ORGANIC CHEMISTRY

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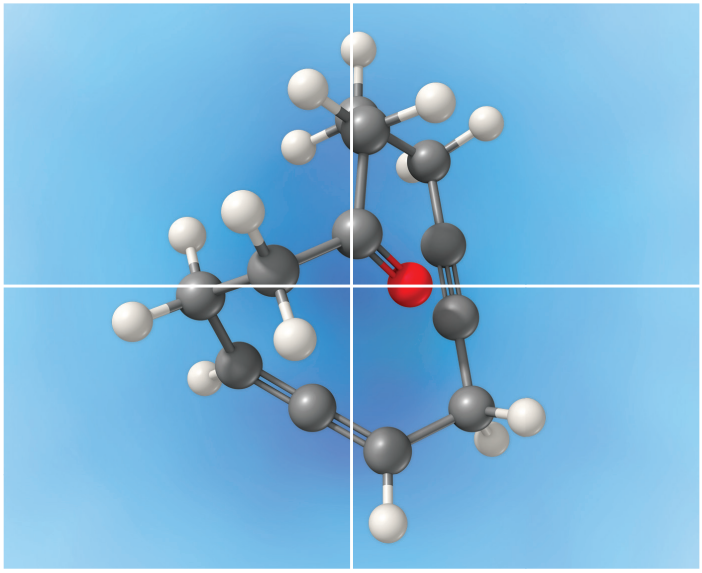

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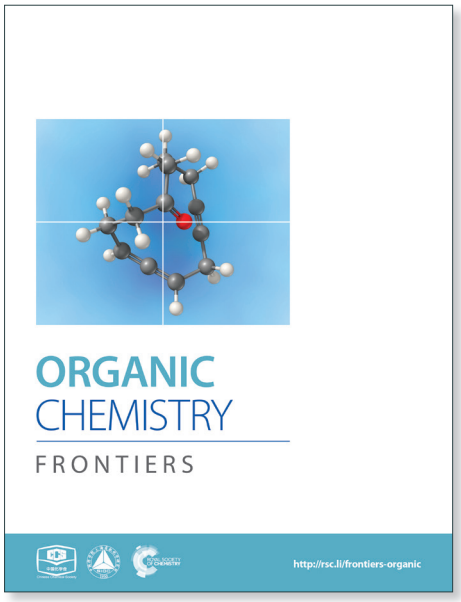

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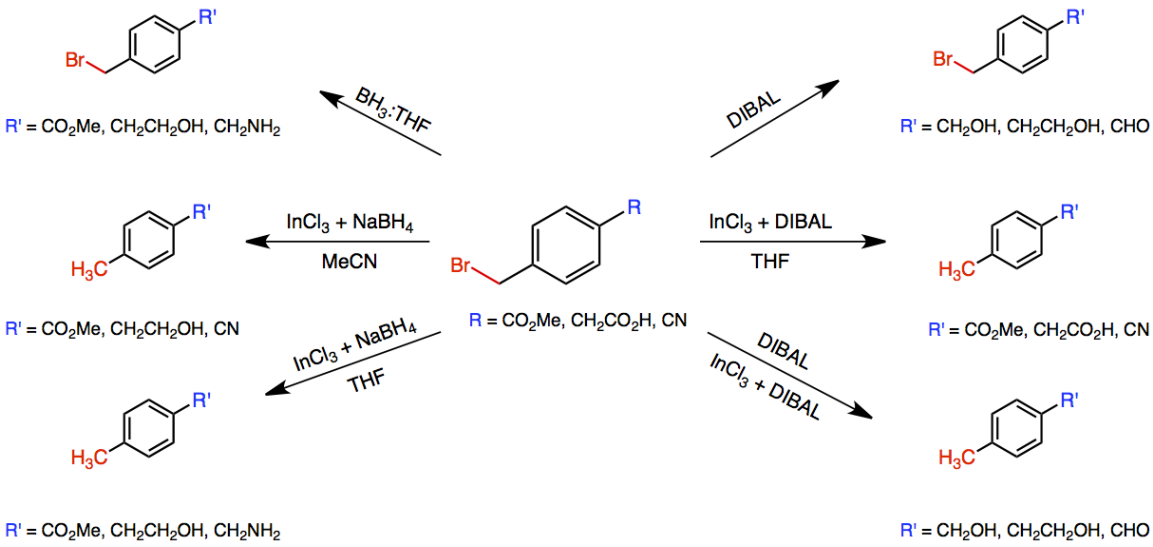
Binary reducing agents containing dichloroindium hydride for the selective, partial, or tandem reductions of bifunctional compounds consisting of halo-nitriles, halo-esters and halo-carboxylic acids†

Rachel Snelling, Jaime Z. Saavedra, Panathda Bayrasy, Yashar Abdollahian, and Bakthan Singaram*[a]

Selective, partial, or tandem reductions of bifunctional compounds containing primary alkyl or benzyl bromides can generate a variety of different products using a mixture of dichloroindium hydride ($HInCl_2$) and an additional hydride, such as borane-tetrahydrofuran (BH_3:THF) or diisobutylaluminum hydride (DIBAL-H). Binary metal hydride systems, containing $HInCl_2$ and BH_3:THF, are readily generated from anhydrous indium trichloride ($InCl_3$) and sodium borohydride ($NaBH_4$) in THF. Dichloroindium hydride can reduce primary halides and in the presence of another hydride, either generated *in situ* or added to the single-pot reaction, can perform tandem reductions of a variety of bifunctional bromides. Together, the hydrides reduce carbon-halogen bonds as well as an electrophilic group, such as a nitrile, ester, or carboxylic acid. The reduction of 4-(bromomethyl)benzonitrile using the $HInCl_2$ and BH_3:THF binary metal hydride system affords 4-methylbenzylamine in excellent yield under ambient conditions and short reaction times. By using the binary metal hydride system consisting of $HInCl_2$ and DIBAL-H, the tandem reduction of 4-(bromomethyl)benzonitrile was achieved affording *para*-tolualdehyde in excellent yield, also under ambient conditions. Reduction of 4-(bromomethyl)phenyl acetic acid by $HInCl_2$ selectively reduced the carbon-halogen bond generating *para*-tolylacetic acid. When using either binary hydride system, both functional groups were reduced generating 4-methylphenethyl alcohol. Methyl 4-(bromomethyl) benzoate underwent a selective or tandem reduction to generate [4-(bromomethyl)phenyl]methanol, methyl 4-methyl benzoate or *para*-tolylmethanol depending on the hydride system used. Consequently, a single bifunctional compound was transformed to a variety of different compounds by simple manipulation of the binary hydride system used without the need of protecting groups, and in most cases, by one-pot procedure.

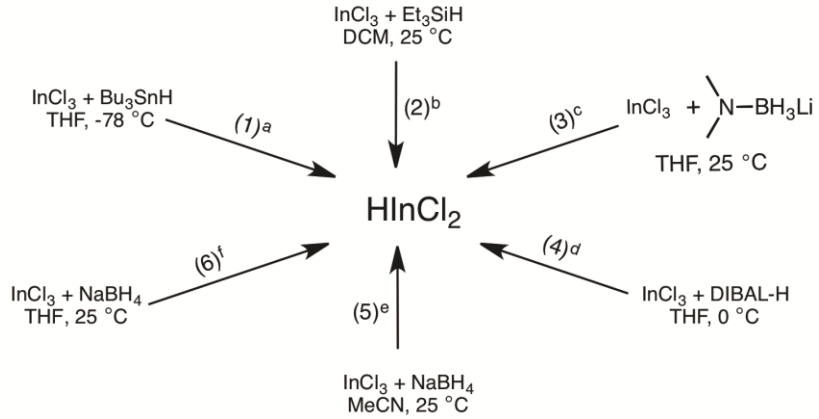


1. Introduction

Chemoselective reduction is an important tool in synthetic organic chemistry. Development of partial, selective, and tandem reaction cascades help reduce or eliminate the need for protecting groups, which can help improve yield while decreasing waste generation.[1a] There are a variety of reducing agents that range in strength for the reduction of many different electrophilic functional groups.[1b] Traditional and common metal hydride reducing agents, such as sodium

borohydride ($NaBH_4$)[2a-c] or lithium aluminum hydride ($LiAlH_4$) [3a-c] have been used and studied extensively. The ability of $LiAlH_4$ to reduce most functional groups limits its use in multifunctional compounds when selective reduction is desired.[3a] Conversely, $NaBH_4$ is a mild reducing agent with limited abilities and does not reduce electrophiles, such as nitriles, carboxylic acids, or esters.[2a] Sodium borohydride is known to reduce aldehydes or ketones in the presence of other functional groups.[2d] New reducing agents, such as dichloroindium hydride ($HInCl_2$), have been developed for selective reduction of an alkyl halide bond in multifunctional compounds.[4a-d] Indium hydride reagents such as $LiInH_4$, $LiPhInH_3$ and $LiPh_2InH_2$, were first prepared from $InCl_3$ and LiH by Wiberg and Schmidt.[5] Subsequently, Butsugan and coworkers suggest these metals hydrides reduce aldehydes and ketones, but esters were not reduced using $LiInH_4$.[6]

There are many methods to generate dichloroindium hydride (Fig. 1). Baba and coworkers synthesized $HInCl_2$ from $InCl_3$ and tributyltin hydride (eqn 1) and used it to reduce variety of functional groups, such as aldehydes, ketones, and alkyl halides.[4d,7a-b] However other methods of generating $HInCl_2$ have been developed to avoid using toxic tributyltin hydride. Baba and coworkers also showed that $HInCl_2$ can be prepared from $InCl_3$ using less toxic triethylsilane (Et_3SiH) [4b, 8] (eqn 2), which can undergo a 1,4-addition to enones[9] in addition to reducing carbon-halogen bonds. Additionally, we have previously explored the preparation of $HInCl_2$ from $InCl_3$ and lithium aminoborohydride (LAB) but this system required careful control of the stoichiometry of the reactants (eqn 3).[10-13] Baba and Oshima have shown that $HInCl_2$ can also be generated from $InCl_3$ and diisobutylaluminum hydride (DIBAL-H) at 0 °C (eqn 4).[14-16] Oshima and coworkers have demonstrated that $HInCl_2$ and catalytic amounts of Et_3B selectively reduced alkyl halides in the presence of aromatic esters and aromatic ketones. Finally, $HInCl_2$ can also be synthesized by the reduction of $InCl_3$ with $NaBH_4$ in acetonitrile (eqn 5) or THF (eqn 6).[12]



[a] Side product was tributyltin chloride. [b] Chlorotriethylsilane was generated, but does not interfere with reduction. [c] 3 equiv of anhydrous $InCl_3$ and 1 equiv of MeLAB were needed to generate $HInCl_2$. Excess LAB reagent would over-reduce $HInCl_2$ to In(0). N,N-dimethylaminoborane and LiCl were generated, but do not hinder reduction. [d] Diisobutylaluminum chloride was generated. [e] 1 equiv of anhydrous $InCl_3$ and 3 equiv of $NaBH_4$ were necessary to generate $HInCl_2$. Acetonitrile trapped the *in situ* formation of borane, creating a single hydride reducing system consisting of only $HInCl_2$. [f] 1 equiv of anhydrous $InCl_3$ and 3 equiv of $NaBH_4$ generated $HInCl_2$. BH_3:THF was generated *in situ*.

Fig. 1 Different methods of generating $HInCl_2$.

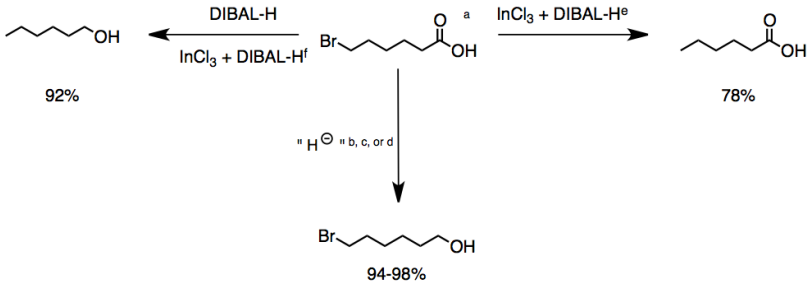
A closer examination of the $InCl_3/NaBH_4$ system by ^{11}B NMR spectroscopy revealed an unique solvent effect.[12] When the synthesis of $HInCl_2$ from $InCl_3$ and $NaBH_4$ was carried out in THF, ^{11}B NMR analysis showed the formation of equimolar amount of BH_3:THF.[12] When the same reaction was performed in acetonitrile (MeCN), the ^{11}B NMR spectrum showed formation of an "N-BH_2" species, arising from *in situ* trapping of borane generated by the solvent.[12] Additionally, we have recently demonstrated that the binary reducing system, prepared from $InCl_3/NaBH_4$ in THF, readily reduced a variety of aliphatic and aromatic nitriles to the corresponding primary amine in excellent yields.[12] Subsequently, we became interested in exploring the use of this binary hydride system to reduce a variety of other bifunctional compounds that contained a primary alkyl or benzyl bromide and an additional electrophilic functionality in a selective, partial, or tandem fashion. We anticipated that $HInCl_2$ present in the binary hydride mixture would reduce primary alkyl or benzyl bromides to the corresponding hydrocarbon, while BH_3:THF would reduce the nitrile group of a halonitrile to the corresponding primary amine and carboxylic acids to the alcohol. We also envisioned that a binary reducing system containing $HInCl_2$ and DIBAL-H can be exploited to reductively manipulate halonitriles, haloesters, and haloacids in selective, partial, or tandem fashion. Herein, we report an operationally simple, selective, partial, or tandem reduction of bifuntional compounds containing alkyl and benzyl halides by binary hydrides often capable of being carried out in a one-pot reaction.

2. Results and discussion

Our goal was to develop chemoselective reduction of bifunctional compounds using a single or binary hydride system. Developing new methodology for selective reduction of multi-functional compounds would help eliminate the use of protecting groups in synthetic organic chemistry, reduce the number of steps in a reaction and ultimately increase the overall yield while reducing waste. Accordingly, bifunctional primary or benzylic halides containing a carboxylic acid, ester, or nitrile were selected in order to further explore the various hydride systems. We used BH_3:THF-$HInCl_2$ and DIBAL-H-$HInCl_2$ as our binary hydride reducing systems. We compared our results with those obtained from reducing the representative bifunctional compounds with single hydride reducing agents, such as BH_3:THF, $HInCl_2$, and DIBAL-H. All the reductions were carried out at 25 ℃ and products were isolated by standard aqueous acid-base workup procedures and identified by NMR spectral analyses.

2.1 Reduction of 6-bromohexanoic acid.

We selected 6-bromohexanoic acid as the representative for the family of aliphatic halo-acids. There are three different outcomes possible in the selective or tandem reduction of 6-bromohexanoic acid, which include 6-bromohexanol, 1-hexanol, or hexanoic acid. Selective or tandem reduction of halogenated carboxylic acids was achieved using a variety of different hydrides and the results are summarized in Scheme 1. The selective reduction of the carboxylic acid gave 6-bromohexanol and can be accomplished using DIBAL-H or BH_3:THF with yields of 94 and 98% respectively. (Scheme 1, b or c). Both reactions were carried out under ambient conditions. For complete reduction, three equivalents of DIBAL-H were needed, whereas only one equivalent of BH_3:THF was needed for quantitative production of 6-bromohexanol. Neither BH_3:THF nor DIBAL-H reduced carbon-halogen bond. Using BH_3:THF was more attractive because of the stoichiometry, facile work-up procedure and higher yield of 6-bromohexanol. However, commercial samples of BH_3:THF are often compromised during the shipping and handling process.[17] Consequently, it is advisable to check the purity of BH_3:THF by ^{11}B NMR or hydride analysis as some of the commercial samples contained only tributoxyborate due to shipping and/or handling. Selective reduction of the carbon-halogen bond, afforded hexanoic acid, and was achieved using two equivalents of $HInCl_2$ synthesized from $InCl_3$ and DIBAL-H in THF. This pathway was the only method that selectively cleaved the carbon-halogen bond while leaving the unprotected carboxylic acid intact and required no radical initiator, such as Et_3B.[4a,14,18a-b] A stepwise reduction of 6-bromohexanoic acid to hexanol was achieved by reducing the acid first using BH_3:THF or DIBAL-H followed by reduction of the crude 6-bromohexanol by $HInCl_2$ generated in a separate flask from $InCl_3$ and DIBAL-H. Unfortunately, the $InCl_3$/$NaBH_4$ in THF system did not afford the tandem reduction of the carbon-halogen and the carboxylic acid group, but instead generated 6-bromohexanol. This is because the reduction of the carbon-bromide bond by $HInCl_2$ was inhibited by BH_3:THF.[12,16] The reduction of 6-bromohexaonic acid with $InCl_3$ and $NaBH_4$ in MeCN, gave a complex mixture of products.



[a] All reactions were run on a 3 mmol substrate scale at 25 ℃ for 4 h under Ar. [b] 3 equivalents of DIBAL-H required for complete reduction of the carboxylic acid group (94%). [c] 1 equivalent of BH_3:THF required for complete reduction of the carboxylic acid group (98%). [d] 1 equivalent of $InCl_3$ and 3 equivalents of $NaBH_4$ in THF were used for the reduction of the carboxylic acid group (94%). [e] 2 equivalents of $HInCl_2$ (from $InCl_3$ and DIBAL-H) required for complete reduction of the C-Br bond. The first for deprotonation of the acidic proton and the second for the cleavage of the C-Br bond (78%). [f] $HInCl_2$ generated in a separate flask from $InCl_3$ and DIBAL-H and added to 6-bromohexanol (92%).

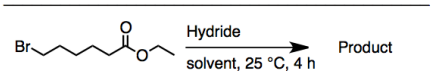
Scheme 1 Selective or tandem reduction of 6-bromohexanoic acid with single or binary hydrides

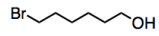
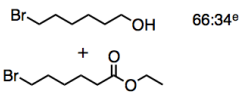
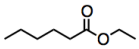
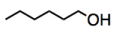
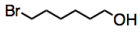
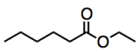
2.2 Reduction of ethyl 6-bromohexanoate.

Ethyl 6-bromohexanoate was selected as the representative example to probe the possibility of tandem and selective reduction of bromo esters using binary reducing agents. Three different products were feasible *via* selective or tandem reductions (Table 1). Selective reduction of the ester carbonyl group, which gave the bromo alcohol, was accomplished

by using two equivalents of DIBAL-H under ambient conditions (Table 1, entry 1). Brown had shown that pure BH_3:THF does not reduce esters. However, commercial BH_3:THF, containing $NaBH_4$ as a stabilizer, afforded some amount of bromo alcohol arising from the reduction of ester group (Table 1, entry 2). We achieved selective reduction of the carbon-bromide bond using two equivalents $HInCl_2$ generated from $InCl_3$ and DIBAL-H to afford ethyl hexanoate, again without the use of a protecting group, radical initiator, or column purification (Table 1, entry 3).[4] In our hands, use of 1.3 equiv of $HInCl_2$ gave incomplete reduction and, in order to achieve full reduction of carbon-bromide bond, we used one equivalent excess hydride rather than using pyrophoric radical initiator triethyl borane.[18a-b] Stepwise reduction of the carbon-bromide bond and ester carbonyl group was carried out using a two-pot procedure. The ester was reduced using DIBAL-H, which gave the halo-alcohol. The isolated halo-alcohol was then reduced using $HInCl_2$, which gave the corresponding aliphatic alcohol (Table 1, entry 4). Indium trichloride ($InCl_3$) and $NaBH_4$ in THF system gave the selective reduction of the ester group and formed the bromo alcohol. Since BH_3:THF alone did not reduce the ester, the excess $NaBH_4$ present must have catalyzed the reduction of the ester and allowed for the formation of 6-bromohexanol albeit in a lower isolated yield. As expected, switching the solvent from THF to acetonitrile (MeCN) resulted in selective reduction of the carbon-bromide bond (Table 1, entry 6). When one equivalent of $HInCl_2$ was used, only starting material was recovered. However when we increased $HInCl_2$ to two equivalents, ethyl hexanoate was afforded in a 92% isolated yield.

Table 1 Selective and tandem reductions of aliphatic halo-esters



Entry[a]	Hydride	Product	Yield[d]
1	DIBAL-H[b]		99%
2	BH_3:THF[b]		66:34[e]
3	$InCl_3$ + DIBAL-H[b]		78%
4	DIBAL-H[c] $InCl_3$ + DIBAL-H		92%
5	$InCl_3$ + $NaBH_4$[b] THF		71%
6	$InCl_3$ + $NaBH_4$[b] MeCN		92%

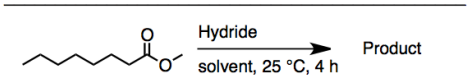
[a] All reactions were run on a 3 mmol substrate scale at 25 ℃ for 4 h under Ar. [b] Reduction was carried out in one-pot. [c] $HInCl_2$ was generated from $InCl_3$ and DIBAL-H in a separate reaction flask and added to haloalkoxy mixture. [d] Isolated Yield. [e] alcohol:ester ratio based on ^{1}H NMR integration.

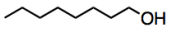
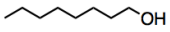
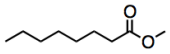
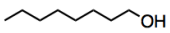
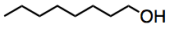
2.3 Reduction of methyl octanoate

Methyl octanoate was used as representative example for the family of aliphatic esters in our study. We were interested in comparing the reductive reactivity of aliphatic esters with the results obtained with aliphatic bromo esters using the binary reducing agents (Table 2). In the reduction of an aliphatic ester, two products were possible: partial reduction to give an aldehyde or complete reduction leading to a primary alcohol. At ambient temperature, complete reduction of ester group was achieved using two equivalents DIBAL-H (Table 2, entry 1). It should be noted that at -78 ℃ DIBAL-H is capable of reducing esters to the corresponding aldehyde with very little over reduction arising from *β*-hydride elimination.[19,20] As with bromo ester, commercial BH_3:THF produced a mixture of octanol and unreacted starting material *via* an incomplete $NaBH_4$ catalyzed ester reduction (Table 2, entry 2). Dichloroindium hydride, generated from $InCl_3$/DIBAL-H in THF or $InCl_3$/$NaBH_4$ in MeCN did not reduce the aliphatic ester group (Table 2, entries 3 and 6). Dichloroindium hydride, as a single hydride reagent, did not reduce the ester (Table 2, entries 3 and 6). However, excess DIBAL-H proceeded to give octanol (Table 2, entry 4). $InCl_3$ and $NaBH_4$ in THF generated the binary reducing system containing both $HInCl_2$ and BH_3:THF.[12] This mixture of hydrides reduced methyl octanoate to 1-octanol in quantitative yield (Table 2, entry 5). Even though both $HInCl_2$ and BH_3:THF were not capable of reducing ester group

on their own, in the binary reducing system the two hydrides acted synergistically and reduced the carbonyl group. Dichloroindium hydride potentially acts as a Lewis acid to activate the ester group and facilitates hydride transfer from BH_3:THF. We have previously observed similar synergistic effects in the reduction of aryl cyanides using a binary reducing system containing both $HInCl_2$ and BH_3:THF.[12]

Table 2 Reduction of aliphatic esters with mono- or binary hydrides



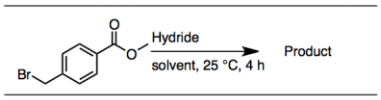
Entry[a]	Hydride	Product	Yield[d]
1	DIBAL-H[b]		99%
2	BH_3:THF[b]	 + 	80:20[e]
3	$InCl_3$ + DIBAL-H	No Reaction	
4	DIBAL-H[c] $InCl_3$ + DIBAL-H		99%
5	$InCl_3$ + $NaBH_4$ THF		99%
6	$InCl_3$ + $NaBH_4$ MeCN	No Reaction	

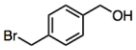
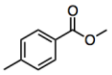
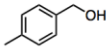
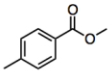
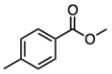
[a-e] Please see footnote for Table 1

2.4 Reduction of benzylic halides containing aromatic ester.

For carboalkoxy benzylic halide family of compounds, methyl 4-(bromomethyl) benzoate was selected. Three different reduction products can arise from methyl 4-(bromomethyl) benzoate, either in a selective or tandem reduction. Diisobutylaluminum hydride selectively reduced the ester group to the corresponding alcohol in excellent yield and was the only method that selectively reduced the ester functionality in the presence of a benzylic bromide (Table 3, entry 1). The stoichiometry of DIBAL-H was important in this reduction. When 3 equivalents of hydride were used, we observed reduction of the ester group as well as significant reduction of the carbon-bromide bond. By decreasing the DIBAL-H to 2.2 equivalents, only the ester group was reduced affording isolated [4-(bromomethyl)phenyl]methanol in 90% yield. Conversely, pure or commercial BH_3:THF alone does not reduce aromatic esters and only the starting material was recovered (Table 3, entry 2). Selective reduction of the carbon-bromide bond can be achieved in a variety of ways. Dichloroindium hydride ($HInCl_2$) generated from $InCl_3$ and DIBAL-H selectively reduced the carbon-halogen bond (Table 3, entry 3) in 78% yield. Indium trichloride and $NaBH_4$ system in THF or MeCN (Table 3, entries 5 and 6) gave methyl *p*-toluate in 99 and 84%, respectively. Although $InCl_3$ and $NaBH_4$ in THF generated both $HInCl_2$ and BH_3:THF, only carbon-halogen bond was cleaved because neither BH_3:THF nor $HInCl_2$ can reduce aromatic esters. The highest yield of methyl *p*-toluate was achieved using the $InCl_3$/$NaBH_4$ reducing system in THF and involved a straightforward work-up procedure. Unfortunately, tandem reduction of the carbon-halogen bond and aromatic ester group was not achieved using $HInCl_2$ and excess DIBAL-H in a sequential addition one-pot procedure. The aluminum alkoxide formed in the ester reduction, was likely insoluble, making the initial product of the tandem reduction unavailable for the second stage of the reduction. *Para*-(bromomethyl) benzyl alcohol can be isolated from the first step and the crude compound can then undergo reduction with $HInCl_2$ gave *para*-methylbenzyl alcohol.

Table 3 Selective and tandem reductions of aromatic halo-esters



Entry[a]	Hydride[b]	Product	Yield[c]
1	DIBAL-H		90%
2	BH_3:THF	No Reaction	
3	$InCl_3$ + DIBAL-H "$HInCl_2$"		78%
4	MeLAB $InCl_3$ + DIBAL-H		90%
5	$InCl_3$ + $NaBH_4$ THF		99%
6	$InCl_3$ + $NaBH_4$ MeCN		84%

[a-b] Please see footnote for Table 1. [c] The tandem reduction was carried out in one-pot, sequential addition beginning with generation of $HInCl_2$ from $InCl_3$ and DIBAL-H and allowed to stir for 1 hour. Methyl 4-(bromomethyl) benzoate was added and allowed to stir for 4 additional hours. 3 equiv methyl-LAB was added for the reduction of the ester and allowed to stir for 4 hours. [d] Isolated Yield.

Because we sought to accomplish the tandem reduction in one-pot procedure, we turned our attention to another reducing agent. Lithium dimethylaminoborohydride (methyl-LAB) is not only known to reduce ester groups, but LAB and $InCl_3$ can generate $HInCl_2$. As previously mentioned, the stoichiometry of methyl-LAB to $InCl_3$ plays a significant role in the formation of $HInCl_2$.[12] In order to successfully generate $HInCl_2$ from $InCl_3$ and methyl-LAB, 3 equivalents of $InCl_3$ were needed for 1 equivalent of LAB reagent, otherwise $HInCl_2$ gets over-reduced to a metal nugget.[12] In order to eliminate the use of excess anhydrous $InCl_3$, we decided to generate $HInCl_2$ from DIBAL-H since this reaction only required 1 equivalent of $InCl_3$ and 1 equivalent of DIBAL-H. With $HInCl_2$ in hand, methyl 4-(bromomethyl) benzoate was added, and the reduction of the benzyl bromide proceeded smoothly. Methyl-LAB was then added resulting in reduction of the ester group (Table 3, entry 4). Immediately upon addition of the LAB reagent, a solid precipitate aggregated to form a metal nugget in the reaction flask. Excess LAB reagent was then added in order to reduce the ester functional group. We speculated that this metallic nugget was indium(0), because we have previously observed the same nugget formation when generating $HInCl_2$ from $InCl_3$ and LAB.[12] Powder X-ray diffraction (PXRD) was used to elucidate the composition of the metal nugget. Analysis of the PXRD data showed the sample was highly crystalline indium metal with no impurities or amorphous phases (Fig. 2).

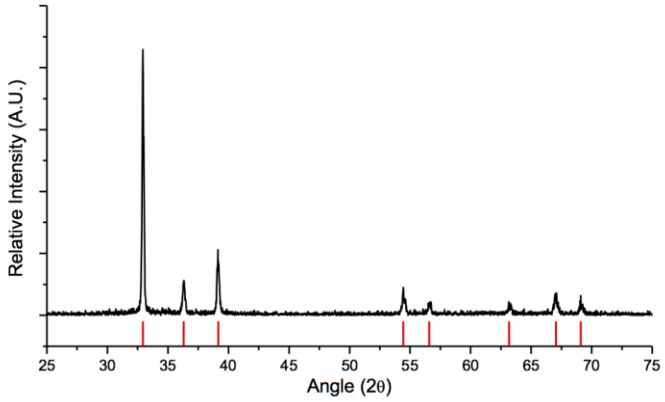
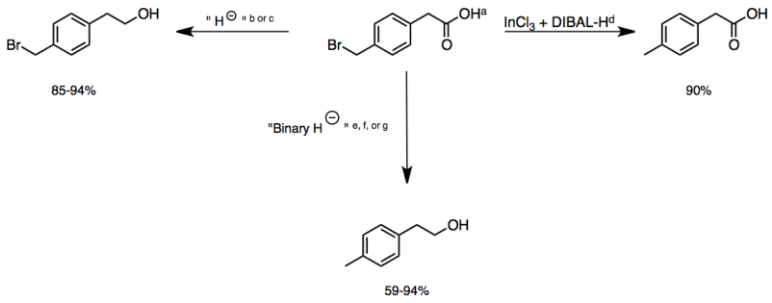


Fig. 2 PXRD spectrum of the indium metal nugget. Red bars at the bottom indicate the theoretical peak positions of indium. (PDF card #01-075-3850)

2.5 Reduction of 4-(bromomethyl)phenyl acetic acid

4-Bromomethy-l-phenyl acetic acid served as representative example for the family of halomethyl-aryl acids. Three different products are possible *via* either selective or tandem reductions (Scheme 2). Both DIBAL-H and BH_3:THF achieved selective reduction of the carboxylic acid group in the presence of the benzyl bromide functionality in 85% and 94% isolated yields, respectively (Scheme 2, b and c). It should be pointed out that only one equivalent of BH_3:THF[21] was required for selective reduction of carboxylic acid, while three equivalents of DIBAL-H were required for the complete reduction of carboxylic acid group at 25 ℃.[22] Selective reduction of carbon-halogen bond was successfully achieved using $HInCl_2$ generated from $InCl_3$ and DIBAL-H and gave *para*-tolylacetic acid in a 90% yield without the need of a protecting group or radical initiator (Scheme 2, d). A one-pot tandem reduction of 4-(bromomethyl)phenylacetic acid was achieved using a variety of different binary metal hydride systems. Examples include $HInCl_2$ generated from $InCl_3$ and an excess of DIBAL-H, as well as $HInCl_2$ from $InCl_3$ and $NaBH_4$ in THF or MeCN. For the tandem reduction, $HInCl_2$ from $InCl_3$ and DIBAL-H followed by 3 equivalents of DIBAL-H gave 4-methylphenethyl alcohol in a 70% isolated yield (Scheme 2, e). The same product was accessed through $InCl_3$ and $NaBH_4$ in THF or MeCN with isolated yields of 94 and 59% respectively (Scheme 2, f and g). The binary reducing system containing $HInCl_2$ and BH_3:THF gave highest isolated yield of 4-methylphenethyl alcohol and involved simple work-up procedure.



[a] Reaction run on a 3 mmol scale at 25 ℃. [b] 3 equiv of DIBAL-H required for complete reduction of carboxylic acid (85%). [c] 1 equiv of BH_3:THF required for complete reduction of carboxylic acid (94%). [d] 6 mmol $HInCl_2$ generated from $InCl_3$ and DIBAL-H and allowed to stir for 1 hour. 3 mmol of the substrate was added to $HInCl_2$ and allowed to stir for 4 hours (90%). [e] Binary hydride system was used for the tandem reduction of 4-(bromomethyl)phenyl acetic acid. 6 mmol $HInCl_2$ generated from $InCl_3$ and DIBAL-H and allowed to stir for 1 hour. 3 mmol of substrate was added to $HInCl_2$ and allowed to stir for 4 hours followed by addition of 9 mmol of DIBAL-H for reduction of the carboxylic acid (70%). [f] Binary hydride system $HInCl_2$ and BH_3:THF was generated from $InCl_3$ and $NaBH_4$ in THF and allowed to mix for 1 hour, followed by the addition of 4-(bromomethyl)phenyl acetic acid and stirred for 4 hours (94%). [g] $HInCl_2$ was generated from $InCl_3$ and $NaBH_4$ in MeCN. Excess $NaBH_4$ reduced carboxylic acid group. Reaction allowed to stir

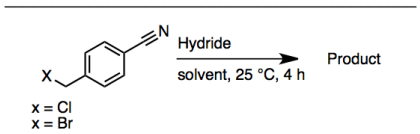
for 1 hour, followed by addition of 4-(bromomethyl)phenyl acetic acid and stirred for 4 more hours (59%).

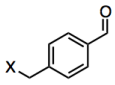
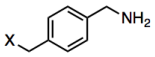
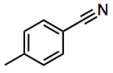
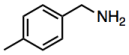
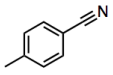
Scheme 2 Selective and tandem reduction of aromatic halo-carboxylic acids

2.6 Reduction of 4-(halomethyl)benzonitrile

4-(bromomethyl)benzonitrile was selected as representative member of the family of aromatic halo-nitriles. The most interesting results of selective, partial and tandem reductions were seen with halogenated substituted aromatic nitriles. Binary reducing agents lead to five different useful compounds. Partial reduction of the nitrile group in both 4-(bromomethyl)benzonitrile and 4-(chloromethyl)benzonitrile were carried out at 25 ℃ and gave the corresponding halomethyl substituted benzaldehyde in isolated yields of 85% and 80%, respectively (Table 4, entry 1). Selective reduction of 4-(bromomethyl)benzonitrile can be achieved using BH_3:THF under THF reflux conditions for 12 hrs to afford 4-(bromomethyl)-phenyl)methanamine (Table 4, entry 2).[21] In our study, this was the only pathway available to selectively convert a nitrile to the corresponding primary amine in the presence of a primary or benzylic halide. 4-(Bromomethyl)benzonitrile was reduced, by sequential addition of DIBAL-H followed by $HInCl_2$, to 4-methylbenzaldehyde through the intermediate formation of the corresponding imine derivative (Table 4, entry 4). When the tandem reduction was carried out under ambient conditions using $InCl_3$ and $NaBH_4$ in THF, $HInCl_2$ reduced the carbon-halogen bond and BH_3:THF reduced the nitrile and gave *para*-tolymethanamine (Table 4, entry 5).[12] For the selective reduction the carbon-halogen bond we used $InCl_3$ and $NaBH_4$ in MeCN system, where borane generated *in situ* was trapped by MeCN and renders the borane unavailable for reduction. Consequently, $InCl_3$/$NaBH_4$ in MeCN gave the selective reduction of the carbon-halogen bond to afford *para*-methylbeznonitrile (Table 4, entry 6).[12] This selective reduction was also achieved using $HInCl_2$ prepared from $InCl_3$ and DIBAL-H (Table 4, entry 3).

Table 4 Selective, partial, and tandem reduction of aromatic halo-nitriles



Entry[a]	Hydride[b]	Product	Yield[c]
1	DIBAL-H		x = Cl, 80% x = Br, 85%
2	BH_3:THF		[d]Ref 21
3	$InCl_3$ + DIBAL-H		x = Cl, 74% x = Br, 85%
4	DIBAL-H[b] $InCl_3$ + DIBAL-H		x = Cl, 63% x = Br, 67%
5	$InCl_3$ + $NaBH_4$ THF		x = Cl, 65% x = Br, 61%[e]
6	$InCl_3$ + $NaBH_4$ MeCN		x = Cl, 68% x = Br, 65%[e]

[a] All reactions were run on a 3 mmol substrate scale at 25 ℃ for 4 h under Ar. [b] Reaction was run in two-pot procedure. DIBAL-H was added to 4-(bromomethyl)benzonitrile and allowed to stir for 4 hours. In a separate pot, $HInCl_2$ was generated and then added to the first reaction mixture. [c] Isolated yield.[d] Ref 21. [e] Ref 12.

3. Conclusions

Dichloroindium hydride containing either BH_3:THF or DIBAL-H has shown promising results as a binary hydride reducing system to achieve selective, partial, and tandem reductions of bifunctional benzylic halides. Primary halides and benzylic halides containing a carboxylic acid, ester, or nitrile functional group were selected for further study. Our goal was to develop chemoselective reductions of these bifunctional compounds using a single or binary hydride system. By developing new methodology for the partial, selective, or tandem reduction of bifunctional compounds the synthesis of a variety of different products can be achieved from a single starting material without the use of protecting groups or pyrophoric radical initiators was demonstrated. With many ways of generating $HInCl_2$, the binary hydride reducing system can be utilized in a deliberate way for chemoselective reduction of a targeted functional group. For example, 4-(bromomethyl)benzonitrile produces five different products, based on the binary hydride system used. Diisobutylaluminum hydride generated 4-(bromomethyl)benzaldehyde in excellent yield, while BH_3:THF gave 4-(bromomethyl)benzylamine. When 4-(bromomethyl)benzonitrile was sequentially reduced with $HInCl_2$ and DIBAL-H, *para*-tolualdehyde was obtained as the product. When the binary reducing system of $HInCl_2$ and BH_3:THF, generated *in situ* from $InCl_3/NaBH_4$ in THF was used, 4-methylbenzylamine was isolated as the tandem reduction product. Meanwhile, when using $HInCl_2$ as a single hydride, whether generated from $InCl_3$ *via* DIBAL-H or $NaBH_4$ in MeCN, only carbon-halogen bond was cleaved and left the nitrile intact. This method also works for other benzyl halides containing electrophilic groups, such as carboalkoxy benzylic bromide which gave three possible different products. This methodology was expanded to both aliphatic and aromatic esters containing a primary or benzylic bromide generating four and three possible different products, respectively. We also included the reductions of monosubstituted compounds for comparison. The results are summarized in Table 5.

Table 5 Summary of selective, partial, or tandem reductions of mono- and bi-substituted compounds with different hydrides

Hydride / Substrate	DIBAL-H	BH_3:THF	$HInCl_2$ (from $InCl_3$ + DIBAL-H)	$HInCl_2$ (from $InCl_3$ + DiBAlH) + DIBAL-H	$HInCl_2$ + BH_3:THF ($InCl_3$ + $NaBH_4$ in THF)	$HInCl_2$ + "BH_3Z" ($InCl_3$ + $NaBH_4$ in MeCN)
n-$C_{11}H_{23}CH_2Br$	NR[a,b]	NR[a,c]	*n*-$C_{11}H_{23}CH_3$[d]	*n*-$C_{11}H_{23}CH_3$[e]	Incomplete Reduction[e,f]	*n*-$C_{11}H_{23}CH_3$[e,f]
	NR[a,b]	NR[a,c]	 [g]	 [g]	Incomplete Reduction[e,f]	 [e,f]
	 [b]	 [c]	NR[a]	 [h]	 [h]	NR[a]
	 [b]	 [c]	NR[a]	 [h]	 [h]	NR[a]
	 [b]	 [c]	 [g,j]	 [g,j]		 [g,j]
	 [b]	 [c]	 [g,j]			 [g,j]
		[i]	NR[a]			NR[a]
	 [b]	 [c]	NR[a]	------	 [e,f]	------
	 [b]	 [c]	NR[a]	------	 [e,f]	------
						[j]
		[i]				
		NR[a]				
	[b]	[c]	[e,f]		[e,f]	[e,f]

[a] NR = No Reaction. [b] Ref Ref 22. [c] Ref 21. [d] Ref 4a. [e] Ref 12. [f] Ref 16. [g] Ref 7a. [h] Reduction of the functional group occurs from DIBAL-H or BH_3:THF. $HInCl_2$ alone does not reduce carboxylic acids. i Ref 6. [j] Mixture of products.

The method described herein has shown promising results towards the partial, selective, and tandem reductions in compounds containing multiple-functional groups without the need for protecting groups. In most cases a one-pot procedure was used along with simple work-up procedures that resulted in good to excellent isolated yields. All the reductions reported in this manuscript were carried out in ambient conditions and with short reaction times. Simple manipulation of the binary reducing system containing $HInCl_2$ can potentially generate a wide variety of different compounds starting from bifunctional primary or benzylic halides.

Notes and references

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[a]*E-mail: Singaram@ucsc.edu*
†Electronic supplementary information (ESI) available: Experimental procedures and the characterization data of the isolated compounds.

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