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Biphasic Synthesis of 2-Phenylpropionic Acid and Ester by Interfacial Carbonylation of α-Methylbenzyl Bromide

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Abstract:

An interfacial synthesis technique has been successfully extended to the carbonylation of α-methylbenzyl bromide in an organic−aqueous sodium hydroxide mixture at 35−60 °C and 1 atm using surface-active palladium−(4-dimethylaminophenyl)diphenylphosphine complex as the catalyst and dodecyl sodium sulfate as the emulsifier. Depending on the reaction conditions, 2-phenylpropionate in the form of sodium salt and an ester was obtained in 0−83% yield, along with varying amounts of side products that included α-methylbenzyl alcohol, 2,3-diphenylbutane, di(α-methylbenzyl)ether, and an asymmetric ether derived from the substrate and an alcoholic medium. When 2-methyl-1-butanol or 2-ethyl-1-hexanol was used as the organic phase, 2-phenylpropionate ester and sodium salt were obtained in 40−83% yield, with a maximum yield obtained at an optimal aqueous base concentration of about 5 M. At a lower aqueous base concentration, more of α-methylbenzyl alcohol was formed, whereas at a higher aqueous base concentration, more of 2,3-diphenylbutane and asymmetric ether were formed. When toluene was used as the organic phase, 2-phenylpropionate salt was obtained in less than 13% yield, and the major side product was α-methylbenzyl alcohol at a low aqueous base concentration and 2,3-diphenylbutane at a high aqueous base concentration. In all cases, the formation of 2,3-diphenylbutane was accompanied by a stoichiometric formation of carbonate. The latter implicates the involvement of an oxidative intermediate—tentatively identified as hypobromous acid—that could deactivate the catalyst complex through ligand degradation. Along with the carbonylation reaction, carbon monoxide also underwent a slow, base-induced hydrolysis reaction to form formic acid. With 2-ethyl-1-hexanol as the organic phase, the carbonylation of α-methylbenzyl bromide showed an apparent temperature-dependent activation energy, a first-order dependence each on the substrate, catalyst, and ligand concentrations up to the catalyst concentration of 0.0020 M and a ligand:catalyst ratio of 3:1, and a variable-order dependence on the carbon monoxide pressure that switched from first to zeroth order as the carbon monoxide pressure was increased above 450 mmHg. A reaction mechanism is proposed which yields model rate and yield expressions in accord with the experimental findings. Results of control experiments with α,α-dibromotoluene in a toluene−aqueous sodium hydroxide mixture indicate that replacement of the α-methyl group in α-methylbenzyl bromide by a second bromo group suppressed the formation of substituted benzyl alcohol and coupled product. They suggest that the broad product distribution in the carbonylation of α-methylbenzyl bromide relative to the carbonylation of benzyl chloride and α,α-dibromotoluene is attributable to the electron-releasing α-methyl group making the substrate susceptible to hydrolysis and coupling reactions.

I. Introduction

Recent studies from our laboratory[1−5] have demonstrated the feasibility and advantages of using an organic−water (hereafter, O−W) interfacial technique to synthesize α-tetralone, phenylacetic and phenylenediacetic acids, poly(2,6-dimethyl-1,4-phenylene oxide), and aromatic polyamides. Interfacial synthesis offers some significant advantages over conventional syntheses (homogeneous or heterogeneous), and these include (1) avoidance of the use of a toxic or environmentally troublesome solvent that may otherwise be needed, (2) use of a pseudo-homogeneous catalyst that is characterized by high reactivity, selectivity, and reproducibility under mild reaction conditions, (3) ease of catalyst recovery unaffected by the solubilities of the reactants and products in either the aqueous or organic phase, (4) possibility of a simultaneous reaction−separation scheme whereby a desired product can be removed to prevent further reaction, (5) ease of operation and control, (6) avoidance of an adverse gelling effect on a polymerization reaction, (7) a higher solubility for a gaseous reactant than in an aqueous system, (8) a higher reaction rate due to the concentrating and intimate-contacting effects of the interface on the reactant(s) and catalyst, and (9) possibility of regio- and stereoselectivity control on account of the directional influence of the interface on molecular orientations.

The last possibility is intriguing because the directional influence of the interface, which could be augmented by a

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(1) Ahn, W. S.; Zhong, Y.; Abrams, C. F.; Lim, P. K.; Brown, P. A. *J. Phys. Chem. B* **1997**, *101* 596−602.
(2) Lim, P. K.; Zhong, Y. Chemically benign synthesis at organic-water interface. In *Green Chemistry—Designing Chemistry for the Environment*; Anastas, P., Williamson, T., Eds.; ACS Symposium Series 626; American Chemical Society: Washington, DC, 1996; pp 168−177.
(3) Zhong, Y.; Godfrey, V. M.; Lim, P. K.; Brown, P. *Chem. Eng. Sci.* **1996**, *51*, 757−767.
(4) Zhong, Y.; Abrams, C. F.; Lim, P. K. *Ind. Eng. Chem. Res.* **1995**, *34*, 1529−1535.
(5) Dautenhahn, P. C.; Lim, P. K. *Ind. Eng. Chem. Res.* **1992**, *31*, 463−469.

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regio- or stereoselective emulsifier or solvent, may provide an additional avenue besides the catalysts and ligands for controlling regio- and stereoselectivities.

Partly to verify the possible stereoselectivity influence of the interface and partly to study the substituent effect on the biphasic carbonylation of benzyl halide, we have extended the biphasic carbonylation of benzyl chloride to α-methylbenzyl bromide. Methyl substitution of one of the two hydrogens at the α-carbon of a benzyl halide introduces a stereoselectivity choice, in addition to the steric and electronic effects. The latter, in conjunction with a solvent effect, brought a wealth of information which is the subject of this paper; the stereoselectivity aspects of the reaction will be reported later in a separate paper. In addition to providing useful information on the substituent effect in the carbonylation of benzyl halide, the synthesis of 2-phenylpropionic acid and esters is also important in its own right. The stereoisomers of 2-phenylpropionic acid are useful as chiral building blocks and resolving agents; they can also serve as a useful model for the general class of 2-arylpropionic acids—as represented by naproxen and ibuprofen—that can function as nonsteroidal antiinflammatory drugs.[6]

II. Experimental Section

The apparatus and procedure for studying the biphasic carbonylation reaction were similar to those which have been used for studying the biphasic carbonylation of benzyl chloride,[3] except for a scale-down of the reactor and reaction mixture and the use of magnetic stirring in place of mechanical stirring. A 300-mL Morton-flask reactor was used in place of a 585-mL reactor, and the total volume of the biphasic reaction mixture was reduced from 150−200 to 40 mL. Control experiments showed no difference in the carbonylation rate between magnetic stirring provided by a 2-in. stir bar spinning at about 800 rpm and mechanical stirring provided by a Dyna-Mix mechanical stirrer rotating at about 1600 rpm. Because the magnetic stirring was more convenient and less prone to leakage, it was used in this study.

The biphasic carbonylation reaction was carried out batchwise using a mixture of an organic liquid and aqueous sodium hydroxide as the biphasic reaction medium, a palladium complex of a surface-active ligand as the catalyst, and dodecyl sodium sulfate (DSS) or some other surfactant as the emulsifier. The reagents used in this study were purchased from Aldrich and were used without further purification or treatment. A representative run was performed as follows: The reactor was charged with 40 mL of a 1:1 organic−aqueous sodium hydroxide mixture and the desired amounts of palladium chloride, emulsifier, and surface-active ligand. It was placed in a water bath and purged with carbon monoxide for about 15 min and then allowed to equilibrate to the set temperature, which was typically 45 °C. Removal of dissolved oxygen from the reaction mixture was found to be essential in getting reproducible results. The reaction was initiated by substrate addition with the help of a syringe through a septumed joint on the reactor. The substrate was added last to the reaction mixture to prevent side reactions from taking place during the temperature equilibrium. The alternate strategy of adding the catalyst last did not work in this case because the side reactions were found to occur in the absence of the catalyst. The carbonylation reaction was followed by monitoring the carbon monoxide uptake with the help of a constant-pressure manometric unit.[7]

The reddish brown color of palladium chloride faded and the uptake of carbon monoxide commenced after a brief induction period. The stirred reaction mixture appeared either opaque white initially or gray eventually, but when stirring was stopped it phase-separated after a few minutes into an organic phase, a clear aqueous phase, and a grayish, interfacial emulsion layer that contained some black particulates. Formation of the latter increased with the coalescence of the dispersed droplets, so that upon the reaction mixture standing overnight, a black film emerged at the interface. A similar surface-dependent saturation−precipitation phenomenon has previously been reported for other surface-active metal complexes.[8]

The carbon monoxide uptake data were augmented by composition data on the reaction mixtures. Samples of the biphasic reaction mixture were withdrawn at timed intervals and quenched in an ice bath to arrest the reactions. After centrifugation, the organic and aqueous fractions of each sample were separated with the aid of a pipet. Known amounts of undecane and molecular sieve (5 Å), which served respectively as the internal standard for GC analysis and drying agent, were added to a measured volume of the organic fraction. Removal of the trace moisture from the organic fraction was essential to obtaining consistent and reproducible GC results. Duplicate samples of the dried organic fraction were analyzed using a Perkin-Elmer GC−MS system that had previously been calibrated with known standards. The GC−MS system consisted of an AutoSystem gas chromatograph equipped with an HP-5 capillary column (cross-linked 5% PHME silicon, length = 25 m, diameter = 0.2 mm, film thickness = 0.33 μm), a Q-Mass 910 mass spectrometer, a DEC 433 data station equipped with a 57 000-compound spectral library, and a HP LaserJet printer.

The concentration of 2-phenylpropionic acid in the aqueous fraction was determined by extracting the acid with toluene and analyzing the resulting toluene solution in the same manner as the organic fraction. A measured volume of the aqueous fraction was acidified with hydrochloric acid to lower its pH to below 1. After cooling, it was contacted successively with the two known portions of toluene to extract the 2-phenylpropionic acid. The two toluene portions were combined and then treated in a similar way as the organic fraction described above.

The partial pressure of carbon monoxide in the reaction was varied by introducing a known amount of inert nitrogen into the vapor phase of the reactor. This was achieved before

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[6] Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095−4131.

[7] Giles, D. W.; Cha, J. A.; Lim, P. K. *Chem. Eng. Sci.* **1986**, *41*, 3129−3140.

[8] Lloyd, P. B.; Ganesan S.; Lim, P. K. *Ind. Engng. Chem. Res.* **1989**, *28*, 577−584.

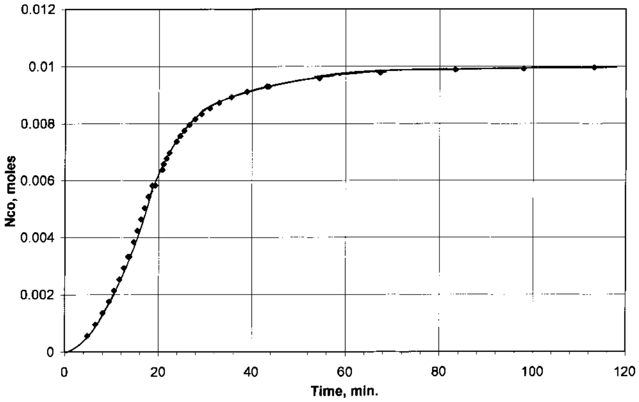

Figure 1. **Representative carbon monoxide uptake profile (see Table 1 for reaction conditions).**

Table 1. **Reaction conditions of the base run for Figures 1−8 and Tables 2−6**

parameter	parameter value
temperature	45 °C
pressure	~760 mmHg
CO partial pressure	~690 mmHg
2-ethyl-1-hexanol (organic phase)	20 mL
5 N NaOH solution (aqueous phase)	20 mL
Ingredients	
dodecyl sodium sulfate (emulsifier)	4.00×10^{-4} g-mol
palladium(II) chloride (catalyst)	1.53×10^{-4} g-mol
4(dimethylamino)phenyldiphenylphosphine (ligand)	3.07×10^{-4} g-mol
α-methylbenzyl bromide (substrate)	1.37×10^{-2} g-mol

the start of the reaction by flushing the reactor and its contents with a mixed stream of carbon monoxide and nitrogen of a known composition. The latter was controlled by adjusting the relative flow rates of carbon monoxide and nitrogen streams through two calibrated rotameters and allowing them to mix at a T-joint. The combined stream was used to purge the reactor and the biphasic mixture; its composition was calculated from the calibrated flow rates of the component streams.

III. Results and Discussion

(A) Carbonylation and Side Reactions. A representative carbon monoxide uptake profile of the biphasic carbonylation of α-methylbenzyl bromide is shown in Figure 1. The corresponding reaction conditions are listed in Table 1, and they constitute the reaction conditions of the base run upon which parametric variations were made in subsequent runs. It is seen that the carbonylation reaction took off after an induction period, during which active reaction intermediates were formed. For detailed kinetic analysis, the reaction rate is taken to be the "steady-state" uptake rate of carbon monoxide following the induction period. Data presented in Table 2 show the influence of the various parameters and procedure on the induction period. It is seen that increasing the reaction temperature and premixing the catalyst and ligand prior to the reaction shortened the induction period. On the other hand, increasing the catalyst, substrate, and base concentrations seemed to increase the induction period.

Table 2. **Variation of the induction period as a function of some key variables (other conditions are specified in Table 1)**

variable	induction period (min)
catalyst concn[a] (M)	
5.08×10^{-4}	6
1.00×10^{-3}	15
1.42×10^{-3}	15
1.99×10^{-3}	13
3.93×10^{-3}	15.5
7.80×10^{-3}	10
substrate concn[a] (M)	
0.0686	5.6
0.171	4.5
0.258	12.1
0.344	15.5
NaOH concn (M)	
1	8
2.5	15
3.75	21
5	15.5
6.1	11.6
7.7	18
10	18
reaction temp (K)	
308	40
313	14.4
318	15.5
323	8.2
premixing catalyst and ligand (313 K)	10

[a] Based on the total liquid volume of 40 mL.

A methyl substitution of one of the two hydrogens at the α-carbon of a benzyl halide profoundly affects the product distribution. Instead of the quantitative yield of phenylcarboxylate which has been obtained in the biphasic carbonylation of a benzyl halide,[3]

$$C_6H_5CH_2X + CO + 2OH^- \rightarrow C_6H_5CH_2COO^- + X^- + H_2O \quad (1)$$

the biphasic carbonylation of α-methylbenzyl bromide,

$$C_6H_5CH(CH_3)Br + CO + 2OH^- \rightarrow C_6H_5CH(CH_3)COO^- + Br^- + H_2O \quad (2)$$

is accompanied by more significant side reactions, which have been identified as follows:

$$C_6H_5CH(CH_3)Br + OH^- \rightarrow C_6H_5CH(CH_3)OH + Br^- \quad (3)$$

$$2C_6H_5CH(CH_3)Br + CO + 4OH^- \rightarrow [C_6H_5CH(CH_3)]_2 + 2Br^- + 2H_2O + CO_3^{2-} \quad (4)$$

$$C_6H_5CH(CH_3)Br + C_6H_5CH(CH_3)OH + OH^- \rightarrow C_6H_5CH(CH_3)OCH(CH_3)C_6H_5 + Br^- + H_2O \quad (5)$$

If the organic portion of the biphasic medium is an alcohol, denoted by ROH, two additional reactions,

$$C_6H_5CH(CH_3)Br + ROH + OH^- \rightarrow C_6H_5CH(CH_3)OR + Br^- + H_2O \tag{6}$$

$$C_6H_5CH(CH_3)Br + CO + ROH + OH^- \rightarrow C_6H_5CH(CH_3)COOR + Br^- + H_2O \tag{7}$$

are involved, of which reaction 6, which produces an ether, is another side reaction. Reaction 7, which produces a 2-phenylpropionate ester, will be considered a desired reaction, along with reaction 2. Thus, the yield of 2-phenylpropionate reported herein will include both the acid and ester forms of 2-phenylpropionate. Reaction 3 produces α-methylbenzyl alcohol, which can react with another substrate to form a symmetrical ether, di(α-methylbenzyl)ether. The organic products are formed in two stereoisomeric forms in reactions 2, 3, 6, and 7 and four stereoisomeric forms in reactions 4 and 5. The stereoselectivity aspect of reactions 2−7 will be addressed in a later paper.

The formation of the coupled product in reaction 4 is accompanied by a stoichiometric formation of carbon dioxide, which appears as a dissolved carbonate in aqueous base. The latter was converted to a white calcium carbonate precipitate in the presence of aqueous calcium chloride. Acid treatment of the precipitate released carbon dioxide, which was confirmed by a limewater test. The carbonate formation suggests the involvement of an oxidizing intermediate which, as will be shown later, may attack the phosphine ligand and deactivate the catalyst complex.

Besides reactions 2 and 4, carbon monoxide also undergoes a base-induced hydrolysis reaction, as reported previously:[3]

$$CO + OH^- \rightarrow HCOO^- \tag{8}$$

Reactions 2, 4, and 7 are catalyzed by palladium, whereas reactions 3, 5, 6, and 8 are not.

The identities of the products—2-phenylpropionic acid, 2-phenylpropionate ester, α-methylbenzyl alcohol, di(α-methylbenzyl)ether, 2,3-diphenylbutane, asymmetric ether, and formic acid—were established by GC−MS and autenticated by comparison with known standards. The ester standards were prepared from 2-phenylpropionic acid and 2-methyl-1-butanol or 2-ethyl-1-hexanol in the presence of 1 N sulfuric acid acting as a catalyst,[9] and the desired esters were obtained in a quantitative yield. Attempts to prepare the esters in the absence of the sulfuric acid brought negative results, i.e., zero yield. The latter finding rules out the possibility that the ester formed in the alcoholic biphasic system was derived from 2-phenylpropionic acid reacting with the alcohol medium as follows:

$$C_6H_5CH(CH_3)COOH + ROH \rightarrow C_6H_5CH(CH_3)COOR + H_2O \tag{9}$$

since the biphasic carbonylation reactions wers carried out under basic conditions. The results suggest instead a palladium-mediated ester formation reaction with the alcohol solvent,

$$C_6H_5\overset{+}{C}H(CH_3)Pd + ROH + OH^- + CO \rightarrow C_6H_5CH(CH_3)COOR + Pd + H_2O \tag{10}$$

Presumably, the palladium-bound carbonium intermediate postulated in the proposed reaction 10, $C_6H_5\overset{+}{C}H(CH_3)Pd$, is derived from a base-catalyzed debromination of the substrate,

$$C_6H_5CH(CH_3)Br + Pd \xrightarrow{OH^-} C_6H_5\overset{+}{C}H(CH_3)Pd + Br^-$$

and may be resonance-stabilized by intramolecular exchange with $C_6H_5C^{\bullet}H(CH_3)Pd^+$ as follows:

$$C_6H_5\overset{+}{C}H(CH_3)Pd \leftrightarrow C_6H_5C^{\bullet}H(CH_3)Pd^+$$

The yield of 2-phenylpropionate ranged from 0 to 83%, depending on the organic phase, catalyst and ligand, carbon monoxide pressure, aqueous base and ionic strength, reaction temperature, and presence of any inhibiting product. Each of these factors is discussed in the following sections.

(B) Dependence on the Organic Phase and Evidence of Catalyst Deactivation. Aside from the catalyst complex and carbon monoxide partial pressure, which directly affect the yield of 2-phenylpropionate (see later), the organic phase is the single most important factor affecting the selectivity of the carbonylation reaction. Thus, with toluene or undecane as the organic phase, the data presented in Table 3 show that side products were formed predominantly via reactions 3 and 4, and 2-phenylpropionic acid was formed by reaction 2 as a minor product with a yield of 13% or less. The low yield of 2-phenylpropionic acid in the carbonylation of α-methylbenzyl bromide in an aqueous−toluene biphasic medium stands in contrast to the quantitative yield of phenylacetic acid in the carbonylation of benzyl chloride in the same biphasic medium.[3]

On the other hand, when 2-methyl-1-butanol and 2-ethyl-1-hexanol were used as the organic phase, the total yield of 2-phenylpropionate in the ester and carboxylate forms, as shown by the data in Table 3a, jumped to 30% and 71%, respectively, even though the alcoholic organic phase introduced an ether formation side reaction, reaction 6. In most cases, however, the yield of ether was minor relative to that of 2-phenylpropionate. The sharp increase in the 2-phenylpropionate yield resulted from the ester formation reaction, reaction 7, which proceeded in parallel with reaction 2 and exceeded the latter's contribution.

While both 2-methyl-1-butanol and 2-ethyl-1-hexanol were more conducive to the carbonylation reactions than toluene, 2-ethyl-1-hexanol gave a substantially higher carbonylation rate and 2-phenyl-propionate yield than 2-methyl-1-butanol. The carbonylation rate and 2-phenylpropionate yield varied in a parallel fashion, each being more than 3 times higher with 2-ethyl-1-hexanol than with 2-methyl-1-butanol. Both alcohols produced a preponderance of the ester over the acid product.

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(9) Solomons, T. W. G. *Organic Chemistry*, 3rd ed.; Wiley: New York, p 794.

Table 3. **Rate and product distribution information**

(a) Rate and Product Distrubiton as a Function of Organic Phase at 318 K[a]

organic solvent	2-ethyl-1-hexanol	2-methyl-1-butanol	toluene	undecane
rate, M/min	1.23×10^{-2}	4.02×10^{-3}	6.22×10^{-4}	7.03×10^{-4}
product distribution, %				
2′-ethyl-1′-hexyl-2-phenylpropionate	52	24	na	na
2-phenylpropionic acid	19	6	0	6
α-methylbenzyl alcohol	6	40	15	36
2,3-diphenylbutane	13	20	44	40
(α-methylbenzyl)(2-ethyl-1-hexyl)ether	2	9	na	na
di(α-methylbenzyl)ether	7	0	41	17

(b) Product Distribution (%) for Aqueous−Toluene Biphasic System at 333 K and Different Aqueous Base Concentrations[a]

NaOH concn (M)	2-phenylpropionic acid	α-methylbenzyl alcohol	2,3-diphenylbutane
2.5	4	90	6
5	13	64	23
10	4	10	86
14	10	7	83

[a] Other conditions are specified in Table 1.

The fact that 2-methyl-1-butanol gave a much higher yield of α-methylbenzyl alcohol and ether than 2-ethyl-1-hexanol (∼60% vs ∼15%) may suggest that the former was more favorable to the benzyl alcohol and ether formation reactions, namely, reactions 3 and 6. Results of control runs in the absence of carbon monoxide confirmed that to be case, but the rate differences between the two alcoholic biphasic systems were modest and could not fully account for the 4-fold difference in the yield of α-methylbenzyl alcohol and ether. Neither reaction 3 nor 6 was affected by palladium. At 45 °C and in a 1:1 alcohol−5 M aqueous sodium hydroxide mixture, the overall psuedo-first-order rate constant with which α-methylbenzyl bromide reacted to form α-methylbenzyl alcohol and ether was 0.0063 min^{-1} with 2-methyl-1-butanol as the organic phase and 0.0051 min^{-1} with 2-ethyl-1-hexanol as the organic phase. Using data on the relative concentrations of α-methylbenzyl alcohol and ether in the product mixture, the overall rate constants can each be broken down into the constituent rate constants. The respective rate constants for the α-methylbenzyl alcohol and ether formation reactions were found to be 0.0034 and 0.0017 min^{-1} with 2-ethyl-1-hexanol as the organic phase and 0.0040 and 0.0023 min^{-1} with 2-methyl-1-butanol as the organic phase.

Other possible causes were considered to account for the markedly different product distributions in the two alcoholic biphasic systems, and catalyst deactivation via oxidative degradation of the catalyst ligand is deemed a plausible cause. Evidence in support of the postulate is provided by an abrupt halt in the carbon monoxide uptake profile, the intermediary of an oxidizing species implicated by the carbonate formation that accompanied the formation of the coupled product, and a sensitivity of the carbonylation reactions to the inhibiting effect of dissolved oxygen. The carbon monoxide uptake duration was much shorter and the cessation of the carbon monoxide uptake was abrupt when 2-methyl-1-butanol was used in place of 2-ethyl-1-hexanol as the organic phase. The contrast was even more pronounced with toluene as the organic phase. In both cases with 2-methyl-1-butanol and toluene as the organic phase, the relative yield of coupled product—and hence the relative amount of the concomitant oxidizing intermediate—was much higher than in the case with 2-ethyl-1-hexanol as the organic phase (20−44% vs 13%, see Table 3a). Mechanistic considerations (see section III-J) suggest that the oxidizing intermediate was probably hypobromous acid (HOBr), a known oxiding agent,[10] and that the phosphine ligand might have been oxidized to the corresponding phosphine oxide that was catalytically inactive. Thus, the high yield of α-methylbenzyl alcohol and ether associated with 2-methyl-1-butanol probably resulted from reactions 3 and 5 continuing long after the catalyst complex had been deactivated.

Table 4. **Effect of emulsifier (DSS) concentration on rate and yield (other conditions are specified in Table 1)**

emulsifier concn[a] (M)	rate, M/min	cumulative CO uptake relative to substrate
0	6.87×10^{-3}	84
0.0050	1.19×10^{-2}	77
0.0100	1.23×10^{-2}	71

[a] Based on the total liquid volume of 40 mL.

Product inhibition by 2-phenylpropionic acid also contributed to catalyst deactivation. The results of a control run, presented in Table 4, show that the presence of 2-phenylpropionic acid in 15 mol % with the initial substrate reduced the carbonylation rate and 2-phenylpropionate yield by about 90% and 67%, respectively. At the same time, the yield of coupled product increased from about 13% to about 30%. Evidently, 2-phenylpropionate ion inhibited the carbonylation reactions by competing against the phosphine ligand for the coordination sites of palladium, and the phosphine-deficient palladium complex was less active and more selective toward the formation of the coupled product. Unlike the inhibiting effect associated with the oxidizing

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(10) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley-Interscience: New York, 1988; pp 563−567.

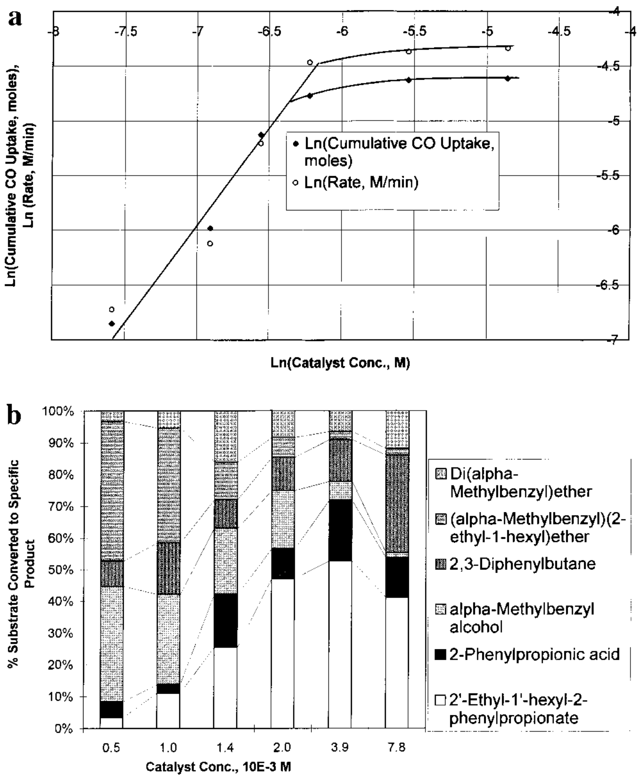

Figure 2. **(a) Rate and cumulative CO uptake dependence on the catalyst concentration at a ligand:palladium ratio of 2:1 (other conditions as specified in Table 1). (b) Dependence of product distribution on the catalyst concentration at a ligand: palladium ratio of 2:1 (other conditions as specified in Table 1).**

intermediate, which was more pronounced with toluene or 2-methyl-1-butanol as the organic phase than with 2-ethyl-1-hexanol as the organic phase, the inhibiting effect of 2-phenylpropionate ion appears to be independent of the nature of the organic phase.

(C) Dependence on the Catalyst and Ligand. As with the carbonylation of benzyl chloride,[3] palladium and (4-*N*,*N*-dimethylaminophenyl)diphenylphosphine were found to be the effective catalyst and ligand for the carbonylation of α-methylbenzyl bromide. Other potential catalysts, such as rhodium bromide, ruthenium bromide, platinum chloride, cobalt carbonyl, and nickel chloride, showed little or no catalytic activity. Other ligand candidates, including tris(4-*N*,*N*-dimethylaminophenyl)phosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(*p*-*N*,*N*-dimethylaminophenyl)-phosphinobutane, and (*S*)-2′-isopropylidene-bis(4-phenyl-2-oxazoline) were either ineffective or less effective.

The dependence of the carbonylation rate, cumulative carbon monoxide uptake, and product distribution on the catalyst concentration are shown in Figure 2. The carbonylation rate, cumulative carbon monoxide uptake, and the 2-phenylpropionate yield vary, more or less, in a parallel fashion. Similar parallel trends are observed with other parametric variations. The reaction order with respect to the catalyst varied from an apparent second order to almost zeroth order as the catalyst concentration was increased above a threshold value of about 0.0020 M. The leveling of the carbonylation rate beyond the catalyst concentration of 0.0020 M suggests that, first, the catalyst probably operated primarily as a dissolved complex, and second, a saturation phenomenon might be limiting the dissolved catalyst complex to about 0.0020 M. Consistent with this explanation, black catalyst particles could be found segregating at the O−W interface when the catalyst concentration exceeded 0.0020 M. The black precipitate showed little catalytic activity.

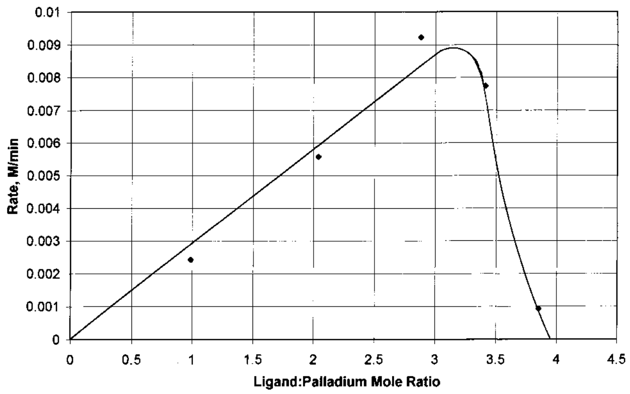

Figure 3. **Rate dependence on the ligand concentration for 1.47×10^{-3} M of catalyst (other conditions as specified in Table 1).**

The apparent second-order dependence on the catalyst below the threshold catalyst concentration of 0.0020 M was, in fact, the product of two first-order dependences, one each on palladium and the phosphine ligand. In the catalyst variation runs of Figure 2, the ligand concentration was varied proportionally with the palladium concentration to keep a constant palladium:ligand ratio of 2.0. Results of ligand variation runs at a fixed palladium concentration (0.0015 M), which are presented in Figure 3, show that up to a ligand:palladium ratio of 3:1, the reaction shows a first-order dependence on the ligand concentration. Above the ligand:palladium ratio of 3:1, the rate falls with a further increase in the ligand concentration, presumably due to the excess ligand competing against the substrate for the remaining coordination sites of palladium. It should be noted that both higher rate and higher yield of 2-phenylpropionate were obtained at the phosphine:palladium ratio of 3:1 than at 2:1. The latter ratio was optimal for the carbonylation of benzyl chloride in the aqueous−toluene biphasic system.[3]

The apparent second-order dependence on the palladium−phosphine complex found in this study differs from a first-order dependence on the same catalyst−ligand system determined previously on the carbonylation of benzyl chloride in the aqueous−toluene biphasic system.[3] The difference may be due to a lower stability constant of the palladium−phosphine complex in the aqueous−alcohol system than in the aqueous−toluene system; i.e., it appears that less of the ligand was complexed to palladium in the aqueous−alcohol system than in the aqueous−toluene system. A lower stability constant of the palladium−phosphine complex in the alcoholic biphasic system may be rationalized in terms of a greater solvating and ligating power of alcohol over the nonpolar toluene and is consistent with a sensitivity

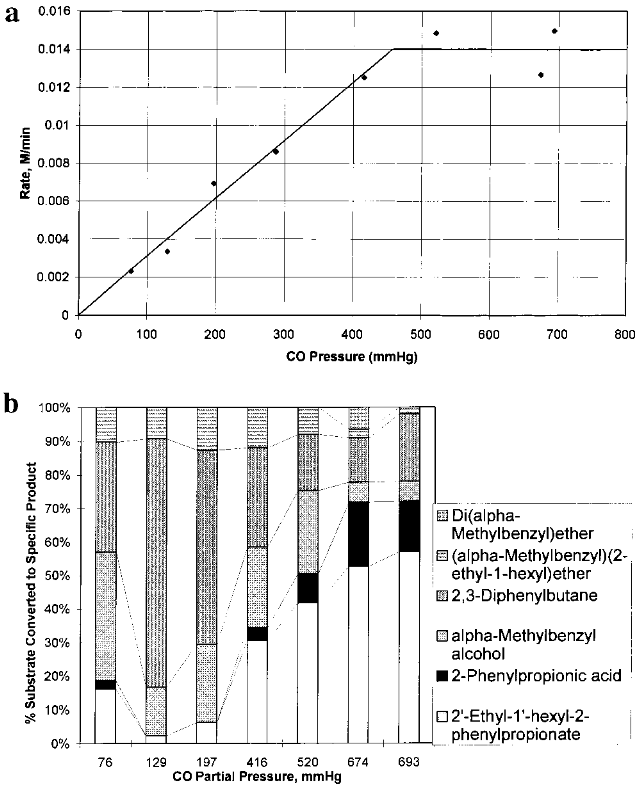

Figure 4. **(a) Rate dependence on the carbon monoxide partial pressure (other conditions as specified in Table 1). (b) Dependence of the product distribution on the carbon monoxide partial pressure (other conditions as specified in Table 1).**

of the catalyst to product inhibition, as shown in the preceding section.

The product distribution data presented in Figure 2 indicate that the yield of 2-phenylpropionate increased while the yields of α-methylbenzyl alcohol and α-methylbenzyl-(2-ethyl-1-hexyl)ether decreased with increasing catalyst concentration up to a catalyst concentration of about 0.0039 M, where the yield of 2-phenylpropionate reached a maximum of about 70%. Catalyst in excess of 0.0039 M brought a sharp rise in the yield of the coupled product and a lower yield of 2-phenylpropionate, while the yields of α-methylbenzyl alcohol and α-methylbenzyl(2-ethyl-1-hexyl)ether continued to decrease. Evidently, catalyst beyond the threshold concentration range of 0.0020−0.0039 M favored the formation of the coupled product. In light of the empirical link found in the preceding section between product selectivity and deficiency of phosphine ligand in the catalyst complex, it appears that the catalyst beyond the threshold concentration range of 0.0020−0.0039 M was deficient in the phosphine ligand.

(D) Dependence on the Carbon Monoxide Pressure. The dependence of the carbonylation rate and product yield on the carbon monoxide partial pressure P_{CO} is shown in Figure 4. In contrast to the carbonylation of benzyl chloride in the aqueous−toluene biphasic system that showed a zeroth-order dependence on the carbon monoxide partial pressure down to a pressure as low as 76 mmHg,[3] the carbonylation of α-methylbenzyl bromide in an alcoholic biphasic medium showed a variable reaction order with respect to carbon monoxide. The reaction order shifted from first order below a P_{CO} of 450 mmHg to zeroth order above it, and the 2-phenylpropionate yield increased with increasing P_{CO}. The increased 2-phenylpropionate yield came at the expense of the two side products over two different pressure ranges: coupled product up to a P_{CO} of 520 mmHg and α-methylbenzyl alcohol above a P_{CO} of 520 mmHg. The trend reversal in the yields of 2-phenylpropionate and the coupled product on going from P_{CO} of 129 to 77 mmHg needs to be confirmed, but it may reflect a change in the catalyst's composition or valence state or the reaction mechanism.

The first-to-zeroth-order switch in the rate profile suggests a switch in either the rate-controlling step(s) of the carbonylation reactions or the dominant catalyst species. It will be shown later that the kinetic results collectively support a switch of the dominant fraction of the catalyst from one that was carbonylated to one that was not carbonylated when the carbon monoxide partial pressure fell below 450 mmHg.

The zeroth-order rate dependence on P_{CO} above 450 mmHg, which may be explained in terms of the palladium complex existing predominantly in a carbonylated form (see section III-J), brings the biphasic carbonylation of α-methylbenzyl bromide partially in line which other biphasic catalytic reactions that show zeroth-order dependence on dissolved gas reactants.[1,3,4] It appears that the segregation of a surface-active catalyst complex at the O−W interface, coupled with the affinity of the catalyst complex for the dissolved gas reactant, creates a localized high concentration of the dissolved gas reactant around the interface and lessens the dependence on the dissolved gas, except at a low concentration. The fact that the zeroth-order regime in the rate profile in this case is preceded by a prominent first-order regime may be attributed to a lower stability constant of the palladium−phosphine complex in the alcoholic biphasic medium and a lower concentration of the catalyst complex at the O−W interface. The implication of the zeroth-order regime is that the pressure requirement of a dissolved gas, catalytic reaction may be lowered substantially by running the reaction in a biphasic mode with the help of a surface-active catalyst complex.

(E) Dependence on the Substrate Concentration. The dependence of the carbonylation rate and cumulative carbon monoxide uptake on the substrate concentration is shown in Figure 5. The carbonylation reactions—as well as the side reactions, as noted earlier—had a first-order dependence on the substrate concentration. The cumulative carbon monoxide uptake increased proportionately with the substrate concentration up to about 0.344 M, whereupon it appeared to level off with further increase in the substrate concentration. The leveling of carbon monoxide uptake was probably due to a buildup of 2-phenylpropionic acid that had an inhibiting effect on the carbonylation reactions (see Table 4), and it implied a falling yield of 2-phenylpropionate above a substrate concentration of 0.344 M.

(F) Dependence on the Aqueous Base Concentration and Ionic Strength. Sodium hydroxide was a more effective base for the carbonylation reactions than either 1,8-diazabicyclo[5,4,0]-undec-7-ene, ammonium hydroxide, or potas-

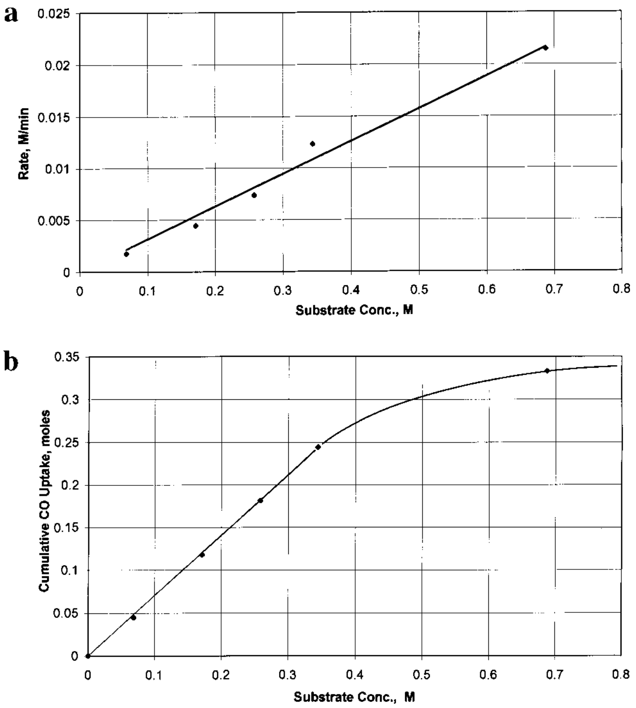

Figure 5. **(a) Rate dependence on the substrate concentration (other conditions as specified in Table 1). (b) Cumulative CO uptake as a function of the initial substrate concentration (other conditions as specified in Table 1).**

sium hydroxide. Little carbonylation reactions occurred with either of the first two bases, and the reactions were slower with the last base. Figure 6 shows that the carbonylation rate and 2-phenylpropionate yield both increased with increasing sodium hydroxide concentration up to 5.0 M and then decreased thereafter. The increase in 2-phenylpropionate yield with increasing base concentration up to 5.0 M came largely at the expense of α-methylbenzyl alcohol. The yield of coupled product increased with increasing base concentration; a similar trend was observed with toluene as the organic phase (see Table 3b). The increased yield of coupled product that came at the expense of 2-phenylpropionate at an aqueous base concentration above 7.7 M may be attributed, at least in part, to a reduced solubility of carbon monoxide in the biphasic medium due to the ionic strength effect.[11]

It is interesting to note that an aqueous phase containing 2.5 M each of sodium hydroxide and sodium chloride gave essentially the same carbonylation rate and 2-phenylpropionate yield as the aqueous phase containing 5.0 M sodium hydroxide. It appears that the increases in rate and 2-phenylpropionate yield resulting from the base concentration increase from 2.5 to 5.0 M were due to a salt effect rather than an intrinsic base effect. Presumably, the aqueous phase contained sufficient base at 2.5 M to meet the basicity need of the dehalogenation reaction, and the excess base above 2.5 M merely contributed to an increased salt effect. The latter apparently brought two effects: a faster phase separation of the emulsified reaction mixture that adversely affected reaction 3 more than other reactions and a stabilization of charged transition-state moieties, such as $R^+Pd^0L(CO)(OH^-)$ and $R^+Pd^0L(CO)(RO^-)$, that favored the carbonylation reactions (see section III−J). Evidence in support of the first effect was provided by Wang et al.,[12] who have reported that the base-catalyzed, biphasic hydrolysis of benzyl chloride gave a decreasing yield of benzyl alocohol relative to dibenzyl ether with an increasing aqueous base concentration.

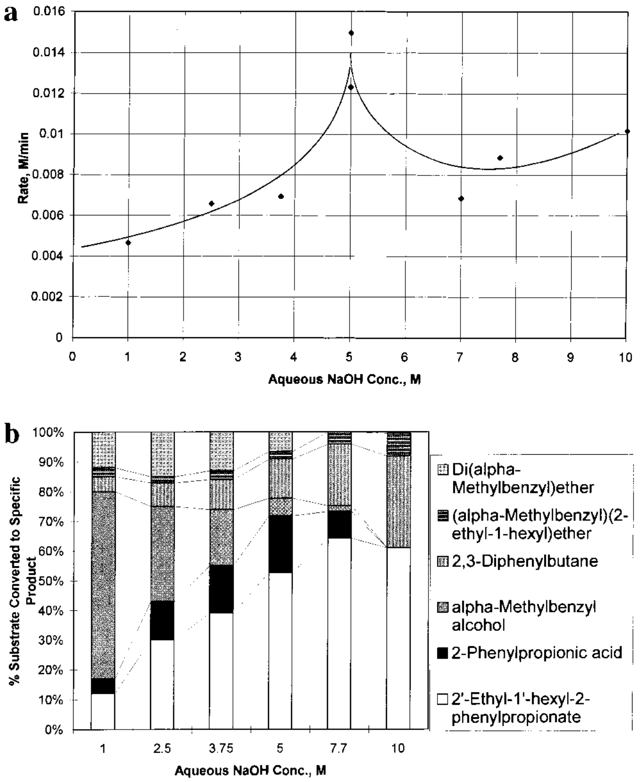

Figure 6. **(a) Rate dependence on the aqueous sodium hydroxide concentration (other conditions as specified in Table 1). (b) Dependence of the product distribution on the aqueous sodium hydroxide concentration (other conditions as specified in Table 1).**

Table 5. **Effect of 2-phenylpropionic acid on the rate and yield of biphasic carbonylation of α-methylbenzyl bromide (other conditions are specified in Table 1)**

dependent variables	fresh catalyst	fresh catalyst with an initial 0.05 M of 2-phenylpropionic acid
cumulative CO uptake relative to substrate, %	71%	40
rate, M/min	1.23×10^{-2}	3.97×10^{-3}

(G) Dependence on the Emulsifier Concentration, O−W Phase Ratio, and Temperature. Data presented in Table 5 show that the carbonylation rate doubled when the DSS concentration was increased from 0 to 0.005 M but then leveled off with further increase in the DSS concentration. Correspondingly, the 2-phenylpropionate yield decreased and then leveled off while the yield of α-methylbenzyl alcohol increased continuously with rising DSS concentration. Evidently, the increase in carbonylation rate brought on by

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[11] Danckwerts, P. V. *Gas−Liquid Reactions*; McGraw-Hill: New York, 1970; pp 18−20.

[12] Wang, T.-T.; Huang, T.-C.; Huang, Yeh, M.-Y. *Chem. Eng. Commun.* **1990**, *92*, 139−151.

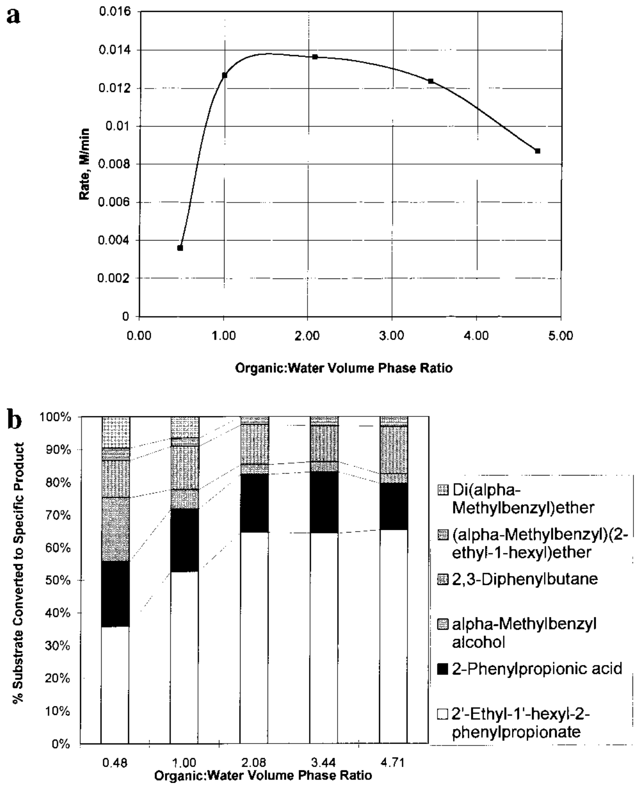

Figure 7. **(a) Rate dependence on the organic−water volume phase ratio (other conditions as specified in Table 1). (b) Dependence of the product distribution on the organic−water volume phase ratio (other conditions as specified in Table 1).**

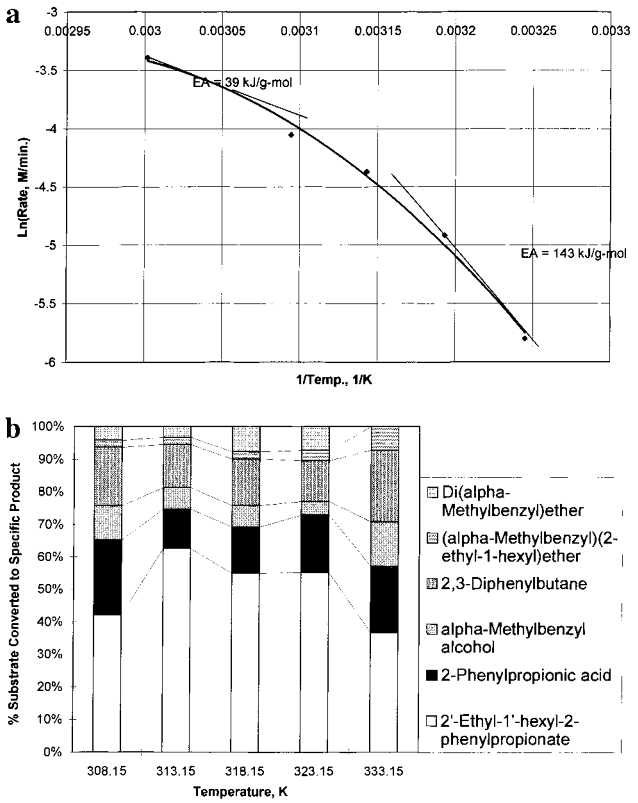

Figure 8. **(a) Rate dependence on the reaction temperature (other conditions as specified in Table 1). (b) Dependence of the product distribution on the reaction temperature (other conditions as specified in Table 1).**

the DSS concentration increase from 0 to 0.005 M was more than offset by the corresponding increase in the rate of reaction 3, so that the 2-phenylpropionate yield decreased. The increased yield of α-methylbenzyl alcohol over the DSS concentration range 0.005−0.010 M was offset by a decreased yield of coupled product so that the yields of 2-phenylpropionate and ether remained essentially constant.

The rate dependence and 2-phenylpropionate yield on the O−W phase ratio and reaction temperature are shown in Figures 7 and 8, respectively. The rate and 2-phenylpropionate yield increased with increasing O−W phase ratio up about 2:1, and then the rate decreased with a further increase in the phase ratio while the 2-phenylpropionate yield leveled off. The results stand in contrast to the optimal O−W phase ratio of 1:1 for the carbonylation of benzyl chloride in the aqueous−toluene system.[3] The 2-phenylpropionate yield at the optimal O−W phase ratio was 83%, which was quite high considering the multiplicity of side reactions. The yield improvement of 2-phenylpropionate in going from an O−W phase ratio of 1:1 to 2:1 apparently resulted from an enhancement of the carbonylation rate and a simultaneous reduction in the rate of reaction 3.

The Arrhenius plot in Figure 8 shows a distinct convex feature with the apparent activation energy varying from 143 kJ/mol at 35 °C to 39 kJ/mol at 60 °C. The convex feature may be rationalized in terms of the product distribution that indicates a higher yield of 2-phenylpropionic acid and coupled product at both ends of the temperature range, 35−60 °C. In view of the fact that 2-phenylpropionic acid and the coupled product are associated with reaction inhibition (see section III−B), it appears that, at both ends of the temperature range, product inhibition was more significant than in the middle temperature range, so that the carbonylation rate was correspondingly lower at both ends of the temperature range. The possibility of mass transfer limitation at the high end of the temperature range could not be ruled out entirely, however, since the magnitude of the apparent activation energy approaches that for a diffusion process.

(H) α-Substituent Effect on the Carbonylation of Benzyl Halide. To map out a more definitive pattern of the α-substituent effect on the carbonylation of benzyl halide, the carbonylation of α,α-dibromotoluene was also studied in a 1:1 toluene−5 N aqueous sodium hydroxide mixture under conditions similar to those listed in Table 1. The second bromine in α,α-dibromotoluene may be treated as a substituent whose effect may be contrasted with that of a hydrogen in benzyl halide and that of methyl substituent in α-methylbenzyl bromide. Compared to hydrogen, both the bromo and methyl substituents are bulkier, but the bromo substituent is electron-withdrawing whereas the methyl substituent is electron-releasing. If the multiplicity of side products—as represented by α-methylbenzyl alcohol and 2,3-diphenylbutane—in the carbonylation of α-methylbenzyl bromide is caused by the α-substituent group being electron-releasing, then a replacement of the α-methyl group by an electron-withdrawing α-bromo group should reduce, if not eliminate, the side product formation.

The expectation was confirmed; i.e., the bromo-substituted analogues of benzyl alcohol and coupled product—specifically, α-bromobenzyl alcohol and 1,2,-diphenyl-1,2-dibromoethane—were not detected in the reaction mixture. The results, however, were complicated somewhat by the fact that the α-bromo group can itself undergo hydrolysis and further carbonylation reactions *after* α,α-dibromotoluene has been quantitatively converted to α-bromophenylacetic acid as follows:

$$C_6H_5CHBr_2 + CO + 2OH^- \rightarrow C_6H_5CHBrCOO^- + Br^- + H_2O \quad (11)$$

Results of control experiments with α-bromophenylacetic acid revealed that, in the toluene—aqueous sodium hydroxide mixture, the intermediate acid product readily underwent hydrolysis and further carbonylation reaction to form mandelic and phenylmalonic acids, respectively, as follows:

$$C_6H_5CHBrCOO^- + OH^- \rightarrow C_6H_5CH(OH)COO^- + Br^- \quad (12)$$

$$C_6H_5CHBrCOO^- + CO + 2OH^- \rightarrow C_6H_5CH(COO^-)_2 + Br^- + H_2O \quad (13)$$

Thus, upon complete conversion of α,α-dibromotoluene, the reaction mixture gave mandelic and phenylmalonic acids as the major products, with no trace of either α-bromobenzyl alcohol or 1,2,-diphenyl-1,2-dibromoethane.

Results of another control experiment also revealed that, for over 9 h at 60 °C, α,α-dibromotoluene underwent no detectable hydrolysis reaction in the toluene—aqueous sodium hydroxide mixture kept under an inert nitrogen atmosphere. The finding ruled out the possibility of α,α-dibromotoluene undergoing the hydrolysis reaction first and then the carbonylation reaction to form mandelic acid. It appears that the mandelic acid was derived exclusively from α-bromophenylacetic acid being formed first (in reaction 11) and then undergoing a hydrolysis reaction (reaction 12).

It should be noted that, while the neutral carboxylic acid group, —COOH, is electron-withdrawing, its deprotonated counterpart, the carboxylate ion, $-COO^-$, is electron-releasing. It follows that the presence of an α-carboxylate group in a benzyl halide should have a similar effect as the electron-releasing α-methyl group in favoring the hydrolysis reaction over the carbonylation reaction. Consistent with this deduction, the final reaction mixture in the carbonylation of α,α-dibromotoluene showed a preponderance of the mandelic acid over the phenylmalonic acid.

Table 6. **Comparison of the activities and product selectivities of the recycled and fresh catalysts (other conditions are specified in Table 1)**

dependent variables	fresh catalyst	recycled catalyst
cumulative CO uptake relative to substrate	71	24[a]
rate, M/min	1.23×10^{-2}	2.79×10^{-3}

[a] This reaction had no induction period.

Taken together, the results on the carbonylation of α-methylbenzyl bromide, benzyl chloride,[3] and α,α-dibromotoluene collectively suggest that the broad product distribution in the carbonylation of α-methylbenzyl bromide is attributable to the electron-releasing nature of the α-methyl substituent group. Evidently, an electron-releasing α-substituent weakens the carbon—halide bond and facilitates the heterolytic dehalogenation in reactions 3 and 6, whereas an electron-withdrawing α-substituent has the opposite effect. The fact that the α-methyl substituent also increased the coupled product formation suggests that an electron-releasing α-substituent may also make the carbon—halide bond more susceptible to homolytic scission and free-radical attack, as depicted below:

$$C_6H_5CH(CH_3)Br + Pd^0OH^- \rightarrow C_6H_5\dot{C}H(CH_3)Pd^+(OH^-) + Br^- \quad (14)$$

$$C_6H_5\dot{C}H(CH_3)Pd^+(OH^-) + C_6H_5CH(CH_3)Br \rightarrow [C_6H_5CH(CH_3)]_2 + Pd^0 + HOBr \quad (15)$$

$$HOBr + CO + 3OH^- \rightarrow Br^- + CO_3^{2-} + 2H_2O \quad (16)$$

The postulated reaction sequence, 14—16, explains the concomitant formation of coupled product and carbonate.

(I) Feasibility of Catalyst Recycle. The segregation of palladium at the O—W interface suggests the possibility of recovering and recycling the catalyst. The possibility was tested in a repeat run using recycled interfacial layer and aqueous phase from a preceding run. Makeup organic phase and substrate were added to the recycled mixture to replace the removed organic phase and the reacted substrate, but no additional catalyst, ligand, or emulsifier was added. The results of the recycled catalyst run are presented in Table 6, along with those of the fresh catalyst run. The rate and desired product yield of the recycled catalyst run were respectively one-fifth and one-third of those of the fresh catalyst run. The low rate and yield of the recycled catalyst run can be attributed to two factors: first, a loss of the phosphine ligand through oxidative degradation and replacement of the organic phase, and second, product inhibition on the catalyst. On account of the modest stability constant of the palladium—phosphine complex in the alcoholic biphasic medium (see section III—B), a significant fraction of the phosphine ligand was likely to have been lost with the replacement of the original organic phase with fresh organic phase. The results of the feasibility study indicate that, for catalyst recycle to be practical in an alcoholic biphasic system, the phosphine ligand ought to have a much greater ligating power and surface affinity than (4-*N*,*N*-dimethylaminophenyl)diphenylphosphine.

(J) Kinetic Model for the Carbonylation of α-Methylbenzyl Bromide in an Alcoholic Biphasic System. A kinetic model for the biphasic carbonylation of α-methylbenzyl bromide in the presence of side reactions is depicted in Scheme 1.

***Scheme 1.* Proposed mechanism for the carbonylation and side reactions**

$$\mathrm{Pd^0OH^-} + \mathrm{CO} \overset{K_1}{\rightleftharpoons} \mathrm{Pd^0(CO)OH^-}$$

$$\mathrm{Pd^0(CO)OH^-} + \mathrm{L} \overset{K_2}{\rightleftharpoons} \mathrm{Y} \equiv \mathrm{Pd^0L(CO)(OH^-)}$$

$$\mathrm{Y} + \mathrm{R'OH} \overset{K_3}{\rightleftharpoons} \mathrm{Z} \equiv \mathrm{Pd^0L(CO)(R'O^-)} + \mathrm{H_2O}$$

Carbonylation Reactions

$$\mathrm{RBr} + \mathrm{Y} \xrightarrow{k_1} \mathrm{R^+Pd^0L(CO)(OH^-)} + \mathrm{Br^-}$$

$$\mathrm{R^+Pd^0L(CO)(OH^-)} \xrightarrow{k_2} \mathrm{RCOOH} + \mathrm{Pd^0L}$$

$$\mathrm{RBr} + \mathrm{Z} \xrightarrow{k_3} \mathrm{R^+Pd^0L(CO)(R'O^-)} + \mathrm{Br^-}$$

$$\mathrm{R^+Pd^0L(CO)(R'O^-)} \xrightarrow{k_4} \mathrm{RCOOR'} + \mathrm{Pd^0L}$$

Coupling and CO_2 Formation Reactions

$$\mathrm{RBr} + \mathrm{Pd^0OH^-} \xrightarrow{k_5} \begin{array}{c} \mathrm{R^+Pd^0OH^-} \\ \downarrow\uparrow \\ \mathrm{(R^\bullet)Pd^0(OH^\bullet)} \end{array} + \mathrm{Br^-}$$

$$\mathrm{RBr} + \mathrm{(R^\bullet)Pd^0(OH^\bullet)} \xrightarrow{k_6} \mathrm{RR} + \mathrm{Pd^0} + \mathrm{HOBr}$$

$$\mathrm{HOBr} + \mathrm{CO} \xrightarrow{k_7} \mathrm{HBr} + \mathrm{CO_2}$$

Benzyl Alcohol and Ether Formation Reactions

$$\mathrm{RBr} + \mathrm{OH^-} \xrightarrow{k_8} \mathrm{ROH} + \mathrm{Br^-}$$

$$\mathrm{R'OH} + \mathrm{OH^-} \overset{K_4}{\rightleftharpoons} \mathrm{R'O^-} + \mathrm{H_2O}$$

$$\mathrm{RBr} + \mathrm{R'O^-} \xrightarrow{k_9} \mathrm{ROR'} + \mathrm{Br^-}$$

In accord with the formation of the two distinct carbonylation products in an alcoholic biphasic medium, namely, 2-phenylpropionic acid and 2-phenylpropionate ester, two parallel carbonylation pathways are proposed which are mediated by palladium−phosphine−carbonyl complexes. The latter complexes are postulated to be the active catalyst complexes, with a modest stabilty constant (K_2) with respect to the phosphine ligand and a higher stability constant (K_1) with respect to carbon monoxide. The postulate is based on the general affinity of palladium−phosphine complexes for carbon monoxide,[13−17] a first-order rate dependence on the palladium below the threshold palladium concentration of 0.0020 M, a first-order rate dependence on the ligand below the threshold ligand:palladium ratio of 3:1, and a zeroth-order rate dependence on the carbon monoxide partial pressure above 450 mmHg. The latter result suggests a major fraction of the palladium complexes existing in the carbonylated form above a carbon monoxide pressure of 450 mmHg. A similar deduction was made in the carbonylation of benzyl chloride in the aqueous−toluene biphasic system at a carbon monoxide pressure above 76 mmHg.[3]

In agreement with the basicity requirement of the carbonylation reactions, the catalyst complexes are presumed to contain a hydroxide or alkoxide group. The postulate of multiple groups being present in the catalyst complexes is consistent with the sensitivity of the carbonylation reactions to product inhibition and coordination saturation at palladium. Interactions between the substrate and the catalyst complexes are believed to be rate-limiting based on the first-order rate dependence on the substrate concentration.

Consistent with the high yield of coupled product and the stoichiometric formation of carbonate in the carbonylation reactions inhibited by 2-phenylpropionic acid or excess hydroxide ions, the sequential formation of the coupled product and carbon dioxide is proposed through the mediation of phosphine-deficient palladium. The intermediacy of hypobromous acid (HOBr)—or, equivalently, the hypobromite ion in the basic medium (BrO^-)—is proposed because, first, hypobromite is a known oxidizing agent[10] capable of oxidizing carbon monoxide to form carbonate in an alkaline medium, and second, the intermediacy of hypobromite is stoichiometrically consistent with the formation of the coupled product, as proposed in reaction 15.

Finally, debromination reactions are proposed between α-methylbenzyl bromide and hydroxide as well as alkoxide ions to account for the formation of the α-methylbenzyl alcohol and ether, respectively. Consistent with the absence of any effect by palladium, the reactions are presumed to proceed spontaneously unaided by palladium.

To rigorously model the biphasic carbonylation reactions, it would be necessary to have quantitative data on the interfacial area and the interfacial concentrations of the catalyst and reacting species. Such data are, unfortunately, not available, and it is necessary to simplify the model. On account of the vigorous stirring used in this study, the reaction mixture may be treated as a uniform emulsion for simplicity. With the dispersion and mass-transfer effects being averaged out by the rapid mixing process, the reactions may effectively be treated as pseudo-homogeneous. With this simplifying assumption, the kinetic model may be shown to yield the following model expressions for the rates of consumption/formation of the various species and the 2-phenylpropionate yield:

$$\frac{-\mathrm{d[RBr]}}{\mathrm{d}t} \simeq \frac{(k_1 + k_3K_3)K_1K_2[\mathrm{Pd}]_\mathrm{o}[\mathrm{L}]_\mathrm{o}[\mathrm{CO}][\mathrm{RBr}] + 2k_5[\mathrm{Pd}]_\mathrm{o}[\mathrm{RBr}]}{1 + k_5/k_6 + K_1[\mathrm{CO}]} + (k_8 + k_9K_4)[\mathrm{RBr}][\mathrm{OH^-}]$$

$$\frac{-\mathrm{d}(N_{\mathrm{CO}}/V)}{\mathrm{d}t} \simeq \frac{(k_1 + k_3K_3)K_1K_2[\mathrm{Pd}]_\mathrm{o}[\mathrm{L}]_\mathrm{o}[\mathrm{CO}][\mathrm{RX}] + k_5[\mathrm{Pd}]_\mathrm{o}[\mathrm{RBr}]}{1 + k_5/k_6 + K_1[\mathrm{CO}]}$$

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(13) Kudo, K.; Hidai, M.; Uchida, Y. *J. Organometallic Chem.* **1971**, *33*, 393−398.

(14) Mednikov, E. G.; Eremenko, N. K.; Slovokhotov, Y. L.; Struchkov, Y. T. *J. Chem. Soc. Chem. Commun.* **1987**, No. *3*, 218−219.

(15) Grevin, J.; Kalck, Ph.; Daran, J. C.; Vaissermann, J.; Bianchini, C. *Inorg. Chem.* **1993**, *32*, 4965−4967.

(16) Toth, I.; Elsevier, C. J. *J. Am. Chem. Soc.* **1993**, *115*, 10388−10389.

(17) Amiens, C.; Decaro, D.; Chaudret, B.; Bradley, J. S.; Mazel, R.; Roucau, C. *J. Am. Chem. Soc.* **1993**, *115*, 11638−11639.

$$\frac{d[\mathrm{RCOOH}]}{dt} + \frac{d[\mathrm{RCOOR'}]}{dt} \simeq \frac{(k_1 + k_3K_3)K_1K_2[\mathrm{Pd}]_o[\mathrm{L}]_o[\mathrm{CO}][\mathrm{RBr}]}{1 + k_5/k_6 + K_1[\mathrm{CO}]}$$

$$\frac{d[\mathrm{RR}]}{dt} = \frac{d[\mathrm{CO_3}^{2-}]}{dt} \simeq \frac{k_5[\mathrm{Pd}]_o[\mathrm{RBr}]}{1 + k_5/k_6 + K_1[\mathrm{CO}]}$$

$$\frac{d[\mathrm{ROH}]}{dt} = k_8[\mathrm{RBr}][\mathrm{OH}^-]$$

$$\frac{d[\mathrm{ROR'}]}{dt} = k_9K_4[\mathrm{RBr}][\mathrm{OH}^-]$$

$$\text{2-phenylpropionate yield} = ([\mathrm{RCOOH}]_f + [\mathrm{RCOOR'}]_f)/[\mathrm{RBr}]_o$$

$$\simeq (k_1 + k_3K_3)K_1K_2[\mathrm{Pd}]_o[\mathrm{L}]_o[\mathrm{CO}]/\{(k_1 + k_3K_3)K_1K_2[\mathrm{Pd}]_o[\mathrm{L}]_o[\mathrm{CO}]_o + 2k_5[\mathrm{Pd}]_o + (1 + k_5/k_6 + K_1[\mathrm{CO}])(k_8 + k_9K_4)[\mathrm{OH}^-]\}$$

In the above expressions, L, RBr, RCOOH, RCOOR′, RR, ROH, and ROR′ denote respectively the phosphine ligand, substrate, 2-phenylpropionic acid, 2-phenylpropionate ester, 2,3-diphenylbutane, α-methylbenzyl alcohol, and ether; $[i]$, N_{CO}, and V denote respectively the molar concentration of species i, the molar uptake of carbon monoxide, and the volume of the biphasic reaction mixture; and subscripts o and f correspond to initial/total and final concentrations, respectively. In deriving the above expressions, the following assumptions have been made: (i) $[\mathrm{Pd}]_o < 0.0020$ M and $[\mathrm{L}]_o/[\mathrm{Pd}]_o < 3$, (ii) each palladium is tied up by a hydroxide or alkoxide ion, and (iii) $K_2(1 + K_3)[\mathrm{L}] < 1$. The last assumption stipulates that the catalyst complex has a modest stability constant with respect to that of the phosphine ligand.

Consistent with the experimental findings, the model predicts (1) a first-order dependence of the carbonylation and side reactions on the substrate concentration, (2) a first-order dependence of the carbonylation reactions on the palladium and ligand concentrations each, and (3) a variable dependence—between zeroth and first order—of the carbonylation reactions on the carbon monoxide pressure.

IV. Comparison with Phase-Transfer Carbonylation Reaction

The biphasic carbonylation reaction described here is similar to a phase-transfer carbonylation reaction[18,19] in that both utilize a biphasic liquid mixture as the reaction medium and both can be effected under mild reaction conditions by the use of palladium−phosphine complexes as the catalysts. However, there are significant differences between the two. In this biphasic reaction, the ligand is designed to be surface-active, and the catalyst complex is intended to segregate and operate at the O−W interface. With a sufficiently surface-active and strongly complexing ligand, the catalyst complex can be recovered in a compact emulsion layer at the interface after the reaction. In the phase-transfer reaction, on the other hand, the phosphine ligand is designed to draw the palladium into the organic phase, where the reaction actually occurs. Catalyst recovery requires the recycling of the entire organic phase and is complicated by the appreciable solubility of the reaction product(s) in the organic phase.

The biphasic reaction described here is sensitive to parameters—such as emulsifier type[3] and concentration, and stirring speed—that affect the interface. The phase-transfer reaction is sensitive to the same parameters only in the mass-transfer limit. The nature and functions of the emulsifier and phase-transfer agent used in the two reactions also differ. The emulsifier is used to enlarge the interface by enhancing phase dispersion, whereas the phase-transfer agent is used to transport a reactant from one bulk phase to another. Either anionic or cationic surfactant could serve as an emulsifier,[3] whereas it would seem from the literature evidence[18,20−22] that only a cationic surfactant or a crown ether could serve as a phase-transfer agent.

V. Comparison between This and Other Biphasic Techniques

The biphasic technique described here is also different from, though complementary to, the another biphasic technique that is based on the use of water-soluble catalyst ligands.[23−26] The latter technique has been developed primarily to allow for separation and recovery of the catalyst from the reaction products. The function of the water-soluble ligand is to keep the catalyst in the aqueous phase while reaction products are being formed and carried off into the organic phase. The reaction is designed to occur in the aqueous phase unless the substrate has a very low aqueous solubility and cannot be drawn into the aqueous phase by the use of a reverse phase-transfer agent. In the latter event, the reaction will occur either at the interface or in the organic phase. In the first case, the catalytic efficiency will be low because only a small fraction of the water-soluble catalyst complex can be found at the interface. In the second case, a phase-transfer agent will be needed to transport the catalyst complex into the organic phase, but this will negate much of the advantage of using a water-soluble ligand for catalyst recovery.

By contrast, in this biphasic technique, the catalyst complex is designed to effect the reaction at the O−W interface. The catalyst ligand is ideally amphiphilic and surface-active, rather than hydrophilic. With the right choice of ligand, the catalyst can be recovered almost quantitatively in a compact emulsion layer at the O−W interface.[4,8,27] Thus, in principle, the catalyst can be recovered in a more concentrated form than in the case with the use of a water-soluble ligand. Moreover, the catalyst recovery is not much affected by the solubilities of the reaction products in either

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(18) Alper, H.; Hashem, K.; Heveling, J. *Organometallics* **1982**, *1*, 775−778.

(19) Okano, T.; Uchida, I.; Nakagaki, T.; Konishi, H.; Kiji, J. *J. Mol. Catal.* **1989**, *54*, 65−71.

(20) Cassar, L.; Foa, M.; Gardano, A. *J. Organometallic Chem.* **1976**, *121*, C55−C56.

(21) Amer, I.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 927−930.

(22) Arzoumanian, H.; Buono, G.; Choukard, M'B.; Petrignani, J.-F. *Organometallics* **1988**, *7*, 59−62.

(23) Kuntz, E. G. *Chemtech* **1987**, *17*, 570−575.

(24) Cornils, B.; Wiebus, E. *Chemtech* **1995**, *25*, 33−38.

(25) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524−1544.

(26) Kalck, P.; Monteil, F. *Adv. Organomet. Chem.* **1992**, *34*, 219−284.

(27) Ganesan, S.; Lloyd, P. B.; Gilleskie, G. L.; Lim, P. K. *Chem. Eng. Sci.* **1989**, *44*, 171−177.

the organic or aqueous phase. In contrast, the catalyst recovery scheme based on the use of a water-soluble ligand is adversely affected if any of the reaction products is appreciably soluble in the aqueous phase.

Additionally, the biphasic technique based on the use of a surface-active catalyst complex may also offer other advantages, including a lower mass-transfer resistance on account of a shorter diffusion pathway, a higher reaction rate due to the segregating and intimate-contacting effects of the interface on the reacting species, and the possibility of a stereoselectivity control through the orientation−alignment effect of the interface on the reacting species and the influence of chiral emulsifier and solvent. It follows from the foregoing considerations that the O−W interfacial technique may be viewed as a logical extension and refinement of the biphasic technique based on the use of water-soluble ligands.

VI. Conclusion

The carbonylation of α-methylbenzyl bromide has been effected interfacially in an organic−aqueous sodium hydroxide mixture with the use of surface-active palladium−(4-dimethylaminophenyl)diphenylphosphine complex as the catalyst and dodecyl sodium sulfate as the emulsifier. The yield of the desired product—2-phenylpropionate in acid and ester forms—varied from 0 to 83%, depending on the reaction conditions. Side products have been identified to be α-methylbenzyl alcohol, 2,3-diphenylbutane, di(α-methylbenzyl)ether, and a second, asymmetric ether that was formed between the substrate and an alcoholic medium. A high 2-phenylpropionate yield was associated with the use of a high-molecular-weight alcohol (2-methyl-1-butanol or 2-ethyl-1-hexanol) as the organic phase, a high carbon monoxide pressure, an intermediate catalyst concentration (∼0.0039 M), an intermediate reaction temperature (∼45 °C), an intermediate sodium hyroxide concentration (5 M) in the aqueous phase, and an optimal organic−water phase ratio of 2:1. With 2-ethyl-1-hexanol as the organic phase, the carbonylation of α-methylbenzyl bromide showed a first-order dependence each on the substrate, catalyst, and ligand concentrations up to the catalyst concentration of 0.0020 M and a ligand: catalyst ratio of 3:1 and a variable-order dependence on the carbon monoxide pressure that switched from first to zeroth order as the carbon monoxide pressure was increased above 450 mmHg. A reaction mechanism is proposed which yields model rate and yield expressions in accord with the experimental findings.

Results of control experiments with α,α-dibromotoluene in a toluene−aqueous sodium hydroxide mixture indicate that replacement of the α-methyl group in α-methylbenzyl bromide by a second bromo group suppressed the formation of substituted benzyl alcohol and coupled product. They suggest that the broad product distribution in the carbonylation of α-methylbenzyl bromide relative to the carbonylation of benzyl chloride and α,α-dibromotoluene is attributable to the electron-releasing α-methyl group making the substrate susceptible to hydrolysis and coupling reactions.

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