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Synthetic Methods

Base-Catalyzed Synthesis of Substituted Indazoles under Mild, Transition-Metal-Free Conditions**

*Isabelle Thomé, Claire Besson, Tillmann Kleine, and Carsten Bolm**

Coupling reactions are among the most versatile and efficient methods for C–C, C–N, and C–O bond formation.[1] They have enriched the toolbox of synthetic chemists with a great number of inter- and intramolecular reactions for the step-economical synthesis of complex and functionalized molecules.

For the synthesis of N-heterocyclic compounds, C–N coupling reactions are highly valuable; consequently, they have quite frequently been used in the preparation of specific polymers, dyes, and biologically active molecules to be used as agrochemicals and drugs. They are most often catalyzed by Pd-, Ni-, or Cu-based complexes, often at elevated temperatures.[2] Especially if applied in the synthesis of pharmaceuticals, the use of such transition-metal catalysts is controversial, since they may remain in the products as trace impurities, which have to be removed in tedious additional steps. Hence, reaction protocols that enable the preparation of compounds through inter- or intramolecular C–N coupling reactions in the absence of transition metals are attractive and considered sustainable.[3] In this context, we previously reported various base-mediated N-, O-, and S-arylation reactions, including intramolecular ring-closing reactions to give heterocyclic products.[4] We now wondered about a transition-metal-free synthetic route to indazoles.

Compounds with an indazole framework display a wide range of pharmacological activities,[5] from antiinflammatory and antiarthritic activity to antifertility activity. Although several procedures for the preparation of indazole derivatives are known,[6] the discovery of new methods that are milder than the classical routes, such as the diazotization or nitrosation of anilines and the condensation of benzaldehydes with hydrazines, is desirable. Those methods often require an excess of a highly toxic or unstable hydrazine,[6d,i,l] hydrazone,[6b,f] nitro,[6e] or diazo[6a,c,j] compound, and the reaction conditions tend to be harsh and involve strong acids or high temperatures.

More recently, transition-metal-catalyzed syntheses of indazoles have also been developed.[7–9] Most involve palladium, copper, and iron salts or complexes, which are used in combination with strong bases, such as lithium hexamethyldisilazide (LiHMDS) or *t*BuONa, at moderate to high temperatures. Furthermore, the metal loading is generally high, and the rather narrow substrate tolerance does not enable the synthesis of 1-unsubstituted 1*H*-indazole derivatives. Among the reported copper-catalyzed processes,[8] a study by Tois, Franzén, and co-workers caught our attention.[8c] They had found that in the presence of a catalytic system consisting of a combination of copper(I) iodide (10 mol%), *N*,*N*′-dimethylethylenediamine (DMEDA; 30 mol%), and an excess of sodium carbonate, 1*N*-tosylindazoles were formed in good yields from the corresponding substituted (*Z*)-2-haloacetophenone *N*-tosylhydrazones.[10] On the basis of our previous work,[4] we hypothesized that an analogous transition-metal-free approach could be developed. Herein, we report the realization of this idea.

For the initial screening and optimization of the reaction conditions, (*Z*)-2-bromoacetophenone *N*-tosylhydrazone (**1aa**) was chosen as the substrate. Following the protocol described by Tois, Franzén, and co-workers, this starting material was accessible in stereochemically homogeneous form through a three-step reaction sequence.[8c,11] For the envisaged transition-metal-free cyclization, various bases and amines were tested, and the reaction parameters (temperature, time) were altered. While our initial attempt to use the previously applied "superbase" system consisting of KOH (or KO*t*Bu) in DMSO remained unsuccessful (Table 1, entries 1 and 2),[12] we were surprised to see that product formation occurred in the presence of a simple DMEDA/K_2CO_3 mixture (Table 1, entry 3). Only a catalytic amount of the diamine (10 mol%) was required for the formation of indazole **2a** in high yield. The best reaction medium was toluene, which was unexpected considering the low solubility of the applied inorganic base in this rather nonpolar solvent.[13] Both DMEDA (**A1**) and K_2CO_3 were essential reagents; in the absence of either, no reaction occurred or the yield of **2a** was significantly lower (Table 1, entries 4–6).[14]

The next surprise related to the reaction temperature. Assuming a low-to-moderate reactivity, we performed the initial cyclization attempts at 135°C (Table 1, entries 1–6). However, subsequent optimization studies revealed that the

[*] I. Thomé, Dr. T. Kleine, Prof. Dr. C. Bolm
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)
E-mail: carsten.bolm@oc.rwth-aachen.de
Dr. C. Besson
Institute of Inorganic Chemistry, RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)

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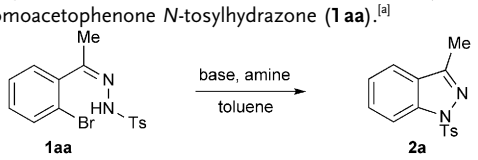
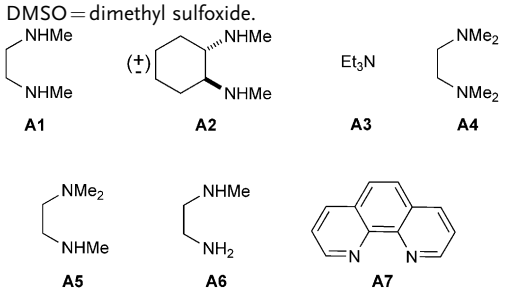
Table 1: Optimization of the reaction conditions for the cyclization of (*Z*)-2-bromoacetophenone *N*-tosylhydrazone (**1aa**).[a]



1aa **2a**

Entry	Base	Amine	*t* [h]	*T* [°C]	Yield [%][b]
1	KOH/DMSO	none	24	135	0
2	KO*t*Bu/DMSO	none	24	135	0
3	K_2CO_3	**A1**	24	135	69
4	K_2CO_3	none	24	135	trace
5	none	**A1**	24	135	26
6	none	none	24	135	0
7	K_2CO_3	**A1**	24	120	73
8	K_2CO_3	**A1**	24	80	76
9	K_2CO_3	**A1**	24	60	56
10	K_2CO_3	**A1**	24	RT	95
11[c]	K_2CO_3	**A1**	24	RT	94/93
12	K_2CO_3	**A2**	24	RT	99
13[c]	K_2CO_3	**A2**	24	RT	96/94
14[d]	K_2CO_3	**A2**	24	RT	88
15	Na_2CO_3	**A2**	24	RT	10
16	Cs_2CO_3	**A2**	24	RT	0
17[e]	K_2CO_3	**A2**	24	RT	99
18	K_2CO_3	**A2**	2.5	RT	99
19[f]	K_2CO_3	**A2**	0.5	50	99
20[g]	none	**A3**	24	RT	0
21	K_2CO_3	**A4**	24	RT	0
22	K_2CO_3	**A5**	24	RT	0
23	K_2CO_3	**A6**	24	RT	0
24	K_2CO_3	**A7**	24	RT	39

[a] The reaction was carried out with an inorganic base (2 equiv) and an amine (10 mol%) unless otherwise stated. [b] The yield of **2a** after flash chromatography is given. [c] The reaction was carried out with 1.5 equivalents or 1.0 equivalent of the inorganic base. [d] The reaction was carried out with 6 mol% of the diamine. [e] Purity of K_2CO_3: >99.9999%. [f] The reaction was carried out under microwave irradiation. [g] The reaction was carried out with triethylamine (2.1 equiv). DMSO = dimethyl sulfoxide.



A1 **A2** **A3** **A4**

A5 **A6** **A7**

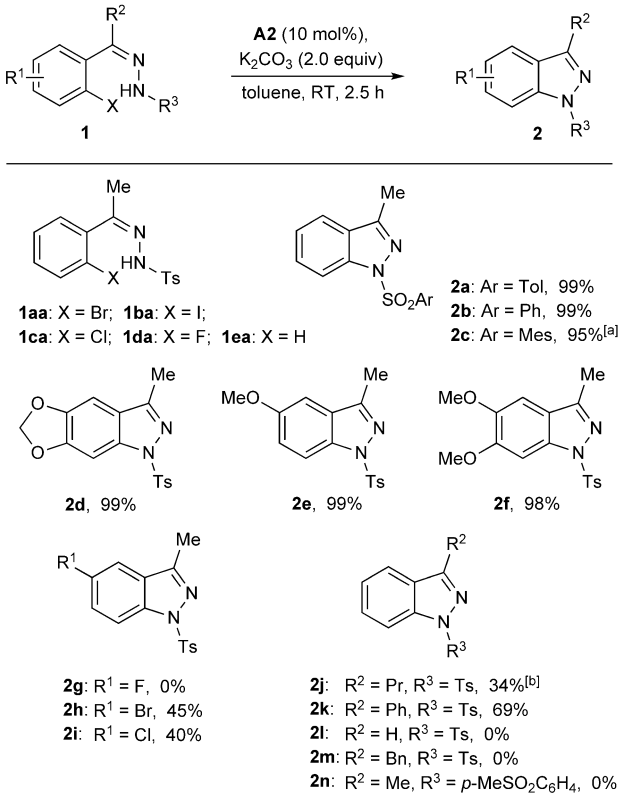
yields were significantly higher at lower temperatures (Table 1, entries 7–10). Finally, it was found that the catalytic reaction was most efficient at room temperature. Thus, when DMEDA (10 mol%) was used in combination with K_2CO_3 (2 equiv) in toluene at room temperature for 24 h, the yield of **2a** was 95% (Table 1, entry 10). A decrease in the amount of the inorganic base to 1.5 or even 1.0 equivalents had almost no effect on the product yield (Table 1, entry 11).[15]

An additional improvement was observed when *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**A2**) was used instead of DMEDA. Now, **2a** was formed in 99% yield (Table 1, entry 12). Also in this case, it was possible to reduce the amount of K_2CO_3 without significantly affecting the yield of **2a** (Table 1, entry 13). With only 6 mol% of **A2** (instead of 10 mol%), the product yield was lower (Table 1, entry 14). Neither Na_2CO_3 nor Cs_2CO_3 could substitute the potassium salt (Table 1, entries 15 and 16). Being aware that in other reactions extreme activities of copper catalysts (in "homeopathic doses") have been observed,[11,15] we applied K_2CO_3 with a purity higher than 99.9999% (Table 1, entry 17). No negative effect was observed, and the yield of **2a** remained 99%. From this result as well as the high yields of **2a** obtained in reactions with **1aa** prepared by other means (see below), we conclude that transition metals do not play a role in this process. Finally, the reaction time could be shortened from 24 to 2.5 h (Table 1, entry 18). Under microwave irradiation (at 50°C), even 30 min were sufficient for **2a** to be formed in excellent yield (Table 1, entry 19).

A remarkable structure/activity relationship was observed with respect to the organic diamine. Only the use of **A1** and **A2** led to highly active systems (Table 1, entries 10 and 12 versus entries 20–24). Neither triethylamine (**A3**) nor the structurally closely related ethylenediamine derivatives **A4**, **A5**, or **A6** afforded suitable catalysts. The use of 1,10-phenanthroline (**A7**) provided **2a** in 39% yield. We assume that various factors, including the basicity and ion-stabilization capability of the amine in combination with steric effects, are responsible for these differences in behavior.

Next, we explored the scope of the cyclization by assaying the reactions of various *Z*-configured 2-haloaryl hydrazones **1** (Scheme 1). The cyclization of the 2-iodoaryl derivative **1ba** proceeded as well as that of the 2-bromoaryl derivative **1aa** and afforded **2a** in 99% yield. In contrast, no conversion of the chloro and fluoro analogues **1ca** and **1da** or of the nonhalogenated compound **1ea** was observed. Consequently, our subsequent studies were focused on the transformation of the respective 2-bromoaryl hydrazones, and all yields of the corresponding products **2** depicted in Scheme 1 refer to the conversion of these substrates.

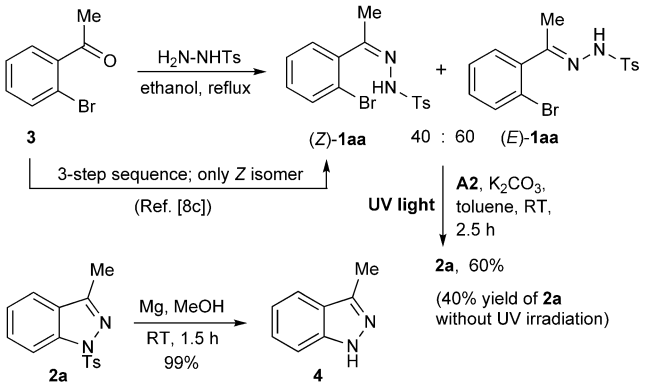
Several variations of the substrate core were tolerated (Scheme 1). For example, replacement of the tolyl group of the *N*-sulfonyl moiety in **1aa** with phenyl or mesityl had almost no effect on the yield of the corresponding indazoles **2b** and **2c**, which were obtained in 99 and 95% yield, respectively. Also, products **2d–f** with electron-donating alkoxy substituents on the arene ring of the indazole core were obtained in excellent yields (≥98%). In contrast, additional halo substituents on the 2-bromoaryl ring of the hydrazone substrate affected the reactions negatively: the desired fluoro-substituted product **2g** was not formed at all, and **2h** and **2i** were formed in low yields. A similar negative effect was observed when the substituent R^2 was varied. Whereas most compounds with a methyl group at this position underwent a very efficient cyclization (≥95%), the yields for **2j** (with R^2 = Pr) and **2k** (with R^2 = Ph) were significantly lower (34 and 69%). When R^2 was a hydrogen atom (*E* isomer) or a benzyl group, none of the desired product (**2l** or **2m**) was observed. Also, a substrate with a *p*-methylsulfonyl-substituted phenyl group on the hydrazone did not undergo cyclization to form **2n**.



Scheme 1. Scope and limitations of the base-catalyzed cyclization. Product yields after chromatography are given. [a] The starting material was a 1:3 *E*/*Z* isomer mixture; the yield given is based on the conversion of the *Z* isomer. [b] The reaction was carried out at 50 °C instead of room temperature. Bn = benzyl, Mes = 2,4,6-trimethylphenyl (mesityl), Ts = *p*-toluenesulfonyl.

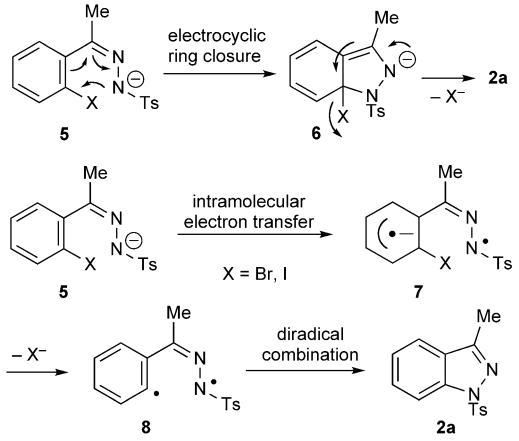
Until this stage, all substrates had been diastereomerically pure with a *Z* configuration at the hydrazone C–N double bond. For their selective preparation, special reaction sequences had to be applied,[8c,11] which we considered as a synthetic limitation.[16] A simple approach to 2-haloaryl hydrazones **1** is the condensation of the corresponding phenone with tosylhydrazine in ethanol. When 2-bromoacetophenone (**3**) was subjected to this reaction, **1aa** was obtained as a mixture of *E* and *Z* isomers in a 3:2 ratio (Scheme 2).[7e,17] The treatment of this mixture with **A2** and K_2CO_3 under the optimized conditions led to **2a** in 40 % yield, which indicated that only the *Z* isomer underwent cyclization, whereas (*E*)-**1aa** remained untouched. The same result was obtained when the entire reaction sequence was performed under one-pot conditions.[18]

With the goal to improve the cyclization yield for the transformation of readily accessible *E*/*Z* mixtures of **1**, we tested an in situ photoisomerization induced by UV light.[19] Indazole **2a** was now obtained in 60 % yield from the standard 3:2 *E*/*Z* mixture of **1aa**. Apparently, as hypothesized, some of the *E* isomer of **1aa** had isomerized to provide additional (*Z*)-**1aa**, which smoothly underwent cyclization to give **2a**. As known from a study reported by Sakamoto and co-workers,[7d] products such as **2a** can be detosylated with magnesium in methanol.[20] In this particular case, the transformation provided 1*H*-indazole **4** in 99 % yield (Scheme 2).



Scheme 2. Cyclization of *E*/*Z* mixtures of **1aa** under irradiation with UV light and detosylation of **2a**.

There are various possible mechanisms for this cyclization, including stepwise and concerted processes involving anionic and radical species. Furthermore, it is important to take into account the roles of the base and the counterion. The effect of these components is difficult to elucidate owing to the heterogeneous appearance of the reaction mixture. As a representative example, we consider the formation of **2a** from hydrazones **1** (Scheme 3). The fact that only *N*-arylsulfonyl-substituted substrates with relatively acidic NH hydrogen atoms reacted, whereas the *N*-aryl hydrazone substrate expected to give **2n** was inactive, indicates that



Scheme 3. Plausible mechanisms for the formation of **2a**.

the deprotonation of the hydrazone moiety of starting materials **2** is the initial step of the process.[21] In this manner, intermediate **5** is formed (which should be stabilized by its allyl diazo anion character). Both the counterion (in this case potassium) and potentially ion-chelating and H-bonding ligands (such as diamines **A1** and **A2**) will affect the reactivity of **5**.[22] Since only bromo and iodo derivatives (**1aa** and **1ba**) cyclized well, whereas the corresponding chloro and fluoro compounds **1ca** and **1da** were inactive, we consider an intramolecular nucleophilic substitution as unlikely. This hypothesis is enforced by the observation that substrates

containing electron-rich aromatic rings reacted most efficiently. Alternatively, **5** could undergo electrocyclic ring closure to yield intermediate **6**, which upon loss of the halide ion would give product **2a** directly. The bases and the counterion might facilitate such an anionic pathway; thus, this sequence of events is reasonable. However, attempts to detect anion **6** by ^{13}C NMR spectroscopy remained unsuccessful, and no signal corresponding to a quaternary carbon atom was observed.

There is, however, another very reasonable alternative, which involves the formation of radicals. Accordingly, intramolecular electron transfer from the allyl diazo anion moiety onto the aryl part of **5** could provide species **7**, which should lose a halide ion in analogy to well-established $S_{RN}1$ reactions.[23] The observed reactivity order of the various halo derivatives **1aa**–**1da** is in accord with this suggestion. Product **2** is then formed by the radical combination of diradical **8**. Investigations of the reaction slurry by ESR spectroscopy showed the presence of an organic radical.[24,25] The broadness of the observed signal (130 G peak-to-peak, $g = 2.012$)[26] and its absence when only the solution was analyzed were in accordance with a solid species, as could be expected for a negatively charged radical anion, such as **7**, which is insoluble in toluene.

In summary, a mild base-catalyzed method for the synthesis of 1*H*-indazole derivatives has been developed. The transition-metal-free procedure involves an inexpensive combination of a catalytic amount of *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine and K_2CO_3. At room temperature, various products were obtained in high yield after only 2.5 h. A UV-light-induced photoisomerization was shown to be advantageous when *E*/*Z* mixtures of starting materials were used. Reasonable mechanisms have been proposed, and the formation of radical intermediates was proven by ESR spectroscopy.

Experimental Section

General procedure: A sealable tube equipped with a magnetic stir bar was charged with the hydrazone (100 mg) and K_2CO_3 (2 equiv). The aperture of the tube was then covered with a rubber septum cap, an argon atmosphere was established, and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (10 mol%) and toluene (1.0 mL) were added by syringe. The septum cap was then replaced with a teflon-coated screw cap, and the heterogeneous reaction mixture was stirred at room temperature. After 2.5 h, ethyl acetate (5 mL) was added, and the mixture was extracted with 1N HCl (10 mL). The organic phase was washed with water and brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the indazole product was purified by silica-gel chromatography (*n*-pentane/ethyl acetate). The identity and purity of the product were confirmed by ^1H and ^{13}C NMR spectroscopic analysis. See the Supporting Information for full details.

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[10] For an overview on the use of *N*-tosylhydrazones in catalysis, see: Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236.

[11] Because the first reaction of the diastereoselective three-step synthesis of **1aa** from 2-bromoacetophenone[8c] involved the use of copper bromide, special care was taken in the purification of product **1aa**. We also tried to keep potential metal contamination as low as possible in other reactions (see also Ref. [18]). For a review related to these issues, see: I. Thomé, A. Nijs, C. Bolm, *Chem. Soc. Rev.* **2012**, *41*, 979.

[12] At 135 °C, the use of KOH/DMSO ($pK_a = 30–32$) or KO*t*Bu/DMSO ($pK_a = 32$) led to decomposition of the starting material. At ambient temperature, no reaction was observed, and the starting material was fully recovered.

[13] No product formation was observed in *N*,*N*-dimethylformamide, DMSO, ethanol, or ethanol/H_2O (1:1).

[14] Even in the absence of the inorganic base, **2a** was formed in 26% yield when (distilled) DMEDA (10 mol%) was used (Table 1, entry 4). Under these conditions, the catalytic activity of the diamine is probably hampered by the formation of increasing amounts of HBr salts.

[15] a) P.-F. Larsson, A. Correa, M. Carril, P.-O. Norrby, C. Bolm, *Angew. Chem.* **2009**, *121*, 5801; *Angew. Chem. Int. Ed.* **2009**, *48*, 5691; b) S. L. Buchwald, C. Bolm, *Angew. Chem.* **2009**, *121*, 5694; *Angew. Chem. Int. Ed.* **2009**, *48*, 5586.

[16] The direct condensation of 2-bromoacetophenone (**3**) with acetohydrazide, benzohydrazide, 4-chlorobenzohydrazide, 2,4-dinitrophenylhydrazide, *N*-phenylhydrazinecarboxamide, and methyl hydrazinecarboxylate gave mainly *E* hydrazones, which did not cyclize under the optimized reaction conditions. Attempts at the *Z*-selective synthesis of 2-bromoacetophenone hydrazones failed.

[17] The isomer ratio was determined by NMR spectroscopy and HPLC analysis, and the respective data were compared with those reported in Ref. [7e]; see also: C. A. Bunnell, P. L. Fuchs, *J. Org. Chem.* **1977**, *42*, 2614.

[18] The "one-pot" condensation reaction of 2-bromoacetophenone (**3**) with tosylhydrazine was carried out in ethanol at reflux. After 2.5 h, the reaction mixture was cooled to room temperature, the solvent was removed in vacuo, and toluene, **A2**, and K_2CO_3 were added. After a further 2.5 h at room temperature, indazole **2a** was isolated in 40% yield. This process was transition-metal-free throughout, and the reaction outcome can be considered as evidence that no transition metals were necessary for the cyclization to give the final products in the indazole syntheses described herein.

[19] For an analogous photoisomerization of *N*,*N*-dimethylhydrazones, see: L. F. Clarke, F. O'Sullivan, A. F. Hegarty, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1649. Attempts to promote the isomerization and cyclization of the *E* isomer of **1aa** and the corresponding starting material for the formation of **2l** by exposure to UV irradiation failed and resulted in decomposition of the starting materials.

[20] For the initial report, see: M. Sridhar, B. A. Kumar, R. Narender, *Tetrahedron Lett.* **1998**, *39*, 2847.

[21] Attempts to use NaH (2 equiv) or KO*t*Bu (1 equiv; as a solid or as a 1M solution in THF) for the deprotonation to enable a diamine-free cyclization remained unsuccessful. The latter reagent, however, was activated by the presence of *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**A2**; 10 mol%) to give **2a** in 94% yield after 2.5 h at room temperature. An analogous observation was made when lithium diisopropylamide (LDA; 1 equiv) was used as the base (instead of K_2CO_3). Only if the diamine was added, a cyclization to give **2a** occurred (75% yield at room temperature after 2.5 h).

[22] Hypothesizing that the diamine plays a role as a phase-transfer catalyst in the inhomogeneous reaction mixture, we performed an experiment with DMEDA in the presence of [18]crown-6 (2 equiv). Under those conditions, the yield of **1aa** dropped to 89% (after 24 h).

[23] For an excellent overview on $S_{RN}1$ reactions, see: R. A. Rossi, A. B. Pierini, A. B. Peñeñory, *Chem. Rev.* **2003**, *103*, 71.

[24] For a detailed summary of all ESR experiments, see the Supporting Information. Notably, trace amounts of nitrosyl radicals were detected in crude and distilled samples of **A1**, **A2**, and **A5**. However, on the basis of the significantly different results of the cyclization experiments with those diamines (see Table 1, entries 10, 12, and 22), we do not believe that these trace impurities play a role (e.g. in initiating a radical chain reaction). This assumption is further supported by the fact that the cyclization was not initiated by the presence of 10 mol% of the nitrosyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).

[25] When 1,1-diphenylethylene (1 equiv) or TEMPO (1 equiv) was added as a radical scavenger, the yield of **2a** dropped to 80 and 15%, respectively. The addition of azobisisobutyronitrile (AIBN; 20 mol%) and Bu_3SnH (2 equiv) blocked the conversion of **1aa**.

[26] The observed signal is centered at $g = 2.012$. This value falls outside the range expected for hydrazyl (2.0032–2.0038) as well as for σ or π aryl anion radicals [2.0020–2.0025 and 2.0026–2.0029, respectively: *Electron Spin Resonance Spectroscopy of Organic Radicals* (Eds.: F. Gerson, W. Huber), Wiley-VCH, Weinheim, **2003**]. The higher *g* value, however, is not unexpected owing to the diradical nature of the postulated intermediate. The broadness of the signal caused by the solid state of the species precludes any quantitative determination of zero-field splitting or hyperfine coupling.

