

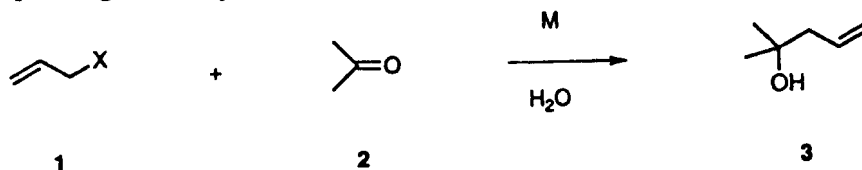
Organometallic-type reactions in aqueous media mediated by indium: Application to the synthesis of carbohydrates

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Abstract: Indium-mediated coupling reaction of carbonyl compounds with allylic halides in aqueous media to give homoallylic alcohols was studied in details regarding its regio- and stereoselectivity. A mechanism accounting for the observations has been proposed. The reaction has been applied to the syntheses of a number of sialic acids including KDN and neu5NAc.

Metal-mediated reactions in aqueous media have recently attracted considerable interest in organic synthesis.¹ Such reactions in aqueous media offer a number of advantages over conventional organometallic reactions in organic solvents: (1) There is the practical convenience, and possible environmental benefits, of not having to use inflammable and anhydrous organic solvents; (2) The tedious task of protection-deprotection chemistry for certain functional groups often encountered in organic synthesis may be obviated; (3) Water-soluble compounds such as carbohydrates can be reacted directly without the need of derivatization; (4) The regio- and stereochemical outcomes of the reactions may well change from organic to aqueous media and this offers new opportunities in synthesis. Several years ago, we began a program to study organometallic-type reactions in aqueous media with a view to exploring the above mentioned possibilities.

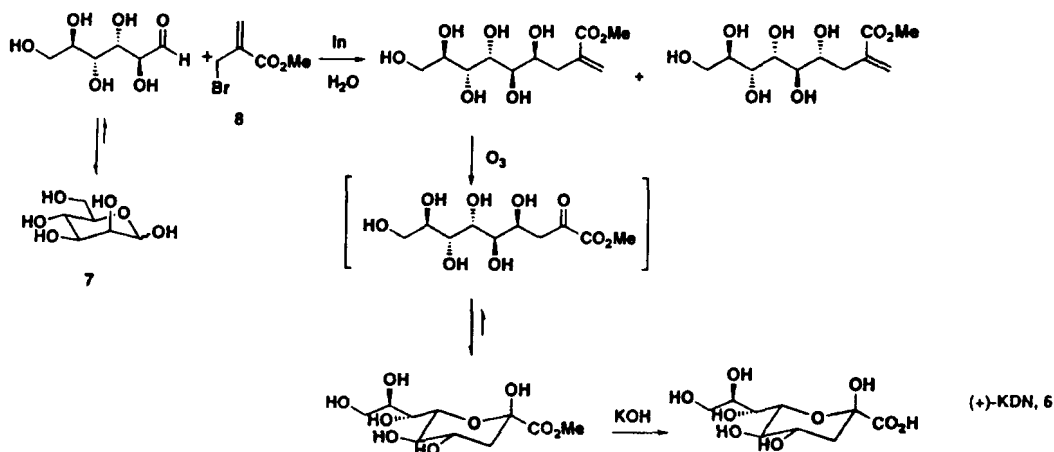
The most explored reaction thus far is the coupling of allylic halides (1) with carbonyl compounds (2) in aqueous media mediated by metal (M) to give the corresponding homoallylic alcohols (3).²



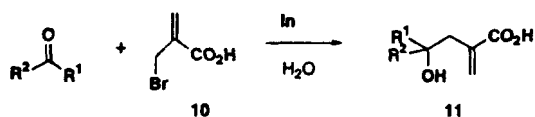
Variations of the allylic theme have been the use of 1,3-dihalopropenes (4)³ to give vinyl epoxides and 2-chloromethyl-3-iodopropene (5)⁴ to give methylenetetrahydrofurans. As for the metal M used, in addition to zinc and tin, indium has been found by us to be the metal of choice.⁵ Indium is considered to be more effective than zinc and tin because the reaction requires no activation, and produce few side products.



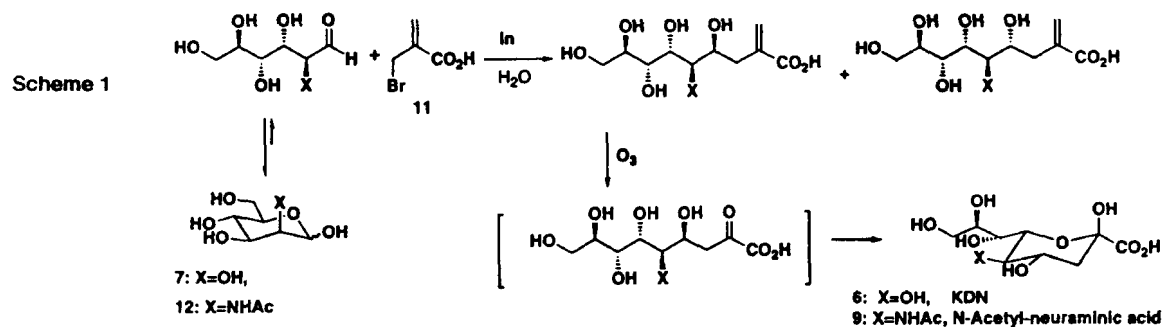
An obvious consequence of the aqueous media is that hydroxy functional groups do not require protection at the carbon-carbon bond formation step. This is particularly useful in the synthesis of carbohydrate molecules. We demonstrated the advantage of such reactions in a concise synthesis of (+)-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN, **6**) that was based on an indium mediated coupling reaction between mannose (**7**) and methyl α -bromomethylacrylate (**8**).⁶



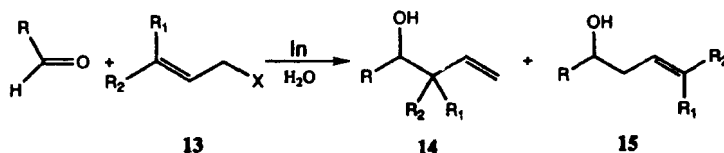
Recently,⁷ a similar approach has been applied by Whitesides and his coworkers to the synthesis of N-acetylneuraminic acid (neu5NAc, **9**), a sialic acid with an important role in a number of biological processes including cell adhesion, recognition and growth regulation. However, in this synthesis, the acid **9** was not isolated, but was converted to the corresponding peracetyl derivative. More recently, we found that the carboxylic acid function is also compatible with the indium-mediated reaction conditions. Thus, α -bromomethylacrylic acid (**10**) reacted directly with carbonyl compounds and indium in water to give the corresponding γ -hydroxy- α -methylene carboxylic acids (**11**) in good yields.⁸



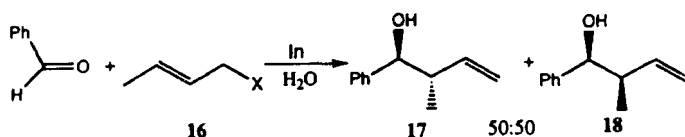
Since acids are often crystalline compounds, they are more readily purified than the corresponding esters. This has led to an even shorter synthesis of sialic acids (KDN **6** and neu5NAc **9**) according to scheme 1. In the case of neu5NAc **9**, it could be obtained as a crystalline solid starting from N-acetylmannosamine **12**.



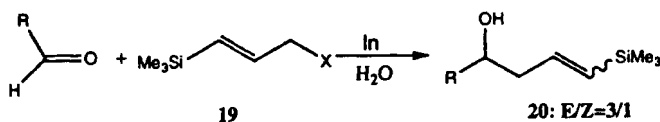
So far, in spite of these applications in synthesis, little is known about the regio- and stereoselectivity of these indium-mediated coupling reactions. In the coupling of aldehydes with an substituted allylic halide such as **13**, the coupled products can be either the α - or the γ -adducts, **14** and **15** respectively.



It is known that⁹ in the coupling of benzaldehyde with crotyl bromide (16), the reaction was γ -regioselective but poorly diastereoselective, giving a mixture of 17 and 18.



On the other hand, we found that for the coupling of aldehydes with 1-trimethylsilylpropenyl bromide (19) under the same conditions, the reaction was α -regioselective in giving a mixture of *E*- and *Z*-vinylsilanes (20). It is clear that if the reaction is to find further application in the synthesis of complex molecules, we must gain a better understanding of the origin of regio- and diastereo-selectivity.



The reactions of a number of γ -substituted allyl bromides with aldehydes under aqueous media mediated by indium were examined. The results are summarised in Table 1. The following conclusions can be drawn. (1) Regioselectivity is not governed by the ability of the substituent to conjugate with the double bond. Thus, both phenyl and ester substituents (21 and 22) gave the de-conjugated adducts. (2) Regioselectivity appears to be governed by the steric size of the substituent, but not by the degree of substitution. Thus, both the *t*-butyl (23) and the silyl substituted (19 and 24) allyl bromides coupled with aldehydes to give the same regio-isomers. (3) In γ -regioselective coupling leading to a mixture of syn- and anti-diastereomers, the diastereoselectivity (anti/syn ratio) is governed by the steric size of the substituent of the aldehydes to give mainly the anti-isomer. This is clear by comparing the coupling of a series of different aldehydes with the same *E*-cinnamyl bromide (21). Anti/syn ratio increased as the size of the aldehyde substituent increased from *n*-octyl to cyclohexyl to iso-propyl. (4) The diastereoselectivity appears to be independent of the stereochemistry of the double bond in the allyl bromide moiety. This is evident from the observation that *Z*-cinnamyl bromide (25) coupled with iso-butylaldehyde to give nearly the same ratio of anti/syn isomers as the coupling of *E*-cinnamyl bromide. The possibility that the *Z*-cinnamyl bromide may have isomerised to the *E*-isomer first before coupling was ruled out since *Z*-cinnamyl bromide could be recovered unchanged if the reaction was allowed to proceed to half completion.

To account for these observations, we propose in broad terms the following mechanism for the indium-mediated coupling reaction in aqueous media (Scheme 2). First, an allyl indium species 26 is formed which exists in equilibrium with its regioisomer 27. Because of this equilibrium, stereochemistry of the double bond in the allylindium species can be isomerised to favour the more stable isomer. In the coupling with aldehyde, the reaction proceeds through a cyclic transition state with the carbonyl oxygen coordinated with indium. In cases where the γ -substituent in the allyl bromide is bulky (e.g. silyl or *t*-butyl), the cyclic transition states preferred are the ones (28 and 29) which minimise the steric interaction between the bulky substituent and the aldehyde, leading to the α -adducts. In other cases, the cyclic transition states (30 and 31) are the ones leading to the γ -adducts, but with the diastereo-selectivity governed by the steric size of the aldehydic substituents in choosing between quasi-equatorial (30) versus quasi-axial (31) positions.

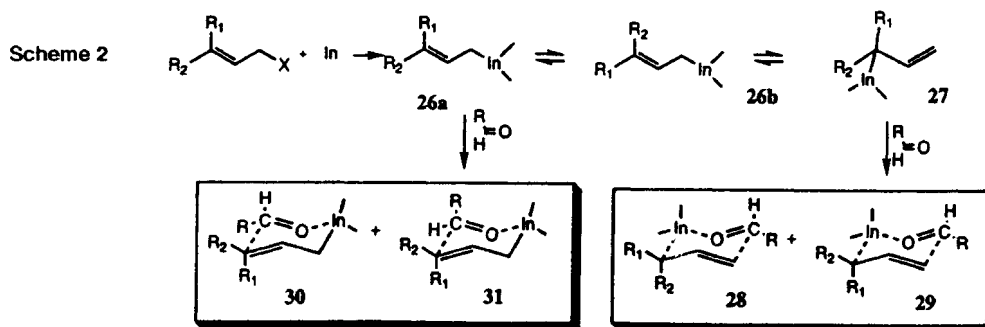
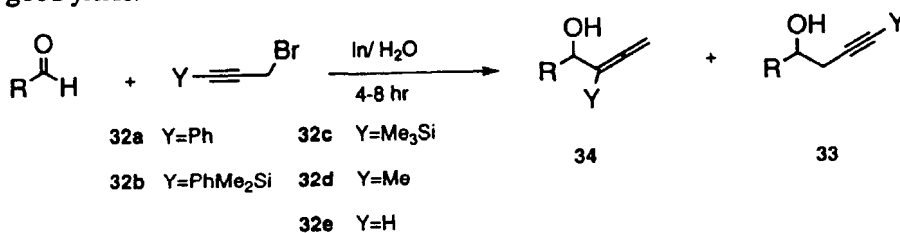


TABLE I: INDIUM MEDIATED ALLYLATION OF CARBONYL COMPOUNDS IN WATER

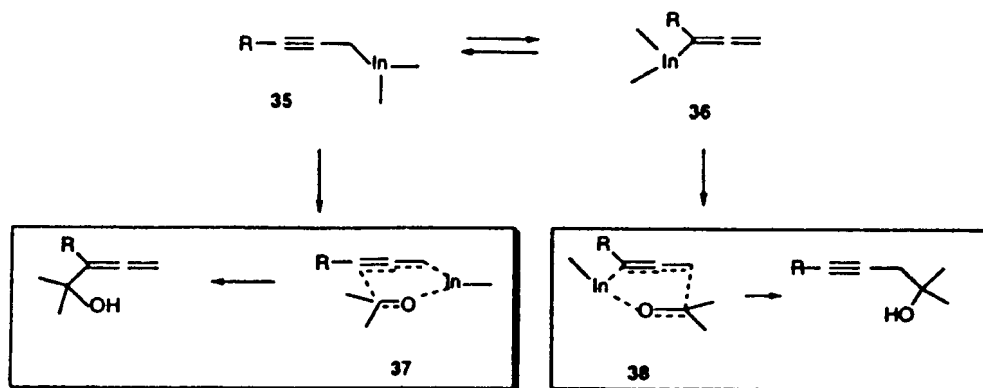
ENTRY	ALLYL BROMIDE	ALDEHYDES	PRODUCT	YIELD(%)
1		Me ₂ CH-CHO		62 (E: Z =75 : 25)
2		Me ₂ CH-CHO		50 (E: Z =68 : 32)
3		PhCHO		88(anti: syn=96:4)
4	21	Me ₂ CH-CHO		88(anti: syn=96:4)
5	21			75(anti: syn=90:10)
6	21	n-C ₈ H ₁₇ -CHO		80(anti: syn=69:31)
7		PhCHO		75(anti: syn=84:16)
8	22	Me ₂ CH-CHO		81(anti: syn=92:8)
9	22			88(anti: syn=72:28)
10		Me ₂ CH-CHO		87 (E: Z =80 : 20)
11		PhCHO		90
12		Me ₂ CH-CHO		86(one isomer)
13	25	Me ₂ CH-CHO		79(anti: syn=90:10)
14		PhCHO		92(anti: syn=50:50)
15	16	Me ₂ CH-CHO		88(anti: syn=84:16)
16	16	Me ₃ C-CHO		87(anti: syn=80:20)

All reactions were carried out at room temperature using the aldehyde(1mmol), allyl bromide(2mmol), In(2mmol) in H₂O(2ml). Isolated yields are reported and selectivities were determined from crude Nmr.

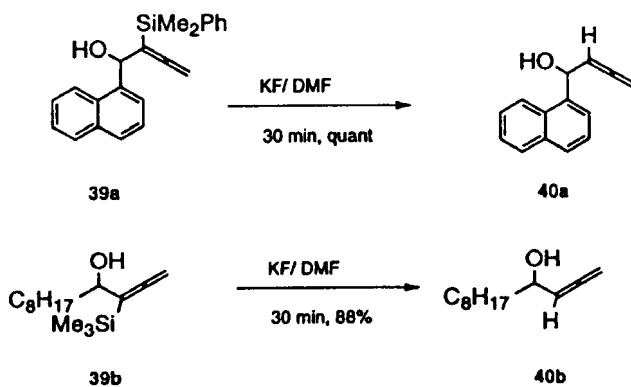
The same consideration can be extended to the indium-mediated coupling of aldehydes with propargyl bromides in aqueous media. Here, only the question of regioselectivity exists. With the parent prop-2-ynyl bromide (32e), indium-mediated coupling with aliphatic or aryl aldehydes in water gave mainly the homopro-2-ynyl alcohols 33 in good yields. In contrast, when the propargyl bromide is γ -substituted with methyl, or phenyl or silyl, the coupling products were predominately or exclusively the allenylic alcohols 34, again in good yields.¹⁰



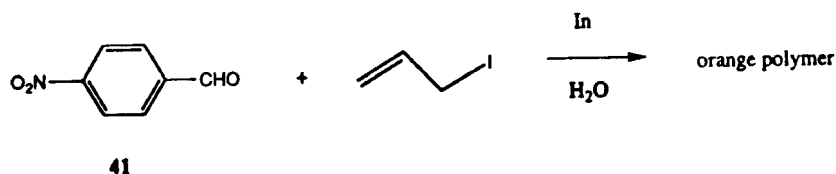
The regioselection can be explained by a modified mechanism involving the indium species. In the equilibrium between the propargyl indium **35** and the allenyl indium **36** species, the direction of the equilibrium depends greatly on the substituent. In the parent case ($R=H$), the equilibrium is very much in favour of the allenyl indium **36**; whereas for the substituted case, the equilibrium is in favour of the propargyl indium **35**. The reaction with the aldehydes may well proceed through similar cyclic transition states **37** and **38**, leading to the respective products.



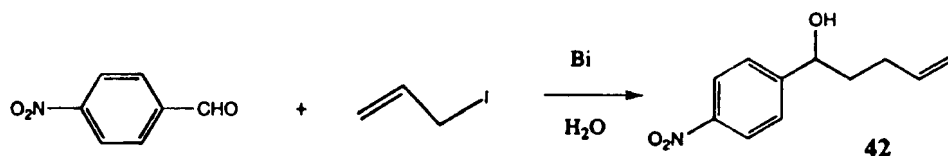
Based on these observations, we have devised an approach to obtain selectively the unsubstituted allenyl alcohols. 1-Silyl-3-bromopropynes (**32b** or **32c**) were coupled with aldehydes to give the corresponding allenyl alcohols **39a** or **39b** which were separated readily from the minor homopropargyl alcohols. Protodesilylation of **39** with KF/DMF gave quantitatively the unsubstituted allenyl alcohols **40a** or **40b** without any contamination of the isomeric homopropargyl alcohol. The protodesilylation reaction by fluoride ion is patterned after a similar reaction on β -hydroxyvinylsilanes.¹¹



While indium offers considerable advantages in the reactions mentioned above, we would be less than honest if we don't outline some of the disadvantages as well. Indium is relatively expensive; this may well prohibit its use in large scale. However, one may surmount this problem by using indium in a catalytic cycle via an electrolytic process or in combination with a less expensive metal. A catalytic process may also overcome the second disadvantage of using indium, namely, the rather high toxicity of indium. Finally, not all function groups are compatible with the use of indium. One example we have encountered is in the attempted coupling of *p*-nitrobenzaldehyde (**41**) with allyl iodide with indium in water. An orange insoluble polymer was obtained, presumably because the nitro function was first reduced by the indium to give the corresponding amino function which then condensed with the aldehyde function.



We found that bismuth, with a first ionisation potential between that of indium and zinc, is able to mediate the coupling between *p*-nitrobenzaldehyde and allyl iodide in water to give the homoallylic alcohol **42** in 70% isolated yield. The reaction required the presence of tetrabutylammonium bromide, otherwise the yield was considerably poorer. The bismuth-mediated coupling is quite sensitive to the structure of the allylic halides used. For example, allyl chlorides or bromides are much less reactive under these conditions, suggesting that the coupling reaction requires a finely-tuned balance between the electron transfer from the metal to the different substrates.



Conclusions We have shown that certain organometallic-type reactions in aqueous media are useful reactions in organic synthesis, particularly in the synthesis of carbohydrate molecules. Factors affecting the regio- and stereoselectivity of these reactions can be understood. The scope of the reactions remain to be extended, and metals other than indium may need to be examined.

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