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Remarkable Electronic Effect on Rhodium-Catalyzed Carbonyl Additions and Conjugated Additions with Arylmetallic Reagents

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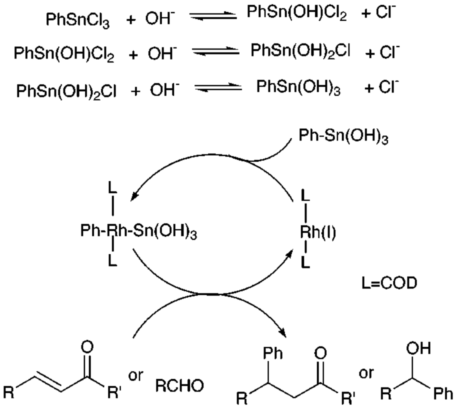
The transition-metal catalyzed coupling reactions of organometallic reagents are of growing importance in modern organic chemistry and are widely used in the synthesis of pharmaceuticals, fine chemicals, petrochemicals, agricultural chemicals, and polymers.[1] The progress of these catalyzed reactions is generally controlled by the nature of the catalyst and its associated ligands. Alternatively, the reactivity can be adjusted by changing the nature of the organometallic reagents, for example by using organozinc,[2] organotin,[3] and organoboron[4] reagents. While the activation of the less reactive organosilicon[5] reagents by fluoride ion is well-known,[6] the electronic properties of substituents (X) on the reactivity of organometallic reagents RMX_n have not been widely studied. On the other hand, it is well recognized that the nature of counterions has a fundamental impact on the acidity of the Lewis acids (e.g., AlR_3, AlR_2X, $AlRX_2$, AlX_3).[7] Herein we wish to report a remarkable effect (by the electronic nature of substituents) on the reactivity of organometallic reagents RMX_n in rhodium-catalyzed carbonyl additions and conjugated additions in air and water.

Recently, as part of our interests of developing organic reactions in aqueous media,[8] we reported a phenylation of aldehydes in water. Phenyltin derivatives (trimethyl and tributyl) reacted effectively with aldehydes in water and under an atmosphere of air to give nucleophilic addition products in the presence of a catalytic amount of rhodium catalyst.[9] Subsequently, we found that in the presence of a rhodium catalyst, α,β-unsaturated esters and ketones react with triphenylbismuth as well as trialkylphenyl- and trialkylvinyltin reagents in aqueous media to give the corresponding conjugated addition products under an air atmosphere.[10] From the atom economy point of view,[11] Ar_mMX_n should be a better choice than $ArMR'_n$, where all the R′ groups were sacrificed. In addition, Ar_mMX_n-based reagents are more readily available and would also provide more alternatives for the operational procedure. However, when the alkyl- and aryl-substituents R′ on the metals were changed to halogens such as chloro and bromo (e.g., $PhSnCl_3$), the reaction ceased completely. Upon the addition of a base, the reaction proceeded again.

Figure 1. Postulated electronic effect on tin.

Scheme 1. Tentative Mechanism for the Rhodium-Catalyzed Carbonyl Addition and Conjugated Addition of Phenyltin Trichloride under Basic Conditions



A tentative mechanism for the effect of the base on the reaction of phenyltin trichloride was proposed in which transient organotin hydroxide intermediates were formed and enhanced the reactivity of the C−Sn bonds in tin reagents (Scheme 1).[12] Under neutral conditions, such a halogen−hydroxy exchange will occur only partially and may not be enough to initiate the reaction. Alternatively, ate-complexes (stannates and borates) were formed in the presence of a base, which enhanced the reactivity of the arylmetallic reagents.

To understand the dramatic change of reactivity due to the switch from alkyl and aryl groups to halogens and the effect of base on the reactions, we speculated that for the group (R′) attached to tin, alkyl groups inductively donate electrons, whereas alkoxy (and hydroxy) and halogen substiuents inductively withdraw electrons but donate electrons to the empty d-orbital of tin by resonance (Figure 1). However, the electron-withdrawing inductive effect out-gains the electron-donating resonance effect in halogens; the resonance effect may be stronger than the inductive effect in alkoxy (and hydroxy).[13] It would then be expected that the desired reactions would proceed if the halogens are replaced by hydroxy or alkoxy groups.

To study this hypothesis, we examined the rhodium-catalyzed phenylation of aldehydes with various phenylstannanes, phenyltin

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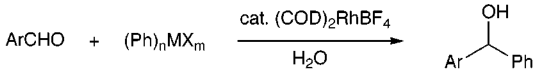
Table 1. Rhodium-Catalyzed Phenylation of Aldehydes with Various Reagents in Water^{a}

entry	**2**	substrate(**1**)	base	yield(%)
1	PhSnCl$_3$	PhCHO	no base	0^{d}
2	PhSnCl$_3$	PhCHO	LiOH	21^{d}
3	PhSnCl$_3$	PhCHO	NaOH	49^{d}
4	PhSnCl$_3$	PhCHO	KOH	71^{d}
5	PhSnMe$_3$	PhCHO	no base	82^{d}
6	PhSnCl$_3$	PhCHO	KOH	43^{b,d}(11)^{c,d}
7	Ph$_2$SnBu$_2$	PhCHO	no base	62^{d}
8	Ph$_3$SnCl	PhCHO	no base	0^{d}
9	Ph$_3$SnOH	PhCHO	no base	31^{d}
10	Ph$_3$SnBu	PhCHO	no base	43^{d}
11	PhSnCl$_3$	*o*-FPhCHO	KOH	83^{e}
12	PhSnCl$_3$	*p*-FPhCHO	KOH	78^{e}
13	PhSnCl$_3$	naphthaldehyde	KOH	63^{d}
14	PhSnCl$_3$	anisoaldehyde	KOH	57^{d}
15	PhBCl$_2$	PhCHO	no base	0^{b,d}
16	PhBCl$_2$	PhCHO	KOH	38^{b,f}
17	PhBCl$_2$	PhCHO	KOH	75^{b,d}

[a] All reactions were performed with 10 mol % of catalyst otherwise mentioned. The ratio of **2** to **1** is 2:1. All yields were isolated ones after column chromatography on silica gel. [b] 5 mol % of the catalyst was used. [c] 2.5 mol % of the catalyst was used. [d] 100 °C. [e] 50 °C. [f] rt.

chloride derivatives, and phenyltin chloride derivatives with a base (eq 1). In the presence of a catalytic amount of Rh(COD)$_2$BF$_4$ at



(1)

1 **2** **3**

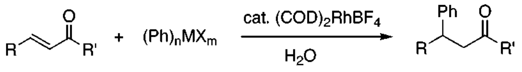
refluxing temperature in water and air, benzaldehyde underwent reaction with trimethylphenyltin and dibutyldiphenyltin (entries 5 and 7, Table 1) to give the corresponding nucleophilic addition product smoothly. On the other hand, under the same reaction conditions, no reaction was observed between benzaldehyde and phenyltin trichloride even after several days. When the reaction was carried out in the presence of potassium hydroxide, a smooth reaction occurred again to give the desired product overnight. A more dramatic effect was observed by using triphenyltin chloride, triphenyl hydroxide, and butyltriphenyltin. No reaction was observed with the chloride, but the reaction with either hydroxide or butyl proceeded smoothly (entries 8−10). Interestingly, the use of different bases also affects the reaction progress (entries 2−4). Although 10 mol % of the catalyst was used initially, the use of a smaller amount of the catalyst (2.5−5 mol %) was also effective although it slowed the reaction slightly (entry 6). With the optimal reaction conditions in hand, several aldehydes were examined with phenyltin trichloride under basic conditions (entries 11−14). The presence of electron-withdrawing groups on aromatic aldehyde appeared beneficial to the reaction, whereas electron-donating substituents on aromatic aldehydes decreased the reactivity and thus required a longer reaction time. Under the basic conditions, aliphatic aldehydes gave low yields of the desired products most likely due to complications such as aldol-condensations.

A similar dramatic electronic effect was observed in the conjugated addition of unsaturated ketones **4**[14] including 1-cyclohexen-2-one, 1-cyclohepten-2-one, and *trans*-1,2-dibenzoylethylene (eq 2) (Table 2). Essentially no reaction was observed even after a long reaction time between phenyltin trichloride and 1-cyclohexene-2-one (entry 1). However, the reaction was highly successful in giving the desired product **5** with either phenyltrimethylstannane (entry 2) or with the combination of phenyltin trichloride and KOH (entries 3−5). Similar results were obtained by using triphenyltin chloride, triphenyltin hydroxide, triphenyltin methoxide, butyltriphenyltin, and tetraphenyltin (entries 6−10, Table 2); whereas no reaction was observed with the chloride, all of the others reacted with tetraphenyltin being the least effective. Such an electronic effect was also observed with organobismuth compounds (entries 11−14). Although PhBiBr$_2$ does not react with 1-cyclohexene-2-one under neutral conditions, conjugated-addition products can be obtained with either triphenylbismuth (and dimethylphenylbismuth) or PhBiBr$_2$ under basic conditions. Such a trend was further displayed with phenylboron reagents.[15] PhBCl$_2$ was inactive under neutral conditions but was highly reactive for both carbonyl additions and conjugated additions under basic conditions (Table 1, entries 15−17; Table 2, entries 15 and 16) (the empty P-orbitals of boron are involved in those cases).

Table 2. Rhodium-Catalyzed Conjugated Additions of Unsaturated Ketones in Water^{a}

entry	(Ph)$_n$MX$_m$	substrate (**4**)	base	yield (%)
1	PhSnCl$_3$	2-cyclohexen-1-one	no base	trace^{c}
2	PhSnMe$_3$	2-cyclohexen-1-one	no base	85^{c}
3	PhSnCl$_3$	2-cyclohexen-1-one	KOH	92(82)^{b,e}
4	PhSnCl$_3$	2-cyclopenten-1-one	KOH	78^{d}
5	PhSnCl$_3$	trans-1,2-dibenzoyl-ethylene	KOH	62^{c}
6	Ph$_3$SnCl	2-cyclohexen-1-one	no base	trace^{c}
7	Ph$_3$SnPh	2-cyclohexen-1-one	no base	11^{c}
8	Ph$_3$SnBu	2-cyclohexen-1-one	no base	62^{c}
9	Ph$_3$SnOH	2-cyclohexen-1-one	no base	52^{c}
10	Ph$_3$SnOMe	2-cyclohexen-1-one	no base	53^{c}
11	Ph$_3$Bi	2-cyclohexen-1-one	no base	84^{d}
12	PhBiMe$_2$	2-cyclohexen-1-one	no base	90^{d}
13	PhBiBr$_2$	2-cyclohexen-1-one	no base	trace^{c}
14	PhBiBr$_2$	2-cyclohexen-1-one	KOH	26^{c}
15	PhBiCl$_2$	2-cyclohexen-1-one	no base	trace^{d}
16	PhBiCl$_2$	2-cyclohexen-1-one	KOH	82^{d}

[a] All reactions were performed with 10 mol % of catalyst otherwise mentioned. The ratio of **2** to **4** is 2:1. All yields were isolated ones after column chromatography on silica gel. [b] 2.5 mol % of the catalyst was used. [c] 100 °C. [d] 50 °C. [e] rt.



(2)

4 **5**

In conclusion, the electronic nature of substituents on metal has a dramatic influence on the reactivity of arylmetallic reagents under rhodium-catalyzed conditions. By using such an electronic effect, successful aqueous phenylation of carbonyl compounds and conjugated addition of unsaturated carbonyl compounds were achieved with phenylmetal halides under basic conditions or with phenylmetal hydroxides (and methoxides). Such an electronic effect may be more profound, and it opens the door for an additional method of controlling the chemo-, regio-, and stereochemistry of transition-metal catalysis.

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Supporting Information Available: Representative experimental procedures for carbonyl phenylation and conjugated additions (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

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