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Regio- and Stereoselective Synthesis of Tri- and Tetrasubstituted Enamides *via* Palladium-Catalyzed Silaboration of Ynamides

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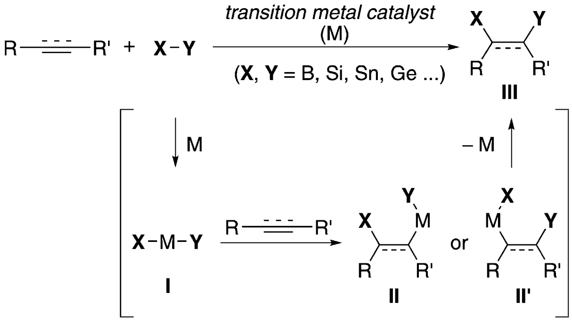
Abstract: The palladium-catalyzed silaboration of ynamides is demonstrated. The silaboration proceeds in a highly regioselective manner to give the corresponding tri- and tetrasubstituted enamide derivatives having both a silyl group and a boryl group on the alkene. Furthermore, the silaborated enamide could be utilized as a coupling partner in Suzuki–Miyaura coupling with aryl iodides to give the corresponding cross-coupling product in good yield.

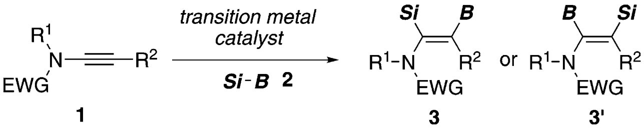
Keywords: boron; metallation; palladium; silicon; ynamides

The transition metal-catalyzed addition of an element-element σ-bond of a bimetallic reagent (**X**–**Y**) to carbon-carbon unsaturated compounds (i.e., bismetallation) is one of the most important methods for the synthesis of 1,*n*-dimetallo compounds, which are expected to be useful building blocks for further organic transformations. Group 10 metals are widely employed for bismetallation reactions.[1] The generally accepted mechanism of bismetallation is shown in Scheme 1. First, oxidative addition of a bimetallic reagent to a low-valent transition metal (M) proceeds to give the the **X**–M–**Y** complex **I**. Insertion of a multiple bond in the substrate into either the M–X or the M–Y σ-bond in **I** occurs to produce intermediate **II** or **II′**, from which reductive elimination affords bismetallated product **III**.

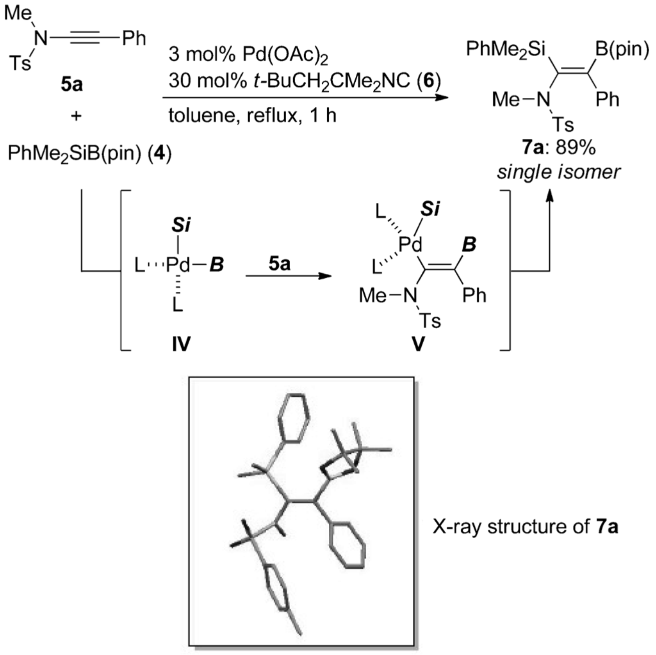


Scheme 1. Transition metal-catalyzed bismetallation of carbon-carbon unsaturated bonds.

The *N*-alkynylamide (ynamide) moiety has been recognized as a versatile building block in recent synthetic organic chemistry,[2–4] and we have already reported a new transformation of ynamides by virtue of the use of transition metal catalysis.[5] The aforementioned bismetallation of ynamides is expected to be an attractive strategy for the synthesis of multi-substituted enamides having two metal components, and palladium-catalyzed silastannylation and bisstannylation of ynamides have been reported to date.[6,7] However, only a terminal alkyne has been employed in those studies, and no examples of the bismetallation of an ynamide having an internal alkyne structure have been reported so far. In this context, we planned the silaboration[8–11] of an ynamide as shown in Scheme 2. Thus, if silaboration of ynamide **1** with silylborane (***Si-B***, **2**) proceeds in the presence of a transition metal catalyst, the silaborated enamide **3** and/or **3′** would be formed. Here, we report the palladium-catalyzed regioselective silaboration of ynamides using commercially available (dimethylphenylsilyl)pinacolatoboron [$PhMe_2SiB(pin)$, **4**][12,13] that led to the formation of a multi-substituted enamide derivative bearing vinyl silicon and vinyl boron moieties.

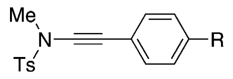
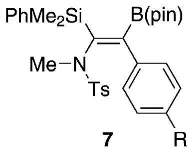
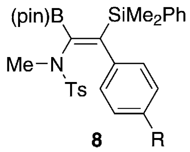
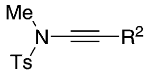
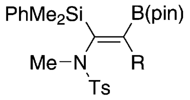
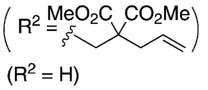


Scheme 2. Bismetallation of ynamide leading to multi-substituted enamides.



Scheme 3. Pd-catalyzed silaboration of ynamide **5a**.

Table 1. Silaboration of tosylamide-derived ynamides.[a]

Run	Ynamide	Yield (Time)
		 **7**  **8**
1	**5b** (R = OMe)	**7b** + **8b**: 83% (5.9:1, 2 h)
2	**5c** (R = CO_2Me)	**7c** + **8c**: 63% (2:1, 21 h)[b]
		
3	**5d** (R^2 = ^{n}Bu)	**7d**: 93% (1 h)
4	**5e** (R^2 = CH_2CH_2OTBS)	**7e**: 80% (1 h)
5	**5f** (R^2 = CH_2OAc)	**7f**: 75% (2 h)
6	**5g** ()	**7g**: 71% (2 h)
7	**5h** (R^2 = H)	**7h**: 81% (1 h)

[a] *Reaction conditions:* $PhMe_2SiB(pin)$ (**4**, 1 equiv.), $Pd(OAc)_2$ (3 mol%), t-$BuCH_2CMe_2NC$ (**6**, 30 mol%), toluene, reflux.

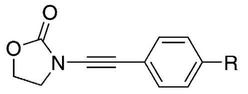
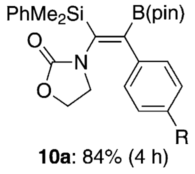
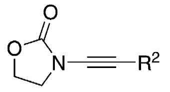
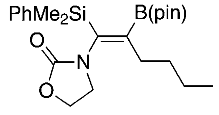
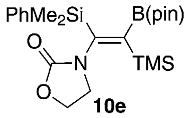
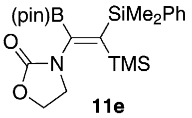
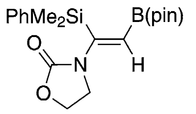
[b] The ratio was determined by ^1H NMR analysis (400 MHz) of the mixture of **7c** and **8c**.

Referring to the previously reported procedure,[8a] ynamide **5a** was reacted with $PhMe_2SiBi(pin)$ (**4**) in the presence of $Pd(OAc)_2$ and isonitrile ligand **6** in toluene under reflux conditions. As a result, silaborated enamide **7a** was obtained as a single regio- and stereoisomer in 89% yield (Scheme 3). The structure of **7a** was unambiguously determined by X-ray crystallographic analysis.[14] It is known that Pd(0)-catalyzed silaboration of alkyne proceeds through insertion of a triple bond into the Pd–B σ-bond of **IV** formed by oxidative addition of **4** to Pd(0).[1h,15] Therefore, this result indicates that regioselective insertion of ynamide **5a** into the Pd–B bond of **IV** occurred to produce intermediate **V**, from which reductive elimination took place stereoselectively to afford the enamide derivative **7a**.

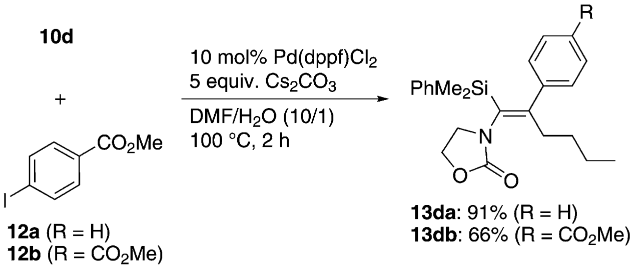
Encouraged by this result, we studied the scope and limitations of silaboration of ynamides (Table 1). When ynamide having a 4-methoxyphenyl group on the alkyne part **5b** was reacted with silylborane **4**, the expected silaborated enamide **7b** and its regioisomer **8b** were produced in 71% yield and 12% yield, respectively (run 1). On the other hand, silaboration of ynamide **5c** bearing an ester group on the aromatic ring afforded **7c** and **8c** in totally 63% yield (ratio of 2 to 1). Alkyl-substituted ynamide **5d** is also applicable to the silaboration, and the corresponding enamide **7d** was obtained in high yield as a single isomer (run 3). Siloxy, acetoxy and alkenyl groups in substituents on the alkyne part (**5e**–**g**) were tolerated under the reaction conditions, giving enamide derivatives **7e**–**g** in good yields in a highly regio- and stereoselective manner (runs 4–6). Furthermore, the reaction of terminal alkyne **5h** with **4** also proceeded smoothly to give tri-substituted enamide **7h** in 81% yield as a sole product (run 7).

Next, silaboration of oxazolidinone-derived ynamides **9** was investigated (Table 2). Ynamides **9a**–

Table 2. Silaboration of oxazolidinone-derived ynamides.[a]

Run	Ynamide	Yield (Time)
		
1	**9a** (R = H)	**10a**: 84% (4 h)
2	**9b** (R = OMe)	**10b**: 82% (2 h)
3	**9c** (R = CO_2Me)	**10c**: 74% (2 h)
		
4	**9d** (R^2 = ^{n}Bu)	**10d**: 89% (4 h)
5	**9e** (R^2 = TMS)	 **10e**  **11e** **10e** + **11e**: 81% (2.1:1, 2 h)
6	**9f** (R^2 = H)	 **10f**: 74% (1 h)

[a] *Reaction conditions:* $PhMe_2SiB(pin)$ (**4**, 1 equiv.), $Pd(OAc)_2$ (3 mol%), t-$BuCH_2CMe_2NC$ (**6**, 30 mol%), toluene, reflux



Scheme 4. Suzuki–Miyaura coupling of enamide **9d** with aryl iodides

c having an aryl group on the alkyne part were subjected to the optimal conditions, giving the corresponding silaborated enamides **10a–c** in high yields (runs 1–3). The silaboration of ynamide **9d** bearing an alkyl group on the alkyne part gave the desired enamide **10d** in 89% yield (run 4). On the other hand, TMS group-substituted ynamide also reacted with **4** in the presence of a palladium catalyst to give expected **10e** in 55% yield and its regioisomer **11e** in 26% yield (run 5). Terminal alkyne **9f** was also applicable to the silaboration, giving **10f** in 74% yield as a single isomer (run 6).[16]

Having established the silaboration of ynamides, we examined the utilization of silaborated enamide as a boronic ester (Scheme 4). Suzuki–Miyaura coupling of the enamide **10d** with iodobenzene (**12a**) was carried out in the presence of Pd(dppf)Cl$_2$ (10 mol%) and Cs$_2$CO$_3$ (5 equiv.) in DMF/H$_2$O at 60 °C. As a result, cross-coupling product **13da** was obtained in 91% yield. On the other hand, the coupling reaction of **10d** and **12b** gave the corresponding enamide derivative **13db** in 66% yield.

In summary, we have found that the Pd-catalyzed silaboration of ynamides having various substituents proceeds to give various tri- and tetra-substituted enamide derivatives in a highly regio- and stereoselective manner. It was also demonstrated that the silaborated enamide could be utilized as a coupling partner in Suzuki–Miyaura coupling, and the corresponding coupling products were obtained in good yields. Further studies along this line are in progress.

Experimental Section

General Procedure for Pd-Catalyzed Silaboration of Ynamides

A solution of an ynamide, PhMe$_2$SiB(pin) (**4**, 1 equiv. to the ynamide), Pd(OAc)$_2$ (3 mol% to the ynamide) and 1,1,3,3-tetramethylbutylisocyanide **6** (30 mol% to the ynamide) in toluene was stirred at 110 °C. The reaction mixture was cooled to room temperature and concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel to give the corresponding silaborated enamide.

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[13] Recently, we reported nickel-catalyzed asymmetric coupling of 1,3-dienes, aldehydes, and $PhMe_2SiBi(pin)$ (**4**). See: N. Saito, A. Kobayashi, Y. Sato, *Angew. Chem.* **2012**, *124*, 1258; *Angew. Chem. Int. Ed.* **2012**, *51*, 1228.

[14] CCDC 884205 contains the supplementary crystallographic data for this paper (**7a**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[15] For a mechanistic study on silaboration of alkynes mediated by a stoichiometric amount of platinum complex, see: T. Sagawa, Y. Asano, F. Ozawa, *Organometallics* **2002**, *21*, 5879. For a related theoretical study on palladium-catalyzed silaboration of 1,2-diene, see: ref.[10i]

[16] Although the reason for the high regioselectivity of silaboration of yanmides is not clear yet, coordination of oxygen functionality of the amide group to the palladium center might affect the direction of the insertion pathway. Furthermore, steric repulsion between the bulky boryl group of **IV** and the amide group of the substrate might operate on the regioselective insertion of the triple bond into the Pd−B σ-bond.