Effect of InCl$_3$ on the addition of Grignard reagents to α,β-unsaturated carbonyl compounds

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Abstract—Control of 1,2- versus 1,4-addition of organometallic reagents to enones remains a long-standing problem. There is still no satisfactory 1,2-directing agent comparable to the 1,4-directing effect of copper salts. We report that the presence of just 5 mol% indium(III) chloride can significantly alter the amount of 1,2-product formed in these reactions. © 2002 Elsevier Science Ltd. All rights reserved.

Carbon–carbon bond formation is the fundamental operation in the construction of organic molecules and the addition of organometallic reagents to carbonyl compounds is one of the most common C–C bond forming reactions. However, when the carbonyl substrate is α,β-unsaturated, a mixture of products may arise (Scheme 1).

Control of 1,2- versus 1,4-addition in such systems is not satisfactory in that no 1,2-directing agent comparable to the 1,4-directing effect of copper(I) salts[1] has been identified thus far—although CeCl$_3$ has had a significant effect in some cases.[2] This is particularly true when Grignard reagents must be used in cases where the corresponding organolithium compounds (which generally give the 1,2-adduct) are commercially unavailable or cause unwanted reactions by acting as bases. With the foregoing in mind, we sought an agent which could regioselectively direct such nucleophile/carbonyl systems, thereby reducing or completely eliminating unwanted side-products. Herein we report our preliminary results, which show that the presence of ≤5 mol% InCl$_3$ as an additive can significantly alter the amount of 1,2-product formed. We chose to study indium compounds because although organoindium chemistry is in

its infancy, a number of interesting and useful synthetic aspects are already known.[3] But only allylation has been studied in much detail and indeed this is by far the best known use for indium in organic synthesis. However, Trost and co-workers[4] found that in palladium-catalysed trimethylenemethane (TMM) cycloadditions (which can be considered as a 1,4-addition followed by cyclisation), the presence of 10 mol% indium(III) acetylacetonate redirected the reaction from a conjugate pathway to a 1,2 route with enones. It was this, allied to the fact that the presence of indium has also been reported to catalyse the reaction of allylic stannanes with carbonyls,[5] which led us to believe that our goal of regioselectivity in the Grignard reaction of enones was attainable.

Following Trost's success using In(III) compounds, we chose InCl$_3$ as an additive in the test reaction of PhMgBr with benzylidene acetone. Gratifyingly, the presence of just 5 mol% InCl$_3$ did indeed alter the outcome of the reaction, increasing the 1,2/1,4-product ratio to 88:12 as compared to 76:24 in the absence of any additive. In order to establish if InCl$_3$ was altering the rate of this reaction, we carried out a simple compe-

Scheme 1.

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tition experiment. Two reactions were performed simultaneously under identical conditions—one in the absence of additive and the other in the presence of 5 mol% InCl$_3$. Both reactions were quenched after 60 min and after workup, analysis by ^{1}H NMR revealed a 98% conversion of enone in the case where InCl$_3$ was present, and 88% conversion when it was not. Thus it was evident that (at least in this case) InCl$_3$ was capable of inducing an increase in the rate of reaction. Consequently we decided to screen a number of Grignard reactions with various enones in the presence of InCl$_3$ (Table 1). It can be seen from Table 1 that in many cases there was a significant alteration in the product distribution when just 5 mol% of InCl$_3$ was added to the reaction.

We can make the following generalisations about the results we have obtained. In the cases of MeMgCl and strikingly with EtMgBr when there is not already exclusive 1,2-product formation in the absence of any additive, the addition of InCl$_3$ causes an increase in the proportion of 1,2-product formed. The opposite is the case (i.e. there is a proportional decrease in the amount of 1,2-product) with allylmagnesium bromide and *tert*-butylmagnesium chloride as the Grignard reagents. However, the situation with phenylmagnesium halide is less clear cut.

Before we can discuss the role of InCl$_3$, some discussion of the 1,2/1,4 ratio in the absence of additive is merited. Clearly there is a large variation between each of the substrate/Grignard combinations indicating that the ratio is both substrate and reagent dependent. It is a phenomenon that has been discussed elsewhere in the literature[6] but a universal theory which adequately explains it has yet to be generally accepted. Holm[7] has carried out a series of kinetic experiments in order to shed some light on the situation. He asserted that only substrates which have or may assume a *cisoid* conformation may react in a 1,4 fashion via a polar mechanism. By invoking the concept of a homolytic reaction mechanism he rationalised why certain *transoid* substrates such as 2-cyclohexenone also underwent 1,4-addition with certain Grignard reagents. However, he did note anomalies within this theory whereby certain Grignard reagents which are unlikely candidates for homolysis were still observed to undergo 1,4-addition with *transoid* substrates.

Initially we had envisaged the role of InCl$_3$ as that of a Lewis acid, whereby it would coordinate to the oxygen of the carbonyl moiety of the enone, thereby rendering it more electrophilic and thus promote attack by the incoming nucleophile at the carbonyl position (Scenario 1). Our initial postulate therefore, was that if we added

Table 1. Effect of added InCl$_3$ on the 1,2/1,4-product ratios[a] in the reaction[b] of Grignard reagents with various enones

Enone	Additive	Grignard				
		MeMgCl	EtMgBr	AllylMgBr	PhMgBr	^{t}BuMgCl
Ph-enone (acetyl)	None	95:5 (97)	15:85 (99)	100:0 (93)	76:24 (100)	52:48 (98)
	InCl$_3$	100:0 (70)	45:55 (86)	90:10 (87)	88:12 (100)	52:48 (94)
Ph-enone-Ph	None	62:38 (100)	7:93 (92)	99:1 (100)	0:100 (86)	95:5 (100)
	InCl$_3$	82:18 (95)	56:44 (55)	100:0 (93)	0:100 (90)	54:46 (100)
Ph-enone-OMe	None	63:37 (91)	3:97 (100)	100:0 (100)	10:90 (100)	77:23 (100)
	InCl$_3$	100:0 (15)	39:61 (91)	96:4 (89)	11:89 (100)	59:41 (88)
cyclohexenone	None	100:0 (83)	3:97 (100)	100:0 (100)	71:29[c] (100)	36:64 (100)
	InCl$_3$	100:0 (60)	49:51 (100)	100:0 (100)	37:63[c] (48)	21:79 (96)
Ph-enone-H	None	100:0 (58)[d]	85:15 (98)	100:0 (99)[d]	100:0 (100)[d]	66:34 (91)[d]
	InCl$_3$	100:0 (50)[d]	98:2 (86)[d]	100:0 (99)[d]	100:0 (94)	58:42 (83)[d]

[a] Determined by ^{1}H NMR; no other products formed unless otherwise stated. Figures in parentheses refer to the percentage conversion of enone as determined by ^{1}H NMR.

[b] Typical procedure was as follows: To a solution of enone (1 equiv.) in dry THF (ca. 1.5 mmol/30 mL) was added InCl$_3$ (0.05 equiv.). The resulting suspension was stirred rapidly and cooled to 0°C. Grignard reagent (1.1 equiv.) was then added all at once via syringe, at which point dissolution of the suspension occurred. The reaction mixture was allowed to warm to ambient temperature over 16 h, after which it was quenched with a saturated ammonium chloride solution (ca. 30 mL), extracted with ether (3×20 mL), dried over sodium sulfate and concentrated in vacuo to give the crude product(s).

[c] PhMgCl was used.

[d] Reduction and other side products formed.

enough InCl$_3$ to each reaction we would be able to induce 1,2-addition in all cases.

However, when we added 100 mol% InCl$_3$ to the reaction of PhMgBr with benzylidene acetone (Table 2, entry 3), we found that no addition to the enone occurred. This was quite puzzling. However, when we closely examined the set of reactions we had originally screened (Table 1), we found that in nearly every case the addition of InCl$_3$ caused a decrease in the conversion of starting material and hence a decrease in the yield of addition products. Thus it was apparent that the InCl$_3$ was competing with the enone for attack by the Grignard nucleophile.

Therefore we had to re-evaluate our initial assumptions about the role of InCl$_3$ and we considered a number of possibilities, two of which are outlined below:

(a) *The Grignard reagent reacts with InCl$_3$ to form an InR$_3$ species which then delivers the R group to the enone*. The reported preparation of many trialkyl- and triaryl-indiums is just this reaction,[8] so this is a likely process in our system. When we carried out a control reaction by adding 3 equivalents of PhMgBr along with 100 mol% of InCl$_3$ (Table 2, entry 4), again we found there was no reaction with the enone. This rules out the possibility of the InR$_3$ species supplying the nucleophile, at least in the phenyl case. Another possibility (where 5 mol% InCl$_3$ is present) is that the InR$_3$ species formed could activate the carbonyl position on the enone for further attack by the remaining Grignard reagent (similar to Scenario 1, above). However, this can only be the case if the InR$_3$ species does not further react with the Grignard reagent to form an 'ate' complex (see below).

(b) *An indium 'ate' species (InR$_4^-$ $^+$MgX) could be formed (which is more reactive than the corresponding InR$_3$ entity[9]) which could then act as the aryl-/alkylating agent*. When we added 4 equivalents of PhMgBr along with 100 mol% of InCl$_3$, we obtained the 1,2-product exclusively, but there was a low conversion of starting material. This would appear to confirm the intermediacy of an 'ate' species, whose regioselectivity is greater

than that of 'ordinary' Grignard reagent, but with a sluggish reactivity in comparison (Scenario 2). However, the situation is not quite as simple as that because there is an alternative scenario (Scenario 3), where InR$_3$ acts as a Lewis acid and the 4th equivalent of Grignard derived nucleophile is directed to the carbonyl (again, similar to Scenario 1).

It is likely that Scenario 2 operates, as the low yield of addition product would indicate that a species less reactive than RMgX is the reactant. That said, however, to the best of our knowledge the only reported indium 'ate' complexes have been made using organolithium reagents, and not organomagnesiums. We also cannot rule out the possibility of both scenarios (2 and 3) occurring in parallel.

The above arguments may be used to explain the effect of added InCl$_3$ on the methyl and ethyl and to a certain extent phenyl Grignard reactions. However, they cannot be used for the allyl and *tert*-butyl reagents. Both of these reagents are potential candidates for reaction via a homolytic mechanism, as they can form radicals which are stabilised by resonance and hyperconjugation, respectively. Therefore, it may be that the presence of InCl$_3$ stabilises the radicals formed thus inhibiting the 'usual' reactions in the absence of any additive. That said, there was no obvious ketyl coloration observed in any of the reactions with or without an indium additive. Alternatively, the putative InR$_3$ Lewis acid in operation in the cases of the reactions with EtMgBr and MeMgCl has never been reported to form from allyl or *tert*-butyl Grignard reagents. Thus, whatever species does form (presumably InR$_2$Cl or InRCl$_2$) in these cases may in fact weakly direct 1,4-addition.

The situation with phenylmagnesium halide is less clear-cut. Although with PhMgBr there is an increase in the proportion of 1,2-product formation in some cases, when PhMgCl was used with 2-cyclohexenone (Table 1), the addition of InCl$_3$ caused a marked decrease in the proportion of 1,2-product. It is too early at this stage to speculate as to why this should be so, although major differences have been seen before in the reaction of acyclic and cyclic α,β-unsaturated ketones.[10]

Table 2. Variation of amount of InCl$_3$ and Grignard reagent[a]
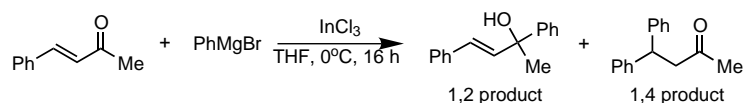
Entry	Equivalents of PhMgBr[b]	Mol% of InCl$_3$[b]	1,2/1,4 Ratio[c]
1	1.1	–	76:24 (100)
2	1.1	5	88:12 (100)
3	1.1	100	– (0)
4	3	100	– (0)
5	4	100	100:0 (27)

[a] Figures in parentheses refer to percentage conversion of enone as determined by ^{1}H NMR.
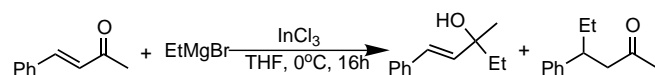[b] W.r.t. benzylidene acetone.
[c] Determined by ^{1}H NMR.

Having established that $InCl_3$ did indeed alter the product distribution in the reaction of Grignard reagents with enones, but with a decrease in conversion in most cases, we wanted to establish if less than 5 mol% $InCl_3$ could still induce a similar redistribution of products, but with less of a drop in conversion. We investigated the reaction of EtMgBr with benzylidene acetone because this combination of Grignard and substrate had shown the most pronounced effect when we had carried out our initial screening. The results of this investigation are shown in Table 3.

As can be seen from these results, there is a correlation between the amount of $InCl_3$ and the decrease in conversion of enone. However, as the $InCl_3$ loading increases from 1 to 20 mol%, there is very little change in the 1,2/1,4-product ratio. Thus, in this limited case it would seem that a reduction in the loading of $InCl_3$ is advantageous with regard to the conversion without a significant diminution of the 1,2 selectivity.

In conclusion, we have shown that the presence of $InCl_3$ can have a marked effect on the regioselective outcome of the reaction of Grignard reagents with enones. However, although it is too early at this stage to comment definitively as to why this is so, we can assert that the effect is not just limited to allylic nucleophiles. Efforts are ongoing to investigate further the scope of indium compounds in these nucleophile/carbonyl systems.

Table 3. Influence of $InCl_3$ on the reaction of 1.1 equiv. of EtMgBr with benzylidene acetone

Mol% $InCl_3$	1,2/1,4 Ratio[a]	% Conversion[b]
–	15:85	99
1	41:59	89
5	45:55	86
10	43:57	80
20	47:53	50

[a] Determined by ^{1}H NMR.
[b] Refers to percentage conversion of enone.

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