Three-Component Synthesis of Substituted η^5-Cyclopentadienyltricarbonylrhenium Complexes: Scope, Limitations, and Mechanistic Interpretations

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Received February 23, 1999

We have investigated the scope and mechanism of the "three-component" synthesis of substituted $CpRe(CO)_3$ complexes which involves the reaction of nucleophiles with diazocyclopentadiene ($C_5H_4N_2$) and a *fac*-$Re(CO)_3^+$ species. We found that only moderately strong nucleophiles (halogen, carboxylates, boronic acids) are suitable for this transformation and that it shows a great sensitivity to the steric and electronic features of the nucleophile. A Hammett-type $\rho\sigma$ analysis of the effect of *para*-substituents on the relative rate of this reaction with several benzoates showed that the reaction is accelerated by electron-donating substituents. A mechanistic analysis, based on structure/reactivity relationships and NMR experiments, indicated that the nucleophile initially reacts with the rhenium precursor. Then, in the rate-determining step, the resulting preassociated rhenium−nucleophile intermediate reacts with $C_5H_4N_2$ via a concerted S_N2-like transition state. The same general mechanistic pathway seems to be followed by two very different classes of nucleophiles, carboxylates and boronic acids, in the synthesis of acyloxy- and carbon-substituted $CpRe(CO)_3$ complexes, respectively. In particular, the lack of reactivity of boronic esters can be explained by the necessary preassociation step between the rhenium and a deprotonated hydroxy group of the nucleophile, which is possible only with free boronic acids.

Introduction

Many metallic radionuclides are nowadays routinely used in nuclear medicine.[1] Some of the most widely used ones are technetium-99m for diagnostic imaging and rhenium-186 and -188 for radiotherapy.[2] It is convenient that the elements technetium and rhenium have very similar chemical behaviors, so that the stable natural isotopes ^{185}Re and ^{187}Re can be reliably studied as models not only for the radioisotopes $^{186}Re/^{188}Re$ but also for ^{99m}Tc.[3]

The synthesis of radiopharmaceuticals possessing specific receptor-binding properties presents a special challenge. Such agents are usually prepared by radiolabeling organic molecules, which act as ligands for specific biological receptors. A critical element in a receptor-binding radiopharmaceutical is the nature of the radionuclide attached to the ligand: it must be a stable chemical species, and it must have a structure that does not interfere with the receptor-binding process. With regard to these issues, very favorable properties are shown by cyclopentadienyl tricarbonyl Re^I and Tc^I complexes $CpM(CO)_3$ (**1**, Figure 1),[4] especially when they are compared to the more widely used inorganic chelate complexes (**2**). First, $CpM(CO)_3$ complexes **1** are chemically and metabolically stable, which allows for easy handling and effective in vivo distribution. Second, they are lipophilic and relatively small, so that they are less likely to interfere with the receptor−ligand binding process, either through polarity or by steric hindrance. Third, unlike many inorganic metal−oxo chelates (**2**), they do not possess additional stereocenters, which often complicate the purification process of radiopharmaceuticals.[5]

Despite these favorable characteristics, however, the use of organometallic systems such as **1** conjugated with bioactive molecules has, so far, been rather limited.[6] Considerable effort has been devoted to the development of new synthetic methods suitable for radiolabeling biologically interesting molecules with this class of

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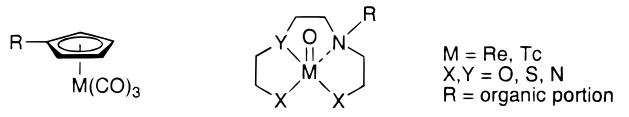
(5) See, for example: Hom, R. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1997**, *62*, 6290−6297, and references therein.

(6) (a) Top, S.; El Hafa, H.; Vessières, A.; Quivy, J.; Vaissermann, J.; Hughes, D. W.; McGlinchey, M. J.; Mornon, J.-P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, *117*, 8372−8380. (b) Spradau, T. W.; Edwards, W. B.; Anderson, C. J.; Welch, M. J.; Katzenellenbogen, J. A. *Nucl. Med. Biol.* **1999**, *26*, 1−7.

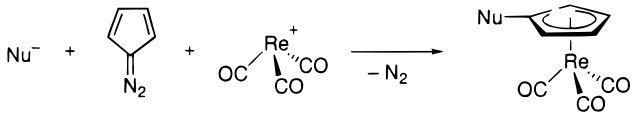
10.1021/om990128t CCC: $18.00
Publication on Web 06/06/1999



1 2

Figure 1. $CpM(CO)_3$ complex (**1**) and a generic metal(V)−oxo inorganic chelate structure (**2**).

Scheme 1. Three-Component Synthetic Approach to Substituted $CpRe(CO)_3$ Complexes



organometallic systems. The first success in this endeavor was achieved by the "double ligand transfer" reaction,[7] a process which, despite high efficiency, has some drawbacks such as harsh conditions and substrate limitations.

Our goal has been to develop fast, efficient, and generally applicable synthetic methods to prepare radiopharmaceuticals containing $CpM(CO)_3$ functional groups. As a starting point, a "three-component" approach (Scheme 1),[8] which involved the simultaneous formation of the Cp−metal and the Cp−nucleophile bonds, was considered. Diazocyclopentadiene ($C_5H_4N_2$)[9] was expected to be an ideal Cp precursor. Because it readily loses molecular nitrogen, it can be considered to be a bifunctional synthon, able to donate six π-electrons to the metal center and to undergo nucleophilic substitution at the ring σ-site. We also wanted to use metal precursors which could be easily obtained from perrhenate and pertechnetate, because these are the chemical forms delivered from generators of Re-186/188 and Tc-99m, respectively. We were particularly attracted by *fac*-$(CH_3CN)_3Re(CO)_3^+$ and *fac*-$(CH_3CN)_3Tc(CO)_3^+$ species, whose efficient preparations had been recently reported,[10] because they already possess the three CO ligands in the proper geometrical orientation. In addition to its easy synthetic accessibility, this $(CH_3CN)_3Re(CO)_3^+$ species proved to be much more reactive than pentacarbonyl halides,[9a] when used with $C_5H_4N_2$ in the synthesis of halogen-substituted $CpRe(CO)_3$.[11]

The nucleophilic species used in this sequence which gave the most promising results, in terms of their potential use in nuclear medicine, were organic carboxylates (which afford acyloxy-substituted $CpRe(CO)_3$ complexes)[11] and boronic acids (which afford carbon-substituted $CpRe(CO)_3$ complexes).[12] Here, we present a detailed analysis of structure/reactivity relationships in the nucleophilic component of this synthesis, spectroscopic evidence for reaction intermediates, and a discussion of the possible mechanistic pathway followed by this reaction.

Table 1. Yields Obtained with Different Heteroatom Nucleophiles 5a−g (eqs 1 and 2)[a]

entry	nucleophile	product	isolated yield (%)[b]
1	Br^- **5a**[c]	**6a**	67
2	I^- **5b**	**6b**	53
3	**5c**	**6c**	69
4	**5d**	**6d**	59
5	**5e**	**6e**	72
6	**5f**	**6f**	60
7	**5g**	**6g**	75

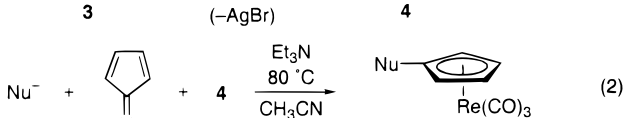
[a] Conditions: **4** (0.050 mmol), nucleophile (0.10 mmol), diazocyclopentadiene (0.060 mmol), CH_3CN (2.5 mL), 80 °C for 45 min. [b] Yields are based on the initial rhenium precursor **3**. [c] In this reaction, **3** was directly used, without treatment with silver triflate, to generate **4**. The $Re(CO)_3^+$ precursor contained 0.15 mmol of Br^-.

Results and Discussion

Heteroatom Nucleophiles. The reactions of a large number of heteroatom nucleophilic species **5a**−**g** (Table 1) with in situ generated $[(CH_3CN)_3Re(CO)_3]^+TfO^-$ (**4**, eq 1) and $C_5H_4N_2$ were examined in acetonitrile at 80 °C (eq 2).[11]

$$(Et_4N)_2[ReBr_3(CO)_3] \xrightarrow[CH_3CN]{AgOTf} [(CH_3CN)_3Re(CO)_3]^+TfO^- \quad (1)$$

3 (−AgBr) **4**



(2)

Initially, we obtained reasonably good yields with halide ions (entries 1, 2, Table 1). However, the halogen-substituted $CpRe(CO)_3$ species derived from these monovalent nucleophiles would require additional functionalization, via palladium-mediated C−C coupling reac-

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(10) (a) Alberto, R.; Schibli, R.; Schubiger, P. A. *Polyhedron* **1996**, *15*, 1079−1089. (b) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, P. A.; Herrmann, W. A.; Artus, G.; Abram, U.; Kaden, T. A. *J. Organomet. Chem.* **1995**, *492*, 217−224. (c) Alberto, R.; Egli, A.; Abram, U.; Hegetschweiler, K.; Gramlich, V.; Schubiger, P. A. *J. Chem. Soc., Dalton Trans.* **1994**, 2815−2820. (d) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, P. A.; Abram, U.; Kaden, T. A. *J. Am. Chem. Soc.* **1998**, *120*, 7987−7988.

(11) Minutolo, F.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4514−4515.

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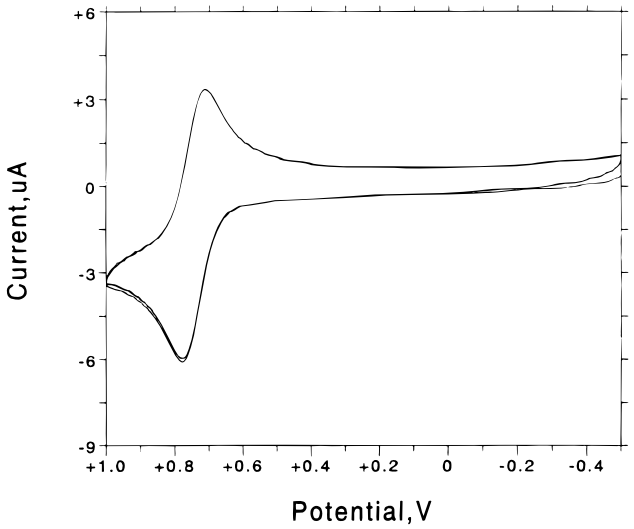


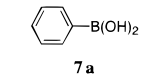
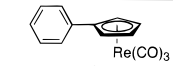
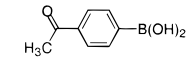
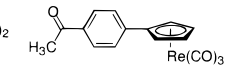
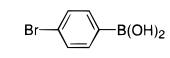
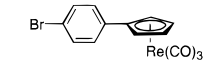
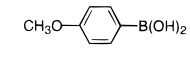
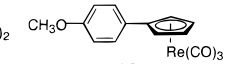
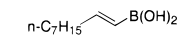
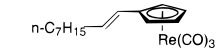
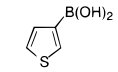
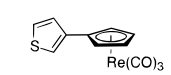
Figure 2. Cyclic voltammogram recorded at a platinum electrode in a CH_3CN solution (0.5 mM, vs Ag/AgCl reference electrode) of ferrocene-conjugated $CpRe(CO)_3$ complex **6g** (scan rate 0.1 V s^{-1}).

tions,[6a,13] in order for it to become attached to a suitable receptor ligand. To overcome this limitation, we first extended this transformation by the use of organic carboxylates (**5c**−**g**), which gave good yields of acyloxy-substituted $CpRe(CO)_3$ systems (entries 3−7, Table 1). This reaction tolerated the presence of protic hydrogens, so carboxylate species could be generated in situ by treating the corresponding carboxylic acid with triethylamine (see Experimental Section). Alcohol, phenol, carbonyl, and amide-NH substituents in the carboxylate nucleophile are also tolerated. This tolerance of active protons provides a great synthetic advantage, because it allows this reaction to be conducted on unprotected biologically active organic molecules.

Although the formation constants of various nucleophiles with the $[Re(CO)_3]^+$ cation are not known, a general characteristic of these reactive nucleophiles (halides and carboxylates) that work well in this reaction appears to be their "moderate" nucleophilicity. The fact that stronger nucleophilic reagents failed to give the desired Cp complex suggests that they underwent irreversible interactions with the metal center or with the coordinated carbonyl groups. Some "strong" nucleophiles that did not work in this reaction are primary amines, thiols, hydrides, hydroxide ions,[14] and alkoxides. On the other hand, "weaker" nucleophiles (e.g., alcohols, phenols, triflate, and nitrate ions) underwent no reaction with the other two components.

The last entry of Table 1 shows that a novel bimetallic complex (**6g**), containing a ferrocene moiety bound to the $CpRe(CO)_3$ unit, could be efficiently prepared by this method in one step from the commercially available carboxylic acid **5g**. Cyclic voltammetry analysis of complex **6g** (Figure 2) showed the well-known reversible

Table 2. Yields Obtained with Different Boronic Acids 7a−g (eqs 1 and 3)

entry	boronic acid	product	isolated yield (%)[a] conditions A[b]	conditions B[c]
1	 **7a**	 **8a**	64	59
2	 **7b**	 **8b**	34	52
3	 **7c**	 **8c**	39	50
4	 **7d**	 **8d**	74	42
5	 **7e**	 **8e**	51	76
6	 **7f**	 **8f**	72	-

[a] Yields are based on the initial rhenium precursor **3** (eq 1). [b] Conditions A: **4** (0.050 mmol), boronic acid (0.50 mmol), Et_3N (1.0 mmol), diazocyclopentadiene (0.060 mmol), CH_3CN (2.5 mL), 80 °C for 45 min. [c] Conditions B: **4** (0.050 mmol), boronic acid (0.10 mmol), Et_3N (0.20 mmol), diazocyclopentadiene (0.060 mmol), CH_3CN (2.5 mL), 80 °C for 14 h.

oxidation of the iron center[15] with $E_{1/2}(Fc/Fc^+) = +0.75$ V (vs Ag/AgCl). Oxidation of the rhenium was not observed at the potentials applied (up to +1.4 V). The redox characteristics of **6g** make it (or its derivatives) a potential candidate for residualizing radionuclides in hypoxic tissues,[16] which are found in various pathological states (solid tumors, stroke, ischemia, cardiovascular obstructions, etc.).

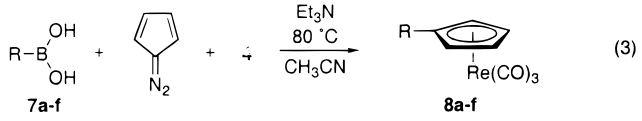
Carbon Nucleophiles. To form a connection between the organometallic complex and the organic unit in potential radionuclides that would be more robust than the ester linking group present in **6c**−**g** (Table 1), we considered using carbon nucleophiles in the "three-component" reaction. If successful, this would allow us to form directly a stable C−C bond as the linking group, which, unlike the esters, would not be prone to undergo hydrolytic or metabolic cleavage in vivo. By a preliminary screening of classical organometallic species (organolithium, organosilicon, organocopper), we found that none of them gave any of the desired Cp complex, presumably because they react irreversibly with the rhenium center or with its carbonyl ligands. Only very weak organometallic reagents, such as boronic acids (**7a**−**f**, eq 3, and Table 2), proved to have the proper reactivity for the synthesis of carbon-substituted $CpRe(CO)_3$ complexes **8a**−**f** under our reaction conditions.[12]

(13) (a) Lo Sterzo, C.; Miller, M. M.; Stille, J. K. *Organometallics* **1989**, *8*, 2331−2337. (b) Lo Sterzo, C.; Stille, J. K. *Organometallics* **1990**, *9*, 687−694.

(14) A remarkably high affinity of the solvated cation $Re(CO)_3^+$ for OH^- has been reported in: Egli, A.; Hegetschweiler, K.; Alberto, R.; Abram, U.; Schibli, R.; Hedinger, R.; Gramlich, V.; Kissner, R.; Schubiger, P. A. *Organometallics* **1997**, *16*, 1833−1840.

(15) Zanello, P. Electrochemical and X-ray Structural Aspects of Transition Metal Complexes Containing Redox-Active Ferrocene Ligands. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH Publishers: New York, 1995; Chapter 7.

(16) Uccelli, L.; Bolzati, C.; Boschi, A.; Duatti, A.; Morin, C.; Pasqualini, R.; Giganti, M.; Piffanelli, A. *Nucl. Med. Biol.* **1999**, *26*, 63−67, and references therein.



(3)

A few representative examples of this transformation are reported in Table 2. All of the aromatic boronic acids generally gave reasonable yields (entries 1−4 and 6, Table 2), although certain substituent effects are evident. Competition reactions confirmed that electron-donating substituents, like the *para*-methoxy group in **7d**, accelerate the reaction, whereas electron-withdrawing substituents, like those in **7b** and **7c,** decrease the reaction rate.[17] A more detailed discussion of this substituent effect is given later. Vinylic boronic acids (**7e**, Table 2, and **9**,[18] Scheme 2) also afforded good yields of the product complexes.

An important feature of this reaction is its tolerance toward a wide variety of functional groups, such as free alcoholic and phenolic hydroxy groups (Scheme 2), carbonyls, and aryl bromides (Table 2). Moreover, no catalyst is required by this transformation, unlike other cross-coupling reactions involving boronic acids, which always require a palladium catalyst.[19] The one-pot synthesis of estradiol analogue **10** (Scheme 2) starting from the vinyl boronic **9** is a good example of the use of this reaction to functionalize a biologically interesting compound with a rhenium organometallic unit, in a simple, fast, and efficient manner.

Substrate Features Affecting Reactivity. As mentioned in the two previous sections, only heteroatom and carbon nucleophiles of *moderate* strength proved to be efficient in this three-component reaction. Other aspects of the specific structures of the nucleophiles also affect reactivity (Figure 3); a careful analysis of these factors provides significant clues to the reaction mechanism.

The presence of strongly coordinating groups such as pyridines (*a*, Figure 3) interferes with the coupling reaction, probably because the metal atom is irreversibly coordinated by the pyridine nitrogen atom and cannot react further with the Cp precursor to form the cyclopentadienyl complex. A similar effect is encountered when even weaker coordinating groups are arranged in a geometry that allows for chelation, as in *b*. In fact, 3-thiopheneboronic acid produced the desired complex in good yield (entry 6, Table 2), whereas its regioisomer 2-thiopheneboronic acid, which can chelate with the metal, did not produce any Cp complex.

Another fundamental requirement is the presence of protic groups (acidic hydroxy groups) which can generate anions in the presence of weak bases such as triethylamine. Although the requirement for deprotonation is rather obvious for carboxylic acids, where the nucleophilic center is the anionic oxygen, in the case of organoboron reagents, where the ultimate nucleophilic center is the carbon atom, it was not immediately understood that deprotonation was also required. As shown in case *c* (Figure 3), only free boronic acids worked in this reaction, whereas boronic esters (which are usually reactive in Pd-catalyzed cross-coupling reactions)[19] are completely unreactive under our conditions. These first three cases suggest that in order for the reaction to proceed, it is essential to have donor sites that can precoordinate reversibly with the rhenium precursor, but that this precoordination must not be too strong, otherwise it prevents the metal center from subsequently becoming coordinated to the Cp ring.

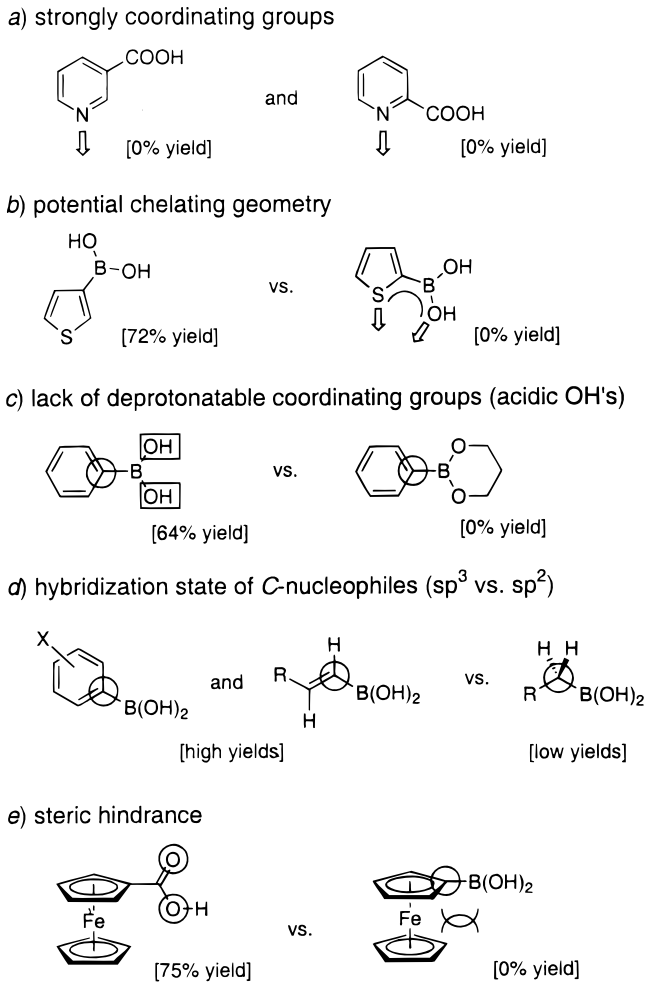
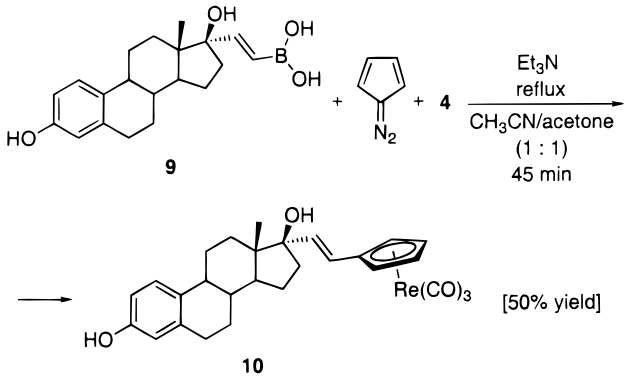


Figure 3. Nucleophile structural features affecting reaction yield (where relevant, nucleophilic sites have been circled).

Scheme 2. One-Step Synthesis of Estradiol Derivative 10 from Boronic Acid 9



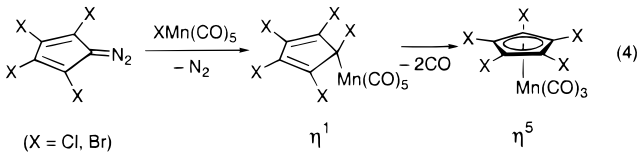
(17) A completely opposite trend is found in typical Pd-catalyzed cross-coupling reactions involving the same class of phenylboronic acids: Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149−151.

(18) (a) Kabalka, G. W.; Gooch, E. E.; Sastry, K. A. R. *J. Nucl. Med.* **1981**, *22*, 908−912. (b) Nakatsuka, I.; Ferreira, N. L.; Eckelman, W. C.; Francis, B. E.; Rzeszotarski, W. J.; Gibson, R. E.; Jagoda, E. M.; Reba, R. C. *J. Med. Chem.* **1984**, *27*, 1287−1291.

(19) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483, and references therein.

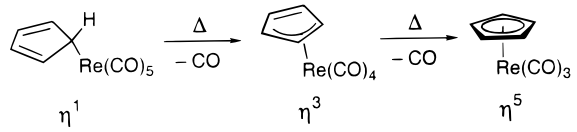
Case *d* in Figure 3 also shows that the reactivity depends on the hybridization of the carbon nucleophiles: aromatic and vinylic boronic acids generally give good yields (Table 2), whereas poor yields were obtained with aliphatic boronic acids.[12] Furthermore, the last example (*e*, Figure 3) shows that nucleophiles containing hindered sp^2-carbon atoms, such as ferroceneboronic acid, do not react at all, whereas a carboxylate analogue of ferrocene (entry 7, Table 1) shows an excellent reactivity. These last two examples indicate that the reaction is very sensitive to steric factors around the active nucleophilic carbon center. Flat sp^2-carbon nucleophiles are preferred over bulkier sp^3-counterparts, but when one face of the sp^2-hybridized nucleophile becomes hindered, as in case *e*, the yield is lowered. All the issues discussed in this initial analysis of structure/reactivity relationships constitute a solid basis for starting our mechanistic investigations.

Mechanistic Considerations: Reaction Intermediates. Understanding the mechanism of this unusual transformation is clearly a challenge. Some guidance is provided by related reactions, the closest precedents being the reactions of tetrahalogenated diazocyclopentadienes with pentacarbonylmanganese halides. In these reactions, η^1-metal pentacarbonyl adducts (eq 4) have been isolated and characterized[20] and were found to transform readily to the more stable η^5-metal tricarbonyl complexes.



(4)

Thermal ring slippage of η^1-$CpRe(CO)_5$ to η^5-$CpRe(CO)_3$ has recently been studied extensively (eq 5),[21] and evidence has been reported for the intermediacy of the η^3-$CpRe(CO)_4$ complex in this process.

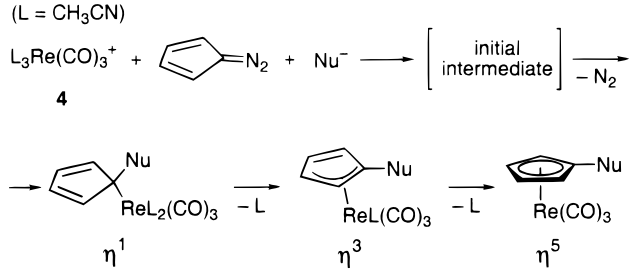


(5)

By analogy with these precedents, we believe that in our case the last two species involved in the reaction pathway before the final formation of the η^5-complex are the corresponding η^1- and the η^3-species (Scheme 3) in which the more labile donor solvent CH_3CN replaces two or one molecule of CO, respectively. Contrary to the literature examples shown in eq 4 and eq 5, we were not able to detect the η^1- and the η^3-intermediates, presumably due to their greater susceptibility toward ligand (CH_3CN) dissociation and ring slippage.

Although the last intermediates in this reaction can be reasonably surmised from these precedents, what happens at the beginning of this transformation still needs to be clarified. In fact, it is likely that the reaction

Scheme 3. Three Component Reaction through the η^1-species and the η^3–η^5 Ring Slippage Sequence



is started by association between two of the three reagents, to form an "initial intermediate" (Scheme 3), which then reacts with the third reagent to give the η^1-complex. In the literature examples shown above (eq 4),[20] diazocyclopentadiene derivatives undergo insertion reactions into polar Re–Cl and Re–Br bonds, losing molecular nitrogen, and generating the first detectable η^1-intermediate. If the same process happens in our reaction, then the initial step must be an association of the $(CH_3CN)_3Re(CO)_3^+$ precursor (**4**) with the anionic nucleophile, forming a polar Re–Nu bond into which diazocyclopentadiene subsequently inserts.

The proposal that the nucleophile reacts first with the $(CH_3CN)_3Re(CO)_3^+$ precursor is supported by IR and NMR experiments. No association reaction and no consumption of reagents were observed by ^1H and ^{13}C NMR spectrometry or solution IR spectroscopy when diazocyclopentadiene was mixed either with the nucleophile or with the rhenium precursor alone. On the other hand, significant spectroscopic changes associated with both the metal and the nucleophile were observed when the rhenium precursor was mixed with the nucleophile.

Figure 4 shows ^{13}C NMR experiments in which a solution of [1-^{13}C]acetic acid in CD_3CN (spectrum *a*; δ 172.72) was treated with triethylamine to generate the acetate anion (spectrum *b*; δ 176.10). Then, 1 equiv of $[(CD_3CN)_3Re(CO)_3]^+TfO^-$, prepared like its *protio*-analogue **4** (eq 1), was added, at which point the carboxylate anion was transformed into four new species (spectrum *c*; δ 176.78, 177.27, 177.49, 180.67). The nature of these intermediates will be discussed below. After addition of diazocyclopentadiene (spectra *d*, *e*, and *f*), all these species, even the longer-lasting one at δ 180.67, were converted into the final η^5-cyclopentadienyl complex [^{13}C]-**6c** (see Table 1), which showed a peak at δ 168.90. The same behavior was found in an identical experiment conducted with [1-^{13}C]-benzoic acid (δ 167.84, data not shown). Here again, several species appeared after treatment of the labeled benzoate (δ 171.92) with the rhenium precursor (δ 171.72, 171.91,[22] 172.60, 175.06), which, after addition of $C_5H_4N_2$, were eventually all converted into the final complex [^{13}C]-**12b** (see Scheme 6), which showed a peak at δ 164.28.

A reasonable explanation for the formation of multiple intermediates from the interaction between carboxylate anions and the solvated $Re(CO)_3^+$ species is presented in Scheme 4. The species involved in the equilibria shown here have precedents in reactions involving Re^I

(20) (a) Herrmann, W. A.; Huber, M. *J. Organomet. Chem.* **1977**, *140*, 55–61. (b) Day, V. W.; Stults, B. R.; Reimer, K. J.; Shaver, A. *J. Am. Chem. Soc.* **1974**, *96*, 4008–4009.

(21) Young, K. M.; Miller, T. M.; Wrighton, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 1529–1537.

(22) The chemical shift of this peak is very similar to the starting benzoate; so, it is also possible that there is still some uncoordinated benzoate and that, as opposed to the case with acetate, only three coordinated species are formed.

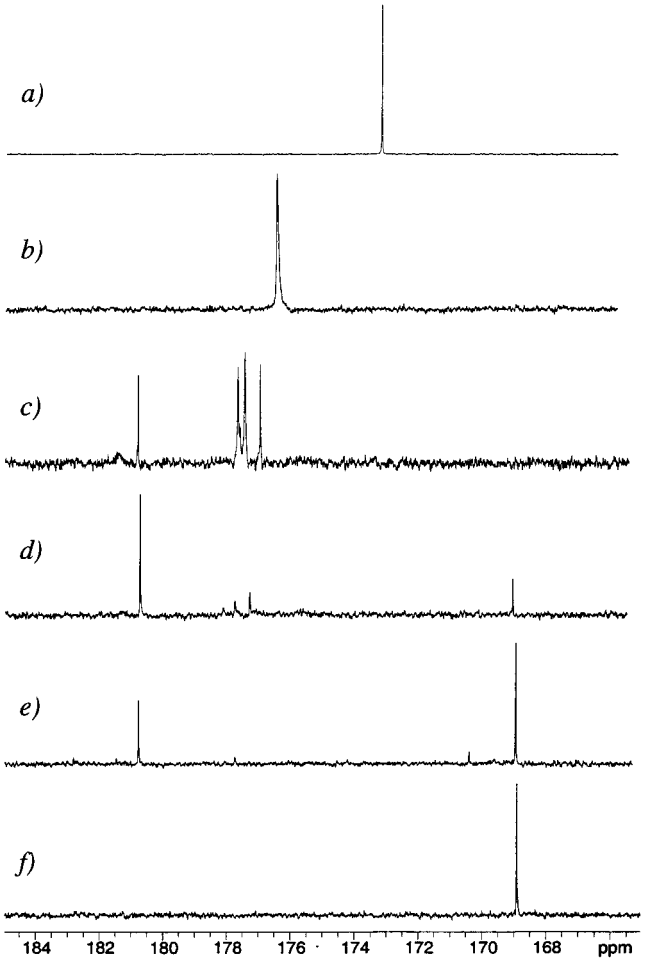
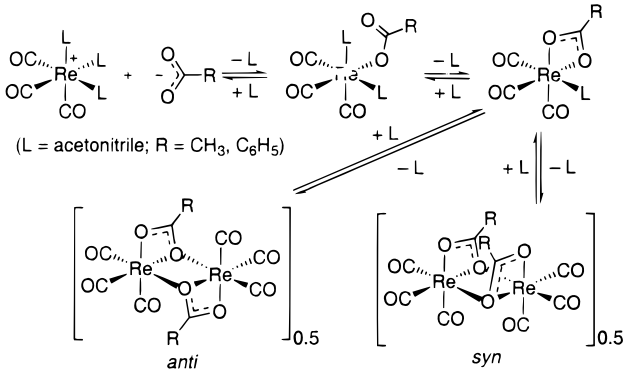


Figure 4. ^{13}C NMR spectra of (a) $CH_3{}^{13}COOH$ (0.097 mmol) in CD_3CN (1.1 mL); (b) after addition Et_3N (0.20 mmol); (c) after addition of $[(CD_3CN)_3Re(CO)_3]^+TfO^-$ (0.10 mmol); (d) after addition of $C_5H_4N_2$ (0.50 mmol), 23 °C, 5 min; (e) sample d after 4.5 h at 23 °C; (f) sample e after 1 h at 70 °C.

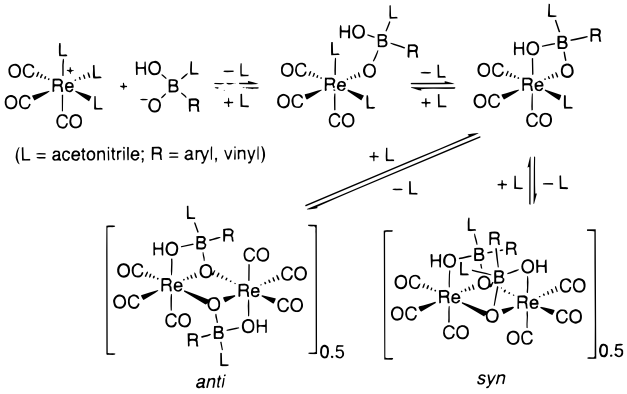
Scheme 4. Species Likely Involved in the Association Process of Acetate and Benzoate Anions with the Rhenium Precursor (Spectrum *c*, Figure 4)[23]



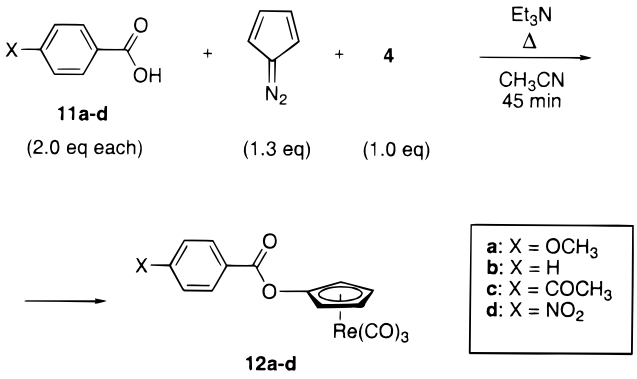
and Tc^I pentacarbonyl species and potentially bidentate ligands of general formula A_2Y (A = O, S, Se; Y = CH, CR, COR, CNR_2, PR_2, AsR_2).[23] As shown in Scheme 4, up to four species (unidentate, chelate, *syn*- and *anti*-dimers) can be formed, and, consistently, NMR shows four different peaks when the carboxylate and the $Re(CO)_3{}^+$ precursor are mixed together (spectrum *c*, Figure 4).

(23) See ref 3, pp 188−190.

Scheme 5. Proposed Equilibria Involving Boronic Acids in the Initial Association Process with the Rhenium Precursor



Scheme 6. Competition Reactions of *para*-Substituted Benzoic Acids 11a−d with the Rhenium Precursor 4 and Diazocyclopentadiene



X-	product ratio	k_X/k_H
CH_3O-	0.41	1.14
H-	0.36	1.00
$CH_3C(O)$-	0.23 (0.67)	0.64
NO_2-	(0.33)	0.31

So far, attempts to characterize these mixtures of intermediates formed in acetonitrile solution by electrospray ionization mass spectrometry (ESI-MS) have failed, most likely because all of these species are neutral and, therefore, difficult to detect by this technique. Only fragments derived from the *fac*-$Re(CO)_3{}^+$ portion could be observed. Analysis of IR spectra of acetonitrile solutions of **4** showed a splitting of the ν_{as}-(CO) band (1935 cm^{-1}) into two broad bands (1934 and 1912 cm^{-1}) after addition of 1 equiv of tetraethylammonium acetate. This result is a clear indication of a change in the coordination environment around the metal center resulting from the Re−acetate association, but since several species are probably simultaneously

Table 3. Relative Rate Constants (k_X/k_H) Found in the Competition Reaction of *para*-Substituted Benzoic Acids 11a−d (Scheme 6) and Hammett Constants σ (eq 6)[24]

entry	nucleophile[a]	X[a]	σ[b]	k_X/k_H[c]	$\log(k_X/k_H)$
1	**11a**	*p*-methoxy	−0.27	1.14	0.057
2	**11b**	H	0.00	(1.00)	(0.00)
3	**11c**	*p*-acetyl	0.50	0.64	−0.19
4	**11d**	*p*-nitro	0.78	0.31	−0.51

[a] See Scheme 6. [b] Reference 24 and eq 6. [c] Values equal to product ratios determined by ^{1}H NMR integration of the reaction product mixture.

present at equilibrium (Scheme 4), nothing further can be deduced from this experiment.

Similar multiple equilibria can be proposed for the reaction with boronic acids. Interestingly, when the addition of the $Re(CO)_3^+$ precursor to (*E*)-1-nonenylboronic acid (**7e**, Table 2) was followed by ^{1}H NMR, the peaks for the vinylic hydrogens suggest the formation of at least four different Re−boronate adducts. This result can be explained by assuming the occurrence of the multiple equilibria shown in Scheme 5, which are analogous to the ones proposed for carboxylates (Scheme 4). The fact that only free boronic acids are reactive, whereas boronic esters are completely unreactive, suggests that this preassociation step is essential for the reaction to proceed. Therefore, we believe that at least one of the several associated intermediates shown in Scheme 4 and Scheme 5 is the species which then reacts with diazocyclopentadiene to give the final product. Because boronic esters cannot form these kinds of preassociated intermediates, they are unable to serve as nucleophiles in the synthesis of the $CpRe(CO)_3$ products.

Substituent Effects on Relative Reaction Rates: Transition State Speculations. The experiments described in the previous section suggest that preequilibria involving coordination of the nucleophile to the metal center are the first steps in the synthesis of the $CpRe(CO)_3$ products. However, thereafter, no further intermediates could be detected until the final η^5-Cp complex is formed. The reaction between the preassociated species (Scheme 4 and Scheme 5) and diazocyclopentadiene is the rate-determining step in the three-component reaction. Therefore, an analysis of factors affecting the reaction rate can provide useful information about the transition state involved. For this purpose, competition reactions between different *para*-substituted benzoic acids (**11a**−**d**, Scheme 6) were conducted, and a Hammett free energy correlation analysis (eq 6)[24]

$$\log\left(\frac{k_X}{k_H}\right) = \rho\sigma \qquad (6)$$

of the effect of the electronic properties of the nucleophile (substituent constants σ, Table 3) on the relative reaction rates was carried out. The results, reported in Table 3, clearly show that electron-donating substituents such as *para*-methoxy (entry 1) accelerate the reaction with respect to unsubstituted benzoate, whereas

(24) (a) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96−103. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195, and references therein.

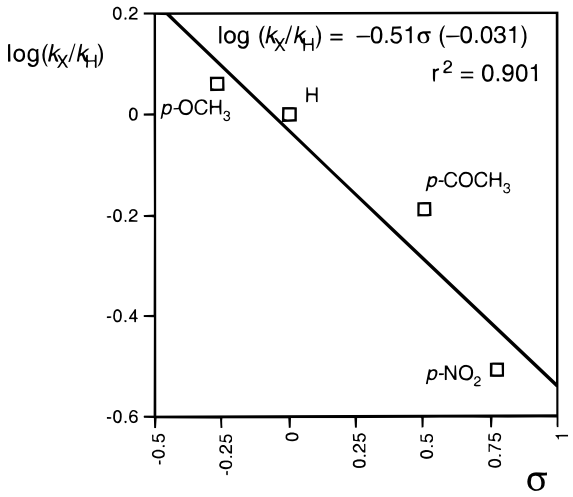


Figure 5. Hammett $\rho\sigma$ plot and least-squares curve-fit equation for the competition reactions involving *para*-substituted benzoates **11a**−**d** (Scheme 6).

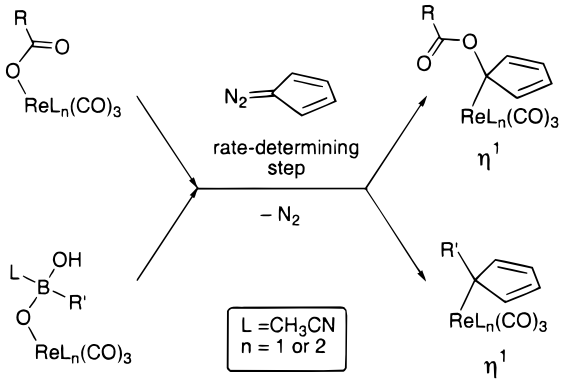
electron-withdrawing substituents slow the reaction (entries 3, 4). These results have been inserted into the Hammett equation (eq 6), which correlates the logarithm of the rate constants with the Hammett σ-constants of the substituent. The reaction constant ρ gives a measure of the sensitivity of the reaction rate to changes in the electronic properties of the reagent.

A $\rho\sigma$ plot of the data from Table 3 is shown in Figure 5, together with a least-squares linear curve-fit and its resulting equation. The calculated reaction constant ρ has a value of −0.51 (Figure 5), which indicates a notable sensitivity of the reaction to the substituent effects. The negative ρ value means that the reaction is accelerated by electron-donating substituents. This result implies that nucleophilic attack by the benzoate is likely involved in the rate-determining step (see below).[25]

As was mentioned earlier, a similar competition reaction was also conducted with different *para*-substituted phenylboronic acids (**7a**−**d**, Table 2),[12] and here again electron-donating substituents such as *para*-methoxy in **7d** accelerated the reaction, whereas electron-withdrawing substituents lowered the reaction rate. In this case, it was not feasible to make a Hammett correlation because of the simultaneous occurrence of a side reaction, protodeboronation, whose rate is also increased by electron-donating substituents.[26] Nevertheless, a direct dependence of the reaction rate on the

(25) The statistical correlation factor for the Hammett linear plot of our data is not excellent ($r^2 = 0.901$, Figure 5), but a certain deviation from the linear correlation can be attributed to several factors: (i) the nucleophilic species involved in the rate-determining step are not free benzoates (for which σ values have been originally tabulated), but are rhenium-coordinated benzoates (see Scheme 7) and therefore might need adjustments in their σ values, which are currently not available; (ii) solvent effects on σ values have been reported in the past (see refs a−d reported below), especially when hydroxylic solvents such as water (solvent in which σ values have been originally tabulated) are replaced by non-hydroxylic solvents such as acetonitrile, used in our reaction. These considerations can explain why there is not a more linear Hammett correlation, although the significance of the nucleophile strength-dependence of the reaction rate, and therefore the active participation of the nucleophile to the rate-determining step, is not questionable. See: (a) Ritchie, C. D.; Lewis, E. S. *J. Am. Chem. Soc.* **1962**, *84*, 591−594. (b) Taft, R. W. *J. Phys. Chem.* **1960**, *64*, 1805−1815. (c) Amis, E. S. *Solvent Effects on Reaction Rates and Mechanisms;* Academic Press: New York, 1966; pp 152−159. (d) Hine, J. *Physical Organic Chemistry;* McGraw-Hill: New York, 1962; pp 88−93.

Scheme 7. Rate-Determining Step: Reaction of Precoordinated Rhenium−Nucleophile Species with Diazocyclopentadiene to Give the Short-Lived η^1-Complex Intermediate



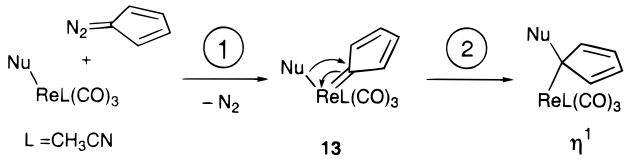
nucleophilic strength can also be confidently affirmed for this class of carbon nucleophiles. Both of these results are very useful in suggesting a possible transition structure involved in the rate-determining step.

The results described in the previous section suggest that a rapid preassociation between the rhenium and nucleophile species occurs before the rate-determining step. We think that among the four possible adducts (Schemes 4, 5), the reactive species for both carboxylates and boronic acids are the unidentate adducts, i.e., those formed by loss of one acetonitrile ligand (Scheme 7, $n = 1$). On the basis of literature precedents (eqs 4, 5),[20,21] we also hypothesized the occurrence of a short-lived η^1-complex (Scheme 3), which rapidly undergoes a ring slippage sequence to form the final η^5-complex. What happens between (Scheme 7, rate-determining step) still needs to be established. We have noticed that the reaction rate increases when higher concentrations of diazocyclopentadiene are used, although exact kinetic experiments have not been run. Nevertheless, this rate dependence indicates that diazocyclopentadiene is participating in the rate-determining step.

One possibility is that the reaction proceeds through a metal−carbene species. Such species can be formed in different ways. However, it is very unlikely that, under our conditions, diazocyclopentadiene directly generates a free carbene by loss of molecular nitrogen, because such a process generally requires rather high temperatures or UV irradiation, and we have found that the reaction proceeds even at room temperature in the dark. Moreover, free carbenes are known to react readily with acetonitrile, producing several nitrile-containing addition products,[27] none of which have been detected under our conditions. Nevertheless, metallocarbenoid species of several transition metals can also be formed upon direct interaction of diazo compounds with the metal precursors (Scheme 8), and they are known to be reactive intermediates for several transformations.[28]

However, there are a few points that rule against this mechanism. In a metallocarbenoid pathway (Scheme 8),

Scheme 8. Hypothetical Intermediacy of Metallocarbenoid Species 13



if the rate-determining step were the formation of the Re−carbene intermediate **13** (step 1), then we should not expect the reaction rate to be accelerated by increasing the strength of the nucleophilic reagent (Nu), because step 1 does not involve any nucleophilic reaction. Furthermore, in the formation of metal−carbene species, the metal precursors react as *electrophiles* with diazo compounds.[28a] Therefore, this step should be accelerated by electron-withdrawing substituents on the nucleophile. These considerations are not consistent with what we found in the competition reaction data reported in Table 3 and with the Hammett correlation of Figure 5.[29]

Another possibility for a metallocarbenoid reaction pathway would be if the transformation of **13** into the η^1-complex were the slow step (step 2, Scheme 8). In this case, the carbene species **13** should be a rather stable low-energy intermediate that we should be able to detect. But, as shown by the NMR experiments reported in Figure 4, no such intermediates were found after addition of diazocyclopentadiene to the rhenium−nucleophile mixture. Moreover, if these species were formed, we should also see a reaction between the $Re(CO)_3^+$ species (**4**, eq 1) and diazocyclopentadiene in the absence of the nucleophile. However, as mentioned above, no reaction occurred between **4** and $C_5H_4N_2$ in the absence of the nucleophile under the reaction conditions. All these considerations indicate that a mechanism involving the occurrence of a metal−carbene species can reasonably be ruled out.[29]

We believe that the mechanism that is most consistent with all of our experimental observations involves a transition state derived from a *concerted* formation of the two bonds on the cyclopentadienylic C-1 carbon with both the nucleophile and the metal center (Scheme 9).

In this mechanism, the bimolecular nucleophilic substitution (S_N2) character of the slow step, driven by the oxygen atom of the carboxylate (*a*, Scheme 9) and by the carbon substituent R′ of the boronic acid (*b*, Scheme 9), can explain the remarkable sensitivity of this reaction toward the nucleophilicity of the reagents. Such S_N2-like transition states are stabilized by extended

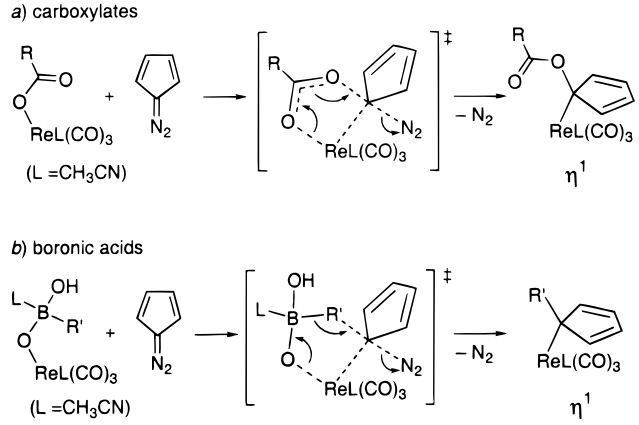
(26) (a) Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666−2670. (b) Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *Can. J. Chem.* **1963**, *41*, 3081−3090.

(27) Griller, D.; Hadel, L.; Nazran, A. S.; Platz, M. S.; Wong, P. C.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2227−2235, and references therein.

(28) (a) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348−356. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263−309. (c) *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Elmsford, NY, 1995; Vol. 12, Chapters 5.1−5.5, and references therein.

(29) An alternative mechanism might involve as the rate-limiting step the loss of a ligand (CH_3CN) from the rhenium center of the preassociated rhenium−nucleophile species, to generate an open coordination site, prior to the association with diazocyclopentadiene. One would expect in this case that electron-donating substituents on the carboxylate would facilitate ligand (CH_3CN) dissociation and would accelerate the overall reaction. The subsequent reaction would need to be rapid: carbenoid formation, nucleophilic attack, and rearrangement. However, the fact that the reaction rate depends on the diazocyclopentadiene concentration rules out the possibility that the loss of acetonitrile from the metal−nucleophile intermediate is the rate-determining step of the reaction.

Scheme 9. Proposed Concerted Transition States for the Reaction of Both Carboxylates (*a*) and Boronic Acids (*b*)

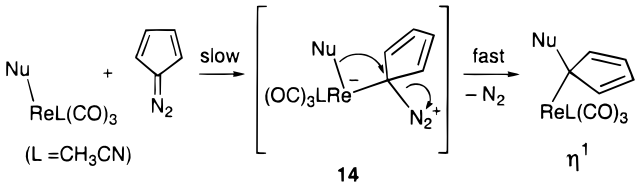


π-conjugation, as would operate in the cyclic diene system of the Cp ring.

Although these mechanistic pathways (*a* and *b*, Scheme 9) are almost identical for carboxylates and boronic acids, the different product outcomes (oxygen-substituted complexes from the former, carbon-substituted complexes from the latter) can be explained as follows. Once precoordinated to rhenium, carboxylates have only one free nucleophilic site, the uncoordinated carboxylic oxygen, which eventually forms a bond with the C-1 atom of the Cp ring of the final complex. On the other hand, precoordinated boronic acids still have two potentially available nucleophilic centers, a hydroxy and a carbon substituent. In this case, because of the great oxophilicity of boron, the carbon substituent is much more easily released and attacks the C-1 atom of the Cp ring, producing carbon-substituted complexes. Boronic acids are also known to undergo transmetalation processes in the presence of palladium or rhodium catalysts in several recently reported reactions.[19,30] Therefore, it is not impossible, even in our reaction, that a boron/rhenium transmetalation step could occur before the coordinated metal center reacts with diazocyclopentadiene. However, transmetalation reactions are known to occur readily for boronic *esters*,[19] just as well as for free boronic *acids*, and in our reaction boronic *esters* proved to be completely unreactive (Figure 3, case *c*). This result suggests that an initial transmetalation step is unlikely in our case and supports the formation of reactive intermediates in which the rhenium is coordinated to the boronic acid through a deprotonated oxygen atom (Scheme 9, eq *b*).

An alternative *stepwise* mechanism involving a high-energy intermediate **14** (Scheme 10) can also be ruled out, because the slow step, which is the initial electrophilic addition of the metal center onto the cyclopentadienyl C-1 carbon, does not involve the nucleophile. In fact, the nucleophile transfer from the rhenium to the Cp ring occurs in the fast step. Therefore, this mechanism should not be accelerated by electron-donating substituents present on the nucleophile, contrarily to what is observed experimentally. We can therefore assume that the *concerted* transition state illustrated in Scheme 9 is the most reasonable.

Scheme 10. Alternative Stepwise Reaction of the Preassociated Re–Nu Species with $C_5H_4N_2$ through the High-Energy Intermediate 14



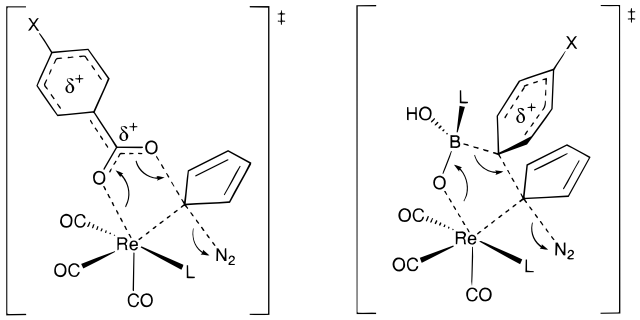


Figure 6. Distribution of the partial positive charge in transition states for *para*-substituted benzoates and phenylboronic acids (L = acetonitrile).

The partial positive charge distribution, and its stabilization or destabilization by the aromatic substituent X in the concerted transition states involving *para*-substituted benzoates and phenylboronic acids, is shown in Figure 6. In both cases it is clear that the electron donation by the aromatic substituent X in the *para* position can effectively stabilize the transition state and, thereby, accelerate the reaction. In the case of carboxylates, the partial positive charge that develops on the carboxylic carbon atom can be efficiently delocalized onto the aromatic ring and onto the *para*-substituent X. Similarly, the partial positive charge that develops on the aromatic ring of phenyl boronic acids can be stabilized by the electron-donating substituent in the *para*-position. In this latter case, the transition state closely resembles the one involved in an aryl-1,2-nucleophilic migration reaction, which, analogously, is known to be accelerated by electron-donating aromatic substituents.[31,32]

Some of the structure–reactivity relationships reported earlier in Figure 3 can be explained on the basis of the transition states proposed here. For example, steric reasons can account for the lower reactivity of aliphatic boronic acids compared to aromatic and vinylic

(30) (a) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3279–3281. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580. (c) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229–4231.

(31) 1,2-Aryl migrations, as occur in nucleophilic displacements with anchimeric assistance, have large, negative ρ values (−1.3 to −6.3). Typical examples are provided in these references: (a) Kingsbury, C. A.; Best, D. C. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3440–3445. (b) Thompson, J. A.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 1778–1789. (c) Kim, C. J.; Brown, H. C. *J. Am. Chem. Soc.* **1969**, *91*, 4286–4287, 4287–4289, 4289–4291. (d) Lancelot, C. J.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1969**, *91*, 4291–4294. (e) Lancelot, C. J.; Harper, J. J.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1969**, *91*, 4294–4296.

(32) As noted in the text, we were unable to measure a ρ value for the direct aryl migration as occurs in the boronic acid substitution, because of competitive protodeboronation. In the case of carboxylates **11a–d**, our ρ value of −0.51 is understandably smaller than the values reported in ref 31, because the electron-donating effect in the nucleophile has to operate through a carboxyl group.

boronic acids (case *d*, Figure 3). In fact, a flat sp^2-hybridized carbon substituent fits very nicely between the Cp ring and the tetracoordinated boron atom in this "sandwich-like" transition state (Figure 6). An sp^3-hybridized carbon substituent is not flat and, therefore, presents more serious steric hindrance, which would increase the energy of the transition state, slowing the reaction or making it less efficient. Even worse is the case of ferroceneboronic acid (case *e*, Figure 3): although it is an sp^2-hybridized boronic acid, one face of the carbon−nucleophilic center is so severely hindered by the second Cp ring and the iron atom that it is unreactive. In fact, it is rather difficult to imagine how such a bulky reagent could even fit into the transition state we have proposed. This mechanism also accounts for stereospecific transformation of (*E*)-vinylboronic acids to (*E*)-vinyl-substituted $CpRe(CO)_3$. In fact, complexes **8e** (Table 2) and **10** (Scheme 2), both derived from (*E*)-vinyl boronic acids, specifically maintain their *trans* double-bond configuration, as shown by their vinylic hydrogens' coupling constants of 15.7 and 15.9 Hz, respectively. No *cis*-isomer was ever observed in either case.

Conclusion

The reaction of diazocyclopentadiene, a *fac*-$Re(CO)_3^+$ precursor, and a nucleophile has proved to be an efficient synthetic method for preparing substituted η^5-$CpRe(CO)_3$ complexes. The reaction shows a great tolerance toward reactive functional groups. The main limitation of this reaction is related to the strength of the nucleophiles used: only *moderate* nucleophilic species, such as halides and carboxylates among heteroatom nucleophiles and boronic acids among carbon nucleophiles, give good yields. The reaction also proved to be rather sensitive to steric factors. These limitations and further structure−reactivity relationships established experimentally are in good agreement with the mechanism herein proposed, which involves an initial rapid association between the nucleophilic species and the tricarbonyl−metal precursor. This association process produces up to four intermediary species in equilibrium, as shown by NMR experiments, although their exact constitution proved difficult to ascertain. According to our proposed mechanism, a preassociated unidentate metal−nucleophile precursor then reacts, in the rate-determining step, with diazocyclopentadiene through a *concerted* S_N2-like transition state to produce a short-lived η^1-complex, which rapidly undergoes a ring slippage through a η^3-species to the final η^5-complex. In these last steps, from the Re−nucleophile intermediates to the final complex, no further intermediates could be detected. This general mechanism should be equally valid for the formation of different complexes such as halogen-, acyloxy-, and carbon-substituted ones, and it accounts for structural features that prevent certain nucleophiles from reacting effectively. The experimental results and the theoretical speculations herein reported constitute a solid basis for starting more rigorous mechanistic studies devoted to accurately establish kinetic parameters (reaction orders, rate constants), as well as for designing experiments to more precisely identify and characterize the reaction intermediates involved in this synthetically useful transformation.

Experimental Section

General Comments. Unless otherwise specified, reagents and solvents used in this study were purchased from commercial sources (Aldrich, Strem, Eastman, Fisher, or Mallinckrodt) and were used without further purification. Acetonitrile and triethylamine were distilled over calcium hydride under nitrogen. Analytical thin-layer chromatography (TLC) was run on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved using UV illumination and/or phosphomolybdic acid (PMA). Flash chromatography was performed according to the method reported in the literature[33] with Woelm silica gel (0.040−0.063 mm) packing. Compound **3** was prepared as described in the literature.[10c] Diazocyclopentadiene was always used as a 1.73 M pentane solution prepared according to Reimer and Shaver.[9b] *For safety reasons, diazocyclopentadiene should always be kept in solution and never used neat.*[9b] 1-Nonenylboronic acid (**7e**) was prepared according to a general procedure reported by Brown and co-workers.[34] A literature procedure[18] for the synthesis of estradiol derivative **9** was followed. Characterization data of halogen-substituted complexes **6a** and **6b** were in good agreement with previously reported data.[9a,13a,35] Purification conditions and characterization data for some acyloxy- (**6c**−**f**)[11] and carbon-substituted (**8a**−**e**, **10**)[12] $CpRe(CO)_3$ complexes have already been reported.

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained with a Mattson Galaxy Series FT-IR 3000 using NaCl plates or KBr pellets. NMR spectra were recorded on a U400 or U500 Varian FT-NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from internal tetramethylsilane or from proton resonances resulting from incomplete deuteration of the NMR solvent. Low-resolution electron impact (EI) mass spectra were obtained on a Finnigan MAT CH5 spectrometer. High-resolution EI mass spectra were obtained on a Finnigan MAT 731 spectrometer. The cyclic voltammogram for **6g** was recorded on a Bioanalytical System BAS-CV 50W electrochemical analyzer with a platinum working electrode. The measurement was performed at ambient temperatures under a nitrogen atmosphere in a 0.1 mM acetonitrile solution of $[n\text{-}Bu_4N]^+[PF_6]^-$ vs Ag/AgCl as the reference electrode. The $E_{1/2}$ value is reported vs Ag/AgCl; the couple is described as reversible (r), as verified from the ratio of the anodic to cathodic current (i_a/i_c), which was within 10% of unity.

Typical Experimental Procedure for the Synthesis of Acyloxy-Substituted $CpRe(CO)_3$ Complexes (6c−g, 12a−d). $(Et_4N)_2[ReBr_3(CO)_3]$ (**3**) (3 39 mg, 0.050 mmol) was dissolved in anhydrous CH_3CN (1.5 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing diazocyclopentadiene (35 μL of a 1.73 M pentane solution, 0.060 mmol), the carboxylic acid (**5c**, **5e**−**g**, **11a**−**d**) (0.10 mmol), and triethylamine (0.20 mmol) in CH_3CN (1 mL). The mixture was heated at 80 °C for 45 min and then concentrated under vacuum. In the case of **5d**, the commercially available sodium salt was used (0.10 mmol); therefore no triethylamine was added to the reaction mixture. The crude reaction product was purified by flash chromatography.

[(Ferrocenyloxy)cyclopentadienyl]tricarbonylrhenium (6g). Yield: 75%, orange solid. Mp: 155 °C. R_f (silica

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gel, Hex/Et_2O 9:1): 0.21. IR (NaCl): cm^{-1} 2021, 1914, 1737, 1445, 1267, 1233, 1092. ^1H NMR (500 MHz, $CDCl_3$): δ 5.63 (*pseudo* t, 2H, J = 2.4 Hz), 5.19 (*pseudo* t, 2H, J = 2.4 Hz), 4.84 (*pseudo* t, 2H, J = 2.0 Hz), 4.51 (*pseudo* t, 2H, J = 2.0 Hz), 4.27 (s, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.69, 168.81, 129.65, 79.37, 74.45, 72.43, 70.52, 70.11, 68.20. MS (EI, 70 eV): *m*/*z* 564 (M, ^{187}Re, 39), 562 (M, ^{185}Re, 25), 358 (M − 3CO − (C_5H_5)Fe − H, ^{187}Re, 10), 356 (M − 3CO − (C_5H_5)Fe − H, ^{185}Re, 6), 213 ($(C_5H_5)Fe(C_5H_4CO)$, 100), 185 ($(C_5H_5)Fe(C_5H_4)$, 39). HRMS (EI, 70 eV): Calcd for $C_{19}H_{13}O_5Fe^{185}Re$ 561.9642. Found: 561.9651. Calcd for $C_{19}H_{13}O_5Fe^{187}Re$: 563.9670. Found: 563.9657. $E_{1/2}$ (Fe^{II}/Fe^{III}): +747 (r) mV.

[(4-Methoxybenzoyloxy)cyclopentadienyl]tricarbonylrhenium (12a). Yield: 78%, colorless solid. Mp: 101 °C. R_f (silica gel, Hex/Et_2O 9:1): 0.12. IR (NaCl): cm^{-1} 2022, 1916, 1742, 1606, 1512, 1466, 1258, 1231, 1168, 1059. ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (AA′XX′, 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 6.95 (AA′XX′, 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.4 Hz), 5.65 (*pseudo* t, 2H, J = 2.4 Hz), 5.21 (*pseudo* t, 2H, J = 2.4 Hz), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.55, 164.40, 163.12, 132.40, 129.71, 120.09, 114.04, 79.63, 74.70, 55.56. MS (EI, 70 eV): *m*/*z* 486 (M, ^{187}Re, 12), 484 (M, ^{185}Re, 7), 458 (M − CO, ^{187}Re, 9), 456 (M − CO, ^{185}Re, 5), 402 (M − 3CO, ^{187}Re, 5), 400 (M − 3CO, ^{185}Re, 3), 135 ($CH_3OC_6H_4CO$, 100). HRMS (EI, 70 eV): Calcd for $C_{16}H_{11}O_6{}^{185}$Re 484.0085. Found: 484.0078. Calcd for $C_{16}H_{11}O_6{}^{187}$Re: 486.0113. Found: 486.0102.

[(Benzoyloxy)cyclopentadienyl]tricarbonylrhenium (12b). Yield: 79%. Colorless solid. Mp: 99 °C. R_f (silica gel, Hex/Et_2O 9:1): 0.17. IR (NaCl): cm^{-1} 2028, 1908, 1745, 1462, 1267, 1062. ^1H NMR (500 MHz, $CDCl_3$): δ 8.07−8.05 (m, 2H), 7.64 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.9 Hz), 5.68 (*pseudo* t, 2H, J = 2.5 Hz), 5.23 (*pseudo* t, 2H, J = 2.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.43, 163.42, 134.29, 130.18, 129.33, 128.76, 127.91, 79.69, 74.78. MS (EI, 70 eV): *m*/*z* 456 (M, ^{187}Re, 16), 454 (M, ^{185}Re, 10), 428 (M − CO, ^{187}Re, 24), 426 (M − CO, ^{185}Re, 14), 372 (M − 3CO, ^{187}Re, 12), 370 (M − 3CO, ^{185}Re, 7), 105 (C_6H_5CO, 100), 77 (C_6H_5, 46). HRMS (EI, 70 eV): Calcd for $C_{15}H_9O_5{}^{185}$Re 453.9980. Found: 453.9966. Calcd for $C_{15}H_9O_5{}^{187}$Re: 456.0008. Found: 455.9994.

[(4-Acetylbenzoyloxy)cyclopentadienyl]tricarbonylrhenium (12c). Yield: 68%, colorless solid. Mp: 106 °C. R_f (silica gel, Hex/Et_2O 7:3): 0.15. IR (NaCl): cm^{-1} 2023, 1916, 1749, 1466, 1256, 1232, 1079. ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (AA′XX′, 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 1.8 Hz), 8.05 (AA′XX′, 2H, J_{AX} = 8.7 Hz, $J_{AA'/XX'}$ = 1.8 Hz), 5.70 (*pseudo* t, 2H, J = 2.4 Hz), 5.24 (*pseudo* t, 2H, J = 2.4 Hz), 2.66 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.24, 193.30, 162.58, 141.17, 131.59, 130.45, 128.83, 128.48, 79.78, 74.81, 26.91. MS (EI, 70 eV): *m*/*z* 498 (M, ^{187}Re, 17), 496 (M, ^{185}Re, 10), 470 (M − CO, ^{187}Re, 21), 468 (M − CO, ^{185}Re, 12), 414 (M − 3CO, ^{187}Re, 14), 412 (M − 3CO, ^{185}Re, 9), 147 ($CH_3C(O)C_6H_4CO$, 100), 119 ($CH_3C(O)C_6H_4$, 12). HRMS (EI, 70 eV): Calcd for $C_{17}H_{11}O_6{}^{185}$Re 496.0085. Found: 496.0071. Calcd for $C_{17}H_{11}O_6{}^{187}$Re: 498.0113. Found: 498.0095.

[(4-Nitrobenzoyloxy)cyclopentadienyl]tricarbonylrhenium (12d). Yield: 62%, pale yellow solid. Mp: 122 °C. R_f (silica gel, Hex/Et_2O 8:2): 0.14. IR (NaCl): cm^{-1} 2022, 1921, 1758, 1527, 1457, 1346, 1260, 1234, 1075. ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (AA′XX′, 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.1 Hz), 8.24 (AA′XX′, 2H, J_{AX} = 9.0 Hz, $J_{AA'/XX'}$ = 2.1 Hz), 5.71 (*pseudo* t, 2H, J = 2.5 Hz), 5.25 (*pseudo* t, 2H, J = 2.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.13, 161.60, 151.21, 133.27, 131.33, 128.30, 123.90, 79.87, 74.86. MS (EI, 70 eV): *m*/*z* 501 (M, ^{187}Re, 57), 499 (M, ^{185}Re, 35), 473 (M − CO, ^{187}Re, 100), 471 (M − CO, ^{185}Re, 69), 445 (M − 2CO, ^{187}Re, 16), 443 (M − 2CO, ^{185}Re, 12), 417 (M − 3CO, ^{187}Re, 12), 415 (M − 3CO, ^{185}Re, 7), 387 (M − 3CO − NO, ^{187}Re, 22), 385 (M − 3CO − NO, ^{185}Re, 12), 371 (M − 3CO − NO_2, ^{187}Re, 8), 369 (M − 3CO − NO_2, ^{185}Re, 4),150 ($O_2NC_6H_4CO$, 88). HRMS (EI, 70 eV): Calcd for $C_{15}H_8NO_7{}^{185}$Re 498.9831. Found: 498.9826. Calcd for $C_{15}H_8NO_7{}^{187}$Re: 500.9858. Found: 500.9846.

Typical Experimental Procedure for the Synthesis of Carbon-Substituted $CpRe(CO)_3$ Complexes (8a−f). Conditions A. Compound **3** (39 mg, 0.050 mmol) was dissolved in anhydrous CH_3CN (1.5 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing diazocyclopentadiene (35 μL of a 1.73 M pentane solution, 0.060 mmol), the boronic acid (**7a**−**f**) (0.5 mmol, 10 eq), and triethylamine (1.0 mmol, 20 equiv) in CH_3CN (1 mL). The mixture was heated at 80 °C for 45 min and then concentrated under vacuum. The crude reaction product was purified by flash chromatography. **Conditions B.** Compound **3** (39 mg, 0.050 mmol) was dissolved in anhydrous CH_3CN (1.5 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing diazocyclopentadiene (35 μL of a 1.73 M pentane solution, 0.060 mmol), the boronic acid (**7a**−**f**) (0.10 mmol, 2 equiv), and triethylamine (0.20 mmol, 4 equiv) in CH_3CN (1 mL). The mixture was heated at 80 °C for 14 h and then concentrated under vacuum. The crude reaction product was purified by flash chromatography.

(3-Thienylcyclopentadienyl)tricarbonylrhenium (8f).[36] Yield: 72% (conditions A). HRMS (EI, 70 eV): Calcd for $C_{12}H_7O_3S^{185}$Re 415.9646. Found: 415.9641. Calcd for $C_{12}H_7O_3S^{187}$Re: 417.9674. Found: 417.9672.

NMR Experiments Reported in Figure 4. Spectrum *a* (δ = 172.72 ppm): commercially available (Aldrich) [1-^{13}C]-acetic acid (5.9 mg, 0.097 mmol) was dissolved in CD_3CN (1.1 mL) in a NMR tube. Spectrum *b* (δ = 176.10 ppm): triethylamine (28 μL, 0.20 mmol) was added. Spectrum *c* (δ = 176.78, 177.27, 177.49, 180.67 ppm): the solution derived from spectrum *b* was added to a vial containing **3** (78 mg, 0.10 mmol) and AgOTf (84 mg, 0.33 mmol); AgBr was removed by filtration, and the supernatant was stirred at room temperature for 45 min, then returned to the NMR tube and analyzed. Spectrum *d* (δ = 168.69, 177.19, 177.63, 180.63 ppm): a pentane solution (1.73 M) of diazocyclopentadiene (0.3 mL, 0.5 mmol) was added, and the mixture was stirred for 5 min at room temperature. Spectrum *e* (δ = 169.69, 180.63 ppm): the solution derived from spectrum *d* was stirred at room temperature for 4.5 h. Spectrum *f* (δ = 169.90 ppm): the solution derived from spectrum *e* was heated to 70 °C (*outside the spectrometer!*) for 1 h; after cooling to room temperature, the resulting dark suspension was analyzed by NMR.

Competition Reaction Procedure for Differently *para*-Substituted Benzoic Acids 11a−d. Relative Kinetic Constant Values (k_X/k_H) Determination. In one experiment, 39 mg (0.050 mmol) of **3** was dissolved in anhydrous CH_3CN (1.5 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing diazocyclopentadiene (35 μL of a 1.73 M pentane solution, 0.060 mmol), **11a** (15 mg, 0.10 mmol), **11b** (12 mg, 0.10 mmol), **11c** (16 mg, 0.10 mmol), and triethylamine (0.60 mmol). The mixture was heated at 80 °C for 45 min and then concentrated under vacuum. The product ratio in the crude reaction mixture was determined by ^1H NMR integration of independently and unambiguously assigned peaks, which gave the following product distribution: **12a** (41%, k_{MeO}/k_H = 1.14), **12b** (36%, k_H/k_H = 1.00), **12c** (23%, k_{Ac}/k_H = 0.64). In a second experiment, 39 mg (0.050 mmol) of **3** were dissolved in anhydrous CH_3CN (1.5 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing diazocyclopentadiene (35 μL of a 1.73 M pentane solution, 0.060 mmol), **11c** (16 mg, 0.10 mmol), **11d** (17 mg, 0.10 mmol), and

(36) Purification conditions and most characterization data of **8f** have already been reported in: Minutolo, F.; Katzenellenbogen, J. A. *Angew. Chem.*, in press.

triethylamine (0.40 mmol). The mixture was heated at 80 °C for 45 min and then concentrated under vacuum. As in the first experiment, ^{1}H NMR integration analysis gave the following product distribution: **12c** (67%, $k_{Ac}/k_H = 0.64$ determined in the first experiment), **12d** (33%, $k_{NO_2}/k_H = 0.31$).

Acknowledgment. We are grateful for support of this research through grants from the National Institutes of Health (5R01 CA25836) and the Department of Energy (DE FG02 86ER60401). NMR spectra were obtained in the Varian Oxford Instrument Center for Excellence in NMR Laboratory. Funding for this instrumentation was provided in part from the W. M. Keck Foundation, the National Institutes of Health (PHS 1 S10 RR104444-01), and the National Science Foundation (NSF CHE 96-10502). Mass spectra were obtained on instruments supported by grants from the National Institute of General Medical Sciences (GM 27029), the National Institutes of Health (RR 01575), and the National Science Foundation (PCM 8121494). We thank Gregory S. Girolami and Thomas B. Rauchfuss for helpful discussions.

OM990128T