Pergamon

Tetrahedron 56 (2000) 2175–2182

TETRAHEDRON

Selective Remote Functionalization of Alkyl Side Chains in the Coupling of Fischer Carbene Complexes with Conjugated Enediynes

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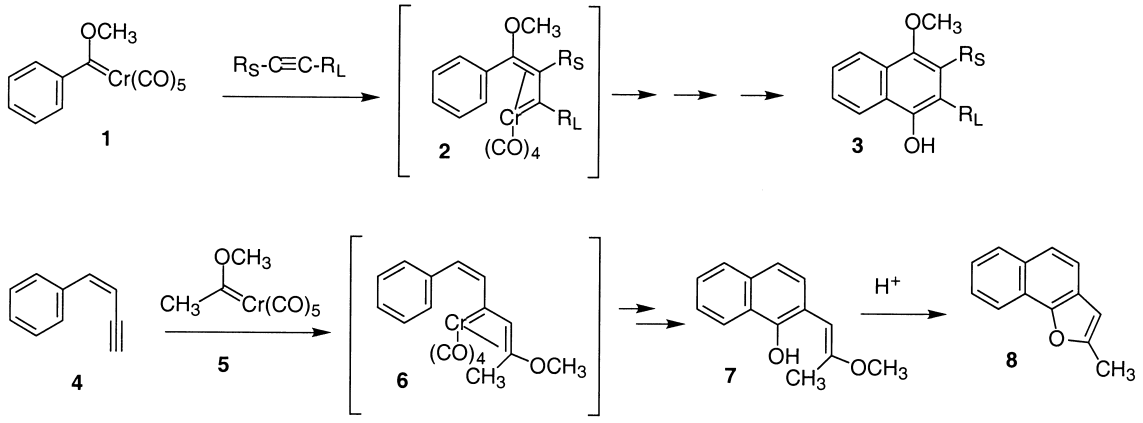
Accepted 7 December 1999

Abstract—The reactions of various enediyne derivatives with Fischer carbene complexes has been examined. In most cases, benzofuran derivatives featuring a functionalized side chain were produced as a result of the coupling reaction. Reactions performed in chlorobenzene produced mostly this class of products. The major product was usually the alkene derivative, although in the presence of chlorine atom sources, chloride derivatives were also observed.

Introduction

Numerous synthetically useful reaction processes involve the coupling of alkynes with carbene complexes, including: (1) the synthesis of aromatic rings via the coupling of alkynes with α,β-unsaturated chromium carbene complexes (also known as the Dötz reaction) (Scheme 1, conversion of **1** to **3**);[1] (2) the synthesis of cyclopentenones via the coupling of alkynes with cyclopropylcarbene and/or alkylcarbene complexes;[2] (3) tandem alkyne-insertion vinylcarbene trapping reactions;[3] and (4) tandem alkyne-insertion vinylketene trapping reactions.[4]

In recent years, a program to design alternatives to reaction processes #1 and #2 has been initiated, emphasizing the independent generation of hypothetical intermediates of these reactions.[5] Generation of α,β,γ,δ-unsaturated carbene complexes (e.g. **6**) through coupling of E-phenylvinylacetylenes (**4**) and simple carbene complexes (e.g. **5**) should lead to benzannulation products; note the structural similarity between intermediates **2** and **6** in Scheme 1. As noted in the earlier study, the coupling of phenylvinylacetylenes and carbene complexes does in fact lead to benzannulation products. The expected products, enol ether-phenols (e.g. **7**) are not stable under the purification conditions, and are isolated as either cyclic ketals or benzofuran derivatives (**8**). Benzannulation through the coupling of conjugated enynes and carbene complexes can be regarded as



Scheme 1.

Keywords: derivatives; Fischer carbene complexes; coupling reaction.

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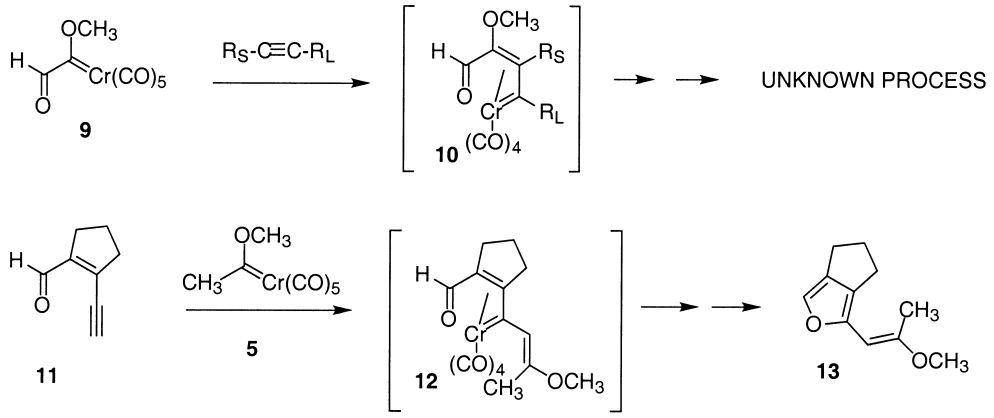
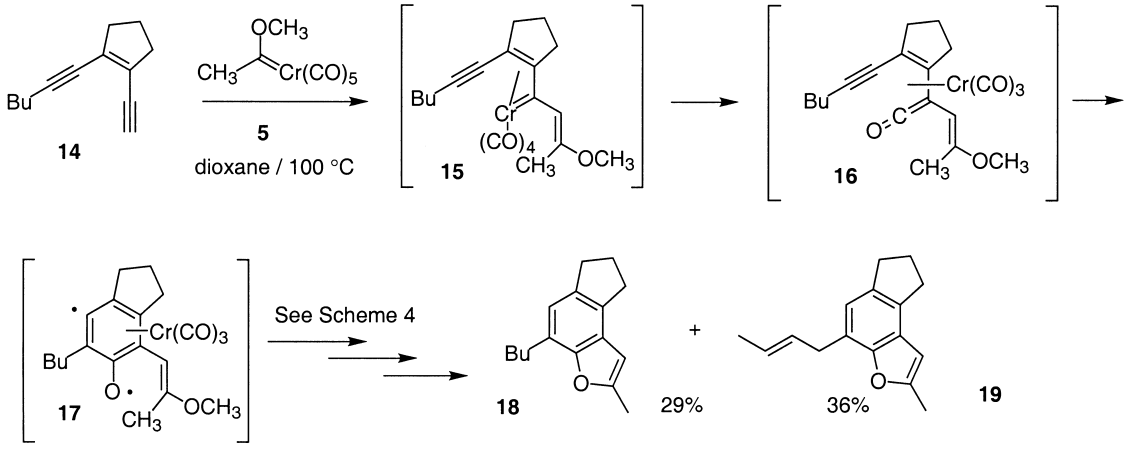


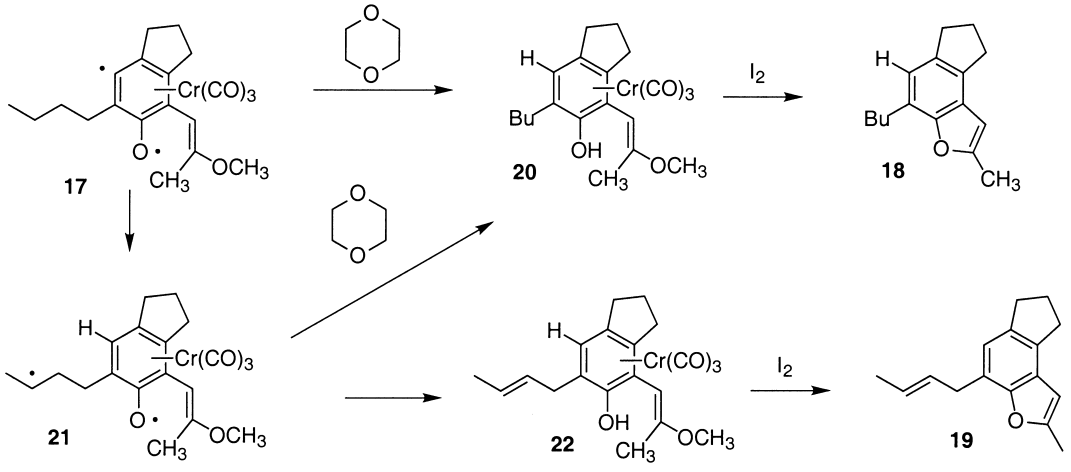
Scheme 2.

a mechanism-based alternative[6] to the direct coupling of alkynes and α,β-unsaturated carbene complexes.

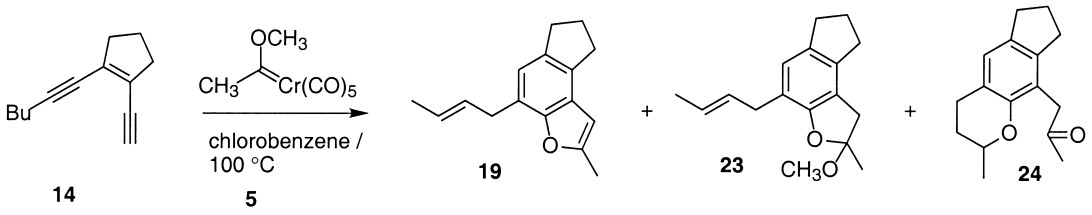
The reaction processes which can be studied using this mechanism-based alternative extend far beyond alternatives to well-documented carbene–alkyne couplings (e.g. the Dötz reaction). For example, the answer to the following question: what are the reaction pathways when the γ,δ-C–C bond of species like **2** and **6** is replaced with a different type of π-bond (illustrated in Scheme 2, compounds **10** and **12**, where the γ,δ-π-bond is a C–O bond), is more easily obtained using the mechanism-based alternative than using the classical approach. The classical approach would require the use of a rare acylcarbene complex[7] (**9**)



Scheme 3.



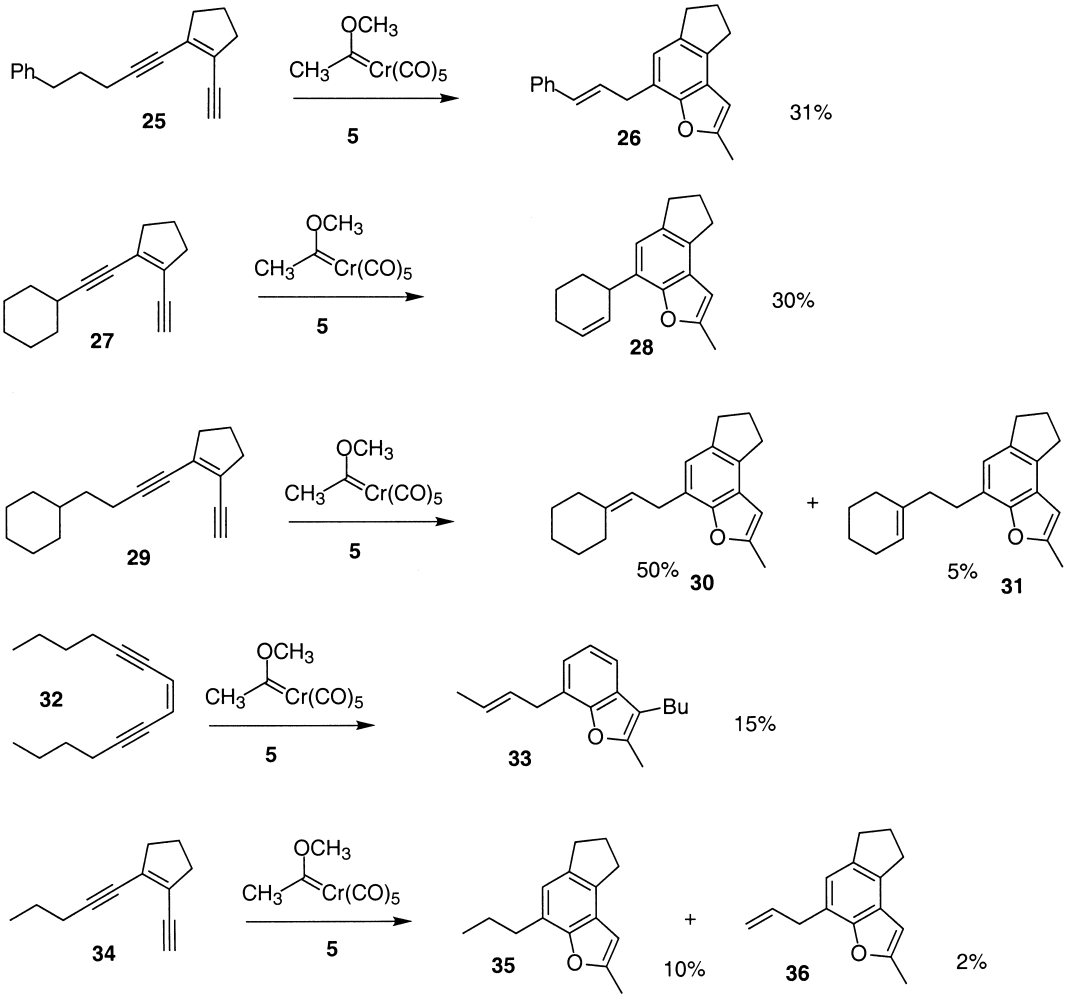
Scheme 4.



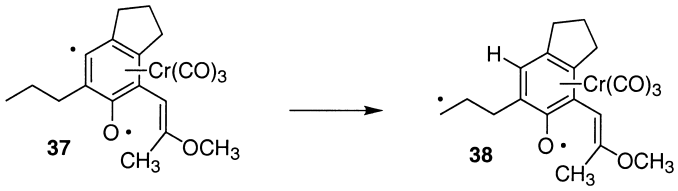
Scheme 5.

and a simple alkyne, while the mechanism-based alternative employs a simple carbene complex and enyne-carbonyl compounds (e.g. **11**), a very well-known class of molecules. As reported in a recent communication, this reaction process gives rise to furan derivatives (**13**).[8]

In a related study, where the γ,δ-π-bond is now part of an alkyne (Scheme 3), the reaction of enediynes (e.g. **14**) with Fischer carbene complex **5** was investigated.[9] This reaction ultimately affords benzofuran derivatives **18** and **19** as the major products of a complex reaction mixture. A mechanism involving selective coupling of the carbene complex with the less substituted alkyne, affording divinylcarbene complex **15**, followed by formation of enyne–ketene intermediate **16** and subsequent Moore cyclization, affording diradical **17**, was proposed. Intramolecular hydrogen atom transfers (Scheme 4) account for the formation of butenyl derivative **19**[10] while intermolecular hydrogen atom transfers from dioxane account for butyl derivative **18**. Enol ether-phenols (or their arene chromium complexes) were converted to the corresponding benzofurans during oxidative workup. Access to diradicals similar to **17** via the intramolecular coupling of alkynes and alkynylcarbene complexes was also reported; in these studies, the diradical intermediates were quenched directly using hydrogen atom donors.[11] The aim of work in this manuscript is to: (1) design reaction conditions which avoid the reduction product **18**; (2) examine the scope of this remote functionalization process



Scheme 6.



Scheme 7.

for a variety of enediyne systems featuring various alkyl groups; and (3) design other reaction processes for the diradical intermediates.

Results

Optimization of the remote functionalization process for coupling of complex 5 and enediyne 14

The goal of these studies is to suppress the intermolecular hydrogen atom donation pathway. The simplest solution to this problem is removal of the hydrogen atom source, dioxane, and replace it with a solvent of lesser hydrogen donating capability. The solvents examined must be compatible with the carbene–alkyne coupling process, and must have no easily-removable hydrogen atoms. Solvents examined include benzene and chlorobenzene, where all of the hydrogens are bound to sp^2 carbon. The coupling reaction did not proceed at an acceptable rate in refluxing benzene, so chlorobenzene was the solvent of choice. The coupling of carbene complex **5** and enediyne derivative **14** in chlorobenzene at 100°C (Scheme 5) afforded a mixture of alkene–benzofuran derivative **19** (4:1 *trans*:*cis*), the corresponding ketal **23**, and the cyclic ether **24**. None of the saturated side chain derivative **18** was observed under these reaction conditions. Simple radical–radical coupling from intermediate diradical **21** of Scheme 4 followed by enol ether hydrolysis can account for formation of cyclic ether derivative **24**. If the crude reaction mixture was treated with iodine prior to chromatographic purification, only benzofuran **19** (4:1 *trans*:*cis*, 60%) and cyclic ether **24** (5%) were obtained.

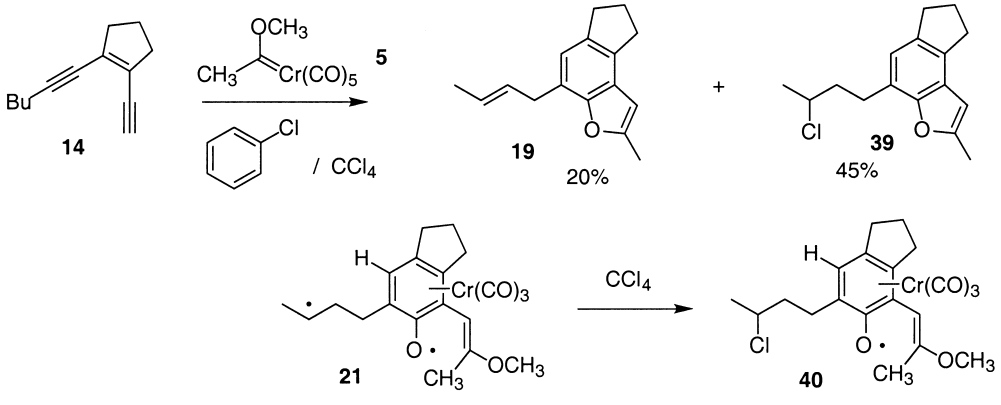
Examination of other alkyl-enediyne substrates

The scope and limit of the remote functionalization process was examined for a variety of other enediyne derivatives[12] (Scheme 6). In the examples depicted in Scheme 6 (in all cases, the product was obtained after iodine treatment), the remote functionalization process occurs with a remarkable degree of regioselectivity in most cases. In the coupling with enediynes **25** and **27**, the reaction cleanly produces the indicated product, accompanied by ≤5% yield of the cyclic ether corresponding to **24**; the *trans*:*cis* selectivity was >90% in all cases where a 1,2-disubstituted alkene was generated. Significant decomposition of the enediyne at the reaction temperature is a competing reaction pathway, and might account for the low yields in some cases. For the coupling with cyclohexylethyl-substituted enediyne **29**, mostly the expected alkylidenecyclohexane derivative **30** was obtained, accompanied by a sizable portion of the cyclohexene isomer **31**; the transformation of **30** to **31** also occurred during storage. Enediyne **32** is the only example where the initial coupling occurs at an internal alkyne, which might account for the lower yield in this case.

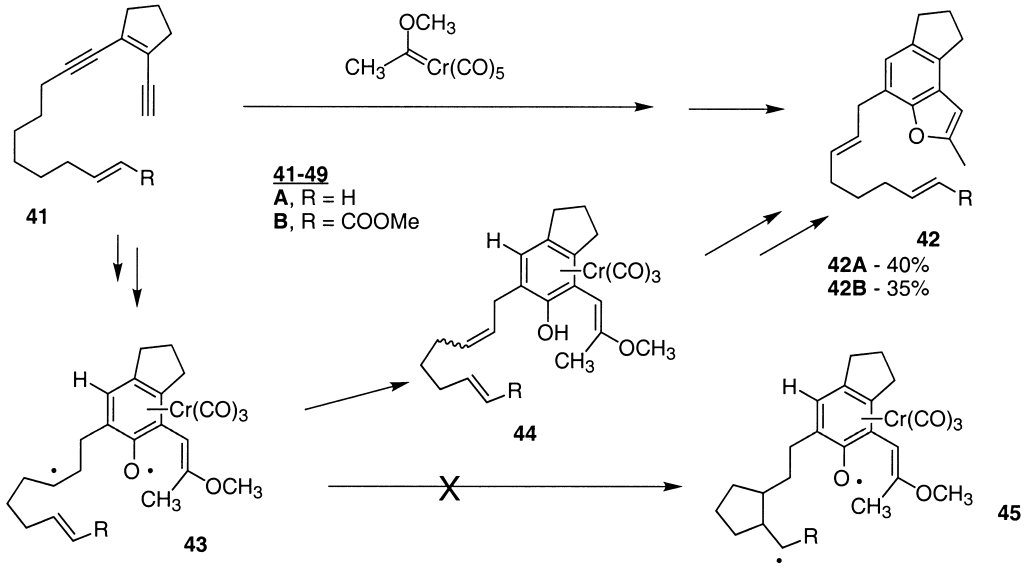
Coupling with the enediyne derivative featuring a propyl side chain (**34**, Scheme 6) proved to be troublesome; in this case predominantly the saturated side chain derivative **35** was observed, accompanied by only trace amounts of the unsaturated compound **36** and a trace amount of the conjugated isomer. A likely problematic step in this case is the first intramolecular hydrogen atom transfer process (Scheme 7). Unlike other substrates examined, a primary radical (**37**) is generated, which might account for the low yield of functionalized products. The overall yield in this reaction is unusually low compared with the other cases, and this might be due to the lack of a hydrogen atom source coupled with the lack of a well-defined reaction pathway.

Design of alternative reaction pathways

An effort to induce processes other than hydrogen atom



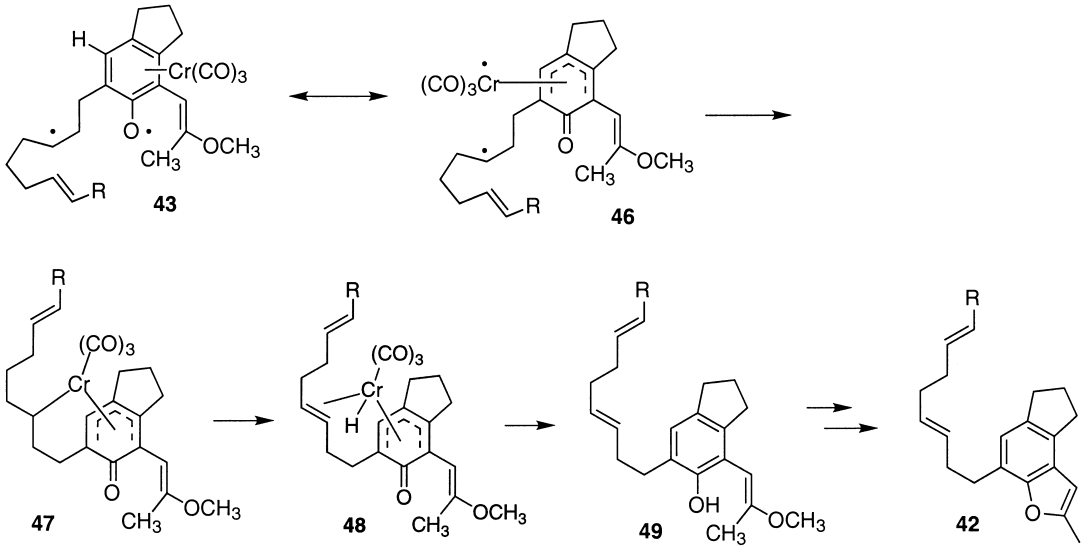
Scheme 8.



Scheme 9.

shifts was also undertaken. The coupling of enediyne **14** and carbene complex **5** was examined in mixtures of chlorobenzene and carbon tetrachloride in an effort to promote chlorination of the free radical intermediate **21**. The reaction in 9:1 chlorobenzene:carbon tetrachloride afforded a mixture of chlorinated derivative **39** and alkene **19** (Scheme 8). A complex intractable reaction mixture was observed from the analogous reaction in 4:1 chlorobenzene:carbon tetrachloride. The carbene complex decomposed within 1 h when heated to reflux in pure carbon tetrachloride, and presumably this reaction pathway accounts for the failure of the coupling reaction in the 4:1 solvent mixture.

Coupling of dienediyne derivatives **41A** and **41B** with carbene complex **5** afforded only the alkene derivatives **42** (Scheme 9) in yields similar to the examples in Scheme 6. These complexes were expected to undergo a radical cyclization process after the first hydrogen atom transfer (**43→45**), however apparently intramolecular transfer of a hydrogen atom to oxygen (**43→44**) is the kinetically-preferred reaction pathway. The results in Schemes 4, 8, and 9 are not consistent with free radical kinetics in similar systems. The rate constant for a secondary alkyl radical undergoing a 5-*exo* trig cyclization is estimated to be $10^5\ s^{-1}$,[13] thus the rate for the second intramolecular hydrogen atom transfer must occur with a rate constant substantially greater than $10^5\ s^{-1}$ since none of the radical cyclization product was observed in the reaction in Scheme 9. However the results in Scheme 8 strongly suggest that the rate constant for the second hydrogen atom transfer is less than the rate constant for intermolecular chloride abstraction, which is estimated to be $2\times10^4\ s^{-1}$ at the concentration of carbon tetrachloride employed (approximately 1 M).[14] An alternative mechanism for the generation of the alkene in the side chain is depicted in Scheme 10. This mechanism involves interaction of the free radical with the chromium



Scheme 10.

tricarbonyl unit, which is expected to have significant free radical character through resonance form **46** (Scheme 10).[15] An alternative mechanism is conversion of the diradical to an alkylchromium species (**47**), followed by β-hydride elimination to form the alkene products. This alternative mechanism involves the intermediacy of alkylchromium species and not free radicals, and might explain the inconsistencies with well-established free radical kinetics.

Conclusions

In summary, we have shown that the remote functionalization process can be controlled very effectively by eliminating hydrogen atom donors from the reaction system, and a diverse array of alkyl substituents have been shown to undergo this process. The alkene forming process appears to be the predominant reaction mode in most cases, and seems to occur in preference to other processes. The observed relative rates for intramolecular hydrogen atom transfer, intermolecular chlorine abstraction, and radical cyclization are not totally consistent which previous studies of free radical processes. An explanation involving free radical intermediates as well as organochromium intermediates has been employed to explain the observed processes. Continued study of the coupling of enediynes with carbene complexes is currently underway in our laboratory.

Experimental

General experimental

Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker AF200 (200 MHz) or Bruker AF400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra were recorded on a Nicolet 5DXC FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak). Mass spectra (MS) were obtained on a VG 7070E spectrometer using electron impact (EI) or chemical ionization (CI) or on a Hewlett-Packard GC-Mass Spec 5970B with Mass Selection Detector; m/e values are reported, followed by the relative intensity in parentheses. Flash column chromatography was performed using thick-walled glass columns and 'flash grade' silica (Bodmann 230–400 mesh). Routine thin layer chromatography (TLC) was performed by using precoated 0.25 mm silica gel plates purchased from Whatman. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. All commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF and dioxane were distilled from sodium-benzophenone ketyl, dichloromethane from calcium hydride prior to use. All reactions were performed in an inert atmosphere created by a slight positive pressure (ca. 0.1 psi) of nitrogen.

General procedure for thermolysis reactions conducted in dioxane

An 0.03–0.05 M chlorobenzene solution of the enediyne (1.0 equiv.) and the carbene complex (1.2 equiv.) was heated to 100°C for 24 h using an oil bath heated to 100°C. The reaction mixture was then allowed to cool to room temperature and the solvent was removed on a rotary evaporator. Hexane (15 mL) was added and the resulting green suspension was filtered through Celite. Iodine (1.5 equiv.) was added to the filtrate and this solution was stirred at room temperature for 24 h. The reaction mixture was poured into aqueous sodium thiosulfate solution in a separatory funnel and the aqueous layer was extracted two times with hexane. The combined hexane layers were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the crude residue was purified by chromatography on silica gel using 19:1 hexane:ethyl acetate as the eluent.

Enediyne syntheses

Enediynes **14**, **25**, **27**, **29**, and **34** were synthesized from 2-bromo-1-cyclopentenecarboxaldehyde[16] in 3 steps:[9] (1) palladium-catalyzed coupling with the appropriate acetylene; (2) reaction with carbon tetrabromide/triphenylphosphine/zinc, which converts the aldehyde (RCHO) to the dibromoalkene (RCH=CBr_2); and (3) reaction with excess butyllithium, which converts RCH=CBr_2 to the corresponding terminal alkyne (RC≡CH). Enediynes **41** were synthesized from 2-bromo-1-cyclopentencarboxaldeyde in 6 steps:[9] (1) reaction with carbon tetrabromide/triphenylphosphine/zinc, which converts the aldehyde (RCHO) to the dibromoalkene (RCH=CBr_2); (2) reaction with excess butyllithium followed by TBDMS-chloride which selectively converts RCH=CBr_2 to the corresponding silylated alkyne (RC≡C-TBDMS) without affecting the original vinylic bromide; (3) palladium-catalyzed coupling with 8-nonyn-1-ol;[17] (4) Swern oxidation; (5) Wittig reaction (CH_2=PPh_3 or Ph_3P=CHCOOMe); and (6) desilylation with tetrabutylammonium fluoride. Enediyne **32** was prepared from *cis* 1,2-dichloroethylene and 1-hexyne according to a literature procedure.[18] In most cases, the enediynes were stable for no more than two weeks when kept in the refrigerator.

Coupling of enediyne 14 with carbene complex 5. The general procedure was followed using enediyne **14** (165 mg, 0.96 mmol) and carbene complex **5** (302 mg, 1.21 mmol) in chlorobenzene (25 mL). Two fractions were obtained after chromatographic purification. The product in the first fraction was benzofuran **19** (130 mg, 60%). The product in the second fraction was cyclic ether **24** (11 mg, 5%).

Benzofuran 19. ^{1}H NMR ($CDCl_3$): *trans isomer* δ 3.52 (d, 2H, J=6.2 Hz), 1.67 (d, 3H, J=5.9 Hz); *cis isomer*: δ 3.60 (d, 2H, J=6.8 Hz), 1.77 (d, 3H, J=6.2 Hz); *the following peaks are overlapping in both isomers:* δ 6.88 (s, 1H), 6.27

(s, 1H), 5.70 (m, 1H), 5.59 (m, 1H), 2.96 (t, 2H, J=7.3 Hz), 2.93 (t, 2H, J=7.3 Hz), 2.44 (s, 3H), 2.13 (quintet, 2H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 155.1, 152.9, 137.9, 132.8, 129.2, 128.3, 126.2, 125.3, 118.9, 101.3, 32.7, 31.2, 27.0, 25.7, 17.8, 14.2; Mass Spec (EI): 226 (M, 100), 227 (20), 225 (35), 212 (10), 211 (38), 201 (10), 199 (20), 197 (20), 186 (17), 185 (75), 184 (13), 183 (42), 172 (17), 171 (22), 169 (19); HRMS calcd for $C_{16}H_{18}O$ 226.13577, found 226.13552.

Cyclic ether 24. ^{1}H NMR ($CDCl_3$): δ 6.84 (s, 1H), 4.07 (m, 1H), 3.61 (s, 2H), 2.80 (m, 6H), 2.12 (s, 3H), 2.02 (quintet, 2H, J=7.3 Hz); 1.64 (m, 2H), 1.35 (d, 3H, J=6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 207.5, 142.9, 135.5, 123.8, 119.6, 116.4, 112.1, 72.4, 42.8, 32.5, 31.6, 29.4, 25.4, 25.2, 21.4, 14.4; Mass Spec (EI): 244 (M, 38), 202 (20), 201(100), 159 (63), 155 (21), 91 (17); HRMS calcd for $C_{16}H_{20}O_2$ 244.1463, found 226.1463.

Coupling of enediyne 25 with carbene complex 5. The general procedure was followed using enediyne **25** (387 mg, 1.66 mmol) and carbene complex **5** (496 mg, 1.98 mmol) in chlorobenzene (27 mL). A single fraction was obtained after chromatographic purification and identified as benzofuran **26** (149 mg, 31%).

Benzofuran 26. ^{1}H NMR ($CDCl_3$): δ 7.27 (m, 5H), 6.93 (s, 1H), 6.46 (m, 2H), 6.28 (s, 1H), 3.75 (d, 2H, J=5.4 Hz), 2.95 (m, 4H), 2.44 (s, 3H), 2.13 (quintet, 2H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$): δ 155.4, 152.6, 138.2, 137.9, 133.4, 131.1, 129.9, 128.2, 127.5, 125.6, 120.9, 119.3, 101.6, 33.3, 32.9, 31.3, 25.9, 14.4; Mass Spec (EI): 288 (M, 100), 245 (23), 185 (19), 184 (10), 171 (10), 114 (12); HRMS calcd for $C_{21}H_{20}O$ 288.1514, found 288.1516.

Coupling of enediyne 27 with carbene complex 5. The general procedure was followed using enediyne **27** (285 mg, 1.44 mmol) and carbene complex **5** (431 mg, 1.72 mmol) in chlorobenzene (30 mL). A single fraction was obtained after chromatographic purification and identified as benzofuran **28** (108 mg, 30%).

Benzofuran 28. ^{1}H NMR ($CDCl_3$): δ 6.93 (s, 1H), 6.27 (s, 1H), 5.92 (dt, 1H, J=12.0, 2.6 Hz), 5.75 (dd, 1H, J=12.0, 2.6 Hz), 3.99 (m, 1H), 2.96 (m, 4H), 2.45 (s, 3H), 2.43 (m, 5H), 1.70 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 155.1, 152.2 137.9, 132.9, 130.0, 128.4, 127.1, 125.4, 117.9, 101.5, 35.2, 32.9, 31.3, 30.6, 25.8, 25.2, 21.3, 14.3; Mass Spec (EI): 252 (M, 100), 224 (28), 223 (16), 207 (21), 181 (20), 172 (21); HRMS calcd for $C_{18}H_{20}O$ 252.1514, found 252.1510.

Coupling of enediyne 29 with carbene complex 5. The general procedure was followed using enediyne **29** (200 mg, 0.90 mmol) and carbene complex **5** (426 mg, 1.70 mmol) in chlorobenzene (30 mL). A single fraction was obtained after chromatographic purification and identified as benzofuran **30**, contaminated with about 10% benzofuran **31** (total of 217 mg, 55%). Treatment of the crude reaction mixture with p-toluenesulfonic acid afforded pure **31**.

Benzofuran 30. ^{1}H NMR ($CDCl_3$): δ 6.90 (s, 1H), 6.27 (s, 1H), 5.33 (t, 1H, J=7.6 Hz), 3.57 (d, 2H, J=7.6 Hz), 2.95 (m, 4H), 2.45 (s, 3H), 2.32 (m, 2H), 2.10 (m, 4H), 1.57 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 155.2, 140.7, 138.0, 132.8, 125.4, 123.4, 122.6, 121.0, 118.8, 101.5, 38.7, 37.7, 32.9, 31.3, 28.7, 27.9, 27.4, 25.9, 22.7, 14.3; Mass Spec (EI): 280 (M, 54), 223 (7), 198 (10), 186 (29), 185 (100), 172 (30); HRMS calcd for $C_{20}H_{24}O$ 280.1827, found 280.1842.

Benzofuran 31. δ 6.90 (s, 1H), 6.27 (s, 1H), 5.49 (m, 1H), 2.95 (m, 6H), 2.45 (s, 3H), 2.32 (m, 2H), 2.10 (m, 4H), 1.57 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 154.9, 152.6, 140.4, 137.7, 132.5, 125.1, 123.1, 120.9, 118.8, 101.2, 38.5, 32.6, 31.1, 30.7, 28.4, 25.6, 25.2, 23.0, 22.5, 14.1.

Coupling of *cis* 7-tetradecen-5,9-diyne (32) with carbene complex 5. The general procedure was followed using enediyne **32** (200 mg, 1.06 mmol) and carbene complex **5** (319 mg, 1.28 mmol) in chlorobenzene (30 mL). A single fraction was obtained after chromatographic purification and identified as benzofuran **33** (35 mg, 14%).

Benzofuran 33. ^{1}H NMR ($CDCl_3$): δ 7.28 (m, 3H), 5.76 (m, 2H), 3.70 (d, 2H, J=7.3 Hz), 2.71 (t, 2H, J=7.3 Hz), 2.51 (s, 3H), 1.81 (d, 3H, J=7.0 Hz), 1.73 (quintet, 2H, J=7.3 Hz), 1.49 (sextet, 2H, J=7.3 Hz), 1.05 (t, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 150.6, 128.9, 128.0, 126.6, 125.3, 124.1, 122.9, 122.2, 116.7, 114.9, 32.6, 32.0, 23.5, 22.6, 18.0, 14.0, 12.1; Mass Spec (EI): 242 (M, 55), 200 (21), 199 (21), 198 (100), 185 (10), 114 (7); HRMS calcd for $C_{17}H_{22}O$ 242.1671, found 242.1666.

Coupling of enediyne 34 with carbene complex 5. The general procedure was followed using enediyne **34** (200 mg, 1.27 mmol) and carbene complex **5** (383 mg, 1.53 mmol) in chlorobenzene (25 mL). Two fractions were obtained after chromatographic purification. The product in the first fraction was saturated benzofuran **35** (25 mg, 10%). The product in the second fraction was unsaturated benzofuran **36** (6 mg, 2%).

Benzofuran 35. ^{1}H NMR ($CDCl_3$): δ 6.87 (s, 1H), 6.25 (s, 1H), 2.94 (m, 4H), 2.82 (t, 2H, J=7.3 Hz), 2.43 (s, 3H), 2.13 (quintet, 2H, J=7.4 Hz), 1.73 (sextet, 2H, J=7.4 Hz), 0.97 (s, 3H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$): δ 154.9, 132.5, 123.2, 118.9, 111.7, 101.2, 32.6, 31.9, 31.2, 25.6, 23.3, 15.5, 14.1; Mass Spec (EI): 214 (M, 54), 199 (12), 186 (16), 185 (100), 171 (9); HRMS calcd for $C_{15}H_{18}O$ 214.1360, found 214.1358.

Benzofuran 36. ^{1}H NMR ($CDCl_3$): δ 6.87 (s, 1H), 6.26 (s, 1H), 6.05 (ddt, 1H, 15.8, 10.4, 6.3 Hz), 5.10 (m, 2H), 3.59 (d, 2H, J=6.3 Hz), 2.94 (m, 4H), 2.43 (s, 3H), 2.12 (quintet, 2H, J=7.3 Hz); Mass Spec (EI): 212 (M, 81), 197 (15), 186 (15), 185 (100), 171 (22).

Coupling of enediyne 14 with carbene complex 5 in the presence of carbon tetrachloride. The general procedure was followed using enediyne **14** (176 mg, 1.02 mmol) and carbene complex **5** (314 mg, 1.26 mmol) in chlorobenzene (27 mL) and carbon tetrachloride (3 mL). Two fractions were obtained after chromatographic purification. The product in the first fraction was benzofuran **19** (53 mg, 20%). The product in the second fraction was chlorinated benzofuran **39** (121 mg, 45%).

Chlorobenzofuran 39. ^{1}H NMR ($CDCl_3$): δ 6.90 (s, 1H), 6.26 (s, 1H), 4.03 (sextet, 1H, J=6.5 Hz), 2.94 (m, 6H), 2.44 (s, 3H), 2.14 (m, 4H), 1.54 (d, 3H, J=6.5 Hz); ^{13}C NMR ($CDCl_3$): δ 155.1, 152.9, 137.9, 133.1, 125.1, 121.4, 119.2, 101.3, 58.3, 40.5, 32.6, 31.1, 27.1, 25.6, 25.3, 14.1; Mass Spec (EI): 262 (M, 31), 244 (9), 186 (54), 185 (100), 183 (12), 171 (13), 165 (11); HRMS calcd for $C_{16}H_{19}OCl$ 262.11246, found 262.11380.

Coupling of enediyne 41A with carbene complex 5. The general procedure was followed using enediyne **41A** (251 mg, 1.11 mmol) and carbene complex **5** (333 mg, 1.33 mmol) in chlorobenzene (15 mL). A single fraction was obtained after chromatographic purification and identified as benzofuran **42A** (122 mg, 40%).

Benzofuran 42A. ^{1}H NMR ($CDCl_3$): δ 6.88 (s, 1H), 6.26 (s, 1H), 5.78 (ddt, 1H, J=17.2, 10.3, 6.8 Hz), 5.60 (m, 2H), 4.97 (br d, 1H, J=17.2 Hz), 4.93 (br d, 1H, J=10.3 Hz), 3.54 (d, 2H, J=5.0 Hz), 2.95 (m, 4H), 2.44 (s, 3H), 2.14 (quintet, 2H, J=7.3 Hz), 2.05 (m, 4H), 1.46 (quintet, 2H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 154.8, 152.2, 138.8, 137.7, 132.6, 131.1, 128.0, 125.0, 121.3, 118.5, 114.1, 101.1, 33.0, 32.6, 31.9, 31.0, 30.0, 28.5, 25.6, 14.0; Mass Spec (EI): 280 (M, 77), 210 (29), 198 (48), 186 (38), 185 (100), 172 (30); HRMS calcd for $C_{20}H_{24}O$ 280.1827, found 280.1835.

Coupling of enediyne 41B with carbene complex 5. The general procedure was followed using enediyne **41B** (350 mg, 1.23 mmol) and carbene complex **5** (352 mg, 1.40 mmol) in chlorobenzene (23 mL). A single fraction was obtained after chromatographic purification and identified as benzofuran **42B** (137 mg, 35%).

Benzofuran 42B. ^{1}H NMR ($CDCl_3$): δ 6.95 (dt, 1H, J=15.7, 6.7 Hz), 6.87 (s, 1H), 6.26 (s, 1H), 5.79 (d, 1H, J=15.7 Hz), 5.56 (m, 2H), 3.71 (s, 3H), 3.54 (d, 2 H, J=5.6 Hz), 2.95 (m, 4H), 2.44 (s, 3H), 2.13 (m, 6H), 1.53 (quintet, 2H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 167.3, 155.2, 149.6, 138.0, 133.1, 130.8, 129.0, 128.5, 125.4, 121.2, 119.0, 111.9, 101.5, 51.4, 32.8, 31.9, 31.6, 31.3, 27.8, 25.7, 25.6, 14.3; Mass Spec (EI): 338 (M, 81), 279 (21), 210 (33), 186 (34), 185 (100), 171 (37); HRMS calcd for $C_{22}H_{26}O_3$ 338.1882, found 338.1890.

Acknowledgements

We thank the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and New Mexico State University for financial support of these research activities. We thank Ms Caroline Ladd of the University of Maryland for acquisition of Mass Spectral Data.

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