Organic Syntheses

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Discussion Addendum for:
PALLADIUM CATALYZED CROSS-COUPLING OF (*Z*)-1-HEPTENYLDIMETHYLSILANOL WITH 4-IODOANISOLE: (*Z*)-(1-HEPTENYL)-4-METHOXYBENZENE
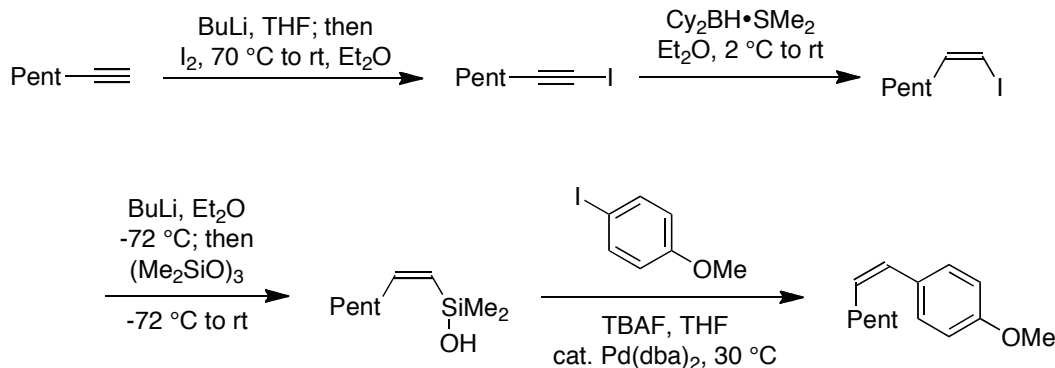
Prepared by Scott E. Denmark* and Jack Hung-Chang Liu.[1]
Original article: Denmark, S. E.; Wang, Z. *Org. Synth.* **2005**, *81*, 42.

The cross-coupling of organosilanols has emerged as a viable alternative to the classical methods of Suzuki (boronic acids), Stille (stannanes) and Negishi (organozincs).[2] The major developments over the past years have been the significant expansion of the scope of the organosilanol (or silanol precursor) and the introduction of non-fluoride activation of the silanols. Both advances will be summarized here.

Scope of Organosilanol Donor

Over the past ten years, a wide range of organosilanols have been prepared[3] and shown to be competent partners in the fluoride-activated cross coupling with aromatic and olefinic halides (including bromides[4]) and triflates.[5] Most notable has been the extension to pyranylsilanols,[6] cyclic siloxanes generated by intramolecular hydrosilylation,[7] intramolecular silylformylation,[8] and ring-closing metathesis[9] (Figure 1). The latter tandem process (RCM-cross-coupling) was featured in a total synthesis of (+)-brasilenyne (Figure 2).[10] In addition, silylcarbocyclization-formylation[11] allowed for the construction of the pyrrolidine core of isodomoic acids G and H (Figure 3).[12] The final cross-coupling step involved a fluoride mediated process that employed a buffered form of TBAF (octahydrate).
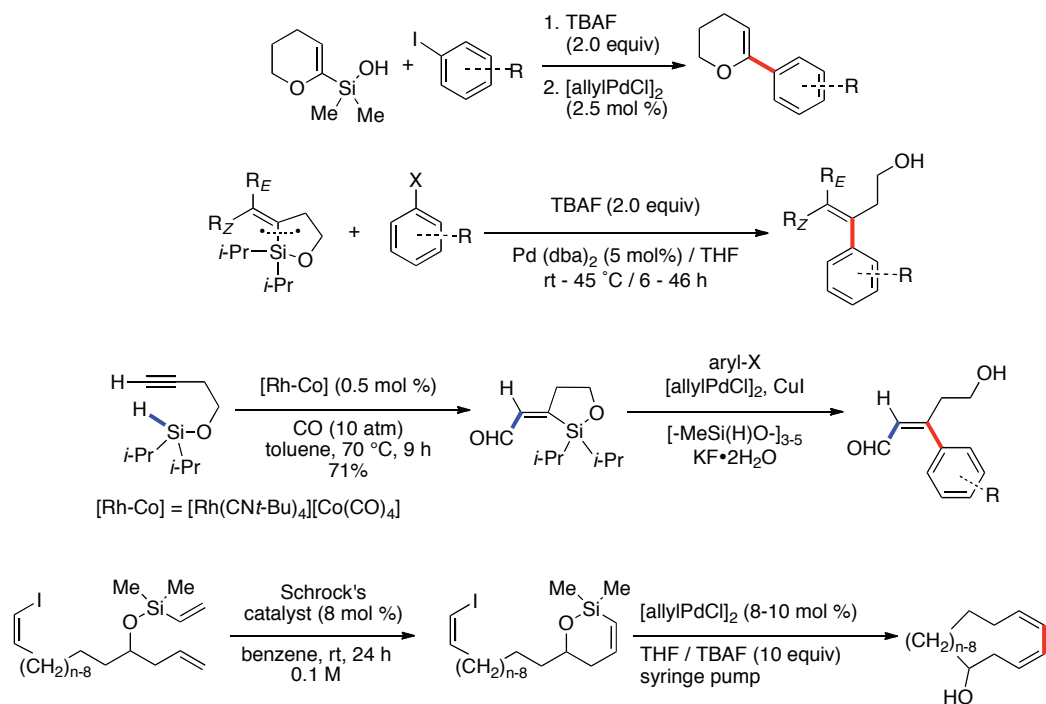
Figure 1. Newer variations of fluoride-promoted, silicon-based-cross coupling reactions.
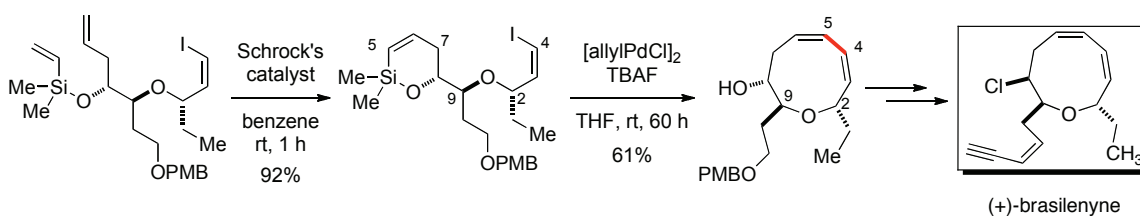

Figure 2. Fluoride-promoted intramolecular alkenyl-alkenyl cross-coupling for the syntheses of brasilenyne.
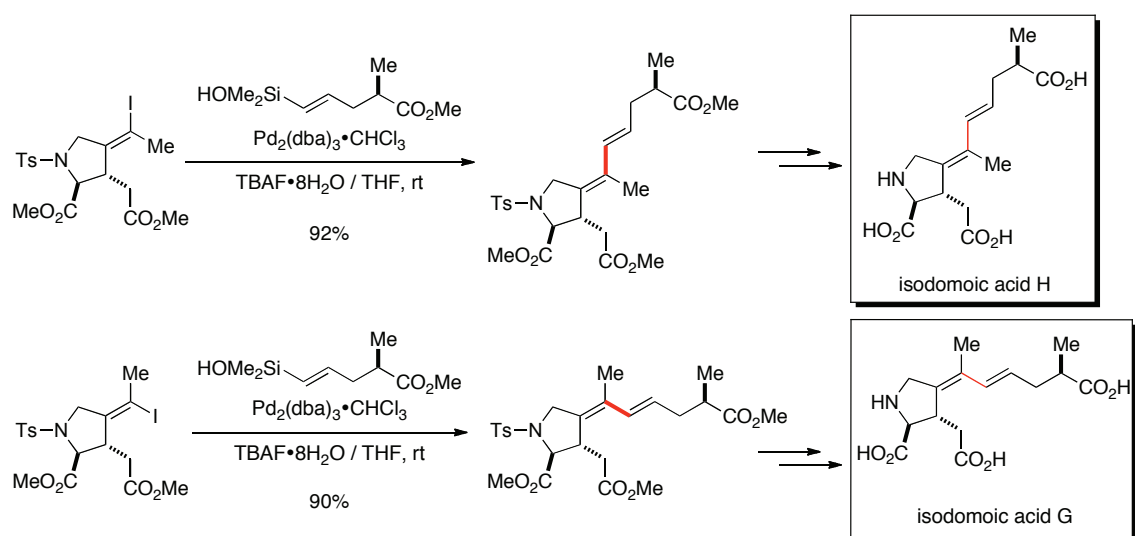

Figure 3. Fluoride-promoted intermolecular alkenyl-alkenyl cross-coupling for the syntheses of isodomoic acids G and H.

Fluoride-Free Cross-Coupling Reactions

By far the most important advance in the past five years has been the discovery of a preparatively useful and mechanistically distinct[13] pathway for cross-coupling of organosilanols that employs various Brønsted bases as activators.[2d] This discovery has allowed for a wider range of coupling partners to be incorporated and also for milder reaction conditions to be employed. For example is it now possible to effect the cross-coupling of simple alkenylsilanols and alkynylsilanols (with KOTMS),[14] arylsilanols (with Cs_2CO_3),[15] and 2-indolylsilanols (with KOt-Bu),[16] and isoxazolinylsilanols (with KOt-Bu)[17] (Figure 4).
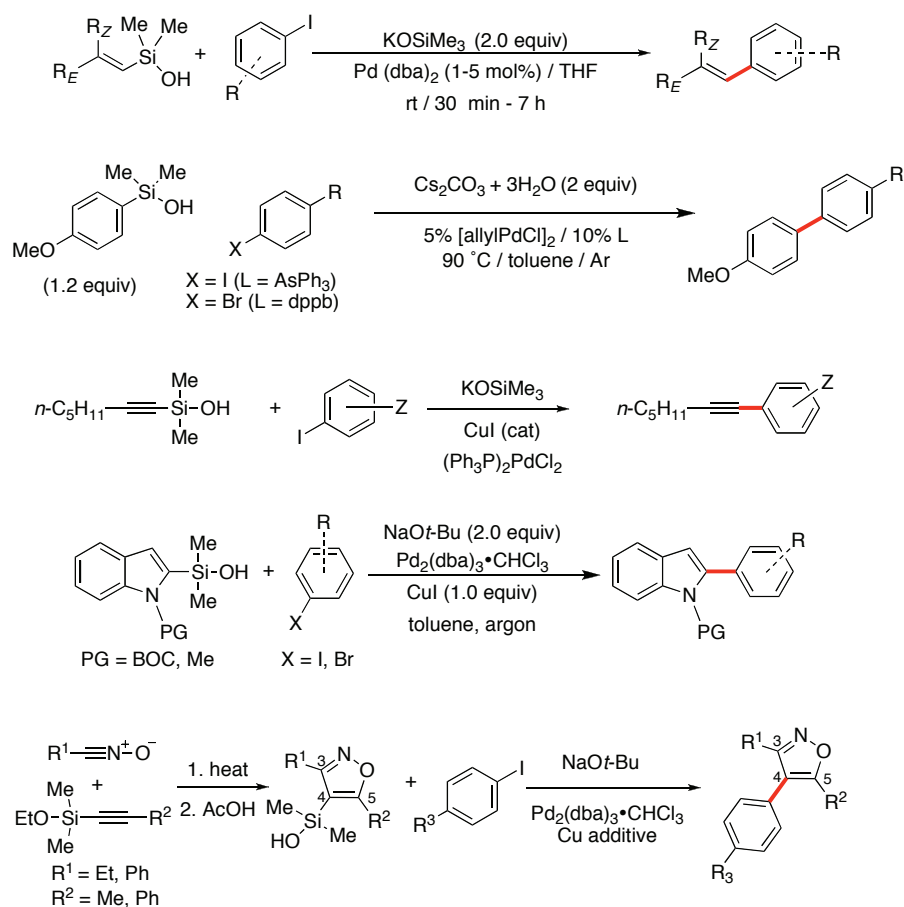

Figure 4. Variations of fluoride-free, cross-coupling reactions.

The ability to couple silanols under fluoride-free conditions has allowed the introduction of the preformed silanolate salts as viable coupling partners. The salts can be easily prepared by deprotonation with NaH or KH and are, in general, stable, free flowing powders. The silanolates couple directly without the need for added bases or activators. Accordingly, heterarylsilanolates derived from indoles, thiophenes, furans[18] as well as a

wide range of aromatic silanolates[19] have been successfully employed. Finally, alkenylsilanolates also undergo high yielding and highly stereospecific cross-coupling with aryl chlorides[20] (Figure 5).

Figure 5. Cross-coupling reactions of preformed silanolate salts.

The demonstration of both fluoride and non-fluoride activation for silicon-based cross-coupling has led to the development of a conjunctive reagent that allows for sequential coupling at separate ends of a 1,4-butadiene unit.[21] This application was featured in the total synthesis of RK-397 (Figure 6).[22]

Figure 6. Sequential cross-coupling of a 1,4-bissilyl-1,3-butadiene.

The construction of the key aryl glycosidic bond en route to papulacandin D highlights the synthetic utility of the Brønsted base activation method (Figure 7).[23] The glycal silanol would not withstand activation by fluoride and the resorcinol coupling partner is highly deactivated. Nevertheless, the desired coupling could be achieved by the action of sodium *tert*-butoxide at 50 °C in the presence of Pd$_2$(dba)$_3$•CHCl$_3$. The coupled product contains the entire carbon framework of the sugar fragment of papulacandin D.
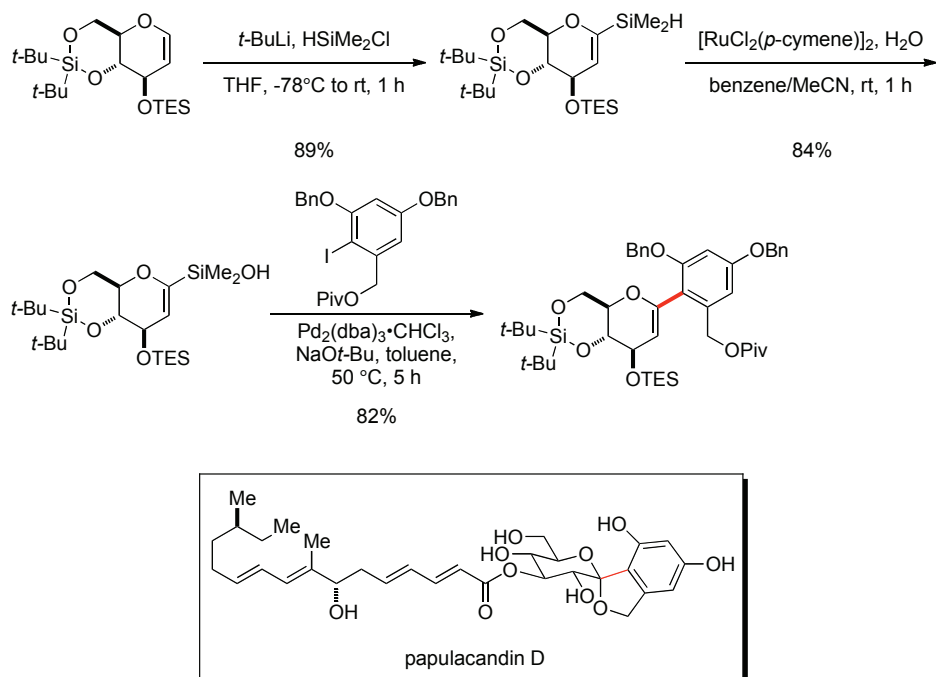

Figure 7. Fluoride-free alkenyl-aryl cross-coupling for the total synthesis of papulacandin D.

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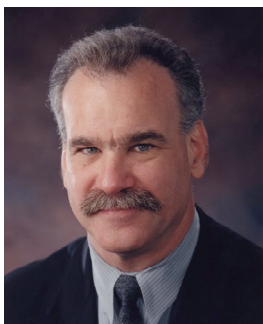
Scott E. Denmark was born in Lynbrook, New York on 17 June 1953. He obtained an S.B. degree from MIT in 1975 and his D.Sc.Tech. (with Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois. He was promoted to associate professor in 1986, to full professor in 1987 and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry and the origin of stereocontrol in fundamental carbon-carbon bond forming processes.

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