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HOMOGENEOUS AND PHASE TRANSFER CATALYZED CARBONYLATION REACTIONS

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My Ph.D. research at McGill University was concerned with the conductivities of amines and other organic compounds in formic acid. One aim of this research was to determine the relationship between Stokes Law and conductivities in formic acid [1]. A requirement for the Ph.D. degree was the presentation of a seminar on a subject unrelated to that of one's research project. On reading the literature, I found the chemistry of iron carbonyls exciting, particularly the outstanding work by the late Rollie Pettit on dieneiron carbonyl complexes. Following the presentation of a seminar on this topic, I discussed with Professor Jack Edward, my research supervisor, several possible projects in the area of iron carbonyls and he was most supportive of my pursuit of research in organometallic chemistry. (The research in physical organic chemistry, on which I worked for over a year, was soon completed). Edward's flexiblity in permitting me to work in an area of chemistry in which he was a novice (as was I!), and his continued encouragement, were decisive in the development of my career as an organometallic chemist.

Phase transfer catalyzed carbonylation reactions

As a research advisor, I did not forget Jack Edward's ability to be flexible in one's approach to research. For instance when Herve des Abbayes, a postdoctoral fellow from France, came to work with me at Ottawa, he suggested that we attempt to apply the concept of phase transfer catalysis to organometallic chemistry. The most common type of phase transfer reaction is that involving an aqueous base, an organic phase, and a quaternary ammonium salt as the transfer agent. Organometallic phase transfer catalysis seemed to me to be a very promising area of research and initial experiments quickly bore fruit.

The reduction of nitro compounds induced by triiron dodecacarbonyl, and the synthesis of novel sulfur donor ligand *ortho*-metallated complexes from thioketones, were chosen as model systems for the phase transfer reactions. The nitro to amine conversion is of industrial interest and the *ortho*-metallated complexes are important intermediates in the preparation of thiolactones, amongst other organic compounds [2]. Both phase transfer processes were rapid, and superior to those effected under

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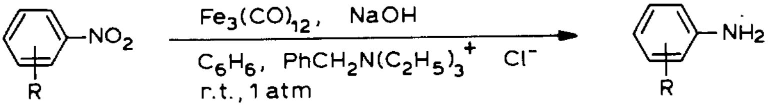
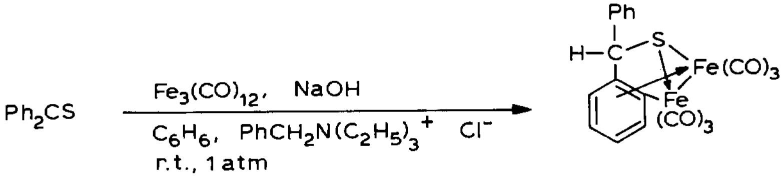
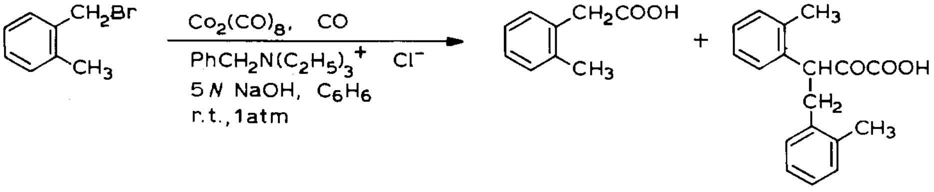




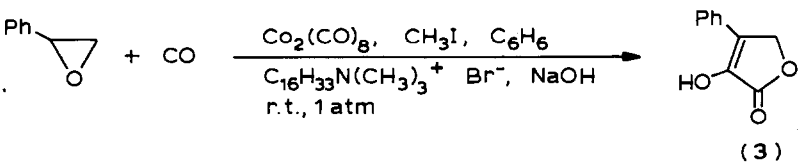
homogeneous conditions [3,4]. The key to success of the phase transfer technique in this and in other reactions is the facile generation of metal containing anions in the organic phase, and the subsequent reaction of the relatively unsolvated anions with appropriate substrates.

While these reactions were interesting in that they were the first examples of organometallic phase transfer catalysis, they were stoichiometric with respect to triiron dodecacarbonyl. The more desirable transformation is that where the metal complex, as well as the phase transfer agent, function as catalysts. A reaction of considerable importance is the cobalt carbonyl-catalyzed carbonylation of benzylic halides to give acids, which under homogeneous conditions normally requires the use of elevated temperatures and pressures, an excess of base, extended reaction times, and, with few exceptions, affords acids in low to moderate yields. Work in the author's laboratory [5] and at Montedison [6] showed that halides were convertible into acids under very mild conditions by phase transfer methods. In addition, we observed a novel double carbonylation reaction in the case of *o*-methylbenzyl bromide whereby the alkylated α-keto acid **2** was isolated together with the anticipated monoacid **1**. Double carbonylation reactions of halides, under both phase transfer and homogeneous conditions, have been extensively investigated in recent years [7].



(1) (2)

It is believed that the key intermediate in the carbonylation reaction is an acylcobalt tetracarbonyl complex, $RCOCo(CO)_4$. One can intercept such an intermediate by simply effecting the reaction in the presence of either unsaturated or strained ring substrates. For example, use of methyl iodide as the halide and styrene oxide as the strained ring reactant in the cobalt carbonyl catalyzed carbonylation reaction resulted in the incorporation of two molecules of carbon monoxide, to give the enol **3** of the α-keto lactone [8]. The driving force for both double carbonylation reactions, i.e. to give **2** and **3**, is probably the ability of an intermediate phenacyl-



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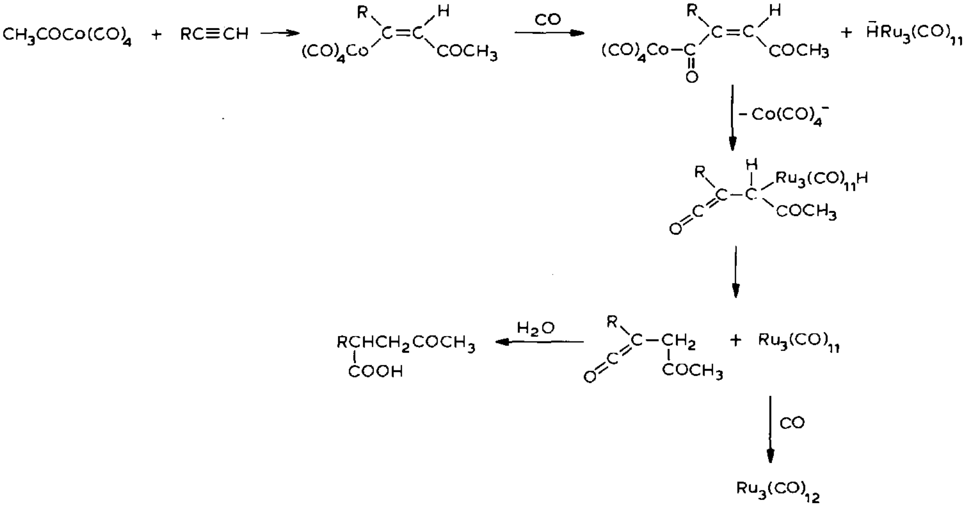
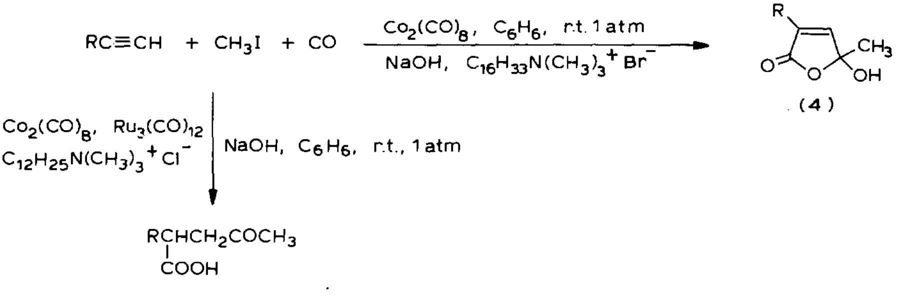


SCHEME 1

cobalt carbonyl complex to undergo enolization, thereby facilitating a second insertion of carbon monoxide, this time into a vinyl cobalt–carbon bond.

Another useful reaction is that of the in situ generated acylcobalt complex with alkynes resulting in the formation of 2-butenolides (4) [9]. If the reaction is repeated

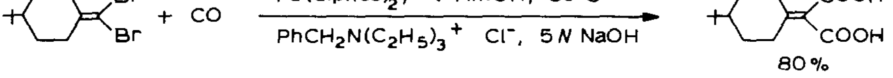


(4)

(5)

using ruthenium carbonyl as well as cobalt carbonyl as metal catalysts, then γ-keto acids (**5**) are obtained in good yields (**5** does not arise from **4**) [10]. As illustrated in Scheme 1, the presumed function of the in situ generated ruthenium hydride catalyst, $HRu_3(CO)_{11}^-$, is to add to an α,β-unsaturated acylcobalt carbonyl and regenerate cobalt tetracarbonyl anion. This was the first example of bimetallic phase transfer catalysis, where the two metal catalysts are playing roles at different stages in the conversion of reactants to products.

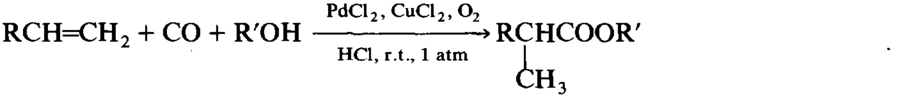
Palladium complexes are also valuable catalysts for the biphasic and phase transfer catalyzed carbonylation of halides. One interesting reaction is that of vinylic dibromides, where biscarbonylation to the unsaturated diacid can be attained in high yield [11]. See reference 12 for some other examples of palladium and cobalt catalyzed phase transfer processes.



Homogeneously catalyzed carbonylation reactions

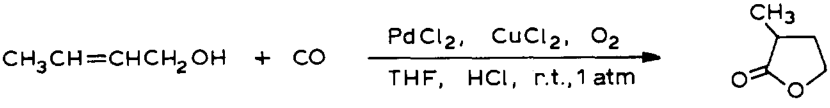
While phase transfer catalyzed carbonylation reactions are of genuine value in organic synthesis, homogeneously catalyzed processes are also of importance. Simple and novel routes to carboxylic esters has been one focus of our research. Three methods merit comment:

(i) The metal catalyzed hydroesterification and hydrocarboxylation of olefins has been the subject of numerous patents and literature publications. Straight-chain esters, some of which are of value as fatty acid ester derivatives, are usually the major products of the reaction. But several branched chain esters are also of importance, including methyl isobutyrate (convertible to methyl methacrylate) and ibuprofen, which is more pharmacologically active than aspirin. Therefore, it was of interest to develop a selective synthesis of branched chain esters and acids. A regiospecific, remarkably mild approach to such esters and acids can be achieved by means of palladium(II) catalyzed oxidative carbonylation of olefins under acidic conditions [13]. This transformation is now typically run at room temperature and



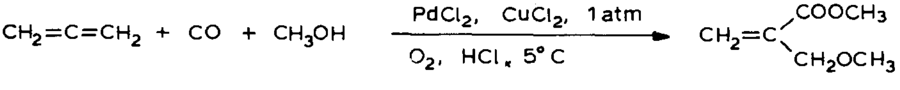
$$RCH{=}CH_2 + CO + R'OH \xrightarrow[HCl,\ r.t.,\ 1\ atm]{PdCl_2,\ CuCl_2,\ O_2} \underset{\displaystyle CH_3}{RCHCOOR'}$$

atmospheric pressure by bubbling carbon monoxide and oxygen through an alcohol solution of palladium chloride, cupric chloride, acid, and olefin. In the case of hydrocarboxylation [14], tetrahydrofuran containing a limited amount of water was used as the solvent medium. This reaction is applicable to a variety of olefins as well as monoalcohols and diols. Using diols, the reaction is regioselective and chemoselective for the monofunctionalization of the diol moiety [15]. Unsaturated alcohols, including allylic alcohols, experience intramolecular cyclization to lactones (e.g. 6) under these conditions [16]. Other unsaturated substrates also react in a facile



(6)

manner, a noteworthy example being allene, which undergoes alkoxy alkoxycarbonylation to give a functionalized methyl methacrylate [17].



$$CH_2{=}C{=}CH_2 + CO + CH_3OH \xrightarrow[O_2,\ HCl,\ 5°C]{PdCl_2,\ CuCl_2,\ 1\,atm} CH_2{=}C\begin{matrix}\nearrow COOCH_3 \\ \searrow CH_2OCH_3\end{matrix}$$

(ii) Alkoxy transfer reactions from metal alkoxides to halides and other organic substrates, in the presence of carbon monoxide and a metal catalyst, appeared to be a viable method for ester production. Our first experiments were done using borate esters and benzylic bromides, which reacted with carbon monoxide in the presence of the dimer of chloro(1,5-hexadiene)rhodium ($[1,5\text{-}HDRhCl]_2$), to give primary,

$$3ArCH_2Br + 3CO + B(OR')_3 \xrightarrow[75°C,\ 1\ atm]{[1,5\text{-}HDRhCl]_2} 3ArCH_2COOR' + BBr_3$$

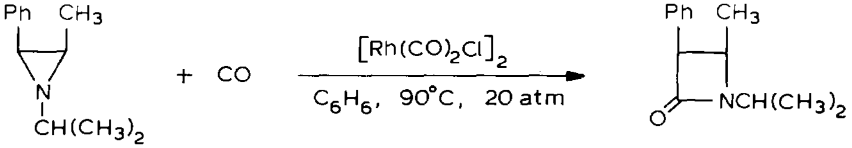
secondary, or tertiary esters in high yields [18]. This transformation also occurs for benzylic chlorides, provided that potassium iodide is present [19]. In order to extend the reaction to other halides, such as simple alkyl mono- and di-halides, a bimetallic catalyst system ($[1,5\text{-HDRhCl}]_2/\text{Pd(PPh}_3)_4$) must be used [20]. Alkoxides of aluminum, titanium, and zirconium also react successfully under similar conditions to those used for borate esters [21].

(iii) Little is known about the desulfurization and carbonylation of organic sulfur compounds. It was envisaged that since there are non-halide routes to mercaptans, the successful conversion of the latter into esters would represent a new non-halide approach to these compounds. Indeed, cobalt carbonyl catalyzes the carbonylation of benzylic and aryl mercaptans (thiophenols) in aqueous alcohol to give esters in

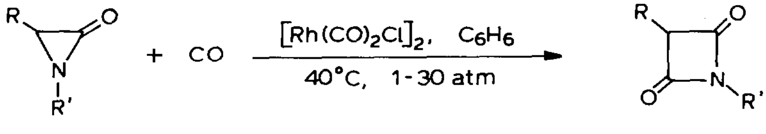
$$\text{RSH} + \text{CO} + \text{R'OH} \xrightarrow[\substack{850\text{-}900\ \text{psi} \\ 190^\circ\text{C, 24 h}}]{\text{Co}_2(\text{CO})_8,\ \text{H}_2\text{O}} \text{RCOOR'} + \text{H}_2\text{S}$$

reasonable yields. Hydrogen sulfide is the reaction by-product [22]. This reaction is sensitive to the solvent, since substitution of benzene for alcohol results in desulfurization, carbonyl sulfide also being obtained [23].

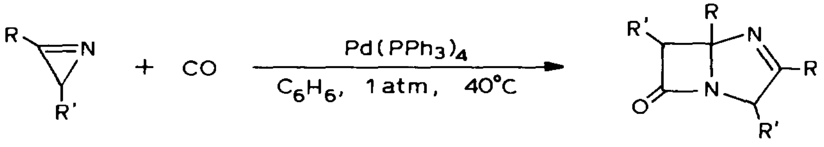
One of the reactions described above is the conversion of unsaturated alcohols into lactones, an important class of heterocycles. Another approach to heterocyclic compounds containing a carbonyl group is the simple incorporation of carbon monoxide into a reactant heterocycle. This stitching reaction has been particularly successful with, but not limited to, nitrogen heterocycles. For example, rhodium(I) catalyzed carbonylation of aziridines affords monocyclic β-lactams in excellent yields [24]. The reaction is both a regiospecific and stereospecific one [25], α-Lactams also



react regiospecifically affording azetidine-2,4-diones [26].



Finally, the palladium(0) catalyzed carbonylation of azirines to bicyclic β-lactames is a spectacular example of a metal-induced coupling and carbonylation reaction [27]. The carbonylation-ring expansion by conflation of carbon monoxide and



heterocyclic substrates is a general method of synthetic potential.

In conclusion, metal-catalyzed carbonylation reactions, under homogeneous and phase transfer conditions, can lead to new reactions, and to novel approaches to useful compounds. Much remains to be learned concerning the mechanisms of these reactions.

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