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Terminal Olefin Cross-Metathesis with Acrolein Acetals

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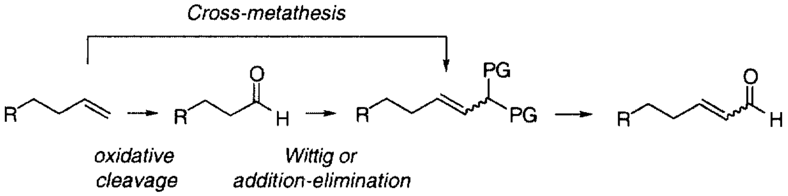
Abstract: New olefin metathesis methodology for the homologation of terminal olefins to protected α,β-unsaturated aldehydes is described. Acrolein acetals, including asymmetric derivatives, are robust cross-metathesis substrates as evidenced by reaction yields of 80-90% at catalyst loadings of 2-5 mol % $(PCy_3)_2Cl_2Ru{=}CHPh$ (**1**). © 1999 Elsevier Science Ltd. All rights reserved.

The preparation of α,β-unsaturated aldehydes can be accomplished by Wittig[2] homologation of aldehydes employing reagents such as $Ph_3P{=}CHCHO$[3] or with acetal[4] or imine[5] protected two-carbon ylides. Addition-elimination methods have also been used to homologate aldehydes.[6,7,8] In cases where a terminal olefin is serving as an aldehyde precursor, a cross-metathesis approach offers a means for direct homologation (Scheme 1). Herein, we report an efficient olefin metathesis protocol for converting a terminal olefin to the corresponding α,β-unsaturated aldehyde using ruthenium benzylidene **1**[9] and acrolein acetals.

Scheme 1



Although acrylonitrile has been successfully employed in molybdenum-catalyzed cross-metathesis reactions,[10] conjugated olefins including acrolein were found to be unreactive in reactions using catalytic ruthenium benzylidene **1**. Unconjugated acrolein acetals, on the other hand, were found to be viable metathesis substrates.[11] Our initial investigations employed the commercially available acrolein diethyl acetal (**2**) and 9-decen-1-ol benzoate (**3**) (Scheme 2). An optimization study led to the following observations: α,β-unsaturated aldehyde **4** was obtained in 75-80% yield using either 2.5 or 5 mol % **1** and 2 equiv. of acetal **2** (entries 2 and 3). Although the acid-sensitive diethyl acetal cross-metathesis product could be isolated with chromatography using Et_3N-treated silica gel, it was more convenient to recover the α,β-unsaturated aldehyde after formic acid hydrolysis.[12] We observed that reactions using older samples of diethyl acetal gave low yields, presumably due to small amounts of hydrolysis-derived acrolein. Increasing the number of acetal equivalents (entry 4) was found to suppress the formation of product **4**, presumably due to engaging the propagating ruthenium carbene in unproductive acetal homodimerization.

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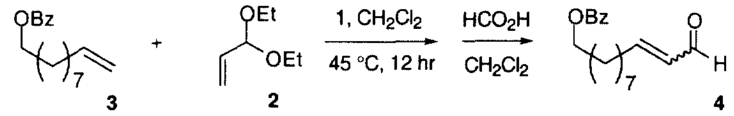
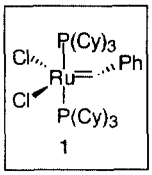
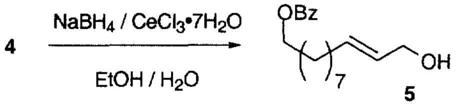
Using a Luche reduction,[13] α,β-unsaturated aldehyde **4** was converted to allylic alcohol **5** in a highly *E*-selective manner. This 3-step allylic alcohol synthesis is an improvement, in terms of both yield and *E*-selectivity, upon our recently disclosed 2-step metathesis procedure using protected (*Z*)-2-butene-1,4-diols.[14]

Scheme 2

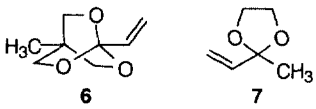




entry	[**3**]	equiv. **2**	mol% **1**	isolated yield **4**
1	0.1 M	4	5	72%
2	0.1 M	2	5	75%
3	0.2 M	2	2.5	81%
4	0.1 M	65 (neat)	5	<10%



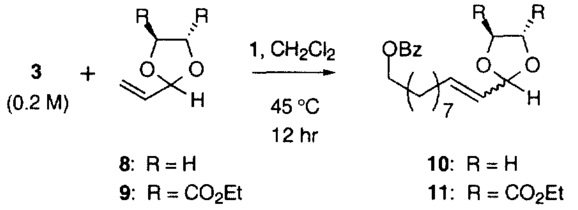
94% (26:1 *E/Z*)



unreactive substrates

The reactivity of acetal **2** was unexpected, as it was originally thought that allylic disubstitution would hinder the cross-metathesis reaction. Extending this methodology to substrates with allylic trisubstitution could, in principle, provide access to additional functional groups such as α,β-unsaturated esters and methyl ketones. However, attempts at Ru-catalyzed cross-metathesis of **3** with orthoester **6**[15] or ketal **7**[16] proved unsuccessful.

Scheme 3



entry	mol% **1**	isolated yield
5	1	**10**: 74%
6	2	**10**: 87%
7	2.5	**10**: 93%
8	5	**10**: 91%
9	2.5	**11**: 86%

Cross-metathesis reactions between terminal olefin **3** and 2-vinyl-1,3-dioxolane (**8**), a commercially available acrolein acetal with enhanced acid-stability compared to diethyl acetal **2**, gave good to excellent yields of the dioxolane-protected α,β-unsaturated aldehyde **10** (Scheme 3). Under these conditions, a 74% isolated yield of **10** was obtained with the catalyst loading reduced to as little as 1 mol % **1** (entry 5). Yields of 87-91% (7:1 *E/Z*) were obtained for reactions using catalyst loadings of 2-5 mol % **1** (entries 6-8).[17]

Extending the scope of the reaction to include asymmetric acrolein acetals was considered worthwhile because chiral α,β-unsaturated acetals are useful synthetic intermediates.[18] Accordingly, diethyl vinylidene-L-tartrate (**9**) was prepared[19] and found to provide an *E*-selective (6.7:1 *E/Z* by ^{1}H NMR) cross-metathesis product **11** in excellent yield (Scheme 3, entry 9).

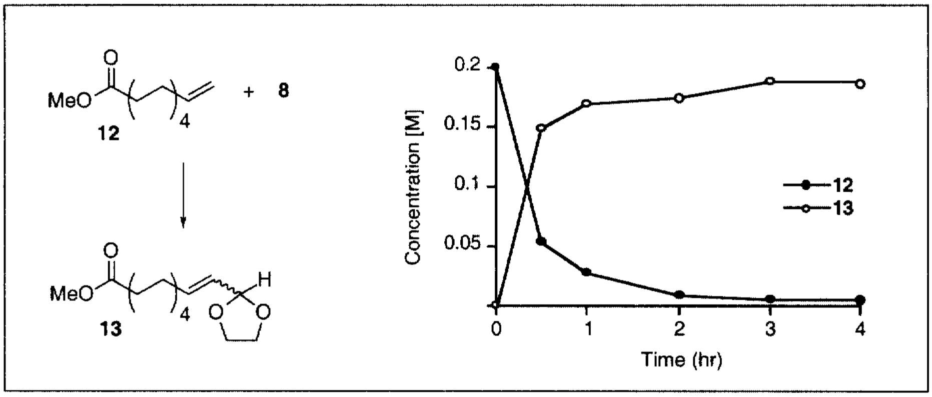
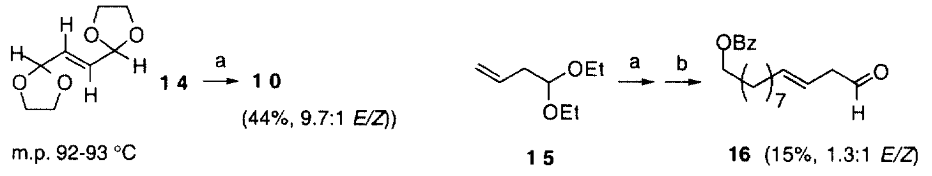


Figure 1. Reaction profile for cross-metathesis reaction employing alkene **12** (0.2 M), vinyl dioxolane **8** (2 equiv.), and 2.5 mol % catalyst **1** (45 °C, CH_2Cl_2). The concentration of **13** consists of a ca. 7:1 *E/Z* olefin composition throughout the course of the reaction. Data obtained from GC/MS analysis of reaction aliquots (1,4-dichlorobenzene as internal standard, data corrected for relative response).

A GC/MS assay was used to measure the qualitative rate of cross-metathesis. Figure 1 shows a representative reaction profile for a standard reaction employing 2.5 mol % **1**, 2 equiv. vinyl dioxolane **8**, and 0.2 M methyl 10-undecylenate **12**. The data show the reaction is essentially complete (>90%) after 3 hours.

Attempting to build upon our earlier work,[14] which demonstrated certain advantages to using symmetric disubstituted olefins as cross-metathesis partners, we prepared fumaraldehyde bis(ethylene glycol acetal) (**14**)[20] by Ru-catalyzed dimerization[14] of vinyl dioxolane **8**. However, bis-acetal **14** was not as reactive as vinyl dioxolane **8** in cross-metathesis reactions with terminal olefin **3**, presumably due to steric factors (Scheme 4). Interestingly, the *E/Z* ratio improved when the bis-acetal was employed (**14**: *E/Z* = 9.7:1; **8**: *E/Z* = 7:1).



Scheme 4. Reagents and Conditions: (a) 5 mol % **1** / 0.2 M **3** / CH_2Cl_2 / 45 °C; (b) HCO_2H-CH_2Cl_2 (1:8) / RT.

Extending the methodology to the construction of β,γ-unsaturated aldehydes *via* cross-metathesis was also explored. Unfortunately, 3-butenal diethyl acetal **15** does not appear to be a promising substrate for Ru-catalyzed cross-metathesis reactions. Yields and *E/Z* selectivities of the corresponding β,γ-unsaturated aldehydes were generally poor (Scheme 4).[21]

In conclusion, acrolein acetals **2**, **8**, and **9** have been shown to be remarkably reactive in cross-metathesis reactions with terminal olefins. This method offers a mild alternative to traditional homologative methods for preparing α,β-unsaturated aldehydes. The use of asymmetric acrolein equivalents, coupled with emergent asymmetric metathesis catalysts,[22,23] suggests a means for effecting catalytic kinetic resolutions *via* cross-metathesis. Current investigations are directed toward this end, and results will be reported in due course.[24]

References and Notes.

1. Current address: Department of Chemistry, Pomona College, Claremont, CA, 91711.
2. For recent reviews, see: (a) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 1, Chapter 3, pp 755-782. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.
3. Bestmann, H. J.; Vostrowsky, O.; Paulus, H.; Billman, W.; Stransky, W. *Tetrahedron Lett.* **1977**, 121-124.
4. Daubresse, N.; Francesch, C.; Rolando, C. *Tetrahedron* **1998**, *54*, 10761-10770.
5. Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788-3789.
6. Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365-7367.
7. Wittig, G.; Reiff, H. *Angew. Chem., Intl. Ed. Engl.* **1968**, *80*, 8-15.
8. Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36-56.
9. Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.
10. Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162-5163.
11. For a recent example of an acrolein acetal used in a ring-closing metathesis reaction, see: Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084-9085.
12. All compounds exhibited satisfactory spectroscopic data (^{1}H/^{13}C NMR, HRMS).
13. Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1981**, 4077-4080.
14. O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, 7427-7430.
15. Gassman, P. G.; Chavan, S. *J. Chem. Soc., Chem. Comm.* **1989**, 837-839.
16. Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449-1457.
17. **General Procedure for Cross-Metathesis Reactions.** An oven-dried flask is charged with a magnetic stir bar and ruthenium benzylidene **1** (11 mg, 2.5 mol %), and capped with a septum under nitrogen atmosphere. Dry, degassed CH_2Cl_2 (2.5 ml) and terminal olefin **3** (0.5 mmol, 1 equiv.) are added in succession. Vinyl dioxolane **8** (1.0 mmol, 2 equiv.) is added and the septum is quickly replaced with a condenser connected to a nitrogen bubbler. The flask is immersed in an oil bath and refluxed (bath temperature: 45 °C) for a period of 12 hr or until the reaction is judged complete by TLC.
18. For an example of an asymmetric Simmons-Smith reaction, see: Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447-6458.
19. Tsuzuki, T.; Koyama, M.; Tanabe, K. *Bull. Chem. Soc. Japan* **1967**, *40*, 1008-1013.
20. Sokolov, G. P.; Hillers, S. *Khim. Geterotsikl. Soedin.* **1969**, *1*, 32-35.
21. Certain homoallylic substituents (Br, OMe, OBn) are known to deactivate catalytic cross-metathesis reactions. See Ref. 10 and: Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998-10999.
22. (a) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499-2500. (b) Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824-832.
23. Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041-4042.

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