

Intramolecular Silicon-Assisted Cross-Coupling Reactions: General Synthesis of Medium-Sized Rings Containing a 1,3-*cis-cis* Diene Unit

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The Pd-catalyzed cross-coupling reaction of organosilanes has recently emerged a viable alternative to the well-established Stille coupling of organostannanes¹ and Suzuki coupling of organoboranes.² Following the pioneering work of Hiyama,³ functionalized organosilanes have been successfully employed for expansion of this new method.⁴ Recent disclosures from these laboratories⁵ have demonstrated the synthetic potential of simple organosilanes as effective donors in Pd-catalyzed cross-coupling reactions.

Although significant progress has been recorded in the intermolecular process, the intramolecular cross-coupling reactions of organosilanes have yet to be investigated. In a recent report we described the combination of ring-closing metathesis (RCM) and cross-coupling reactions to construct allylic, homoallylic, and bishomoallylic alcohols in geometrically defined form.^{5c} If the siloxane product of RCM contained a suitably disposed electrophile, then the ensuing intramolecular cross-coupling would afford medium-sized rings with an internal, 1,3-*cis-cis* diene unit. The synthesis of medium-sized rings,⁶ particularly with a conjugated diene unit is well-known to be challenging because of unfavorable entropic and enthalpic factors.⁷ Herein we report the successful realization of this approach for the stereocontrolled construction of 9-, 10-, 11- and 12-membered rings.^{8,9}

The strategy involves the generation of cyclic silyl ethers by Mo-catalyzed ring-closing metathesis and their subsequent participation as the nucleophilic partners in Pd-catalyzed intramolecular cross-coupling with an alkenyl iodide appended at a remote position. In these siloxanes, variables, *m* and *n* combine to determine the size of the ring and the location of the hydroxyl group relative to the diene unit (Table 1).

To test the feasibility and generality of the overall transformation, the substrates, **3** were prepared from alcohols **1** by silylation with commercially available chlorodimethylvinylsilane (Table 1). From our earlier studies, we knew that RCM of vinylsilyl ethers required the use of Schrock's molybdenum complex **4**. Gratifyingly, substrate **2** also underwent the RCM process smoothly with **4** which tolerates the vinyl iodide functionality.¹⁰ Not surprisingly, the yields of these reactions are not influenced by chain length.

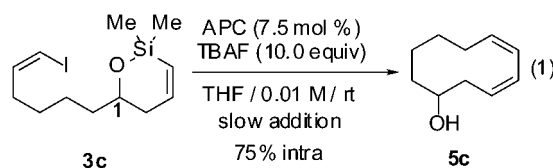
Optimization of the Pd-catalyzed intramolecular cross-coupling with **3c** employed allylpalladium chloride dimer (APC, 3 mol %) as catalyst and a 1.0 M THF solution of tetrabutylammonium fluoride (TBAF, 2.0 equiv) as activator. Typical conditions which would favor intra- versus intermolecular coupling (high dilution or slow addition of substrate) did not promote this intramolecular process well (14% conversion). Therefore, to maintain efficient fluoride activation, promote transmetalation and maintain a low concentration of **3c**, the amount of TBAF solution was increased (10.0 equiv). To our delight, the percentage of desired product, **5c**, increased to 45%. Whereas no improvement accrued from changing

Table 1. Preparation of Cross-Coupling Precursors^a

<i>m, n</i>	silyl ether	yield, % ^b	siloxane	yield, % ^b
1, 1	2a	86	3a	83
2, 1	2b	95	3b	81
3, 1	2c	94	3c	82
4, 1	2d	93	3d	81
5, 1	2e	93	3e	83
2, 2	2f	95	3f	80

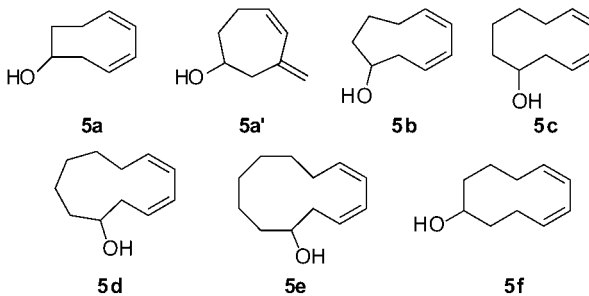
^a Conditions: (a) chlorodimethylvinylsilane (1.2 equiv), Et₃N (1.5 equiv), CH₂Cl₂, 0 °C to rt, 0.5–1.0 h. (b) **4** (8.0 mol %), benzene (0.1 M), rt, 24 h. ^b Yields of analytically pure materials.

the amount of TBAF solution, we did find that the catalyst loading did have a dramatic effect on the success of this intramolecular process. Thus, by employing 7.5 mol % of APC, the percentage of **5c** in the coupling products jumped to 75% (eq 1).



The scope of this silicon-assisted intramolecular cross-coupling process with regard to ring size was examined under the optimal conditions, 7.5–10.0 mol % of APC and 10.0 equiv of TBAF solution, at room temperature. The results reveal good generality for the construction of 9-, 10-, 11-, and 12-membered cycloalkadienes (Table 2). With the exception of **3a**, all of the substrates examined gave the corresponding medium-sized rings bearing the *cis,cis*-1,3-diene unit stereospecifically in respectable yield from highly flexible starting material without significant conformational constraint. Notably, site modulation of hydroxy group was successfully achieved by adjustment of chain length and ring size of silyl ether. Substrate **3a** afforded a mixture of desired product **5a** and cine rearrangement product **5a'** in a 1:1 ratio presumably due to the more difficult construction of a cyclooctadiene.

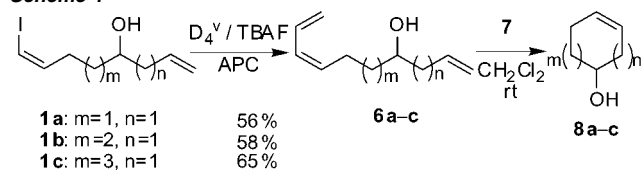
Obviously, the iodoalcohols **1** could also be converted to cycloalkadienes **5** by an inverted sequence of cross-coupling followed by RCM of the triene. To demonstrate the tactical advantage of intramolecular cross-coupling, we prepared the trienes **6** and assayed their potential for RCM to dienes (Scheme 1).^{11,12} Initial studies on the RCM of trienes, **6a** and **6b**, using Grubbs alkylidene

Table 2. Pd-Catalyzed Intramolecular Cross-Coupling Reactions of **3**^a


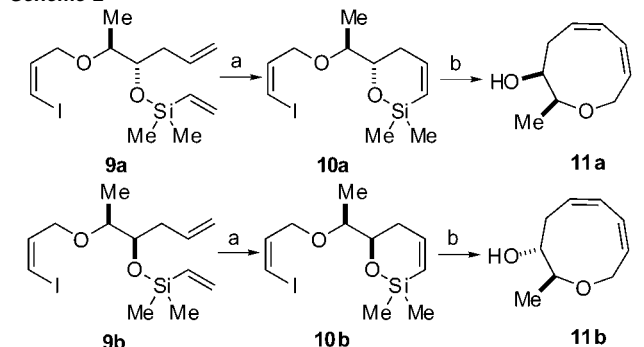
entry	3	APC, mol %	time, h ^b	product 5 , yield/% ^c
1	3a	7.5	60	5a+5a' (60%, 1:1) ^{d,e}
2	3b	7.5	45	5b (70%)
3	3c	7.5	45	5c (63%)
4	3d	10.0	75	5d (55%)
5	3e	10.0	75	5e (72%)
6	3f	10.0	60	5f (71%)

^a All reactions were performed on a 1.0 mmol scale (0.1 M in THF), with TBAF (10.0 equiv), at room temperature. ^b Addition time. ^c Yield of analytically pure materials. ^d Yield of chromatographically homogeneous material. ^e The ratio was determined by ¹H NMR analysis.

complex **7** produced only the 6- and 7-membered ring compounds **8a** and **8b** at room temperature. Furthermore, none of closure products of **6c** were observed under these conditions or in refluxing CH₂Cl₂. Clearly, closure on the internal double bond of the diene to afford smaller rings predominated.

Scheme 1

To demonstrate the versatility and effectiveness of this process, we next investigated extension to medium-sized heterocycles. Medium ring ethers have attracted a great deal of attention as synthesis targets in view of their occurrence in several classes of marine natural product structures.¹³ The diastereomeric silyl ethers **9a** and **9b**, (prepared in seven steps from propargyl alcohol) were selected to test this application by generation of the corresponding 9-membered oxacyclic dienes,¹⁴ **11a** and **11b** (Scheme 2). Ring-closing metatheses of both **9a** and **9b** proceed smoothly to afford cyclic silyl ethers, **10a** and **10b**. Interestingly, the two diastereomers reacted with equal facility and yield. More importantly, subsequent

Scheme 2^a

^a Reagents and conditions: (a) **4** (10.0 mol %), benzene (0.1 M), rt, 36 h, **10a** (81%); **10b** (80%). (b) APC (7.5 mol %), TBAF (10.0 equiv), rt, 45 h, **11a** (72%); **11b** (77%).

exposure of the siloxanes under the optimal conditions established above promoted the intramolecular cross-coupling effectively. Again, both diastereomers, **11a** and **11b**, were obtained in good yield with no difference in rate or efficiency.

In conclusion, we have demonstrated that Pd-catalyzed, silicon-assisted intramolecular cross-coupling provides an effective and potentially powerful method for construction of medium-sized rings with an internal 1,3-*cis-cis* diene unit. Noteworthy features of this process include: (1) a highly stereospecific intramolecular coupling process, (2) flexible positioning of the hydroxy group, and (3) potential extension to other medium-sized carbocycles and heterocycles. Further application of this strategy for the syntheses of natural products is currently in progress.

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Supporting Information Available: Full characterization of all starting materials and products along with representative procedures for the coupling reactions (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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