Tetrahedron Vol. 41, No. 24, pp. 5839 to 5853, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

THE DEVELOPMENT OF AN ORGANOTRANSITION METAL SYNTHESIS OF QUINONES

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(*Received in USA* 14 *May* 1984)

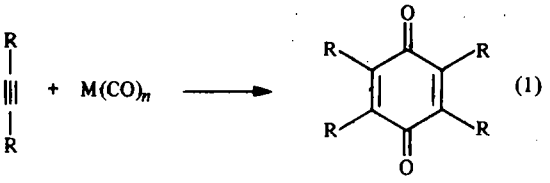
Abstract—A new and very general synthesis of quinones is described from conception to the current state of maturity. The chemistry relies on a convergent joining of a transition metal complex and an alkyne to provide benzoquinones (from maleoylmetal complexes) and naphthoquinones (from phthaloylmetal complexes). Significant aspects of this chemistry are its generality (terminal, internal, electron rich, and electron deficient alkynes react), its mildness (reactions can be run between room temperature and 80°) and its functional group compatibility (aldehydes, ketones, esters, nitriles, olefins, halides acetals, ketals, etc. survive).

To the uninitiated organic chemist the use of organotransition metal chemistry in organic chemistry may seem like 'black magic'. Furthermore, there are some organic chemists who respond with scepticism to synthetic organic transformations that emphasize transition metal chemistry, because they incorrectly presume that all organotransition metal reactions are very air-sensitive and require special handling techniques. Finally, there is a misconception among some organic chemists that any change in the ligands around the transition metal will dramatically alter the course of a reaction and there is no logical way to predict how ligand changes will influence reactivity.

Through the specific chemistry described in this article we wish to emphasize three attributes of the use of organotransition metal chemistry in organic synthesis that may help dissuade the previous misconceptions. First, organotransition metal chemistry can provide the organic chemist with a very mild means of forming carbon–carbon bonds under neutral reaction conditions. Often the carbon–carbon bonds will be formed in selective reactions that are compatible with a wide variety of unprotected functional groups. Secondly, the ability to alter the ligands around the metal and influence the reactivity of organotransition metal complexes by steric and electronic perturbations is a very useful control element in the chemistry. Finally, organotransition metal chemistry provides the organic chemist with novel ways to 'disconnect' the carbon skeleton of a target molecule that allow practical synthetic alternatives to the traditional nucleophile–electrophile combinations or concerted thermal processes required for most carbon–carbon bond formations.

BACKGROUND

Quinones or quinone–metal complexes are often formed when alkynes are treated with stoichiometric transition metal carbonyl reagents (equation 1).



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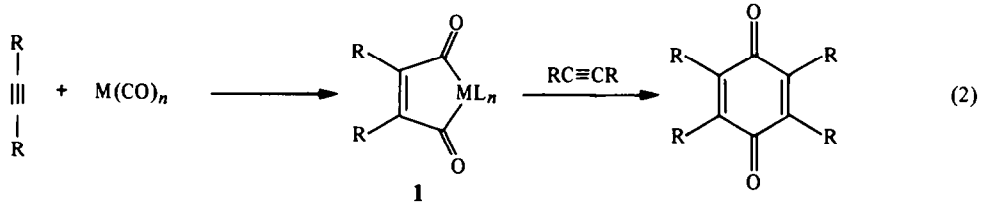
Examples based on Fe,[1–5] Co,[6,7] Mo,[8] Mn,[9] Rh[10,11] and Pt[12] have been described and catalytic variants of this chemistry leading to hydroquinones are known.[13a]

This general and mild means of forming four carbon–carbon bonds between two alkyne and two carbon monoxide molecules has been rationalized to proceed through the initial formation of a maleoylmetal complex, **1**, which then reacts with an alkyne, perhaps by way of an insertion–reductive elimination sequence, to give the quinone product (equation 2).[13b,14]



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Strong support for this pathway to quinones comes from the widespread isolation of maleoymetal complexes, **1**,[15–26] often from alkyne–$M(CO)_n$ reactions which also produce quinones.[6,10,11] Prior to our work in this field there was no direct observation of the reaction of maleoylmetal complexes with alkynes to give quinones; however, a critical link between maleoylmetal complexes and quinones was provided by Kang *et al.*[10] in 1968. They showed that an amorphous solid isolated from the reaction of 2-butyne with $[Rh(CO)_2Cl]_2/CO$ gave maleoylrhodium complex, **2**, on treatment with PPh_3 and the same amorphous solid formed a mixture of 2,3-dimethyl-5,6-diethylbenzoquinone and tetraethylbenzoquinone when treated with 3-hexyne (Scheme 1).

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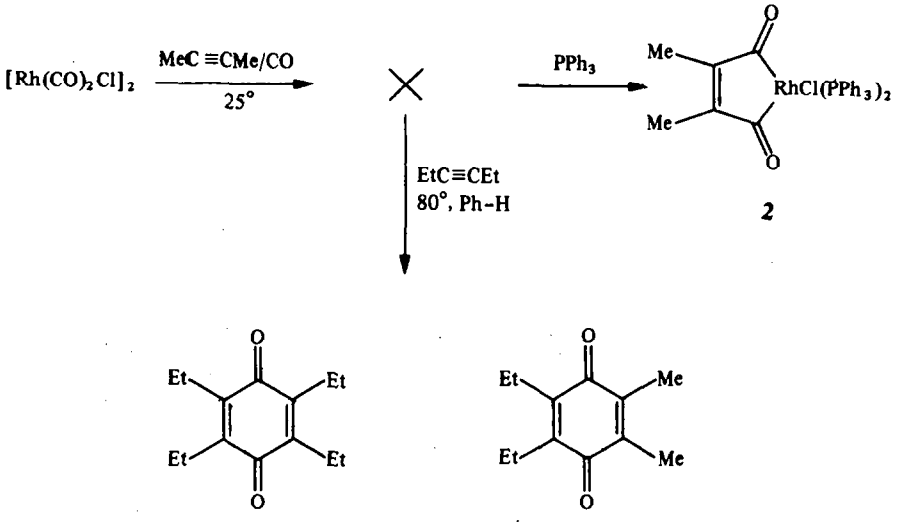
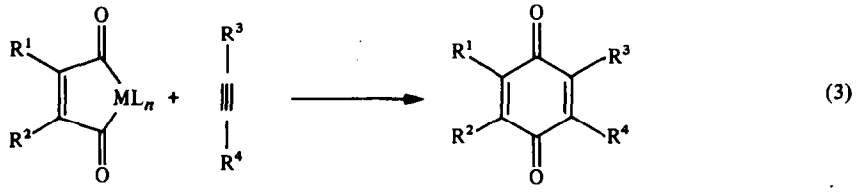


Scheme 1.

The observation of 2,3-dimethyl-5,6-diethylbenzoquinone in the reaction described by Kang *et al.*,[10] and the fact that quinones almost invariably form when alkynes are treated with metal carbonyl reagents suggested to us that a powerful route to unsymmetrical quinones with controlled substitution patterns may lay hidden in this organotransition metal chemistry. If a practical and general synthesis of maleoylmetal complexes could be discovered, then reaction with alkynes might provide a convergent route to highly substituted and functionalized benzoquinones (equation 3). A similar sequence leading to naphthoquinones could be envisaged beginning with phthaloylmetal complexes, 3 (equation 4). If conditions could be discovered that would allow the regioselective synthesis of these substituted quinones in high yield, then the total synthesis of quinone based natural products of diverse molecular structures could be realized using one common synthetic method.

NAPHTHOQUINONE SYNTHESIS

We chose to begin our search for a convergent quinone synthesis in the napthoquinone system and, therefore, a practical synthesis of phthaloylmetal complexes, 3, was required. Of the two compounds known when we began this project, Ni complex 4[27] was formed in much higher yield and under more practical conditions than the Fe complex 5[16] (Scheme 2), so our initial studies focused on the reaction of 4 with alkynes under a variety of conditions. Neither thermolysis, photolysis, reduction nor added ligands gave any indication of naphthoquinone formation from 4 with alkynes; however, traces of 2,3-diethyl-1,4-naphthoquinone were seen when 4 was activated with $AgBF_4$ in the presence of 3-hexyne. It is of synthetic interest that high yields of Ni and Pd complexes related to 4 could be prepared from phthaloyl chloride (equations 5 and 6);† however, no useful naphthoquinone syntheses were found with any of these compounds. Also, phthaloyl chloride could, in principle, provide an efficient route to the phthaloyliron complex, 5, by reaction with $Na_2Fe(CO)_4$, but it has been shown previously that this reaction leads instead to biphthalide (equation 7).[28]



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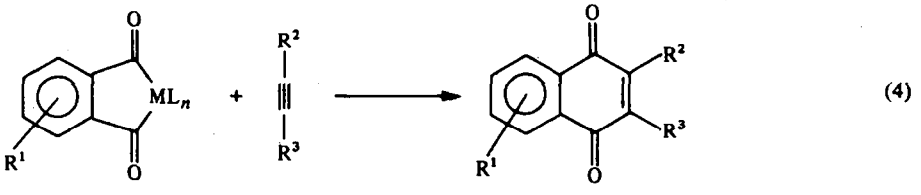

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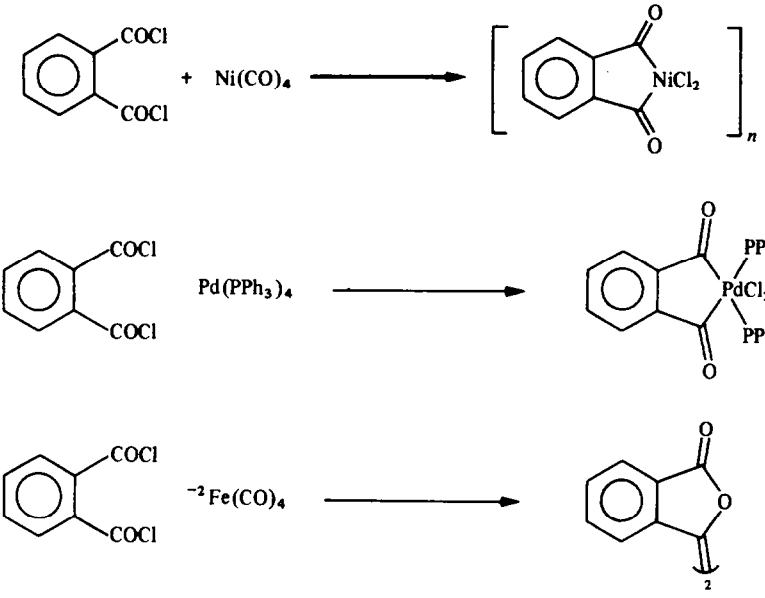
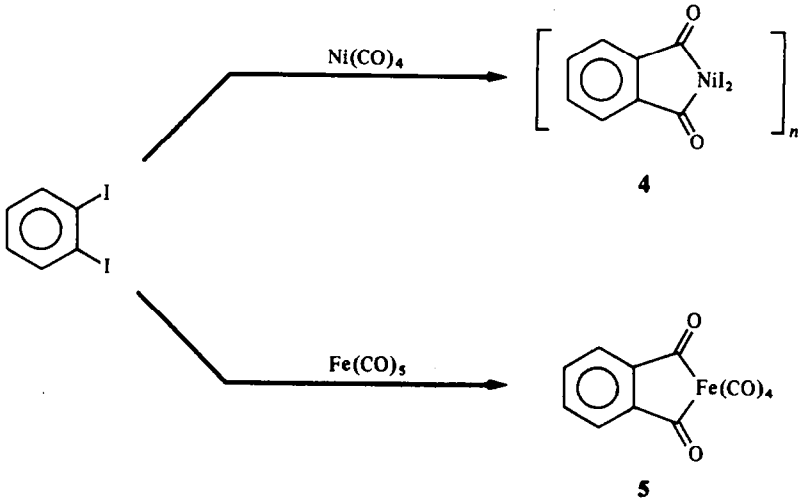
† These compounds showed IR and NMR spectra in accord with the proposed structures and similar to the data for Ni complex 4. However, they were never fully characterized because no useful quinone-forming chemistry was developed from them.

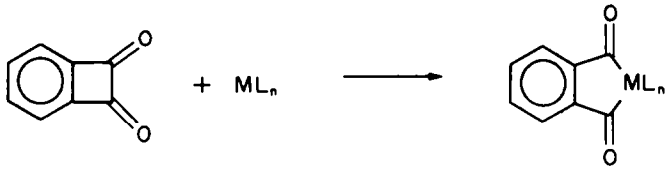


To study properly the synthesis of naphthoquinones from phthaloylmetal complexes, we required a method of synthesis of the organometallic compounds that would allow easy variation of the metal and ligands to survey rapidly their influence on the reaction. Since organic strained-ring compounds can be cleaved by low valent transition metal complexes,[29] we reasoned that reaction of benzocyclobutenedione with various metal reagents might provide a general route to the desired compounds. The known insertion[30] of $Pt(PPh_3)_4$ between the aromatic ring and a carbonyl group of benzocyclobutenedione did not dissuade us from looking at other low valent metal complexes and our search led to the high yield synthesis of the phthaloylmetal complexes **5–8** shown in Table 1.[31] Phthaloyliron complex **5** is a yellow, crystalline, chromatographable solid which had been prepared previously in low yield (12%) by extended photolysis of $Fe(CO)_5$–*o*-di-iodobenzene in acetone.[16] The current preparation reproducibly gave high yields of complex **5** when conducted in a sealed system to maintain internal CO pressure. The yellow Rh species, **6**, was synthesized in high yield from $ClRh(PPh_3)_3$ and an X-ray crystal structure determination established a trigonal bipyramidal geometry. Isostructural phthaloylcobalt complex **7** was prepared under very mild conditions (40° in C_6H_5Cl for 24 hr) and is the most practical of all the compounds for scale-up. We have often prepared the red–brown complex **7** on a > 50 g scale using as the Co starting material, $ClCo(PPh_3)_3$, prepared in high yield from $CoCl_2$, Zn and PPh_3 in MeCN.[32] Finally, benzocyclobutenedione reacted with $CpCo(CO)_2$ in refluxing xylene to give the yellow cyclopentadienyl **8** in high yield after chromatography. It must be emphasized that all of the phthaloylmetal complexes we have prepared are stable to air and moisture. They are all organic soluble, crystalline solids which can be stored in bottles with no special precautions and they



Scheme 2.

Table 1. Synthesis of phthaloylmetal complexes from benzocyclobutenedione



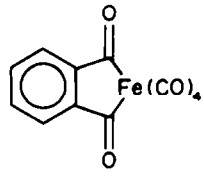
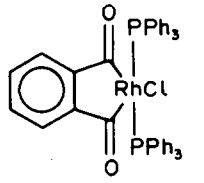
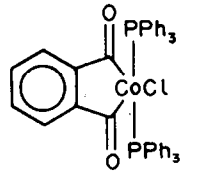
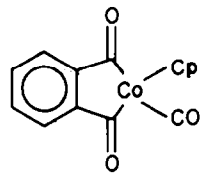
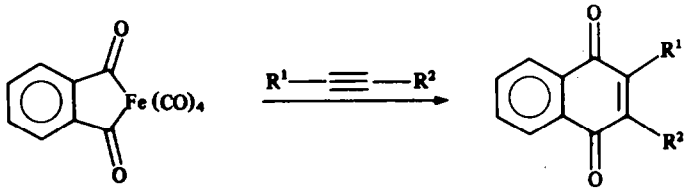
ML_n	Complex		Yield (%)
$Fe(CO)_5$		**5**	85
$ClRh(PPh_3)_3$		**6**	95
$ClCo(PPh_3)_3$		**7**	92
$CpCo(CO)_2$		**8**	90

Table 2. Naphthoquinones from phthaloyliron complex 5



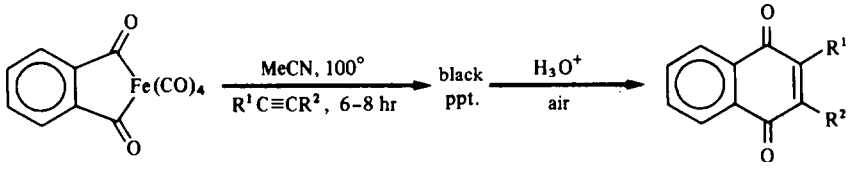
Entry	Alkyne	1,4-Naphthoquinone	Yield (%)
1	MeC≡CMe	2,3-Dimethyl	99
2	EtC≡CEt	2,3-Diethyl	95
3	PhC≡CPh	2,3-Diphenyl	88
4	PhC≡CMe	2-Methyl-3-phenyl	100
5	*n*-BuC≡CH	2-*n*-Butyl	95
6	PhC≡CH	2-Phenyl	94
7	*t*-BuC≡CMe	2-*t*-Butyl-3-methyl	37
8	EtC≡Callyl	2-Ethyl-3-(3-propenyl)	75
9	EtOC≡CEt	2-Ethoxy-3-ethyl	—
10	*n*-BuC≡CTMS	2-*n*-Butyl-3-(TMS)	22
11	$PhC{\equiv}C(CH_2)_2OH$	2-(2-Hydroxyethyl)3-phenyl	81
12	$MeC{\equiv}CCO_2Et$	2-Carboethoxy-3-methyl	74
13	EtC≡CCOMe	2-Acetyl-3-ethyl	68

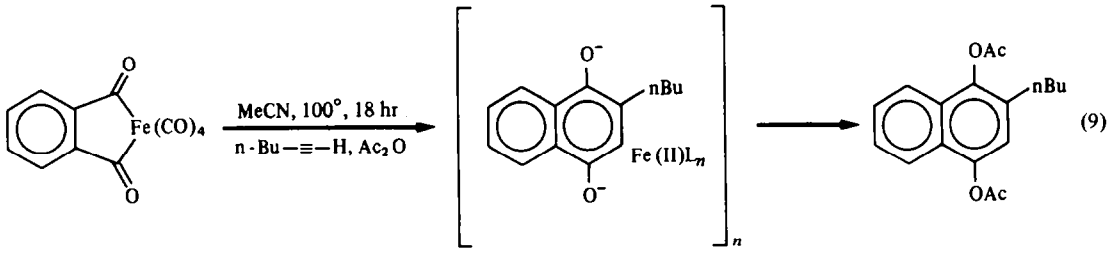
are prepared under an N_2 atmosphere in normal glassware using conditions no different to those used to prepare Grignard reagents. The organic starting material, benzocyclobutenedione, is also readily available (see below), thus imposing no restraint to the synthesis of phthaloylmetal complexes.

To test for the desired naphthoquinone synthesis, the inexpensive Fe and Co systems, **5** and **7** were surveyed for reactivity towards alkynes. Phthaloyliron complex **5** reacted with internal, terminal and electron deficient alkynes in MeCN at 100° to form a black, insoluble precipitate from which high yields of naphthoquinones were obtained on acidification in the presence of air (equation 8, Table 2).[33] Lower yields were encountered with sterically hindered alkynes (1-trimethylsilyl-1-hexyne and 2,2-dimethyl-3-pentyne) and an electron rich alkyne (ethyl-1-butynyl ether) failed to give any naphthoquinone product. The black precipitate referred to above was presumed to be a hydroquinone oxidation state precursor to the naphthoquinone product and support for this presumption was obtained by the formation of the hydroquinone diacetate of 2-*n*-butyl-1,4-naphthoquinone in 80% yield when acetic anhydride was included in the reaction of iron complex **5** with 1-hexyne (equation 9).

Phthaloylcobalt complex **7** proved unreactive towards alkynes until activated with $AgBF_4$ (equation 10).[33] The original (but incorrect, see below) premise for adding $AgBF_4$ was to remove the chloride from the ligand sphere of the Co and allow the alkyne to co-ordinate to the metal in its place. Although the requirement of $AgBF_4$ detracted somewhat from the practical application of phthaloylcobalt complex **7** in naphthoquinone synthesis, the fact that high yields of a wide variety of naphthoquinones could be synthesized using this method further emphasized the underlying generality of the organotransition metal route to quinones. Using the $AgBF_4$ mediated Co variation of this method, naphthoquinones were directly obtained from all but electron deficient alkynes (Table 3).

Even though the Co system required $AgBF_4$ for activation, the mild and easy preparation of the starting phthaloylcobalt complex made it our method of choice for most of our further studies. We considered





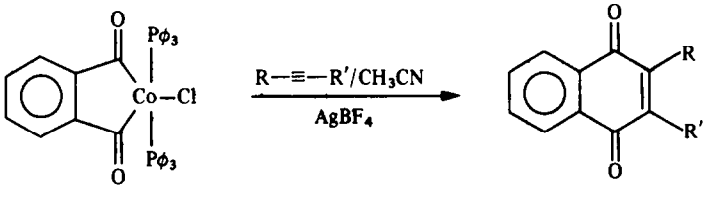
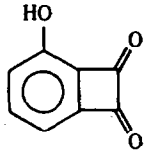


Table 3. Naphthoquinones from phthaloylcobalt complex **7**

Entry	Alkyne	Product	Yield (%)
1	MeC≡CMe	2,3-Dimethyl-1,4-naphthoquinone	73
2	EtC≡CEt	2,3-Diethyl-1,4-naphthoquinone	90
3	PhC≡CPh	2,3-Diphenyl-1,4-naphthoquinone	68
4	PhC≡CMe	2-Methyl-3-phenyl-1,4-naphthoquinone	78
5	*n*-BuC≡CH	2-*n*-Butyl-1,4-naphthoquinone	65
6	PhC≡CH	2-Phenyl-1,4-naphthoquinone	57
7	*t*-BuC≡CMe	2-*t*-Butyl-3-methyl-1,4-naphthoquinone	72
8	EtC≡Callyl	2-Ethyl-3-(3-propenyl)-1,4-naphthoquinone	80
9	EtOC≡CEt	2-Ethoxy-3-ethyl-1,4-naphthoquinone	89
10	*n*-BuC≡CSiMe$_3$	2-*n*-Butyl-3-(trimethylsilyl)-1,4-naphthoquinone	68
11	PhC≡C(CH$_2$)$_2$OH	2-(2-Hydroxyethyl)-3-phenyl-1,4-naphthoquinone	27
12	MeC≡CCO$_2$Et	2-Carbethoxy-3-methyl-1,4-naphthoquinone	0
13	EtC≡CCOMe	2-Acetyl-3-ethyl-1,4-naphthoquinone	0

improvements of the conditions for quinone synthesis to be important, but chose first to address the issue of regiochemistry in the naphthoquinone preparation. To study the regiochemistry of the quinone formation and to extend the utility of our synthetic method, we required a practical route to substituted benzocyclobutenediones. Our published solution to this problem provided simple syntheses of multigram quantities of benzocyclobutenediones **9–12** as well as the unsubstituted parent compound.[34] More recently, we have found the benzyne route to substituted benzocyclobuteneones[35] to provide a convenient, alternative entry to substituted benzocyclobutenediones (equation 11).



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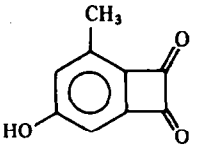

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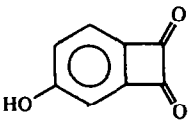

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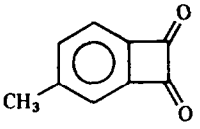

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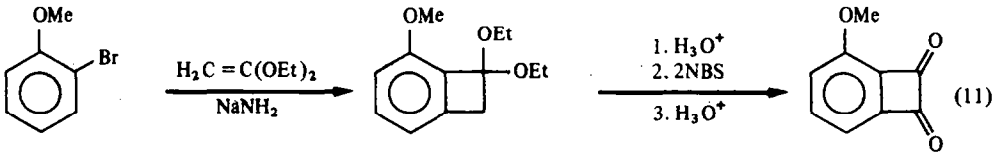
Propargyl alcohol (**14**) was readily elaborated to the highly functionalized, benzocyclobutenedione **15** in 75% yield (Scheme 3). Insertion of Co into the benzocyclobutenedione ring occurred cleanly with no complications to give phthaloylcobalt complex **16**. We reasoned that an intramolecular naphthoquinone formation from **16** would occur selectively to give one regioisomer because of conformational constraints imposed by the intramolecular nature of the process. In the event, macrocyclic quinone **17** was reproducibly formed in 45–50% isolated yield from **16** on treatment with $AgBF_4$ in MeCN. Formation of the required pyran ring was accomplished simply, in high yield, by Zn–conc. HCl reduction of **16** followed by an oxidative work-up (Ag_2O) which gave pyranonaphthoquinone (**18**) in 83% yield as a mixture of *trans* and *cis* isomers (3 : 1 ratio, respectively). We presume this facile reaction proceeds through the intermediary of an *o*-quinone methide formed from **18** under the acidic, reducing conditions. The total synthesis of nanaomycin A was completed by removal of the phenolic substituent with $AlCl_3$ (95%) followed by hydrolysis of the nitrile to the acid (70%). Pure racemic nanaomycin A was obtained by one recrystallization of the crude mixture which contained *ca* 30% of the *cis* stereoisomer. The successful synthesis of nanaomycin A using the phthaloylcobalt



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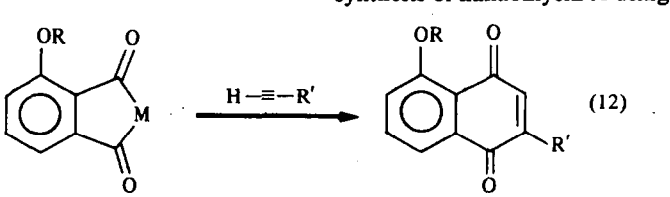

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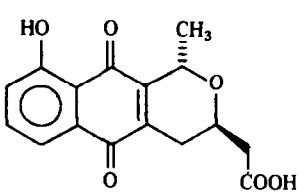

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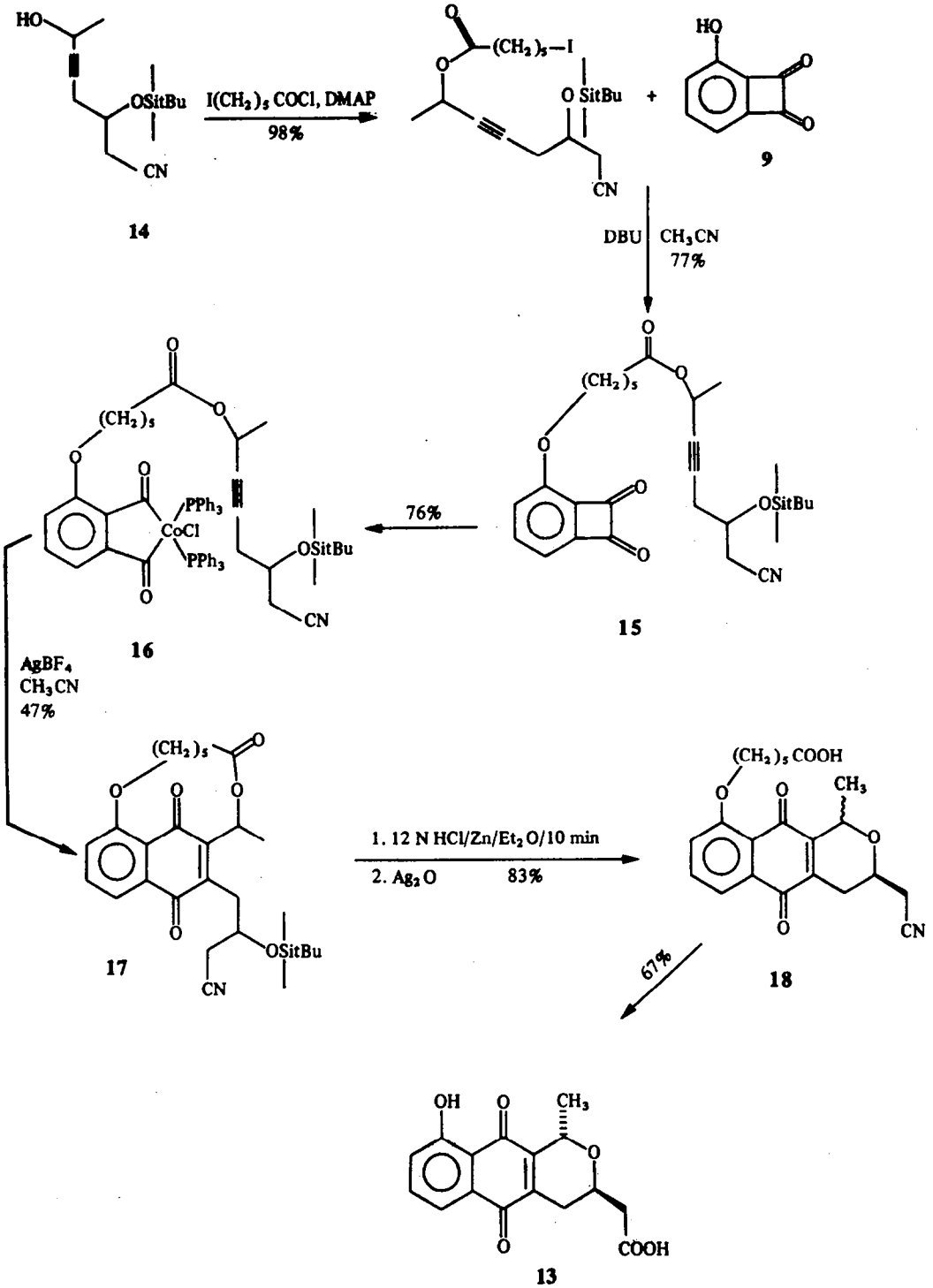
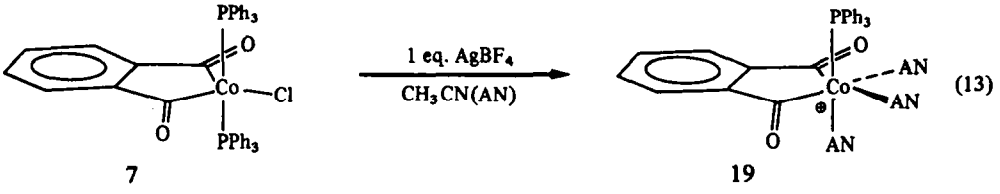


Scheme 3.

method reinforced our confidence that very highly functionalized quinones could be prepared by this chemistry and the sequence of reactions **15** → **16** → **17** in Scheme 3 underlines the unique selectivity achievable using organotransition metal chemistry in organic synthesis.

Since the phthaloylcobalt complexes were easily synthesized on large scale and in high yield, even from polyfunctional benzocyclobutenediones such as **15**, we decided to look closely at the need for $AgBF_4$ in the formation of quinones from these complexes with the hope of finding a milder and less expensive means of

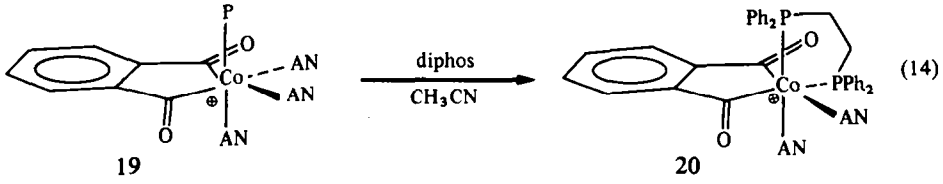
inducing the quinone reaction.[32] On treating Co complex **7** with 1 equivalent of $AgBF_4$ in MeCN, $AgCl \cdot PPh_3$ was precipitated and a solution of the amber, 6-co-ordinate, tris(acetonitrile)cobalt cation, **19**, was obtained (equation 13). Additional studies showed that cation **19** did react with alkynes to give quinones and other results strongly suggested that a facile dissociation of the unique MeCN ligand *below* the plane of the phthaloyl ring was responsible for the reactivity in the quinone forming reaction. Complexes with ligands strongly held above and below the plane of the phthaloyl ring did not react, even if in plane ligand dissociation was facile. Although cation **19** would not crystallize, it was converted to the very stable and crystalline diphos[bis(1,2-diphenylphosphine)ethane] analogue **20**, in 99% yield (equation 14). An X-ray crystal structure determination established the geometry shown[37] and, consistent with the presence of a labile MeCN ligand below the plane of the phthaloyl ring, diphos cation **20** reacted in high yield with a variety of alkynes to give quinones (Table 4).



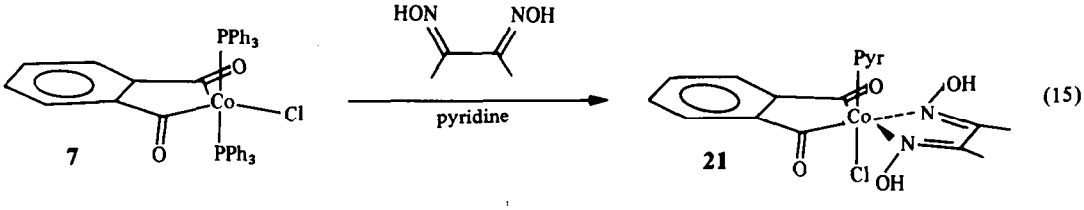
7 19

Specifically, terminal, trimethylsilyl and propargyl alkynes generally gave higher yields of the corresponding naphthoquinones with complex **20**.

If facile dissociation of a ligand above or below the phthaloyl ring plane is a requirement for quinone formation (by alkyne co-ordination in place of the departing ligand), then simple modification of the ligands of the parent Co complex **7** might provide a practical, alternative to the use of $AgBF_4$ for activation. Analysis of the situation using organometallic concepts suggested that conversion of 5-co-ordinate **7** into a 6-co-ordinate complex would facilitate ligand dissociation ($18e^- \rightarrow 16e^-$ easier than $16e^- \rightarrow 14e^-$) and that incorporation of a *chelating* ligand in the plane of the phthaloyl ring would retard ligand dissociation in that plane leaving the out of plane ligands free to dissociate. After some investigation, we discovered that dimethylglyoxime in pyridine converted **7** into the air-stable-6-co-ordinate, phthaloylcobalt complex **21**, in very high yield (equation 15).[37] Confirmation of structure **21** was obtained by X-ray crystal structure determination.



19 20

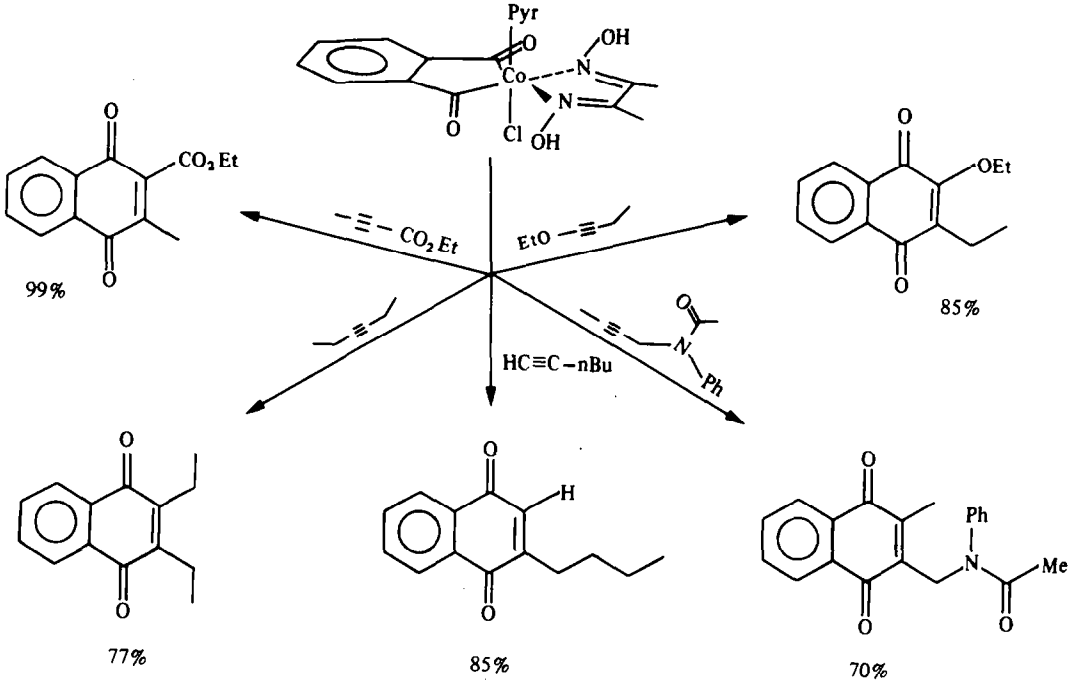


7 21

Diphos cation **20** is a very stable solid and can be stored indefinitely in a stoppered container with no signs of decomposition. In some cases, quinone formation from diphos cation **20** was superior to the *in situ* use of $AgBF_4$ and phthaloylcobalt complex **7**. Reaction of **21** with alkynes occurred smoothly at 80° in CH_2Cl_2, acetone, or 1,2-dichloroethane within 8 hr and gave high isolated yields of quinones (Scheme 4) in support of the previous mechanistic rationalization. Addition of $CoCl_2 \cdot 6H_2O$ to the reaction mixture had a

Table 4. Naphthoquinones from diphos cation **20**

Alkyne	Product	Conditions (hr, °)	Isolated yield (%)
HC≡C-*n*-Bu	2-*n*-Butyl-1,4-naphthoquinone	2, 80	90
EtC≡CEt	2,3-Diethyl-1,4-naphthoquinone	2, 80	85
$Me_3SiC{\equiv}C$-*n*-Bu	2-*n*-Butyl-3-(trimethysilyl)-1,4-naphthoquinone	4, 80	86
MeC≡CCH_2OEt	2-(Ethoxymethyl)-3-methyl-1,4-naphthoquinone	2, 80	63
MeC≡$CCH(OEt)_2$	2-(Diethoxymethyl)-3-methyl-1,4-naphthoquinone	2, 80	51
EtC≡$C(CH_2)_2OTHP$	3-Ethyl-2-(2-(tetrahydrodropyranyloxy)ethyl)-1,4-naphthoquinone	2, 80	73



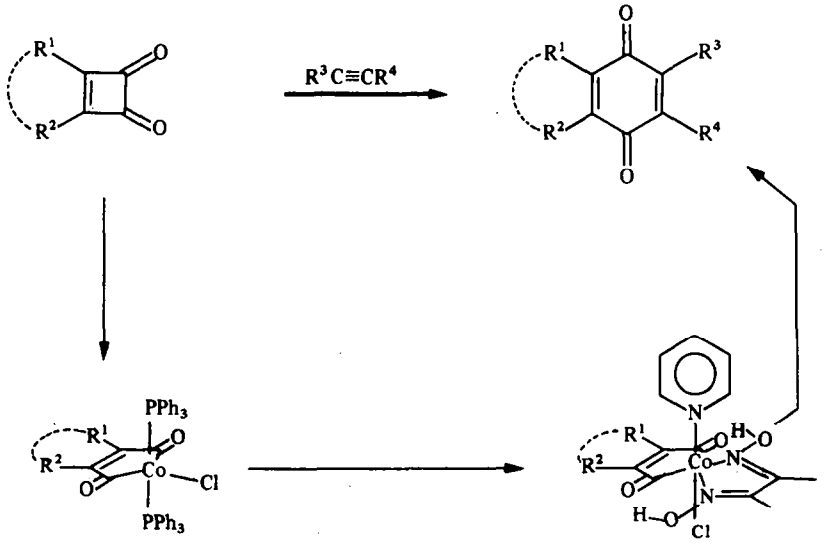
Scheme 4.

beneficial influence on reaction times and product yields. Our original premise for adding $CoCl_2 \cdot 6H_2O$ to the reaction was to coordinate any liberated pyridine or dimethylglyoxime that might have inhibited the reaction, but we have no proof that this was occurring. It should be noted that the dimethylglyoxime complexes reacted with alkynes ranging from electron rich to electron poor. No other complexes we have prepared to date have proved as general in reactivity.

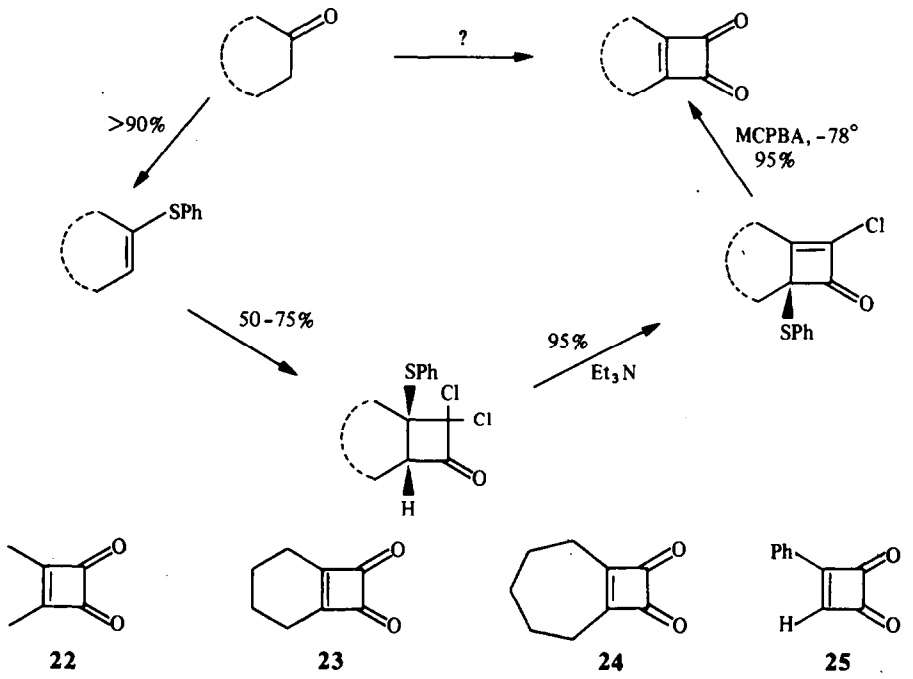
As alluded to in the introduction to this paper, the ability to control the reactivity of these organotransition metal complexes by variation of the ligands was a very powerful and useful control element in the chemistry. As will be seen below, the technique of modifying the parent Co complexes with dimethylglyoxime in pyridine proved very general in scope.

BENZOQUINONE SYNTHESIS

With a very general synthesis of naphthoquinones in hand, we considered applying our knowledge of phthaloylmetal complexes to the maleoyl series in pursuit of an equally general benzoquinone synthesis (Scheme 5). Successful attainment of this goal, if coupled with significant regiochemical control in both



Scheme 5.



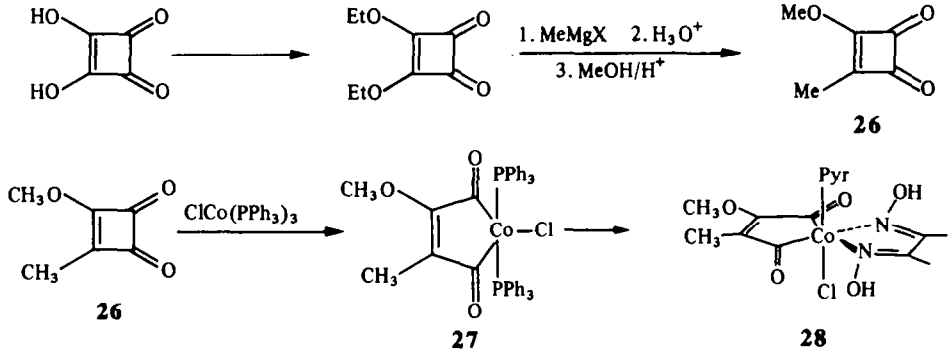
Scheme 6.

the naphthoquinone and benzoquinone series, would allow us to synthesize a wide range of important quinone-based natural products.

Analogy with our phthaloylmetal system suggested that cyclobutenediones would react with low-valent transition metal complexes to give maleoylmetal complexes. An original synthesis of the organic starting materials was developed and is shown in Scheme 6.[38] Using this chemistry, cyclobutenediones **22–25** were easily synthesized on a multigram scale and reaction of **22–24** with $ClCo(PPh_3)_3$ in benzene between room temperature and 60° gave very high yields of the corresponding maleoylcobalt complexes as air-stable, crystalline, red–brown solids.

Ligand modification of the bis(triphenylphosphine) complexes with dimethylglyoxime in pyridine gave high yields of the 6-co-ordinate complexes in exact analogy with the phthaloylcobalt series and subsequent reaction with 1- and 3-hexyne produced very good yields of the corresponding benzoquinones (Table 5).[39] Each of the quinone forming reactions was complete in 90 min when conducted in acetone at 80° in the presence of 1 equivalent of $CoCl_2 \cdot 6H_2O$. In the absence of $CoCl_2 \cdot 6H_2O$ the reactions took 5 hr to reach completion and the yields were slightly lower.

To study the regiochemistry of this benzoquinone synthesis, 3-methoxy-4-methyl-3-cyclobutene-1,2-dione (**26**) was chosen as the unsymmetrical cyclobutenedione counterpart in the reaction, because the methoxy–methyl substitution pattern of the resulting benzoquinones is common with naturally occurring quinones. 3 - Hydroxy - 4 - methyl - 3 - cyclobutene - 1,2 - dione has been synthesized by a number of procedures,[40,41] but the recent availability of squaric acid in large quantities at reasonable prices from Dayton Tinker† has made the procedure shown in equation 16 the preparative method of choice.[42]

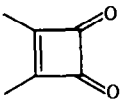
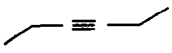
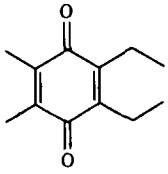
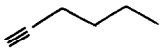
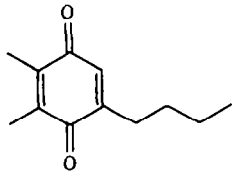
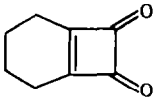
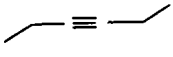
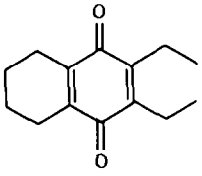
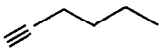
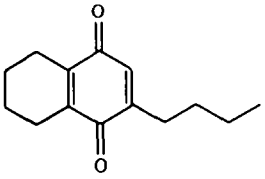
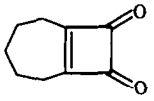
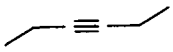
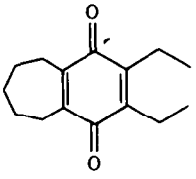
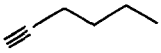
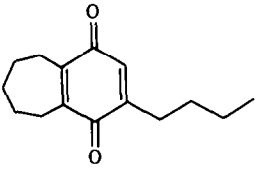


(17)

Cyclobutenedione **26** reacted with $ClCo(PPh_3)_3$ to give the corresponding bis(triphenylphosphine)-maleoylcobalt complex **27** and treatment with dimethylglyoxime in pyridine then provided the required 6-co-ordinate Co complex **28** (equation 17). The regiochemistry of reaction of **28** was surveyed with a variety of alkynes in CH_2Cl_2 at 100°. Under these

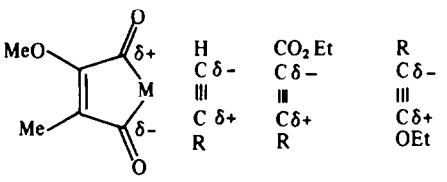
† Dayton Tinker Corporation, 143 Westpark Road, Dayton, OH 45459, U.S.A. The current price of squaric acid is $220/kg.

Table 5. Conversion of cyclobutenediones into benzoquinones

Cyclobutenedione	Co complexes PPh_3 (%)	Co complexes dmg (%)	Alkyne	Benzoquinone	Isolated yield (%)
	90	83			81%
					85%
	99	90			85%
					79%
	86	86			88%
					84%

conditions reactions were complete within 6 hr (Table 6).[39] Addition of $CoCl_2 \cdot 6H_2O$ was avoided in these reactions because the additive caused a perturbation of the regiochemical results. This interesting effect is currently under study.

An overview of the results listed in Table 6 shows that a range of alkynes would participate in the benzoquinone synthesis and that moderate to excellent regiochemical control was observed in this preliminary survey. The significant regiochemical ratio observed with 1-ethoxy-1-propyne suggested that electronic effects play a dominant role in the regiochemistry. In fact, all of the major regioisomers shown in Table 6 can be rationalized by the polarization model depicted in structure **29**. Although the current regiochemical results are encouraging, total synthesis applications



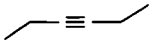
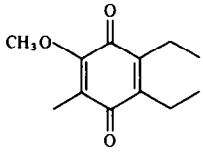
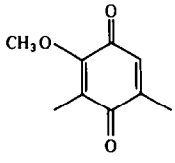
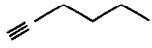
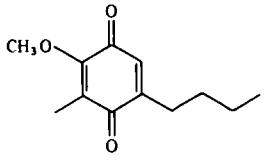
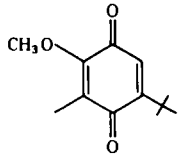
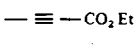
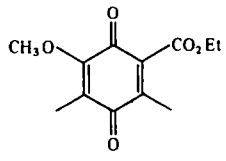
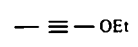
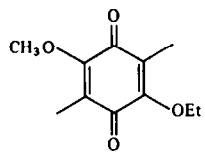
29

will require better selectivity. Again, the ability to vary the ligands about the metal may prove to be a useful control element since variation of the α-dioxime ligand in maleoylcobalt complex **28** does influence the regiochemical outcome of the reaction with alkynes (L. S. Liebeskind and S. Iyer, unpublished).

CONCLUSIONS

We have developed a very general synthesis of quinones which is based on organotransition metal chemistry. The mildness of conditions, broad functional group compatibility and extreme generality of the process are uniquely attributable to the use of transition metals to perform the carbon–carbon bond formations. While the chemistry described in this article will never find use in the synthesis of bulk

Table 6. Benzoquinone regiochemistry

Co complexes PPh_3 (%)	Co complexes dmg (%)	Alkyne	Benzoquinone major regioisomer	Regioisomer ratio	Isolated yield (%)
63	87			—	80%
				5:1	81%
				3.7:1	89%
				2.8:1	73%
				3.7:1	64%
				13.5:1	81%

chemicals, it should provide a powerful synthetic method for structure–function studies of biologically active quinones and for the total synthesis of valuable natural products. It also provides the experimentalist with a simple and versatile method for the synthesis of theoretically interesting quinones. Perhaps the most important lesson we have learned from our development of an organotransition metal synthesis of quinones is that remarkable and useful organic chemistry can be discovered if one is willing to explore organotransition metal chemistry from the 'metal' point of view as well as from the organic perspective.

EXPERIMENTAL

Synthesis of phthaloyliron complex **5**[31]

To a 60 ml Fischer–Porter resealable Pyrex tube were added benzocyclobutenedione (1.06 g, 8.00 mmol), C_6H_6 (29 ml), and $Fe(CO)_5$ (15.7 g, 80 mmol). The tube was sealed and placed 3 in. from a 150 W GE spotlight for 48 hr. The disappearance of the dione was monitored by TLC. The tube was cooled in a dry ice–Me_2CO bath and opened. Volatiles were removed in the hood with an aspirator and the residue was passed quickly through a 3 cm × 0.75 m silica gel column eluting with CH_2Cl_2. After removal of solvents, 2.0 g (83%) of Fe complex **51** was obtained as a yellow solid. M.p. 135° dec. (CH_2Cl_2–hexane) (lit.[16] 137°). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3000, 2125, 2060, 2035, 1710, 1660, 1585, 1190, 865. ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 7.9–7.4 (m). Mass spectrum: *m/z* 300 [M^+].

General procedure for the synthesis of the naphthoquinones from phthaloyliron complex **5**[33]

To a heavy-walled glass reaction tube (3 ml), sealable by means of a two-piece threaded Al coupling and internal Teflon sealing disk, were added Fe complex **5** (60 mg, 0.20 mmol), the desired alkyne (1.5 equivalents), acetonitrile (0.75 ml) and a small magnetic stirring bar. After stirring at 100° for 6 hr, the reaction was allowed to cool and was partitioned between CH_2Cl_2 and 1.2 M HCl. The organic layer was dried (Na_2SO_4), filtered and condensed on a rotary evaporator, and the residues were chromatographed on 20 × 20 cm × 0.5 mm preparative layer silica gel plates eluting with mixtures of CH_2Cl_2–hexane.

Synthesis of $CoCl(PPh_3)_3$[32]

To a vigorously stirred slurry of $CoCl_2(PPh_3)_2$ (19 g, 0.03 mol) and PPh_3 (7.6 g, 0.03 mol) in dry degassed MeCN was added Zn (1.9 g, 0.03 mol) in one portion. After stirring the soln under N_2 at room temp for 2 hr, the blue colour of $CoCl_2(PPh_3)_2$ was replaced with a bright green slurry of $CoCl(PPh_3)_3$. After addition of 400 ml of N_2-sat EtOH–H_2O (1:1) to complete pptn, the product was collected by filtration under N_2 using a Schlenk apparatus. The resulting solid was washed with 250 ml of absolute EtOH and then slurried under N_2 with 500 ml of N_2-sat 2 M HCl for 1 hr. The solid was filtered under N_2 and washed with H_2O (250 ml) and EtOH (2 × 250 ml), and then dried at room temp under a vacuum to yield $CoCl(PPh_3)_3$ (18.7 g, 71%). The product, a bright green solid, was moderately air stable and was best stored under N_2.

Synthesis of phthaloylcobalt complex **7**[32]

Benzocyclobutenedione (10 g, 76 mmol), $CoCl(PPh_3)_3$ (100 g, 114 mmol), and 100 ml of dry, N_2-sat chlorobenzene were heated with stirring under N_2 in an oil bath maintained at 40° until the benzocyclobutenedione had disappeared as monitored by TLC (silica gel, CH_2Cl_2, *ca* 24 hr). After the mixture had cooled to room temp crude, red–brown **7** was collected by suction filtration and then washed with a minimum amount of MeCN to remove unreacted $CoCl(PPh_3)_3$ followed by washing with hexane. The product was then dissolved in CH_2Cl_2 and filtered, and the CH_2Cl_2 was removed on a rotary evaporator to yield 52.5 g of **7**. Yield: 92%. M.p. 245–246° (CH_2Cl_2–hexane). IR $\nu_{max}^{KBr,CO}$ cm^{-1}: 1635. ^{1}H-NMR (Me_2CO-d_6, 270 MHz): δ 7.75–7.45 (m, 12H), 7.40–7.07 (m, 18H), 6.82 (dd, J = 5.5, 3.2 Hz, 2H), 6.65 (dd, J = 5.5, 3.2 Hz, 2H). (Found: C, 70.10; H, 4.64; Cl, 4.92. Calc for $CoC_{44}H_{34}ClP_2O_2$: C, 70.34; H, 4.57; Cl, 4.73%.)

Synthesis of quinones from Co *complex* **7**

2,3-Diethyl-1,4-naphthoquinone.[33] To a heavy-walled glass reaction tube, sealable by means of a two-piece threaded Al coupling and internal Teflon sealing disk, was added $AgBF_4$ (343 mg, 1.76 mmol) under N_2. The Co complex **7** (660 mg, 0.88 mmol), 3-hexyne (108 mg, 1.32 mmol), a small magnetic stirring bar and MeCN (3 ml) were then added and the reaction vessel was sealed. The heavy-walled glass tube was immersed in an oil bath maintained at 100° and the reaction was stirred magnetically. After 3 hr, the reaction mixture was filtered with the aid of CH_2Cl_2 and condensed on a rotary evaporator. The residue was passed through a 15 × 3 cm silica gel column using CH_2Cl_2. The resulting yellow soln was evaporated to dryness and the residue was chromatographed by medium-pressure LC (Merck Lobar prepacked column, hexane–CH_2Cl_2 3:2), to yield 169 mg (90%) of 2,3-diethyl-1,4-naphthoquinone. M.p. 70–71°, from petroleum ether (lit.[43] m.p. 72–73°).

Synthesis of the nanaomycin A *precursors*[36]

Preparation of phthaloylcobalt complex **16** (*mixture of diastereomers*). To a 25 ml round-bottomed flask equipped with a magnetic stirring bar were added **15** (668 mg, 1.31 mmol), $Co(PPh_3)_3Cl$ (2.30 g, 2.61 mmol) and C_6H_6 (13 ml). After flushing with N_2 the flask was sealed with a septum cap and kept at 40° for 6 hr under continuous stirring. After this time the contents of the flask were added to 50 ml of Et_2O and the excess $Co(PPh_3)_3Cl$ which pptd was removed by filtration. Removal of the solvents on a rotary evaporator left the crude **16** which was purified by rapid chromatography (Florisil, 2 × 6 cm, CH_2Cl_2–EtOAc, 1:1) followed by trituration of the resulting brown oil with petroleum ether (3 × 100 ml) to leave 1.12 g (76%) of **16** as a red–brown oil (mixture of diastereomers). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 2275, 1738, 1633, 1605. ^{1}H-NMR (60 MHz, $CDCl_3$): δ 7.48–6.75 (m, 30H), 6.62–5.92 (m, 3H), 5.26 (br, q, 1H, J = 6 Hz), 4.38–3.42 (m, 3H), 2.53 (d, 2H, J = 6 Hz) 2.65–2.05 (m, 4H), 1.95–1.08 (m, 6H), 1.43 (d, 3H, J = 6 Hz), 0.90 (s, 9H), 0.12 (s, 6H).

Preparation of macrocyclic naphthoquinone **17** (*mixture of diastereomers*). To a flame-dried 15 ml round-bottomed flask equipped with a magnetic stirring bar were added **16** (113 mg, 0.10 mmol) and MeCN (3 ml). The mixture was placed under N_2 and stirred while a soln of $AgBF_4$ (97.3 mg, 0.50 mmol) in MeCN (2 ml) was added dropwise via a syringe. A reflux condenser equipped with an N_2 inlet was attached to the flask and the mixture was refluxed under N_2 for 5 hr. After cooling to room temp, the volatiles were removed on a rotary evaporator and the crude reaction mixture was filtered through a short silica gel column (2 × 6 cm, CH_2Cl_2 then Et_2O). After removal of solvents the crude product was chromatographed (E. Merck preparative silica gel plate, 0.5 mm, Et_2O) to give 24 mg (47%) of **17** as a yellow oil (mixture of diastereomers). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 2270, 1730, 1672, 1595. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.63–7.50 (m, 2H), 7.29–7.22 (m, 1H), 5.62, 5.59 (two overlapping q, 1H total, J = 7 Hz each), 4.58–4.28 (m, 2H), 4.07–3.87 (m, 1H), 3.15–2.98 (m, 1H), 2.72–2.11 (m, 5H), 1.83, 1.82 (two d, 3H total, J = 7 Hz each), 1.74–1.07 (m, 6H), 0.88, 0.87 (two s, 9H total), 0.13, 0.12, 0.07, 0.02 (all s, 6H total). Mass spectrum (70 eV): *m/z* (rel. int.) 511 [$M]^+$ (0.90), 455 (19), 454 (50), 436 (18), 341 (19), 340 (53), 299 (31), 115 (23), 97 (36), 75 (76), 69 (100), 55 (42); mass spectral MW calc for $C_{28}H_{37}O_6NSi$: 511.2387, found: 511.2379.

Synthesis of phthaloylcobalt diphos cation **20**.[32] Into a flamed round-bottomed flask under N_2 was weighed $AgBF_4$ (1.132 g, 5.81 mmol) followed by **7** (4.372 g, 5.81 mmol) and then 58 ml of MeCN. The heterogeneous mixture was stirred at room temp under N_2 until the red–brown colour of **7** had disappeared, leaving an amber soln and white ppt (1 hr; larger scale required longer time). The mixture was filtered under N_2 with the aid of MeCN and bis(1,2-diphenylphosphino)ethane (2.315 g, 5.81 mmol) was added to the filtrate. The reaction was

stirred for 1 hr at room temp under N_2. The MeCN was removed on a rotary evaporator. The residue was dissolved in a minimum amount of hot MeCN and Et_2O was added dropwise until the cloudiness just disappeared on swirling, at which point the soln was allowed to stand until crystallization began whereupon it was completed by the addition of more Et_2O as described above until no more solid formed. The orange product was collected by filtration to yield 4.423 g of **20** (95%). M.p. 180–181.5°. IR $\nu_{max}^{CH_2Cl_2,CO}$ cm^{-1}: 1650. ^{1}H-NMR (CD_2Cl_2): δ 7.60–6.90 (m, 24H), 3.47–2.57 (m, 4H), 2.13 (dd, 3H, J = 3.1 Hz), 1.77 (s, 6H); ^{31}P-NMR (CH_2Cl_2) two broad absorptions at +43.1 and +38.35 ppm relative to 85% H_3PO_4. (Found: C, 60.29; H, 4.72; N, 5.25. Calc for $CoC_{40}H_{37}BF_4N_3O_2P_2$: C, 60.09; H, 4.67; N, 5.26%.)

Synthesis of quinones from diphos cation **20**

2-n-*Butyl*-1,4-*naphthoquinone*.[32] Complex **20** (320 mg, 0.4 mmol), 1-hexyne (49 mg, 0.6 mmol) and 4 ml of CH_2Cl_2 were stirred under N_2 in a sealed tube for 2 hr in an oil bath maintained at 80°. After being cooled, the reaction vessel was opened and the mixture transferred to a separation funnel with the aid of 25 ml of CH_2Cl_2. The organic layer was washed with 50 ml of 1.2 M HCl, dried (Na_2SO_4), filtered and condensed to a small vol. The crude product was filtered through a short plug of silica gel (5 × 1 in) and then chromatographed by medium-pressure LC (hexane–CH_2Cl_2, 3:2) to yield 77 mg (90%) of 2-*n*-butyl-1,4-naphthoquinone identical with an authentic sample.[33]

Synthesis of phthaloylcobalt dimethylglyoxime complex **21**[37]

Complex **7** (3.61 g, 0.005 mol), dimethylglyoxime (0.640 g, 0.006 mol) and 25 ml of pyridine were stirred at room temp for 12 hr. Et_2O (75 ml) was added and the resulting soln was allowed to stand overnight in an N_2 atmosphere. Suction filtration followed by an Et_2O wash (20 ml) afforded **21** (1.78 g, 88%) as a yellow–brown solid. M.p. 187–188° dec. (MeCN–Et_2O). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1605, 1570, 1475 (br); ν_{max}^{KBr} cm^{-1}: 1600, 1565, 1450 (br). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 13.76 (s, 2H), 8.30 (dd, 2H, J = 6, 1.4 Hz), 7.91 (dd, 2H, J = 5.5, 3.3 Hz), 7.49 (overlapping tt; 1OH, J = 8, 1.4 Hz), 7.45 (overlapping dd, 2H, J = 5.5, 3.3 Hz), 7.03 (dd, 2H, J = 8, 6 Hz), 2.32 (s, 6H). (Found: C, 48.31; H, 4.21; N, 10.05. Calc for $C_{17}H_{17}CoN_3ClO_4$: C, 48.41; H, 4.06; N, 9.97%.)

Synthesis of quinones from dimethylglyoxime complex **21**

2,3-*Diethyl*-1,4-*naphthoquinone*.[37] Complex **21** (126.5 mg, 0.30 mmol), 3-hexyne (36.8 mg, 0.45 mmol), $CoCl_2 \cdot 6H_2O$ (7.14 mg, 0.30 mmol) and 3 ml of CH_2Cl_2 were stirred in a sealed tube immersed in an oil bath at 80° for 8 hr. After cooling, the reaction vessel was opened and the mixture was filtered through a short plug of silica gel (5 × 1 in) with the aid of hexane–ether (3:2). The resulting yellow soln was reduced to *ca* 1 ml and chromatographed (E. Merck silica gel preparative plates, 2.0 mm hexane–Et_2O, 4:1) to yield 55.2 mg (86%) of 2,3-diethyl-1,4-naphthoquinone identical with a previously prepared sample.

Synthesis of bis(triphenylphosphine)maleoylcobalt complexes[39]

The complex forming reactions were carried out in an appropriately sized round-bottomed flask which was flame-dried while being purged with N_2. The flask was then charged with a substituted cyclobutenedione (1 equivalent), $CoCl(PPh_3)_3$ (1.5 equivalents), C_6H_6 as a solvent and a small stirring bar. The flask was then sealed with a rubber septum, placed in a 50° oil bath and stirred vigorously. The N_2 atmosphere was maintained by connection to an N_2 manifold via a syringe needle inserted through the septum. The reaction was monitored for disappearance of dione by GLC analysis of aliquots obtained via a syringe. After GLC analysis indicated completion of the reaction, C_6H_6 was removed in a rotary evaporator. The resulting solid residue was washed with small (10–20 ml) portions of absolute EtOH until the wash solvent showed no traces of green. The red–brown solid which remained was washed with Et_2O, dissolved in CH_2Cl_2 and filtered to remove Co insolubles. Subsequent removal of solvent in a rotary evaporator afforded the maleoylcobalt complexes as air-stable, red–brown solids. These compounds were almost always isolated with an accompanying molecule of solvation and yields were calculated based on MWs of the Co complexes, which included the molecule of solvation in proper stoichiometries as determined by ^{1}H-NMR.

Maleoylcobalt complex from 3,4-*dimethylcyclobut*-3-*ene*-1,2-*dione*

Reaction of **22** (11.19 mg, 10.20 mmol) and $CoCl(PPh_3)_3$ (13.50 g, 15.30 mmol) in 100 ml of C_6H_6 according to the general procedure (8 hr) afforded 7.44 g (90%) of the Co complex as a brick-red solid containing one $C_2H_4Cl_2$ molecule of solvation after crystallization. M.p. 185–186° (dec.) ($C_2H_4Cl_2$–hexane). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 11612. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.85–7.50 (overlapping m, 12H), 7.50–7.15 (overlapping m, 18H), 1.55 (s, 4H), 0.88 (s, 6H). (Found: C, 64.09; H, 5.06; Cl, 12.60. Calc for $C_{42}H_{36}Cl_2CoO_2P_2(C_2H_4Cl_2)$: C, 63.82; H, 4.87; Cl, 12.85%.)

Synthesis of dimethylglyoxime maleoylcobalt complexes[39]

A maleoylbis(triphenylphosphine)cobalt chloride complex (1.0 equivalent) was stirred with 1.1 equivalents of dimethylglyoxime (DMG) in pyridine at room temp for 8 hr. The mixture was added dropwise to 10 vols of Et_2O and allowed to stand for 1 hr in order to complete ppt of the maleoylcobalt DMG complex. The complex was isolated by suction filtration and washed with Et_2O until the smell of pyridine no longer persisted. The maleoylcobalt complexes obtained in this manner were sufficiently pure to serve as analytical samples. None of the complexes gave useable m.ps as they decomposed over a 10–20° range.

Preparation of the dimethylglyoxime cobalt complex from 3,4-*dimethylcyclobut*-3-*ene*-1,2-*dione*

Reaction of the previous Co complex (1.00 g, 1.23 mmol) and dimethylglyoxime (157 mg, 1.35 mmol) in 5 ml of pyridine as described in the general procedure afforded 408 mg (83%) of the complex as a pale yellow solid. IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1589, 1570, 1475 (br). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 13.69 (s, 2H), 8.21 (dd, 2H, J = 6.25, 1 Hz), 7.54 (tt, 1H, J = 7.5, 1 Hz), 7.06 (apparent t, dd, 2H, J = 7.5, 6.25 Hz), 2.28 (s, 6H), 2.08 (s, 6H). (Found: C, 45.07; H, 4.68; N, 10.53. Calc for $C_{15}H_{19}ClCoN_3O_4$: C, 45.07; H, 4.79; N, 10.51%.)

Synthesis of benzoquinones from dimethylglyoxime maleoylcobalt complexes[39]

All reactions were carried out in heavy-walled glass reaction tubes sealed by means of a two-piece threaded Al coupling and an internal Teflon sealing disc. The reaction tube, equipped with a small magnetic stirring bar, was flame dried while being purged with N_2. To this reaction tube were added, under N_2, the reactants and the desired solvent. The reaction tube was sealed immediately after charging and placed in an oil bath maintained at the desired temp. After the desired time, the mixture was cooled to room temp and flash chromatographed on a 4 × 1 in silica gel column with hexane–Et_2O (2:1). The resulting soln was concentrated *in vacuo* and chromatographed (E. Merck silica gel preparative plate, 2.0 mm) to afford the benzoquinone.

Preparation of 2,3-*diethyl*-5,6-*dimethyl*-1,4-*benzoquinone*. The Co complex described above (120 mg, 0.3 mmol), $CoCl_2 \cdot 6H_2O$ (71 mg, 0.3 mmol) and 3-hexyne (47 μl, 0.45 mmol) in 3 ml of Me_2CO were reacted for 1.5 hr at 80° as described in the general procedure. Chromatography (hexane–Et_2O, 10:1), afforded 47 mg (81%) of 2,3-diethyl-5,6-dimethyl-1,4-benzoquinone as a yellow oil. IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1640. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 2.49 (q, 4H, J = 7.35 Hz), 2.01 (s, 6H), 1.07 (t, 6H, J = 7.35 Hz). Ms (70 eV): *m/z* (rel. int.) 192 $[M]^+$ (38), 177 (20), 164 (17), 149 (100), 121 (21), 97 (15), 91 (26), 83 (23), 81 (22), 79 (22), 71 (25), 69 (38), 67

(35), 65 (16), 62 (19). (Found: C, 74.82; H, 8.42. Calc for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.)

Acknowledgement—We thank the National Cancer Institute, D.H.E.W. (grant CA 26374) for support of this work.

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