Iron-Mediated Electrophilic Amination of Organozinc Halides using Organic Azides

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Abstract: A wide range of alkyl-, aryl- and heteroarylzinc halides were aminated with highly functionalized alkyl, aryl, and heterocyclic amines. The reaction proceeds smoothly at 50°C within 1 h in the presence of FeCl₃ (0.5 equiv) to furnish the corresponding secondary amines in good yields. This method was extended to peptic azides and provided the aryalted 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] in which the amine plays the role of a nucleophile, such as the Buchwald–Hartwig amination,[2] 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[3] and more recently from Berman and Johnson[4] have led to a number of electrophilic aminations, for example, using N-hydroxylamines derivatives as electrophilic aminating reagents.[5] Recently, we have shown that the cobalt-catalyzed amination of organozinc halides and pivalates by N-hydroxylamine benzoates furnishes polyfunctional tertiary amines.[6] 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.[7] In early work by Pearson and Trost[8] and others,[9] such reactions have been performed using Grignard reagents. We envisioned that organozinc halides of type 2 would be especially attractive, since these organometallics are compatible with the presence of various functional groups.[10] 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).

In preliminary experiments, we treated aryl azide (1a) with 4-anisylzinc chloride (2a), prepared from the corresponding Grignard reagent by transmetalation with ZnCl₂, in THF at 25°C.[11] 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(III), 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 FeCl₃ was more active than FeCl₂ (entries 9–10).[12] Varying the stoichiometry showed that 0.5 equiv of FeCl₃ led to the best result, furnishing 5a in 68% yield of isolated product (entry 11). 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 with organic azides in the presence of a transition metal catalyst.

| Entry | Catalyst (loading) | Yield [%] |
|-------|-------------------|-----------|
| 1     | –                 | 0%        |
| 2     | CuCN·2LiCl (20 mol%) | < 5% |
| 3     | CuCl₂ (20 mol%)   | < 5%      |
| 4     | CoCl₂ (20 mol%)   | < 5%      |
| 5     | CoCl₂ (20 mol%)   | < 5%      |
| 6     | CrCl₃ (20 mol%)   | < 5%      |
| 7     | NiCl₂ (20 mol%)   | < 5%      |
| 8     | PdCl₂ (20 mol%)   | < 5%      |
| 9     | FeCl₂ (20 mol%)   | 51%       |
| 10    | FeCl₂ (20 mol%)   | 55%       |
| 11    | FeCl₃ (50 mol%)   | 68% (74%[c]) |
| 12    | FeCl₃ (75 mol%)   | 32%       |

[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, various highly functionalized diarylamines (5b–h), containing functional groups such as halides, esters, cyano groups, N-morpholino amides, and a primary amide group (CONH₂), 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, OCF₃, 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.

Interestingly, the required heterocyclic zinc reagents can be generated through selective metalation of a heterocyclic precursor. Thus, 3,6-dichloropyridazine (6) was readily zinicated with TMPZnCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl) 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 4a, 5z) azides. Despite the presence of TMP-H, generated during the zinication, 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 via lithiation using n-BuLi and subsequent trapping with TsN₃. Further reaction with arylzinc...
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 adaman-tyamine 5ab in 80% yield (Scheme 5a). This reaction was also extended to peptidic azides and azido esters (Scheme 5b, R2 = 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).

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 1r with p-anisylzinc chloride (2a) in the presence of 50 mol% FeCl3 (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 of isolated product (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 iPrMgCl·LiCl (−78 °C, 30 sec) and subsequent transmetalation using ZnCl2, 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).

In summary, we have developed a general electrophilic amination of polyfunctional organozinc halides with organic azides, mediated by FeCl3 (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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