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Selective reductions with stable indium trihydride reagents

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Abstract

The carbene and tertiary phosphine adducts of indane, [InH_3{CN(Mes)C_2H_2N(Mes)}] and [InH_3{P(C_6H_{11})$_3$}] (Mes = 2,4,6-trimethylphenyl), have been used to reduce unsaturated organic functionalities. The success and selectivity of these reductions relative to those carried out with lighter group 13 hydride complexes is discussed. © 2000 Elsevier Science Ltd. All rights reserved.

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Boro- and alumino-hydride reagents have been exhaustively utilised in organic synthesis and a large number of fundamental advances have been made in examining the selectivity of these toward the hydrometallation of functional groups.[1] The use of hydride complexes of the heavier group 13 elements in organic synthesis has not been equally developed. This situation has arisen from the increasing frailty of the metal–hydrogen bond as the group is descended, which has resulted in a paucity of species available for study. Despite this, some gallium hydride complexes, e.g. [GaH_3{P(C_6H_{11})$_3$}], have been applied to the reduction of organic carbonyl containing functionalities.[2] Moreover, in recent years several indium hydride species have displayed selectivity in the reduction of a variety of bi- and poly-functional compounds.[3] However, the indium hydride reagents that have been studied are poorly characterised, difficult to handle and most are thermally unstable and air-sensitive.

We have recently synthesised the first indium trihydride species,[4,5] for example [InH_3{P(C_6H_{11})$_3$}] **1** and [InH_3{CN(Mes)C_2H_2N(Mes)}] **2**, both of which have been crystallographically characterised. The air and room temperature stability of **1** and **2** has prompted us to apply these complexes to organic synthesis. This is of interest as indium has an electronegativity between that of aluminium and gallium. Therefore it might be expected that the In–H bond should have a polarity between that of the analogous Al–H and Ga–H bonds. Consequently, there should be a degree of chemoselectivity in the reduction of organic functionalities using indium hydride reagents. In addition indium has a greater covalent radius (1.5 Å) than

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either aluminium or gallium (1.25 Å) which means that indane complexes, like alane but unlike gallane complexes, should prefer to participate in hypervalent (five or six coordinate) bonding. This preference for higher co-ordination numbers may give rise to a high degree of diastereoselectivity in the reduction of bifunctional substrates. In this report we compare the diastereo-, chemo- and regioselectivity of reductions utilising **1** and **2** relative to similar reductions involving alane and gallane reagents.

The Lewis-base adducts **1** and **2** can be readily prepared in high yield via the ligand displacement of NMe_3 from $[InH_3(NMe_3)]$ or elimination of LiH from $LiInH_4$, respectively.[5] Reductions were performed under an inert atmosphere with equimolar proportions of reductant to substrate (except where indicated) in anhydrous toluene with warming from −78°C to room temperature and stirring overnight (ca. 15 h) before quenching with dilute acid. Product ratios were determined by ^1H NMR and in the case of liquid products, GCMS analyses. The results are summarised in Table 1. The substrates studied are those commonly used to evaluate reducing agents.[6]

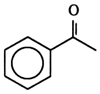
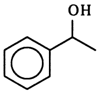
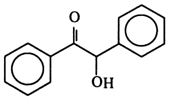
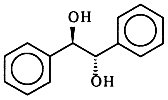
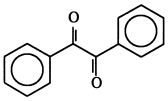
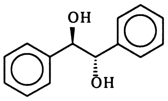
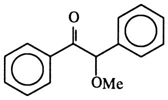
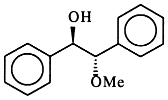
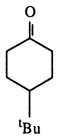
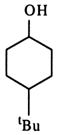
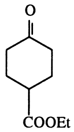
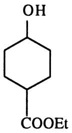
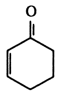
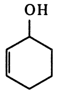
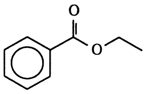
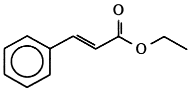
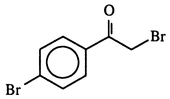
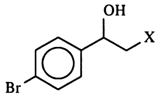
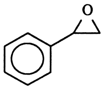
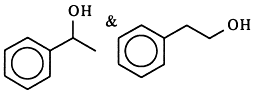
Reductions of simple ketones such as acetophenone (I) were shown to go to completion. Activated ketones such as benzoin, benzil and benzoin methyl ether (II–IV) were also reduced in high yield with excellent diastereoselectivity. This is akin to the unstable indium hydride complexes $LiInH_4$[3a,b] and $[InHCl_2(THF)]$,[3c] although **1** does appear to effect substantially better yields. The diastereoselective reductions of II–IV suggest a strong chelation of the substrate to the indium centre of the complex, which allows a directed hydride delivery leading to the observed result. Decreasing the amount of **1** to 0.33 molar equivalents had little effect on the diastereoselectivity of the reduction of II, although only a 74% conversion was observed. Reductions of II and III with **2** proceeded with a similar selectivity to those with **1** but with lower conversions, which is not surprising given the considerable steric bulk of the carbene ligand used to stabilise **2**.

The diastereoselectivity observed for reduction of 4-*tert*-butylcyclohexanone (V) with equimolar proportions of **1** or **2** resulted in a predominance of the *trans* alcohol, the yield of the former reduction being quantitative. This is as per many aluminium and gallium hydride reagents[2,7] and is consistent with Cieplak's model for stabilisation of the transition state via antiperiplanar allyic bonds.[8]

The attempted reduction of ethyl-4-oxocyclohexanecarboxylate (VI) with 1 equivalent of **1** proceeded in moderate yield (60%) without reduction of the ester moiety. By contrast the reduction of ethyl benzoate performed with $[AlH_3(NMe_3)]$ provides the benzyl alcohol in 80% yield under similar conditions.[2] This intimates the milder reducing nature of indane adducts relative to that of similar alane species as predicted on electronegativity grounds. Tricyclohexylphosphine indane, **1**, quantitatively reduces 2-cyclohexenone (VII) to its alcohol without any conjugate addition. This is contrary to the reducing ability of $[InHCl_2(THF)]$ which has been shown to effect a 1,4-reduction with the allylic carbonyl of chalcone.[3c] In addition, both **1** and **2** were shown to be ineffective towards the reduction of ethyl benzoate (VIII) and ethyl cinnamate (IX), whilst $LiInH_4$, $LiPhInH_3$ and $LiPh_2InH_2$ are known to reduce similar esters.[3a]

In probing the regioselectivity of reduction with **1**, 2,4′-dibromoacetophenone (X) was chosen as a substrate due to comparative data being available on its reduction with Lewis-base adducts of borane, alane and gallane.[2] As per the debromination qualities of $[InHCl_2(THF)]$,[3c] **1** was shown to reduce the ketone moiety in high yield (76%), with concomitant cleavage of the adjacent carbon–bromine bond in 57% of cases. This is intermediate between the behaviour of alane and gallane complexes, the former of which effects quantitative α C–Br cleavage whilst the

Table 1
Reduction of organic compounds with $[InH_3\{P(C_6H_{11})_3\}]$, **1** (bold) and $[InH_3\{CN(Mes)C_2H_2N(Mes)\}]$, **2**

Entry	Substrate	Product(s)	Selectivity/%	Yield/%
I			–	**100** 100
II			**> 99** > 99	**100** 63
III			**> 99** > 99	**69** 57
IV			**> 99**[b]	**65**
V			**81:19 trans:cis** 72:28 trans:cis	**100** 73
VI[a]			**76:24 trans:cis**	**60**
VII[a]			**> 99**	**100**
VIII[a]		No Reduction	–	–
IX[a]		No Reduction	–	–
X			**X=Br 43** **X=H 57**	**76**
XI			**56 & 44**[c]	**80**

[a] 1:1 stoichiometry employed to elucidate chemoselectivity of reductant.
[b] RS/SR, *anti*-2-methoxy-1,2-diphenylethanol obtained with >99% d.e.
[c] 1-phenylethanol 56%, 2-phenylethanol 44%.

latter effects minimal cleavage. The corresponding borane adduct, [$BH_3(NMe_3)$], is completely inactive towards the substrate. These differences can again be explained by the intermediate electronegativity of indium relative to aluminium and gallium which gives rise to an intermediate M–H bond polarity and therefore reactivity. This contrast is compounded by the regiochemistry of the reduction of styrene oxide (XI) with **1**. The proportion of 2-phenylethanol formed in this reduction (44%) suggests the participation of an alkoxyindium transition state that possesses a benzylic carbocation prior to hydride transfer. This is similar to the behaviour of quinuclidine–alane (37% primary alcohol).[2] However, in keeping with the electropositive nature of MH_3 adducts, the secondary alcohol is also formed in roughly equivalent yield (56%). Tricyclohexylphosphine gallane reduces styrene oxide to the secondary alcohol with >99% selectivity, which again places the indane complex, **1**, in between alane and gallane complexes in terms of its regioselectivity[2].

In summary, we have proven the utility of indium trihydride complexes as selective reducing agents. Overall, they appear to behave in an intermediate fashion to their aluminium and gallium trihydride analogues, which was predicted based on the physical properties of the metal involved. We believe our success in synthesising air and room temperature stable Lewis-base adducts of indane will lead to such complexes being added to the organic chemist's arsenal of selective reducing agents. The study described here is currently being extended, placing emphasis on the isolation of intermediates, as we believe the nature of these will shed light on the mechanisms involved. The results of these investigations will be reported in subsequent publications.

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