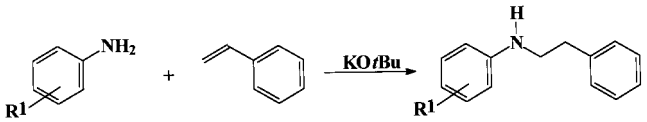
Base-Catalyzed Synthesis of *N*-(2-Arylethyl)anilines and Base-Promoted Domino Synthesis of 2,3-Dihydroindoles**

Matthias Beller,* Claudia Breindl, Thomas H. Riermeier, Martin Eichberger, and Harald Trauthwein

Dedicated to Professor Klaus Kühlein on the occasion of his 60th birthday

The hydroaminination of olefins to amines is in terms of atom economy the most efficient and most elegant method for the production of amines.[1] Hydroaminations of styrenes to 2-(arylethyl)amines are of particular interest, since this class of substances is of great importance as lead structures for psychodysleptics, strong analgesics, analeptics, antihistaminics, and anorectics.[2] Among the numerous pharmaceutical products that contain an $ArCH_2CH_2NR_2$ structual element are Fentanyl, Fenfluramin, Dimetinden, and Doxapram. Despite the fundamental advantages of hydroaminations—such as price, availabilitiy of the starting materials, and the avoidance of waste products—only a few base-catalyzed[3] and more recently metal-catalyzed aminations[4] of aromatic olefins are known. We have therefore investigated to what extent bases not used previously catalyze the hydroamination of styrene and functionalized styrenes. Furthermore, we were interested in the application of hydroaminations as part of new domino processes.[5]

Initially we were interested in the reaction of substituted anilines with styrene to give *N*-(2-phenethyl)anilines (Scheme 1), since the products could be converted comparatively easily into interesting heterocycles.[6] *N*-(2-Phenethyl)-anilines are also of current importance as pharmaceuticals—for example, Tromaril, which exhibits anti-inflammatory activity. Base-catalyzed reactions of aniline and styrene have been investigated previously by Wegeler and Pieper[3a] as well as by Schlott et al.[3c] Under "typical" reaction conditions (5–10 mol% *n*BuLi or lithium amide; THF, reflux) of base-catalyzed hydroaminations of styrene with aliphatic amines no reaction takes place, whereas a conversion of 70% of aniline is observed in the presence of 5–15 mol% sodium at 180–185 °C. With β-methylstyrene, under these reaction conditions the hydroamination product forms only in 10% yield.



Scheme 1. Base-catalyzed hydroaminations of styrene with substituted anilines.

As model system for the application of alternative base catalysts we investigated the reaction of styrene with aniline in more detail (Table 1). Here a 1:1 mixture of the starting materials in tetrahydrofuran as solvent in the presence of 10 mol% of a base catalyst was allowed to react in a pressure tube at 120 °C. After several hours the reaction mixture was allowed to cool to room temperature and terminated through the addition of water.

Table 1. Variation of the base catalyst in the reaction of styrene **2** with aniline **1**.[a]

Entry	Base	Cat. [mol %]	*T* [°C]	Amine: olefin	Yield[b] [%]
1	*n*BuLi	10	100	1:1	–
2	*n*BuLi/K_2CO_3	10/10	120	1:1	69
3	KO*t*Bu	10	120	1:1	85
4	LiO*t*Bu	10	100	1:1	–
5	NaO*t*Bu	10	100	1:1	–
6	K_2CO_3	10	100	1:1	–
7	KO*t*Bu	10	120	5:1	99
8	KO*t*Bu	5	120	2:1	96

[a] All reactions were carried out in Ace pressure tubes; reaction time 20 h; solvent THF. [b] Determined by GC analysis with hexadecane as internal standard.

In agreement with published results,[3c] no reaction of the starting materials occurred in the presence of 5–10 mol% *n*BuLi or lithium amide in THF under reflux. Even when the reaction was carried out at 120 °C under pressure no products were formed (Table 1, entry 1). It is assumed that the nucleophilicity of the lithium anilides which is lower than that of aliphatic amides, is no longer sufficient for an attack at the double bond of the styrene. Thus, we decided to prepare more ionic and therefore more reactive potassium anilides in situ, in order to increase the reactivity of the amide. Since the direct application of potassium anilides is not viable because of the sensitivity of the substances, we investigated to what extent an amination can be achieved by the addition of potassium salts to the above-mentioned reaction mixture. In fact styrene and aniline react in the presence of 10 mol% *n*BuLi and 10 mol% potassium carbonate regioselectively to give *N*-(2-phenethyl)aniline in 69% yield. We explain this finding by way of a side reaction in which the metal on the lithium anilides is exchanged to give trace amounts of the more reactive potassium anilides; the formation of mixed lithium–potassium anilides is likely.[7] Surprisingly, a subsequent screening of base catalysts showed that potassium *tert*-butylalcoholate is particularly suitable as catalyst for the hydroamination of styrene with aniline (Table 1). For instance, the corresponding *N*-(2-phenethyl)aniline **3** is obtained regioselectively in 85% yield together with traces of the doubly alkylated aniline (Table 1, entry 3) by using

[*] Prof. M. Beller, M. Eichberger[+]
Institut für Organische Katalyseforschung (IfOK)
an der Universität Rostock e.V.
Buchbinderstraße 5-6, D-18055 Rostock (Germany)
Fax: (+49) 381-4669324
E-mail: Matthias.Beller@ifok.uni-rostock.de
C. Breindl
Lehrstuhl für Anorganische Chemie
der Technische Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-289-13473
Dr. T. H. Riermeier, Dr. H. Trauthwein
Aventis Research and Technologies
Industriepark Höchst G830, D-65926 Frankfurt (Germany)
[+] Deceased 1997.

[**] Anti-Markownikov Functionalizations of Unsaturated Compounds, Part 4. We thank Dr. J. Herwig (Celanese) for helpful discussions and advice. Part 3: M. Beller, C. Breindl, *Tetrahedron* **1998**, *54*, 6359.

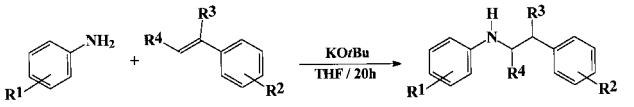
  1433-7851/98/3724-3389 $ 17.50+.50/0

10 mol % KO*t*Bu in THF at 120 °C (> 99.9 % regioselectivity). If an excess of aniline is used (2 – 5 equivalents relative to styrene), **3** is formed in 96 – 99 % yield and with > 99 % selectivity (Table 1, entries 7, 8). The amount of catalyst can be reduced to 5 mol % without any adverse effects on the product yields. An important advantage of the new procedure compared to the classical nucleophilic substitution of phenethyl halides with primary amines is the excellent chemoselectivity with which the secondary amine product **3** is obtained. For instance, no tertiary amination product even in trace amounts is detected with five equivalents aniline (relative to styrene).

In order to investigate the practicability of potassium *tert*-butylalcoholate as hydroamination catalyst, the reaction of aniline with styrene was carried out on a 50-g scale without the use of pressure in a glass flask in toluene as solvent under reflux with a reaction time of 24 h. After distillation **3** was obtained without further optimization in 62 % yield (59 g).

The scope of application of the new base catalyst for hydroaminations is demonstrated in the reaction of substituted anilines with different styrenes that are functionalized at the ring and the double bond (Table 2).

Table 2. KO*t*Bu-catalyzed hydroamination of aryl olefins with substituted anilines.[a]

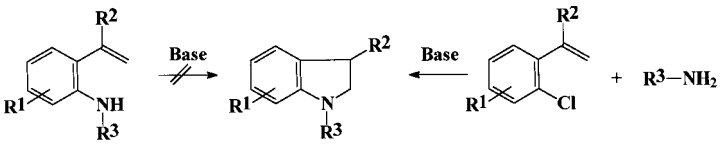


Entry	Amine	Olefin			Yield[b]	Product
	R^1	R^2	R^3	R^4	[%]	
1	H	H	H	H	85	**3**
2	4-F	H	H	H	75	**4**
3	2-OMe	H	H	H	85	**5**
4	H	4-Cl	H	H	72	**6**
5[c]	H	H	Me	H	34	**7**
6[c]	H	H	H	Me	50	**8**

[a] Reaction conditions: Amine (0.011 mol), olefin (0.011 mol), and 10 mol % KO*t*Bu (0.12 g) were heated in THF (10 mL) at 120 °C for 20 h in an Ace pressure tube. [b] Determined by GC analysis with hexadecane as internal standard. [c] Reaction temperature 160 °C.

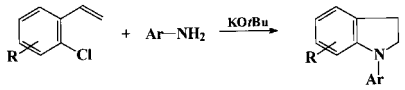
Aniline (Table 2, entry 1) and substituted anilines with electron-withdrawing or electron-donating substituents, even in the critical *ortho* position (Table 2, entries 2, 3) react in good yields (75 – 85 %) to give the desired products. Interestingly, hydroamination of α-methylstyrene and β-*trans*-methylstyrene (Table 2, entries 5, 6) can also be achieved, although the yields (34 and 50 %, respectively) are not optimized in this case.

In addition to the intermolecular base-catalyzed hydroamination, we have pursued the development of intramolecular variants of the method. As shown in Scheme 2, this has led to a new route to 2,3-dihydroindoles (indolines). The partial structure of the indole and of the indoline is found in numerous natural products and pharmacologically active substances such as Bufotenine or Lysergide.[2] Simple and viable synthesis routes to such substances are therefore of general interest.[8] Preliminary attempts at the realization of our concept as exemplified by the cyclization of 2-isopropenylaniline in the presence of different bases were however disapppointing, thus, we pursued an alternative route: By applying 2-halostyrenes a ring closure should be possible after hydroamination of the double bond by nucleophilic substitution of the suitably placed leaving group at the arene or by palladium-catalyzed C – N bond formation.[9] In fact the cyclization of 2-chlorostyrene with aniline (1.5 equiv) in the presence of three equivalents of potassium *tert*-butylalcoholate in toluene at 135 °C in the pressure tube gives *N*-phenyl-2,3-dihydroindole in 53 % yield! Under these reaction conditions, which have not been optimized, a series of substituted anilines can be converted (Table 3). Electron-withdrawing and electron-donating substituents on the aniline are tolerated without changing the yields. Structural variations are also possible on the styrene, for instance, *N*-(4-fluorophenyl)-4-chloro-2,3-dihydroindole is obtained by the reaction of commercially available 2,6-dichlorostyrene and 4-fluoroaniline in 50 % yield (isolated product, Table 3, entry 4). In order to minimize side reactions of the chloro substituents under the reaction conditions, the amount of amine in this reaction was reduced to 1.2 equivalents (relative to 2,6-dichlorostyrene) and that of the base to 1.5 equivalents (relative to 2,6-dichlorostyrene). In all domino reactions up to 10 % of the corresponding dehydrogenated reaction product (*N*-aryl indole) was clearly identified as a side product. The hydrogen acceptor necessary for this dehydrogenation appears to be the styrene used. The corresponding indoles are accessible in > 50 % yields by in situ dehydrogenation of the indolines with a suitable oxidation system.[10]



Scheme 2. Base-catalyzed and base-promoted cyclizations to give 2,3-dihydroindoles. R^2 = H, CH_3; R^3 = H, aryl.

Table 3. Domino hydroamination aryne cyclization reaction to give *N*-aryl indolines.



Entry	R	Ar	Yield [%]	Product
1	H	C_6H_5	53	**9**
2	H	4-FC_6H_4	54	**10**
3	H	2-$MeOC_6H_4$	58	**11**
4	6-Cl	4-FC_6H_4	50	**12**

With regard to the mechanism the new domino reaction proceeds by a base-catalyzed hydroamination and a subsequent intramolecular aryne reaction. Based on the comparison of the reactions of 2- and 3-chlorostyrene with aniline it could be shown that the cyclization indeed proceeds via an aryne intermediate. Both chlorostyrenes form the same aryne intermediate, thus *N*-phenyl-2,3-dihydroindole (**9**) is obtained

  1433-7851/98/3724-3390 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 24

in yields of between 50 and 55% regardless of the position of the halogen substituent.

A comparison of the new domino hydroamination aryne cyclization reaction with known cyclizations of 2-(2-chlorophenyl)ethylamines[11] clearly shows the superiority of the new method. The yields of the indoline products obtained are superior to the reported values by about a factor of 3.

KO*t*Bu-catalyzed hydroaminations of aromatic olefins with anilines make pharmacologically interesting *N*-(2-arylethyl)-anilines accessible with 100% atom economy and in a particularly viable manner in good to excellent yields. The excellent chemo- and regioselectivities are an important advantage over classical syntheses of N-substituted anilines. The use of 2- or 3-substituted halostyrenes as starting materials has enabled the synthesis of N-substituted indolines by a novel domino reaction. Very recent experiments indicate that this reaction is not limited to anilines, but that aliphatic amines also undergo analogous reactions.[12]

Experimental Section

Synthesis of *N*-phenyl-2,3-dihydroindole (**9**): In an Ace pressure tube (38 mL) 2-chlorostyrene (0.28 g, 2.0 mmol) and aniline (0.28 g, 3.0 mmol) were dissolved in toluene (10 mL) under argon. After addition of potassium *tert*-butylalcoholate (0.67 g, 6.0 mmol), the sealed reaction vessel was placed in an oil bath preheated to 135 °C and the reaction mixture was stirred vigorously. After 36 h the mixture was allowed to cool to room temperature and water (20 mL) was added with stirring. The aqueous phase was extracted three times with dichloromethane (10 mL). Subsequently the combined organic phases were dried over magnesium sulfate, and the solvent was removed under vacuum. The resulting crude product was separated by column chromatography with hexane as eluent. Compound **9** was obtained in 53% (0.21 g) yield. ^{1}H NMR (360 MHz, 25 °C, $CDCl_3$): $\delta = 7.32$ (dd, $^3J(H,H) = 8.0$, 7.1 Hz, 2H, *m*-Ph-H), 7.21 (d, $^3J(H,H) = 8.0$ Hz, 2H, *o*-Ph-H), 7.14 (d, $^3J(H,H) = 7.1$ Hz, 1H, Ar), 7.12 (d, $^3J(H,H) = 8.0$ Hz, 1H, Ar), 7.05 (dd, $^3J(H,H) = 8.0$, 7.5 Hz, 1H, Ar), 6.94 (t, $^3J(H,H) = 7.1$ Hz, 1H, *p*-Ph-H), 6.73 (dd, $^3J(H,H) = 7.5$, 7.1 Hz, 1H, Ar), 3.92 (t, $^3J(H,H) = 8.4$ Hz, 2H, NCH_2), 3.10 (t, $^3J(H,H) = 8.4$ Hz, 2H, CH_2); ^{13}C{^{1}H} NMR (90 MHz, 25 °C, $CDCl_3$): $\delta = 147.1$ (quart. Ph), 144.2 (quart. Ar-C-N), 131.2 (quart. Ar-C), 129.1 (*m*-Ph), 127.1 (Ar), 125.0 (Ar), 120.9 (Ar), 118.8 (Ar), 117.7 (*o*-Ph), 108.2 (*p*-Ph), 52.1 (NCH_2), 28.2 (CH_2); MS (70 eV): *m*/*z* (%): 195 (5) [M^+], 165 (70), 116, 91 (100), 77.

Received: May 12, 1998 [Z11845IE]
German version: *Angew. Chem.* **1998**, *110*, 3571 – 3573

Keywords: aminations · arynes · cyclizations · domino reactions · potassium

[1] Reviews: a) T. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675; b) J.-J. Brunet, D. Neubecker, F. Niedercorn, *J. Mol. Catal.* **1989**, *49*, 235; c) D. M. Roundhill, *Chem. Rev.* **1992**, *92*, 1; d) D. Steinborn, R. Taube, *Z. Chem.* **1986**, *26*, 349.

[2] E. Mutschler, *Arzneimittelwirkungen,* 7th ed., Wissenschaftliche Verlagsgesellschaft, Stuttgart, **1996**.

[3] R. Wegler, G. Pieper, *Chem. Ber.* **1950**, *83*, 1; b) N. Imai, T. Narita, T. Tsuruta, *Tetrahedron Lett.* **1971**, *38*, 3517; c) R. J. Schlott, J. C. Falk, K. W. Narducy, *J. Org. Chem.* **1972**, *37*, 4243; d) T. Narita, T. Yamaguchi, T. Tsuruta, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3825; e) T. Narita, N. Imai, T. Tsuruta, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1242; f) T. Fujita, K. Suga, S. Watanabe, *Aust. J. Chem.* **1974**, *27*, 531.

[4] a) B. Åkermark, J. E. Bäckvall, L. S. Hegedus, K. Zetterberg, *J. Org. Chem.* **1974**, *72*, 127; b) L. S. Hegedus, J. M. McKearin, *J. Am. Chem. Soc.* **1982**, *104*, 2444; c) A. L. Casalnuovo, J. C. Calabrese, D. Milstein, *J. Am. Chem. Soc.* **1988**, *110*, 6738; d) M. Deeba, M. E. Ford, T. A. Johnson, D. W. in *Catalysis of Organic Reactions*, Marcel Dekker, New York, **1990**, p. 241; e) D. Selent, D. Scharfenberg-Pfeiffer, G. Reck, R. Taube, *J. Organomet. Chem.* **1991**, *415*, 417; f) M. R. Gagné, L. Brad, V. P. Conticello, M. A. Giardello, C. L. Stern, T. J. Marks, *Organometallics* **1992**, *11*, 2003; g) A. L. Seligson, W. C. Trogler, *Organometallics* **1993**, *12*, 744; h) Y. Li, T. J. Marks, *Organometallics* **1996**, *15*, 3770; i) R. C. Larock, T. R. Hightower, L. A. Hasvold, K. P. Peterson, *J. Org. Chem.* **1996**, *61*, 3584; j) R. Dorta, P. Egli, F. Zurcher, A. Togni, *J. Am. Chem. Soc.* **1997**, *119*, 10857.

[5] Selected reviews on domino reactions: L. F. Tietze, U. Beifuß, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.

[6] a) D. Lesieur, S. Yous, P. Depreux, J. Andrieux, G. Adam, D. H. Caignard, B. Guardiola (ADIR et Cie., France), EP-B 527687 A2, **1992** [*Chem. Abstr.* **1993**, *118*, 254750e]; b) Z. Budai, P. Benko, L. Pallos (Egyesult Gyogyszer, Hungary), HU-B 155783 [*Chem. Abstr.* **1969**, *71*, 21854n]; c) J. G. Berger, W. K. Chang, J. A. Kozlowski, G. Zhou (Schering Corp., USA), US-A 5530125 A, **1992** [*Chem. Abstr.* **1994**, *120*, 134315m].

[7] a) L. Lochmann, J. Trekoval, *J. Organomet. Chem.* **1979**, *179*, 123; b) P. G. Williard, G. J. MacEwan, *J. Am. Chem. Soc.* **1989**, *111*, 7671; c) F. M. Mackenzie, R. E. Mulvey, *J. Am. Chem. Soc.* **1996**, *118*, 4721.

[8] a) B. Robinson, *The Fischer Indole Synthesis*, Wiley-Interscience, New York **1982**; b) L. S. Hegedus, *Angew. Chem.* **1988**, *100*, 1147; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113; c) G. W. Gribble, *Contemp. Org. Synth.* **1994**, *1*, 145; d) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**.

[9] a) F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969; b) J. F. Hartwig, S. Richards, D. Barañano, F. Paul, *J. Am. Chem. Soc.* **1996**, *118*, 3626; c) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217; d) J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7010; e) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215; f) N. P. Reedy, M. Tanaka, *Tetrahedron Lett.* **1997**, *38*, 4807; g) M. Beller, T. H. Riermeier, C.-P. Reisinger, W. A. Herrmann, *Tetrahedron Lett.* **1997**, *38*, 2073; h) M. S. Driver, J. F. Hartwig, *Organometallics* **1997**, *16*, 5706; i) S. Wagaw, R. A. Rennels, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 8451; j) M. Beller, T. H. Riermeier, A. Zapf, *Top. Catal.* **1997**, *4*, 301; k) R. A. Singer, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 213; l) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722.

[10] a) K. Aoki, A. J. Peat, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 3068; b) M. Beller, C. Breindl, T. H. Riermeier, unpublished results.

[11] a) R. Huisgen, H. König, *Chem. Ber.* **1959**, *92*, 203; b) R. Huisgen, H. König, N. Bleeker, *Chem. Ber.* **1959**, *92*, 424; c) H. König, R. Huisgen, *Chem. Ber.* **1959**, *92*, 429; d) H. Iida, S. Aoyagi, C. Kibayashi, *J. Chem. Soc. Perkin 1* **1975**, 2502.

[12] M. Beller, C. Breindl, unpublished results.

  1433-7851/98/3724-3391 $ 17.50+.50/0