Chemistry Letters

# Catalytic Addition Reactions of Alkylazaarenes to Vinylsilanes

Yasuhiro Yamashita, Kodai Minami, and Shū Kobayashi*

Advance Publication on the web March 17, 2018
doi:10.1246/cl.180132

# Catalytic Addition Reactions of Alkylazaarenes to Vinylsilanes

Yasuhiro Yamashita,[1] Kodai Minami [1] and Shū Kobayashi*[1]
[1]*Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033*

E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp

Strong Brønsted-base-catalyzed addition reactions of alkylazaarenes with vinylsilanes are reported. The reactions of alkylpyridines and their analogues with vinylsilanes proceed in moderate to high yields in the presence of catalytic amounts of LiTMP, LiCl, and MS 4Å. This is a general method that can be applied to catalytic addition reactions of alkylazaarenes with vinylsilanes.

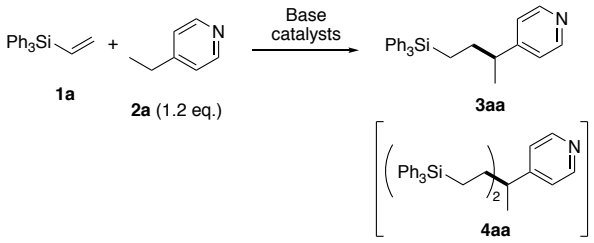
Keywords: Strong base, Alkylazaarene, Vinylsilane

Azaarenes are one of the most common structural motifs in natural products and biologically active compounds, pharmaceuticals, agrochemicals, etc.[1] Accordingly, efficient methods for functionalization of azaarenes are extremely important in organic synthesis, and various kinds of reactions have been reported. Among the large number of azaarenes, pyridine derivatives are the most common family and the most widely exploited.[2] Introduction of carbon units to the α-positions of alkylazaarenes is a useful method to obtain functionalized azaarene derivatives. Catalytic carbon–carbon bond-forming reactions at the α-position of alkylazaarenes have already been investigated.[3] However, most of the catalytic reactions require transition-metal catalysts and high reaction temperature; furthermore, the reaction position is limited to the *ortho*-benzylic C–H bond. Therefore, general methods to functionalize alkylazaarenes at their benzylic positions under mild reaction conditions are highly desired.

Brønsted-base-catalyzed carbon–carbon bond-forming reactions are fundamental and traditional methods in synthetic organic chemistry. The reactions proceed under proton transfer conditions, and they are regarded as an ideal chemical process from an atom economy perspective. However, use of weakly acidic carbon pronucleophiles (p$K_a$ >30 in DMSO) in the Brønsted-base-catalyzed reactions remains limited. Our group recently reported strong Brønsted-base-catalyzed carbon–carbon bond-forming reactions of weakly acidic carbonyl and related compounds as carbon pronucleophiles, where catalytic Mannich-type reactions and 1,4-addition reactions proceeded in high yields with good to high stereoselctivities.[4] Furthermore, quite recently we found that catalytic 1,4-addition reactions of alkylazaarenes proceeded smoothly in a similar fashion.[5] Indeed, although α-hydrogen atoms of alkylazaarenes are not acidic (the hydrogen atom of 4-methylpyridine has p$K_a$ 35 in DMSO),[6] the reactions proceeded well. On the other hand, however, available electrophiles in the system were limited to only *N*-arylimines and α,β-unsaturated carbonyl compounds, and expansion of available electrophiles is highly desired. Vinylsilanes are stable substituted alkenes, and the silyl groups can be converted into several functional groups.[7] The silyl groups are also known to stabilize anions formed at their α-positions; therefore, vinylsilanes can accept nucleophiles at their β-positions more easily than alkyl-substituted alkenes. Catalytic addition reactions of a vinylsilane with alkylpyridines were reported by Pines et al. in 1969;[8,9] however, sodium or potassium metal was employed in these reactions, and a significant amount of byproduct formed under the conditions. General catalytic addition reactions of alkylpyridines to vinylsilanes have not yet been established.[10] Here, we report the results of our studies on the catalytic addition reactions of alkylazaarenes to vinylsilanes under strongly basic catalyst conditions.[11]

We first investigated the catalytic addition reaction of 4-ethylpyridine (**2a**) with triphenylvinylsilane (**1a**) in the presence of 10 mol% potassium hexamethyldisilazide (KHMDS) in diethyl ether ($Et_2O$) at 0 °C (Table 1). Whereas the reaction proceeded sluggishly when only KHMDS was used (entry 1), the desired product **3aa** was obtained in 61%

**Table 1.** Optimization of the reaction conditions[a]



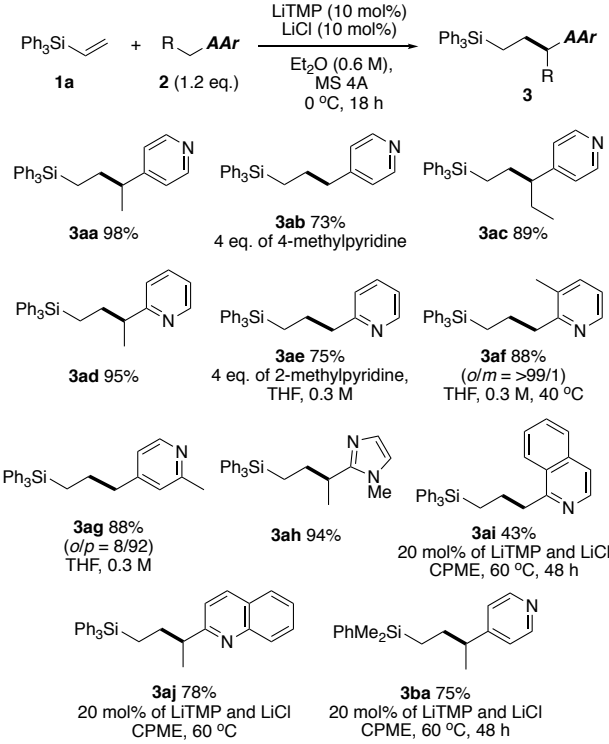

| Entry | Metal amide (mol%) | Additive (mol%) | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | KHMDS (10) | – | $Et_2O$ | 3 |
| 2 | KHMDS (10) | 18-crown-6 (11) | $Et_2O$ | 61[c] |
| 3 | LiTMP (10) | – | $Et_2O$ | 63 |
| 4 | LDA (10) | – | $Et_2O$ | 59 |
| 5 | LiHMDS (10) | – | $Et_2O$ | 0 |
| 6 | LiTMP (10) | – | THF | 60 |
| 7 | LiTMP (10) | – | CPME | 57 |
| 8 | LiTMP (10) | – | toluene | 52 |
| 9 | LiTMP (10) | LiCl (10) | $Et_2O$ | 84 |
| 10 | LiTMP (10) | LiCl (10), MS 4Å | $Et_2O$ | quant. (98)[d] |
| 11 | LiTMP (10) | MS 4Å | $Et_2O$ | 68 |
| 12 | LiTMP (5) | LiCl (5), MS 4Å | $Et_2O$ | 79 |

[a] The reaction of **1** (0.30 mmol) with **2** (0.36 mmol) was performed in 0.6 M at 0 °C for 18 h under Ar atmosphere unless otherwise noted. [b] The yield was determined by $^1$H NMR analysis using durene as internal standard. [c] Double adduct **4aa** (10%) was obtained. [d] Isolated yield.

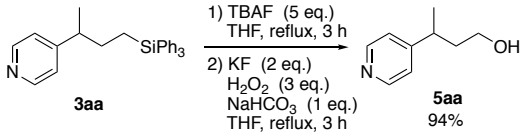
yield by using KHMDS and 18-crown-6 ether; however, undesired byproduct **4aa** was obtained in a significant amount (entry 2). On the other hand, remarkably, lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was found to promote the reaction effectively in the absence of a crown ether without formation of **4aa** (entry 3). Other lithium amides, namely lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LiHMDS), were also employed as catalysts. Whereas LDA showed almost the same reactivity (entry 4), LiHMDS did not catalyze the reaction at all because of its lower Brønsted basicity (entry 5). The effect of solvents was then examined. Slightly lower yield was obtained when a less polar solvent, toluene, was used, but the use of alternative ether solvents THF and cyclopentyl methyl ether (CPME) gave almost the same results as obtained with $Et_2O$ (entries 6–8). Interestingly, it was found that addition of a lithium salt improved the yield; thus, when 10 mol% lithium chloride (LiCl) was used, an increased yield of 84% was obtained (entry 9). LiCl might affect an aggregation state of LiTMP to enhance its reactivity.[12] Further improvement of the yield was achieved by using molecular sieves 4Å (MS 4Å), and the desired adduct was obtained in 98% isolated yield (entry 10). The combined use of LiCl and MS 4Å was essential (entry 11). A good yield was also obtained when the catalyst loading was decreased to 5 mol% (entry 12). It was thus established that the LiTMP–LiCl–MS 4Å system promoted the desired addition reaction effectively without formation of byproduct **4aa**.

The substrate scope of the addition reaction was then examined (Table 2). When 4-methylpyridine (**2b**, 4-picoline) was used as azaarene instead of 4-ethylpyridine, the desired reaction proceeded, but formation of the double adduct was observed. A good yield of the product **3ab** was obtained when 4 equivalents of the pyridine **2b** was used to suppress the side reaction. 4-Propylpyridine (**2c**) also worked well to afford **3ac** in high yield. Next, 2-alkylpyridines were examined as pronucleophiles. When 2-ethylpyridine (**2d**) was employed, the reaction proceeded in high yield to afford the product **3ad**. In the reaction of 2-methylpyridine (**2e**), the use of 4 equivalents of **2e** was also effective to suppress byproduct formation, and the desired product **3ae** was obtained in good yield. Regioselective reactions were then investigated. When 2,3-dimethylpyridine (**2f**) was used as pronucleophile, the desired reaction proceeded only at the 2-methyl group to afford **3af** in high yield. The selectivity could be explained based on much more acidic nature of an α-hydrogen atom of the 2-methyl group than that of the 3-methyl group due to different stabilization pattern of the formed anion via delocalization after deprotonation. Furthermore, when 2,4-dimethylpyridine **2g** was used, the reaction proceeded with high regioselectivity at the 4-position to afford the product **3ag**. That is also because α-hydrogen atom of the 4-methyl group could be more acidic than that of 2-methyl group.[13] Other types of alkylazaarenes were then employed. 2-Ethyl-1-methylimidazole (**2h**) reacted with **1a** to afford the product **3ah** in high yield. When 1-methylisoquinoline (**2i**) and 2-ethylquinoline (**2j**) were used, the reactivities were decreased in both cases, and the desired products **3ai** and **3aj** were obtained in moderate to good yields. Other vinylsilanes were then examined. The reaction of **2a** with dimethylphenylvinylsilane (**1b**) proceeded in good yield under heating conditions because of the low reactivity of **1b**. The number of phenyl groups on the silicon atom might affect the stabilizing ability of the α-anion and influenced the total reactivity. It was found that many alkylazaarenes could be employed for the catalytic addition reactions with vinylsilanes in the presence of the LiTMP catalyst system.

**Table 2.** Scope of the reaction with respect to alkylazaarenes




The obtained product was converted into alcohol **5aa** under oxidative conditions (Scheme 1). By treating **3aa** with tetrabutylammonium fluoride (TBAF) and subsequently with KF and $H_2O_2$, the silyl group was oxidized to afford **5aa** in high yield. The pyridine nitrogen atom was not oxidized under the reaction conditions.




**Scheme 1** Transformation of **3aa**

In conclusion, strong Brønsted-base-catalyzed addition reactions of alkyl azaarenes with vinylsilanes were developed. The reactions of alkylpyridines and their analogues with vinylsilanes proceeded in moderate to high yields in the presence of catalytic amounts of LiTMP, LiCl, and MS 4Å. This is a general method to perform catalytic addition reactions of alkylazaarenes with vinylsilanes. The

triphenylsilyl group was successfully converted into a hydroxyl group under oxidative conditions without any effect on the pyridine nitrogen atom. Further studies on reactions with other alkenyl compounds as well as asymmetric catalysis are ongoing.

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS) and Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the Japan Science and Technology Agency (JST).

Supporting Information is available on http://dx.doi.org/10.1246/cl.

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