ORGANIC LETTERS

2001
Vol. 3, No. 11
1749−1752

Sequential Ring-Closing Metathesis and Silicon-Assisted Cross-Coupling Reactions: Stereocontrolled Synthesis of Highly Substituted Unsaturated Alcohols

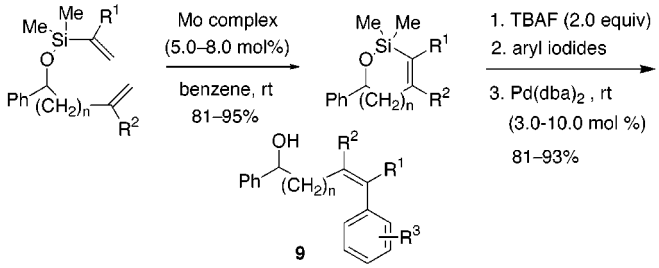
Scott E. Denmark* and Shyh-Ming Yang

Roger Adams Laboratory, Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801

denmark@scs.uiuc.edu

Received April 5, 2001

ABSTRACT



A sequential ring-closing metathesis/silicon-assisted cross-coupling sequence has been developed. Alkenyldimethylsilyl ethers of ω-unsaturated alcohols undergo facile ring closure with Schrock's catalyst to afford five-, six-, and seven-membered cycloalkenylsiloxanes bearing substituents on both alkenyl carbons. These siloxanes were highly effective coupling partners with various aryl and alkenyl halides and in the presence of Pd(0) afforded styrenes and dienes in high yield and specificity and with good functional group compatibility.

The formation of carbon−carbon bonds by transition-metal-catalyzed cross-coupling reactions, especially by palladium catalysts, has emerged as a general and powerful method in organic synthesis.[1] Among the most notable and commonly employed methods are the Suzuki coupling of organoboranes, Stille coupling of organostannanes, and Negishi coupling of organozinc compounds. In recent years, the coupling reactions of organosilicon compound have provided a viable alternative.[2,3] Following the pioneering work of Hiyama[2,3a] and Ito,[3b,c] the utility of this method has been expanded by, inter alia, modulation of the silicon species, the use of additives, and implementation of new catalysts.[3] Recent reports from these laboratories[4] have demonstrated that simple organosilicon components including silacyclo-

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic Syntheses*; Wiley: Chichester, U.K., 1995. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.

(2) For a recent review, see: Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471. (c) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.

(3) For recent examples of silicon-based cross-coupling, see: (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918 (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. (c) Suginome, M.; Kinugasa, H.; Ito, Y. *Tetrahedron Lett.* **1994**, *35*, 8635. (d) Mowery, M. E.; DeShong, P. J. *J. Org. Chem.* **1999**, *64*, 1684. (e) Mowery, M. E.; DeShong, P. J. *J. Org. Chem.* **1999**, *64*, 3266. (f) Lam. P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M.; DeShong, P.; Lark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. (g) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hayama, T. *Org. Lett.* **1999**, *1*, 299. (h) Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 749. (i) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (j) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309.

10.1021/ol015950j CCC: $20.00
Published on Web 05/09/2001

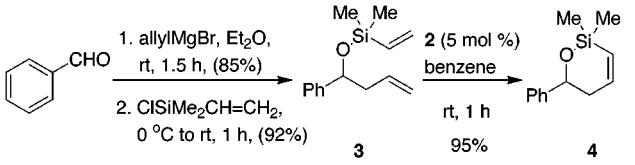
butanes,[4a−d] silanols,[4e] silyl hydrides,[4f] cyclic silyl ethers,[4g] and even oligosiloxanes[4h] can serve effectively as the donor in Pd-catalyzed cross-coupling reactions. Among the practical features of this process are (1) efficiency and mildness of reaction conditions, (2) stereospecificity with respect to both of addends, and (3) broad functional group compatibility.

One of the most important advantages of the silicon-based cross-coupling is the diversity of methods available for the introduction of the silafunctional unit into the organic substrate. Moreover, the ability to introduce the silicon donor in a regio- and stereocontrolled fashion is a prerequisite for stereocontrolled construction of alkenes. We have recently illustrated this aspect of the method by the use of intramolecular hydrosilylation/cross-coupling to efficiently and stereoselectively prepare homopropargylic alcohols.[4g] In that study, a temporary silicon tether was employed to set the geometry of an alkylidenylsiloxane by hydrosilylation. We now report a variant of the silicon-tether concept to the generation of cycloalkenylsiloxanes by Mo-catalyzed ring-closing metathesis (RCM) and their subsequent participation as the nucleophilic partners in Pd-catalyzed cross-coupling.[5]

Ring-closing metathesis (RCM) catalyzed by Mo or Ru complexes has revolutionized the way in which of carbocycles and heterocycles are constructed.[6] In view of the not uncommon use of silyl ethers as tether anchor points, we recognized the opportunity for the combination of RCM and Pd-catalyzed cross-coupling chemistry by the use of alkenylsilyl ethers. The few reported examples of RCM of allylic silyl ethers employ Grubbs ruthenium alkylidene complex $[Cl_2(Cy_3P)_2Ru{=}CHPh]$ (**1**) as the catalyst.[7] However, RCM of the sterically more demanding vinylsilyl ether dienes requires the less sterically sensitive molybdenum carbene complex $[(CF_3)_2MeCO]_2Mo(=CHCMe_2Ph)(=NC_6H_3\text{-}2,6\text{-}i\text{-}Pr_2)$ (**2**), developed by Schrock et al.[8]

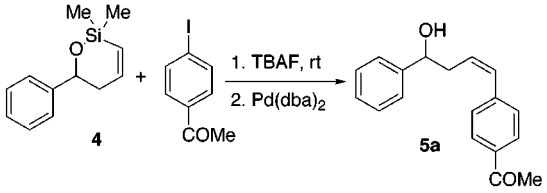
To test the feasibility of the overall transformation, we prepared vinylsilyl ether, **3**, which was prepared by addition of allylmagnesium bromide to benzaldehyde followed by silylation with commercially available chlorodimethylvinylsilane, Scheme 1. Initial studies on the RCM reaction of **3** using the Grubbs alkylidene complex **1** failed; none of the desired product, **4**, was observed by ^{1}H NMR analysis. All variations in conditions, including change of solvent (CH_2Cl_2 or benzene) and/or temperature (room tempearture, 45 °C, or 80 °C) were unsuccessful. Even the more reactive 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium complexes failed to promote the RCM reaction.[9] Gratifyingly, substrate **3** did undergo the RCM process by using the molybdenum complex **2** as the catalyst.[10] After careful optimization a near quantitative yield of **4** was obtained with 5 mol % of **2** in benzene at ambient temperature.

Scheme 1



Optimization of the Pd(0)-catalyzed coupling with siloxane **4** and 4-iodoacetophenone employed the conditions developed in our previous studies with alkenyl silanols[4e] (Table 1). Thus, siloxane **4** was combined with a 1.0 M THF solution of tetrabutylammonium fluoride (TBAF·3H_2O, Fluka) at room temperature, followed by the addition of 4-iodoacetophenone and 5 mol % of $Pd(dba)_2$ sequentially. The reaction proceeded cleanly to completion in only 10 min (Table 1, entry 1). Decreasing the loading of $Pd(dba)_2$ (3

Table 1. Optimization of the Cross-Coupling of **4** with 4-Iodoacetophenone[a]



entry	$Pd(dba)_2$, mol %	TBAF, equiv	time, min	yield,[b] %
1	5.0	2.0	10	89
2	3.0	2.0	30	86
3	1.0	2.0	180	80[c]
4	5.0	1.0	180	65[d]

[a] All reactions employed 1.1 equiv of **4** and 1.0 equiv of 4-iodoacetophenone at room temperature. [b] Yield of isolated **5a**. [c] 5% of 4-iodoacetophenone was recovered. [d] 19% of 4-iodoacetophenone was recovered.

(4) (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (b) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491. (c) Denmark, S. E.; Wang, Z. *Synthesis* **2000**, 999. (d) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495. (e) Denmark. S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (f) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221. (g) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61. (h) Denmark, S. E.; Wang, Z. *J. Organomet. Chem.* **2001**, *624*, 372. (h) Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073.

(5) To the best of our knowledge, the cross-coupling of cycloalkenylsiloxanes has not been reported.

(6) For recent reviews, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, 1998.

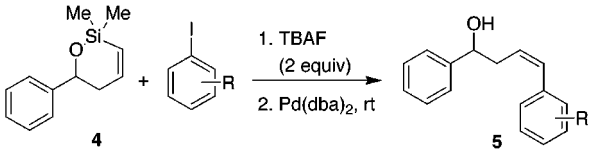
(7) (a) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257. (b) Taylor, R. E.; Schmitt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601. (c) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861. (d) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411. (e) Using $[RuCl_2(=C=C=CPh_2)(PCy_3)_2]$ or $[RuCl_4(=C=C=CPh_2)(PCy_3)(\eta^6\text{-}MeC_6H_4\text{-}4\text{-}i\text{-}Pr)]$ as the catalyst, see: Fürstner, A.; Hill, A. F.; Liebl, M.; Wilton-Ely, J. D. E. T. *Chem. Commun*. **1999**, 601. (f) For asymmetric studies using chiral Mo complex as the catalyst, see: Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251.

(8) (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (b) Ahmed, M.; Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A.; Salter, M. M. *Tetrahedron* **1999**, *55*, 3219. (c) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508. (d) The ruthenium carbene complex **1** is more sensitive to the substitution pattern of alkenes than molybdenum catalyst **2**, see: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

mol %, entry 2) only marginally affected the rate of the coupling process. However, with a lower catalyst loading (1.0 mol %, entry 3) or less TBAF (1.0 equiv, entry 4), the reaction did not go to completion and a significant amount of 4-iodoacetophenone was recovered.

With suitable conditions for both processes in hand, we turned our attention to expanding the scope of this process with various aryl iodides. Both the nature and position of substituents on the aromatic ring were studied. The results compiled in Table 2 reveal high compatibility with the common functional groups tested. For all aryl iodides examined, the reaction gave uniformly high yields. Noteworthy features of this process include the following: (1) electron-withdrawing or -donating groups exhibit similar reactivity (entries 1 and 2), (2) the steric effect of ortho substituents is minimal (entry 4) except in the cases where a possible chelation between the substituent and the palladium may slow the reductive elimination step (entries 5−7), (3) the reaction tolerates diverse functional groups such as ester, ether, nitro, and even free hydroxy group, and (4) the reactions of all iodides were stereospecific.[11]

Table 2. Palladium-Catalyzed Cross-Coupling of **4** with Aryl Iodides[a]

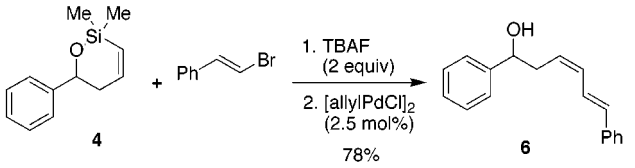


entry	R	$Pd(dba)_2$, mol %	time, min	product	yield,[b] %
1[c]	4-COMe	5.0	10	**5a**	90
2	4-OMe	3.0	30	**5b**	92
3	3-CO_2Et	3.0	30	**5c**	93
4	2-Me	3.0	30	**5d**	89
5	2-NO_2	3.0	90	**5e**	86
6	2-CH_2OH	5.0	180	**5f**	90
7	2-CO_2Me	5.0	360	**5g**	84

[a] All reactions employed **4** (1.1 equiv), TBAF (2.0 equiv), aryl iodide (1.0 equiv), and $Pd(dba)_2$ (3.0−5.0 mol %) in THF at room temperature. [b] Yields of analytically pure materials. [c] Yield of chromatographically homogeneous material.

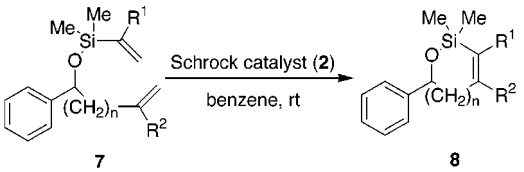
The cross-coupling of **4** was also successful with (*E*)-2-bromostyrene (Scheme 2). The reaction rate and yield were slightly lower than that obtained with aryl iodides. After 5 h, **6** could be isolated in 78% yield with 2.5 mol % of $[allylPdCl]_2$ as the catalyst.

Scheme 2



The next objective was to explore the influence of tether length (i.e., ring size) and substituents on the RCM/cross-coupling process. The allylic ether **7a** (a five-membered ring precursor) suffered RCM under the standard conditions (5 mol % of Mo complex in benzene, 1 h); however, only 75% conversion could be obtained in 1 h. This problem was solved by increasing the catalyst loading; using 7 mol % of catalyst, the complete consumption of **7a** was achieved within 3 h to afford the product **8a** in 89% yield (Table 3, entry 1). However, for the preparation of seven-membered siloxane **8d**, the reaction only went to 91% completion, giving an 81% yield under these conditions. With a monosubstituted alkene or monosubstituted vinylsilane (entries 2 and 3), the RCM process proceeded slowly compared to **4** albeit ultimately to completion. Unfortunately, substitution on both the alkene and vinylsilane (entry 4) did not lead to successful closure (even under harsher conditions), presumably as a result of the significant increase in steric demand.

Table 3. Molybdenum-Catalyzed Ring-Closing Metathesis of **7**[a]



entry	substrate, *n*	R^1	R^2	catalyst, mol %	time, h	product	yield,[b] %
1	**7a**, 0	H	H	7.0	3	**8a**	89
2	**7b**, 1	H	Me	8.0	15	**8b**	91
3	**7c**, 1	C_6H_{13}	H	7.0	12	**8c**	90
4	**7d**, 1	C_6H_{13}	Me				
5[c]	**7e**, 2	H	H	7.0	12	**8d**	81

[a] Reactions were performed at 0.1 M concentration. [b] Yields of analytically pure materials. [c] 91% conversion was observed by ^{1}H NMR analysis.

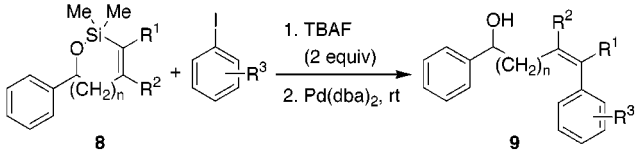
A variety of aryl iodides bearing various functional groups was selected to expand the utility of this transformation. The

(9) Recently, the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium complex exhibited high reactivity in RCM, especially for di-, tri-, or tetra-substituted cyclic alkenes; see: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(10) The molybdenum complex **2** is commercially available (Strem) and can be prepared according to the reported procedure with consistent purity and reactivity; see: (a) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287. (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (c) Oskam, J. H.; Fox, H. H.; Yap, K. B.; McConville, D. H.; O'Dell, R.; Lichtenstein, B. J.; Schrock, R. R. *J. Organomet. Chem.* **1993**, *459*, 185. (d) Fox, H. H.; Lee, J.-K.; Park, L. Y.; Schrock, R. R. *Organometallics* **1993**, *12*, 759.

(11) The coupling products showed slight decomposition under distillation; however, we were able to secure them in an analytically pure form after silica gel chromatography. Although the stereospecificity could not be determined by GC, no isomer was found by ^{1}H NMR analysis.

Table 4. Palladium-Catalyzed Cross-Coupling of **8** with Aryl Iodides[a]



8 **9**

entry	substrate, *n*	R^1	R^2	R^3	$Pd(dba)_2$, mol %	time, h	product	yield,[b] %
1	**8a**, 0	H	H	4-CO_2Et	3.0	0.5	**9a**	85
2	**8b**, 1	H	Me	2-Me	3.0	0.75	**9b**	83
3[c]	**8c**, 1	C_6H_{13}	H	3-CO_2Et	10.0	24	**9c**	81
4	**8d**, 2	H	H	4-OMe	3.0	0.5	**9d**	85[d]

[a] All reactions employed **8** (1.1 equiv), TBAF (2.0 equiv), aryl iodide (1.0 equiv), and $Pd(dba)_2$ (3.0 mol %) at room temperature unless otherwise specified. [b] Yields of analytically pure materials. [c] $Pd(dba)_2$ (2.5 mol %/3 h) and (0.25 mmol/3 h) were added portionwise. [d] Yield of chromatographically homogeneous material.

results collected in Table 4 reveal that (1) the different sizes of cyclic alkenyl silanes exhibit similar reactivity in the coupling reaction (entries 1 and 4) and (2) substitution on the *β-trans*-position of the silyl group did not affect the reactivity significantly (entry 2). The α-substituted alkenyl silane **8c** did undergo the coupling process; however, a significantly reduced reaction rate compared to the related silanes was observed. Moreover, the reaction mixture contained a substantial amount of self-coupling product of ethyl 3-iodobenzoate. The use of additives[4c] or slightly elevated temperatures did not improve the results. Fortunately, the addition of the iodide in portions satisfactorily suppressed the formation of the self-coupling product.[4g] Moreover, increasing the loading and portionwise addition of the Pd(0) complex also provided complete conversion and kept the palladium from precipitating in this slow coupling reaction.

A comparison between these results and those described previously reveals that monosubstitution of alkenyl silanes (silacyclobutanes[4a−d] and silanols[4e]) in either the α- or *β*-position does not effect the rate of the cross-coupling process significantly. The disubstituted alkenyl silanes including cyclic siloxanes[4g] and silyl hydrides[4f] are also very reactive in coupling process except in the case of the substitution on both of the α- and *β-cis*-positions, for example, **8c**. The steric influence may slow the coupling reaction and allow a competitive homocoupling of the aryl iodides to intervene.

In conclusion, we have successfully demonstrated sequential RCM/cross-coupling reactions with readily available silyl ethers. The cycloalkenylsiloxane serves as a competent donor undergoing rapid and high-yielding cross-coupling with various aryl and alkenyl halides. In addition, the ring size and substitution on the olefin have similar behavior in the coupling process as was seen in acyclic cases. Extension of this method to double intramolecular RCM/cross-coupling processes is in progress.

Acknowledgment. We are grateful to the National Science Foundation for generous financial support (NSF CHE 9803124). We thank Professor Amir Hoveyda (Boston College) for providing details for the preparation of catalyst **2**.

Supporting Information Available: Full characterization of all products and detailed procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015950J