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Stereospecific and Chemoselective Copper-Catalyzed Deaminative Silylation of Benzylic Ammonium Triflates

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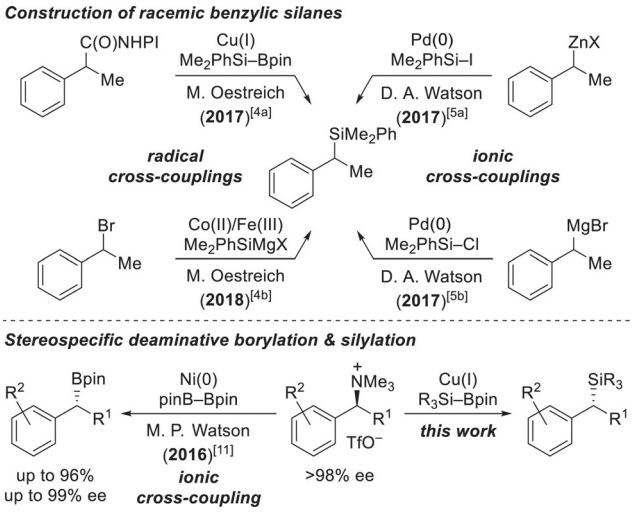
Abstract: *A method for the synthesis of benzylsilanes starting from the corresponding ammonium triflates is reported. Silyl boronic esters are employed as silicon pronucleophiles, and the reaction is catalyzed by copper(I) salts. Enantioenriched benzylic ammonium salts react stereospecifically through an S_N2-type displacement of the ammonium group to afford α-chiral silanes with inversion of the configuration. A cyclopropyl-substituted substrate does not undergo ring opening, thus suggesting an ionic reaction mechanism with no benzyl radical intermediate.*

Catalytic methods for the asymmetric synthesis of α-chiral silanes using silicon nucleophiles have gone through a tremendous development in recent years.[1] However, enantioselective C(sp^3)–Si bond formation by cross-coupling of either the aforementioned silicon nucleophiles or, in a reverse approach, silicon electrophiles with aliphatic coupling partners is still essentially unknown.[2,3] As shown for *benzylic* precursors in the racemic series, our group[4] as well as Watson and co-workers[5] have developed mechanistically different cross-coupling reactions (Scheme 1, top).[2,6] Our efforts to render these radical reactions enantioconvergent have been fruitless so far.[7] We therefore turned away from alkyl halides and redox-active carboxylic acid derivatives and considered the use of quaternary ammonium salts as electrophiles.[8] These are stable towards light and oxygen and easily accessible in high enantiomeric purity.[9] Watson and co-workers have demonstrated their stereospecific displacement[10–12] for C(sp^3)–C(sp^2)[10] and C(sp^3)–B[11] bond formation (Scheme 1, bottom left). A related C(sp^3)–Si cross-coupling of these ammonium salts is unprecedented and would offer an alternative to Markovnikov hydrosilylation of styrenes.[13] We disclose here a copper-catalyzed deaminative silylation of those benzylic quaternary ammonium salts with inversion of the configuration (Scheme 1, bottom right).

We began our investigation by testing the typical protocol of our earlier ionic silylation[3] in the reactions of racemic



Scheme 1. Synthesis of racemic benzylsilanes and stereospecific deaminative cross-couplings. NHPI = *N*-hydroxyphthalimide.

ammonium triflate **1a** and iodide **2a** with silyl boronic ester[14] Me_2PhSi-Bpin (**3a**). After a systematic screening of reaction conditions (see the Supporting Information for details), an excellent yield was obtained at 0 °C for triflate **1a** with 10 mol % CuBr as the catalyst and NaO*t*Bu as the base (Table 1, entry 1). The corresponding iodide **2a** was less reactive,[10a] affording the benzylsilane **4aa** in moderate yield (entry 2). As expected, the alkoxide base had a profound effect on the reaction outcome (entries 3–5), and without base, there was no reaction (entry 6). Both higher and lower loadings of Me_2PhSi-Bpin/NaO*t*Bu resulted in diminished yields (entries 7 and 8). Reactions were sluggish at temperatures other than 0 °C (entries 9 and 10). The yield dropped with 5.0 mol % CuBr (entry 11), and there was an alkoxide-promoted background reaction[15] in the absence of the copper catalyst but conversion was low (entry 12). The use of other silicon nucleophiles[4b,16] led to inferior yields (entries 13 and 14).

With the optimized setup in hand, we examined the scope of the nucleophilic substitution for secondary as well as primary and tertiary benzylic ammonium triflates in the racemic series (Scheme 2). The reaction proceeded well with representative silyl boronic esters **3a–c** (**1a**→**4aa–ac**). Methyl substitution at the aryl group was tolerated in the *para* (as in **1b**), *meta* (as in **1c**), and *ortho* (as in **1d**) positions but the yield was rather low for **1d**→**4da**. A broad range of electronically modified aryl groups was compatible, but we could not identify any particular trend (**1e–k**→**4ea–ka**). Bromine substitution in the *para* position was an exception since this substrate underwent hydrodebromination (not

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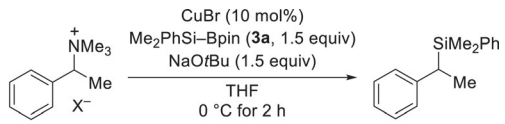
Table 1: Selected examples from the optimization of the reaction conditions.[a]

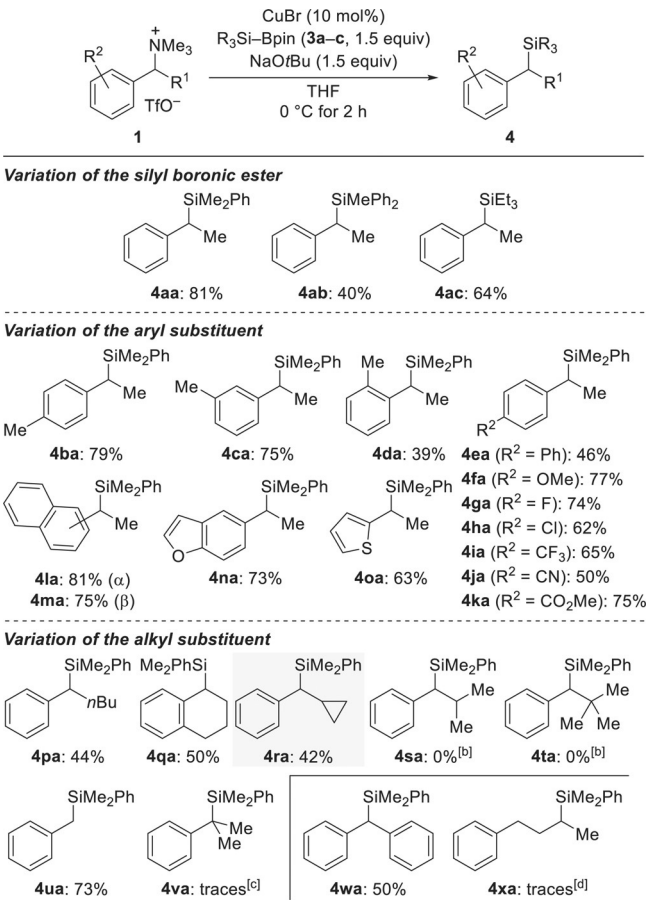


Entry	X	Variation	Yield [%][b]
1	OTf (**1a**)	none	92
2	I (**2a**)	18 h instead of 2 h	64
3	OTf (**1a**)	NaOMe instead of NaO*t*Bu	46
4	OTf (**1a**)	LiO*t*Bu instead of NaO*t*Bu	64
5	OTf (**1a**)	KO*t*Bu instead of NaO*t*Bu	0
6	OTf (**1a**)	w/o NaO*t*Bu, 18 h	0
7	OTf (**1a**)	1.1 equiv of $Me_2PhSiBpin$/NaO*t*Bu	59
8	OTf (**1a**)	2.0 equiv of $Me_2PhSiBpin$/NaO*t*Bu	41
9	OTf (**1a**)	25 °C, 2 h	65
10	OTf (**1a**)	−78 °C, 20 h	34
11	OTf (**1a**)	w/ 5.0 mol% CuBr, 2 h	45
12	OTf (**1a**)	w/o CuBr, 18 h	9
13	OTf (**1a**)	w/ $(Me_2PhSi)_2Zn$	35
14	OTf (**1a**)	w/ $Me_2PhSiMgX$	66

[a] All reactions performed on a 0.25 mmol scale. [b] Determined by GLC analysis with 1,3,5-trimethoxybenzene as an internal standard.

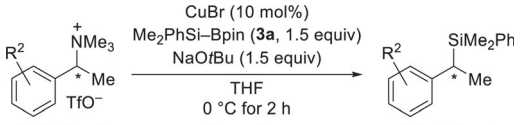
shown); we had observed this before under similar conditions.[3,17] Benzylic substrates containing naphthyl groups (as **1l** and **1m**) as well as heteroaryl groups (as **1n** and **1o**) reacted in good yields. A longer aliphatic chain at the benzylic position resulted in lower yield (**1p**→**4pa**); the same applied to a cyclic substrate (**1q**→**4qa**). Importantly, cyclopropyl-substituted **1r** yielded **4ra** in 42% with no ring opening (gray box); this supports an ionic mechanism and excludes the intermediacy of a benzyl radical. However, increasing the steric demand of the alkyl substituent further (isopropyl in **1s** and *tert*-butyl in **1t**) thwarted the nucleophilic displacement and defunctionalization was observed. The parent primary substrate reacted in good yield (**1u**→**4ua**) but, with regard to the assumed S_N2-type mechanism, the tertiary benzylic ammonium salt **1v** decomposed and only furnished traces of **4va**. For completion, diaryl-substituted **1w** converted into **4wa** in 50% yield. Conversely, dialkyl-substituted **1x**, that is, an unactivated ammonium triflate, only formed the desired silane **4xa** in trace amounts. Me_2PhSi-Me (= Me_3PhSi) was found to be the major product, which is proof that a primary site (methyl) reacts preferentially over an unactivated secondary position. This is indeed the current limitation of the method. The formation of that byproduct was also seen to a much lesser extent in the reactions of the benzylic substrates and accounts for the lower yields for a few substrates.

We next studied the stereospecificity of this nucleophilic substitution (Table 2). A number of highly enantioenriched benzyl ammonium triflates **1** were transformed into the desired benzyl silanes **4** with essentially no loss of enantiomeric purity. Substitution of the aryl ring with electron-donating (entry 4) or electron-withdrawing (entries 5 and 7) groups had no effect on the stereospecificity. The absolute configuration of **4aa** was assigned as *S* by Tamao–Fleming



Scheme 2. Copper-catalyzed nucleophilic substitution of benzylic ammonium triflates.[a] [a] Yields are isolated material after purification by flash chromatography on silica gel. Me_2PhSi-$SiPhMe_2$ is always obtained as a byproduct but can be selectively oxidized[18] for easier separation from the less polar benzylsilanes. [b] Mainly defunctionalization was observed. [c] Defunctionalization and decomposition was observed. [d] Me_3PhSi formed as the major product.

Table 2: Stereospecific copper-catalyzed nucleophilic substitution of benzylic ammonium triflates with a silicon nucleophile.[a]



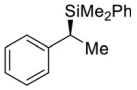
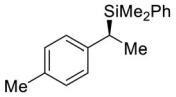
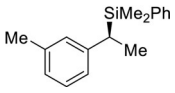
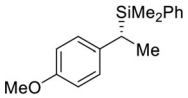
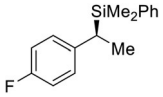
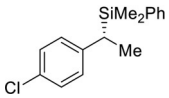
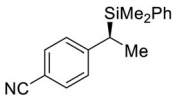
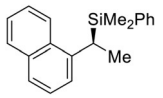
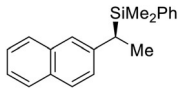
Entry	Ammonium triflate	*ee* [%]	Benzylsilane	Yield [%][b]	*ee* [%][c]
1	(*R*)-**1a**	>99[d]	 (*S*)-**4aa**	79	>99
2	(*R*)-**1b**	98[e]	 (*S*)-**4ba**	77	98

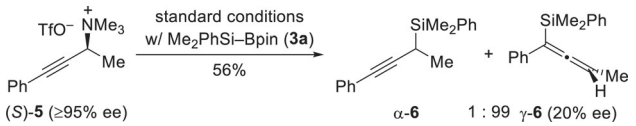
Table 2: (Continued)

Entry	Ammonium triflate	*ee* [%]	Benzylsilane	Yield [%][b]	*ee* [%][c]
3	(*R*)-**1c**	98[e]	 (*S*)-**4ca**	76	98
4	(*S*)-**1f**	98[d]	 (*R*)-**4fa**	75	97
5	(*R*)-**1g**	98[d]	 (*S*)-**4ga**	71	98
6	(*S*)-**1h**	98[d]	 (*R*)-**4ha**	64	98
7	(*R*)-**1j**	>95[e,f]	 (*S*)-**4ja**	48	97[g]
8	(*R*)-**1l**	99[d]	 (*S*)-**4la**	82	99
9	(*R*)-**1m**	99[d]	 (*S*)-**4ma**	77	97

[a] All reactions performed on a 0.25 mmol scale. [b] Yield of isolated product after purification by flash chromatography on silica gel. [c] Determined by HPLC analysis on chiral stationary phases after Tamao–Fleming oxidation. [d] Starting amine is commercially available in enantiomerically enriched form. [e] Determined by HPLC analysis on a chiral stationary phase at the stage of the free amine after amide formation with 4-nitrobenzoic acid chloride (see the Supporting Information for details). [f] Racemization during amide formation; the enantiomeric excess is derived from the diastereomeric excess (de) of the highly diastereoenriched precursor[10b] (Ellman's *tert*-butanesulfinyl amines[9a]). [g] The enantiomeric excess was determined at the stage of the silane; no Tamao–Fleming oxidation required.

oxidation and comparison of the optical rotation of the resulting (*S*)-1-phenylethanol with the reported value (see the Supporting Information for details).[19] Hence, the stereochemical course of the transformation of (*R*)-**1a** into (*S*)-**4aa** is inversion, which is in agreement with our previously reported ionic nucleophilic silylation of α-triflyloxy nitriles and esters.[3]

We then moved to other activated ammonium triflate salts. Since the synthesis of unknown secondary allylic ammonium salts failed in our hands, a primary derivative was tested successfully (see the Supporting Information for details). In turn, a secondary propargylic ammonium triflate could be prepared with high enantiomeric excess, and both linear- and branched-selective stereospecific substitution reactions with Grignard reagents have been reported.[20] We subjected (*S*)-**5** to the usual procedure and obtained allene γ-**6** in reasonable yield, noting the chemical instability of (*S*)-**5** (Scheme 3). In contrast to Tortosa's work[20b] and our own method[21] with a phosphate leaving group, the enantiomeric excess of (*R*)-γ-**6** was significantly eroded; several runs of the reaction showed that the *ee* value varied, probably as result of the partial decomposition of (*S*)-**5**.



Scheme 3. Copper-catalyzed silylation of a propargylic ammonium salt.

In summary, we have developed a nucleophilic silylation of benzylic ammonium triflates, which represents the first example of a deaminative silylation. Our procedure offers an alternative pathway for the synthesis of racemic benzylsilanes and exhibits good functional-group tolerance. The reaction is stereospecific and likely to proceed by an S_N2-type mechanism. The extension of this approach to allylic or propargylic ammonium salts will require further optimization and is currently under investigation in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: copper · nucleophilic substitution · silanes · stereospecificity · transmetalation

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