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MIDA−Vinylsilanes: Selective Cross-Couplings and Applications to the Synthesis of Functionalized Stilbenes

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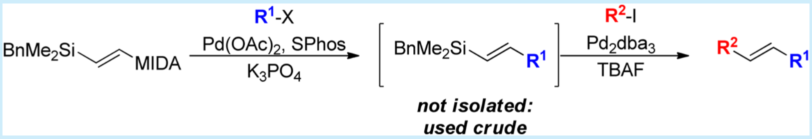
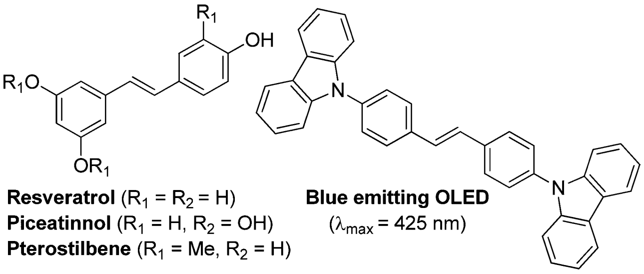
S Supporting Information



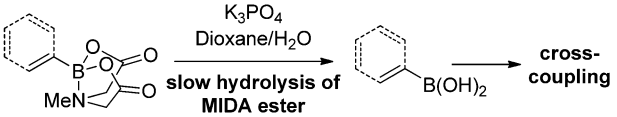
ABSTRACT: A rapid and stereodefined synthesis of MIDA−boryl vinylsilanes has been achieved through the hydrosilylation of an alkynylboronic ester. The *E* products which contain a silyl and boryl group can be selectively cross-coupled in a two-step bidirectional sequence to provide a rapid and high-yielding synthesis of complex styrenes.

Stilbenes and their derivatives have been known to have numerous applications in both medicinal and material chemistry.[1] Stilbenoids such as resveratrol, piceatinnol, and pterostilbene show a broad range of therapeutic activity against cancer, hepatitis C, and diabetes alongside exhibiting anti-inflammatory and cardioprotective properties.[2] Additionally, the photophysical properties of stilbenes have been extensively studied,[3] finding use in organic light emitting diodes (OLED's),[4] optical brighteners, and photoresistors.[5]



The synthesis of stilbenes has traditionally been dominated by the Wittig reaction and its derivatives;[6,7] however, these rely on easy access to the corresponding phosphonium salts and aldehydes alongside compatibility with the basic conditions. One solution is the use of palladium catalyzed cross-coupling reactions such as the Heck,[8] Suzuki−Miyaura,[9] Stille,[10] and Hiyama couplings.[11] Although more functional group tolerant than the Wittig-type reactions, these can lose modularity due to the intermediacy of styryl organometallic or halide species. Even though there are numerous methods in use to prepare stilbenes, the establishment of new routes to their synthesis in a robust and selective manner remains highly desirable.

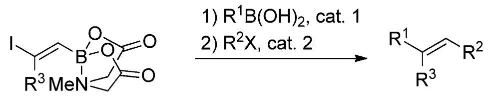
MIDA boronates, pioneered by Burke and co-workers, offer synthetic chemists a reliable, bench-stable, functional handle which can be used as in Suzuki cross-couplings.[12] These act as protected boronic acids which can be readily synthesized and purified through column chromatography. They are tolerant of many standard Suzuki−Miyaura coupling conditions and can be can be unmasked through the use of aqueous K_3PO_4 slowly releasing the corresponding boronic acid which then performs the cross-coupling reaction (eq 1). This strategy has been used to form polyenes, biaryl (and heterobiaryl) compounds, *Z*-stilbenes, and 1,1-disubstituted alkenes.[12]



(1)

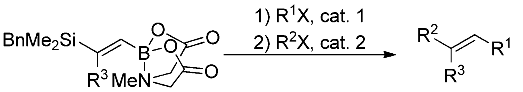
Because of the very specific and controlled hydrolysis conditions required to unmask the active boronic acid, other palladium-catalyzed reactions can be performed in the presence of MIDA boronates. Indeed, Suzuki−Miyaura coupling reactions using an exogenous boronic acid can be carried out on vinyl and aryl halides containing an MIDA boronate.[12] Following this initial Suzuki coupling, a second coupling reaction can be performed using very specific hydrolysis conditions (eq 2). This has been used for the synthesis of polyenes natural products such as amphotericin B[12a] and synechoxanthin.[12j] We envisaged that this approach could be further augmented by the formation and use of vinyl groups that contain both an MIDA boronate and a silane whereby

Burke (ref 12): selective sequential Suzuki coupling



(2)

This work: selective sequential Suzuki & Hiyama coupling



(3)

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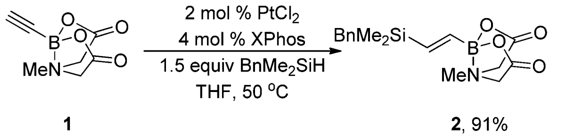
sequential Suzuki and Hiyama couplings could be performed to form complex styrenes in a rapid and modular fashion (eq 3). Boryl vinylsilanes have been previously reported and can be synthesized through the hydroboration of a silylacetylene[13] via a lithium−tin exchange reaction of the corresponding silyl vinylstannane, followed by trapping with a borate[14] or by a silylboration of an alkyne.[15] Although effective, many of these approaches rely on the use of highly air and moisture sensitive boranes such as 9-BBN or Cy_2B groups which cannot be purified or stored and there are no reports of Hiyama couplings with these moieties.[16] Herein we report the development of bidirectional strategy based on the hydrosilylation of alkynyl MIDA boronic esters and subsequent selective cross-coupling reactions.

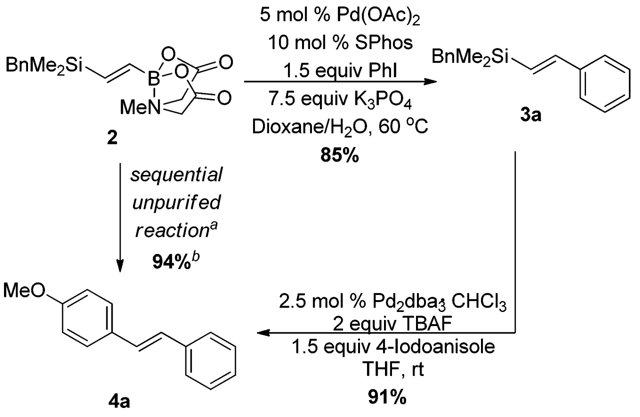
We needed to develop a rapid and reliable method for the formation of the requisite vinyl groups and we examined the use of platinum catalyzed hydrosilylations. We have previously reported the hydrosilylation of propargylic and allylic alcohols using a $PtCl_2$/XPhos system which provides the corresponding silanes in excellent yields and selectivity.[17] These conditions were excellent for the hydrosilylation of readily available ethynyl MIDA boronate ester **1**,[18] providing the desired vinyl silane **2** in excellent yield. We chose to utilize the benzyldimethylsilane as this would be optimal for the Hiyama coupling using Trost-type conditions.[19]



(4)

With the MIDA−vinylsilane in hand, we turned our attention to the sequential cross-coupling reaction sequence (Scheme 1).

Scheme 1. Sequential Suzuki−Hiyama Cross-Couplings

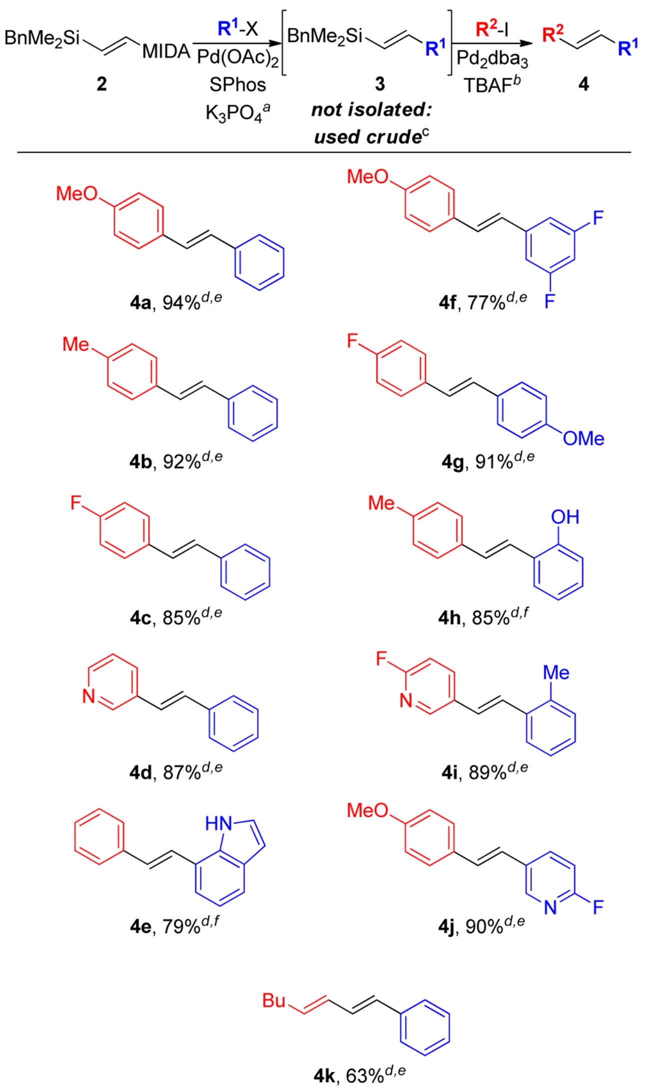


[a] Filtered through pad of Celite, concentrated, and used directly for the second coupling reaction. [b] Isolated yield over two steps.

The challenge was in identifying conditions that would allow for the facile hydrolysis of the MIDA boronate ensuring the silane remained intact. We subjected **2** to conditions previously reported by Burke and co-workers and were delighted to observe that the Suzuki product was produced in 85% yield.[12] The vinylsilane **3** was then subjected to Hiyama coupling conditions[11] resulting stilbene product **4a** in 91% yield. As both reactions were very efficient and high yielding, we performed a "telescoped" version whereby the reaction mixture from the first coupling was filtered through Celite and subjected to the next set of coupling conditions, following a solvent swap. Gratifyingly we found that this approach led to higher yields of **4a** with a 94% overall yield being obtained from **2**.[20] Employing either route, the product was formed as a single regioisomer with complete transfer of alkene geometry from the hydrosilylation step.

With these conditions in hand, we began examining the scope of the reaction and found that this protocol was very robust (Scheme 2). Both electron-rich and electron-deficient substrates performed well in both the Suzuki and Hiyama couplings, and heterocycles could be incorporated. Ortho substituents were also tolerated alongside free phenols, indoles, and electrophilic pyridines. In all cases, excellent yields were obtained over the two steps to provide highly substituted styrenes. Complete selectivity was obtained with no sym-

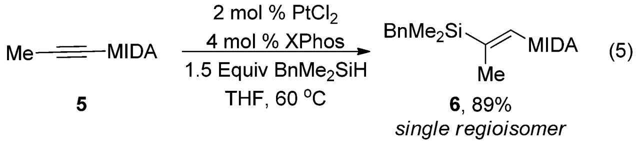
Scheme 2. Substrate Scope



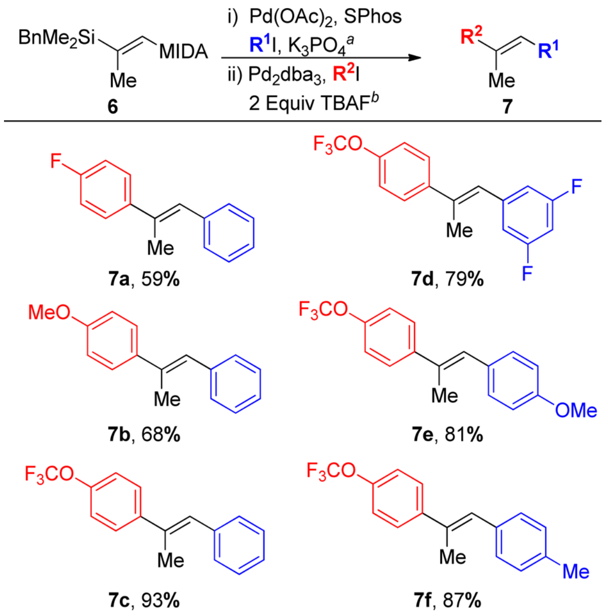
[a] 5 mol % $Pd(OAc)_2$, 10 mol % SPhos, 1.2 equiv of R^1X (X = I, Br), 7.5 equiv of K_3PO_4; 1,4-dioxane/H_2O, 60 °C, 12 h. [b] 2.5 mol % Pd_2dba_3, 1.2 equiv of R^2I, 2 equiv of TBAF, THF, 25 °C, 12 h. [c] Filtered through pad of Celite, concentrated, and used directly for the second coupling reaction. [d] Isolated yields over entire coupling sequence. [e] Suzuki coupling performed using aryl iodide. [f] Suzuki coupling performed using aryl bromide.

metrical products being observed and the geometric integrity of the *E* alkene was maintained. We also examined the vinyl−vinyl coupling variant as this can lead to erosion of alkene geometry. Gratifyingly, we found that 1-iodohex-1-ene could be coupled in the Hiyama step to provide a single geometric isomer of diene **4k**.

We also investigated the selective formation of unsymmetrical trisubstituted stilbenes. First, we performed the hydrosilylation of propynyl MIDA ester **5** which proceeded in excellent yield and produced a single regio- and geometric isomer of the methyl-substituted silane **6** (eq 5). The addition appears to be directed by sterics with the large size of the MIDA boronic ester dictating the formation of **6** as a single isomer.[21] With **6** in hand, we then performed the same Suzuki−Hiyama protocol which was utilized in the unsymmetrical case (Scheme 3). Once again, the reaction proceeded well and provided a range of products **7** with both electron-rich and -deficient groups participating well, providing high overall yields as a single regioisomer. The geometric integrity from the hydrosilylation reaction was maintained in all cases with a >98:2 *E*:*Z* ratio observed. This protocol has provided ready access to novel trisubstituted styrenes which could have applications in medicinal chemistry and organic electronics.



Scheme 3. Synthesis of Trisubstituted Olefins



[a] 5 mol % $Pd(OAc)_2$, 10 mol % SPhos, 1.2 equiv of R^1I, 7.5 equiv of K_3PO_4; 1,4-dioxane, 60 °C, 12 h; filtered through pad of Celite, concentrated, and used directly for the second coupling reaction. [b] 2.5 mol % Pd_2dba_3, 1.2 equiv of R^2I, 2 equiv TBAF, THF, 25 °C, 12 h. [c] Isolated yields over both coupling steps.

In conclusion, we have developed a rapid and robust coupling sequence for the synthesis of stilbenes taking advantage of the differential reactivity of vinyl silanes and MIDA boronic esters. The reaction is very tolerant of functionality and provides products as a single regio and geometric isomer. This is the first report of a bench stable silyl vinylbornic ester which can be used in a bidirectional coupling strategy. The applications of this method are currently being explored in total synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, full characterization of all compounds reported, and copies of NMR spectra (^1H and ^{13}C). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) Vinylpinacol boronic esters can be reacted selectively in the presence of MIDA boronic esters. See ref 12j.

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(18) Compound **1** is commercially available from Sigma-Aldrich (catalog no. 700231) or can be readily synthesized on gram scale (ref 12i).

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