Advances in indium-catalysed organic synthesis

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Covering: 1st May 1995 to 31st March 2000.

1   Introduction

Since the landmark review by Cintas in 1995 the organic chemistry community has witnessed an explosion of interest in the utility of indium reagents in synthesis.[1] A large proportion of this work has focused on the use of stoichiometric organo-indium reagents to promote organic reactions in aqueous media. Indeed, the phenomenal growth of indium-mediated Barbier type reactions in water has prompted a recent detailed review of the area.[2] The recent emergence of indium(III) complexes as efficient Lewis acid catalysts presents new and exciting opportunities for organoindium chemistry. This review highlights the advances in indium *catalysed* organic synthesis made throughout the period 1st May 1995 to 31st March 2000.

2   Acylation

The Lewis acid catalysed acylation of amines and alcohols with acetic anhydride is a mild alternative to basic and nucleophilic catalysts. The extremely efficient acylation of a diverse range of substrates has been noted using very low catalyst loadings (0.1 mol%) of the commercially available complex indium(III) triflate (Scheme 1).[3] Thus, secondary alcohol **1** is acetylated under mild conditions affording a very high yield of product **2** in less than thirty minutes at room temperature. Similarly, aniline **3** was protected in quantitative yield to form **4**.

The practical utility of this methodology is reflected in the high yielding acetylation of polyhydroxy compounds. As shown
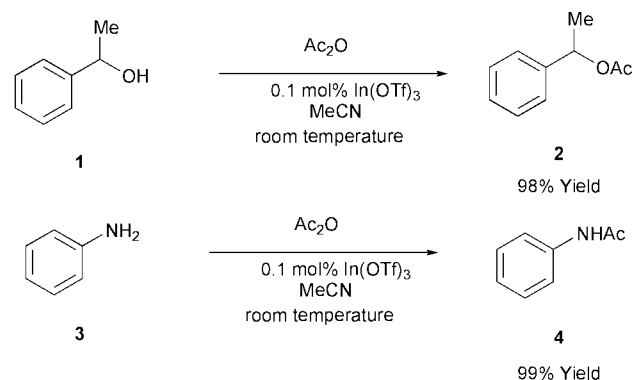
in Scheme 2, the exhaustive acetylation of D-mannitol **5** occurs in 94% yield affording **6** using the same low loadings of indium catalyst.
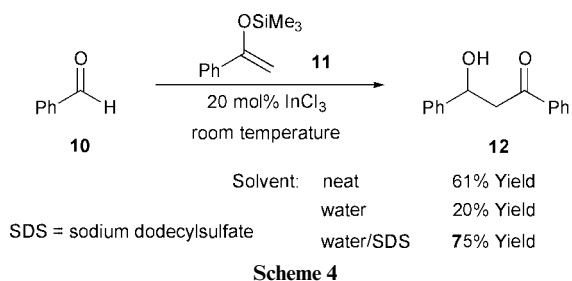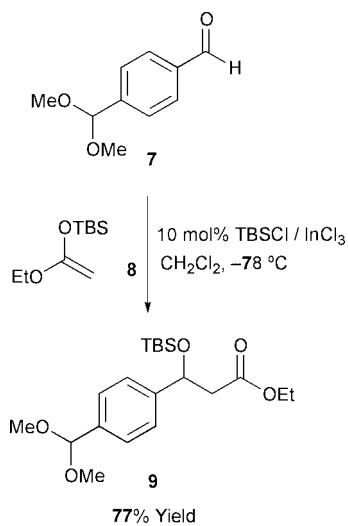
Scheme 2
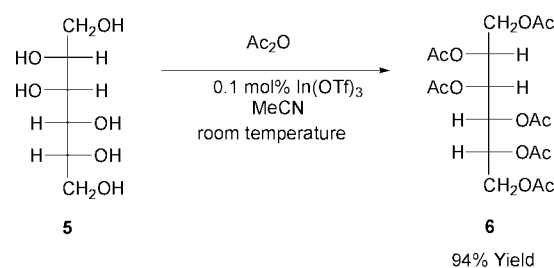
## 3   Addition to carbonyls

Over the last decade the indium-catalysed Mukaiyama aldol reaction has been the subject of some controversy. In 1991 it was first reported that both indium metal and indium(I) iodide promoted the aldol condensation between α-halo ketones and aldehydes.[4] Kobayashi and co-workers subsequently disclosed that indium(III) chloride in combination with chlorotrimethylsilane catalyses the aldol reaction between aldehydes (and the corresponding dimethyl acetals) with trimethylsilyl enol ethers.[5] This catalyst system had previously been found to be effective in the reaction of *O*-trimethylsilyl monothioacetals with triethylsilane to afford good yields of the corresponding sulfides.[6] Further work by Kobayashi demonstrated that the aldol reaction was strongly influenced by the substituents on the silicon of the silyl enol ether such that one could achieve the preferential activation of aldehydes in the presence of the corresponding acetals. To illustrate this phenomenon (a reversal of what is generally accepted), the mixed acetal–aldehyde substrate **7** smoothly reacts with *tert*-butyldimethylsilyl enol ether **8** to afford the corresponding aldol adduct **9** whilst the acetal part of **7** remains untouched (Scheme 3).

In 1996 Teck-Peng Loh and co-workers in Singapore reported the indium(III) chloride catalysed Mukaiyama aldol reaction affording good yields of products at room temperature using water as solvent.[7] This report was not consistent with results obtained by Kobayashi who concluded that the hydrolysis of silyl enol ethers is superior to the desired condensation in the same indium(III) chloride catalysed Mukaiyama aldol reaction.[8] A subsequent reinvestigation of the reaction revealed that reasonable yields of product could be obtained under neat (solvent-free) conditions albeit with severe substrate limitation. This is shown by reaction of benzaldehyde **10** with silyl enol ether **11** to give aldol product **12** (Scheme 4). Further to this, it was found that the reaction proceeded smoothly in water in the presence of a small amount of surfactant.
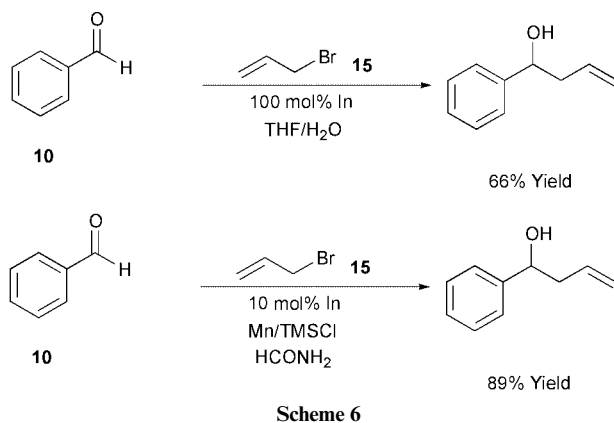
The many advantages of using water as a solvent for catalytic carbon–carbon bond formation continues to drive research in this area and the group of Teck-Peng Loh have reported an

Scheme 1

Scheme 3

7

10 mol% TBSCl / InCl$_3$
CH$_2$Cl$_2$, −78 °C

8

9
77% Yield

Scheme 4

OSiMe$_3$
Ph
11

20 mol% InCl$_3$
room temperature

10

12

SDS = sodium dodecylsulfate

| Solvent: | neat | 61% Yield |
| | water | 20% Yield |
| | water/SDS | 75% Yield |

efficient aldol reaction between commercially available aqueous formaldehyde and silyl enol ether **13** furnishing **14** which is promoted by indium(III) chloride (Scheme 5).[9]

Scheme 5

CH$_2$O (37% in water)
40 mol% InCl$_3$
room temperature

13

14
73% Yield
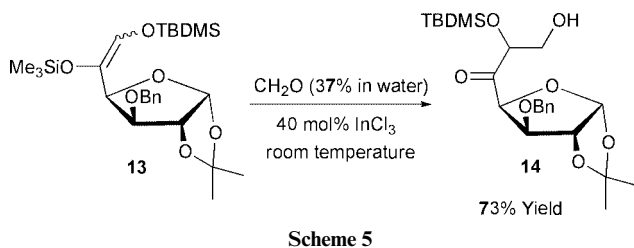
By far the greatest number of indium-mediated organometallic reactions involve the allylation of carbonyl compounds. Although rare (compared with magnesium and zinc) the stoichiometric amount of indium used is often tolerated as the metal has demonstrated remarkable reactivity in aqueous media. Similar allylation reactions using a catalytic amount of indium(III) chloride in combination with zinc or aluminium have been reported but at the expense of reactivity.[10] Indium(III) iodide has recently been employed as a catalyst for the addition of allylstannanes to carbonyl groups in organic solvents.[11] The major drawback to this methodology is the necessity to prepare the tin compounds in a separate step. Efficient methodology for the indium-catalysed allylation of carbonyl compounds has recently been disclosed. The method is based on the transmetallation of indium alkoxides by trimethylsilyl chloride and the *in situ* reduction of indium(III) species by manganese.[12] As described in Scheme 6, this system allows the efficient allylation of benzaldehyde **10** with allyl bromide **15** in the presence of trimethylsilyl chloride, manganese and a catalytic amount of indium powder. Formamide was shown to be the most efficient solvent for the reaction and the optimised conditions allow higher yields of product to be obtained than by using stoichiometric indium.

Scheme 6

Br **15**
100 mol% In
THF/H$_2$O

10

66% Yield

Br **15**
10 mol% In
Mn/TMSCl
HCONH$_2$

10

89% Yield

The diastereoselectivity of the reaction is observed to be high which is postulated to be a consequence of a chelation-controlled mechanism. This is illustrated by the allylation of benzoin methyl ether **16** which afforded the *syn* adduct **17** with >96% selectivity (Scheme 7).

Scheme 7

Ph
Ph
OMe
16

Br **15**
10 mol% In
Mn/TMSCl
HCONH$_2$

Ph
Ph
OMe
17

88% Yield
>96% *syn*
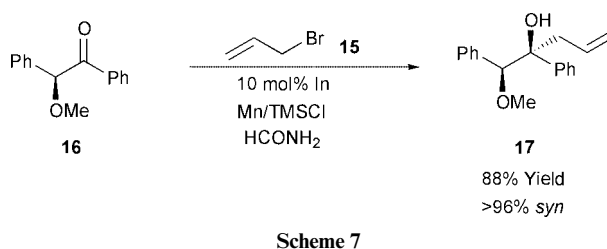
Teck-Peng Loh has established that the commercially available complex indium(III) fluoride is an effective catalyst for the addition of trimethylsilyl cyanide **18** to aldehydes in water as depicted in Scheme 8. Thus, pyridine-3-carbaldehyde **19** is converted to **20** in good overall yield. In the presence of a stoichiometric amount of indium(III) chloride a lower yield was obtained. Under similar conditions ketones do not react providing a chemoselective process.[13]

Scheme 8

CHO

TMSCN **18**
30 mol% InF$_3$
H$_2$O
room temperature

19

20
80% Yield
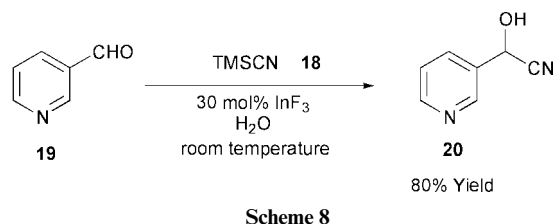
4 Addition to imines

To circumvent the problems associated with synthesis and purification of imines an elegant one-pot Mannich-type reaction has been developed employing indium(III) chloride as catalyst.[14] The reaction between aldehyde **21**, amine **22** and silyl enol ether **23** is catalysed by 20 mol% of indium(III) chloride in water and affords the product β-amino ester **24** in high yield (Scheme 9). The approach is also useful for the synthesis of β-amino ketones.

A similar strategy has been used by Ranu and co-workers in the one-pot synthesis of α-amino phosphonates from the reaction of a carbonyl compound, amine and diethyl phosphite **25**.[15] The method is operationally simple and applicable to aldehydes and ketones. The reaction is tolerant of sensitive functional groups and chelating groups such as pyridine in **21** which reacts with aniline **3** and **25** under mild conditions to afford the highly functionalised product **26** in high yield (Scheme 10). The reaction of a ketone such as cyclohexanone **27** and **28** with **25** required the reaction being heated to a higher
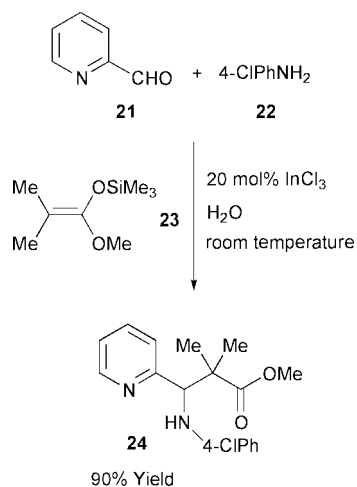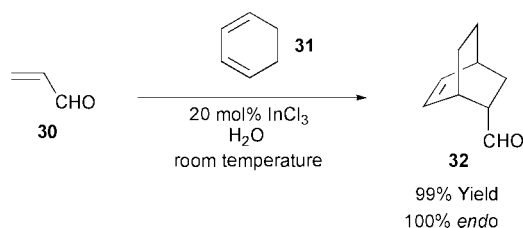
Scheme 9
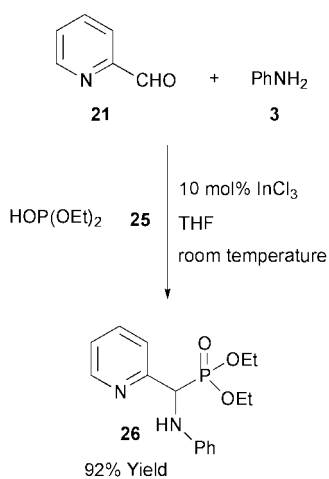
Scheme 10
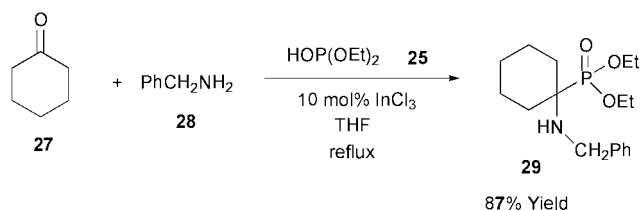
temperature but efficient conversion to product is still observed, as shown by the preparation of **29** in respectable yield.

5 Diels–Alder reactions

The synthetically important Diels–Alder reaction is known to show increased reactivity rates in water. This is enhanced in the presence of a water-stable Lewis acid. The reliable indium(III) chloride has been found to catalyse the Diels–Alder reaction between various dienes and dienophiles in water.[16] A representative example is shown in Scheme 11. Acrylaldehyde **30** reacts with cyclohexadiene **31** to afford the cycloaddition product **32** in high isolated yield as a single stereoisomer.
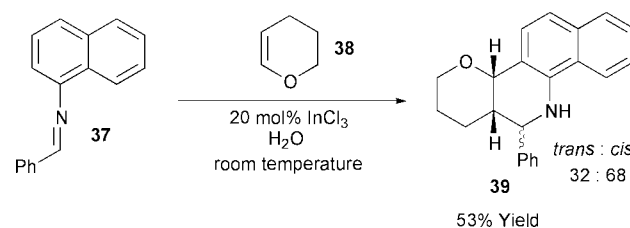

Scheme 11

The Frost group has noted the high catalytic activity of indium(III) triflate in hetero Diels–Alder reactions.[17] Initial work examined the reaction between benzaldehyde **10** and 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (Danishefsky's diene) **33** (Scheme 12). In the presence of 10 mol% of indium(III) triflate the two components react to afford the product **34** in just thirty minutes at −20 °C. The efficiency of this process prompted the investigation of the closely related imino Diels–Alder reaction between imine **35** and **33**. The catalyst loading could be lowered to 0.5 mol% and the reaction is still effectively complete within thirty minutes at room temperature furnishing **36**. Several examples are reported including a three component coupling of aldehyde, amine and diene demonstrating the advantageous stability of indium complexes in the presence of water and primary amines.
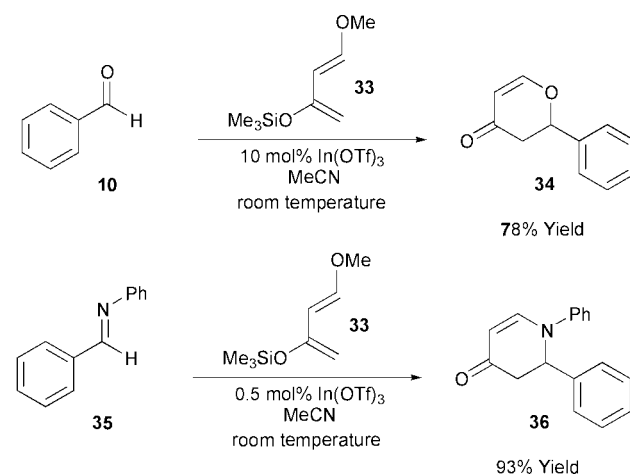
Scheme 12

Imines derived from aromatic amines can act as heterodienes. The group of Perumal have been foremost in utilising indium(III) chloride to catalyse this process. The reaction of Schiff's bases with cyclopentadiene, cyclohexen-2-one and cyclohepten-2-one results in the rapid synthesis of cyclopenta-quinolines, azabicyclooctanones and azabicyclononanones respectively.[18] As illustrated in Scheme 13, this protocol allows for the facile synthesis of functionalised phenanthridine derivative **39** from **37** and 3,4-dihydro-2H-pyran **38**.[19]
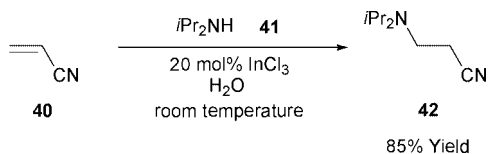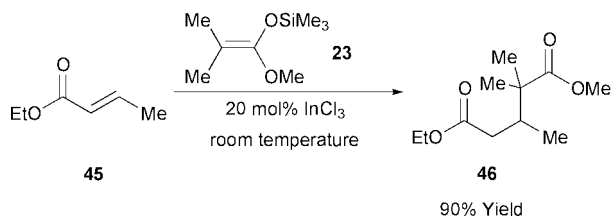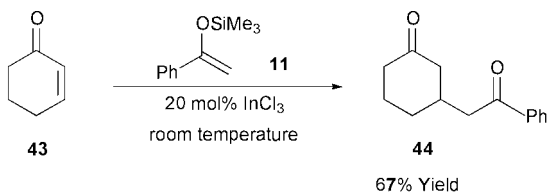

Scheme 13

6 Michael reactions

A catalytic amount of indium(III) chloride effectively promotes the Michael reaction between amines and α,β-ethylenic compounds in water and under mild conditions.[20] As an illustration of this methodology, when the reaction of acrylonitrile **40** with diisopropylamine **41** was performed in the presence of indium(III) chloride, the monosubstituted product **42** was obtained as the only product in high yield (Scheme 14). The catalyst can be recovered and reused without a decrease in yield.

In the absence of water (under neat conditions) indium(III) chloride is also an effective catalyst for the Michael reaction of silyl enol ethers with α,β-unsaturated carbonyl compounds.[21] This is shown in Scheme 15 where cyclohex-2-enone **43** is
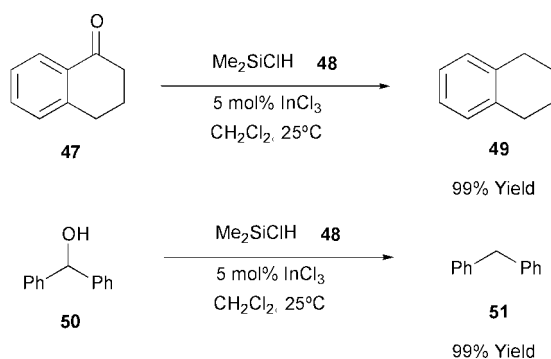
Scheme 14

Scheme 15

reacted with **11** to afford the the diketone product **44**. Furthermore, alkenoate **45** is smoothly converted to product **46** upon indium catalysed addition of **23**.
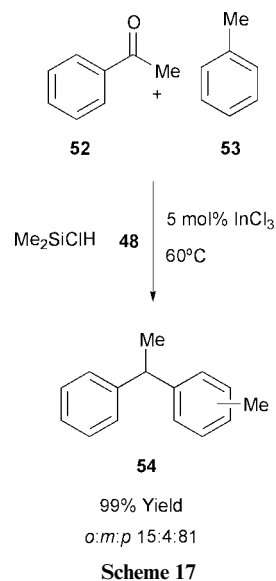
7 Reductions

The combination of chlorodimethylsilane **48** and an indium catalyst is extremely effective for reductive deoxygenation processes. An illustration of the utility of this method is in the deoxygenation of tetralone† **47**, the product **49** being obtained in quantitative yield.[22] Although the indium(III) chloride catalysed protocol is depicted in Scheme 16 several indium sources proved to be effective, including indium powder. The strategy is equally effective for the reduction of *sec*-benzylic alcohols as demonstrated by the transformation of **50** to the deoxygenated product **51**. It is of particular note that the combination system is so selective towards carbonyls that the reduction conditions tolerate functionalities such as halogen, ester and ether.
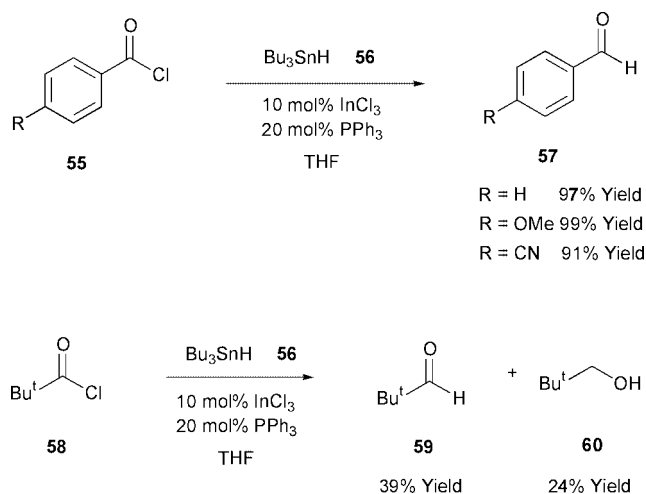

Scheme 16

The same catalytic combination proved equally effective in the reductive Friedel–Crafts alkylation of aromatics with ketones or aldehydes (Scheme 17).[23] The reaction of acetophenone **52** with toluene **53** in the presence of chlorodimethylsilane **48** and indium(III) chloride furnished the reduced product **54** in quantitative yield as a mixture of regioisomers (predominantly *para*).

The generation of dichloroindium hydride from tributyltin hydride **56** and indium(III) chloride allows the reduction

† The IUPAC name for tetralone is 3,4-dihydronaphthalen-1(2*H*)-one.

Scheme 17

of carbonyl compounds and the dehalogenation of alkyl bromides.[24] The selective reduction of acyl halides to aldehydes is much harder to achieve mainly due to over-reduction of the produced aldehyde. Baba and co-workers have reported a solution which allows the reduction of a range of acid chlorides **55** to the corresponding aldehydes **57**. The over-reduction could be suppressed by the addition of 20 mol% of triphenylphosphine leading to high yields of product (Scheme 18).[25] Although neither electron-withdrawing nor electron-releasing substituents on the aromatic acyl chlorides effected the conversion, bulky aliphatic acid chlorides such as **58** afforded low yields of product **59** accompanied by formation of significant amounts of the over-reduction product **60**.
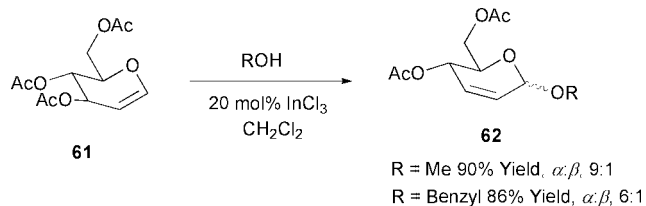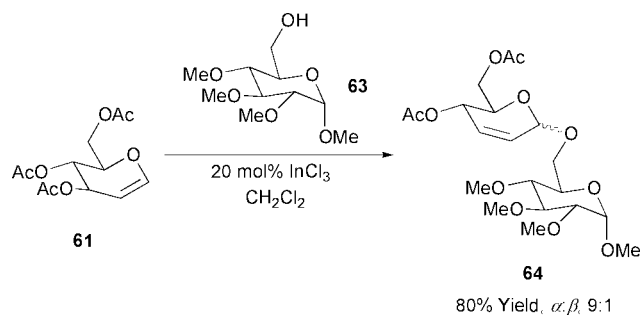

Scheme 18

8 Miscellaneous

Indium(III) chloride is reported to be an efficient catalyst for the synthesis of alkyl and aryl 2,3-unsaturated glycopyranosides utilising the Ferrier rearrangement.[26] As illustrated in Scheme 19, treatment of tri-*O*-acetyl-D-glucal **61** with alcohols in the presence of 20 mol% of indium(III) chloride at room temperature led to glycosidation products **62** in excellent yields and good anomeric selectivity.

The reaction was extended to 1,2,3,4-tetra-*O*-methyl-α-D-glucopyranoside **63**, which was coupled to **61** to afford the disaccharide **64** in 80% yield with the α-anomer as the major product (Scheme 20).

Scheme 19

R = Me 90% Yield, α:β, 9:1
R = Benzyl 86% Yield, α:β, 6:1

80% Yield, α:β, 9:1

Scheme 20

The Ranu group have reported a simple and efficient procedure for the rearrangement of substituted epoxides catalysed by indium(III) chloride as shown in Scheme 21.[27] Aryl-substituted epoxides isomerise with complete regioselectivity to form a single carbonyl compound. With close to thirty examples the methodology offers a high yielding synthesis of benzylic aldehydes and ketones with complete predictability. This is illustrated by the preparation of **66** from epoxide **65**.

92% Yield
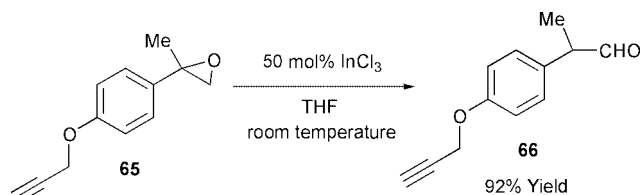
Scheme 21

9 Conclusion

Indium complexes have emerged as extremely valuable catalysts for a range of synthetic transformations. Catalytic reactions in water or aqueous media have attracted a lot of attention from the chemical community and indium exhibits unique activity in this area owing to its high coordination number and fast coordination–dissociation equilibrium. The future of this area lies in the development of an enantioselective indium catalyst that is air and water-stable.

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