N-Dealkylation of aliphatic amines and selective synthesis of monoalkylated aryl amines†

Dirk Hollmann, Sebastian Bähn, Annegret Tillack and Matthias Beller*

Received (in Cambridge, UK) 25th February 2008, Accepted 7th April 2008
First published as an Advance Article on the web 8th May 2008
DOI: 10.1039/b803114b

Highly selective alkyl transfer processes of mono-, di- and trialkyl amines in the presence of the Shvo catalyst have been realized; in addition, a general method for *N*-alkylation of aniline with di- and trialkyl amines is presented.

Metabolic *N*-dealkylation is an important biotransformation in nature. Such processes are catalyzed by monooxygenases such as Cytochrome P 450,[1] although these enzymes are mainly known for oxidation reactions such as hydrocarbon hydroxylation and alkene epoxidation.[2] Ever since the identification of the first dealkylation catalyst,[3] the understanding and the development of new systems is of significant interest, albeit only a few methods are known.[4]

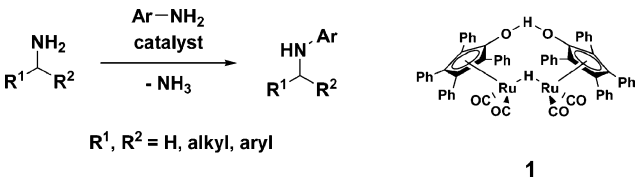
In recent years, the synthesis of aniline derivatives has received high attention. Aromatic amines play an outstanding role as biologically active compounds.[5] In addition, for industry the development of improved syntheses is of enormous interest. Among the various methods, the widely used palladium- and copper-catalyzed aminations of aryl halides (Buchwald–Hartwig aminations) became the most general method to form C–N bonds of aromatic amines.[6,7] Apart from well established aryl halides, tosylates and triflates, simple anilines constitute available and cheap substrates.

Recently, we have described the first arylation of aliphatic amines with anilines leaving ammonia as the only side-product (Scheme 1).[8] In the presence of the so-called Shvo catalyst **1**[9,10] a variety of functionalized anilines and primary amines react smoothly to give the corresponding aryl amines in excellent yields.[11]

In this communication we present our new studies of the dealkylation of aliphatic amines combined with the selective synthesis of monoalkylated aniline derivates. For the first time it is shown that starting from primary, secondary and tertiary amines, a complete and selective transfer of all alkyl groups takes place highly selectively.

As a starting point of our investigations we compared the amination of aniline with *n*-hexylamine, di-*n*-hexylamine and tri-*n*-hexylamine. To our surprise, all the different hexylamines are converted in high yields (75–87%) to the same *N*-hexylaniline (Scheme 2)! Especially remarkable is the activation and alkyl transfer of the tertiary amine.

Upon optimization we found that two equivalents of aniline per hexyl group in the presence of 1 mol% of the Shvo catalyst



Scheme 1 Arylation of aliphatic amines using the Shvo catalyst **1**.

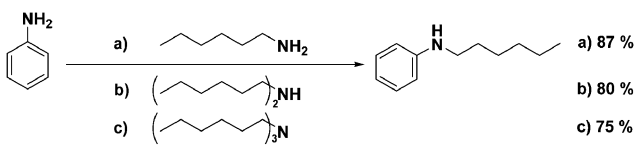
in *tert*-amyl alcohol gave the best results. Notably, a mixture of mono-, di- and tri-*n*-hexylamine is also converted highly selectively to give *N*-hexylaniline (Scheme 3).

We believe that the reaction proceeds through a hydrogen borrowing mechanism as proposed by Williams,[12] which involves dehydrogenation of the amine, imine formation, nucleophilic attack by the aniline, elimination of ammonia, and final hydrogenation. To confirm this mechanism, a reaction was carried out with labeled aniline-^{15}N and dibenzylamine. The resulting *N*-benzylaniline was obtained in 96% isolated yield and showed >99% of ^{15}N-labelling (Table 1, entry 5).[13]

Of note, in this alkyl transfer reactions the hydrogen donors for the final hydrogenation step are the primary, secondary and tertiary amines. Hence, no additional hydrogen or hydrogen transfer reagent is required in the process. Advantageously there is no need for high-pressure equipment which is used often in hydrogenation reactions such as reductive amination.

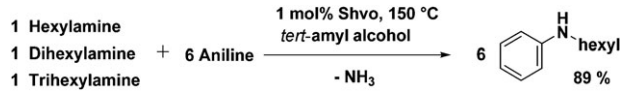
As shown in Scheme 4 under the reaction conditions, equilibrium between the mono-, di- and trialkyl amines is observed. All alkyl amines are converted into each other and can be monitored until the reaction is finished (reversible steps).[14,15] However, by reaction of the respective imines or iminium species with aniline, the corresponding *N*-hexylaniline is formed in an irreversible step. Thus, reaction of tri-*n*-hexylamine with aniline yields exclusively *N*-hexylaniline and di-*n*-hexylamine. Then, the next alkyl group is transferred. Finally, the reaction of *n*-hexylamine with aniline, results in the formation of ammonia (irreversible step).

Next, we were interested in the generality of the dealkylation process and their application in the *N*-alkylation of aniline with various di- and trialkyl amines. Using polyalkylated short-chain amines, this method provides a convenient access



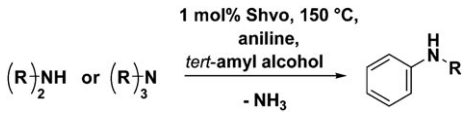
Scheme 2 Amination of aniline with different alkyl amines (isolated yields are based on hexyl groups).

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, D-18059 Rostock, Germany.
E-mail: matthias.beller@catalysis.de; Tel: +49 381 1281 113
† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b803114b



Scheme 3 Amination of aniline with a mixture of hexylamines (isolated yields are based on hexyl groups).

Table 1 Amination of aniline with di- and trialkyl amines



Entry	Amine	Product	Yield (%)
1	Triethylamine	R =	95
2	Dipropylamine	R =	96
3	Diisopropylamine	R =	92
4	Dibenzylamine	R = Ph	98
5	Dibenzylamine	R = Ph	92[b]
6	Tribenzylamine	R = Ph	21[c]
7	Dicyclohexylamine	R =	99
8	H_2N O	R = O	92
9	HN (O)2	R = O	91
10	N (O O)3	R = O O	74

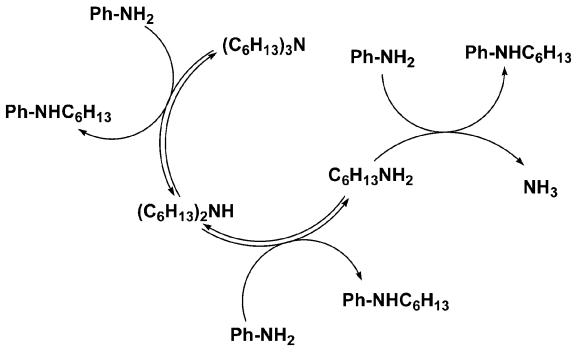
[a] *Reaction conditions*: 1 mol% Shvo catalyst per alkyl group, 1 mmol mono-, di- or trialkyl amine, 2 mmol aniline per alkyl group, 24 h, *tert*-amyl alcohol, 150 °C. Isolated yields are based on alkyl groups. [b] Aniline-^{15}N; product content of ^{15}N > 99%. [c] 78% recovered tribenzylamine.

to monoalkylated anilines with short-chain alkyl groups. For comparison, in the Buchwald–Hartwig reaction, these compounds have to be synthesized from the corresponding volatile amines using a sealed tube technique,[16] benzylmethylamine or methylammonium chloride.[17]

Instead of ethylamine (bp, 16.6 °C), propylamine (bp, 48 °C), isopropylamine (bp, 33.5 °C), we are able to use the convenient non-volatile triethylamine, dipropylamine and diisopropylamine (Table 1, entries 1–3). Excellent yields of 92–98% are observed. In addition, different alkyl amines and aminoalkoxyethers are converted in excellent selectivity and high yields (Table 1, entries 4, 5, 7–10). So far, only the full conversion of tertiary benzylic amine poses a challenge (Table 1, entry 6).

In summary, we have presented the first selective *N*-alkylation with mono-, di- and trialkyl amines. This tool provides a general access to the synthesis of monoalkylated aryl amines *via* alkyl transfer and acts as a model for metabolic *N*-dealkylations. This novel reaction is highly atom efficient leaving only ammonia as side-product and can be conveniently carried out. Further applications with functionalized anilines as well as other alkyl amines can be easily envisioned.

This work has been supported by the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (DFG BE 1931/16-1, Leibniz-price) and the state of Mecklenburg-Vorpommern.



Scheme 4 Equilibrium and selective transfer of alkyl groups.

Notes and references

1. P. Hlavica, *Drug Metab. Rev.*, 2002, **34**, 451.
2. Review of P450 enzymes: D. Meyer, T. Leifels, L. Sbaragli and W.-D. Woggon, *Biochem. Biophys. Res. Commun.*, 2005, **338**, 372; W.-D. Woggon, *Top. Curr. Chem.*, 1997, **184**, 39; *Cytochrome P450 Structure, Mechanism and Biochemistry*, ed. P Ortiz de Montellano, Plenum Press, New York, London, 2nd edn, 1995.
3. T. Omura and R. J. Sato, *J. Biol. Chem.*, 1964, **239**, 2370.
4. In organic synthesis only a few dealkylation reactions are known: for the von Braun reaction, Polonovski demethylation reaction, and others, see: K. McCamley, J. A. Ripper, R. D. Singer and R. J. Scammells, *J. Org. Chem.*, 2003, **68**, 9847, and references therein.
5. *The Chemistry of Anilines*, ed. Z Rappoport, Wiley-Interscience, New York, 2007, vol. 1.
6. For recent examples of palladium-catalyzed aminations, see: E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; C. A. Fleckenstein and H. Plenio, *Organometallics*, 2007, **26**, 2758; S. P. Nolan, *Chem.–Eur. J.*, 2006, **12**, 5142; J. F. Hartwig, *Synlett*, 2006, 1283; O. Navarro, N. Marion, J. Mei, S. L. Buchwald, C. Mauger, G. Mignani and U. Scholz, *Adv. Synth. Catal.*, 2006, **348**, 23; Q. Shen, S. Shekhar, J. P. Stambuli and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2005, **44**, 1371. For reviews, see: B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 1599; J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi, Wiley-Interscience, New York, 2002, vol. 1, p. 1051; B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125.
7. Copper-catalyzed aminations of aryl halides, see: M. Taillefer, N. Xia and N. Ouali, *Angew. Chem., Int. Ed.*, 2007, **46**, 934; D. Jiang, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2007, **72**, 672; X. Guo, H. Rao, H. Fu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2006, **348**, 2197; H. Zhang, Q. Qai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164; I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400.
8. D. Hollmann, S. Bähn, A. Tillack and M. Beller, *Angew. Chem., Int. Ed.*, 2007, **46**, 8291.
9. R. Karvembu, R. Prabhakaran and N. Natarajan, *Coord. Chem. Rev.*, 2005, **249**, 911; Y. Shvo, D. Czarkie and Y. Rahamim, *J. Am. Chem. Soc.*, 1986, **108**, 740; Y. Shvo and R. M. Laine, *J. Chem. Soc., Chem. Commun.*, 1980, 753.
10. A. Comas-Vives, G. Ujaque and A. Lledos, *Organometallics*, 2007, **26**, 4135; J. S. M. Samec, A. H. Ell, J. B. Åberg, T. Privalov, L. Eriksson and J.-E. Bäckvall, *J. Am. Chem. Soc.*, 2006, **128**, 14293; J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237; J. B. Åberg, J. S. M. Samec and J.-E. Bäckvall, *Chem. Commun.*, 2006, 2771; C. P. Casey, G. A. Bikzhanova, Q. Cui and I. A. Guzei, *J. Am. Chem. Soc.*, 2005, **127**, 14062; J. S. M. Samec, L. Mony and J.-E. Bäckvall, *Can. J. Chem.*, 2005, **83**, 909; J. S. M. Samec, A. H. Ell and J.-E. Bäckvall, *Chem. Commun.*, 2004, 2748; C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi and M. Kavana, *J. Am. Chem. Soc.*, 2001, **123**, 1090.
11. In an ACE-pressure tube under an argon atmosphere the Shvo catalyst (0.02 mmol) and the corresponding alkyl amine (2 mmol

of alkyl groups) were dissolved in *tert*-amyl alcohol (0.5 ml) and aniline (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 was easily purified by column chromatography with pentane–ethyl acetate (20 : 1).

12. For an excellent review of the hydrogen borrowing methodology, see: M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555.
13. Similar observations have been made in the amination of alcohols: D. Hollmann, A. Tillack, D. Michalik, R. Jackstell and M. Beller, *Chem.–Asian J.*, 2007, **3**, 403; A. Tillack, D. Hollmann, D. Michalik and M. Beller, *Tetrahedron Lett.*, 2006, **47**, 8881; M. H. S. A. Hamid and J. M. J. Williams, *Chem. Commun.*, 2007, 725; G. Cami-Kobeci, P. A. Slatford, M. K. Whittlesey and J. M. J. Williams, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 535.
14. A. Miyazawa, K. Saitou, K. Tanaka, T. M. Gädda, M. Tashiro, G. K. S. Prakash and G. L. Olah, *Tetrahedron Lett.*, 2006, **47**, 1437.
15. C. W. Jung, J. D. Fellmann and P. E. Garrou, *Organometallics*, 1983, **2**, 1042.
16. J. J. Li, Z. Wang and L. H. Mitchell, *J. Org. Chem.*, 2007, **72**, 3606.
17. M. Kreis, C. J. Friedmann and S. Braese, *Chem.–Eur. J.*, 2005, **11**, 7387.