Amination

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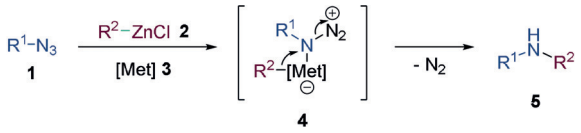
Iron-Mediated Electrophilic Amination of Organozinc Halides using Organic Azides

*Simon Graßl, Johannes Singer, and Paul Knochel**

Abstract: *A wide range of alkyl-, aryl- and heteroarylzinc halides were aminated with highly functionalized alkyl, aryl, and heterocyclic azides. The reaction proceeds smoothly at 50 °C within 1 h in the presence of $FeCl_3$ (0.5 equiv) to furnish the corresponding secondary amines in good yields. This method was extended to peptidic azides and provided the arylated substrates with full retention of configuration. To demonstrate the utility of this reaction, we prepared two amine derivatives of pharmaceutical relevance using this iron-mediated electrophilic amination as the key step.*

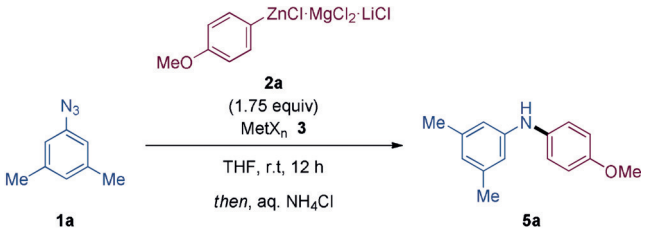
The preparation of polyfunctional amines is central to organic synthesis.[1] Nucleophilic aminations[2] in which the amine plays the role of a nucleophile, such as the Buchwald–Hartwig amination,[3] have been widely used for the preparation of aryl and heteroaryl amines. In contrast, electrophilic aminations are much less developed. Pioneering work by Narasaka and co-workers[4] and more recently from Berman and Johnson[5] have led to a number of electrophilic aminations, for example, using *N*-hydroxylamines derivatives as electrophilic aminating reagent.[6] Recently, we have shown that the cobalt-catalyzed amination of organozinc halides and pivalates by *N*-hydroxylamine benzoates furnishes polyfunctional tertiary amines.[7] In the search for electrophilic amination reactions leading to secondary amines, we envisioned the use of organic azides of type **1** as electrophilic nitrogen sources.[8] In early work by Pearson and Trost[9] and others,[10] such reactions have been performed using Grignard reagents. We envisioned that organozinc halides of type **2** would be especially attractive, since these organometallics[11] are compatible with the presence of various functional groups.[12] In general, organozinc reagents are not very reactive, so we anticipated that transition-metal catalysts (Met; **3**) may be required for achieving the desired amination via transition state **4**, leading to secondary amines of type **5** (Scheme 1).



Scheme 1. Tentative pathway for the electrophilic amination of organozinc halides with organic azides in the presence of a transition metal catalyst.

In preliminary experiments, we treated aryl azide (**1a**) with 4-anisylzinc chloride (**2a**), prepared from the corresponding Grignard reagent by transmetalation with $ZnCl_2$, in THF at 25 °C.[12] In the absence of a transition-metal catalyst, no amination was observed (Table 1, entry 1). Metal salts derived from Cu^{I}, Cu^{II}, Cr^{II}, Cr^{III}, Ni^{II}, Pd^{II} provided only traces of the secondary amine **5a** (entries 2–8). However, Fe^{II} or Fe^{III} catalysis gave valuable results, and $FeCl_3$ was more active than $FeCl_2$ (entries 9–10).[13] Varying the stoichiometry showed that 0.5 equiv of $FeCl_3$ led to the best result, furnishing **5a** in 68% yield of isolated product (entry 11–12). Further optimization of the reaction conditions showed that performing the amination at 50 °C led to complete conversion to **5a** within 1 h in 74% yield of isolated product (entry 11).

Table 1: Optimization of the electrophilic amination of organozinc halides **2** with organic azides **1**, leading to secondary amines of type **5**.



Entry	Catalyst (loading)	Yield [%]
1	–	0
2	CuCN·2 LiCl (20 mol%)	<5%
3	$CuCl_2$ (20 mol%)	<5%
4	$CrCl_3$ (20 mol%)	<5%
5	$CoCl_2$ (20 mol%)	<5%
6	$CrCl_2$ (20 mol%)	<5%
7	$NiCl_2$ (20 mol%)	<5%
8	$PdCl_2$ (20 mol%)	<5%
9	$FeCl_2$ (20 mol%)	51[a]
10	$FeCl_3$ (20 mol%)	55[a]
11	$FeCl_3$ (50 mol%)	68[b] (74[b,c])
12	$FeCl_3$ (75 mol%)	32[a]

[a] GC-yield. [b] Yield of isolated product. [c] 50 °C, 1 h

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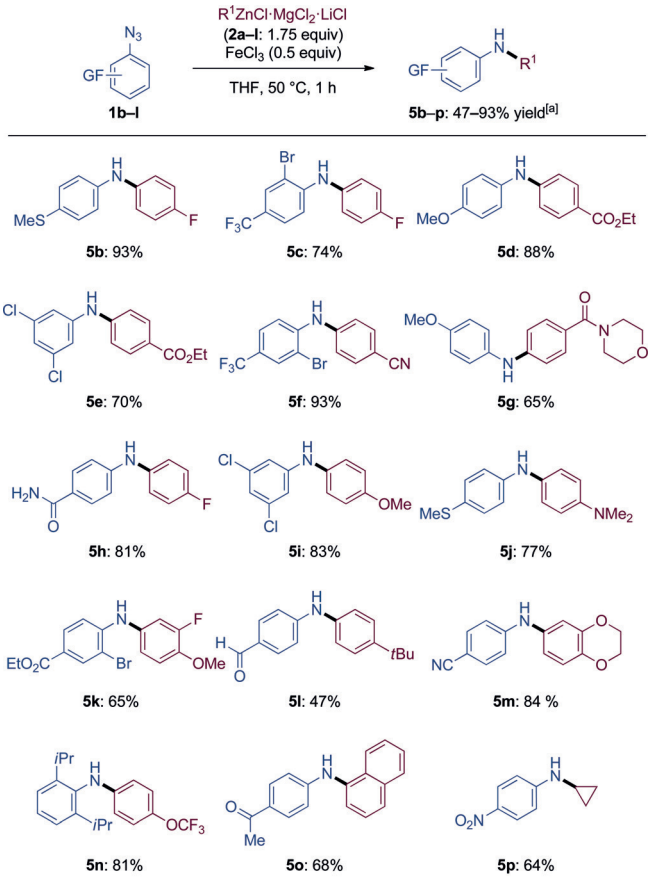
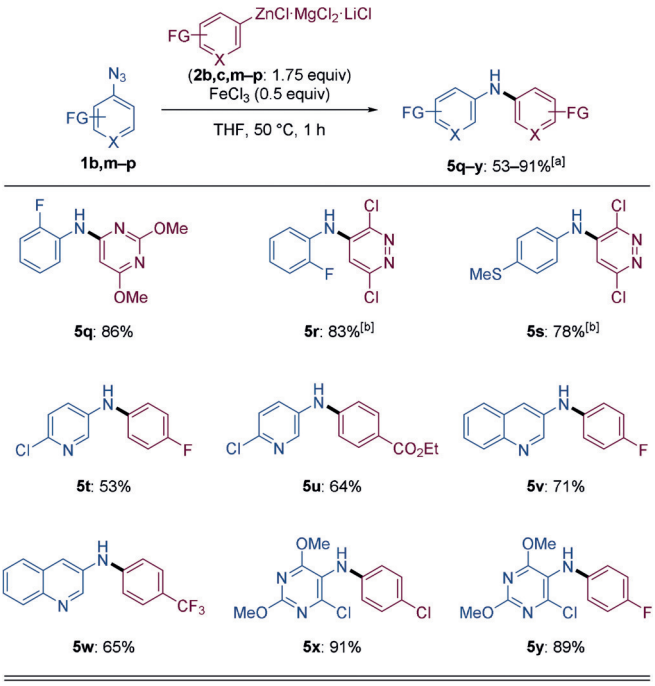
These amination conditions were satisfactory for a wide range of organic azides **1** as well as organozinc halides **2** (Scheme 2). Remarkably, arylzinc chlorides bearing electron-withdrawing groups, and therefore being less nucleophilic, still react under our standard conditions (50 °C, 1 h). Thus,



Scheme 2. Scope with respect to functionalized aryl azides of type **1** and arylzinc halides of type **2** in the iron-mediated electrophilic amination reaction. [a] Yields of isolated product; R^1 = aryl, alkyl.

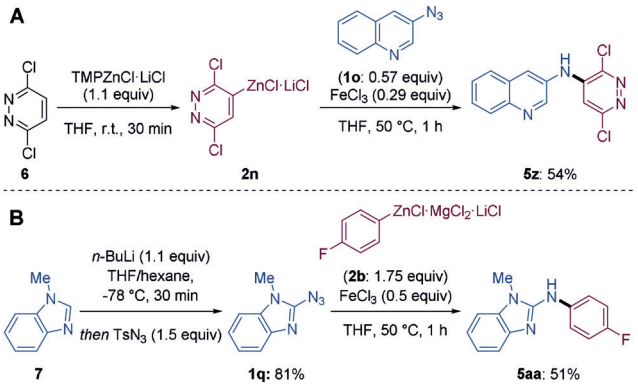
various highly functionalized diarylamines (**5b–h**), containing functional groups such as halides, esters, cyano groups, *N*-morpholino amides, and a primary amide group ($CONH_2$), were prepared in high yields (65–93 % yield). As expected, electron-rich arylzinc reagents react smoothly under the described conditions, leading to diarylamines **5i–o** bearing functional groups such as dimethylamino, OCF_3, formyl, or acetyl groups (47–84 % yield). Alkylzinc reagents also showed to be suitable substrates and cyclopropylzinc chloride (**2l**) was aminated by 4-nitrophenylazide in 64 % yield. Interestingly, no electron transfer from the zinc reagent to the nitro group is observed.[14]

The preparation of secondary amines bearing N-heterocyclic groups is of prime importance for pharmaceutical applications.[15] Therefore, heterocyclic zinc reagents **2m**,**n** or heterocyclic azides **1n–p** were subjected to this novel iron-mediated amination, and the heterocyclic amines **5q–y** were obtained (53–91 % yield, Scheme 3).



Scheme 3. Preparation of functionalized heteroaryl amines **5** using heterocyclic azides of type **1** and heteroarylzinc halides of type **2**. [a] Yields of isolated product. [b] The used organozinc chlorides do not contain $MgCl_2$.

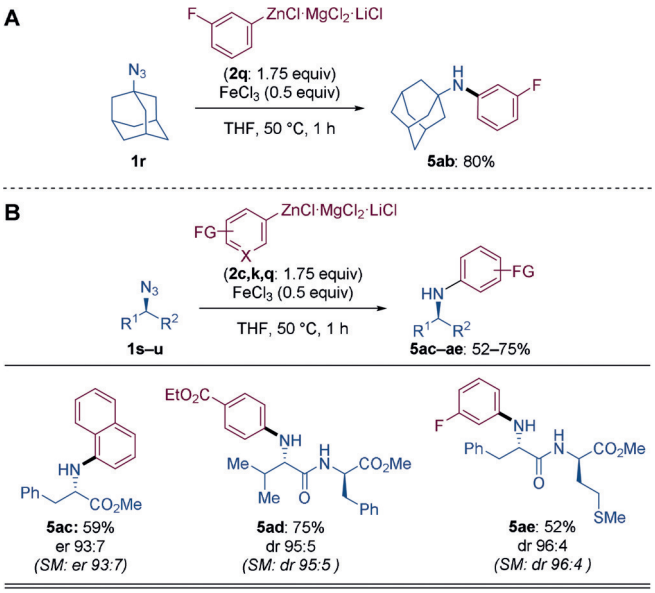
Interestingly, the required heterocyclic zinc reagents can be generated through selective metalation of a heterocyclic precursor. Thus, 3,6-dichloropyridazine (**6**) was readily zincated with TMPZnCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl)[16] at 25 °C for 30 min, leading to the heterocyclic zinc species **2n**, which was then aminated with various aryl (Scheme 3, **5r–s**) and heteroaryl (Scheme 4 a, **5z**) azides. Despite the presence of TMP-H, generated during the zincation, the amination proceeds without interference. Additionally, heterocyclic azides, such as *N*-methyl benzimidazole (**7**), were generated according to the method reported by Fujieda and co-workers[17] via lithiation using *n*-BuLi and subsequent trapping with TsN_3. Further reaction with arylzinc



Scheme 4. A) Metalation of 3,6-dichloropyridazine (**6**) and subsequent iron-mediated electrophilic amination. B) Generation of 2-azido-*N*-methyl benzimidazole (**1q**) and subsequent amination to provide amine **5aa**.

chloride **2b** gave the desired secondary amine in 51% yield (Scheme 4b, **5aa**).

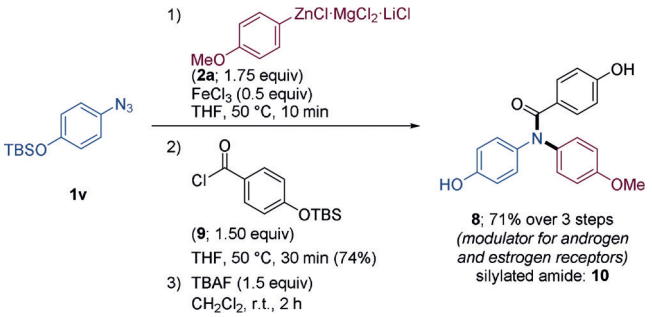
Finally, alkyl azides, including bulky azides like 1-adamantyl azide **1r**, react smoothly with arylzinc derivatives such as 3-fluorophenylzinc chloride (**2q**), leading to the adamantylamine **5ab** in 80% yield (Scheme 5a). This reaction was also extended to peptidic azides and azido esters (Scheme 5b, R^2 = OMe or NH-alkyl), which were arylated under the standard conditions, providing the polyfunctional chiral amines **5ac–ae** with full retention of configuration (Scheme 5b).



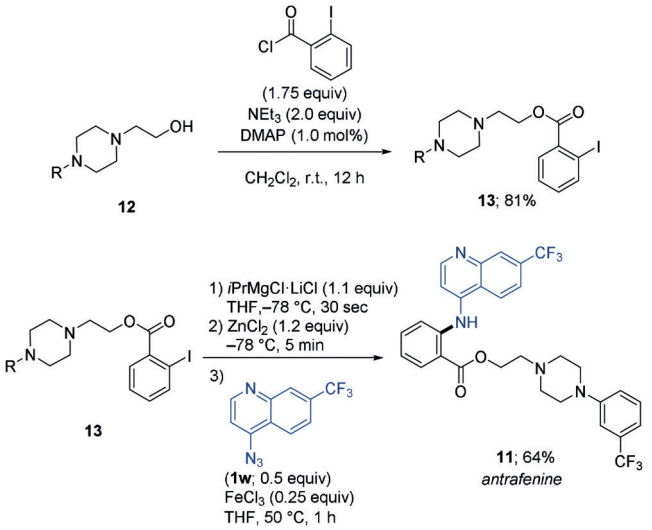
Scheme 5. A) Iron-mediated amination of organozinc chloride **2q** using the bulky alkyl azide 1-azidoadamantane (**1r**), leading to amine **5ab** in 80% yield of isolated product. B) Electrophilic amination of arylzinc halides **2c**,**k**,**q** using α-azido ester **1s** and peptidic azides **1t–u**, providing the arylated substrates in 52–75% yield of isolated product under full retention of configuration.

As an application, we have prepared two amine derivatives of pharmaceutical relevance. The first target was amide **8**, a modulator of androgen and estrogen receptors, reported by Dalton and co-workers.[18] Treatment of aryl azide **1v** with *p*-anisylzinc chloride (**2a**) in the presence of 50 mol% $FeCl_3$ (50 °C, 10 min) led to an intermediate amine, which then was directly acylated using acid chloride **9**, providing the protected amide **10** in 74% yield (Scheme 5). After desilylation (with TBAF) the desired product **8** was obtained in 71% overall yield (Scheme 6).

In a second application, we prepared the analgesic antrafenine (**11**). Starting from amino alcohol **12**, the iodide **13** was obtained in 81% yield after acylation. Following, a very fast iodine–magnesium exchange using *i*PrMgCl·LiCl (−78 °C, 30 sec) and subsequent transmetalation using $ZnCl_2$, the corresponding organozinc chloride was obtained. This was submitted to an electrophilic amination with heterocyclic azide **1w**, leading to antrafenine (**11**) in 64% yield (Scheme 7).



Scheme 6. Preparation of androgen and estrogen receptor modulator **8** using the iron-mediated electrophilic amination. TBAF = tetrabutylammoniumfluoride.



Scheme 7. Preparation of the analgesic antrafenine **11**, using the iron-mediated electrophilic amination. R = 3-CF_3-C_6H_5.

In summary, we have developed a general electrophilic amination of polyfunctional organozinc halides with organic azides, mediated by $FeCl_3$ (0.5 equiv). The reactions are generally complete within 1 h at 50 °C, providing highly functionalized secondary amines. As a mechanistic guideline we propose a transition state of type **4** (Scheme 1). Iron salts seem to have a unique ability to efficiently trigger this amination. Further scope extension, as well as mechanistic investigations, are currently underway in our laboratories.

Conflict of interest

The authors declare no conflict of interest.

Keywords: azides · electrophilic amination · iron-mediated amination · organozinc halides · secondary amines

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[1] A. Ricci, *Modern amination methods*, Wiley-VCH, Weinheim, **2008**.
[2] a) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247 – 9301; b) P. Ruiz-Castillio, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564 – 12649; c) J. X. Qiao, P. Y. S. Lam, in *Boronic Acids*, 2nd ed., Wiley-VCH, Weinheim, **2011**, pp. 315 – 361.
[3] a) A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901 – 7902; b) F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969 – 5970.
[4] a) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505 – 4519; b) H. Tsutsui, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1997**, *26*, 317 – 318.
[5] A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680 – 5681.
[6] a) Z. Zhou, L. Kürti, *Synlett* **2019**, https://doi.org/10.1055/s-0037-1611861; b) B. N. Hemric, A. Chen, Q. Wang, *J. Org. Chem.* **2019**, *84*, 1468 – 1488; c) C. E. Hendrick, K. J. Bitting, S. Cho, Q. Wang, *J. Am. Chem. Soc.* **2017**, *139*, 11622 – 11628; d) J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li, N. Jiao, *Chem. Eur. J.* **2017**, *23*, 563 – 567; e) C. E. Hendrick, Q. Wang, *J. Org. Chem.* **2017**, *82*, 839 – 847; f) X. Dong, Q. Liu, Y. Dong, H. Liu, *Chem. Eur. J.* **2017**, *23*, 2481 – 2511; g) M. Corpet, C. Gosmini, *Synthesis* **2014**, *46*, 2258 – 2271.
[7] a) S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann, P. Knochel, *Org. Lett.* **2019**, *212*, 494 – 497; b) Y.-H. Chen, S. Graßl, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 1108 – 1111; *Angew. Chem.* **2018**, *130*, 1120 – 1124.
[8] a) P. Starkov, T. F. Jamison, I. Marek, *Chem. Eur. J.* **2015**, *21*, 5278 – 5300; b) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040 – 1052; c) E. Ciganek, in *Organic Reactions 72*, Wiley-VCH, Weinheim, **2009**, pp. 1 – 366; d) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188 – 5240; *Angew. Chem.* **2005**, *117*, 5320 – 5374.
[9] B. M. Trost, W. H. Pearson, *J. Am. Chem. Soc.* **1983**, *105*, 1054 – 1056.
[10] a) B. V. S. Reddy, N. S. Reddy, Y. J. Reddy, Y. V. Reddy, *Tetrahedron Lett.* **2011**, *52*, 2547 – 2549; b) J. S. Yadav, B. V. S. Reddy, P. Borkar, P. J. Reddy, *Tetrahedron Lett.* **2009**, *50*, 6642 – 6645; c) J. S. Yadav, C. Madhuri, B. V. S. Reddy, G. S. K. K. Reddy, G. Sabitha, *Synth. Commun.* **2002**, *32*, 2771 – 2777; d) H. M. S. Kumar, B. V. S. Reddy, S. Anjaneyulu, J. S. Yadav, *Tetrahedron Lett.* **1999**, *40*, 8305 – 8306.
[11] a) A. D. Benischke, M. Ellwart, M. R. Becker, P. Knochel, *Synthesis* **2016**, *48*, 1101 – 1107; b) P. Knochel, N. Millot, A. L. Rodriguez in *Organic Reactions* 58, Wiley-VCH, Weinheim, **2004**, pp. 417 – 759.
[12] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117 – 2188.
[13] a) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778 – 789; b) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170 – 3387; c) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217 – 6254.
[14] I. Sapountzis, P. Knochel, *J. Am. Chem. Soc.* **2002**, *124*, 9390 – 9391.
[15] a) K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Wiley-VCH, Weinheim, **1997**; b) S. A. Lawrence, *Amines: Synthesis Properties and Applications*, University Press, Cambridge, **2004**.
[16] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837 – 1840.
[17] S. Ohta, N. Tsuno, S. Nakamura, N. Taguchi, M. Yamashita, I. Kawasaki, M. Fujieda, *Heterocycles* **2000**, *53*, 1939 – 1955.
[18] J. T. Dalton (Pearl Cohen), US 2007/0265296A1, **2007**.

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