

Preparation of Tertiary Amines from Tris(2-cyanoethyl)amine Using Three Successive Cobalt-Catalyzed Electrophilic Aminations with Organozinc Halides

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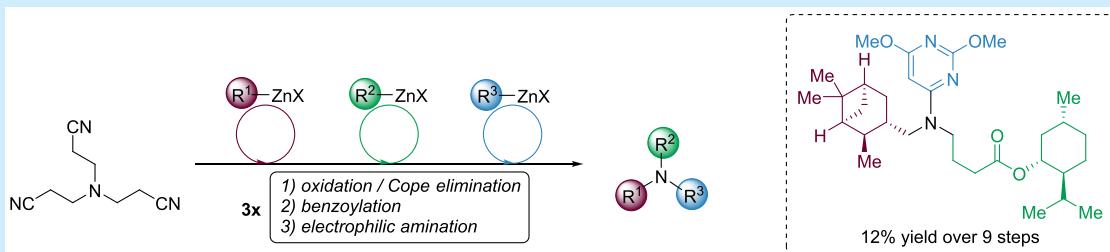
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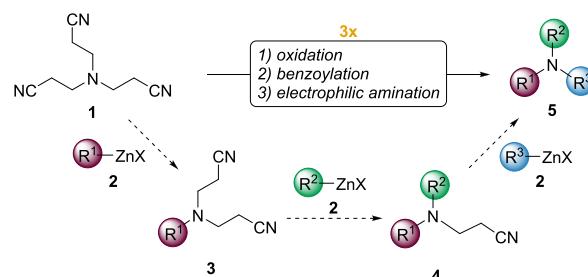


ABSTRACT: We report a stepwise preparation of triple alkylated or arylated tertiary amines, starting from commercially available tris(2-cyanoethyl)amine using three successive reaction sequences involving a selective oxidation (formation of an *N*-oxide followed by a Cope elimination) leading to an intermediate hydroxylamine, a benzoylation, and a cobalt-catalyzed electrophilic amination with organozinc halides.

The formation of carbon–nitrogen bonds is a central challenge for the elaboration of pharmaceuticals and agrochemicals.¹ In recent decades, several new amine preparations have been developed.² Therein, the palladium-catalyzed nucleophilic aminations reported by Buchwald³ and Hartwig⁴ tremendously improved the scope of especially aryl and heteroaryl amine synthesis.⁵ Lately, electrophilic aminations, pioneered by Narasaka⁶ and Johnson,⁷ have proven to display a valuable alternative, since cheaper and less toxic catalysts derived from Cu, Ni, Co, or Fe may be used.⁸ These aminations utilize electrophilic nitrogen sources, such as organic azides,⁹ *N*-chloro amines,¹⁰ or *N*-hydroxylamine benzoates¹¹ in combination with various organometallic reagents as nucleophiles. Recently, we reported a preparation of *N*-hydroxylamine benzoates, based on a Cope elimination on amines bearing a 2-cyanoethyl moiety.¹² This method proved to be very robust, enabling the late-stage functionalization of various polyfunctionalized amines.¹³ Therefore, we have envisioned using tris(2-cyanoethyl)amine (1) as a precursor for a triple electrophilic amination using three different organozinc reagents of type 2, providing tertiary amines of type 5. Due to their broad availability, high stability, and excellent tolerance toward sensitive functional groups, organozinc reagents would be desirable nucleophiles for this transformation.¹⁴ This would enable construction of a variety of tailored tertiary amines, bearing three chosen organic moieties (R^1 , R^2 , R^3 ; Scheme 1). Using other amination procedures, such a task is often challenging, since over-

alkylation and -arylation of primary amines are frequently observed side reactions.¹⁵

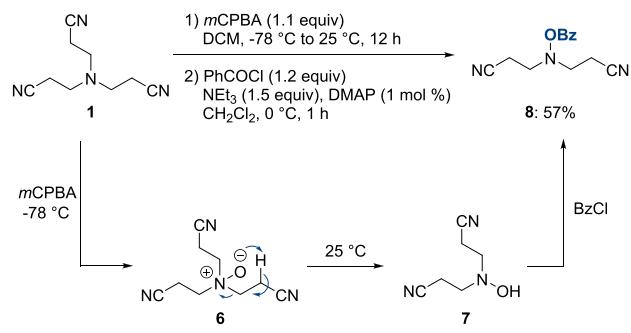
Scheme 1. General Iterative Preparation of Functionalized Tertiary Amines of Type 5 Starting from Amine 1 and Organozinc Halides 2



Herein we report an iterative sequence, which furnishes tertiary amines using three different organozinc reagents of type 2 and tris(2-cyanoethyl)amine (1) as the nitrogen source. Thus, we have treated amine 1 with *m*CPBA at $-78\text{ }^\circ\text{C}$, leading to the *N*-oxide 6, which reacts at $25\text{ }^\circ\text{C}$ to the corresponding hydroxylamine 7 (Scheme 2). After benzoyla-

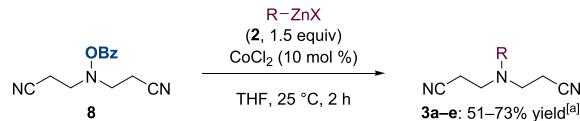
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Scheme 2. Preparation of Hydroxylamine Benzoate 8 Starting from Amine 1 and Proposed Mechanistic Pathway



tion using benzoyl chloride and triethylamine, the *N*-hydroxylamine benzoate **8** was obtained in 57% yield. This benzoate **8** was submitted to a cobalt-catalyzed electrophilic amination with alkylzinc halides of type **2**. Thus, the amination of organometallics **2a–c** provided, after amination with benzoate **8** in the presence of CoCl_2 , the tertiary amines **3a–c** in 61–73% yield (Scheme 3, entries 1–3).

Scheme 3. Cobalt-Catalyzed Electrophilic Amination of Alkyl Organozinc Reagents **2a–e Using *N*-Hydroxylamine Benzoate **8**, Leading to Tertiary Amines of Type **3****



Entry	Organozinc reagent of type 2	Product of type 3	Yield ^[a]
1			65%
2			73%
3			61%
4			51%
5			66%

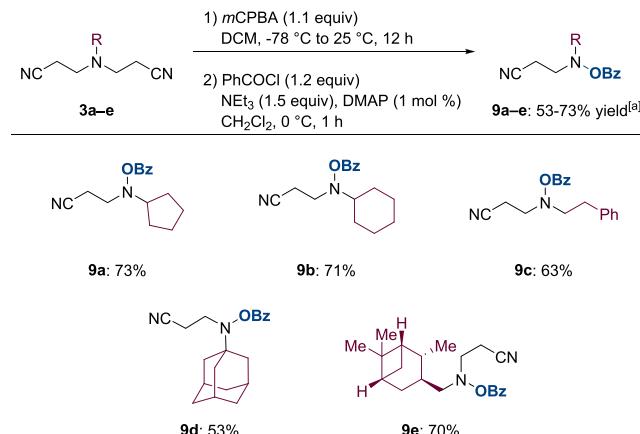
^aAll reported yields are isolated yields of analytically pure products.

Remarkably, even the sterically hindered adamantylzinc bromide (**2d**) was readily aminated with hydroxylamine **8**, leading to amine **3d** in 51% yield (entry 4). Also, the pinene-derived organometallic **2e** provided, after a cobalt-catalyzed amination with benzoate **8**, the desired tertiary amine **3e** in 66% yield (entry 5). As reported in the literature, hydroxyl-

amine benzoates derived from aromatic amines are not stable and undergo a [3,3]-sigmatropic rearrangement of the OBz moiety to the aryl ring.¹⁶ Therefore, only alkylzinc reagents were used for the first two functionalizations.

Next, we applied the oxidation procedure to the alkylated tertiary amines of type **3**. As expected, selective formation of the corresponding hydroxylamine was straightforward, which after benzoylation provided the benzoates **9a–e** in 53–73% yield (Scheme 4). Those have been coupled a second time,

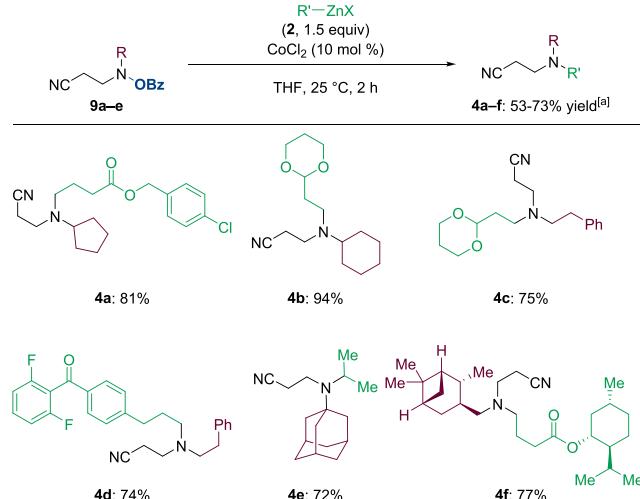
Scheme 4. Preparation of *N*-Hydroxylamine Benzoates of Type **9 Starting from Amines of Type **3****



^aAll reported yields are isolated yields of analytically pure products.

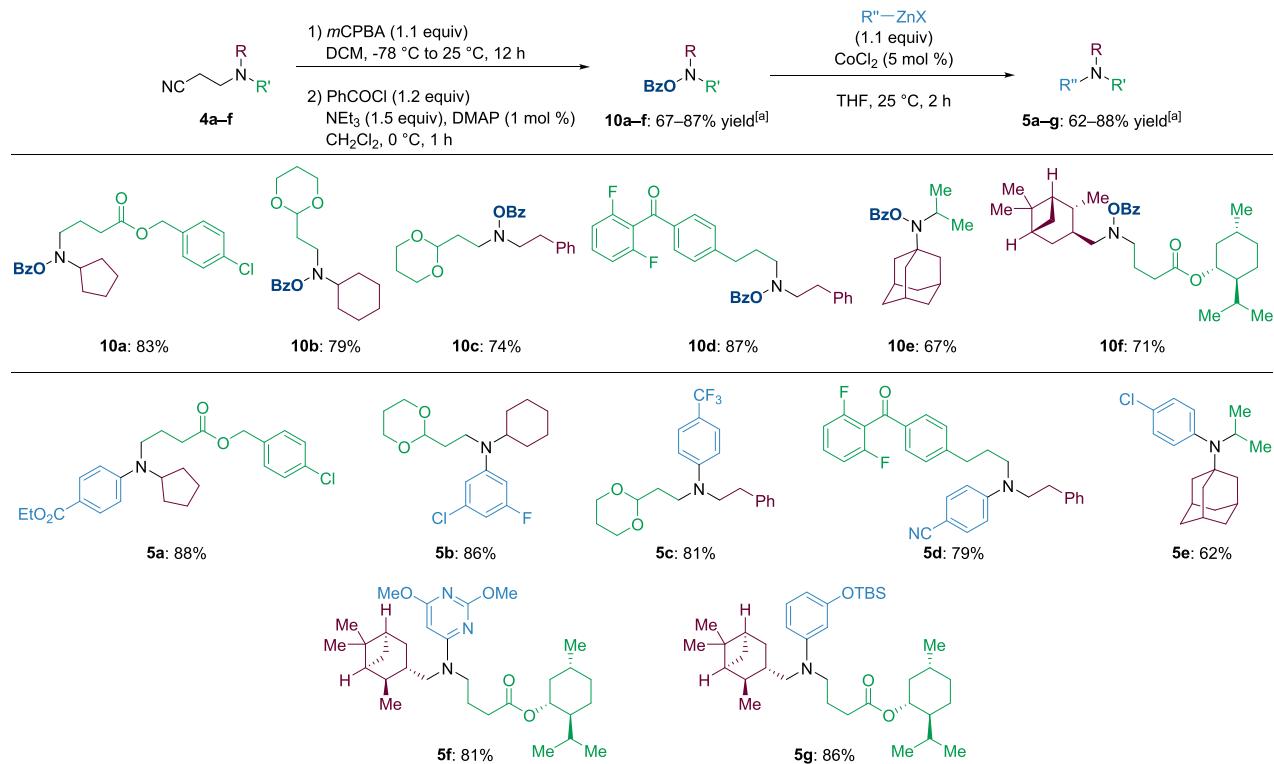
using various alkylzinc reagents of type **2**. Thus, treatment of cyclopentylamine benzoate **9a** with polyfunctional organozinc reagent **2f** in the presence of a cobalt catalyst led to the double functionalized amine **4a** in 87% yield (Scheme 5). Also, the benzoates **9b–c** were smoothly alkylated using the functionalized organozinc reagents **2g–h**, providing the tertiary amines **4b–d** in 74–94% yield. Noteworthy, the sterically hindered *N*-hydroxylamine benzoate **9d** was successfully reacted with isopropylzinc chloride (**2i**), providing the bulky tertiary amine

Scheme 5. Electrophilic Amination of Organozinc Reagents of Type **2 Using Benzoates of Type **9** in the Presence of CoCl_2**



^aAll reported yields are isolated yields of analytically pure products.

Scheme 6. Preparation of N-Hydroxylamine Benzoates of Type 10 Starting from Amines of Type 4 and Electrophilic Amination of Organozinc Reagents of Type 2 Using Benzoates of Type 10 in the Presence of CoCl_2



^aAll reported yields are isolated yields of analytically pure products.

4e in 72% yield.¹⁷ In addition, the pinene-derived benzoate 9e was alkylated with the menthol-derived organozinc reagent 2j, leading to the tertiary amine 4f in 77% yield.

With these double alkylated amines of type 4 in hand, we focused on the last functionalization. Therefore, the amines of type 4 have been treated with *m*CPBA, followed by benzoylation, providing to the unsymmetrical hydroxylamine benzoates 10a–f in 67–87% yield (Scheme 6). These have been submitted to a cobalt-catalyzed electrophilic amination with various functionalized aryl- and heteroarylzinc reagents of type 2. Thus, arylzinc chloride 2k was aminated with hydroxylamine benzoate 10a in the presence of CoCl_2 , providing the triple functionalized tertiary amine 5a in 88% yield (Scheme 6). Also, benzoates 10b–d are readily arylated with organozinc chlorides 2l–n, leading to the corresponding aniline derivatives 5b–d in 79–86% yield. As expected, various functional groups, such as esters, nitriles, and a diaryl acetate, were tolerated in this transformation. Interestingly, adamantly hydroxylamine benzoate 10e smoothly reacted with 4-chlorophenylzinc chloride (2o), affording the corresponding amine 5e in 62% yield. Remarkably, the pinene-derived hydroxylamine benzoate (10f) reacted in the presence of a cobalt catalyst with the aryl- and heteroarylzinc chlorides 2p–q to give the arylated amines 5f–g in 81–86% yield.

In summary, we have developed a procedure to construct triple alkylated or arylated tertiary amines, starting from commercially available tris(2-cyanoethyl)amine (1). This iterative method involves standard steps such as an oxidation (generating after a Cope elimination a hydroxylamine), a benzoylation, and a cobalt-catalyzed electrophilic amination of organozinc reagents of type 2. Thus, various polyfunctionalized

tertiary amines have been prepared in good yields. Further scope extensions are currently underway in our laboratories.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c00297>.

Full experimental details and characterization of all isolated products (¹H NMR spectra, ¹³C NMR spectra, and mass analysis) (PDF)

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Notes

The authors declare no competing financial interest.

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