

Quasi-Nature Catalysis: Developing C–C Bond Formations Catalyzed by Late Transition Metals in Air and Water

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ABSTRACT

This Account outlines the recent efforts of developing catalysis under the ambient conditions of air and water for synthetic purposes from the author's laboratory. The discussions are focused on catalytic reactions (mostly C–C bond formations) other than oxidations via late transition metals. It includes the following aspects: (1) copper-catalyzed C–C bond formations; (2) palladium-catalyzed C–C bond formations; (3) rhodium-catalyzed C–C bond formations; (4) ruthenium-catalyzed olefin isomerizations and C–H activations. The mechanism, limitations, and synthetic applications of these reactions are also discussed.

Introduction

The use of late transition metals for catalyzing reactions is of growing importance in modern organic chemistry.¹ These catalyses are widely used in the synthesis of pharmaceuticals, fine chemicals, petrochemicals, agricultural chemicals, polymers, and plastics. Among the various catalytic reactions, the formations of C–C, C–O, C–N, and C–H bonds are particularly important in synthesis. Conventionally, organometallic chemistry and transition-metal catalysis are carried out under an inert gas atmosphere and the exclusion of moisture has been essential.²

On the other hand, the catalytic actions of transition metals under ambient conditions of air and water have played a key role in various enzymatic reactions including biocatalysis, biodegradation, photosynthesis, nitrogen fixation, digestions, and the evolution of bioorganisms.³ All these "natural" catalytic reactions occur under aqueous conditions in an air atmosphere, which is in sharp contrast to most transition-metal-catalyzed reactions commonly used in the laboratory. Although many transition-metal-catalyzed oxidations such as the renown Wacker oxidation process⁴ are carried out in air and water, this account concerns mostly catalytic reactions involving a carbon–metal (C–M) bond that leads to the formation of carbon–carbon bond in air and water.

Chao-Jun Li, born in 1963, received a B.S. (1983) and an M.S. (1988) from Zhengzhou University and the Chinese Academy of Sciences, respectively. He completed his Ph.D. study (1989–1992) at McGill University and was an NSERC (Canada) Postdoctoral Fellow at Stanford University. Since 1994, he has been on the faculty of Chemistry Department at Tulane University as an assistant professor, associate professor (1998), and full professor (2000–present). His current research activities are focused on green chemistry, organic reactions in water, transition-metal catalyses, and natural product syntheses.

In a recent Account, Roesky and co-workers elegantly discussed the reactivity of C–M bonds involving main group metals toward water by examining the bonding characteristics of s-block and p-block organometallic compounds.⁵ For p-block organometallic compounds, the increased covalent nature of C–M bonds dramatically decreased their sensitivity toward water. On the other hand, the reactivity of C–M bonds of d-block organometallic compounds was much more complicated as well as synthetically more versatile than those of both the s-block and p-block organometallic compounds due to the participation of d-orbitals in bonding. There is no doubt that many more interesting catalytic reactions can be discovered by the exclusion of competing hydrolysis and oxidation due to the presence of air and water. However, the ambient feature offers convenience in chemical synthesis involving small-scale combinatorial synthesis, large-scale manufacturing, and catalyst recycling. Such advantages have been well demonstrated by the recent large volume of work with water-soluble catalysts,^{6,7} such as catalytic hydrogenation,⁸ hydroformylation (e.g., the well-known Rhone-Poulenc process),⁹ palladium-catalyzed carbon–carbon bond formation reactions,¹⁰ and ruthenium-catalyzed metathesis reactions.¹¹ This Account describes the development of synthetically useful catalytic coupling reactions under the ambient conditions of both air and water, which comes down to the competitive reactivity of C–M bonds toward water (hydrolysis), air (oxidation), and organic substrates (often an electrophile to generate the desired product) (Figure 1). Through a delicate balance of these reactivities, this Account demonstrates that various air- and water-sensitive catalytic reactions can in fact be carried out in air and water.

Background

Since Wolinsky et al.¹² made the observation in 1977 that the allylation reaction of carbonyl compounds with allyl bromide mediated by zinc could be carried out in 95% ethanol and *tert*-butyl alcohol, a growing interest in metal-mediated Barbier–Grignard type carbonyl addition in water has been seen.¹³ One particularly interesting characteristic of such reactions is that they can also be carried out in air. Chan¹⁴ and Whitesides¹⁵ have elegantly demonstrated the potentials of such reactions with synthetic applications in carbohydrate chemistry. However, most of the successes have been limited to the use of organic halides involving an activated C–X bond (such as allyl halides). This is primarily due to the fact that a highly reactive metal is required to break a nonactivated carbon–halogen bond and, with a highly reactive metal, various competing side reactions (such as the reduction of water, the reduction of starting materials, and the hydrolysis of the organometallic intermediate, even if it is successfully generated) will prevail. On the other hand, the chemistry of d-block transition metals is much more complex and rich in diversity. The methods for forming C–M bonds

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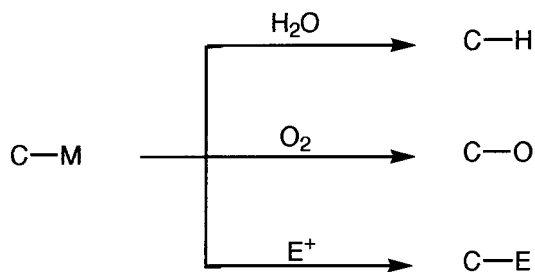
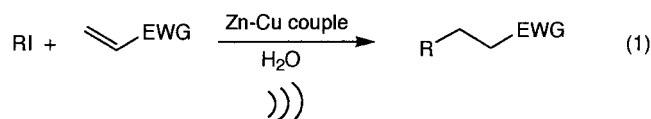


FIGURE 1.

involving d-block metals (late transition metals in particular) are both rich and facile. In addition, the C–M bonds related to these metals can be tuned readily to balance their stability toward air and water and their reactivity toward organic substrates. This Account illustrates the efforts to extend the aqueous Barbier–Grignard-type reaction to nonactivated organic halides via late-transition-metal catalysis in air and water.

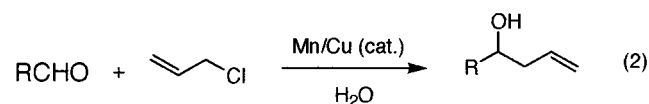
Copper-Catalyzed C–C Bond Formations in Air and Water

An early effort was made to activate a nonactivated C–X bond by using a copper catalyst together with a metal mediator (such as tin or zinc), to mediate a coupling between an aldehyde and a simple alkyl halide in air and water. The efforts were, by and large, unsuccessful. Chan demonstrated that alkyl halides tend to undergo copper-catalyzed Wurtz-type coupling and dehalogenation in water.¹⁶ However, Luche found that when a zinc–copper couple was used, alkyl halides reacted with conjugated carbonyl compounds and nitriles to give 1,4-addition products in good yields under sonication conditions in aqueous media (eq 1).¹⁷ A moderate diastereoselectivity



was observed in these reactions where a mixture of diastereomers could be generated.¹⁸ The difference between carbonyl addition and conjugated addition could be due to the increased reactivity of the transient alkyl-copper species toward the conjugated carbon.

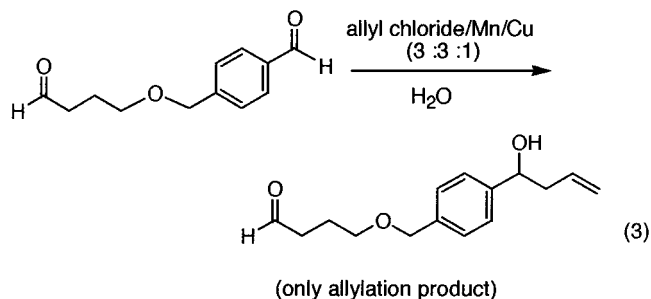
A more recent study by Li and Chan¹⁹ showed the combination of manganese and copper to be a highly *regioselective* mediator for the allylation of aryl aldehydes in water alone (eq 2). No reaction was observed with either



manganese or copper alone as the mediator and only a catalytic amount of copper was required for the reaction. The use of Cu(0), Cu(I), and Cu(II) as the copper source were all effective. Under such reaction conditions, better yields of allylation products were obtained with allyl chloride than with allyl bromide and iodide. This was

attributed to the formation of Wurtz-type coupling product with the bromide and iodide.

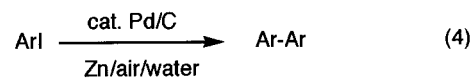
An exclusive selectivity was also observed when both aliphatic and aromatic aldehyde functionalities were present in the same molecule (eq 3). In the presence of



acetic acid or ammonium chloride, manganese was found to effect pinacol-coupling reactions in water.²⁰ The reaction proceeded also selectively with aryl aldehydes.

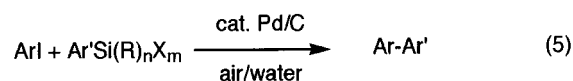
Palladium-Catalyzed C–C Bond Formation in Air and Water

The utilization of a palladium catalyst is due to an effort in effecting coupling between carbonyls and organic halides involving a sp^2 -carbon–halogen bond. Through the Heck reaction, Suzuki reaction, Sonigashira reaction, and Stille reaction, palladium is known to be particularly effective in activating sp^2 -carbon–halogen bonds even in aqueous media.²¹ Thus, efforts were made to couple aryl and vinyl halides with carbonyl compounds in water by using a catalytic amount of palladium and a stoichiometric amount of another metal. When iodobenzene was reacted with benzaldehyde and zinc together with a catalytic amount of palladium on charcoal in air and water, the desired carbonyl addition product was not generated, instead a Ullmann-type phenyl–phenyl coupling product was obtained (eq 4).²² The presence of crown ethers²³ or



poly(ethylene glycol)s²⁴ were found to be beneficial for obtaining the Ullmann-type product.

A simple synthesis of unsymmetrical biaryls through palladium-catalyzed coupling of arylsilanes with aryl halides was also developed in air and water.²⁵ The reaction of methylphenyldichlorosilane with a variety of aryl halides was examined under the Pd/C catalyzed conditions to generate the unsymmetrical biaryls (eq 5). This



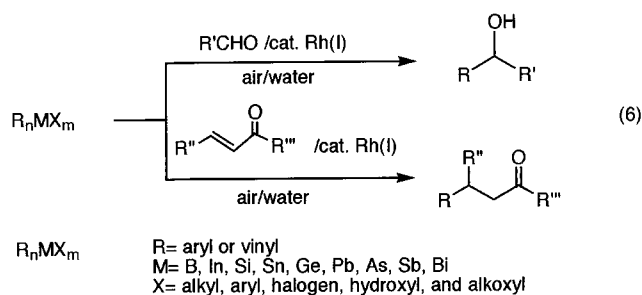
provided a convenient alternative to the use of hypervalent silicon reagents reported by Hiyama²⁶ and DeShong²⁷ and highly activated silicon reagents developed by Denmark for related cross couplings.²⁸

Rhodium-Catalyzed C—C Bond Formations in Air and Water

The use of palladium catalysts provided a way of activating organic halides involving a sp^2 -carbon-halogen bond in air and water; however, further reaction of the transient organometallic intermediate with aldehyde or α,β -conjugated carbonyl compounds were not successful with the palladium catalytic system (to generate synthetically useful products). Thus attention was shifted to the addition of the sp^2 -C—M organometallic intermediate onto carbonyls. To choose the proper organometallic reagent and achieve the desired reactions, the corresponding organometallic reagent must be stable in air and water. Based on previous literature, a variety of aryl and vinyl derivatives of metals including B, In, Si, Sn, Ge, Pb, As, Sb, and Bi were chosen. However, these reagents themselves do not react with carbonyl compounds directly and require a catalyst for such purposes.

Various transition-metal catalysts available in the laboratory were screened. Among the transition-metal complexes tested, $Rh_2(COD)_2Cl_2$ and $Rh(COD)_2BF_4$ provided the desired aldehyde addition and conjugated addition products smoothly.²⁹ The use of $Ni(acac)_2$ as the catalyst was also effective but provided the desired product in very low yield (<10%). No reaction was observed with other catalysts. In an independent study, Miyaura and co-workers also reported the rhodium-catalyzed arylation of carbonyls with arylboronic esters under aqueous conditions (although under an inert atmosphere).³⁰ Subsequently, the two Rh(I) catalysts were examined for both carbonyl addition and conjugated addition studies (eq 6).

The reactions were found highly dependent on both



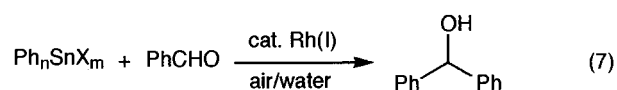
electronic and steric effects. For the carbonyl additions, aromatic aldehydes often provided better results than aliphatic aldehydes under the present reaction conditions. With aromatic aldehydes, the presence of electron-withdrawing groups appeared beneficial to the reaction, whereas the presence of electron-donating substituents decreased their reactivities. Increased steric hindrance around the reaction site also decreased the yield of the desired product. For the conjugated addition, both ketones (linear and cyclic) and esters were effective as the electron-withdrawing functional groups. When either a mono- or disubstituted unsaturated C=C was involved, the reaction proceeded rapidly. In some cases, a mixture of several products including both the conjugated addition and Heck-type reaction products were observed for the monosubstituted derivatives. Either no reaction was ob-

Table 1. Electronic Effect on Rhodium-Catalyzed Carbonyl Additions

entry	reagents	substrate	base	yield, %
1	$PhSnCl_3$	PhCHO	no base	0
2	$PhSnCl_3$	PhCHO	KOH	71
3	$PhSnMe_3$	PhCHO	no base	82
4	Ph_2SnBu_2	PhCHO	no base	62
5	Ph_3SnCl	PhCHO	no base	0
6	Ph_3SnOH	PhCHO	no base	31
7	Ph_3SnBu	PhCHO	no base	43

served or very low yields of the products were obtained with trisubstituted derivatives.

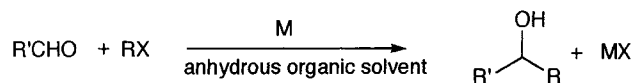
The carbonyl addition and the conjugated addition were found to be highly sensitive to both the metal and the groups attached to the metal. Except for organoarsen and organoantimony reagents, aryl or vinyl derivatives of all other metals (and metalloids) examined were able to generate the desired carbonyl addition and conjugated addition products with varied efficiencies. Among them, aryl and vinyltin, silicon, boron, lead, and bismuth derivatives were found to be the most effective. The corresponding indium and germanium reagents provided only low yields of the products. A strong effect (by the electronic nature of substituents) on the reactivity of the organometallic reagents was observed in the rhodium-catalyzed carbonyl additions and conjugated additions in air and water. Taking the organotin reagents as an example (Table 1), in the presence of a catalytic amount of $Rh(COD)_2BF_4$ at refluxing temperature in air and water, benzaldehyde underwent nucleophilic addition with trimethylphenyltin and dibutyldiphenyltin to give the corresponding nucleophilic addition product smoothly (eq 7). On the other



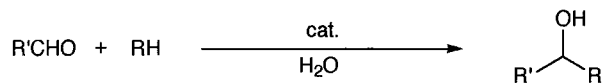
hand, under the same reaction conditions, no reaction was observed between benzaldehyde and phenyltin trichloride even after several days. When the reaction was carried out in the presence of potassium hydroxide, a smooth reaction occurred again to give the desired product overnight. A more dramatic effect was observed by using triphenyltin chloride, triphenyltin hydroxide, and butyltriphenyltin. No reaction was observed with the chloride derivative, but the reaction with either hydroxide or butyl derivatives proceeded smoothly. The use of different bases also affects the reaction progress. Various bases such as lithium hydroxide, sodium hydroxide, and potassium hydroxide were tested (which showed the same trend as the basicity), and potassium hydroxide appeared to be the most effective for this reaction. A similar dramatic electronic effect was observed in the conjugated addition of unsaturated ketones including 1-cyclohexen-2-one, 1-cyclohepten-2-one, and *trans*-1,2-dibenzoyl ethylene. A similar electronic effect was also observed with organobismuth, organolead, organoindium, and organoboron compounds.

Scheme 1

I. Classical Grignard-type reaction



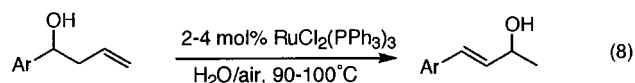
II. Grignard-type reaction via C-H Activation in aqueous media



Ruthenium-Catalyzed C–H Activation in Air and Water

The use of ruthenium is mostly related to searching for cleaner C–C bond formation in air and water via C–H activations. Despite the tremendous usefulness of the Grignard reaction and its related modifications in synthesis, the standard practice for carrying out such reactions involving the reactions of carbonyl compounds with organic halides mediated by a stoichiometric amount of metals is less than satisfactory (Scheme 1, route I). Such a practice would generate both a stoichiometric amount of halide waste and a stoichiometric amount of metal waste. It also requires multistep synthesis of the halides, which further generates a fair volume of waste due to reactions and separations. On the other hand, an alternative Grignard-type reaction between carbonyl compounds and a hydrocarbon via catalytic C–H activation³¹ in water by using a water-soluble catalyst (Scheme 1, route II), if successful, would provide a cleaner solution for a Grignard-type reaction and organic synthesis. Furthermore, the reaction would provide a theoretical 100% atom efficiency.³²

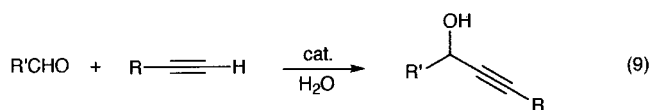
The first investigation was on the activation of the allylic C–H bond by using ruthenium catalysts in water. The initial intention was to overcome the difficulties encountered in coupling reactions between carbonyl compounds and organic halides involving a sp^2 -carbon–halogen bond by an alternative approach involving a simple isomerization of the readily accessible homoallyl alcohols to the more difficult allyl alcohol. $\text{RuCl}_2(\text{PPh}_3)_3$ was chosen since the complex is compatible with water and air. Through the catalysis of $\text{RuCl}_2(\text{PPh}_3)_3$, the functional groups of homoallylic alcohols are repositioned to give allylic alcohols with controlled regioselectivity (eq 8).³³ The selectivity in product formation was found to be



affected by the reaction temperature and the amount of the catalyst being used. A higher reaction temperature and the use of a smaller amount of the catalyst are preferable for the formation of allylic alcohols. The reaction process was postulated as a tandem olefin migration–allylic rearrangement. Under the same reaction conditions, the functional groups of allylic alcohols undergo allylic rear-

rangements. With a water-soluble ruthenium catalyst, a living catalytic system is possible in which the catalyst has been recycled many times.³⁴

The second investigation is on the addition of alkynyl-metal reagents to aldehydes, a fundamental reaction in synthesis.³⁵ Most methods employ a stoichiometric amount of organometallic reagents such as organolithium or organomagnesium for forming alkynylmetal reagents from alkynes³⁶ or alkynyl halides³⁷ in anhydrous organic solvent. Because aldehydes also react with organometallic reagents readily, the preparation of alkynyllithium and organomagnesium reagents must be carried out as a separate step. These new studies show an effective addition reaction of phenylacetylene to aldehydes in aqueous solution via C–H activation where various aldehydes reacted with phenylacetylene catalyzed by a bimetallic Ru–In catalytic system to give Grignard-type nucleophilic addition products in water—with one to catalyze the overall reaction and the other to activate the carbonyl (eq 9).³⁸ This



appears to serve the dual purpose of being able to perform aqueous Barbier–Grignard-type reactions involving a sp C and achieving such reactions via a C–H activation in water.

Tentative Explanation of Air and Water Stability

During the study, a subtle phenomenon was observed: catalytic reactions are less air sensitive in water than in organic solvent. The insensitivity and stability of C–M bonds related to late transition metals toward water can be explained by the hard–soft and acid–base principle, in which water molecules (hard) interfere very little with the late transition metals (soft).³⁹ However, the exact nature of the apparent increased stability toward air in water in these catalytic reactions is not very clear.

Conclusion and Outlook

We have shown in this account that catalysis via late transition metals cannot only be carried out in water but can also take place under an atmosphere of air. The open-air feature offers convenience in chemical synthesis involving small-scale combinatorial synthesis, large-scale manufacturing, and catalyst recycling. In the area of environmental science and technology, transition-metal-catalyzed reactions in air and water offer convenient ways to use catalytic remediation of large areas of polluted water in open fields as well as reduce the consumption of potential polluting organic solvents in chemical manufacturing. Such reactions could also shed some light on the mechanism of biological and evolutionary processes in nature.⁴⁰ We hope that this Account will generate interest in the field.

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