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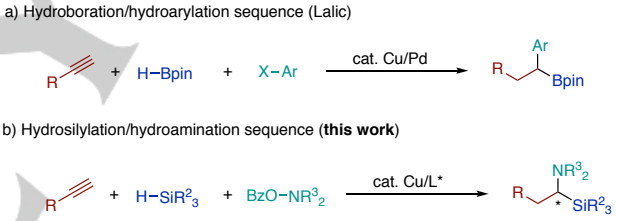
Cu-Catalyzed Reductive *gem*-Difunctionalization of Terminal Alkynes via Hydrosilylation/Hydroamination Cascade: Concise Synthesis of α-Aminosilanes

Soshi Nishino,[a] Koji Hirano,*[a] and Masahiro Miura*[a]

Dedication ((optional))

Abstract: A copper-catalyzed reductive *gem*-difunctionalization of terminal alkynes with hydrosilanes and hydroxylamines has been developed. The reaction proceeds via hydrosilylation/hydroamination cascade, and the readily available and simple terminal alkynes can be transformed into the corresponding α-aminosilanes of medicinal interest in a single operation. Additionally, the use of chiral bisphosphine ligand successfully makes the reaction enantioselective to deliver the optically active α-aminosilanes with good enantiomeric ratios.

The terminal alkyne is simple and abundant but one of the indispensable chemical entities in modern organic synthesis because of its high and versatile reactivity associated with two π bonds.[1] Particularly, metal-catalyzed addition-type reactions can add various functional groups across the alkyne platform. Among them, the catalytic, simultaneous introduction of two functional groups (difunctionalization) has received significant attention because it can rapidly increase the molecular complexity. Whereas the catalytic *vic*-difunctionalization reactions have been widely studied, the introduction of two functions at the alkyne terminus (*gem*-difunctionalization) is less explored. The catalytic double hydroboration[2] and hydrosilylation[3] were reported to form the corresponding *gem*-diborylalkanes and -disilylalkanes, respectively, but only the same functional groups (boryl or silyl) could be installed. Buchwald[4] and Mankad[5] independently developed the copper-catalyzed reductive hydroamination and reductive hydroacylation of terminal alkynes, respectively. However, one of functional groups added to the terminal carbon is a hydrogen atom. Only one successful example of *gem*-difunctionalization with two different non-hydrogen functional groups is the copper/palladium co-catalyzed hydroboration/hydroarylation sequence with pinacolborane and aryl halides, which was recently reported by Lalic (Scheme 1a).[6] Thus, this research field still remains underdeveloped. Herein, we report a copper-catalyzed hydrosilylation/hydroamination sequence with hydrosilanes and hydroxylamines: the silyl and amino groups are added in the *gem*-relationship, and the corresponding α-aminosilanes are obtained from the terminal alkynes in a single operation (Scheme 1b). Additionally, an appropriate chiral bisphosphine ligand makes the reaction enantioselective to form the optically active α-aminosilanes[7] with good enantiomeric ratio (e.r.), which are of interest in medicinal chemistry, as exemplified by angiotensin-converting enzyme (ACE) inhibitor and serine protease human neutrophil elastase (HNE) inhibitor.[8] Our group and Buchwald independently reported the related Cu-catalyzed aminoboration[7d] and hydroamination[7e] of vinylsilanes; however, in which the starting vinylsilanes need to be prepared from terminal alkynes in advance. In sharp contrast, the present sequential Cu catalysis allows the terminal alkynes to be starting platforms. We note that during the course of this study, Engle and Liu reported the related copper-catalyzed sequential hydroboration/hydroamination of terminal alkynes, giving the α-aminoboronates.[9]



Scheme 1. Metal-catalyzed reductive *gem*-difunctionalization of terminal alkynes with two different non-hydrogen functional groups. pin = pinacolate. Bz = benzoyl.

On the basis of the reported copper-catalyzed hydrosilylation[10] and hydroamination,[11,12,13] our optimization studies commenced with 5-phenyl-1-pentyne (**1a**; 3.0 equiv), Ph_2SiH_2 (**2a**; 3.0 equiv), and *O*-benzoyl-*N*-benzyl-*N*-*tert*-butylhydroxylamine (**3a**) as model substrates, and several phosphine ligands were screened, in conjunction with CuCl catalyst (10 mol%), LiO*t*Bu base (3.0 equiv), and 1,2-dichloroethane (DCE) solvent (Scheme 2). In an early experiment, treatment of **1a** with **2a** and **3a** under the CuCl/dppbz catalysis afforded a small but meaningful amount of α-aminosilane **4aaa** (2% ^{1}H NMR yield) along with the reduced byproduct **6a**. Prompted by the preliminary result, we investigated several dppbz-type ligands.[14] The introduction of substituents at the ortho- or para-position on the benzene ring gave almost negligible impact, and concomitant formation of vinylsilane **5aa**, alkene **6a,** and alkylsilane **7aa** byproducts were observed. In sharp contrast, dppbz ligands modified with the bulky *tert*-butyl group at the meta-position greatly increased the reactivity and selectivity (DTBM-dppbz and *t*Bu-dppbz). Moreover, the more sterically demanding Me_3Si-substituted TMS-dppbz showed the best performance to form the desired **4aaa** in 97% ^{1}H NMR yield. Subsequent fine-tuning revealed that the reaction also proceeded well with the decreased amount

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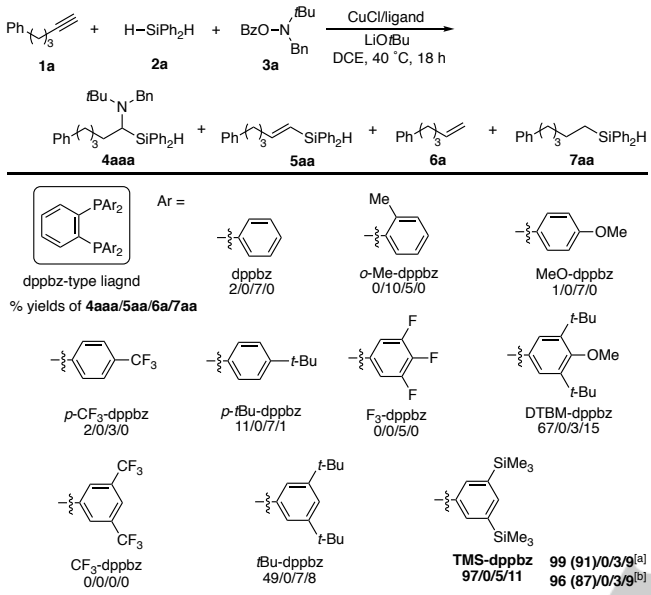
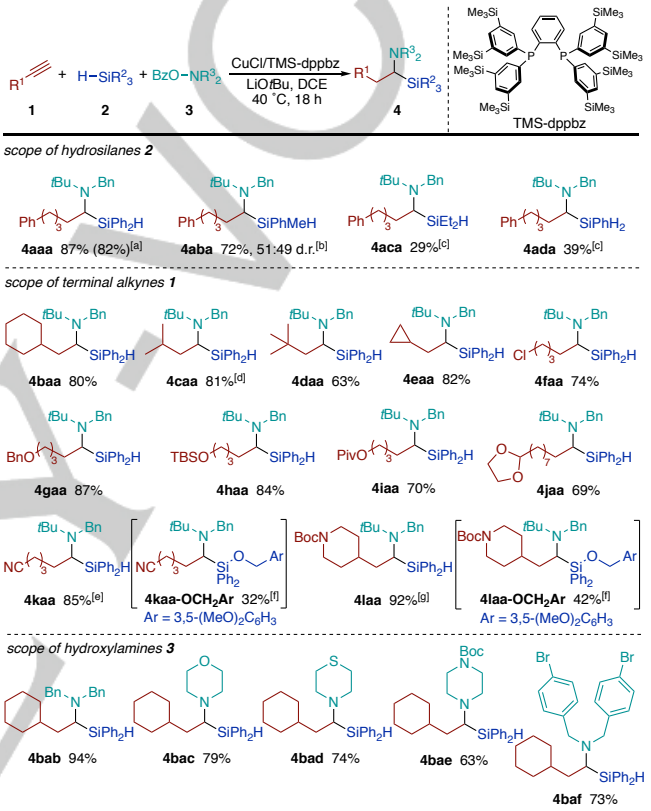
of **1a** (2.0 equiv) or LiO*t*Bu (2.0 equiv) to deliver **4aaa** in 91 or 87% isolated yield, respectively. Some additional observations are to be noted: attempts with other monodentate and bidentate ligands suffered from much lower selectivity; LiO*t*Bu is indispensable for the high conversion; no reaction occurred in the absence of any Cu salts (see the Supporting Information for more detailed optimization studies).



Scheme 2. Representative ligand optimization studies for Cu-catalyzed hydrosilylation/hydroamination sequence of terminal alkyne **1a** with dihydrosilane **2a** and hydroxylamine **3a**. Conditions: **1a** (0.45 mmol), **2a** (0.45 mmol), **3a** (0.15 mmol), CuCl (0.015 mmol), ligand (0.015 mmol), LiO*t*Bu (0.45 mmol), DCE (1.5 mL), 40 ˚C, 18 h, N_2. ^{1}H NMR yields based on 0.15 mmol with CH_2Br_2 internal standard are shown. Isolated yields are in parentheses. [a] With LiO*t*Bu (0.30 mmol). [b] With **1a** (0.30 mmol).

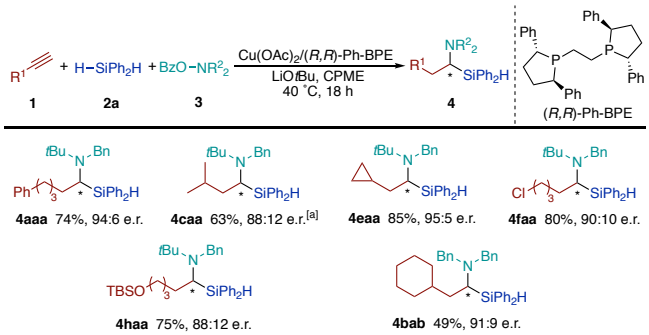
With optimal conditions in hand, we investigated the generality of copper-catalyzed sequential process (Scheme 3). We initially tested some hydrosilanes **2**: secondary $PhMeSiH_2$, Et_2SiH_2, and primary $PhSiH_3$ also worked to form the corresponding α-aminosilanes **4aba**–**4ada**, but in the latter two cases the products were too unstable for chromatographic purification to be isolated. On the other hand, tertiary silanes such as Ph_2MeSiH and $(EtO)_2MeSiH$ did not provide any products because of no hydrosilylation activity. The corresponding simply hydroaminated product, that is enamine,[4] was also not detected (data not shown). The scope of terminal alkynes **1** was substantially broad. The more sterically demanding cyclohexylacetylene (**1b**), isopropylacetylene (**1c**), and *tert*-butylacetylene (**1d**) underwent the reaction smoothly to form the desired **4baa**–**4daa** in good yields. The cyclopropylacetylene (**1e**) was converted to **4eaa** with the cyclopropyl ring left intact. Moreover, the copper catalyst was compatible with several functional groups including alkyl chloride, benzyl ether, silyl ether, pivaloyl ester, and acetal to deliver the *gem*-functionalized products **4faa**–**4jaa** in 69–87% isolated yields. The nitrile and NBoc moieties were also tolerated under the standard reaction conditions, but the products were somewhat sensitive to silica gel and partially decomposed during purification (**4kaa** and **4laa**); however, they could be isolated in an analytically pure form after conversion into the silyl benzyl ethers (**4kaa-OCH$_2$Ar** and **4laa-OCH$_2$Ar**).[15] The cyclohexylacetylene (**1b**) could also be coupled with acyclic *N,N*-dibenzylamine as well as cyclic morpholine, thiomorpholine, and Boc-protected piperazine to deliver the corresponding α-aminosilanes **4bab**–**4bae** in good yields. The 4-bromobenzylamine **2f** also provided **4baf** with the aryl-Br remaining untouched. Furthermore, the reaction was conducted on a 1.0 mmol scale without any difficulty (**4aaa**), indicating the scalability and reproducibility of the copper catalysis.



Scheme 3. Cu-catalyzed hydrosilylation/hydroamination sequence of terminal alkynes **1** with hydrosilanes **2** and hydroxylamines **3**. Conditions: **1** (0.30 mmol), **2** (0.45 mmol), **3** (0.15 mmol), CuCl (0.015 mmol), TMS-dppbz (0.015 mmol), LiO*t*Bu (0.45 mmol), DCE (1.5 mL), 40 ˚C, 18 h, N_2. Isolated yields are shown. [a] On 1.0 mmol scale. [b] With **1** (0.45 mmol) and LiO*t*Bu (0.30 mmol). [c] ^{1}H NMR yields. [d] With **1c** (0.45 mmol). [e] Contaminated with 22% of deaminated product **7ka**. [f] Isolated after treatment with 3,5-dimethoxybenzyl alcohol and K_2CO_3. See the Supporting Information for details. [g] Contaminated with 17% of deaminated product **7la**. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Piv = *tert*-butylcarbonyl, TBS = *tert*-butyldimethylsilyl.

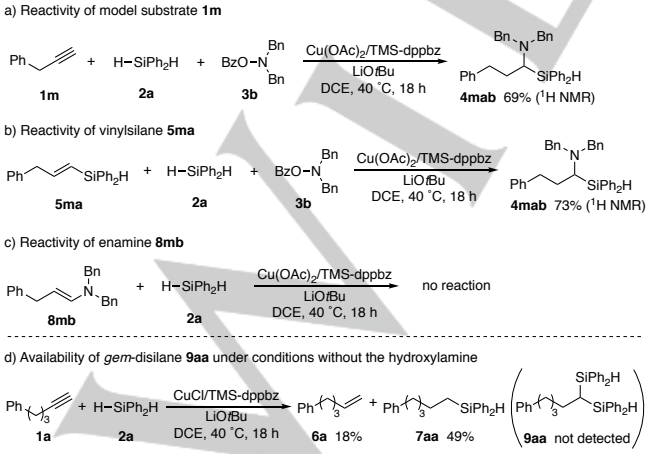
Our next target was the enantioenriched α-aminosilane by the enantioselective hydrosilylation/hydroamination cascade. After the evaluation of chiral ligands and various reaction parameters, we were pleased to find that the optically active **4aaa** was obtained in 74% isolated yield with 96:4 e.r. under the $Cu(OAc)_2$/(*R,R*)-Ph-BPE catalysis combined with cyclopentyl methyl ether (CPME) solvent (Scheme 4). The **4aaa** was readily purified by silica gel column chromatograph but unstable for chiral HPLC analytical conditions; therefore, the e.r. value was determined after the conversion into the corresponding silyl ether **4aaa-OCH$_2$Ar** (vide supra).[16] Sterically hindered

secondary alkyl-substituted terminal alkynes also underwent the enantioselective *gem*-difunctionalization to from **4caa**, **4eaa**, and **4bab** with 88:12–95:5 e.r. The asymmetric catalysis was tolerated with the alkyl chloride and silyl ether moieties, and the corresponding functionalized chiral α-aminosilanes **4faa** and **4haa** were formed in good yields with acceptable enantioselectivity.



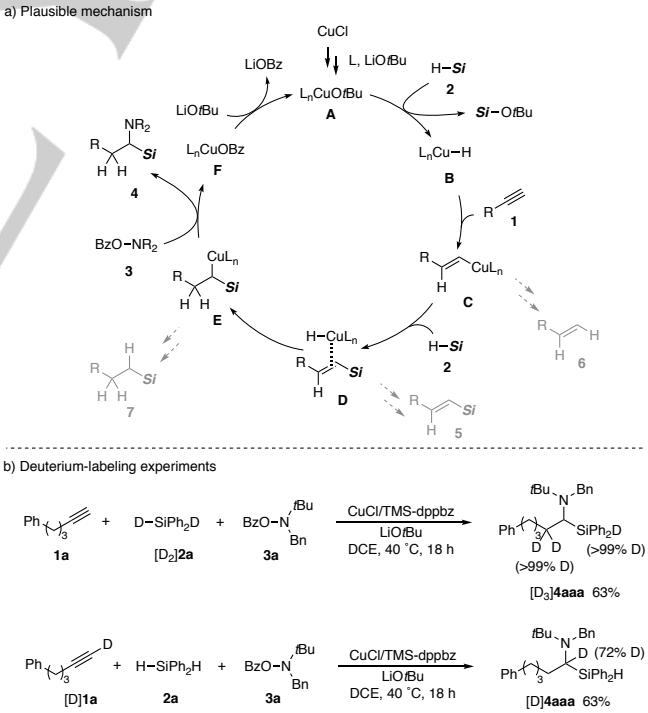
Scheme 4. Cu-catalyzed enantioselective hydrosilylation/hydroamination sequence of terminal alkynes **1** with diphenyldihydrosilane (**2a**) and hydroxylamines **3**. Conditions: **1** (0.30 mmol), **2a** (0.45 mmol), **3** (0.15 mmol), $Cu(OAc)_2$ (0.015 mmol), (*R,R*)-Ph-BPE (0.018 mmol), LiO*t*Bu (0.45 mmol), CPME (0.30 mL), 40 °C, 18 h, N_2. Isolated yields of **4** are shown. The enantiomeric ratios (e.r.) were determined by HPLC analysis on a chiral stationary phase after conversion into **4-OCH$_2$Ar**. [a] With **1c** (0.45 mmol).

To get insight into the mechanism, we then evaluated the reactivity of potential intermediates (Scheme 5).[18] First, we confirmed the viability of propargylbenzene (**1m**) under almost identical conditions to form the α-aminosilane **4mab** in 69% ^{1}H NMR yield (Scheme 5a). Second, we independently prepared the corresponding vinylsilane **5ma** and enamine **8mb** and checked their reactivity: whereas **5ma** was converted to **4mab** in 73% yield (Scheme 5b), no reaction occurred with **8mb** (Scheme 5c). On the other hand, the *gem*-disilane **9aa**[17] was also another putative intermediate but not detected at all even when the terminal alkyne **1a** was subjected to otherwise identical conditions without the hydroxylamine: only the terminal alkene **6a** and alkylsilane **7aa** were formed (Scheme 5d). These outcomes suggest the most plausible intermediacy of the vinylsilane.



Scheme 5. Evaluation of potential intermediates.

Based on the aforementioned results, we are tempted to propose that the mechanism of reaction is as follows (Scheme 6a). Initially, the active copper alkoxide species **A** is generated in situ from CuCl, LiO*t*Bu, and the ancillary ligand L. Subsequent σ-bond metathesis with the hydrosilane **2** (**A** to **B**) and insertion of the terminal alkyne **1** form the vinylcopper intermediate **C**, where the regioselectivity is controlled by steric factors and the more bulky copper is located at the terminal position.[19] The second σ-bond metathesis with the hydrosilane **2**[9] and insertion via the vinylsilane-coordinated copper hydride **D** afford the alkylcopper **E**. In the vinylsilane insertion step, hyperconjugation between the Cu–C σ orbital and proximal Si–C σ* orbital can work well to lead to the one regioisomer **E** selectively.[7d,e,20] Final electrophilic amination with the hydroxylamine **3**[21] gives the α-aminosilane **4**, and salt metathesis with LiO*t*Bu regenerates the starting copper alkoxide **A** to complete the catalytic cycle. When using the chiral (*R,R*)-Ph-BPE ligand, the second hydrocupration (**D** to **E**) is the enantioselectivity-determining step, and the corresponding enantioenriched α-silylalkylcopper **E** is eventually transformed into the optically active **4**. The byproducts **6** and **7** observed during the optimization studies could arise from protonolysis of organocopper intermediates **C** and **E**, respectively, while the dissociation of L_nCuH from π-complex **D** produces the vinylsilane **5**. The results of control experiments with deuterium-labeled hydrosilane [D_2]**2a** and terminal alkyne [D]**1a** are also consistent with the proposed mechanism (Scheme 6b).



Scheme 6. a) Plausible mechanism for Cu-catalyzed hydrosilylation/hydroamination sequence of terminal alkynes **1** with hydrosilanes **2** and hydroxylamines **3**; b) deuterium-labeling experiments. L = TMS-dppbz or (*R,R*)-Ph-BPE.

In conclusion, we have developed a copper-catalyzed reductive *gem*-difunctionalization of terminal alkynes with

hydrosilanes and hydroxylamines. The reaction proceeds via hydrosilylation/hydroamination sequence, and the corresponding α-aminosilanes are obtained in a single operation. Additionally, the asymmetric synthesis is also possible to deliver the enantioenriched α-aminosilanes of interest in medicinal chemistry.[22] Improvement of the reaction efficiency as well as enantioselectivity and expansion of this reaction concept to other type alkyne difunctionalizations are currently underway.

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Conflict of Interest

The authors declare no conflict of interest.

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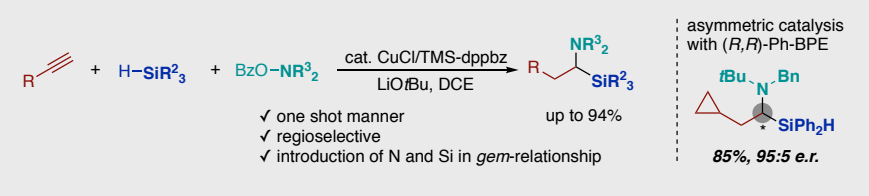

Si(lent) N(ight) in Alkyne: A Cu/TMS-dppbz-catalyzed hydrosilylation/hydroamination cascade of simple terminal alkynes with hydrosilanes and hydroxylamines proceeds chemoselectively to deliver the reductive *gem*-difunctionalization products, α-aminosilanes, in a single operation. Additionally, the chiral (*R,R*)-Ph-BPE ligand makes the reaction asymmetric to directly form the corresponding optically active α-aminosilanes, which are Si mimics of enantioenriched α-amino acids and of interest in medicinal chemistry.

S. Nishino, K. Hirano, M. Miura**

Page No. – Page No.

Cu-Catalyzed Reductive *gem*-Difunctionalization of Terminal Alkynes via Hydrosilylation/Hydroamination Cascade: Concise Synthesis of α-Aminosilanes