

Das Reagenz · The Reagent

Indium Metal: A Reagent for C–C-Bond Formation by Organometallic Reactions in Aqueous Medium

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Indium metal is known since 1863 [1], but its regular use in organic synthesis was initiated less than a decade ago. Indium powder is not a cheap reagent but it is commercially available at a reasonable price (comparable to silver [2]). The material can be handled without special precautions; it is neither toxic nor sensitive to water or air (the latter at room temperature only) [1, 3]. The reducing power of this reagent ($\text{In}^{3+}/\text{In}^0$, $E^0 = -0.34 \text{ V}$) is lower than that of other popular reducing reagents used in organometallic reactions like tin ($\text{Sn}^{2+}/\text{Sn}^0$, $E^0 = -1.38 \text{ V}$), chromium(II) ($\text{Cr}^{3+}/\text{Cr}^{2+}$, $E^0 = -0.41 \text{ V}$), zink ($\text{Zn}^{2+}/\text{Zn}^0$, $E^0 = -0.76 \text{ V}$), aluminium ($\text{Al}^{3+}/\text{Al}^0$, $E^0 = -1.66 \text{ V}$), and magnesium ($\text{Mg}^{2+}/\text{Mg}^0$, $E^0 = -2.37 \text{ V}$). But its first ionization potential (5.79 eV) is lower than the one of the other metals mentioned above (Al: 5.98 eV, Mg: 7.65 eV, Zn: 9.39 eV, Sn: 7.34 eV). Since the organometallic reactions discussed below presumably proceed by a single electron transfer (SET) mechanism [4, 5e], indium is an effective reagent in spite of its E^0 -value.

1 History

The first organoindium compound, diphenylindium chloride, was described in 1927 [6]. The ability of such organoindium compounds to react as nucleophiles with organic electrophiles [7] like carbonyl compounds and Michael systems was discovered in 1940. It was also found, that these compounds are sensitive to oxygen [7, 8]. Efforts to reduce the basicity of organometallic reagents by the usage of less electropositive metals in order to prevent side reactions like enolization of carbonyl-compounds while maintaining the nucleophilicity of the organometallic reagent initiated the use of activated indium (Rieke) in Reformatsky reactions in 1975 [9]. However, it took another 13 years until in 1988 Araki and Butsugan recognized that normal indium powder [10] can also be used for bromides and iodides. Since then indium is increasingly used in highly chemo- and regioselective reactions [11]. In 1991 Chan reported that organometallic reactions with indium are possible in aqueous medium (even without protecting gas), another breakthrough for the use of indium [12].

2 The Principles

The first reactions with indium were carried out under exclusion of oxygen in dry polar, aprotic solvents like DMF. In most of these applications of indium metal an organoindium compound (sesquihalide **1**, [13, 8]) is prepared *in situ* from indium powder and an activated halide (α -halo esters and allylic halides; bromides and iodides preferentially) and added to organic electrophiles.



Unlike as in the preparation of allylic or propargylic grignard or organolithium compounds, with indium no Wurtz-type coupling is observed [8]. Only two of the three groups R in **1** are transferred to the carbonyl compound [11, 14, 10], therefore the ratio of indium:halide:electrophile is 2:3:2.

The reactions in aqueous medium [5e,g] offers several advantages: (a) no need to dry (inflammable) solvents by sometimes hazardous or time-consuming procedures, (b) hydroxyl groups don't need to be protected, (c) compounds insoluble in organic solvents (*e.g.* carbohydrates) can react directly (d) changes in the stereoselectivity are possible. In these reactions usually indium powder is added to a solution where both the halide and the electrophile are present.

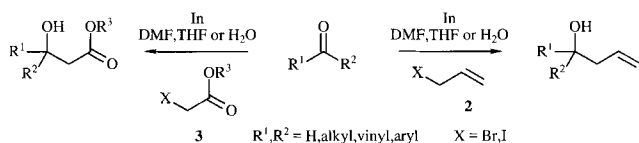
Two other metals frequently applied in organometallic reactions in aqueous medium are zinc and tin, but indium offers the advantage that not necessarily an activation by acid catalysts, heat or sonication is required [12].

The following sections will provide examples of the different transformations that can be achieved with indium metal [5].

3 Reactions with Aldehydes and Ketones

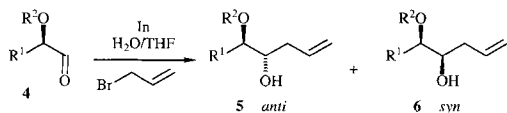
The first organic reaction discovered with organoindium compounds was the addition to carbonyl groups of aldehydes

and ketones [7, 9, 10]. So far this is probably the most widespread application of these organometallic substrates. There exist numerous examples for both the Barbier-type reaction of allylic halides **2** and the Reformatsky-type reaction of α -halogen esters **3** [15].



The diastereoselectivity of this reaction (especially in aqueous medium) was investigated intensively during the past two years, mainly by Paquette *et al.* [2, 16]. They demonstrated that chelate control also operates in water. The main stereochemical characteristics known so far are summarized below:

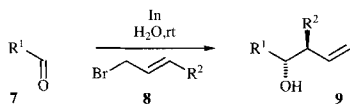
a) With O-protected α -oxy aldehydes ($R^1 \neq H$, **4a**) the *anti*-isomer **5** dominated, with a free hydroxyl group ($R^1 = H$, **4b**) the *syn*-isomer **6** is preferred [16a].



The *anti*-diastereoselectivity of protected derivatives can be enhanced by the addition of $Yb(OTf)_3$ [16c].

b) The corresponding β -hydroxy aldehydes formed *anti*-1,3-diols preferentially, no good selection was achieved with the protected derivatives [2].

c) When achiral aldehydes **7** are reacted with γ -substituted allylic halides **8** the *anti*-isomer **9** dominates [16b].



Here $La(OTf)_3$ was shown to increase the rate of the reaction and to improve the *anti*-selectivity [16d].

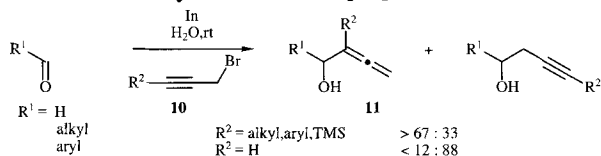
d) With allyl bromides bearing an etheral stereogenic center at 2-position, an 1,4-asymmetric induction in favor for the 1,4-*syn* product was observed [16f,h].

e) In the formation of stereotriads high levels of diastereoselectivity were recently reported [16j].

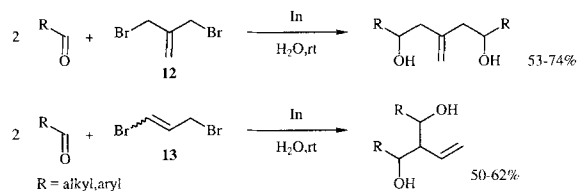
f) During the addition to α -alkoxy cyclohexanones, better and in special cases reversed diastereoselectivities were observed [16e].

So far there exists only one report on enantioselective indium-induced Reformatsky reactions, stoichiometric amounts of chiral aminoalcohols were used [17].

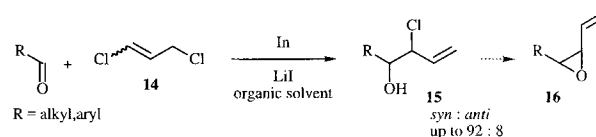
The substituted propargyl bromides **10** provided the allenylcarbinols **11** as major products, without substituent the reverse selectivity was observed [18].



An interesting extension to form trimethylenemethane dianion respectively *gem*-allyl dianion equivalents from **12** or **13** in water was reported by Li [19].



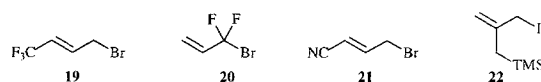
But with the dichloride **14** in organic solvents only one halogen reacted, the *syn*-chlorohydrin **15**, which *e.g.* can be converted to vinyloxydides **16**, was the major product [20].



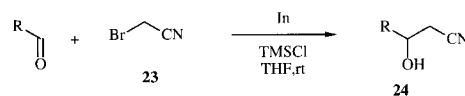
α,α -Dibromo ester **17** directly formed the oxirane **18** [21]. With other dihalides the reactions were less selective.



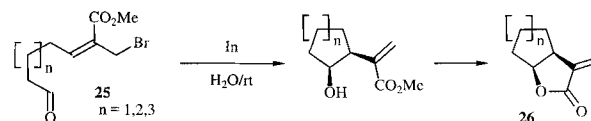
Other possible substituents on the allyl halide are CF_3 **19** [22a], CF_2R (**20**) [22b], CN (**21**) [22c] and allylsilanes CH_2SiMe_3 (**22**) [22d].



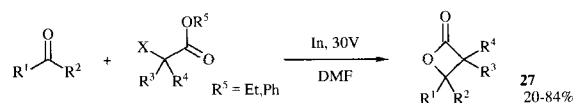
With $TMSCl$ as additive even bromoacetonitrile **23** reacts, β -hydroxy nitriles **24** are produced [23].



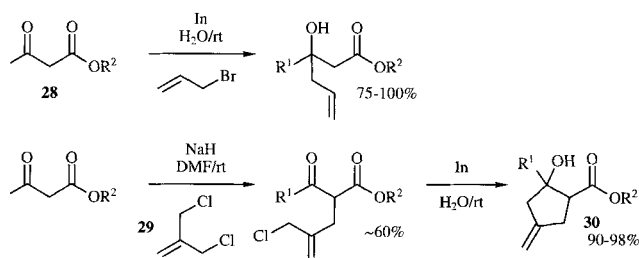
Intramolecular reactions lead to carbocycles, with **25** stereoselectively the lactones **26** were obtained [24].



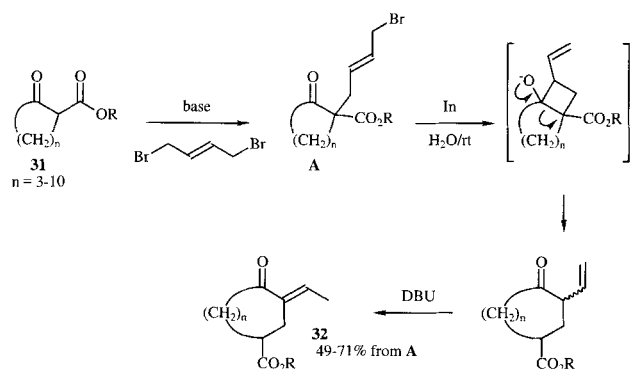
Schick developed an unique electrochemical synthesis of di-, tri-, and tetrasubstituted β -lactones **27** by a Reformatsky reaction [25].



The indium reagents also added to the keto groups of 1,3-dicarbonyl compounds **28**, which are known to be deprotonated by other organometallic reagents [26]. When dihalides **29** are used in these reactions, a [3+2] annulation forms cyclopentanes **30** by a two-step procedure [27].

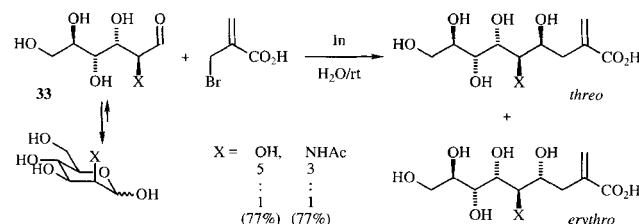


With cyclic substrates **31** an interesting two-carbon ring enlargement reaction, leading to seven- to fourteen-membered rings (**32**), was observed [28].



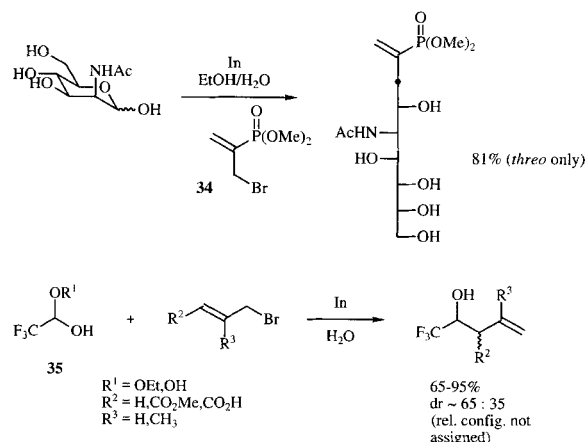
4 Reactions with Hemiacetals and Unprotected Carbohydrates

One of the most fascinating reaction of organoindium sesquihalides is the alkylation of unprotected carbohydrates (like **33**) in aqueous medium developed by Whitesides and by Chan, which proceeds with good *threo*-diastereoselectivity [29].



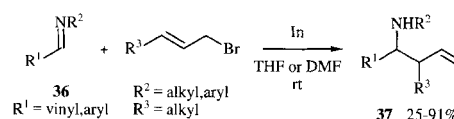
This principle has been applied to the synthesis of (+)-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) and *N*-acetylneuraminic acid [29f]. Similar reactions were also possible with phosphonates like **34** [29g].

This principle also allows the allylation of unstable aldehydes like trifluoroacetaldehyde **35** which can conveniently be used as stable hemiacetals or hydrates [29k].



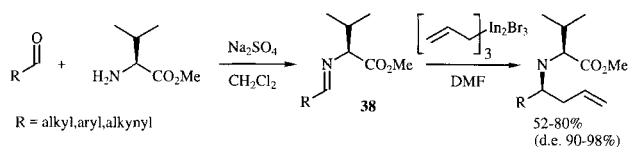
5 Reactions with Aldimines

With aldimines **36** and allylic bromides, the homoallylic amines **37** can be prepared [30].

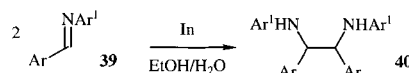


In DMF as solvent with R¹ = alkyl, the *N*-formylated products were formed [30b]. The diastereoselectivity ranges from erythro:threo = 55:45 to 65:35.

Slightly better diastereoselectivities were observed with aldimines **38** derived from (*S*)-valine esters. Diastereomeric ratios of 3:1 could be reached [30c]. Further improvement was achieved by a one-pot procedure of Loh, where **38** is generated *in situ* and then preformed allylindium sesquibromide is added [30d]. Thus a *d.e.* of 98% was reached.

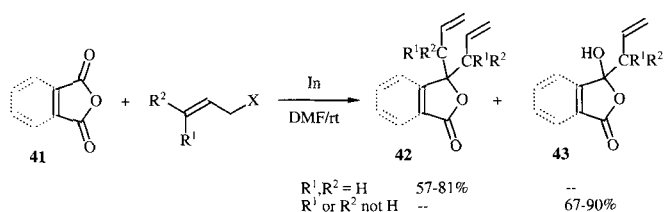


It should be noted that on the other hand in aqueous ethanol aldimines **39** are dimerized to a DL and meso mixture of vicinal diamines **40** by indium [31].

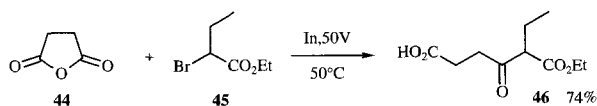


6 Reactions with Carboxylic Acid Anhydrides

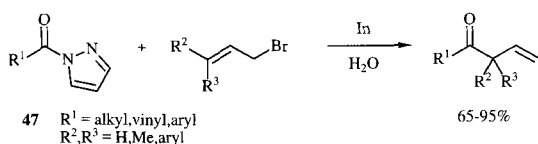
The indium mediated allylation of acid anhydrides **41** provides, depending on the substituents at the allyl group, either butenolides **42** or hydroxy lactones **43** [32a].



With 2-bromoalkanoates **45** and succinic anhydride **44**, Schick was able to prepare the ketones **46** by electrochemically assisted reactions with indium as sacrificial anode [32b].

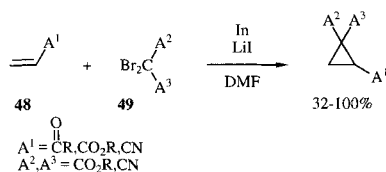


A more general approach to such ketones is the reaction of acylpyrazoles **47** [32c].



7 Cyclopropanations

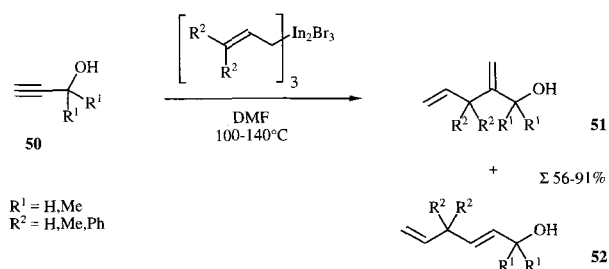
With activated methylene dibromides **49**, a cyclopropanation of electron-deficient olefins **48** is possible in the presence of lithium iodide [33].



In the case of two different substituents A^2 and A^3 , usually a mixture of diastereomers was observed [33, 21]. With electron rich alkenes, only very low yields were obtained.

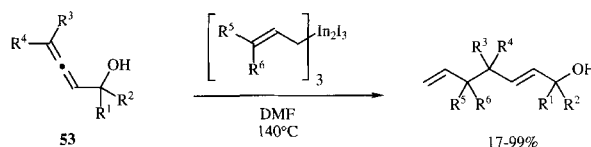
8 Carboindations of Alkynes and Allenes

At elevated temperatures allylic indium sesquihalides are able to carbometallate propargylic alcohols **50** in a regio- and stereo- selective manner [34]. Only terminal alkynes react.

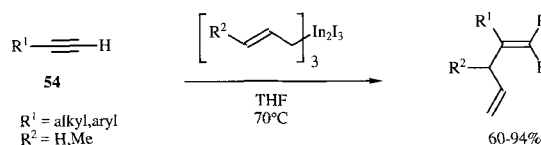


While the allylindium reagent always couples at the γ -carbon, the regioselectivity of the *syn*-addition to the alkyne is dependent on the substituents attached to both the allylindium and the alkynol. The ratio of two constitutional isomers **51** and **52** ranges from 0:100 to 86:14. The naturally occurring monoterpene yomogi alcohol was synthesized by this methodology [34a].

When allenols **53** were used, a completely regioselective addition was observed [34c]. Unfortunately in the case of two different substituents R^3 and R^4 , only a modest diastereoselectivity was observed (3:1 to 2:1).



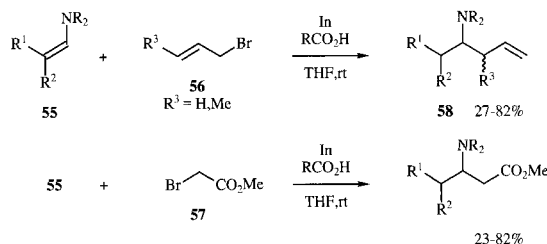
Recently it was reported that in THF also terminal alkynes **54** without hydroxyl group as activating group can be carbometallated [34d].



Interestingly, the regioselectivity of this addition is reversed with $\text{R} = \text{TMS}$!

9 Enamines

Homoallylamines **58** (compare section 5) can be prepared by the reaction of enamines **55** with allylic bromides **56** (methyl bromo acetate **57** also reacts) in the presence of metallic indium [35]. Once again the diastereoselectivity of this process is modest (2:1).



The presence of a carboxylic acid accelerates the reaction, which probably proceeds *via* an addition of the indium sesquihalide to the iminium salt formed by the protonation of the enamine. Unlike in other reactions mentioned above, here all three allyl groups of the sesquihalide are transferred to the organic substrate.

10 Future Prospects

The exploitation of indium in organic synthesis has just begun.

and one can expect many more useful transformations to be developed. Investigations in the field of diastereoselective reactions have just started, enantioselective reactions still have to be developed. Also an area of great interest, but beyond the scope of this article, is the application of indium(III) chloride as Lewis acid in aqueous medium [36].

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