Addition of Olefins to Aromatic Ketones Catalyzed by Rh(I) Olefin Complexes

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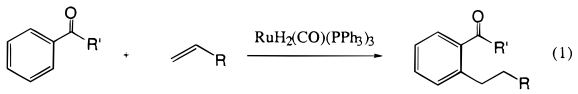
Abstract: The rhodium bis-olefin complex $[C_5Me_5Rh(C_2H_3SiMe_3)_2]$, **1**, has been shown to be a catalyst for the selective addition of olefins to the ortho position of aromatic ketones. The addition of vinyltrimethylsilane to benzophenone was studied by NMR spectroscopy, which indicated that **1** was the catalyst resting state for this process. This reaction was applied to a series of olefins (allyltrimethylsilane, 1-pentene, norbornene, 2,2′-dimethyl-3-butene, cyclopentene, and vinyl ethyl ether) and aromatic ketones (benzophenone, 4,4′-dimethoxybenzophenone, 3,3′-bis(trifluoromethyl)benzophenone, dibenzosuberone, acetophenone, *p*-chloroacetophenone, and *p*-(trifluoromethyl)acetophenone). The dependence of the turnover frequency on substrate concentration was investigated. In the presence of excess ketone the formation of a benzophenone complex, **5**, $[(C_5Me_5Rh)_2$-η^4-η^4-$C_6H_5C(O)Ph]$ was observed after consumption of olefin. Active catalyst is regenerated upon addition of olefin to **5**. On the basis of kinetic experiments and labeling studies using acetophenone-d_8, a mechanism for this catalysis is proposed. In the reaction of acetophenone with vinyltrimethylsilane and **1**, the formation of ethylene and the trimethylsilyl enolate of acetophenone was observed together with the alkyl−aryl coupling product. This side reaction is specific for vinyltrimethylsilane.

Introduction

Transition metal catalyzed carbon−carbon bond formation based on the initial oxidative addition of carbon−halogen or carbon−heteroatom bonds has been developed to a remarkable degree of sophistication and applicability with respect to potential use in organic synthesis. On the other hand, catalytic processes which allow the formation of carbon−carbon bonds based on the oxidative addition of carbon−hydrogen bonds are still rare.[1−3] Reactions of low-valent complexes of iridium, rhodium, and ruthenium traditionally have been used to gain a detailed mechanistic understanding of transition metal mediated carbon−hydrogen bond activation. The application of these results in new catalytic carbon−carbon bond forming reactions has been mainly developed with ruthenium complexes.[4−13] For example, the activation of sp^2-C−H bonds in aromatic or vinylic substrates by ruthenium(0) followed by the insertion of an olefin and reductive elimination to generate a new carbon−carbon bond has been the focus of recent efforts to develop catalytic applications. As a major advance in this area, Murai and coworkers in a series of papers have reported the regioselective addition of olefins to aromatic carbonyl compounds to generate ortho-alkylation products mediated by a ruthenium catalyst[14−22] (eq 1).



(1)

The catalysis is performed at 90−140 °C in aromatic solvents and generally exhibits good turnover numbers. A wide range of aromatic ketones can be used in this process. The presence of the carbonyl moiety diverts the metalation to the ortho position and is believed to result in a chelating interaction that assists the reductive elimination of product from a Ru^{II} aryl−

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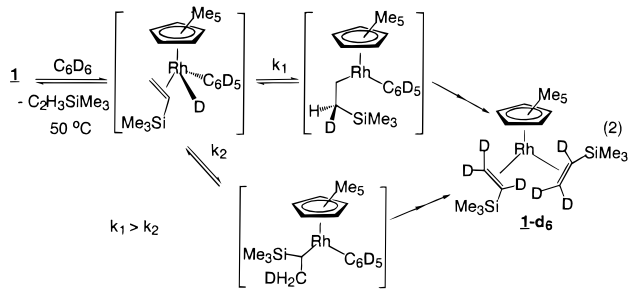
alkyl intermediate.[23−27] This chemistry has also been extended to vinylic C−H bonds in certain α,β-unsaturated ketones and esters.[28,29]

Rhodium or iridium complexes, on the other hand, have found only limited application in catalytic carbon−carbon bond forming reactions.[30−37] While rhodium systems of the type [C_5Me_5RhL] have been crucial in developing an understanding of the oxidative addition reaction of C−H bonds, they have had limited application toward the goal of catalytic functionalizations.[38−41]

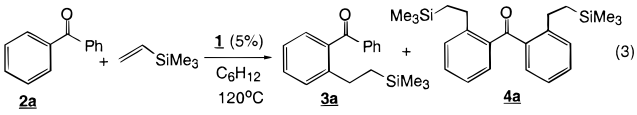
To effect carbon−carbon coupling reactions, the strategy applied here was to utilize bis-olefin complexes, for example, [$C_5Me_5Rh(C_2H_3SiMe_3)_2$], **1**, which allow thermal access to the 16-electron species [C_5Me_5Rh(olefin)]. Oxidative addition of C−H bonds to this species generates a complex of the type [C_5Me_5Rh(olefin)(R)(H)] in which coupling reactions between olefin and R can be envisioned to occur. This approach is based on the observation that the parent ethylene complex [$C_5Me_5Rh(C_2H_4)_2$] will incorporate deuterium into the ethylene ligand when heated in benzene-d_6 (78 °C, 2 h, 25% decrease in intensity).[42,43] This process follows a mechanism that involves initial ethylene dissociation followed by the reversible activation of benzene and insertion of olefin which results in scrambling of the deuterium label from the solvent into the coordinated ethylene. Increasing the steric bulk of the coordinated olefin in catalyst **1** results in a decrease of the barrier for olefin loss and thus more facile generation of the reactive intermediate [C_5Me_5RhL]. The increased reactivity of **1** relative to the bis-ethylene complex is illustrated in a thermolysis experiment in benzene-d_6 that results in selective deuterium incorporation into coordinated olefin under mild conditions[44] (eq 2).



In this paper, we report the use of **1** as a catalyst for the addition of olefins to aromatic ketones to selectively generate ortho-alkylated aromatic ketones.

Results and Discussion

A. Alkylation of Benzophenone with Vinyltrimethylsilane Catalyzed by [$C_5Me_5Rh(C_2H_3SiMe_3)_2$], 1. Prior to surveying a range of substrates, we conducted a detailed NMR study of the addition of vinyltrimethylsilane to benzophenone employing **1** as the catalyst to yield mono- and dialkylated products **3a** and **4a** (eq 3). A 1:1 molar ratio of benzophenone and



vinyltrimethylsilane and **1** (0.01 g, 2.3×10^{-5} mol, 5 mol %) in cyclohexane-d_{12} was heated in a sealed NMR tube at 120 °C and monitored by ^{1}H NMR spectroscopy. The formation of ortho-alkylated product **3a** was observed with a turnover frequency of ca. 0.65 TO/h (Figure 1, Experimental Section). Characteristic for ketone **3a** are resonances for the $-CH_2-$ protons at 2.65 (m, 2H) and 0.84 (m, 2H) and a new $-SiMe_3$ resonance at −0.08 (s, 9H). As in the case of the Murai system, only alkylation at the ortho position is observed and only the β-silyl addition product is formed ("anti-Markovnikov" addition). The only rhodium species observed during catalysis is complex **1**, indicating that this species is the catalyst resting state.

It was also informative to follow the reaction in toluene-d_8 at 120 °C (1:1 molar ratio of substrates, 5 mol % **1**). Free vinyltrimethylsilane showed considerable deuterium incorporation as the reaction proceeded. After 22 h, both vinylic sites showed ca. 80% deuteration as judged by use of an internal standard. At this point 36% conversion of substrates to **3a** had occurred and significant deuteration of the $-CH_2-$ groups was evident (ca. 25%) due to deuteration of the vinylsilane prior to reaction as well as deuteration of **3a** after formation.[45] The deuteration of the olefin and the product **3a** are explained with a reversible H/D exchange sequence as shown in eq 2.[44] This observation is consistent with the assignment of **1** as the catalyst resting state. Reversible C−H bond activation by [$C_5Me_5Rh(C_2H_3SiMe_3)$] (in rapid equilibrium with **1**), followed by reversible olefin insertion into Rh−D (see eq 2) must occur on a faster time scale than productive ketone−olefin coupling.[46] Coupling products based on the activation of toluene were not observed.

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(45) The turnover frequency is 0.7 TO/h and compares well with the results for the reaction in cyclohexane.

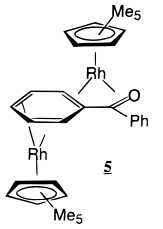
(46) The degree of deuterium incorporation into free olefin and product **3a** are on the same order of magnitude, which indicates that activation of toluene-d_8 followed by reversible H/D exchange are faster than productive aryl−alkyl coupling.

When the catalysis is carried out to high conversions, the double alkylation product **4a**[47] is observed in addition to the expected product **3a** (eq 3). For example, after 18 h in a reaction with 5 mol % catalyst at 120 °C, 83% conversion to products was observed. Of these products 18% corresponded to **4a**. Indicative for **4a** was an ^{1}H NMR resonance at 2.76 ppm (m, 4H, $-CH_2-$). Synthesis of the mono-addition product **3a** was best accomplished in the presence of excess benzophenone, which prevented formation of **4a**. On the other hand, **4a** could be selectively prepared in a reaction employing excess vinyltrimethylsilane with **2a** (2 mol % **1**; olefin-to-ketone ratio of 2.5, cyclohexane-d_{12}). After one week at 120 °C ketone **4a** was the sole product with **3a** being formed initially in the catalysis.[48] The second equivalent of olefin added regioselectively to the unsubstituted aromatic ring. This observation was supported by using 4,4′-dimethoxybenzophenone, **2b**, as the substrate. The first alkylation generates an unsymmetrical ketone with two inequivalent $-$OMe groups (^{1}H NMR). Addition of the second equivalent of vinyltrimethylsilane generates a benzophenone derivative with equivalent methoxy groups indicating addition to the second aryl group.[49]

Catalyst lifetimes are long provided excess olefin is present. With use of a 1:1 molar ratio of substrates (5 mol % **1**, 120 °C, C_6D_{12}) the turnover/time plot is linear to 95% conversion (0.65 TO/h, Figure 1, Experimental Section). This behavior suggests that the turnover frequency is first order in ketone and inverse order in olefin, which is consistent with the proposal of reversible olefin loss from the catalyst resting state followed by reaction of [$C_5Me_5Rh(C_2H_3SiMe_3)$] with ketone. While quantitative kinetics were not carried out, qualitative experiments verified that the TOF was suppressed in the presence of excess vinyltrimethylsilane and accelerated with added ketone. For example, by using a 1:2.5 molar ratio of vinylsilane:ketone the initial TOF was observed to increase to ca. 2 TO/h. To further probe catalyst stability a reaction employing 1 mol % **1** and a 1:1 molar ratio of substrate was carried out (C_6D_{12}, 120 °C). After 110 h, ca. 95% conversion to products had occurred and NMR analysis of the solution indicated that **1** is still present and accounts for 90% of the original loading.

Thermolysis in the presence of excess benzophenone under conditions of catalysis (120 °C) results in catalyst deactivation after complete conversion of olefin. Analysis of the ^{1}H NMR spectrum of a reaction mixture generated in this fashion showed, in addition to ketone **3a** and excess benzophenone, a series of resonances in the Cp* region indicating an ill-defined deactivation process to generate a series of rhodium-containing species.

This was further investigated in a reaction of **1** with excess benzophenone (10 equiv) in cyclohexane-d_{12} at lower temperature (55 °C). After 4 h, 65% of **1** was converted to generate **3a** (92%) and **4a** (8%) and a single rhodium-containing species, complex **5**, with Cp* resonances at 1.62 and 1.91 ppm in the ratio of 1:1. No free olefin remained in the reaction mixture, which changed color from orange to brown during this process. After 8 h at 55 °C complete conversion of **1** to **5** was observed with nearly all olefin converted to **3a**. Complex **5** was isolated as a brown solid by column chromatography. In addition to the Cp* resonances, signals in the aryl region accounting for five protons are observed as well as resonances at 2.82 (dd, 1H), 3.18 (d, 1H), 3.28 (d, 1H), 5.60 (m, 1H), and 5.81 ppm (m, 1H). No $-SiMe_3$ resonances are present. Clearly the deactivation product is composed of 1 equiv of benzophenone and two nonequivalent [C_5Me_5Rh] moieties. To date we have been unsuccessful in obtaining crystals of this species. A proposed structure that is consistent with the NMR data is shown below (**5**).



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A notable feature of the above reaction is the very mild conditions (55 °C, 8 h) under which product is formed when no free olefin is present. This is clearly a consequence of the high concentration of the intermediate [$C_5Me_5Rh(C_2H_3SiMe_3)$] in solution in the absence of added free vinyltrimethylsilane. This result also suggests that slow addition of olefin to a reaction mixture generated in this fashion can result in catalytic ketone formation at these low temperatures compared to the temperatures required in the catalytic process described above. Complex **5** is not a true deactivation product unlike the rhodium complexes generated in the presence of excess benzophenone under higher temperature thermolysis conditions. The addition of excess vinyltrimethylsilane to a cyclohexane solution of **5** at 50 °C results in the formation of **1** without the formation of additional ketone **3a**; after 2 h slow catalytic olefin addition to generate **3a** is observed in this reaction if the olefin concentration remains low. Complex **5** essentially functions as an alternative to **1** to deliver the 14-electron fragment [C_5Me_5Rh] for further catalysis.

B. Addition of Olefins to Benzophenones and Acetophenones. A survey of the reactivity of several olefins toward benzophenone (and derivatives) and acetophenones was carried out. Results are summarized in Table 1 and correspond to reactions run under standard, unoptimized conditions. Reactions were conducted at 120 °C, 5 mol % catalyst loading, and with a 1:1 molar ratio of substrates. In selected cases it was possible to reduce the catalyst loading significantly (vide infra).

Entry 1 involving benzophenone and vinyltrimethylsilane has been discussed extensively above. The use of the bulkier 3,3-dimethyl-1-butene (entry 2) results in more rapid turnover as might be expected due to more facile dissociation from the Rh(I) center.[50] After 1 h 65% conversion is observed with 3,3,-dimethyl-1-butene whereas with vinyltrimethylsilane 11 h are required for 49% conversion.

Another particularly reactive olefin is norbornene, which is both bulky (disubstituted) and strained. In this case the reaction was followed by ^{1}H NMR spectroscopy (1:1 substrate ratio, 5 mol % **1**). Complete conversion to **3g** was observed after 3.5 h at 70 °C in cyclohexane-d_{12} (for a turnover−time plot see the Experimental Section). The TOF for the formation of **3g** was moderate in the initial stage of catalysis (1 TO/h for 1.5 h) and increased by an order of magnitude to 10 TO/h (1.5−2.5 h) as

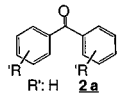
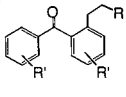
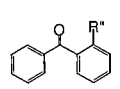
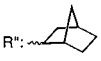
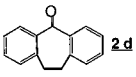
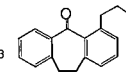
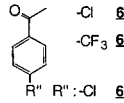
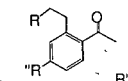
(47) Organic products have been isolated by chromatography and characterized by NMR spectroscopy and elemental analysis or HRMS; see Supporting Information.

(48) The formation of even higher alkylation products is observed if reaction times are increased, indicating that the catalyst is long-lived even though additional alkylation is slower. Indicative for these products are the ^{1}H NMR resonances for the methylene groups α to the aryl ring (**3a**, δ 2.65, **4a**, δ 2.83; higher alkylation products, δ 3.11).

(49) The relatively high ratio of higher alkylated products suggests that the second alkylation might occur without prior release of the initially alkylated **2a**. Also, the observation of secondary alkylation products in the deactivation process (vide infra) suggests this notion.

(50) Independent synthesis of a rhodium olefin complex with 3,3-dimethyl-1-butene was not successful. In situ NMR studies indicate the formation of such complexes as intermediates.

Table 1. Catalytic Addition of Olefins to Aromatic Ketones Catalyzed by **1** [5 mol % **1** (0.01 g, 2.3×10^{-5} mol), 120 °C, cyclohexane, ketone:olefin ratio 1:1][a]

entry	ketone	olefin	product	conversion [%] (reaction time[1])
1	 R': H **2a**		**3a** R: -SiMe$_3$	49 (11) 99 (23)[2]
2		 	**3b** R: -CMe$_3$	65 (1) 91 (18)
3			**3c** R: -C$_3$H$_7$	31 (1.5) 60 (24)
4			**3d** R: -CH$_2$SiMe$_3$	42 (12)
5			**3e** R: -OEt	10 (1) 10 (12)
6		 	**3f** R": 	22 (1) 55 (12)
7			**3g** R": 	quant. (1.5)[3]
8	R': 4,4'- OMe **2b**		**3h** R: -SiMe$_3$	38 (11) 99 (23)
9	R': 3,3' - CF$_3$ **2c**		**3i** R: -SiMe$_3$	75 (8)[4]
10	 **2d**		 **3j**	12 (38) 92 (72)
11	R": -H **6a**		R: -SiMe$_3$ R": -H **7a**	60 (72)[5]
12	-Cl **6b**		-Cl **7b**	35 (24) 75 (72)
13	 -CF$_3$ **6c**		-CF$_3$ **7c**	51 (24) 89 (72)
14	R" R": -Cl **6b**		R": -Cl **8a**	21 (1) 72 (12)
15	-CF$_3$ **6c**	R: -CMe$_3$	-CF$_3$ **8b**	60 (1) 91 (12)

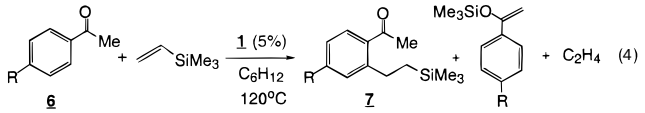
[a] (1) Parentheses: reaction time (hours). (2) Conversion corresponds to **3a** (88%) and **4a** (11%). (3) Endo/exo distribution see text. (4) Olefin addition to 2,5-disubstituted isomer. (5) Conversion of **6a** to products; side product 30%; see text (eq 4).

catalysis proceeded. A decrease of the TOF was again observed close to complete conversion. After 1.5 h, 85% conversion of vinyltrimethylsilane (introduced with **1**) to **3a** was observed, which explains the significant increase in TOF for the formation of **3g**. After complete conversion of norbornene, 16% *endo*-**3g** and 84% *exo*-**3g** were observed in the reaction mixture.[51] The high reactivity of norbornene allowed the decrease of catalyst loading to 0.5 mol % with 92% conversion to *exo/endo*-**3g** (exo: 82%) after 18 h at 80 °C.

Cyclopentene on the other hand was converted less effectively to **3f** (entry 6, Table 1); catalyst deactivation to unassigned products was observed. The addition of α-olefins to **2a** as in entries 3 and 4 (Table 1) showed fair conversions to ketones **3c** and **3d**. Exclusive anti-Markovnikov addition was observed to generate the linear products, even though isomerization to internal olefins in the case of entry 3 was observed during the reaction.[52] The vinyl ether in entry 5 was converted to product but conversion was low and early catalyst deactivation was observed.[53]

In general, substituted benzophenones showed similar reactivities (entries 8−10) for the addition reaction. The −OMe-substituted system (entry 8) had somewhat lower reactivity while the −CF_3-substituted system (entry 9) showed somewhat increased reactivity. With reductive elimination being the turnover-limiting step the electron-deficient benzophenone derivative is expected to accelerate this process. In entry 10, however, the conformational flexibility has been significantly reduced and a decrease in the rate of addition to olefin was observed. The required geometry for the transition state of the reductive elimination reaction might be less accessible with this substrate. Even though this reaction is slow, high conversions can be obtained at longer times.

C. Catalytic Conversion of Acetophenones. Acetophenones are also substrates for catalytic hydroarylation (entries 11−16). A noteworthy difference was observed in the addition reaction of vinyltrimethylsilane to acetophenones **6a**−**c**. The conversion to hydroarylation products **7a**−**c** was slow and analysis of the reaction by NMR spectroscopy indicated that additional products were generated in this process. For example, in the reaction of *p*-chloroacetophenone, **6b**, with vinyltrimethylsilane (5 mol % **1**, cyclohexane-d_{12}, ratio 1:1, 120 °C) 24% conversion to **7b** was observed after 12 h in addition to 22% conversion of **6b** to a new species. In addition to a resonance for free ethlyene in solution (s, 5.3 ppm, C_6D_{12}) two new doublets are observed at 4.38 and 4.85 ppm (J = 3 Hz) along with resonances in the aromatic and the −$SiMe_3$ region. Comparison to an authentic sample[54] established this side product as the silyl protected enolate (eq 4, see the Supporting Information for a sample NMR spectrum).



6 **7** (4)

The formation of ethylene during this side reaction decreases catalytic activity. Ethylene coordinates quite strongly to the rhodium system and is less labile under the reaction conditions. With acetophenone, catalysis stops after approximately 60% conversion. With *p*-(trifluoromethyl)acetophenone, **6c**, the silyl transfer was of minor importance and high conversion to **7c** was observed (entry 13).

A possible mechanism for catalytic silyl transfer to generate a silyl enolate and ethylene from vinyltrimethylsilane and acetophenone is illustrated in Scheme 1. Several significant features of catalytic hydroarylation with **1** as a catalyst are illustrated in this side reaction. Olefin complex **1** reacts readily to activate sp^3-CH bonds in substrates such as acetone indicated by catalytic H/D exchange as illustrated in eq 2 for benzene.[44] The reversible activation of the acetophenone −CH_3 group was observed by using labeling experiments (vide infra) and supports formation of intermediate **A** via step i in Scheme 1. Reductive elimination from **A** of two sp^3-alkyl groups to generate a γ-silyl ketone is not likely in this system. Alternatively β-silyl elimination from **A** (step ii) generates intermediate **B** from which a lower barrier for the reductive elimination reaction is available by generating a C−Si bond. Ethylene dissociation in the presence of excess vinyltrimethylsilane regenerates **1**. The

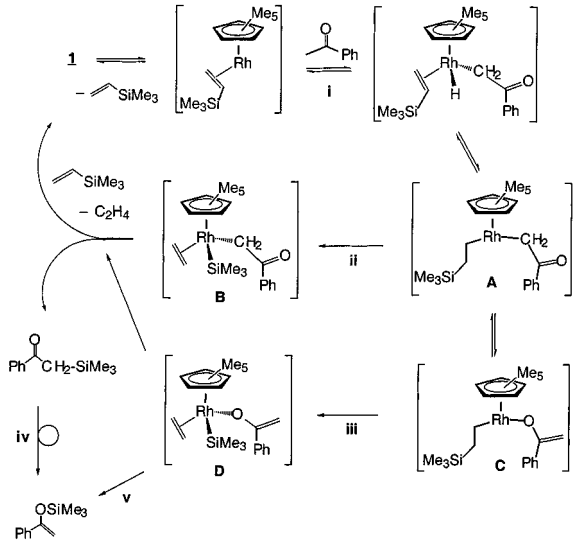
(51) It is curious to note that the ratio of endo to exo products in this reaction increases as the reaction proceeds with *exo*-**3g** being the exclusive addition product in the early stages of catalysis, which suggests that intermediates such as **5** or mixed olefin complexes generated from **1** and norbornene show different reactivity as the presumed bis-norbornene rhodium complex, which is assigned as the resting state during norbornene conversion.

(52) Analogous results are observed by Murai and co-workers using the Ru system in the reaction of 1-hexene (see refs 14−22).

(53) Addition product **3e** was characterized in situ by ^{1}H NMR spectroscopy and mass spectroscopy. ^{1}H NMR (C_6D_6, 300 MHz, 20 °C) δ 0.98 (t, 3H, −CH_3); 3.25 (q, 2H, OCH_2); 3.15 (t, 2H, −CH_2−); 3.62 (t, 2H, −CH_2−); 7.95 (m, 2H, Ar); 7.04−7.18 (m, Ar.). MS/EI: 254.18.

(54) (a) *p*-Chloroacetophenone was treated with LDA at low temperatures and quenched with $ClSiMe_3$. The enolate was isolated by vacuum distillation. The corresponding $SiMe_3$ protected enolate of acetophenone is commercially available. (b) A referee has suggested that formation of the silyl enolate might occur through a mechanism involving the addition of a rhodium hydride to the vinyl silane followed by β-silyl elimination and release of ethylene to generate a Rh−silyl complex. Insertion of ketone into the Rh−silyl bond followed by β-elimination would generate the silyl enolate and regenerate the rhodium hydride. While we cannot strictly rule out this mechanism, it is not apparent how a Rh−H species could be generated as the chain carrier in this system.

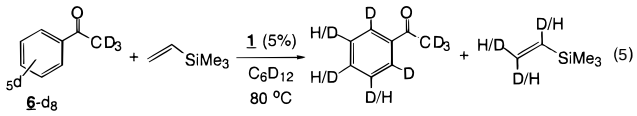
Scheme 1. Proposed Mechanism for Silylenolate Formation during Catalytic Hydroarylation of Acetophenone with Vinyltrimethylsilane with Use of **1** as Catalyst



thermal rearrangement of α-silyl ketones to silyl-protected enolates (step iv) has been reported (Brook rearrangement) and is likely to occur under these conditions to generate the final products. Another attractive option involves isomerization of **A** to generate an O-bound rhodium enolate complex (species **C**) that will, after silyl elimination (step iii) and Si−O reductive elimination (step v), generate the silyl enolate directly. At this point it is difficult to distinguish between these mechanistic alternatives.[54b] But in favor of pathway iii, it is significant to point out that in all cases investigated silyl−aryl coupling with vinyltrimethylsilane and **1** as catalyst has not been observed, which is notable since the reductive elimination of an aryl−silyl bond is expected to be more facile as recently observed by Berry and co-workers.[38] The presence of the carbonyl group in the catalytic process investigated here is not only important for reducing the barrier for reductive elimination in C−C coupling and controlling the regioselectivity of alkylation but also seems to be responsible for the specific side reaction observed in the addition of vinyltrimethylsilane to acetophenone.

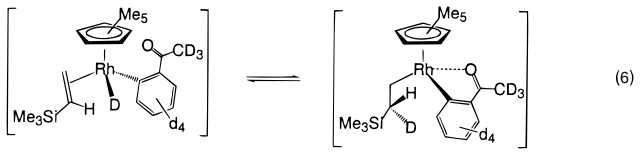
Using 3,3-dimethyl-1-butene as the olefin gave good conversion to products **8a** and **8b**,[55] which confirmed that this side reaction is specific for vinyltrimethylsilane and acetophenones. As in the benzophenone case, double alkylation can be observed and such a product has been isolated from a reaction of **6c** with an excess of vinyltrimethylsilane.

D. Reaction of Acetophenone-d_8 with Vinyltrimethylsilane. Mechanistic information was obtained from the results of the reaction of acetophenone-d_8 with vinyltrimethylsilane (5 mol % **1**, 0.01 g, substrate ratio 1:1, cyclohexane-d_{12}) at 80 °C, conditions under which product formation is *not* observed. (For a plot showing the change of intensity of the residual ^{1}H NMR resonances of acetophenone-d_8 during this process see the Experimental Section, Figure 3). The residual resonance for the ortho sites of acetophenone-d_8 did *not* change during the 35 h this reaction was followed by ^{1}H NMR spectroscopy. In contrast, the resonances for the meta and para sites were increased 15-fold in intensity during this process, which corresponds to roughly 30% incorporation of protio label into these sites. H/D exchange delivered deuterium from acetophenone into free vinyltrimethylsilane and decreased the ^{1}H NMR signal intensity without converting the olefin to products. All ^{1}H vinylic sites were reduced in intensity on the same time scale to generate perdeuteriovinyltrimethylsilane (eq 5).



(5)

These results show that activation of the meta and para C−H bonds followed by olefin insertion is reversible and results in H/D exchange by a mechanism similar to that shown in eq 2.[56] In contrast, no H/D exchange is observed in the ortho position, yet this is the sole site of alkylation. There are two plausible explanations for this observation. One possibility is that the barrier for the overall process of oxidative addition of the ortho C−D(H) bond and migratory insertion to generate a Rh(III) alkyl aryl intermediate (see eq 2) is much higher than the corresponding barrier for the meta and para C−D(H) bonds. An alternative, illustrated in eq 6, is that oxidative addition/migratory insertion



(6)

occurs reversibly but a chelate interaction in the alkyl aryl Rh(III) intermediate renders the methylene hydrogens (in this case −CHD−) diastereotopic and therefore the deuterium which migrates to the olefin must, by microscopic reversibility, also return to the rhodium in the reverse β-elimination step. Thus, even though the C−H oxidative addition/migratory insertion process is reversible, no H/D exchange occurs.

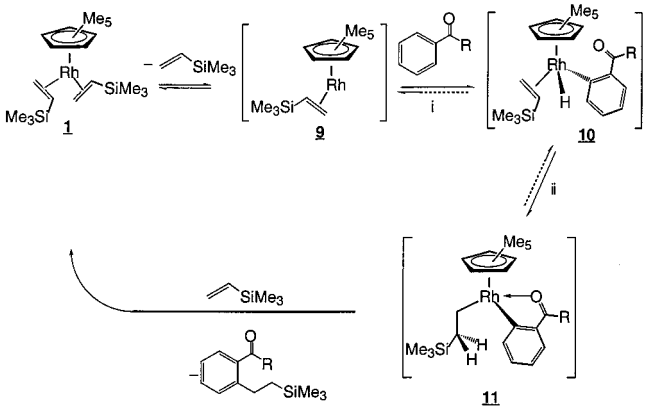
We have no firm evidence to distinguish these possibilities. However, we have observed that with other monosubstituted benzenes[44] (e.g., toluene, chlorobenzene) H/D exchange in the ortho position is only slightly slower than in meta and para positions and the exchange occurs at much lower temperatures than is required for the catalytic coupling reaction of acetophenone with vinyltrimethylsilane. Thus, we currently favor the latter explanation, that is oxidative addition/migratory insertion of the ortho C−H(D) bond is reversible but not detectable via an H/D exchange experiment. If this explanation is correct, it suggests that in the catalytic cycle reductive elimination from the alkyl−aryl intermediate is the turnover limiting step.

On the basis of the results obtained to date, some statements can be made concerning the overall catalytic cycle (see Scheme 2). The increase in turnover frequency with increase in ketone concentration and suppression of the turnover frequency with added olefin suggests a reversible loss of olefin to produce an intermediate (**9**) that is trapped by ketone. For simplicity we show this trapped species as the oxidative addition adduct, **10**. (A simple ketone adduct of **9** may well intervene between **9** and **10**). Olefin insertion generates **11** in which chelation of the carbonyl group provides an 18-electron intermediate. Such species have precedent. Cyclometalations which afford metal

(55) Ketone **8b** was characterized *in situ* after catalysis and shows spectroscopic features comparable to similar fully characterized products (see ref 16 and Supporting Information). ^{1}H NMR (C_6D_6, 300 MHz, 20 °C) δ 0.88 (s, 9H, CMe_3); 1.32 (m, 2H, CH_2); 2.68 (m, 2H, CH_2); 1.96 (s, 3H, Me); 7.38 (s, 1H, Ar); 7.11 (d, 1H, Ar); 6.92 (d, 1H, Ar). MS/EI: 272.16.

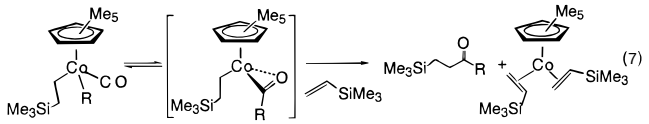
(56) No site selectivity regarding the olefin was observed, which suggests that olefin insertion into a Rh hydride can occur with both regiochemistries under these conditions. This is especially remarkable since the exclusive products observed are based on anti-Markovnikov olefin addition. Olefin-hydride insertion might be directed by the carbonyl group with respect to regiochemistry; no direct evidence for this is available.

Scheme 2. Proposed Mechanism for Catalytic Olefin Addition to Aromatic Ketones



complexes stabilized by intramolecular coordination of a carbonyl group have been observed in a variety of ruthenium complexes.[23,58−64]

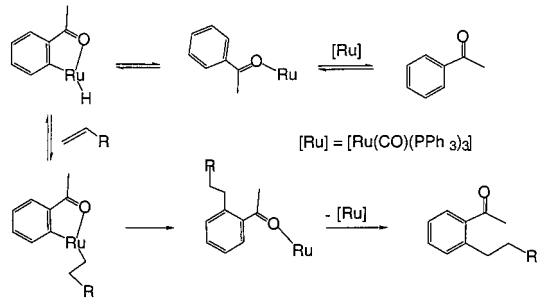
The barrier to reductive elimination is apparently reduced by this chelate interaction which results in exclusive ortho alkylation. This is consistent with proposals by Murai regarding the ruthenium-catalyzed alkylation and by others.[57] This is also consistent with our recent study of catalytic hydroacylation with similar cobalt complexes where it was found that reductive elimination of ketone is most likely mediated by an η^2-acyl interaction (eq 7).[65,66] Maitlis and co-workers have reported the formation of acetophenone from $[C_5Me_5Rh(CO)(Me)(Ph)]$ in a reductive elimination reaction that most likely involves η^2-acyl assistance.[67]



E. Conclusions. The catalytic process reported here introduces rhodium complex **1** as an efficient catalyst for the addition of a variety of olefins regioselectively to the ortho positions of aromatic ketones. Mechanistic details of this reaction have been studied with benzophenone and vinyltrimethylsilane as substrates. The turnover-limiting step is likely the reductive elimination reaction to generate the alkylated ketone product. Deactivation routes and side reactions for acetophenones have been described and support the mechanistic scheme developed for this reaction.

Several significant differences are apparent in a comparison of the ruthenium system developed by Murai and co-workers and the rhodium system introduced here. The reaction conditions for both catalytic systems are similar (Murai system: 135 °C, refluxing toluene, 1−24 h.). While optimization of the catalytic process in the Ru system has resulted in generally good turnover numbers, the rhodium system investigated here shows interesting potential for further developments in this area, especially considering the mild conditions for the reaction of norbornene and the reactivity in the presence of excess benzophenone. Both systems show in general high regioselectivity for addition to the olefin to generate the anti-Markovnikov product. Olefin isomerization is observed in situ with the rhodium as well as with the ruthenium system, but aromatic alkylation generates only the linear addition products for substrates such as 1-pentene or 1-hexene. The catalyst activation procedure in the ruthenium system is believed to be an initial olefin hydrogenation step that generates a ruthenium(0) olefin complex; in the system investigated here rhodium bis-olefin complexes are the catalyst resting states. The proposed mechanism for catalytic alkylation of aromatic ketones catalyzed by $[RuH_2(CO)(PPh_3)_3]$ is illustrated in Scheme 3.

Scheme 3. Murai Mechanism for Ruthenium-Catalyzed Hydroarylation of Olefins



A key difference in the mechanisms of Schemes 2 and 3 is that in the ruthenium-catalyzed process carbonyl coordination is presumed to be the first step, which directs the C−H bond activation to the ortho position of the aromatic substrate.[68] H/D exchange experiments establish that para and meta C−H bonds are *not* activated in the Ru system. These rhodium complexes, on the other hand, are not discriminating in the C−H bond activation step and activation of all sites (ortho, meta, para) of the substrate is observed. Murai has established that C−H bond activation is fast and reversible in the Ru system and that the reductive elimination of the alkylated product is the turnover-limiting step. We believe the same feature applies to the rhodium system, but no conclusive evidence is available yet concerning this point. In both systems, chelation of the carbonyl group to the metal center lowers the barrier for reductive elimination to product.

Experimental Section

General Considerations. All manipulations of air- and/or water-sensitive compounds were performed by using standard high-vacuum or Schlenk techniques. Argon and nitrogen were purified by passage through columns of BASF R3-11 catalyst (Chemalog) and 4 Å molecular sieves. Solid organometallic compounds were transferred in an argon-filled Vacuum Atmospheres drybox. ^{1}H and ^{13}C NMR chemical shifts were referenced to residual ^{1}H NMR signals and to the ^{13}C NMR signals of the deuterated solvents, respectively. NMR probe temperatures were measured by using an anhydrous ethylene glycol sample. Elemental analyses were performed by Atlantic Microlabs, Inc., of Norcross, GA.

Materials. All solvents used for synthesis were deoxygenated and dried via passage over a column of activated alumina.[69] Tetrahydrofuran

(57) Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031.
(58) (a) Komiya, S.; Ito, T.; Cowie, M.; Yamamoto, A.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 3874. (b) Tolman, C. A.; Ittel, S. D.; English, A. D.; Jesson, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 1742
(59) Rothwell, I. P. *Acc. Chem. Res.* **1988**, *21*, 153.
(60) Ryabov, A. D. *Synthesis* **1985**, 233.
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(64) Mawby, R. J.; Saunders: D. R. *J. Chem. Soc.* **1984**, 2133.
(65) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965.
(66) Bergman, R. G. *Acc. Chem. Res.* **1980**, *13*, 113.
(67) Sunley, G. J.; Fanizzi, F. P.; Saez, I. M.; Maitlis, P. M. *J. Organomet. Chem.* **1987**, *330*, C27.

(68) Labeling studies have shown that C−H bond activation is only observed in the ortho positions of acetophenone with use of the ruthenium catalyst; the other sites are not activated (see ref 16).

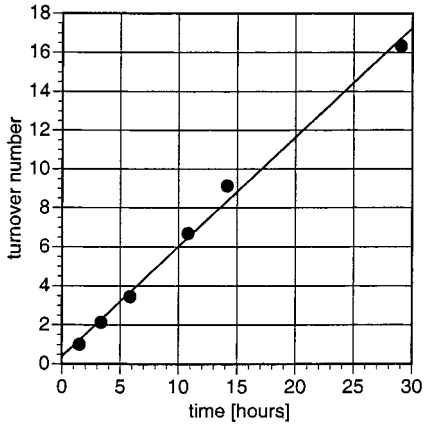

Figure 1. Conversion of benzophenone **2a** with Vinyltrimethylsilane (ratio 1:1) to **3a** catalyzed by **1** (0.01 g, 2.3×10^{-5} mol, 5 mol %) at 120 °C. $k_{TOF} = 0.6$ TO/h.

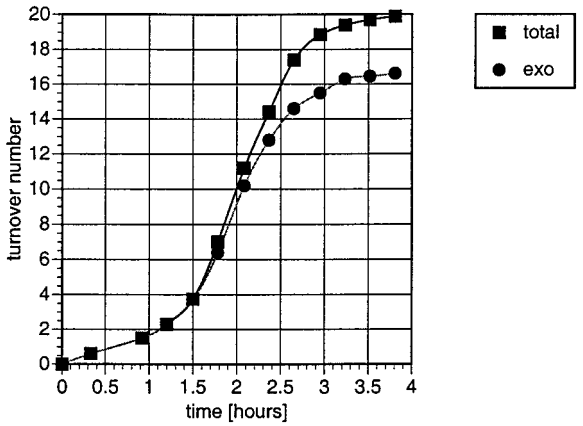

Figure 2. Catalytic conversion of norbornene and benzophenone to **3g** at 70 °C in cyclohexane-d_{12} (0.01 g **1**, 2.3×10^{-5} mol, 5 mol %, substrate ratio 1:1).

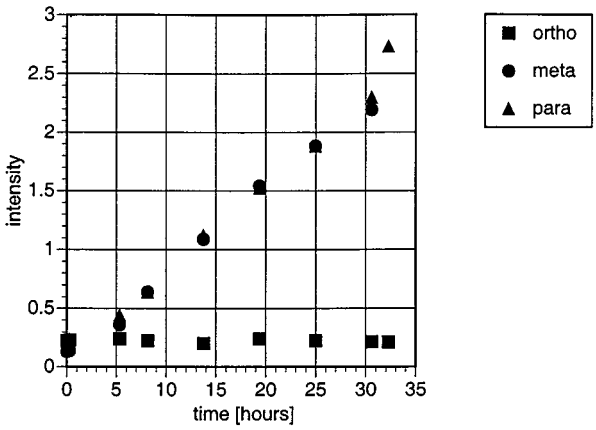

Figure 3. Increase in intensity of the residual resonances for acetophenone-d_8 during thermolysis at 80 °C in the presence of vinyltrimethylsilane and **1** (5 mol %, ratio of olefin to acetophenone 1:1).

was distilled from sodium benzophenone−ketyl prior to use. [C_5Me_5-$Rh(C_2H_3SiMe_3)_2$] was prepared following a previously reported procedure.[44] The procedure is also described in the Supporting Information. All substrates listed in Table 1 were commercially available from Aldrich. Benzene-d_6, toluene-d_8, and cyclohexane-d_{12} were dried over potassium benzophenone−ketyl, acetone-d_6, and acetophenone-d_8 over CaH_2, vacuum transferred, and degassed by repeated freeze−pump−thaw cycles.

Catalytic Alkylation of Benzophenone: Kinetic Analysis. A solution of **1** (0.01 g, 2.28×10^{-5}mol) in cyclohexane-d_{12} (0.6 mL) was treated with 20 equiv of benzophenone and 20 equiv of vinyltrimethylsilane. Both reagents were added in a drybox to an NMR tube equipped with a Teflon screw top. This tube was inserted into the heated probe of an AMX 300 NMR spectrometer and spectra were taken with time as the reaction proceeded. A plot of turnover number vs time is illustrated in Figure 1. Complete conversion was observed. An alternative procedure involved the same sample preparation followed by thermolysis in a temperature-controlled oil bath. The sample tube was removed at various intervals and analyzed by NMR spectroscopy at 20 °C.

In a series of similar experiments turnover frequencies on the order of 1 TO/h were observed. In all cases the reaction mixtures remained homogeneous and no deactivation was observed. The only rhodium-containing species present during these reactions was **1**.

Analogously, reactions were carried out with different ratios of vinyltrimethylsilane to benzophenone. The appropriate amount of substrate was added by weight and the turnover process was analyzed by NMR spectroscopy. TOF = 0.6 TO/h (5 mol % **1**, 1:1 substrate ratio) and TOF = 0.03 TO/h (5 mol % **1**, 1:2.5 ratio of ketone to olefin); TOF = 1.4 TO/h (5 mol % **1**, 1.4:1 ratio of ketone to olefin); TOF = 2.0 TO/h (5 mol % **1**, 2.5:1 ratio of ketone to olefin).

Catalytic Addition of Norbornene to Benzophenone. In a similar reaction norbornene and benzophenone, **2a**, were heated at 70 °C in cyclohexane-d_{12} with **1** (0.01 g, 2.3×10^{-5} mol, 5 mol %) as catalyst. The reaction was followed by NMR spectroscopy and the conversion to *endo/exo*-**3g** was plotted vs time in addition to the conversion to only *exo*-**3g**. After complete conversion, *endo*-**3g** accounts for 16% of the product. In addition, vinyltrimethylsilane was converted to **3a** during this process. The initial turnover frequency of 1 TO/h increased as catalysis progressed and an intermediate TOF of 10 TO/h was observed. Close to complete conversion the turnover frequency decreased.

H/D Exchange with Acetophenone-d_8. Acetophenone-d_8 and vinyltrimethylsilane were mixed with **1** (0.01 g, 2.3×10^{-5} mol, 5 mol %) in cyclohexane-d_{12} and heated to 80 °C and followed with time by ^{1}H NMR spectroscopy. Conversion to ketone **8a** or side products according to eq 4 was not observed under these conditions. H/D exchange based on reversible acetophenone activation and olefin insertion resulted in an increase of the residual acetophenone resonances and a decrease of the olefinic resonances of vinyltrimethylsilane. Resonances were normalized based on the integration of **1** (relative to one proton) and plotted vs time in Figure 3 for the change of the acetophenone resonances. The change of the integration for the decreasing olefinic resonances showed that no site selectivity is observed and all three vinylic protons of vinyltrimethylsilane were reduced to 65% after 30 h under the indicated reaction conditions. The solvent was not activated during this process and was therefore not a source for deuterium exchange.

The residual resonance for the ortho sites of acetophenone did not change in intensity during this reaction, while the para and meta sites showed considerable H/D exchange that resulted in an increase that accounted for roughly three protons based on the original intensity after 30 h. The residual resonance of the $-CD_3$ group in the ^{1}H NMR spectrum increased in intensity during this process (3-fold based on the original intensity).

Catalytic Alkylation of Aromatic Ketones. Complex **1** (0.01 g, 2.3×10^{-5} mol) was added to an NMR tube equipped with a Teflon screw cap or a thick-walled glass tube with a Teflon screw top and dissolved in cyclohexane (-d_{12} or -h_{12}, if solubility required a different solvent (entry 8, Table 1) benzene was used). To this was added the required amount of ketone and olefin (in general 4.6×10^{-4} mol each) by weight wiht a syringe. The sealed containers were removed from the drybox and kept at 120 °C immersed in an oil bath. Samples prepared in NMR tubes were monitored during catalysis. The residual solvent resonance was used as an integration standard. After the reactions were terminated all volatiles were removed and the reaction mixture was analyzed by NMR spectroscopy to determine conversion. Column chromatography (flash-chromatography) on alumina gave in general pure material as judged by NMR spectroscopy. When vinyltrimethylsilane was not used as the olefin, small impurities based on

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the initial conversion of vinyltrimethylsilane originating from complex **1** were present in some samples and proved difficult to separate by chromatography. NMR data (^{1}H and ^{13}C) and data from elemental analysis or mass spectroscopic analysis are summarized in the Supporting Information.

Acknowledgment is made to the National Institutes of Health (Grant GM 28938) for financial support. C.P.L. thanks the Fonds der Chemischen Industrie, Germany, for a Kekulé fellowship.

Supporting Information Available: Spectroscopic and analytical data for the organic products of Table 1; ^{1}H NMR spectrum for complex **5**; sample NMR spectrum for the side reaction in the conversion of acetophenones (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA990702S