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Direct reductive amination of carbonyl compounds using bis(triphenylphosphine) copper(I) tetrahydroborate

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Abstract—A direct reductive amination protocol for aldehydes/ketones using bis(triphenylphosphine) copper(I) tetrahydroborate as a novel reducing agent in the presence of sulfamic acid has been developed. The reagent chemoselectively reduces the imine moiety and does not affect other reducible functionalities such as chloro, nitro, cyano and methoxy.

Amines and their derivatives are important functionalities in various natural products and unnatural synthetic targets. Due to its unique biological properties the amine moiety has played a central role in the chemotherapeutics of numerous diseases.[1] Lower aliphatic amines are used as organic intermediates for the synthesis of drugs, bactericides, herbicides, rubber accelerators, corrosion inhibitors and surface-active agents.[2–4] Considering their significant applications in the fields of medicinal, bioorganic, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of amines.

The reductive amination of aldehydes and ketones is one of the most useful methods for the synthesis of secondary and tertiary amines. The importance of reductive amination procedures is exemplified by the enormous number of its synthetic uses.[5] Direct reductive amination (DRA) procedures, where the carbonyl compound is treated in a one-pot fashion with the amine and a reducing agent is an extremely useful method. The two commonly used DRA processes are based either on a hydride reagent or catalytic hydrogenation. Hydride reagents such as $NaBH_4$[6] borane–pyridine,[7] borohydride exchange resin (BER),[8] zinc–acetic acid,[9] sodium borohydride–magnesium perchlorate,[10] $ZnBH_4$–$ZnCl_2$,[11] $NaBH(OAc)_3$,[12] silica gel–$ZnBH_4$,[13] dibutyltin chloride hydride[14] and $NaBH_3CN$[15] have been developed for this conversion. However, most of these reagents have one or other disadvantages. The use of $NaBH_3CN$ carries the risk of having residual cyanide in the product, while pyridine–borane is thermally unstable and must be handled with extreme care. Also, catalytic hydrogenation protocols are incompatible with a number of other reducible functional groups such as nitro, cyano and C–C multiple bonds. Therefore, the search for a milder and more efficient system for performing direct reductive amination has been the subject of recent focus.

In an effort to develop a convenient system for the DRA reaction, we focussed our attention on the use of complex hydrides. The size of the complex transition metal borohydrides, together with their solubility in non-hydroxylic organic solvents, makes them ideal for studies on selective reduction. An example of one such reagent is bis(triphenylphosphine) copper(I) tetrahydroborate (**1**) which has been used in the reduction of acid chlorides to aldehydes.[16,17] Unlike $NaBH_4$, **1** provides only one hydride equivalent per mole and the reagent appears to tolerate a variety of functional groups such as nitro, cyano, ester and C–C multiple bonds. As a result of its unique features, **1** has found applicability in many natural product syntheses. The ease of preparation of **1**, compatibility with various functional groups, indefinite shelf life and stability towards air and moisture prompted us to investigate its activity in direct reductive amination reactions.

Keywords: Reductive amination; Bis(triphenylphosphine) copper(I) tetrahydroborate; Carbonyl compounds; Amines.
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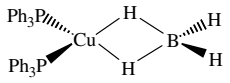
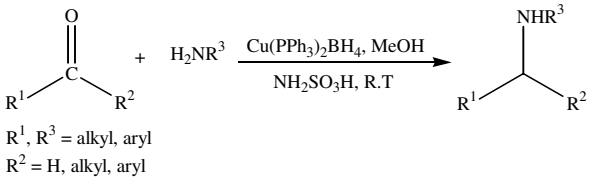


Bis(triphenylphosphine) copper(I) tetrahydroborate (**1**)

Herein, we report bis(triphenylphosphine) copper(I) tetrahydroborate[18] as a complex transition metal borohydride for the direct reductive amination of aldehydes and ketones in the presence of sulfamic acid. The reaction was carried out in methanol under mild operating conditions (Scheme 1).

Initially, the condensation of benzaldehyde with aniline was chosen as the model reaction, to examine the effect of the reductant. The reaction was carried out in a 1:1.2:1 mol ratio of aniline, benzaldehyde and $Cu(PPh_3)_2BH_4$ in methanol at room temperature. Under neutral conditions, no substantial reduction of the corresponding imine was observed. We then turned our attention towards the use of additives to promote the reaction. Since most DRA reactions are favoured under acidic conditions, the addition of 1 equiv of sulfamic acid led to higher yields of the desired product. Sulfamic acid was used because of its mild acidity, non-volatility, non-corrosive nature and cheap commercial availability.



Scheme 1. DRA of aldehydes and ketones with primary and secondary amines.

The influence of solvents on the DRA of aldehydes and ketones was also investigated (Table 1). Solvents such as chloroform and THF led to no conversion due to the

Table 1. Influence of solvent on the DRA of carbonyl compounds

Entry	Solvent	Time (h)	Yield[a] (%)
1	Chloroform	6	—
2	Tetrahydrofuran	6	—
3	Methanol	1.5	96
4	Ethanol	4	92
5	Toluene	6	92

[a] Reaction conditions: benzaldehyde = 1.2 mmol, aniline = 1 mmol, sulfamic acid = 1 mmol, complex **1** = 1 mmol, solvent = 5 ml. Yields based on GC analysis.

Table 2. Reductive amination of aldehydes and ketones[a]

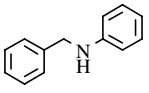
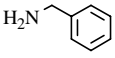
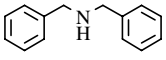
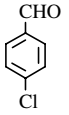
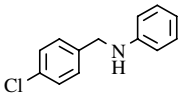
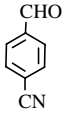
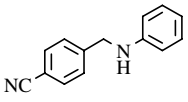
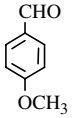
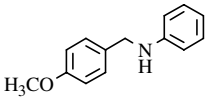
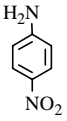
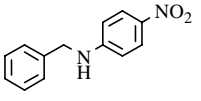
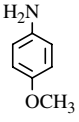
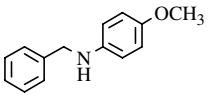
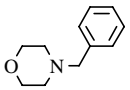
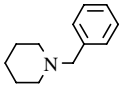
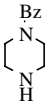
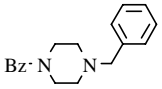
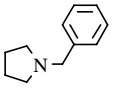
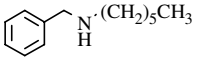
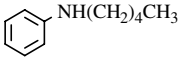
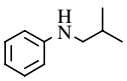
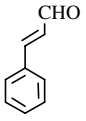
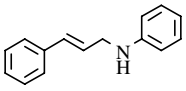
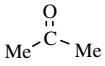
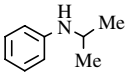
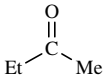
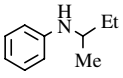
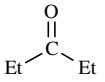
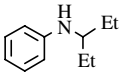
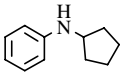
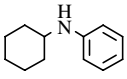
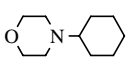
Entry	Carbonyl compound	Amine	Time (h)	Product	Isolated yield[b]
1			1.5		94
2			2		92
3			1.5		93
4			1.5		90
5			2		88
6			4		83
7			3		91
8			2		92

Table 2 (*continued*)

Entry	Carbonyl compound	Amine	Time (h)	Product	Isolated yield[b]
9			3		93
10			1.5		94
11			3		92
12		$CH_3(CH_2)_5NH_2$	4		87
13			1.5		89
14			1.5		88
15			2		84
16			1.5		88
17			2		88
18			3		82
19			4		92
20			4		91
21			4		90
22		$CH_3(CH_2)_5NH_2$	4		87

[a] Reaction conditions: carbonyl compound = 6 mmol, amine = 5 mmol, sulfamic acid = 5 mmol, **1** = 5 mmol, solvent = methanol (15 ml).
[b] Isolated yields.

good solubility of complex **1** in the respective solvent. However, when methanol, ethanol and toluene were employed, better results were obtained, which was in agreement with literature reports,[16a] suggesting that complex **1** is highly active when the reactions are carried out in a medium in which **1** is insoluble.

To evaluate the general applicability of this reagent, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 2, entries 1–22).[19] The reaction of aniline with benzaldehyde (entry 1) gave a 94% yield of *N*-benzylaniline within 1.5 h. Similarly, primary and secondary aliphatic amines (entries 2, 8–12) when reacted with benzaldehyde afforded the corresponding *N*-benzyl derivatives in excellent yields. Another important feature of this protocol was the survival of a variety of reducible functional groups such as chloro, cyano, nitro and methoxy (entries 3–7). The system also allowed the DRA of cinnamaldehyde, to *N*-cinnamyl aniline in an excellent yield without affecting the double bond (entry 15). Similarly aliphatic aldehydes such as valeraldehyde and isobutyraldehyde were also aminated effectively (entries 13–14).

To check the overall compatibility of this protocol, the direct reductive amination of ketones was also carried out. A variety of ketones such as acetone, butan-2-one and cyclohexanone were efficiently aminated with various aliphatic and aromatic amines under mild conditions to afford the corresponding amines (entries 16–22) in good to excellent yields.

In summary, bis(triphenylphosphine) copper(l) tetrahydroborate has proved to be an excellent reagent for direct reductive amination of both aldehydes and ketones having different steric and electronic properties. The ease of making, handling, storing and using **1**, together with its compatibility with a large number of functional groups, makes this reagent an attractive and general alternative to the present range of methods for the direct reductive amination procedures. There is also considerable scope for modifying the reagent with a chiral phosphine ligand with the prospect of asymmetric induction.

Acknowledgement

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18. *Preparation of bis (triphenylphosphine) copper(I) tetrahydroborate*: Finely powdered copper(I) chloride (10 g, 0.1 mol) was added to a stirred solution of triphenylphosphine (54 g, 0.205 mol) in chloroform (375 ml) over 5 min. The reaction mixture was stirred until the copper chloride had dissolved (15 min), then treated with a suspension of sodium tetrahydroborate (3.8 g, 0.1 mol) in ethanol (40 ml) and stirred for a further 15 min, and then added to water (75 ml). The chloroform layer was washed with water (2×65 ml), dried (magnesium sulphate) and treated with diethyl ether (500 ml). Bis(triphenylphosphine) copper(I) tetrahydroborate precipitated immediately and was collected by filtration and washed with ether to give white needles of **1**, mp 172–174 °C.
19. *Typical procedure for DRA of aldehydes and ketones*: To a solution of carbonyl compound (6 mmol), amine (5 mmol) and sulfamic acid (5 mmol) in 15 ml of methanol was added $Cu(PPh_3)_2BH_4$ (5 mmol) over a period of 5 min. The reaction mixture was magnetically stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and the filtrate was evaporated to yield a crude product, which was purified using silica gel (60–120 mesh) column chromatography with petroleum ether–ethyl acetate as the eluent to afford the pure amine.