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Communication

Pd/Ming-Phos-Catalyzed Asymmetric Three-Component Arylsilylation of *N*-Sulfonylhydrazones: Enantioselective Synthesis of *gem*-Diarylmethine Silanes

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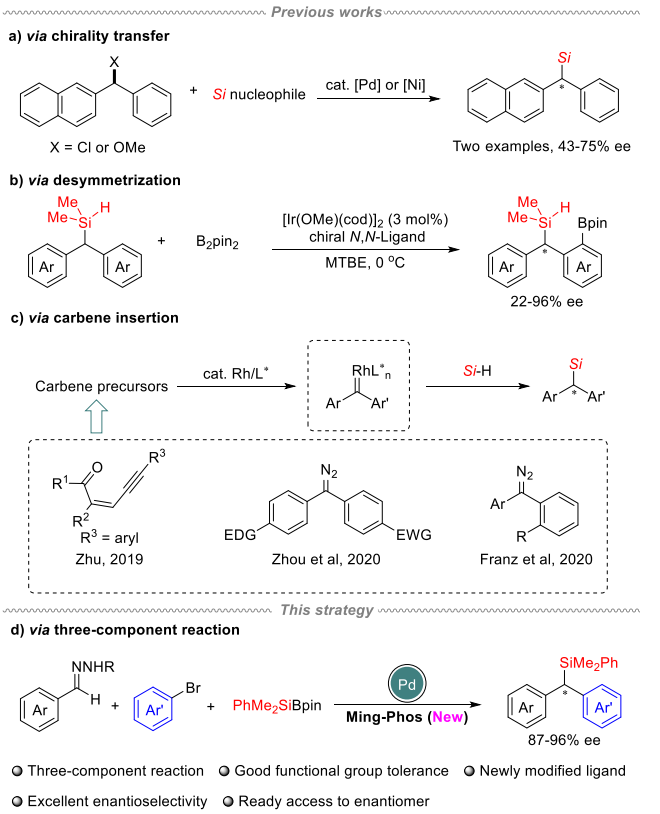
ABSTRACT: A Pd-catalyzed enantioselective three-component reaction of *N*-sulfonylhydrazones, aryl bromides, and silylboronic esters is developed, enabling the synthesis of chiral *gem*-diarylmethine silanes in high enantioselectivity with the use of a newly identified **Ming-Phos**. Compared with *N*-tosyl, the more easily decomposed *N*-mesitylsulfonyl is more suitable as the masking group of electron-rich hydrazone to improve the reaction efficiency. The reaction features a broad scope concerning both coupling partners, high enantioselectivity, and mild reaction conditions. The ready access to enantiomers and utility of this catalytic method are also presented.

Chiral organosilanes are very useful molecular skeletons due to their practical applications in medicinal chemistry and materials science.[1] Silicon motifs can also be used in essential transformations, such as the Hiyama coupling reaction, oxidation, and C−H activation.[2] As a result, catalytic methods for the enantioselective synthesis of chiral benzyl silanes have advanced tremendously, including the asymmetric hydrosilylation of alkenes,[3] transition metal-catalyzed chirality transfer reactions,[4] and asymmetric carbene insertion.[5] Nevertheless, most transformations are limited to arylalkylmethine silanes. The catalytic, efficient, and enantioselective assembly of chiral *gem*-diarylmethine silanes, those with two sterically similar aromatic substituents, poses considerable challenges, and only a handful of examples have been reported,[6] though the diarylmethane skeleton is commonly found in many bioactive compounds.[7] Among the strategies used, reactions through chirality transfer have been sporadically reported, including the palladium-catalyzed reaction of benzylic chloride with silyl boronate and the nickel-catalyzed reaction of benzylic methyl ether with silyl Grignard reagent (Scheme 1a),[6c,4b] both of which gave chiral *gem*-diarylmethine silanes with moderate enantiopurity. In addition to the chirality transfer strategy, Hartwig and co-workers[8] reported an iridium-catalyzed desymmetrization of prochiral *gem*-diarylmethine silanes with B_2pin_2, and recently, Hong and co-workers[9] further optimized some of the reaction results (Scheme 1b). The rhodium-catalyzed enantioselective insertion of carbenes into Si−H is an alternative and more straightforward method (Scheme 1c). In 2019, Zhu and co-workers[10] described an elegant method to produce enantioenriched α-furyl-substituted *gem*-diarylmethanesilanes using conjugated enynones as carbene precursors. Then, Zhou and co-workers[11] made a breakthrough in synthesizing enantioenriched *gem*-diarylmethanesilanes from diaryldiazome thanes. The significant electronic difference between the two aromatic rings is the key to obtain high enantioselectivity. Meanwhile, Franz and cowokers[12] reported

Scheme 1. Diverse Pathways for the Synthesis of Chiral *gem*-Diarylmethine Silanes



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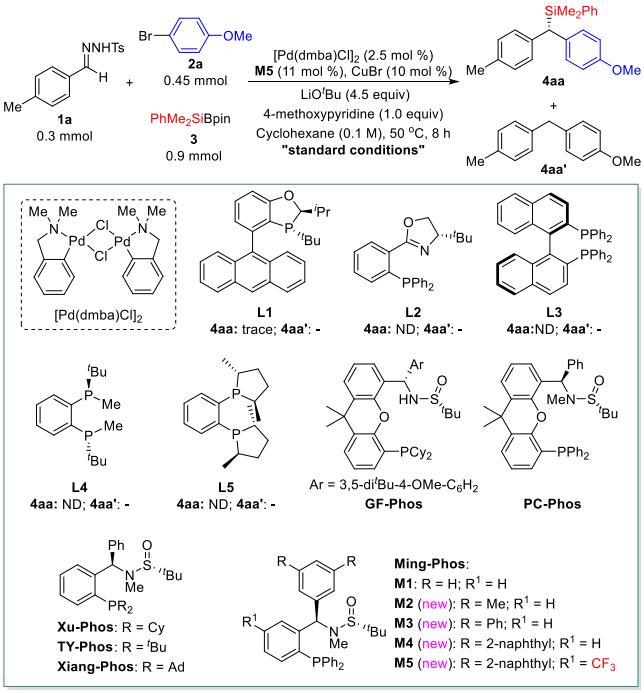
a similar reaction to produce silanes with a carbon- and a silicon-stereogenic center but using the steric difference of the two aryl groups, in which the *ortho* substituent is crucial. Given the ideal of silicon as a carbon isostere in drug discovery,[1a−e] it remains necessary to develop more general methods for the preparation of chiral *gem*-diarylmethine silanes.

Considering the prevalence of aldehyde derived hydrazones as carbene precursors and their rich chemistry in C−C bond formations,[13] as well as silylboronic esters as commercially available reagents in silicon chemistry,[14] we envisaged whether the enantioselective three-component reaction to obtain chiral *gem*-diarylmethine silanes can be realized by exploiting *N*-sulfonylhydrazones, aryl bromides, and silylboronic esters as reaction partners. In order to accomplish this design, the following challenges must be overcome: (1) How to obtain the target product with a desired yield when two of the three components may interplay to generate byproducts.[15] (2) How to obtain excellent enantioselectivity. We describe herein the development of a novel Pd-catalyzed enantioselective three-component arylsilylation of *N*-sulfonylhydrazones using a newly identified **Ming-Phos** (Scheme 1d).

Inspired by the excellent performance of our developed **Sadphos** in the asymmetric palladium catalysis and hydrazone involved three component cross-coupling reaction,[16−21] our investigations began with *N*-tosylhydrazone **1a**, 4-bromoanisole **2a**, and silylboronic ester **3** as model substrates. A survey of various reaction conditions identified [Pd(dmba)Cl]$_2$, CuBr, **Ming-Phos M5**, LiO^{t}Bu, 4-methoxypyridine, and cyclohexane as crucial parameters to give **4aa** in 68% isolated yield and 94% ee (Table 1, entry 1). We discovered that the formation of **4aa′** is the primary factor reducing the yield, and the direct coupling of **2a** with **3** to form aryl silanes was also detectable. Indeed, commercially available ligands **L1**−**L5** exhibited poor catalytic activity, indicating that the ligand is crucial for reactivity and enantioselectivity. For the **Sadphos** ligand kit, **GF-Phos**, **PC-Phos**, **Xu-Phos**, **TY-Phos**, and **Xiang-Phos** delivered **4aa** with unsatisfactory results (Table 1, entries 2−6). To our delight, the reaction using **Ming-Phos M1** provided **4aa** with 54% yield and 86% ee (Table 1, entry 7), and a further increase in the bulkiness of **Ming-Phos** and decrease in the electron density of phosphine could improve the yield and enantioselectivity (Table 1, entries 8−10). Other parameters varying from the standard conditions were also evaluated, leading to either lower yields or inferior ee values (see the Supporting Information for details). Control experiments showed palladium catalysts were critical to afford the chiral silane (Table 1, entries 11). Notably, both copper salts and 4-methoxypyridine were pivotal for the reaction efficiency, which might promote the formation of the Cu-SiMe$_2$Ph specie for transmetalation (Table 1, entries 12−13).[22]

The optimal reaction conditions were next implemented to examine the scope of the substrates (Table 2, top). An array of aryl *N*-tosylhydrazones was tested at the outset. Generally, good functional group tolerance was achieved for *para*- and *meta*-substituents of *N*-tosylhydrazones (**4aa**−**4qa**), smoothly affording the desired chiral *gem*-diarylmethine silanes. The electronic effect of the *para*-substituents has a significant impact on the yield, and especially, the target compounds were almost undetectable when using *N*-tosylhydrazones with strong electron-donating groups. High enantioselectivities were obtained for *ortho*-substituted substrates, albeit with relatively lower yields, which might be due to the relatively lower rate for the migratory insertion (**4ra**−**4ta**). Heteroarylhydrazones, like

Table 1. Optimization of the Reaction Conditions



entry	variation from "standard conditions"	yield **4aa** (%)[a]	yield **4aa′** (%)[a]	ee (%)[c]
1	none	74 (68[b])	11	94
2	**GF-Phos** instead of **M5**	40	ND[d]	24
3	**PC-Phos** instead of **M5**	43	ND	64
4	**Xu-Phos** instead of **M5**	14	7	−24
5	**TY-Phos** instead of **M5**	8	7	20
6	**Xiang-Phos** instead of **M5**	11	6	22
7	**M1** instead of **M5**	54	7	86
8	**M2** instead of **M5**	56	13	91
9	**M3** instead of **M5**	60	14	92
10	**M4** instead of **M5**	62	21	91
11	no [Pd(dmba)Cl]$_2$	ND	ND	
12	no CuBr	17	47	90
13	no 4-methoxypyridine	20	2	83

[a]^{1}H NMR yield using 1,1,2,2-tetrachloroethane as the internal standard. [b]Isolated yield. [c]Determined by HPLC analysis with a chiral stationary phase. [d]ND = not detected

3-thienyl one, provided the corresponding product in moderate yield with 89% ee (**4ua**).

Next, we turned our attention to the reaction of various aryl bromides **2** with *N*-tosylhydrazone **1a** and silylboronic ester **3**. The results showed that aryl bromides bearing both electron-withdrawing and electron-donating groups proceeded well to deliver **4ab**−**4ak** in moderate yields with high ees. Some functional groups, such as OBn (**4af**), CO$_2$R (**4ag** and **4ai**), and acetal (**4aj**), were incorporated, allowing the products to be amenable to further transformations. Moreover, heterocycles such as benzofuran and indole could also be tolerated (**4ol**−**4om**). As we mentioned above, *para*-strong electron-donating *N*-tosylhydrazones were unsuitable for this catalytic system, probably due to the slower dissociation rate into the diazo species.[23] After an extensive screening of different substituents of hydrazones, it was found that sterically congested *N*-mesitylsulfonylhydrazones could address this issue. Thus, the chiral diarylmethine silanes, containing two *para*-electron-rich aryl groups, such as **4vd**, **4vf**, and **4wa**, were

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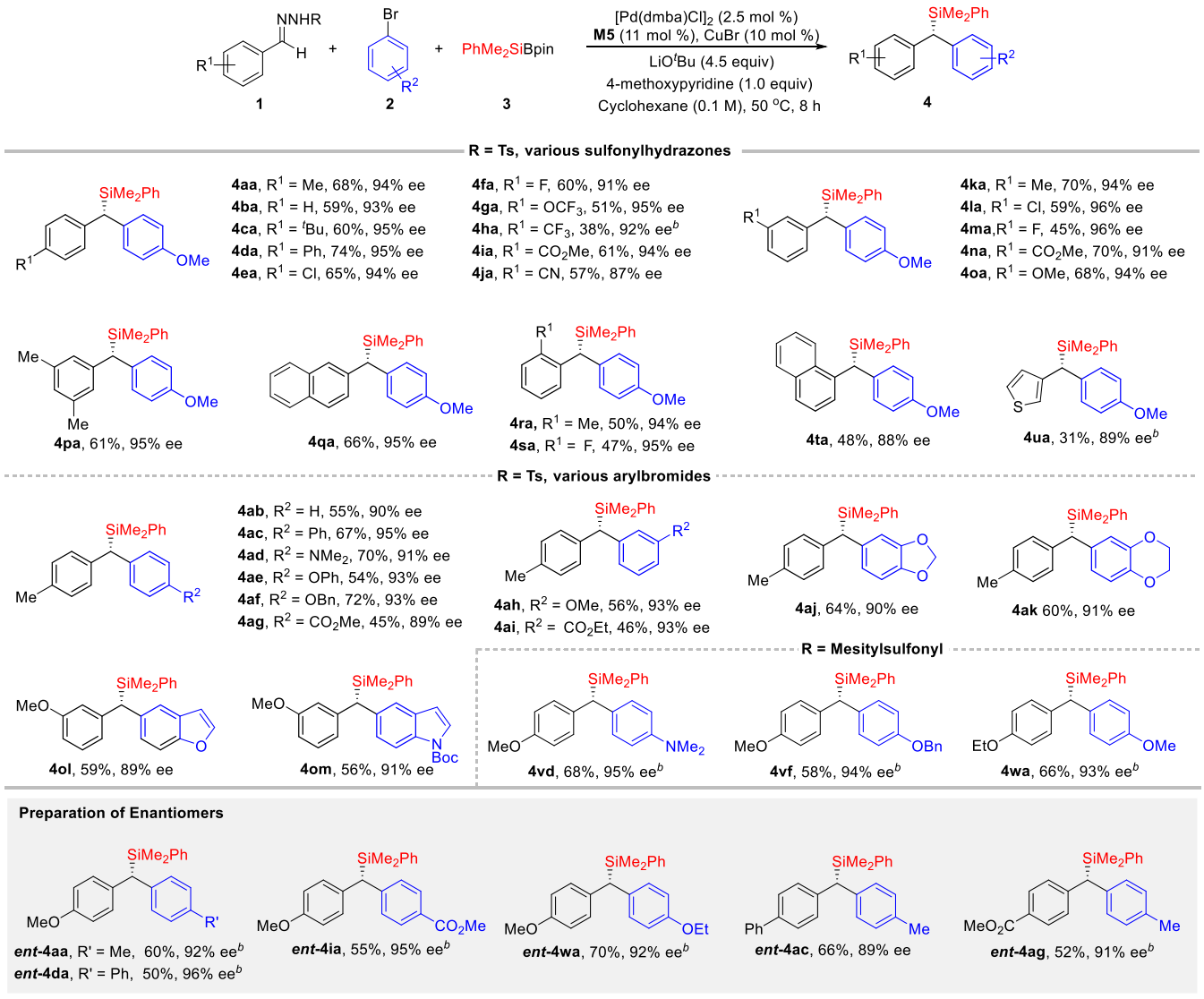
Table 2. Substrates Scope (Top) and Preparation of Enantiomers (Bottom)[a]



[a]Unless noted otherwise, the reactions were performed with **1** (0.30 mmol), **2** (0.45 mmol), **3** (0.90 mmol), $[Pd(dmba)Cl]_2$ (2.5 mol %), **M5** (11 mol %), CuBr (10 mol %), LiO^tBu (4.5 equiv), and 4-methoxypyridine (1.0 equiv) in cyclohexane (3.0 mL) at 50 °C for 8 h. Isolated yields are given. Enantioselectivities were determined by chiral HPLC. [b]With **2** (0.6 mmol) and **3** (1.2 mmol) for 12 h.

delivered in moderate yields and high ees. It is noteworthy that this type of chiral diarylmethine silane could not be easily accessible through the carbene Si−H insertion approach. The absolute configuration of **4ad** was unambiguously confirmed by X-ray crystallography.[24]

One obvious advantage of the three-component coupling is that it provides a convenient approach to access both enantiomers by simply exchanging the aromatic moieties of hydrazones and aryl bromides. Through this strategy, we constructed six enantiomers, employing *N*-mesitylsulfonylhydrazone (*ent*-**4aa**, *ent*-**4da**, *ent*-**4ia**, *ent*-**4wa**) and *N*-tosylhydrazones (*ent*-**4ac**, *ent*-**4ag**), respectively, all of which were prepared in good yields and high enantioselectivities (Table 2, bottom)

To illustrate the practicality of this three-component reaction, a larger scale synthesis of **4aa** was carried out (Scheme 2). The product was isolated in 61% yield with 94% ee under the standard conditions. Enantioenriched silane **4ab** could be converted to the corresponding chiral benzylic alcohol **5** using Fleming−Tamao oxidation.[25] Then, (*R*)-neobenodine, a bioactive molecule with anticholinergic and antihistaminic properties, was prepared. The treatment of **4aa** with $HBF_4{\cdot}Et_2O$ in DCM at room temperature for 4 h and then the reduction by $LiAlH_4$ could afford hydrosilane **6**, which could go downstream for derivatization. For example, compound **6** was hydrolyzed by Pd/C catalyst to provide silanol **7**.[12] Moreover, the $Pd(P^tBu_3)_2$ catalyzed coupling reaction of **6** with **1a** was achieved to furnish compound **8**.[6e] Notably, all transformations were developed without any erosion of the chirality.

Some control experiments were then conducted to gain insights into the reaction mechanism. Surprisingly, byproduct **4aa′** was not detected when silylboronic ester **3** was absent (Scheme 3a). Combined with the detection of **4aa′** in standard conditions, we can conclude that the transmetalation of carbene-coordinated palladium species with Cu-$SiMe_2Ph$ may precede the group migratory insertion. We also examined the reaction between *N*-tosylhy-drazone **1a** and silylboronic ester **3**

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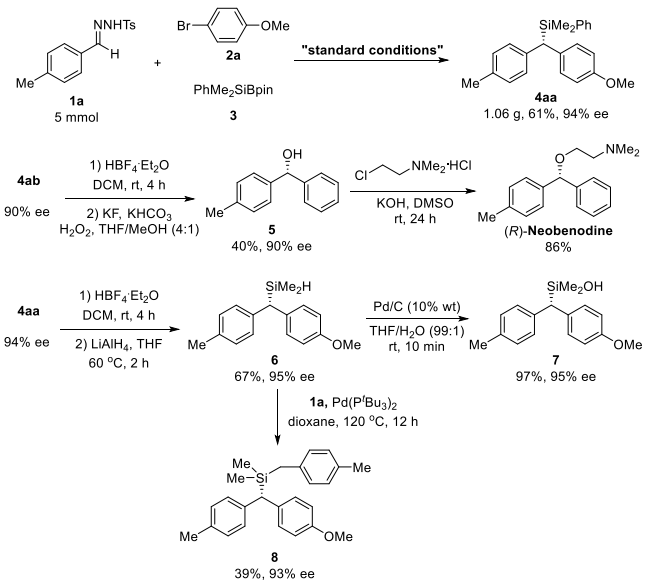
Scheme 2. Scale-up Synthesis and Applications

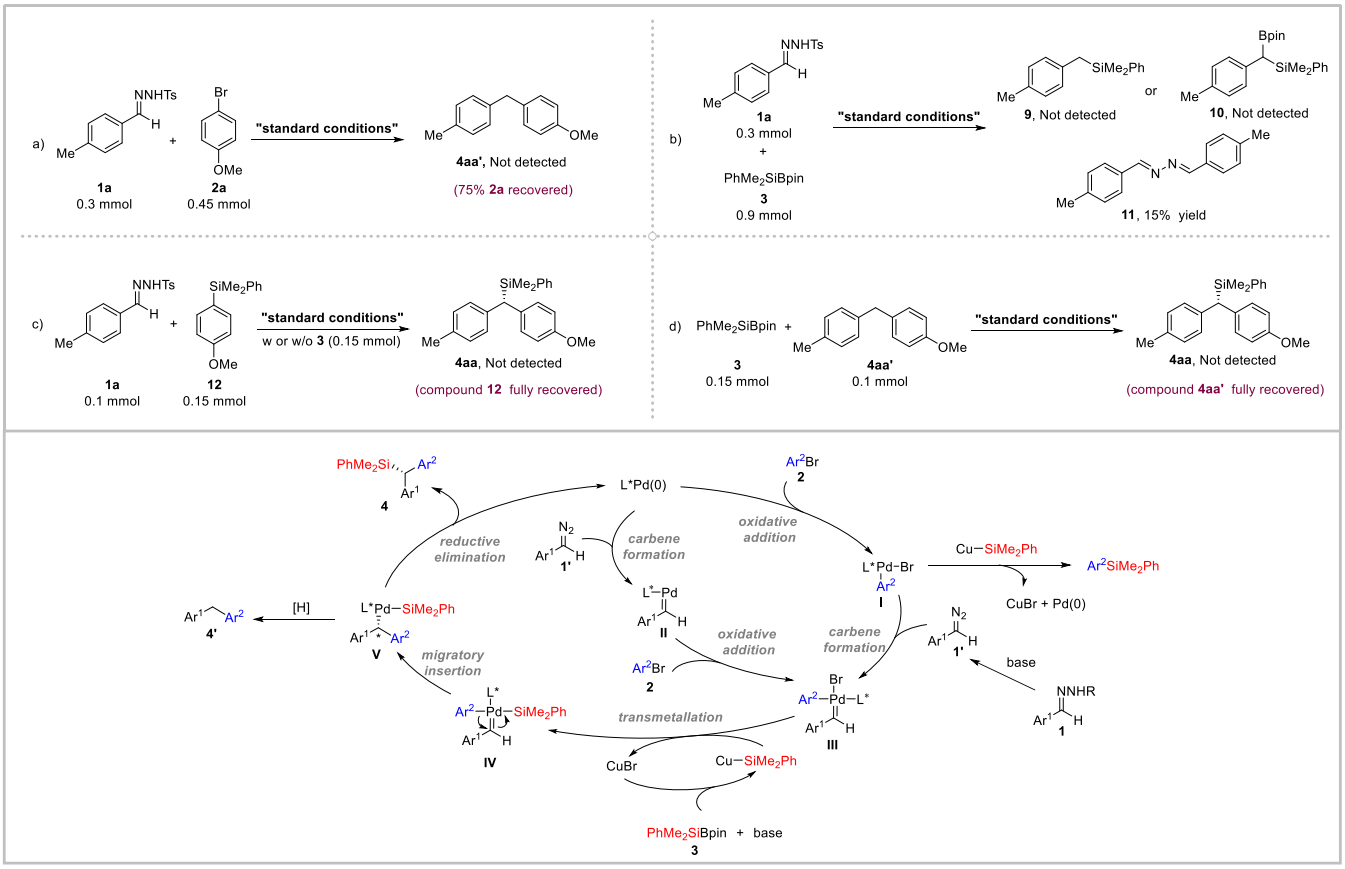


under the standard conditions. Products of hydrosilylation or silylborylation of carbene were not detected either (Scheme 3b). This result indicated that the carbene migratory insertion is more likely to occur with an aryl group. To explore the possibility of a two-step route, we utilized byproducts **12** and **4aa′** to react with the corresponding unintroduced components (Scheme 3c,d). Product **4aa** was not detected in both experiments, which excluded the above-mentioned assumption.

On the basis of the previous reports and the experimental results,[5a,16,26] a plausible reaction mechanism is outlined (Scheme 3, bottom). The oxidative addition of aryl bromides **2** to Pd(0) to form intermediate **I**, followed by the reaction with in situ generated **1′**, afforded the Pd carbene intermediates **III**. As an alternative, the Pd carbene intermediates **II** are generated by the coordination of Pd(0) with **1′**, which undergoes oxidative addition with **2** to furnish the Pd carbene intermediates **III**. In another cycle, silylboronic ester **3** is activated by copper salt. Subsequently, the transmetalation proceeds between Pd carbene intermediate **III** and Cu-SiMe$_2$Ph to generate intermediate **IV**. As a critical step of stereoscopic construction, carbene migratory insertion occurs with Ar^2 to form chiral benzylic Pd complex **V**. Lastly, stereoretentive reductive elimination affords enantioenriched **4** and regenerates Pd(0). The byproduct **4′** is generated through the direct protonation of the complex **V**.

In summary, we have disclosed a new method to build up chiral *gem*-diarylmethine silanes through a Pd-catalyzed enantioselective three-component reaction starting from *N*-sulfonylhydrazones, aryl bromides, and silylboronic esters. The newly indentified **Ming-Phos M5** is imperative to induce excellent enantioselectivity, while copper salts integrated with the additive 4-methoxypyridine were beneficial to improve the reaction efficiency. This reaction showcases high enantioselectivity, good functional group tolerance, and ready access to enantiomers. In addition, a feasible mechanism is proposed on the basis of several control experiments.

Scheme 3. Control Experiments (Top, a−d) and Proposed Mechanism (Bottom)



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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c07037.

Experimental details, characterization data, HPLC spectra, and NMR spectra (PDF)

Accession Codes

CCDC 2181904 and CCDC 2201094 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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