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Chromene Chromium Carbene Complexes in the Syntheses of Naphthopyran and Naphthopyrandione Units Present in Photochromic Materials and Biologically Active Natural Products

Manish Rawat, Victor Prutyanov, and William D. Wulff*

Contribution from the Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received October 8, 2005; E-mail: wulff@chemistry.msu.edu

Abstract: The carbene complex 5-(2,2-dimethyl-2*H*-chromene)methoxylmethylene chromium pentacarbonyl will undergo a benzannulation reaction with phenylacetylene, 1-pentyne, 3-hexyne, and trimethylsilylacetylene to give 7-hydroxy-10-methoxy-3*H*-naphtho[2.1-b]pyrans as the primary product. These compounds are difficult to obtain pure due to their sensitivity to air. If the benzannulation reaction is performed in conjunction with protection of the phenol function at C-7, then good to excellent yields of 7-alkoxy-10-methoxy-3*H*-naphtho[2.1-b]pyrans are afforded. If the 7-hydroxy products are captured by triflic anhydride, then the resulting aryl triflate can be used to access 3*H*-naphtho[2.1-b]pyrans bearing C-7 carbon substituents. The 7-hydroxy products can be oxidized to 3*H*-naphtho[2,1-b]pyran-7,10-diones which are stable. The chromenyl carbene complex reacts with 1,6-bis(triisopropylsilyl)-1,3,5-hexatriyne to give a 2,3-dihydro-2,2-dimethylbenzo[*de*]chromene, a product type that has not been seen before in the reaction of Fischer carbene complexes with alkynes. A mechanism is proposed for this process that involves α,β-hydride elimination from a chromacyclobutane intermediate. Chromenyl tungsten complexes react with alkynes to give products that result from cyclization without CO insertion.

I. Introduction

The 3*H*-naphtho[2,1-b]pyran and related 3*H*-naphtho[2,1-b]-pyran-7,10-dione ring systems are important core units in a number of natural products[1] and also in photochromic compounds.[2] A number of natural products contain the 3*H*-naphtho-[2,1-b]pyran-7,10-dione core. Cannon and co-workers isolated nine quinones related to this family from the roots of *conospermum teretifolium*.[1b] Kimpe has recently isolated compound **5** as a natural product with the naphthopyran core, although it is oxygenated at the 7- and 10-positions (Scheme 1).[1c] The natural product **5** was isolated from the roots of *Pentas bussei*, a plant found in Kenya. The decoction of the roots is used as a remedy for gonorrhea, syphilis, and dysentery. Conocurvone is a unique natural product in that it contains three naphthopyrandione units, and this fact may be related to its remarkable anti-HIV activity.[1a] 3*H*-Naphtho[2,1-b]pyrans are known to exhibit photochromic properties which occur with the photo-induced electrocyclic ring-opening to the *ortho*-quinone methide **4**.[2] Photochromic compounds have found wide applications in which a sunlight-induced reversible color change or darkening is desired, e.g., for the manufacture of ophthalmic lenses, contact lenses, solar protection glasses, filters, camera optics, transmission devices, agrochem films, glazing, decorative objects, or information storage by optical inscription (coding).[2] The properties of molecules of the type **3** have been actively studied with such applications in mind. Several SAR studies of these molecules have resulted in the finding that the nature and the position of the substituents in the 3*H*-naphtho[2,1-b]pyrans have a significant impact on the absorption properties of these compounds.[2] Although a number of patents and publications on various naphthopyran derivatives have appeared in the past two decades, detailed studies with alkyl, aromatic, and heteroatom substituents at all positions have not been done. This is likely due, at least in part, to the limited methods to generate these compounds.

II. Background

Most of the studies of the effects of substitution of the naphthopyran nucleus on the photochromic behavior has been done at the positions 1 through 6.[2] We envisioned that a family of naphthopyrans with substitution in positions 7−10 could be accessed through the reaction of a 5-chromenyl chromium carbene complex of the type **7** with alkynes (Scheme 2).[3] This reaction would be expected to generate the naphthopyran **8** with an alkoxy group in the 10-position and a hydroxy group in position 7. Positions 8 and 9 could be introduced by proper choice of the alkyne. For terminal alkynes, the regiochemical incorporation of the alkyne in reactions with carbene complexes

(1) (a) Decosterd, L. A.; Parsons, I. C.; Gustafson, K. R.; Cardellina, J. H., II; McMahon, J. B.; Cragg, G. M.; Murata, Y.; Pannell, L. K.; Steiner, J. R.; Clardy, J.; Boyd, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 6673−6679. (b) Cannon, J. R.; Joshi, K. R.; McDonald, I. A.; Retallack, R. W.; Sierakowki, A. F.; Wong, L. C. H. *Tetrahedron Lett.* **1975**, *16*, 2795−2798. (c) Bukuru, J. F.; Van, T. N.; Puyvelde, L. V.; Mathenge, S. G.; Mudida, F. P.; Kimpe, N. D. *J. Nat. Prod.* **2002**, *65*, 783−785.

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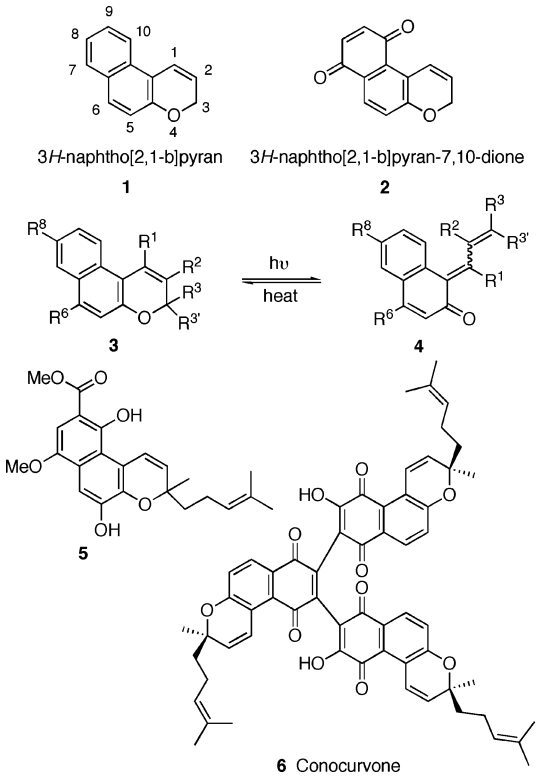
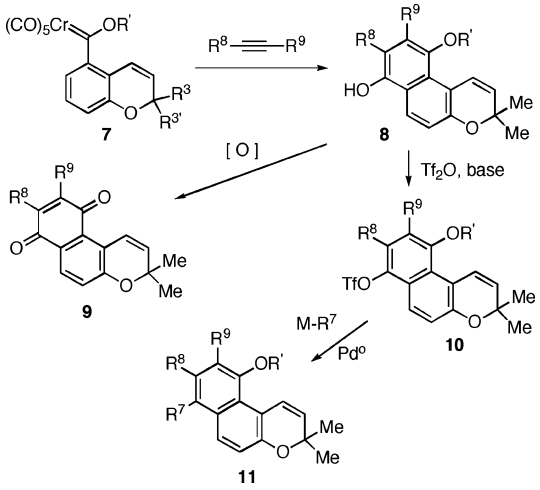
10.1021/ja0568852 CCC: $33.50

Scheme 1

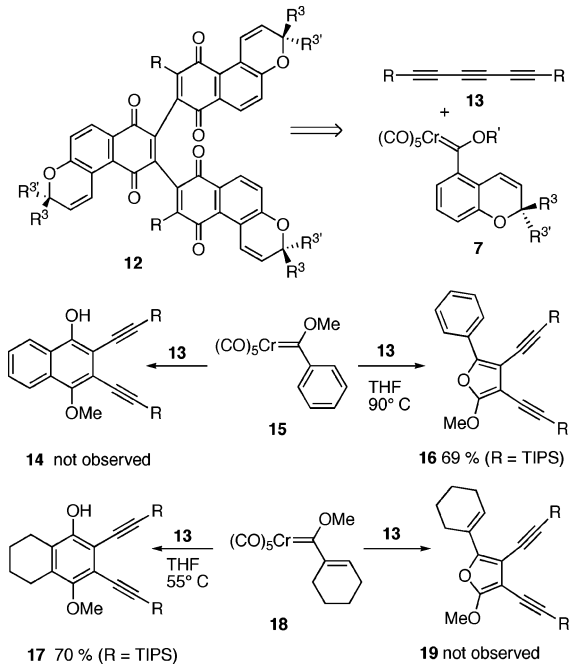


Scheme 2



is known to be very high with a single isomer produced where the alkyne substituent would be adjacent to the phenol function (C-8).[4] For internal alkynes, the regiochemical control is usually determined by the relative size of the substituents. For example, 1-phenyl-1-propyne has been observed to give a 40:1 mixture of regioisomers with the phenyl group preferentially incorporated next to the phenol function.[5] In some instances, electronics can be used to control the regiochemical incorporation of the alkyne.[6] The benzannulation product **8** could serve as a direct source of the naphthopyrandione core **9** and, furthermore, would provide the additional flexibility for the preparation of a variety of naphthopyran derivatives substituted at position 7 via various coupling reactions of the triflate **10**.

Scheme 3



While the reaction of chromenyl complex **7** with simple alkynes should be able to provide access to naphthopyrandiones of the type **9**, the reaction of complex **7** with conjugated triynes of the type **13** has the potential of providing rapid access to tris-naphthopyrandiones of the type **12** and, if this is the case, then a rather straightforward route for the total synthesis of Conocurvone **6** (Scheme 3). We have recently reported the first examples of the reaction of carbene complexes with conjugated triynes and were surprised to find that while the reaction of one equivalent of the cyclohexenyl complex **18** with triyne **13** (R = Si(*i*-Pr)$_3$) gave the expected benzannulation product **17**, the same reaction of the phenyl complex **15** gave the furan product **16** where CO insertion had occurred but not cyclization to the phenyl ring.[7] Both reactions did occur by the expected selective reaction with the less sterically hindered central alkyne unit of the triyne **13** (R = Si(*i*-Pr)$_3$), although other triynes did not show this regioselectivity. Based on these limited results, it might be expected that the chromenyl complex **7** might behave more like the phenyl complex **15** than the cyclohexenyl complex **18** and thus not be able to provide for a direct route to tris-quinones of the type **12**. Nonetheless, our limited experience with the reactions of carbene complexes with triynes suggested that surprise is the norm and not the exception. Indeed, this proved to be the case with the chromenyl complex **7**. The results

(3) For recent reviews on carbene complexes in organic chemistry, see: (a) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, R. G. A., Wilkinson, G., Eds.; Pergemon Press: 1995; Vol. 12, pp 469−547. (b) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105−4128. (c) de Meijer, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964−4002. (d) Dötz, K. H.; Tomuschatt, P. *Chem. Soc. Rev.* **1999**, *28* 187−198. (e) Herndon, J. W. *Coord. Chem. Rev.* **1999**, *181*, 177−242. (f) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, New York, 1999.

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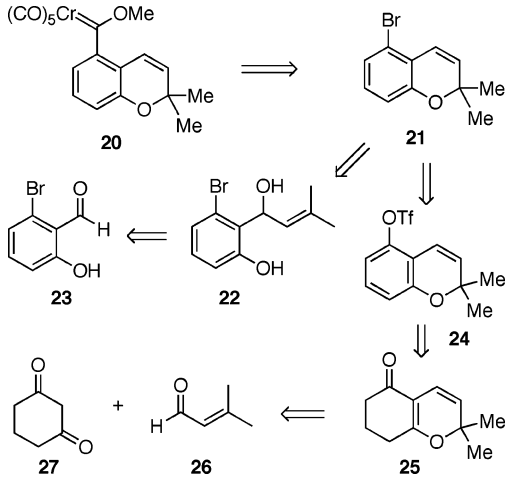
(5) Waters, M. L.; Bos, M. E.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 6403−6413.

(6) (a) Chamberlin, S.; Wulff, W. D.; Waters, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 3113−3114. (b) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Chem. Soc., Chem. Commun.* **1999**, 2107−2108.

(7) Jiang, M. X.-W.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 5970−5971.

Scheme 4



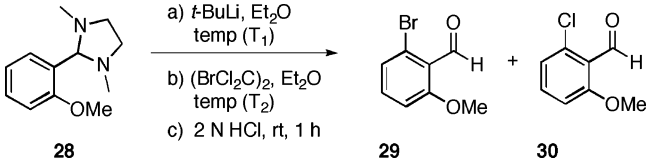
of studies described herein show that while the reaction of complex **7** with simple alkynes does in fact provide for a facile entry to naphthopyrans and naphthopyrandiones, the reaction of the chromenyl complex **7** with conjugated triynes led to an unprecedented reaction involving alkyne insertion and a subsequent addition/rearrangement process involving the double bond of the pyran ring.

III. Results and Discussion

Synthesis of the Chromium Cromenyl Carbene Complex 20. Fischer carbene complexes with aryl substituents are typically made from the corresponding aryl halides.[3] In the case of carbene complex **20**, this will require the aryl halide **21** (Scheme 4). A three-step synthesis of **21** has been reported that begins with the regioselective alkylation of 3-bromophenol with prenyl bromide,[8] but in our hands, this reaction under the reported conditions gave an inseparable mixture of products which included mono- and dialkylated species. We thus decided to evaluate new approaches for the synthesis of the chromenyl bromide **21** (Scheme 4). One involves the construction of the pyran ring by an acid-catalyzed cyclization of the allylic alcohol **22** which in turn should be accessible from the aldehyde **23**. The second approach begins with the base-catalyzed cyclization of 1,3-cyclohexanedione **27** with 3-methyl-2-butenal.

The aldehyde **23** that is needed for the synthesis of carbene complex **20** as outlined in Scheme 4 has previously been prepared by Couture and co-workers.[9] Their synthesis involved the directed-metalation of imidazolidine **28** and then bromination with dibromotetrachloroethane followed by acid workup to provide 2-bromoanisaldehyde **29** in 79% yield (Table 1). When this reaction was repeated under the reported conditions, a 2:1 mixture of 2-bromoanisaldehyde and 2-chloroanisaldehyde was obtained in 35% yield (entry 1). It was found that the ratio of **29:30** showed a noticeable dependence on the temperature of the reaction (Table 1). Optimal conditions required *ortho*-lithiation at −40 °C and the addition of the brominating agent at −78 °C which gave a 69% yield of **29** (entry 8) and only a trace amount of **30** (**29:30** = 50:1). Final conversion to aldehyde **23** was accomplished by demethylation of **29** with boron tribromide which provided 2-bromosalicylaldehyde **23** in excellent yield (94% yield).

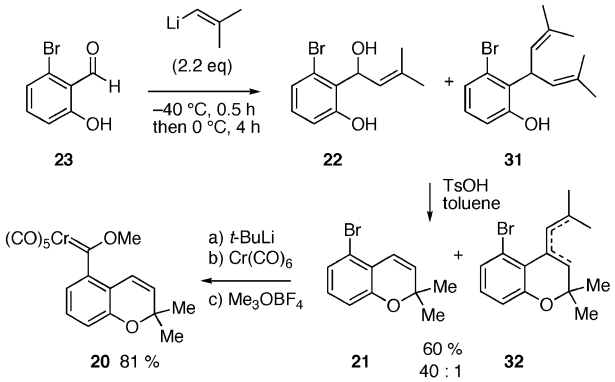
Table 1. Directed Metalation/Bromination of Aminal **28**[a]



entry	*t*-BuLi (equiv)	T_1 (°C)	T_2 (°C)	ratio **29:30**[b]	yield (%) **29** + **30**[c]
1	3.0	rt	rt	2:1	35
2	3.0	rt	rt	3.3:1	48
3	3.0	rt	rt	3.3:1	41
4	3.0	rt	rt		≤10[d]
5	3.0	14	14 to rt	3.3:1	43
6	3.0	0	0 to rt	5.6:1	52
7	3.0	−20	−20 to rt	5.6:1	72
8	3.0	−40	−70 to rt	50:1	69

[a] All reactions were at 0.1 M in **28** and used 3.0 equiv of bromination agent. [b] Determined in isolated mixture. [c] Isolated yield of the mixture. [d] ≤10% yield was observed with either NBS or bromine as bromination agent.

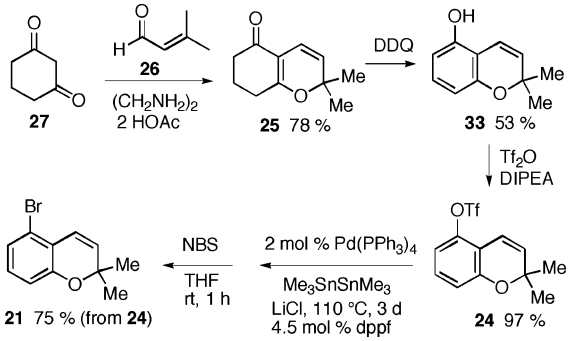
Scheme 5



Completion of the synthesis of carbene complex **20** requires the acid-catalyzed cyclization of the allylic alcohol **22**, a process that is known for related allylic alcohols.[10] The addition of 2 equiv of 2-methyl-1-propenyllithium to the hydroxybenzaldehyde **23** produced a mixture of the desired allylic alcohol **22** and the dienyl arene **31** (Scheme 5). With no purification, the crude reaction mixture was subjected to acid-catalyzed cyclization which afforded a 5:1 mixture of the desired bromochromene **21** and of the 4-substituted chromene **32** which was obtained as a mixture of olefin isomers. Further purification by Kugelrohr distillation improved the ratio of **21:32** to 40:1 and provided **21** in 60% overall yield from aldehyde **23**. The synthesis of the carbene complex **20** was achieved by the standard Fischer procedure as indicated in Scheme 5. Treatment of **21** with 2 equiv of *tert*-butyllithium and subsequent reaction with chromium carbonyl and finally methylation with Meerwein's salt gave carbene complex **20** in 81% yield as a red crystalline solid. The chromenyl chromium carbene complex **20** is remarkably stable for an aryl chromium complex and could be separated from the small amount of carbene complex generated from the

(8) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953.
(9) Couture, A.; Deniau, E.; Grandclaudon, P.; Christophe, H. J. *Org. Chem.* **1998**, *63*, 3128−3132.
(10) (a) Talley, J. J. *Synthesis* **1983**, 845−846. (b) Cruz-Almanza, R.; Perez-Flores, F.; Cardenas, J.; Vazquez, C. Fuentes, A. *Synth. Commun.* **1994**, *24*, 1009. (c) Chauder, B. A.; Kalinin, A. V.; Snieckus, V. *Synthesis* **2001**, 140−144.

Scheme 6

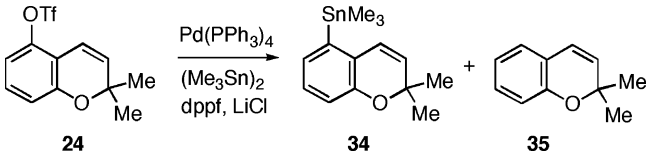


bromide **32** by silica gel chromatography. In this way, carbene complex **20** could be obtained in pure form in six steps from *o*-anisaldehyde in 24% overall yield.

An alternative approach to the synthesis of the carbene complex **20** begins with cyclohexan-1,3-dione and aldehyde **26** (Scheme 6). The base-catalyzed condensations of 1,3-diones and α,β-unsaturated aldehydes are known to give pyrans.[11] The reaction of cyclohexan-1,3-dione with prenyl aldehyde in the presence of ammonium salt of 1,2-diaminoethane gives the pyran **25** in 78% yield. Subsequent DDQ oxidation gave the benzopyran **33** which was then treated with triflic anhydride to give the aryl triflate **24**. The key conversion of the aryl triflate **24** to the bromide **21** was planned to utilize chemistry we had previously developed for the conversion of aryl triflates to aryl halides via a two-step sequence involving coupling of the aryl triflate with a distannane and then conversion of the aryl stannane to an aryl bromide with NBS or bromine.[12] An alternative method for the conversion of **24** to **21** involves the reaction of triflate **24** with tributyl stannyl cuprate;[13] however, a variety of conditions were explored, but all failed to give any coupling product and instead this reaction only resulted in the recovery of triflate **24** and/or phenol **33**.

The palladium-catalyzed coupling of aryl triflate **24** with hexamethylditin was a slow reaction and gave mixtures of the desired aryl stannane **34** and the proto-destannylated chromene **35** (Table 2). Very little reaction was seen in THF at 60 °C, and thus it was necessary to raise the reaction temperature. The solvent was thus changed to 1,4-dioxane, and it was also found beneficial to add bis-(diphenylphosphinyl)ferrocene (dppf) to provide a stable palladium complex at the higher temperatures. Dioxane was the superior solvent as dibutyl ether gave considerable precipitation of palladium black and DMF gave substantial amounts of the reduction product **35**. At the optimal conditions of 110 °C for 96 h, the reaction went to completion and gave a 90:10 ratio (by GC) of the desired stannane **34** to the reduced product **35** along with a small amount of a third unidentified product. Purification of the stannane **34** was not possible by silica gel chromatography as the desired product **34** coeluted with the reduced product **35** and with the triphenylphosphine from the catalyst. It was therefore found most convenient to directly treat the crude reaction mixture containing the stannane **34** with NBS in THF at room temperature for 1 h which gave

Table 2. Pd Catalyzed Triflate/Distannane Coupling of **24**[a]



entry	solvent	temp (°C)	time (h)	% conv	ratio **34:35**
1	THF	60	48	3[b]	
2	dioxane	105	8	10	
3	dioxane	105	48	77	47:53
4	dioxane	110	96	100	90:10
5	dibutyl ether	120	8	2	
6	DMF	160	0.2	100	26:74
7	DMF	110	110	100	30:70

[a] Unless otherwise specified, all reactions were carried out at 0.1 M in **24** with a ratio of reagents: **24**/$(Me_3Sn)_2$/$Pd(PPh_3)_4$/dppf/LiCl = 1:0.9:0.02:0.45:6. [b] dppf not used.

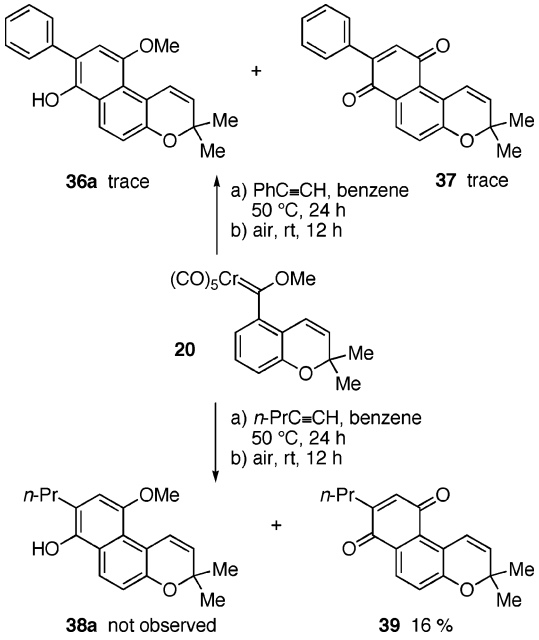
the bromochromene **21** in pure form in 75% overall yield from the triflate **24**. This alternate route for the synthesis of carbene complex **20** provides the complex in six steps in 24% overall yield, a situation identical with the first route involving aldehyde **23** (Scheme 4). The choice between the two thus comes down to the cost of reagents, and by this criteria, the first route is the most desirable.

Reaction of the Chromenyl Carbene Complex 20 with Acetylenes. Our studies of the benzannulation reactions of the chromenyl carbene complex **20** with alkynes were initially quite disappointing. The reaction of complex **20** with phenylacetylene was performed under typical conditions. The reaction was carried out in benzene at 50 °C until the carbene complex was consumed (24 h) at which point the crude reaction mixture was stirred in air for 12 h at room temperature to allow for the oxidative decomplexation of any chromium tricarbonyl fragment from the product. Surprisingly, neither the expected phenol **36a** or its corresponding quinone **37** could be detected in more than trace amounts in the crude reaction mixture. The same reaction of complex **20** with 1-pentyne gave a crude reaction mixture that did not contain any of the expected phenol **38a** and the only product that could be purified from the mixture was the quinone **39** in 16% yield. The failure to isolate any of the phenols **36a** and **38a** was surprising, since, in our experience, it is rare that phenol products from the reactions of Fischer carbene complexes and alkynes are air-sensitive enough that they would not survive exposure to air during the workup of these reactions. It is even more unusual that the exposure of these phenols to air did not lead to the formation of substantial amounts of the corresponding quinones **37** or **39**.

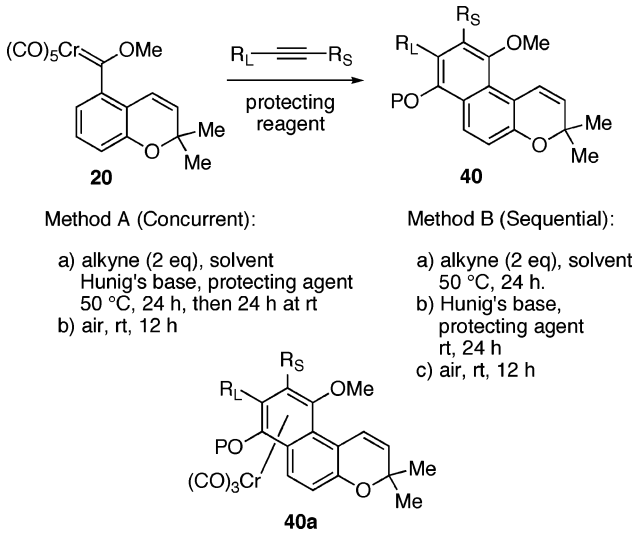
If the failure of the reactions shown in Scheme 7 is due to the sensitivity of the phenols **36a** and **38a** to air, then a possible solution might be able to protect the phenols in-situ which would lead to the isolation of the aryl ethers **40** (Scheme 8). The primary product from the reaction of chromium carbene complex **20** with alkynes is expected to be the chromium tricarbonyl complex **40a** (P = H) with the chromium complexed to the newly formed benzene ring. Normally, these chromium tricarbonyl complexed phenols are air sensitive, and the chromium tricarbonyl group is quickly lost when the reaction mixture is opened to air. Since chromium tricarbonyl complexes of aryl

(11) (a) Tietze, L.-F.; Kiedrowski, G.; Berger, B. *Synthesis* **1982**, 683−684. (b) Schuda, P. F.; Price, W. A. *J. Org. Chem.* **1987**, *52*, 1972−1979.
(12) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S., Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277−279.
(13) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795−4798.

Scheme 7

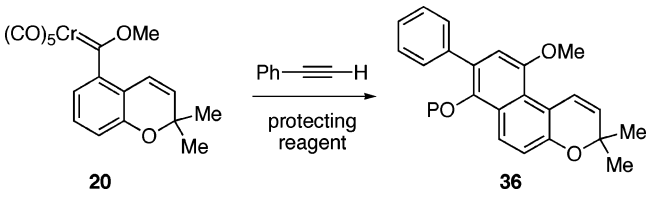


Scheme 8



ethers are air stable, it might be expected that in situ protection of the phenol function produced in these reactions would result in the isolation of the protected phenol chromium tricarbonyl complex **40a** (P ≠ H). However, in nearly all known examples of in situ protection of phenol chromium tricarbonyl complexes produced from the reaction of aryl carbene complexes, the chromium tricarbonyl group is lost.[14] It should be added that, in contrast to the reaction of aryl complexes, the in situ protection of the phenols produced from the reaction of alkenyl complexes occurs with the isolation of the chromium tricarbonyl complexed protected phenols in high yields.[14] This dichotomy is apparently due to the greater ease of displacement of η^6-naphthalene ligands compared with η^6-benzene ligands. Thus, based on what is known in the literature, the reaction of the chromenyl complex **20** with alkynes with in situ protection of the phenol function is expected to lead to the isolation of the

Table 3. Benzannulation of Complex **20** with Phenylacetylene[a]



entry	method[b]	protecting reagent	product	P	% yield **36**[c]
1	A	none	**36a**	H	trace
2	A	TBSCl	**36b**	TBS	27
3	A	TBSCl	**36b**	TBS	45[d]
4	A	TBSOTf	**36b**	TBS	57[e]
5	A	TMSCl	**36c**	TMS	65
6	B	TMSCl	**36c**	TMS	25[f]
7	B	TMSCl	**36c**	TMS	62
8	A	TMSOTf	**36c**	TMS	25
9	A	Ac_2O	**36d**	Ac	57
10	A	Ac_2O	**36d**	Ac	57[g]
11	A	MOMCl	**36e**	MOM	60

[a] Unless otherwise specified, all reactions were in benzene at 0.05 M in **20** for 24 h at 50 °C. Ratio of reagents: **20**/phenylacetylene/protecting reagent/Hunig's base = 1:2:3:5. [b] See Scheme 8. [c] Isolated yield. After silica gel chromatography. [d] Reaction at rt for 6 d. [e] Reaction at 60 °C; **36b** was isolated as a mixture and its yield was determined by ^{1}H NMR. [f] Not freeze−pump−thaw deoxygenated after Hunig's base and TMSCl were added. g DMAP (5 mol %) also added.

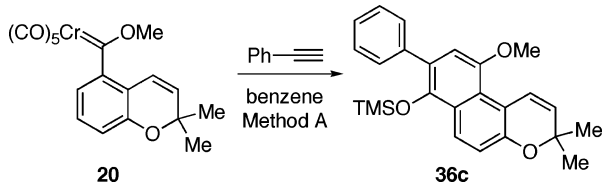
protected phenol **40** without the chromium tricarbonyl group. Concurrent and sequential protocols have been developed for in situ protection (Scheme 8), and both were evaluated for complex **20**.

The reaction of the chromenyl carbene complex **20** with phenylacetylene was examined with a number of different electrophiles under both the concurrent and sequential procedures (Table 3). All the reactions in Table 3 were performed in benzene at 0.05 M in **20** with 2 equiv of alkyne, 3 equiv of protecting agent, and 5 equiv of Hunig's base. To ensure the absence of oxygen, each reaction (except where specified) was deoxygenated by the freeze−pump−thaw method at the beginning of the reaction (three cycles) and after addition of the Hunig's base and protecting agent (two cycles, sequential method). The optimal silylating agent proved to be trimethylsilyl chloride which provided the silylated phenol **36c** in 65% yield as the metal-free arene (entry 5). The reaction of Fischer carbene complexes with alkynes can produce a large number of different products (dozens) depending on the substrates and conditions.[3] Thus, the isolation of the protected phenols **36** demonstrates that the major pathway for the reaction of the chromenyl complex **20** leads to the normal phenol product and is supportive of the contention that the phenol **36** is sensitive to air under the reaction conditions. This is also supported by the lower yield of **36c** observed under the sequential protocol where the reaction mixture is not deoxygenated after the addition of Hunig's base and protecting agent (entry 6 vs entry 7). This result could be consistent with an air sensitivity of the phenol **36a** or to the air sensitivity of the chromium tricarbonyl complex of **36a**. It is surprising that this reaction is so sensitive to air, since many reactions of carbene complexes with alkynes can be performed without freeze−thaw deoxygenation resulting in no significant loss in yield.[15] Similar yields of the protected phenol **36** could

(14) (a) Fogel, L.; Hsung, R. P.; Wulff, W. D.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 5580−5581. (b) Chamberlin, S.; Wulff, W. D.; Bax, B. *Tetrahedron* **1993**, *49*, 5531−5547.

(15) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293−9319.

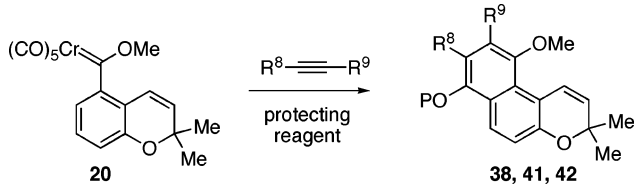
Table 4. Solvent and Temperature Effects on Reaction of **20**[a]



entry	temp (°C)	solvent	% yield **36c**[b]
1	50	THF	50
2	50	CH_3CN	55
3	50	benzene	65
4	75	benzene	67
5	100	benzene	68
6	125	benzene	68

[a] Unless otherwise specified, all reactions were 0.05 M in **20** for 24 h. Ratio of reagents: **20**/phenylacetylene/TMSCl/Hunig's base = 1:2:3:5. [b] Isolated yield after silica gel chromatography.

Table 5. Benzannulation of Complex **20** with Acetylenes[a]



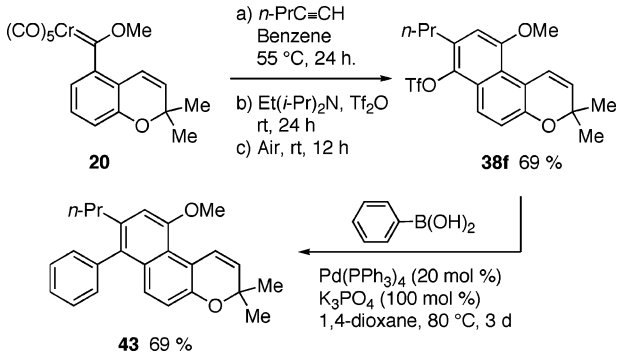
entry	method[b]	protecting reagent	R^8	R^9	product	P	% yield **38**, **41**, **42**[c]
1		none	*n*-Pr	H	**38a**	H	16[d]
2	A	TMSCl	*n*-Pr	H	**38c**	TMS	97
3	B	TMSCl	*n*-Pr	H	**38c**	TMS	50[e]
4	B	TMSCl	*n*-Pr	H	**38c**	TMS	89
5	A	TBSCl	*n*-Pr	H	**38b**	TBS	88[f]
6	A	Tf_2O	*n*-Pr	H	**38f**	Tf	*g*
7	B	Tf_2O	*n*-Pr	H	**38f**	Tf	69
8	A	TMSCl	Et	Et	**41c**	TMS	96[h]
9	A	TBSCl	Et	Et	**41b**	TBS	85
10	A	TMSCl	TMS	H	**42c**	TMS	89
11	A	TBSCl	TMS	H	**42b**	TBS	*g*
12	A	MOMCl	TMS	H	**42e**	MOM	85
13	A	MOMCl	TMS	H	**42e**	MOM	70[i]

[a] Unless otherwise specified, all reactions were in benzene at 0.1 M in **20** for 24 h at 50 °C. Ratio of reagents: **20**/acetylene/protecting reagent/Hunig's base = 1:2:3:5. [b] See Scheme 8. [c] Isolated yield after silica gel chromatography. [d] Only 16% yield of quinone **39** was isolated. [e] Not freeze−pump−thaw deoxygenated after the addition of base and protecting reagent. [f] Includes a 10% yield of the quinone **39**. [g] Complex mixture observed which was not analyzed. [h] Isolated by filtration through Celite. [i] Reaction at rt for 5 d.

be obtained with acetic anhydride and chloromethylmethyl ether as trapping agents. The structure of **36d** was confirmed by X-ray diffraction. The reactions of Fischer carbene complexes with alkynes can be sensitive to solvent and temperature.[15] However, as indicated by the data in Table 4, the reaction of complex **20** with phenylacetylene is not at all sensitive to temperature and only slightly sensitive to solvent with benzene giving slightly higher yields than THF or acetonitrile.

The trapping of the phenol generated from the reaction of complex **20** with 1-pentyne was much more efficient than with phenylacetylene giving a 97% yield of the TMS ether **38c** (Table 5). The air sensitivity of the intermediates in this reaction is thus clear by comparison of this result with that from the reaction with no trap (entry 1 vs 2) and with the reaction in which deoxygenation was not performed after the addition of protecting

Scheme 9



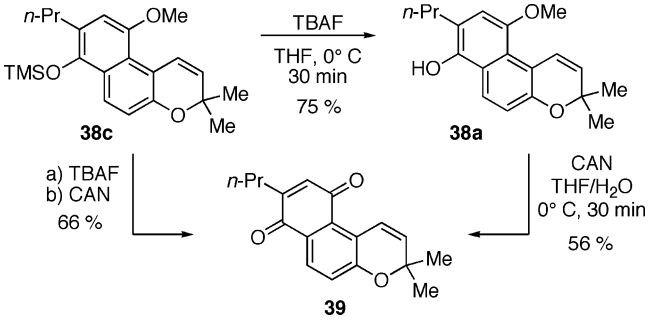
agent and base (entry 3 vs 4). Very efficient trapping was also observed from the reactions with 3-hexyne and trimethylsilylacetylene giving the protected phenols **41c** and **42c** in 96% and 89% yields, respectively. All of the trimethysilylaryl ethers in Tables 4 and 5 are stable to silica gel except **41c**. In this case, the reaction of **20** and 3-hexyne was very clean, and simple filtration through Celite gave essentially pure material. The TBS-protected analogue **41b** obtained from the reaction of **20** with 3-hexyne in the presence of TBSCl is stable to silica gel and can be obtained in pure form. In contrast, the trapping of the reactions of 1-pentyne and trimethylsilylacetylene with TBSCl is not clean giving **38b** along with some of the quinone **39** for the former and a very complex reaction mixture with the latter. Electrophiles other than silyl halides can be used as demonstrated by the isolation of the aryl triflate **38f** in 69% from the reaction of **20** with 1-pentyne and also by the isolation of the MOM ether **42e** in 85% yield from the reaction of **20** with trimethylsilylacetylene.

As outlined in Scheme 2, we anticipated that the triflation of the phenol function in **8** may allow for the introduction of carbon substituents in the 7-position of the 3*H*-naphtho[2,1-b]pyrans **1**. Thus a significant finding in this regard is that the phenol obtained from the reaction of carbene complex **20** with 1-pentyne could be trapped with triflic anhydride to give the aryl triflate **38f** in 69% yield. It is curious that the trapping of the phenol from this reaction with triflic anhydride was successful under sequential (Method B) but not concurrent (Method A) protocols (Table 5, entries 6 and 7). Trimethylsilyl chloride gives approximately the same yields under either reaction method for either 1-pentyne (Table 5, entries 2 and 4) or phenylacetylene (Table 3, entries 5 and 7). The origin of this effect is not understood at this time. There was some concern with the prospect of success for the Suzuki coupling of the aryl triflate **38f** given the fact that the triflate function is flanked by substituents on either side. This concern was misplaced as triflate **38f** underwent Suzuki coupling with phenylboronic acid under standard conditions[16] to give the 7-phenyl-substituted naphthopyran **43** in 69% yield (Scheme 9).

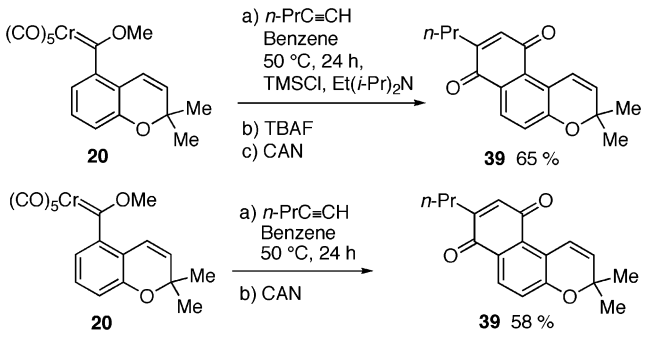
Deprotection of the trimethylsilyl ether **38c** was performed to more properly determine the stability of the phenol **38a**. Treatment of **38c** with TBAF in THF at 0° for 30 min gave the phenol **38a** in 75% yield after purification by silica gel chromatography (Scheme 10). Although phenol **38a** was obtained in relatively pure form, it contained a small amount

(16) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

Scheme 10



Scheme 11

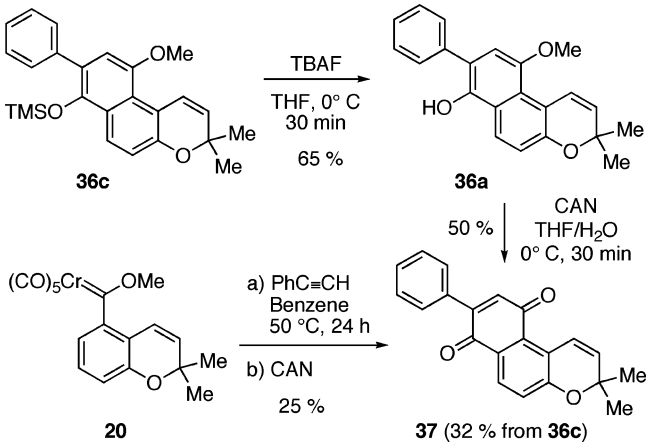


of impurity and decomposed at a rate such that the impurity could not be removed with repeated chromatographic purifications. Oxidation of phenol **38a** with ceric ammonium nitrate (CAN) gave the quinone **39** in 56% yield. The quinone **39** was stable and robust to both air and light and was completely characterized. Given the sensitivity of the phenol **38a**, the best method for access to the quinone **39** was treatment of the trimethylsilyl ether **38c** with TBAF and then treatment of the crude phenol **38a** with CAN which results in a 66% yield of the quinone **39**.

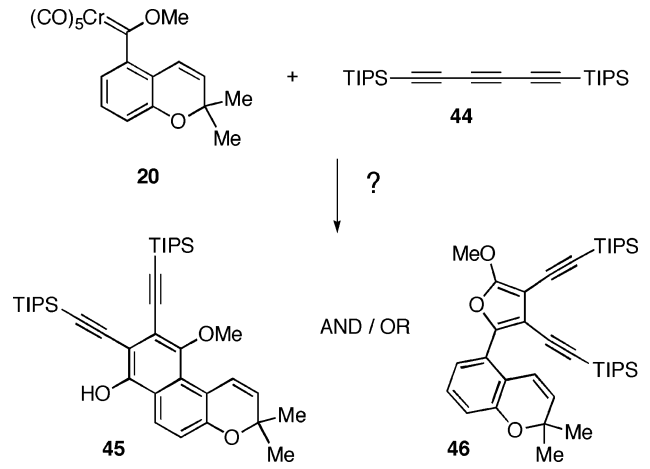
The direct conversion of the carbene complex **20** to the quinone **39** was examined with and without in situ generation of the trimethylsilyl ether **38a** (Scheme 11). After the reaction of complex **20** and 1-pentyne was carried out at 50° for 24 h in the presence of trimethylsilyl chloride and Hunig's base, the reaction was worked up to provide the crude silyl ether **38c**. This silyl ether was not purified but directly treated with TBAF, and then the resultant phenol **38a** was directly oxidized to the quinone **39** without purification. The overall yield for this conversion of complex **20** to quinone **39** was 65% yield which is essentially identical with the overall yield that was observed when the silyl ether **38c** was isolated and purified (97% × 66% = 64%). This is to be compared with the direct conversion of carbene complex **20** to the quinone **39** without in situ trapping of phenol **38a** with trimethylsilyl chloride which is only marginally less effective (58%).

Deprotection of the silyl ether **36c** obtained from the reaction of complex **20** with phenylacetyelene gave the phenol **36a** in 65% yield (Scheme 12). Like the phenol **38a**, the phenol **36a** was relatively unstable and was not fully characterized but rather oxidized with CAN to give the quinone **37** in 50% yield. The quinone **37** could be obtained directly from the reaction of the carbene complex **20** and phenylacetylene in the absence of any trapping agent in 25% yield if the crude reaction mixture is oxidized with CAN. This is essentially the same overall yield from carbene complex **20** that is observed when the trimethylsilyl ether **36c** is isolated and purified (65% × 32% = 21%). This lower yield of quinone **37** compared with quinone **39** suggests that the phenol **36a** from phenylacetylene is more sensitive to decomposition than the phenol **38a** from 1-pentyne. It further suggests that it may be possible to optimize the yield of quinones from these reactions if the process is optimized for the oxidizing agent especially when considering that the reactions with 1-pentyne, 3-hexyne, and trimethysilyl acetylene give high yields of the trapping products with trimethylsilyl chloride (Table 5).

Scheme 12



Scheme 13



Reaction of Chromenyl Carbene Complex 20 with Triynes. Based on our limited studies on the reaction of Fischer carbene complexes with conjugated triynes, the reaction of the chromenyl carbene complex **20** with the bis-silyl substituted triyne **44** would be expected to give either the phenol product **45** or the furan product **46** (Scheme 13).[7] As summarized in Scheme 3, the reaction of the phenyl complex **15** with **44** gives the furan **15**, whereas the reaction of the cyclohexenyl complex **18** gives the phenol **17** in 70% yield. Thus based on these observations and the fact that the chromenyl complex **20** is an aryl-substituted carbene complex, we would expect that the furan **46** would be the major product formed from the reaction of complex **20** with triyne **44**.

The reaction of carbene complex **20** with triyne **44** gave neither the phenol **45** nor the furan **46** as was expected. Instead, this reaction lead to the formation of the naphthalene deriative **47a** that results from incorporation of the triyne and then

Scheme 14

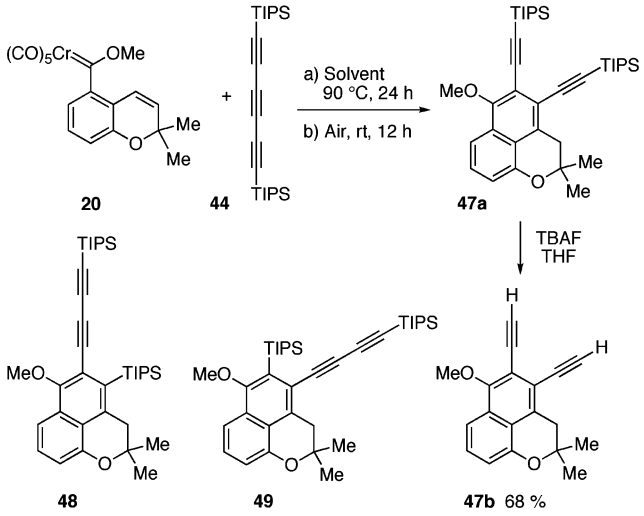


Table 6. Reaction of Complex **20** with Triyne **44**[a]

entry	solvent	% yield **47a**[b]
1	benzene[c]	74
2	benzene[d]	71
3	benzene	80
4	CH_2Cl_2	88
5	THF	75
6	CH_3CN[e]	
7	DMF[e]	

[a] Unless otherwise specified all reactions were carried out at 0.05 M in **20** with 1.0 equiv of **44**. [b] Isolated yields after purification by silica gel chromatography. [c] TMSCl (2 equiv) and Hunig's base (4 equiv) were used. [d] MOMCl (2 equiv) and Hung's base (4 equiv) were used. [e] Complex mixture observed which contained at most a trace of **47a**.

cyclization to the double bond of the chromene ring (Scheme 14). Two regioisomers of **47a** would also be possible from this reaction which would result from the different modes of incorporation of the triyne. The regioisomers **48** and **49** were ruled out as possibilities with the cleavage of the silyl groups in the product from the reaction. Only isomer **47a** could give a desilylated product that had two different acetylene protons. Treatment of **47a** with TBAF gave the bis-alkyne **47b** in 68% yield with two alkynyl proton singlets at $\delta = 3.55$ and 3.56 ppm.

The reactions of complex **20** and triyne **44** were initially performed in the presence of trapping agents in an effort to trap the phenol **45** with the thought that it may be unstable like **38a** and **36a**. The reaction was run in benzene in the presence of base and trimethylsilyl chloride and methyl chloromethyl ether (Table 6, entries 1 and 2). The only product that was observed to be silica gel mobile in these reactions was the alkene addition product **47a**. The yield of **47a** was higher if the trapping agents were omitted (Table 6, entry 3). The best yield of the addition product **47a** was found in methylene chloride (88%), whereas the use of the polar coordinated solvents acetonitrile and DMF lead to a complex mixture of products in which **47a** was present in at most trace amounts.

Mechansitic Discussion. A possible mechanism[17] is shown for the formation of the alkene addition product **47a** in Scheme 15 along with the other products that could have arisen from this reaction, the furan **46**, the phenol **45**, the indene **54**, and the cyclopropane **57**. Loss of a carbon monoxide ligand from the carbene complex **20** and addition to the central alkyne unit in triyne **44** would be expected to give the h^1,h^3-vinyl carbene complex **50** as either the E- and Z-isomer or as a mixture. It is also possible that the E- and Z-isomers of **50** are in equilibrium with respect to product formation.[17c] The phenol product **45** can only arise from the E-isomer of **50** via the ketene complex **51**, and previous work[18] suggests that the furan product **46** arises from the Z-isomer of **50** via the ketene complexes **52**. For the reactions of carbene complexes and alkynes in general, one of the most common side-products that arises from the E-isomer of the vinyl carbene complexed intermediate is an indene product, and in the case of the triyne **44**, this would be the indene derivative **54**. This product was not detected in the reaction of complex **20** with triyne **44**, nor was the phenol **45** or the furan **46** observed from this reaction. The alkene addition product **47a** appears to derive from the chromacyclobutane intermediate **56** that would be expected from an intramolecular [2 + 2] cycloaddition of the chromium−carbon double bond in **55** with the alkene in the chromene ring. The formation of a chromacyclobutane has been widely envoked in the reaction of carbene complexes with alkenes as the penultimate intermediate in the formation of cyclopropanes via reductive elimination.[19] No cyclopropane product was observed in the reaction of **20** with **44**, although the possibility exists that the alkene insertion product **47a** is a secondary product of the reaction resulting from an acid-catalyzed isomerization of **57**. Although relatively rare, chromacyclobutane intermediates have been reported to undergo β-hydride elimination and then reductive elimination of hydride to give an alkene product instead of cyclopropane products.[20] This type of process could account for the formation of the alkene insertion product **47a** via reductive elimination from the chromium(II) hydride intermediate **58**.

The reaction manifold outlined in Scheme 15 was also explored with quantum calculations. The geometries of the reactants, intermediates, and products were fully optimized with the Spartan 5.1.3 program by the semiempirical PM3tm method. The PM3tm optimized geometries were subjected to BP86 single-point (SP) calculations with the DN* basis set as implemented in the Spartan program. The details of these calculations can be found in the Supporting Information, and the results are consistent with experiment. The formation of all four products, **45**, **46**, **54**, and **47a**, are all predicted to be exothermic with **47a** as the most favored. The E-isomer of the vinyl carbene intermediate **50** was found to be more stable than the Z-isomer. Of the three intermediates that could eminate from (*E*)-**50**, all of the intermediates on the pathway to **47a**, namely **55**, **56**, **57**, and **58**, were lower in energy than either **51** or **53**.

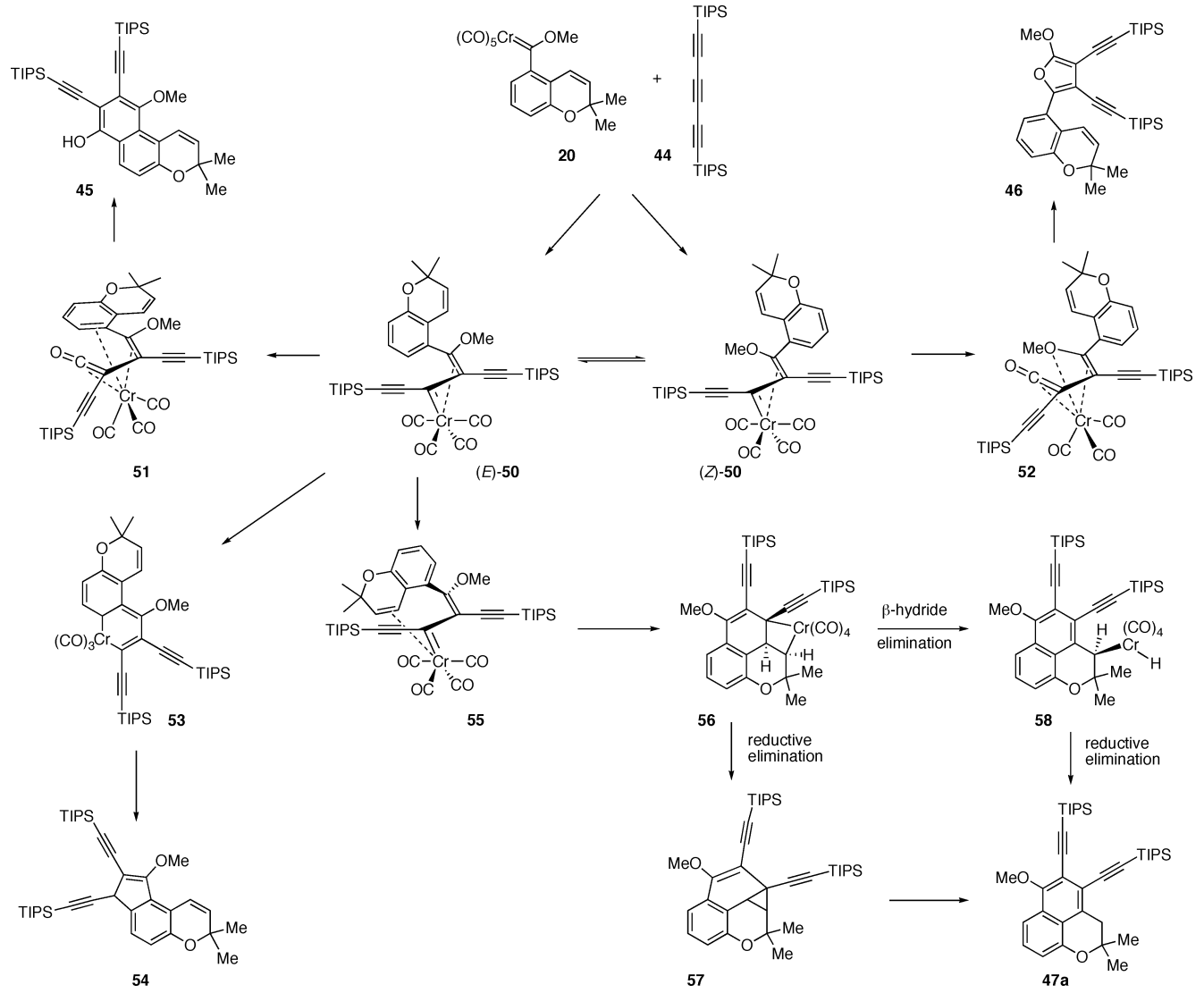
(17) For references to mechanistic issues and leading references, see: (a) Gleichmann, M. M.; Dötz, K. H.; Hess, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10551−10560. (b) Torrent, M.; Duran, M.; Sola, M. *J. Am. Chem. Soc.* **1999**, *121*, 1309−1316. (c) Waters, M. L.; Bos, M. E.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 6403−6413. (d) Barluenga, J.; Aznar, F.; Gutierrez, I.; Martin, A.; Garcia-Granda, S.; Llorca-Baragano, M. A. *J. Am. Chem. Soc*. **2000**, *122*, 1314−1324.

(18) (a) McCallum, J. S.; Kunng, F.-A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346−2360. (b) Parlier, A.; Rudler, M.; Rudler, H.; Goumont, R.; Daran, J.-C.; Vaissermann, J. *Organometallics* **1995**, *14*, 2760−2774.

(19) For reviews, see: (a) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Able, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol 12, p 387. (b) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411−432.

(20) (a) Wienand, A.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1129. (b) Hwu, C.-C.; Wang, F.-C.; Yeh, M.-C. P.; Sheu, J.-H. *J. Organomet. Chem.* **1994**, *474*, 123−128. (c) Barluenga, J.; Gonzalez, R.; Fananas, F. J. *Organometallics* **1997**, *16*, 4525−4526. (d) Woodgate, P. D.; Sutherland, H. S. *J. Organomet. Chem.* **2001**, *628*, 155−168.

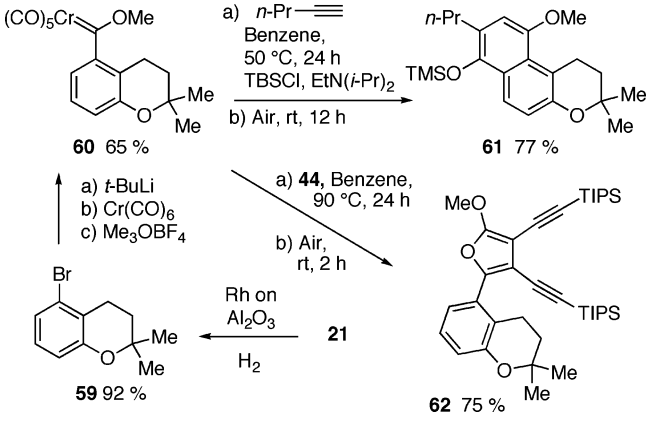
Scheme 15



The results show that the β-hydride elimination pathway via **58** is preferred over the cyclopropanation pathway via **57** by ~12 kcal/mol. Although the energy of (*E*)-**50** is lower than that for (*Z*)-**50**, the second lowest pathway is that to the furan product **46**, since the intermediate **52** is lower in energy than either the intermediates **51** or **53**.

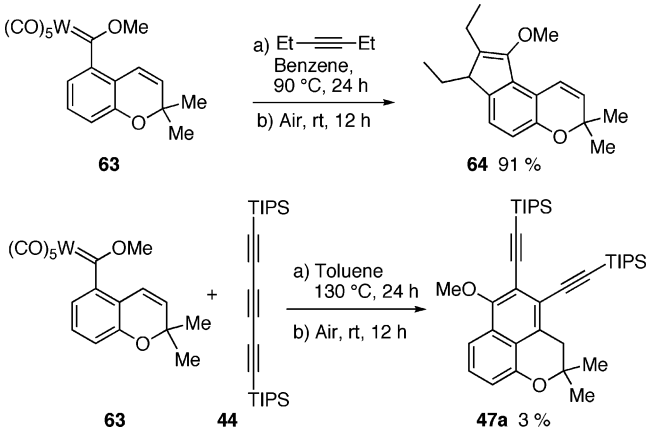
Reaction of the Dihydrochromenyl Complex 60 with Alkynes. The reaction of the carbene complex **20** with several internal and terminal alkynes proceeds to give the normal benzannulated product (Table 5), and thus the reaction with the triyne **44** to give the alkene inserted product **47a** was quite unexpected and thwarted the idea for a straightforward access to conocurvone (Scheme 3). If the double bond in complex **20** was removed, the formation of the alkene insertion product would be obviated and then the question would revert to whether the reaction with triyne **44** would give the normal phenol product or the furan product (Scheme 13). The dihydrochromene carbene complex **60** was prepared as outlined in Scheme 16. The double bond in the bromochromene **21** was selectively reduced in the presence of the aryl bromide with rhodium on alumina[21] to give the aryl bromide **59** in 92% yield. As expected the dihydrochromene carbene complex **60** will react with 1-pentyne in the presence of TBSCl as trapping agent to give the normal benzannulated product **61** in 77% yield. The key issue is the reaction with the triyne **44** which was found to proceed to cleanly give the furan product **62**. This result is consistent with the calculations described above and adds to the growing evidence that aryl complexes are selective for furan products

Scheme 16



(21) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363−3366.

Scheme 17



in their reactions with triyne **44** and alkenyl complexes are selective for the phenol products.[7]

Reaction of the Tungsten Chromenyl Complex 63 with Alkynes. The formation of the alkene insertion product **47a** from complex **20** and triyne **44** occurs without the insertion of a carbon monoxide ligand. When the alkene in **20** is removed, i.e., complex **60**, then CO insertions occurs and the phenol product **61** is formed upon reaction with 1-pentyne. It thus appears that CO insertion is interrupted and prevented by coordination of the metal to the alkene and the formation of the intermediate **55** (Scheme 15). In an effort to generalize this alkene insertion process and to expand its scope from triynes to simple alkynes, we decided to investigate the reactions of the tungsten complex **63**, the analogue of chromium complex **20**. The reason is that, relative to chromium complexes, tungsten complexes are well-known to have much less of a propensity for producing CO inserted products in their reactions with alkynes.[22] Thus, the tungsten should alter the competition between the CO insertion and alkene coordination pathways in the tungsten intermediate corresponding to **50**-**E** in Scheme 15 in favor of alkene coordination and thus the formation of the alkene insertion product **47a**. While the reaction of the tungsten complex **63** with 3-hexyne did not produce any CO insertion products, the alkene insertion pathway did not compete with indene formation that derives from a cyclization to the arene ring in intermediate **50**-**E** to give the indene product **54** perhaps via the intermediacy of the metallocycle **53**. The reaction of tungsten complex **63** with 3-hexyne gives the indene product **64** in 91% yield. Furthermore, it was found that the tungsten complex **63** would not react with the triyne **44** to give significant amounts of the alkene insertion product **47a**. There is no reaction at 90 °C, and at 130 °C the triyne **44** (1 equiv) was completely consumed but the only silica gel mobile products observed were **47a** (3%) and a 30% recovery of the carbene complex **63**. This suggests that the tungsten complex **63** is oligiomerizing the triyne **44**, a process that has been often noted in the reaction of tungsten carbene complexes with alkynes.[23]

(22) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102−126.

IV. Conclusion

It has been shown that the reactions of chromenyl carbene complexes of chromium with alkynes can provide for a direct entry to 3*H*-naphtho[2,1-b]pyrans and 3*H*-naphtho[2,1-b]pyran-7,10-diones that are highly substituted in the C-ring. This chemistry should be useful in the synthesis of natural products and photochromic materials containing these two rings systems. The degree and nature of the substituents at the C7−C10 positions in the C-ring can be controlled by the nature of the alkyne and by post-benzannulation modification of the oxygen substituent at C-7 (and thus presumably also at C-10). Although it was found that the reaction of chromenyl complexes with conjugated triynes will not be useful for the construction of the central quinone unit in conocurvone (it may still be useful for the two end quinone units), this reaction, nonetheless, proved to be quite interesting as it occurs to give a product type that has not been previously observed for the reactions of Fischer carbene complexes with alkynes. This reaction leads to a non-CO insertion benzannulation onto the remote double bond presence in the carbene complex. A mechanism is proposed for this process that involves a β-hydride elimination from a chromacyclobutane intermediate. Synthetic applications of the reactions with chromenyl carbene complexes with alkynes will be reported in due course.

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Supporting Information Available: Procedures for the preparation of new compounds, characterization data for all new compounds, and details on QM calculations of the reaction of complex **20** with triyne **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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