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One-step facile synthesis of deuterium labeled aldehydes from tertiary amides using $Cp_2Zr(D)Cl$

Jared T. Spletstoser, Jonathan M. White and Gunda I. Georg*

Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, University of Kansas, Lawrence, KS 66045-7582, USA

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Abstract—The synthesis of deuterium labeled aldehydes was accomplished in an expedient and facile manner through the reduction of amides using commercially available $Cp_2Zr(D)Cl$. The reactions proceeded rapidly (ca. 15 min) and in high yields (70–99%).

Deuterium labeled aldehydes and their derivatives are frequently found in a variety of biochemical and chemical applications.[1–3] Specifically, deuterioaldehydes have been used to show that the enzymatic reduction of acetaldehyde by yeast alcohol dehydrogenase is stereospecific.[3] Furthermore, deuterioaldehydes were used to determine deuterium isotope effects in imine formation reactions to probe transition-state structures.[2] Although several methods are available for the synthesis of deuterioaldehydes, most involve multi-step procedures, costly reagents, or extended reaction times.[4–12] Some representative examples of deuterioaldehyde preparation methods include: Rosenmund reduction of acid chlorides (moderate yields with low deuterium incorporation),[4] lithium aluminum deuteride reduction followed by oxidation (two steps, moderate yields, and substrate specific),[5] aldehyde conversion to the dithiane followed by *n*-butyllithium H–D exchange (three-steps and requires strong basic conditions),[7] reduction of dihydro-1,3-oxazines (four steps and is specific for α, β-unsaturated and aliphatic aldehydes).[10] Methods have been developed to overcome these limitations, but are often highly substrate dependent.[11] Most of the methods reported to date for the synthesis of deuterioaldehydes requires either heat[4,7–9] or the use or generation of strong bases,[7,8,10,12] usually at low temperatures. Thus, the need to develop an efficient and general method for the synthesis of deuterium labeled aldehydes that operates under mild conditions remains.

Previous findings in our laboratory have shown that the Schwartz reagent provides an efficient method to reduce a variety of tertiary amides, including *N*,*O*-dimethylhydroxamates[13] (Weinreb amides) to the corresponding aldehydes.[14] This reaction has been shown to proceed on a variety of substrates and has also revealed an extraordinary selectivity profile. Furthermore, this reduction operates under very mild conditions and with fast reaction times (at room temperature, typically in under 15 min). We therefore sought to further expand the use of this chemistry for the preparation of deuterium labeled aldehydes (Fig. 1). Fortunately, deuterium labeled Schwartz reagent is commercially available ($Cp_2Zr(D)Cl$). Thus, the application of $Cp_2Zr(D)Cl$ was explored and the results are detailed herein.

As shown in Table 1, a variety of amides was efficiently reduced by $Cp_2Zr(D)Cl$ in good overall yield. Further, the reactions proceeded very rapidly—comparable to the results seen with $Cp_2Zr(H)Cl$. The reaction is selective for tertiary amides and is unaffected by electronic substituents (comparing entry 1 and 2, electron donating and electron withdrawing compounds, respectively). Compatibility is observed for aromatic, aliphatic, and heteroaromatic systems. Further, the tertiary amide is selectively reduced in the presence of the nitrile (entry 3), as well as the secondary *tert*-butoxycarbonyl (BOC) protected amide (entry 6). As is known with the hydrido

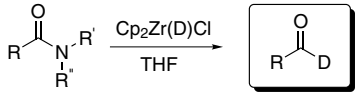

Figure 1. General reduction of tertiary amides to deuterium labeled aldehydes.

Keywords: Schwartz reagent; Zirconium; Amide; Reduction; Deuterium labeled aldehyde; $Cp_2Zr(D)Cl$.

* Corresponding author. Tel.: +1-7858644498; fax: +1-7858645326; e-mail: georgeku.edu

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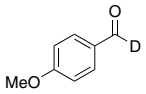
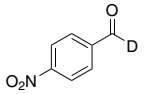
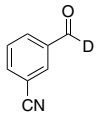
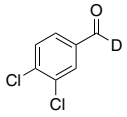
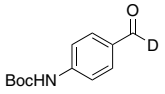
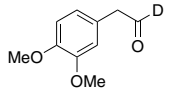
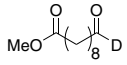
Table 1. Reaction scope

Entry	Product	Yield (%)	Reaction time (min)	Starting amide
1		90	10	–NEt_2
2		70	15	–NEt_2
3		85	10	–NEt_2
4		93	5	–N(OMe)Me
5		92	10	–N(OMe)Me
6		91	5	–N(OMe)Me
7		92	5	–NEt_2
8		89	10	–N(OMe)Me
9		80	20	–NEt_2

reagent, the tertiary amides are reduced in the presence of esters as well.[14] This feat is not possible with DIBAL-D and has not been reported to occur with any other reagent to the best of our knowledge. These are meaningful points, as alternative methods cannot achieve the same selectivities. For example, lithium aluminum deuteride (LAD) is one method that can be used for the preparation of deuterium labeled aldehydes. Unfortunately, the use of LAD with compounds containing the aforementioned functional groups is not possible. The same is true for DIBAL-D, another reagent used to generate deuterium labeled aldehydes. In all cases, no over-reduction to the corresponding alcohol was observed.

A typical procedure is as follows: $Cp_2Zr(D)Cl$[15] (380 mg, 1.5 mmol) was suspended in THF (2 mL) under argon at ambient temperature to which *N*,*N*-diethyl-4-methoxybenzamide (210 mg, 1.0 mmol) in THF (1 mL) was added in one-portion. The reaction mixture was stirred and monitored by TLC. Typical reactions were completed in 15 min—see Table 1 for specific reaction periods. Upon reaction completion (10 min), the mixture was concentrated and directly purified via silica gel column chromatography to provide the aldehyde (123 mg, 0.9 mmol) in 90% yield (see Table 1 for specific yields).

Spectral data of aldehydes from entries 1, 2,[16] and 8[12] were in accordance with their reported values. The remaining products were fully characterized by ^1H and ^{13}C NMR, IR, and MS. Deuterium incorporation was $\geqslant 95\%$ as determined by ^1H NMR for all products.

In summary, an efficient and high-yielding method for the preparation of deuterium labeled aldehydes has been developed. This method has the advantage of being nonsubstrate specific and works on a variety of tertiary amides, including Weinreb amides, and proceeds with no observed over-reduction of the aldehyde.

References and notes

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