

A Practical in situ Generation of the Schwartz Reagent. Reduction of Tertiary Amides to Aldehydes and Hydrozirconation

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(5) Supporting Information



ABSTRACT: A new, highly efficient in situ protocol $(Cp_2ZrCl_2/LiAlH(OBu-t)_3)$ is described for the generation of the Schwartz reagent which provides a convenient method for the amide to aldehyde reduction and the regioselective hydrozirconation—iodination of alkynes and alkenes. Highlighted are chemoselective reductions of benzamides derived by directed *ortho* metalation (DoM) chemistry, allowing the synthesis of valuable 1,2,3-substituted benzaldehydes. The single-step, three-component process proceeds in a very short reaction time, shows excellent functional group compatibility, and uses inexpensive and long-storage stable reducing reagents.

F irst prepared in 1969,¹ the Schwartz reagent, Cp₂Zr(H)Cl, has developed into a stalwart reagent for hydrozirconation, reduction, and other functional group transformations.² In 2000, Georg reported that the Schwartz reagent is very effective for the mild and general reduction of tertiary amides to aldehydes.³ However, although the Schwartz reagent is commercially available, it is expensive and problematic for long-term storage due to its sensitivity to air, light, and moisture.^{2c,d} Moreover, this reagent is feebly soluble in common inert solvents. These drawbacks lower the effective use of the Schwartz reagent and limit its application. Previously reported in situ procedures for independent generation of the Schwartz reagent for hydrozirconation⁴ and amide reduction^{4d} by using different hydride sources such as LiAlH₄,^{4a} NaAlH₂(OCH₂CH₂OCH₃)₂ (Red-Al),^{4a} t-BuMgCl,^{4a,b} LiEt₃BH,^{4c} and DIBAL-H^{4d} led to the formation of a heterogeneous reagent (Figure 1, process A) that is typically contaminated with unreacted reductant (which may react with



Figure 1. Comparison of (A) two-step and (B) three-component, onepot in situ Schwartz reagent reduction processes.

substrate and intermediates), over-reduced Cp₂ZrH₂, and other salts.^{2c,d} To overcome these deficits,^{2c,d,5} we envisaged that an ideal, three-component, one-pot procedure for the in situ generation and use of the Schwartz reagent would embody the following features (Figure 1, process B): provides a freshly prepared reagent ready for immediate use, effects chemoselective reduction of Cp₂ZrCl₂ without reaction with substrates and organozirconium intermediates, and does not lead to over-reduction.

Herein we report on the formulation and development of an in situ generated Schwartz reagent process for the reduction of amides to aldehydes and hydrozirconation—iodination of alkenes and alkynes by using LiAlH(OBu-t)₃ as reductant which meets all the ideal requisites of Figure 1, process B.⁶ We further demonstrate its connection to the powerful regioselective directed *ortho* metalation (D*o*M) and cross-coupling methodologies, separate⁷ and combined,⁸ for aromatic amides allowing the regioselective construction of polysubstituted aromatic and heteroaromatic aldehydes with contiguous and uncommon patterns that are difficult to obtain by classical routes.

Following our successful use of the Georg procedure in the course of our Ergot alkaloid synthetic studies,^{6a} we were confronted by the deficiencies of the commercial Schwartz

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reagent mentioned above which stimulated the discovery and development of the synthetic chemistry reported herein.

In initial studies, we were motivated to assess the new in situ method with the well-defined Georg procedure for the reduction of *N*,*N*-diethylbenzamides to benzaldehydes.^{3a,c} We aimed to establish new methodology which tolerates the presence of other powerful directed *ortho* metalation groups (DMGs), functional groups (FGs) which act as cross coupling partners, as well as other FGs which had not been examined previously^{3a,c} (Scheme 1). Thus, in a comparative set of





^aYields are of isolated products. Equivalents of Cp₂ZrCl₂:LiAlH(OBu-t)₃ (1:1) /times of reduction (in minutes) are shown in parentheses. ^bData for Schwartz reagent (Cp₂Zr(H)Cl) reduction employing the Georg procedure. ^cReduction via inverse addition: a solution of Cp₂ZrCl₂ (1.4 equiv) was added to a solution of substrate and LiAlH(OBu-t)₃ (2.4 equiv). ^dAccompanied by the corresponding 3-(NHCbz)benzyl alcohol (24%). ^eAccompanied by the corresponding 3-*n*-PrO-benzaldehyde (7%).

experiments, when subjected to the Georg conditions (1.5 equiv of Schwartz reagent/THF/rt), a *p*-carbomethoxybenzamide underwent chemoselective reduction to give the benzaldehyde 2a in 92% yield within 25 min while the in situ procedure (1.6 equiv of Schwartz reagent) afforded 2a in the same yield within 2 min. In other comparative studies, the in situ method was shown to have an advantage in yield and time

of reaction, e.g., 2d, 2e, 2i, 2j, 2l-n, and 2q-s. A variety of FGs (CO₂Me, CN, NMe₂, NHBoc, NHCbz, NO₂, OCH₂CH= CH₂, OCONEt₂, OSiEt₃, OP(O)(NEt₂)₂, OTf, P(O)(OEt)₂, S(O)t-Bu, SO₂Ph, F, Cl, Br)^{2n,9} are tolerant to these Schwartz reduction conditions, including the powerful DMGs OCO-NEt $_2^{7c,10a}$ and OP(O)(NEt $_2)_2^{10b}$ which offer useful data for further synthetic design based on DoM chemistry. The partial over-reduction for an NHCbz benzamide using the Georg method (aldehvde product 2e, 76% yield accompanied by the corresponding alcohol, 24% yield) was not observed under the in situ conditions (quant yield of 2e). Interestingly, the valiant N-Boc was found to be stable to the Schwartz reduction conditions (2f), and the coexistence of an amide-alkene FG, which was complicated by hydrozirconation under the Georg conditions (2i), was not compromised under the in situ 2 min protocol to give product 2i in 91% yield. As an example of the chemoselective reduction of a heterocycle, a picolinamide afforded the corresponding aldehyde 2s in a useful yield.¹¹ Furthermore, a reverse addition procedure was developed for high-yield reduction of amide substrates bearing acidic hydrogens: a solution of Cp₂ZrCl₂ (1.4 equiv) was added to a solution of substrate and LiAlH(OBu-t)₃ (2.4 equiv) of which 1 equiv of reductant presumably served to deprotonate the substrate (2b and 2h). Reduction of aliphatic amides also proceeded smoothly in high yields (2t-x) under the in situ conditions, including a branched aliphatic amide which furnished 2u under prolonged reaction times.

Having established the optimum conditions for the in situ method, a series of differentially *N*,*N*-disubstituted benzamides were investigated (Table 1). Thus, while a *N*,*N*-diethylamide **3a** underwent reduction in high yield in 2 min under the standard

Table 1. in situ Schwartz Reagent Reduction of Differentially Substituted Tertiary Amides 3a–i



^{*a*}Yields are of isolated products. ^{*b*}Cumyl = 2-phenylpropan-2-yl.

conditions (entry 1), the corresponding *N*,*N*-diisopropylamide **3b** required a prolonged reaction time and excess reductant to obtain a good yield of the aldehyde product **2r** (entry 2). Less-hindered, mono *ortho*-substituted benzamides **3c**, **3d**, and **3g**-**i** were reduced in high yields (entries 3, 4, and 7–9). Notable are the cases **4h** and **4i** (entries 8 and 9), which demonstrate for the first time the stability of aryl iodides under the reduction conditions. However, the corresponding bulky substituted amides such as *N*,*N*-diisopropyl- and *N*-ethyl-*N*-cumylamides **3e** and **3f** were resistant to reduction while, in comparison, these cases underwent reduction in moderate yields under the Georg conditions (entries 5 and 6).¹²

In order to demonstrate the utility of a linked DoM– Schwartz reduction tactic for the synthesis of valuable and difficult to access benzaldehydes, a variety of DoM-derived and -related amide substrates were investigated (Scheme 2).





^{*a*}Yields are of isolated products. ^{*b*}Data for Schwartz reagent $(Cp_2Zr(H)Cl)$ reduction employing the Georg procedure.

Inherently, all ortho-substituted N,N-diethylbenzamides performed well under the reduction conditions to give the corresponding benzaldehydes 5a-i in good yields. P- and Sisubstituents were found to be tolerated as seen from products 5a and 5b,e, respectively. Although the hindered o-PPh₂ benzamide was reduced in moderate yield under the standard conditions, the use of excess reductant (1.8 equiv) furnished aldehyde 5a in 93% yield. Similarly, use of an excess amount of reductant (1.8 equiv) drove the reduction of a hindered 2,3disubstituted benzamide to completion to furnish aldehyde product 5e in 97% isolated yield. 1-Aryl-2-naphthamides were smoothly reduced (5f,g). While a thiophenene-ylbenzamide (5h) behaved unexceptionally, surprisingly, a di-ortho-substituted furanamide was reduced to the corresponding aldehyde 5i in good yield under the standard conditions.¹³ A possible rationalization is the less encumbered environment of an amide between two furan ring substituents compared to the corresponding aryl amide due to bond angle differences of the respective substituents.¹⁴ Besides the *N*,*N*-diethyl aromatic amides, the DoM-derived N,N-dimethyl and N-methyl-N-

phenylbenzamides **3h** and **3i** (Table 1) behaved very well in the in situ Schwartz reduction process. These results establish a useful benzamide DoM-in situ Schwartz reduction connection for the preparation of unusual contiguously substituted benzaldehydes of potential further synthetic value.¹⁵

After the amide to aldehyde reduction study, we expanded the new in situ method to hydrozirconation chemistry. For a brief targeted investigation, we chose the conversion of alkynes to (*E*)-iodoalkenes which was previously reported in a threestep (preparation of Schwartz reagent and hydrozirconation at 0 °C; iodination at -78 °C) one-pot process using Cp₂ZrCl₂/ DIBAL-H.^{4d} The results, summarized in Scheme 3, demon-





strate that aliphatic and aromatic alkynes **6a–c** are regio- and stereoselectively converted to the expected (*E*)-iodoalkenes **7a–c** in high yields under simpler reaction conditions. Notably, in contrast to the low reaction temperatures (0 and -78 °C) required for the comparative method,^{4d} the in situ method is conducted at room temperature with high efficiency, e.g., **7a** is obtained in 91% yield by both methods. Further, hydrozirconation–iodination of an alkene **6d** under the same conditions furnished iodoalkane **7d** in excellent yield and high regioselectivity. Thus, the in situ protocol appears to be an advantageous procedure for the provision of (*E*)-iodoalkenes and iodoalkanes which are useful for the important Negishi cross-coupling regimen.¹⁶

In summary, stimulated by the Georg report,^{3a} we have discovered and developed an advantageous in situ protocol $(Cp_2ZrCl_2/LiAlH(OBu-t)_3)$ for the generation of the Schwartz reagent which provides a general, convenient, and economic method for the reduction of aliphatic, aromatic, and heteroaromatic tertiary amides to the corresponding aldehydes and the regioselective hydrozirconation-iodination of alkynes and alkenes. The reaction demonstrates advantages of a very short reaction time, excellent functional group compatibility, and use of inexpensive and long-storage stable reducing reagents. Of considerable significance is the DoM-Schwartz protocol. The large number of benzamide precursors of benzaldehyde products 2d, 2f, 2j-n, 2p, and 2q (Scheme 1) represent prototypes bearing additional DMGs, on which DoM chemistry⁷ prior to reduction can lead to unusually substituted aromatics. More recommendable are the contiguously substituted products 5b-e and 5i (Scheme 2), which have seen abundant use in modern synthetic practice.¹⁷ From these considerations, substantially greater synthetic utility and application of these results is anticipated. Considerable generalization and mechanistic studies will be reported in due course.

Organic Letters

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for new compounds and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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