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Synthesis of Functionalized Olefins by Cross and Ring-Closing Metatheses

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The generation of olefins with electron-withdrawing functionality, such as α,β-unsaturated aldehydes, ketones, and esters, remains a difficult task in organic chemistry. A practical method to approach this problem would involve olefin metathesis,[1] utilizing well-defined alkylidenes such as $((CF_3)_2MeCO)_2(ArN)Mo{=}CH(t\text{-}Bu)$ (**1**)[2] and $(PCy_3)_2Cl_2Ru{=}CHPh$ (**2**).[3] However, the generation of olefins with vinylic functionality through the use of cross-metathesis[4] (CM) has met with limited success. In one of the few reports of this reaction, Crowe and Goldberg[5] demonstrated that acrylonitrile participated in cross-metathesis reactions with a variety of terminal olefins. Other π-conjugated olefins, such as enones and enoic esters, were not functional group compatible with alkylidene **1** and failed to react with **2** in cross-metathesis. Recently, the highly active ruthenium-based olefin metathesis catalyst **3**,[6] which contains a 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand, was found to efficiently catalyze the cross-metathesis of 1,1-geminally disubstituted olefins.[7] Because ruthenium alkylidene **3** displayed unique activity toward previously metathesis-inactive substrates, we decided to investigate the metathesis of α-functionalized olefins. In this communication, we report the single-step synthesis of α-functionalized olefins by intermolecular cross-metathesis and intramolecular ring-closing metathesis using ruthenium alkylidene **3**.

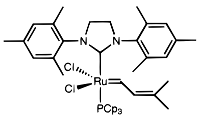

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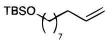
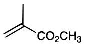
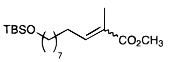
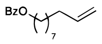
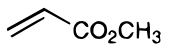
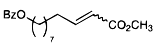
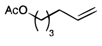
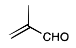
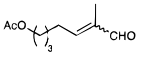
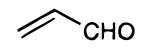
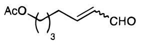
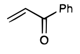
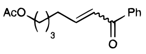
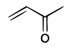
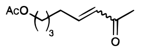
Table 1. Cross-Metathesis Reactions with Esters, Aldehydes and Ketones[a]

entry	terminal olefin	α-functionalized olefin (equiv.)		product	isolated yield(%)	*E/Z*[b]
1	 **4**	 **7**	(0.5)	 **13**	62	>20:1
2	 **5**	 **8**	(2.0)	 **14**	91	4.5:1
3	 **6**	 **9**	(0.5)	 **15**	92	>20:1
4	**6**	 **10**	(2.0)	 **16**	62	1.1:1
5	**6**	 **11**	(2.0)	 **17**	99	>20:1
6	**6**	 **12**	(2.0)	 **18**	95	>20:1

[a] Reactions with 5 mol% of **3**. Reactions with geminally disubstituted olefins utilize the same stoichiometry as those reported in ref 7. [b] Ratio based on NMR spectra.

In the exploration of a variety of 1,1-geminally disubstituted olefins as substrates for CM, we discovered that methyl methacrylate **7** participates in CM with terminal olefin **4** to generate the trisubstituted enoic ester **13** in moderate yield with excellent stereoselectivity (Table 1, entry 1). This positive result led us to examine the cross-metathesis of various α-carbonyl containing compounds (Table 1). Particularly noteworthy are the generally excellent yields attained with ketones and aldehydes (Table 1, entries 3−6). Extended reaction times were necessary in order to ensure these high yields.[8]

Additionally, the efficiency of the reactions suggest that the highly unstable β-carbonyl-carbene species $[Ru]{=}CH(CO)R$ is not involved in the cross-metathesis. It was recently shown that ester-carbene complexes decompose within a few hours at room temperature, in contrast to the long lifetime of catalyst **3** in cross metathesis.[9] The typically low degree of conversion to an ester-carbene, coupled with its instability, strongly suggests that β-carbonyl-carbenes are not responsible for the bulk of product formation.[10]

Overall, the stereoselectivities of the reactions are excellent, making them synthetically practical. Although numerous factors control the stereochemistry of the ultimate products, simple steric arguments provide a first level of analysis. Presumably the alkyl chain (from the unfunctionalized olefin) and the carbonyl group

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(1) For a recent review of olefin metathesis see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(2) (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.

(3) (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.

(4) Recent developments in cross-metathesis include: (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998−10999. (b) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117−2120. (c) Brummer, O.; Ruckert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441−446. (d) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427−7430. (e) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091−1094. (f) Roy, R.; Dominique, R.; Das, S. K. *J. Org. Chem.* **1999**, *64*, 5408−5412. (g) Blanco, O. M.; Castedo, L. *Synlett* **1999**, 557−558. (h) Huwe, C. M.; Woltering, T. J.; Jiricek, J.; Weitz-Schmidt, G.; Wong, C.-H. *Bioorg. Med. Chem.* **1999**, *7*, 773−788. (i) Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405−5408. (j) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58−71.

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

(6) Scholl, M.; Ding, S.; Lee C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. The dimethylvinyl carbene **3** is prepared by analogy to the synthesis of the benzylidene reported therein. Details are included in the Supporting Information.

(7) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753.

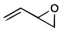
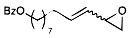
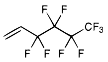
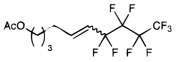
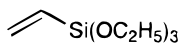
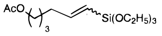
(8) In entry 3 (Table 1), productive CM was still observed (^1H NMR) to be occurring after 8 hours. As previously reported in a related CM system using Ru catalyst **2**, productive cross-metathesis continues to be observed after 10 hours.[4j] This result is also consistent with previous experiments which indicate that the propagating species, the methylidene derivative of **3**, has a lifetime in excess of 12 hours: Ulman, M.; Grubbs, R. H. Unpublished results.

(9) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. Manuscript in preparation.

(10) NMR scale experiments were performed in J. Young valve NMR tubes under an N_2 atmosphere, with 20 equivalents of functionalized olefin to 1 equivalent of **3** in CD_2Cl_2. After 1 hour at 45 °C, the reaction of **3** and methyl acrylate forms less than 7% of the ester carbene, which decomposes rapidly (4 hours). Characteristic ^1H NMR shifts include: 17.87 ppm (methylidene of **3**); 17.33 ppm (ester-carbene, $Ru{=}CHCO_2Me$).

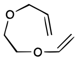
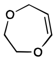
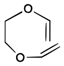
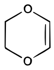
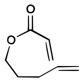
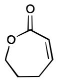
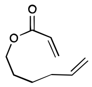
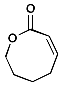
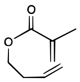
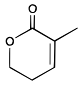
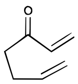
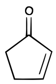
10.1021/ja9939744 CCC: $19.00

Table 2. Cross-Metathesis Reactions with Substrates Containing Non-Carbonyl Functional Groups[a]

entry	terminal olefin	α-functionalized olefin (equiv.)		product	isolated yield (%)	*E*/*Z*[b]
1	**5**	 **19**	(2.0)	 **22**	38	5:1
2	**5**	**19**	(4.0)[c]	**22**	55	5:1
3	**6**	 **20**	(2.0)	 **23**	34	2.3:1
4	**6**	 **21**	(2.0)	 **24**	81	11:1

[a] Reactions with 5 mol% of **3**. [b] Ratio based on NMR spectra. [c] Added over a 12 h period.

Table 3. Ring-Closing Metathesis of Functionalized Dienes[a]

entry	α-functionalized diene	product	isolated yield (%)
1	 **25**	 **31**	49
2	 **26**	 **32**	0
3	 **27**	 **33**	97
4	 **28**	 **34**	92
5	 **29**	 **35**	86
6	 **30**	 **36**	93

[a] Using 5 mol % of **3**.

are well separated in the metathesis intermediates leading to product formation. Adding a geminal methyl group (entries 1 and 3) radically amplifies this *trans* tendency. Various ketones also appear to contain bulk close enough to the metal center to overwhelmingly favor the *trans* orientation in the products (entries 5 and 6). Replacing the ketone with an aldehyde group evidently removes this steric interaction, allowing the *cis/trans* ratio to approach unity. Alternatively, in light of the long lifetime of these catalysts,[7] the ratios could also result from subsequent isomerization of the initial products.

Other functional groups at the vinylic position were also investigated in cross-metathesis, and the results are summarized in Table 2. Butadiene monoxide **19** and electron-deficient fluorinated alkene **20** participate in cross-metathesis in moderate yields (entries 1−3). The slow addition of four equivalents of epoxide **19** over 12 h increased the yield of cross-product **22** with the balance of **5** as its homodimer. Similar to the successful CM of highly oxygenated vinyl boronic esters,[4j] vinyl siloxanes are also very good cross-metathesis partners using **3** (Table 2, entry 4), but yielded only 36% of cross-product **24** with ruthenium benzylidene **2**.[11] These siloxanes provide useful synthons for further reactions, such as Suzuki-type aryl halide cross-couplings.[12]

It should be noted that vinylic halides, pthalimides, sulfones, silanes, acetates, ethers, alkyltins, and acrylonitriles were not reactive in cross-metathesis using **3**. Some homodimerization of terminal olefins **4**−**6** were observed in these reactions, but no significant CM products were formed. This lack of reactivity may result from the sequestering of the catalyst in a stabilized Fischer-type carbene complex, which either rapidly decomposes or fails to react further.[13]

To compare reactivities of intra- and intermolecular metathesis, RCM reactions of substrates bearing vinyl functional groups were performed, and the results are summarized in Table 3. In contrast to the unsuccessful cross-metathesis of vinyl ethers, the RCM of mixed ether **25** proceeded in moderate yield to give the cyclic adduct **31** (Table 3, entry 1). Interestingly, substrates bearing both a vinyl ether and allylic ether were previously found to be inactive for ring-closing metathesis using ruthenium benzylidene **2**.[14] However, with **3**, formation of unreactive Fischer-type carbenes is reduced if **3** reacts preferentially with the allylic ether. Consistent with this suggestion is the inability of **3** to ring-close substrate **26** where both alkenes are vinyl ethers (Table 3, entry 2). Substrates **27**−**30** underwent RCM cleanly and in excellent yield. Six, seven and eight membered α,β-unsaturated lactones (Table 3, entries 3−5) and cyclopentenone **36** were formed in excellent yields, including a notable trisubstituted case **35**.[15]

In conclusion, the cross-metathesis and ring-closing metathesis of a variety of electron-deficient olefins employing ruthenium alkylidene **3** has been described. These findings further demonstrate the high activity and functional group compatibility of **3**, which significantly expands the range of olefins that can participate in the olefin metathesis reaction.

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Supporting Information Available: Full experimental details and spectral data for compounds **3**−**36** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA9939744

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[11] CM of vinyl silanes with styrene has recently been demonstrated using **2**: See Pietraszuk, C.; Marciniec, B.; Fischer, H. *Organometallics* **2000**, *19*, 913−917.

[12] (a) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051−6054. (b) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309−1310. (c) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688.

[13] For typical experimental conditions in NMR reactions, see ref 10. For 9-vinylcarbazole, the new Fischer carbene species has the following characteristic resonances: ^{1}H NMR: 16.64 ppm; ^{31}P NMR: 30.06 ppm. After 40 min at 45 °C, all **3** has been consumed. For ethyl vinyl ether, the new Fischer carbene has characteristic resonances: ^{1}H NMR: 13.62 ppm; ^{31}P NMR: 27.07 ppm. Even after 4.5 h at 45 °C, some **3** remains visible by ^{1}H NMR.

[14] Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623−9626.

[15] The formation of five- and six-membered α,β-unsaturated lactones, with **2** and a Lewis acid, has been previously reported. See Ghosh, A. K.; Capiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651−4654.