

## CHAPTER 2

### THE SYNTHESIS OF PHENOLS AND QUINONES VIA FISCHER CARBENE COMPLEXES

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*Organic Reactions, Vol. 70*, Edited by Larry E. Overman et al.

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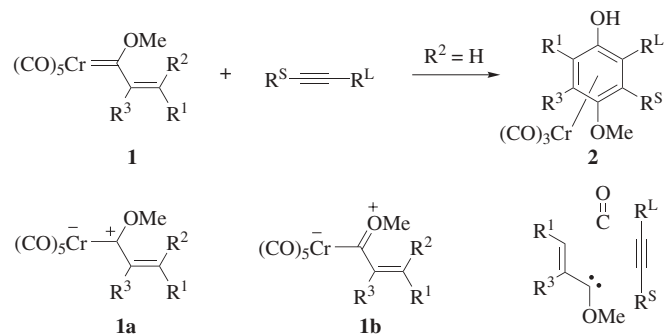
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#### ACKNOWLEDGMENTS

We express our gratitude to our coworkers at Michigan State University for assistance in proofreading this chapter. We also thank the many students and postdoctoral fellows who have contributed over the years to much of the original research that we cite. We are grateful to the National Science Foundation and National Institutes of Health for financially supporting the study of the chemistry of carbene complexes conducted in our laboratories over the last twenty-three years. Finally, we certainly extend our thanks to Bob Joyce (now deceased) and Linda Press for their invaluable help in assembling the tables, and to Scott E. Denmark for his patience, encouragement, and professional oversight of this chapter.

#### INTRODUCTION

Fischer carbene complexes can be broadly defined as those transition-metal carbene complexes that have a low oxidation state, have an electrophilic carbene carbon, and usually have a heteroatom-stabilizing substituent on the carbene carbon. The reactivity of Fischer complexes of the type **1** is consistent with the resonance structures **1a** and **1b** (Scheme 1). These complexes were first prepared by E. O. Fischer and were, in fact, the first examples of any type of transition-metal carbene complexes to be reported.<sup>1</sup> The reaction of a Fischer carbene complex with an alkyne was first reported by Dötz and was found to give a chromium tricarbonyl complexed 4-alkoxy-substituted phenol (Scheme 1).<sup>2</sup> The



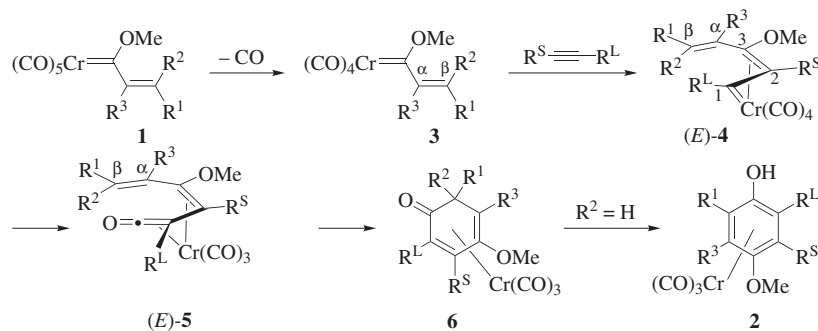
Scheme 1

outcome was unexpected because the reaction was anticipated to give a cyclopropene by transfer of the carbene ligand to the alkyne.<sup>3</sup> The reaction of Fischer carbene complexes with alkynes is facile, occurring just above ambient temperature, and resulting in the assembly of a benzene ring from the three carbons of the  $\alpha,\beta$ -unsaturated carbene complex, the two carbons of the alkyne, and the carbon of a carbon monoxide ligand (Scheme 1). The synthetic value of this reaction stems from its broad scope, the generally high yields for the process, and the fact that the products can function as intermediates for the synthesis of a variety of aromatic compounds including *para*-quinones. It is the most synthetically valuable of the large number of reactions of Fischer carbene complexes that have been developed for applications in synthetic organic chemistry.

Most of the previous reviews of the reactions of Fischer carbene complexes with alkynes have appeared as part of larger reviews on the applications of Fischer carbene complexes in organic synthesis that include a number of different reactions.<sup>4-41</sup> The first major review was published only a few years after the discovery of the reaction,<sup>10</sup> and shortly thereafter a detailed review appeared which focused on the work of a single research group.<sup>16</sup> The literature on the reaction of Fischer carbene complexes with alkynes up to 1988 is roughly contained in three reviews that cover all reactions of Fischer carbene complexes.<sup>10,16,20</sup> A comprehensive review has appeared that includes the reaction of Fischer carbene complexes with alkynes for the period 1988 to 1993.<sup>24</sup> This chapter is the first comprehensive review that is limited to the synthesis of phenols and quinones from the reactions of Fischer carbene complexes with alkynes. The literature is covered as cited in *Chemical Abstracts* up to September, 2004.

#### MECHANISM AND OVERVIEW

The mechanism by which (4-alkoxyphenol)chromium tricarbonyl complexes **2** are produced from the reaction of Fischer carbene complexes is not known in complete detail. A summary of the current understanding of the reaction of  $\alpha,\beta$ -unsaturated Fischer carbene complexes **1** with alkynes is presented in Scheme 2.



Scheme 2

The first and rate-limiting step of the reaction was long ago proposed on the basis of kinetic studies to be a carbon monoxide dissociation from the starting carbene complex to give the 16-electron unsaturated species **3**.<sup>42</sup> Subsequent reaction with the alkyne is suggested to give the  $\eta^1, \eta^3$ -vinyl carbene-complexed intermediate (*E*)-**4**. Recently, this view has been called into question by a theoretical study that concluded that the first step is an insertion of the alkyne to give a pentacarbonyl species and then a rate limiting loss of CO to give the unsaturated vinyl carbene complex (*E*)-**4**.<sup>43</sup> This report is controversial<sup>44</sup> because it is inconsistent with kinetic studies that demonstrated that the first step of the reaction is loss of CO, and that the second step depends on the alkyne concentration.<sup>42</sup> The  $\eta^1, \eta^3$ -vinyl carbene-complexed intermediate (*E*)-**4** has been suggested to exist in a number of different forms. Most early mechanistic proposals include a [2 + 2] cycloaddition of the alkyne and carbene complex to give a metallacyclobutene intermediate that undergoes subsequent electrocyclic ring opening to give an  $\eta^1$ -vinyl carbene-complexed intermediate related to (*E*)-**4** (see structure (*E*)-**17** in Scheme 6) but not having the chromium coordinated to carbons 2 and 3.<sup>5,9</sup> It was suggested in 1987 that the  $\eta^1$ -complex (*E*)-**17** is coordinatively unsaturated and may prefer to exist as the 18  $e^-$  ( $\eta^1, \eta^3$ -vinyl)carbene complex (*E*)-**4**.<sup>13</sup> Subsequently, extended Hückel calculations found that the  $\eta^1$ - and  $\eta^1, \eta^3$ -vinyl carbene complexes are of comparable energy and also ruled out a metallacyclobutene intermediate as a precursor to (*E*)-**4**.<sup>45,46</sup> The intermediate **4** must have an *E*-configuration about the C2-C3 double bond to enable phenol formation, and evidence suggests that this configuration is favored by the electron-releasing methoxy group.<sup>47</sup> One recent density functional theory calculation (DFT) found that the  $\eta^1, \eta^3$ -complex (*E*)-**4** is more stable,<sup>48</sup> while another recent DFT study found that the  $\eta^1$  complex (*E*)-**17** (Scheme 6) is more stable.<sup>49,50</sup> It has been experimentally shown that the  $\eta^1, \eta^3$  and  $\eta^1$  forms can interconvert.<sup>51,52</sup> A third isomeric form of (*E*)-**4** has been proposed recently on the basis of spectroscopic evidence in which the chromium is coordinated to a carbon-carbon double bond originally present in an alkenyl carbene complex.<sup>53,54</sup> The intermediacy of this species in the formation of phenols has been supported by DFT calculations that find this configuration to

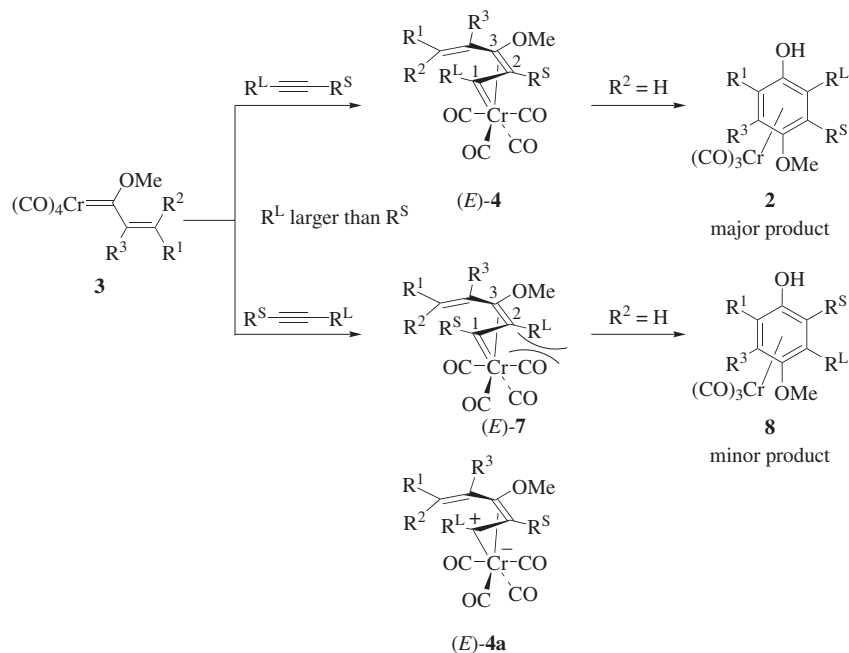
be the most stable of the isomers of **4**.<sup>49,50,55</sup> An  $\eta^1, \eta^3$ -vinyl carbene-complexed intermediate has been isolated from the reaction of a cationic tungsten carbene complex bearing a Cp ligand.<sup>56</sup>

The insertion of CO was originally proposed to give the ( $\eta^4$ -vinyl) ketene complex (*E*)-**5** which upon electrocyclic ring closure and tautomerization gives the observed phenol complexes **2**.<sup>57</sup> DFT studies support the intermediacy of vinyl ketene complex (*E*)-**5** for aryl complexes.<sup>48</sup> However, for the same studies on alkenyl carbene complexes there is no local minimum for the vinyl ketene complex but rather CO insertion and electrocyclic ring closure occur in the same step.<sup>48-50</sup> The isolation of ( $\eta^4$ -vinyl) ketene complexes has been reported for the reaction of alkynes with carbene complexes that do not have an  $\alpha, \beta$ -unsaturated substituent.<sup>58,59</sup> The last step in the reaction is proposed to be the tautomerization of cyclohexadienone complex **6**, and support for this intermediate comes from the isolation of a non-tautomerized ( $R^2 = H$ ) complex from a molybdenum carbene complex.<sup>60</sup> Metal-free and metal-complexed cyclohexadienones can be obtained from these reactions if tautomerization is not possible ( $R^2, R^1 \neq H$ ).<sup>61,62</sup>

Information about the rates and reversibility of these processes has been difficult to obtain because a rate-limiting CO dissociation is followed by rapid conversion into product, which also explains the inability to detect reaction intermediates.<sup>63,64</sup> One DFT study suggests that both the alkyne insertion and CO insertion steps should be irreversible.<sup>48</sup> Another DFT study finds that the alkyne insertion should be irreversible, but information on the CO insertion step was not provided.<sup>49,50</sup> A detailed study of the reaction of a (2-furyl) carbene complex with 1-pentyne concludes that at least one of these steps must be irreversible.<sup>65</sup> More recent studies on the reaction of a 2-methoxyphenyl complex finds that the constitutional isomers of the vinyl carbene complex (*E*)-**4** (see structures **4** and **7**, Scheme 3) undergo interconversion faster than CO insertion although it could not be determined if this interconversion takes place by reversible insertion of the alkyne or some other mechanism.<sup>66</sup>

Unsymmetrical acetylenes react with  $\alpha, \beta$ -unsaturated Fischer carbene complexes to give two constitutionally isomeric phenol products as represented by compounds **2** and **8** (Scheme 3). In most reaction scenarios, the predominant product can be predicted on the basis of the steric bulk of the alkyne substituents such that the major product has the largest substituent of the alkyne incorporated adjacent to the hydroxy group of the phenol.<sup>67-70</sup> With internal alkynes, mixtures of isomers that vary with the sizes of the substituents are observed. With terminal alkynes the reaction generally proceeds with greater than 100:1 selectivity, but lower selectivities are occasionally observed (10:1).

The source of the steric influence of the alkyne substituents on regioselectivity has been suggested to result from the interaction of these substituents with carbon monoxide ligands in the  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate (Scheme 3, **4** vs. **7**). Extended Hückel calculations reveal that the substituent at the 2-position of this intermediate is at least 1 Å closer to its nearest CO ligand than the substituent on the 1-position.<sup>46</sup> It is not clear whether the preference for isomer **4** over **7** is a result of kinetic or thermodynamic control. Perturbation of



Scheme 3

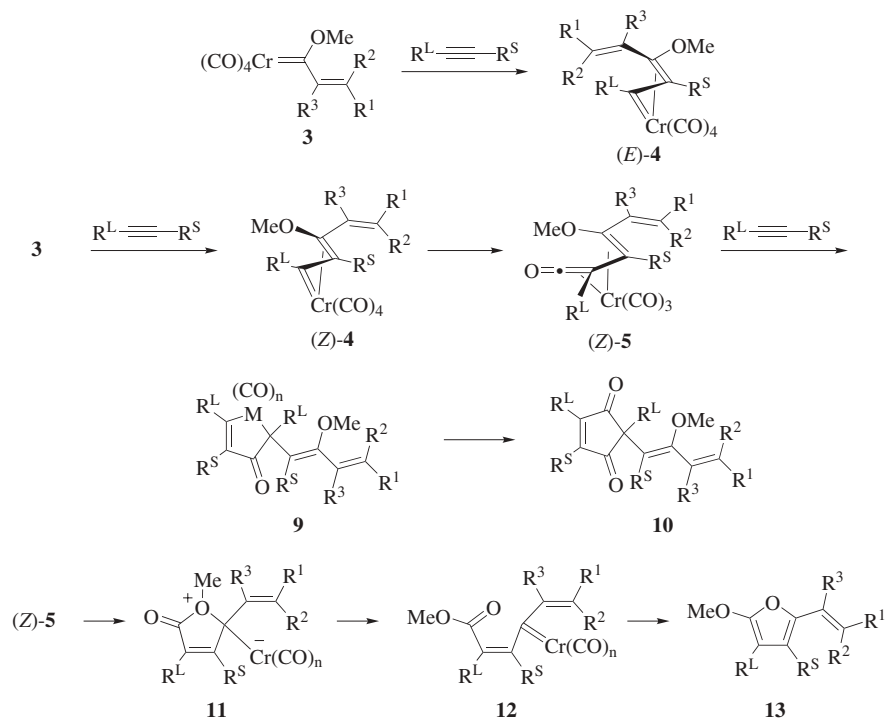
the regioselectivity by electronic effects has been reported rarely. To date, only ketone<sup>71</sup> and tributylstannyl<sup>72,73</sup> substituents on the alkyne are known to influence regioselectivity to the point that electronic factors predominate over steric factors. The source of these electronic effects have been interpreted in terms of the resonance structure (*E*)-4a for the  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate. A recent report describes the regioselective reaction with internal boryl alkynes, which may be due to electronic rather steric effects.<sup>74,75</sup>

Even if the key intermediates in the reaction are those shown in Scheme 2, this information is usually not sufficient to predict the product distribution. The reactions are quite sensitive to solvent, temperature, concentration, the nature of the metal and its ligands, and on any functionalities present in either the carbene complex or the alkyne. The optimal conditions for a given carbene complex and alkyne are best determined experimentally with the aid of the known set of reactions that are presented in the Tabular Survey.

One of the main problems in the reaction of  $\alpha, \beta$ -unsaturated Fischer carbene complexes with alkynes is the large number of chemical structures that are possible products. The chemoselectivity, or the selectivity for a certain product type, has been carefully examined and the number of products that have been reported for this reaction are too numerous to list here, but are included in the Tabular Survey. However, for those reactions targeting phenols, the most common structures observed as co-products are furans,<sup>65,76,77</sup> vinylcyclopentadienones,<sup>78</sup>

cyclobutenones,<sup>76,13</sup> indenenes (cyclopentadienes),<sup>76,79</sup> and two-alkyne phenols, which are phenols derived from the carbene carbon, a carbon monoxide ligand, and two equivalents of the alkyne.<sup>80,81</sup> The mechanistic origin of each of these side-products will be briefly discussed below to the extent that such information is known.

A mechanistic accounting for the formation of the vinylcyclopenten-1,3-dione product **10** and the furan product **13** is presented in Scheme 4. These products result from the insertion of the alkyne to give the *Z*-isomer of the  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate **4**. The alkyne normally inserts to give the *E*-isomer of **4** and this preference has been shown to be a result of the electronic influence of the methoxy group.<sup>47</sup> Consequently, the vinylcyclopenten-1,3-dione **10** and furan product **13** are usually observed in less than 20% combined yield, although under certain circumstances they are the major products of the reaction. Furan formation results from insertion of a carbon monoxide ligand to give the *Z*-isomer of the vinyl ketene complex **5**, and then attack of the methoxy group on the ketene to give the zwitterion **11**. Carbon-oxygen bond fragmentation gives the non-stabilized carbene-complexed intermediate **12**, which is not observed but is presumably attacked rapidly by the carbonyl oxygen with subsequent loss of chromium to give the furan.<sup>65,77</sup> Although two reasonable possibilities have

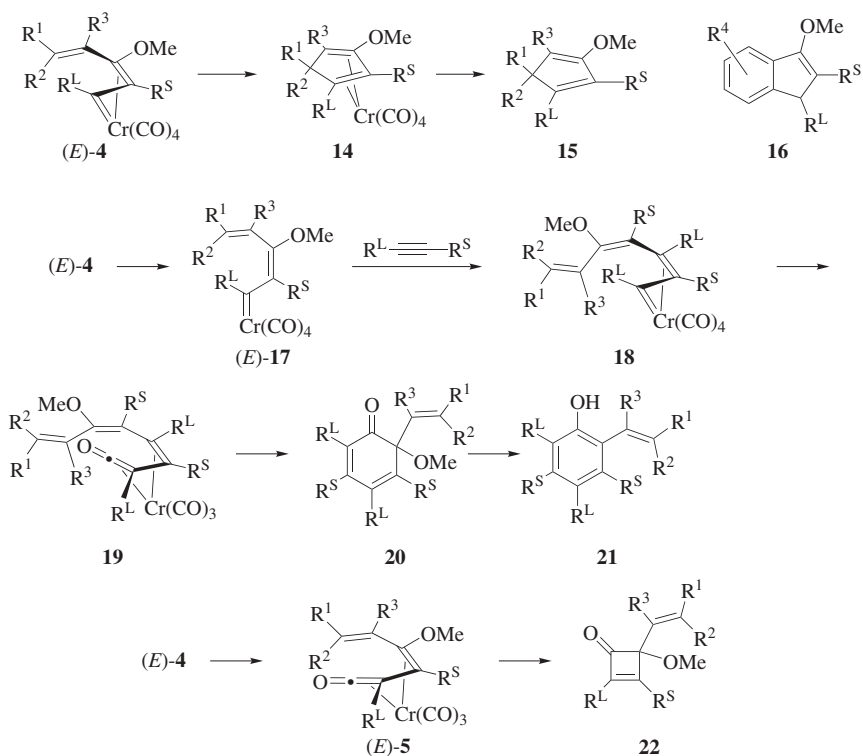


Scheme 4



been suggested for the formation of the vinylcyclopenten-1,3-dione **10**, the most likely pathway is thought to involve a reductive coupling of the carbon-carbon double-bond of the ketene with a second molecule of the alkyne to give metallocyclopentenone **9**. Subsequent CO insertion and reductive elimination would render the observed product **10**.<sup>78,60</sup>

For many reactions of interest, the formation of the indene product can be the most detrimental, decreasing the yields of the desired phenol product. The indene product results from the failure of carbon monoxide to insert into the vinyl carbene-complexed intermediate (*E*)-**4** to produce the vinyl ketene complexed intermediate (*E*)-**5** (Scheme 5). Instead, cyclization occurs to give a five-membered ring (**14**), which upon loss of the metal gives the cyclopentadiene **15**. This product is actually rarely seen with alkenyl-substituted chromium carbene complexes and is usually only observed as a side-product in the reaction of aryl complexes, where it is often isolated as the metal-free indene **16**. The phenol to indene (cyclopentadiene) ratio is more favorable for phenol formation with chromium than with molybdenum and tungsten complexes.<sup>60,63,71,82</sup> Phenol formation is also more often seen with electron-poor complexes than with electron-rich complexes,<sup>79,83</sup> and in less polar solvents rather than in more polar

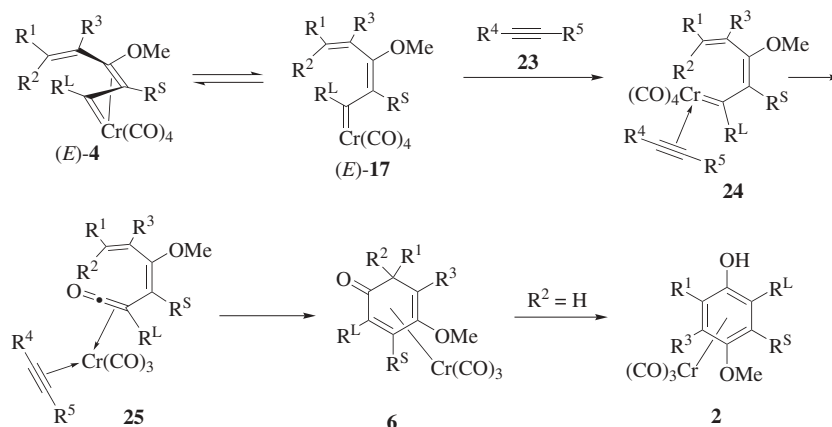


solvents.<sup>13</sup> Concentration and temperature can also influence this ratio such that lower temperatures and higher concentrations favor phenol formation.<sup>84</sup>

The two-alkyne phenol product **21** results from the incorporation of two equivalents of the alkyne. It is believed that the formation of this product begins with the decomplexation of the double-bond in the saturated 18-electron  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate (*E*)-**4** to give the unsaturated 16-electron  $\eta^1$ -analogue (*E*)-**17** (Scheme 5).<sup>80</sup> Calculations have shown that these two intermediates are nearly identical in energy and that the barrier to their interconversion is quite low.<sup>45,46</sup> This observation has been confirmed experimentally.<sup>51,52</sup> The site of unsaturation in (*E*)-**17** makes possible the reaction with a second alkyne to give the  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate **18** that has two equivalents of the alkyne incorporated. CO insertion would give the vinyl ketene complex **19** and electrocyclic ring closure would give the cyclohexadienone **20**, which can sometimes be isolated but is usually reduced in situ by chromium(0) to give phenol **21**. This mechanism suggests that the formation of two-alkyne phenols is concentration dependent and experiments reveal that the phenol **21** is most often significant as a side-product at high concentrations and with sterically unencumbered alkynes. Just as the  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate (*E*)-**4** can decomplex from the double bond to give the  $\eta^1$ -vinyl carbene complexed intermediate (*E*)-**17** and then insert an alkyne, so can the  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate **18**. This process is presumably the mechanism by which Group 6 carbene complexes, especially those of tungsten, can cause oligomerization and polymerization of alkynes.<sup>85</sup>

Finally, the cyclobutanone product **22** is thought to be the result of an electrocyclic ring closure of the vinyl ketene complex (*E*)-**5**. The formation of this product is often maximized in acetonitrile where coordination of the solvent to the metal may foster cyclization.<sup>13</sup> It has not been determined whether the two-alkyne phenol product **21** and the cyclobutanone product **22** can be formed from the *E*- $\eta^1, \eta^3$ -vinyl carbene complexed intermediate **4**, or formed from the *Z*-isomer, or from both.

The formation of the phenol product can often be sensitive to the concentration of the reactants. Extensive investigation revealed that this dependency is linked to the concentration of the alkyne and not to that of the carbene complex.<sup>13,60,84</sup> Increased concentration of the alkyne leads to increased proportions of the phenol product relative to the indene (cyclopentadiene) product. An explanation was put forth that involves the coordination of a molecule of the alkyne to the metal center in the 16 electron  $\eta^1$ -vinyl carbene complexed intermediate (*E*)-**17**, which already has a molecule of the alkyne incorporated. Because an alkyne can be either a 2- or 4-electron donor ligand, the coordination of alkyne **23** is proposed to facilitate the insertion of a carbon monoxide ligand (Scheme 6). The alkyne can switch from a 2-electron donor in **24** to a 4-electron donor in **25**, and thus maintains a saturated, 18-electron metal center during the CO insertion step. Electrocyclic ring closure and loss of the acetylene would then produce the phenol chromium tricarbonyl complex **2** as the product. This alkyne-promoted enhancement of phenol formation is termed the "allochemical effect"<sup>84</sup> if the alkyne **23** is the



Scheme 6

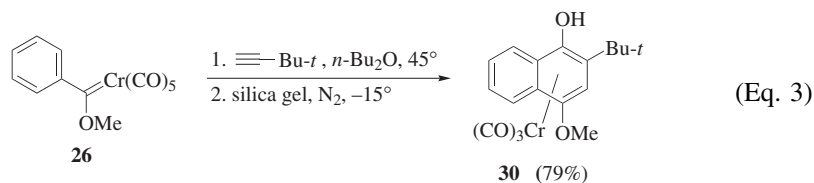
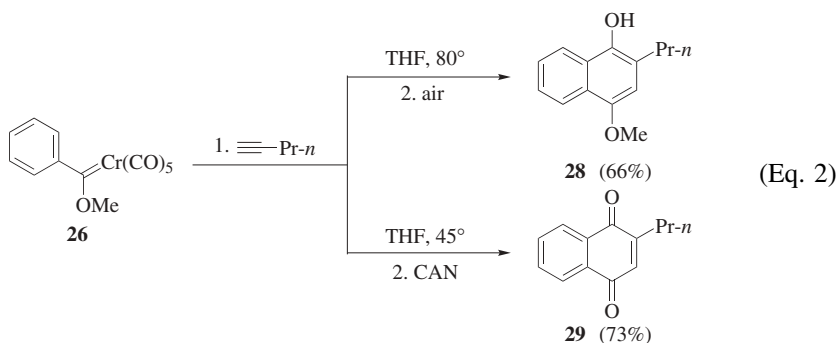
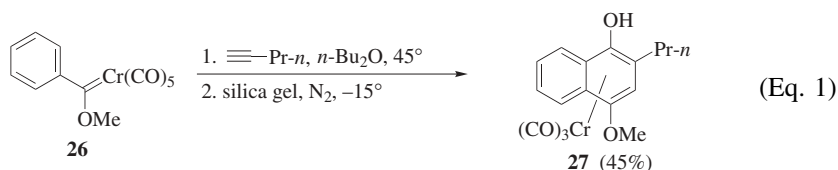
same as the first alkyne that has already been incorporated into (*E*)-**17**, and the “xenochemical effect”<sup>86</sup> if the two alkynes are different. This allochemical effect and the process that leads to the formation of the 2-alkyne phenol product **21** (Scheme 6) are closely related. In the former the alkyne coordinates to the metal of (*E*)-**17** but does not insert and in the latter the alkyne inserts into (*E*)-**17** to give the intermediate **18**.

## SCOPE AND LIMITATIONS

### Benzannulation

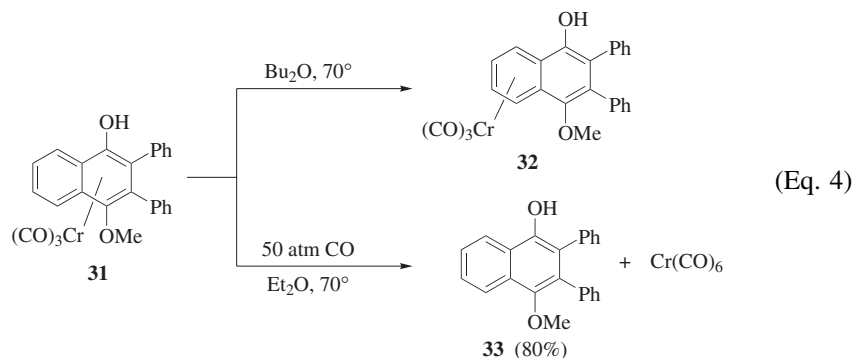
**Product Isolation.** The primary product of the reaction between an alkyne and an  $\alpha,\beta$ -unsaturated Fischer carbene complex (e.g., **26**) is an arene chromium tricarbonyl complex with the chromium coordinated to the newly formed benzene ring. The phenoxy function present in these products renders the molecule sensitive to air and special precautions are needed to isolate these complexes. The arene complex **27** is isolated in 45% yield by purification on silica gel at  $-15^\circ$  under an inert atmosphere (Eq. 1).<sup>87</sup> However, this result does not represent the actual yield because naphthol **28** can be isolated in 66% yield after oxidation in air<sup>60</sup> and quinone **29** is obtained in 73% yield after an oxidative workup with ceric ammonium nitrate (Eq. 2).<sup>13</sup> The lower yield of complex **27** is due to air oxidation which occurs despite the precautions taken. Most arene chromium tricarbonyl complexes from this reaction are quite air-sensitive and will lose the metal within minutes upon exposure to atmospheric conditions. This air-sensitivity is in contrast to that of Fischer carbene complexes, which are normally stable to air and only undergo extensive air oxidation when left in solution for a day or more. Relatively air-stable arene chromium tricarbonyl complexes are obtained from reactions of carbene complexes with acetylenes

bearing large substituents as illustrated in the isolation of complex **30** in 79% yield (Eq. 3).<sup>68</sup> Many such arene complexes with hindered substituents adjacent to the phenol are quite stable to air and some will survive chromatography on silica gel at room temperature in the presence of air with little or no decrease in yield.<sup>88</sup>

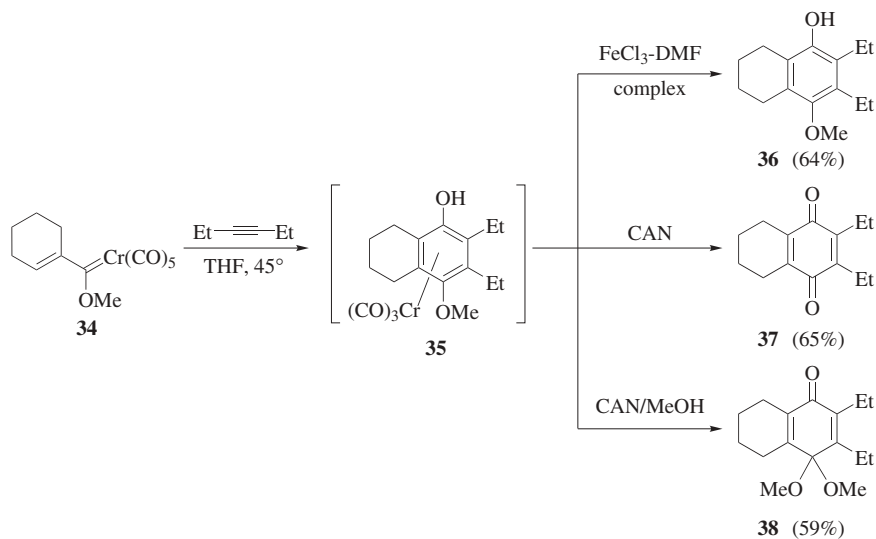


The reaction of complex **26** with diphenylacetylene at 45° produces the arene complex **31** with the chromium tricarbonyl group on the newly formed benzene ring.<sup>2</sup> This product results from kinetic control because heating this complex to 70° results in migration of the chromium tricarbonyl group to the other ring of the naphthalene nucleus giving complex **32**. This observation requires that the chromium remains bound to the organic fragment during the entire course of the reaction. Complex **31** is also used to demonstrate a method for removal of the chromium tricarbonyl unit from the product that does not involve an oxidation of the metal. Ligand displacement with carbon monoxide can effectively provide the metal-free phenol **33** in good yield (Eq. 4).<sup>76</sup> A related ligand displacement method with triphenylphosphine has been reported.<sup>90</sup> Another important aspect of deprotection with CO in addition to the mild conditions is that this method sequesters the chromium as its hexacarbonyl complex in high yield, thus providing for a convenient recycling of the chromium (chromium hexacarbonyl is the starting material from which most Fischer carbene complexes are produced).

Because chromium hexacarbonyl is relatively insoluble in ether, it can be recovered by simple filtration.



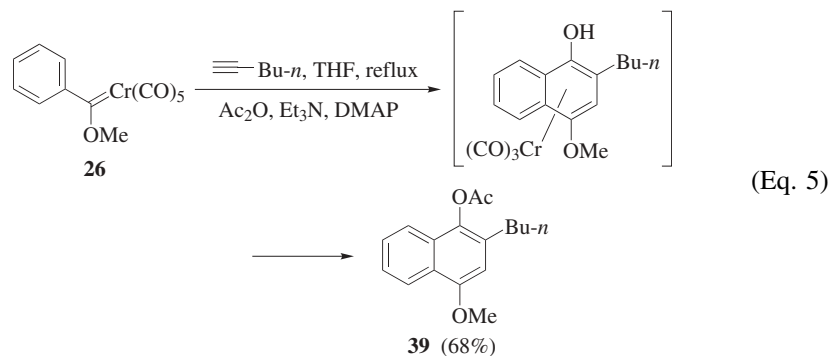
In most synthetic applications the metal-free organic product is desired and the method of workup is chosen to provide a clean and rapid removal of the metal as well as to provide the product in a particular oxidation state or particular form of functional group differentiation, as illustrated in the reaction of the cyclohexenyl complex **34** with diethylacetylene (Scheme 7).<sup>69</sup> Oxidative workup with ferric chloride-DMF removes the metal from complex **35** but does not oxidize the hydroquinone mono-ether, resulting in product **36**. Pyridine *N*-oxide has also been used for this purpose.<sup>91</sup> Oxidation with ceric ammonium nitrate removes the metal and oxidizes the product to the quinone **37**. Ceric(IV) oxidation in methanol gives the quinone mono-acetal **38**. Other oxidants that have been

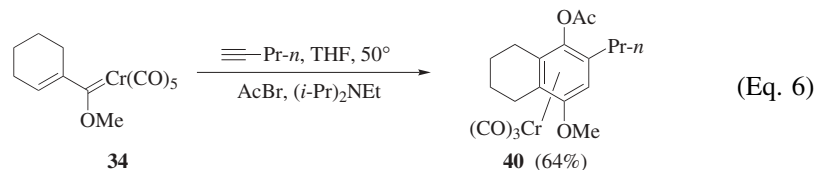


Scheme 7

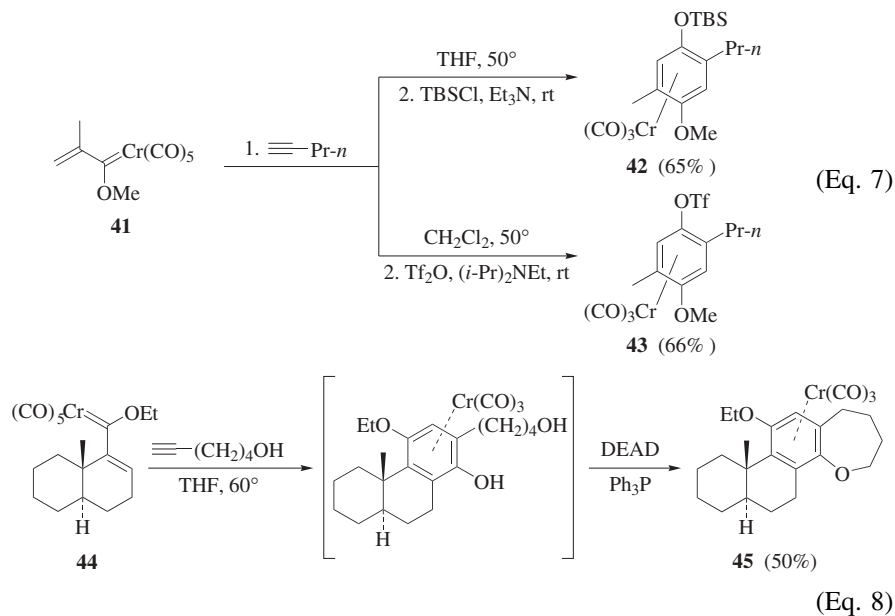
used include lead oxide,<sup>92</sup> nitric acid,<sup>76</sup> silver oxide,<sup>93</sup> and iodine.<sup>67</sup> The ferric chloride-DMF complex is not selective in the oxidation of naphthol chromium tricarbonyl complexes, removing the metal and oxidizing the product to a naphthoquinone. Other than air, no oxidant has been reported that will selectively remove the metal from a naphthol chromium tricarbonyl complex without also oxidizing the naphthol to a naphthoquinone. Air oxidation is usually effective for obtaining naphthols from naphthol complexes but exposure to air for extended times, or additional irradiation with ultraviolet light may be required for certain complexes. Ligand displacement with CO can be a useful alternative for the clean isolation of naphthols.

In general, it has been possible to efficiently protect the phenoxy function while retaining the chromium tricarbonyl group in products from the reactions of alkenyl complexes. However, this process has not been as successful for the reactions of aryl complexes, probably because of the increased lability of naphthol chromium tricarbonyl complexes toward ligand displacement compared to that of phenol chromium tricarbonyl complexes. For example, the reaction of phenyl complex **26** with 1-hexyne in the presence of acetic anhydride and triethylamine gives the acetylated product **39**, which has lost the metal (Eq. 5).<sup>94</sup> In contrast, cyclohexenyl complex **34** undergoes benzannulation with 1-pentyne followed by in situ acylation to give tricarbonyl(*O*-acetoxyarene)chromium complex **40** in 64% yield (Eq. 6).<sup>95</sup> *O*-Acetyl complexes can sometimes be obtained from aryl carbene complexes if the naphthyl chromium tricarbonyl complexes are first isolated.<sup>73</sup> Whereas *O*-acetoxy-naphthalene chromium tricarbonyl complexes cannot be obtained by the one-pot method, the in situ acylation of these products is useful because *O*-acylated naphthols are often less sensitive to air oxidation than their corresponding naphthols. For this reason, in situ acylation is often used to produce acylated products from both alkenyl and aryl complexes and the transformation indicated in Eq. 5 has been developed as an *Organic Syntheses* procedure.<sup>94</sup> With alkenyl complexes, the metal-free *O*-acylated products are obtained from a tandem process in which the benzannulated product is exposed to air before the acylating reagents are added.



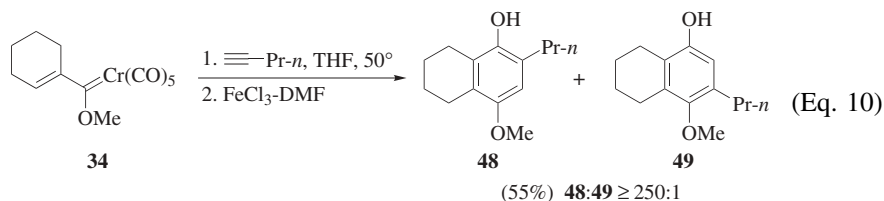
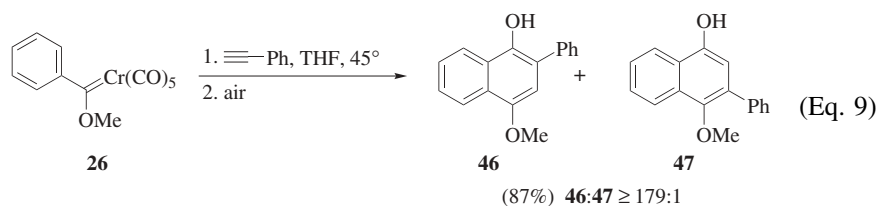


Several other methods for derivatization of the phenoxy function have been reported for the direct preparation of differentially-protected (hydroquinone)chromium tricarbonyl complexes. The silylated chromium tricarbonyl complex **42**<sup>95</sup> and the triflated complex **43**<sup>96</sup> have both been prepared from carbene complex **41** and 1-pentyne (Eq. 7). The yields of these complexes are approximately the same for both one-step and two-step processes. Silylated complexes can also be obtained from aryl complexes in a one-pot process with certain alkynes.<sup>73,97</sup> Other electrophiles that have been used include triisopropylsilyl triflate and methoxymethyl chloride.<sup>95</sup> Two reports of functionalization of the phenol by an intramolecular Mitsunobu reaction have been described.<sup>98,99</sup> In the reaction of the octalin carbene complex **44**, the metal is retained in product **45**, which is formed as a single diastereomer (Eq. 8).<sup>99</sup>

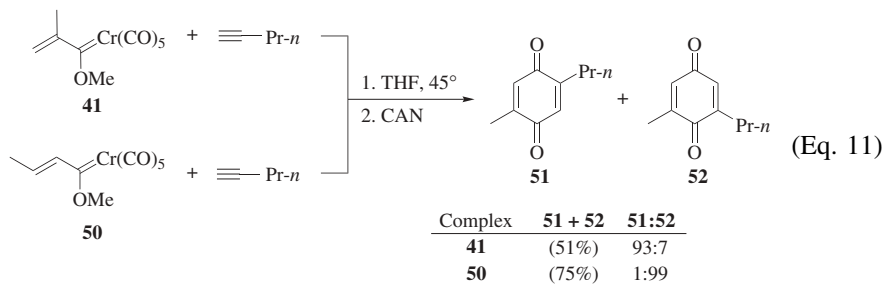


**Regioselectivity.** In general, the regioselectivity of the reaction is controlled by steric effects and the level of regioselectivity is related to the difference in steric bulk of the two alkyne substituents.<sup>67-70</sup> The major isomer derives from the incorporation of the larger substituent into the position adjacent to the phenolic hydroxy group. The largest difference in substituent sizes occurs when one of them is hydrogen, and thus the highest selectivities are found with these alkynes.

The regioselectivity with terminal alkynes is almost always extremely high with both aryl and alkenyl complexes alike. This high selectivity is illustrated by the reaction of phenyl complex **26** with phenylacetylene, which gives at least a 179 : 1 selectivity for phenol **46** in preference to phenol **47** (Eq. 9).<sup>100</sup> Likewise, reaction of cyclohexenyl complex **34** with 1-pentyne gives phenol **48** in preference to phenol **49** with at least 250 : 1 selectivity (Eq. 10).<sup>101</sup>



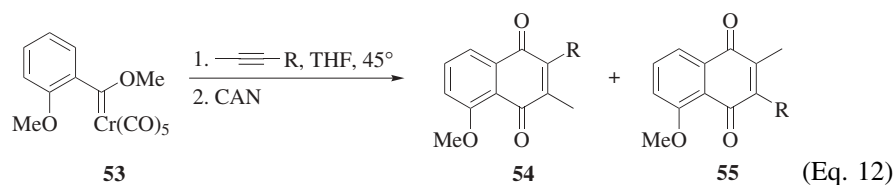
The pair of reactions of carbene complexes **41** and **50** with 1-pentyne provides a direct comparison of the regioselectivity of these complexes with the same alkyne because these two reactions share the same set of two possible isomeric quinones (but not phenols) (Eq. 11).<sup>69</sup> Interestingly, whereas the *trans*-1-propenyl complex **50** gives the typically high regioselectivity observed with terminal alkynes, the 2-propenyl complex **41** only gives a 93 : 7 selectivity for quinones **51** and **52**. This ratio represents the lowest regioselectivity that has been observed in the reaction of an alkenyl complex with a non-electronically perturbed terminal alkyne and no explanation for it has been offered. The regioselectivity of this reaction can be increased to 97 : 3 if the reaction is performed with 1-tributylstannyl-1-pentyne.<sup>72</sup>



The effect of the difference in steric size of the two alkyne substituents on the regioselectivity of the reaction is illustrated in Eq. 12.<sup>67</sup> 2-Pentyne gives a 1.5 : 1 mixture of the isomeric quinones **54** and **55** upon reaction with the



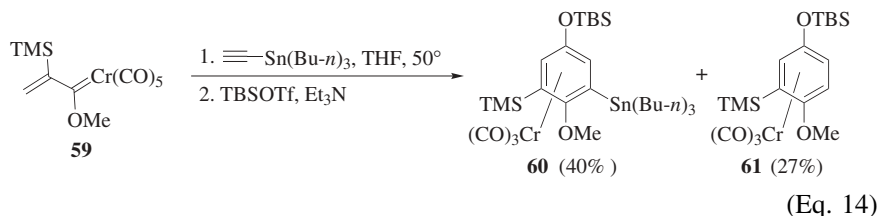
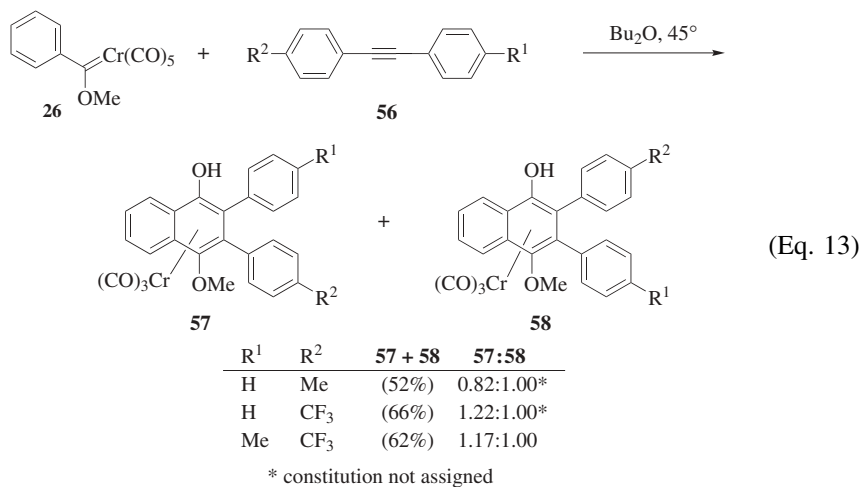
2-methoxyphenyl complex **53** (Eq. 12). This ratio is increased to 4.8:1 with 4-methyl-2-pentyne. On the basis of the difference in the size of the two substituents, higher regioselectivity was expected for the reaction with 1-phenylpropyne and the value of 41:1 has been recorded for this reaction.<sup>66</sup> This selectivity drops to 18:1 when the temperature is increased from 45° to 90°. This is the only example in which regioselectivity as a function of temperature has been reported.



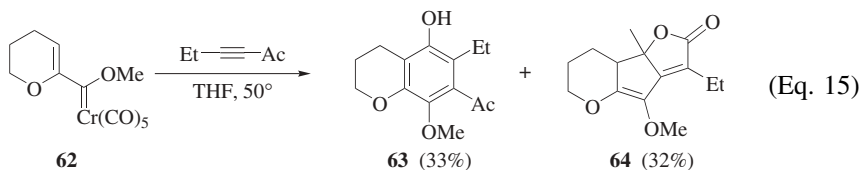
R	Temp	54:55
Et	45°	1.5:1
<i>i</i> -Pr	45°	4.8:1
Ph	45°	41.0:1
Ph	90°	18.0:1

Regioselectivity is rarely influenced by electronic perturbations of the alkyne. Very small differences in the regioselectivity of the reaction of complex **26** with substituted diphenylacetylenes **56** are found where nearly equal ratios of phenol complexes **57** and **58** are observed despite significant electronic differences in the two arene rings of **56** (Eq. 13).<sup>42</sup> Electronic factors can, under some circumstances, exert a strong influence on regioselectivity.<sup>71-73</sup> If the alkyne is substituted by a stannyl group, the regioselectivity of incorporation of the alkyne occurs as if the stannyl group were not present. Occasionally the regioselectivity is enhanced over that observed for the terminal alkyne. For example, the reaction of complex **41** with 1-tributylstannyl-1-pentyne gives, after oxidative workup, a 97:3 mixture of quinones **51** and **52** (Eq. 11).<sup>72</sup> The reaction of tributylstannylacetylene with complex **59** followed by in situ protection with *tert*-butyldimethylsilyl triflate gives the stannyl-substituted chromium tricarbonyl complex **60** in 40% yield, and the destannylated complex **61** in 27% yield (Eq. 14).<sup>72</sup> The major product **60** has the stannyl group incorporated adjacent to the methoxy group (3-position). This orientation is opposite to the regioselectivity previously seen with all terminal acetylenes. Minor product **61** could have resulted from loss of the stannyl group in either the 2- or 3-position. The reaction with 2-deuterio-1-tributylstannylacetylene proceeds with a 2:1 selectivity in favor of the "abnormal" isomer **60**. The origin of this effect is attributed to  $\beta$ -stabilization of the positive charge on C1 of the vinyl carbene complexed intermediate (*E*)-**4a** when the stannyl group is on C2 of (*E*)-**4a** (Scheme 3). Although silicon has a lesser ability to stabilize  $\beta$ -carbocations than does tin,<sup>102</sup>

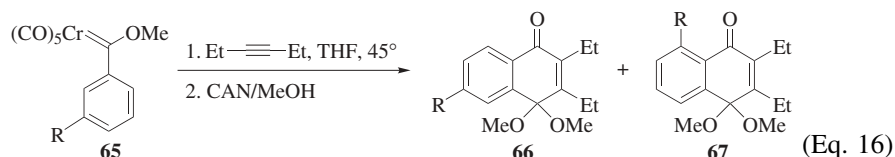
it is nonetheless surprising that a similar electronic effect has not been observed for silicon.<sup>69,72,73</sup>



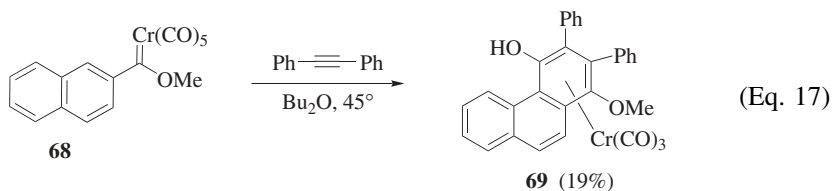
A disubstituted alkyne with a ketone function in conjugation with the alkyne reacts with high regioselectivity to give products in which the ketone function is introduced into the phenol adjacent to the methoxy group (Eq. 15).<sup>71</sup> Reaction of complex **62** with hex-3-yn-2-one gives products **63** and **64**, both as a result of the same regiochemical incorporation of the alkyne. Compound **64** is formed via cyclization of the vinyl ketene in a crossed fashion. Ester functions do not impart a strong enough effect when conjugated with an alkyne to influence the regioselectivity and as a result mixtures of isomers are observed.<sup>47,70</sup> It is curious that a ketone, which is separated from the alkyne by two methylenes, has an effect on the regioselectivity, albeit to a lesser extent than is observed with conjugated ketones (Eq. 47).<sup>103</sup> A recent report on the regiochemical outcome of the reactions of internal boryl alkynes may involve electronic control of the regioselectivity by boron.<sup>74,75</sup>



Site selectivity in reactions of unsymmetrically substituted phenyl carbene complexes has been examined to some extent. In all of the reactions of 3-substituted phenyl carbene complexes **65**, the major isomer **66** results from cyclization away from a meta substituent (Eq. 16).<sup>67</sup> A very curious observation is that the magnitude of the site-selectivity observed with the 3-methoxy complex **65b** is highly dependent on whether a terminal or internal alkyne is used.<sup>67</sup> The reaction with 3-hexyne is four times less selective than the reaction with 1-pentyne. An explanation for this behavior has not been advanced. The electronic nature of the meta substituent also has a strong effect. The 3-trifluoromethylphenyl complex **65c** is ten times as selective as the 3-methoxy complex **65b**. The same reaction with the 3-methyl complex **65a** gives a 1.2:1 mixture of **66a** and **67a**. Because the trifluoromethyl group is not significantly different in size than a methyl or methoxy group, it is clear that a strongly electron-withdrawing group directs the cyclization to the more remote para position. Two isomers are also possible in the cyclization of the 2-naphthyl complex **68**. However, reaction with diphenylacetylene affords only a single isomer, namely a phenanthrene rather than an anthracene (Eq. 17).<sup>104</sup> The actual chemical yield of this reaction is likely to be quite high and the low yield of **69** is likely a consequence of the air instability of this arene chromium tricarbonyl complex containing an unprotected phenolic hydroxy group. Cyclization to the 1-position of the naphthalene is a typical reactivity pattern for various types of cyclizations of 2-substituted naphthalenes because this option disrupts the aromaticity in only one of the naphthalene rings. This direction of cyclization of 2-substituted naphthyl carbene complexes has been confirmed in a different system by X-ray crystal structure analysis.<sup>105</sup>

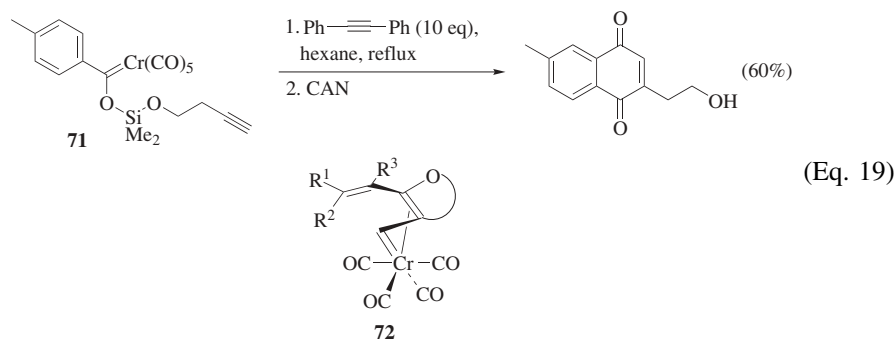
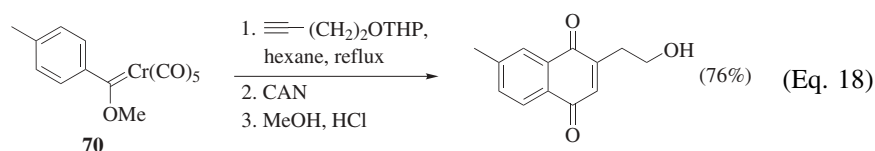


	R	<b>66</b> + <b>67</b>	<b>66</b> : <b>67</b>
<b>65a</b>	Me	(79%)	1.2:1
<b>65b</b>	OMe	(81%)	2.1:1
<b>65c</b>	CF <sub>3</sub>	(55%)	25.5:1

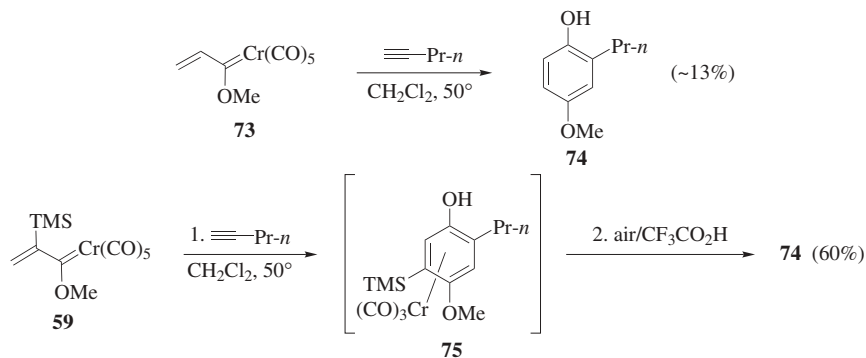


The normal site selectivity of the reaction of Fischer carbene complexes with alkynes can be reversed if the alkyne is tethered through the heteroatom-stabilizing substituent. Either isomer of the quinone from the reaction of 4-methylphenyl carbene complex and 3-butyneol can be obtained cleanly as shown

in Eqs. 18 and 19.<sup>86</sup> Carbene complex **70** and the free alkyne give the expected quinone isomer in 76% yield. The regiochemical outcome is reversed for the tethered complex **71** because the vinyl carbene complexed intermediate **72** in this reaction has the unsubstituted end of the alkyne at the C1 position. Note that in the absence of a tether, a terminal alkyne will preferentially be incorporated to give vinyl carbene intermediate (*E*)-**4** rather than (*E*)-**7** (Scheme 3) for the reasons discussed above. It is interesting to note that the intramolecular reaction of complex **71** gives high yields only in the presence of ten equivalents of diphenylacetylene. This phenomenon is observed for a number of intramolecular examples and is termed the xenochemical effect.<sup>86</sup> The xenochemical effect is related to the allochemical effect<sup>84</sup> in that the product distribution is a function of the alkyne concentration, but it differs in that the distribution is a function of the concentration of an alkyne that does not become incorporated into the product (Scheme 6).



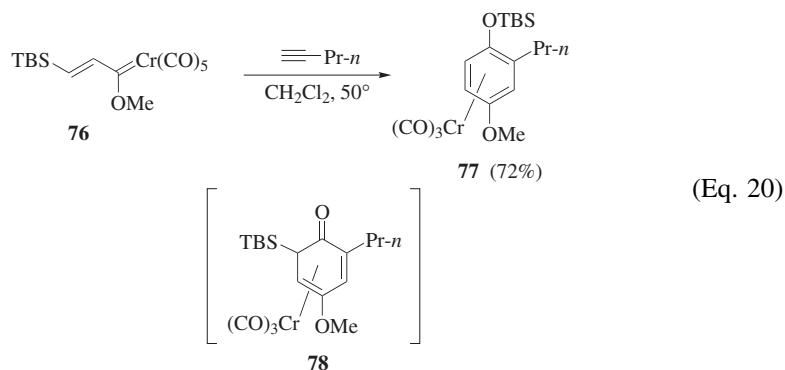
**Alkenyl, Aryl, and Alkynyl Chromium Complexes.** The only alkenyl chromium carbene complex that will not react with alkynes to give useful yields of annulated products is the unsubstituted parent vinyl carbene complex **73** (Scheme 8). The reaction of complex **73** with 1-pentyne gives approximately a 13% yield of phenol **74**.<sup>106</sup> The origin of the failure of this reaction is not understood but it is known that complex **73** is unstable with respect to polymerization and can only be isolated in pure form below its melting point (15°).<sup>107-109</sup> The  $\alpha$ -silyl-substituted vinyl complex **59** (Scheme 8) has been developed as a synthetic equivalent for the parent vinyl complex.<sup>110</sup> The reaction of **59** with 1-pentyne followed by exposure to air and trifluoroacetic acid affords phenol **74** in 60% yield. Both the 2-propenyl and trans-1-propenyl complexes react with alkynes to give useful yields of the cyclized product (Eq. 11). The cis-1-propenyl



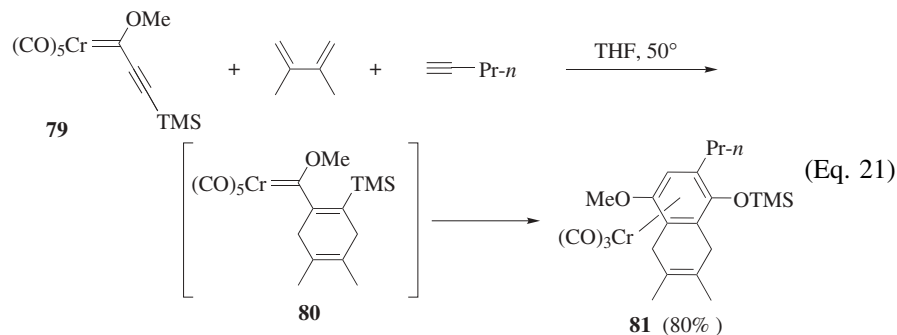
Scheme 8

complex also reacts with alkynes to give phenol products but the *cis*- and *trans*-1-propenyl complexes could not be compared since the former isomerizes to the *trans* complex at a rate competitive with the reaction with 1-pentyne.<sup>69</sup> Interestingly,  $\beta,\beta$ -disubstituted complexes do not isomerize during their reactions with alkynes.<sup>111</sup>

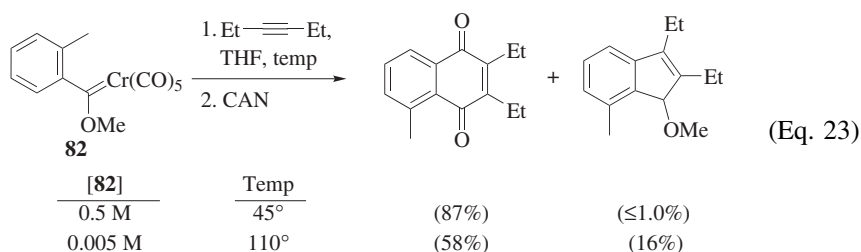
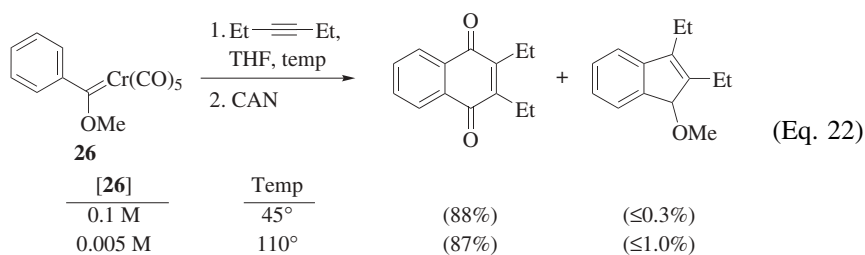
The  $\beta$ -silyl-substituted complex **76** can also serve as a synthetic equivalent for the parent and has the additional advantage that the silicon migrates to the phenolic oxygen both obviating the need for protodesilylation and producing an air-stable arene chromium tricarbonyl complex directly from the reaction (Eq. 20).<sup>110</sup> This process occurs because migration of silicon to oxygen is faster than tautomerization of the hydrogen in intermediate **78**. Benzannulation of a  $\beta$ -silyl-substituted carbene complex can be coupled with a Diels-Alder reaction of an alkynyl carbene complex as illustrated in the one-step preparation of the dihydronaphthyl complex **81** (Eq. 21).<sup>95,112</sup> In this process, the diene reacts with alkynyl complex **79** faster than with the alkyne to give the Diels-Alder adduct **80**, which then reacts with 1-pentyne with silyl migration to give the arene complex **81** in 80% yield.

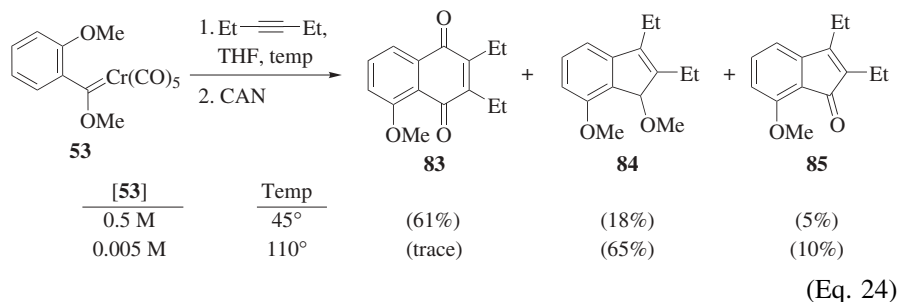


(Eq. 20)

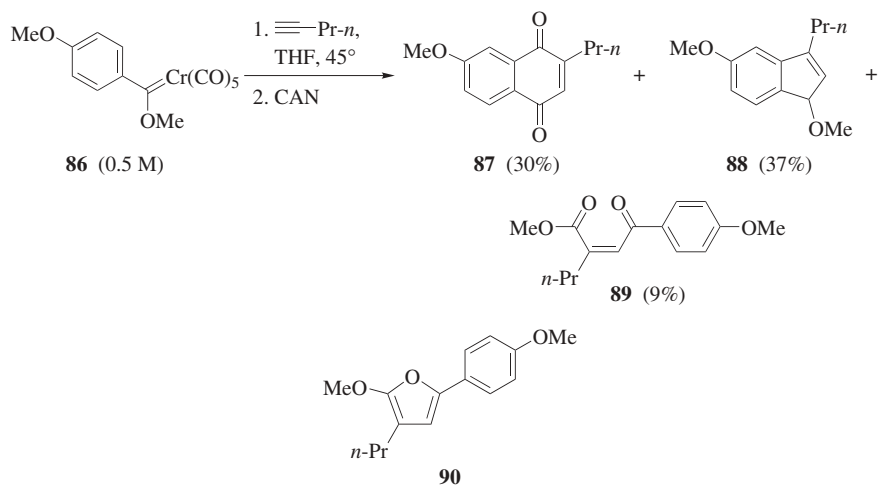


A wide range of substituents on the phenyl ring in an aryl carbene complex can be tolerated in the reaction. The introduction of a methyl group at the 2-position (**82**) has very little effect on the yield of quinone product (Eq. 22 vs. Eq. 23).<sup>84</sup> However, the methyl substituent does have some effect on the reaction run at lower concentration and higher temperatures where both quinone and indene products are observed. A methoxy group at this position has an even greater effect (Eq. 24).<sup>84</sup> Even if the reaction of the 2-methoxyphenyl complex **53** is run at high concentration and low temperature to maximize the six-membered ring product, indenenes **84** and **85** are still formed in a combined 23% yield. More dramatically, at low concentrations and high temperatures only a trace of the quinone is observed. The yield of quinone **83** can be improved (77–91%) by utilizing a large excess of alkyne or employing a less coordinating solvent (benzene or 2,5-dimethyltetrahydrofuran).<sup>84</sup>

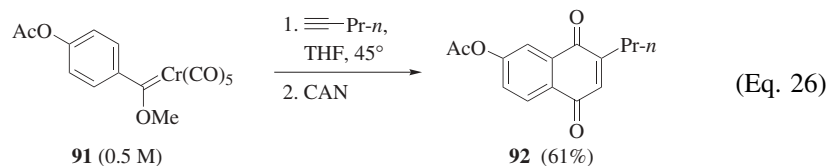




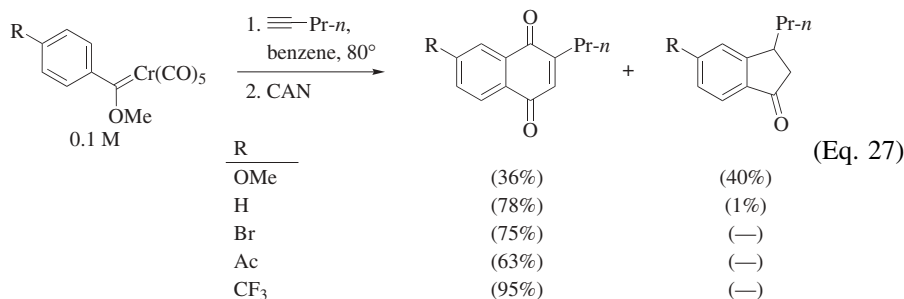
The effect of the methoxy group at the 2-position may be due to a combination of coordination, electronic, and steric effects. Interestingly, the 4-methoxyphenyl complex **86** displays a different sensitivity to concentration and alkyne substitution than does the 2-methoxyphenyl complex **53** and thus the effects of the methoxy group cannot be strictly electronic (Eq. 25).<sup>84</sup> The 4-methoxy complex reacts with 1-pentyne to give a 30% yield of quinone **87** along with indene **88** and keto ester **89**, whereas, the reaction of the 2-methoxyphenyl complex under the same conditions gives the quinone as the predominant product (not shown).<sup>84</sup> The keto ester **89** is not a primary product of the reaction but rather results from air oxidation of furan **90**, which is often seen as a by-product in this reaction but is usually difficult to isolate.<sup>65,76,77</sup> The influence of the 4-methoxy group can only be electronic and the degree of its effect is significant because the reaction of the unsubstituted phenyl complex **26** gives a 73% yield of the quinone **29** (Eq. 2) and the 4-acetoxy complex **91** gives a 61% yield of the quinone **92** (Eq. 26).<sup>84</sup>



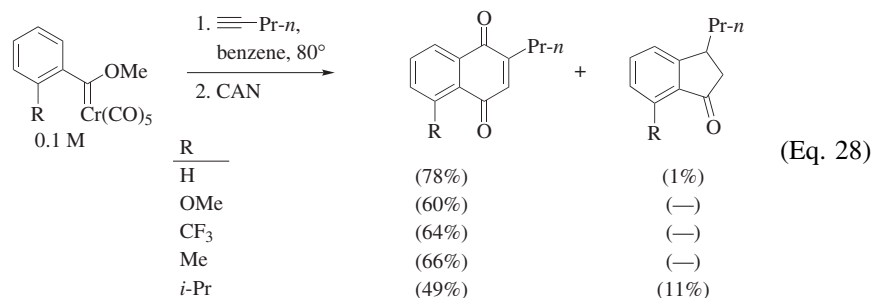
(Eq. 25)



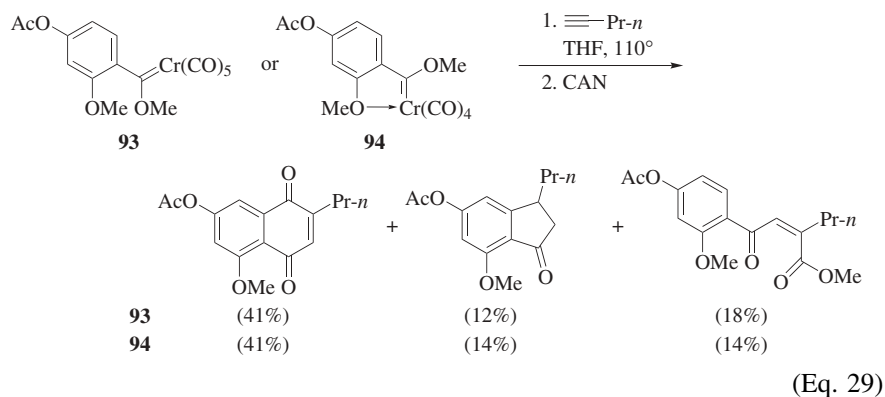
Almost all of the substituent effect studies that have been carried out on the reaction of substituted phenyl complexes involve alkyl or alkoxy groups. Complexes bearing electron-withdrawing groups have rarely been studied because they are not available by the standard methods of synthesis. Fischer carbene complexes are typically prepared by reaction of chromium hexacarbonyl with the corresponding aryllithium compounds. Thus, functionality that is not compatible with an organolithium reagent cannot be easily introduced into an arylcarbene complex. A recent study provides one of the few direct comparisons of the effects of electron-withdrawing and electron-donating groups on the reactions of phenyl carbene complexes (Eqs. 27 and 28).<sup>113</sup> Reactions of a number of para-substituted complexes with 1-pentyne were examined in benzene. The complex bearing the electron-releasing methoxy group gives low yields of quinone product and an equal amount of the indanone product (the distribution is slightly different in benzene and THF; Eqs. 25 vs. 27). The effect of the bromo substituent is negligible, whereas the trifluoromethyl group has a dramatic effect, affording a 95% yield of the quinone. The observation of a positive effect of an electron-withdrawing group was anticipated from published mechanistic studies.<sup>47</sup> However, the yield from the 4-acetylphenyl complex is not consistent with these studies and this may be because of the instability of this complex. The reaction of the phenyl complex bearing a trifluoromethyl group in the 2-position with 1-pentyne gives a much reduced yield of quinone.<sup>113</sup> In fact, all 2-substituted phenyl complexes give reduced yields independent of the electronic nature of the substituent. The larger the substituent the more the yield decreases (methyl vs. *iso*-propyl).<sup>113</sup> The reduced yields observed with 2-substituted complexes could be the result of steric destabilization of the planar conformation of the vinyl ketene complex (*E*)-**5** that is necessary for cyclization (Scheme 2).





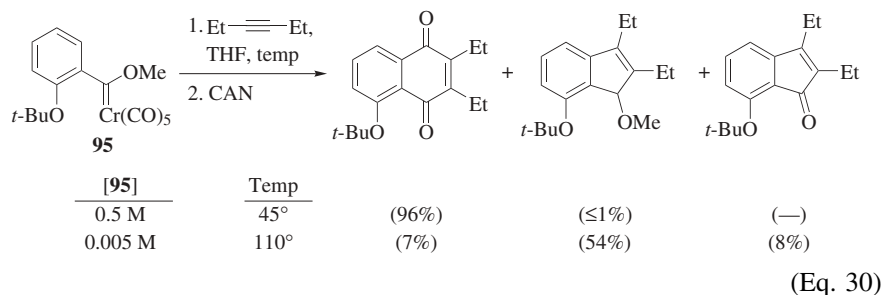


The reactions of a number of internally coordinated tetracarbonyl carbene complexes have been investigated but the effects of such coordination on product distribution have not been carefully determined in many systems. Given the sensitivity of the reactions of the 2-methoxy-substituted phenyl carbene complex **53** to concentration, temperature, and solvent (Eqs. 24 and 28), it is necessary that comparisons be made with full awareness of the exact reaction conditions. One system in which a comparison under precise control of conditions has been made is the reaction of the 2-methoxy-4-acetoxyphenylcarbene complex **94** (Eq. 29).<sup>84</sup> The chelated complex **94** can be generated in high yield by heating **93** in THF. The reaction of both complexes at 110°, and at 0.005 M in carbene complex with 1.5 equivalents of alkyne gives an essentially identical profile of the three products. From this experiment it can be concluded that it makes no difference whether 2-O-substituted phenyl carbene complexes are used as either the pentacarbonyl or the coordinated tetracarbonyl complexes. Often, the transient formation of an internally coordinated complex can be observed during the course of a reaction of a non-coordinated complex with an alkyne.



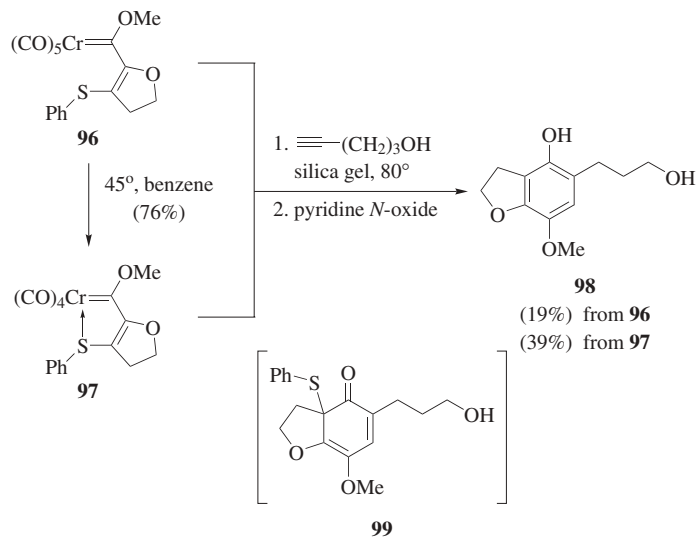
Although the reactions of complexes **93** and **94** demonstrate that the product distribution is not dependent on whether the methoxy group is coordinated prior to the reaction, the results in Eqs. 24 and 30 suggest that coordination by the methoxy group at some point in the reaction may take place. The chromium should be much less able to coordinate to a *tert*-butoxy group than to a methoxy

group. Thus, if coordination of the methoxy group is responsible for the differences in the reactions of phenyl complex **26** and the 2-methoxyphenyl complex **53** (Eqs. 22 and 24), then the reaction of the 2-*tert*-butoxyphenyl complex **95** (Eq. 30) should have a product distribution more similar to that of **26** than to that of **53**. On the other hand, if the effect is strictly electronic, then the two oxygenated complexes **53** and **95** should produce the same distribution. The result is intermediate between these extremes. It is clear that hindered protecting groups on the oxygen substituent allow preferential formation of the quinone product. The reaction of 2-*tert*-butoxyphenyl complex **95** with 3-hexyne at 0.5 M and 45° affords a 96% yield of the quinone with less than 1% of the indene (Eq. 30), whereas under the same conditions the 2-methoxyphenyl complex **53** affords only a 61% yield of the quinone and 23% of the indene (Eq. 24).<sup>84</sup> Note that the data in Eq. 28 predict that the yield of quinone from the reaction of complex **95** would be less than that for **53** (Eq. 24) given the size of the 2-substituent. However, the reactions in Eq. 28 are performed in a different solvent and are carried out on a terminal alkyne. Internal and terminal alkynes can have quite different product distributions (see below).



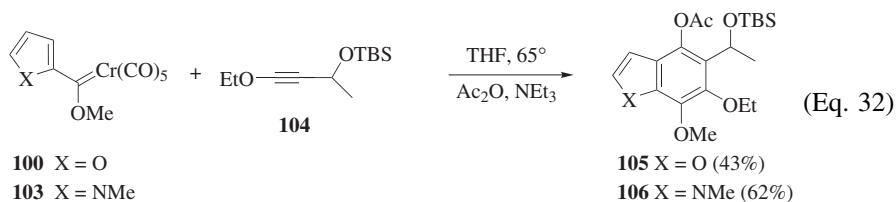
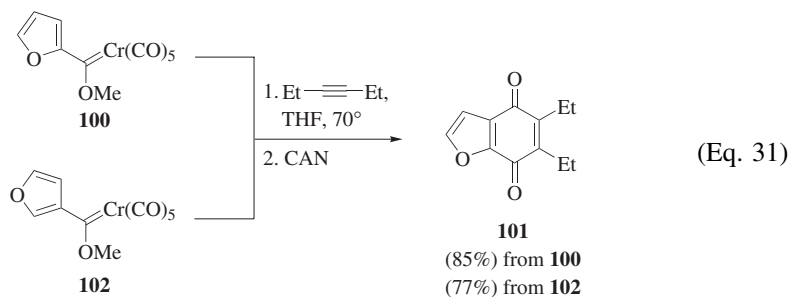
The sulfur-coordinated complex **97** has been prepared and its reaction with 4-pentyn-1-ol has been compared with that of the non-coordinated complex **96** (Scheme 9).<sup>91</sup> The reactions are carried out by adsorption on silica gel and the internally coordinated complex gives a 39% yield of the phenol **98**, double that of the non-coordinated complex. No other products are reported for this reaction and the fate of the remainder of the substrate is not known. The coordinated complex is more stable than the non-coordinated complex, and thus the increased yield may be due to competing decomposition of complex **96**. It is likely that the loss of sulfur arises from an in situ reduction of the cyclohexadienone **99** by chromium(0) to give **98**.<sup>80</sup>

A variety of heteroaryl Fischer carbene complexes give good yields of annulated phenols and quinones. The reaction of the 2-furyl complex **100** with 3-hexyne provides the quinone **101** in 85% yield after oxidative workup with CAN (Eq. 31).<sup>114</sup> The reaction of the 3-furyl complex **102** gives the same quinone in 77% yield with no detectable amount of an isobenzofuran that would result from the alternate sitespecificity in the cyclization.<sup>104,114</sup> The furan complex **100** reacts with the functionalized alkyne **104** in the presence of acetic anhydride to give



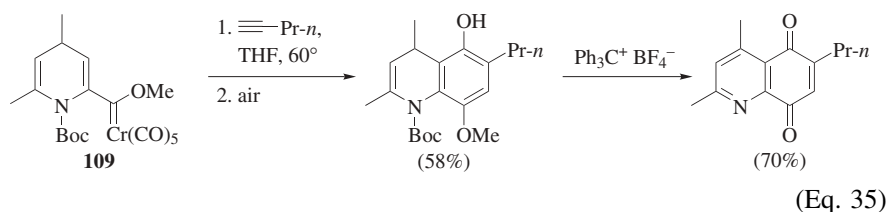
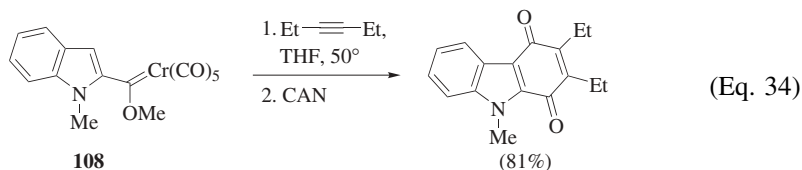
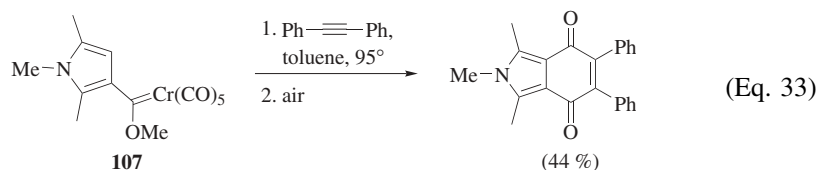
Scheme 9

the benzannulated product **105** (Eq. 32).<sup>115</sup> The same reaction of the 2-pyrrolyl complex **103** is more efficient, providing the highly functionalized indole **106** in 62% yield.<sup>115,116</sup>



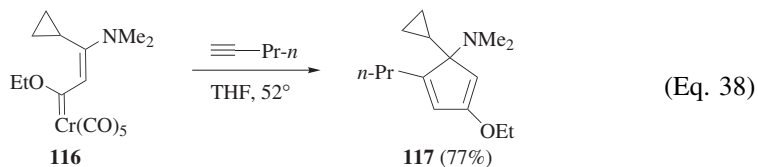
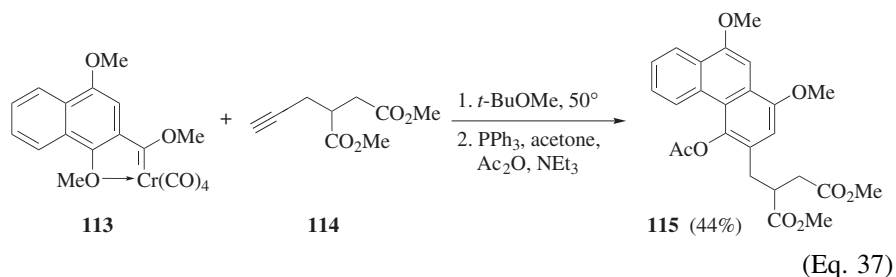
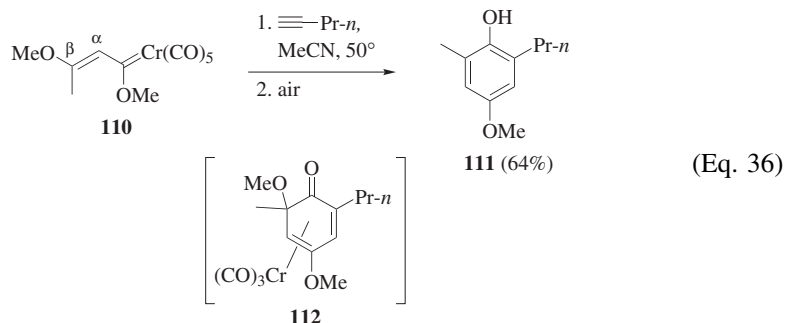
The site selectivity of the annulation of a 3-pyrrolyl carbene complex can be reversed by blocking the 2-position. This was demonstrated in the reaction of the 2,5-dimethyl-3-pyrrolyl complex **107** with diphenylacetylene to give a substituted isindolequinone (Eq. 33).<sup>117</sup> The synthetic utility of indole-substituted

carbene complexes is illustrated in the reaction of the 2-indolyl complex **107**, which reacts with 3-hexyne to give a carbazoloquinone in 81% yield (Eq. 34).<sup>62</sup> Pyridylcarbene complexes have proved difficult to make<sup>118–120</sup> and for this reason dihydropyridyl complexes of the type **109** were developed as synthetic equivalents for 2-pyridyl complexes (Eq. 35).<sup>121</sup> Subsequent to annulation with an alkyne, the pyridine ring may be reoxidized with trityl tetrafluoroborate, which also oxidizes the hydroquinone ring to give substituted quinolinoquinones.

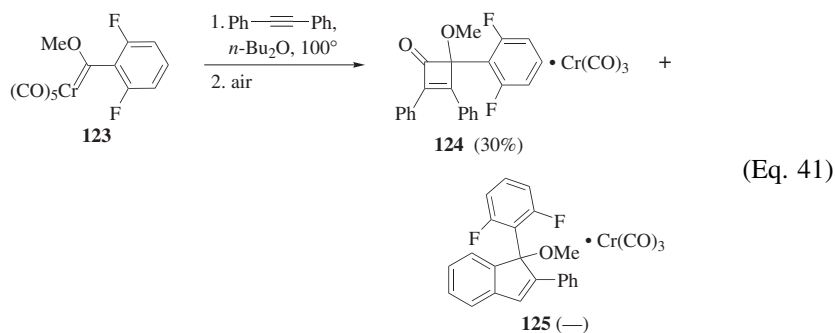
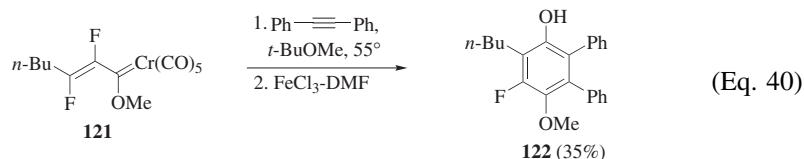
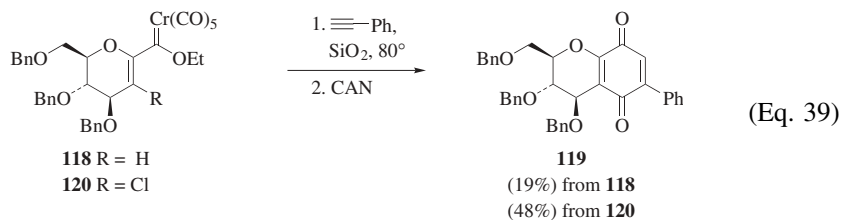


There have been occasional reports of the benzannulation of Fischer carbene complexes bearing heteroatoms at a position beta to the carbene carbon. Examples already discussed include the  $\beta$ -silyl substituted complexes **76** and **80** (Eqs. 20 and 21)<sup>112,110</sup> and a  $\beta$ -thio ether complex **96** (Scheme 9).<sup>91</sup> The sulfone complex corresponding to **96** also undergoes benzannulation with loss of the sulfone to give phenolic products related to **98** where the sulfur is lost in the aromatization.<sup>91</sup> Only two examples of cyclization of complexes bearing  $\beta$ -oxygen substituents are known. In the first, the  $\beta$ -methoxyalkenyl complex **110** reacts with 1-pentyne to give phenol **111** in 64% yield (Eq. 36).<sup>122</sup> The loss of the methoxy group from the cyclohexadiene complex **112** is likely a result of reduction by chromium(0) to give a chromium(II) phenolate complex.<sup>80</sup> The second example is the reaction of the internally coordinated naphthyl complex **113** with the alkyne **114** to give the substituted phenanthrene **115** (Eq. 37).<sup>105</sup> This example demonstrates the strong preference for cyclization of a 2-naphthyl complex to the  $\alpha$ -position. With complex **113**, this preference is strong enough to force cyclization to occur ipso to the methoxy despite the fact that the other ortho position is unsubstituted. An amino group in the  $\beta$ -position leads to the exclusive formation of cyclopentadiene products. This reaction has been examined extensively and is illustrated by the

reaction of complex **116** which gives the cyclopentadiene **117** in 77% yield (Eq. 38).<sup>123</sup> Depending on the conditions and substrates, a variety of products have been observed from the reaction of  $\beta$ -amino complexes.<sup>30</sup>

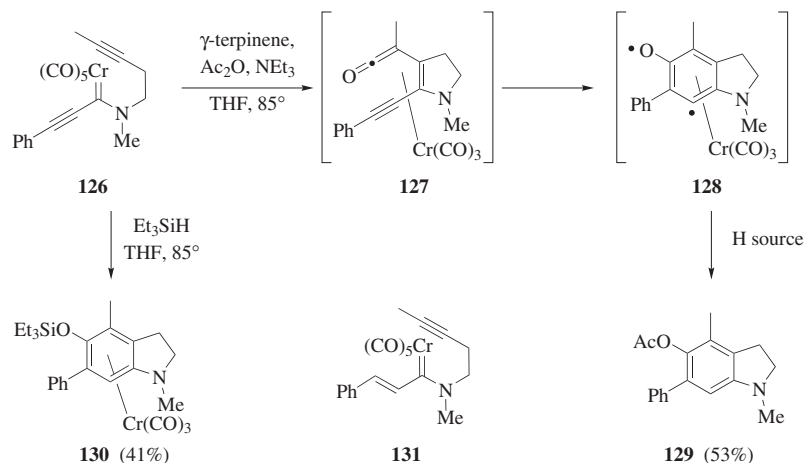


Cyclization occurs onto an  $\alpha,\beta$ -unsaturated carbene complex that bears a  $\beta$ -halogen substituent. The two known examples involve fluorine and chlorine substituents. The  $\beta$ -chloroalkenyl complex **120** reacts with phenylacetylene to give a significantly higher yield of the quinone **119** than the corresponding unchlorinated complex **118** (Eq. 39).<sup>124</sup> The  $\alpha,\beta$ -difluoro complex **121** reacts in a similar fashion to afford (after cyclization and reductive cleavage of the fluorine) phenol **122** in 35% yield (Eq. 40).<sup>125</sup> Cyclization does not occur if the  $\beta$ -fluoro substituent is on a benzene ring.<sup>126</sup> The reaction of the 2,6-difluorophenyl complex **123** with diphenylacetylene affords the cyclobutenone **124** as the major product (Eq. 41).<sup>126</sup> A second product, **125**, results from cyclization, not onto the phenyl group of the carbene complex, but onto the phenyl group of the alkyne. Both products from this reaction are obtained as chromium tricarbonyl complexes but in each case it was not determined which of the aryl rings is coordinated.



The benzannulation of  $\alpha$ -alkynyl complexes has been reported and is illustrated in Scheme 10.<sup>127</sup> Mechanistically, this reaction must be quite distinct from that of alkenyl- and arylcarbene complexes (Scheme 1). Intramolecular reaction of the pendant alkyne in complex **126** and carbon monoxide insertion is proposed to give an alkynyl-substituted vinyl ketene complex of the type **127**. Cyclization of this vinyl ketene complex then gives a diradical intermediate, which upon hydrogen abstraction gives a benzannulated product. Note that the indoline **129** obtained from thermolysis of complex **126** is the same product that could be produced from the alkenyl complex **131** by the normal mechanism. However, complexes of the type **131** do not give phenols but rather cyclize without CO insertion to give a cyclopentadiene unit that is embedded into an azabicyclo[3.3.0]octane.<sup>128</sup> The indoline **129** cannot be isolated as its chromium tricarbonyl complex. However, if the reaction of **126** is carried out in the presence of triethylsilane as hydrogen donor, the silyloxyindolinylchromium tricarbonyl complex **130** is isolated in 41% yield. Recently, an alternative entry to diradical intermediates of the type **128** from saturated carbene complexes has been reported, and the synthetic utility of these intermediates has been further explored.<sup>129,130</sup>

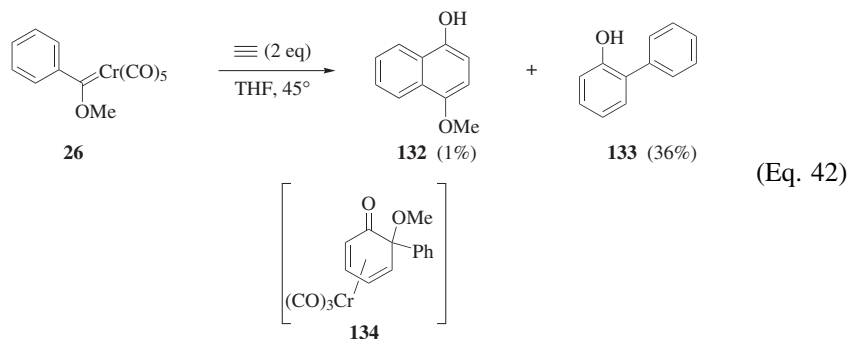
**Alkyne Components.** The reactions of  $\alpha,\beta$ -unsaturated Fischer carbene complexes with alkynes will tolerate a broad range of functional groups present in the alkyne. Less tolerant are alkynes that are conjugated to strongly electron-withdrawing or electron-donating groups and also alkynes that are very bulky.



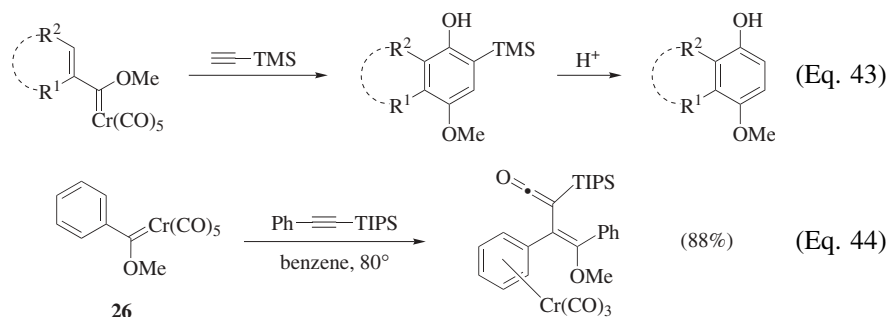
Scheme 10

Coordination of functional groups on the alkyne to the metal can lead to side-product formation. Functional groups on the alkyne that survive under the reaction conditions include alkenes, alkynes (hindered), halides, silanes, stannanes, ethers, thio ethers, seleno ethers, acetals, epoxides, ketones, esters, amides, nitriles, nitro groups, sulfoxides, and sulfones. Alcohols can be tolerated by the reaction in some instances (see below).

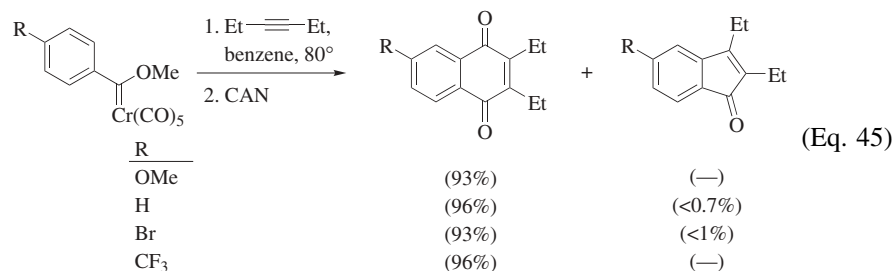
The reaction of Fischer carbene complexes with acetylene fails to give useful amounts of the normal benzannulation product. For example, the reaction of complex **26** with two equivalents of acetylene affords a 1% yield of naphthol **132** and a 36% yield of the two-alkyne phenol **133** (Eq. 42).<sup>131</sup> The two-alkyne phenol results from incorporation of the carbene carbon, a carbon monoxide ligand, and two equivalents of the alkyne. The primary product is the cyclohexadienone complex of the type **134**, which is reduced by chromium(0) to the phenol.<sup>80</sup> The yield of the two-alkyne phenol drops sharply with substituted alkynes. The reaction of **26** with propyne provides useful yields of the naphthols and only 4% of the two-alkyne phenol corresponding to **133**.<sup>131</sup>



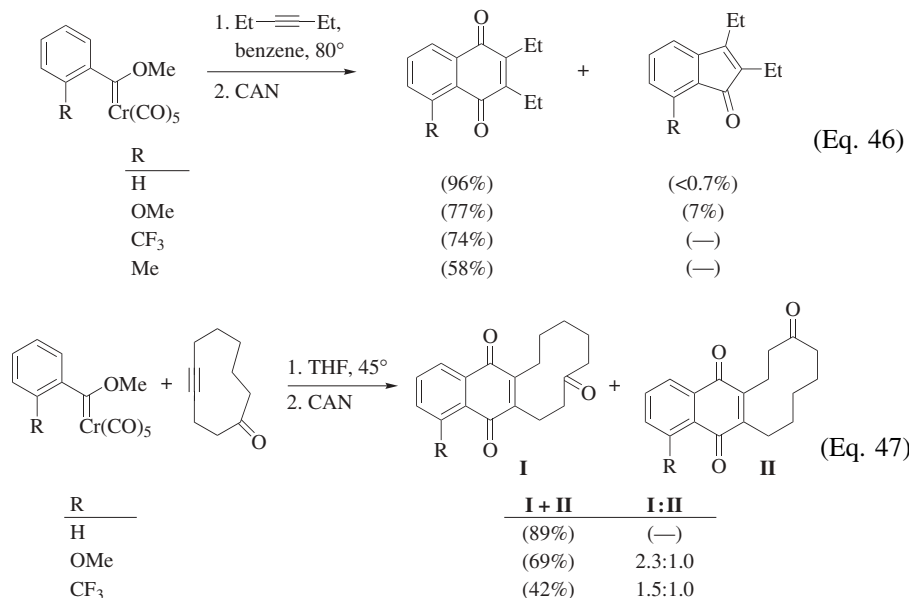
Trimethylsilylacetylene can serve as a synthetic equivalent for acetylene because it affords high yields of the normal benzannulated product and can be subject to clean proto-desilylation (Eq. 43, Scheme 8).<sup>69,101,110</sup> Bulky silyl-substituted alkynes can lead to the isolation of vinyl ketenes that are stabilized by the  $\alpha$ -silyl substituent.<sup>57,61,132-134</sup> Thus, reaction of phenyl complex **26** with phenyl(triisopropylsilyl)acetylene gives the vinyl ketene in 88% yield (Eq. 44).<sup>134</sup> Whereas stannyl-substituted alkynes do not yield stable vinyl ketenes, they have been reported to cause a reversal in the site selectivity of alkyne incorporation into phenolic products (Eq. 14).<sup>72,73</sup>



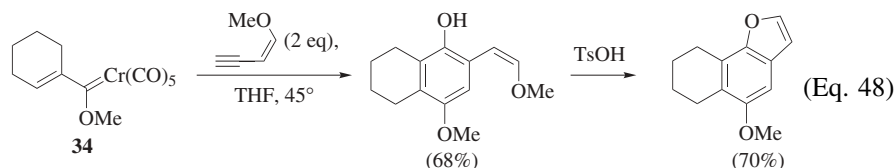
The efficiency of phenol formation from unfunctionalized alkynes is quite different for internal and terminal alkynes. The reactions of 4-substituted phenyl carbene complexes in benzene with 3-hexyne (Eq. 45) are compared to the same reactions with 1-pentyne (Eq. 27).<sup>113</sup> Reactions with 3-hexyne produce greater than 90% yields of quinone products for all 4-substituted phenyl complexes including those with electron-deficient as well as electron-donating substituents. The yields are also generally higher for reactions of ortho-substituted complexes with 3-hexyne compared to 1-pentyne (Eq. 46 and Eq. 28). However, as in the reaction of 1-pentyne (Eq. 27), the yields from reactions of 3-hexyne with ortho-substituted complexes are also suppressed relative to those of the unsubstituted phenyl complex (Eqs. 45 and 46). There are two reports of the reactions of cyclic alkynes, and the example shown in Eq. 47 is of interest because it reveals that a carbonyl group separated from an alkyne function by two methylenes can influence the regioselectivity.<sup>103,135</sup>





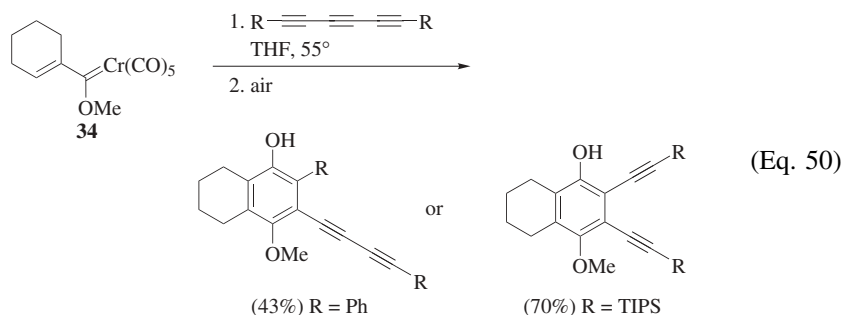
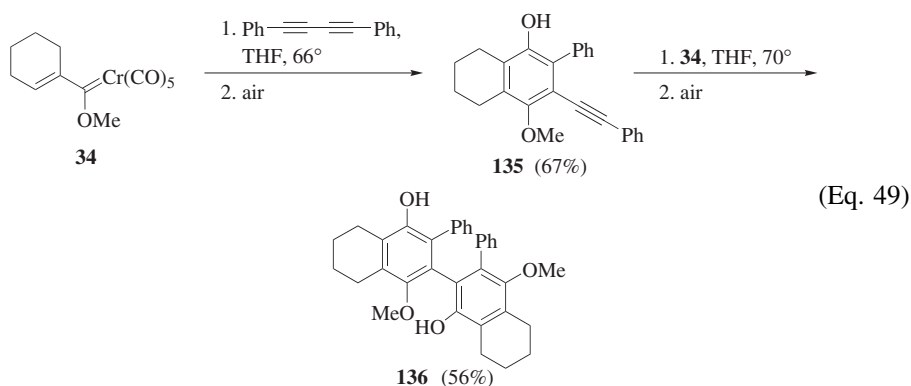


Although alkenes react with Fischer carbene complexes to produce cyclopropanes,<sup>136</sup> they do so too slowly to compete with the benzannulation reaction. Thus, the reaction of Fischer carbene complex **34** with (*Z*)-1-methoxybut-1-en-3-yne results in a good yield of the phenol (Eq. 48).<sup>69</sup> The compatibility of alkenes with the benzannulation reaction has also been demonstrated in an intermolecular competition experiment. The yield of the quinone from the reaction of complex **53** and 3-hexyne (Eq. 24) is unchanged (58%) when carried out in the presence of four equivalents of ethyl vinyl ether<sup>137</sup> even though, in the absence of 3-hexyne, ethyl vinyl ether gives good yields of cyclopropane.<sup>138</sup>



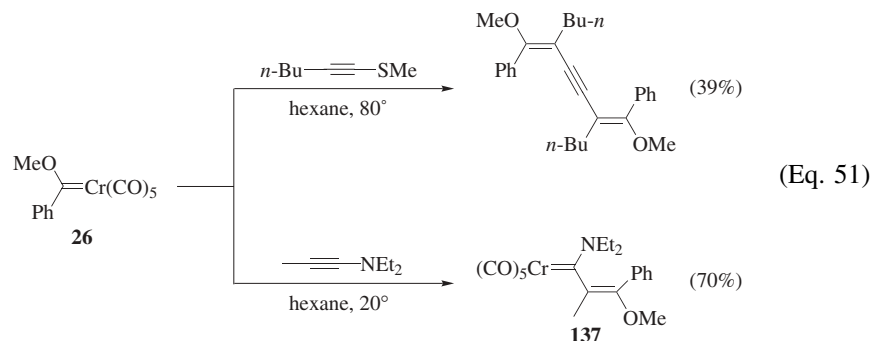
Conjugated 1,3-diyne reacts with one equivalent of a Fischer carbene complex to provide the benzannulated product in which one of the alkynes has been incorporated in a process that is unaffected by the presence of the other alkyne. After decomplexation of the metal from the phenol **135** by exposure to air, a second benzannulation can be carried out to give biaryl product **136** in good yield (Eq. 49).<sup>100</sup> Interestingly, product **136** cannot be obtained by direct reaction of the diyne with an excess of the carbene complex. It thus appears that the presence of a chromium tricarbonyl group on the mono-annulated product **135** hinders subsequent reaction with a second equivalent of carbene complex. The reactions

of conjugated 1,3,5-triynes are complicated by the ability of a carbene complex to react either with the central alkyne unit or with one of the two terminal alkyne units. Steric interactions predict that the reaction would be selective for the central alkyne. The cyclohexenyl complex **34** reacts at the central alkyne with 1,3,5-triynes that are capped with triisopropylsilyl groups. Surprisingly, the triyne capped with a phenyl group gives rise to exclusive incorporation of a terminal alkyne unit (Eq. 50).<sup>139</sup>

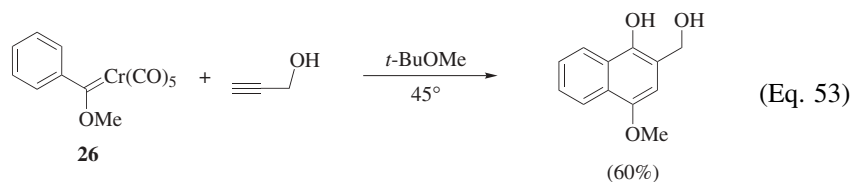
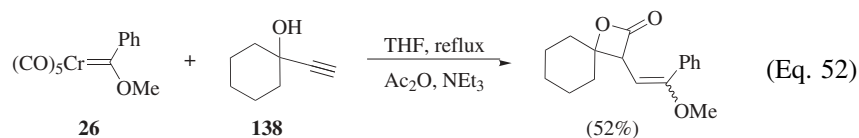


Heteroatom-substituted alkynes do not always react with Fischer carbene complexes to give phenolic products. Ynamines are reactive towards Fischer carbene complexes and react below room temperature to give simple non-cyclized insertion products.<sup>140,141</sup> This reaction occurs by a mechanism that is different from that for simple alkynes. The reaction is first order in both carbene complex and ynamine.<sup>141</sup> The insertion products undergo a thermally induced cyclization that leads to indene products and not to phenols, presumably due to the electron-rich nature of  $\alpha,\beta$ -unsaturated complexes of type **137** (Eq. 51).<sup>142</sup> In contrast to ynamines, alkoxy-substituted alkynes such as **104** do react with carbene complexes to give phenols (Eq. 32). Terminal alkoxy acetylenes also yield insertion products analogous to **137**.<sup>143</sup> Alkynyl thio ethers do not react with chromium carbene complexes in the same way as either ynamines or alkoxy acetylenes, but rather give very unusual dienyne products that are unprecedented in all

the reactions of carbene complexes with alkynes (Eq. 51).<sup>144</sup> Tungsten complexes react with thioalkynes to give insertion products analogous to **137**.<sup>145</sup> Haloacetylenes react with Fischer carbene complexes to generate complex mixtures of products.<sup>72,146</sup>

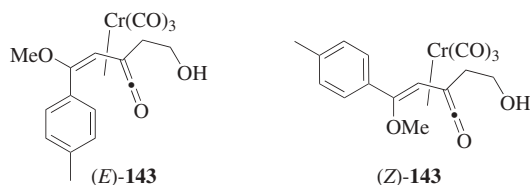
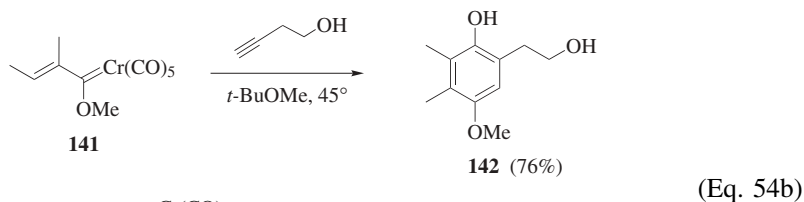
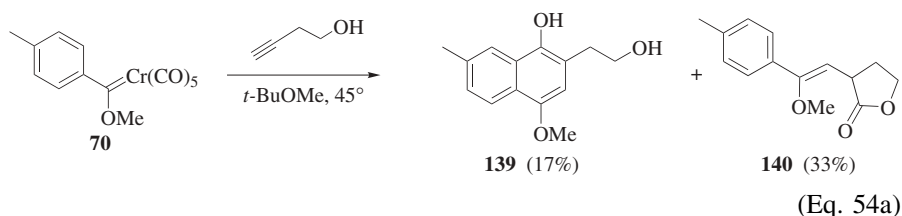


The presence of an alcohol function on the alkyne can sometimes be tolerated, but can also lead to intramolecular trapping of the complexed vinyl ketene intermediate to give lactones. This behavior is dependent on the length and substitution of the tether between the alkyne and the alcohol function and on the nature of the carbene complex. A dramatic example of this dependence is the reaction of the two propargylic alcohols shown in Eqs. 52 and 53. Propargyl alcohol gives only the phenol (Eq. 53),<sup>147</sup> whereas substituted propargylic alcohols give  $\beta$ -lactones as the exclusive products (Eq. 52).<sup>148</sup> This divergence has been attributed to the Thorpe-Ingold effect.<sup>148</sup> Interestingly, alkynes similar to **138** that contain a 4-membered ring can afford either ring-expanded or cyclobutenone products.<sup>149</sup>

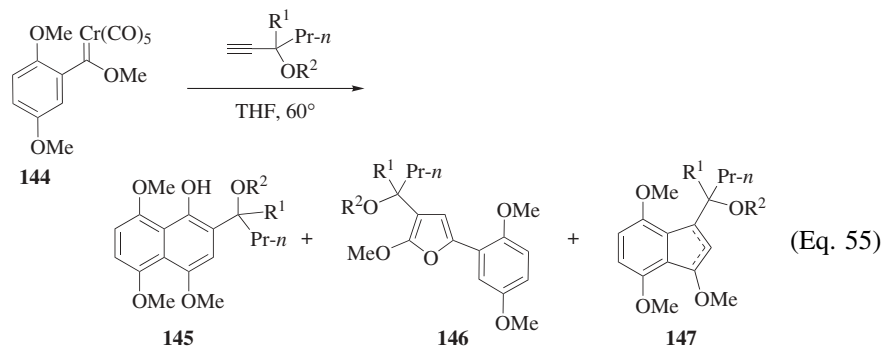


Homopropargylic alcohols afford substantial amounts of lactone product with aryl complexes but not with alkenyl complexes.<sup>147</sup> Whereas the reaction of 4-methylphenyl complex **70** affords naphthol **139** in only 17% yield along with the lactone **140** in 33% yield (Eq. 54a), the reaction of alkenyl complex **141** with 3-butyne-1-ol affords phenol **142** in good yield (Eq. 54b).<sup>147</sup> Lactone **140** is depicted as the *Z*-enol ether rather than as the *E*-enol ether that was originally reported. Subsequent work established that the enol ether from the reaction

of 4-pentyn-1-ol with complex **70** was assigned incorrectly as the E-enol isomer and thus it is considered likely that the enol ether configuration of **140** was also incorrectly assigned as the E-isomer.<sup>65</sup> The Z-isomer of the complexed vinyl ketene intermediate **143** cannot cyclize to the naphthol **139**. Because the E-isomer of **140** is not observed, it can be assumed that for the E-isomer of ketene complex **143**, intramolecular trapping of the ketene by the hydroxy group cannot compete with cyclization to phenol **139**. Longer-chain alcohols give much less of the ketene-trapped product. The reactions of complex **70** with 4-pentyn-1-ol and 5-hexyn-1-ol give the corresponding naphthols in 44 and 75% yields, respectively.<sup>147</sup>

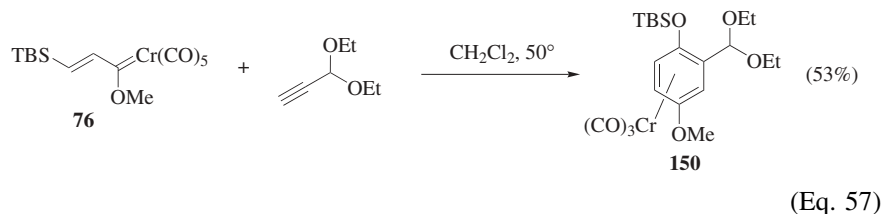
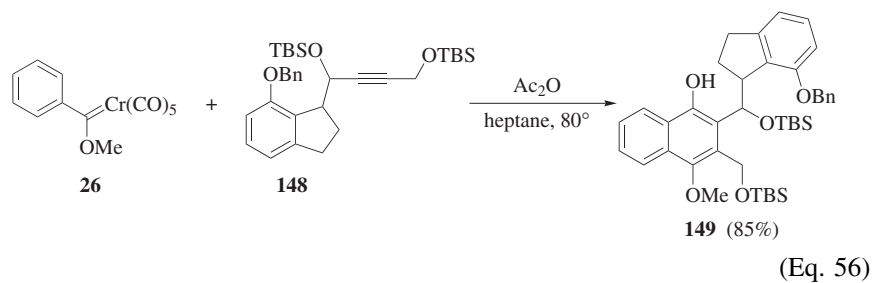


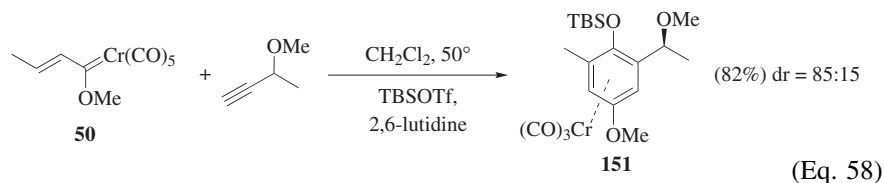
The presence of a propargyl ether function can be detrimental to benzannulation especially for the reaction of electron-rich aryl carbene complexes. Whereas the *tert*-butyldimethylsilyl ether of 1-hexyn-3-ol reacts with complex **144** to give only the naphthol product **145**, the corresponding methyl ether gives a mixture of naphthol **145** and furan **146** (Eq. 55).<sup>150</sup> These examples suggest that coordination of the propargyl oxygen to chromium during the reaction is somehow responsible for the formation of furans. An increase in the level of substitution at the propargylic position is also detrimental to the reaction but not as a result of furan formation. For example, the indene product **147** is formed in 28% yield from the reaction of complex **144** with the quaternary TBS-protected propargyl ether prepared from 3-methyl-1-hexyn-3-ol.<sup>150</sup> This steric effect is also observed for alkynes that do not bear propargylic oxygen substituents.<sup>84</sup>



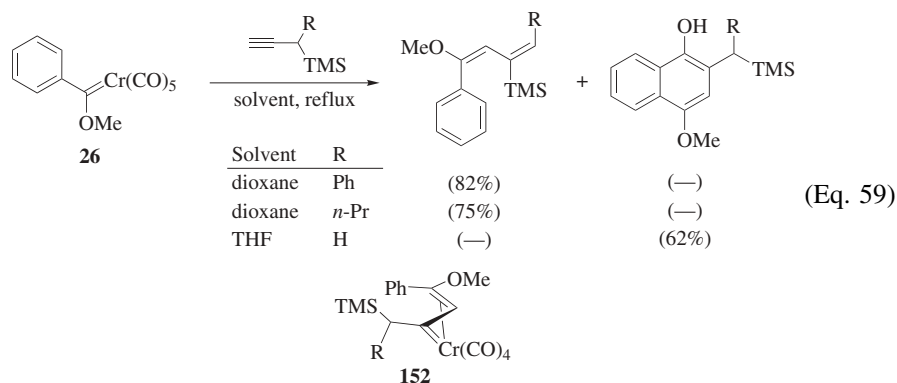
R <sup>1</sup>	R <sup>2</sup>	145	146	147
H	Me	(24%)	(16%)	(—)
H	TBS	(46%)	(—)	(—)
Me	TBS	(30%)	(—)	(28%)

Propargyl ether functions can lead to high yields of naphthol products if the oxygen carries a *tert*-butyldimethylsilyl group and the aryl ring of the carbene complex is not electron-rich. This behavior is illustrated in the reaction of phenyl complex **26** with bis-propargyl ether **148**, which provides the naphthol **149** in 85% yield (Eq. 56).<sup>151</sup> The phenol functionality is not acetylated, but if acetic anhydride is not present the reaction falls. Alkenyl complexes are much less susceptible to side product formation with propargyl ethers. The reaction of carbene complex **76** with propynal diethyl acetal gives a 53% yield of the chromium tricarbonyl complex **150** (Eq. 57).<sup>110</sup> Complexation of the propargyl ether oxygen is not a problem for the reaction of *trans*-1-propenyl complex **50** as it is for the reaction of the aryl complex **144** (Eq. 55) given that an 82% yield of the phenol complex **151** is produced in this reaction (Eq. 58).<sup>88</sup> Homopropargyl ether functions can also interfere with the benzannulation reaction.<sup>152</sup>



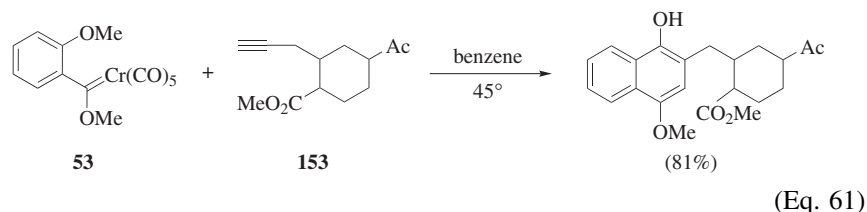
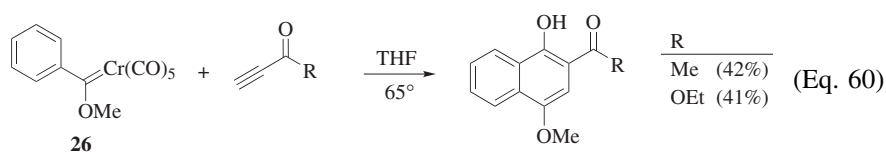


Propargylsilanes react to give phenols but only if they are unsubstituted at the propargylic carbon. The reaction of the phenyl complex **26** with 1-trimethylsilyl-2-propyne gives the normal phenol product in 62% yield (Eq. 59).<sup>153</sup> However, phenols are not observed if an additional substituent is present in the 1-position of the propyne.<sup>154,155</sup> These propargylsilanes stereoselectively produce only the E,E-dienes. This type of product may be formed when the normal cyclization process is thwarted by a  $\beta$ -silyl elimination from the intermediate  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate **152** with subsequent reductive elimination resulting in the formation of a carbon-silicon bond.

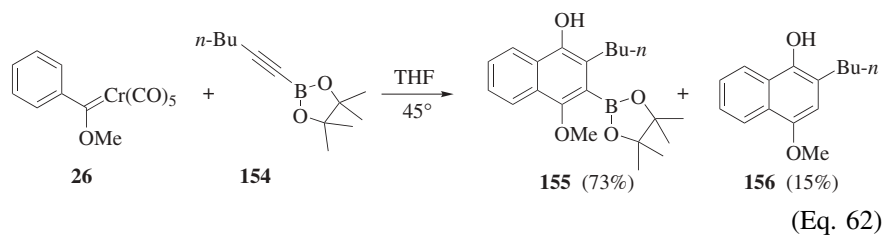


Reactions of alkynes that are conjugated to ketone or ester groups do give phenol products but in diminished yields when compared to unfunctionalized alkynes. The reaction of phenyl complex **26** with 3-butyne-2-one affords the naphthol product in 42% yield (Eq. 60).<sup>70</sup> No other products are reported from this reaction. The reaction of the same complex with ethyl propynoate affords the naphthol in 41% yield.<sup>70</sup> These are the highest yields reported to date with any alkoxy carbene complex having a terminal alkyne or alkyne ester; however, there is a high-yielding reaction of ethyl propynoate and an amino complex.<sup>156,157</sup> Higher yields of naphthols can be obtained from conjugated alkynyl esters if the alkyne is internal.<sup>70</sup> The ester functionality has little influence on regioselectivity when the alkyne is internal. The reaction of conjugated alkynyl ketones in an internal alkyne also gives higher yields but of two predominant products, as illustrated by the reaction of **62** where an unusual tricyclic lactone **64** is produced along with the normal product **63** (Eq. 15).<sup>71</sup> Both products are formed by the same regiochemistry of incorporation of the alkyne. The reaction of complex **53**

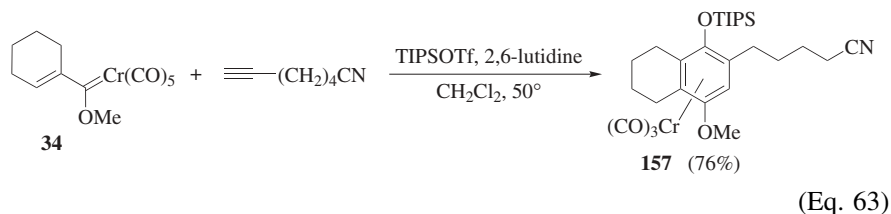
with alkyne **153** illustrates that the presence of non-conjugated ketone and ester groups is usually tolerated (Eq. 61).<sup>158</sup>



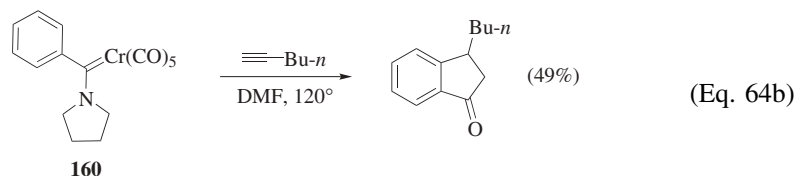
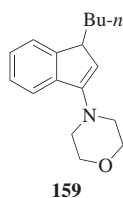
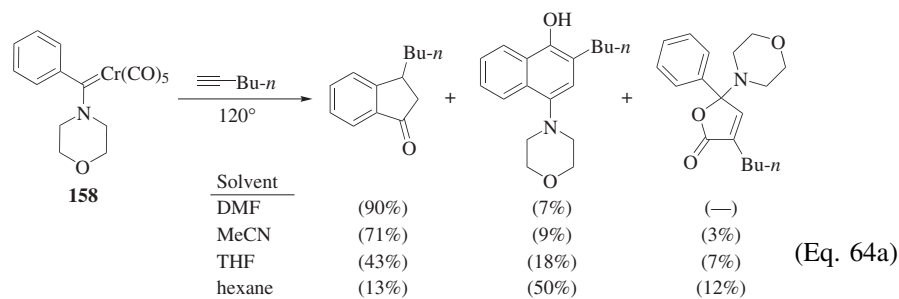
Alkynyl borate esters participate in the benzannulation reaction. The reaction of phenyl complex **26** with alkynylborate **154** affords a single isomer of the naphthol **155** along with a small amount of the protodeboronated product **156** (Eq. 62).<sup>74,75</sup> This reaction has considerable synthetic potential because it represents an example of a regioselective insertion with an internal alkyne. Moreover, the pinacol boronate products are suitable for Suzuki cross-coupling reactions.



The benzannulation reaction is also compatible with a number of groups that could coordinate to the metal and interfere with the reaction such as thioethers<sup>91,114,159</sup> (Scheme 9) and nitriles. Interestingly, the reaction of the cyclohexenyl complex **34** with the 6-cyano-1-hexyne (Eq. 63)<sup>12,159</sup> occurs to give a slightly higher yield of the desired product than does the reaction of this complex with 1-pentyne (Eq. 10).

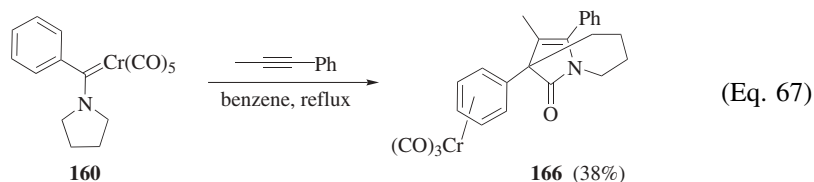
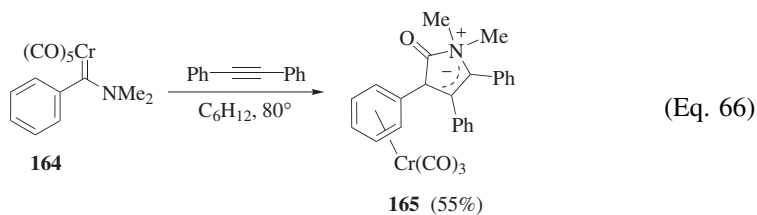
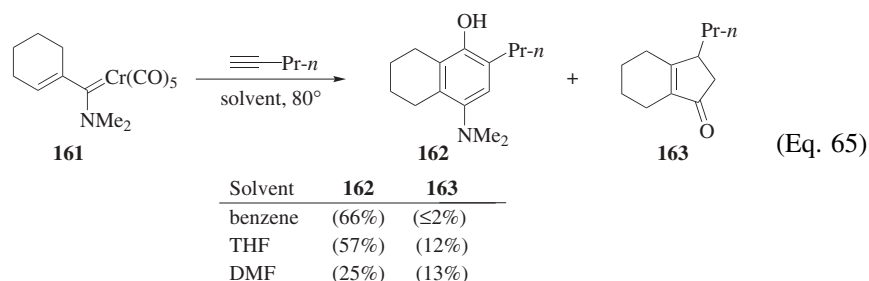


**Heteroatom Stabilizing Substituents.** The most thoroughly studied class of non-oxygen-stabilized carbene complexes is that of the amino carbene complexes. These complexes are more electron-rich and as a consequence have stronger bonds to the carbon monoxide ligands, which in turn leads to decreased proportions of products that incorporate carbon monoxide. The reactions of amino carbene complexes with alkynes in DMF have been developed as an efficient method for the synthesis of indenenes.<sup>79</sup> The effect of solvent on this reaction is illustrated in the combination of the morpholine complex **158** with 1-hexyne. In THF, the phenol and indanone products are formed in 18% and 43% yields, respectively, whereas in DMF the latter is favored over the former by a factor of 13 : 1 (Eqs. 64a and 64b).<sup>160</sup> The indanone is a secondary product of the reaction that results from hydrolysis of the indene **159** upon purification on silica gel. The highest yield of the naphthol (50%) is obtained when the reaction is run in hexane. The efficiency of indene formation is highly dependent on the nature of the substituents on nitrogen. Reaction of the pyrrolidino complex **160** with 1-hexyne in DMF gives the indanone in 49% yield (Eq. 64b),<sup>79</sup> whereas reaction of the dimethylamino complex corresponding to **160** with 1-pentyne in DMF gives only a 32% yield of the indanone product.<sup>83</sup> Internal alkynes usually give higher proportions of indenenes than do terminal alkynes. However, with morpholino carbene complex **158** there is not much difference. The reaction of this complex with 1-hexyne in DMF gives a 90% yield of the indenone product (Eq. 64a) and under the same conditions it gives a 96% yield of indanone product with 3-hexyne.<sup>79</sup>



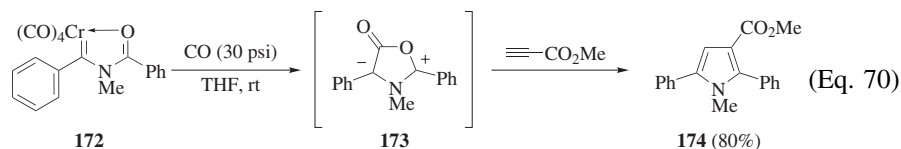
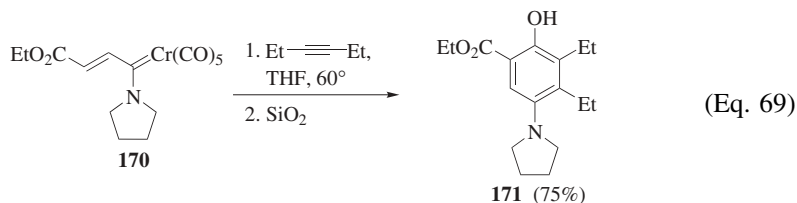
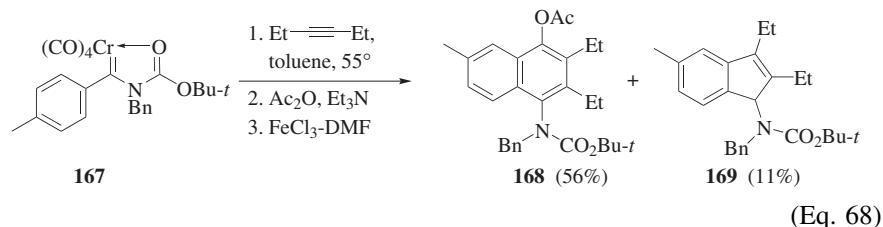


Phenols can be obtained from the reaction of amino carbene complexes bearing non-aromatic substituents.<sup>54,83</sup> Reaction of the cyclohexenyl complex **161** with 1-pentyne in benzene affords the phenol **162** in 66% yield with no detectable amount of the five-membered ring product **163** (Eq. 65).<sup>83</sup> The formation of phenols from aminoalkenyl complexes is limited to terminal alkynes. The reaction of complex **161** with 3-hexyne gives a complex mixture of products, none of which is the expected phenol.<sup>83</sup> Reactions of amino complexes with alkynes can give a number of unusual products that are derived from internal trapping of the vinyl ketene complex by the amino group.<sup>22</sup> This trapping leads to zwitterionic species of the type **165**, which can be isolated from the reaction of complex **164** with diphenylacetylene in refluxing cyclohexane (Eq. 66).<sup>161</sup> Many other reactions of this type lead to products that result from a Stevens-type rearrangement of this zwitterionic intermediate that gives rise to lactams. This rearrangement is usually seen with groups of greater migratory propensity than methyl. An example is the reaction of the pyrrolidino carbene complex **160** with 1-phenylpropyne to give the bicyclic lactam **166** in 38% yield (Eq. 67).<sup>77</sup>



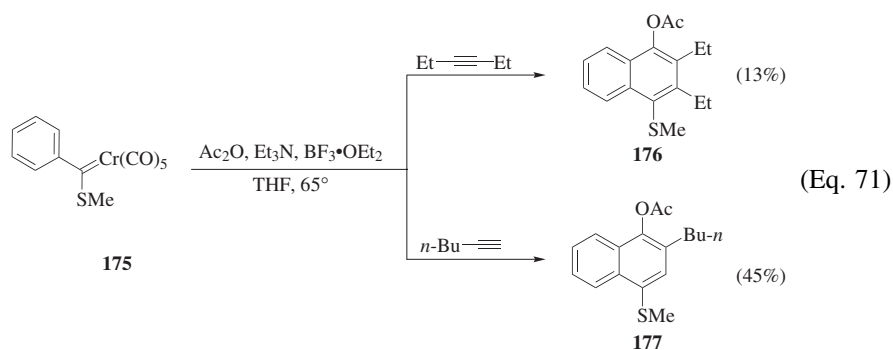
The propensity of amino complexes to give indenenes instead of phenols can be alleviated by installing a carbonyl group on the nitrogen<sup>162,163</sup> or by incorporating the nitrogen atom into a pyrrole.<sup>164</sup> Both of these modifications attenuate the electron-donating capacity of the nitrogen atom to the carbene carbon. The *tert*-butyl carbamate complex **167** reacts with 3-hexyne to give predominantly the

phenol-derived product **168** in 56% yield along with an 11% yield of the indene **169** (Eq. 68).<sup>162</sup> Similar reaction of the methoxy complex **26** gives the quinone in 88% yield (Eq. 22).<sup>84</sup> Although the reaction of an *N,N*-dialkylamino complex corresponding to **167** has never been investigated under these conditions with 3-hexyne, no *N,N*-dialkylamino aryl carbene complex has ever been reported to react with an internal alkyne in any solvent to give a phenol. Alternatively, electron density can be removed from an amino complex through the carbon substituent to give enhanced yields of phenols. The alkenyl amino complex **170** bearing an ester group gives good to excellent yields of phenols even with internal alkynes as illustrated by the formation of phenol **171** in 75% yield (Eq. 69).<sup>156,157</sup> In the absence of electron-withdrawing groups, alkenylamino complexes fail to give phenols with internal alkynes.<sup>83</sup> In contrast to the carbamate complex **167**, certain *N*-acyl complexes react with alkynes to give pyrroles. Complex **172** reacts with methyl propiolate to give the pyrrole **174** in a process that has been shown to involve a [3 + 2] cycloaddition of the alkyne with in situ generated münchnone **173** (Eq. 70).<sup>165</sup>

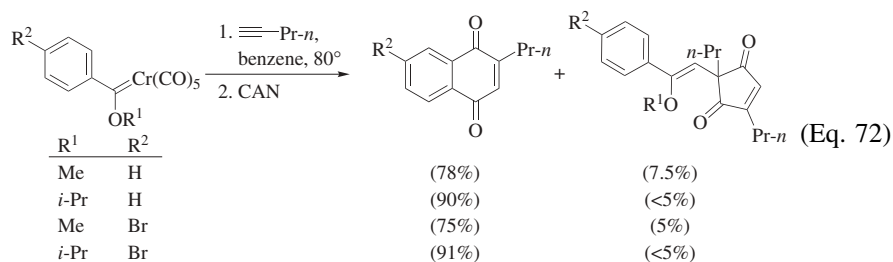


A limited number of reports have described the reactions of sulfur-stabilized Fischer carbene complexes with alkynes. Although it has been reported that this reaction can proceed without the assistance of a Lewis acid,<sup>166</sup> most of the studies have employed boron trifluoride etherate to afford the best, albeit still low, yields.<sup>167,168</sup> The thiomethyl phenyl complex **175** reacts with 3-hexyne in the presence of five equivalents of boron trifluoride etherate and five equivalents of acetic anhydride to give the acetylated phenol **176** in 13% yield (Eq. 71).<sup>167</sup> The reaction of **175** with 1-hexyne under the same conditions is more efficient, giving the acetylated phenol **177** in 45% yield.<sup>167</sup> It is interesting to note that

the reaction of the thioethyl analog of **175** with 3-hexyne in THF affords a 46% yield of the naphthol in the absence of Lewis acids.<sup>166</sup>

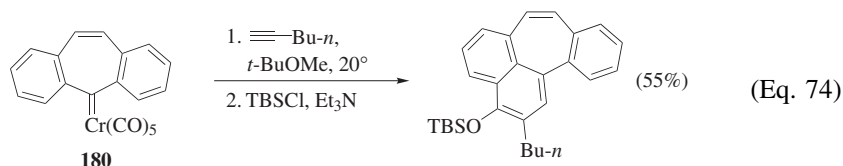
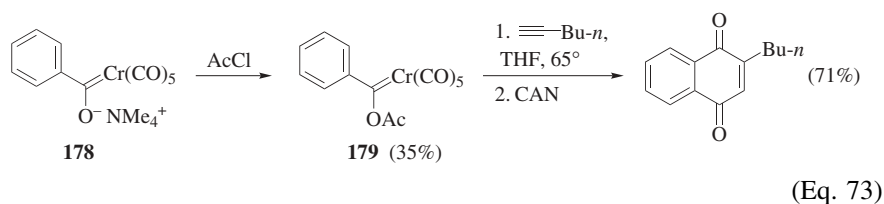


The benzannulation of alkoxy carbene complexes has been carried out almost universally on either methoxy or ethoxy complexes. There is little data available on the effect of the alkoxy group on either the yield or the product distribution from reactions with alkynes. When the same reaction has been reported with two different alkoxy groups, the results often conflict.<sup>88,91,100,159</sup> In the only systematic study on the effect of the size of the alkoxy group, it was found that the yields of quinone product are higher for isopropoxy groups compared to methoxy groups in reactions of aryl complexes with 1-pentyne (Eq. 72).<sup>113</sup> This effect was not general because no difference is seen for electron-donating substituents in the 4-position or for any type of substituent in the 2-position. The deleterious consequences of 2-substitution in an aryl complex (Eq. 28) cannot be offset by substitution of isopropoxy for methoxy.<sup>113</sup> The benzannulation of aryloxy carbene complexes provides yields similar to those of alkoxy complexes, however, there has been no direct comparison.<sup>47,169</sup>

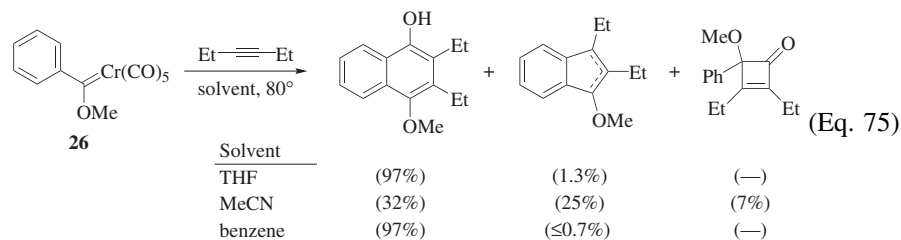


Given the thermal instability of acetoxy complexes,<sup>170,171</sup> it is surprising that complex **179**,<sup>172</sup> in this example generated from complex **178**, reacts with 1-hexyne (Eq. 73) to give the same yield of the benzannulation product as does the reaction of the corresponding methoxy complex **26** (Eq. 5).<sup>94</sup> Other acetoxy complexes fail to provide any cyclized product upon reaction with alkynes.<sup>114</sup> The only class of complexes that has two carbon substituents on the carbene

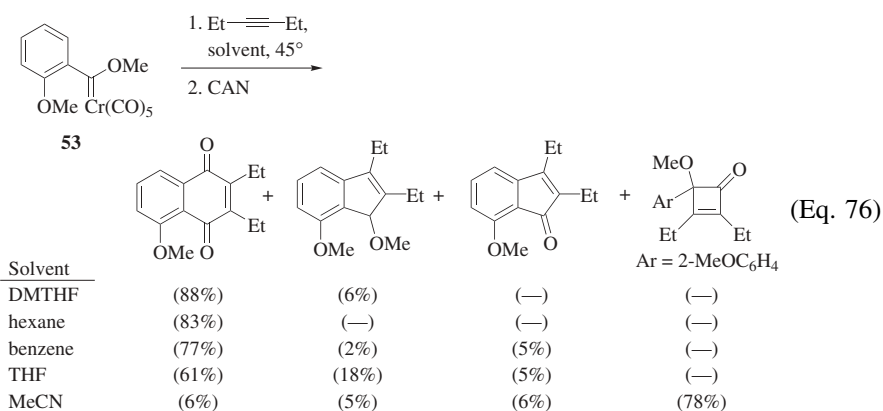
carbon and which are isolable are those bearing two aryl groups. The reactions of these complexes generally give low yields of phenols upon reaction with alkynes.<sup>47,87,143</sup> In contrast, the dibenzocycloheptatriene complex **180** reacts with 1-hexyne to give a 55% yield of the benzannulation product after protection as its TBS ether (Eq. 74).<sup>173,174</sup>



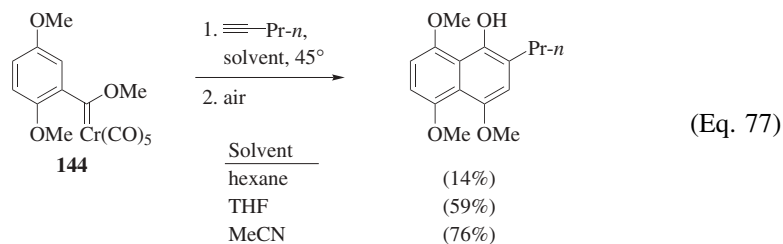
**Reaction Media and Conditions.** The nature of the solvent can have a significant effect on the product distribution from reactions of Fischer carbene complexes with alkynes. This effect is most often observed for the reaction of aryl alkoxy carbene complexes and is rarely seen for alkenyl alkoxy carbene complexes, although the reactions of alkenyl amino carbene complexes are sensitive to the nature of the solvent (Eq. 65).<sup>83</sup> The general observation of the correlation between efficiency of phenol formation and the nature of the solvent is that the highest chemoselectivity for phenol formation is found in non-polar and/or non-coordinating solvents.<sup>12,13,60,84</sup> The effects of solvent on the benzannulation reaction is usually more pronounced for internal alkynes than for terminal alkynes. As an example, the reaction of phenyl complex **26** with 3-hexyne gives higher yields of the naphthol in THF and in benzene than in acetonitrile, in which an indene is formed as a mixture of double-bond isomers in 25% yield along with a cyclobutenone in 7% yield (Eq. 75).<sup>60</sup> The use of polar solvents in combination with other changes can lead to reactions that give high selectivity for products other than phenols. For example, reactions of amino carbene complexes in DMF can give synthetically useful yields of indenenes (Eq. 64a).<sup>79,160</sup>



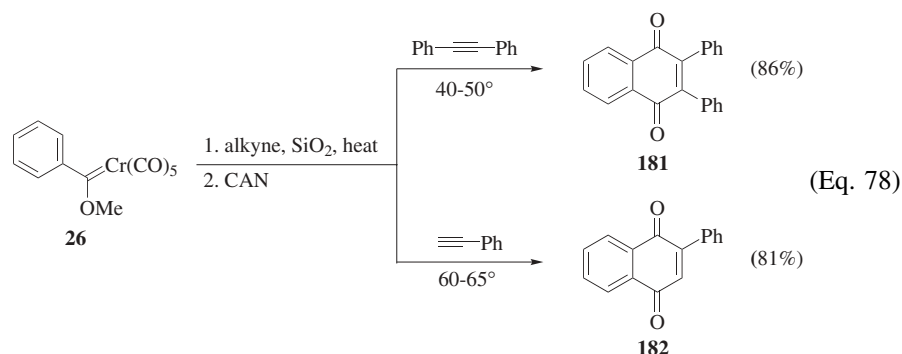
Reactions of 2-methoxyphenyl complex **53** are much more sensitive to the solvent than those of the unsubstituted phenyl complex **26**. The product distribution from the reaction of complex **53** with 3-hexyne is especially responsive to the ability of the solvent to coordinate to the metal during the course of the reaction (Eq. 76).<sup>84</sup> Non-coordinating solvents such as hexane and benzene give significantly higher yields of the quinone than does THF. Furthermore, the yield of the quinone drops precipitously in acetonitrile where the cyclobutenone is the major product and is isolated in 78% yield. An indication of the importance of the coordination of the solvent to the metal during the reaction can be seen in the data from the reaction in 2,5-dimethyltetrahydrofuran (DMTHF) in which the yield of quinone is significantly higher than it is in THF.



The rule that non-polar and non-coordinating solvents give the highest chemo-selectivity for phenols is rarely violated. One exception is the reaction of the 2,5-dimethoxyphenyl complex **144** with 1-pentyne, which gives a 76% yield of phenol in acetonitrile and only a 59% yield in THF (Eq. 77).<sup>175</sup> Even more surprising is the drop in yield to 14% when the reaction is performed in hexane. Another exception is the reaction of the phenyl complex **26** with diphenylacetylene, which in heptane<sup>76</sup> gives an equal mixture of phenol and indene products, but in THF<sup>84</sup> affords the phenol almost exclusively. The solvent can also have profound effects on the intramolecular reactions of carbene complexes with alkynes leading to products not seen in intermolecular reactions.<sup>176</sup>

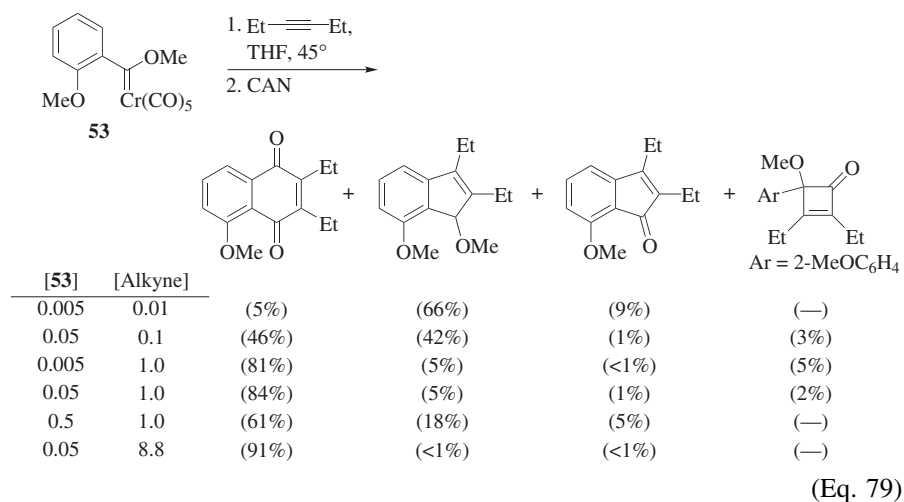


Reactions of Fischer carbene complexes with alkynes have also been examined without solvent.<sup>177,178</sup> As an example, the reaction of phenyl complex **26** with 1.5 equivalents of diphenylacetylene is performed by dissolving the two reactants in ether, adding silica gel, and removing the solvent to leave a dry powder which is heated under nitrogen at 40–50° for 3 hours (Eq. 78). The yield of the quinone **181** after oxidation is comparable to the yield reported for the same reaction in THF.<sup>84</sup> The reaction of complex **26** with 1.5 equivalents of phenylacetylene carried out in the same manner gives the quinone **182** in 81% yield, which is comparable to the yield reported for this reaction in THF where the corresponding naphthol **46** was isolated (Eq. 9).<sup>100</sup> This technique has not been widely examined; however, a few dry-state reactions on silica gel give improved yields of phenolic products compared to the same reactions performed in solution,<sup>91,98,124,179</sup> whereas it is less effective for other reactions.<sup>75,180</sup>

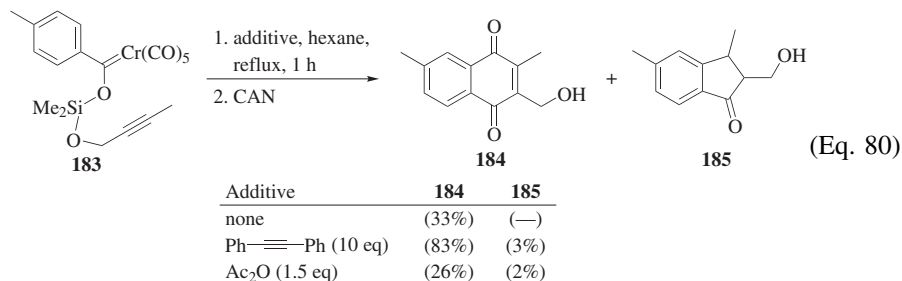


The distribution of products from the reaction of Fischer carbene complexes with alkynes can be dependent on the concentration such that the preference for the phenolic product increases at higher concentrations.<sup>13,60,84</sup> The sensitivity of the product distribution on the concentration is greater for aryl complexes than for alkenyl complexes, and greater for internal alkynes than for terminal alkynes. One system that is particularly sensitive to concentration is the reaction of the 2-methoxyphenyl complex **53** with 3-hexyne.<sup>84</sup> At 1.0 M in alkyne the distribution between phenol and indene products is not particularly sensitive to the concentration of the carbene complex (Eq. 79).<sup>84</sup> However, the distribution is strongly dependent on the concentration of the alkyne as can be seen from the data at 0.005 M in carbene complex where a 100-fold increase in the concentration of the alkyne increases the yield of quinone from 5% to 81%. An additional increase in concentration of the alkyne to 8.8 M (neat 3-hexyne) affords the quinone as the exclusive product. A careful analysis of the concentration dependence of the reaction of a molybdenum complex also reveals that the product distribution is a function of the concentration of the alkyne and not of the carbene complex.<sup>60</sup> This phenomenon has been termed the allochemical effect and is explained by an alkyne-assisted insertion of carbon monoxide into the vinyl carbene intermediate to give the vinyl ketene intermediate (Scheme 6).<sup>84</sup> The  $\eta^1, \eta^3$ -vinyl carbene complexed intermediate (*E*)-**4** is an 18-electron complex and coordination of an

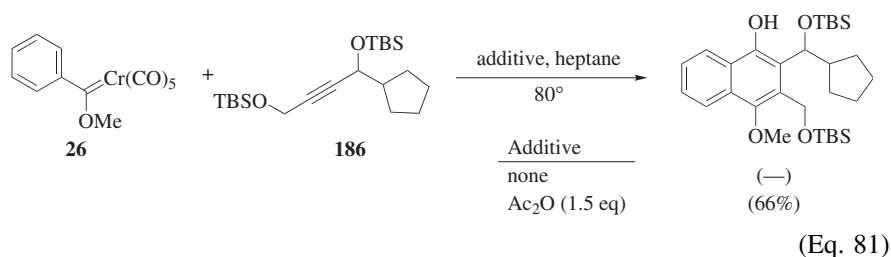
alkyne must be preceded by a dissociation of the double-bond to generate the  $\eta^1$ -vinyl carbene intermediate (*E*)-**17** (Scheme 6). An alkyne can be either a 2- or 4-electron donor and because carbon monoxide insertion results in the formation of an unsaturated complex, it has been proposed<sup>84</sup> that the alkyne ligand in complex **24** can accelerate the CO insertion if it switches from a 2- to a 4-electron donor during the process such that **25** is a saturated 18-electron complex (Scheme 6).



A related phenomenon, termed the “xenochemical effect”, has been observed in which the yield of phenolic product from reaction with an alkyne is dependent on the concentration of a second added alkyne that does not become incorporated into the product.<sup>86</sup> This is schematically indicated in Scheme 6. The xenochemical effect is a special case of the allochemical effect where the alkyne  $R^4CCR^5$  is not the same as the alkyne that has already been incorporated ( $R^LCCR^S$ ). Thus far it has only been observed in intramolecular reactions, and a dramatic example is in the reaction of complex **183** to give the quinone **184** and indanone **185**. The yield increases from 33 to 83% if 10 equivalents of diphenylacetylene are added to the reaction mixture (Eq. 80). The yield of quinone **184** could be increased somewhat by employing 3-hexyne as the xenochemical agent. However, competition is seen with the intermolecular benzannulation of 3-hexyne at the expense of the intramolecular benzannulation. Examples have also been reported for an intramolecular reaction of manganese carbene complexes (see Eq. 89 in the following section).<sup>181,182</sup> One might expect to find intermolecular examples of the xenochemical effect if the two alkynes were of much different reactivity. Finally, concentration is also an important factor in the distribution between phenolic products and products resulting from the incorporation of more than one alkyne. Examples include the formation of two-alkyne phenols (**21** in Scheme 5),<sup>80,81</sup> vinylcyclopentenediones (**10** in Scheme 4),<sup>60,78</sup> and polyacetylene.<sup>85</sup>



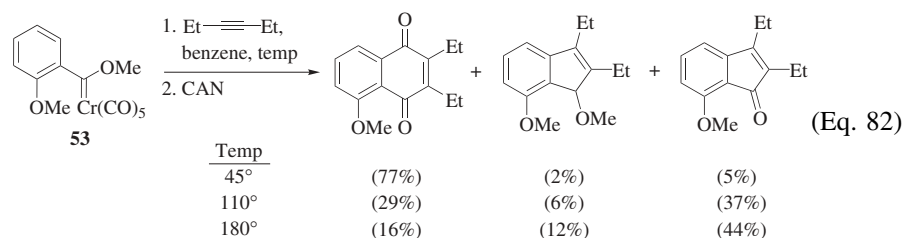
Another interesting additive effect that has not been widely reported, but which nonetheless could be synthetically quite important, is the effect of added acetic anhydride.<sup>116,183</sup> This effect is illustrated by the reaction of complex **26** with alkyne **186**, which fails to give any of the phenolic product in refluxing heptane, but in the presence of one equivalent of acetic anhydride affords the expected product in 66% yield (Eq. 81). Note that the product is not acetylated. Acetic anhydride does not have any effect on the yield of quinone from the intramolecular reaction of **183**.<sup>86</sup> The effect of acetic anhydride has only been reported for a small number of reactions and while it certainly does not work in all reactions,<sup>84</sup> or may not even work on a majority of reactions, when it does work the effect can be substantial and thus should be considered when optimizing a benzannulation reaction. An even less well studied additive is carbon monoxide. Small increases in the yield of quinone product can be observed for some complexes when the reaction is performed under a carbon monoxide atmosphere,<sup>184</sup> as has been observed for 2-alkoxyaryl carbene complexes (10-15% increase).



The effect of temperature on chemoselectivity has been examined for some reactions. The reaction of complex **53** with 3-hexyne over a 135° temperature range reveals that, whereas the mass balance is fairly consistent over this range, the proportion of phenolic product varies dramatically (Eq. 82).<sup>84</sup> In these studies, phenolic products are favored at lower temperature and are increasingly replaced by indene products as the temperature is raised. The unsubstituted phenyl complex **26** and the 2-methylphenyl complex **82** are not as sensitive to changes in temperature, but the latter is sensitive to a combination of temperature and concentration (Eqs. 22 and 23).<sup>84</sup> The effects of temperature on the reactions of alkenyl complexes have not been extensively studied.<sup>60</sup> The effect of temperature on the regioselectivity of the reaction of Fischer carbene complexes with



alkynes has only been examined in one example and it was found that the level of the regioselectivity drops by a factor of two for a 45° increase in temperature (Eq. 12).<sup>66</sup>

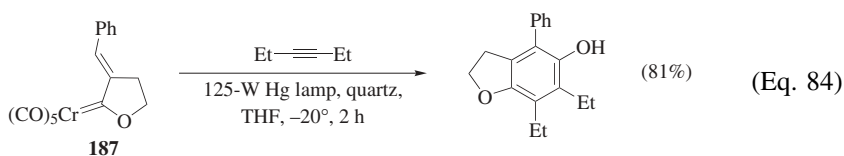
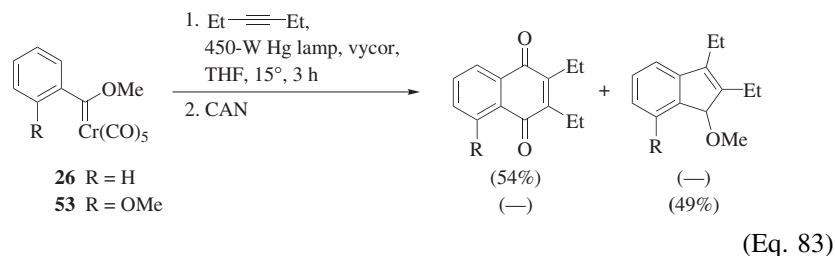


Although lower temperatures favor the formation of phenols compared to indenenes, there is a limit to which the temperature can be lowered to achieve reasonable rates. The rate-limiting step is the loss of a CO ligand (Scheme 2).<sup>42</sup> For most pentacarbonyl chromium carbene complexes, a reasonable rate for the thermal reaction can only be achieved at temperatures no lower than approximately 40–50°.

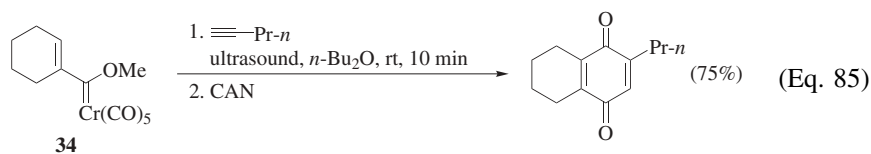
Reactions of amino carbene chromium complexes<sup>79</sup> and alkoxy carbene tungsten complexes<sup>60,63</sup> require higher temperatures than those of alkoxy carbene chromium complexes and both give a greater proportion of indene. This phenomenon has been attributed to the slower initial CO dissociation for amino complexes.<sup>48</sup> This shift in product distribution to indenenes for these reactions may be due to a combination of electronic effects in the carbene complexes and the temperature of the reaction, but these effects have not been sorted out. Molybdenum complexes react faster than chromium complexes and also give a higher proportion of indene products.<sup>185,60</sup> Thus, for molybdenum complexes it is clear that the increased propensity for indene formation is due to the nature of the metal.

Other methods for facilitating the loss of CO include photolysis, ultrasound irradiation, and microwave irradiation, and all three have been examined for the reaction of carbene complexes with alkynes. Photolysis has been used to probe for reactive intermediates in this reaction for both chromium and tungsten complexes.<sup>63,64</sup> The effect of photolysis of chromium carbene complexes on the yield of phenol products is variable. The reaction of complex **26** with 3-hexyne is mediated by irradiation with a 450 Watt Hg lamp and occurs at reasonable rates at 15° and at –78°, but the highest reported yield of the quinone is 54% at 15° (Eq. 83).<sup>13</sup> It is clear that ultraviolet irradiation can do more than just lower the barrier of CO dissociation since the photo-induced reaction of the 2-methoxyphenyl complex **53** with 3-hexyne gives no trace of phenolic product and instead the indene product is obtained in 49% yield. This result is in contrast to the thermally-induced reaction in the same solvent (Eq. 79).<sup>13</sup> Much higher yields of phenolic products have been reported from the photolysis of heteroaryl complexes and heteroaryl-substituted alkenyl complexes.<sup>186</sup> The photo-induced reaction of complex **187** with 3-hexyne affords the phenolic product in 81% yield and is important because reactions of complexes of this type provide the only known

examples of a successful photo-induced benzannulation of a chromium complex in which the corresponding thermal reaction fails (Eq. 84).<sup>187,188</sup> Photolysis is also known to greatly facilitate or make possible the benzannulation reactions of manganese complexes in inter- and intramolecular reactions.<sup>181,182</sup> The photolysis of  $\beta,\beta$ -disubstituted iminocarbene complexes in the presence of alkynes leads to the formation of 2*H*-pyrroles.<sup>189,190</sup>



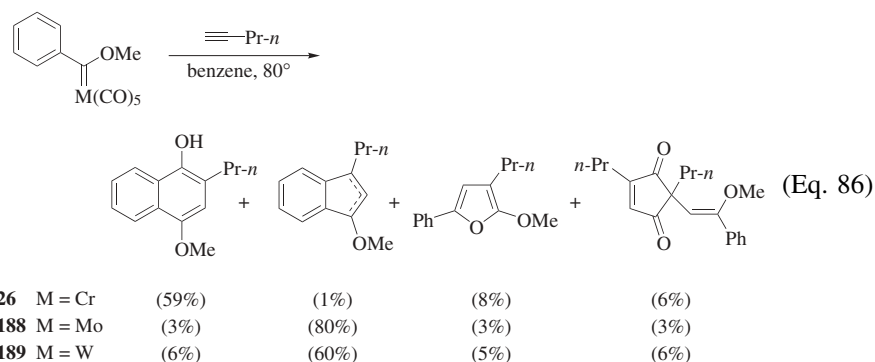
There are also a few examples of ultrasound-promoted reactions, an illustration being the reaction of complex **34** with 1-pentyne (Eq. 85).<sup>177</sup> This reaction provides the quinone product in essentially the same yield as the corresponding thermal reaction,<sup>13</sup> but the time and temperature are greatly reduced. Other reports include improvement in yields and rate for the benzannulation of aryl-oxy complexes<sup>169</sup> and similar improvements in the key step in the synthesis of parvaquone.<sup>191</sup>



The synthesis of phenols from the reactions of Fischer carbene complexes with alkynes has also been facilitated with microwave irradiation in a commercial reactor at 130° for 5 minutes.<sup>192</sup> Despite the relatively high temperatures employed, the reactions give yields comparable to the corresponding thermal reactions. Other agents that have been reported to mediate the reaction of carbene complexes with alkynes include [(COD)RhCl]<sub>2</sub>, which has been reported to facilitate the reaction of  $\beta$ -aminovinyl complexes with alkynes,<sup>193–195</sup> and boron trifluoride etherate, which has been reported to facilitate the benzannulation of thio carbene complexes (Eq. 71).<sup>167,168</sup>

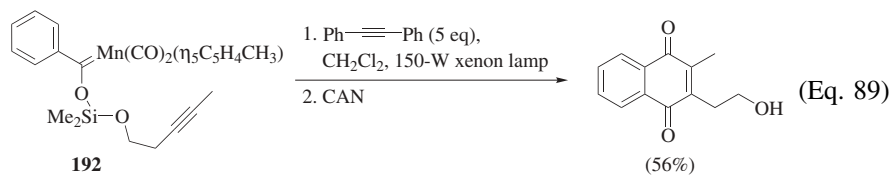
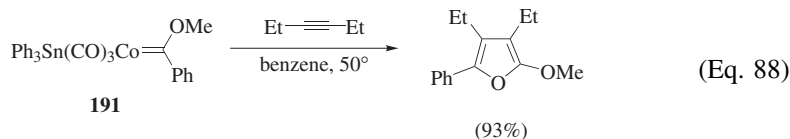
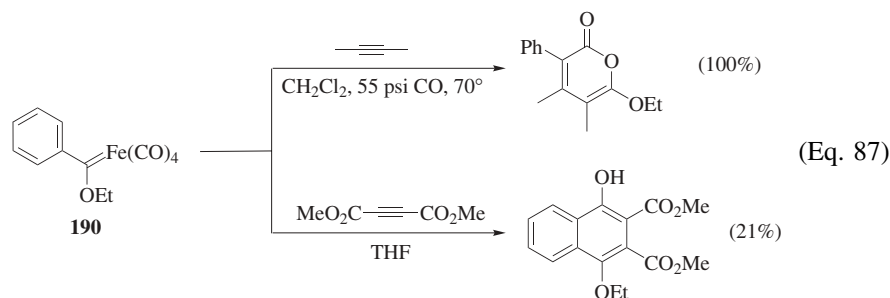
**Metal and Ligand Complement.** Fischer carbene complexes are known for a large number of transition-metals and the reactions of many of these have been

investigated with alkynes. However, of the Group 6 metals, chromium remains the metal of choice for the synthesis of phenols and quinones. The reactions of tungsten and molybdenum carbene complexes with alkynes are much less chemoselective for the phenolic product<sup>60,63,82,185</sup> as exemplified by the reaction of unsubstituted phenyl complexes **188** and **189** with 1-pentyne (Eq. 86).<sup>60</sup> The situation can be quite different with alkenyl complexes. For example, higher yields of the phenols can be obtained for certain molybdenum and tungsten alkenylcarbene complexes than with the corresponding chromium complexes.<sup>60</sup> One disadvantage of molybdenum complexes is that they are less stable than the chromium complexes. Nonetheless, molybdenum complexes can be employed without special precautions if used immediately after preparation. Tungsten complexes are more stable than the chromium complexes but suffer from the fact that alkyne polymerization<sup>63,85</sup> can be a serious side-reaction, thus requiring significant excesses of the alkyne. The reactions of tungsten and molybdenum alkenyl complexes with internal alkynes are not as chemoselective for phenols as are their reactions with terminal alkynes and thus these reactions usually give mixtures of products.<sup>60</sup>



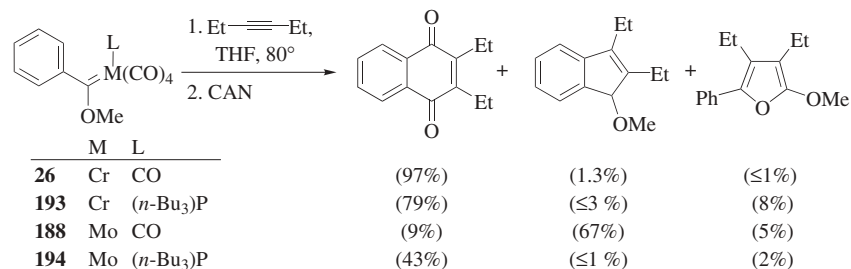
A few non-Group 6 Fischer carbene complexes have been investigated for their reactivity with alkynes but none provide for a synthesis of phenols that is as general as that of chromium complexes. Iron tetracarbonyl carbene complexes such as **190** give only phenols upon reaction with dimethyl acetylenedicarboxylate (Eq. 87).<sup>196</sup> The more typical outcome of the reaction of iron complexes with alkynes is the production of furans<sup>196,197</sup> or the formation of pyrones (Eq. 87).<sup>198</sup> A ruthenium Fischer carbene complex has been reported to give a quinone.<sup>199</sup> The reaction of stannyl tricarbonyl cobalt carbene complexes (e.g., **191**) with alkynes gives 2-alkoxyfurans as the only observable products as in the reaction of stannyl complex **191** with 3-hexyne (Eq. 88). This process has been used in the synthesis of bovolide.<sup>200</sup> Cyclopentadienyl dicarbonyl manganese carbene complexes will only react with alkynes upon ultraviolet irradiation and then only with non-carbon groups on the oxygen substituent of the carbene carbon. The intramolecular reaction of the siloxycarbene complex **192** gives a quinone upon photolysis and oxidative workup (Eq. 89). However, if the siloxy group is

replaced by a methyl group, no quinone formation is detected either by thermolysis or photolysis.<sup>181,182</sup> Note that intramolecular benzannulation of the manganese complex **192** is facilitated by the xenochemical effect (Scheme 6). The yields are approximately doubled by the addition of 5 equivalents of diphenylacetylene.



Replacing one of the carbon monoxide ligands of a Fischer carbene complex with a phosphine affects the benzannulation reaction with alkynes.<sup>87,13,201</sup> Only a small effect is seen in the reaction of phenyl complex **26** with 3-hexyne when a CO ligand is replaced with a tri-*n*-butylphosphine (Eq. 90).<sup>201</sup> In a related study with diphenylacetylene, replacement of a CO ligand by either the electron-rich tri-*n*-butylphosphine or with the electron-poor tris-(*para*-fluorophenyl)phosphine also has only a minor effect on the outcome of the reaction.<sup>201,87</sup> In contrast, a tri-*n*-butylphosphine ligand greatly affects the reaction of the phenyl molybdenum complex **188** with 3-hexyne (**194**, Eq. 90).<sup>133,201</sup> The major product changes from the indene with the pentacarbonyl complex **188** to the quinone with the tri-*n*-butylphosphine complex **194**. The origin of this effect has not been determined, but this is one of only three known examples of phenol formation from an aryl molybdenum carbene complex.<sup>60,82,185,201</sup> In principle, the use of phosphine ligands could provide a method to lower the temperature requirement of the benzannulation reaction. It has been demonstrated that a triphenylphosphine (but not trialkylphosphine) dissociates faster than CO from a Fischer carbene complex.<sup>202</sup> Although there are no known examples of the benzannulation

of tetracarbonyl(triphenylphosphine) aryl or alkenyl complexes, the two-alkyne annulation reaction has been reported for an alkyl carbene complex with a triphenylphosphine ligand and a rate acceleration was observed (see section on Two-Alkyne Annulation).<sup>133</sup>

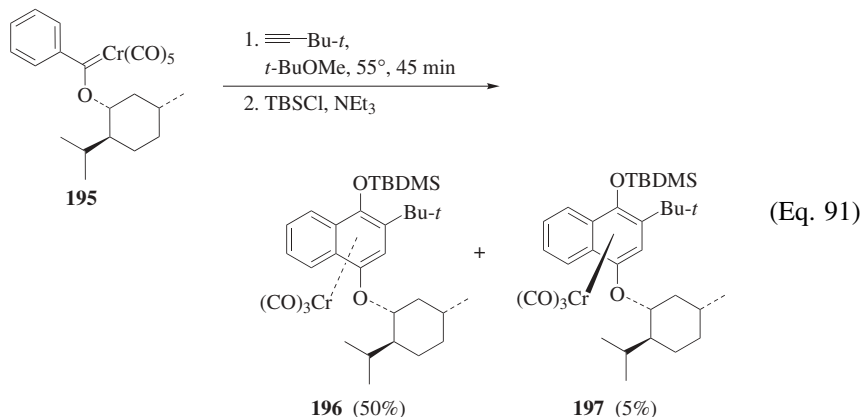


(Eq. 90)

There are many more examples in which a carbon monoxide ligand has been replaced by an oxygen or sulfur donor atom as the result of the coordination of an alkoxy group, a thio ether, or a carbonyl oxygen. Some examples include the methoxy-chelated complexes **94** (Eq. 29)<sup>84</sup> and **113** (Eq. 37),<sup>105</sup> the thioether-chelated complex **97** (Scheme 9),<sup>91</sup> and the carbonyl-chelated complexes **167** and **172** (Eqs. 68 and 70).<sup>162,165</sup> Only one example is known in which a carbon monoxide ligand is replaced by an isonitrile ligand, and an indene product results from reaction of this complex with an alkyne.<sup>203</sup>

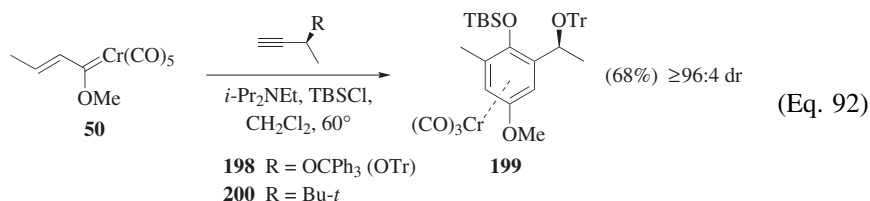
**Diastereoselectivity.** A new stereogenic element is formed when the arene chromium tricarbonyl group is created. There are three modes of stereoinduction involving diastereoselective installation of the chromium tricarbonyl group. These three possibilities arise when the stereocenter of the arene chromium tricarbonyl group is created in the presence of stereocenters that already exist either on the alkyne, on the oxygen substituent of the carbene carbon, or on the carbon substituent of the carbene carbon. The development of stereoselective benzannulation procedures is dependent on the invention of a general method for the protection of the phenol function and the resulting production of air-stable arene chromium tricarbonyl complexes.<sup>95</sup>

The only success that has been achieved with a carbene complex bearing a chiral alcohol is illustrated by the reaction of the phenyl [(−)-menthyloxy]carbene complex **195** with 3,3-dimethyl-1-butyne to give a 10 : 1 mixture of the diastereomers **196** and **197** (Eq. 91).<sup>97,204</sup> Although this reaction does give a similar selectivity with 3-hexyne,<sup>73</sup> it gives low selectivity with 1-pentyne.<sup>205</sup> The corresponding reactions of alkenyl [(−)-menthyloxy]carbene complexes fail to give significant stereoselectivity with a number of acetylenes including *tert*-butylacetylene.<sup>97,205</sup>



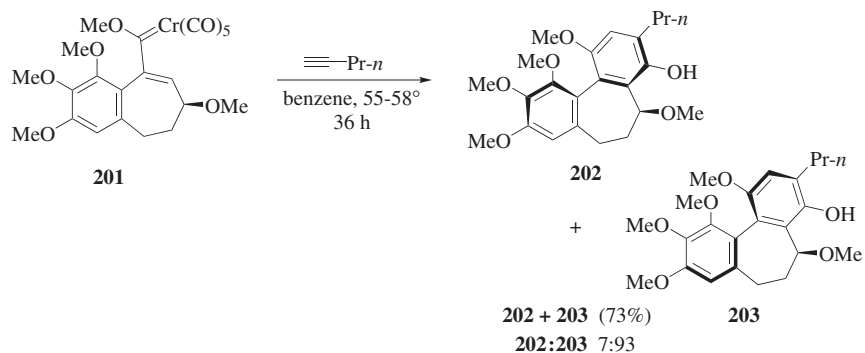
Another mode of stereocontrol involves asymmetric induction from a stereogenic center on the alkyne to the newly formed planar element of chirality. Very high asymmetric induction is observed for the reaction of certain alkenyl carbene complexes with propargyl ethers. The reaction of the  $\beta$ -substituted vinyl carbene complex **50** with alkyne **198** ( $\text{R} = \text{CPh}_3$ ) gives the arene chromium tricarbonyl complex **199** in 68% yield and  $\geq 96:4$  stereoselectivity (Eq. 92).<sup>88</sup> The high stereoselectivities observed may have a stereoelectronic origin as revealed by variations in the ether substituent of the propargyl ether **198** and by the fact that the alkyne **200** gives nearly an equal mixture of diastereomers upon reaction with complex **50**.<sup>88,206</sup> This stereoinduction is limited to  $\beta$ -substituted alkenyl carbene complexes. The same reaction with alkenyl carbene complexes bearing an  $\alpha$ -substituent gives low stereoselectivity.

The third mode for stereoinduction in the benzannulation reaction involves chiral carbene complexes that have a stereogenic center in the carbon substituent of the carbene carbon. This reaction has been examined for cyclohexenyl complexes bearing substituents in the 3- and 6-positions and the diastereoselectivity varies from low to modest.<sup>207</sup> High diastereoselectivity has been observed from the reaction of complex **44** with 5-hexyn-1-ol which gives a single diastereomer of **45** after an intramolecular Mitsunobu cyclization (Eq. 8).<sup>99</sup> Other examples of this mode of stereoselection include the use of the benzannulation reaction in the formation of cyclophanes,<sup>208</sup> chiral biaryls,<sup>209</sup> annulenes,<sup>98</sup> and carbohydrate-derived carbene complexes.<sup>210</sup>



Asymmetric induction is also observed in reactions where the chromium tricarbonyl unit is not retained in the newly formed arene ring. In a study directed

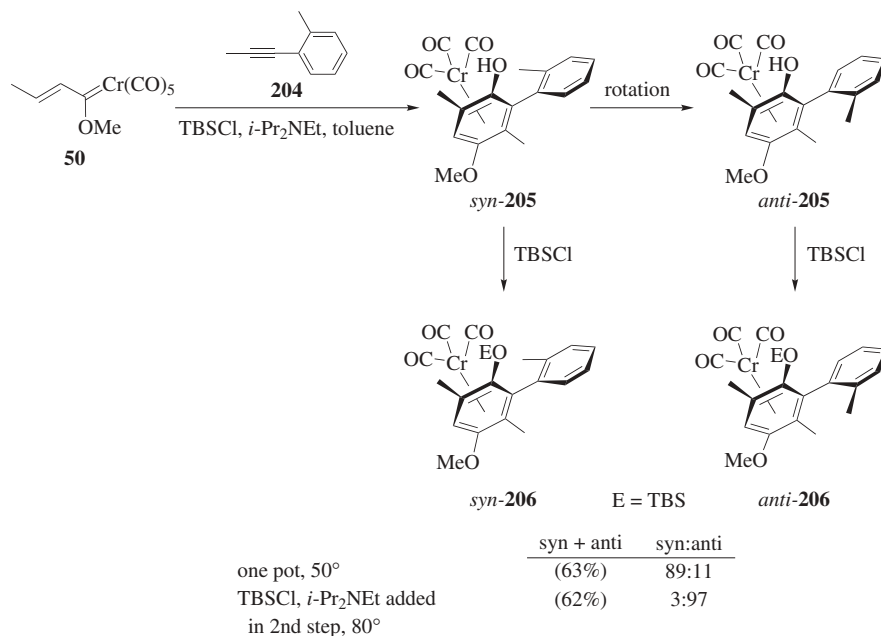
to the synthesis of allocolchicinoids, the reaction of the carbene complex **201** with 1-pentyne selectively gives the benzannulated product **203** in which there is central to axial stereoinduction leading to the preferential formation of one of the two possible atropisomers **202** and **203** (Eq. 93).<sup>211</sup> Another example of this type of asymmetric induction is presented in the next section (Eq. 98).<sup>100</sup>



(Eq. 93)

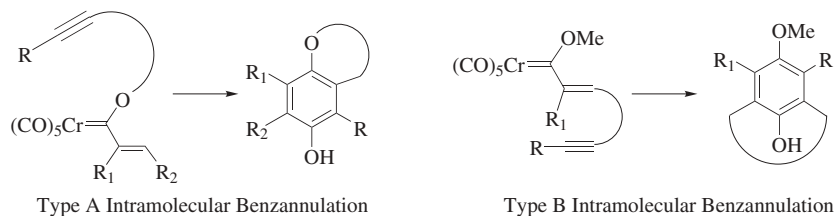
Asymmetric induction can also be achieved from the newly formed plane of chirality of the arene chromium tricarbonyl complex to an axis of chirality formed in the same reaction. The combination of  $\alpha,\beta$ -unsaturated carbene complexes with 2-substituted aryl acetylenes simultaneously generates planar and axial elements of chirality.<sup>212</sup> As an example, if the reaction of complex **50** and aryl propyne **204** is carried out in toluene at 50° in the presence of *tert*-butyldimethylsilyl chloride and (*i*-Pr)<sub>2</sub>NEt, the arene chromium tricarbonyl complex **206** is obtained in an 89 : 11 mixture of syn- to anti-isomers (Scheme 11). This diastereoselectivity can be reversed to give a 97 : 3 ratio in favor of the anti-isomer if the benzannulation and silylation steps are carried out sequentially. These observations are consistent with a kinetic formation of the syn-phenoxy complex **205**. Under simultaneous silylation conditions the phenol is silylated before rotation about the chiral axis can occur to give the anti-phenoxy complex **205**. Under sequential silylation conditions, complete isomerization to the anti-phenoxy complex can occur if the first step is performed at 80° (the two step reaction at 50° gives a 95 : 5 mixture of anti:syn isomers). Subsequent silylation then yields the silylated complex *anti*-**206**. The reactions of aryl acetylenes of the type **204** with a chiral substituent replacing the methyl group on the benzene can give rise to asymmetric induction from the stereocenter in the alkyne to a newly formed axis of chirality in the benzannulated product.<sup>213</sup>

**Intramolecular Reactions.** The most thoroughly studied intramolecular reactions of  $\alpha,\beta$ -unsaturated Fischer carbene complexes involve those in which the alkyne is tethered through the heteroatom substituent (Type A). The thermolysis of the complexes **207** provides good yields of fused cyclic aryl ethers for the generation of dihydrobenzofurans, dihydrobenzopyrans, and

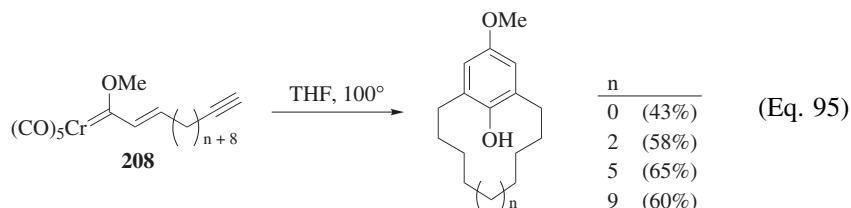
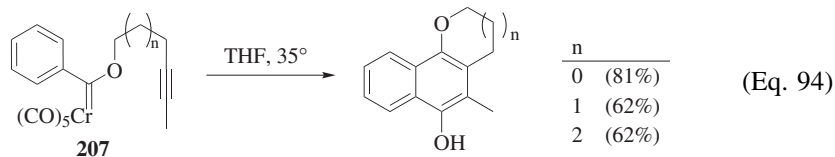


Scheme 11

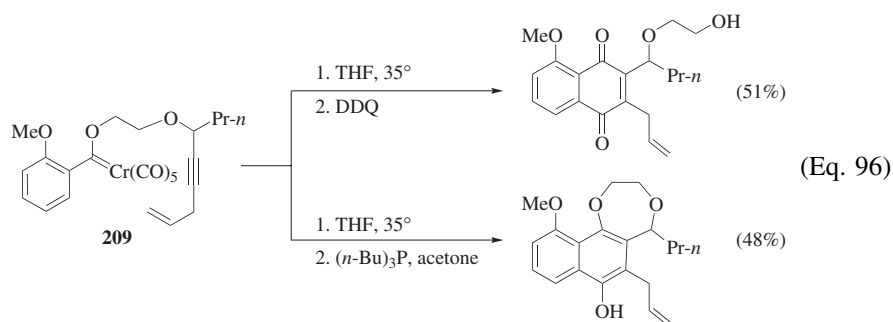
tetrahydrobenzoxepins, respectively (Eq. 94).<sup>214</sup> The extension to formation of eight-membered rings has not been reported. There are a few examples of intramolecular cyclizations wherein the alkyne is tethered to an alkenyl or aryl substituent of the carbene carbon (Type B).<sup>215,216</sup> These reactions do not always give the normal phenolic products, but often good yields of the phenol can be obtained (Eq. 95). If the alkyne is tethered to the  $\beta$ -carbon of an alkenyl complex as in **208**, the product of the reaction is a metacyclophane.<sup>215</sup> The yield of the phenol is modest for the cyclophane with an eight-methylene bridge (43%), but above that, the yield increases and levels off at 60%. If the alkyne is connected to the  $\alpha$ -carbon, and if it is sufficiently long, then paracyclophanes are formed, but the strain introduced with shorter tethers can lead to the formation of products that are unprecedented in intermolecular reactions including bicyclo[3.1.0]hexenones and *m*-alkoxyphenols.<sup>217,176</sup>





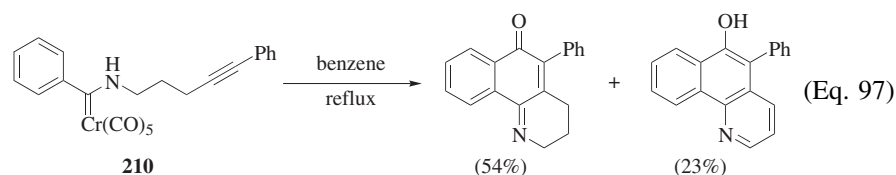


A significant difference between the two modes of intramolecular cyclization (especially with terminal alkynes) is that the regiochemistry is reversed in Type A but is normal in Type B reactions. A consequence is that terminal alkynes do not give as high yields of phenols for the Type A process as for Type B. These low yields can be overcome by capping the alkyne with a trimethylsilyl group.<sup>114</sup> Intramolecular benzannulation with alkynes attached through removable tethers has been used to control the regiochemistry of reactions of internal alkynes (Eq. 19). A synthesis of deoxyfrenolicin featured the intramolecular benzannulation of carbene complex **209**, which upon oxidative workup gives a naphthoquinone, and upon workup involving a ligand displacement gives a naphthol (Eq. 96).<sup>86,90,218</sup> An intermolecular reaction with a similarly functionalized alkyne gives the opposite constitutional isomer.<sup>90</sup>

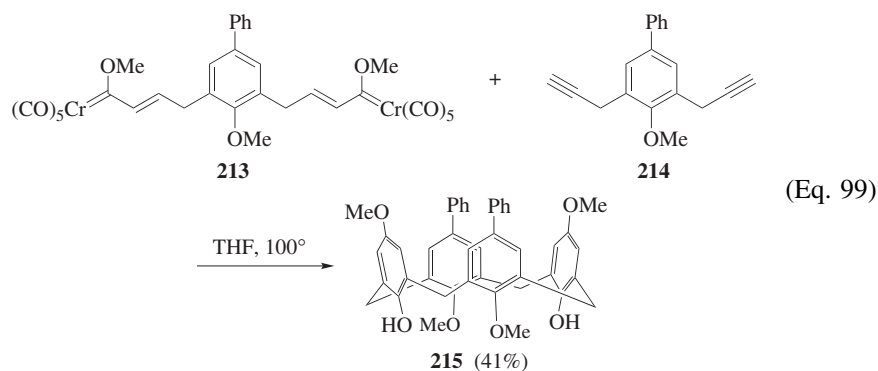
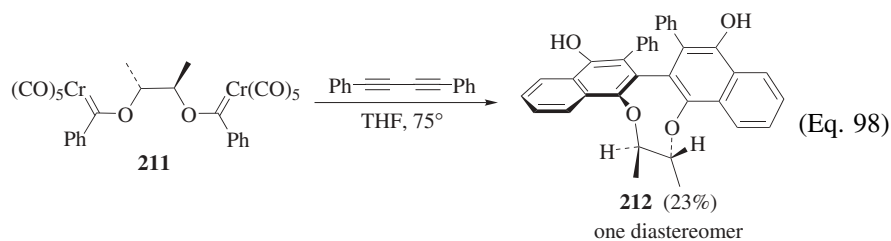


Intramolecular benzannulations also impact the chemoselectivity of the reaction. For intermolecular reactions, alkenyl amino carbene complexes and alkynes can sometimes yield phenolic products (Eq. 65),<sup>83</sup> but aryl amino carbene complexes rarely afford phenols as the major product and instead usually afford indenenes.<sup>79,160</sup> However, as illustrated by the reaction of complex **210**, the intramolecularity of a benzannulation reaction can cause a switch from indenenes to phenols for amino carbene complexes (Eq. 97).<sup>219</sup> Other examples of intramolecular

reactions of amino complexes give phenolic products,<sup>23,128,220,221</sup> whereas others give indene products.<sup>128,222</sup>

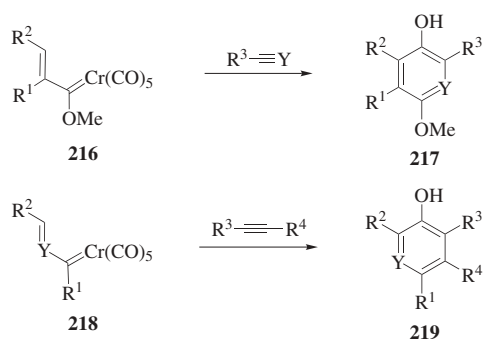


Intramolecular benzannulations have also been demonstrated in the reactions of bis(carbene) complexes with bis(alkynes). The first benzannulation from the reaction of the bis(carbene) complex **211** and 1,4-diphenylbutadiyne is intermolecular but the second step must be intramolecular (Eq. 98).<sup>100</sup> The intramolecularity of the second step leads to the formation of a  $C_2$ -symmetric product unlike that observed for the product from the intermolecular reaction (Eq. 49).<sup>100</sup> Despite the low yields observed for the reaction of complex **211**, this reaction has potential for the asymmetric synthesis of chiral biaryls given that only a single diastereomer of the binaphthol **212** is formed (Eq. 98). A bis(carbene) complex can also be employed in a double-benzannulation of a non-conjugated diyne as a route to calix[4]arenes. The reaction of bis(carbene) complex **213** with diyne **214** gives calix[4]arene **215** in 41% yield in a process in which two of the benzene rings of the calixarene are made at the same time as the macrocycle. (Eq. 99).<sup>223</sup>



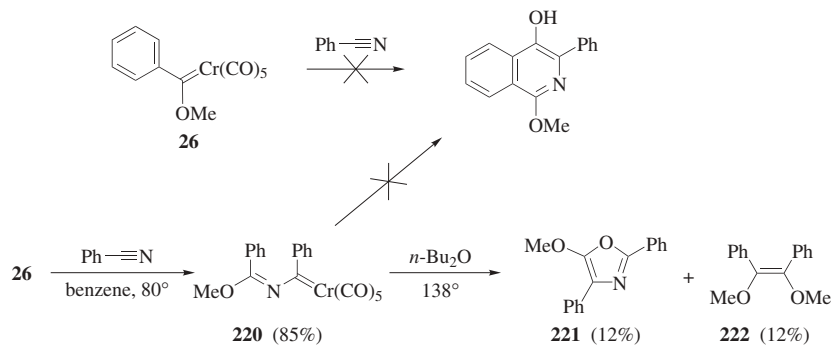
### Heteroannulation

Heteroaromatic rings containing a hydroxyl function have been produced from the reaction of  $\alpha,\beta$ -unsaturated carbene complexes by two routes (Scheme 12). In reactions with carbene complexes of type **216**, substitution of one of the triply-bonded carbon atoms of the alkyne with a heteroatom leads to the heterocycles **217**. Alternatively, heterocycles **219** can be formed by the reactions of alkynes with carbene complexes of the type **218** in which the  $\alpha$ -carbon of the  $\alpha,\beta$ -unsaturated substituent has been replaced by a heteroatom. Although the latter approach has been proven so far to be the more general, the following discussion will begin with the reactions of "hetero-alkynes."



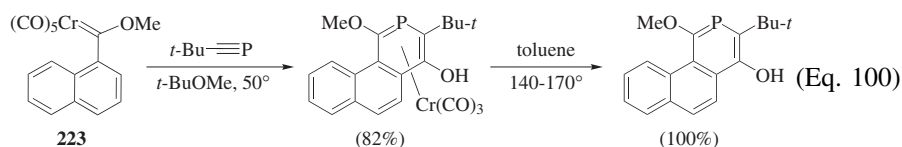
Scheme 12

Reaction of aryl carbene complexes with nitriles do not produce functionalized isoquinolines. Instead, imidatocarbene complexes such as **220** result from the insertion of the nitrile function into the chromium-carbon bond of the starting carbene complex (Scheme 13).<sup>224,225</sup> At higher temperatures (138°) the only products formed are the oxazole **221** and the alkene **222**.<sup>226,227</sup> The latter is likely due to thermal decomposition of phenyl complex **26**, which is formed by expulsion of benzonitrile from complex **220**.<sup>228</sup>

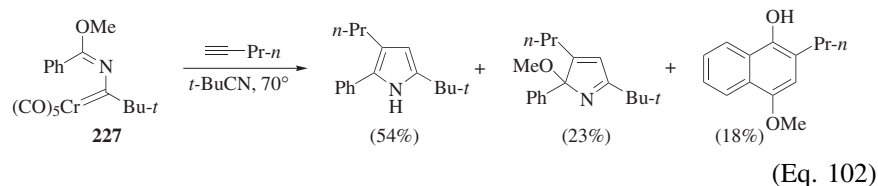
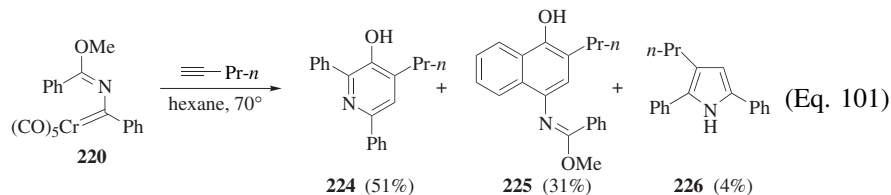


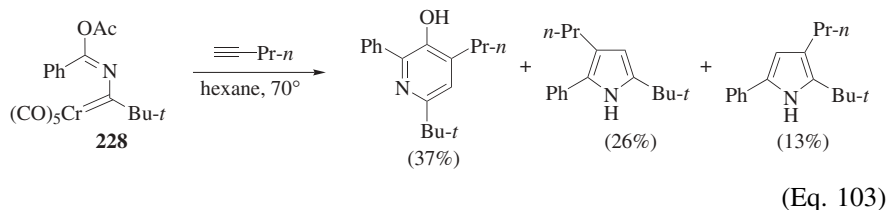
Scheme 13

Whereas the reaction of carbene complexes with nitriles does not produce six-membered heterocycles, these products can result from reactions of carbene complexes with phosphalkynes.<sup>229–231</sup> Reaction of the 1-naphthyl carbene complex **223** with 2,2-dimethylpropylidynephosphane gives a phosphabenzene chromium tricarbonyl complex in 82% yield (Eq. 100).<sup>229,231</sup> The metal can be removed in quantitative yield by ligand exchange with toluene. Despite the high yield observed for this reaction, significant yields of phospharenes could not be obtained with other carbene complexes. The predominant product from most of these reactions are oxaphospholes.

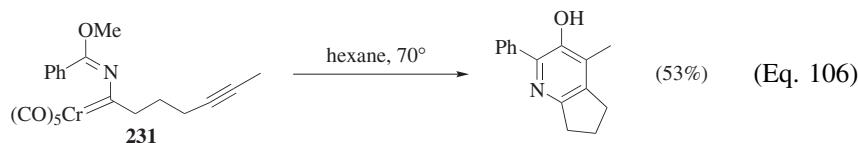
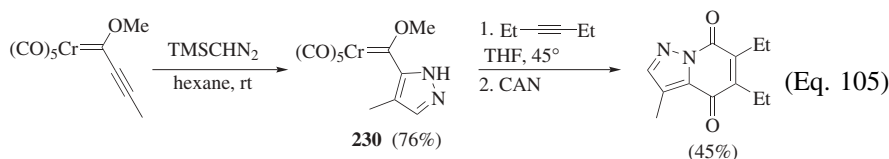
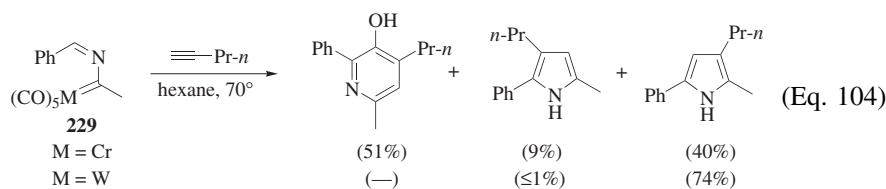


Although thermolysis of complex **220** does not produce a six-membered heterocycle (Scheme 13), its reaction with alkynes gives 3-hydroxypyridines.<sup>226,232</sup> The 3-hydroxypyridine **224** is produced in 51% yield along with the non-CO inserted pyrrole **226** (Eq. 101).<sup>232</sup> A third product (**225**) is formed by cyclization to the phenyl group on the carbene carbon in **220** rather than to the imino group. This complication does not exist for complex **227**; however, its reaction with 1-pentyne only gives five-membered ring products containing nitrogen (Eq. 102).<sup>226</sup> The naphthalene product from this reaction results from extrusion of *tert*-butyl nitrile to give phenyl complex **26**, which then undergoes reaction with 1-pentyne. This reaction is carried out in *tert*-butyl nitrile as solvent to suppress extrusion. The same reaction in THF gives only the naphthalene product.<sup>233</sup> Extrusion of *tert*-butyl nitrile from complex **228** would give a non-stabilized carbene complex and this apparently disfavors extrusion since a naphthalene is not observed from the reaction of complex **228** with 1-pentyne (Eq. 103).<sup>232</sup> The observation that the more electron-deficient complex **228** gives a six-membered ring product incorporating a CO ligand while the more electron-rich complex **227** only gives non-CO inserted products is consistent with the differences observed for reactions of alkoxy- and aminocarbene complexes.



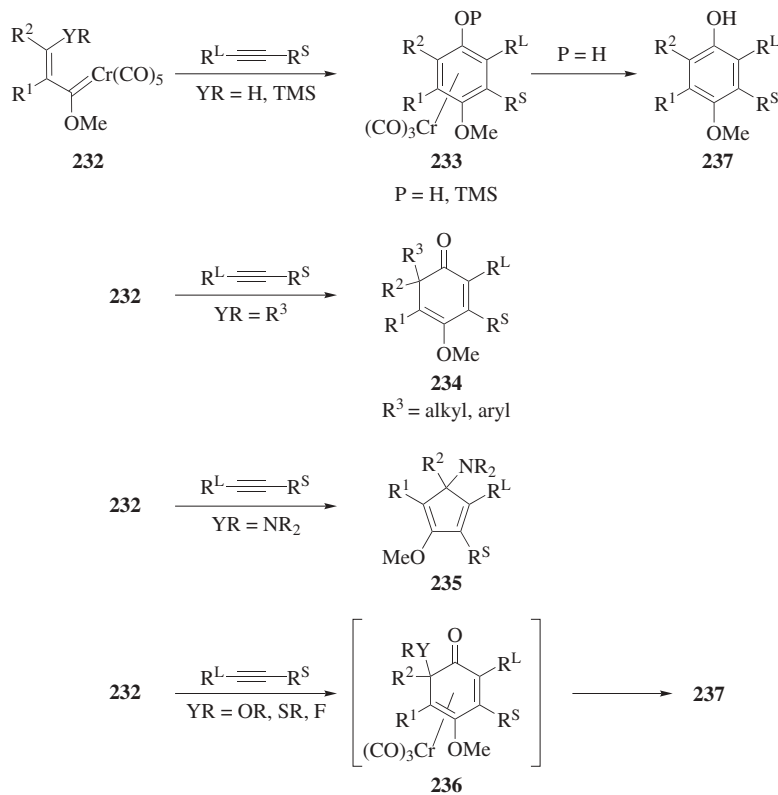


The imino complex **229** (Eq. 104) gives a higher proportion of 3-hydroxypyridine product than does the imidato complex **228** (Eq. 103).<sup>232-236</sup> Chromium imino complexes of the type **229** produce mixtures of 3-hydroxypyridines and pyrroles, whereas the tungsten analogs give only pyrroles in a highly chemo- and regioselective synthesis of these heterocycles (Eq. 104).<sup>234</sup> The reaction of  $\beta,\beta$ -disubstituted imino complexes of the type **229** (obtained from ketones) with alkynes has been reported to give 2*H*-pyrroles under photolytic conditions.<sup>189,190</sup> The only examples of heteroannulation onto a heterocyclic substituent of a carbene complex involve the reactions of pyrazole complexes of the type **230** (Eq. 105).<sup>237</sup> Moderate yields of pyrazolopyridinoquinones are obtained upon reaction with alkynes. The intramolecular assembly of a 3-hydroxypyridine from the complex **231** affords a 53% yield of a ring-fused 3-hydroxypyridine (Eq. 106).<sup>232</sup>



### Cyclohexadienone Annulation

Cyclohexa-2,4-dienones can be the predominant products from the reactions of alkynes with  $\alpha,\beta$ -unsaturated carbene complexes of the type **232** that bear two carbon substituents in the  $\beta$ -position (Scheme 14).<sup>61</sup> Complexes of the type **232** with  $YR = R_3Si$  give silylated phenols of the type **233** in high yield, often as their chromium tricarbonyl complexes (Eqs. 20 and 21).<sup>95,110,112,159</sup> These products result from the carbon to oxygen migration of the silicon substituent in

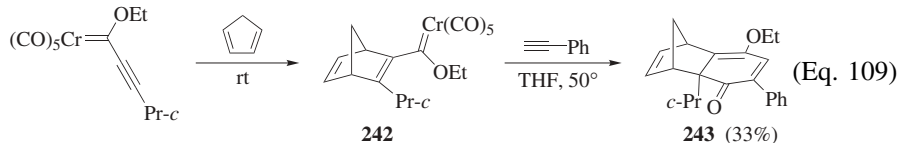
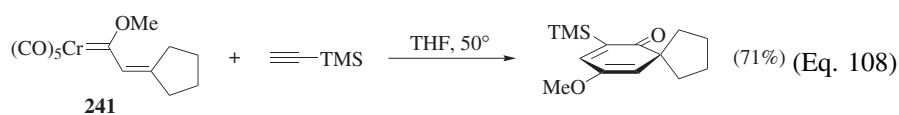
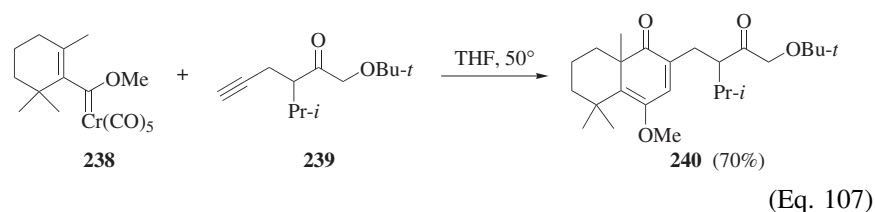


Scheme 14

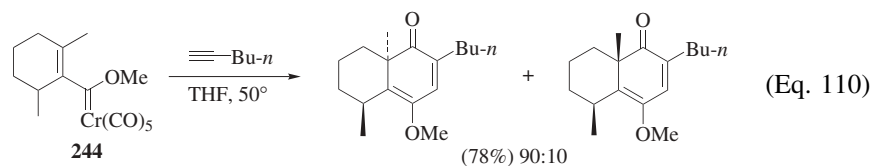
intermediate **236**. If the carbene complex bears an oxygen, sulfur, chlorine, or fluorine substituent in the  $\beta$ -position, phenol **237** is produced by cleavage of the carbon-YR bond in intermediate **236** shown in Scheme 14 (Scheme 9,<sup>91</sup> Eq. 36,<sup>122</sup> Eq. 37,<sup>105</sup> Eq. 39,<sup>124</sup> Eq. 40<sup>125</sup>). The reactions of complexes bearing  $\beta$ -amino substituents do not give phenols or cyclohexadienones but rather yield predominantly cyclopentadienes of the type **235** (Scheme 14).<sup>123,30</sup> Given the higher reduction potential of carbon-carbon bonds and the lower migratory propensity of carbon versus silicon or hydrogen, the reaction of complexes of the type **232** with YR as a carbon substituent usually give the cyclohexadienone product **234**, although carbon migration may occur (see below).

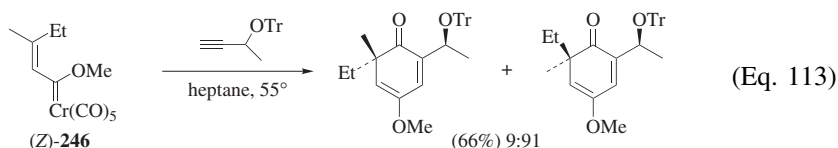
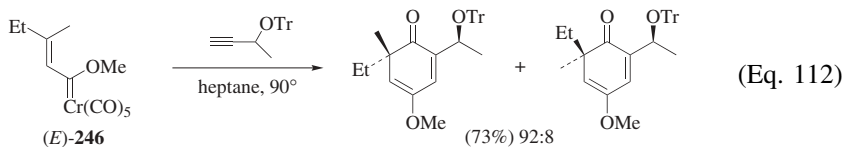
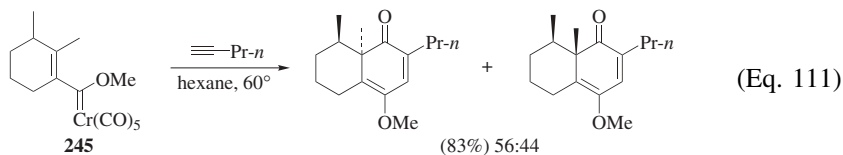
The reactions of complexes **238**, **241**, and **242** illustrate the versatility of the cyclohexadienone annulation (Eqs. 107–109). The reaction of hindered complex **238** with keto alkyne **239** gives the decalindienone **240** in 70% yield (Eq. 107).<sup>238</sup> The quaternary carbon that is produced in the cyclohexadienone annulation becomes a spirocyclic center if the carbene complex is derived from a methylenecycloalkane such as complex **241** (Eq. 108).<sup>239</sup> The tetracyclic cyclohexadienone **243** is constructed from simple starting materials utilizing a

Diels-Alder reaction of a Fischer carbene complex as well as the cyclohexadienone annulation (Eq. 109).<sup>240</sup>

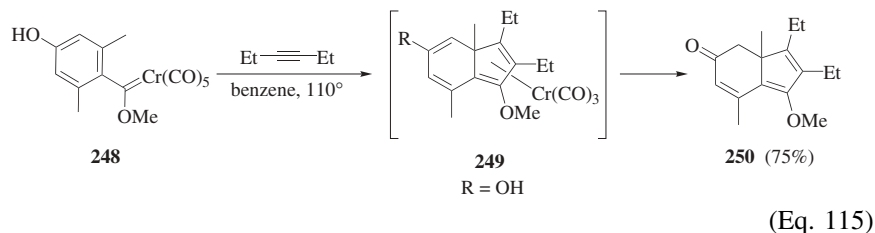
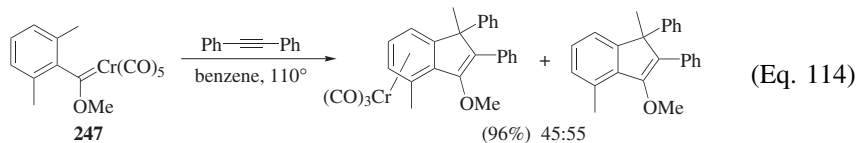


The cyclohexadienone annulation reaction can produce a new stereogenic center at the quaternary carbon if the two  $\beta$ -substituents of the carbene complex are not the same, as illustrated in Eq. 109.<sup>240</sup> In such reactions the potential exists for relative asymmetric induction between the preexisting stereocenters in either the carbene complex or the alkyne and the newly formed stereocenter in the cyclohexadienone. Although the stereoselectivity of these reactions has not been extensively examined, examples of both types of induction can be found in the literature. Reaction of the 2,6-dimethylcyclohexenyl complex **244** gives a 90 : 10 selectivity for the *trans*-configured cyclohexadienone (Eq. 110),<sup>61</sup> in contrast to the reaction of the 2,3-dimethylcyclohexenyl complex **245**, which renders a nearly equal mixture of isomers (Eq. 111).<sup>207</sup> A proposal to account for this difference in stereoselectivity has been presented. Significant levels of 1,4-asymmetric induction are observed for reactions with propargyl ethers (Eqs. 112 and 113).<sup>111</sup> This reaction is stereospecific as demonstrated by the reaction of the *Z*- and *E*-isomers of carbene complex **246**. The *E*-isomer gives a 92 : 8 mixture of diastereomers, whereas the *Z*-isomer gives a 9 : 91 mixture of the same cyclohexadienones. This result requires that the *Z*- and *E*-isomers of the  $\beta,\beta$ -disubstituted carbene complex **246** do not isomerize under the reaction conditions, which is surprising in light of the fact that the *cis*- and *trans*-1-propenyl carbene complexes have been found to isomerize under the reaction conditions.<sup>69</sup>



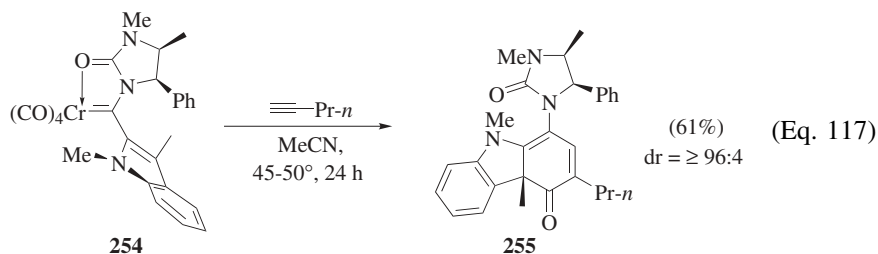
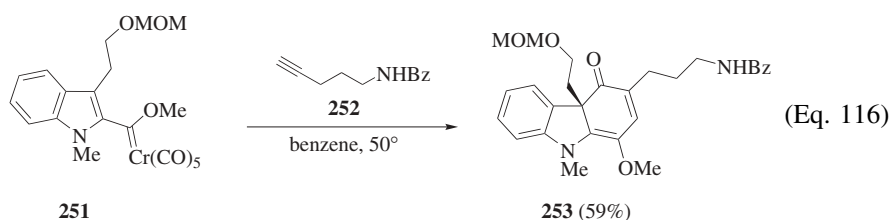


The reactions of aryl carbene complexes that have all-carbon substituents in positions beta to the carbene carbon often do not give cyclohexadienone products. For example, the reaction of the 2,6-dimethylphenyl carbene complex **247** with diphenylacetylene gives a 96% yield of the indene product, which is isolated as a mixture of the metal-free indene and its chromium tricarbonyl complex (Eq. 114).<sup>241,242</sup> Although this reaction does not give a naphthol in which the methyl group has migrated to oxygen, this reaction does give an indene in which the methyl group has undergone a 1,5-sigmatropic rearrangement. Part of the driving force for this migration is the restoration of the aromaticity of the benzene ring that was lost when cyclization occurred to give the intermediate **249** (R = H, Eq. 115). A recent study finds that the 1,5-sigmatropic migration of methyl can be prevented by a keto-enol tautomerization in intermediate **249** (R = OH).<sup>243</sup> An example of this tautomer-arrested annulation is the reaction of complex **248** with 3-hexyne, which affords the highly functionalized indenone **250** in 75% yield (Eq. 115). Some intramolecular variants of these reactions lead to CO insertion and the formation of vinyl ketene intermediates, which upon cyclization give cyclohexadienone products.<sup>243</sup>





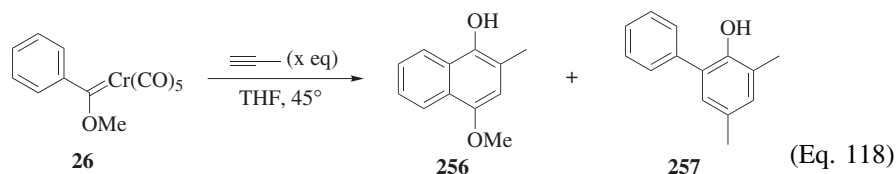
Cyclohexadienones can be obtained in good yields from other  $\beta,\beta$ -blocked aryl carbene complexes. Both 2-indolyl and 3-indolyl carbene complexes that have carbon substituents beta to the carbene complex give moderate to high yields of cyclohexadienone annulation products.<sup>62</sup> As an example, the 2-indolyl complex **251** reacts with alkyne **252** to give the 4*H*-carbazol-4-one **253** in 59% yield (Eq. 116). The only example of an asymmetric cyclohexadienone reaction involving a chiral auxiliary on the carbene complex has been reported for an indolyl carbene complex. The reaction of chiral carbene complex **254** with 1-pentyne gives the 4*H*-carbazol-4-one **255** with a greater than 96:4 selectivity for the diastereomer shown (Eq. 117).<sup>244</sup>



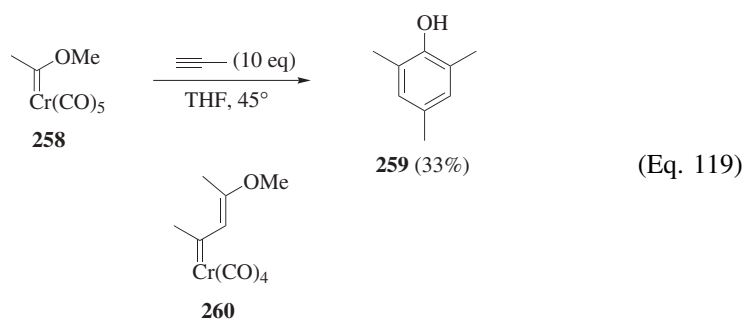
### Two-Alkyne Annulation

The original discovery of the formation of phenols from the reaction of Fischer carbene complexes with acetylenes involved the incorporation of only one molecule of alkyne. However, phenolic products can also be formed from the reaction of a Fischer carbene complex with two molecules of an alkyne. This structural type was first observed as a minor product in the cyclohexadienone annulation.<sup>61</sup> An example of the competition between the formation of the two different phenolic products is presented in the reaction of phenyl complex **26** with propyne to give naphthol **256** along with phenol **257**, which is derived from two molecules of propyne (Eq. 118).<sup>131,245</sup> The yield of the “two-alkyne” phenol **257** initially increases with the number of equivalents of alkyne employed in the reaction and then falls off, presumably because of competing polymerization of the alkyne. The two-alkyne phenol is the major product with acetylene under all conditions (Eq. 42).<sup>131</sup> The unsaturated substituent of the carbene complex is not incorporated into the two-alkyne phenol and thus alkyl-substituted carbene complexes such as **258** can also give “two-alkyne” phenol products. The

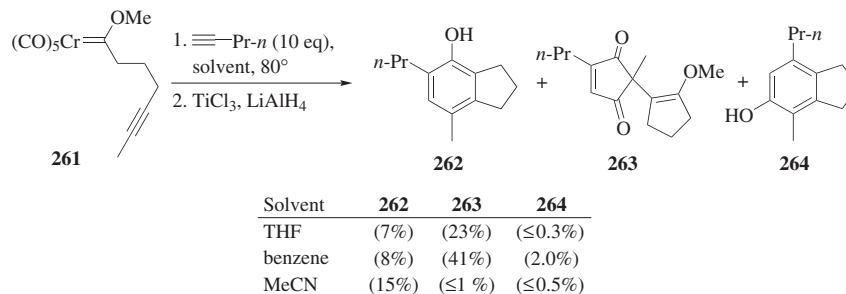
latter reacts with propyne to give the phenol **259**, which is likely formed via the intermediate vinylcarbene complex **260** into which a second molecule of alkyne inserts (Eq. 119).<sup>131</sup> A more thorough presentation of the mechanistic path to the two-alkyne phenol product can be found in Scheme 5.



x	<b>256</b>	<b>257</b>
2	(45%)	(4%)
40	(10%)	(44%)
neat	(0.3%)	(28%)

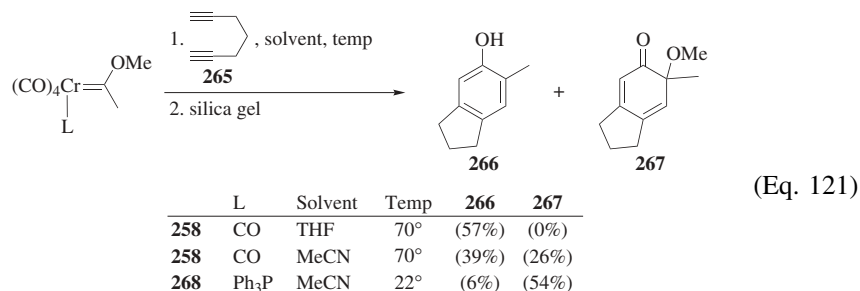


The utility of the intermolecular “two-alkyne phenol” annulation is limited by typically poor yields as indicated in Eqs. 118 and 119. Furthermore, this variant is limited to small alkynes such as propyne or acetylene (Eq. 42). More success has been achieved with intramolecular variations of this process (Eqs. 120–123). The possibilities for intramolecular reaction are three-fold: (1) the tethering of the carbene complex to one of the alkynes, (2) the tethering together of the two alkynes, and (3) the tethering of both alkynes to the carbene complex. The first combination is limited in its ability to produce the two-alkyne phenol product as illustrated by the formation of phenol **262** from the reaction of complex **261** with 1-pentyne (Eq. 120).<sup>246</sup> This particular intramolecular variation in benzene can produce good to moderate yields of 2-vinylcyclopentenedione **263**, a rather complex product derived from the incorporation of two equivalents of alkyne and two equivalents of carbon monoxide (Scheme 4).<sup>78</sup> Also observed in this reaction is the isomeric “two-alkyne phenol” **264**, which results from incorporation of the carbon monoxide into the benzene ring para to the carbon derived from the carbene carbon. Increased amounts of this para “two-alkyne phenol” are observed at lower substrate concentrations<sup>78,246</sup> and with amino carbene complexes.<sup>58</sup>

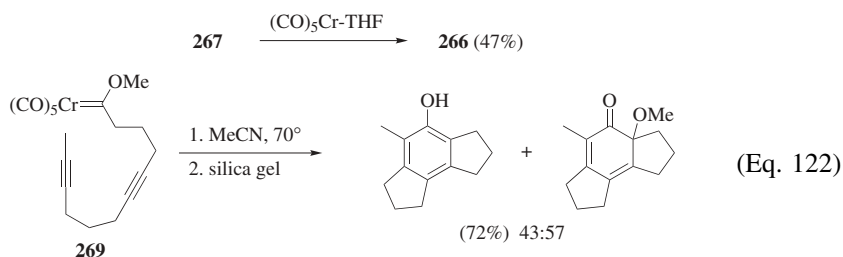


(Eq. 120)

Synthetically useful yields of “two-alkyne phenols” can be obtained from the reaction of Fischer carbene complexes with diynes. This feature is illustrated by the reactions of complexes **258** and **268** with 1,6-heptadiyne (**265**) which, depending on the solvent, gives mixtures of the phenol **266** and the cyclohexadienone **267** (Eq. 121).<sup>80,133</sup> The cyclohexadienone **267** can be reduced to the phenol **266** by chromium(0), supporting the mechanism proposed for phenol formation (Scheme 5). The phenol is the major product in THF, but in acetonitrile increased amounts of the cyclohexadienone are isolated. This outcome is thought to be attributable to the ability of acetonitrile to sequester the chromium(0). Good yields of the cyclohexadienone product can be obtained with the phosphine-substituted complex **268**, which can react with the diyne without the need for heating. In a related process, phenols of the type **266** can also be produced by the reaction of diynes and Fischer carbene complexes.<sup>81</sup> The double intramolecular reaction of carbene complexes bearing tethered diynes can give good yields of tricyclic phenols as illustrated by the thermolysis of complex **269** in acetonitrile (Eq. 122).<sup>245,247</sup>

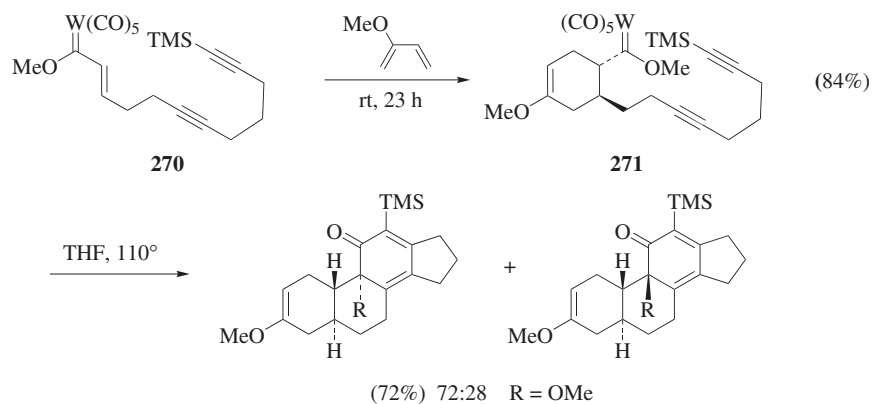


(Eq. 121)



(Eq. 122)

A tandem Diels-Alder/“two-alkyne annulation” has been developed as a strategy for the synthesis of steroid analogs.<sup>245,247</sup> Diels-Alder reaction of endiynyl carbene complex **270** with 2-methoxybutadiene proceeds at room temperature to give the cycloadduct **271** in 84% yield (Eq. 123). The tungsten complex is employed because the double intramolecular two-alkyne annulation of chromium complexes gives lactone side products, the amount of which is dependent on the geometric constraints of the tether. Tungsten complexes require higher temperatures for reaction but, nonetheless, give good yields of two-alkyne phenols. Thermolysis of **271** in THF produces the cyclohexadienone in 72% yield as a 3 : 1 mixture of diastereomers.<sup>245</sup>

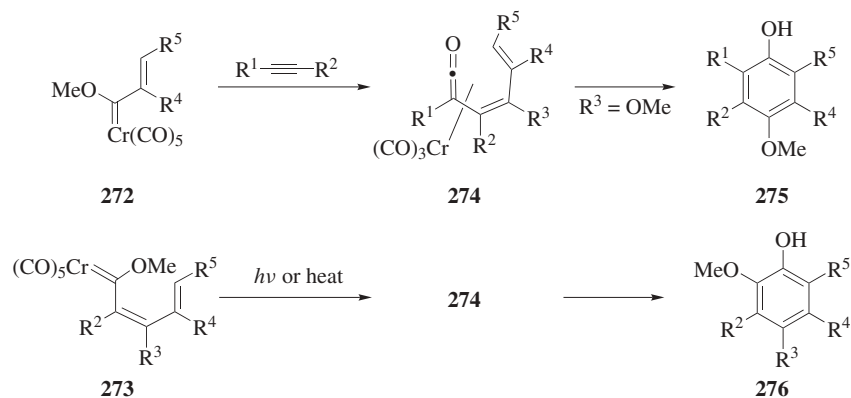


(Eq. 123)

### Ortho-Benzannulation/Cyclization of Doubly Unsaturated Complexes

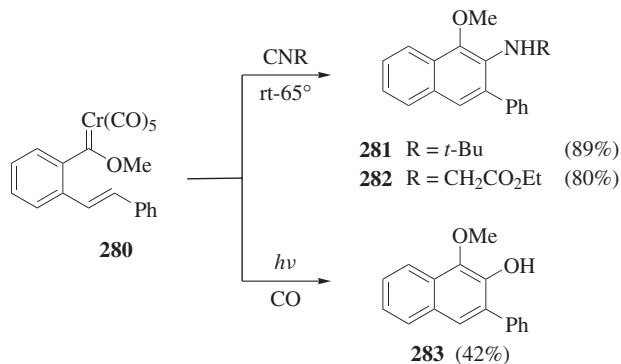
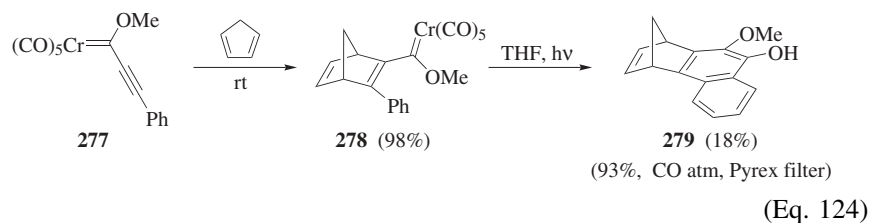
The penultimate intermediate in the formation of phenols from the thermal reaction of Fischer carbene complexes with alkynes is a doubly unsaturated ketene complex of the type **274** (Scheme 15). The typical reaction involves the carbene complex **272** and an alkyne to give the 4-methoxyphenol **275**. On the basis of the extensive photochemical studies of Fischer carbene complexes,<sup>248,249,37</sup> it was anticipated that an alternative method for access to ketene complex **274** would be the photolysis of the doubly unsaturated carbene complex **273**.<sup>250,251</sup> Photolysis should promote a CO insertion to give ketene complex **274**, and subsequent cyclization would then lead to the 2-methoxyphenol **276**. These two methods would thus be complementary as to the substitution patterns in the phenol product. Recently, the thermal conversion of certain types of complex **273** into phenols **276** has been observed.<sup>252,253</sup>

Photo-induced ortho-benzannulation of carbene complex **278** (prepared by a Diels-Alder reaction of alkynyl complex **277** with cyclopentadiene) gives the ring-fused 2-methoxynaphthol **279** in 18% yield (Eq. 124).<sup>250,251</sup> The yield of this reaction is dramatically improved (93%) when the reaction is carried out in a Pyrex vessel under an atmosphere of carbon monoxide.<sup>254</sup> 2-Methoxyanilines

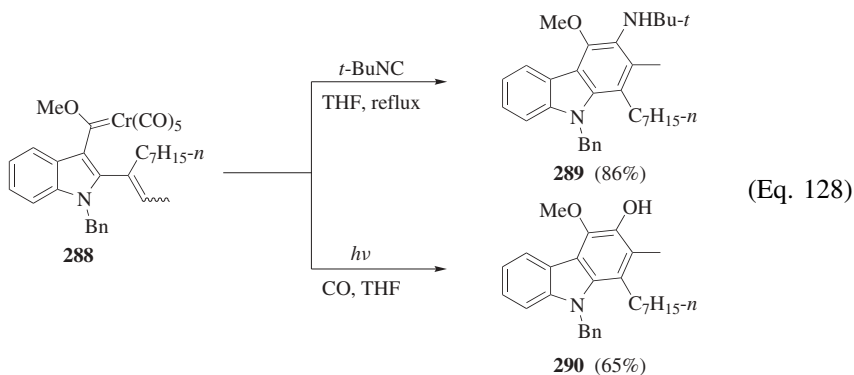
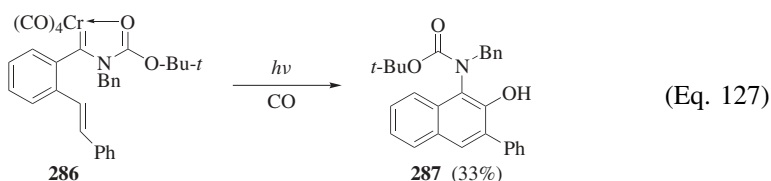
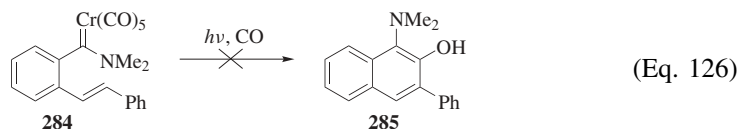


Scheme 15

and 2-methoxyaminonaphthalenes are produced by thermal reaction of doubly unsaturated carbene complexes with isocyanides.<sup>255</sup> This reaction presumably proceeds via the iminoketene analog of **274** (Scheme 15). For example, complex **280** reacts with *tert*-butyl isocyanide to give the aminonaphthalene **281** in 89% yield, and with ethyl 2-cyanoacetate to give **282** in 80% yield, in contrast to photo-induced CO insertion into **280**, which gives the naphthol **283** in 42% yield (Eq. 125).

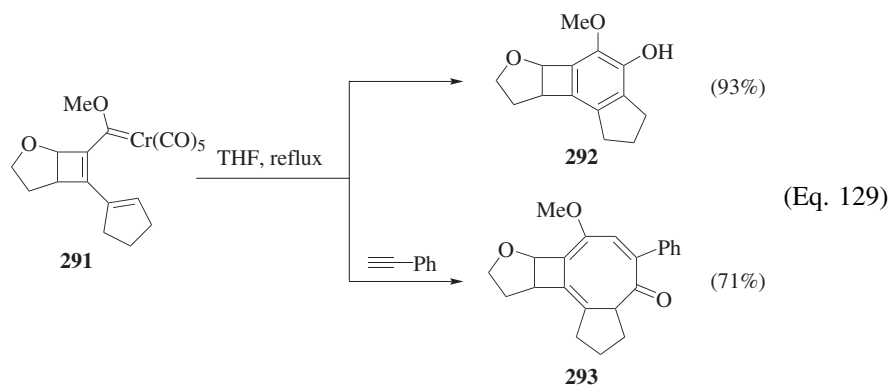


The photo-induced ortho-benzannulation reaction is not generally extendable to dialkylamino-substituted carbene complexes. The photolysis of complex **284** in the presence of CO does not give any detectable amount of the amino naphthol **285** (Eq. 126).<sup>256</sup> However, if the amino group of the carbene complex is incorporated as a carbamate, photolysis of complexes such as **286** give amino naphthols like **287** (Eq. 127).<sup>256</sup> A similar observation has been made for the scope of the thermal benzannulation of amino complexes with alkynes (Eq. 68).<sup>162,163</sup> The most general method for the synthesis of 2-amino phenols from this reaction is the thermolysis of isonitriles.<sup>255,257</sup> For example, the amino carbazole **289** is obtained in 86% yield from thermal reaction of indole carbene complex **288** with *tert*-butyl isonitrile,<sup>258</sup> compared to the 65% yield of alkoxy carbazole **290** that was obtained from the photolysis of **288** in the presence of CO (Eq. 128). Both the CO and isonitrile insertion/cyclization products from indolyl carbene complexes of the type **288** were used in the total synthesis of carbazoquinocin C.<sup>258</sup>

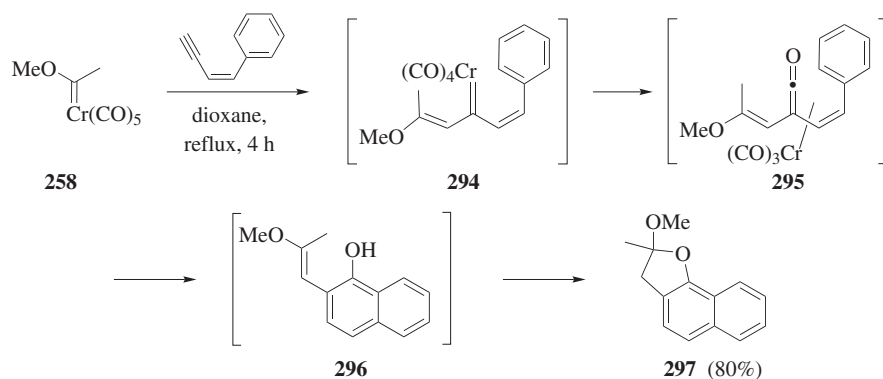


The formation of ortho-alkoxy phenols from doubly unsaturated carbene complexes can be effected thermally in good yield with certain complexes.<sup>252,253</sup> Whereas thermolysis of complex **278** in refluxing heptane affords only the *o*-methoxyphenol **279** in 29% yield (Eq. 124),<sup>254</sup> thermolysis of complex **291**

in THF produces the *o*-methoxyphenol **292** in 93% yield (Eq. 129). This thermal reaction was found to be synthetically viable only for a variety of cyclobutenylcarbene complexes, presumably because of the strain in the four-membered ring.<sup>253</sup> These cyclobutenyl complexes are also unique in that their reactions with alkynes produce eight-membered ring compounds like **293**.<sup>54</sup>



An alternative entry into dienyl ketenes of the type **274** (Scheme 15) involves reactions of Fischer carbene complexes with alkynes that are conjugated to doubly unsaturated groups.<sup>51,129,130,259,260</sup> The reaction of complex **258** with (*Z*)-4-phenyl-3-buten-1-yne gives the naphthalene derivative **297** in 80% yield (Scheme 16).<sup>51</sup> In these reactions, the vinyl ketene intermediate **295** is formed by addition of the carbene complex **258** to the terminal alkyne function to give the new complexed vinyl carbene intermediate **294**. Subsequent CO insertion to give **295** followed by cyclization affords phenol **296**, which is isolated as cyclized product **297**.<sup>51</sup>



Scheme 16

## APPLICATIONS TO SYNTHESIS

A large number of reactions of Fischer carbene complexes have been employed in organic synthesis and undoubtedly the reaction that has been most widely used in organic complex molecule synthesis is the benzannulation reaction with alkynes. The benzannulation reaction has been used in the total syntheses of a variety of natural products including vitamins K<sub>3</sub> and K<sub>1(20)</sub>,<sup>261</sup> vitamins in the K<sub>1</sub> and K<sub>2</sub> series,<sup>262</sup> vitamin E,<sup>263</sup> nanaomycin A and deoxyfrenolicin,<sup>86,90,152,218</sup> 7-ethoxyprococene,<sup>69</sup> khellin,<sup>264,115</sup> sphondin,<sup>114</sup> thiosphondin,<sup>114</sup> heratomin,<sup>114</sup> angelicin,<sup>114,265</sup> visnagan,<sup>167</sup> 12-*O*-methylroyleanone,<sup>266</sup> 5-lipoxygenase inhibitors,<sup>267</sup> fredericamycin A,<sup>151,183,268,269</sup> egonol,<sup>270</sup> parvaquone,<sup>191</sup> calphostins A, B, C, and D,<sup>271,272</sup> shikonin,<sup>273–275</sup> 7-methoxyeleutherin,<sup>276</sup> bis-*N*-dimethylmuryquinone,<sup>75</sup> carbazoquinocin C,<sup>258</sup> and landomycinone.<sup>277</sup>

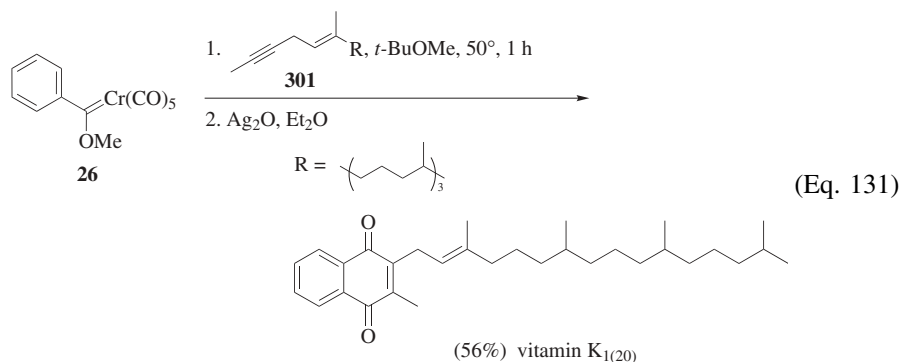
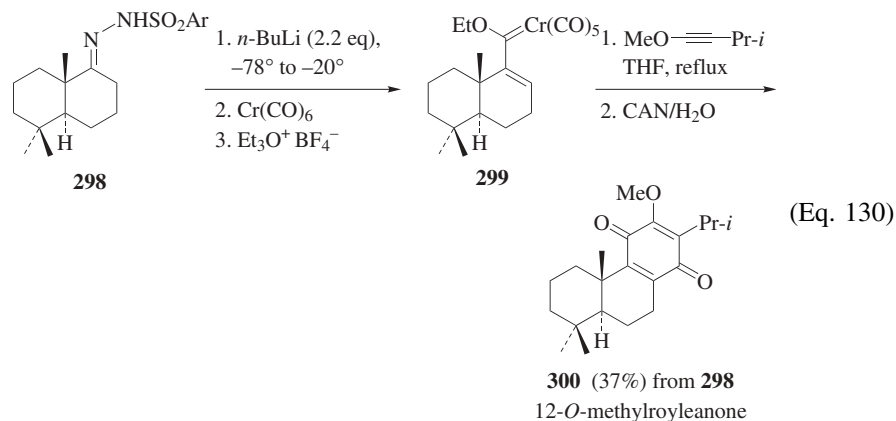
The benzannulation reaction has also been used for the synthesis of the anthracyclinone antitumor antibiotics including the formal synthesis of daunomycinone<sup>278,12,112</sup> and 11-deoxydaunomycinone<sup>158,279–281</sup>. An alternate strategy for the formal synthesis of daunomycinone and 4-demethoxydaunomycinone has also been reported,<sup>279,281–284</sup> but subsequently this synthesis has been called into question.<sup>105</sup>

Strategic models have been examined for the synthesis of several natural products including frenolicin and granaticin,<sup>214</sup> olivin and chromomycinone,<sup>285,286,113,265</sup> aspidosperma alkaloids,<sup>62,242</sup> mitomycin A,<sup>287</sup> taxodione,<sup>238</sup> nogalarol,<sup>288</sup> 11-ketosteroids,<sup>245,247</sup> oxasteroids,<sup>289</sup> gilvocarcins,<sup>290</sup> anthracyclines,<sup>159</sup> angucyclinone SF 2315A,<sup>103</sup> berberine alkaloids,<sup>291</sup> indolocarbazole natural products,<sup>292,293</sup> benzocarbazole natural products,<sup>220</sup> modified carbohydrates,<sup>294,124</sup> *C*-aryl glycosides,<sup>295,296</sup> menogaril,<sup>175,297</sup> rubromycin,<sup>298</sup> and allocolchicinoids.<sup>299,211</sup>

A selected set of total syntheses that feature the reaction of Fischer carbene complexes with alkynes is presented below and in each example the presentation begins with the key benzannulation step. The synthetic target is usually a natural product, but one example highlights benzannulation in the synthesis of a ligand for use in asymmetric catalysis. The examples were chosen to illustrate the utility of the benzannulation of alkenyl, aryl, and heteroaryl complexes, the intramolecular benzannulation, and the ortho benzannulation.

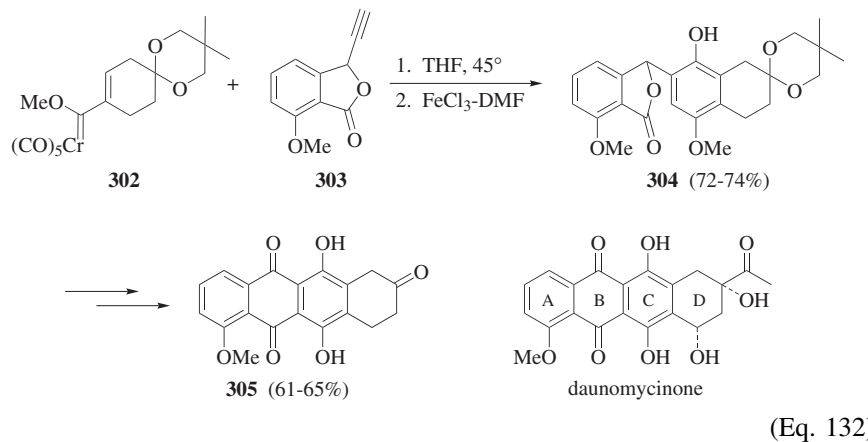
The syntheses of 12-*O*-methylroyleanone<sup>266</sup> and vitamin K<sub>1(20)</sub><sup>262</sup> result directly from the benzannulation of alkenyl complex **299** and phenyl complex **26**, respectively (Eqs. 130 and 131). Decalenyne complex **299** is prepared from the hydrazone **298** upon in situ generation of the corresponding vinyl lithium. The reaction of this complex with 1-methoxy-3-methyl-1-butyne gives the target quinone **300** in 37% overall yield from **298**. The synthesis of vitamin K<sub>1(20)</sub> is actually quite straightforward once the phytyl chain is appended to the proper alkyne function. The reaction of alkyne **301** with the phenyl carbene complex **26** gives a 56% yield of vitamin K<sub>1(20)</sub> after oxidation of the 4-methoxyphenol product with silver oxide.<sup>262</sup> The same alkyne can be used in the synthesis of vitamin E.<sup>300</sup>



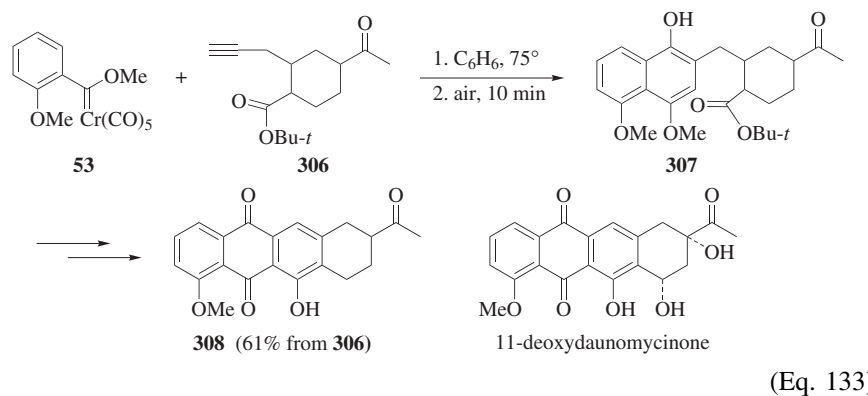


Alkenyl and aryl carbene complexes have both been used in the synthesis of anthracycline antitumor antibiotics. Daunomycinone and 11-deoxydaunomycinone are aglycones of members of the anthracycline family of antitumor antibiotics, which include agents that are among the clinically most important compounds in cancer chemotherapy (Eqs. 132 and 133). The syntheses of daunomycinone<sup>278,12</sup> and 11-deoxydaunomycinone<sup>158</sup> via Fischer carbene complexes are illustrative of the power of the benzannulation reaction to solve two of the most significant problems related to the synthesis of this family of compounds: (1) the control of the relative orientation of the A vs. D rings, and (2) a convergent method to both the 11-oxy and 11-deoxy members of the anthracycline family.<sup>301</sup>

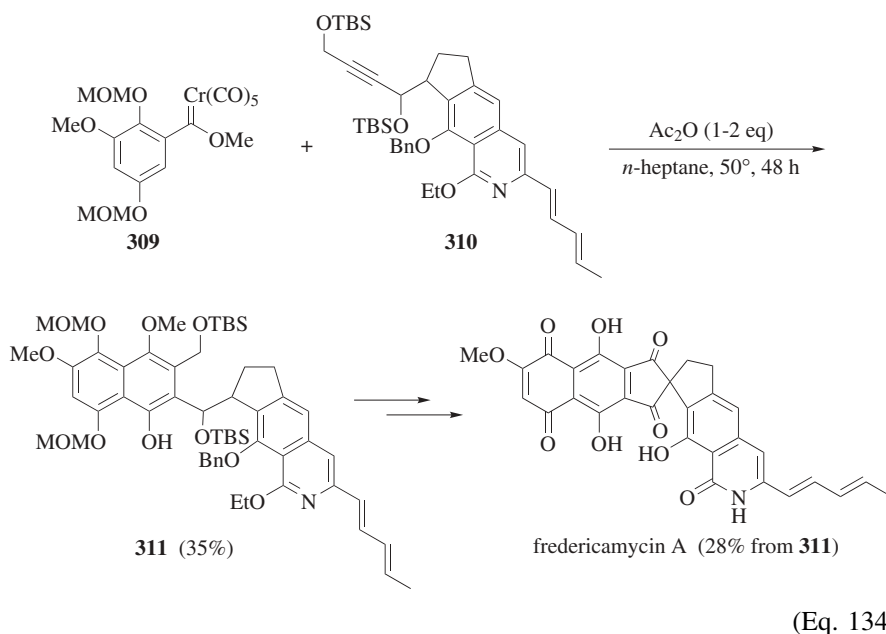
The construction of the tetracyclic quinone **305** from carbene complex **302** and alkyne **303** represents a formal synthesis of daunomycinone because its synthesis from **305** has been previously reported.<sup>302</sup> This reaction gives a single constitutional isomer of **304** and locks in the correct relative regiochemistry of two ends of the tetracyclic target **305**. The regioselectivity is expected to be quite high because the related reaction of the cyclohexenyl complex **34** with 1-pentyne gives greater than 250:1 selectivity (Eq. 10).



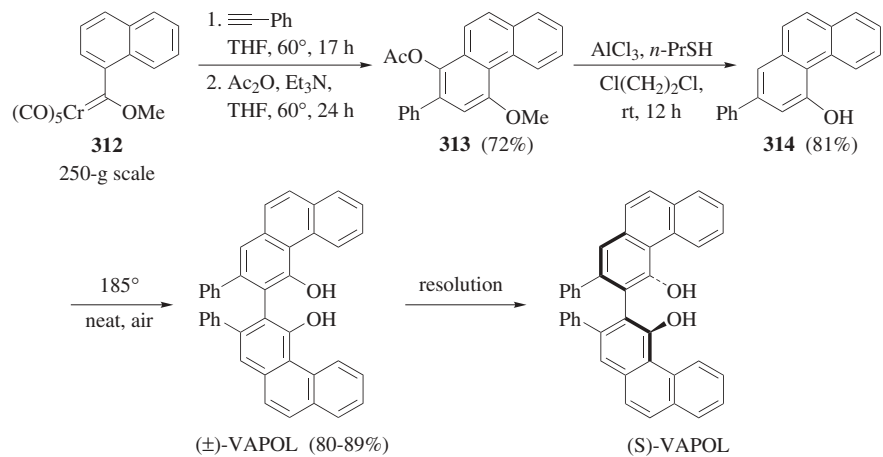
The synthesis of 11-deoxydaunomycinone is accomplished with an inverted strategy compared to that for daunomycinone in that it incorporates the aromatic A-ring in the carbene complex and the saturated D-ring in the alkyne (Eq. 133).<sup>158</sup> A tetracyclic intermediate can be made in a one-pot process involving a tandem benzannulation/Friedel-Crafts sequence of carbene complex **53** and alkyne **306**. Benzannulation is carried out in benzene and after completion, the reaction mixture is opened to air to oxidatively liberate product **307** from the metal. Triflic anhydride and sodium acetate are added to protect the phenol and then triflic acid is added to effect the Friedel-Crafts cyclization. Final adjustments to the oxidation state give the tetracyclic target **308** in 61% overall yield from alkyne **306**. Intermediate **308** has been previously converted into 11-deoxydaunomycinone in four steps.<sup>303</sup> The complete synthesis of 11-deoxydaunomycinone, including the four additional steps from intermediate **308**, is achieved in 8.5% overall yield from commercially available starting materials. This synthesis clearly demonstrates the efficiency of the benzannulation reaction of Fischer carbene complexes in organic synthesis.



The synthesis of fredericamycin A is a formidable task not only due to the complexity of the molecule but also because a highly oxygenated aryl carbene complex is required (Eq. 134). Depending on the substitution pattern and the nature of the substituents, these complexes can be problematic in the benzannulation reaction.<sup>151,183,268,269</sup> The 2,3,5-trioxygenated phenyl carbene complex **309** is no exception. In fact, the importance of the “acetic anhydride” effect (Eq. 81)<sup>116</sup> was made apparent in the course of this synthesis. The key benzannulation in the synthesis of fredericamycin A is the reaction of complex **309** with alkyne **310** to give the desired phenol **311** in 35% yield. In the absence of acetic anhydride no product is observed.

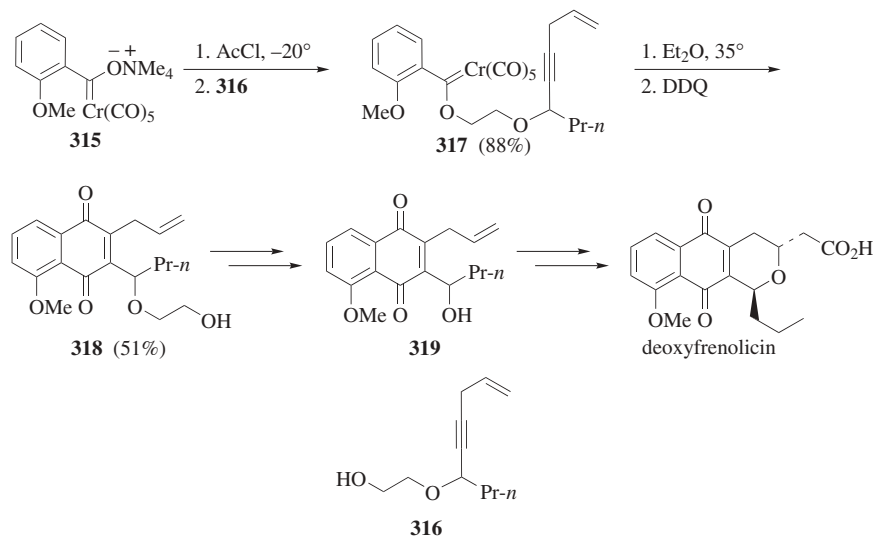


The synthesis outlined in Eq. 135 is not of a natural product, but rather of a compound that was designed and synthesized for the purpose of serving as the chiral ligand VAPOL for catalytic asymmetric synthesis. The synthesis begins with the benzannulation reaction of the 1-naphthylcarbene complex **312** and phenylacetylene,<sup>89</sup> which is carried out on a 250-gram scale to give a 72% yield of phenanthrene **313** after acetylation of the phenol.<sup>304</sup> Cleavage of the methyl ether occurs with simultaneous reduction of the acetoxy group to give 2-phenyl-4-phenanthrol (**314**) in 81% yield. Heating **314** in the presence of air at 185° gives the VAPOL ligand directly as a product of oxidative phenolic coupling. The racemic VAPOL can be resolved into its enantiomers by salt formation of a cyclic phosphoric acid derivative with (–)-cinchonidine. VAPOL has found general use in asymmetric catalysis.<sup>305–309</sup>



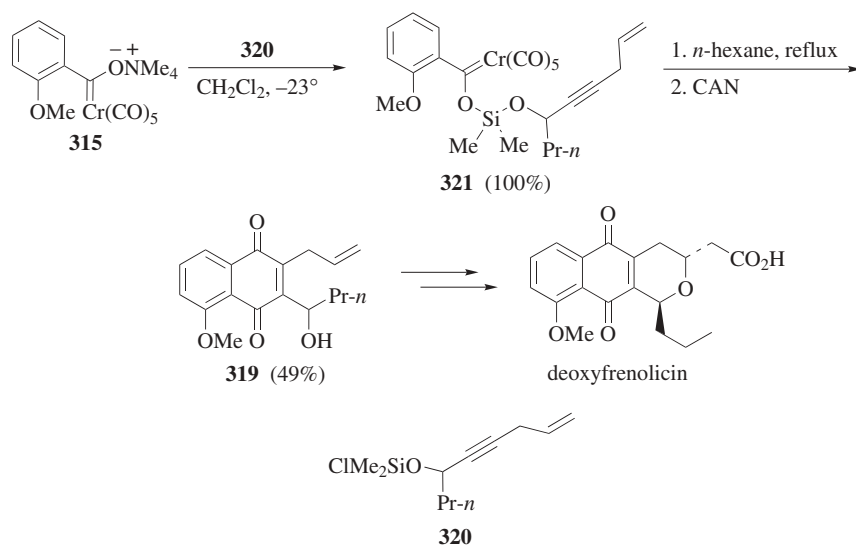
(Eq. 135)

The structural features of deoxyfrenolicin are sufficiently seductive to have inspired one formal and two total syntheses utilizing the benzannulation reaction. Since deoxyfrenolicin has a naphthalene core that is substituted in both the 2- and 3-positions, retrosynthesis to an aryl carbene complex requires a benzannulation reaction with an internal alkyne, a reaction known not to be regioselective. The first total synthesis solved the regiochemistry problem by tethering the alkyne **316** to the aryl carbene complex **315** via a  $\beta$ -alkoxyethoxy group that serves as the heteroatom stabilizing group (Eq. 136).<sup>90,214,218</sup> The key intermediate is the carbene complex **317**, which upon thermolysis and oxidative workup gives naphthoquinone **318** as a single constitutional isomer.



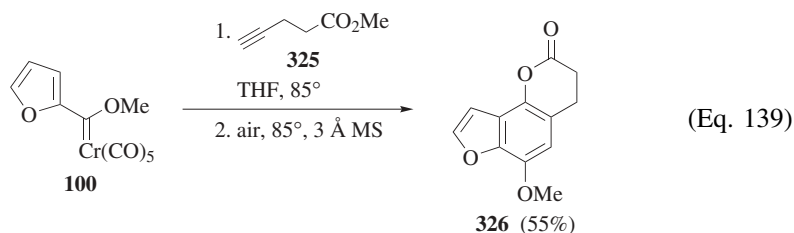
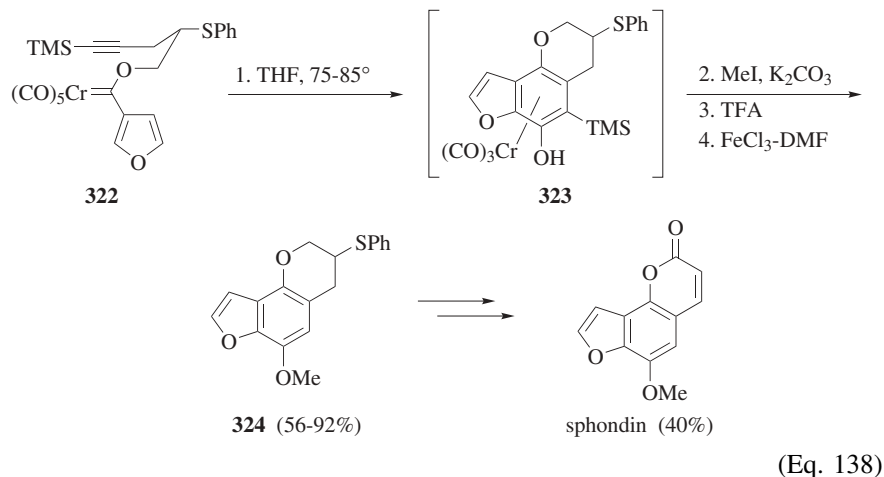
(Eq. 136)

This synthesis can be shortened and improved in overall efficiency by employing the silicon tether in carbene complex **321**, generated in situ from complex **315** and chloro(alkynyloxy)silane **320**. Complex **321** is heated in hexane to give the key intermediate **319**, which undergoes several subsequent steps to complete a formal synthesis of deoxyfrenolicin (Eq. 137).<sup>86</sup> Note that in this intramolecular reaction the product can be liberated from the silicon tether without oxidation at the alcohol function. A second total synthesis of deoxyfrenolicin has been reported in which the problem of regiochemistry is circumvented by employing a terminal alkyne. The substituent in the 3-position is introduced by an oxa-Pictet-Spengler reaction.<sup>152</sup>

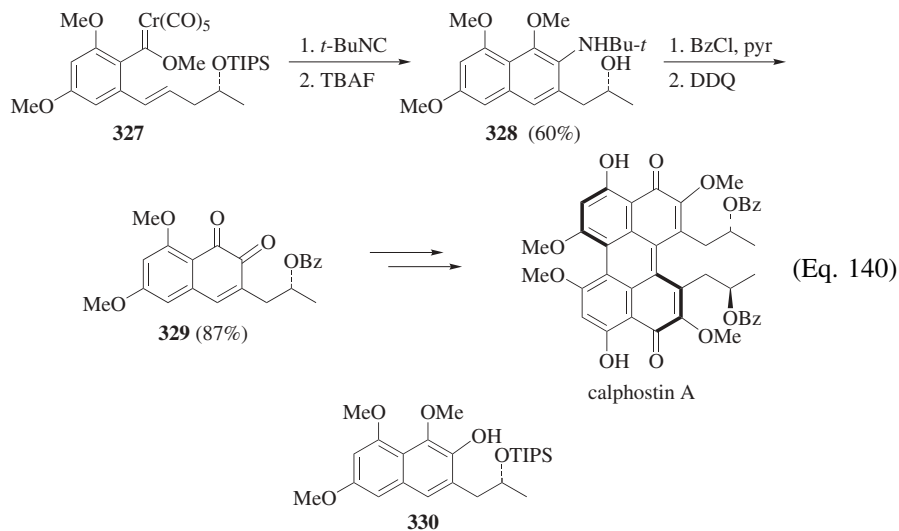


(Eq. 137)

The total synthesis of sphondin has been achieved by both an inter- and intramolecular benzannulation. The intramolecular approach involves the 3-furyl carbene complex **322** that has the alkyne tethered through the oxygen substituent of the carbene complex (Eq. 138).<sup>114,265</sup> Thermolysis of **322** leads to in situ formation of the arenechromium tricarbonyl complex **323**, which is methylated, proto-desilylated, and finally oxidatively liberated from remaining metal fragments to afford the benzofuran **324** in yields that range from moderate to excellent. The presence of the trimethylsilyl group in the intramolecular benzannulation is critical because extremely poor yields are observed for this reaction with terminal alkynes.<sup>90,114,214</sup> A more efficient synthesis of sphondin can be achieved by an intermolecular benzannulation of the 2-furyl complex **100** and alkyne **325** to generate the benzofuran **326** in 55% yield (Eq. 139).<sup>114</sup> Oxidation of **326** with DDQ produces sphondin in 40–57% yield.

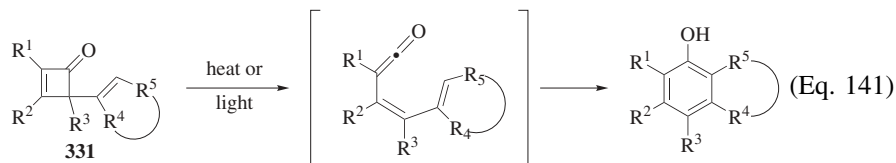


The calphostin family of natural products are potent inhibitors of protein kinase C. The synthesis of calphostin A illustrates a situation where the thermal isonitrile insertion/cyclization is superior to the photo-induced CO insertion/cyclization procedure (Eq. 125).<sup>255</sup> The presence of adjacent oxygenated carbons in one of the rings in these molecules suggested an approach utilizing the ortho-benzannulation of a Fischer carbene complex (Eq. 140).<sup>271,272</sup> The key intermediate for this synthesis is the 2-alkenyl substituted aryl complex **327**. The central disconnection in the retrosynthetic analysis leads to the ortho-quinone intermediate **329**. The photo-induced ortho-benzannulation fails to provide a synthetically viable synthesis since photolysis of complex **327** gives low yields of the ortho-methoxy phenol **330**. However, the alternative procedure involving the thermal reaction of complex **327** with an isonitrile gives the *o*-methoxynaphthylamine **328** in 60% yield. After protection of the alcohol function, **328** is oxidized to the *o*-quinone **329** in 87% yield. Quinone **329** is dimerized with trifluoroacetic acid in the presence of oxygen to give an intermediate, which upon deprotection affords calphostin A. The synthetic strategy developed for the synthesis of calphostin A has also been applied to the synthesis of calphostins B, C, and D.<sup>271,272</sup>

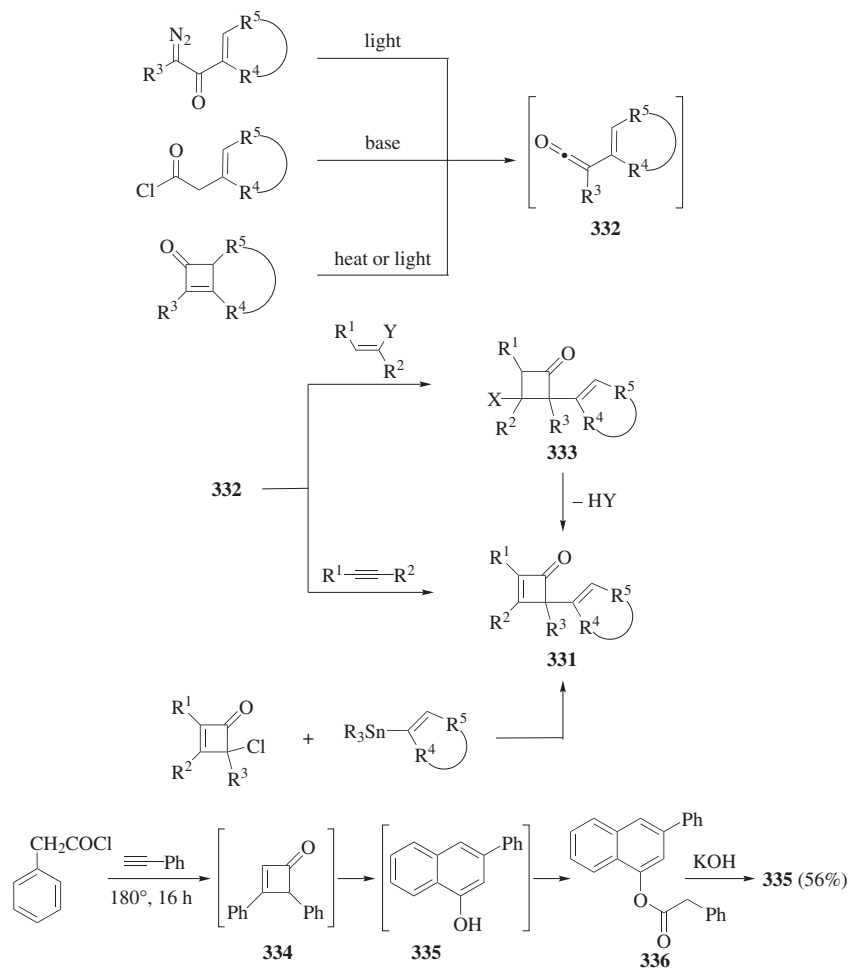


#### COMPARISON WITH OTHER METHODS

The synthesis of phenols and quinones by the reaction of Fischer carbene complexes with alkynes is broadly applicable, and provides good to excellent overall synthetic efficiency for a range of substituted phenols, naphthols, and higher polycyclic phenols. There are many other methods for construction of aromatic ring systems in general, and also for phenols and quinones in particular.<sup>310</sup> A few of these methods are closely related mechanistically to the benzannulation of carbene complexes in that they involve electrocyclic ring closure of a dienyl ketene intermediate that, however, is not coordinated to a metal center. Most of these processes involve the generation of cyclobutenones of the type **331**, and their electrocyclic ring opening to a dienyl ketene and subsequent cyclization (Eq. 141).



Many of the methods for the construction of cyclobutenones involve the [2 + 2] cycloaddition of a ketene with an alkyne (**332** to **331**, Scheme 17). This reaction can be synthetically useful with stable ketenes such as diphenylketene,<sup>311,312</sup> but not generally with simple alkynes and ketenes. One example involves the reaction of phenylacetyl chloride with phenylacetylene.<sup>313</sup> Thermally induced elimination of HCl at 180° produces phenylketene, which undergoes cyclization to the cyclobutenone **334**. Under the reaction conditions, **334** undergoes ring



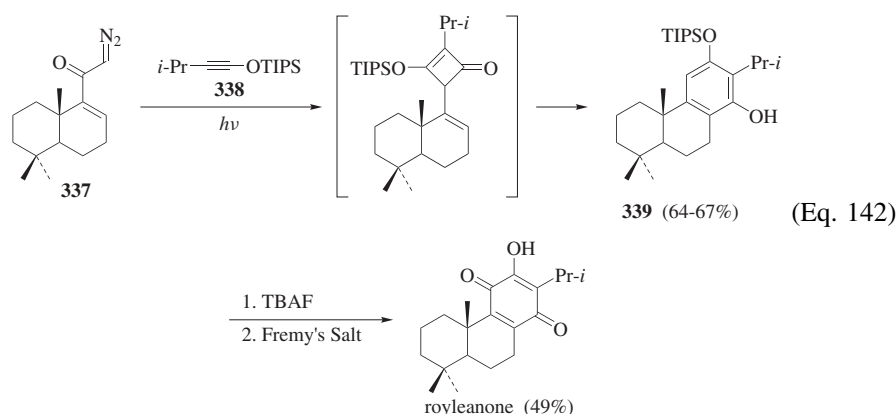
Scheme 17

opening and then cyclization to afford naphthol **335**, which in the presence of the acid chloride is acylated to provide ester **336**. Hydrolysis gives a 56% yield of naphthol **335**. The limitation of the [2 + 2] cycloaddition of ketenes with alkynes can be overcome in a two-step process involving the [2 + 2] cycloaddition of a ketene with an enol ether to provide **333** (Y = OR), followed by elimination of an alcohol to generate the phenol precursor **331**.<sup>314,315</sup> An alternative approach to cyclobutenones of the type **331** is the installation of the unsaturated substituent on the sp<sup>3</sup> carbon by a Stille coupling reaction of chlorocyclobutenones.<sup>316</sup>

A synthetically reliable synthesis of phenols via cyclobutenones has been developed on the basis of the [2 + 2] cycloaddition of ketenes with alkynyl ethers, thio ethers, and ynamines.<sup>317,318</sup> This process involves the cascade of



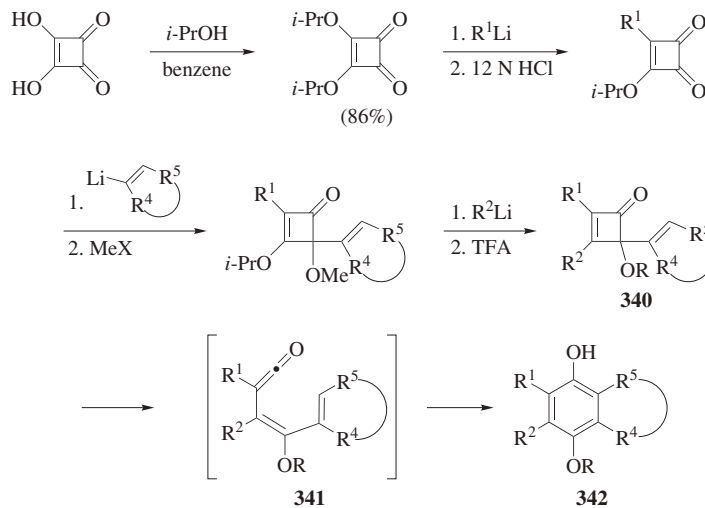
four pericyclic reactions and has been utilized in syntheses of a number of natural products. The synthesis of royleanone outlined in Eq. 142 involves a cascade of three pericyclic reactions beginning with the [2 + 2] cycloaddition of alkyne **338** with a ketene generated from the Wolff rearrangement of the diazo ketone **337**.<sup>319</sup> This reaction affords phenol **339** in 64–67% yield and subsequent silyl deprotection and oxidation completes the synthesis of royleanone. This synthesis is to be compared with the synthesis of *O*-methyl royleanone from carbene complex **299** (Eq. 130).<sup>266</sup> The synthetic route to the methyl ether via the carbene complex is a few steps shorter and proceeds with somewhat higher overall yield.<sup>319</sup>



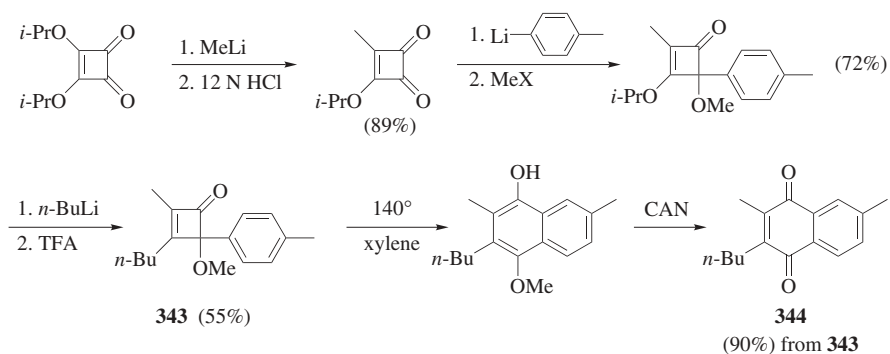
A flexible synthesis of 4-alkoxyphenols and quinones grew out of the synthesis of phenols from cyclobutenones as outlined in Scheme 18.<sup>320–325</sup> Alkoxyphenols would be the expected products when  $R^3$  in cyclobutenone **331** is an alkoxy group, that is, when cyclobutenones of the type **340** are employed (Scheme 18). Cyclobutenones **340** bearing an alkoxy substituent on the  $sp^3$  carbon tend to give higher yields of phenols upon thermolysis because the alkoxy group has a propensity for outward rotation in the electrocyclic ring opening. Thus, the unsaturated substituent preferentially undergoes inward rotation to give the ketene intermediate **341** having the correct geometry for cyclization to phenol **342**.<sup>326</sup> Cyclobutenones of the type **340** are best prepared from squaric acid.<sup>327,328</sup>

One of the key advantages of this quinone synthesis is the regiocontrolled construction of quinones as exemplified in the synthesis of quinone **344** in an overall yield of 90% from the intermediate **343** (Scheme 19).<sup>329</sup> The synthesis of the same quinone from the reaction of a 4-methylphenyl-substituted Fischer carbene complex with 2-heptyne would give a mixture of isomers in which quinone **344** would be expected as the minor isomer. Thus, although this quinone synthesis is longer than the one involving Fischer carbene complexes, it offers a much higher level of regiochemical control that is not possible with Fischer carbene complexes.

Much of the work on methods for quinone synthesis involving cyclobutenones and cyclobutenediones described above grew out of an earlier method that featured an oxidative addition of a transition-metal to a cyclobutenedione to give a metalla-cyclopentadienone followed by coupling with an alkyne to produce

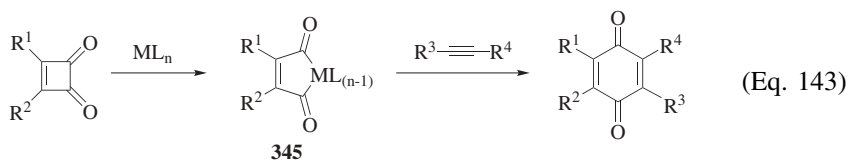


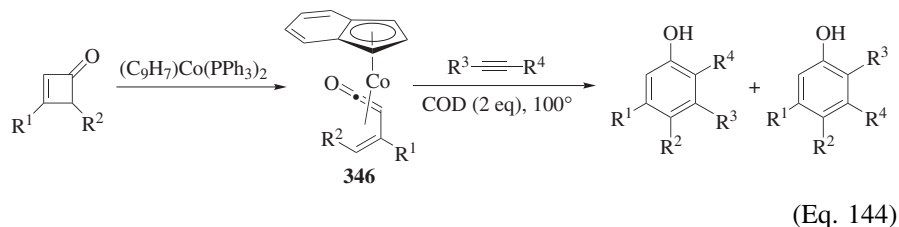
Scheme 18



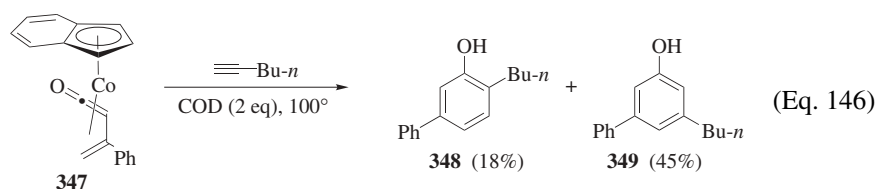
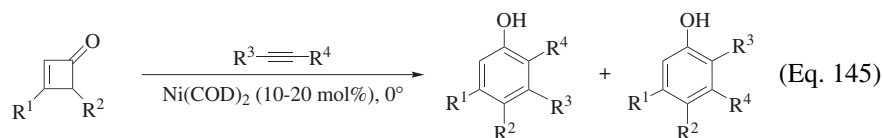
Scheme 19

quinones (Eq. 143).<sup>330,331</sup> This method can be extended to cyclobutenones where, depending on the nature of the metal, either metallacyclopentenones<sup>332</sup> or vinyl ketene complexes of the type **346** can be isolated (Eq. 144).<sup>333</sup> Subsequent reaction of complex **346** with an alkyne gives a mixture of constitutionally isomeric phenols.

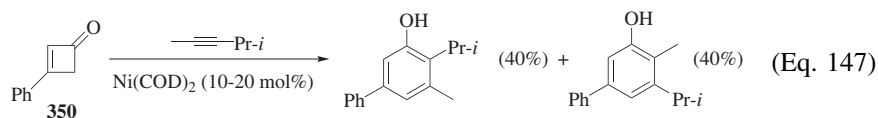




The reaction can also be performed catalytically with substoichiometric amounts of bis(cyclooctadiene)nickel resulting in facile formation of the same phenols at much reduced temperatures (Eq. 145).<sup>334</sup> Reactions of the isolated vinyl ketene complexes **346** with alkynes give good to moderate yields of phenols (Eq. 144). However, the regioselectivity is low as indicated in the reaction of **347** with 1-hexyne, which gives a 2.5 : 1 mixture of phenols **348** and **349** (Eq. 146).<sup>333</sup>

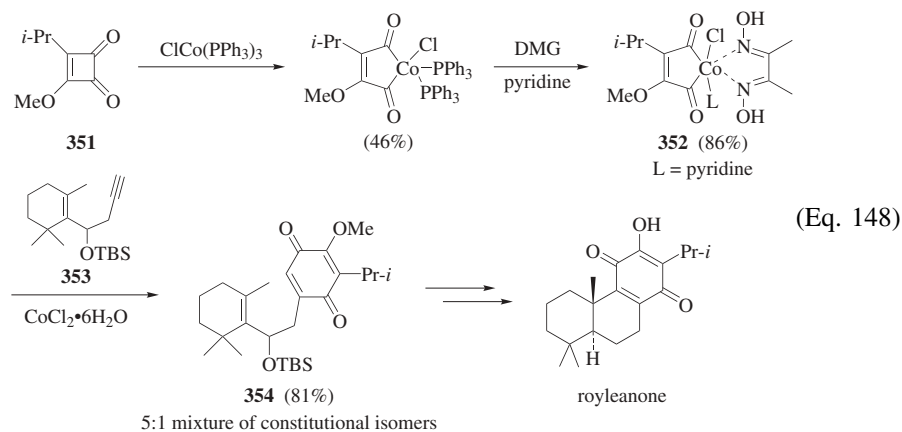


Reactions of cyclobutenones with alkynes catalyzed by Ni(0) fail to give phenolic products with terminal alkynes, but afford good to high yields with internal alkynes. The steric difference between the two substituents of the alkyne has essentially no impact on regioselectivity as noted in the reaction of cyclobutenone **350** with 4-methyl-2-pentyne, which gives an equal mixture of the two possible isomeric products (Eq. 147).<sup>334</sup>



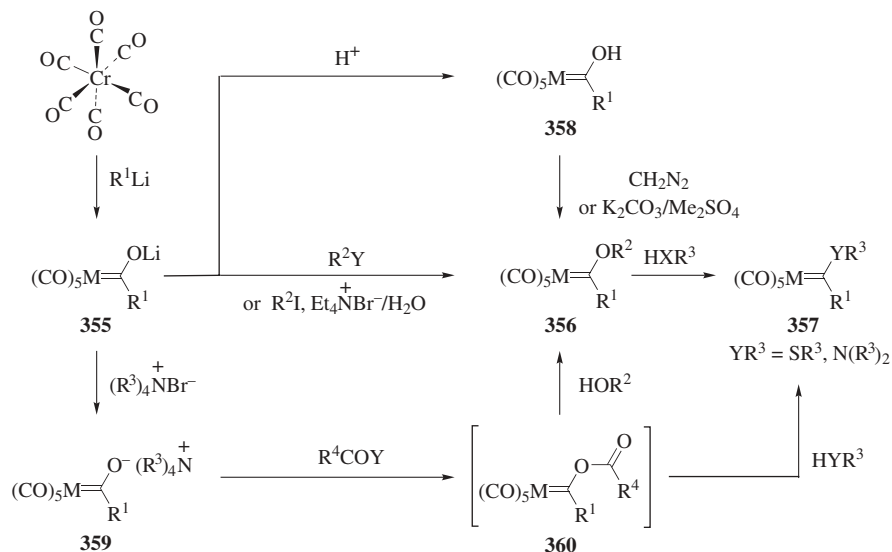
The most widely studied of the organometallic-based quinone syntheses is that involving metallacyclopentenediones of the type **345** derived from cyclobutenediones (Eq. 143). Application of this process to the synthesis of an intermediate for the natural product royleanone is illustrative (Eq. 148).<sup>335</sup> Reaction of cyclobutenedione **351** with tris(triphenylphosphine)chlorocobalt gives the corresponding metallacycle in 46% yield. Replacement of the phosphine ligands in the metallacycle with dimethylglyoxime produces the more reactive (toward alkynes)

complex **352**.<sup>336</sup> The key step in the synthesis is the reaction of complex **352** with alkyne **353** to give the quinone **354** as a 5 : 1 mixture of constitutional isomers.



#### PREPARATION OF CARBENE COMPLEXES

The most widely used method for the synthesis of Fischer carbene complexes remains the original method reported by Fischer, which involves the addition of an organolithium reagent to a metal carbonyl complex (Scheme 20).<sup>1</sup> The alkoxy complexes **356** can be obtained directly from the metal acylate **355** by in situ alkylation with trialkyloxonium salts,<sup>337</sup> alkyl fluorosulfonates,<sup>338</sup> or alkyl trifluoromethanesulfonates.<sup>339</sup> The carbon monoxide ligands in lithium acylates will rapidly exchange with free carbon monoxide and also with the acyl carbon, thus providing an efficient method for the preparation of isotopically-labeled compounds.<sup>340</sup> The reactions of acylate complexes **355** with less reactive electrophiles such as methyl iodide are not generally useful, although the direct preparation of complexes **356** with alkyl iodides in a two-phase system has been developed.<sup>341</sup> Reactivity toward a given electrophile can be increased by conversion of the lithium acylate **355** to the tetraalkylammonium acylate **359**. This enhancement is illustrated by the reaction of **359** with acid halides to generate the acyloxy complexes **360**.<sup>170</sup> These complexes are not generally stable to isolation under ambient conditions, but their reactivity can be utilized in the preparation of a variety of complexes by substitution reactions with alcohols, amines, and thiols.<sup>171</sup> The preparation of complexes of the type **356** via the acyloxy complexes **360** is more efficient when the latter are generated with an acid halide from the ammonium salt **359** than from the lithium salt **355**. Fischer was the first to demonstrate that amino and thio complexes of the type **357** could be prepared by the direct treatment of alkoxy complexes with amines and thiols.<sup>9</sup> The alkylation of **355** with dimethyl sulfate is slow and inefficient. However, high yields have been reported with this inexpensive alkylating agent from the reaction of the potassium acylate generated in situ from the hydroxy complex **358** and potassium

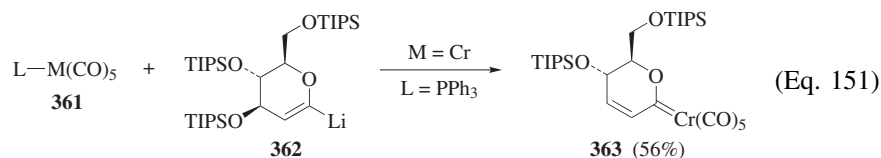
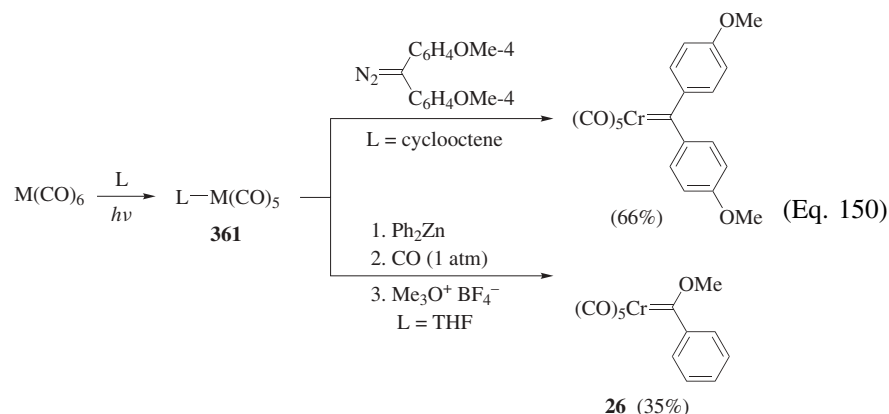
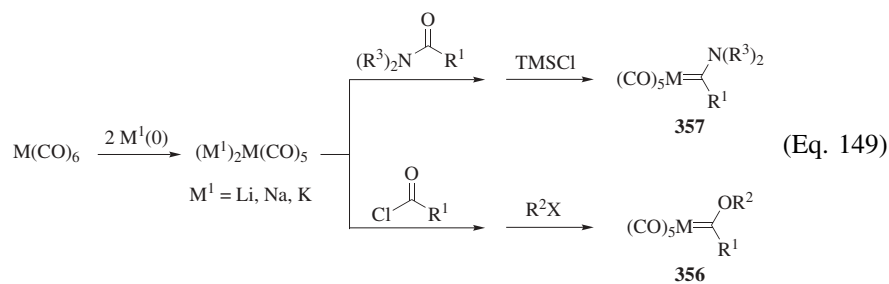


Scheme 20

carbonate.<sup>89</sup> Alkylation of the hydroxy complex with diazomethane was, in fact, the first method by which a Fischer carbene complex was produced.<sup>1</sup>

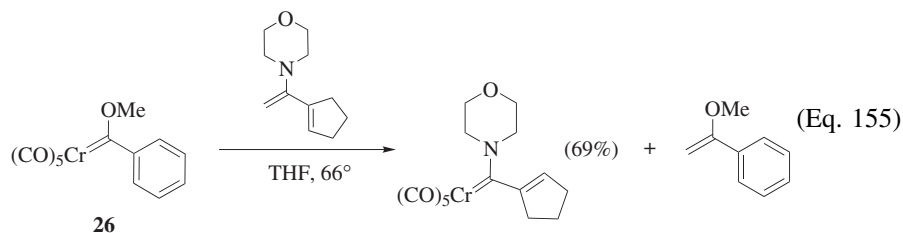
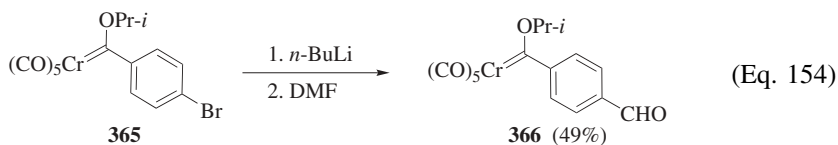
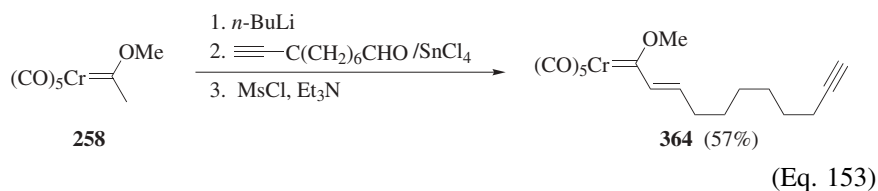
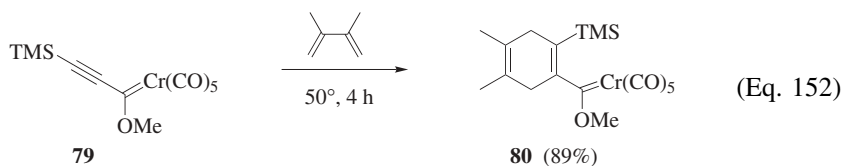
A number of "non-Fischer" methods for the synthesis of Group 6 pentacarbonyl carbene complexes have been developed and, while a comprehensive discussion of these methods is not possible here, a few select examples are shown (Eqs. 149–151). The most important of these involves the reaction of the pentacarbonyl Group 6 metal dianions with acid halides<sup>342</sup> and amides,<sup>343</sup> which can lead to efficient synthesis of alkoxy and amino carbene complexes (Eq. 149). Although these methods were originally developed with disodium salts, the dipotassium salt is the preferred choice because of the ease of purification of the resulting carbene complex.<sup>344</sup> Fischer carbene complexes can be prepared efficiently by the reaction of diazo compounds with metal pentacarbonyl derivatives of the type **361** that have an easily dissociable ligand (Eq. 150).<sup>345</sup> This method does not appear to be applicable to the preparation of complexes that have oxygen substituents on the carbene carbon.<sup>346</sup> Although Grignard reagents and other organometallic reagents less reactive than organolithiums do not provide useful yields of carbene complexes by the Fischer procedure, these reagents can potentially lead to Fischer complexes by addition to the more reactive metal precursors of the type **361** that have a labile ligand. Such a process has been reported for organozinc compounds.<sup>347</sup> After the addition of diphenylzinc to **361** (L = THF), the resulting chromium pentacarbonyl monoanion is exposed to an atmosphere of CO, presumably leading to the formation of the zinc acylate corresponding to **355**, which upon subsequent alkylation gives phenyl complex **26** (Eq. 150). Finally, a rather interesting synthesis of the stabilized complex **363** has

been reported from the reaction of the vinyl lithium derivative **362** and complex **361** ( $L = PPh_3$ ) in which the addition product suffers a conjugate elimination of triisopropylsiloxide to give the  $\alpha,\beta$ -unsaturated complex **363** (Eq. 151).<sup>143</sup>



Another important route to  $\alpha,\beta$ -unsaturated Fischer carbene complexes is the conversion of one carbene complex into another. It is not possible to even summarize the large number of classes of reactions in this category. The examples provided illustrate the types of transformations resulting in  $\alpha,\beta$ -unsaturated Fischer carbene complexes that could serve in the preparation of phenols and quinones (Eqs. 152–155). The first method (Eq. 152) involves the Diels-Alder reaction of an alkynyl carbene complex that provides cycloadduct **80**, which has been used to produce a benzannulated product (Eq. 21).<sup>112</sup> Certainly one of the most important reactions in this category is the aldol condensation of alkyl carbene complexes to give trans-1-alkenyl complexes as is illustrated by the synthesis of complex **364** (Eq. 153).<sup>348</sup> A number of useful procedures for this process have been developed over the years.<sup>156,239,348–351</sup> The carbene complex **366** obviously could not be directly prepared by the standard Fischer procedure

starting with 4-bromobenzaldehyde (Eq. 154).<sup>113</sup> The metal-halogen exchange in the 4-bromophenyl carbene complex **365** is only successful if the isopropoxy group is present to prevent attack on the carbene carbon.<sup>352</sup> Finally, the metathesis reaction of electron-rich alkenes can be a useful method for the synthesis of either amino-<sup>353</sup> or alkoxy-substituted<sup>354</sup> Fischer carbene complexes (Eq. 155).



### EXPERIMENTAL CONDITIONS

The reactions of Fischer carbene complexes with alkynes are best performed in non-polar solvents at temperatures of 45–80° under an inert atmosphere. Lower concentrations are usually required for intramolecular reactions and also to inhibit certain side-products in intermolecular reactions. However, most side-processes can be avoided by higher reaction concentrations. Many of the published procedures include deoxygenation of the reaction mixture by the freeze-thaw method. This procedure is usually taken for precautionary reasons when exploring a new reaction and looking for all primary products. For example, the 2-alkoxyfuran side-products are quite sensitive to air and often do not survive prolonged exposure. Deoxygenation by the freeze-thaw method is usually not needed for most reactions. Instead, flushing the flask with nitrogen is sufficient. In many reactions

where the yields have been compared with and without careful deoxygenation, only slight if any differences have been noted. This observation is particularly important in the development of large-scale reactions where deoxygenation by the freeze-thaw method would be impractical (see the experimental procedure for the preparation 4-methoxy-2-phenylphenanthren-1-yl acetate).

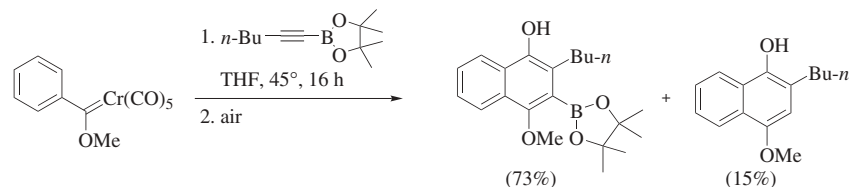
Most Fischer chromium carbene complexes are only slightly sensitive to air and can be purified by chromatography on silica gel in the presence of air with negligible losses. In large-scale preparations, purification can be accomplished by crystallization because many complexes are solids. Crystallized complexes can be stored in a refrigerator in a vial or bottle flushed with nitrogen for indefinite periods, sometimes up to several years. For some of the more air-sensitive complexes, reactions are most successful if the complex is purified just prior to use by chromatography on silica gel in the presence of air. It is extremely rare to encounter a complex that is so air sensitive that chromatography on silica gel under an inert atmosphere is required.

Air oxidation of chromium carbene complexes produces chromium(III) and even trace amounts can cause broadening in the NMR spectra. Filtration through a short plug of silica gel with  $\text{CDCl}_3$  directly into an NMR tube removes the contaminant sufficiently enough to produce high quality spectra even when the filtration is done in air. Some complexes produce trace amounts of chromium(III) upon reaction with  $\text{CDCl}_3$  and thus  $\text{C}_6\text{D}_6$  is the preferred solvent in that event. CAUTION: *Although chromium is an essential element in the +3 oxidation state, high levels of chromium(III) are toxic. In addition, the reaction of chromium carbene complexes with alkynes can produce chromium hexacarbonyl as a product of the reaction. This compound is a toxic and relatively volatile solid. Thus, these reactions should be carried out in ventilated hoods taking the normal precautions for handling toxic materials.*

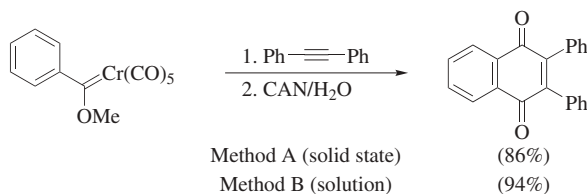
#### EXPERIMENTAL PROCEDURES

The following set of experimental procedures was chosen to illustrate a number of facets of the reactions of Fischer carbene complexes with alkynes. Methods for product isolation, of particular importance in most applications of the procedure, are reviewed in the section on Scope and Limitations. As is more fully illustrated by the following Experimental Procedures, there is a range of experimental protocols available for the production of a diverse set of functionalized products from these reactions including phenols, protected phenols, quinones, quinone acetals, arene chromium tricarbonyl complexes, and cyclohexadienones. The reaction of Fischer carbene complexes with alkynes can be a very complicated reaction that can lead to a vast array of products, potentially detracting from its synthetic utility for generating phenols and quinones. The identity of the products reflects both the choice of reaction conditions and the actual protocol employed. In most of the following procedures, the procedure and conditions have been optimized for the normal benzannulation product.





**2-Butyl-4-methoxy-3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)naphthalen-1-ol (Benzannulation with an Alkynylborane).**<sup>75</sup> To a solution of pentacarbonyl(methoxyphenylmethylene)chromium (102 mg, 0.327 mmol) in THF (6.4 mL) was added 2-(hex-1-ynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (204 mg, 0.980 mmol) via syringe under nitrogen. The reaction mixture was stirred at 45° for 14 hours and concentrated by rotary evaporation. Purification of the resulting residue by silica gel chromatography provided 4-methoxy-2-*n*-butyl-1-naphthol (11 mg, 15%) and the title compound (85 mg, 73%). The latter was crystallized from hexanes to provide an amber solid, mp 116–116.5°: IR 3445, 2991, 2977, 1662, 1142 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.42 (s, 12H), 1.47–1.72 (m, 4H), 2.73 (app t, *J* = 7.9 Hz, 2H), 3.91 (s, 3H), 4.93 (br s, 1H), 7.39–7.53 (m, 2H), 7.95–8.03 (m, 1H), 8.05–8.13 (m, 1H); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) δ 14.1, 24.7, 24.9, 30.2, 33.0, 63.5, 84.0, 121.6, 122.0, 124.3, 125.2, 125.9, 126.6, 144.4, 153.9. Anal. Calcd for C<sub>21</sub>H<sub>29</sub>BO<sub>4</sub>: C, 70.80; H, 8.20. Found: C, 70.67; H, 8.36.

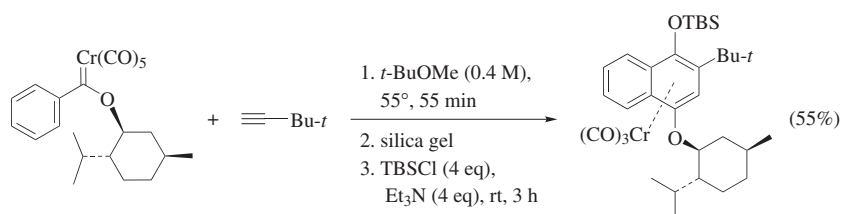


**2,3-Diphenyl-1,4-naphthoquinone (Comparison of Thermal Reaction in THF Solution with Solid-Phase Reaction on Silica Gel).**<sup>84,177</sup>

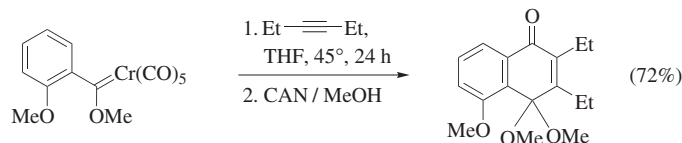
**Method A.** A suspension of pentacarbonyl(methoxyphenylmethylene)chromium (65 mg, 0.208 mmol), silica gel (2.58 g), and diphenylacetylene (46 mg, 0.258 mmol) in hexane or Et<sub>2</sub>O was stirred for 5 minutes at room temperature and the solvent was removed in vacuo. The round-bottomed flask containing the resulting orange powder was purged with nitrogen, immersed in a heated oil bath, and the contents were stirred at 40–50° until all the complex had been consumed (as indicated by TLC analysis of extracts of small aliquots of solid mixture, 3 hours). On completion of the reaction, the adsorbent was extracted with Et<sub>2</sub>O and the extracts filtered through a pad of Kieselguhr. The resulting crude phenol product was taken up in Et<sub>2</sub>O (10 mL) and treated with an aqueous ceric ammonium nitrate solution (8 eq) for 30 minutes at room temperature. The quinone was purified on a silica gel column with a 3:2 mixture of petroleum ether/CH<sub>2</sub>Cl<sub>2</sub> as eluent. 2,3-Diphenyl-1,4-naphthoquinone was obtained as a yellow crystalline

solid (56 mg, 86%), mp 139–140° (lit.<sup>355</sup> mp 141–142°): FTIR (CH<sub>2</sub>Cl<sub>2</sub>) 1670, 1601 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.10 (m, 4H), 7.23 (m, 6H), 7.81 (m, 2H), 8.21 (m, 2H).

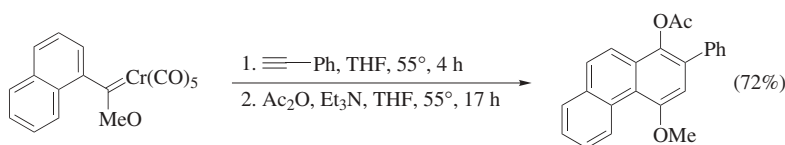
**Method B.** A solution of pentacarbonyl(methoxyphenylmethylene)chromium (0.156 g, 0.500 mmol) and diphenylacetylene (0.178 g, 1.00 mmol) in THF (1.0 mL) was deoxygenated by the freeze-thaw method and heated at 70° for 12 hours under an argon atmosphere. The reaction mixture was diluted with THF (10 mL) and water (10 mL) and then ceric ammonium nitrate (1.8 g) was added. After 20 minutes the aqueous layer was extracted twice with Et<sub>2</sub>O and the combined organic fractions were washed with water and brine, then dried over Mg<sub>2</sub>SO<sub>4</sub>. The crude reaction mixture was chromatographed on a silica gel column with a mixture of Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, and hexanes (1 : 1 : 10) to give 0.146 g (0.47 mmol) of the title compound as a yellow solid in 94% yield.



**{*tert*-Butyl-[2-*tert*-butyl-4-(2-isopropyl-5-methylcyclohexyloxy)naphthalen-1-yloxy]dimethylsilanyloxy}tricarbonylchromium(0) (Asymmetric Benzannulation of *O*-Menthyl Complexes).<sup>97</sup>** A solution of pentacarbonyl [[[1*S*,2*R*,5*S*]-5-methyl-2-(1-methylethyl)cyclohexyl]oxy]phenylmethylene]chromium (2 mmol) and of 3,3-dimethyl-1-butyne (8 mmol) in *tert*-butyl methyl ether (5 mL) was degassed in three cycles and warmed at 55° for 55 minutes. After cooling to room temperature and filtration over silica gel, (*tert*-butyl)chlorodimethylsilane (8 mmol) and triethylamine (8 mmol) were added and the solution was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/CH<sub>2</sub>Cl<sub>2</sub> = 5 : 1, -10°) to give 0.66 g (1.1 mmol, 55%) of the title arene complex as a red solid: *R*<sub>f</sub> = 0.27 (petroleum ether/CH<sub>2</sub>Cl<sub>2</sub> = 5 : 1); dr = 91 : 9 (based on <sup>1</sup>H NMR signals for H-3: 5.71 (s)/5.60 (s) ppm); [α] = -690° (c = 0.9, CHCl<sub>3</sub>); IR (petroleum ether) 1958, 1890, 1877 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.34, 0.53 (s, 6H), 0.80, 0.93, 1.01 (d, *J* = 7.0 Hz, 3H), 1.09 (s, 9H), 1.52 (s, 9H), 1.15–1.70 (m, 3H), 1.75 (m, 2H), 2.11 (qd, *J* = 7.0, 2.6 Hz, 1H), 2.65 (m, 1H), 4.00 (ddd, *J* = 10.6, 9.8, 5.3 Hz, 1H), 5.60 (s, 1H), 7.33 (ddd, 1H, *J* = 9.1, 6.5, 1.0 Hz, 1H), 7.45 (ddd, *J* = 8.9, 6.5, 1.0 Hz, 1H), 8.05 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ -1.0, 0.4, 16.9, 20.8, 22.2, 19.9, 23.6, 26.0, 27.0, 30.9, 31.5, 34.2, 34.9, 39.3, 48.1, 76.9, 79.7, 99.0, 101.0, 108.6, 123.4, 125.4, 126.6, 127.8, 128.9, 130.6, 234.4; MS (70 eV) *m/z* (% relative intensity): 604 (5, M<sup>+</sup>), 548 (1, M<sup>+</sup> - 2 CO), 520 (100, M<sup>+</sup> - 3 CO), 468 (1, M<sup>+</sup> - Cr(CO)<sub>3</sub>). Anal. Calcd for C<sub>33</sub>H<sub>48</sub>O<sub>5</sub>SiCr: C, 65.53; H, 8.00. Found: C, 65.43; H, 7.91.

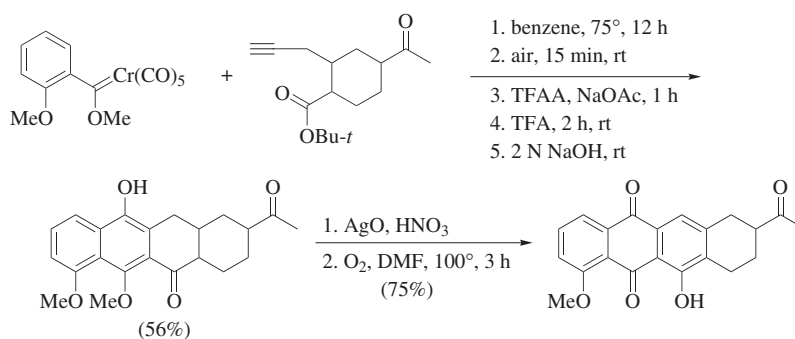


**2,3-Diethyl-4,4,5-trimethoxy-4H-naphthalen-1-one (Oxidative Workup to Quinone Monoacetals).**<sup>12</sup> A solution of pentacarbonyl[methoxy(2-methoxyphenyl)methylene]chromium (0.690 g, 2.02 mmol) and 3-hexyne (0.207 g, 2.52 mmol) in THF (20 mL) was deoxygenated by the freeze-thaw method ( $-196^{\circ}/0^{\circ}$ , 3 cycles). The mixture was stirred under argon at  $45^{\circ}$  and monitored by TLC. The crude mixture was poured into a solution of ceric ammonium nitrate (7.5 eq) in anhydrous MeOH (100 mL) and stirred over powdered anhydrous  $\text{Na}_2\text{CO}_3$  (1 g). After 30 minutes the solution was diluted with of 2% aqueous  $\text{Na}_2\text{CO}_3$  (200 mL) then extracted with several portions of  $\text{Et}_2\text{O}$ . After removal of the volatiles the crude product was purified by chromatography on activity IV basic alumina with a mixture of  $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{hexanes}$  (1 : 1 : 4,  $R_f = 0.13$ ) to give the title compound in 72% yield as a white solid, mp  $88-89.5^{\circ}$  (ether/hexane);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.14 (t,  $J = 7.5$  Hz, 3H), 1.24 (t,  $J = 7.5$  Hz, 3H), 2.51 (q, 2H), 2.57 (q, 2H), 2.92 (s, 6H), 3.94 (s, 3H), 7.15 (d,  $J = 8.6$  Hz, 1H), 7.47 (t,  $J = 8.0$  Hz, 1H), 7.79 (d,  $J = 7.7$  Hz, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  13.3, 14.0, 19.4, 20.0, 51.2, 56.1, 99.5, 115.2, 118.5, 125.1, 130.0, 134.4, 142.1, 154.8, 157.3, 183.2; MS  $m/z$  (% relative intensity): 290 (18,  $\text{M}^+$ ), 275 (16), 261 (100), 259 (52), 231 (78), 135 (78), 115 (85), 91 (60), 77 (88).



**4-Methoxy-2-phenylphenanthren-1-yl Acetate (Benzannulation and In Situ Protection as an Aryl Acetate).**<sup>304</sup> An oven-dried, 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a septum was charged with pentacarbonyl(methoxy-1-naphthalenylmethylene)chromium (250 g, 0.69 mol). To this was added dry THF (1.4 L) via cannula under an inert nitrogen atmosphere. The resulting dark-red solution was purged with nitrogen for 30 minutes. The septum was replaced by a pressure-equalizing dropping funnel containing a nitrogen purged solution of phenylacetylene (91 mL, 0.83 mol) and dry THF (29 mL). The flask and its contents were heated to  $55^{\circ}$  with a heating mantle and then the phenylacetylene solution was added dropwise over a 3-hour period. The reaction mixture was stirred at  $55^{\circ}$  for an additional 1 hour or until TLC indicated that the chromium carbene complex was totally consumed. At this point triethylamine (289 mL, 2.07 mol) and acetic anhydride (196 mL, 2.07 mol) were added to the flask and the resultant mixture was stirred at  $55^{\circ}$  for 17 hours. The dark brown reaction mixture was cooled to ambient

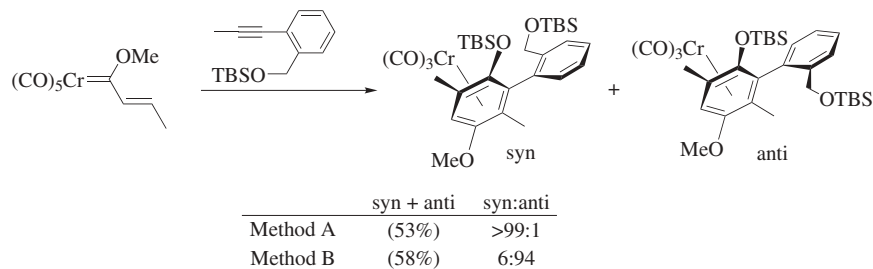
temperature, decanted into a 2-L round-bottomed flask, and the volume reduced to 1/4 of the original volume under reduced pressure (rotary evaporator). The greenish yellow precipitate was collected by filtration on a 13-cm Büchner funnel under reduced pressure and washed with EtOAc ( $3 \times 200$  mL) to afford the first crop of the yellow product. The green solid remaining in the 3-L flask was washed with EtOAc ( $3 \times 100$  mL) and the solvent decanted. The solid residue remaining was discarded, the decanted EtOAc washings were combined with the filtrate from the first crop, and the combined organic layers washed with 1 L of water and 1 L of brine. The organic layer was suction filtered through a 3-cm bed of wet packed silica gel in a 12-cm diameter Büchner funnel to remove the green chromium residue. The brown filtrate was reduced to 1/4 of its original volume under reduced pressure and the resultant precipitate was collected by filtration and washed with EtOAc ( $3 \times 50$  mL) to afford a second crop of the product as a yellow solid. The filtrate was then further concentrated to afford a third crop. The three crops were combined to provide the title compound as a light yellow solid (171 g, 72% yield based on the carbene complex). The product was further purified by flash column chromatography using EtOAc/hexane (1:9) to give a white solid, mp 160–161°;  $R_f = 0.23$  (EtOAc/hexane = 1:9); IR (neat) 3056, 2929, 2844, 1762, 1598, 1498, 1451, 1367, 1213, 1196, 1174, 1157, 1100, 1049, 815, 745, 700  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.19 (s, 3H), 4.14 (s, 3H), 7.13 (s, 1H), 7.36 (t,  $J = 7.3$  Hz, 1H), 7.43 (t,  $J = 7.6$  Hz, 2H), 7.53–7.63 (m, 4H), 7.70 (d,  $J = 8.9$  Hz, 1H), 7.78 (d,  $J = 9.0$  Hz, 1H), 7.85 (d,  $J = 7.8$  Hz, 1H), 9.62 (d,  $J = 8.8$  Hz, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  20.7, 56.0, 109.6, 119.5, 120.9, 126.3, 126.9, 127.5, 127.6, 128.3, 128.4, 128.6, 129.1, 129.3, 130.1, 131.9, 132.5, 137.3, 138.0, 156.6, 169.7; MS  $m/z$  (% relative intensity): 342 (8,  $\text{M}^+$ ), 300 (100), 285 (46), 268 (8), 255 (6), 239 (10), 226 (12), 191 (2), 155 (27), 126 (18); exact mass ( $m/z$ ) calcd for  $\text{C}_{23}\text{H}_{18}\text{O}_3$ , 342.1256; found, 342.1253. Anal. Calcd for  $\text{C}_{23}\text{H}_{18}\text{O}_3$ : C, 80.68; H, 5.30. Found: C, 80.76; H, 5.42.



**2-Acetyl-11-hydroxy-6,7-dimethoxy-2,3,4,4a,12,12a-hexahydro-1H-naphthalen-5-one and 8-Acetyl-7,8,9,10-tetrahydro-11-hydroxy-1-methoxytetra-cene-5,12-dione (One-Pot Benzannulation/Friedel-Crafts Reactions Followed by Oxidation).**<sup>158</sup> A solution of pentacarbonyl[methoxy(2-methoxyphenyl)]

methylene]chromium (0.176 g, 0.516 mmol) and *tert*-butyl 4-acetyl-2-(prop-2-ynyl)cyclohexanecarboxylate (0.163 g, 0.619 mmol) in benzene (6 mL) was deoxygenated by the freeze-thaw method ( $-196^{\circ}$  to room temperature, 3 cycles). The reaction mixture was heated under an argon atmosphere at  $60^{\circ}$  for 30 hours and then opened to air for 15 minutes. A major spot on TLC ( $R_f = 0.34$ ,  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane} = 1:1:1$ ) indicated the presence of the benzannulated product. NaOAc (98.0 mg, 0.715 mmol) was added and the mixture was stirred at room temperature for 5 minutes before trifluoroacetic anhydride (2.0 mL) was introduced. The acetylation reaction was complete in one hour after stirring at room temperature ( $R_f = 0.42$ ,  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane} = 1:1:1$ ). Trifluoroacetic acid (3 mL) was added and the resulting mixture was stirred at room temperature for 2 hours to effect the Friedel-Crafts cyclization. Only one spot was present on TLC ( $R_f = 0.29$ ,  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane} = 1:1:1$ ). To hydrolyze the trifluoroacetate, NaOH solution (4 M) was slowly added until the solution became basic ( $\text{pH} > 11$ ). After the mixture was stirred at room temperature for a half hour, HCl was added to neutralize the reaction mixture ( $R_f = 0.13$ ,  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane} = 1:1:1$ ). The mixture was extracted with  $\text{Et}_2\text{O}$  ( $6 \times 30$  mL) and the organic phases were combined and dried over  $\text{MgSO}_4$ . After removal of the volatiles, 2-acetyl-2,3,4,4a,12,12a-hexahydro-11-hydroxy-6,7-dimethoxytetracen-5(1*H*)-one was isolated by flash chromatography ( $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane} = 1:1:1$ ) in 56% overall yield.

The tetracenone intermediate was not characterized, but rather directly oxidized by treatment with silver oxide (1.28 g, 10.3 mmol) and nitric acid (2.0 N, 10.3 mL, 20.6 mmol) in acetone (20 mL) at room temperature for 30 minutes ( $R_f = 0.14$ ). After addition of buffer solution ( $\text{pH} 7$ , 10 mL) and  $\text{CH}_2\text{Cl}_2$  (50 mL), the organic phase was washed with brine and water, and dried over  $\text{MgSO}_4$ . Evaporation of the volatiles under reduced pressure gave an orange residue which was aromatized by a gentle purge with oxygen in DMF (10 mL) at  $100^{\circ}$  for 2 hours. After removal of the DMF by heating under reduced pressure, the product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane} = 1:1:1$ ,  $R_f = 0.44$ ) to give the title compound (0.109 g, 0.311 mmol, 75% yield) as an orange solid and as the sole product; mp  $222\text{--}225^{\circ}$  (lit.<sup>356</sup> mp  $222\text{--}225^{\circ}$ ). If the tetracenone intermediate is not purified, the final product was isolated in 61% overall yield from the alkyne in a one-pot seven step process. IR (neat) 2957, 2921, 2854, 1701, 1665, 1622, 1585, 1460, 1436, 1415, 1384, 1353, 1287, 1269, 1260, 1249, 1235, 1213, 1176, 1053  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.71–1.82 (m, 1H), 2.23–2.31 (m, 1H), 2.27 (s, 3H), 2.69–2.84 (m, 2H), 2.95–3.08 (m, 3H), 4.06 (s, 3H), 7.33 (d,  $J = 8.4$  Hz, 1H), 7.53 (s, 1H), 7.71 (t,  $J = 8.1$  Hz, 1H), 7.94 (d,  $J = 7.5$  Hz, 1H), 13.35 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.8, 24.5, 28.2, 31.5, 46.8, 56.7, 114.0, 118.0, 119.5, 120.1, 120.9, 129.7, 132.7, 135.6, 135.9, 144.2, 160.8, 160.8, 182.7, 188.8, 210.1; MS  $m/z$  (% relative intensity): 350 (100,  $\text{M}^+$ ), 335 (6), 308 (30), 307 (97), 306 (12), 304 (25), 291 (12), 290 (12), 289 (15), 275 (5), 189 (6), 178 (4), 166 (4), 115 (5), 77 (4), 69 (5); exact mass ( $m/z$ ) calcd for  $\text{C}_{21}\text{H}_{18}\text{O}_5$ , 350.1154; found, 350.1169.

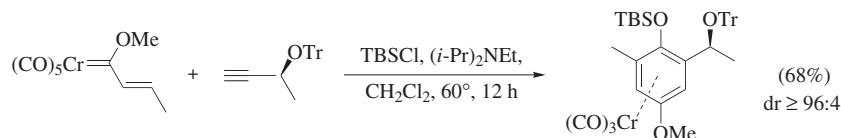


**Tricarbonyl[6-(*tert*-butyldimethylsilyloxy)-2'-(*tert*-butyldimethylsilyloxy)-oxymethyl]-3-methoxy-2,5-dimethylbiphenyl]chromium(0) (Simultaneous and Stereoselective Creation of Axial and Planar Elements of Chirality).<sup>212</sup>**

**Method A.** A magnetic stir bar was placed in a flame-dried, single-necked flask that had been modified by replacement of the 14/20 joint with a 10-mm threaded high-vacuum stopcock. The stopcock was replaced by a rubber septum and the flask was back-filled with argon. *N,N*-diisopropylethylamine (0.162 g, 1.25 mmol, distilled from KOH and freshly filtered through basic alumina) was added via syringe. Pentacarbonyl[(*ZZ*)-1-methoxy-2-butenylidene]chromium (0.102 g, 0.37 mmol, freshly purified or freshly prepared) was added to the reaction flask followed by a solution of (2-(prop-1-ynyl)benzyloxy)(*tert*-butyl)dimethylsilane (0.065 g, 0.25 mmol) in toluene (1.0 mL) and then (*tert*-butyl)chlorodimethylsilane (0.113 g, 0.75 mmol) was added via syringe. The septum was replaced by the threaded stopcock and the reaction mixture was deoxygenated using the freeze-thaw method (three cycles). The reaction flask was left to warm to room temperature, after which it was back-filled with argon, sealed with the stopcock, covered with aluminum foil, and heated to 50° for 24 hours. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator and subjected to silica gel chromatography. Elution with a mixture of pentane and CH<sub>2</sub>Cl<sub>2</sub> (3:1) gave the title compound (88 mg, 53% yield) as a yellow oil which was determined by <sup>1</sup>H NMR to be ≥99:1 syn:anti. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz) δ -0.64 (s, 3H), -0.17 (s, 3H), 0.17 (s, 6H), 0.80 (s, 9H), 0.97 (s, 9H), 1.86 (s, 3H), 2.22 (s, 3H), 3.78 (s, 3H), 4.97 (d, *J* = 7.8 Hz, 1H), 5.34 (d, *J* = 7.8 Hz, 1H), 5.72 (s, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H).

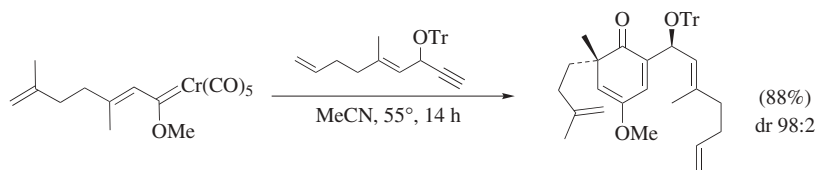
**Method B.** A magnetic stir bar was placed in a flame-dried, single-necked flask that had been modified by replacement of the 14/20 joint with a 10-mm threaded high-vacuum stopcock. The stopcock was replaced by a rubber septum and the flask was back-filled with argon. Pentacarbonyl[(*ZZ*)-1-methoxy-2-butenylidene]chromium (105 mg, 0.38 mmol) was added together with a solution of (2-(prop-1-ynyl)benzyloxy)(*tert*-butyl)dimethylsilane (65 mg, 0.25 mmol) in toluene (1.0 mL). The septum was replaced by the threaded stopcock and the reaction mixture was deoxygenated using the freeze-thaw method (-196° to room temperature, three cycles). At the end of the third cycle (room temperature), the reaction flask was back-filled with argon, sealed with the stopcock,

covered with aluminum foil, and heated in an oil bath at 50° for 48 hours. After cooling to room temperature, the reaction flask was placed under a positive flow of argon, and *N,N*-diisopropylethylamine (0.218 mL, 1.25 mmol) and (*tert*-butyl)chlorodimethylsilane (0.113 g, 0.75 mmol) were added to the reaction flask. The flask was deoxygenated by the freeze-thaw method (−196° to room temperature, two cycles) and heated for an additional 24 hours at 50°. After being cooled to room temperature, the reaction mixture was concentrated on a rotary evaporator and the product was purified by silica gel chromatography (pentane/CH<sub>2</sub>Cl<sub>2</sub> = 3 : 1) to provide the title compound as a yellow oil (92 mg, 58%). The product was determined by <sup>1</sup>H NMR to be a 96 : 4 mixture of anti to syn diastereomers. The same ratio was found in the <sup>1</sup>H NMR of the crude reaction mixture. The diastereomers are not separable by TLC or silica gel chromatography. Anti-isomer: IR (neat) 2930, 2857, 1955, 1880, 1463, 1409, 1255, 1159, 1119, 1077, 914, 837, 778 cm<sup>−1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz) δ −0.49 (s, 3H), −0.04 (s, 3H), −0.03 (s, 3H), 0.04 (s, 3H), 0.73 (s, 9H), 0.85 (s, 9H), 1.80 (s, 3H), 2.20 (s, 3H), 3.70 (s, 3H), 4.28 (d, *J* = 13.6 Hz, 1H), 4.56 (d, *J* = 13.6 Hz, 1H), 7.40 (m, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H).



**{*tert*-Butyl[4-methoxy-2-methyl-6-(1-trityloxyethyl)phenoxy]dimethylsilyloxy}tricarboylchromium(0) (Central to Planar Chirality Transfer from a Chiral Propargyl Ether).**<sup>88</sup> Pentacarbonyl[(2*Z*)-1-methoxy-2-butenylidene]chromium (0.263 mmol) and a small magnetic stir bar were placed in a flame-dried, single-necked flask that had been modified by replacement of the 14/20 joint with a 10-mm threaded high-vacuum stopcock (Kontes No. 826610). The stopcock was replaced with a rubber septum and the flask was evacuated and back-filled with argon. One half of the volume of anhydrous CH<sub>2</sub>Cl<sub>2</sub> required for a 0.05 M solution of the carbene complex, optically pure (*S*)-(but-3-yn-2-yloxy)triphenylmethane (1.9 eq), *N,N*-diisopropylethylamine (5.0 eq, freshly distilled or passed through a pipette-size basic alumina column), (*tert*-butyl)chlorodimethylsilane (3.0 eq), and the remaining solvent were added via syringe. The septum was replaced with the threaded stopcock, and the reaction mixture was degassed using the freeze-thaw method (three to four cycles). Then the reaction flask was back-filled with argon, sealed with the stopcock, and the reaction mixture was heated at 60° for 6–20 hours or until all the carbene complex was consumed. After cooling to room temperature, the reaction mixture was analyzed by TLC (CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1, UV/PMA), concentrated under reduced pressure, and subjected to column chromatography (gradient elution from 0–75% CH<sub>2</sub>Cl<sub>2</sub> in hexane or pentane, column size 1.5 × 30 cm) to give the title compound (239.7 mg, 68% yield) as a yellow waxy foam,

$R_f = 0.42$  ( $\text{CH}_2\text{Cl}_2/\text{hexane} = 1:1$ ). The diastereomeric purity was determined to be greater than 96:4 by  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis with the aid of samples of each diastereomer.  $[\alpha]^{20}_{436} -298.3^\circ$  ( $c\ 5.70 \times 10^{-5}$ ,  $\text{CH}_3\text{OH}$ );  $[\alpha]^{20}_{\text{D}} -114.0^\circ$  ( $c\ 5.70 \times 10^{-5}$ ,  $\text{CH}_3\text{OH}$ ); IR (neat) 2928, 2855, 1941, 1858, 1452, 1429, 1235, 1153, 1041, 1026, 893, 829  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.14 (s, 3H), 0.15 (s, 3H), 0.76 (s, 9H), 1.51 (d,  $J = 6.3$  Hz, 3H), 2.05 (s, 3H), 3.52 (s, 3H), 4.82 (d,  $J = 2.5$  Hz, 1H), 4.85 (q,  $J = 6.3$  Hz, 1H), 5.51 (d,  $J = 2.5$  Hz, 1H), 7.12 (t,  $J = 7.0$  Hz, 3H), 7.16 (t,  $J = 7.7$  Hz, 6H), 7.36 (d,  $J = 7.5$  Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ )  $\delta$  -2.9, 17.7, 18.8, 25.8, 26.7, 56.2, 66.3, 81.6, 83.3, 88.3, 99.1, 114.1, 127.5, 127.6, 128.0, 128.1, 129.1, 129.3, 136.0, 144.6, 235.5; EIMS  $m/z$  (% relative intensity): 675 (11,  $\text{M}^+ + 1$ ), 590 (56), 538 (10), 347 (3), 330 (4), 289 (3), 243 (100), 228 (3), 207 (3), 183 (9), 165 (34), 126 (5), 105 (28); exact mass ( $m/z$ ) calcd for isomer  $\text{C}_{38}\text{H}_{42}\text{CrO}_6\text{Si}$ : 674.2156, found 674.2143.

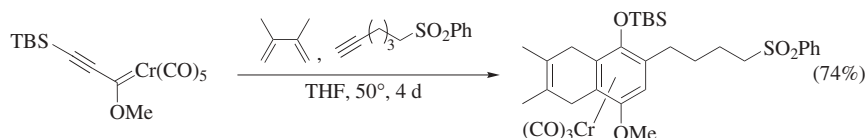


**4-Methoxy-6-methyl-6-(3-methylbut-3-enyl)-2-(3-methyl-1-trityloxyhepta-2,6-dienyl)cyclohexa-2,4-dienone (1,4-Asymmetric Induction in Cyclohexa-dienone Formation).**<sup>357</sup>

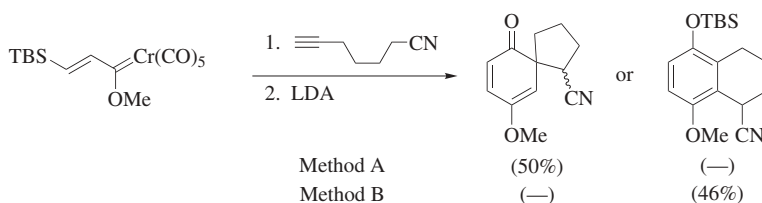
Pentacarbonyl[methoxy-1-(2,5-dimethylhexa-1,5-dienyl)methylene]chromium (0.552 mmol) and ((*E*)-5-methylnona-4,8-dien-1-yn-3-yloxy)triphenylmethane (0.28 g, 0.718 mmol, 1.3 eq) were placed in a 100-mL, flame-dried, single-necked flask that had been modified by replacement of the 14/20 joint with a 10-mm threaded high-vacuum stopcock. The stopcock was replaced by a rubber septum and the flask was evacuated and back-filled with argon. To this flask was added MeCN (50 mL), the septum was replaced by the threaded stopcock, and the reaction mixture was deoxygenated by the freeze-thaw method (three cycles). The flask was back-filled with argon, sealed with the stopcock at room temperature, and heated to 55° for 14 hours. After cooling to room temperature, the reaction mixture was opened to the air, the solvent was changed to  $\text{Et}_2\text{O}$ , and the solution was stirred for 3 hours in air. The crude mixture was concentrated, and the product purified by column chromatography (silica gel, hexane/ $\text{CH}_2\text{Cl}_2 = 1:1$ ) to yield the title compound (0.28 g, 88% yield) as a light yellow solid, dr = 98:2 as determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis with the aid of a sample of a mixture of diastereomers.  $R_f = 0.31$  (hexane/ $\text{CH}_2\text{Cl}_2 = 1:1$ ); IR (neat) 1646, 1598, 1448, 1384  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.94 (s, 3H), 1.32 (m, 3H), 1.53 (s, 3H), 1.59 (s, 3H), 1.81 (m, 1H), 2.01 (m, 2H), 2.13 (m, 2H), 3.48 (s, 3H), 4.46 (s, 1H), 4.55 (s, 1H), 4.69 (d,  $J = 3$  Hz, 1H), 4.93 (d,  $J = 10.1$  Hz, 1H), 5.01 (d,  $J = 16.8$  Hz, 1H), 5.07 (d,  $J = 9$  Hz, 1H), 5.33 (d,  $J = 9$  Hz, 1H), 5.77 (m, 1H), 6.66 (d,  $J = 3$  Hz, 1H), 7.71 (m, 9H), 7.47 (d,  $J = 8$  Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.0, 22.4, 27.1, 32.2, 32.3, 39.0, 41.2, 48.5, 54.5, 66.9,



87.8, 109.3, 109.5, 114.4, 125.3, 127.0, 127.6, 128.8, 136.0, 136.2, 138.3, 138.5, 144.6, 145.4, 150.4, 202.8.



**[[2-(4-Benzenesulfonylbutyl)-4-methoxy-6,7-dimethyl-5,8-dihydronaphthalen-1-yloxy]-*tert*-butyldimethylsilyloxy]tricarbonylchromium(0) (Tandem Diels-Alder/Benzannulation Reaction).**<sup>95</sup> Pentacarbonyl[3-[(1,1-dimethylethyl)dimethylsilyl]-1-methoxy-2-propynylidene]chromium (0.388 g, 1.037 mmol) and 1-(hex-5-ynylsulfonyl)benzene (0.166 g, 1.55 mmol) were combined in a mixture of THF (10 mL) and 2,3-dimethylbutadiene (3.5 mL). The solution was degassed (four cycles), and heated at 50° under argon for six days. Concentration and chromatographic purification on silica gel (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/hexanes = 1 : 1 : 6) gave the title compound as a yellow solid (0.409 g, 0.764 mmol, 74% yield), mp 136.5 – 138.0°; R<sub>f</sub> = 0.23 (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/hexanes = 1 : 1 : 4); IR (neat film) 1946, 1860, 1463, 1355, 1306, 1257, 1150, 1133 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.28 (s, 3H), 0.34 (s, 3H), 0.94 (s, 9H), 1.65 – 1.85 (m, 4H), 1.73 (s, 3H), 1.75 (s, 3H), 2.24 (dt, *J* = 13.8, 7.0 Hz, 1H), 2.61 (dt, *J* = 13.8, 7.0 Hz, 1H), 3.07–3.13 (m, 5H), 3.20–3.30 (m, 1H), 3.67 (s, 3H), 4.87 (s, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.87 (d, *J* = 7.1 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ –3.1, –2.1, 18.4, 18.5, 18.7, 22.4, 25.9, 28.9, 29.8, 30.8, 32.5, 55.8, 56.0, 73.8, 96.8, 102.0, 103.6, 121.4, 122.0, 125.9, 127.9, 129.3, 133.8, 136.2, 138.9, 234.7; MS *m/z* (% relative intensity): 650 (10, M<sup>+</sup>), 566 (45), 514 (100), 457 (100), 372 (20), 331 (20), 317 (75). Anal. Calcd for C<sub>32</sub>H<sub>47</sub>CrO<sub>7</sub>SSi: C, 59.06; H, 6.50. Found: C, 58.67; H, 6.14.



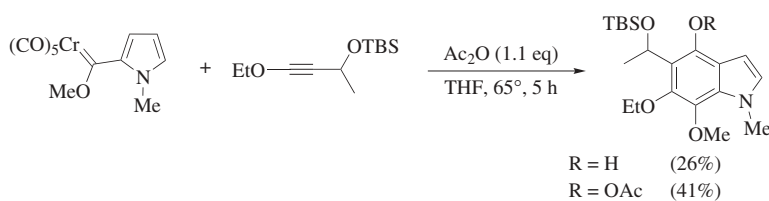
**7-Methoxy-10-oxospiro[4.5] deca-6,8-diene-1-carbonitrile and 5-(*tert*-Butyldimethylsilyloxy)-8-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (Tandem Benzannulation/Aromatic Nucleophilic Substitution).**<sup>159</sup>

**Method A.** Pentacarbonyl[(2*E*)-3-[(1,1-dimethylethyl)dimethylsilyl]-1-methoxy-2-propenylidene]chromium (0.2125 g, 0.565 mmol), 6-cyano-1-pentyne (0.0666 g, 0.621 mmol), and a small stir bar were placed in a 100-mL flask that had been modified by replacement of the 14/20 joint with a 10-mm

threaded high-vacuum stopcock. The contents of the flask were dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (11.3 mL) and deoxygenated by the freeze-thaw method. The flask was back-filled with argon at room temperature, the stopcock was replaced, and the flask sealed and heated at  $65^\circ$  under argon for 20 hours. The reaction flask was cooled to  $0^\circ$  and opened to high vacuum to strip the volatiles, followed by 2 hours at room temperature under high vacuum. The crude benzannulated product was taken up into THF (30 mL), then the flask was degassed and back-filled with argon. Under an argon stream, the threaded stopcock was replaced with a rubber septum. The flask was then cooled to  $-78^\circ$ . A deoxygenated THF solution of lithium diisopropylamide (0.847 mmol, 1.5 eq) was cooled to  $-78^\circ$  and added by cannula. The reaction mixture was stirred at  $-78^\circ$  for 1.5 hours. A  $-78^\circ$  degassed THF solution of iodine (1.15 g, 4.52 mmol, 8.0 eq) was added to the reaction mixture. After stirring the resulting solution for 1 hour at  $-78^\circ$ , the cold bath was removed. After 2.5 hours of stirring at room temperature, the mixture was poured into  $\text{Et}_2\text{O}/10\%$  aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ . The aqueous layer was extracted once with  $\text{Et}_2\text{O}$ . The combined organic layers were dried with brine and  $\text{MgSO}_4$ , filtered, and concentrated. Chromatography on silica gel ( $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{hexanes} = 1:1:6$ ) gave two separable diastereomers of the spirocyclic title compound in a combined yield of 50%; major (0.0298 g, 0.147 mmol) and minor (0.0234 g, 0.115 mmol). If the arene chromium tricarbonyl complex produced by the benzannulation reaction was first purified (69%) and then subjected to the aromatic nucleophilic addition in a second step, then the major diastereomer of the spirocyclic product was obtained in 33% overall yield and the minor in 17% overall yield. The major isomer was isolated as a colorless solid, mp  $88-90^\circ$ ;  $R_f = 0.19$  ( $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{hexane} = 1:1:4$ ); IR (neat film) 2240, 1670, 1641, 1582, 1453, 1408, 1250, 1032, 824  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.83 (quint,  $J = 6.3$  Hz, 1H), 1.94–2.00 (m, 2H), 2.04–2.16 (m, 2H), 2.39–2.46 (m, 1H), 3.31 (t,  $J = 9.1$  Hz, 1H), 3.66 (s, 3H), 5.27 (d,  $J = 2.5$  Hz, 1H), 6.09 (d,  $J = 10.1$  Hz, 1H), 6.90 (dd,  $J = 10.1, 2.7$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.9, 30.8, 39.6, 40.8, 55.1, 57.9, 105.9, 119.7, 126.6, 142.3, 150.9, 201.7; MS  $m/z$  (% relative intensity): 203 (70,  $\text{M}^+$ ), 188 (15), 175 (25), 171 (10), 161 (30), 147 (90), 137 (100), 133 (50), 122 (40), 117 (40), 105 (50), 91 (65), 77 (90); exact mass ( $m/z$ ) calcd for  $\text{C}_{12}\text{H}_{13}\text{NO}_2$ , 203.0946; found 203.0915.

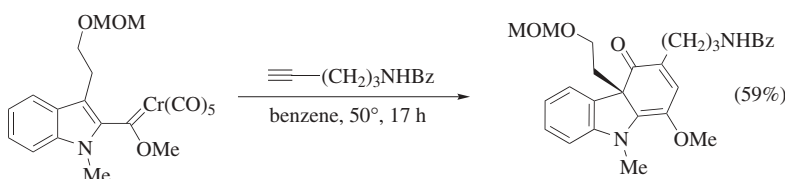
The minor isomer was isolated as an amber oil:  $R_f = 0.14$  ( $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{hexane} = 1:1:4$ ); IR (neat film) 2240, 1669, 1642, 1585, 1464, 1408, 1242  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.74–1.78 (m, 1H), 1.83–1.91 (m, 1H), 2.12–2.19 (m, 2H), 2.21–2.29 (m, 1H), 2.38–2.46 (m, 1H), 2.76 (t,  $J = 9.5$  Hz, 1H), 3.63 (s, 3H), 4.93 (d,  $J = 2.6$  Hz, 1H), 6.04 (d,  $J = 10.1$  Hz, 1H), 6.83 (dd,  $J = 10.2, 2.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.4, 30.1, 38.5, 40.5, 55.0, 58.5, 107.6, 119.5, 126.7, 141.5, 151.3, 202.0; MS  $m/z$  (% relative intensity) 203 (45,  $\text{M}^+$ ), 188 (10), 175 (15), 171(5), 161 (25), 147 (25), 137 (90), 121 (25), 107 (40), 91 (45), 77 (100); exact mass ( $m/z$ ) calcd for  $\text{C}_{12}\text{H}_{13}\text{NO}_2$ , 203.0946; found 203.0948.

**Method B.** Pentacarbonyl[(2*E*)-3-[(1,1-dimethylethyl)dimethylsilyl]-1-methoxy-2-propenylidene]chromium (0.1555 g, 0.414 mmol) and 6-cyano-1-pentyne (0.071 g, 0.66 mmol) were combined as described in Method A and heated at 65° for 21 hours. The procedure for the nucleophilic addition was the same as for the one-pot conversion to spirocycle, except that (1) the annulation residue was taken up into only 8.5 mL of THF (~0.05 M), and (2) 10 minutes after the addition of lithium diisopropylamide to the reaction mixture, the dry ice/acetone bath was replaced with an ice-water bath. After 1 hour at 0°, a deoxygenated solution of iodine (0.79 g, 3.11 mmol, 7.5 eq) in THF (5 mL) was added at 0°. The mixture was stirred at room temperature for 3 hours prior to workup as described above. Chromatography (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1 : 10) yielded the tetrahydronaphthalene title compound in 38% yield (0.0497 g, 0.157 mmol). If the arene chromium tricarbonyl complex from the benzannulation reaction was first purified (69%) and then subjected to the aromatic nucleophilic addition in a second step, the tetrahydronaphthalene product was obtained in 46% yield for the two steps. The product was a colorless solid, mp 72–74°: *R<sub>f</sub>* = 0.52 (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1 : 4); IR (neat film) 2237, 1594, 1476, 1252, 1090, 905, 861 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.22 (s, 3H), 0.23 (s, 3H), 1.02 (s, 9H), 1.80–1.84 (m, 1H), 1.88–1.94 (m, 1H), 1.95–2.04 (m, 1H), 2.25 (br d, *J* = 13.0 Hz, 1H), 2.47 (ddd, *J* = 17.7, 11.4, 5.7 Hz, 1H), 2.86 (br d, *J* = 17.4 Hz, 1H), 3.84 (s, 3H), 4.06 (br s, 1H), 6.59 (d, *J* = 8.7 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ -4.2, 18.2, 19.1, 23.6, 25.0, 25.7, 26.1, 55.7, 107.6, 117.1, 119.9, 121.7, 129.3, 147.2, 151.3; MS *m/z* (% relative intensity) 317 (65, M<sup>+</sup>), 261 (20), 233 (100), 218 (10), 159 (15), 144 (5), 129 (5), 115 (10); exact mass (*m/z*) calcd for C<sub>18</sub>H<sub>27</sub>NO<sub>2</sub>Si, 317.1811; found 317.1828.



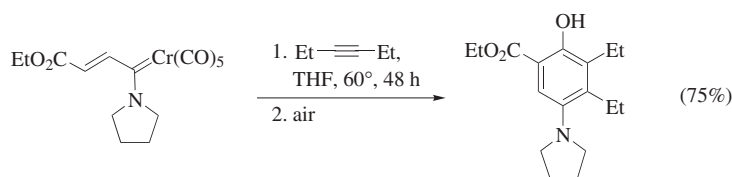
**Methyl 5-{1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-6-ethoxy-4-hydroxy-7-methoxyindole and its Acetate (Benzannulation of a Heteroaryl Carbene Complex).**<sup>115,116</sup> A solution of pentacarbonyl[methoxy(1-methyl-1*H*-pyrrol-2-yl)methylene]chromium (1.0 g, 3.2 mmol), (4-ethoxybut-3-yn-2-yloxy)(*tert*-butyl)dimethylsilane (1.5 g, 4.8 mmol), and acetic anhydride (0.3 mL, 3.2 mmol) in THF (150 mL) was heated at 65° under argon for 5 hours. The mixture was cooled, and the solvent was removed by rotary evaporation to give a black oil. Purification by flash column chromatography (silica gel, 250 g, Et<sub>2</sub>O/hexanes = 3 : 7) gave the title compound as a brown oil (309 mg, 26% yield) and its corresponding acetate as a brown oil (553 mg, 41% yield). Spectral data for the 4-acetoxyindole: IR (neat) 3334, 1637, 1494, 1324, 1288, 1056 cm<sup>-1</sup>; <sup>1</sup>H NMR

(CDCl<sub>3</sub>)  $\delta$  -0.07 (s, 3H), 0.16 (s, 3H), 0.92 (s, 9H), 1.41 (t,  $J$  = 7.0 Hz, 3H), 1.51 (d,  $J$  = 6.3 Hz, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 4.09 (q,  $J$  = 7.0 Hz, 2H), 5.45 (q,  $J$  = 6.3 Hz, 1H), 6.49 (d,  $J$  = 3.1 Hz, 1H), 6.78 (s,  $J$  = 3.1 Hz, 1H), 8.86 (s, 1H); MS  $m/z$ : 379 (M<sup>+</sup>), 363, 247, 218. Anal. Calcd for C<sub>20</sub>H<sub>33</sub>NO<sub>4</sub>Si: C, 63.28; H, 8.76; N, 3.69. Found: C, 63.25; H, 8.81; N, 3.52.



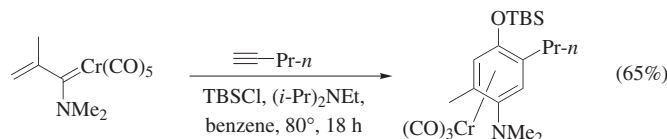
***N*-{3-[1-Methoxy-4a-(2-methoxymethoxyethyl)-9-methyl-4-oxo-4a,9-dihydro-4*H*-carbazol-3-yl]propyl}benzamide (Cyclohexadienone Annulation of an Aryl Carbene Complex).<sup>62</sup>**

Pentacarbonyl[methoxy[3-[2-(methoxymethoxy)ethyl]-1-methyl-1*H*-indol-2-yl]methylene]chromium (121 mg, 0.27 mmol) was combined with *N*-(pent-4-ynyl)benzamide (76.8 mg, 0.41 mmol) in benzene (27.0 mL). The mixture was deoxygenated by the freeze-pump-thaw method and then was stirred at 50° under argon for 17 hours. Once cool, the flask was opened to air and stirred for 1 hour at room temperature. The solution was concentrated and the residue was chromatographed on 60 mL of silica gel (Et<sub>2</sub>O/hexane = 9 : 1). The principal deep purple band was collected to afford the title compound (77 mg, 0.16 mmol, 59% yield) as a viscous oil: IR (CHCl<sub>3</sub>) 2929, 2851, 1653, 1609, 1580, 1547, 1488, 1464, 1363, 1101, 993, 913 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.73–1.87 (m, 2H), 2.09 (br t,  $J$  = 6.8 Hz, 2H), 2.33–2.42 (m, 2H), 3.21 (s, 3H), 3.33 (t,  $J$  = 6.8 Hz, 2H), 3.34–3.50 (m, 2H), 3.50 (s, 3H), 3.64 (s, 3H), 4.39 (d,  $J$  = 6.4 Hz, 1H), 4.40 (d,  $J$  = 6.4 Hz, 1H), 6.71 (d,  $J$  = 7.8 Hz, 1H), 6.93 (t,  $J$  = 7.3 Hz, 1H), 6.96 (s, 1H), 7.03 (br s, 1H), 7.24 (t,  $J$  = 7.7 Hz, 1H), 7.38 (t,  $J$  = 7.7 Hz, 2H), 7.44 (t,  $J$  = 7.3 Hz, 1H), 7.83 (d,  $J$  = 7.9 Hz, 2H), 7.86 (d,  $J$  = 7.3 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  25.6, 29.4, 31.2, 38.6, 46.4, 55.1, 60.9, 61.5, 63.2, 96.3, 107.0, 120.2, 122.3, 125.1, 126.9, 127.3, 128.2, 128.3, 128.4, 129.5, 131.0, 134.7, 141.8, 146.7, 167.2, 201.6; Anal. Calcd for C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.26; H, 7.03; N, 5.76.



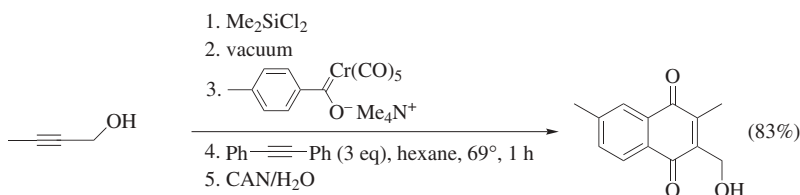
**Ethyl 3,4-Diethyl-2-hydroxy-5-(1-pyrrolidinyl)benzoate (Phenol Formation from an Activated Aminocarbene Complex).**<sup>156–157</sup> To a solution of pentacarbonyl[(2*E*)-4-ethoxy-4-oxo-1-(1-pyrrolidinyl)-2-butenylidene]chromium

(74 mg, 0.2 mmol) in THF (7 mL) was added an excess of diethylacetylene. The mixture was stirred at 60° for 48 hours and then cooled to room temperature and stirred with silica gel (1 g) for 30 minutes. The solid was filtered off and the solvent and excess alkyne were removed under reduced pressure. The resulting residue was subjected to flash chromatography on silica gel (hexane/EtOAc = 3 : 1) to yield the title compound (44 mg, 75% yield) as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.22 (m, 6H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.93 (m, 4H), 2.77 (m, 4H), 3.00 (m, 4H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.52 (s, 1H), 10.94 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.1, 14.3, 15.3, 19.5, 21.3, 24.5, 53.9, 61.0, 109.4, 118.3, 131.2, 141.1, 147.7, 156.5, 170.5. Anal. Calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub>: C, 62.53; H, 6.89; N, 4.56. Found C, 62.69; H, 6.72; N, 4.53.



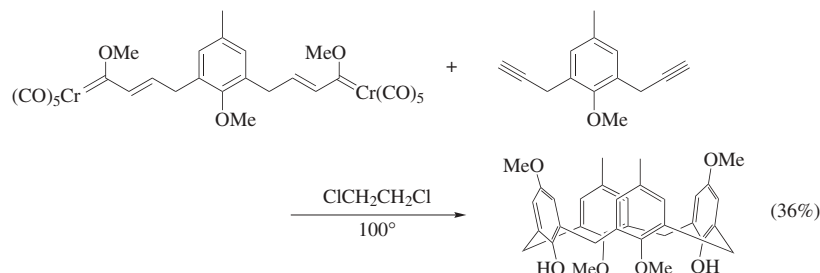
**{[4-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-propylphenyl]dimethylamino}tricarbonylchromium(0) (Generation of an Aniline Chromium Tricarbonyl Complex).**<sup>83</sup> Pentacarbonyl[1-(dimethylamino)-2-methyl-2-propenylidene]chromium (75.0 mg, 0.26 mmol) and a small magnetic stir bar were placed in a flame-dried, single-necked flask that had been modified by replacement of the 14/20 joint with a 10-mm threaded high-vacuum stopcock (Kontes No. 826610). The stopcock was replaced with a rubber septum and the flask was evacuated and back-filled with argon. One-half of the total amount of anhydrous benzene (1.0 mL) required for a 0.25 M solution of the carbene complex, 1-pentyne (48.5  $\mu$ L, 0.49 mmol, 1.9 eq), *N,N*-diisopropylethylamine (135.3  $\mu$ L, 0.78 mmol, 3.0 eq, freshly distilled and/or passed through a pipette-size basic alumina column), (*tert*-butyl)chlorodimethylsilane (78.1 mg, 0.52 mmol, 2.0 eq), and the remaining solvent were added via syringe. The septum was replaced with the threaded stopcock, and the reaction mixture was deoxygenated using the freeze-thaw method ( $-196^\circ$  to room temperature, three to four cycles). The reaction flask was back-filled with argon at the end of the last cycle, sealed with the stopcock, and heated at 80° for 17 hours. After cooling to room temperature, the reaction mixture was analyzed by TLC (CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1, UV/PMA), concentrated under reduced pressure, and the residue was subjected to column chromatography on silica gel (10-50% CH<sub>2</sub>Cl<sub>2</sub> in hexane) to give the title compound as a yellow solid (74.8 mg, 65% yield), mp 74–75°. Recrystallization from Et<sub>2</sub>O:pentane gave yellow needles: *R<sub>f</sub>* = 0.43 (CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1); IR (neat) 2959, 2932, 2861, 1951, 1868, 1473, 1364, 1266, 1172, 945, 862, 842, 784 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ 0.31 (s, 3H), 0.41 (s, 3H), 1.02 (s, 9H), 1.03 (t, *J* = 7.5 Hz, 3H), 1.59 (m, 2H), 2.19 (m, 1H), 2.24 (s, 3H), 2.61 (s, 6H), 2.63 (m, 1H), 5.05 (s, 1H), 5.50 (s, 1H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ -4.2, -3.8, 14.3, 18.4, 18.6, 24.8, 25.8, 32.7, 45.1, 86.1, 89.5, 102.0, 106.1, 126.5, 135.8, 236.0;

EIMS  $m/z$  (% relative intensity): 443 (46,  $M^+$ ), 387 (25), 359 (100), 307 (64), 250 (9), 120 (14); exact mass ( $m/z$ ) calcd for  $C_{21}H_{33}CrNO_4Si$ , 443.1584; found, 443.1566. Anal. Calcd for  $C_{21}H_{33}CrNO_4Si$ : C, 56.86; H, 7.50; N, 3.16; Cr, 11.73. Found C, 56.64; H, 7.84, N, 3.05; Cr, 11.56.

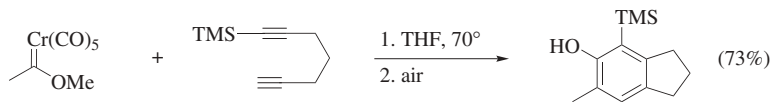


**2-Hydroxymethyl-3,6-dimethyl-1,4-naphthoquinone (Intramolecular Benzannulation with an In Situ Generated Tether).<sup>86</sup>**

2-Butyn-1-ol (500 mg, 7.1 mmol) was added dropwise at room temperature to neat dichlorodimethylsilane (9.10 g, 70.5 mmol). Immediate removal of HCl and excess dichlorodimethylsilane in vacuo provided (but-2-ynoxy)chlorodimethylsilane in quantitative yield and requiring no additional purification. The in situ preparation of pentacarbonyl[[[(2-butyloxy)dimethylsilyl]oxy](4-methylphenyl)methylene]chromium was accomplished by dropwise addition of a solution of (but-2-ynoxy)chlorodimethylsilane (84 mg, 0.52 mmol) in  $CH_2Cl_2$  (3 mL) to a stirred solution of [tetramethylammonium][[(4-(1-methylphenyl)oxido)methylene]pentacarbonyl chromium] (200 mg, 0.52 mmol) in  $CH_2Cl_2$  (20 mL). After several minutes, tetramethylammonium chloride was removed by filtration and the solvent was removed in vacuo to give the siloxy carbene complex in quantitative yield. This complex was taken up in hexane (50 mL,  $[Cr] = 0.01$  M) and diphenylacetylene (922 mg, 5.2 mmol, 10.0 eq) was added. The reaction mixture was heated to reflux with stirring and monitored by IR spectroscopy until the carbonyl ligand stretching bands of the starting siloxycarbene complex disappeared ( $\sim 1$  hour). The reaction mixture was left to cool to room temperature under an inert atmosphere after which the solvent was removed by rotary evaporation in air. The residue was taken up in  $Et_2O$  (40 mL) and treated with a solution of ceric ammonium nitrate (0.5 M, 10 mL) in 0.1 N aqueous nitric acid (10 eq). The combined aqueous and organic layers were stirred vigorously for 10 minutes. The aqueous phase was then extracted with  $Et_2O$  ( $3 \times 25$  mL), and the combined organic extracts were dried over  $MgSO_4$  and concentrated. The products were separated by flash chromatography (petroleum ether/ $EtOAc = 65 : 35$ ). The excess diphenylacetylene eluted rapidly and was recovered quantitatively. Further elution gave the title compound (93 mg, 83% yield): IR ( $CDCl_3$ ) 1665, 1622, 1602  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ),  $\delta$  2.21 (s, 3H), 2.46 (s, 3H), 4.72 (s, 2H), 6.76 (br s, 1H), 7.48 (d,  $J = 7.8$  Hz, 1H), 7.82 (s, 1H), 7.90 (d,  $J = 7.8$  Hz, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  12.2, 21.8, 58.0, 126.4, 126.9, 129.4, 131.8, 134.5, 141.9, 144.7, 145.2, 185.4, 186.0. Anal. Calcd for  $C_{13}H_{12}O_3$ : C, 72.21; H, 5.59. Found: C, 72.14; H, 5.91.

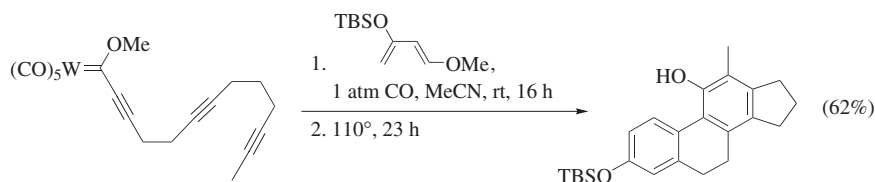


**5,17-Dimethyl-11,23,26,28-tetramethoxy-25,27-dihydrocalix(4)arene (Calix[4]arene Formation via a Triple Annulation).**<sup>223</sup> 1,3-Bis-[2'-propenyl(methoxy)methylene]pentacarbonylchromium (0)-2-methoxy-5-methylbenzene (0.188 g, 0.28 mmol) and 2-methoxy-5-methyl-1,3-di(prop-2-ynyl)benzene (0.055 g, 0.28 mmol) were dissolved in 1,2-dichloroethane (112 mL) in a flame-dried, 250-mL Schlenk flask under argon. The solution was deoxygenated by the freeze pump thaw method ( $-196^{\circ}$  to room temperature, three cycles) and then backfilled with argon at ambient temperature. The flask was sealed with a threaded high-vacuum Teflon stopcock and heated to  $100^{\circ}$  for 20–40 minutes during which time the deep red solution turned yellow. The yellow solution was stirred overnight exposed to air to facilitate demetalation of the arene chromium tricarbonyl complex. The solvent was removed under vacuum, the residue dissolved in EtOAc (50 mL), and the solution filtered through a short pad of silica gel. Further washing of the silica gel pad with EtOAc and evaporation of the solvent gave the crude calixarenes. Purification was accomplished by flash chromatography on silica gel (EtOAc/hexanes = 1 : 3), giving the title calix(4)arene (0.054 g, 0.101 mmol, 36% yield) as a white solid and as a single conformer. This compound was crystallized from acetonitrile and subjected to single crystal X-ray diffraction analyses that revealed that it exists as the cone conformer, mp  $>298^{\circ}$  (dec.)  $R_f = 0.32$  (EtOAc/hexanes = 1 : 3); IR ( $\text{CH}_2\text{Cl}_2$ ) 3297, 3055, 2988, 2937, 2835, 1600, 1481, 1433, 1285, 1228, 1124, 1055, 1009  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.03 (s, 6H), 3.27 (d,  $J = 13.2$  Hz, 4H), 3.74 (s, 6H), 3.93 (s, 6H), 4.27 (d,  $J = 12.9$  Hz, 4H), 6.61 (s, 4H), 6.72 (s, 4H), 7.59 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  20.9, 31.5, 55.8, 63.5, 113.7, 129.1, 129.7, 132.7, 134.3, 146.9, 151.3, 152.2; HRMS ( $m/z$ ): calcd for  $\text{C}_{34}\text{H}_{36}\text{O}_6$ , 540.2512; found 540.2512. Anal. Calcd for  $\text{C}_{34}\text{H}_{36}\text{O}_6$ : C, 75.53; H, 6.71. Found: C, 75.62; H, 6.60.



**6-Methyl-4-(trimethylsilyl)indan-5-ol (Regioselective Two-Alkyne Phenol Annulation).**<sup>80</sup> A deoxygenated solution of pentacarbonyl[methoxy(methyl)methylene]chromium (164 mg, 0.67 mmol) and (hepta-1,6-diynyl)trimethylsilane

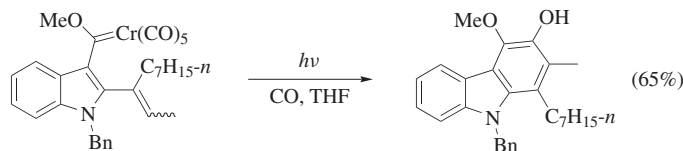
(108 mg, 0.66 mmol) in THF (7 mL) was heated at 50° for 20 hours. The mixture was then stirred in air at room temperature for 1 hour followed by filtration through a bed of Celite. After removal of the volatiles from the filtrate, the crude product was purified by chromatography on silica gel (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1 : 50) to first give the recovered carbene complex (14 mg) and then the title compound (106 mg, 0.48 mmol, 73% yield): IR (CHCl<sub>3</sub>) 3600, 2970, 1560, 1400 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.37 (s, 9H), 2.02 (m, 2H), 2.20 (s, 3H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.92 (t, *J* = 7.2 Hz, 2H), 4.73 (s, 1H), 7.01 (s, 1H); MS *m/z* (% relative intensity) 220 (30, M<sup>+</sup>) 205 (30), 204 (100), 189 (50); exact mass (*m/z*) calcd for C<sub>13</sub>H<sub>20</sub>OSi, 220.1283; found 220.1287. Anal. Calcd for C<sub>13</sub>H<sub>20</sub>OSi: C, 70.88; H, 9.09. Found: C, 71.20; H, 9.23.



**3-(*tert*-Butyldimethylsilyloxy)-12-methyl-7,15,16,17-tetrahydro-6*H*-cyclopenta[*a*]phenanthren-11-ol (Tandem Diels-Alder Two-Alkyne Phenol Annulations).**<sup>245</sup>

A 100-mL, single-necked flask equipped with a threaded high-vacuum stopcock was charged with pentacarbonyl(1-methoxy-2,6,11-tridecatrynylidene)tungsten (0.147 g, 0.28 mmol), ((*E*)-4-methoxybuta-1,3-dien-2-yloxy) (*tert*-butyl)dimethylsilane (0.0902 g, 0.42 mmol), and MeCN (5.6 mL). The solution was deoxygenated three times via the freeze-thaw method, the flask was back-filled with 1 atm of carbon monoxide and sealed, and the contents of the flask were stirred at room temperature for 16 hours. The flask was opened and the reaction mixture was diluted with MeCN (50.6 mL). The solution was degassed twice using the freeze-thaw method, and then the flask was back-filled with one atmosphere of carbon monoxide at room temperature, sealed, and placed in an oil bath at 110° for 23.5 hours. The crude reaction mixture was filtered through Celite, and after removal of solvents, the product was purified by flash chromatography on silica gel (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1 : 30, then 1 : 1 : 4) to give the title compound as a colorless oil (0.0635 g, 0.17 mmol, 62% yield); *R<sub>f</sub>* = 0.38 (Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/hexane = 1 : 1 : 16); IR (neat) 3567, 3028, 2952, 2894, 2857, 1608, 1495, 1471, 1419, 1287, 1247, 1224, 1169, 1073, 999, 969, 852, 839, 781 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.25 (s, 6H), 1.02 (s, 9H), 2.10 (quintet, *J* = 7.5 Hz, 2H), 2.23 (s, 3H), 2.65 (m, 2H), 2.68 (m, 2H), 2.88 (quintet, *J* = 7.5 Hz, 4H), 5.20 (s, 1H), 6.74 (m, 1H), 6.76 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ -4.1, 12.6, 18.2, 24.6, 25.7, 26.5, 30.0, 31.3, 32.2, 117.8, 118.2, 119.3, 119.9, 126.4, 126.6, 132.0, 132.7, 140.7, 142.8, 149.2, 154.0; MS *m/z* (% relative intensity): 380 (100, M<sup>+</sup>), 339 (14), 323 (36), 161 (8), 75 (29), 57 (14); exact mass (*m/z*) calcd for C<sub>24</sub>H<sub>32</sub>O<sub>2</sub>Si, 380.2173; found, 380.2162. Anal. Calcd for C<sub>24</sub>H<sub>32</sub>O<sub>2</sub>Si: C, 75.74; H, 8.48. Found: C, 75.36; H, 8.58.





***N*-Benzyl-1-heptyl-4-methoxy-2-methyl-9*H*-carbazol-3-ol (Photoinduced ortho-Benzannulation).**<sup>258</sup> A solution of pentacarbonyl[[2-(1-ethylideneoctyl)-1-(phenylmethyl)-1*H*-indol-3-yl]methoxymethylene]chromium (472 mg, 0.815 mmol) in THF (150 mL) in a quartz photoreactor was purged with nitrogen for 15 minutes and then purged with carbon monoxide for another 15 minutes. The solution was irradiated with a 450 W medium-pressure mercury lamp for 30 minutes at room temperature. The resulting solution was kept under a carbon monoxide atmosphere for 12 hours. The solvent was then evaporated to give a red oily residue. The residue was purified by column chromatography (EtOAc/hexanes = 3:97) to give the title compound (223 mg, 65% yield) as a light brown solid, mp 102–104°: IR (CH<sub>2</sub>Cl<sub>2</sub>) 3544, 2959, 2928, 2857 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.91 (t, *J* = 6.9 Hz, 3H), 1.20–1.40 (m, 8H), 1.42–1.64 (m, 2H), 2.38 (s, 3H), 2.74–2.84 (m, 2H), 4.06 (s, 3H), 5.65 (s, 1H), 5.66 (s, 2H), 7.04 (d, *J* = 6.8 Hz, 2H), 7.19–7.30 (m, 5H), 7.34–7.40 (m, 1H), 8.20 (dd, *J* = 7.8, 1.3 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 12.0, 14.1, 22.6, 28.2, 29.1, 29.8, 31.8, 31.8, 48.7, 60.5, 108.8, 114.7, 119.2, 121.0, 122.1, 123.0, 124.3, 125.4, 127.1, 128.8, 134.2, 138.7, 138.8, 140.6, 142.1; EIMS *m/z* (% relative intensity) 415 (65), 330 (20), 240 (80), 91 (100). Anal. Calcd for C<sub>28</sub>H<sub>33</sub>NO<sub>2</sub>: C, 80.93; H, 8.00; N, 3.37. Found C, 81.23; H, 7.84; N, 3.48.

#### TABULAR SURVEY

The literature coverage includes that cited in *Chemical Abstracts* up to mid-September of 2004, but some additional references past this time have been included. All reactions in the literature that involve the reaction of an  $\alpha,\beta$ -unsaturated Fischer carbene complex with an alkyne are included whether or not a phenol or quinone product was formed in the reaction, i. e., every example is included where a phenol or quinone product could have been produced. Not all reactions of saturated alkyl carbene complexes with alkynes are included; only those where reaction occurs to give a phenol product or phenol-derived product. The reactions of alkyl carbene complexes that give phenol products are largely the two-alkyne phenol products, which are to be found in Table 24 on miscellaneous reactions, or in Table 21 on carbene complexes with tethered alkynes.

The product distribution from the reactions of carbene complexes with alkynes can often be very sensitive to the concentration and, thus, for purposes of comparison, the concentration of the carbene complex and the number of equivalents of alkyne are given in the tables when they are reported. Most of the tables are organized by the carbon number of the alkyne that appears in the first column and then by the carbon number of the carbene complex that appears in the second

column. Tables 21 and 23 are organized by the carbon number of the carbene complex which appears in the first column. In some instances, the carbene complex that participates in the reaction is generated in situ and the organization is by the carbon number of the precursor carbene complex. The tables are subdivided by the nature of the metal, whether the alkyne is terminal or internal, and by the type of heteroatom-stabilizing group on the carbene complex. Thus the reactions of chromium, tungsten, and molybdenum complexes occur in separate tables. The reactions of chromium complexes are also separated into oxygen-, amino- and imino-, and sulfur-stabilized complexes. The exceptions to this organization are the tables on intramolecular reactions (Table 21), non-heteroatom-stabilized complexes (Table 22), and doubly unsaturated complexes (Table 23), where all examples of different metals and/or heteroatom complexes appear.

The yields for the reactions are given in parentheses, followed by a ratio of product if applicable. A dash (—) indicates that no yield is reported in the reference.

The following abbreviations have been used in the tables:

Ad	adamantyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CC	carbene complex
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp'	methylcyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomer excess
DEAD	diethylazodicarboxylate
DDQ	2,3-dichloro-5,6-dicyano- <i>f</i> -benzoquinone
DMAP	<i>N,N</i> -dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMTH	2,5-dimethyltetrahydrofuran
dr	diastereomeric ratio
ds	diastereomer selectivity
EE	2-ethoxyethyl
HMPA	hexamethylphosphoric triamide
LAH	lithium aluminum hydride
MEM	methoxyethoxymethyl
MOM	methoxymethyl
naphth	naphthyl
N-morph	<i>N</i> -morpholino
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl

pyr	pyridine, pyridinyl
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol	tolyl
Tr	triphenylmethyl (trityl)
tr	trace
Ts	<i>p</i> -toluenesulfonyl

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