Palladium Chloride Catalyzed Dicarbonylation of Terminal Alkynes

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Received January 3, 1991

Terminal alkynes react with formic acid and/or water in a catalytic system using $PdCl_2$ and $CuCl_2$ to give monosubstituted maleic anhydrides and the corresponding maleic and fumaric acids. The catalysis takes place at room temperature and requires gentle bubbling of carbon monoxide and oxygen through the reaction medium. Among the solvents tested, THF is the most suitable one; the total yields of the carbonylated products range from 30 to 75%. Phosphines and phosphites completely inhibit the reaction.

Introduction

The origins of transition-metal-catalyzed carbonylation of alkynes date back to the investigations of Reppe and Roelen in the late 1930s and the early 1940s.[1] The reports of these pioneering studies stimulated considerable research activity in this area between 1950 and 1965, producing a large number of patents and leading to some commercial processes. Of the latter, the most important has been the large scale production of acrylic acids and esters, which are used as precursors to high molecular weight polymers.

Pino and Braca[2] have reviewed the early stages in the development of this field and have concluded that alkyne carbonylation is an inherently complex reaction which gives different products depending on such factors as the type of metal catalyst, the solvent, temperature and pressure, presence of hydrogen sources such as H_2 and H_2O, type of acid or other promoters, and the pH of the reaction medium. Possible products include ketones, aldehydes, esters, acids, lactones, hydroquinones, and oligomers of both the starting alkyne and the products.

The most widely used catalysts for alkyne carbonylation are the carbonyl complexes of groups 8-10 metals, of which $Ni(CO)_4$ and $Co_2(CO)_8$, or their precursors, have been the most important catalysts and the only ones used industrially. In general, these systems require high temperatures (100-200 °C) and pressures (30-200 atm); milder conditions (25-100 °C, 1-10 atm) usually lead to stoichiometric reactions. Among other transition metals, palladium has shown the highest and most interesting reactivity toward alkyne carbonylation. The first use of Pd catalysts was reported in a German patent issued in 1962[3] and was soon followed by many other publications.[4-10] The main difference in the reactivities of Pd, Ni, and Co is that Pd-catalyzed carbonylation of alkynes usually leads to dicarbonylation, while Ni- and Co-catalyzed processes give mainly monocarbonylated products. A common feature of most Pd-catalyzed systems is that metallic palladium separates during the reaction and only by using such oxidants as $CuCl_2/O_2$ or thiourea/air[5] can these reactions proceed catalytically.[2]

One of us has previously reported the use of $PdCl_2$ in catalytic alkene hydrocarboxylation with water,[11] alkene hydrocarboalkoxylation with alcohols[12] and formate esters,[13] and alkyne dicarboalkoxylation in alcohols.[14] Having found that the combination of $PdCl_2/CuCl_2/CO/O_2/HCl$ catalyzes these and other related reactions[15,16] under very mild conditions, we sought to extend our studies to the carbonylation of alkynes with water, formic acid, and formate esters. This paper presents the results of the $PdCl_2$-catalyzed dicarbonylation of terminal alkynes with formic acid and water.

Experimental Section

General Comments. The solvents were distilled from appropriate drying agents under N_2. The alkynes (Farchan) were dried and distilled before use; acetone-d_6 (MSD) and HCOOH (Aldrich) were used as supplied. $PdCl_2$ and $CuCl_2$ were purchased from commercial sources and were used as received. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200-MHz spectrometer. The chemical shifts were measured in ppm relative to the resonances of the residual protons (for ^1H) and the carbonyl carbon (for ^{13}C) of acetone-d_6, both of which are internally calibrated against tetramethylsilane. IR spectra were recorded on a Perkin-Elmer 783 spectrometer. GC/MS analyses were performed on a VG 7070E mass analyzer.

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General Procedure for Catalytic Reactions. The reactions were carried out in a two-neck flask containing the solvent (5–10 mL), PdCl₂ (0.15 mmol), CuCl₂ (0.15–0.30 mmol), the alkyne (1.5 mmol), and 90% HCOOH or water (2.3–3.0 mmol). The CO/O₂ gas mixture (3:1, 9 mL/min) was bubbled through the reaction mixture via a gas inlet adaptor extending down below the surface of the solvent. The reaction mixture was stirred for 3–8 h at room temperature and was worked up by evaporating the solvent and extracting the residual material with diethyl ether/water; the ethereal layer was then dried over MgSO₄, and the solvent was removed.

Product Analysis. Quantitative analysis was carried out by ¹H NMR spectroscopy (acetone-d₆) with maleic acid as an internal standard. Integration of the vinylic proton resonances of the carbonylated products (ca. 6.95 ppm for the monosubstituted maleic anhydrides 1, 6.75 ppm for the corresponding fumaric acids 3, and 5.95 ppm for the corresponding maleic acids 2) against that of the standard (ca. 6.40 ppm) gave both the total yields and the product ratios. The products were then isolated by standard basification/neutralization extractions and/or column chromatography (silica gel, 1:2 methylene chloride/hexane followed by 1:1 ethyl acetate/hexane) and characterized on the basis of IR, ¹H and ¹³C NMR, and GC/MS spectra.

Control Experiment for the Hydrolysis of the Maleic Anhydride Derivative with HCOOH. The substituted maleic anhydride isolated from the carbonylation of 1-octyne (1, R = –(CH₂)₅CH₃) was used in place of the terminal alkyne under catalytic reaction conditions: THF (5 mL), PdCl₂ (0.12 mmol), CuCl₂ (0.24 mmol), 90% HCOOH (5.40 mmol), and 1 (0.71 mmol). A 3:1 mixture of CO/O₂ was bubbled through the stirring reaction mixture for 6 h. The solvent was then evaporated, and the residual material was analyzed by ¹H NMR spectroscopy (acetone-d₆), which indicated the presence of a 97:3 mixture of the starting anhydride (1) and the corresponding maleic acid (2), respectively; no trace of the corresponding fumaric acid (3) was detected (Table VI). Thus, under typical reaction conditions and in the presence of excess formic acid, only 3% of the maleic anhydride derivative may be hydrolyzed to the corresponding maleic acid.

Control Experiment for the Hydrolysis of the Maleic Anhydride Derivative with Water. The above experiment was repeated with water instead of 90% HCOOH: THF (5 mL), PdCl₂ (0.12 mmol), CuCl₂ (0.23 mmol), H₂O (3.0 mmol), and 1 (0.62 mmol). Analogous workup and analysis revealed an 89:11 mixture of 1 and 2; no 3 was detected (Table VI). Thus, under typical reaction conditions and in the presence of excess water, as much as 11% of the maleic anhydride derivative may be hydrolyzed to the corresponding maleic acid.

Control Experiment for the Dehydration of the Maleic Acid Derivative. The substituted maleic acid isolated from the carbonylation of 1-octyne (2, R = –(CH₂)₅CH₃) was used in the following reaction: THF (5 mL), PdCl₂ (0.19 mmol), CuCl₂ (0.19 mmol), 90% HCOOH (0.94 mmol), and 2 (0.50 mmol). A 3:1 mixture of CO/O₂ was bubbled through the stirring reaction mixture for 6 h. The solvent was then evaporated, and the residual material was analyzed by ¹H NMR spectroscopy (acetone-d₆), which indicated the presence of an 89:11 mixture of the starting maleic acid (2) and the corresponding anhydride (1), respectively; no fumaric acid derivative (3) was detected (Table VI). Thus, under typical reaction conditions with formic acid, up to 11% of the maleic acid derivative formed during the carbonylation reaction may dehydrate to the corresponding anhydride.

Attempted Carbonylation of *trans*-2-Octenoic Acid. PdCl₂ (42 mg, 0.24 mmol) and CuCl₂ (62 mg, 0.46 mmol) were stirred in THF (20 mL), and a 3:1 mixture of CO/O₂ was bubbled through the mixture. After 10 min, *trans*-2-octenoic acid (302 mg, 2.13 mmol) and 90% HCOOH (174 mg, 3.77 mmol) were added, and the stirring was continued for 6 h. Workup as usual gave a pale yellow liquid (298 mg) whose ¹H NMR spectrum was that of the starting acid. Therefore, *trans*-2-octenoic acid does not carbonylate to give maleic or fumaric derivatives under the reaction conditions for catalytic dicarbonylation of alkynes.

Synthesis and IR Spectrum of the Yellow Complex. Bubbling CO through a stirred suspension of PdCl₂ (29 mg, 0.16 mmol) and CuCl₂ (50 mg, 0.37 mmol) in THF (15 mL) for 4 h produced a sparingly soluble, yellow solid. The reaction mixture was filtered under CO by using standard Schlenk techniques, and

Table I. Pd-Catalyzed Dicarbonylation of H–CC–R with HCOOH or H₂O[a]

			product distribution,[b] %		
run	R	yield,[b] %	1	2	3
1	Ph	75 (68)	100	0	0
2	t-Bu	49	95	5	0
3	CH(Me)Et	66	66	26	8
4	(CH₂)₂Ph	53	75	0	25
5	(CH₂)₃Ph	65	69	0	31
6	(CH₂)₃Cl	59	70	5	25
7	(CH₂)₃CN	30	62	11	27
8	(CH₂)₃CH₃	54	65	5	30
9	(CH₂)₅CH₃	68 (59)	60	5	35

[a] In a typical experiment the following reagents were used with the indicated stoichiometries: PdCl₂ (0.15 mmol), CuCl₂ (0.15–0.30 mmol), H—C≡C—R (1.50 mmol), and 90% HCOOH (2.30–3.00 mmol). The reactions were carried out in THF (5–10 mL) for 3–8 h at room temperature; a CO/O₂ (9 mL/min:3 mL/min) gas mixture was bubbled through the reaction mixture. [b] The reaction mixture was worked up by evaporating the solvent, extracting the residual material with Et₂O/H₂O, drying the ethereal layer over MgSO₄, and removing the solvent. The yields are based on the starting alkyne used and were determined from the ¹H NMR spectra (acetone-d₆) of the worked-up reaction mixtures, using maleic acid as the standard. Integration of the vinylic proton signals of the carbonylated products (ca. 6.95 ppm for 1, 6.75 ppm for 3, and 5.95 ppm for 2) against that of the standard (ca. 6.40 ppm) gives the total yield and the product ratios. Isolated yields were obtained in two cases and are reported in parentheses.

the yellow solid thus isolated was stored under CO. The IR (Nujol) spectrum of the solid showed a strong absorption at 1985 cm⁻¹.

Catalytic Activity of the Yellow Complex. Bubbling CO through a stirred suspension of PdCl₂ (33 mg, 0.19 mmol) and CuCl₂ (42 mg, 0.31 mmol) in THF (15 mL) for 3 h produced a slightly soluble, yellow solid. 1-Octyne (206 mg, 1.81 mmol) and water (65 mg, 3.61 mmol) were added to the yellow mixture, and a 10:1 CO/O₂ mixture was bubbled through for 10 h, during which the color of the mixture turned black. Workup as usual gave a pale yellow solid, and ¹H NMR spectroscopy with maleic acid as the internal standard indicated a 51% total yield of the carbonylated products 1–3 in a 39:15:46 ratio. Thus, the yellow complex can act as a catalyst precursor in the dicarbonylation of alkynes.

Results and Discussion

Phenylacetylene reacts with 90% HCOOH, PdCl₂ (10 mol %), CuCl₂ (10–20 mol %), and a mixture of CO/O₂ gases to produce phenylmaleic anhydride in 75% yield; under the same conditions, 3,3-dimethylbutyne affords a 49% combined yield of *tert*-butylmaleic anhydride and *tert*-butylmaleic acid in a 95:5 ratio, respectively. In contrast, 1-octyne gives a mixture of hexylmaleic anhydride and the corresponding maleic and fumaric acids (eq 1).

$$H\text{—}\!\equiv\!\text{—}R + HCOOH/H_2O + PdCl_2/CuCl_2 \xrightarrow[\substack{CO/O_2 \\ 1\ atm}]{THF,\ room\ temp} \quad (1)$$
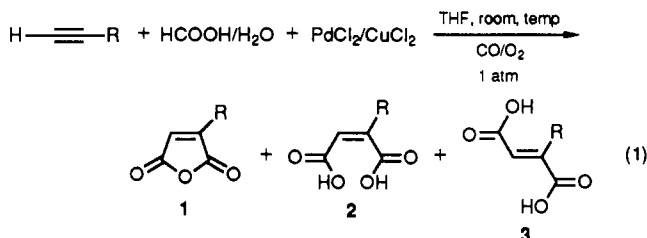
Table I summarizes the results of the reactions of terminal alkynes with 90% formic acid. These results indicate that the proportion of the fumaric derivative 3 is strongly influenced by the steric bulk of the alkyne substituent, with the bulky groups Ph, *t*-Bu, and CH(Me)Et giving little or no 3 (Table I, runs 1-3) and the less bulky groups giving 25–35% (Table I, runs 4-9). With straight-chain alkyl substituents, the (Z):(E) ratio (i.e., the ratio of maleic to fumaric derivatives) is (2–3):1; this is in

Table II. Solvent Effects on Dicarbonylation of Alkynes[a]

PdCl₂	CuCl₂	1-octyne	90% HCOOH	solvent	yield, %	ratio 1:2:3
1	2.0	9.4	19	THF	68	60:5:35
1	2.0	9.7	20	acetone	57	36:37:27
1	2.2	10.1	21	dioxane	44	54:8:38
1	2.0	9.4	19	CH₃CN	42	17:56:27
1	2.0	10.3	22	EtOAc	25	50:9:41
1	2.1	9.9	24	C₆H₆	11	59:24:17
1	2.1	10.1	21	CHCl₃		
1	2.0	10.0	20	CH₂Cl₂		

[a] The reactions were carried out at room temperature for 6 h. See footnote b of Table I and the Experimental Section for details on yield assessments. Taken together, the values given in columns 1–4 represent the molar ratio of the reactants (e.g. 1:2.0:9.4:19 for PdCl₂:CuCl₂:1-octyne:90% HCOOH).

contrast to the 1:4 ratio reported by Heck[6] in the dicarboalkoxylation of 1-heptyne with $PdCl_2/HgCl_2$. The presence of a chloro group away from the triple bond in the starting alkyne seems to have no effect on the reaction (Table I, run 6), whereas a cyano group in the same position reduces the yield (Table I, run 7); this effect might be due to the blocking of a coordination site on the metal center of the catalyst by the pendant CN group. With propynoic acid and its esters (H–CC–COOR; R = H, Me, Bu) intractable materials are obtained in which no carbonylation products could be identified; this result is in agreement with Heck's finding[6] that polar substituents on both alkenes and alkynes cause substantial deactivating effects on Pd-catalyzed carbonylations of these substrates. The reaction does not proceed with the internal alkynes 2-heptyne and 4-methyl-2-pentyne; these results are somewhat surprising in light of the earlier finding[14] that internal alkynes are hydrocarboalkoxylated with $PdCl_2/CuCl_2/HCl/ROH$ to give disubstituted alkyl acrylates.

Solvent Effects. The present catalytic system is quite sensitive to a number of factors including the solvent. As seen from Table II, the suitability of the solvent follows the order THF > acetone > dioxane > CH₃CN > EtOAc > C₆H₆; there is no reaction in CHCl₃ and CH₂Cl₂. No obvious correlation seems to exist between the solvent polarity and its suitability for the reaction. For instance, while CH₃CN is the most polar of the solvents tested, it is not the most suitable one for the reaction; this might be due to the well-known ability of this solvent to compete with substrates for coordination to palladium. The complete inhibition of catalysis in CHCl₃ and CH₂Cl₂ might be due to the low miscibility of HCOOH/H₂O and the low solubility of PdCl₂ and CuCl₂ in these solvents.

Effects of Additives. Alkali-metal halides and I₂ have been used as promoters for Pd-catalyzed alkyne carbonylations.[7,8] In the present system, however, LiCl was found to have no promoting effect, while NaI inhibited the catalysis both in the presence and absence of CuCl₂. Small amounts of I₂ did not influence the reaction, but larger amounts suppressed the dicarbonylation and gave small amounts of an unidentified product.

Bystrom, Larsson, and Akermark[17] have recently reported that addition of PPh₃ to a catalytic system consisting of Pd(OAc)₂, Cu(OAc)₂, hydroquinone, and O₂ inhibits the catalytic acetoxylation of olefins; this effect was attributed to the oxidation of the phosphine by oxygen. We have examined the effects of using the phosphines PPh₃, PCy₃, and Ph₂P–(CH₂)₄–PPh₂ and the phosphites P(OPh)₃ and P(O-i-Pr)₃ in various ratios with respect to PdCl₂, with or without CuCl₂/O₂; the catalysis was com-

pletely inhibited in all cases. Therefore, the carbonylation proceeds best in the absence of any ligand or solvent that can compete with CO and the alkyne for coordination sites on the catalyst.

Turnover Numbers. Table III summarizes the reaction yields and turnover numbers for various Pd:alkyne ratios. It is interesting to note that the yields are similar for stoichiometric (1:1) and catalytic (1:10) ratios, while higher than 1:10 ratios lead to lower percent yields but more or less the same turnover numbers. The main reason for the low turnover numbers is a competing polymerization side reaction, which becomes significant with higher Pd:alkyne ratios. Also, the continuous bubbling of CO and O₂ through the reaction mixture causes some loss of alkyne by evaporation, especially when more volatile alkynes are used. A partial solution to both these problems is to keep the alkyne concentration low by adding it dropwise (Table III, run 2).

Effects of CO/O₂ and the Metals. The gases CO and O₂ are very crucial to the catalysis. Without CO no carbonylation takes place even when sufficient amounts of HCOOH are present (Table IV, run 1); instead, the alkyne undergoes cyclotrimerization and polymerization. Furthermore, it is necessary to bubble the CO *through* the reaction mixture, otherwise lower yields are obtained when the gases are contained in a balloon attached to the reaction flask (Table IV, run 2). A 3:1 ratio of CO/O₂ was used in most reactions, but experiments showed that this ratio is not very important (Table IV, runs 3 and 4). This is perhaps not surprising since these gases are usually in large excess with respect to the other components of the system (e.g., with a 3:1 ratio of CO/O₂, the ratio of Pd: CO:O₂ is roughly 1:(500–1000):(200–300)).

With PdCl₂ alone, without oxygen and CuCl₂, the carbonylation reaction proceeds stoichiometrically (Table IV, run 5), while in the absence of PdCl₂ no carbonylation takes place (Table IV, run 6). These results indicate that, of the two metal salts used, PdCl₂ is undoubtedly the catalyst precursor. In catalytic systems employing some combination of PdCl₂ and CuCl₂/O₂, the latter are generally assumed to act as Wacker-type regenerators (oxidants) of the "deactivated" palladium catalyst:

$$Pd^0 + 2CuCl_2 \rightarrow Pd^{II} + Cu_2Cl_2 \qquad (2)$$

$$Cu_2Cl_2 + \frac{1}{2}O_2 + 2HCl \rightarrow 2CuCl_2 + H_2O \qquad (3)$$
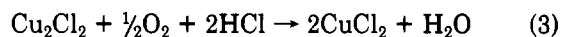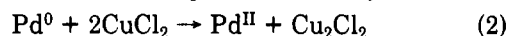
According to the above reactions, CuCl₂ is the main oxidant for regenerating Pd⁰; HCl and oxygen are needed to replenish CuCl₂ but can be replaced by excess CuCl₂. Interestingly, however, HCl has detrimental effects on our system, while oxygen is much more necessary for the catalysis than is CuCl₂. For instance, the relative amount of CuCl₂ present in the reaction does not seem to be a crucial factor (Table IV, runs 7–9), and even in the complete absence of CuCl₂ at least 4 catalytic turnovers are observed (Table IV, run 10). In contrast, excluding just oxygen from the system completely inhibits the catalysis even when excess CuCl₂ is used (Table IV, run 11), while introducing oxygen into the system initiates the catalysis.

These results have important implications for the mechanism of catalyst regeneration in this system, and perhaps in many other Pd(II)/Cu(II)/O₂ (Wacker-type) systems. They seem to suggest that oxygen can oxidize Pd⁰ to Pd^{II} independently of CuCl₂. A search of the literature has revealed a number of other reports[18–20] sup-

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Table III. Effect of the Pd:Alkyne Ratio on Dicarbonylation of Alkynes[a]

run	PdCl₂	CuCl₂	alkyne	90% HCOOH	time, h	yield, %	ratio 1:2:3	turnover no.
1	1	1.1	1-octyne, 1.0	2.5	1	75	58:11:31	
2	1	1.1	1-octyne, 9.4	19	6	77[b]	60:3:37	7.2
3	1	2.0	1-octyne, 40	72	10	17	40:20:40	6.8
4	1	2.0	H–CC–Ph, 20	40	14	50	100:0:0	10.0
5	1	9.9	H–CC–Ph, 22	45	14	40	100:0:0	8.8
6	1	1.2	H–CC–(CH₂)₃Cl, 48	82	11	15	43:25:32	7.2

[a] See footnote b of Table I and the Experimental Section for Details on yield assessments. Taken together, the values given in columns 2–5 represent the molar ratio of the reactants, (e.g. 1:1.1:1.0:2.5 for PdCl₂:CuCl₂:1-octyne:90% HCOOH (run 1)). [b] 1-Octyne and HCOOH were added dropwise over a 3-h period.

Table IV. Effects of Gases and Metal Ratios on Dicarbonylation of Alkynes[a]

run	PdCl₂	CuCl₂	1-octyne	HCOOH or H₂O	CO/O₂	yield, %	ratio 1:2:3
1	1	2.0	9.9	HCOOH, 26	O₂ only	b	
2	1	2.1	9.7	HCOOH, 21	3:1[c]	45	62:9:29
3	1	1.7	9.7	H₂O, 19	10:1	51	39:14:47
4	1	2.0	8.1	H₂O, 17	1:6	53	20:43:37
5	1		11.0	H₂O, 29	CO only	6	35:30:35
6		1.0	10.0	HCOOH, 20	3:1		
7	1	0.56	11.0	HCOOH, 23	3:1	68	57:5:38
8	1	2.5	10.3	HCOOH, 23	3:1	68	57:5:38
9	1	5.5	10.5	HCOOH, 22	3:1	66	54:5:41
10	1		9.8	H₂O, 21	3:1	43	26:21:53
11	1	16	14.0[d]	HCOOH, 33	CO only	2	100:0:0

[a] See footnote b of Table I and the Experimental Section for details on yield assessments. Taken together, the values given in columns 2–5 represent the molar ratio of the reactants (e.g. 1:2.0:9.9:26 for PdCl₂:CuCl₂:1-octyne:HCOOH (run 1)). [b] Polymers formed. [c] The gases were contained in a balloon attached to the reaction flask. [d] Ph—C≡C-H was used.

porting this possibility. The most widely accepted view is that the insertion of O₂ into the Pd–H bond of an intermediate species forms a palladium hydroperoxo complex which, in turn, gives Pd(II) and water (vide infra).

If, indeed, oxygen is the true oxidant in this system, then CuCl₂, which is certainly beneficial for the overall catalytic process, must have a different function. One distinct possibility is that CuCl₂ may be involved in the formation of a heterometallic (Pd/Cu) species which participates in the catalysis in some capacity. This possibility has been raised earlier by Fenton and Steinwand[21] who proposed a Pd/Cu complex as the main catalytic species in the carbonylation of alcohols to oxalates. Hosokawa, Murahashi, and co-workers[18a] have also argued that a Pd–Cu intermediate is involved in the oxidative cyclization of 2-allylphenols catalyzed by Pd(OAc)₂/Cu(OAc)₂/O₂. Furthermore, we have observed that the interaction of PdCl₂, CuCl₂, and CO in the absence of alkyne and HCO-OH leads to a yellow solid which can serve as a catalyst precursor with catalytic activity comparable to that of PdCl₂/CuCl₂. That this compound contains CO ligand(s) is apparent from a single, strong absorption at 1985 cm⁻¹ in the IR (Nujol) spectrum of this solid and the fact that it does not form in the absence of CO. The full characterization of this material, however, has thus far eluded us because it is quite insoluble in most solvents, very unstable in the absence of CO, and does not form crystals. The following tentative structures are postulated as possible candidates for this species:
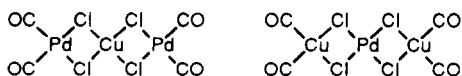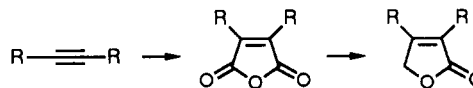
Anhydride Formation.
An interesting feature of the present catalytic system is its tendency to give substituted maleic anhydrides as the major reaction products. Most

previous studies of alkyne carbonylation have resulted in the formation of the corresponding maleic and fumaric acids (with water as nucleophile) and esters (with alcohols as nucleophiles), in addition to other monocarbonylated products. To our knowledge, the only other reports of alkyne dicarbonylation to anhyrides are Heck's[6] stoichiometric reaction using PdCl₂/HgCl₂/Ph–CC–H/H₂O/acetone, and the catalytic synthesis of dimethylenesuccinic anhydrides by Tsuji[4e] and Kiji:[8]
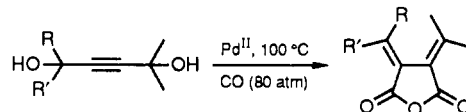
In addition, there have been reports of Pd-[9] and Rh-catalyzed[10] carbonylation of alkynes to furan-2(5H)-ones, which are believed to arise from the in situ reduction of the corresponding maleic anhydrides:

The use of HCOOH in our system seemed at first to be the most probable cause for the preferential formation of anhydrides. We set out to examine this possibility by attempting to ascertain the specific roles of water and HCOOH in the catalytic system. When HCOOH was replaced by water in an otherwise standard reaction, a 53% total yield was obtained with a 1:2:3 ratio of 44:19:37 (Table V, run 1). Therefore, water is a sufficiently good nucleophile for bringing about anhydride formation, even though HCOOH gives somewhat higher total yields and proportions of anhydride. Indeed, even when no water or HCO-OH was added to the reaction mixture ("blank" reaction), a significant yield was obtained (Table V, run 2). This result indicated that the reaction medium contained relatively large amounts of water, perhaps as the residual moisture in the solvent, the gases, or the reagents used. To our surprise, however, no matter how rigorously the

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Table V. Effect of Water, Acids, and Bases on the Dicarbonylation of Alkynes[a]

run	PdCl$_2$	CuCl$_2$	1-octyne	reagents	time, h	yield, %	ratio 1:2:3
1	1	2.5	9.3	H$_2$O, 18.5	5	53	44:19:37
2	1	1.2	10.0		4	41	54:12:34
3	1	1.0	10.8	4A molecular sieves	10	6	80:0:20
4	1	1.2	9.6	MgSO$_4$	5	12	71:0:29
5	1	1.9	21.9	90% HCOOH, 49; 4A molecular sieves	5	5	24:54:22
6	1	1.1	9.5	90% HCOOH, 25; MgSO$_4$	3	56	54:5:41
7	1	2.0	10.1	98–100% HCOOH (pK_a = 3.75), 20	7	57	62:10:28
8	1	2.1	9.9	oxalic acid (pK_a = 1.27), 20	15	68	36:25:39
9	1	2.1	10.5	malonic acid (pK_a = 2.85), 20	11	56	26:48:26
10	1	1.9	9.9	acetic acid (pK_a = 4.74), 21	11	48	37:37:26
11	1	1.9	9.7	boric acid (pK_a = 9.24), 19	12	61	31:39:30
12	1	2.1	9.4	concentrated HCl (pK_a = -2.2), 40	10	14[b]	30:20:50
13	1	2.1	10.9	H$_2$O, 18; EtN(i-Pr)$_2$, 6.6	5		

[a] The reactions were run as described in footnote a of Table I and the Experimental Section, using the reagents specified above. Taken together, the values given in columns 2–5 represent the molar ratio of reactants (e.g. 1:2.5:9.3:18.5 for PdCl$_2$:CuCl$_2$:1-octyne:H$_2$O (run 1)). [b] Other unidentified products were also observed.

solvent and the reagents were dried and/or distilled prior to their use, and in spite of scrubbing the gases, the blank reactions (i.e., the reaction with no added water or HCOOH) repeatedly resulted in about 40% yields. Only when 4A moleculr sieves were present in the reaction medium *during the entire course of the reaction* was it possible to almost completely suppress the carbonylation reaction (Table V, run 3). MgSO$_4$ had a similar effect (Table V, run 4), although it did not suppress the reaction to the same extent probably because it is less effective as a dessicant. Therefore, it seems that water is generated in situ during the reaction and that the use of oxygen is responsible for this in some manner. As noted above, the formation of water from oxygen has been invoked by others[18-20] and might result from hydroperoxo complexes formed by the insertion of O$_2$ into a metal hydride bond.[22]

Having found that water can also result in anhydride formation, it was then necessary to understand why HCOOH gives higher total yields and anhydride proportions. In other words, is HCOOH a more effective nucleophile than water, or does it act merely as a promoter for the reaction of water? In order to determine whether HCOOH plays a direct role in the carbonylation reaction, it was necessary to carry out an experiment with only HCOOH, taking measures to ensure that any in situ generated water would be removed. Thus, a standard HCOOH reaction was run in the presence of 4A molecular sieves. This reaction gave almost no carbonylation (Table V, run 5), leading us to conclude that water, not HCOOH, is the true nucleophile in the carbonylation reaction. This conclusion, however, was not supported by the outcome of an analogous HCOOH reaction with MgSO$_4$, which gave a 56% yield (Table V, run 6). The large difference in the yields of these two reactions is difficult to explain. On the one hand, the high yield of the MgSO$_4$ reaction might be due not to the reaction of HCOOH, but rather to the relatively lower effectiveness of MgSO$_4$ in removing water from the reaction medium. On the other hand, it is possible that 4A molecular sieves inhibit the reaction more effectively because they trap *both* water and HCOOH, while MgSO$_4$ traps only water, allowing HCOOH to react and the reaction to proceed almost unhindered.

If HCOOH does not act as a nucleophile, its role might be to provide H$^+$ ions, which could be conducive to the catalysis; in that case, there should be acids other than HCOOH with similar effects on the reaction. As seen from the results of Table V (runs 7–12), oxalic, boric, acetic, and

Table VI. Hydrolysis and Dehydration Control Experiments

entry	starting material	products 1:2:3
1	1/HCOOH	97:3:0
2	1/H$_2$O	89:11:0
3	2/HCOOH	11:89:0

malonic acids lead to reaction yields which are comparable to that of HCOOH and higher than the yield of the blank reaction (i.e., the reaction with no added water or HCOOH); HCl leads to much lower yields and other products. Therefore, acidic conditions are indeed favorable for the catalysis, while bases completely inhibit the reaction (Table V, run 13). There is, however, no correlation between the pK_a values of the acids used and their effects on either the yield or the anhydride proportion. This is in accord with the results of Whiting et al.[23] who found that the Ni(CO)$_4$-promoted synthesis of acrylic acid from alkynes was independent of the pK_a of the acids used.

To sum up, the presence of HCOOH is beneficial for the catalysis in terms of both yields and anhydride proportion. Our results, however, do not clarify the precise reason(s) for these effects, and the role of HCOOH in the catalysis remains unknown.

Carbonylation Mechanism. Although the maleic anhydride derivative 1 is the major product in all standard catalytic reactions, the proportions of the three products can vary significantly (Table I). As mentioned earlier, the proportion of the fumaric acid derivative 3 is affected by the steric bulk of the alkyne substituent. The possible implications of this steric factor for the mechanism of alkyne insertion will be discussed later (vide infra). In addition, for a given alkyne, more of the maleic acid derivative 2 forms when larger amounts of water are present in the reaction medium. This can be seen from the plot of the relative amounts of water present in the reaction mixture versus the product distribution (Figure 1). This plot also shows that the increase in the proportion of 2 comes almost completely at the expense of the corresponding anhydride derivative 1. The simplest explanation for this observation would be a post facto hydrolysis of the preformed anhydride (eq 4).

$$\text{H}\text{---}\equiv\text{---}\text{R} \xrightarrow{\text{CO}} \mathbf{1} \xrightarrow{\text{H}_2\text{O}} \mathbf{2} \quad (4)$$
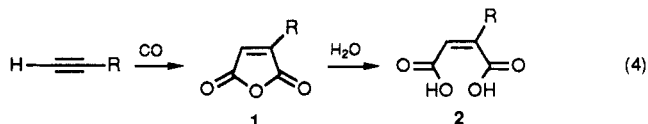
(22) (a) Johnston, L. E.; Page, J. A. *Can. J. Chem.* **1969**, *47*, 4241. (b) Robert, H. L.; Symes, W. R. *J. Chem. Soc. A* **1968**, 1450.

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Scheme I
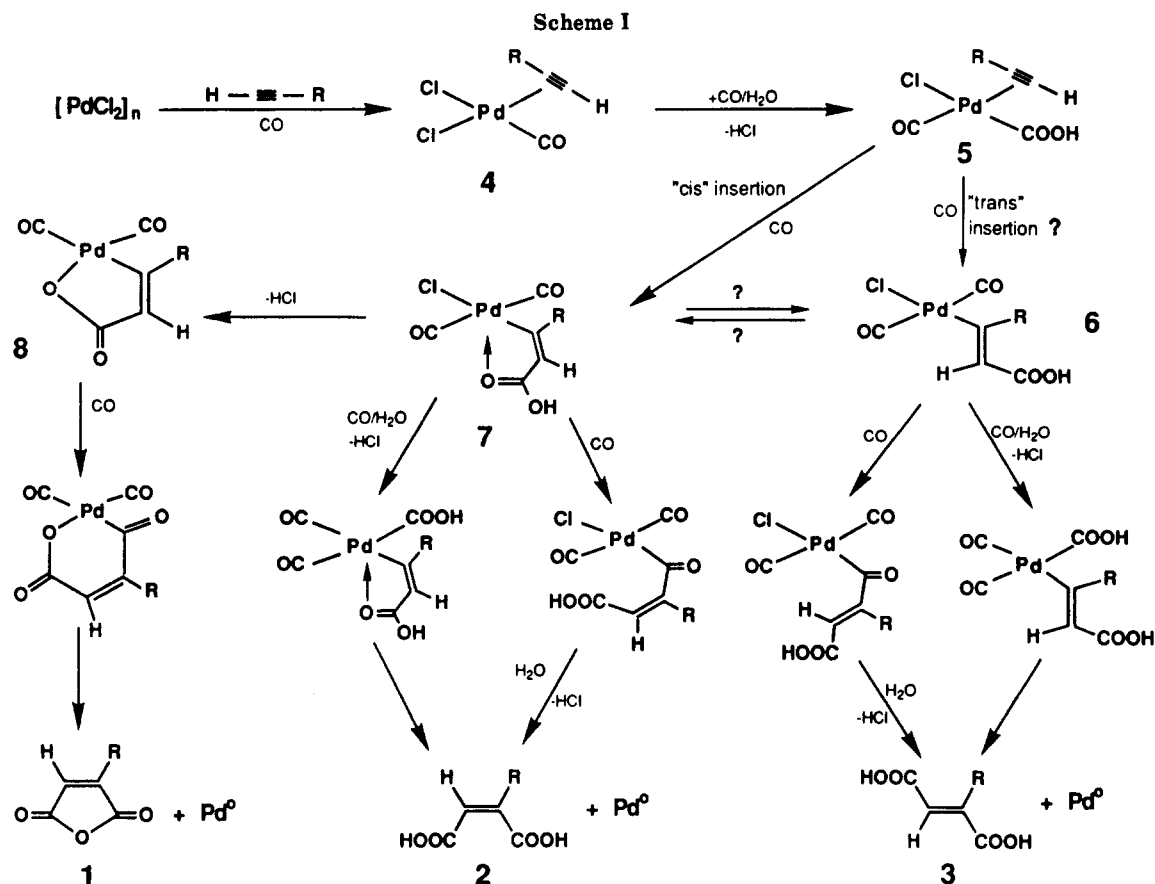
This reasoning, however, is not supported by the following experimental results. When pure anhydride 1 was stirred for 6 h under the conditions of the catalytic runs, a 97:3 mixture of the starting anhydride and the corresponding maleic acid 2, respectively, was recovered (Table VI, entry 1). Even when this experiment was repeated in the presence of excess water, an 89:11 mixture of 1:2 was obtained (Table VI, entry 2). Therefore, once the anhydride 1 is produced in the reaction, it does not hydrolyze significantly to the corresponding diacid 2. Conversely, once the diacid 2 is formed, it does not dehydrate appreciably to the corresponding anhydride 1 or isomerize to give the fumaric acid derivative 3 (Table VI, entry 3).

These results indicate that, under the conditions of the catalytic reactions, 1 and 2 do not interconvert significantly or isomerize to give 3. Therefore, we can conclude that, to a large extent, these three reaction products originate from three distinct, but interdependent, reaction pathways whose relative contributions to the overall reaction are, to a good approximation, reflected in the product ratios. This conclusion forms the basis of our proposed mechanism for the dicarbonylation of terminal alkynes (Scheme I).

The mechanism shown in Scheme I is, in principle, very similar to that proposed by Heck[6] for the dicarboalkoxylation of alkynes. Thus, coordination of CO and the alkyne to PdCl₂ can form complex 4. Nucleophilic attack of water on the coordinated CO would give, after loss of HCl and the incorporation of another CO, the hydroxycarbonyl species 5. The next step is the insertion of the coordinated alkyne into the metal–carboxyl bond, giving either 6 ("trans" insertion) or 7 ("cis" insertion); the stereochemistry of this insertion step will be discussed in the next section. Complex 6 undergoes another nucleophilic attack by water and loss of HCl to give a vinyl carboxyl complex, which then reductively eliminates the fumaric acid derivative 3 and Pd⁰. Alternatively, 6 can
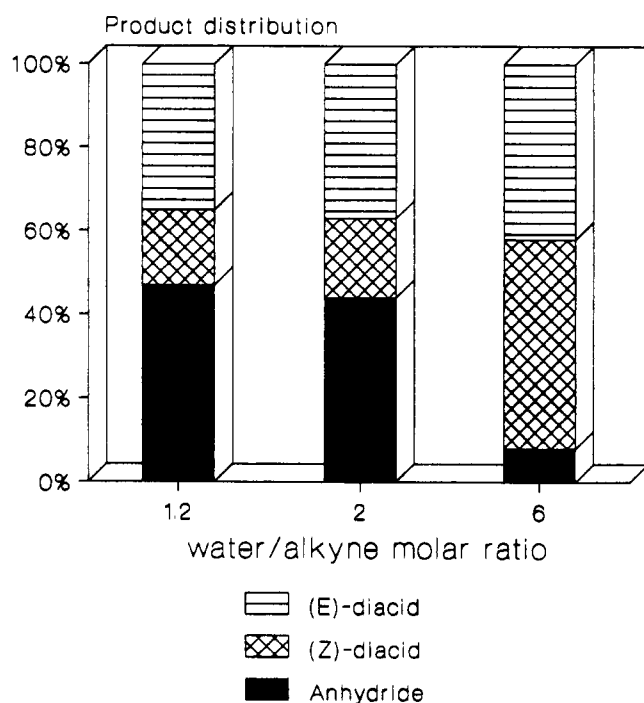

Figure 1. Relationship between the water:alkyne molar ratio and the product distribution.

undergo "migratory insertion" of CO into the metal–vinyl bond first, followed by the nucleophilic attack of water to give 3.

The vinyl complex 7 can undergo nucleophilic attack, loss of HCl, and reductive elimination to give the maleic acid derivative 2; alternatively, migratory insertion, followed by nucleophilic attack and reductive elimination, would lead to the same product. Another possibility for

7 is the oxidative addition of the carboxyl O–H bond to give 8 after losing HCl. (Of course, 8 can also form as a result of the protonation of the metal center in 7 by the carboxyl proton, loss of HCl, and the coordination of the carboxylate anion.) The palladium-containing lactone, 8, is believed to be the main precursor to the maleic anhydride derivatives 1. Nickel- and palladium-containing lactones similar to 8 have been synthesized and characterized by Yamamoto and co-workers,[24] who also showed that these complexes undergo carbonylation to give the corresponding cyclic anhydrides (eq 5). Therefore, it is reasonable to assume that 8 undergoes carbonylation and reductive elimination to give 1.

$$\text{(5)}$$

$$M = Ni, Pd$$
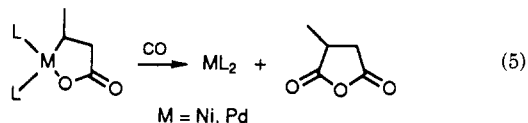
According to the overall reaction mechanism, the products 1 and 2 both originate from the species 7, and while 1 equiv of water is required for the formation of 2 from 7, no water is required for the formation of 1. Therefore, it is not surprising that the presence of excess water in the reaction medium changes the ratio of 1:2 in favor of 2, without seriously affecting the proportion of 3 in the product distribution (Figure 1).

The above mechanism does not involve the formation of monocarbonylated products (enoic acids) as intermediates to the dicarbonylated products. This is based on the observation that *trans*-2-octenoic acid is not carbonylated under the catalytic reaction conditions:
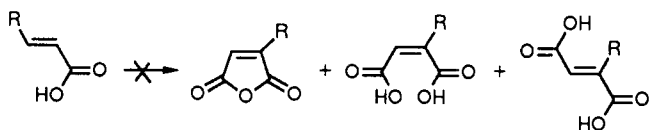
Finally, the reduced palladium must be oxidized in order for the catalysis to proceed. As discussed earlier, our experimental results are consistent with a process in which oxygen is the main oxidant. One such process, involving a hydroperoxo complex, has been described by others.[18-20] A slightly revised version of this process can be represented by the sequence of steps

$$Pd^0 + HCl \rightleftharpoons$$
$$Cl\text{-}Pd\text{-}H \xrightarrow{O_2} Cl\text{-}Pd\text{-}OOH \xrightarrow{HCl} PdCl_2 + HOOH$$
$$HOOH \rightarrow H_2O + 0.5O_2$$
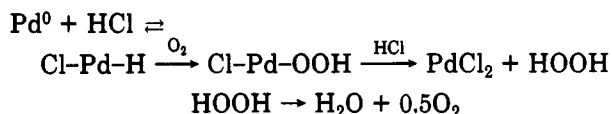
The source of HCl molecules is the nucleophilic attack of water on the coordinated carbonyl ligands, followed by loss of HCl (Scheme I).

Insertion Mechanism. The mechanism depicted in Scheme I accounts for the formation of the fumaric derivative 3 by invoking an overall trans insertion of the alkyne into the carboxyl ligand to form the vinyl complex 6. Strictly speaking, such a trans insertion is not the only possible route for the formation of 3; in some cases, the product which appears to be the result of a trans insertion is in fact obtained from the (Z)–(E) isomerization of the cis insertion product. One relevant example is the HCo-(CO)₄-catalyzed hydrogenation of dimethyl acetylenedicarboxylate, where it was shown[25] that the major product, dimethyl fumarate, results not from a trans insertion but

from a (Z)–(E) isomerization of the cis insertion product, dimethyl maleate. More recently, palladium has also been shown[26] to affect such (Z)–(E) isomerizations with mixtures of styrenes. Therefore, it is possible that the cis insertion products are the *kinetic* products of the reaction, while the *formal* trans insertion products are the *thermodynamic* products.

In our system, however, it has been observed that, once formed, the cis addition products 1 and 2 do not isomerize to 3 under the reaction conditions (Table VI); hence, these types of (Z)–(E) isomerizations cannot explain the formation of 3. This raises the possibility that a trans insertion is the source of 3; an important question here is how such trans insertions might take place.

A review of the literature on the insertion of alkynes into transition-metal–hydride and –alkyl bonds reveals an abundance of precedents for the overall trans addition reaction, which occurs either as the exclusive mode of addition or in conjunction with the cis addition.[27-34] In spite of this abundance of examples, however, there are very few detailed mechanistic studies and little is known about the mechanism of trans insertions. Some workers have favored a concerted cis insertion of the alkyne into the metal hydride or alkyl bond in the initial stage, followed by a cis-trans isomerization of the thus formed vinyl ligand. For instance, Stone et al.[30c] and Schwartz et al.[31] proposed a so-called dipolar mechanism of the cis-trans isomerization of the vinyl ligand formed initially by a cis insertion:
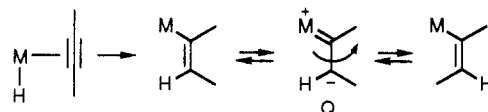
The species Q can be thought of as a metastable intermediate or simply as an extreme case of resonance delocalization. The main thrust of this mechanism is the notion that the vinyl C=C bond weakens enought to allow a rotation which results in the trans insertion product. A similar version of this mechanism has been proposed by Bergman[28a] for the insertion of alkynes into metal–alkyl bonds.

Although the above mechanism has proved useful in explaining the insertion stereochemistry in some cases, it has not received universal acceptance. Clark et al.,[33] for instance, have proposed radical mechanisms for some insertion reactions. In contrast, Otsuka et al.[34] have argued that most transition-metal reaction mechanisms can not be adequately described in purely ionic, radical, or concerted terms and most likely involve some combination of all of these concepts. They have put forth[34b] a concerted, kinetically and stereoelectronically controlled insertion

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mechanism with a four-centered, bimolecular transition state that may be partially ionic or radical in character, depending on subtle stereoelectronic effects.

At this stage, we cannot favor any one of the above mentioned mechanisms for the trans insertion reaction that is believed to be the source of product **3** in our system. Our results can be explained by both the four-centred concerted mechanism put forth by Otsuka et al. and by the following cis–trans isomerization postulate:
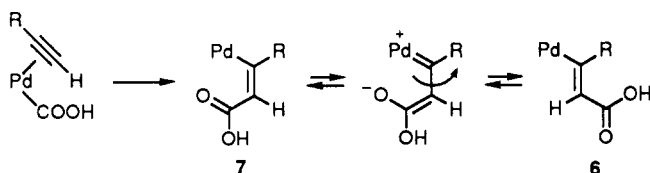
The equilbrium distribution of **6** and **7** would presumably be determined by a number of factors, including the steric interactions between the R and acid groups. Thus, less of the trans insertion product **6**, and hence the fumaric

derivative **3**, would be expected with bulky R groups; this is borne out by the results (Table I).

Nucleophile/Electrophile Double Additions to (1-Methoxynaphthalene)tricarbonylchromium(0). Application in a Formal Synthesis of the Aklavinone AB Ring

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The Cr(CO)₃ group complexed selectively to the nonsubstituted ring of 1-methoxynaphthalene to give (1-methoxynaphthalene)Cr(CO)₃ (**5**). Nucleophilic addition of a series of sulfur-stabilized carbanions to **5** were studied. In general, this reaction, after oxidation, gave mixtures of all four regioisomeric disubstituted naphthalenes. 2-(Methyldithianyl)lithium (**9**) and [(phenylthio)methyl]lithium (**12**) predominantly added to the β-position of the coordinated ring of **5**. The α positions were slightly favored with the more stabilized carbanions [2-(trimethylsilyl)dithianyl]lithium (**14**) and [tris(methylthio)methyl]lithium (**16**), and, unlike nucleophiles **9**, **12**, and dithianyllithium (**6**), these carbanions rearranged on warming to –10 °C to give good selectivity for addition to C(5). In a synthetic application, **16** was added to complex **5**, followed by alkylation of the anionic benzocyclohexadienyl intermediate with methyl iodide, CO insertion and reductive elimination to give, with 6:1 regioselectivity, the *trans*-1,2-disubstituted-1,2-dihydro-5-methoxynaphthalene **19a**. This reaction introduced in a regio- and stereoselective manner an ester equivalent and an acetyl group to C(5) and C(6) of the 1-methoxynaphthalene complex. Methanolysis of the orthothioformate, double bond isomerization, reduction of the acetyl group, and introduction of the 2-OH group via epoxidation yielded the target aklavinone AB ring intermediate **2**.

Introduction

Recently, a novel trans stereoselective addition of a carbon nucleophile and an acyl group across an arene double bond was developed in these laboratories (eq 1).[1]
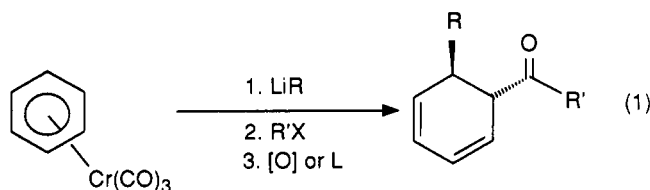
It involves the activation of the arene via complexation to

the electrophilic Cr(CO)₃ group followed by a sequential addition of a carbanion and an alkyl halide to the complex. Nucleophiles add to the complexed arene from the side opposite the metal, and subsequent alkylation takes place at the metal center and is followed by CO insertion and regio- and stereoselective acyl transfer to the endo face of the cyclohexadienyl ligand.

It is well established that substituted arene complexes readily undergo carbanion addition in a highly regioselective manner.[2] The double addition, if successful with these substrates, could lead to useful alicyclic intermedi-

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