New Approaches to Olefin Cross-Metathesis

Helen E. Blackwell,† Daniel J. O'Leary,‡ Arnab K. Chatterjee,† Rebecca A. Washenfelder,‡ D. Andrew Bussmann,‡ and Robert H. Grubbs*,†

Contribution from the Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, and Department of Chemistry, Pomona College, Claremont, California 91711

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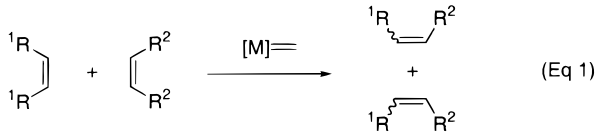
Abstract: New methodology for the selective cross-metathesis (CM) of terminal olefins employing ruthenium benzylidene **1** is described.[1] CM with symmetric internal olefins was found to provide a useful means for homologating terminal olefins to protected allylic alcohols, amines, and esters. Due to the limited commercial availability of symmetric internal olefins, a two-step CM procedure was developed in which terminal olefins were first homodimerized prior to the CM reaction. Terminal olefins with allylic methyl substituents were observed to provide CM products in diminished yield albeit with markedly improved *trans*-selectivity. Reaction rates were measured for CM reactions utilizing butenediol and allyl alcohol derivatives, and the results demonstrated distinct advantages in reaction rate and stereoselectivity for reactions employing the disubstituted olefins. In the course of studies of substrates with allylic oxygen substituents, a new CM application was discovered involving the metathesis of acrolein acetal derivatives with terminal olefins. Acrolein acetals, including asymmetric variants derived from tartaric acid, proved to be exceptionally robust and *trans*-selective CM substrates. In related work, a pinacol-derived vinyl boronate was also found to be a reactive CM partner, providing a novel means for converting terminal olefins into precursors for the Suzuki coupling reaction.

Introduction

Olefin Metathesis. Carbon−carbon bond forming reactions are among the most important family of reactions in organic synthesis. One particularly interesting carbon−carbon bond forming reaction is olefin metathesis, which is the metal-catalyzed exchange of alkylidene moieties between alkenes (eq 1).[2]

Olefin Metathesis:



(Eq 1)

Historically, olefin metathesis has been studied both from a mechanistic standpoint[3] and in the context of polymer synthesis (i.e., in ring opening metathesis polymerization, or ROMP).[2a,4] In contrast, the application of olefin metathesis to the synthesis of complex organic molecules and natural products was limited due to the incompatibility of ill-defined, "classical" catalysts with the diverse functionality encountered in organic synthesis.[2a] Recently, however, ring-closing olefin metathesis (RCM) of acyclic dienes has received considerable attention as a highly efficient methodology for the synthesis of functionally diverse carbocycles and heterocycles.[5] This is primarily due to the development of well-defined transition metal catalysts over the past decade. The two olefin metathesis catalysts that have seen the most extensive use are the ruthenium benzylidene **1** developed by Grubbs *et al*.[6] and the molybdenum alkylidene **2** developed by Schrock *et al*.[7] The relatively high activities and functional group tolerance of both catalysts **1** and **2**, coupled with their commercial availability, has dramatically increased their application in organic synthesis.

Olefin Cross-Metathesis. The volume of work reported in the areas of RCM, ROMP, and novel combinations thereof has dramatically overshadowed that reported for olefin cross-metathesis (CM). This unique method for the intermolecular

* Address correspondence to this author.
† California Institute of Technology.
‡ Pomona College.

(1) For preliminary accounts of this work, see: (a) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427−7430. (b) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091−1094. (c) Blackwell, H. E. Ph.D. Thesis, California Institute of Technology, 1999.

(2) For general olefin metathesis references, see: (a) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, 2nd ed.; Academic: San Diego, 1997. (b) Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York: 1991; Vol. 5, Chapter 9.3.

(3) For details of the present accepted mechanism of olefin metathesis involving formation of a metallocyclobutane intermediate, see: Herrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161−176.

(4) For leading references, see: (a) Feldman, J.; Schrock, R. R. *Prog. Inorg. Chem.* **1991**, *39*, 1−74. (b) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907−915.

(5) For recent reviews of RCM in organic synthesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (c) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833−1836. (d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−552.

(6) PCy_3 = tricyclohexylphosphine. For the preparation and characterization of catalyst **1**, see: (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (c) Belderrain, T. R.; Grubbs, R. H. *Organometallics* **1997**, *16*, 4001−4003.

(7) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378−8387. (c) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899−6907.

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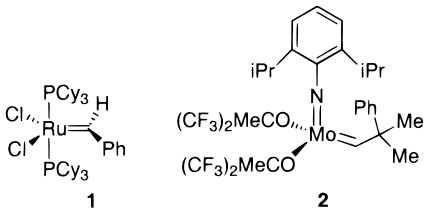
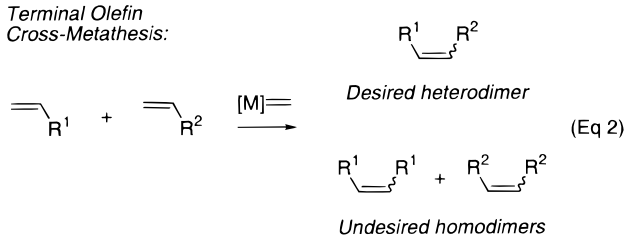


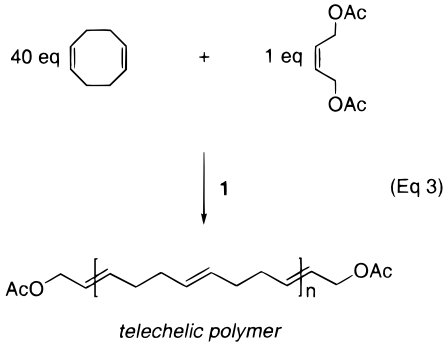
formation of carbon−carbon double bonds has not yet found widespread application in organic synthesis because general reaction conditions that give high product and/or *trans*/*cis* selectivity have not been developed. The simplified CM reaction between two terminal olefins is depicted in eq 2.



Generally, this reaction proceeds to yield three unique products: one desired heterodimeric product and two undesired homodimeric products, each as a mixture of olefin isomers. The majority of the work reported to date in the area of CM has focused upon terminal olefin substrates, because employing asymmetrically-substituted internal olefins as starting materials can add further unwanted complexity to the final product mixture. A predominance of the early reports of CM employing "classical" catalysts[8] involved the synthesis of insect pheromone natural products: these compounds are frequently isolated from natural sources as a specific ratio of *cis* and *trans* isomers, and therefore CM proved to be a moderately effective route toward synthesizing these product mixtures.[9] However, for application to synthetic organic chemistry in general, control of *trans*/*cis* ratios and product selectivity is essential.

The advent of well-defined ruthenium and molybdenum metathesis catalysts **1** and **2** has generated renewed interest in developing methods for the selective CM of terminal olefins. Crowe *et al*. have demonstrated that π-substituted terminal olefins such as styrene[10] and acrylonitrile[11] can be used to efficiently functionalize terminal olefins employing molybdenum catalyst **2**. Crowe has also reported a useful terminal olefin cross-coupling procedure utilizing nucleophilic alkenes such as allyltrimethylsilane.[12,13] Recently, Blechert *et al*. have shown that certain sterically hindered terminal olefins do not undergo self-metathesis, but rather can be selectively functionalized with a variety of commercially available terminal olefins using both catalysts **1** and **2**.[14,15] The novel ruthenium-catalyzed homologation of homoallylglycine derivatives *via* CM has been reported by Gibson *et al*.[16] Efficient crossed yne−ene[17] and ring-opening cross-metathesis (ROM) reactions[18,19] using catalysts **1** and **2** have also been demonstrated. Finally, CM is being employed with increasing frequency in the synthesis of solution-phase combinatorial libraries of highly functionalized dimeric molecules.[20]

Outlined herein are several new approaches for the selective CM of unhindered terminal olefins. Our approach, using symmetric disubstituted olefins as coupling partners, was inspired in part by the synthesis of telechelic polymers[21] *via* tandem ROMP coupled with the CM of disubstituted internal olefins (eq 3). Blechert *et al*. have also used this approach in



the ROM of strained cyclic olefins with symmetrically disubstituted olefins.[18b] To further probe the viability of this approach for applications in organic synthesis, we have explored the Ru-catalyzed homologation of unhindered terminal alkenes *via* CM with functionally diverse, disubstituted internal olefins.

(8) Issues of poor selectivity plagued early CM efforts employing "classical" catalysts. For a recent review of CM using "classical" catalysts, see: Finkel'shtein, E. S.; Bykov, V. I.; Portnykh, E. B. *J. Mol. Catal.* **1992**, *76*, 33−52.

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(11) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162−5163.

(12) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117−2120.

(13) For the ruthenium-catalyzed CM of functionalized terminal olefins with allyldimethylsilyl-derivatized polystyrene resin, see: Schuster, M.; Lucas, N.; Blechert, S. *Chem. Commun.* **1997**, 823−824.

(14) Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441−446.

(15) Highly functionalized silsesquioxanes and spherosilicates have been prepared *via* the CM of various alkenes with vinyl-substituted silsesquioxane and spherosilicate frameworks employing molybdenum alkylidene **2**. The lack of homodimerization of the vinyl-substituted silicon frameworks was attributed to steric bulk. See: Feher, F. J.; Soulivong, D.; Eklund, A. G.; Wyndham, K. D. *J. Chem. Soc., Chem. Commun.* **1997**, 1185−1186.

(16) (a) Gibson, S. E.; Gibson, V. C.; Keen, S. P. *Chem. Commun.* **1997**, 1107−1108. (b) Baigini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, *16*, 2485−2499.

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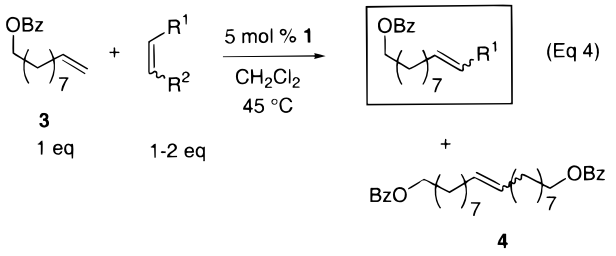
Table 1. CM Reactions with Symmetrically Disubstituted Olefins

entry	substrate	equiv	product: %[a]	*E/Z*[b]
1	$R_1 = R_2 = CH_2OAc$ (cis)	2	**5**: 89	4.7:1
2	$R_1 = R_2 = CH_2OAc$ (cis)	1	**5**: 77	5:1
3	$R_1 = CH_2OAc$, $R_2 = H$	4	**5**: 81	3:1
4	$R_1 = CH_2OAc$, $R_2 = H$	2	**5**: 80	4:1
5	$R_1 = CH_2OAc$, $R_2 = H$	1	**5**: 59	5.7:1
6	$R_1 = R_2 = CH_2OC(O)CF_3$ (cis)	4	**6**: 63[c]	2.8:1
7	$R_1 = R_2 = CH_2OH$ (cis)	2	**7**: 56[d]	5:1
8	$R_1 = R_2 = CH_2O$*t*Bu (cis)	2	**8**: 90	7:1
9	$R_1 = R_2 = CH_2O$trityl (cis)	2	**9**: 75[e]	8:1
10	$R_1 = R_2 = CH_2OCH_2Ph$ (cis)	2	**10**: 71[f]	9:1
11	$R_1 = R_2 = CH_2OTBS$ (cis)	2	**11**: 77[g]	10:1
12	$R_1 = R_2 = CH_2CH_2CH_3$ (cis)	2	**12**: 72	3:1
13	$R_1 = R_2 = CH_2NHBoc$ (cis)	4	**13**: 71	3:1
14	$R_1 = R_2 = CH_2C(O)OMe$ (trans)	2	**14**: 74	3.3:1
15	$R_1 = R_2 = CH_2C(O)NMe(OMe)$ (trans)	4	**15**: 17	1.9:1
16	$R_1 = R_2 = CH_2CH_2OTBS$ (trans)	2	**16**: 49[g]	2.8:1

[a] Isolated product yields. [b] Determined by ^{1}H NMR integration. [c] Yield determined after NEt_3 deprotection of the allyl trifluoroacetate ether (to afford allylic alcohol **7**). [d] Reaction run at room temperature. [e] Yield determined after the formic acid deprotection of the allyl trityl ether to afford **7**. [f] Yield determined after H_2/Pd-C hydrogenation−hydrogenolysis of allyl benzyl ether. [g] Yield determined after TBAF deprotection of allyl TBS ether.

Results and Discussion

Initial Results. 9-decen-1-yl benzoate (**3**)[22] was chosen as a model terminal olefin substrate because of its low volatility and its UV chromophore significantly aided synthetic manipulations. Treatment of benzoate **3** with 1−2 equiv of a symmetric internal olefin and 5 mol % ruthenium benzylidene **1** in refluxing dichloromethane provided the desired CM products in good yields (eq 4). The CM reactions proceeded largely to completion



over 12 h, and any benzoate homodimer side-product (**4**, 5−10%) could be easily recovered and recycled in a subsequent cross-metathesis step. In all of the cases examined thus far, the reaction has favored the formation of the *trans* olefin isomer.

Our initial efforts focused upon elaborating benzoate **3** to the corresponding allylic alcohol derivatives (Table 1).[23] The commercially available *cis*-2-butene-1,4-diol diacetate (entry 1) provided the homologated allylic acetate **5** in excellent yield (89%, 4.7:1 *E/Z*) using 2 equiv of internal olefin. When only 1 equiv of diacetate was employed, the yield of **5** decreased (77%) and no significant change in the *trans*/*cis* ratio was observed (entry 2). Interestingly, the use of 2 equiv of diacetate was found to be more efficient than simply using 1, 2, or 4 equiv of allyl acetate (entries 3−5).[24] Employing the diol acetate as solvent (55 equiv, 45 °C, 12 h) increased the isolated yield of **5** to 91%, although with diminished *trans* olefin content (3:1 *E/Z*). In contrast, the use of neat allyl acetate provided only a marginal amount (10%) of the desired cross-product (data not shown), presumably due to the statistically favored dimerization of allyl acetate by **1** dominating the catalytic cycle, and the likely formation of a less stable ruthenium methylidene species.[25] The *cis*-2-butene-1,4-diol bis-trifluoroacetate[26] (entry 6) afforded a reduced yield of the homologated allylic trifluoroacetate **6** (63%, 2.8:1 *E/Z*), yet with an *E/Z* ratio approximating that of the allylic acetate **5**.

Direct reaction of benzoate **3** with 1,4-butenediol (entry 7, Table 1) occurred in dichloromethane at room temperature to yield allylic alcohol **7** (54%, 5:1 *E/Z*), despite the limited solubility of the diol. Elevating the temperature led to apparent decomposition of alkylidene **1**. No improvement in the isolated yield of **7** was observed when the reaction was conducted as a homogeneous mixture in chloroform. Several diether derivatives of *cis*-1,4-butenediol (entries 8−11) were found to provide better CM yields and improved *trans* selectivity. For example, the bis-*tert*-butyl,[27] bis-trityl,[28] bis-benzyl ether,[29] and bis-TBS[30] substrates provided CM products with *E/Z* ratios ranging from 7:1 to 10:1. While no attempts were made to separate the olefin stereoisomers in the present study, the increased *trans* selectivity observed in the CM of benzoate **4** with the bis-TBS diol now represents a synthetically useful protocol for the direct installation of *E*-allylic alcohol functionality.

Purely aliphatic functionality could be readily incorporated employing this CM methodology: for example, the CM of *cis*-3-hexene with **4** (entry 12) yielded the ethyl functionalized internal olefin cross-product **12** in good yield (72%, 3:1 *E/Z*). The compatibility of nitrogen-containing substrates was next probed through the CM of Boc-protected *cis*-1,4-diaminobutene[31] (entry 13). Boc-protected allylic amine **13** was isolated in good yield (71%, 3:1 *E/Z*), which demonstrates CM as a straightforward route to the introduction of nitrogen functionality.

All of the CM reactions discussed up to this point involved *cis*-disubstituted internal olefins. We chose to employ *cis* olefins at the outset because it had been observed previously that ruthenium alkylidene **1** is more reactive toward the more sterically accessible *cis* olefin.[25] However, *trans*-disubstituted internal olefins were also found to be reactive coupling partners for CM with terminal olefins.[32] Dimethyl *trans*-3-hexene-1,6-dioate[33] (entry 14) provided the desired homoallylic ester cross product (**14**) as the major product (74%, 3:1 *E/Z*; recovered

(22) Prepared according to a general literature procedure: Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1981**, *46*, 5252−5253.

(23) Full experimental details of the CM and self-metathesis reactions and full characterization of the products (^{1}H NMR, ^{13}C NMR, and HRMS) can be found in the Supporting Information.

(24) This is the exact opposite effect that Blechert *et al*. observed in the ROM of cyclic olefins with monosubstituted olefins versus disubstituted olefins. A large excess (up to 10-fold) of the less reactive disubstituted olefin was required to suppress the ROMP of the strained cyclic olefin substrates, while only 1 equiv of the corresponding monosubstituted olefin was required to effect analogous yields. See ref 18b.

(25) Ullman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484−2489.

(26) Prepared according to a standard literature procedure: Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1954**, *37*, 443−450.

(27) Prepared using a general method: Alexakis, A.; Gardette, M.; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2951−2954.

(28) Prepared using a general method: Chaudary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *2*, 95−98.

(29) Prepared by a general procedure: Forster, R. C.; Owen, L. N. *J. Chem. Soc., Perkin Trans. 1* **1978**, 822−829.

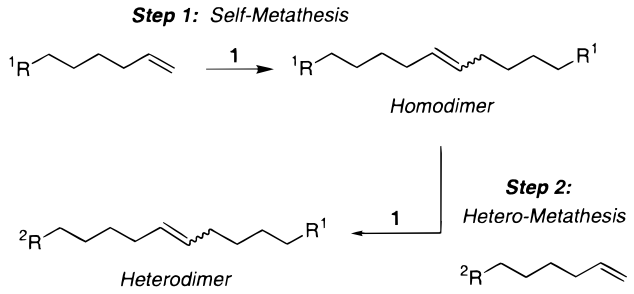
(30) Prepared using a general method: Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

(31) Prepared according to a modified literature procedure. See: Zuwen, H.; Nadkarni, D. V.; Sayre, L. M.; Greenaway, F. T. *Biochim. Biophys. Acta* **1995**, *1253*, 117−127.

(32) This corroborated well with the observation of Blechert *et al*. that *trans*-disubstituted internal olefins are reactive substrates for ROM. See ref 18b.

(33) Prepared according to a literature procedure: Gassman, P. G.; Bonser, S. M.; Mlinaric-Majerski, K. *J. Am. Chem. Soc.* **1989**, *111*, 2652−2662.

Scheme 1



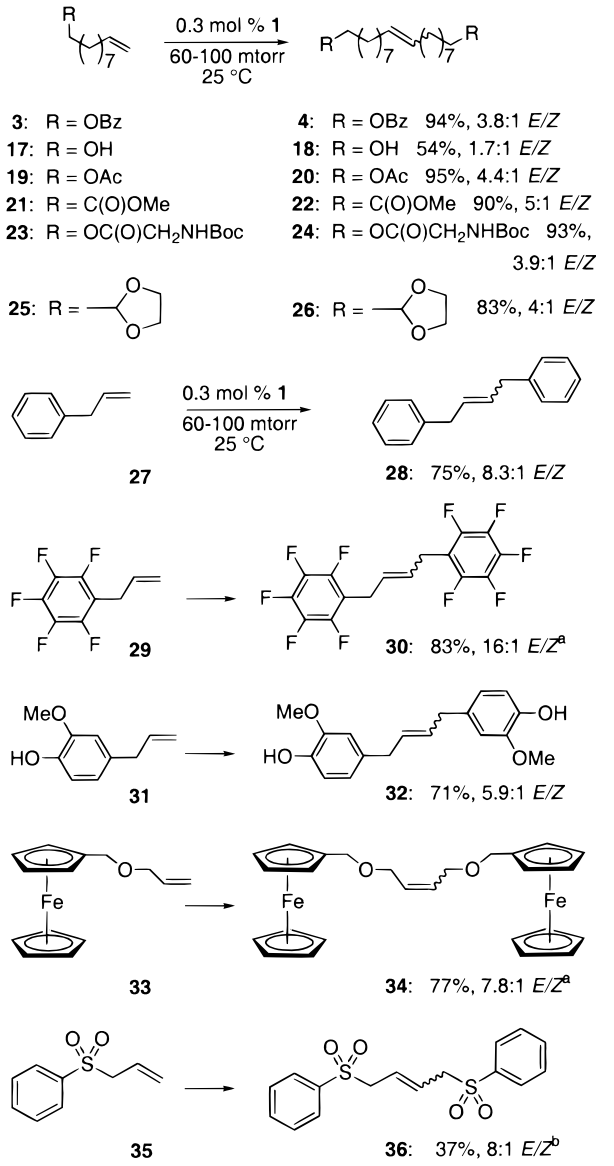
homodimer **4**: 23%). However, in an attempt to introduce Weinreb amide functionality through CM, we found that *trans*-1,6-bis[methyl(methoxy)amido]hex-3-ene[34] (entry 15) was a poor substrate for CM, affording **15** in only 17% yield and with poor *trans* selectivity (1.9:1 *E/Z*). As substantial homodimeric cross-product **4** was not generated, we speculate that the coordination of the amide to the catalyst was inhibiting the catalytic reaction. *Trans*-1,6-bis(*tert*-butyldimethylsilyloxy)hex-3-ene[35] (entry 16) was likewise unreactive. These results are consistent with the observations of Crowe *et al*., which indicated that certain homoallylic substituents on terminal olefins can deactivate catalytic CM reactions.[10,11]

Two-Step Procedure for Terminal Olefin Cross-Metathesis. These initial results suggested that either *cis*- or *trans*-disubstituted olefins could be employed as efficient coupling partners in CM reactions. Accordingly, we investigated the use of a two-step procedure[21,36] for terminal olefin CM as outlined in Scheme 1. First, a terminal olefin was self-metathesized by treatment with ruthenium alkylidene **1**. The mixture of disubstituted olefin isomers generated was then subjected to CM with another terminal olefin employing the methodology described above. The synthesis of a large pool of functionally diverse, homodimeric internal olefins *via* this first self-metathesis procedure is shown in Scheme 2.[37]

For the majority of the terminal olefin substrates studied, homodimerization with 0.3 mol % **1** *in vacuo* (25 °C, 24 h) provided predominantly *trans*-disubstituted olefins in good to excellent yields (Scheme 2). The solvent-free conditions, low catalyst loading, and high yields make homodimerization *via* self-metathesis employing ruthenium alkylidene **1** an exceptional methodology for the synthesis of high molecular weight, symmetrical disubstituted olefins. Furthermore, most of the homodimeric products were crystalline solids, which expedited their purification from alkylidene **1**.

Performing self-metathesis under vacuum has the benefit of removing the stoichiometric gaseous byproduct of the reaction, ethylene, and therefore pushes the self-metathesis reaction toward completion. Employing a static vacuum that is periodically refreshed, the solvent-free method can also be used to homodimerize more volatile substrates such as allylbenzene (**27**).

Scheme 2



[a] Homodimers synthesized in solution (0.1 M, 5 mol % **1**, 45 °C). [b] 1.0 mol % **1** used.

Self-metathesis of the protected derivatives of 9-decen-1-ol (**3**, **19**, **21**, and **23**[38]) afforded the corresponding homodimers (**4**, **20**, **22**, and **24**) in excellent yields. Methyl 10-undecylenate (**21**) and the ethylene glycol acetal of 10-undecenal (**25**) were also found to undergo facile homodimerization reactions. In contrast, homodimerization of neat, unprotected 9-decen-1-ol (**17**) generated only a modest yield of diol **18** with low *trans* selectivity. This result is indicative of alcohol **17** potentially sequestering catalyst **1** by chelation, and effectively shutting down the catalytic cycle before a thermodynamic *trans*/*cis* ratio of products was achieved.[39]

Aromatic, organometallic, and sulfone-containing homodimeric products (**28**, **30**, **32**, **34**, and **36**) could be prepared in moderate to good yield *via* self-metathesis (Scheme 2).[40]

(34) Prepared *via* a DCC coupling between *trans*-β-hydromuconic acid and *N*,*O*-dimethylhydroxylamine hydrochloride. See: Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(35) Prepared according to a general literature procedure: Zhdanov, R. I.; Zhenodarova, S. M. *Synthesis* **1975**, 222−245.

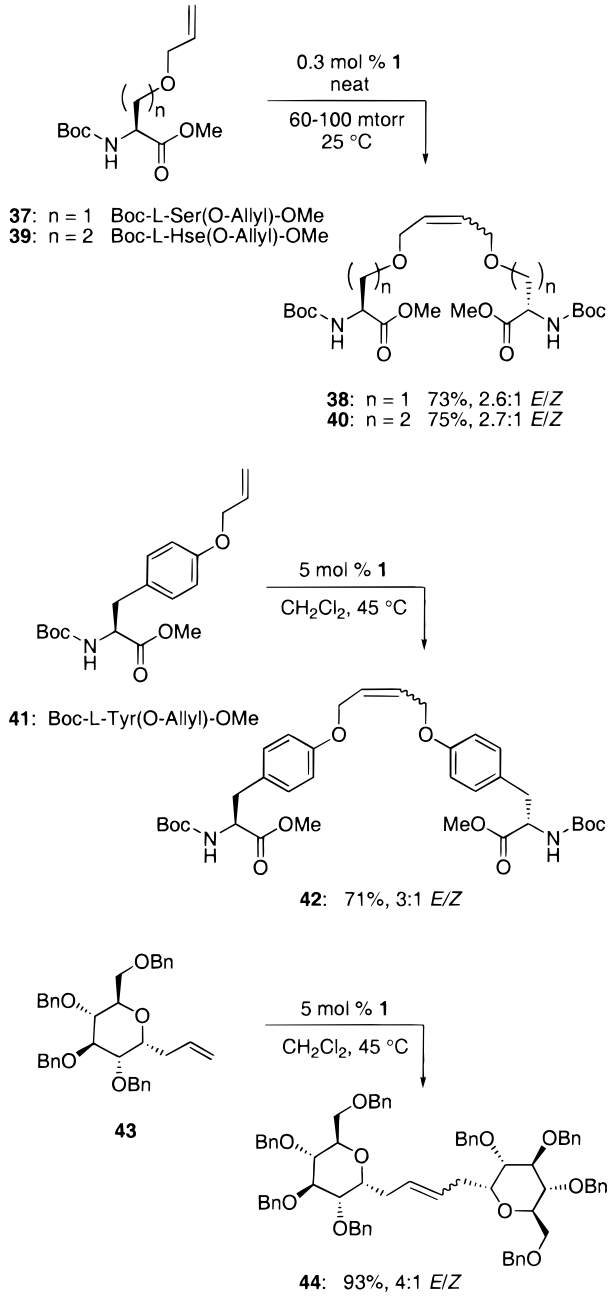
(36) Nubel, P. O.; Yokelson, H. B.; Lutman, C. A.; Bouslog, W. G.; Behrends, R. T.; Runge, K. D. *J. Mol. Catal. A* **1997**, *115*, 43−50.

(37) The self-metathesis of terminal olefins employing "classical" olefin metathesis catalysts has been utilized previously in the synthesis of symmetrically disubstituted olefins. The majority of these applications involved the synthesis of structurally simple, aliphatic internal alkenes. See: (a) Marciniec, B.; Gulinski, J. *J. Organomet. Chem.* **1984**, *266*, C19−C21. (b) Marciniec, B.; Maciejewski, H.; Gullinski, J.; Rzejak, Z. *J. Organomet. Chem.* **1989**, *362*, 273−279. (c) Marciniec, B.; Pietraszuk, C.; Foltynowicz, Z. *J. Organomet. Chem.* **1994**, *474*, 83−87.

(38) Prepared *via* a DCC coupling between *N*-Boc-glycine-OH and 9-decen-1-ol.

(39) Moderate *trans* selectivity has been consistently observed in almost all intermolecular metathesis accounts employing benzylidene **1** to date. This selectivity is consistent with preferential formation of *trans*-α,β-disubstituted metallocyclobutane intermediates. We made the assumption that the predominant olefin regioisomer for these symmetrical homodimers was *trans* in our NMR spectroscopic analyses.

Scheme 3[a]

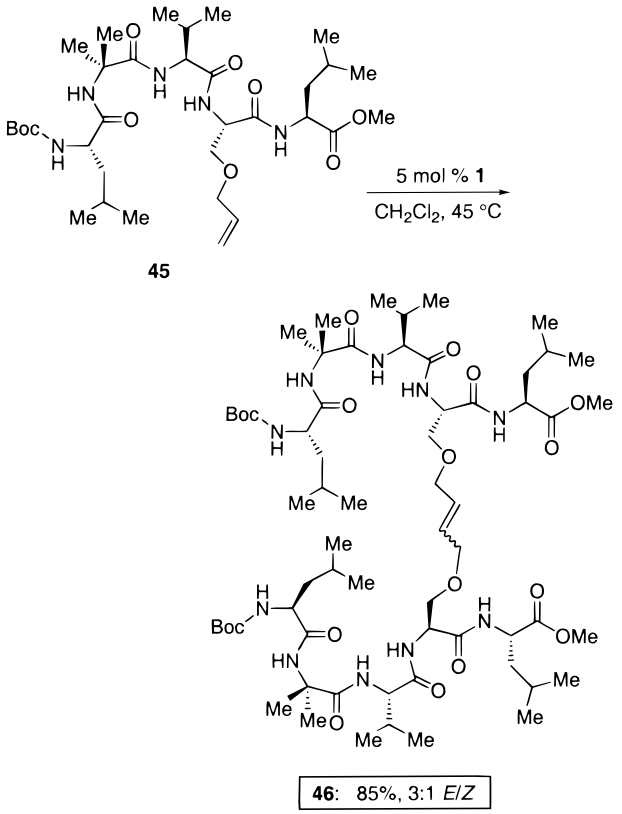


[a] *E/Z* ratios determined by ^{1}H and ^{13}C NMR analyses.[39]

Volatile substrates such as allylpentafluorobenzene (**29**) and 1-ferrocene methanol (*O*)-allyl ether (**33**)[41] can also be efficiently homodimerized using the standard solution-phase CM conditions introduced above (0.1 M, 5 mol % **1**, 45 °C, ca. 12 h). Notably, treatment of allylpentafluorobenzene (**29**) with benzylidene **1** generated homodimeric product **30** with 16:1 *E/Z* olefin content[42] (by ^{1}H NMR); reasons for this increased *trans* selectivity remain to be discerned.

Due to the ongoing interest in our laboratory of employing olefin metathesis in the context of peptide and carbohydrate synthesis, we next turned our attention to the synthesis of a series of novel amino acid, carbohydrate, and peptide homo-

Scheme 4[a]



[a] *E/Z* ratio determined by ^{1}H and ^{13}C NMR analyses.[39]

dimers by self-metathesis (Schemes 3 and 4). These experiments further confirmed the exceptional functional group tolerance of ruthenium alkylidene **1**. Terminal olefin functionality can be readily installed into amino acid side chains by the incorporation of allyl ethers. (*O*)-Allyl ethers of protected L-serine (**37**), L-homoserine (**39**), and L-tyrosine (**41**) derivatives were straightforward to prepare (Scheme 3), and upon treatment with alkylidene **1** afforded good yields of their respective homodimers with moderate *trans* selectivity (ca. 3:1 *E/Z*).[43] As amino acid derivatives **37** and **39** were low viscosity oils, self-metathesis was performed *in vacuo* as described above (Scheme 2); the high viscosity of protected tyrosine derivative **41** required the self-metathesis reaction to be performed in solvent for optimal yield of homodimer **42** (71%). While side chain-bridged amino acids **38**, **40**, and **42** could be generated *via* self-metathesis, treating Boc-L-allylglycine-OMe under the analogous reaction conditions (*in vacuo* or in CH_2Cl_2) yielded less than 5% of the respective homodimer (data not shown); these data[44] are consistent with the observations of Gibson *et al*. that greater separation between the olefin and amino acid is required for efficient CM.[16] Finally, in extending CM methodology to carbohydrate substrates, we observed the crystalline 2,3,4,6-tetra-*O*-benzyl-1-α-*C*-allylglucoside[45] **43** to undergo facile self-

(40) Allyl benzene (**27**) has been previously reported by Benner *et al*. to be an excellent substrate for the synthesis of combinatorial libraries *via* CM. See ref 20d.

(41) The allyl ether was introduced into 1-ferrocene methanol using a standard literature procedure: Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.

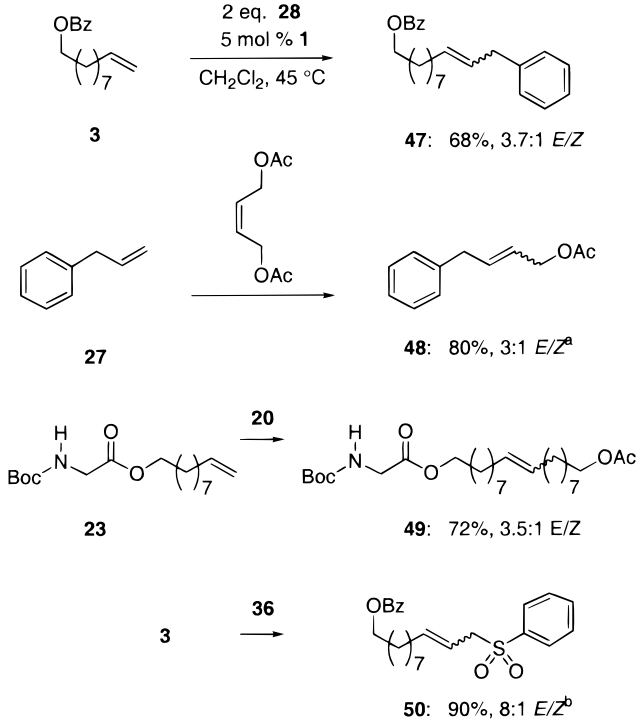
(42) Evidence for assigning the major isomer as *trans* is based upon comparison of ^{1}H NMR and mp data (**30**: 91 °C, lit. mp 94−94.5 °C) with the known *E*-1,4-bis(pentafluorophenyl)-2-butene: Filler, R.; Choe, E. W. *Can. J. Chem.* **1975**, *53*, 1491−1495.

(43) (*O*)-Allyl ethers of L-serine, L-homoserine, and L-tyrosine have been previously employed in the synthesis of peptide macrocycles *via* RCM. See: (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614. (b) Blackwell, H. E.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3281−3284.

(44) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689−1690.

(45) For the synthesis of *C*-allylglucoside **43**, see: Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.

Scheme 5



[a] Using 2.7 mol % **1**. [b] Using 2.5 mol % **1**.

metathesis in solution, affording the novel α,α-linked dimer **44** in high yield (93%, 4:1 *E/Z*).[46]

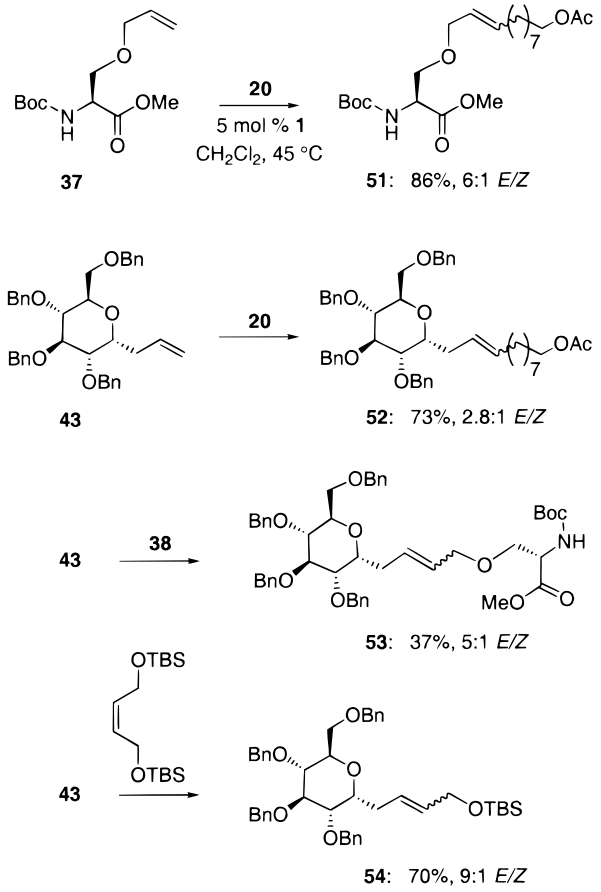
In an attempt to probe the general applicability of olefin self-metathesis for the generation of more complex molecular architectures, we introduced terminal olefin functionality into a hydrophobic pentapeptide framework (**45**) through incorporation of L-serine (*O*)-allyl ether.[43] Treatment of pentapeptide alkene **45** with ruthenium alkylidene **1** under standard solution-phase self-metathesis conditions generated the side chain-bridged homodimer **46** in good yield. Interestingly, the *trans*/*cis* selectivity appeared to approximate that for the CM of the free amino acid (**37**). The facile synthesis of **46** demonstrates the utility of self-metathesis methodology for the synthesis of unique, acyclic peptidic architectures containing non-native C−C linkages; cyclic peptide olefin counterparts have been previously generated employing the intramolecular metathesis variant, RCM.[47]

Finally, to demonstrate the efficacy of our two-step CM protocol, selected symmetrical disubstituted olefins prepared by self-metathesis (Schemes 2−4) were further processed in the CM with terminal olefins. We selected internal and terminal olefin substrates which exhibited varied functionalities and sterics to explore the scope and limitations of this two-step procedure (and selective CM overall). Accordingly, many of the substrates were based upon the structurally diverse amino acid, carbohydrate, and peptide structures shown in Schemes 3 and 4.[48] Furthermore, several of the terminal olefins in Schemes 3 and 4 were utilized as substrates for CM, either with self-metathesized homodimers or simple *cis*-1,4-butenediol substrates from Table 1. Representative examples of this second CM

(46) For recent CM and RCM applications in carbohydrate synthesis, see: (a) Feng, J.; Schuster, M.; Blechert, S. *Synlett* **1997**, 129−130. (b) El Sukkari, H.; Gesson, J.-P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043−4046. (c) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424−425. (d) Calimente, D.; Postema, M. H. D. *J. Org. Chem.* **1999**, *64*, 1770−1771. (e) Postema, M. H. D.; Calimente, D. *Tetrahedron Lett.* **1999**, *40*, 4755−4759.

(47) For leading references to peptide RCM, see refs 5a and 43.

Scheme 6



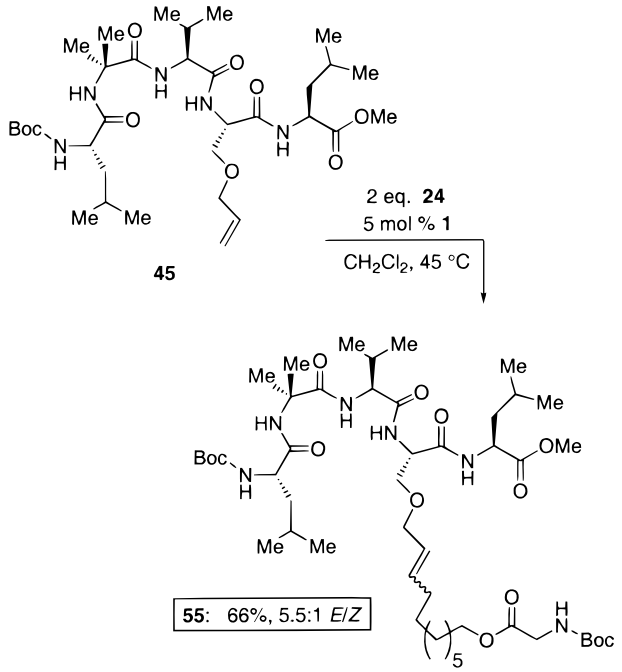
processing step are shown in Schemes 5 and 6. Overall, the heterodimeric products were formed selectively and with moderate to good *trans* selectivity. Standard solution-phase CM conditions were employed throughout (0.1 M in terminal olefin, 2 equiv disubstituted olefin, CH_2Cl_2, 5 mol % **1**, 45 °C), and the reactions were generally complete in 12 h.

Allyl benzene homodimer **28** was reacted with 9-decen-1-yl benzoate **3** (Scheme 5) to yield the benzyl-functionalized internal olefin **47** in good yield (68%, 3.7:1 *E/Z*). Allyl benzene (**27**) itself was also demonstrated to undergo facile CM with butenediol diacetate (87%, 3:1 *E/Z*). 9-Decen-1-yl Boc-glycinate **23** was observed to react with 9-decen-1-yl acetate homodimer **20** to afford the differentially functionalized 9-eicosene (**49**) in good yield (72%, 3.5:1 *E/Z*). Finally, the homodimer of allyl phenyl sulfone was found to be a very reactive CM partner, providing heterodimer **50** in high yield (90%, 7:1 *E*/*Z*).

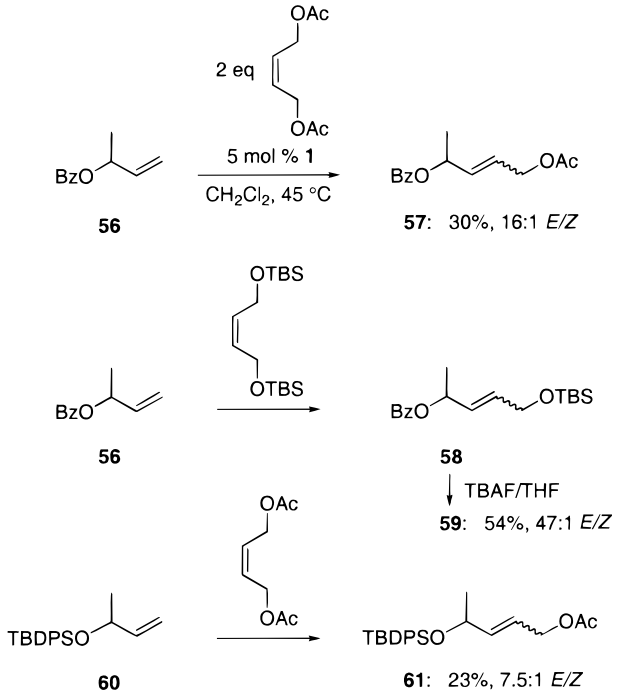
As illustrated in Scheme 6, treatment of Boc-L-serine(*O*-allyl)-OMe (**37**) with bis-acetate **20** generated lipophilic amino acid derivative **51** in high yield with improved *trans* selectivity (86%, 6:1 *E/Z*). The related lipophilic sugar **52** could be prepared in similar fashion through the CM of *C*-allylglucoside **43** with bis-acetate **2** (73%, 2.8:1 *E/Z*). CM of glucoside **43** with Boc-L-serine(*O*-allyl)-OMe homodimer **38** generated a low yield of the amino acid/sugar heterodimer **53** (37%, 5:1 *E/Z*).[49] In analogy to the synthesis of TBS-ether **11** (Table 1), silyl ether derivatized sugar **54** was generated in good yield with pronounced *trans* selectivity (70%, 9:1 *E/Z*).

To study the scope of CM in the functionalization of more complex substrates, we chose to investigate the CM of pentapeptide **45** with disubstituted internal olefins (Scheme 7). Treatment of **45** with the 9-decen-1-yl Boc-glycinate dimer **24** under standard solution-phase CM conditions afforded the

Scheme 7



Scheme 8



glycinate functionalized peptide **55** in moderate yield with modest *trans* selectivity (66%, 5.5:1 *E/Z*). This reaction further demonstrated the general applicability of CM as mild methodology for the introduction of diverse functionality tethered through a carbon−carbon bond. In summary, it appeared that our two-step procedure for the CM of selected internal olefins was not only effective but also, in view of the wide variety of substrates studied, substantially broad in scope.

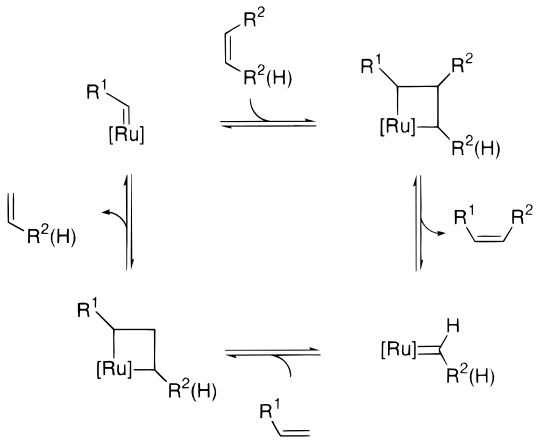
Cross-Metathesis of Terminal Olefins with Allylic Methyl Substituents. To further study the influence of steric effects on the *trans*/*cis* selectivity of CM employing catalyst **1**, a series of CM reactions was conducted on terminal olefins with allylic methyl substituents (Scheme 8).[50] At the outset of our studies, it was anticipated that allylic substitution would introduce steric hindrance close to the olefin group, and potentially direct CM toward the less sterically hindered *trans* product. This was consistently observed in the small group of substrates studied. The increased steric hindrance of the terminal olefin, however, was also observed to significantly reduce the CM yields. 3-Buten-2-yl benzoate (**56**)[22] was selected as the initial model terminal olefin substrate. CM of **56** with 2 equiv of *cis*-1,4-butenediol bis-acetate under standard solution-phase conditions generated cross-product **57** with high *trans* selectivity, albeit in modest yield (30%, 16:1 *E/Z*). This result was in direct contrast to that observed for the CM of 9-decen-1-yl benzoate (**3**) and the bis-acetate (Table 1, entry 1), where the cross-product **5** was generated in considerably higher yield with lower *trans* selectivity (89%, 4.7:1 *E/Z*), indicating that allylic methyl substituents do direct *trans* selective CM. Notably, the *E/Z* ratio for heterodimer **57** was almost four times greater than that for **5**.

CM of allyl-substituted benzoate **56** with the bulky *cis*-1,4-butenediol bis-OTBS gave similar results, affording the coupling product **58** in improved yield with dramatic *trans* selectivity (54%, 47:1 *E/Z*). Again, the *E/Z* ratio for **58** was approximately four times greater than that observed for the CM of 9-decen-1-yl benzoate (**3**) with the bis-OTBS compound (**11**, 10:1 *E/Z*, Table 1, entry 11). This combination of the allylic methyl substitution on **56** and the bulky TBS protecting groups generated a very selective CM reaction. In attempting to discern how the steric bulk of the allylic-substituted terminal olefin effected the regioselectivity of CM, we prepared 3-buten-2-*O*-*tert*-butyldiphenylsilyl ether (**60**).[51] CM of ether **60** with the bis-acetate generated a low yield of cross-product **61** with reduced *trans* selectivity (**61**, 7.5:1 *E/Z*). This result suggested that the increased steric bulk of silyl ether **60** in comparison to benzoate **56** had reduced its reactivity with catalyst **1**; the concomitant loss of *trans* selectivity, however, indicated that steric bulk was not the only factor governing stereoselective CM.

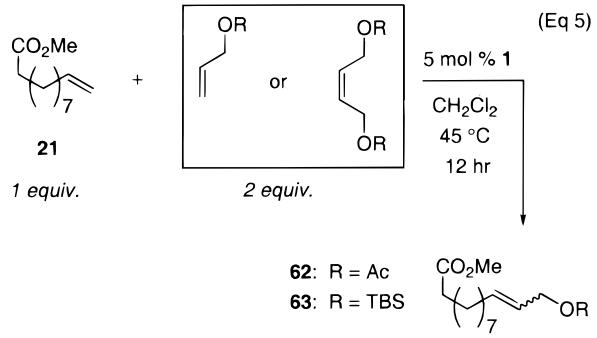
Reactivity of Disubstituted Olefins versus Monosubstituted Olefins. The results presented thus far demonstrate that both *cis*- and *trans*-disubstituted olefins are effective substrates for CM. Employing an excess of the disubstituted olefin relative to the terminal olefin component in CM was observed to lead to good yields of the desired heterodimeric product. In certain cases, we observed higher yields employing the disubstituted olefins instead of the monosubstituted counterpart. While using an excess of one olefin component should statistically push the reaction toward the heterodimeric product (if both olefins have comparable reactivities), we believed at the outset that employing an excess of the disubstituted olefin component in CM would statistically favor formation of an alkyl-substituted ruthenium alkylidene over the unsubstituted ruthenium methylidene. Because the methylidene formed from **1** had been shown to decompose considerably faster than other ruthenium alkylidene species,[25] we anticipated that preferential formation of an alkylidene species employing substituted olefins would extend the metathesis activity of **1** and potentially lead to higher yields of the desired heterodimeric product. As illustrated in Scheme 9, when one reactant is a disubstituted alkene it is possible to have a CM catalytic cycle that does not involve a methylidene intermediate. Alternatively, when both reactants are terminal olefins (as indicated by the (H) adjacent to the second R^2 in Scheme 9), the catalytic cycle generates a ruthenium methylidene for each productive CM reaction.

To further probe the use of disubstituted olefins in CM reactions, we conducted four side-by-side CM reactions with methyl 10-undecenylate (**21**), 5 mol % **1**, and 2 equiv each of

Scheme 9



(1) allyl acetate, (2) allyl OTBS, (3) *cis*-1,4-butenediol bis-acetate, and (4) *cis*-1,4-butenediol bis-OTBS (eq 5). The



advantage of employing certain internal olefins in CM reactions is evident from the graphs shown in Figures 1 and 2.

Reaction profiles for the formation of heterodimeric CM products **62** and **63** and subsequent disappearance of starting material **21** are shown in Figure 1. For both the acetate (Figure 1a,b) and the OTBS (Figure 1c,d) series, CM with the disubstituted olefin afforded higher yields of the respective heterodimer product. In the case of the bis-acetate substrate, almost all of olefin **21** is consumed in 2 h, while consumption takes almost 6 h for the allyl acetate reaction. For the silyl ether substrates, the starting material **21** was consumed considerably faster but the reactivity pattern was similar: **21** was consumed in under 15 min for the bis-OTBS reaction, while it took almost 2 h for the reaction of olefin **21** with allyl OTBS to proceed to completion.

The enhanced reaction rates observed with the disubstituted olefins could be due to a statistical effect, in that 2 equiv of a disubstituted olefin has twice the number of potential alkylidenes to transfer when compared with 2 equiv of a terminal olefin. To examine this possibility, a reaction employing 4 equiv of the allyl OTBS substrate was subjected to a rate study (Figure 1c). This reaction was observed to proceed at a slower overall rate and provide a slightly diminished yield when compared with the reactions employing 2 equiv of allyl OTBS or 2 equiv of the bis-OTBS substrate. This former effect is most likely a consequence of the catalytic ruthenium species being engaged in the unproductive self-metathesis of the excess allyl OTBS starting material.

In monitoring the formation of methyl ester homodimer **22** for the OTBS reaction series (Figure 2a), a negligible amount of **22** was formed in the reaction with the bis-OTBS substrate, while the formation of homodimer **22** was occurring at a slow, but steady rate in the CM with allyl OTBS. Analogous results for homodimer formation **22** in the CM of the acetate series were also obtained (data not shown). From these results, it appeared that secondary metathesis of the heterodimers **62** and **63** and homodimer **22** was not occurring at an appreciable rate. Interestingly, the *trans*/*cis* ratio of heterodimer **63** was observed to be higher throughout the course of the reaction with the bis-OTBS substrate relative to allyl OTBS (Figure 2b). A higher *trans*/*cis* ratio was also observed in the formation of acetate heterodimer **62**. While definitive reasons for the latter ratio were not realized, the qualitative GC-MS analysis of these four reactions strongly suggested that employing these disubstituted olefins provided more chemo- and stereoselective CM relative to reactions employing monosubstituted olefins.

Catalyst Initiation Rates. After the bis-OTBS substrate was found to provide enhanced CM reaction rates and yields, we next became interested in determining a qualitative measure of catalyst initiation rates for this and several other olefin substrates. Although a study of the initiation rates of ruthenium alkylidene **1** by a variety of alkyl-substituted olefins has been published,[25] we were uncertain as to the effect of allylic oxygen functionality on these rates.

Three reactions (Scheme 10) were examined by ^{1}H NMR spectroscopy, and the results are shown in Figure 3. For these experiments, the temperature and concentration of catalyst and substrate was adjusted to provide reasonable rates and signal-to-noise ratios for NMR quantitation. Benzylidene **1** was initiated by terminal olefin **21** and allyl-OTBS at approximately the same rate, with 90% of the catalyst initiated within 5 min at room temperature. In contrast, the bis-OTBS substrate reacted with benzylidene **1** at a slower rate, requiring approximately 90 min to reach 90% initiation. The gradual increase in concentration of the methylidene species **65** was largely a consequence of the experimental conditions: the gaseous reaction byproduct ethylene was not being purged as it normally would under open reflux conditions.[52] We conclude from these studies that terminal olefins bearing allylic oxygen functionality initiated the catalyst with a rate comparable with that of "isolated" terminal olefins (i.e., olefins far removed from other functional groups). Therefore, we believed the benefit of using disubstituted olefins in certain CM applications was the result of minimizing the available pool of terminal olefins which can give rise to the less stable ruthenium methylidene species.

CM Reactions Involving Two "Isolated" Olefins. We discovered in later studies with more complex substrates that the benefit of employing disubstituted olefins in CM did not appear to be general. While a systematic study was not conducted, we observed that as the number of carbon units between the olefin and any functional or sterically bulky group was increased, CM of the *two monosubstituted* olefins, instead of one monosubstituted and one disubstituted olefin, afforded competitive yields of the desired heterodimeric cross-product. For example, cross-coupling reactions using 9-decen-1-yl *N*-Boc glycinate (**23**) and various equivalents of 9-decen-1-yl acetate (**19**) or the internal olefin homodimer **20** demonstrated no benefit to employing the disubstituted olefin for CM instead of the corresponding terminal olefin (Scheme 11). Using 1 or 2 equiv of olefin **19** or **20** afforded similar yields of heterodimer **49**. Furthermore, employing 0.5 equiv of disubstituted olefin **20** was not analogous to 1 equiv of monosubstituted olefin **19** (28% vs 45% yield of heterodimer **49**), which indicated the lower overall reactivity of the disubstituted olefin. While these data did not invalidate our two-step CM procedure described above, it did suggest that, in the case of structurally "isolated" olefins, the

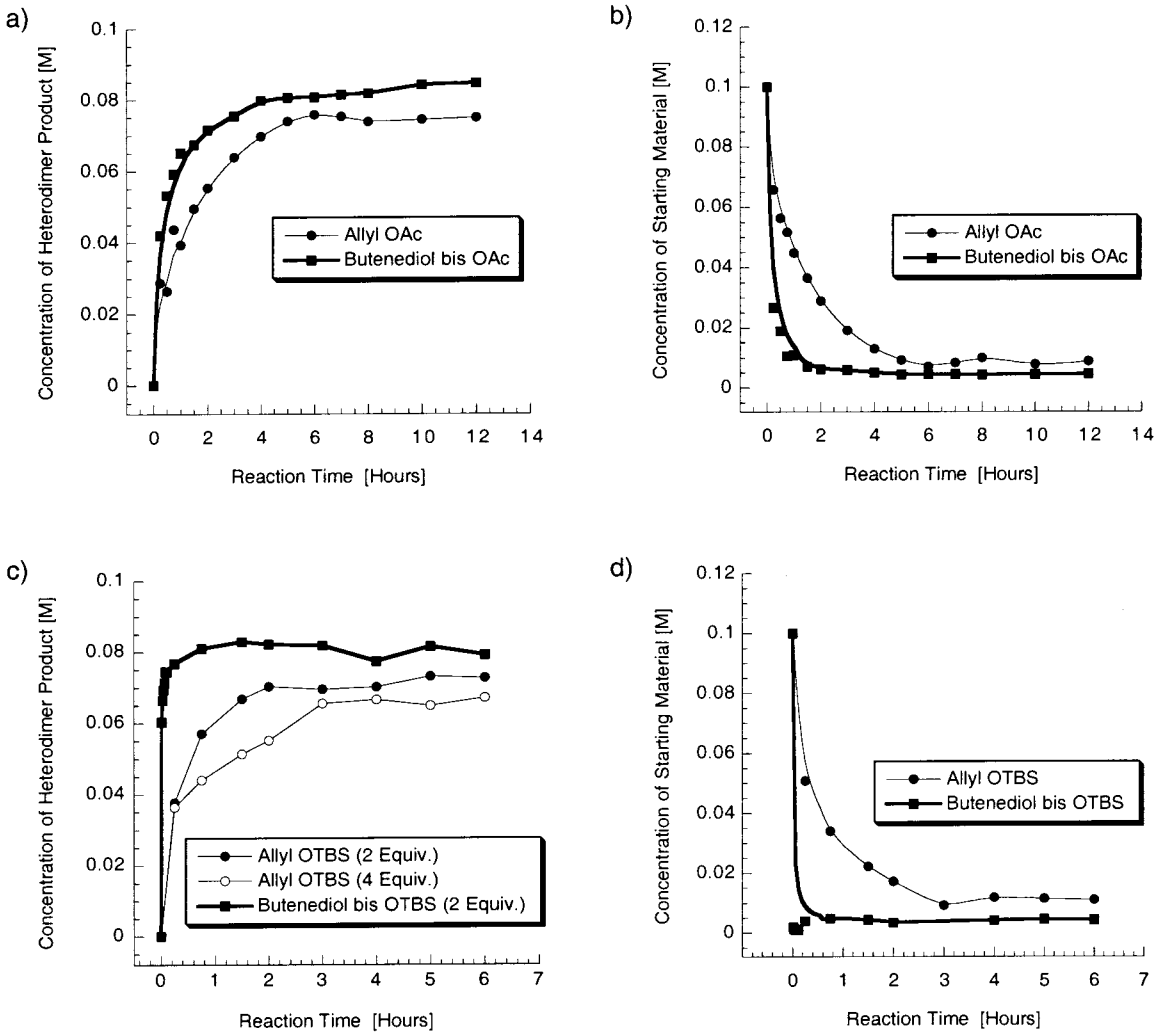


Figure 1. GC-MS reaction profiles for the CM of alkene **21** with mono- and disubstituted olefins. (a) Concentration of heterodimeric product **62** formed vs reaction time in the CM of **21** and allyl acetate and *cis*-1,4-butenediol bis-acetate. (b) Disappearance of **21** vs reaction time in the CM of **21** and allyl acetate and *cis*-1,4-butenediol bis-acetate. (c) Concentration of heterodimeric product **63** formed vs reaction time in the CM of **21** and allyl OTBS (2 and 4 equiv) and *cis*-1,4-butenediol bis-OTBS (2 equiv). (d) Disappearance of **21** vs reaction time in the CM of **21** and allyl OTBS and *cis*-1,4-butenediol bis-OTBS. Data obtained from GC-MS analysis of reaction aliquots (1,4-dichlorobenzene as internal standard, data corrected for relative response).

first self-metathesis step was not essential. Finally, the comparable yields of **49** obtained when equivalent amounts of either the mono- or disubstituted olefin (**19** or **20**) were employed suggested that preferential formation of a ruthenium alkylidene over the methylidene may not be governing the reaction outcome in the CM of structurally "isolated" olefins.

These results were in contrast to those observed in the GC-MS and ^{1}H NMR analysis of CM with protected allylic alcohols above (Figures 1−3), indicating that functionality allylic to the olefin could be influencing metathesis. We speculate that the heightened heterodimer yields employing disubstituted olefins with electron-donating allylic functionality are related to the alkylidenes generated upon metathesis. Relatively bulky, electron-donating substituents on alkylidenes have been shown previously to accelerate metathesis processes;[25] therefore, the preferential formation of a more active alkylidene employing an excess of the disubstituted olefin could be the reason for the observed higher CM yields.[53−55]

Cross-Metathesis of Terminal Olefins with Acrolein Acetals. In the course of examining the activity of substrates for CM with allylic oxygen functionality, we discovered that certain acrolein acetals were particularly robust substrates for CM with terminal olefins yielding protected α,β-unsaturated aldehydes. The preparation of α,β-unsaturated aldehydes has been accomplished previously by Wittig[56] homologation of aldehydes employing reagents such as $Ph_3P{=}CHCHO$[57] or with acetal[58] or imine[59] protected two-carbon ylides. Addition−elimination methods have also been used to homologate aldehydes.[60−62] In cases where a terminal olefin is serving as

(48) Terminal olefin derived sugars and amino acids have previously been employed in CM with other terminal olefins. See refs 13 and 46b.

(49) For recent syntheses of carbon−carbon linked glycosyl amino acids, see: (a) Dondoni, A.; Marra, A.; Massi, A. *J. Chem. Soc., Chem Commun.* **1998**, 1741−1742. (b) Dondoni, A.; Massi, A.; Marra, A. *Tetrahedron Lett.* **1998**, *39*, 6601−6604. (c) Hu, Y.-J.; Roy, R. *Tetrahedron Lett.* **1999**, *40*, 3305−3308.

(50) Racemic allylic-substituted terminal olefins were employed in these CM studies.

(51) Prepared according to a literature procedure: Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975−2977.

(52) The methylidene content was found to diminish when the NMR tubes were periodically purged with argon.

(53) Chelation of functionality in the allylic position of the metal alkylidene to the metal center should be disfavored because this would form a strained, four-membered ring.

(54) The poorer performance of disubstituted "isolated" olefins in CM reactions could also be due to a slower rate of CM, a rate that becomes competitive with the intrinsic rate of catalyst decomposition.

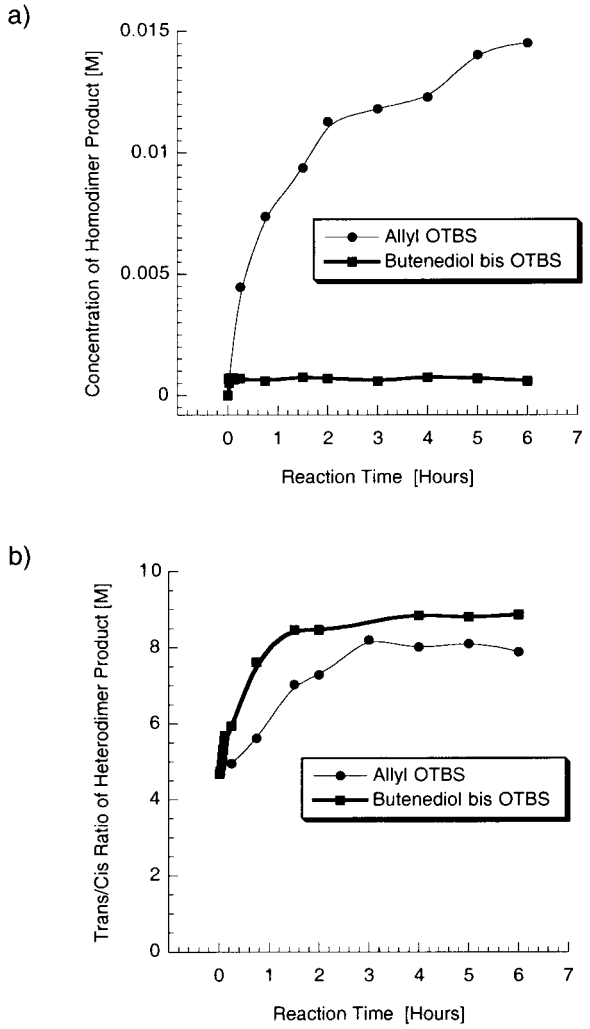


Figure 2. GC-MS reaction profiles for the CM of alkene **21** with allyl OTBS and *cis*-1,4-butenediol bis-OTBS. (a) Concentration of homodimeric product **22** formed vs reaction time in the CM of **21** and allyl OTBS and *cis*-1,4-butenediol bis-OTBS. (b) *Trans*/*cis* ratios of heterodimeric product **63** vs reaction time in the CM of **21** and allyl OTBS and *cis*-1,4-butenediol bis-OTBS. Data obtained from GC-MS analysis of reaction aliquots (1,4-dichlorobenze as internal standard, data corrected for relative response).

an aldehyde precursor, a cross-metathesis approach offers a direct means for homologation (Scheme 12).

Although acrylonitrile has been successfully employed in molybdenum alkylidene **2** catalyzed CM reactions,[11] 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.[63,64] Our initial investigations employed

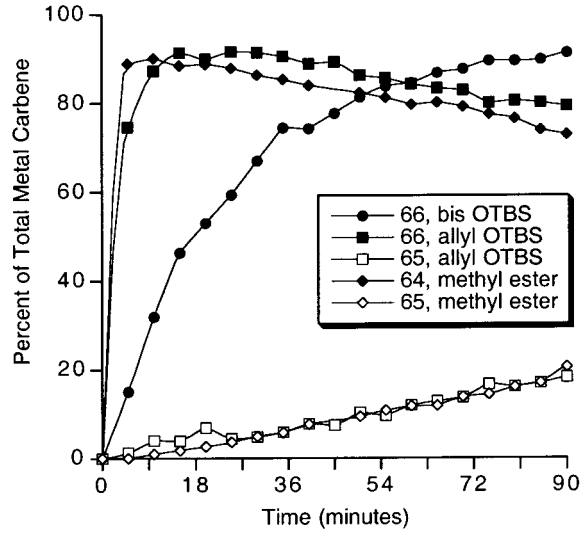
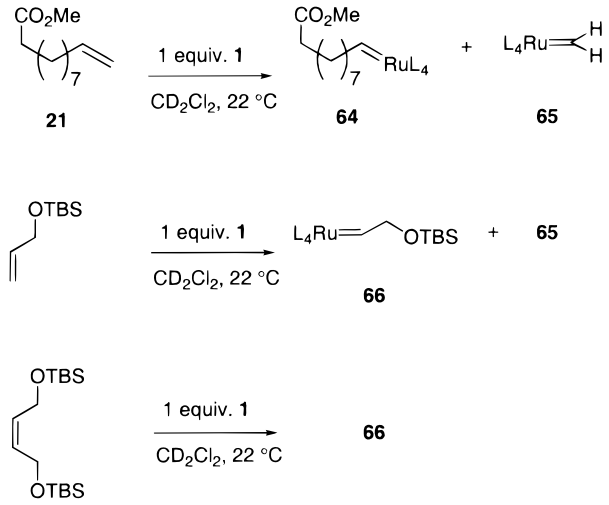


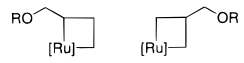
Figure 3. Catalytic species formed by reacting catalyst **1** (10 mM) with either methyl undecylenate **21**, allyl OTBS, or *cis*-1,4-butenediol bis-OTBS, each 100 mM in CD_2Cl_2 at 22 °C. Alkylidene formation in methyl undecylenate reaction (filled diamonds), allyl OTBS reaction (filled squares), and *cis*-1,4-butenediol bis-OTBS (filled circles). Methylidene formation in methyl undecylenate reaction (diamonds), allyl OTBS reaction (squares). Percent of total catalytic species determined by ^{1}H NMR integration of carbene resonances at 18−20 ppm.

Scheme 10[a]



[a] L = ligand on metal center.

(55) Another role of the disubstituted olefin may be to limit formation of a particular metallacycle that reduces catalytic efficiency because it is either less unreactive or readily decomposes. Because this type of role relates directly to the nature of the olefin substituent, it appears to be more consistent with the unique behavior exhibited by olefins containing proximal polar or sterically bulky groups. Two possibilities for the "unfavored" metallacycle, requiring a monosubstituted olefin for its formation, are as follows:



(56) 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.

(57) Bestmann, H. J.; Vostrowsky, O.; Paulus, H.; Billman, W.; Stransky, W. *Tetrahedron Lett.* **1977**, 121−124.

(58) Daubresse, N.; Francesch, C.; Rolando, C. *Tetrahedron* **1998**, *54*, 10761−10770.

(59) Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788−3789.

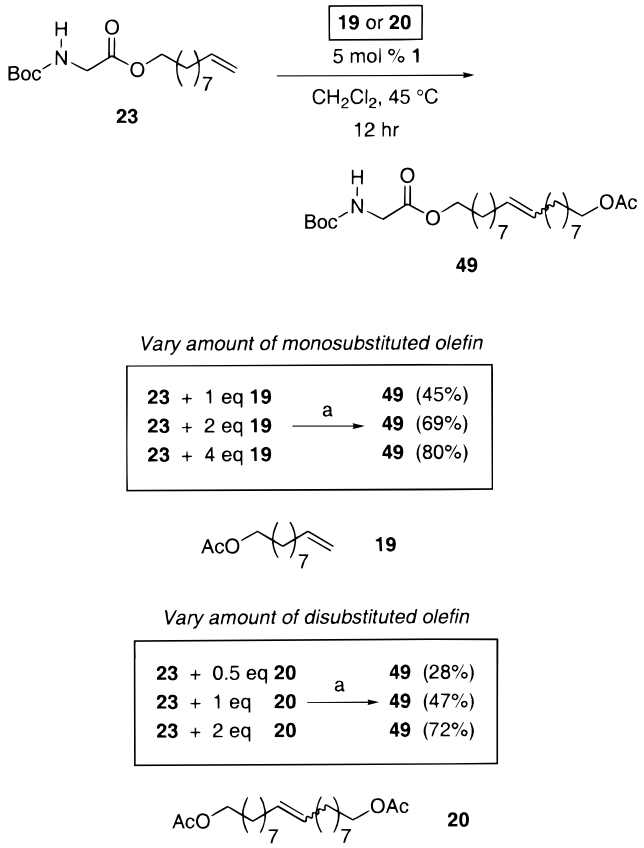
(60) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365−7367.

(61) Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *80*, 8−15.

(62) 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.

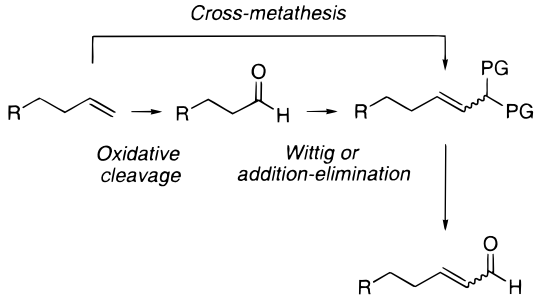
(63) For a recent example of an acrolein acetal used in an RCM reaction, see: (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084−9085. For the recent report of the ROM of cyclopropenone ketal with terminal olefins, see: (b) Michaut, M.; Parrain, J.-L.; Santelli, M. *Chem. Commun.* **1998**, 2567−2568.

Scheme 11[a]



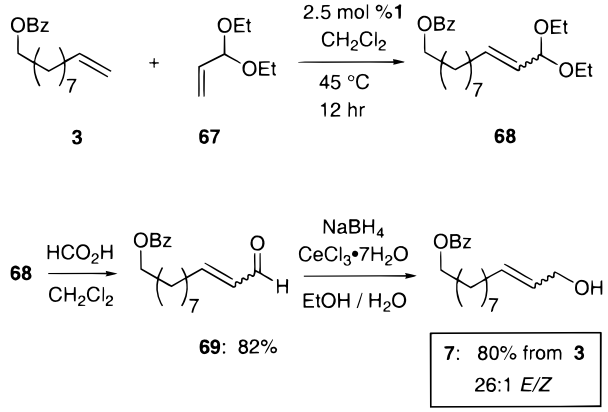
[a] 5 mol % **1**, CH_2Cl_2, 45 °C, 12 h.

Scheme 12

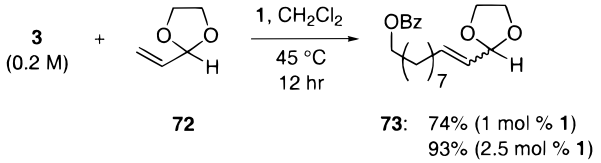


the commercially available acrolein diethyl acetal (**67**) and our standard terminal olefin substrate, 9-decen-1-yl benzoate (**3**) (Scheme 13). α,*β*-Unsaturated aldehyde **69** was obtained in 82% yield using 2.5 mol % **1** and 2 equiv of acetal **67**. Although the acid-sensitive diethyl acetal cross-metathesis product (**68**) could be isolated with chromatography employing Et_3N-treated silica gel, it was more convenient to recover the α,*β*-unsaturated aldehyde **69** after formic acid hydrolysis. Using a Luche reduction,[65] α,*β*-unsaturated aldehyde **69** was converted to allylic alcohol **7** in an efficient and highly *trans*-selective manner (Scheme 13). This three-step allylic alcohol synthesis was an improvement, in terms of both yield and *trans* selectivity, upon our CM procedure using protected *cis*-2-butene-1,4-diols described above (Table 1).

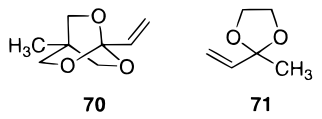
Scheme 13



Scheme 14



The reactivity of acetal **67** was unexpected, as it was originally thought that allylic disubstitution would hinder the CM 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 ruthenium-catalyzed CM of benzoate **3** with ortho ester **70**[66] or ketal **71**[67] proved unsuccessful, potentially due to their relative steric bulk in comparison to acetal **67** above.



CM reactions between terminal olefin **3** and 2-vinyl-1,3-dioxolane (**72**), a commercially available acrolein acetal with enhanced acid-stability compared to diethyl acetal **67**, gave excellent yields of the dioxolane-protected α,*β*-unsaturated aldehyde **73** (Scheme 14). For example, a 74% isolated yield of protected aldehyde **73** was obtained with the catalyst loading reduced to as little as 1 mol % **1**. The yield could be improved to 93% (7:1 *E*/*Z*) with a catalyst loading of 2.5 mol % **1** (Scheme 14), with the reaction proceeding to 90% conversion after 3 h.[1b]

Attempting to build upon our earlier work, which demonstrated certain advantages to using symmetrically disubstituted olefins as CM partners (see above), we prepared fumaraldehyde bis(ethylene glycol acetal) (**74**)[68] by homodimerization of vinyl dioxolane **72** employing ruthenium benzylidene **1** under standard solution-phase CM reaction conditions (Scheme 15). However, bis-acetal **74** did not prove as reactive as vinyl dioxolane **72** in CM reactions with terminal olefin **3**, presumably due to steric factors. Interestingly, however, the *trans*/*cis* ratio improved when

(64) Allylbenzene has recently been reported to efficiently undergo CM reactions with acrolein, acrolein dimethyl acetal, and acrylonitrile catalyzed by ruthenium benzylidene **1**. We have not observed productive CM with olefin **3** and either acrolein or acrylonitrile in our laboratory. See: Blanco, O. M.; Castedo, L. *Synlett* **1999**, 557−558.

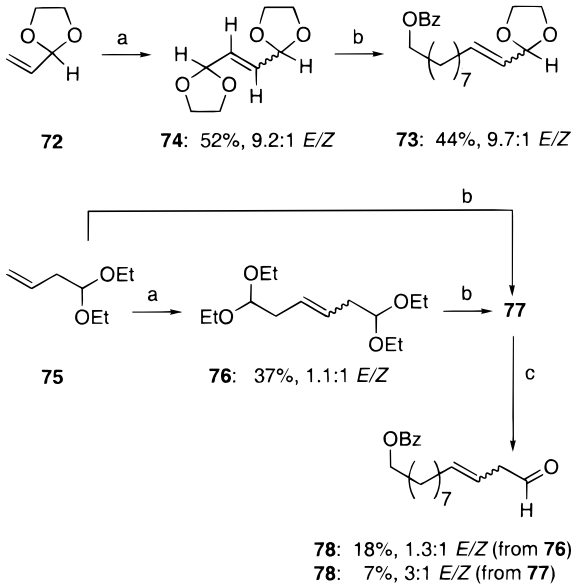
(65) Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1981**, 4077−4080.

(66) Prepared *via* a literature procedure. See: Gassman, P. G.; Chavan, S. *J. Chem. Soc., Chem. Commun.* **1989**, 837−839.

(67) Prepared *via* a literature procedure. See: Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449−1457.

(68) Cyclic diacetals of fumaraldehyde have been prepared previously. See: Sokolov, G. P.; Hillers, S. *Khim. Geterotsikl. Soedin.* **1969**, *1*, 32−35.

Scheme 15[a]



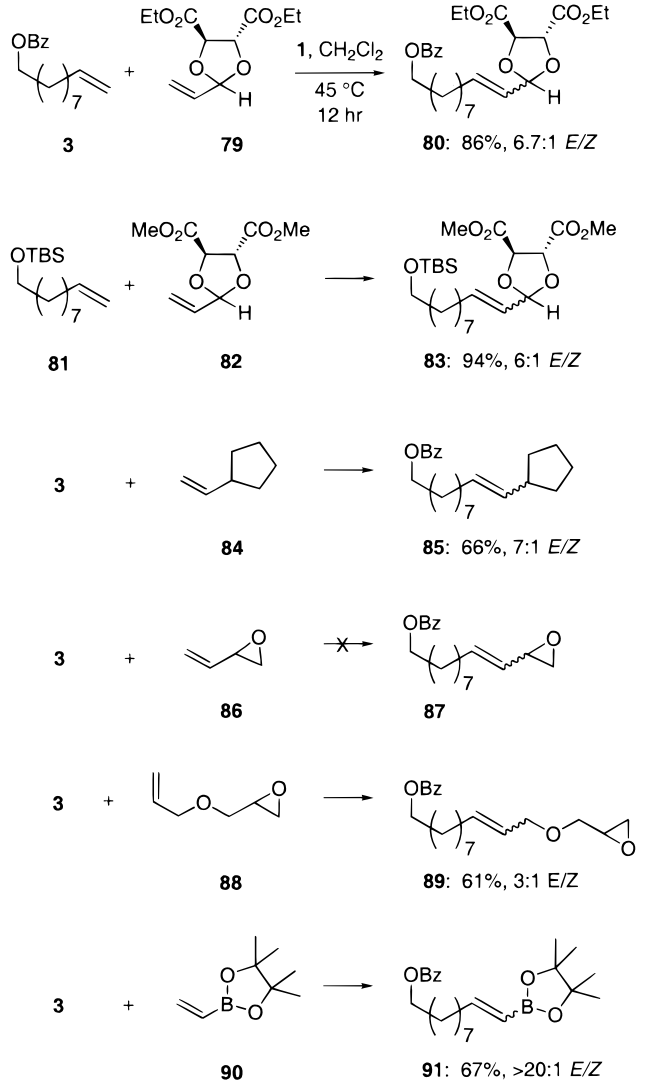
[a] Reagents and conditions: (a) 0.2 M in acetal, 5 mol % **1**, CH_2Cl_2, 45 °C. (b) 2 equiv of acetal component, 0.2 M **3**, 5 mol % **1**, CH_2Cl_2, 45 °C. (c) $HCO_2H-CH_2Cl_2$ (1:8), 25 °C.

the hindered bis-acetal **74** was employed (**73**: $E/Z = 9.7{:}1$ from **74**; **73**: $E/Z = 7{:}1$ from **72**).

Application of this CM acetal methodology to the construction of β,γ-unsaturated aldehydes *via* CM was next explored (Scheme 15). Unfortunately, the homologue of acetal **67**, 3-butenal diethyl acetal **75**, did not appear to be a promising substrate for CM. CM of benzoate **3** with 3-butenal diethyl acetal **75** or its homodimer **76**, followed by acetal hydrolysis afforded only low yields of the β,γ-unsaturated aldehyde **78** with poor *trans*/*cis* selectivity. These results could again be rationalized by the observation that certain homoallylic substituents on terminal olefins deactivate catalytic CM.[10,11] Specifically, formation of the alkylidene from acetal **75** allows for the formation of a potential five-membered chelate between one of the oxygens of **75** and the ruthenium **1** metal center, which could act to inhibit catalysis.

Extending the scope of the reaction to include asymmetric acrolein acetals was considered worthwhile because chiral α,β-unsaturated acetals are useful synthetic intermediates.[69] Accordingly, diethyl vinylidene-L-tartrate (**79**) was prepared[70] and found to provide a *trans* selective (6.7:1 *E/Z* by ^{1}H NMR) CM product **80** in excellent yield (86% after acetal hydrolysis) approximating that of vinyl dioxolane CM product **73** (Scheme 16).[71] Due to difficulties encountered in product purification for this combination of substrates, a variation using the dimethyl vinylidene-L-tartrate (**82**) and TBS-protected 9-decen-1-ol (**81**) was examined to determine an isolated yield for the CM reaction. Satisfyingly, the CM reaction was found to proceed in 94% isolated yield of cross product **83** with 6:1 *trans*/*cis* selectivity. The use of asymmetric acrolein equivalents, coupled with emergent asymmetric metathesis catalysts,[72] suggests a novel means for effecting catalytic kinetic resolutions *via* CM.

Scheme 16. Synthesis of Tartrate-Derived Acetals, Vinyl Boronate, and Epoxide Substrates via CM



Given the success of vinyl dioxolanes in CM reactions, structural variations of the five-membered ring were also examined. Vinyl cyclopentane (**84**) was tested as a CM substrate to compare the carbocyclic five-membered-ring system with the dioxolane systems above. Olefin **84** was found to provide a CM product in good yield and with *E*-selectivity (**85**: 66%, 7:1 *E/Z*). These yields were interesting when compared with results described earlier for the CM of terminal olefins with allylic methyl substituents: for example, 3-butene-2-ol derivatives **56** and **60** were observed to undergo CM reactions with difficulty (Scheme 8). In contrast, the results obtained with cyclic substrates **72**, **79**, **82**, and **84** revealed that ring-constrained allylic disubstitution can be accommodated in CM reactions initiated by ruthenium benzylidene **1**.

If ring constraint was an important factor for the success of these CM reactions, we reasoned that allylic epoxides such as butadiene monoxide (**86**) should be viable CM substrates. Unfortunately, this substrate did not react to any appreciable

(69) For an example of an asymmetric Simmons−Smith reaction using tartrate-derived α,β-unsaturated acetals, see: Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447−6458.

(70) Tsuzuki, T.; Koyama, M.; Tanabe, K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1008−1013.

(71) The *trans*/*cis* ratio was determined by ^{1}H NMR of the crude tartrate CM product **80**. The yield of tartrate CM product **80** was determined after acid hydrolysis of the acetal to afford aldehyde **69**.

(72) (a) Fujimura, O.; dela Mata, F. J.; Grubbs, R. H. *Organometallics* **1996**, *15*, 1865−1871. (b) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499−2500. (c) Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824−832. (d) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041−4042. (e) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720−9721.

extent. Other epoxide-containing substrates can be employed in CM reactions, however, as evidenced by the successful reaction of allyl glycidyl ether (**88**) with benzoate **3** to form cross-product **89** in 61% yield (3:1 E/Z).

Finally, in view of the success of vinyl dioxolanes in CM reactions, a cyclic vinyl boronate was tested as a CM substrate.[73] A pinacol-derived vinyl boronate (**90**)[74] was found to react with terminal olefin **3** to furnish cross-product **91** in good yield (67%) and with excellent *trans*-selectivity (>20:1 *E/Z*). Their use in CM provides a novel "one-step" method for converting terminal olefins into substrates for the Suzuki coupling reaction, a transformation with proven utility in complex natural product total syntheses.[75,76] Efforts to extend the use of vinyl boronates in CM applications are currently underway in these laboratories.

Summary and Future Prospectives

In conclusion, cross-metathesis reactions involving internal disubstituted olefins and certain terminal olefins with allylic disubstituton appear to be a promising method for the direct homologation of terminal olefins. The desired heterodimeric cross-products could be generated in good to excellent yields employing 1 equiv of terminal olefin, a 2-fold excess of the second component, and 1−5 mol % ruthenium benzylidene **1**. Furthermore, the cross-metathesis reactions were shown to be systematically more *trans* selective as the steric bulk at the allylic position of either the internal olefin or the terminal olefin was increased. Details of the current rationale behind the improved chemoselectivity of allylic oxygen functionalized olefins have been presented. The cross-metathesis methodology described herein should be of particular use for the functionalization of advanced intermediates in organic syntheses, for the synthesis of diverse combinatorial libraries, and for the construction of dimeric molecules for use as tools in molecular biology.[77] The CM homodimerization procedure employing benzylidene **1** also allows rapid access to functionally diverse chain transfer agents for the synthesis of novel telechelic polymers by ROMP. Future work is directed toward the installation of other functional groups *via* CM such as protected phosphorus,[78] sulfur,[79] and alkyne functionality, all of which allow for further post-metathesis synthetic manipulation. Routes toward dendritic architectures *via* selective CM are also being pursued in our laboratory. Finally, the simplicity and power of CM as an intermolecular carbon−carbon bond forming reaction is only now being appreciated; we anticipate that as selective CM routes are disclosed, the volume of CM applications in synthesis will dramatically escalate.

(73) For a recent example of the synthesis of cyclic alkenylboronates *via* RCM employing ruthenium catalyst **1**, see: Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995−7996.

(74) Prepared according to a literature procedure: Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599−3602.

(75) Suzuki, A. *Pure Appl. Chem.* **1986**, *58*, 629−638.

(76) Converting a terminal olefin to a vinylboronic acid or protected variant for the Suzuki coupling reaction often requires a three-step procedure involving (1) oxidative cleavage to the aldehyde, (2) subsequent reaction with dimethyl diazomethylphosphonate to provide the terminal alkyne, and (3) finally, conversion to the vinylboronate by hydroboration. For a recent example, see: Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1652−1655.

(77) The natural product FK506 was recently homodimerized employing **1** through its endogenous C(28) allyl group to yield a cell-permeable protein dimerizer, FK1012. See: Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 5106−5109.

(78) For the RCM of alkenyl phosphonates employing **1**, see: Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939−3942.

(79) Preliminary results from these laboratories show that alkenyl ester derivatives of cysteine are active substrates for CM.

Experimental Section

General Experimental Details. NMR spectra were recorded on either a JEOL GX-400, Bruker Avance-400, or Bruker AM-500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter at 589 nm and are reported as $[\alpha]_D$ (concentration in grams/100 mL of solvent). Low- and high-resolution mass spectra were provided by either the Southern California Mass Spectrometry Facility (University of California, Riverside) or the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230−400 mesh) from EM Science.[80] *cis*-3-Hexene was purchased from Chemsampco, Gray Court, SC. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.[81] Catalyst **1** was prepared according to a published procedure.[6]

Peptide Synthesis. *N*-Boc-L-serine(*O*-allyl) methyl ester (**36**), *N*-Boc-L-homoserine(*O*-allyl) methyl ester (**38**), and *N*-Boc-L-tyrosine(*O*-allyl) methyl ester (**37**) were prepared according to a modified literature procedure.[82] Peptide **44** was synthesized by conventional solution-phase synthesis methods using a racemization free fragment condensation strategy. Couplings were mediated by *N*,*N*-dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBT).[83] The Boc group was used to protect the N-terminus, and the C-terminus was protected as a methyl ester. Deprotections were performed using 1:1 trifluoroacetic acid/CH_2Cl_2 and saponification, respectively. All intermediates were characterized by ^{1}H NMR and TLC, and if necessary purified by column chromatography on silica gel.

Representative Procedure for Solution-Phase Cross-Metathesis Reaction. Compound 5. 9-Decen-1-yl benzoate (**3**) (69 μL, 0.25 mmol) was added *via* syringe to a stirring solution of *cis*-1,4-bis(acetyloxy)-but-2-ene (79 μL, 0.5 mmol) and **1** (21 mg, 0.025 mmol, 10 mol %) in CH_2Cl_2 (2.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 3 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 9:1, 4:1, and 2:1 hexane/ethyl acetate (100 mL aliquots). A pale yellow oil was obtained (68 mg, 82% yield, 5:1 *trans*/*cis* as determined by integration of peaks at 4.50 and 4.61 ppm in the ^{1}H NMR spectrum). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (2H, d, J = 7.2 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.42 (2H, t, J = 7.8 Hz), 5.78−5.72 (1H, broad m), 5.57−5.50 (1H, broad m), 4.50 (2H, d, J = 6.4 Hz), 4.30 (2H, t, J = 6.7 Hz), 2.06−2.02 (2H, broad m), 2.03 (3H, s), 1.75 (2H, m), 1.44−1.31 (10H, broad m). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 170.7, 166.5, 150.5, 136.4, 135.2, 132.6, 130.5, 129.4, 128.2, 123.7, 123.3, 65.1, 64.9, 60.2, 32.1, 29.2, 29.1, 28.9, 28.7, 28.6, 27.4, 25.9, 20.9. R_f = 0.36 (9:1 hexane/ethyl acetate); HRMS (FAB) calcd for $C_{20}H_{28}O_4$ $[M - H]^+$ 333.2066, found 333.2067.

Representative Reduced Pressure Procedure for Self-Metathesis Reaction. Compound 4. 9-Decen-1-yl benzoate (**3**)[84] (349 mg, 1.34 mmol) and **1** (3.5 mg, 4 μmol, 0.3 mol %) were combined in a 1 dram

(80) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(81) The solvent columns are composed of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

(82) For the allylation procedure, see: Sugano, H.; Miyoshi, M. *J. Org. Chem.* **1976**, *41*, 2352−2353. For the methyl ester formation, see: Hirai, Y.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1989**, *111*, 3062−3063.

(83) Bodansky, M. *Peptide Chemistry*; Springer-Verlag: New York, 1988; pp 55−146 and references therein.

(84) Prepared according to a general literature procedure: Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1981**, *46*, 5252−5253.

vial. A magnetic stir bar was added to the vial, which was placed inside a vacuum chamber and held under vacuum (60−100 mTorr) accompanied by stirring for 36 h at room temperature. The thick burgundy-colored oil was observed to steadily produce gas during the course of the reaction. The reaction mixture was dissolved in 1.0 mL of CH_2Cl_2 and applied to a silica gel column (2 × 10 cm, eluting with CH_2Cl_2 (375 mL)). Pure fractions were concentrated to give a clear, colorless, viscous oil which formed a white solid over time (312 mg, 94% yield, 3.8:1 *trans*/*cis* as determined by integration of peaks at 5.38 and 5.35 ppm in the ^{1}H NMR spectrum). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.03 (4H, d, J = 7.2 Hz), 7.53 (2H, t, J = 7.3 Hz), 7.42 (4H, t, J = 7.2 Hz), 5.38 (2H, m), 4.30 (4H, t, J = 6.7 Hz), 2.10−1.90 (4H, m), 1.75 (4H, quint, J = 7.2 Hz), 1.50−1.20 (20H, m). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 166.3, 132.5, 130.4, 130.2, 129.7, 129.4, 128.1, 64.9, 32.4, 29.6, 29.4, 29.2, 29.1, 28.9, 28.6, 27.0, 25.9. R_f = 0.50 (9:1 hexane/ethyl acetate); HRMS (FAB) calcd for $C_{32}H_{44}O_4$ $[M + H]^+$ 493.3239, found 493.3318.

Representative Solution-Phase Self-Metathesis Reaction. Compound 46. Pentapeptide **45** (100 mg, 0.10 mmol) was added to a stirring solution of **1** (1.2 mg, 1.0 μmol, 1 mol %) in CH_2Cl_2 (0.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 20 h. The reaction mixture was then reduced in volume to 0.25 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 3:1, 5:1, and 9:1 ethyl acetate/hexane (100 mL aliquots), and finally with 100% ethyl acetate (200 mL). An off-white crystalline solid was obtained (61 mg, 62% yield, 2.8:1 *trans*/*cis* as determined by the relative intensities of peaks at 129.1 and 129.0 ppm in the ^{13}C NMR spectrum). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.47 (2H, d, J = 6.6 Hz), 7.27 (2H, d, J = 9.1 Hz), 7.11 (2H, d, J = 6.3 Hz), 6.83 (2H, s), 5.66 (2H, m), 5.37 (2H, m), 4.66 (2H, m), 4.54 (2H, m), 4.24 (2H, m), 4.05−3.93 (6H, br m), 3.81 (2H, m), 3.70 (8H, s), 2.42 (2H, m), 1.70−1.59 (12H, br m), 1.46 (30H, m), 0.99−0.89 (36H, br m). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 175.7, 175.6, 173.6, 173.5, 172.9, 171.7, 170.4, 170.3, 156.6, 129.1, 129.0, 80.8, 71.1, 69.7, 66.8, 60.4, 57.0, 55.0, 54.1, 52.3, 51.1, 40.7, 40.3, 29.8, 29.3, 28.4, 27.1, 24.8, 24.6, 24.0, 23.0, 22.97, 22.0, 21.8, 19.4, 17.3. R_f = 0.08 (3:1 ethyl acetate/hexane); $[\alpha]_D$ = −13.67 (CH_2Cl_2, *c* 0.34); LRMS (FAB) calcd for $C_{64}H_{114}N_{10}O_{18}$ $[(M) - Boc]^+$ 1211.8, found 1211.9.

Representative Acrolein Acetal Cross-Metathesis Reaction. Compound 83. Dimethyl vinylidene-L-tartrate[70] (215 μL, 1.0 mmol) and 9-decen-1-(*tert*-butyldimethylsilane)-yl (165 μL, 0.5 mmol) were simultaneously added *via* syringe to a stirring solution of **1** (12 mg, 0.014 mmol, 2.9 mol %) in CH_2Cl_2 (2.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 5:1 hexane/ethyl acetate (200 mL). A clear oil was obtained (214 mg, 94% yield, 9:1 *trans*/*cis* as determined by the relative intensities of the peaks at 125.3 and 124.8 ppm in the ^{13}C NMR spectrum). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.00 (1H, m), 5.55 (2H, m), 4.82 (1H, d, J = 3.7 Hz), 4.73 (1H, d, J = 3.7 Hz), 3.80 (6H, s), 3.57 (2H, t, J = 6.6 Hz), 2.07 (2H, m), 1.50−1.21 (12H, m), 0.87 (9H, s), 0.02 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 170.6, 170.2, 141.1, 125.3, 124.8, 108.1, 102.7, 63.8, 53.4, 53.3, 33.4, 32.6, 30.0, 29.9, 29.7, 29.0, 26.5, 26.3, 18.9, 14.8. R_f = 0.23 (9:1 hexane/ethyl acetate); HRMS (FAB) calcd for $C_{23}H_{42}O_7Si$ $[M + H]^+$ 459.2778, found 459.2776. Calcd elemental analysis: C, 60.23; H, 9.23. Found: C, 59.98; H, 9.15.

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Supporting Information Available: Experimental procedures and full characterization (^{1}H and ^{13}C NMR, HRMS/elemental analysis, mp, $[\alpha]_D$) of the cross- and self-metathesis products; ^{1}H NMR spectra for **4**, **5**, **7**, **8**, **10**, **12**−**16**, **18**, **20**, **22**, **24**, **26**, **28**, **30**, **32**, **34**, **38**, **40**, **42**, **44**, **46**−**49**, **51**−**55**, **57**, **59**, **61**, **73**, **74**, **76**, **78**, **85**, **89**, and **91** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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