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Nonoxidative Transition-Metal-Carbon Bond Cleaving Reactions and Their Application in a Transition-Metal Mediated Cyclopentenone Synthesis.

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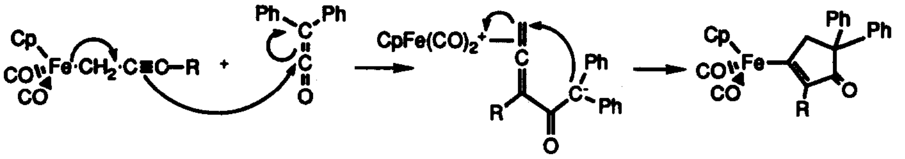
Abstract: Cycloaddition reactions of cyclopentadienyl iron dicarbonyl 2-alkynyl complexes (1) with diphenyl ketene (2) yields transition-metal substituted cyclopentenones (4). The transition metals can subsequently be cleaved from the cyclopentenones under a variety of oxidative and nonoxidative reaction conditions.

The methods most often used by chemists to remove ligands from transition-metal complexes are oxidative carboxylation, halogenolysis and protonolysis.[1] While these methods have been shown to yield useful organic products in many cases, their utility in synthesis is limited because the reaction conditions are many times harshly oxidative and/or acidic. Given the number of organic groups that now work with transition-metal complexes containing metal-carbon σ bonds, one area we are particularly interested in developing in organic/organometallic chemistry is discovering new nonoxidative methods for the removal of ligands from transition metals. The initial substrates that we chose for these nonoxidative cleavage reactions were cyclopentenone complexes (4) synthesized via a 3 + 2 cycloaddition of cyclopentadienyl iron dicarbonyl 2-alkynyl complexes (1) with diphenyl ketene (2) first reported by Wojcicki in 1977.[2] Cycloaddition reactions between transition-metal 2-alkynyl and η^1-allyl complexes and unsaturated electrophilic reagents have been studied in detail over the last 20 years by a number of research groups.[3] The ease of preparation of a variety of 2-alkynyl complexes[4] and ketenes[5] could make this an attractive route to cyclopentenones if efficient methods for removing the cyclopentenone from the metal could be developed. In this initial report we will focus on the metal-carbon bond cleaving reactions.

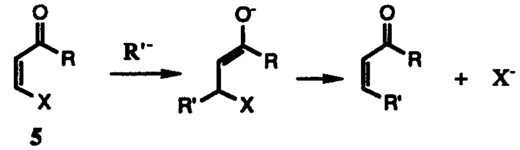


1 2 3 4

a) R = Ph, 82%
b) R = Me, 74%

We have repeated Wojcicki's original reported cycloaddition reactions with diphenyl ketene (2) and they produce $CpFe(CO)_2$ substituted cyclopentenones (4a & 4b) in very good isolated yield. These complexes (4a & 4b) are air-stable yellow-brown solids which can be chromatographed on alumina or silica gel.

There are many examples in the organic literature of Michael type additions to β-heteroatom substituted α,β-unsaturated carbonyl systems (7) which result in the replacement of the β-heteroatom with the Michael nucleophile.[6] Since the $CpFe(CO)_2$ anion could function as a leaving group (X^-) from the metal substituted cyclopentenones (4), we treated these complexes with both Me_2CuLi and Ph_2CuLi and got very high isolated



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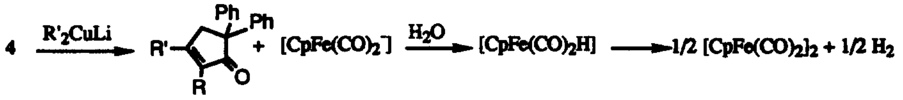
What about X = CpFe(CO)$_2$⁻?

yields of the 3-methyl and 3-phenyl substituted cyclopentenones (**6**).[7] Upon addition of the metallocyclopentenone to the cuprate, the solution turns the characteristic brown color seen when the highly air sensitive CpFe(CO)$_2$⁻ anion (**7**) is generated from [CpFe(CO)$_2$]$_2$.[8] Aqueous workup presumably yields iron hydride (**8**) which is known to decompose thermally to yield the CpFe(CO)$_2$ dimer[9] (**9**)(isolated (70%) in addition to the cyclopentenone (**6b**)). This reaction is unique among metal-carbon bond cleaving reactions in that not only does this reaction replace a metal-carbon bond with a carbon-carbon bond, it also provides us with a transition-metal complex (**9**) which is the original starting material used in the synthesis of the alkynyl complexes (**1**).

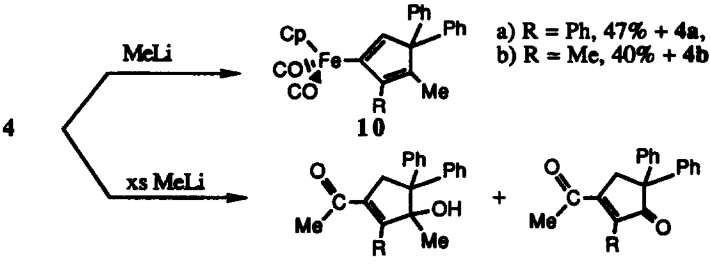


6 a) R=R'=Ph, 72% **7** **8** **9** from b, 70%

b) R=Ph, R'=Me, 76%

c) R=R'=Me, 82%

Given the success of the cuprate experiments outlined above, we were interested in exploring the reactivity of these cyclopentenone complexes (**4**) with alkyl lithiums. There have been isolated reports of carbon-carbon bond forming reactions occurring when metal carbonyl alkyl complexes have been treated with carbon nucleophiles[10] and we wanted to investigate possible alkyl lithium induced carbon-carbon bond forming reactions of complexes (**4**). Treatment of **4a** with MeLi (1.2 eq) at 0°C (3 min) produced **10a** (22%) and recovered **4a** (45%). Treatment of **4a** with MeLi (1.2 eq) at 0°C (2 h) produced **10a** (27%), **11a** (9%), and recovered **4a** (35%). When we increased the amount of MeLi used to two equivalents for long (3 h) or short (3 min) reaction times, we isolated 2-(cyclopentadienyl iron dicarbonyl) substituted cyclopentadienes (**10**) in 40-50% yield and lesser amounts of unreacted **4**. However, when these cyclopentenone complexes (**4**) were treated with a large excess (5 equivalents) of methyl lithium, the major products isolated were 3-acetyl-cyclopentenols (**11**).[11]



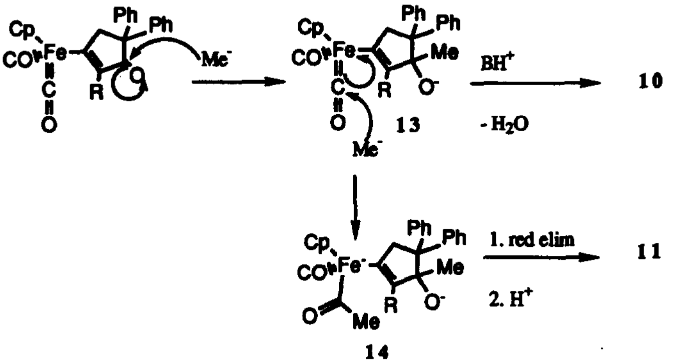
a) R = Ph, 47% + **4a**, 6%
b) R = Me, 40% + **4b**, 22% + **6b**, 2%

10

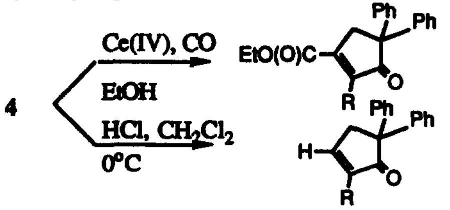
11
a) R = Ph, 51%
b) R = Me, 38%

12
b) R = Me, 10%

These nonstoichiometric reactions of methyl lithium with **4** were unexpected and may be due to alkyl lithium aggregation since the tetrameric alkyl lithium aggregates have been shown to give quite different results when treated with 1-4 equivalents of electrophiles.[12] To explain the formation of these two different types of products (**10** and **11**), we envision possible reaction pathways as outlined below. We assume that methyl lithium would rapidly attack the α,β-unsaturated carbonyl system in a 1,2 fashion to generate an intermediate of structure (**13**). In the presence of a large excess of methyl lithium, a rapid attack on a complexed CO would yield acetyl complex (**14**) which could undergo reductive elimination to generate **11**. Isolation of some acetyl substituted cyclopentenone (**12**) would indicate that attack at the metal carbonyl can be competitive with attack on the cyclopentenone carbonyl.[10] In the absence of a large excess of methyl lithium, elimination of the tertiary alcohol formed after protonation of **13** on workup (Addition of MeLi to a solution of **4b** in d_8 THF does not generate **10b** directly.) to yield cyclopentadienes (**10**) is the major reaction path. As expected complexes **10** were unaffected by MeLi and can be ruled out as possible precursors to **11**.



We have also found that the cyclopentenone framework can be liberated from complexes (**4**) using ceric ammonium nitrate or HCl.[1] Oxidative carboxylation produced 3-carboethoxy-2-cyclopentenones (**15**) in moderate to good yields on a preparatively useful scale (2 - 4 mmol) and acid cleavage yielded 2-methyl-5,5-diphenyl-2-cyclopentenone (**16**) (53%).



15 a) R = Ph, 45%; b) R = Me, 63%

16 b) R = Me, 53%

We are beginning to explore reactions of propargyl complexes with ketenes other than diphenyl ketene. We will continue to explore new methods for cyclopentenone generation from complexes of general structure (**4**) and apply this methodology in the synthesis of specific cyclopentenone targets.

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7. Copper iodide (2 mmol) was added to THF (6 mL) in a flame dried flask under nitrogen. After cooling to -10°C, alkyl lithium (4 mmol) was added via syringe. The solution was then stirred for 0.5 h at -10°C and iron complex (4) (0.5 - 1 mmol, dissolved in THF (9 mL)) was added dropwise to the cuprate. The solution was allowed to stir at 0°C for 2 h after this addition. The reaction was then quenched by the addition of a saturated NaCl solution (20 mL) and extracted with diethyl ether (3 x 20 mL). The extracts were dried (Na_2SO_4) and the solvent removed by rotary evaporation. The crude product was chromatographed on silica gel (10:1, petroleum ether:acetone) to yield **6a** as a light yellow gum; IR ($CDCl_3$) 3062, 3031, 2959, 2928, 1710, 1599, 1495, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) 7.55-7.12 (m, 20H), 3.90 (s, 2H). EI MS 386 (32), 357 (11), 310 (100), 267 (16). EI HRMS calcd. for $C_{29}H_{22}O$: 386.1671; Found: 386.1671; **6b** as a white solid mp: 145-147°C (acetone/petroleum ether), IR ($CDCl_3$) 3065, 2950, 1710, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) 7.46-7.21 (m, 15H), 3.48 (s, 2H), 2.29 (s, 3H). EI HRMS calcd. for $C_{24}H_{20}O$: 324.1513; Found: 324.1513. Anal. calcd. for $C_{24}H_{20}O$; C: 88.89; H: 6.17. Found; C: 88.78, H: 6.19 and **6c** as a light yellow waxy solid: mp 49-51°C (acetone/petroleum ether), IR ($CDCl_3$) 3063, 2962, 2926, 1697, 1651, 1601, 1580, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) 7.36-7.10 (m, 10H), 3.29 (s, 2H) 2.11 (s, 3H), 1.76 (s, 3H). Anal. calcd. for $C_{19}H_{18}O$; C: 87.02, H: 6.87. Found; C: 86.77, H: 6.97.
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11. Iron complex (4) (0.5 - 1 mmol) was dissolved in THF (7 mL) in a flame dried flask under nitrogen. Methyl lithium (2.5 - 5 mmol) was added and the solution was stirred for 3 min before being quenched with saturated NaCl as above. Workup and silica gel chromatography 10:1 (petroleum ether:acetone) as described above yielded **11a** as a light yellow gum: IR ($CDCl_3$) 3550, 3059, 3029, 2982, 2930, 1674, 1598, 1495, 1443 cm^{-1}; ^1H NMR ($CDCl_3$) 7.55-7.10 (m, 15H), 3.43 (apparent q, AB CH_2, J= 19.0 Hz, 2H), 2.11 (s, 1H, exchanges w/D_2O), 1.84 (s, 3H), 1.23 (s, 3H). EI HRMS calcd. for $C_{26}H_{24}O_2$: 368.1785. Found: 368.1772. Anal. calcd. for $C_{26}H_{24}O_2$; C: 84.78, H: 6.52. Found; C: 84.57, H: 6.60. From **4b**, **12b** was isolated as a yellow gum: IR ($CDCl_3$) 3063, 2930, 1709, 1675, 1206 cm^{-1}; ^1H NMR ($CDCl_3$) 7.43 - 7.09 (m, 10H), 3.56 (d, J = 2.1 Hz, 2H), 2.52 (s, 3H), 2.09 (t, J = 2.1 Hz, 3H); EIMS 290(100) 204 (46); HRMS calcd. for $C_{20}H_{18}O_2$: 290.1307; Found: 290.1308 followed by **11b** as a light yellow gum: IR ($CDCl_3$) 3561, 3061, 3035, 2980, 2936, 1679, 1652, 1602, 1492, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) 7.52-7.20 (m, 10H), 3.28 (apparent q, AB CH_2, J= 16.7 Hz, 2H), 2.36 (s, 3H), 2.17 (s, 1H, exchanges with D_2O), 2.16 (s, 3H), 1.12 (s, 3H); HRMS calcd. for $C_{21}H_{22}O_2$: 306.1620; Found: 306.1618.
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