JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

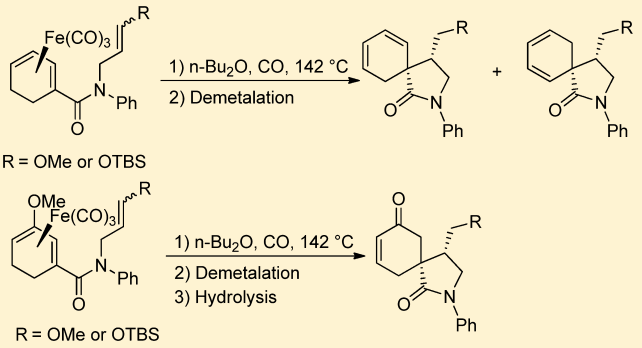
Stereocontrolled Intramolecular Iron-mediated Diene/Vinyl Ether Cyclocoupling Reactions

Anthony J. Pearson,* Sheng Zhang, and Huikai Sun

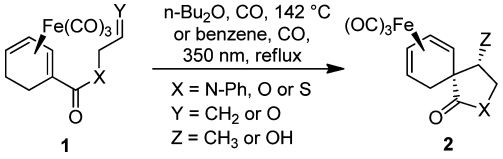
Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, United States

Supporting Information

ABSTRACT: A stereocontrolled intramolecular iron-mediated diene/olefin cyclocoupling reaction has been explored using vinyl ethers as the olefin partners. Spirolactams with functionalized (alkoxymethyl) side chains can be formed under thermal conditions. With a methoxy substituent on the diene, demetalation and hydrolysis of the cyclocoupling product afforded a single diastereomer.



Transition metal-promoted cyclocoupling reactions of alkenes and alkynes have a rich history and occupy an important place in organic synthesis methodology. These processes often complement their more traditional organic counterparts in terms of stereochemistry and one's ability to carry out reactions that are symmetry forbidden or compromised by more facile competing processes. While such transformations in the coordination sphere of a metal are usually not concerted single-step processes, they are nevertheless usually stereospecific, a result of continual attachment of the reacting ligand(s) to the metal as the key bond-forming steps proceed.[1] Our group has developed a stereocontrolled intramolecular iron-mediated diene/olefin cyclocoupling reaction, equivalent to a [6 + 2] ene reaction, which forms spirolactones, spirothiolactones and spirolactams under thermal or photothermal conditions (eq 1, Y = CH_2, Z = CH_3).[2] We



(1)

recently extended this reaction to include aldehydes (**1**, Y = O) as the 2π component,[3] which affords hydroxyl substituted spirolactams (**2**, Z = OH) that embody in the organic moiety key structural features of natural products such as the spirostaphylotrichins.[4] The work described in this report aims to further expand the scope of the cyclocoupling reaction to include vinyl ethers as the 2π component, which would result in spirocyclic molecules having (protected) hydroxymethyl side chains. We examined both methoxy- and *t*-butyldimethylsilyl vinylethers on the side chain to access differently protected hydroxymethyl groups; we also examined the use of methoxy-substituted cyclohexadieneiron complexes that we have previously shown to afford a single diastereomer cyclohexenone after demetalation and hydrolysis.[5]

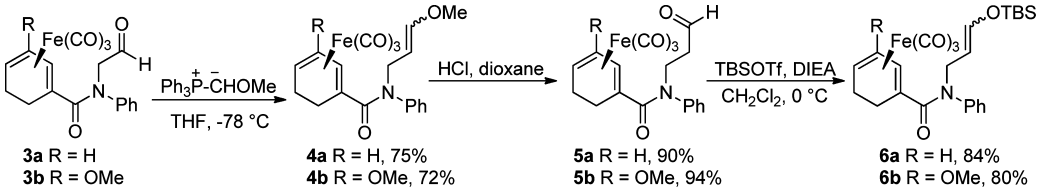
Previously reported[3] aldehydes **3a** and **3b** were each reacted with (methoxymethyl)triphenyl-phosphorane to afford methoxy vinyl ethers **4a** (*E*/*Z* = 2:1) and **4b** (*E*/*Z* = 2:1) (Scheme 1). We also planned to study the cyclizations of silyl ether analogs of complexes **4**, because a silyl protecting group is easier to remove from the anticipated cyclization products when required. Since the requisite silyl vinyl ethers can be accessed from the aldehydes that are produced by hydrolysis of the methyl vinyl ethers, we chose to use this method rather than a more direct approach for the present study. Treatment of **4a** and **4b** with 2 N HCl in dioxane afforded aldehydes **5a** and **5b**, which were reacted with *t*-butyldimethylsilyl trifluoromethanesulfonate in the presence of Hünig's base to give **6a** (*E*/*Z* = 7:1) and **6b** (*E*/*Z* = 5.5:1) in 84 and 80% yield, respectively.

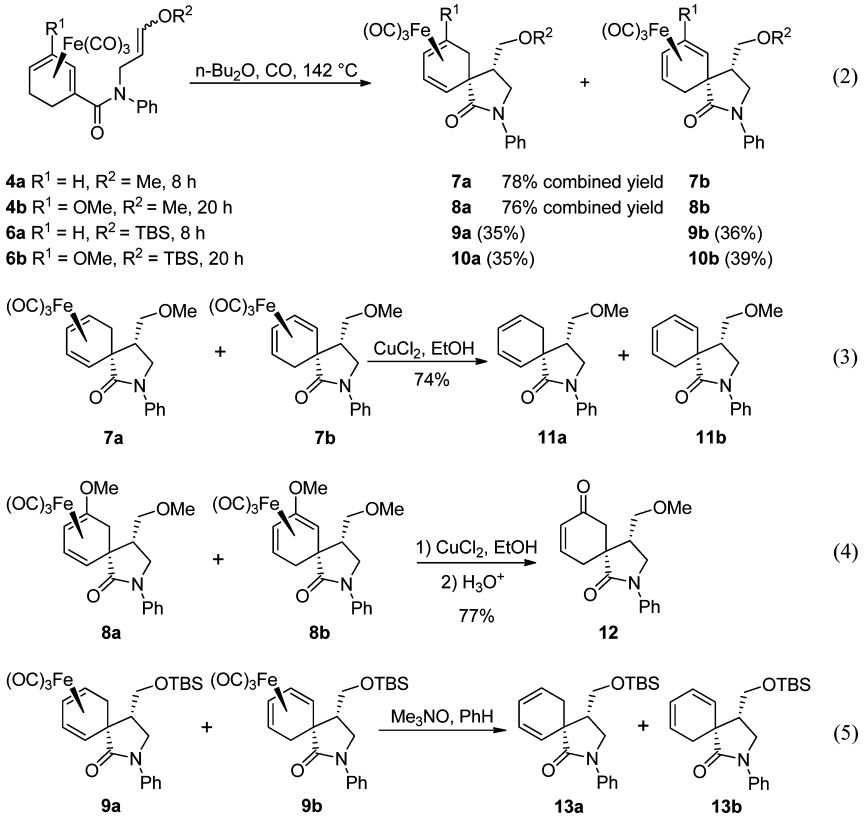
With substrates **4a**/**b** and **6a**/**b** in hand, we investigated their reactivity in the diene/alkene cyclocoupling reaction. Refluxing **4a** in *n*-Bu_2O (0.02 mmol/mL) under CO atmosphere at 142 °C for 8 h generated an inseparable mixture of **7a**/**b** (eq 2; isomers **a** result from thermal rearrangement of the initial products, isomers **b**[2]). The mixture was demetalated with ethanolic $CuCl_2$[6] to afford an inseparable mixture of **11a**/**b** (eq 3). Subjection of **4b** to the same thermal cyclization conditions for 20 h similarly gave an inseparable mixture of **8a**/**b** in 76% combined yield (eq 2). Demetalation and *in situ* hydrolysis of the mixture of **8a**/**b** afforded a single product, α,β-unsaturated ketone **12** (eq 4). Complex **6a** was also subjected to thermal cyclization conditions and gave two separable regioisomers, **9a**

Received: August 16, 2012
Published: September 5, 2012

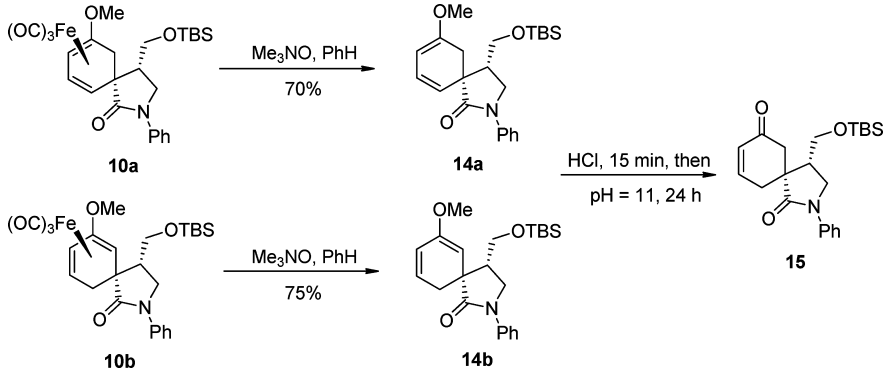
   dx.doi.org/10.1021/jo301721d | *J. Org. Chem.* 2012, 77, 8835–8839

Scheme 1





Scheme 2



and **9b** (eq 2). Demetalation of the mixture **9a**/**b** with $CuCl_2$ gave a complex mixture of products (according to TLC inspection), possibly due to partial hydrolysis of the TBS ether, which were not isolated and characterized. Demetalation of the individual complexes using trimethylamine N-oxide[7] gave **13a** and **13b** in 74 and 72% yield, (eq 5; the mixture of complexes can also be demetalated to afford a mixture of **13a**/**b**). Exposure of **6b** to thermal cyclization conditions for 20 h generated two separable regioisomers **10a** and **10b**. Stirring the mixture of **10a**/**b** with $CuCl_2$ in EtOH gave a complex mixture of products (TLC), as expected from our experience with **9a**/**b**. Consequently **10a** and **10b** were demetalated separately with trimethylamine N-oxide to afford dienes **14a** and **14b** (Scheme 2). We studied the hydrolysis of **14a** and **14b** separately. While **14b** was hydrolyzed quickly by stirring with oxalic acid for 10 min to afford ketone **15** cleanly, under the same conditions **14a** afforded a mixture of several products according to TLC, among which the major product was not **15**; after 24 h under the same conditions, the TBS group was found to be completely removed, but still a mixture of products was

dx.doi.org/10.1021/jo301721d | J. Org. Chem. 2012, 77, 8835−8839

obtained. Next we examined the hydrolysis of **14a**/**b** using aqueous HCl in methanol. Dienol ether **14b** was cleanly hydrolyzed to **15** in 10 min. Under the same conditions, **14a** still afforded a mixture of several products (by TLC) after 15 min reaction time. After adjusting the pH to 11 using NaOH solution, stirring was continued for 24 h, and **15** was isolated as the major product. To expedite the overall conversion to the final enone, the mixture of **14a** and **14b** was hydrolyzed to **15** in a yield of 67% using this procedure (Scheme 2).

EXPERIMENTAL SECTION

High Resolution Mass Spectrometry (HRMS). HRMS measurements were made in-house using a magnetic sector instrument. Iron carbonyl complexes often do not give a molecular ion, owing to facile loss of one or more CO ligands. However, we have found that evaporation of solvent from a solution of the iron complex in ethyl acetate prior to sample introduction overcomes this problem and gives appropriate molecular ions for most complexes; we do not currently have an explanation for this observation.

General Procedure for the Thermally Induced Cyclization. The appropriate amide was dissolved in freshly distilled *n*-butyl ether (0.02 mmol/mL) under Ar in a dried glass round-bottom flask. The solution was degassed by bubbling with Ar for 10 min and then with CO for 10 min. The solution was refluxed under a balloon of CO for 8−20 h. The cooled reaction mixture was filtered through Celite and was concentrated in vacuo. Flash chromatography yielded the desired products.

General Procedure for Demetalation. Method A: To a solution of the iron complex in benzene was added trimethylamine oxide (30 equiv). The reaction mixture was stirred for 24 h at rt and then was filtered through Celite and concentrated *in vacuo*. Separation by flash chromatography afforded the pure products. Method B: To a small vial was added the iron carbonyl complex (0.1 mmol) and sat. $CuCl_2$ solution in EtOH (2.5 mL). The solution was stirred at rt for 18−24 h and then was concentrated *in vacuo*. After water (4 mL) was added to the residue, the mixture was extracted with ether (3 mL × 3). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude products were purified by flash chromatography.

*[N-(3-Methoxyallyl)-N-phenylcyclohexa-1,3-dienecarboxamide]-tricarbonyliron (**4a**).* To a mixture of (methoxymethyl)-triphenylphosphonium chloride (310 mg, 0.91 mmol) in THF (6 mL) under Ar at −78 °C, was added KHMDS (0.5 M in toluene, 2.0 mL, 0.99 mmol). Stirring was continued at this temperature for 1 h, then a solution of aldehyde **3a** (230 mg, 0.60 mmol) in THF (2.0 mL) was added and the reaction was held at −78 °C for 1 h. The mixture was allowed to warm to rt and stirring was continued for 1 h. The reaction mixture was carefully quenched with water (4 mL), extracted with Et_2O (6 mL × 3), and the combined extract was washed with brine (3 mL × 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (Hex:EA/8:1) afforded **4a** as two isomers (185 mg, 75%) as a yellow oil. R_f = 0.22 (Hex:EA/8:1; Hex = hexanes, EA = ethyl acetate). ^{1}H NMR (400 MHz, C_6D_6): δ 7.00−6.96 (m, 5H), 6.90−6.87 (m, 5H), 6.17 (d, J = 12.8 Hz, 1H), 5.48 (d, J = 6.4 Hz, 1H), 5.29−5.26 (m, 2H), 5.02−4.95 (m, 1H), 4.81−4.76 (m, 1H), 4.70−4.65 (m, 1H), 4.49−4.36 (m, 2H), 4.17−4.13 (m, 2H), 3.81 (dd, J = 14.0, 8.0 Hz, 1H), 3.00 (s, 3H), 2.78 (s, 3H), 2.52 (d, J = 3.6 Hz, 2H), 2.14−2.02 (m, 2H), 1.45−1.39 (m, 2H), 1.12−1.03 (m, 4H). ^{13}C NMR (100 MHz, C_6D_6): δ 211.5, 172.1, 171.8, 151.4, 148.7, 144.8, 144.2, 129.7, 129.5, 127.1, 126.9, 102.7, 97.9, 86.9, 83.6, 83.5, 73.3, 73.0, 63.2, 63.1, 59.0, 55.3, 50.7, 46.3, 26.2, 26.1, 25.6, 25.5. HRMS (EI) calcd for $C_{20}H_{20}FeNO_5$ $[M + H]^+$ 410.0691, found 410.0679.

*[3-Methoxy-N-(3-methoxyallyl)-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (**4b**).* To a mixture of (methoxymethyl)triphenylphosphonium chloride (617 mg, 1.8 mmol) in THF (10 mL) under Ar at −78 °C was added KHMDS (0.5 M in toluene, 4.6 mL, 2.3 mmol). Stirring was continued at this temperature for 1 h, then a solution of aldehyde **3b** (400 mg, 0.97 mmol) in THF (2.0 mL) was added and the reaction was held at −78 °C for 1 h. The mixture was allowed to warm to rt and stirring was continued for 1 h. The reaction mixture was carefully quenched with water (4 mL), extracted with Et_2O (10 mL × 3), and the combined extract was washed with brine (5 mL × 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (Hex:EA/9:1) afforded **4b** as two isomers (307 mg, 72%) as a yellow oil. R_f = 0.2 (Hex:EA/9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.31 (m, 4H), 7.29−7.20 (m, 2H), 7.18−7.10 (m, 4H), 6.18 (d, J = 13.0 Hz, 1H), 5.82 (d, J = 4.6 Hz, 1H), 5.38−5.34 (m, 2H), 4.84 (ddd, 13.0, 8.1, 7.0 Hz, 1H), 4.52−4.42 (m, 2H), 4.39 (dd, J = 14.0, 7.0 Hz, 1H), 4.21−4.12 (m, 1H), 3.77 (dd, J = 14.0, 8.1 Hz, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.38 (s, 3H), 3.37−3.34 (m, 2H), 3.32 (s, 3H), 1.72−1.55 (m, 3H), 1.19−1.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 173.5, 151.1, 148.6, 143.8, 143.3, 138.4, 138.4, 129.8, 129.6, 128.5, 128.0, 127.8, 127.4, 102.2, 97.6, 68.9, 68.9, 60.7, 60.5, 59.7, 56.0, 55.9, 55.9, 54.2, 51.1, 46.6, 27.0, 26.8, 24.5. HRMS (EI) calcd for $C_{21}H_{22}FeNO_6$ $[M + H]^+$ 440.0797, found 440.0796.

*[3-Methoxy-N-(3-oxopropyl)-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (**5b**).* A solution of **4b** (178 mg, 0.40 mmol) in dioxane (6 mL) was treated with 2 N HCl (2 mL) at rt for 1.5 h. Et_2O (50 mL) was added, and the solution was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (Hex:EA/4:1) afforded **5b** (160 mg, 94%) as a yellow oil. R_f = 0.3 (Hex:EA/4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 7.46−7.37 (m, 2H), 7.35−7.28 (m, 1H), 7.23−7.15 (m, 2H), 5.28 (s, 1H), 4.29−4.19 (m, 1H), 3.71−3.60 (m, 1H), 3.38 (s, 3H), 3.41−3.36 (m, 1H), 2.84−2.74 (m, 1H), 2.62−2.52 (m, 1H), 1.65−1.55 (m, 1H), 1.14−1.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 174.3, 143.4, 138.4, 130.2, 128.1, 128.0, 68.9, 59.9, 56.0, 54.2, 46.6, 42.3, 26.9, 24.4. HRMS (EI) calcd for $C_{20}H_{20}FeNO_6$ $[M + H]^+$ 426.0640, found 426.0629.

*[N-(3-((tert-Butyldimethylsilyl)oxy)allyl)-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (**6a**).* To a solution of aldehyde **5a** (30.0 mg, 76 μmol) and DIPEA (19.6 mg, 152 μmol) in CH_2Cl_2 (2 mL) at 0 °C under Ar, was added dropwise a solution of TBSOTf (30.1 mg, 114 μmol) in CH_2Cl_2 (0.2 mL). After the reaction solution was stirred at 0 °C for 2 h, it was quenched with sat. sodium bicarbonate (2 mL), and then extracted with CH_2Cl_2 (2 mL × 3). The combined organic extract was washed with brine (2 mL) and dried over Na_2SO_4. Flash chromatography (Hex:EA/8:1) afforded **6a** as two isomers (32.4 mg, 84%, E/Z = 7/1) as a yellow oil. R_f = 0.3 (Hex:EA/8:1). E isomer: ^{1}H NMR (400 MHz, C_6D_6): δ 7.11−7.05 (m, 2H), 6.98−6.94 (m, 3H), 6.30 (d, J = 12.0 Hz, 1H), 5.45−5.38 (m, 1H), 5.34 (d, J = 4.4 Hz, 1H), 4.55 (dd, J = 14.0, 7.2 Hz, 1H), 4.30−4.22 (m, 1H), 3.92 (dd, J = 14.0, 8.4 Hz, 1H), 2.61−2.59 (m, 1H), 2.17−2.10 (m, 1H), 1.56−1.48 (m, 1H), 1.19−1.09 (m, 2H), 0.88 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (100 MHz, C_6D_6): δ 211.5, 172.0, 145.2, 144.2, 129.6, 127.0, 106.5, 87.0, 83.6, 73.2, 63.1, 49.9, 46.3, 26.1, 15.6, 18.4, −3.4, −5.3. Z isomer: ^{1}H NMR (400 MHz, C_6D_6): δ 7.11−7.05 (m, 2H), 6.98−6.94 (m, 3H), 6.10 (d, J = 5.6 Hz, 1H), 5.45−5.38 (m, 1H), 5.08−5.03 (m, 1H), 4.75 (dd, J = 14.0, 6.4 Hz, 1H), 4.61−4.57 (m, 1H), 4.29−4.22 (m, 1H), 2.61−2.59 (m, 1H), 2.17−2.10 (m, 1H), 1.56−1.48 (m, 1H), 1.19−1.09 (m, 2H), 0.78 (s, 9H), −0.10 (s, 3H), −0.16 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 211.5, 171.8, 144.8, 141.2, 129.5, 126.9, 106.2, 86.9, 83.5, 73.1, 63.0, 46.3, 25.7, 25.5, 18.2, −3.4, −5.6. HRMS (EI) calcd for $C_{24}H_{28}FeNO_5Si$ $[M - CH_3]^+$ 494.1086, found 494.1067.

*[N-(3-((tert-Butyldimethylsilyl)oxy)allyl)-3-methoxy-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (**6b**).* To a solution of aldehyde **5b** (49.4 mg, 91 μmol) and DIPEA (23.6 mg, 183 μmol) in CH_2Cl_2 (3 mL) at 0 °C under Ar, was added dropwise a solution of TBSOTf (30.1 mg, 114 μmol) in CH_2Cl_2 (0.2 mL). After the reaction solution was stirred at 0 °C for 2 h, it was quenched with sat. sodium bicarbonate (2 mL), and then extracted with CH_2Cl_2 (2 mL × 3). The combined organic extract was washed with brine (2 mL) and dried over Na_2SO_4. Flash chromatography (Hex:EA/8:1) afforded **6b** as two isomers (39.3 mg, 80%, E/Z = 5.5/1) as a yellow oil. R_f = 0.33 (Hex:EA/8:1). E isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.39 (m, 2H), 7.34−7.30 (m, 1H), 7.20−7.15 (m, 2H), 6.13 (d, J = 12.0 Hz, 1H), 5.43 (s, 1H), 5.07 (ddd, J = 12.0, 8.3, 7.0 Hz, 1H), 4.43 (dd,

dx.doi.org/10.1021/jo301721d | J. Org. Chem. 2012, 77, 8835−8839

14.1, 7.0 Hz, 1H), 3.89 (dd, 14.1, 8.3 Hz, 1H), 3.46 (s, 3H), 3.44−3.40 (m, 1H), 1.75−1.62 (m, 3H), 1.22−1.11 (m, 1H), 0.84 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 145.1, 143.3, 138.5, 129.9, 128.7, 127.7, 106.0, 69.1, 56.0, 54.4, 50.4, 27.0, 25.9, 24.7, 18.6, −5.0, −5.0. *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.36 (m, 2H), 7.31−7.28 (m, 1H), 7.24−7.20 (m, 2H), 6.20 (d, J = 5.7 Hz, 1H), 5.30 (s, 1H), 4.73−4.66 (m, 1H), 4.52−4.45 (m, 1H), 4.30 (dd, 14.4, 8.0 Hz, 1H), 3.46 (s, 3H), 3.44−3.40 (m, 1H), 1.75−1.62 (m, 3H), 1.22−1.11 (m, 1H), 0.74 (s, 9H), −0.01 (s, 3H), −0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 144.0, 141.5, 138.5, 129.7, 128.3, 127.6, 105.3, 69.1, 56.0, 54.4, 46.6, 27.1, 25.8, 24.7, 18.3, −5.2, −5.3. HRMS (EI) calcd for $C_{26}H_{34}FeNO_6Si$ $[M + H]^+$ 540.1505, found 540.1512.

*[4-(Methoxymethyl)-2-phenyl-2-azaspiro[4.5]deca-6,8-dien-1-one]tricarbonyliron (**7a** and **7b**).* According to the general procedure for thermally induced cyclization, a solution of **4a** (35.5 mg, 86.7 μmol) in n-Bu_2O (4.5 mL) was heated at 142 °C under CO for 8 h. Flash chromatography (Hex:EA/8:1) afforded a mixture of two isomers **7a** and **7b** (27.7 mg, 78%) as a yellow oil. R_f = 0.23 (Hex:EA/8:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.60 (m, 4H), 7.37−7.32 (m, 4H), 7.14−7.10 (m, 2H), 5.59−5.56 (m, 2H), 5.51−4.92 (m, 1H), 5.32−5.30 (m, 1H), 4.05 (dd, J = 4.0, 3.2 Hz, 1H), 3.81−3.70 (m, 4H), 3.54 (dd, J = 4.2, 4.2 Hz, 1H), 3.46−3.48 (m, 2H), 3.38 (s, 3H), 3.30−3.23 (m, 2H), 3.23 (s, 3H), 3.01 (dd, J = 2.4, 1.2 Hz, 1H), 2.78 (dd, J = 6.8, 1.2 Hz, 1H), 2.05−2.02 (m, 1H), 1.94−1.91 (m, 1H), 2.10−1.90 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 211.5, 176.2, 176.1, 139.8, 139.6, 128.8, 128.7, 124.4, 124.3, 119.4, 119.3, 88.7, 86.9, 84.6, 82.1, 71.3, 71.0, 63.8, 63.3, 61.1, 59.4, 59.1, 59.0, 51.7, 50.9, 48.7, 48.1, 44.5, 41.7, 40.0, 32.2. HRMS (EI) calcd for $C_{20}H_{20}FeNO_5$ $[M + H]^+$ 410.0691, found 410.0675.

*[9-Methoxy-4-(methoxymethyl)-2-phenyl-2-azaspiro[4.5]deca-6,8-dien-1-one]tricarbonyliron (**8a**) and [7-methoxy-4-(methoxymethyl)-2-phenyl-2-azaspiro[4.5]deca-6,8-dien-1-one]tri- carbonyliron (**8b**).* According to the general procedure for thermally induced cyclization, a solution of **4b** (85.1 mg, 0.19 mmol) in n-Bu_2O (10 mL) was heated at 142 °C under CO for 20 h. Flash chromatography (Hex:EA/10:1) afforded mixture of **8a** and **8b** (65 mg, 76%) as a yellow oil. R_f = 0.25 (Hex:EA/10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.60 (m, 4H), 7.37−7.28 (m, 4H), 7.14−7.07 (m, 2H), 5.50 (d, J = 4.5 Hz), 5.21−5.18 (m, 1H), 4.99 (dd, J = 6.2, 4.5 Hz, 1H), 4.04 (dd, J = 10.2, 6.8 Hz, 1H), 3.78−3.74 (m, 2H), 3.73 (s, 3H), 3.72−3.67 (m, 2H), 3.53 (s, 3H), 3.51−3.44 (m, 2H), 3.39−3.36 (m, 1H), 3.36 (s, 3H), 3.27 (s, 3H), 3.00 (d, J = 1.9 Hz, 1H), 2.75−2.70 (m, 2H), 2.56−2.48 (m, 1H), 2.45 (d, J = 15.1 Hz, 1H), 2.42−2.35 (m, 1H), 2.20 (d, J = 15.1 Hz, 1H), 1.89 (dd, J = 14.8, 1.7 Hz, 1H), 1.74 (dd, J = 14.8, 3.2 Hz, 1H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.6, 176.7, 176.0, 141.4, 139.9, 129.1, 129.1, 124.6, 119.7, 119.6, 119.3, 79.7, 73.4, 71.8, 71.4, 67.5, 60.3, 59.4, 56.7, 55.3, 53.7, 53.7, 50.7, 49.1, 48.8, 48.0, 44.4, 41.9, 40.4, 34.0. HRMS (EI) calcd for $C_{21}H_{22}FeNO_6$ $[M + H]^+$ 440.0797, found 440.0789.

*[4-(((tert-Butyldimethylsilyl)oxy)methyl)-2-phenyl-2-azaspiro-[4.5]deca-6,8-dien-1-one]tricarbonyliron (**9a** and **9b**).* According to the general procedure for thermally induced cyclization, a solution of **6a** (50 mg, 0.10 mmol) in n-Bu_2O (5 mL) was heated at 142 °C under CO for 8 h. Gravity column chromatography (Hex:EA/12:1) afforded individual isomers **9a** (17.5 mg, 35%) as a crystalline solid and **9b** (18.1 mg, 36%) as an oil. **9a**: R_f = 0.22 Hex:EA/12:1). Mp: 132−135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J = 8.8, 1.2 Hz, 2H), 7.36−7.31 (m, 2H), 7.13−7.09 (m, 1H), 5.56−5.54 (m, 1H), 5.33−5.30 (m, 1H), 4.11 (dd, J = 4.2, 4.0 Hz, 1H), 3.70−3.62 (m, 3H), 3.43−3.39 (m, 1H), 3.00 (dd, J = 6.0, 1.2 Hz, 1H), 2.38−2.34 (m, 1H), 2.11 and 2.04 (ABX, J = 16.0, 2.4 Hz, 2H), 0.76 (s, 9H), −0.03 (s, 3H), −0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 176.3, 139.9, 128.7, 124.0, 119.1, 88.7, 82.2, 64.2, 63.5, 62.2, 50.7, 49.1, 43.5, 32.4, 25.6, 17.9, −5.7, −5.8. HRMS (EI) calcd for $[M+H]^+$ ($C_{25}H_{32}FeNO_5Si$) 510.1399, found, 510.1363. **9b**: R_f = 0.20 Hex:EA/12:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.6 Hz, 2H), 7.34 (dd, J = 8.4, 7.6 Hz, 2H), 7.11 (dd, J = 7.6, 7.2 Hz, 1H), 5.62−5.59 (m, 1H), 5.50 (dd, J = 5.6, 5.2 Hz, 1H), 3.96 (dd, J = 10.4, 4.0 Hz, 1H), 3.86−3.80 (m, 2H), 3.71 (dd, J = 10.0, 3.2 Hz, 1H), 3.22 (dd, J = 3.2, 2.0 Hz, 1H), 2.87 (d, J = 6.0 Hz, 1H), 2.25−2.21 (m, 1H), 2.03 and 1.91 (ABX, J = 15.2, 2.0 Hz, 2H), 0.84 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.8, 176.2, 139.7, 128.7, 124.2, 119.2, 86.7, 84.9, 61.8, 60.9, 59.6, 51.8, 48.1, 46.5, 40.1, 25.8, 18.1, −5.5, −5.6. HRMS (EI) calcd for $C_{24}H_{28}FeNO_5Si$ $[M-CH_3]^+$ 494.1086, found 494.1084.

*[4-(((tert-Butyldimethylsilyl)oxy)methyl)-9-methoxy-2-phenyl-2-azaspiro[4.5]deca-6,8-dien-1-one]tricarbonyliron (**10a**) and [4-(((tert-butyldimethylsilyl)oxy)methyl)-7-methoxy-2-phenyl-2-azaspiro[4.5]deca-6,8-dien-1-one]tricarbonyliron (**10b**).* According to the general procedure for thermally induced cyclization, a solution of **6b** (40 mg, 74 μmol) in n-Bu_2O (5 mL) was heated at 142 °C under CO for 20 h. Flash chromatography (Hex:EA/15:1 then 8:1) afforded two isomers **10a** (14 mg, 35%)as a crystalline solid and **10b** (15.5 mg, 39%) as an oil. **10a**: R_f = 0.23 (Hex:EA/12:1). Mp: 142−144 °C. ^{1}H NMR (400 MHz, $(CD_3)_2O$): δ 7.84−7.79 (m, 2H), 7.43−7.36 (m, 2H), 7.17−7.10 (m, 1H), 5.69 (d, J = 4.7 Hz, 1H), 5.20 (dd, J = 6.3, 4.7 Hz, 1H), 4.37 (dd, J = 10.3, 7.2 Hz, 1H), 3.98 (dd, J = 10.7, 4.0 Hz, 1H), 3.91 (dd, J = 10.7, 2.8 Hz, 1H), 3.75 (d, J = 10.3 Hz, 1H), 3.62 (s, 3H), 3.10 (dd, J = 6.3, 1.2 Hz, 1H), 2.66 (d, J = 15.4 Hz, 1H), 2.54−2.49 (m, 1H), 2.29 (d, J = 15.4 Hz, 1H), 0.80 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2O$): δ 213.2, 175.5, 140.7, 128.6, 123.6, 120.2, 119.0, 79.6, 74.0, 63.0, 62.0, 56.1, 50.4, 49.5, 43.5, 34.3, 25.3, 17.8, −6.3, −6.4. HRMS (EI) calcd for MH^+ ($C_{26}H_{34}FeNO_6Si$) 540.1505, found 540.1487. **10b**: R_f = 0.26 Hex:EA/8:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.62 (m, 2H), 7.35−7.29 (m, 2H), 7.12−7.07 (m, 1H), 5.24−5.21 (m, 1H), 3.93 (dd, J = 10.2, 3.9 Hz, 1H), 3.86 (dd, J = 10.2, 6.8 Hz, 1H), 3.82 (dd, J = 10.2, 6.5 Hz, 1H), 3.74 (s, 3H), 3.72 (dd, J = 10.2, 1.8 Hz, 1H), 3.16 (d, J = 2.1 Hz, 1H), 2.74−2.70 (m, 1H), 2.30−2.24 (m, 1H), 1.92−1.87 (m, 1H), 1.74 (dd, J = 14.8, 3.2 Hz, 1H), 0.83 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 141.7, 140.0, 129.0, 124.4, 119.4, 67.8, 62.3, 55.4, 53.8, 48.8, 48.2, 46.3, 40.6, 26.1, 18.4, −5.2, −5.3. HRMS (EI) calcd for $C_{26}H_{34}FeNO_6Si$ $[M + H]^+$ 540.1505, found 540.1497.

*4-(Methoxymethyl)-2-phenyl-2-azaspiro[4.5]deca-6,8-dien-1-one (**11a** and **11b**).* According to method B of the general procedure for demetalation, the mixture of **7a** and **7b** (31 mg, 75.8 μmol) was stirred with sat. $CuCl_2$ solution in EtOH (2.05 mL) for 18 h. The crude product was purified by flash chromatography (Hex:EA/5:1) to afford a mixture of two isomers (15.1 mg, 74%) as an oil. R_f = 0.40 (Hex:EA/5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73−7.69 (m, 4H), 7.42−7.28 (m, 4H), 7.19−7.15 (m, 2H), 6.16 (m, 2H), 6.00−5.95 (m, 2H), 5.90−5.88 (m, 1H), 5.82−5.81 (m, 1H), 5.74 (dt, J = 11.2, 0.8 Hz, 1H), 5.59 (dt, J = 10.8, 0.8 Hz, 1H), 3.95−3.88 (m, 2H), 3.74−3.30 (m, 2H), 3.63−3.57 (m, 2H), 3.46−3.41 (m, 2H), 3.46−3.41 (m, 2H), 3.36 (s, 3H), 3.34 (s, 3H), 3.04 (dt, J = 18.0, 2.8 Hz, 1H), 2.68 (dt, J = 18.0, 6.0 Hz, 1H), 2.61−2.57 (m, 1H), 2.56−2.48 (m, 1H), 2.41 (dd, J = 18.0, 5.6 Hz, 1H), 2.31 (dd, J = 18.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 177.0, 139.6, 139.5, 128.9, 127.0, 126.7, 125.6, 125.1, 124.5, 124.2, 123.6, 123.0, 119.7, 119.6, 72.0, 71.9, 59.1, 59.0, 49.0, 48.6, 48.3, 43.5, 42.5, 31.7, 26.0. HRMS (EI) calcd for $C_{17}H_{19}NO_2$ $[M]^+$ 269.1416, found 269.1418.

*4-(Methoxymethyl)-2-phenyl-2-azaspiro[4.5]dec-8-ene-1,7-dione (**12**).* According to method B of the general procedure for demetalation, the mixture of **8a** and **8b** (30.5 mg, 68.5 μmol) was stirred with sat. $CuCl_2$ solution in EtOH (2 mL) for 22 h. Flash chromatography (Hex:EA/2:1) afforded **12** (15 mg, 77%). R_f = 0.30 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68−7.62 (m, 2H), 7.42−7.35 (m, 2H), 7.20−7.14 (m, 2H), 6.94 (ddd, J = 10.2, 5.4, 2.8 Hz, 1H), 6.17−6.13 (m, 1H), 3.94 (dd, J = 10.3, 7.2 Hz, 1H), 3.70 (dd, J = 10.3, 4.1 Hz, 1H), 3.43 (dd, J = 9.4, 5.4 Hz, 1H), 3.36 (dd, J = 9.4, 1.8 Hz, 1H), 3.28 (s, 3H), 2.89−2.81 (m, 2H), 2.59−2.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 174.7, 146.8, 139.3, 130.1, 129.2, 129.1, 125.1, 120.0, 71.7, 59.2, 50.3, 48.6, 40.9, 40.7, 34.1. HRMS (EI) calcd for $C_{17}H_{19}NO_3$ $[M]^+$ 285.1365, found 285.1363.

*[4-(((tert-Butyldimethylsilyl)oxy)methyl)-2-phenyl-2-azaspiro-[4.5]deca-6,8-dien-1-one]tricarbonyliron (**13a** and **13b**).* According to method B of the general procedure for demetalation, **9a** (17 mg, 33.4 μmol) and **9b** (18 mg, 35.3 μmol) were each stirred separately

dx.doi.org/10.1021/jo301721d | J. Org. Chem. 2012, 77, 8835−8839

with Me_3NO (30 equiv) in benzene (1 mL) at rt for 24 h. Flash chromatography (Hex:EA/10:1 and 12:1) afforded **13a** (9.1 mg, 74%) and **13b** (9.4 mg, 72%), respectively, each as a film. **13a**: R_f = 0.25 (Hex:EA/10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68−7.63 (m, 2H), 7.37−7.32 (m, 2H), 7.15−7.09 (m, 1H), 6.09 (dd, J = 9.5, 4.9 Hz, 1H), 5.95−5.90 (m, 1H), 5.80−5.75 (m, 1H), 5.71−5.67 (m, 1H), 3.86 (dd, J = 9.8, 7.4 Hz, 1H), 3.78 (dd, J = 10.3, 4.2 Hz, 1H), 3.67 (dd, J = 9.8, 7.2 Hz, 1H), 3.61 (dd, J = 10.3, 8.4 Hz, 1H), 2.68−2.60 (m, 1H), 2.42−2.31 (m, 2H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 139.8, 129.0, 127.4, 125.6, 124.7, 124.6, 123.8, 119.8, 63.0, 48.7, 48.5, 45.9, 26.0, 26.0, 18.4, −5.2, −5.3. HRMS (EI) calcd for M^+ ($C_{22}H_{31}NO_2Si$) 369.2124, found, 369.2119. **13b**: R_f = 0.22 (Hex:EA/12:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.67 (m, 2H), 7.40−7.34 (m, 2H), 7.16−7.12 (m, 1H), 6.12 (dd, J = 9.7, 5.1 Hz, 1H), 5.98−5.93 (m, 1H), 5.86−5.80 (m, 1H), 5.66−5.62 (m, 1H), 3.91 (dd, J = 10.0, 7.5 Hz, 1H), 3.78 (dd, J = 10.3, 4.2 Hz, 1H), 3.69 (dd, J = 10.0, 5.4 Hz, 1H), 3.65 (dd, J = 10.3, 8.0 Hz, 1H), 2.93 (dt, J = 17.8, 3.9 Hz, 1H), 2.53−2.46 (m, 1H), 2.28 (dd, J = 17.8, 5.6 Hz, 1H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 140.0, 129.1, 128.7, 126.8, 125.1, 124.7, 124.0, 123.8, 119.9, 62.8, 49.2, 48.7, 43.7, 32.0, 26.1, 18.4, −5.1, −5.2. HRMS (EI) calcd for $C_{22}H_{31}NO_2Si$ $[M]^+$ 369.2124, found 369.2114.

*4-(((tert-Butyldimethylsilyl)oxy)methyl)-9-methoxy-2-phenyl-2-azaspiro[4.5]deca-6,8-dien-1-one (**14a**) and 4-(((tert-Butyldimethylsilyl)oxy)methyl)-7-methoxy-2-phenyl-2-azaspiro[4.5]-deca-6,8-dien-1-one (**14b**).* According to method B of the general procedure for demetalation, **10a** (13 mg, 24.1 μmol) and **10b** (14 mg, 26.0 μmol) were each stirred separately with Me_3NO (30 equiv.) in benzene (1 mL) at rt for 24 h. Flash chromatography (Hex:EA/10:1 and 12:1) afforded **14a** (6.7 mg, 70%) and **14b** (7.8 mg, 75%), respectively, each as a film. **14a**: R_f = 0.25 (Hex:EA/10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.65 (m, 2H), 7.40−7.33 (m, 2H), 7.16−7.10 (m, 1H), 6.08 (dd, J = 9.4, 6.1 Hz, 1H), 5.37 (d, J = 9.4 Hz, 1H), 4.96 (dd, J = 6.1, 2.2 Hz, 1H), 3.90 (dd, J = 9.8, 7.2 Hz, 1H), 3.82 (dd, J = 10.4, 4.2 Hz, 1H), 3.68 (dd, J = 9.8, 5.9 Hz, 1H), 3.65−3.59 (m, 1H), 3.61 (s, 3H), 2.89−2.82 (m, 1H), 2.41−2.28 (m, 2H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 157.5, 140.0, 129.1, 126.3, 124.7, 120.2, 120.0, 92.0, 62.4, 55.3, 50.6, 48.9, 45.4, 30.2, 26.2, 18.5, −5.1, −5.2. HRMS (EI) calcd for M^+ ($C_{23}H_{33}NO_3Si$) 399.2230, found, 399.2226. **14b**: R_f = 0.22 (Hex:EA/12:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.68 (m, 2H), 7.41−7.34 (m, 2H), 7.17−7.11 (m, 1H), 5.94−5.88 (m, 1H), 5.85−5.80 (m, 1H), 4.51 (s, 1H), 3.90 (dd, J = 10.0, 4.4 Hz, 1H), 3.77 (dd, J = 10.0, 7.5 Hz, 1H), 3.68 (dd, J = 10.0, 4.6 Hz, 1H), 3.66 (dd, J = 10.0, 2.2 Hz, 1H), 3.58 (s, 3H), 2.89−2.82 (m, 1H), 2.49−2.42 (m, 1H), 2.27 (dd, 17.7, 5.6 Hz, 1H), 0.84 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 155.4, 140.1, 129.1, 127.8, 124.6, 124.0, 119.8, 90.6, 63.1, 54.6, 49.4, 49.1, 43.8, 32.6, 26.1, 18.5, −5.1, −5.2. HRMS (EI) calcd for $C_{23}H_{33}NO_3Si$ $[M]^+$ 399.2230, found 399.2228.

*4-(((tert-Butyldimethylsilyl)oxy)methyl)-2-phenyl-2-azaspiro[4.5]-dec-8-ene-1,7-dione (**15**).* To a solution of a 1:1 mixture of **14a** and **14b** (10.1 mg, 25.3 μmol) in MeOH (1 mL) were added 5 drops of 1 M HCl and the solution was stirred for 15 min. Aqueous NaOH (0.1 M) was added to adjust the pH to 11 and stirring was continued for 24 h. The reaction mixture was extracted with ether (3 mL × 3), and the combined organic layers were washed with brine (2 mL) and dried over Na_2SO_4. Flash chromatography (Hex:EA/4:1) afforded **15** (6.5 mg, 67%) as a film. R_f = 0.22 (Hex:EA/4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69−7.64 (m, 2H), 7.41−7.34 (m, 2H), 7.19−7.13 (m, 1H), 6.96−6.89 (m, 1H), 6.18−6.12 (m, 1H), 3.96 (dd, J = 10.1, 7.4 Hz, 1H), 3.73−3.66 (m, 2H), 3.61 (dd, J = 10.1, 6.5 Hz, 1H), 2.90 (d, J = 16.8 Hz, 1H), 2.83−2.75 (m, 1H), 2.66 (d, J = 16.8 Hz, 1H), 2.51−2.36 (m, 2H), 0.80 (s, 9H), 0.02 (s, 3H), −0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 174.9, 146.7, 130.3, 129.2, 125.0, 119.9, 62.7, 50.3, 48.9, 42.3, 40.8, 34.3, 26.0, 18.4, −5.3, −5.3. HRMS (EI) calcd for $C_{22}H_{31}NO_3Si$ $[M]^+$ 385.2073, found 385.2071.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*ajp4@case.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (CHE-0743234) and Case Western Reserve University for financial support of this research.

■ REFERENCES

(1) For selected reviews, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Ojima, I.; Tzamariiudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (c) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (d) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129. (e) Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477. (f) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25. (g) Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521. Other examples: (h) Trost, B. M.; Shen, H. C.; Schulz, T.; Koradin, C.; Schirok, H. *Org. Lett.* **2003**, *5*, 4149 and references cited therein.

(2) (a) Pearson, A. J.; Zettler, M.; Pinkerton, A. A. *J. Chem. Soc., Chem. Commun.* **1987**, 264. (b) Pearson, A. J.; Zettler, M. W. *J. Am. Chem. Soc.* **1989**, *111*, 3908. (c) Pearson, A. J.; Zettler, M. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1243. (d) Pearson, A. J.; Alimardanov, A.; Pinkerton, A. A.; Parrish, D. A. *J. Org. Chem.* **1998**, *63*, 6610.

(3) Pearson, A. J.; Sun, H. *J. Org. Chem.* **2007**, *72*, 7693.

(4) Sandmeier, P.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 975 and references cited therein.

(5) Pearson, A. J.; Dorange, I. B. *J. Org. Chem.* **2001**, *66*, 3140.

(6) Thompson, D. J. *J. Organomet. Chem.* **1976**, *108*, 381.

(7) Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* **1974**, 336.