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Tetrahedron Letters 46 (2005) 7401–7405

Tetrahedron Letters

# An improved protocol for the selective hydroaminomethylation of arylethylenes

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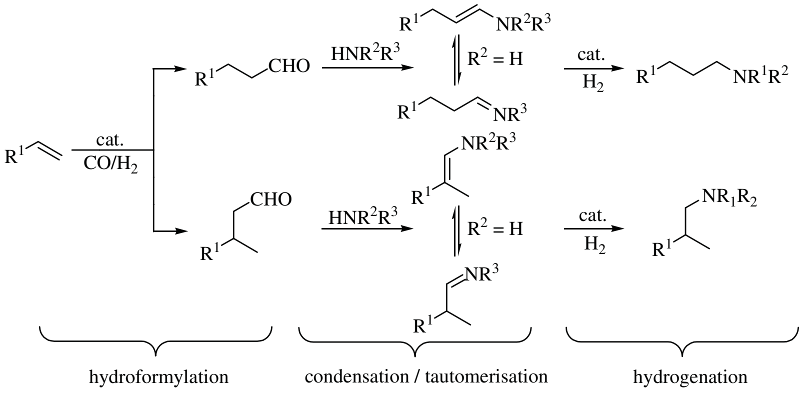
Received 30 May 2005; revised 17 August 2005; accepted 22 August 2005
Available online 12 September 2005

**Abstract**—The hydroaminomethylation of arylethylenes with anilines proceeds under mild conditions in the presence of $[Rh(cod)_2BF_4]$ and dppf as catalyst system to give the corresponding branched amphetamine derivatives in good selectivity and yield.

Amines are important products for bulk as well as fine chemical and pharmaceutical industries. Among the various methods known for the synthesis of amines the so-called hydroaminomethylation of olefines is highly atom-economic and efficient. This domino reaction consists of an initial hydroformylation followed by a reductive amination (Scheme 1).[1] Although the method is known for more than 50 years, only in the last decade the potential of this transformation has been explored in more detail. Here, especially the work of Eilbracht and co-workers is noteworthy.[2]

In general, hydroaminomethylations permit the synthesis of secondary or tertiary amines from terminal and internal olefins.[3] The reaction is tolerant to a variety of potentially reactive functional groups. This aspect has been utilized, for example, in the hydroaminomethylation of methallylic alcohols and steroids.[4] Despite recent improvements of hydroaminomethylation catalysts,[5] control of all aspects of selectivity (chemo-, regio- and enantioselectivity) is still a challenge.[6]

For some time, we are interested in the synthesis of biologically important arylethylamines,[7] which are known to exhibit pharmacological activity such as antihistaminic and sympathomimetic properties.[8] Obviously, the hydroaminomethylation of styrene offers an easy access to this class of compounds. However, comparably



**Scheme 1.** Hydroaminomethylation of olefins.

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*Keywords*: Amines; Catalysis; Hydroaminomethylation.

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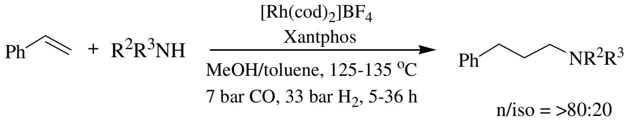
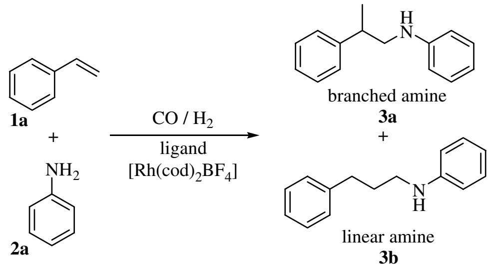
doi:10.1016/j.tetlet.2005.08.107



**Scheme 2.** Hydroaminomethylation to 3-arylpropylamines.

few investigations have been carried out so far. For example, Rische and Eilbracht reported very good yield and selectivity to the corresponding branched amines at high pressure and temperature (110 bar; 110 °C) in the presence of [Rh(cod)Cl]$_2$.[2e] Later on, Alper and coworkers have used a zwitterionic rhodium complex as catalyst.[9] This system was active under milder conditions (<80 bar; 80 °C), but the observed regioselectivity towards the branched amines was only moderate to good. Kostas reported the reaction of styrene with morpholine catalyzed by a cationic rhodium complex with a P,N-ligand system. Again, the reaction was carried out at high pressure (100 bar) giving the corresponding branched amine in good yield and selectivity.[10] It is interesting to note that in all these reactions the branched amphetamine derivative is formed preferentially due to the increased thermodynamic stability of the intermediate benzylrhodium complex. However, the hydroaminomethylation of styrene with piperidine catalyzed by a cationic rhodium complex in the presence of Xantphos as ligand gave the linear arylpropylamine in good yield (Scheme 2).[5]

**Table 1.** Hydroaminomethylation of styrene with aniline[a]



| Entry | Ligand | Additive | Yield of amines[b] (%) | *iso*/*n*-ratio[c] |
|---|---|---|---|---|
| 1 | — | HBF$_4$ | 2 | 85:15 |
| 2 | PPh$_3$ | — | 7 | 98:2 |
| 3 | PPh$_3$ | HBF$_4$ | 52 | 99:1 |
| 4 | Xantphos | — | 29 | 78:22 |
| 5 | Xantphos | HBF$_4$ | 94 | 85:15 |
| 6 | dppe | — | 12 | 61:39 |
| 7 | dppe | HBF$_4$ | 49 | 86:14 |
| 8 | dppent | — | 10 | 93:7 |
| 9 | dppent | HBF$_4$ | 35 | >99:1 |
| 10 | dppf | — | 30 | 80:20 |
| 11 | dppf | HBF$_4$ | 96 | 88:12 |

[a] Reaction conditions: 10 mmol styrene, 10 mmol aniline, 0.25 mol % [Rh(cod)$_2$BF$_4$], 0.25 mol % diphosphine or 0.5 mol % PPh$_3$, 30 mL THF, 1 mmol HBF$_4$, 5 bar $P_{CO}$, 25 bar $P_{H2}$, 60 °C, 18 h.

[b] Yield was determined by GC analysis with *iso*-octane as internal standard.

[c] Selectivity was determined by GC analysis.

Here, we present for the first time the use of a rhodium/diphosphine catalyst system for the hydroaminomethylation of arylethylenes with anilines.

As a start of our investigation, we tested different combinations of [Rh(cod)$_2$BF$_4$] with phosphines in the model reaction of styrene with aniline (Table 1).[11] It is important to note that only 2% of amines **3a** and **4a** were obtained when the reaction was carried out in the absence of phosphine.

Interestingly, in all cases the addition of a catalytic amount of tetrafluoroboric acid significantly enhanced the yield of amines with a slight increase in the *iso*/*n*-ratio. Although the effectiveness of the acid is not fully known, the enhancement of the yield can be partly attributed to the formation of iminium ions, which are smoothly reduced to the corresponding amines. It is likely that this effect will be useful for other hydroaminomethylations, too.

Apart from the acid, the nature of the phosphine ligand influences both the selectivity and the yield of amines. A cationic rhodium precursor in association with the ligand dppf allowed us vide supra to obtain amines **3a**, **4a** in almost quantitative yield with a good *iso*/*n*-ratio.

Next, the rhodium-catalyzed hydroaminomethylation of styrene with aniline in the presence of dppf was

**Table 2.** Variation of reaction conditions[a]

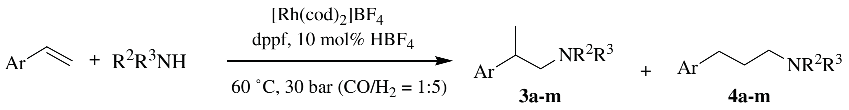
| Entry | Rhodium precursor | CO/H$_2$ (bar) | Temperature (°C) | Solvent | Yield of amine[b] (%) | *iso*/*n*-ratio[c] |
|---|---|---|---|---|---|---|
| 1 | [Rh(cod)$_2$BF$_4$] | 5/25 | 60 | THF | 96 | 88:12 |
| 2 | [Rh(cod)$_2$BF$_4$], H$_2$O | 5/25 | 60 | THF | 20 | 74:26 |
| 3 | [Rh(nbd)$_2$BF$_4$] | 5/25 | 60 | THF | 97 | 93:7 |
| 4 | [Rh(acac)(CO)$_2$] | 5/25 | 60 | THF | 74 | 92:8 |
| 5 | [Rh(cod)$_2$BF$_4$] | 5/25 | 40 | THF | 81 | 92:8 |
| 6 | [Rh(cod)$_2$BF$_4$] | 5/25 | 120 | THF | 99 | 66:34 |
| 7 | [Rh(cod)$_2$BF$_4$] | 3.5/26.5 | 60 | THF | 99 | 91:9 |
| 8 | [Rh(cod)$_2$BF$_4$] | 3.5/50 | 60 | THF | 89 | 90:10 |
| 9 | [Rh(cod)$_2$BF$_4$] | 15/15 | 60 | THF | 99 | 86:14 |
| 10 | [Rh(cod)$_2$BF$_4$] | 5/25 | 60 | MeOH | 88 | 95:5 |
| 11 | [Rh(cod)$_2$BF$_4$] | 5/25 | 60 | Toluene | 96 | 90:10 |

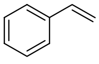
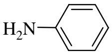
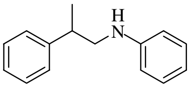
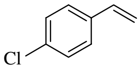
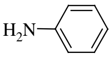
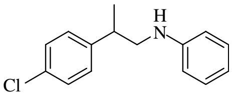
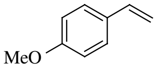
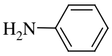
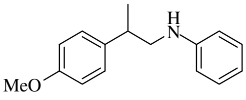
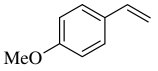
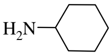
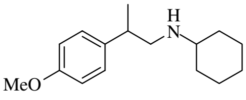
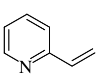
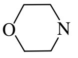
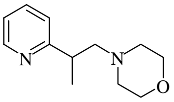
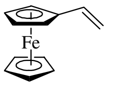
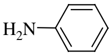
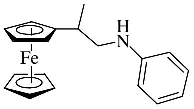
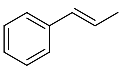
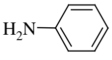
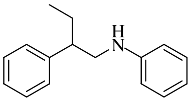
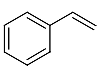
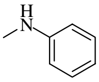
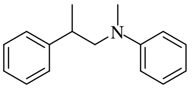
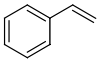
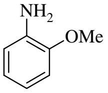
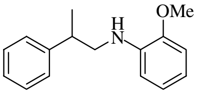
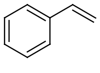
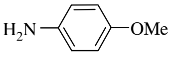
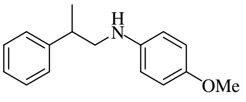
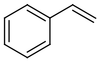
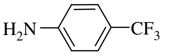
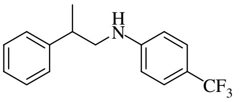
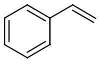
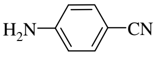
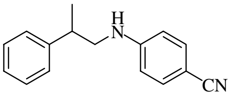
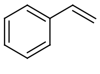
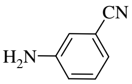
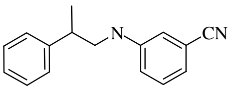
[a] Reaction conditions: 10 mmol styrene, 10 mmol aniline, 0.25 mol % of rhodium precursor, 0.25 mol % dppf, 30 mL of solvent, 1 mmol HBF$_4$, 18 h.

[b] Yield was determined by GC analysis with *iso*-octane as internal standard.

[c] Selectivity was determined by GC analysis.

**Table 3.** Hydroaminomethylation of styrenes with various amines[a]



| Entry | Olefin | Amine | Major product | Yield of amines[b] (%) | *iso*/*n*-ratio[c] |
|---|---|---|---|---|---|
| 1 |  |  |  | 96<br>**3a**, **4a** | 88:12 |
| 2 |  |  |  | 98<br>**3b**, **4b** | 85:15 |
| 3 |  |  |  | 97<br>**3c**, **4c** | 88:12 |
| 4 |  |  |  | 17<br>**3d**, **4d** | 59:41 |
| 5 |  |  |  | 66<br>**3e**, **4e** | 99:1 |
| 6 |  |  |  | 55<br>**3f**, **4f** | 81:19 |
| 7[d] |  |  |  | 50<br>**3g**, **4g** | 93:7 |
| 8 |  |  |  | 75<br>**3h**, **4h** | 85:15 |
| 9 |  |  |  | 97<br>**3i**, **4i** | 88:12 |
| 10<br>11[e] |  |  |  | 65<br>60<br>**3j**, **4j** | 90:10<br>96:4 |
| 12 |  |  |  | 99<br>**3k**, **4k** | 83:17 |
| 13<br>14[f] |  |  |  | 59<br>99<br>**3l**, **4l** | 78:22<br>80:20 |
| 15[f] |  |  |  | 98<br>**3m**, **4m** | 85:15 |

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[a] Reaction conditions: 10 mmol olefin, 10 mmol amine, 0.25 mol % [Rh(cod)$_2$BF$_4$], 0.275 mol % dppf, 30 mL THF, 1 mmol HBF$_4$, 5 bar $P_{CO}$, 25 bar $P_{H2}$, 60 °C, 18 h.

[b] Yield was determined by GC analysis with *iso*-octane as internal standard.

[c] Selectivity was determined by GC analysis.

[d] 72 h, 0.5 mol % [Rh(cod)$_2$BF$_4$], 0.55 mol % dppf.

[e] 40 °C.

[f] 74 h.

investigated with regard to critical reaction parameters such as solvent, temperature, rhodium precursor and pressure. Selected results are shown in Table 2. The purity of the rhodium precursor strongly influences the yield of the reaction (Table 2, entries 1 and 2). In general, yields of amines are better when the reaction was carried out in the presence of a cationic rhodium precursor. It is important to note that our catalytic system is efficient even at 40 °C (Table 2, entry 5), which is important because the regioselectivity towards the branched amine is significantly better at lower temperature (Table 2, compare entries 1 and 6). Modification of the total pressure seems to have only a slight effect on both the yield and the regioselectivity.

Finally, we tested the efficiency of the catalytic system in the hydroaminomethylation of arylethylenes with various amines. The results are summarized in Table 3. *para*-Substituted styrenes react with aniline in the presence of the catalytic system quantitatively to give the corresponding amines (Table 3, entries 2 and 3). Apparently, electronic effects of the substituents in the 4-position of styrene have only little influence on the yield and selectivity of the reaction. However, hydroamino-methylation of 4-methoxystyrene with cyclohexylamine afforded only 17% of **3d** and **4d** with a low *iso*/*n*-ratio (Table 3, entry 4).

Reaction of 2-vinylpyridine with morpholine proceeds with an excellent regioselectivity to give 66% of **3e** and **4e** (Table 3, entry 5). This is a rare successful example of using a heteroaromatic olefin as substrate in hydroaminomethylations. In the reaction of vinylferrocene with aniline amines, **3f**, **4f** are obtained in 55% with a good *iso*/*n*-ratio (Table 3, entry 6). In case of sterically more demanding β-methylstyrene, longer reaction time and more catalyst are necessary to obtain a reasonable yield (50%) of **3g**, **4g** (Table 3, entry 7). It is noteworthy that the hydroaminomethylation of this internal olefin occurs with high regioselectivity. Hydroaminomethylation of styrene with *N*-methylaniline afforded **3h**, **4h** in 75% (Table 3, entry 8). This demonstrated the feasibility of using secondary amines in the reaction. In addition, different substituted anilines have been hydroaminomethylated easily (Table 3, entries 9–11). 2-Anisidine afforded 97% of **3i** and **4i** with an *iso*/*n*-ratio of 88:12. Under the same reaction conditions, 65% of **3j** and **4j** are obtained from 4-anisidine. Here, side-products formed by bishydroaminomethylation were observed. Amine **3k** and **4k** are obtained in excellent yield from styrene and 4-trifluoromethylaniline (Table 3, entry 12). Finally, reaction of styrene with 3- and 4-aminobenzonitrile afforded **3l** and **3m**. A longer reaction time allowed us to obtain both products nearly quantitatively (Table 3, entries 13–15).

In conclusion, we have shown that [Rh(cod)$_2$BF$_4$]/dppf in the presence of HBF$_4$ catalyzes the hydroaminomethylation of aromatic olefins with different amines with good regioselectivity towards the branched products. The described catalyst system permits for the first time hydroaminomethylation of styrenes under mild conditions (low pressure; 60 °C). The reported procedure should be useful for the synthesis of a wide variety of known and new amphetamine derivatives.

## Acknowledgements

This work has been supported by the State of Mecklenburg-Western Pommerania, and the 'Bundesministerium für Bildung und Forschung (BMBF)'. We thank Mrs. C. Mewes, Mrs. H. Baudisch, Mrs. A. Lehmann and Mrs. S. Buchholz (all IfOK) for their excellent support.

## References and notes

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11. General procedure: Hydroaminomethylation reactions were carried out in a Parr stainless steel autoclave (100 mL). In a typical experiment (Table 1, entry 10), a Schlenk flask was charged with [Rh(cod)$_2$BF$_4$] (0.25 mol %),

dppf (0.25 mol %) and THF (30 mL) under argon atmosphere. The solution was stirred at room temperature for 1 h, then styrene (10 mmol), aniline (10 mmol) and tetrafluoroboric acid (0.2 mL 54% wt % solution in diethyl ether) were added. The solution was transferred to the autoclave and the autoclave was pressurized with CO (5 bar) and hydrogen (25 bar). The reaction was carried out at 60 °C for 18 h. Then, the autoclave was cooled at 5 °C and depressurized. After transfer to a Schlenk flask, the mixture was analyzed by gas chromatography using *iso*-octan as internal standard. All branched amines were fully characterized by $^1$H NMR, $^{13}$C NMR, MS and HRMS.

*N*-Phenyl-2-(4-methoxyphenyl)propylamine (**3c**): $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.51–7.41 (m, 4H, Ph), 7.21–7.18 (m, 2H, Ph), 7.02 (tt, $J = 1.0$ and 7.3 Hz, 1H, Ph), 6.90–6.85 (m, 2H, Ph), 4.1 (s, 3H, $OCH_3$), 3.90 (br s, 1H, NH), 3.56 (dd, $J = 12.3$ and 6.2 Hz, 1H, $CH_2$–N), 3.56 (dd, $J = 12.3$ and 8.3 Hz, 1H, $CH_2N$), 3.31 (m, 1H, C*H*–$CH_3$), 1.62 (d, $J = 7.1$ Hz, 3H, $CH_3$). $^{13}$C NMR (161 MHz, $CDCl_3$): $\delta$ 158.0 (Ph), 148.1 (Ph), 136.3 (Ph), 129.0 (2Ph), 127.9 (2Ph), 117.0 (Ph), 113.9 (2Ph), 112.8 (2Ph), 55.0 (O–$CH_3$), 50.1 (*C*$H_2$–NH), 38.1 (CH–$CH_3$), 19.8 ($CH_3$). GC–MS (EI, 70 eV) $m/z = 241$ [$M^+$], 181, 135, 106, 91, 69, 65, 52. HRMS Calcd for $C_{16}H_{19}NO$: 241.14627. Found 241.14627.

*N*-(2-Pyridin-2-yl-propyl)morpholine (**3e**): $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.55–7.45 (m, 1H, CH), 7.11–7.06 (m, 2H, 2 CH), 7.06–7.01 (m, 1H, CH), 3.67–3.63 (m, 2H, $CH_2N$), 3.59–3.54 (m, 2H, $CH_2N$), 3.10–3.01 (m, 1H, C*H*$CH_3$), 2.72–2.67 (m, 1H, C*H*$_2$N), 2.60 (dd, $^1J = 12.2$ Hz, $^2J = 6.9$ Hz, 1H, C*H*$_2$N), 2.49–2.42 (m, 2H, $CH_2O$), 2.38–2.33 (m, 2H, $CH_2O$), 1.23 (d, $J = 6.9$ Hz, 3H, $CH_3$). $^{13}$C NMR (161 MHz, $CDCl_3$): $\delta$ 164.8 (Py), 148.9 (CH), 136.0 (CH), 122.9 (CH), 121.8 (2Ph), 66.8 (*C*$H_2$N), 64.7 (*C*$H_2$N), 58.6 (*C*$H_2$N), 53.7 ($CH_2O$), 53.4 ($CH_2O$), 35.4(*C*H$CH_3$), 18.8 ($CH_3$). GC–MS (EI, 70 eV): $m/z = 206$ [$M^+$], 188, 174, 161, 132, 120, 106, 100, 93, 78, 70, 52, 42, 28. HRMS Calcd for $C_{12}H_{18}N_2O$: 206.14191. Found 206.14180.

*N*-Phenyl(2-ferrocenylpropyl)amine (**3f**): $^1$H NMR (400 MHz, $d_6$-acetone) $\delta$ 7.2–7.1 (m, 2H, Ph), 6.7–6.6 (m, 3H, Ph), 4.7 (m, 1H, NH), 4.16 (m, 7H, 5H Cp+2H subst Cp), 4.12 (m, 2H, subst Cp), 3.22 (m, 1H, C*H*$_2$–NH), 3.09 (m, 1H, C*H*$_2$–NH), 2.82 (m, 1H, C*H*$CH_2$), 1.34 (d, $J = 6.9$ Hz, 2H, $CH_2$). $^{13}$C NMR (161 MHz, $d_6$-acetone) $\delta$ 149.5 (quat Ph), 129.7 (Ph), 116.9 (Ph), 113.1 (Ph), 93.6 (quat Cp), 69.0 (Cp), 67.94 (subst Cp), 67.84 (subst Cp), 67.76 (subst Cp), 66.4 (subst Cp), 51.9 ($CH_2$), 33.2 (CH), 19.1 ($CH_3$). GC–MS (EI, 70 eV) $m/z = 319$ [M+], 213, 153, 106, 89, 77, 46, 28. HRMS Calcd for $C_{19}H_{21}NFe$: 319.10233. Found 319.10198.