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Application of Olefin Cross-Metathesis to Organometallics. Synthesis of Unsaturated Ferrocenyl Alcohols and Ketones

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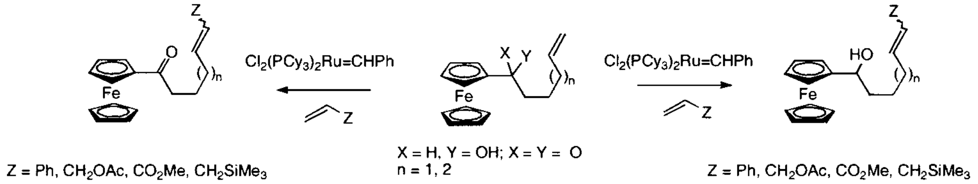
ABSTRACT



The application of olefin cross-metathesis to terminally unsaturated α-hydroxy- and α-ketoferrocenes is reported. Both substrates provided the terminally functionalized olefins in moderate to good yield. These examples represent the first cases of cross-metathesis of substrates containing an organometallic functional group.

With the advent of well-characterized catalysts, olefin metathesis has become a viable and powerful method for the construction of carbon−carbon bonds and, as a consequence, this reaction has received a significant amount of attention.[1] Much of the recent effort in this field has focused on catalyst development aimed at improving the reactivity, selectivity, and stability of the carbene complexes.[2] In addition, the expansion of the range of substrates that successfully engage in this transformation is constantly being reported.[3,4] Not surprisingly, this reaction has been employed as a key step in the total synthesis of several complex natural products.[5,6] While the intramolecular variant of this reaction, ring-closing metathesis, has seen expanded use in synthesis, the intermolecular variant between two different alkenes, i.e., cross-metathesis, has received significantly less attention.[7] Herein, we report the first application of cross-metathesis for the preparation of terminally functionalized olefins containing an organometallic group (Figure 1).[8]

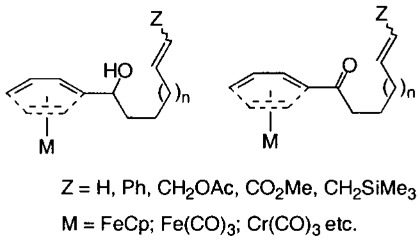


Figure 1. General structures of the target organometallics.

In the course of several planned studies, we needed rapid access to a number of α-hydroxy- and α-keto-substituted

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[1] For recent reviews of this area see: (a) Schuster, M.; Blechert, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans 1* **1998**, 372. (d) Ivin, K. J. *J. Mol. Catal. A: Chem.* **1998**, *133*, 1. (e) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29.

[2] For recent catalyst developments see: (a) Huang, J. K.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F.; Herrman, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (c). Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

[3] For the use of phosphorus-containing templates see: (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939. (b) Hanson, P. R.; Stoiavona, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297. (c) Trevitt, M.; Gouverneur, V. *Tetrahedron Lett.* **1999**, *40*, 7333.

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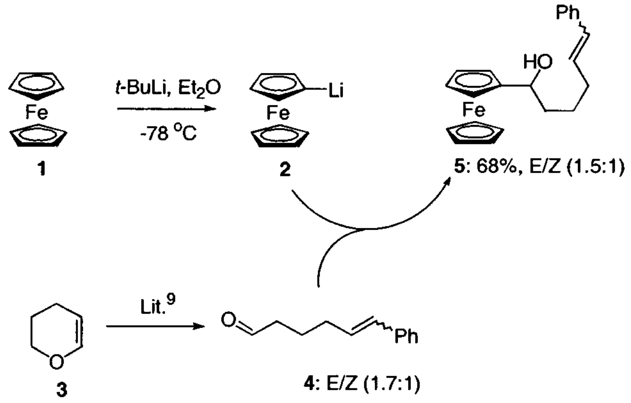
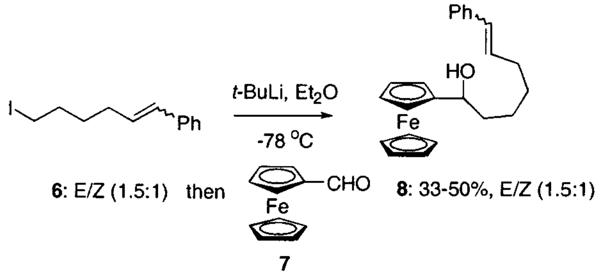
organometallics that possessed diversely functionalized terminal olefins. In the early stages of this program, alcohols **5** and **8** were synthesized through the sequences indicated in Schemes 1 and 2. Alcohol **5** was prepared in 68% yield (28% overall from **3**) by reaction of aldehyde **4**, prepared from dihydropyran according to the procedure of Moeller and co-workers, with lithioferrocene.[9,10] On the other hand, alcohol **8** was prepared in a variable 33−50% yield by conversion of iodide **6**, prepared by standard methods, into the organolithium and then reaction with ferrocenecarboxaldehyde (11−16% overall from **3**).[11,12] Although these routes provided the requisite target compounds, several aspects of these syntheses were rather unsatisfactory. First, for each substituent to be evaluated, an aldehyde related to **4** (three steps) or an iodide related to **6** (three steps) would have to be prepared and then further manipulated to provide the target organometallics, rendering the overall synthetic routes rather lengthy. Second, for the more reactive substituents, e.g., Y = CO_2R and CN, problems with chemoselectivity were envisioned during the preparation of organolithiums. Third, the approach to **8** had drawbacks associated with reproducibility and low overall yields. With these points in mind, an alternative approach was required and, of the options considered, olefin cross-metathesis appeared to represent an attractive and versatile solution. Therefore, we have investigated the application of this tactic to ferrocenyl-containing olefins.[8]

Scheme 1

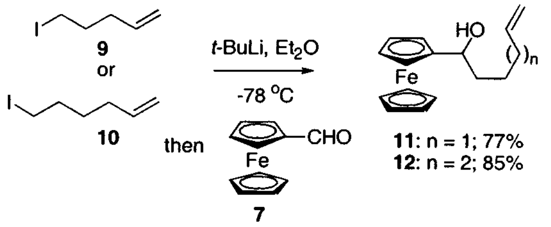


Scheme 2



As part of an ongoing project, alcohols **11** and **12** had been prepared in 72% and 85% yield, respectively, by the reaction of the appropriate organolithium with ferrocenecarboxaldehyde **7** (Scheme 3).[13] With the ferrocenyl alcohols in hand, exploratory experiments were performed with alcohol **11** and trimethylallylsilane (2 equiv) in the presence of Grubbs' catalyst ($Cl_2(PCy_3)_2Ru{=}CHPh$). Under "typical"

Scheme 3



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(4) For the use of sulfur-containing templates see: (a) Shon, Y.-S.; Lee, T. R. *Tetrahedron Lett.* **1997**, *38*, 1283. (b) Miller, J. F.; Termin, A.; Kock, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158. (c) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.

(5) For RCM approaches to the manzamine alkaloids see: (a) Pandit, U. K.; Borer, B. C.; Bieraugel, H. *Pure Appl. Chem.* **1996**, *68*, 659. (b) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (c) Pandit, U. K.; Overkleft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959.

(6) For RCM approaches to the epothilones see: (a) Yang, Z.; He, D.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166. (b) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523. (c) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733. (d) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 3553.

(7) See ref 1e for a review of cross-metathesis. See also: (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998. (b) Crowe, W. E.; Golberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162. (c) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117. (d) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427. (e) Blanco, O. M.; Castedi, L. *Synlett* **1999**, 557. (f) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091. (g) Hu, Y.-J.; Roy, R. *Tetrahedron Lett.* **1999**, *40*, 3305.

(8) Although we are not aware of any previous reports of cross-metathesis reactions involving organometallics, there are some reports of ring-closing metathesis reactions of substrates containing $FcCH_2$ as a protecting group; see: (a) Guibe, F.; Garro-Helion, F. *Chem. Commun.* **1996**, 641. (b) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677. In addition, Grubbs has reported that vinylferrocene undergoes metathesis with $(TFA)_2(PPh_3)_2Ru{=}CH{=}CPh_2$ to produce $(TFA)_2(PPh_3)_2Ru{=}CHFc$ in low (36%) yield; see: Wu, Z.; Nguyen, S. T.; Gubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 550. See also: Buretea, M.; Tilley, T. D. *Organometallics* **1997**, *16*, 1507. Martín-Alvarez, J. M.; Hampel, F.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1999**, *18*, 955.

(9) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; Dallas, G. N. *J. Am. Chem. Soc.* **1991**, *113*, 7372.

(10) Rebiera, F.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1990**, *31*, 5970.

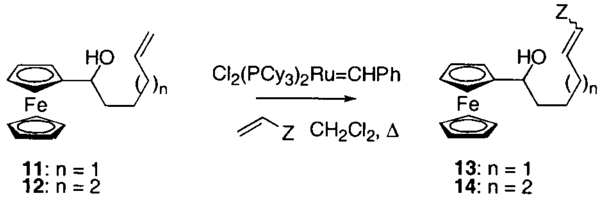
(11) Bailey, W. F.; Gavaskar, K. V. *Tetrahedron* **1994**, *20*, 5970.

(12) The low yield observed in this reaction is presumed to be a consequence of a competing intramolecular cyclization of the anionic center onto the double bond.[11] Interestingly, it was observed that yields tended to be higher when older samples of *t*-BuLi were employed. We speculate that the presence of lithium hydroxide modulates the reactivity of the generated organolithium.

(13) (a) Bailey, W. F.; Gagnier, R. P.; Patricia, J. J. *J. Org. Chem.* **1984**, *49*, 2098. (b) Gavelli, N.; Vierling, P. *J. Org. Chem.* **1992**, *57*, 3046.

conditions of 5 mol % catalyst loadings in dichloromethane at reflux, it was found that cross-metathesis occurred, but with relatively low efficiencies. By systematically increasing the catalyst load by 5 mol % increments, it was found that 20 mol % of catalyst allowed a smooth reaction to take place with complete consumption of starting alcohol, producing the desired cross-metathesis product in 59% isolated yield (*E*:*Z* 1.6:1) along with 23% of the self-metathesis product (Table 1).[14] With reasonable conditions defined, the scope of the reaction was investigated with other olefins. It was found that alcohol **11** underwent efficient metathesis with both styrene and allyl acetate, giving the products in 56% and 70% yield, respectively.[15] Interestingly, when acrylonitrile and acrolein were investigated, none of the cross-metathesis product could be isolated. Only unreacted starting material and a small amount of the alcohol self-metathesis product (6%) was isolated. This result is somewhat surprising, given that acrylonitrile is generally one of the most effective partners in cross-metathesis reactions.[7] In the case of methyl acrylate when the reaction was conducted under the standardized conditions, two products were isolated in addition to unreacted starting material, the self-metathesis product (15%) and the cross-metathesis product (15%). The yield of the cross-metathesis product could be improved somewhat by increasing the number of equivalents of methyl acrylate used from 2 to 10; in this way 26% of the cross-metathesis product could be isolated. As it turns out, alcohol **11** proved to be the least effective in its reaction with methyl acrylate; alcohol **12** and ketones **15** and **16** were somewhat more reactive. It is not clear at this time why the yields of electron-deficient olefins are attenuated compared to other classes of substrates. The homologous alcohol **12** participates in the cross-metathesis reaction with the same range of substrates, although it appears that the efficiency is somewhat reduced, with the exception of methyl acrylate.

Table 1. Yields and Isomer Ratios for the Cross-Metathesis Reactions of Alcohols **11** and **12**

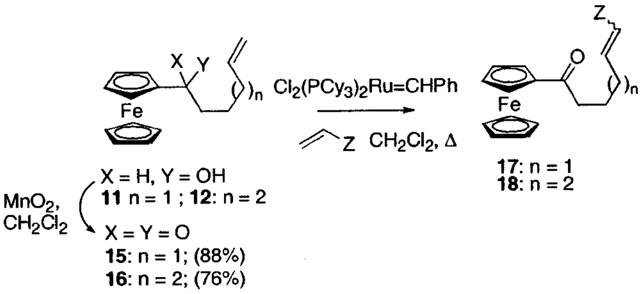


Z	$n = 1^{a,b}$	$n = 2^{a,b}$
Ph	56 (17:1)	54 (18:1)
CH_2SiMe_3	59 (1.6:1)	45 (1.7:1)
CH_2OAc	70 (3:1)	63 (3:1)
CO_2CH_3	26 (*E* only)[c]	42 (*E* only)[c]

[a] The values given in parentheses correspond to the E/Z ratios in the products, determined from the integration of appropriate signals in the ^1H NMR spectra of the purified product. [b] In addition to the cross-metathesis products, 10−30% of the self-metathesis product was isolated. [c] Ten equivalents of methyl acrylate was employed in this case.

As indicated earlier, access to the corresponding ketones was also of interest. Although these compounds could be derived through oxidative means from the appropriate alcohol, application of the cross-metathesis reaction to the appropriate substrate would represent a more efficient and divergent method for the synthesis of these compounds. Therefore, the α-ketoferrocene derivatives **15** and **16**, prepared by the MnO_2 oxidation of the corresponding alcohol, have been evaluated. When the ketones were subjected to the conditions previously defined for the alcohols, they engaged smoothly in cross-metathesis reactions with similar efficiencies with the same range of substrates (Table 2). Perhaps the only result of note is the cross-metathesis reaction between ketone **16** and styrene, where an enhanced *E*:*Z* ratio was observed. Although we presently have no rationale for this observation, it appears to be reproducible.

Table 2: Yields and Isomer Ratios for the Cross-Metathesis Reactions of Ketones **15** and **16**



Z	$n = 1^{a,b}$	$n = 2^{a,b}$
Ph	65 (17:1)	52 (25:1)
CH_2SiMe_3	62 (1.5:1)	58 (1.4:1)
CH_2OAc	58 (2.3:1)	68 (3:1)
CO_2CH_3	38 (*E* only)[c]	37 (*E* only)[c]

[a] The values given in parentheses correspond to the *E*/*Z* ratios in the products, determined from the integration of appropriate signals in the ^1H NMR spectra of the purified product. [b] In addition to the cross-metathesis products, 10−30% of the self-metathesis product was isolated. [c] Ten equivalents of methyl acrylate was employed in this case.

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(14) **Representative Procedure.** A CH_2Cl_2 (18 mL) solution containing the ferrocene derivative (0.21 mmol), the alkene (0.42 mmol), and Grubbs' catalyst (34 mg, 0.04 mmol) was heated at reflux until the starting materials were consumed (TLC analysis, 17−24 h). The solvent was removed, and the residue was purified by flash column chromatography (SiO_2, 5% ethyl acetate in hexanes), providing the product as an orange oil (see Tables 1 and 2). **Compound 18** (Z = Ph): IR ($CHCl_3$) ν_{max} 1667; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4−7.3 (2H, m), 7.3−7.2 (2H, m), 7.2−7.1 (1H, m), 6.42 (1H, d, $J = 15.8$ Hz), 6.25 (1H, dt, $J = 7.0, 15.8$ Hz), 4.78 (2H, t, $J = 1.9$ Hz), 4.48 (2H, t, $J = 1.9$ Hz), 4.16 (5H, s), 2.27 (2H, t, $J = 7.4$ Hz), 2.28 (2H, ddt, $J = 1.4, 7.0, 7.3$ Hz), 1.8−1.7 (2H, m), 1.6−1.5 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 137.9, 130.6, 130.2, 128.6, 126.9, 126.0, 79.2, 72.2, 69.8, 69.4, 39.6, 33.0, 29.3, 24.3; EI-MS (*m*/*z*) 372 (M^+, 8), 228 (100).

(15) Attempts to engage allyl alcohol in the cross-metathesis reaction were unsuccessful, possibly as a result of competing isomerization reactions. We and others have noted the ability of certain secondary allylic alcohols to undergo isomerization to ketones; see: (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123. (b) Browning, R. G.; Lovely, C. J. Unpublished observations.

In summary, we have demonstrated that both α-hydroxy- and α-ketoferrocenes can participate in olefin cross-metathesis reactions with comparable efficiencies. As a consequence, concise approaches to a number of terminally functionalized olefins have been developed. The range of substrates that participate in this reaction appears to be less general than in nonorganometallic cases. Currently, we are investigating the capacity of other organometallic derivatives to participate in this reaction and the ability of other carbene complexes to catalyze this reaction with a view to increasing the reaction efficiency in recalcitrant cases. We will report on these experiments in due course.

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