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ORGANOMETALLIC REACTIONS IN AQUEOUS MEDIA WITH INDIUM[1]

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*Abstract: Allylation reactions of aldehydes and ketones occurred smoothly with indium metal in aqueous media. Compared to similar reactions with zinc and tin, the reaction with indium proceeds without the need of any promoter. The reaction can be extended to the synthesis of 2-methylene-γ-lactone **6** via the condensation of carbonyl compounds with 2-bromomethylacrylate **4**.*

Recently, there has been considerable interest in performing organometallic reactions in aqueous media.[1,2] A number of potential advantages have been cited, including; (1) the ease of reactions in obviating the need for inflammable anhydrous organic solvents and inert atmosphere; (2) protection of "reactive" hydroxy functional group is no longer required; (3) compounds (e. g. carbohydrates) insoluble in organic solvents can react directly and (4) change in stereoselectivity due to solvent effect.[3]

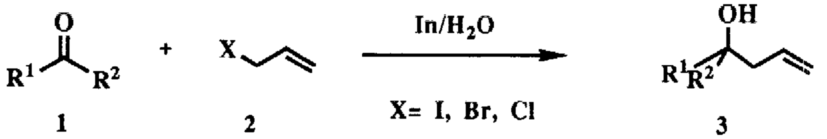
The choice of metals in organometallic reactions in aqueous media is quite limited however. The reactive alkali and alkaline earth metals cannot be used because of their vigorous reactions with water itself. Metals which form aqueous insoluble oxides readily are also unlikely candidates. So far, the most commonly used metals in aqueous organometallic reactions are zinc and tin.[1,2] Very often, acid catalysts,[2b] heat[2c] or sonication[2a] are required to induce the reactions to occur.

In this connection, indium metal offers some intriguing possibilities. Compared to other metals, indium has not been much explored in organometallic reactions.[4] It was only recently that indium has been used in Reformatsky reactions,[5] allylations[6] and cyclopropanations[7] of carbonyl compounds. While these results are interesting, the use of indium in organic solvents offered no obvious advantages over other conventional organometallic reactions. On the other hand, it is known that indium is unaffected by boiling water or alkali.[8] It does not form oxides readily in the air. Furthermore, its first ionization potential (Table 1) is much lower than that of zinc or tin, and for that matter, even magnesium. If aqueous organometallic reactions proceed by a single electron transfer (SET) mechanism as we suspect,[9] indium may well be effective in such reactions.

Table 1. First to Fourth Ionization Potential of Some Metals

Metal	Ionization Potential (eV)			
	I	II	III	IV
Indium	5.785	18.86	28.03	54.4
Aluminum	5.984	18.82	28.44	119.96
Magnesium	7.646	15.035	80.143	109.29
Zinc	9.39	17.96	39.7	
Tin	7.34	14.63	30.49	40.72

We report here that indium can indeed effect allylation of aldehydes and ketones in water at room temperature in high yield (Table 2). The reaction procedures are extremely simple. A mixture of carbonyl compound (1 mmol), allyl halide (1.5 mmol) and indium (1 mmol) in water (20 ml) was stirred at room temperature in a stoppered flask for 1-6 hrs. The product was extracted with ether and purified in the usual manner. The reaction required no protection of inert atmosphere. Allyl bromide appeared to be as good as allyl iodide in undergoing the reaction. Even the less reactive allyl chloride (entry 3) can be used, but the reaction required longer reaction time and gave poorer yield. Hydroxy group elsewhere in the molecule did not require protection (entries 15, 16). Allylation of ketones occurred readily though required longer reaction time than aldehydes.



(eq. 1)

Compared to the use of zinc and tin where acid catalysts, heat or sonication were often required, reactions with indium metal need no promoter. In cases where reactions with zinc or tin gave poor yields, the use of indium generally improved the yields (compare entries 3 and 4, as well as 10-14). By-products such as alcohols (due to reduction of the carbonyl compounds by the metal) and pinacols (due to coupling of the carbonyl compounds) which were often observed in zinc or tin reactions were conspicuously absent in the indium reactions. Furthermore, in the presence of acid sensitive group such as acetal (entry 17), reaction by indium gave cleanly

Table 2. Allylation of Aldehydes and Ketones Mediated by Indium in Aqueous Media

Entry	R^1	R^2	X	Metal	A/allylX/M	Time(hrs)	Yield	Syn:anti
1	Ph	H	Br	In	1/1.5/1	3	97	
2	Ph	H	I	In	1/1.5/1	3	95	
3	Ph	H	Cl	In	1/1.5/1	5	60	
4	Ph	H	Cl	Sn	1/1.5/1	5	$0^{a,b}$	
5	ClPh	H	Br	In	1/1.5/1	1	94	
6	CH_3CHOH	H	Br	In	1/1.5/1	3	85	67:33
7	$CH_3CH(ODCB)$	H	Br	In	1/1.5/1	3	75	24:76
8	$CH_3(CH_2)_2CH(OBn)$	H	Br	In	1/1.5/1	3	80	24:76
9	$PhCH(CH_3)$	H	Br	In	1/1.5/1	3	90	78:22
10	Ph	CH_3	Br	In	1/1.5/1	5	72	
11	Ph	CH_3	Br	Zn	1/1.5/1	5	18^c	
12	Ph	CH_3	Br	Sn	1/1.5/1	3	0^a	
13	$-(CH_2)_5-$		Br	In	1/1.5/1	6	68	
14	$-(CH_2)_5-$		Br	Sn	1/1.5/1	6	0^a	
15	$HOCH_2C(CH_3)_2$	H	Br	In	1/1.5/1	3	85	
16	$HO(CH_2)_4$	H	Br	In	1/1.5/1	3	95	
17	$(CH_3O)_2CHCH_2$	CH_3	Br	In	1/2/1.5	6	70	
18	$(CH_3O)_2CHCH_2$	CH_3	Br	Zn	1/2/2	6	0	
19	$(CH_3O)_2CHCH_2$	CH_3	Br	Sn	1/2/2	6	10^d	

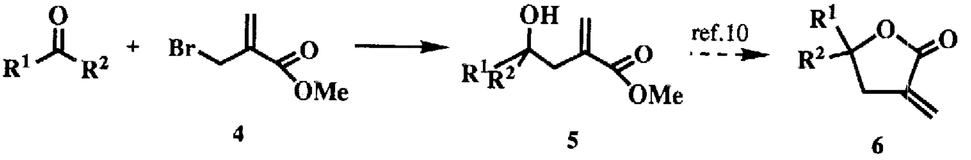
All the reactions were performed at 1 mmol scale at room temperature in water by stirring the reaction mixtur for the proper time, otherwise mentioned; [a]mediated by tin at 80^0C, [b]promoted by sonication; [c]mediated by zinc with sonication; [d]by ^{1}Hnmr.

Table 3. Preperation of 2-methylene-γ-hydroxy Esters.

Entry	RCHO	halide	Metal	Temp.	Time	Yield
1	PhCHO	$BrCH_2C(CH_2)CO_2CH_3$	In	r.t.	5	96
2	PhCHO	$BrCH_2C(CH_2)CO_2CH_3$	Zn	US^a	5	26
3	PhCHO	$BrCH_2C(CH_2)CO_2CH_3$	Zn	$r.t.^b$	6	52
4	$HOCH_2(CH_3)_2CHO$	$BrCH_2C(CH_2)CO_2CH_3$	In	r.t.	5	85
5	$HOCH_2(CH_3)_2CHO$	$BrCH_2C(CH_2)CO_2CH_3$	Zn	US^a	5	17

All the reactions was performed at 1 mmol scale in water with RCHO/halide/M = 1: 1: 1; a: sonication; b: catalysed by NH_4Cl.

allylation of the carbonyl group without affecting the acetal. The same reaction with zinc under all the usual conditions(entry 18) did not give any allylation product and little recovery of the starting acetal ketone, whereas allylation with tin promoted by saturated NH_4Cl gave less than 10% yield of the product (entry 19). Addition of HBr (or other acids) and use of ultrasonic radiation to catalyze the Sn reaction led to a mixture of several products.



(eq. 2)

The allylation with indium can be extended to the reactions of carbonyl compounds with methyl (2-bromomethyl) acrylate (**4**) to give the corresponding hydroxy acrylic esters **5**, a precursor for 2-methylene-γ-lactone **6** which is an important structural unit in a variety of natural products. The reactions proceeded smoothly with indium at room temperature in a few hours (Table 3). The same reaction with zinc has not been reported and gave only low yields in our hands with all the usual reaction conditions including catalysts and sonication. Reactions with tin required long reaction time of refluxing in acid and gave poorer yields.[10]

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