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Preparation of Aryl–Alkylamines via Electrophilic Amination of Functionalized Arylazo Tosylates with Alkylzinc Reagents

Pradipta Sinha, Christiane C. Kofink, and Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-Universität,
Butenandtstrasse 5-13, 81377 München, Germany

paul.knochel@cup.uni-muenchen.de

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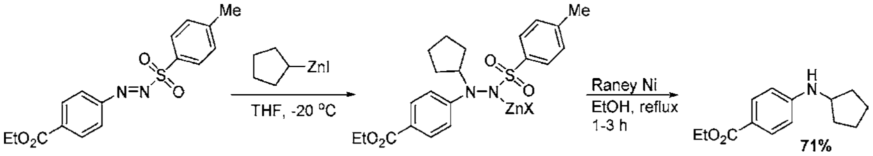
ABSTRACT



A new electrophilic amination reaction of functionalized arylazo tosylates with alkylzinc halides or dialkylzinc reagents in THF leads to the corresponding hydrazines. A facile cleavage of the N–N bond is achieved using Raney nickel in refluxing ethanol, leading to substituted secondary aryl–alkylamines in 45–79% yield.

Electrophilic amination is an attractive method for preparing polyfunctional amines. Organometallic reagents, such as Grignard, or organolithium reagents have been most frequently used for performing these reactions.[1] Only a few examples have been reported so far in the literature using organozinc reagents. These reagents have the advantage of being compatible with a broad range of functional groups.[2] Recently, Erdik has reported the electrophilic amination of triarylzincates with benzenediazonium tetrafluoroborates.[3] Johnson has shown that organozinc reagents can act as potential nucleophiles in the presence of copper and nickel catalysts with *O*-benzoyl hydroxylamines, leading to tertiary amines.[4] The use of functionalized organozinc reagents opens a synthetic route for the preparation of highly functionalized amines, being complementary to the palladium-catalyzed nucleophilic amination reaction.[5]

Recently, we have reported the reactions of functionalized Grignard reagents with nitroarenes and arylazo tosylates, which allow the synthesis of polyfunctionalized diarylamines.[6] Herein, we wish to report a new facile method for

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(1) For general electrophilic amination, see: (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947. (b) Boche, G. In *Houben-Weyl, Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995. (c) Mulzer, J.; Altenbach, H. J.; Brown, M.; Krohn, K.; Reissig, H. U. *Organic Synthesis Highlights*; VCH: Weinheim, Germany, 1991; pp 45−53. (d) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505. (e) Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, *59*, 682. For stoichiometric addition of organometallic reagents, see: (f) Skriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 298. (g) Kitamura, M.; Suga, T.; Chiba, S.; Narasaka, K. *Org. Lett.* **2004**, *6*, 4619. (h) Bernardi, P.; Dembech, P.; Fabbri, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1999**, *64*, 641. (i) An, D. K.; Hirakawa, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 3737. (j) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (k) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620. (l) Alberti, A.; Canè, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677. For the use of organozinc reagents, see: (m) Canè, F.; Brancaleoni, D.; Dembech, P.; Ricci, A.; Seconi, G. *Synthesis* **1997**, *5*, 545. (n) Erdik, E.; Daskapan, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3139.

(2) For a review, see: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(3) Erdik, E.; Kocoglu, M. *Main Group Met. Chem.* **2002**, *25*, 621.

(4) (a) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364. (c) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, *11*, 1799. (d) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680.

(5) (a) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 699−760. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 107−168. (d) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, pp 1051−1096.

(6) (a) Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390. (b) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 897.

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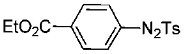
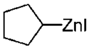
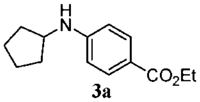
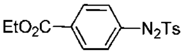
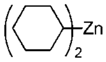
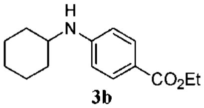
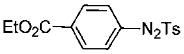
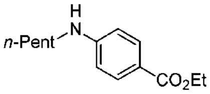
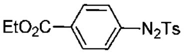
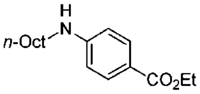
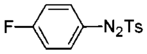
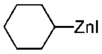
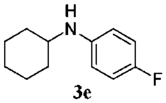
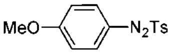
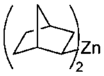
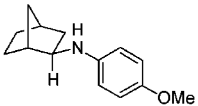
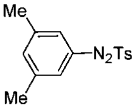
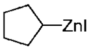
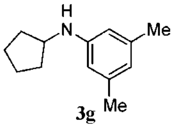
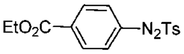
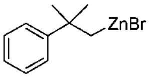
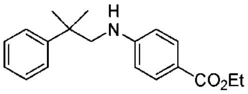
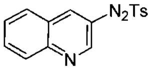
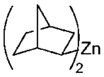
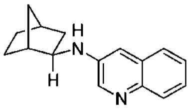
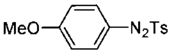
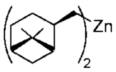
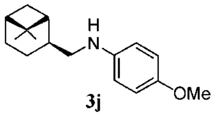
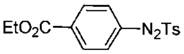
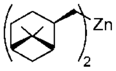
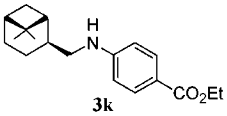
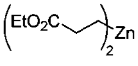
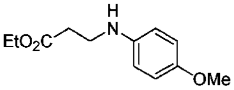
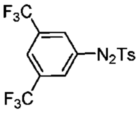
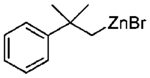
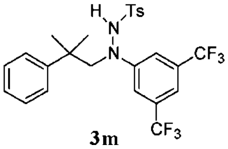
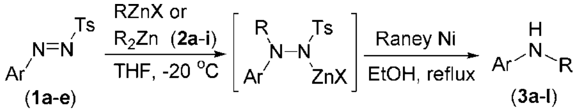
Table 1. Synthesis of Aryl−Alkylamines **3a**−**3m** from the Reaction of Arylazo Tosylates **1a**−**1f** with Alkylzinc Reagents **2a**−**2i**

entry	ArN_2Ts	$RZnX / R_2Zn$	product	yield (%)[a]
1	 **1a**	 **2a**	 **3a**	71
2	 **1a**	 **2b**	 **3b**	62
3	 **1a**	*n*-Pent-ZnI **2c**	 **3c**	55
4	 **1a**	*n*-Octyl-ZnI **2d**	 **3d**	52
5	 **1b**	 **2e**	 **3e**	75
6	 **1c**	 **2f**	 **3f**	71[b]
7	 **1d**	 **2a**	 **3g**	76
8	 **1a**	 **2g**	 **3h**	79
9	 **1e**	 **2f**	 **3i**	62[b]
10	 **1c**	 **2h**	 **3j**	67
11	 **1a**	 **2h**	 **3k**	50
12	 **1c**	 **2i**	 **3l**	45
13	 **1f**	 **2g**	 **3m**	41

[a] Isolated yield of analytically pure product. [b] A 4:1 ratio of *exo*:*endo* isomers was obtained.

the preparation of secondary aryl−alkylamines via an electrophilic amination reaction of organozinc reagents (RZnX or R_2Zn)[7] with functionalized arylazo tosylates (ArN_2Ts)[8] (Scheme 1). This method is applicable to a wide range of polyfunctional substrates due to its excellent compatibility and mild reaction conditions.

Scheme 1. General Reaction Sequence



Preliminary studies showed that the reaction of a 4-phenylazo tosylate ethyl ester (**1a**) with cyclopentylzinc iodide (**2a**) in dry THF at −20 °C leads to the corresponding hydrazine (Scheme 1). However, as reported earlier,[6] the reductive cleavage of the N−N bond using allyl iodide in *N*-methylpyrrolidinone (NMP), followed by the treatment with zinc dust in a mixture of trifluoroacetic acid/acetic acid (1:5 v/v), affords the desired secondary amine **3a** only in 40% yield. Searching for an efficient route to perform the reductive cleavage of the N−N bond, we found that Raney nickel in refluxing ethanol gave amine **3a** in 71% isolated yield within 3 h (Scheme 1, Table 1).

These optimized reaction conditions allow us to synthesize a wide range of highly functionalized secondary aryl−alkylamines (**3a**−**3l**) in good to excellent yields (Table 1). Both alkylzinc iodides and dialkylzinc reagents can be used in this addition reaction, which enables us to prepare diastereoselective aryl−alkylamines. Thus, the reaction of cyclopentylzinc iodide (**2a**) and dicyclohexylzinc (**2b**) with the arylazo tosylate (**1a**) gives rise to the aryl−cycloalkylamines **3a** and **3b**, respectively, in 71 and 62% yield (entries 1 and 2). The reaction of *n*-alkylzinc compounds, such as *n*-pentylzinc iodide (**2c**) and *n*-octylzinc iodide (**2d**), with 4-phenylazo tosylate ethyl ester (**1a**) leads to the formation of aryl-*n*-alkylamines **3c** and **3d** in 52−55% yield (entries 3 and 4).

Ethyl esters of (alkylamino)benzoic acids, such as **3c** and **3d**, have a serum sterol and triglyceride lowering activity (in vivo). Furthermore, such compounds decrease the activity of the enzyme fatty acyl CoA:cholesterol acyltransferase (ACAT) (in vitro) and therefore decrease the accumulation of cholesteryl esters in the arterial wall.[9]

The electrophilic amination reaction also takes place in the presence of an electron-withdrawing fluoride substituent in the aromatic ring of the arylazo tosylate and affords the corresponding amine **3e** in 75% yield (entry 5). The reaction is found equally efficient in the presence of electron-donating substituents on the arylazo tosylate. Thus, the reaction of 4-methoxyphenylazo tosylate (**1c**) leads to amine **3f** in 71% yield, and 3,5-dimethylphenylazo tosylate (**1d**) provides amine **3g** in 76% yield (entries 6 and 7). Remarkably, this method also offers an easy access to secondary amines bearing a neophyl group, $PhC(Me)_2CH_2$, which is usually difficult to introduce by nucleophilic substitution. The reaction of neophylzinc bromide (**2g**), prepared via the transmetalation of neophyllithium by zinc bromide, with 4-phenylazo tosylate (**1a**) leads to the formation of the desired amine **3h** in 79% yield (entry 8). This methodology is successfully applied to bicyclic diorganozinc compounds, such as di-2-norbornylzinc (**2f**) and dimyrtanylzinc (**2h**) (entries 6 and 9−11). It is noteworthy that, di-2-norbornylzinc (**2f**), prepared by the described procedure,[10] reacts with 4-methoxyphenylazo tosylate (**1c**) and provides the desired secondary amine **3f** in 71% yield with an *exo*:*endo* ratio of 80:20 (entry 6). Similarly, product **3i** is obtained by the reaction of di-2-norbornylzinc (**2f**) with the quinoline arylazo tosylate **1e** (62%, entry 9). Interestingly, the presence of an ester group in the organozinc reagent **2i** also furnishes the expected secondary amine **3l** in 45% yield (entry 12). However, in the case of a highly electron-deficient arylazo tosylate system bearing two CF_3 groups **1f**, the reductive workup fails and only the intermediate addition product **3m** can be isolated in 41% yield (entry 13).

Remarkably, this procedure can be further utilized for the synthesis of chiral amines starting from chiral organozinc compounds (Scheme 2).[11] The chiral alkylzinc derivative **2j** can be prepared from 1-(2-methoxyphenyl)cyclopentene (**4**) via hydroboration with (−)-$IpcBH_2$, followed by a boron−zinc exchange with *i*-Pr_2Zn. The chiral organozinc reagent **2j** subsequently reacts with arylazo tosylate (**1a**) leading to the chiral secondary amine **3n** in 40% isolated yield with an enantiomeric excess of 85% and a diastereoselectivity of 98% (Scheme 2).

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[7] (a) Knochel, P.; Calaza, M. I.; Hupe, E. In *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 619−670. (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414. (c) Knochel, P.; Jones, P.; Langer, F. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, UK, 1999; pp 179−212. (d) Knochel, P.; Millot, N.; Rodrriguez, A. L.; Tucker, C. In *Organic Reactions*; Overman, E. L., Ed.; John Wiley & Sons: New York, 2001; Vol. 58.

[8] For the preparation of arylazo tosylate, see: Karzeniowski, S. H.; Gokel, G. W. *Tetrahedron Lett.* **1977**, 3519, and see ref 6b.

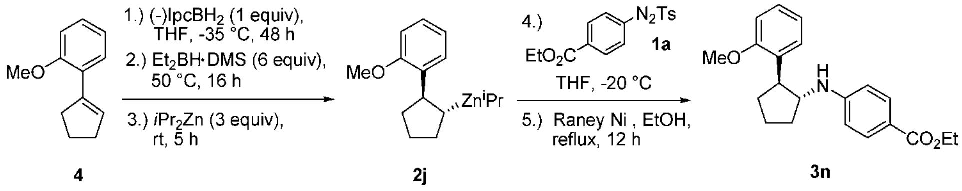
[9] Albright, J. D.; DeVries, V. G.; Largis, E. E.; Miner, T. G.; Reich, M. F.; Schaffer, S. A.; Shepherd, R. G.; Upeslacis, J. *J. Med. Chem.* **1983**, *26*, 1378 and references therein.

[10] Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79.

[11] (a) Hupe, E.; Calaza, M. I.; Knochel, P. *J. Organomet. Chem.* **2003**, 136. (b) Hupe, E.; Calaza, M. I.; Knochel, P. *Chem.*−*Eur. J.* **2003**, *9*, 2789. (c) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111. (d) Hupe, E.; Knochel, P. *Org. Lett.* **2001**, *3*, 127. (e) Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687.

[12] Typical procedure: preparation of cyclopentyl-(3,5-dimethylphenyl)-amine **3g**. In a flame-dried argon-flushed 25 mL two-neck round-bottom flask equipped with a magnetic stirrer and septum, cyclopentylzinc iodide **2a** (0.92 mL, 1.2 mmol, 1.31 M in THF) was dissolved in dry THF (1 mL) and cooled to −20 °C. 3,5-Dimethylphenylazo tosylate **1d** (288 mg, 1.0 mmol) was dissolved in dry THF (2 mL) and added dropwise to the organozinc reagent. The reaction mixture was stirred at −20 °C for 30 min to form the intermediate zinc hydrazide. The solvent was removed, and the residue was dissolved in ethanol (5 mL). Raney nickel (activated catalyst 50%, in water; Acros Chemical) (2.5 g) was added, and the reaction mixture was refluxed for 1.5 h. The reaction mixture was allowed to cool to room temperature, and the Raney nickel residue was separated by filtration. Ethanol was removed in vacuo and the residue extracted with diethyl ether (2 × 10 mL), washed with brine (2 × 10 mL), and dried over sodium sulfate. Purification by flash chromatography (*n*-pentane/diethyl ether 99:1) yielded 144 mg (76% isolated yield) of **3g** as a light-yellow viscous liquid.

Scheme 2. Synthesis of the Chiral Amine **3n**



isolated yield 40%
ee 85%
trans : *cis* 98:2

In summary, we have reported a mild procedure for the synthesis of various secondary aryl−alkylamines bearing a broad variety of functional groups attached at the aromatic ring.[12] This method can also be used for the preparation of chiral aryl−alkylamines (Scheme 2). Further work is underway to explore the reactivity of organometallic reagents toward other electrophilic amino synthons.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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