DOI: 10.1002/adsc.201000575

Dimethyl Sulfoxide/Potassium Hydroxide: A Superbase for the Transition Metal-Free Preparation of Cross-Coupling Products

Yu Yuan,[a,*] Isabelle Thomé,[b] Seok Hwan Kim,[b,c] Duanteng Chen,[a] Astrid Beyer,[b] Julien Bonnamour,[b] Erik Zuidema,[b] Sukbok Chang,[c] and Carsten Bolm[b,*]

[a] College of Chemistry and Chemical Engineering, Yangzhou University, 225002 Yangzhou, People's Republic of China
[b] Institut für Organische Chemie der RWTH Aachen University, Landoltweg 1, 52056 Aachen, Germany
Fax: (+49)-241-809-2391; phone: (+49)-241-809-4675; e-mail: carsten.bolm@oc.rwth-aachen.de
[c] Department of Chemistry and Molecular-Level Interface Research Center, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea

Received: July 21, 2010; Revised: August 25, 2010; Published online: October 28, 2010

Abstract: Potassium hydroxide (KOH) in dimethyl sulfoxide (DMSO) forms a superbasic medium that allows one to access cross-coupling products from reactions between aryl halides with various sulfur-, oxygen- and nitrogen-based nucleophiles under transition metal-free conditions.

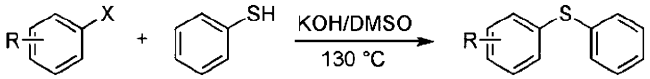
Keywords: arylation; catalysis; cross-coupling; dimethyl sulfoxide/potassium hydroxide (DMSO/KOH); superbase; transition metal-free conditions

Cross-coupling reactions belong to the most relevant transformations in modern organic synthesis.[1] For N-, O-, and S-arylations numerous protocols have been developed, and most commonly palladium complexes and copper salts are utilized as catalysts.[2] To our surprise, many other metal species such as salts, oxides and nanoparticles of indium,[3a,b] zinc,[3a] cadmium,[3c] lanthanum,[3d] just to mention a few, have recently been reported to be catalytically active as well.[4] Looking at the reaction conditions and comparing details indicated that two components played a critical role in most of these prosesses: KOH and DMSO. N-,[5] O-,[6] S-,[7] and C-arylations[8] are also known to occur without the support of a metal catalyst. For electron-poor aryl fluorides, chlorides and bromides, the reactions proceed through the well-known S_NAr mechanism.[9] For these transformations, dipolar aprotic solvents such as DMF, NMP and DMSO are the media of choice, especially when anionic nucleophiles are arylated.[10] Less activated aryl halides that do not readily undergo nucleophilic aromatic substitution by the S_NAr mechanism, can be used as arylating agents of nucleophiles under strongly basic reaction conditions. In this case, the reactions involve reactive aryne intermediates that are formed by *ortho*-deprotonations of the aryl halides followed by halide eliminations.[11]

In many cases, strong bases such as metal amides or metal *tert*-butoxides are used to facilitate the reactions. We wondered if also the simple and inexpensive mixture of KOH and DMSO would be a medium for arylation reactions of S-, O-, and N-based nucleophiles. This combination of base and solvent has extensively been investigated by Trofimov.[12] His studies of the physical organic properties and reactivity of KOH/DMSO mixtures revealed an extraordinary basicity (pK_a 30–32) that was suggested to result from a synergism of two bases.[13] To describe the phenomenon, the term 'superbase media' was introduced. In the light of the presented literature data we hypothesized that this *in situ* formed superbase would be active enough to allow arylations of nucleophiles leading to cross-coupling products under transition metal-free conditions. Here, we report our findings of this study.[14]

As a starting point, arylations of thiols using KOH in DMSO were studied (Table 1).[15] To our delight, reactions between thiophenol and electron-poor aryl halides were greatly facilitated leading to the corresponding cross-coupling products in good to high yields (entries 1 and 2).[16,17] The reactions had to be performed at 130 °C, because at lower temperature (110 °C) the conversions remained incomplete. Also less activated iodo- and bromobenzenes coupled well providing diphenyl sulfide in 95 and 96% yield, respectively (entries 3 and 4). Chlorobenzene, which was expected to be more reactive in a substitution reaction proceeding by the S_NAr mechanism, afforded the product in only 60% yield (entry 5). This result as well as the formation of regioisomeric mixtures in reactions of the more electron-rich 2- and 4-substituted tolyl and anisyl halides (entries 6–11) pointed to the involvement of aryne-type intermediates.

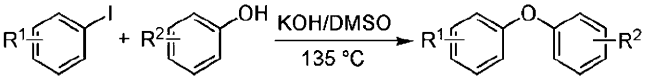
Table 1. Intermolecular S-arylations.[a]



Entry	R	X	Time [h]	Yield [%][b]	Isomeric ratio[c,d]
1	4-NO_2	I	6	55	
2	2-NO_2	I	24	98	
3	H	I	6	95	
4	H	Br	24	96	
5	H	Cl	24	60	
6	4-Me	I	24	95	*p*:*m* = 51:49
7	4-Me	Br	24	98	*p*:*m* = 51:49
8	2-Me	I	24	92	*p*:*m* = 52:48
9	2-Me	Br	24	90	*p*:*m* = 52:48
10	4-OMe	I	24	88	*p*:*m* = 50:50
11	4-OMe	Br	24	56	*p*:*m* = 51:49
12	3-OMe	I	24	70	

[a] *Reaction conditions:* aryl halide (1.1 mmol), thiophenol (1.0 mmol), KOH (2.0 mmol), DMSO (2 mL), 130 °C, argon atmosphere.
[b] After column chromatography.
[c] Determined using gas chromatography.
[d] *p* = para, *m* = meta, *o* = ortho.

Table 2. Intermolecular O-arylations.[a]



Entry	R^1	R^2	Time [h]	Yield [%][b]	Isomeric ratio[c]
1[d]	4-NO_2	H	24	82	
2[d,e]	4-NO_2	H	24	81	
3[d]	4-NO_2	4-OMe	24	52	
4	4-NO_2	4-OMe	24	85	
5	4-NO_2	4-NO_2	24	27[f]	
6	4-Me	H	72	50	*m*:*p* = 46:54
7	2-Me	H	48	52	*o*:*m* = 49:51

[a] *Reaction conditions:* aryl halide (1.0 mmol), phenolic substrate (0.5 mmol), KOH (1.0 mmol), DMSO (1 mL), 135 °C, argon atmosphere.
[b] After column chromatography.
[c] *p* = para, *m* = meta, *o* = ortho.
[d] Aryl halide (0.5 mmol) and phenolic substrate (1 mmol) were used.
[e] Cs_2CO_3 was used instead of KOH.
[f] Together with 8% of 4-nitrothioanisole.

For both *ortho*- and *para*-substituted electron-rich aryl halides, the isomeric ratio of the products was essentially 1:1. Although for 3-methoxyiodobenzene the aryne mechanism would allow for the formation of three different isomers, only a single isomer of the final product was obtained (entry 12), in line with previous studies involving this substrate.[11] The 3-methoxy group activated this substrate towards both the direct halide substitution by the S_NAr mechanism and the deprotonation of the substrate needed for the aryne formation. In the second case, deprotonation should occur on *ortho*- and *para*-positions to the methoxy group, which seems to be completely inhibited by the strong inductive and resonance effect of methoxy group. In contrast, 4-methoxyiodobenzene, which has protons on the *meta*-position of the methoxy group for the formation of aryne afforded two isomers.

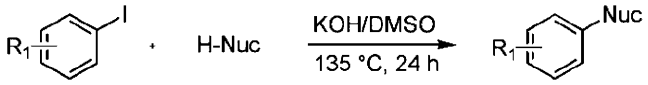
Encouraged by these results, other C–X bond-forming reactions were studied. Less acidic ($pK_a = 18.0$[18a]) and nucleophilic phenol could be arylated with 4-nitroiodobenzene in KOH/DMSO providing the corresponding diaryl ether in 82% yield (Table 2, entry 1). For this substrate combination, even the weaker base Cs_2CO_3 could be employed (entry 2). The more electron-rich 4-methoxyphenol was coupled with KOH as base (entries 3 and 4). In this case, the relative amounts of the two substrates and the base proved to be important. Probably, more base was needed to propagate the deprotonation of this less acidic substrate ($pK_a = 19.1$[18a]). The low yield in the reaction between 4-nitroiodobenzene and 4-nitrophenol (entry 5) could be explained by an extensive decomposition of the product under the reaction conditions. After 24 h, the desired diaryl ether was obtained in only 27% yield, along with 8% of 4-nitrothioanisole.[19] When the reaction mixture was allowed to react for additional 48 h, the thiomethyl-substituted compound was the only product (51% yield).

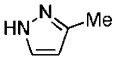
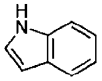
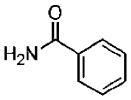
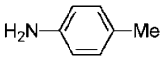
The reactions between phenol and the more electron-rich 4-methyl- and 2-methylphenyl iodides required longer reaction times (entries 6 and 7). As observed in the S-arylations and indicative for an aryne mechanism, approximately 1:1 mixtures of regioisomers were obtained with these aryl halides. Attempts to arylate benzylic and aliphatic alcohols with either electron-rich or electron-poor aryl halides remained unsuccessful. Probably, the solvent/base system was not basic enough to sufficiently deprotonate these nucleophiles under the applied conditions.[18b]

Next, reactions of commonly used nitrogen-based nucleophiles were investigated. For two reasons these were expected to be more challenging. Firstly, most substrates had higher pK_a values in DMSO than the thiols and phenols studied above,[18c] and consequently, their deprotonations were more difficult. If the aryne formation was too facile compared to the generation of the anionic nucleophile, decomposition of the aryl halide could occur. Secondly, in the case of heterocyclic or anilinic substrates, the negative charge generated upon deprotonation was (partly) delocalized over the aromatic ring, leading to a significant decrease of the anion nucleophilicity.

Despite these uncertainties, 3-methylpyrazole ($pK_a \approx 20$[18c]) reacted with 4-nitroiodobenzene and iodo-

Table 3. Intermolecular N-arylations.[a]



Entry	R_1	H-Nuc	Yield [%][b]
1	4-NO_2		51
2	H		28
3	4-NO_2		0
4	H		31
5	H		10
6	4-NO_2		0
7	H		0
8	4-NO_2		0
9	4-NO_2		57
10	H		44

[a] *Reaction conditions:* aryl halide (1.0 mmol), nucleophile (0.5 mmol), KOH (1.0 mmol) in DMSO (1 mL), 135 °C, 24 h.

[b] After column chromatography.

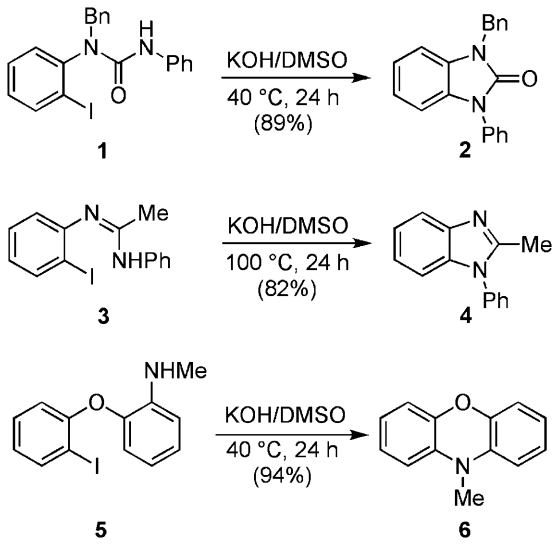
benzene providing the corresponding products in 57 and 28% yield, respectively (Table 3, entries 1 and 2). Surprisingly, indole was not arylated with 4-nitroiodobenzene (entry 3), despite being only slightly more basic ($pK_a = 21.0$[18c]) than 3-methylpyrazole. Probably the deprotonation of indole occurred, but the resulting anion was not nucleophilic enough. Consequently, 4-nitroiodobenzene decomposed faster than it could react with the indolate. Confirming this hypothesis, the more stable iodobenzene and the deprotonated indole reacted providing the expected product (entry 4), albeit in low yield (31%). Probably because of their high pK_a values in DMSO (of 23.3 and 30.6,[18c] respectively) in combination with a reduced nucleophilicity of the anionic intermediates due to charge delocalization, use of benzylamide and 4-methylaniline as N-nucleophile proved unproductive (enties 5–7). 2-Oxazolidinone ($pK_a = 20.8$[18d]) decomposed under the reaction conditions (entry 8).

In light of these results we were initially surprised to note that under the same reaction conditions pyrrolidine (with a pK_a of 44 in DMSO[18e]) was arylated by both electron-poor and electron-rich aryl halides (entries 9 and 10). However, these results could be explained assuming that the highly localized and high-energy lone pair of pyrrolidine allowed it to participate in the reaction without prior deprotonation, as generally accepted for the nucleophilic aromatic substitution of electron-poor aryl halides with sp^3-hybridized amines.[5b] Consequently, deprotonation might occur after the nucleophilic attack, altering the reaction path for this substrate to a significant extend.

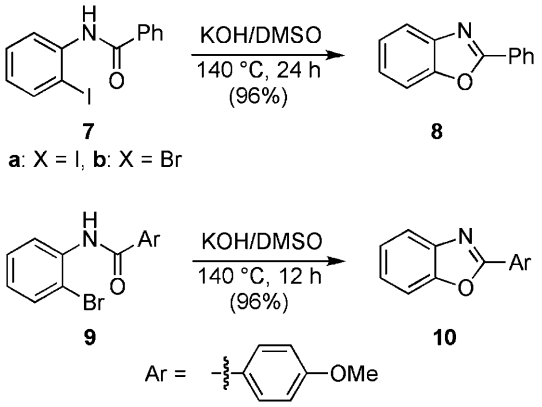
Because of the interest in metal-free routes towards heterocyclic compounds for the production of pharmaceutical and agrochemical compounds,[20] we applied the KOH/DMSO-based protocol to the formation of heterocycles through intramolecular N-arylation. To this end, compounds **1**, **3** and **5** were synthesized by transition metal-free procedures, and subsequently subjected to the mixture of KOH and DMSO. To our delight, the intramolecular C–N couplings proved highly efficient in all three cases, leading to the formation of the corresponding 5- and 6-membered heterocycles **2**, **4** and **6** in yields of 89, 82 and 94%, respectively (Scheme 1). In two cases the reaction temperature could even be as low as 40 °C, without affecting the overall yield. Note that for the cyclization of compound **5** the presence of the N-methyl substituent proved crucial. Hence, the analogous compound containing a primary amino group did not cyclize. When the methyl group was replaced by an acetyl moiety, the cyclization proceeded under loss of the acetyl group affording a light-sensitive product, which readily decomposed.

Finally, intramolecular O-arylations were tested. Using *N*-(2-iodophenyl)benzamide (**7a**) as starting material, the corresponding benzoxazole **8** was isolated in 96% yield after stirring for 24 h at 140 °C in DMSO/KOH (Scheme 2). Almost the same yield (94%) was achieved when K_2CO_3 was used instead of KOH. Only 11% yield of **8** resulted from the cyclization of arylbromide **7b** in DMSO/KOH.[21]

To our surprise, 4-methoxybenzamide **9** proved much more reactive, and this bromo-substituted derivative led to the corresponding benzoxazole **10** in 96% yield after only 12 h (in KOH/DMSO at 140 °C). Diminished yields were observed at lower temperatures.



Scheme 1. Intramolecular N-arylations.



Scheme 2. Intramolecular O-arylations.

In conclusion, we have shown that a simple and inexpensive mixture of KOH in DMSO can be used for transition metal-free arylations of nucleophiles. The *in situ* generated superbasic medium allows efficient C–S, C–O, and to a lesser extent, C–N bond formations. As was observed in other studies on nucleophilic aromatic substitutions,[11] the product yield and regioselectivity strongly depend on the basicity and nucleophilicity of the nucleophile and the nature of the aryl halide. Intramolecular reactions proved especially efficient, allowing the transition metal-free formation of heterocycles at close to ambient temperature.[22]

Experimental Section

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AVANCE 600, a Varian Mercury 300 or a Varian Inova 400 spectrometer, in $CDCl_3$ using TMS as an internal standard. Infrared spectra were recorded on a Bruker TENSOR 27 FT-IR spectrophotometer (KBr) or on a Perkin–Elmer FT-IR Spectrum 100 (neat). HR-MS were recorded on a FinniganMAT 95 spectrometer (ESI). Elemental analyses were measured on an Elementar Vario EL instrument. GC was performed on an AGILENT 6890N GC chromatograph.

General Procedure for S-Arylations

A typical experiment was carried out in a Schlenk tube fitted with a condenser. The aryl halide (1.1 mmol) was added to the mixture of KOH (112 mg, 2.0 mmol) and the thiol (1.0 mmol) in freshly distilled DMSO (2 mL) under argon. The mixture was stirred at 130 °C, and the reaction was monitored by GC and TLC. When the conversion was complete, the reaction mixture was cooled to room temperature. After pouring the mixture into water, ethyl acetate was added and the two phases were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent the residue was purified by column chromatography to obtain the corresponding product. The spectral data of all products corresponded to reported data or those obtained for commercial samples of the products.

General Procedure for the Intermolecular O- and N-Arylations

In a typical experiment, a sealable tube equipped with a magnetic stir bar was charged with the aryl halide (1.0 mmol), KOH (56 mg, 1.0 mmol) and, if a solid, the O- or N-nucleophile (0.5 mmol). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. Dry DMSO (1 mL) and other liquid reaction components were then added by syringe. The septum was replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath at 135 °C for the stated reaction time. After pouring the mixture into water, ethyl acetate was added and the two phases were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent the residue was purified by column chromatography to obtain the corresponding product.

The spectral data of all products corresponded to reported data or those obtained for commercial samples of the products.

Procedures for the Intramolecular N-Arylations (Affording Previously Unknown Products)

1-Benzyl-3-phenyl-1*H*-benzoimidazole-2(3*H*)-one (2): 1-Benzyl-1-(2-iodophenyl)-3-phenylurea (**1**)[23] (100 mg, 0.233 mmol) and KOH (26 mg, 0.47 mmol, 2.0 equiv.) were placed in a sealable tube, and dry DMSO (1.5 mL) was added under an argon atmosphere. The tube was sealed with a teflon-coated screw cap, and the mixture was stirred at 40 °C for 24 h. Then, the reaction mixture was cooled to room temperature and water (2 mL) and ethyl acetate (4 mL) were added. The two phases were separated and the aqueous layer was extracted with ethyl acetate (3×3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The product was purified by silica gel column chromatography (pentane/ethyl acetate 10:1) to afford the product as a pale yellow solid; yield: 62 mg (0.21 mmol, 89%); mp 99.8–100.7 °C. ^{1}H NMR (400 MHz, DMSO): $\delta = 7.58$ (d, $J = 4.2$ Hz, 4H), 7.49–7.43 (m, 1H), 7.41 (d, $J = 7.1$ Hz, 2H), 7.35 (t, $J = 7.4$ Hz, 2H), 7.29–7.24 (m, 1H), 7.21 (d, $J = 7.4$ Hz, 1H), 7.12–7.06 (m, 1H), 7.04 (d, $J = 4.0$ Hz, 2H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, DMSO): $\delta = 152.4$, 136.5, 134.2, 129.2, 128.7, 128.6, 128.4, 127.4, 127.30, 127.25, 125.8, 121.7, 121.3, 108.5, 108.1, 43.8; IR (KBr): $\nu = 3054$, 1701, 1593, 1484, 1397, 1223, 1172, 739, 697 cm^{-1}; MS (EI): *m/z* (%) = 301 ([M+H]$^+$, 21), 300 ([M]$^+$, 100), 209 (5), 167 (10), 91 (57), 65 (5); elemental analysis calcd. for $C_{20}H_{16}N_2O$: C 79.98, H 5.37, N 9.33; found: C 79.76, H 5.34, N 9.26.

10-Methyl-10*H*-phenoxazine (6): A sealable tube equipped with a magnetic stir bar was charged with 2-(2-iodophenoxy)-*N*-methylaniline (**5**, 100 mg, 0.31 mmol, 1.0 equiv.) and KOH (35 mg, 0.62 mmol, 2.0 equiv.). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. Dry DMSO (1 mL) was added by syringe. The septum was then

replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath at 40 °C for 24 h. The mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The resulting solution was directly filtered through a pad of silica. Water (2 mL) and ethyl acetate (4 mL) were added. Then the two phases were separated. The aqueous layer was extracted with ethyl acetate (3× 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the *N*-arylated product, which was purified by silica gel chromatography (pentane/ethyl acetate 10:1) to afford the corresponding product as a pale orange liquid; yield: 57 mg (0.29 mmol, 94%). ^{1}H NMR (300 MHz, DMSO): δ = 6.91–6.82 (m, 2H), 6.69 (d, J = 6.4 Hz, 6H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ = 145.1, 135.1, 124.6, 121.3, 115.3, 112.5, 31.1. IR ($CHCl_3$): ν = 2918, 1489, 1360, 1269, 740 cm^{-1}; HR-MS (ESI): m/z = 197.0835, calcd. for $C_{13}H_{11}NO$: 197.0839.

General Procedure for the Intramolecular O-Arylations

As for the intermolecular O-arylations, but using 0.5 mmol of the aryl halide and 56 mg (1.0 mmol) of KOH in DMSO (1.0 mL) at 140 °C. The spectral data of the products corresponded to reported data.

Synthetic Procedures and Analytical Data for Other Previously Unknown Products

***N′*-(2-Iodophenyl)-*N*-phenylacetimidamide (3):** To a solution of *N*-(2-iodophenyl)acetamide[24] (700 mg, 2.68 mmol) and 2,6-lutidine (0.68 mL, 0.63 g, 5.90 mmol, 2.2 equiv.) in dry dichloromethane was slowly added triflouromethanesulfonic anhydride (0.49 mL, 0.83 g, 2.50 mmol, 1.1 equiv.) at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 45 min. Then, aniline (0.37 mL, 0.37 g, 4.02 mmol, 1.5 equiv.) was added dropwise, and the solution was stirred for 17 h. Subsequently, an aqueous solution of $NaHCO_3$ (10 mL) and dichloromethane (10 mL) were added. The aqueous layer was extracted with dichloromethane (3×5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure the product was purified by column chromatography (pentane/ethyl acetate 9:1) to give **3** as a white solid; yield: 490 mg (1.46 mmol, 54%); mp 132.0–132.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.8 Hz, 1H), 7.57 (br.s, 2H), 7.36–7.24 (m, 4H), 7.06 (br. s, 2H), 6.74 (t, J = 7.9 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 153.6, 138.9, 128.9, 124.1, 123.2, 121.6, 120.8, 93.2, 19.1. IR (KBr): ν = 3020, 1545, 1216, 1015, 758, 718, 690 cm^{-1}; MS (EI): m/z (%) = 337 ([M+H]$^+$, 3), 336 ([M]$^+$, 15), 335 (12), 244 (61), 209 (37), 203 (17), 118 (62), 77 (100), 65 (34); elemental analysis: calcd. for $C_{14}H_{13}IN_2$: C 50.02, H 3.90, N 8.33; found: C 49.92, H 3.85, N 8.27.

2-(2-Iodophenoxy)-*N*-methylaniline (5): To a solution of 2-(2-iodophenoxy)aniline[25] (2.92 g, 9.35 mmol) in DMSO (100 mL) iodomethane (1.33 g, 0.58 mL, 9.35 mmol) was added. The reaction mixture was stirred at room temperature and, the conversion was monitored by TLC. After the reaction was completed, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (3×150 mL). The combined organic phases were washed using water (3× 100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by flash chromatography on silica gel using a mixture of pentane and diethylether as eluent to afford the corresponding product as a pale yellow liquid; yield: 1.06 g (3.27 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 1.0 Hz, 1H), 7.66 (dd, J = 10.8, 4.2 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.29–7.20 (m, 4H), 7.12 (t, J = 7.0 Hz, 1H), 4.31 (s, 1H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 142.7, 141.4, 139.7, 129.7, 124.7, 116.9, 111.2, 87.5, 30.6; IR (neat): ν = 3430, 2965, 2918, 2852, 1609, 1575, 1516, 1464, 1433, 1329, 1257, 1226, 1181, 1163, 1018, 744 cm^{-1}; HR-MS (ESI): m/z = 326.0036, calcd. for $C_{13}H_{13}INO$: 326.0031.

Acknowledgements

This research was supported by the Fonds der Chemischen Industrie and, in part, by the Cluster of Excellence funded by the Excellence Initiative of the German federal and state governments. We also acknowledge RWTH Aachen University for financing a pre-doctoral Short Term Scientific Stay for S. H. K. and thank Ms. S. Kohlhepp for valuable synthetic contributions.

References

[1] *Metal-catalyzed Cross-Coupling Reactions*, (Eds: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, 2nd edn., **2004**.

[2] Reviews: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337; d) J.-P. Corbert, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; e) M. Carril, R. SanMartin, E. Domínguez, *Chem. Soc. Rev.* **2008**, *37*, 639; f) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, *120*, 3140; *Angew. Chem. Int. Ed.* **2008**, *47*, 3096; g) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; h) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450; i) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; j) V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellog, *Org. Process Res. Dev.* **2010**, *14*, 30; k) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.

[3] For selected contributions, see: a) V. P. Reddy, K. Swapna, A. V. Kumar, K. R. Rao, *J. Org. Chem.* **2009**, *74*, 3189 (In, Zn, Sc, Bi); b) V. P. Reddy, A. V. Kumar, K. Swapna, K. R. Rao, *Org. Lett.* **2009**, *11*, 1697 (In); c) L. Rout, P. Saha, S. Jammi, T. Punniyamurthy, *Adv. Synth. Catal.* **2008**, *350*, 395 (Cd); d) S. N. Murthy, B. Madhav, V. P. Reddy, Y. V. D. Nageswar, *Adv. Synth. Catal.* **2010**, *352*, early view, DOI: 10.1002/adsc.200900691 (La); e) S. N. Murthy, B. Madhav, V. P. Reddy, Y. V. D. Nageswar, *Eur. J. Org. Chem.* **2009**, 5902 (La); f) K. Swapna, A. V. Kumar, V. P. Reddy, K. R. Rao, *J. Org. Chem.* **2009**, *74*, 7514 (Fe); g) V. K.

Akkilagunta, V. P. Reddy, K. R. Rao, *Synlett* **2010**, 1260 (Fe).

[4] For copper-catalyzed arylations in DMSO with KOH as base, see: a) L. Rout, T. K. Sen, T. Punniyamurthy, *Angew. Chem.* **2007**, *119*, 5679; *Angew. Chem. Int. Ed.* **2007**, *46*, 5583; b) L. Rout, S. Jammi, T. Punniyamurthy, *Org. Lett.* **2007**, *9*, 3397; c) S. Jammi, S. Sakthivel, L. Rout, T. Mukherjee, S. Mandal, R. Mitra, P. Saha, T. Punniyamurthy, *J. Org. Chem.* **2009**, *74*, 1971; d) P. Saha, T. Ramana, N. Purkait, A. Ali, R. Paul, T. Punniyamurthy, *J. Org. Chem.* **2009**, *74*, 8719; e) J. Zhang, Z. Zhang, Y. Wang, X. Zheng, Z. Wang, *Eur. J. Org. Chem.* **2008**, 5112; f) V. P. Reddy, A. V. Kumar, K. Swapna, K. Rao, *Org. Lett.* **2009**, *11*, 951; g) D. Singh, A. M. Deobald, L. R. S. Camargo, G. Tabarelli, O. E. D. Rodrigues, A. L. Braga, *Org. Lett.* **2010**, *12*, 3288; h) C.-K. Chen, Y.-W. Chen, C.-H. Lin, H.-P. Lin C.-F. Lee, *Chem. Commun.* **2010**, *46*, 281; i) D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan, J. You, *Angew. Chem.* **2009**, *121*, 8885; *Angew. Chem. Int. Ed.* **2009**, *48*, 8729; j) A. Tlili, N. Xia, F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 8881; *Angew. Chem. Int. Ed.* **2009**, *48*, 8725.

[5] Selected examples of metal-free N-arylations: a) J. D. Roberts, D. A. Semenow, H. E. Simmons Jr., L. A. Carlsmith, *J. Am. Chem. Soc.* **1956**, *78*, 601; b) S. D. Ross, *J. Am. Chem. Soc.* **1959**, *81*, 2113; c) H. Bader, A. R. Hansen, F. J. McCarty, *J. Org. Chem.* **1966**, *31*, 2319; d) M. Beller, C. Breindl, R. H. Riermeier, A. Tillack, *J. Org. Chem.* **2001**, *66*, 1403; e) L. Shi, M. Wang, C.-A. Fan, F.-M. Zhang, Y.-Q. Tu, *Org. Lett.* **2003**, *5*, 3515; f) R. Varala, E. Ramu, M. M. Alam, S. R. Adapa, *Synlett* **2004**, 1747; g) J. Hirst, G. Hussain, I. Oyido, *J. Chem. Soc. Perkin Trans. 2* **1986**, 397; h) J. L. Bolliger, C. M. Frech, *Tetrahedron* **2009**, *65*, 1180; i) M. Poirier, S. Goudreau, J. Poulin, J. Savole, P. L. Beaulieu, *Org. Lett.* **2010**, *12*, 2334.

[6] Selected examples of metal-free O-arylations: a) C. A. Kingsbury, *J. Org. Chem.* **1964**, *29*, 3262; b) J. I. G. Cadogan, J. K. A. Hall, J. T. Sharp, *J. Chem. Soc. C* **1967**, *1860*; c) G. Bartoli, P. E. Todesco, *Tetrahedron Lett.* **1968**, *47*, 4867; d) T. Yamatani, M. Yasunami, K. Takase, *Tetrahedron Lett.* **1970**, *20*, 1725; e) I. D. H. Stocks, J. A. Waite, K. R. H. Wooldridge, *J. Chem. Soc. C* **1971**, 1314; f) J. S. Bradshaw, R. H. Hales, *J. Org. Chem.* **1971**, *36*, 318; g) G. Bartoli, F. Ciminale, P. E. Todesco, *J. Org. Chem.* **1975**, *40*, 1975; h) R. B. Bates, K. D. Janda, *J. Org. Chem.* **1982**, *47*, 4374.

[7] Selected examples of metal-free S-arylations: a) J. S. Bradshaw, E. Y. Chen, R. H. Hales, J. A. South, *J. Org. Chem.* **1972**, *37*, 2051; b) R. Varala, E. Ramu, M. M. Alam, S. R. Adapa, *Chem. Lett.* **2004**, *33*, 1614.

[8] Selected examples of metal-free C-arylations: a) R. Zhang, F. Zhao, M. Sato, Y. Ikushima, *Chem. Commun.* **2003**, 1548; b) F. Li, Q. Wang, Z. Ding, F. Tao, *Org. Lett.* **2003**, *5*, 2169; c) S. Yanagisawa, K. Ueda, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 4673; d) R. Luque, D. J. Macquarrie, *Org. Biomol. Chem.* **2009**, *7*, 1627; e) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 0000, DOI: 10.1021/ja103050x.

[9] J. March, *Advanced Organic Chemistry*, 3rd edn., Wiley-Interscience, New York, **1985**, p 576.

[10] a) J. Miller, A. J. Parker, *J. Am. Chem. Soc.* **1961**, *83*, 117; b) A. J. Parker, *Chem. Rev.* **1969**, *69*, 1; c) C. F. Bernasconi, M. Kaufmann, H. Zollinger, *Helv. Chim. Acta* **1966**, *49*, 2563.

[11] For reviews see: a) S. V. Kessar, in: *Comprehensive Organic Synthesis*, Vol. 4, (Eds.: B. M. Trost, I. Fleming), Pergamon Press, **1991**, p 483; b) R. Huisgen, J. Sauer, *Angew. Chem.* **1960**, *72*, 91.

[12] For a review, see: B. A. Trofimov, *Sulfur Rep.* **1992**, *11*, 207 and references therein.

[13] For extraordinary properties of other base combinations see: a) P. A. A. Klusener, L. Brandsma, H. D. Verkruijsse, P. von R. Schleyer, T. Friedl, R. Pi, *Angew. Chem.* **1986**, *98*, 458; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 465; b) L. Brandsma, A. G. Mal′kina, L. Lochmann, P. V. Schleyer, *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 529; c) M. Schlosser, *Pure Appl. Chem.* **1988**, *60*, 1627; d) P. Caubere, *Chem. Rev.* **1993**, *93*, 2317. For the use of superbases in organocatalysis, see e) *Superbases for Organic Synthesis*, (Ed. T. Ishikawa), John Wiley and Sons, Ltd., West Sussex, UK, **2009**.

[14] Recently, cross-couplings with ppm quantities of metal salts have been reported. For examples, see: a) S. L. Buchwald, C. Bolm, *Angew. Chem.* **2009**, *121*, 5694; *Angew. Chem. Int. Ed.* **2009**, *48*, 5586; b) P.-F. Larsson, A. Correa, M. Carril, P.-O. Norrby, C. Bolm, *Angew. Chem.* **2009**, *121*, 5801; *Angew. Chem. Int. Ed.* **2009**, *48*, 5691; c) E. Zuidema, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 4181; d) J. Bonnamour, M. Piedrafita, C. Bolm, *Adv. Synth. Catal.* **2010**, *352*, 1577. In order to ensure that trace metals were not affecting the arylations reported here, new glass-ware and plastic spatulas were used in each reaction (N- and O-couplings). Furthermore, only reagents with high purities (99+%) were applied and metal reagents were avoided in synthetic steps wherever possible. With respect to the S-arylations the following values for metal quantities were obtained by atom absorption spectroscopy: For KOH 10 ppm of Pd, <1 ppm of Cu, 2 ppm of Ni; for NaOH 5 ppm of Pd, <1 ppm of Cu, 3 ppm of Ni; for KO-*t*-Bu 8 ppm of Pd, <1 ppm of Cu, <1 ppm of Ni; for K_2CO_3 10 ppm of Pd, <1 ppm of Cu, 3 ppm of Ni; for LiOH-H_2O 8 ppm of Pd, <1 ppm of Cu, 1 ppm of Ni. From all available data we have no indication that such trace metal amounts have an effect on the reported transformations under the given conditions.

[15] While this manuscript was in preparation, a related system for C–S cross-couplings based on the use of KOH and polyethylene glycol was reported. Z. Duan, S. Ranjit, X. Liu, *Org. Lett.* **2010**, *12*, 2430.

[16] Also other bases than KOH were effective in promoting the formation of diphenyl sulfide in DMSO under these conditions. The following yields were obtained: 35% (NaOH), 85% (NaH), 90% (KO-*t*-Bu), 56% (LiOH-H_2O) and 25% (K_2CO_3).

[17] Rao reported the formation of diphenyl disulfide under these conditions. a) This result was not confirmed by our findings. We see our observations in line with those reported by Adapa and co-workers who studied transition metal-free diaryl sulfide formations with CsOH-

H_2O in DMSO at 120 °C starting from aryl halides and thiols. b) Relevant for this discussion are also Adapa's arene selenenylations starting from aryl halides and diphenyl diselenide mediated by CsOH-H_2O in DMSO at 110 °C (R. Varala, E. Ramu, S. R. Adapa, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 140). Interestingly, Rao and co-workers reported a very similar system for the latter reaction using CuO nanoparticles as catalysts (with KOH as base in DMSO at 110 °C).[4f].

[18] a) F. G. Bordwell, R. J. McCallum, W. N. Olmstead, *J. Org. Chem.* **1984**, *49*, 1424; b) W. N. Olmstead, Z. Margolin, F. G. Bordwell, *J. Org. Chem.* **1980**, *45*, 3295; c) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456; d) F. G. Bordwell, H. E. Fried, *J. Org. Chem.* **1991**, *56*, 4218; e) F. G. Bordwell, G. E. Drucker, H. E. Fried, *J. Org. Chem.* **1981**, *46*, 632.

[19] For a discussion on the formation of aryl methyl thioethers in reactions of halonaphthalenes with *tert*-butoxide in a *tert*-butanol/DMSO medium at 140 °C, see: R. H. Hales, J. S. Bradshaw, D. R. Pratt, *J. Org. Chem.* **1971**, *36*, 314. Also in reactions of iodobenzene with allyl alcohol, allylamine or dimethyl sulfide in KOH/DMSO mixtures at elevated temperatures we detected thioethers.

[20] For selected examples of metal-free C–X bond formation leading to heterocyclic compounds see: a) A. Correa, I. Tellitu, E. Domínguez, I. Moreno, R. SanMartin, *J. Org. Chem.* **2005**, *70*, 2256; b) A. Correa, I. Tellitu, E. Domínguez, R. SanMartin, *J. Org. Chem.* **2006**, *71*, 8316; c) E. Feng, H. Huang, Y. Zhou, D. Ye, H. Jiang, H. Liu, *J. Comb. Chem.* **2010**, *12*, 422; d) D. Bernardi, L. A. Ba, G. Kirsch, *Synlett* **2007**, 2121; e) N. Barbero, R. SanMartin, E. Domínguez, *Tetrahedron* **2009**, *65*, 5729; f) R. Martínez, D. J. Ramón, M. Yus, *J. Org. Chem.* **2008**, *73*, 9778; g) Y.-X. Chen, L.-F. Qian, W. Zhang, B. Han, *Angew. Chem.* **2008**, *120*, 9470; *Angew. Chem. Int. Ed.* **2008**, *47*, 9330; h) J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González, *J. Am. Chem. Soc.* **2003**, *125*, 9028.

[21] In a study of this reaction focusing on iron catalysis it was found that with Cs_2CO_3 in DMF at 135 °C the uncatalyzed cyclization of **7b** gave **8** in 42% yield. At 120 °C only trace of **8** were found under those conditions. J. Bonnamour, C. Bolm, *Org. Lett.* **2008**, *10*, 2667.

[22] It should be noted that this particular base/solvent system has found extensive application in metal-catalyzed cross-coupling processes.[3,4] In some of these studies, DMSO/KOH was reported as being the only successful solvent/base combination. The results presented here demonstrate that under those conditions particular care should be taken and that possible metal-free "background" reactions mediated by the superbase KOH/DMSO should be considered.

[23] J. Clayden, H. Turner, M. Pickworth, T. Adler, *Org. Lett.* **2005**, *7*, 3147.

[24] J. M. Travins, R. C. Bernotas, D. H. Kaufman, E. Quinet, P. Nambi, I. Feingold, C. Huselton, A. Wilhelmsson, A. Goos-Nilsson, J. Wrobel, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 526.

[25] S.-M. Lu, H. Alper, *J. Am. Chem. Soc.* **2008**, *130*, 6451.

