Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 345–350

The development and scope of a versatile tandem Stille-oxa-electrocyclization reaction

Uttam K. Tambar, Taichi Kano, John F. Zepernick and Brian M. Stoltz*

The Arnold and Mabel Beckman Laboratory for Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, United States

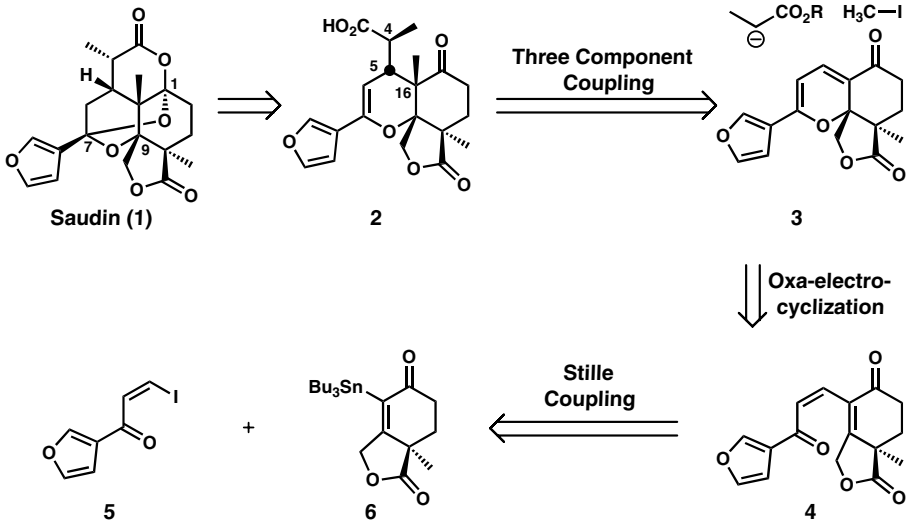
Received 8 October 2006; accepted 15 November 2006

Abstract—A palladium-catalyzed tandem Stille-oxa-electrocyclization reaction has been developed for the convergent preparation of highly substituted polycyclic pyran systems. The strategy presented in this letter is an alternative to the known methods for constructing similar pyran systems. The substrate scope of this diastereoselective transformation is explored.

Metal-mediated coupling reactions are essential tools for the synthetic chemist and are among the most important methods for forming carbon–carbon bonds. Tandem reactions are also useful since they can rapidly and efficiently build up complex molecular architectures. With these key features in mind, a palladium-catalyzed tandem Stille-oxa-electrocyclization has been developed in our group based upon work toward the total synthesis of saudin (**1**).[1]

The key disconnection in our synthetic strategy for saudin (**1**) is the opening of the 2*H*-pyran **3** via a retro-oxa-electrocyclization to reveal oxatriene **4**, followed by disconnection across the C(5)–C(16) bond via a Stille coupling (Scheme 1). This reveals the relatively simple coupling partners **5** and **6**.

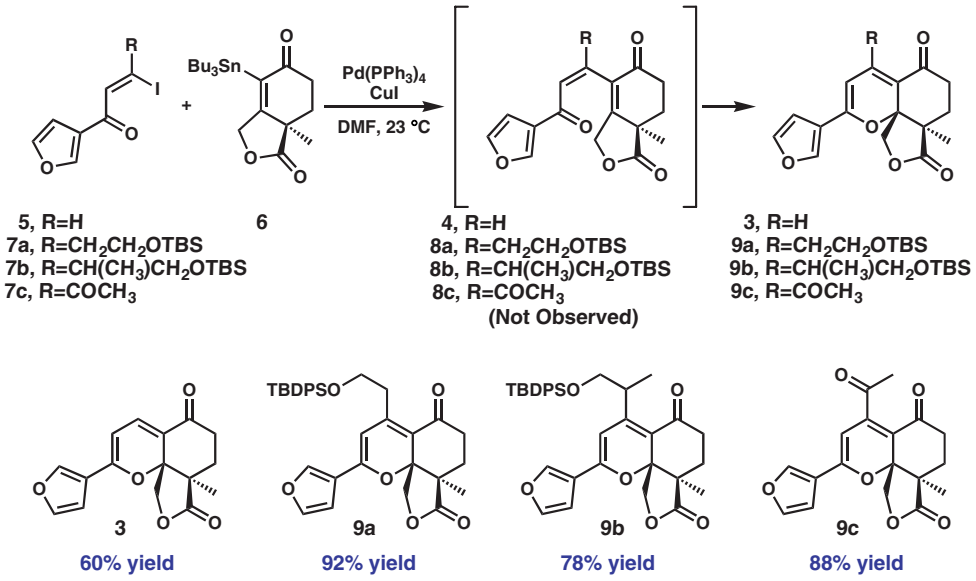
When iodoenones **5** and **7a**–**c** were treated with stannane **6** under Cu(I)-accelerated Stille conditions, the desired



Scheme 1.

* Corresponding author. Tel.: +1 626 395 6064; fax: +1 626 564 9297; e-mail: stoltz@caltech.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.097



Scheme 2.

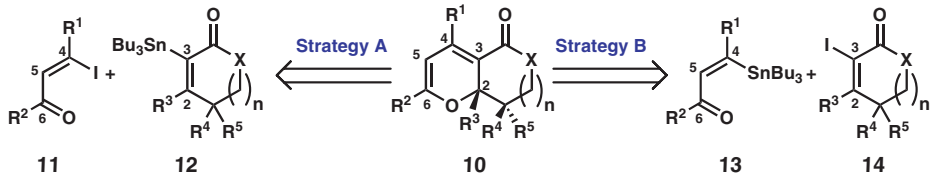
coupling reactions occurred (Scheme 2). However, products **4** and **8a–c** were not observed. Instead, the substrates reacted further, undergoing an oxa-electrocyclization to yield substituted pyrans **3** and **9a–c**. This tandem reaction, which rapidly builds up the core structure of saudin, was selected for further investigation to evaluate its utility as a more general synthetic methodology.

The tandem Stille-oxa-electrocyclization has several interesting features: it is highly diastereoselective, convergent, and requires mild reaction conditions with low catalyst loading. These mild conditions are particularly noteworthy given the sterically hindered nature of the coupling partners. The reaction is also of interest since oxa-electrocyclizations are relatively under-utilized in organic synthesis.[2] Recently there have been notable, though isolated, examples used in the syntheses of torreyanic acid by Porco and co-workers,[3] the epoxyquinols by Hayashi and co-workers,[4] the antimalarial naphthoquinones by Trauner,[5] EI-1941-2 by Porco and co-workers,[6] and Hsung's approach to a number of natural products including rhododaurichromanic acids A and B and arisugacin A.[7]

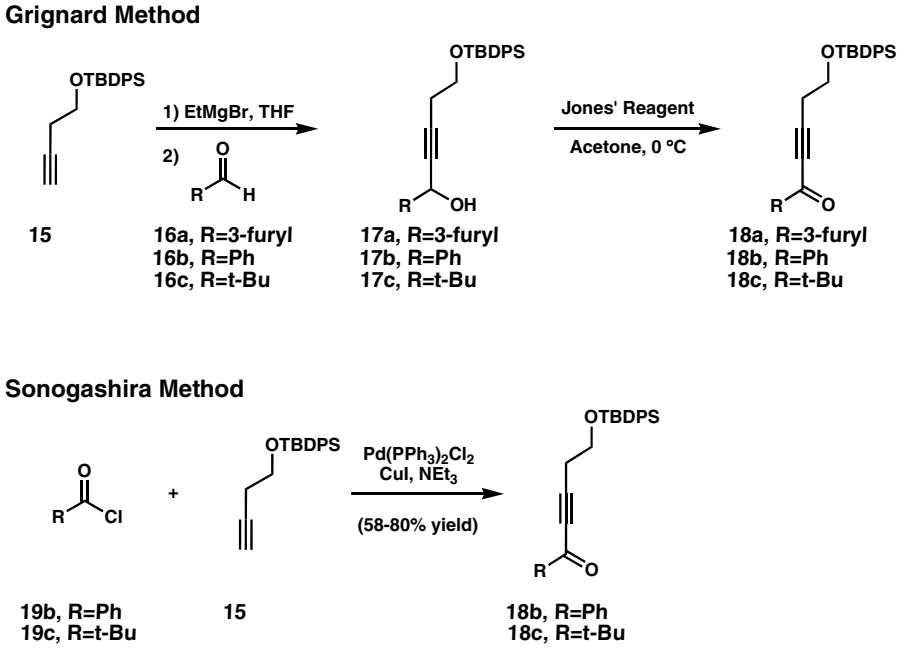
In pursuing this reaction as part of a general synthetic strategy for the formation of 2*H*-pyrans (**10**), we realized that there are two variants of this methodology: strategy A couples a 4-*cis*-iodoenone (**11**) with a 2-stannylenone (**12**), and strategy B couples a 4-*cis*-stannylenone (**13**) with a 2-iodoenone (**14**) (Scheme 3). Our earlier work had shown the viability of strategy A in the context of our synthetic efforts with saudin. Since different strategies may be better suited for different classes of pyrans, we were interested in expanding our tandem methodology by exploring the viability of strategy B. We were also interested in expanding the scope of this tandem reaction to include pyrans with varying substitution at positions 2, 3, and 6 of the ring system. We would like to now present our results on the development of a more general version of the tandem Stille-oxa-electrocyclization as a method for synthesizing highly substituted pyrans.

Two different routes were utilized to synthesize the 4-*cis*-stannylenone coupling partners for strategy B of our tandem methodology. The first route involved addition of a Grignard reagent into an aldehyde followed by a Jones' oxidation to form alkynones **18a–c** (Scheme 4). Alternatively, the same alkynones were made directly via a Sonogashira coupling between a terminal acetylene and an acid chloride (Scheme 4).[8]

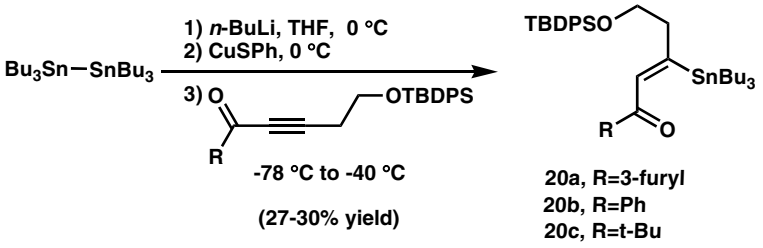
Alkynones **18a–c** were then converted to (*Z*)-vinyl stannanes (Scheme 5). Hexabutylditin was treated with *n*-butyl lithium, followed by the addition of copper thiophenol. This generated (Bu_3Sn)CuSPhLi in situ, which was then reacted with alkynones **18a–c** to give vinyl



Scheme 3.



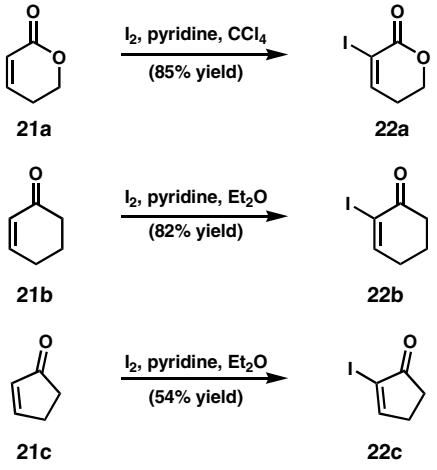
Scheme 4.



Scheme 5.

stannanes **20a–c** with exclusively the desired olefin geometry.[9]

In order to examine the scope of the reaction, vinyl iodides **22a–c** were synthesized from the readily available enones **21a–c** (Scheme 6). These iodoenones feature varying ring sizes and differing amounts of steric bulk around the ring. In addition, vinyl iodide **22a** contains a lactone.

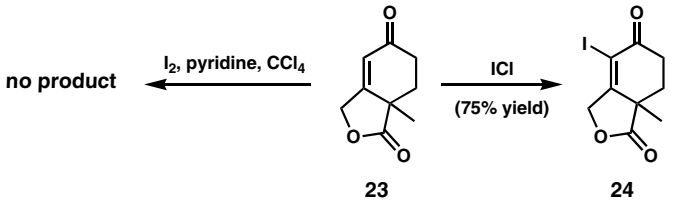


Scheme 6.

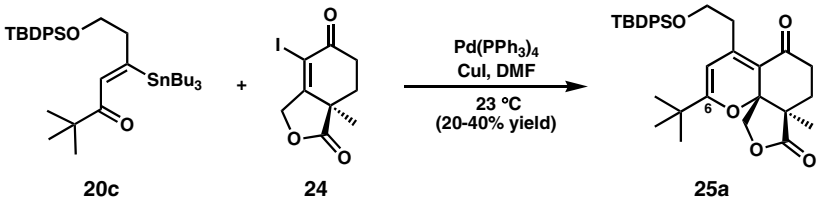
Subjection of enone **23** to the standard iodination conditions did not yield the desired product (Scheme 7). However, treatment with ICl provided iodoenone **24** in good yield.

With a variety of stannanes and iodoenones in hand, the efficiency of the reaction was investigated. Given our previous success with bicyclic stannane **6** (Scheme 2), the bicyclic iodoenone **24** served as a good test substrate to examine various substituents in the 6-position of the resulting 2*H*-pyran. Stannane **20c** successfully underwent both the Stille coupling and the oxa-electrocyclization in tandem when coupled to iodoenone **24**. However, the reaction conditions that worked so well for strategy A of our tandem reaction were less successful for strategy B (Scheme 8). Pyran **25a** was produced in low and variable yields, presumably because of decomposition of 4-stannyl enone **20c**.

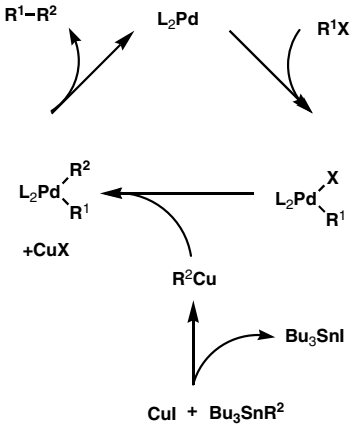
Previous studies in our group demonstrated that copper(I) iodide was necessary for this Stille coupling



Scheme 7.



Scheme 8.

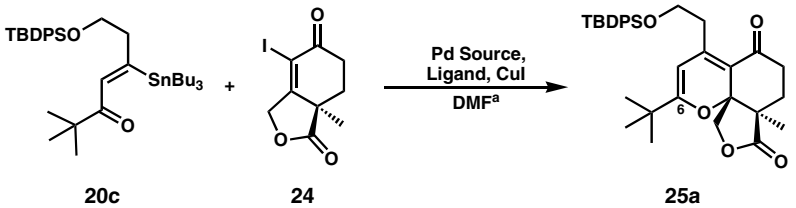


Scheme 9.

to proceed. The copper effect in Stille couplings has been well studied,[10,11] and different mechanisms have been proposed depending upon the reaction medium.[12,13] In the case of very polar solvents such as DMF or NMP, copper(I) salts are believed to undergo Cu/Sn transmetallation, resulting in the formation of an organocopper species (Scheme 9).

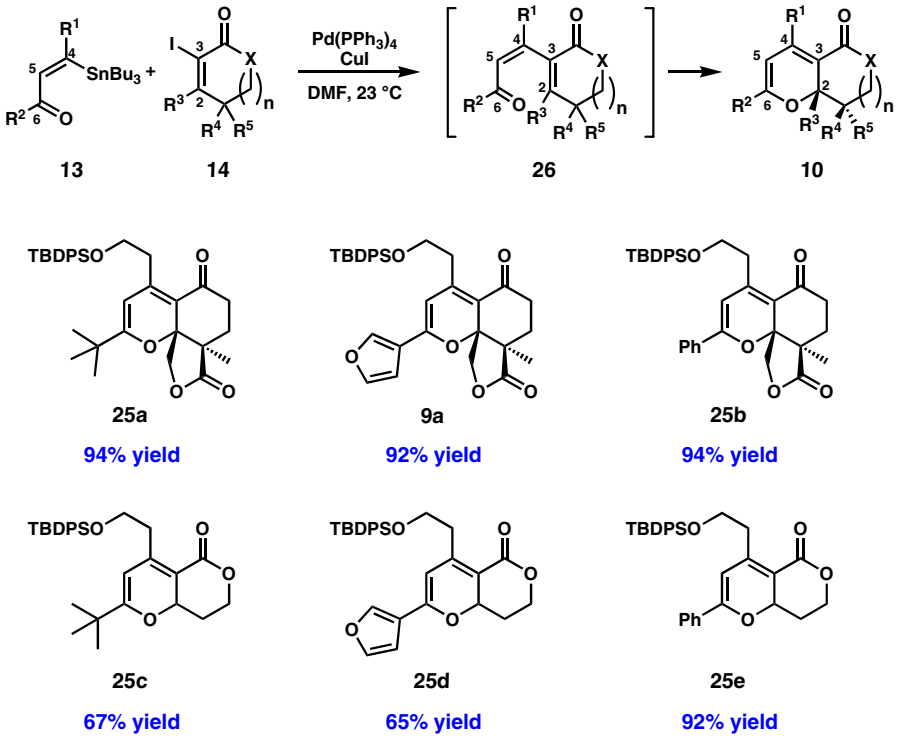
In an attempt to further optimize our reaction, the amount of copper(I) iodide was varied. When substoichiometric amounts of copper(I) iodide were used, the stannane was not consumed, which suggested that somehow the presence of stoichiometric copper was leading to an undesired side reaction of the vinyl stannane (Table 1, entries 2 and 3). In two control experiments, iodoenone **24** was excluded from the reaction (Table 1, entries 4 and 5). Decomposition of vinyl stannane **20c** was observed in the presence of copper(I) iodide (Table 1, entry 4), while no decomposition was seen in the absence of copper(I) iodide (Table 1, entry 5). From these results, it was hypothesized that copper(I) was undergoing oxidation to a copper(II) species, which is known to facilitate the homocoupling of vinyl stannanes.[14] In order to test this hypothesis, the reaction was run in

Table 1.



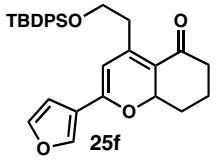
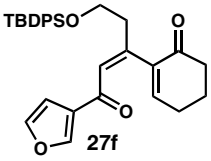
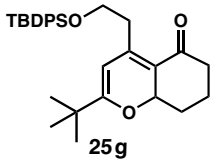
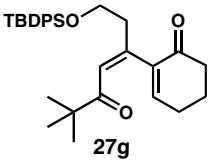
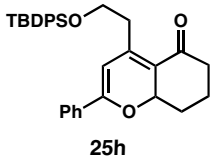
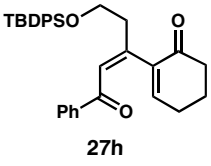
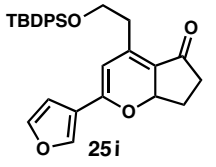
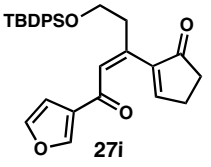
Entry	Pd source	Ligand	CuI (mol %)	Other	Stannane consumed?	Yield
1	$Pd_2(dba)_3$	PPh_3	100		Yes	45%[b]
2	$Pd_2(dba)_3$	PPh_3	5		No	Trace
3	$Pd(PPh_3)_4$		0		No	No reaction
4	$Pd(PPh_3)_4$		100	No iodoenone **24**	Yes	Decomposition
5	$Pd(PPh_3)_4$		0	No iodoenone **24**	No	No reaction
6	$Pd(PPh_3)_4$		100	In glovebox	No	94%[b]

[a] 5 mol % Pd, 20 mol % ligand, 0.1 M in **24**, 1 equiv **24**, 1.2 equiv **20c**.
[b] Isolated yield.



Scheme 10.

Table 2.

Cyclized product	Uncyclized product	Ratio (cyclized:uncyclized)[a]	Yield[b] (%)
 25f	 27f	7:1	90
 25g	 27g	10:1	66
 25h	 27h	10:1	73
 25i	 27i	1:3	62

[a] Ratio determined by ^{1}H NMR spectroscopy.
[b] Isolated yield.

an inert atmosphere glovebox, thus rigorously excluding oxygen. To our delight, the desired product was obtained in high yield (Table 1, entry 6).

Having found that rigorously anaerobic conditions were optimal for this reaction, we examined other substrates.[15] Vinyl stannanes **20a–c** (Scheme 5) were

successfully coupled with vinyl iodides **22a** (Scheme 6) and **24** (Scheme 7) to produce pyrans **25a–e** and **9a** in good to excellent yields (Scheme 10).

When we subjected vinyl iodides **22b** and **22c** (Scheme 6) to our tandem reaction conditions with various vinyl stannanes, the Stille couplings were successful, but the oxa-electrocyclizations yielded an equilibrium mixture of products (Table 2). These equilibrium mixtures were difficult to characterize because the species in solution were rapidly interconverting on the NMR timescale, causing the peaks in the NMR spectrum to be very broad. To alleviate this problem, the ^{1}H NMR spectra were taken at −30 °C. These coupled products were obtained in useful yields and often in a good ratio of cyclized to uncyclized products (Table 2).

In conclusion, the tandem Stille-oxa-electrocyclization reaction is a general method for the synthesis of highly substituted 2*H*-pyrans. Versatility in this methodology has been shown by developing both variants of this reaction (strategy A and strategy B). This work demonstrates the utility of tandem reactions for the construction of complex molecular architectures and also shows the potential of using oxa-electrocyclizations in synthesis.

Acknowledgments

The authors are grateful to the California Institute of Technology, NSF-PECASE, and NDSEG (Graduate Fellowship to UKT) for generous financial support.

Supplementary data

Experimental details and characterization data for all new compounds are available with the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.097.

References and notes

1. (a) Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2413–2416; (b) Tambar, U. K.; Kano, T.; Zepernick, J. Z.; Stoltz, B. M. *J. Org. Chem.* **2006**, *71*, 8357–8364.
2. For a recent example of a Stille-electrocyclization reaction, see: Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 4775–4778.
3. (a) Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484–10485; (b) Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095–5106.
4. Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192–3194.
5. (a) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554–9555; (b) Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276–6283; (c) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757–4778.
6. Kleinke, A. S.; Li, C.; Rabasso, N.; Porco, J. A. *Org. Lett.* **2006**, *8*, 2847–2850.
7. Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23–44.
8. Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777–778.
9. For similar reaction conditions, see: Nielsen, T. E.; Cubillo de Dios, M. A.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 7309–7313.
10. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359–5364.
11. Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
12. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.
13. Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305–1309.
14. Han, X.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1871–1872.
15. *General procedure for tandem Stille-oxa-electrocyclization reactions*. $Pd(PPh_3)_4$ (0.0033 mmol, 5 mol %), CuI (0.057 mmol, 1 equiv), and iodoenone (0.057 mmol, 1 equiv) were weighed into a oven-dried vial. The stannane (0.068 mmol, 1.2 equiv) was concentrated in vacuo from benzene in a separate flask. These materials were then taken into the glovebox. Next, the stannane was dissolved in DMF (0.7 mL) and the resulting solution was transferred into the vial containing the other reagents. The sealed vial was removed from the glove box, and the reaction was stirred for 24 h under the sealed inert atmosphere. Then, water was added and the reaction mixture extracted with ether. The organic layer was dried by passing it over a short silica plug. The material was concentrated in vacuo to yield the crude product, which could then be purified by flash column chromatography on silica gel. Residual tin contaminants were removed by dissolving the flashed material in acetonitrile and washing three times with hexane. Concentrating the acetonitrile layer in vacuo yielded the desired product in high purity.