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Synthesis of Aryl Amine Derivatives from Benzyl Nitriles via Electrocyclization of in Situ Generated *N*-Silyl Ketene Imines

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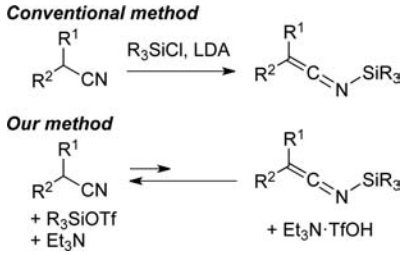
Supporting Information

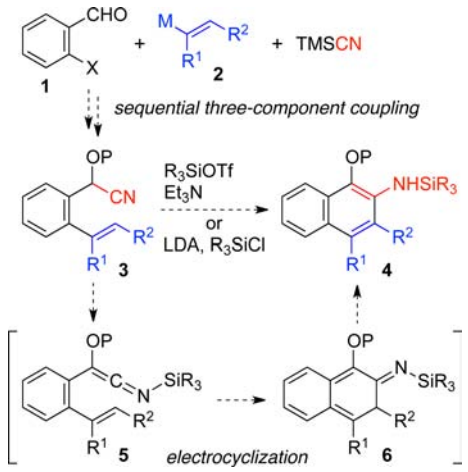
ABSTRACT: The previously unexplored reactivity of *N*-silyl ketene imines in organic synthesis is reported. Benzyl nitriles containing an alkenyl or aryl group at the *ortho* position were smoothly converted into aryl amines in good yields under two sets of mild silylation conditions: (1) nonbasic conditions using $TMSNTf_2$–iPr_2NEt or (2) basic anionic conditions using lithium diisopropylamide–triisopropylsilyl chloride (LDA–TIPSCl). The reaction probably proceeds via in situ generation of an *N*-silyl ketene imine followed by 6π-electrocyclization and aromatization.

N-Silyl ketene imines, nitrile analogues of silyl ketene acetals, have recently attracted attention as suitable α-cyano carbanion equivalents because they react with electrophiles under mild reaction conditions.[1] These species are typically prepared from alkanenitriles via treatment with a bulky trialkylsilyl chloride and a strong base such as lithium diisopropylamide (LDA) (Scheme 1).[2] In sharp contrast to silyl ketene acetals, which are extensively used in organic synthesis,[3] *N*-silyl ketene imines have had limited application in organic synthesis because of the handling difficulties arising from their high tendency to undergo hydrolysis.[1] However, we found that *N*-silyl ketene imines could be generated in situ from nitriles under mild, nonbasic conditions, i.e., treatment with R_3SiOTf–Et_3N.[4] This finding allowed the development of two carbon–carbon bond-forming reactions of nitriles that did not require isolation of labile *N*-silyl ketene imines, namely, tandem *N*-silyl ketene imine formation–intramolecular conjugate addition[4a] and tandem *N*-silyl ketene imine formation–Mannich-type reactions.[4b] Previous synthetic studies on *N*-silyl ketene imines have focused mainly on aldol reactions, Mannich reactions, acylation, and conjugate addition;[1,4] however, their synthetic potential in pericyclic reactions remains unexplored, with only one Diels–Alder reaction with an alkynyl ester having been disclosed.[5] Herein, we report the novel reactivity of *N*-silyl ketene imines in pericyclic reactions, specifically in 6π-electrocyclization, to produce aryl amine derivatives. To the best of our knowledge, this is the first successful application of an *N*-silyl ketene imine to 6π-electrocyclization.

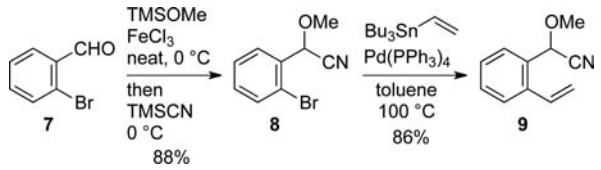
Scheme 1. Generation of *N*-Silyl Ketene Imines from Alkanenitriles



Scheme 2. Electrocyclization Strategy for the Synthesis of Aryl Amines from Benzyl Nitriles



Scheme 3. Synthesis of Nitrile 9



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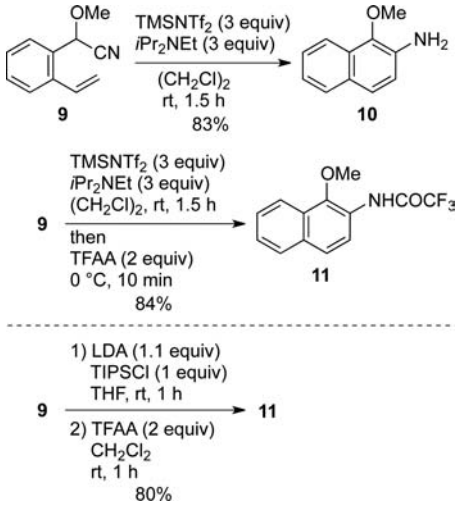
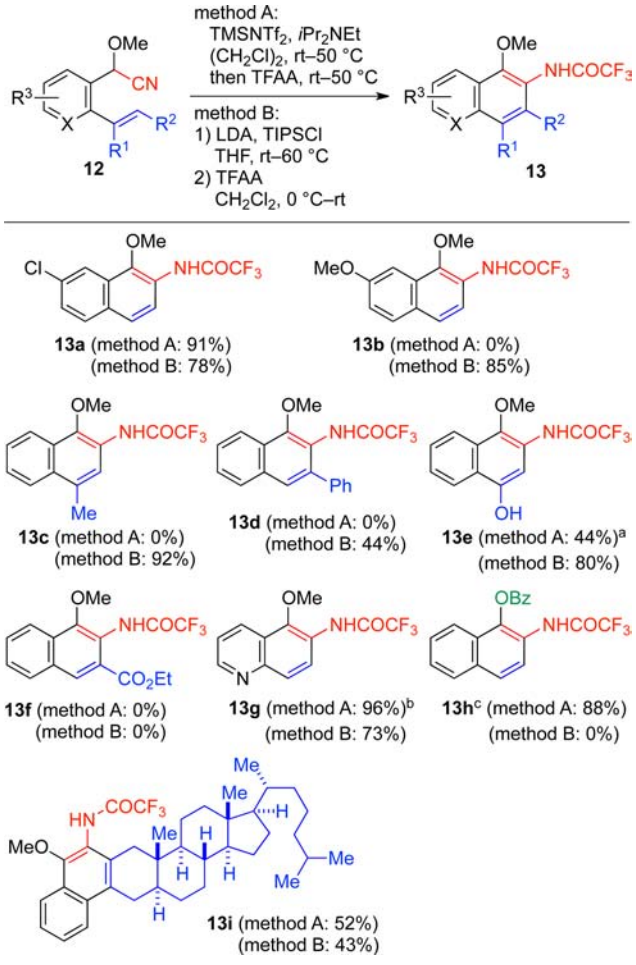
Scheme 4. Optimized Cyclization Conditions



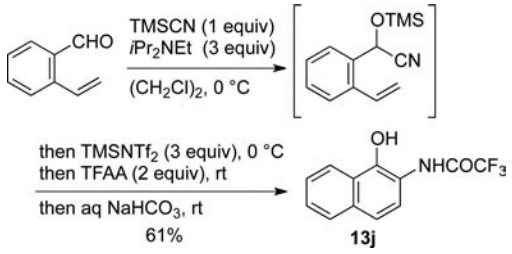
Scheme 5. Substrate Scope



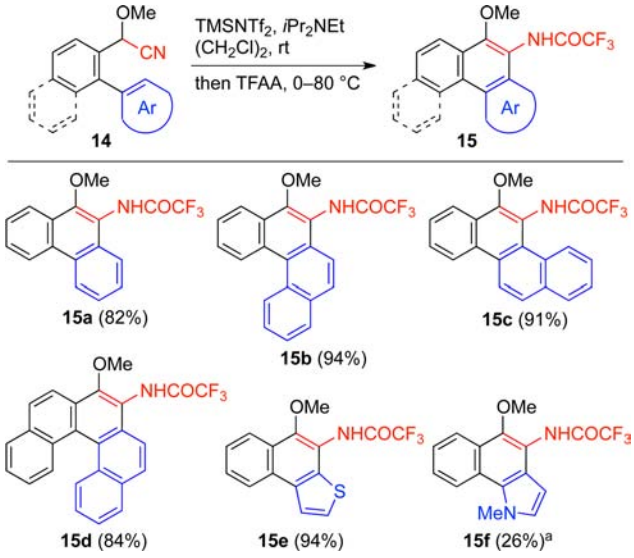
[a]NMR yield. [b]Two-step yield in a stepwise procedure. [c]*O*-Benzoylcyanohydrin was used as a substrate.

We envisaged that under *N*-silyl ketene imine generation conditions (our $R_3SiOTf–Et_3N$ system or the conventional $R_3SiCl–LDA$ system) aryl amines **4** would be directly produced from benzyl nitriles **3**, which bear an alkenyl group at the *ortho* position, via the in situ generation and subsequent 6π-electrocyclization of *N*-silyl ketene imine **5**, followed by aromatization of the resulting imine **6** (Scheme 2).[6] Because a variety of benzyl nitriles **3** could be synthesized by the sequential three-component coupling reactions of 2-halobenzaldehydes **1** with alkenyl metal species **2** and TMSCN, this process would provide a versatile synthetic method for aryl amine derivatives that are ubiquitous in a wide range of biologically active compounds, anion sensors, and dyes.[7]

Scheme 6. Direct Conversion of *o*-Vinylbenzaldehyde to Hydroxy Naphthylamine



Scheme 7. Application to the Synthesis of Polycyclic Aryl and Heteroaryl Amines



[a]78% yield with the LDA–TIPSCl system.

To test the above hypothesis, we began with the reaction of nitrile **9** as a model substrate. This compound was synthesized in two steps from 2-bromobenzaldehyde (**7**) by cyanohydrin methyl ether formation[8] followed by Stille coupling[9] with tributyl(vinyl)stannane (Scheme 3).

With nitrile **9** in hand, we initially examined its cyclization under our nonbasic conditions[4] for the generation of *N*-silyl ketene imines. Through optimization of the reaction conditions (silylating agents, tertiary amines, and temperatures), it was found that the cyclization of **9** upon treatment with $TMSNTf_2$[10] (3 equiv) and iPr_2NEt (3 equiv) in dichloroethane at room temperature proceeded smoothly to give aryl amine **10** in 83% yield (Scheme 4; for details of the optimization, see Table S1 in the Supporting Information).[11] The use of $TMSNTf_2$ as a silylating agent was critical to this reaction, and the use of an excess of reagents was also indispensable, probably because of competing silylation of the resulting amino group. Although **10** could be isolated after purification by column chromatography, this type of amine was slightly labile to air and silica gel (i.e., easily

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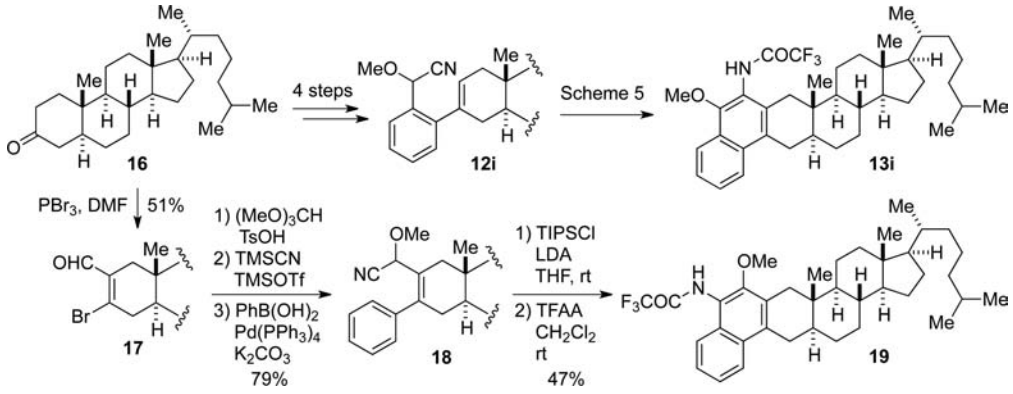
Scheme 8. Cyclization of Allyl Nitrile 18



colored); hence, the resulting amino group was converted into its more stable trifluoroacetamide. The optimized protocol for the conversion of **9** to trifluoroacetamide **11** was as follows. Cyclization of **9** was performed with $TMSNTf_2$ (3 equiv) and iPr_2NEt (3 equiv) in dichloroethane. After verifying the disappearance of **9** by TLC analysis, TFAA (2 equiv) was added to the reaction mixture in one-pot to give **11** in 84% yield. To confirm the reaction mechanism, we also attempted to monitor the reaction of **9** by ^1H NMR. Unfortunately, we could not detect the *N*-silyl ketene imine intermediate,[12,13] which indicated that electrocyclization proceeds spontaneously at room temperature.

Additionally, nitrile **9** underwent cyclization under conventional basic anionic *N*-silyl ketene imine formation conditions, namely, a two-step protocol which involves cyclization using LDA (1.1 equiv) and triisopropylsilyl chloride (TIPSCl) (1 equiv) followed by amidation of the resulting amino group with TFAA (2 equiv) (Scheme 4; for details of the optimization, see Table S2 in the Supporting Information).

With two sets of cyclization conditions in hand (method A: nonbasic $TMSNTf_2$–iPr_2NEt system; method B: basic LDA–TIPSCl system), we then explored the scope with a series of benzyl nitriles **12a**–**i** (Scheme 5). Similar to the synthesis of **9**, these compounds were prepared from *o*-bromobenzaldehyde derivatives by cyanohydrin methyl ether formation and Pd-catalyzed cross-coupling reaction with alkenyl organometallic species or Mizoroki–Heck reaction with ethyl acrylate.[14] Substrates containing an electron-withdrawing group, e.g., chloro, on the aromatic ring gave naphthylamine **13a** in good yields by both methods. Substrates containing an electron-donating group, such as a methoxy group, or a substituent group at the alkenyl group afforded the products (**13b**, **13c**, **13d**) only by method B, while method A led to decomposition of the substrates.[15] The silyl enol ether generated in situ from the corresponding methyl ketone could be used as an alkenyl component in 6π-electrocyclization (cf. **12e**), affording hydroquinone mono methyl ether **13e** in 80% yield by method B. In contrast, the reaction of nitrile **12f**, which contains an α,β-unsaturated ester moiety, did not proceed by either method, and complex mixtures containing a small amount of **12f** were obtained. The presence of a pyridine ring did not affect cyclization by either method (**12g**). Base-sensitive *O*-benzoyl cyanohydrin **12h** underwent cyclization only by method A. Cyclization of the benzyl nitrile derived from steroid (cf. **12i**) produced naphthylamine-fused steroid **13i** in moderate yields by both methods. In addition, an aryl amine derivative containing a free hydroxy group was directly accessible from *o*-vinylbenzaldehyde through the one-pot quadruple reaction sequence, i.e., cyanation–electrocyclization–amidation–deprotection (Scheme 6).

Next, using the one-step $TMSNTf_2$–iPr_2NEt cyclization protocol, various biaryl nitriles **14a**–**f**[14] were tested for their utility in the synthesis of polycyclic aryl and heteroaryl amines because these skeletons are important motifs in materials science (Scheme 7).[16] Gratifyingly, phenanthrene amine **15a**, benzo[*c*]-phenanthrene amine **15b**, and chrysene amine **15c** were all obtained in high yields. Cyclization of binaphthyl **14d** afforded the helicene compound, i.e., dibenzo[*c*,*g*]phenanthrene amine **15d** in 84% yield. In addition to aryl groups, heteroaryl groups such as thiophene (**14e**) and pyrrole (**14f**) could be used as π-components in this reaction, resulting in the smooth formation of naphtho[2,1-*b*]thiophene amine **15e** and benzo[*g*]indole amine **15f**, respectively. Notably, the formation of an indole skeleton was achieved from phenylpyrrole **14f** by 6π-electrocyclization. Thus, the wide variety of aryl amine derivatives that can be readily accessed demonstrates the potential utility and versatility of our method.

Note that an allyl nitrile derivative as well as a benzyl nitrile derivative could be used in the cyclization (Scheme 8). Thus, steroidal allyl nitrile **18**, which was synthesized in four steps from the commercially available ketone **16**, underwent cyclization to afford naphthylamine-fused steroid **19** with the basic LDA–TIPSCl system.[17] Considering that the reaction of benzyl nitrile **12i**, which was also accessed from **16**, provided aryl amine **13i** (cf. Scheme 5), a regiodivergent strategy to fuse the naphthylamine unit at a cyclic ketone was established.

Conventional synthetic methods for aryl amine derivatives,[18] exemplified by aromatic substitution or cross-coupling reactions including Buchwald–Hartwig coupling and Ullmann–Goldberg reactions, suffer from substrate limitation, and multistep reactions are often required to access the substrates, especially for the synthesis of polysubstituted or polycyclic aryl amines. Our method, on the other hand, offers a convenient alternative route to these compounds.

In conclusion, we have developed a novel method for the synthesis of aryl amine derivatives from benzyl nitriles bearing an alkenyl or aryl group at the *ortho* position; the reaction proceeds via in situ generation of an *N*-silyl ketene imine intermediate, followed by 6π-electrocyclization and subsequent aromatization. Because a variety of substrates are readily accessible and the cyclization proceeds in good yield under suitable reaction conditions (a nonbasic $TMSNTf_2$–iPr_2NEt system or basic LDA–TIPSCl system), our methodology is a useful tool for the synthesis of functionalized aryl and heteroaryl amines, including

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polycyclic aryl amines, that are difficult to access by conventional methods.

■ ASSOCIATED CONTENT

Supporting Information

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Optimization of the cyclization conditions, experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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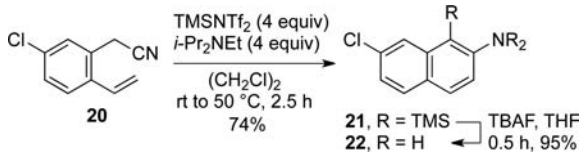
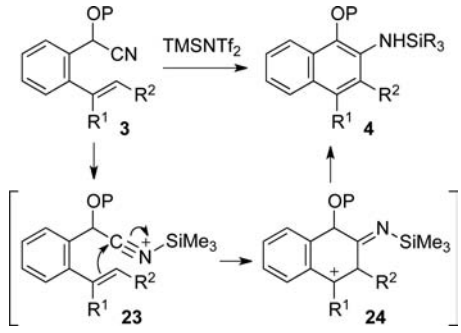
(11) Because Japanese industrial safety and health law prohibits the manufacture of 2-naphthylamine due to its carcinogenicity, we used cyanohydrin methyl ether **9** as a substrate in this investigation. We also examined the cyclization of benzyl nitrile **20**, which resulted in the formation of aryl amine **22** after desilylation with TBAF, as shown below. Thus, oxygen functionality at the α-position of the cyano group is not mandatory for 6π-electrocyclization.



(12) Because $TMSNTf_2$ solely promoted the cyclization of nitrile **9** to **10**, albeit at high temperature (Table S1 in the Supporting Information), an alternative reaction mechanism involving the cationic cyclization of nitrilium ion **23**, as shown below, cannot be ruled out.



(13) As a model, we monitored the reaction of 2-methoxy-2-phenylacetonitrile with $TMSNTf_2$ (1 equiv) and iPr$_2$NEt (1 equiv) in $CDCl_3$ (0.05 M) at rt to 50 °C by ^{1}H and ^{13}C NMR. The corresponding *N*-silyl ketene imine was not detected, probably due to the low concentration of it, which arose from the reversible formation of *N*-silyl ketene imines under equilibrium conditions (see also Scheme 1).[4b]

(14) For details of the synthesis of substrates, see the Supporting Information.

(15) Failure of reactions of **12b**, **12c**, and **12d** by method A might be due to the competitive degradation pathway via the benzyl cation species (cf. **24**)[12] in the cationic cyclization mechanism.

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(17) The yield was <27% yield with the nonbasic $TMSNTf_2$–iPr$_2$NEt system.

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