*-alkylated. Again, in the presence of a large excess of styrene (styrene : amine ratio of 5:1) the reaction, e.g. of *p*-anisidine leads mainly to di- and trialkylation of aniline. While in the reaction of *N*-methylaniline the *ortho*-*C*-alkylation product is formed regioselectively, *N*,*N*-dimethylaniline gives considerably lower yields and selectivities. Apart from aniline *p*-fluoroaniline also does not react under these reaction conditions (Table 2).

Table 2: Friedel-Crafts alkylation of aromatic amines with $HBF_4{\cdot}OEt_2$ (20 mol%) as catalyst[a,b]

					Yield (%)		
Entry	Product	R^1	R^2	R^3	**a**	**B**	**c**
1	**1**	H	H	H	0	0	0
2	**2**	OMe	H	H	8	2	0
3[c]	**2**	OMe	H	H	61	2	0
4	**3**	F	H	H	0	0	0
5	**4**	H	Me	H	75	0	0
6	**5**	H	Me	Me	10	0	4

[a] styrene:amine = 5:1, 20 mol% $HBF_4{\cdot}OEt_2$, toluene, 140 °C, pressure tube, 20 h; [b] yields are determined by gas chromatography using hexadecane as internal standard; [c] styrene:amine = 2:1.

Although it is too early to give a detailed mechanistic explanation for the new rhodium/acid-catalyzed alkylation of aniline we propose that the reaction involves the key intermediates shown in Scheme 2.[5,6] The six-membered cyclic intermediate is more favourable, this accounts for the formation of **1a - 5a** as the main reaction products. The beneficial effect of the rhodium catalyst is explained via a coordination to the arene ring of styrene which results in an activation of styrene towards nucleophiles. This assumption is supported by the observation that simple aliphatic olefins such as cyclohexene and vinylcyclohexene show no reactivity in preliminary catalytic tests.

Alternatively, the *ortho*-alkylation could be explained by an initial *ortho*-metallation of aniline.[13] Indeed, the reaction of [d_7]-aniline with with $[Rh(cod)_2]BF_4$ / 4 PPh_3 shows a C-D activation in the *ortho* and *para* position of aniline. Nevertheless, this reaction pathway seems less viable since the observed Markovnikov selectivity is not explained.

In summary, we have reported the first transition metal-catalyzed alkylation of anilines with aromatic olefins. This reaction allows a simple and straightforward access

to 2-(1-arylethyl)anilines which can be further exploited for the synthesis of a wide range of heterocycles. Remarkably, the combination of both $[Rh(cod)_2]BF_4$ / 4 PPh_3 (2.5 mol%) and $HBF_4{\cdot}OEt_2$ (20 mol%) is necessary to achieve reactions of aniline and *p*-fluoroaniline. On the other hand electron-rich anilines react already in the presence of $HBF_4{\cdot}OEt_2$ (20 mol%) whereby the addition of $[Rh(cod)_2]BF_4$ / 4 PPh_3 (2.5 mol%) increases the yield of alkylated anilines (exception *p*-anisidine at low styrene to anisidine ratio). Extensions of rhodium-catalyzed reaction of anilines with styrenes for the synthesis of quinoline heterocycles will be reported in due course.[14]

Acknowledgement

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(12) Typical experimental procedure: 45 mg (0.11 mmol) $[Rh(cod)_2]BF_4$ and 116 mg (0.44 mmol) PPh_3 were suspended under argon in 5 ml toluene using a pressure tube as reaction vessel. 0.4 ml (4.4 mmol) aniline and 2.52 ml (22 mmol) styrene were added. After adding 120 µl (0.88 mmol) $HBF_4{\cdot}OEt_2$ and hexadecane (GC-standard) the reaction mixture was heated for 20 h at 140 °C. Standard organic workup including chromatography yielded the alkylation products.
All the new compounds were characterized by EA, MS, ^{1}H-NMR and ^{13}C-NMR. Compound **2a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 - 7.07 (m, 5H), 6.82 (d, ^4J(H,H) = 2.5 Hz, 1H), 6.58 (dd, ^3J(H,H) = 8.5 Hz, ^3J(H,H) = 2.5 Hz, 1H), 6.49 (d, ^3J(H,H) = 8.5 Hz, 1H), 4.00 (q, ^3J(H,H) = 7.0 Hz, 1H, C*H*), 3.69 (s, 3H), 3.03 (s, 2H, N*H*), 1.51 (d, ^3J(H,H) = 7.0 Hz, 3H, CH_3); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.4, 145.8, 138.3, 132.3, 129.2, 127.9, 126.8, 117.6, 114.5, 112.1 , 56.1, 40.7, 22.2; MS (70 eV): 227 [M^+], 212 [M^+ - CH_3], 197 [M^+ - 2 CH_3], 180. Compound **3a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19 - 7.07 (m, 5H,), 6.92 (dd, ^3J(H,F) = 10.0 Hz, ^4J(H,H) = 3.0 Hz, 1H), 6.68 (ddd, ^3J(H,F) = 10.0 Hz, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 3.0 Hz, 1H), 6.44 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,F) = 5.0 Hz, 1H), 3.95 (q, ^3J(H,H) = 7.0 Hz, 1H, C*H*), 3.21 (s, 2H, N*H*), 1.48 (d, ^3J(H,H) = 7.0 Hz, 3H, CH_3); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 155.7 (d, ^1J(C,F) = 236.2 Hz), 143.8, 139.1 (d, ^4J(C,F) = 1.9 Hz), 130.7 (d, ^4J(C,F) = 6.8 Hz), 127.8, 126.3, 125.6, 115.9 (d, ^3J(C,F) = 7.7 Hz), 113.0 (d, ^3J(C,F) = 22.3 Hz), 112.3 (d, ^2J(C,F) = 22.4 Hz), 39.2, 20.7; MS (70 eV): 215 [M^+], 200 [M^+ - CH_3], 185, 124, 109, 99, 77. Compound **3b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 - 7.20 (m, 4H), 7.12 (t, ^3J(H,H) = 7.5 Hz, 1H), 6.69 (dd, ^3J(H,F) = 9.0 Hz, ^3J(H,H) = 8.5 Hz, 2H), 6.34 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,F) = 2.4 Hz, 2H), 4.31 (q, ^3J(H,H) = 7.0 Hz, 1H, C*H*), 3.90 (s, 1H, N*H*), 1.41 (d, ^3J(H,H) = 7.0 Hz, 3H, CH_3); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 155.0 (d, ^1J(C,F) = 235.2 Hz), 142.7, 144.2, 125.1, 127.9, 126.3, 114.7 (d, ^2J(C,F) = 22.4 Hz), 113.5 (d, ^3J(C,F) = 7.8 Hz), 53.4, 24.2; MS (70 eV): 215 [M^+], 200 [M^+ - CH_3], 120 [M^+ - C_6H_5], 105, 93, 77.

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