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Cyclization

Cyano-Schmittel Cyclization through Base-Induced Propargyl-Allenyl Isomerization: Highly Modular Synthesis of Pyridine-Fused Aromatic Derivatives

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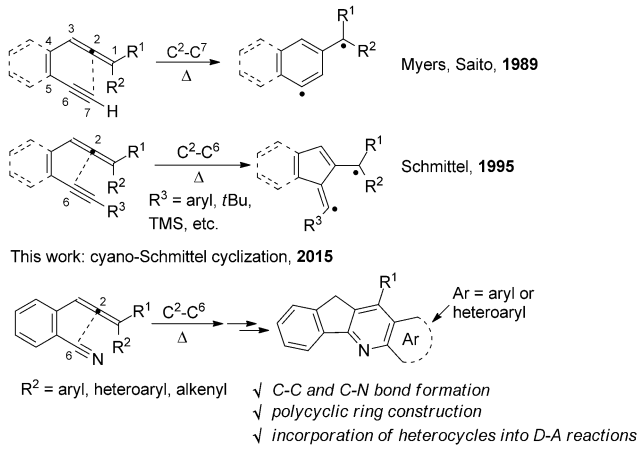
Abstract: The cyano-Schmittel cyclization of in situ-generated cyano-allenes has been carried out. The DFT calculation results suggest that the diradical pathway plays a major role in this cyclization. The reactions can be conveniently performed in a one-pot manner through cascade Sonogashira coupling of terminal cyano-ynes with organic halides, followed by base-promoted propargyl-allenyl isomerization/cyclization, leading to an efficient access to pyridine-fused polycyclic architectures. In particular, a large variety of aryl or heteroaryl rings such as furans, thiophenes and pyridines can be incorporated into the follow-up cyano-Diels–Alder reactions, highlighting the great synthetic utility of this chemistry.

Introduction

Thermal cycloaromatizations of enediynes[1] and enyne-allenes[2,3] have attracted much attention over the last two decades due to their fundamentally intriguing reaction mechanism and potential medical applications, such as in the design of antitumor antibiotic agents.[4] Theoretical and experimental studies revealed that these reactions proceed mainly via diradical intermediates.[5] Two different processes, namely, Myers–Saito (C^2—C^7)[2] and Schmittel (C^2—C^6)[3] cyclizations, are usually involved in enyne–allene systems, which depend on the nature of the substituents on alkyne terminus (Scheme 1). The synthetic potential of these thermal enyne–allene cyclizations has been extended to their hetero-analogues. Most of the studies focused on heteroatom substitution on the allene moiety, such as enyne–ketenes,[6a,b] enyne–carbodiimides,[6c,d] enyne–ketenimines[6e] and enyne–isocyanates,[6f] whereas little attention has been paid to modification of the alkyne moiety. It is expected that if the alkyne moiety in enyne–allenes is replaced by a nitrile functionality, cycloaromatization of the resulting cyano-allenes might also be a feasible transformation; however, such reactions are quite rare. The development of such transformations would be of great interest for the synthesis of polyfused heterocycles through C–C and C–N bond formation. Earlier reports indicated that thermal reactions of (*Z*)-2,4,5-hexatrienenitriles failed to provide the desired pyridine products even at high reaction temperatures of 150–260 °C.[7] A cyano Myers-type cyclization of the in situ-formed cyano-allenyl sulfone to isoquinoline has been reported; however, only one example was described with <20% yield.[8] Wang et al.[9a] reported that cycloaddition of cyano and arylallenes formed in situ could be used for the synthesis of the parent ring cores of camptothecin; however, the reaction was restricted to 2(1*H*)-pyridone-bridged system.[9a,b] Recently, Danheiser et al. found that thermolysis of cyanodiynes at 140–200 °C could afford substituted pyridines, which involves an intramolecular Diels–Alder reaction between in situ-generated vinylallene and nonconjugated cyano group.[9c] In this paper, we report a successful example of Schmittel-type cyclization of cyano-involved aza-enyne-allenes. Our work disclosed that thermal cycloaddition of cyano-allenes could be a common and general reaction pattern, which may become an ideal and important protocol for the construction of pyridine rings. Remarkably, it is also interesting



Scheme 1. Thermal cyclization of enyne–allenes and cyano-allenes.

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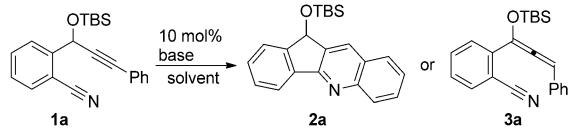
to find that not only aryl groups but also heteroaryl groups such as furans, thiophenes, and pyridines can be incorporated into the follow-up cyano-Diels–Alder reactions successfully to furnish the fused products, which greatly expands the scope and the synthetic utility of this chemistry.[10] It is noted that there is no report for cyano-Diels–Alder reactions in which a heteroaryl ring acts as a part of the diene.

Results and Discussion

In the course of our research on transition-metal-catalyzed transformation of functionalized alkynes, we occasionally found that *o*-(cyano)phenyl propargyl ether **1a** cyclized smoothly in the presence of a base only without the need of metal catalysts. The product was identified as indeno[1,2-*b*]quinoline **2a** (Table 1). The results indicated that a cycloaddition involving phenyl-yne and cyano moiety was efficiently achieved, although the process might be accompanied with a temporary disruption of aromaticity. The unique reaction mode and potential bioactivity of indenoquinolines[11] prompted us to investigate this reaction in detail under various conditions. The results are summarized in Table 1. For example, heating a solution of **1a** in toluene in the presence of 10 mol% Cs_2CO_3 or KO*t*Bu afforded **2a** in 92% and 82% yields, respectively (Table 1, entries 1 and 2). However, the use of K_2CO_3 or DABCO as the base either could not afford the desired product, or gave **2a** in low yield (entries 3 and 4). A catalytic amount of Et_3N appeared to be less effective (entry 5); however, when Et_3N was used as the solvent, **2a** could be formed quantitively (entry 6). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) also proved to be an efficient catalyst for this reaction, leading to **2a** in 93% yield (entry 7). The reaction could also be performed in 1,2-dichloroethane (DCE) or THF, providing **2a** in 95% and 74% yields, respectively (entries 9 and 10). Interestingly, the reaction of **1a** with 10 mol% DBU at room temperature for 40 min afforded the cyano-allene **3a**, which was generated through base-catalyzed propargyl-allenyl isomerization[9a,b,12] in 98% yield (entry 11). Compound **3a** was relatively stable at room temperature, and could be isolated in a pure form. KO*t*Bu could also induce the isomerization of **1a** to **3a** efficiently at −78 °C (entry 12). These experiments indicated that the formation of cyano-allene **3a** was the initial step in this cascade reaction, and possibly **3a** was an intermediate leading to **2a** through formal [4+2] cycloaddition. Without the base, the reaction did not take place even after heating the mixture at 180 °C for 6 h, implying that the reaction proceeded exclusively through the allenic intermediate. It is known that the cyano group rarely participates in the electrocyclization reactions as an enophile or dienophile such as in Diels–Alder reactions.[9,13] There are few reports of the [4+2] cycloaddition of nitriles with 1,3-dienes, which usually require harsh conditions[13a,b] or are restricted to activated nitriles bearing electron-withdrawing groups.[13c,d] Thus, this new finding may serve as an attractive synthetic strategy for the synthesis of heterocycles from unactivated nitriles.

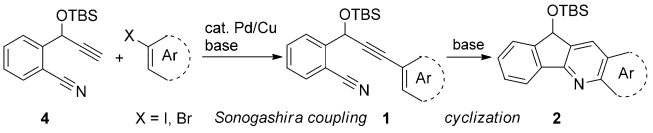
Table 1. Formation of indenoquinoline **2a** and cyano-allene **3a** catalyzed by base.



Entry	Base	Solvent	Temp [°C]	Time	Yield[a] of **2a** [%]	Yield[a] of **3a** [%]
1	Cs_2CO_3	toluene	80	18 h	92	–
2	KO*t*Bu	toluene	80	8 h	82	–
3	K_2CO_3	toluene	80	6 h	–(98)	–
4	DABCO	toluene	80	18 h	25 (75)	–
5	Et_3N	toluene	80	18 h	6 (93)	–
6	–	Et_3N	80	12 h	98	–
7	DBU	toluene	80	6 h	93	–
8	DBU	toluene	50	18 h	31	–
9	DBU	DCE	80	5 h	95	–
10	DBU	THF	80	9 h	74	–
11	DBU	toluene	RT	40 min	–	98
12	KO*t*Bu	THF	−78	10 min	–	95
13	–	toluene	180	6 h	–(100)	–

[a] Yields are of isolated products. The yields of the recovered **1a** are shown in parentheses.

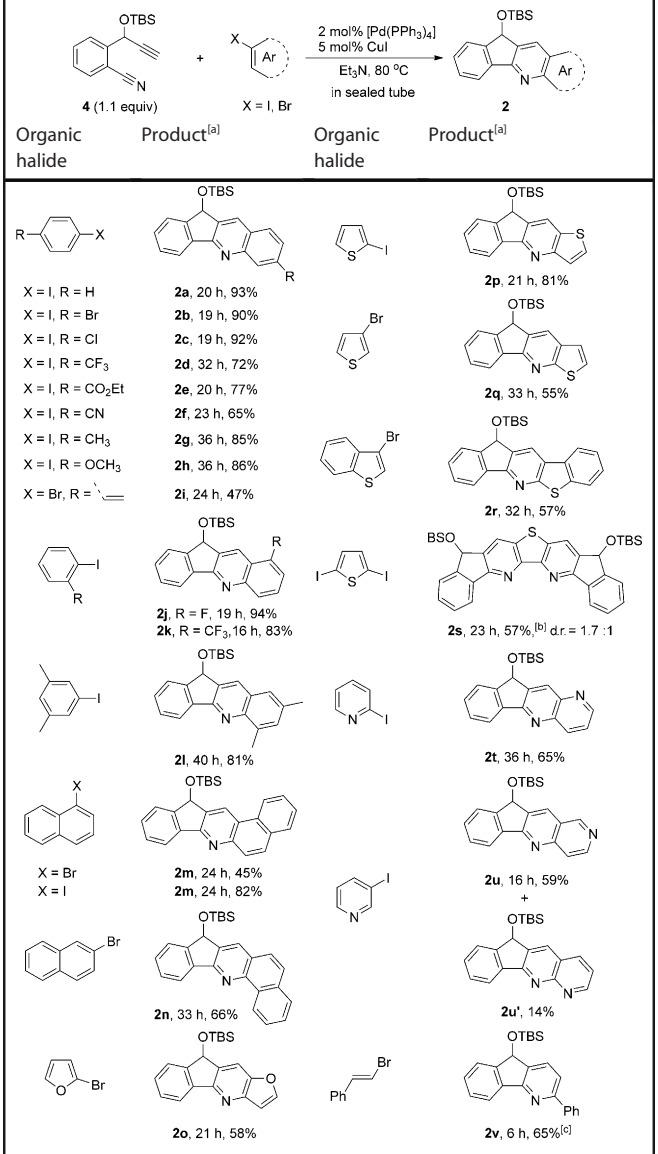
During the study of the generality and scope of the reaction, we became interested in developing a more direct route to indenoquinolines from readily available precursors of terminal alkyne **4** and organic halides through a cascade Sonogashira coupling/cycloaddition process shown in Scheme 2, which would greatly enhance the efficiency of the synthesis by avoiding the isolation of internal alkyne **1**.



Scheme 2. One-pot synthesis of indenoquinolines from terminal alkyne **4** and organic halides.

After detailed optimization of the catalysts and solvents, we were delighted to find that the use of 2 mol% of $[Pd(PPh_3)_4]$ and 5 mol% of CuI with Et_3N as the solvent gave very good results. The results are summarized in Table 2. The present method could be applied successfully to a wide variety of aryl/heteroaryl halides and alkenyl halides. Aryl iodides, when bearing electron-withdrawing or electron-donating groups on the aryl rings, all reacted well with **4**, providing the cyclized products **2b**–**2l** in good to excellent yields. The functionalities such as *p*-Br, *p*-Cl, *p*-CF_3, *p*-CO_2Et, *p*-CN, *p*-Me, *p*-MeO, *o*-F, and *o*-CF_3 were well tolerated during the reaction, leading to **2b**–**2h** and **2j**–**2k** in 65–94% yields. Aryl bromide bearing a vinyl group on the aryl ring was also compatible, furnishing **2i** in 47% yield, while the vinyl group remained intact. The sterically demanding substrates, such as 1-iodo-3,5-dimethylbenzene, also worked well to furnish **2l** in 81% yield. In this case, a longer

Table 2. One-pot synthesis of polycycles **2** from terminal alkyne **4** and organic halides.

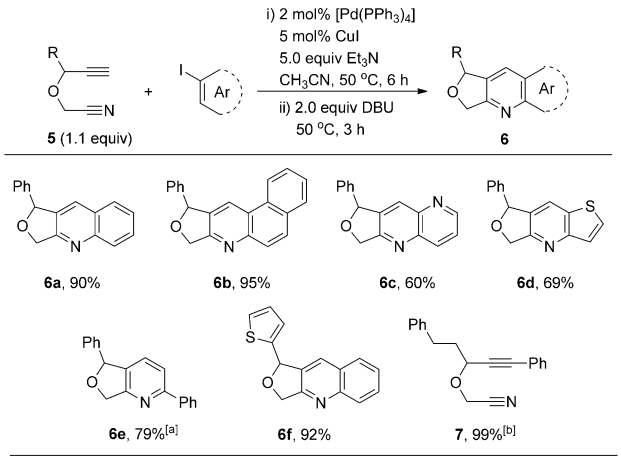


[a] Yields are of isolated products. [b] The reaction was carried out in Et_3N/toluene using 2.2 equiv of **4**, 5 mol% $[Pd(PPh_3)_4]$ and 5 mol% CuI. [c] Desilylated product was also obtained in 30% yield.

reaction time of 40 h was required. However, the use of 2-iodo-1,3,5-trimethylbenzene only afforded a complex mixture at 80 °C. 1-Bromo- or 1-iodo-naphthalene were also suitable for this reaction, and in the latter case, the desired product **2m** was obtained in higher yield of 82%, possibly due to the higher reactivity of iodide in the Sonogashira reaction. In the case of 2-bromonaphthalene, two regioisomers might be formed by cyclization through its C-1 or C-3 position. However, only one regioisomer **2n** was obtained in 66% yield, indicating that C–N bond formation occurred selectively at the C-1 position of the naphthyl substituent.

Heteroacenes bearing furan or thiophene rings constitute one of the most common classes of small-molecular electronic materials.[14] Our method could be readily extended to furanyl or thienyl halides, leading to furan or thiophene-fused products **2o**–**2s** in 55–81% yields. When 2-iodothiophene or 3-bromothiophene were employed, the reaction proceeded smoothly to give **2p** and **2q** with the *anti* or *syn*-fused thiophene rings in 81% and 55% yields, respectively. The results further demonstrated the diversity and flexibility of this method, because different types of polycyclic heterocycles could be easily constructed just by changing the halide position in heteroaryl halide substrates. Interestingly, the use of 2,5-diiodothiophene gave **2s**, featuring seven-fused carbo- and heterocyclic rings, in 57% yield, which might find utilities in materials science. Interestingly, 2-pyridyl iodide also turned out to be an effective substrate for this reaction to give **2t** in 65% yield, in which the pyridyl group was successfully embedded in a naphthyridine framework. It should be noted that the pyridine ring rarely undergoes the [4+2] cycloaddition reaction due to its low reactivity.[10a, 12d] The reaction of 3-iodopyridine with **4** afforded a mixture of two regioisomers **2u** and **2u'** in 59% and 14% yields, respectively, indicating that both of the C-2 and C-4 position of 3-iodopyridine are reactive during the reaction. The alkenyl bromide (*E*)-bromostyrene was well-accommodated, leading to 5*H*-indeno[1,2-*b*]pyridine **2v** in 65% yield, along with 30% of desilylated product. The structures of indenoquinolines were unambiguously confirmed by X-ray crystallography of **2a**, **2b**, **2n**, and **2t**.[15]

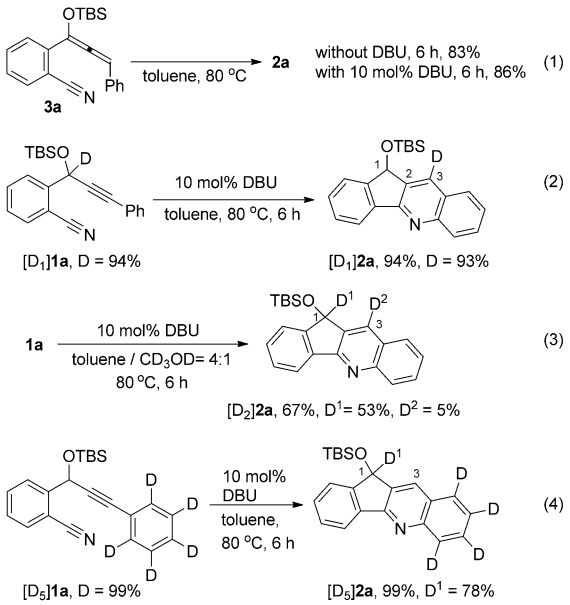
We next explored the possibility of the cascade reactions between linear-type cyano-ynes such as 4-oxa-1-cyano-6-yne **5** with organic halides (Scheme 3). However, under similar conditions to the one-pot synthesis of **2**, only the product derived from Sonogashira coupling was observed. After many efforts, we found that if the reaction was carried out in a stepwise manner by first achieving Pd-catalyzed Sonogashira reaction in Et_3N/CH_3CN, followed by addition of **2** equiv of DBU, the desired quinoline product **6** could be formed in good to excellent yields. The reaction also showed excellent scope with re-



Scheme 3. One-pot synthesis of polycycles **6** from 4-oxa-1-cyano-6-yne **5** and organic halides.Yields are of isolated products. [a] (*E*)-β-Bromostyrene was used. [b] The second step was carried out at 80 °C for 5 h.

spect to aryl/heteroaryl halides, as well as alkenyl bromides. Varying the substituent at the propargylic position with an alkyl group led to the formation of only the coupled product **7**, and no desired cyclization product was observed, possibly due to the fact that the allenic intermediate could not be formed efficiently in this case. The results indicate that the presence of an aryl substituent at the propargylic position is crucial for successful transformation.

To understand the reaction mechanism, various control experiments were carried out. We first investigated the thermal behavior of the isolated cyano-allene **3a**. Heating a solution of **3a** in toluene at 80 °C for 6 h afforded the desired indenoquinoline **2a** with a lower yield of 83% (compared to the results shown in Table 1, entry 7). The lower yield for **2a** may result from the instability of **3a**. In the presence of 10 mol% DBU, a similar reaction rate and yield to **2a** were observed (Scheme 4, [Eq. (1)]), indicating that DBU did not play a role in



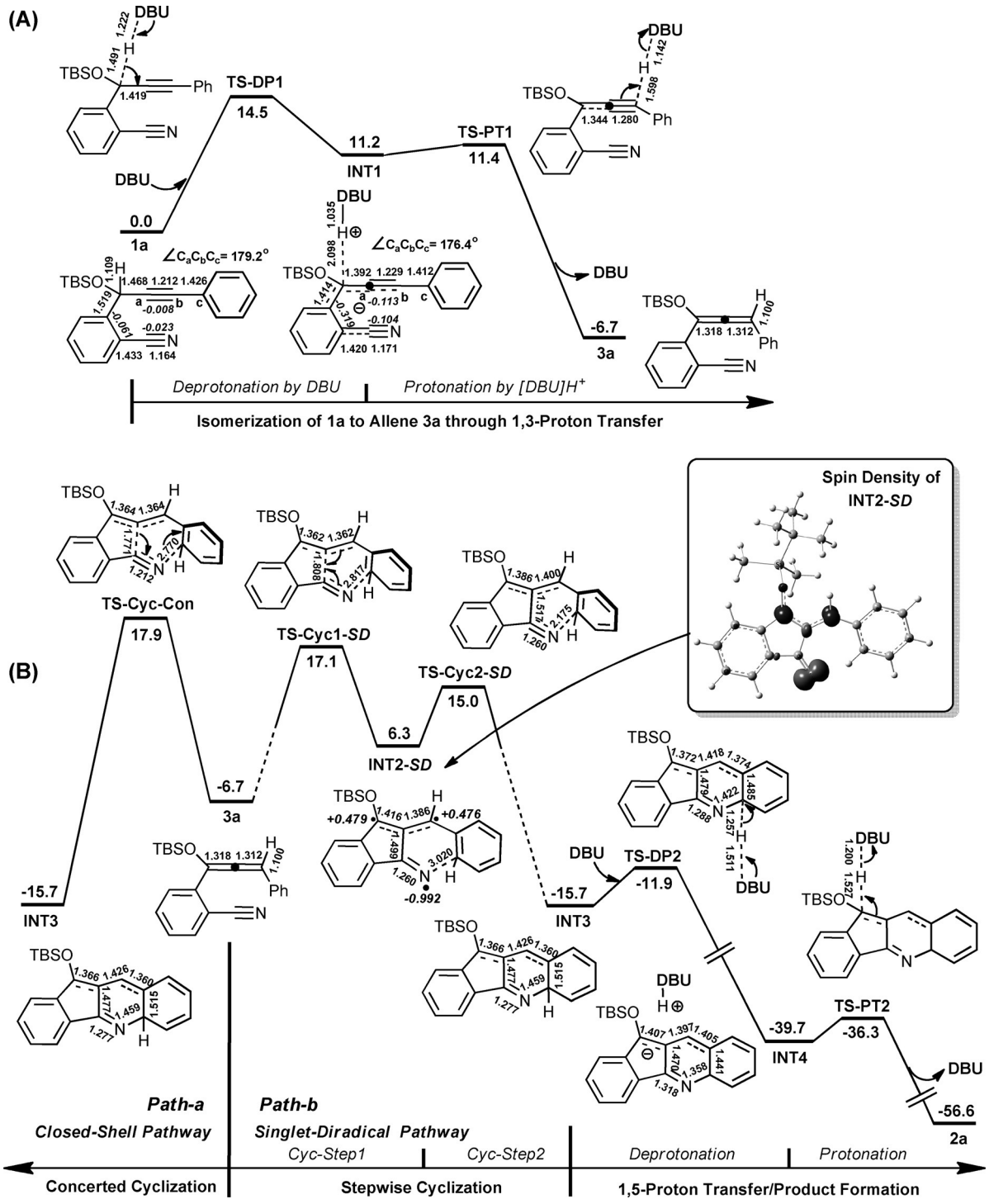
Scheme 4. Control experiments.

accelerating the cycloaddition reaction. We next performed isotope-labeling experiments. Treatment of [D_1]**1a** with a deuterium labeled at the propargylic position with a catalytic amount of DBU at 80 °C provided [D_1]**2a** in 94% yield without a significant loss of deuterium, and in which deuterium was located at the C-3 position (Scheme 4, [Eq. (2)]). Reaction of **1a** in a mixed solvent of toluene/CD_3OD afforded the deuterated product [D_2]**2a** in 67% yield (Scheme 4, [Eq. (3)]). The incorporation of a deuterium at C-1 might be caused by H/D exchange of the benzylic proton in cyclized product under basic conditions (see below). The slight deuterium label at C3 indicated that H/D exchange of the propargylic proton in the substrate was involved only to a small extent during the isomerization process. The above results indicate that a fast 1,3-H shift in initial propargyl–allenyl isomerization process occurs, which may proceed through deprotonation and formation of a contact ion pair followed by reprotonation.[12c] The use of [D_5]**1a** bearing five deuterium atoms on the aromatic ring led to [D_5]**2a** in 99% yield, in which one of the deuterium atoms moved to the C-1 position on the five-membered ring (Scheme 4, [Eq. (4)]). In this case, the deuterium incorporation of D^1 decreased to 78%, possibly due to the benzylic D/H exchange between the cyclized product and water in the reaction mixture. Indeed, addition of 5.0 equiv D_2O and 10 mol% DBU to non-deuterated **2a** and stirring at 80 °C for 5 h resulted in an incorporation of deuterium at the C1-position on the five-membered ring. The absence of deuterium at C3 indicates that the subsequent 1,5-H shift process may not involve a double 1,3-H shift.

To disclose the reaction mechanism for the transformation of **1** to **2** catalyzed by DBU, density functional theory (DFT)[16] studies have been performed with GAUSSIAN09 program[17] using the (U)M06[18] and the 6-31+G** basis set. Harmonic vibration frequency calculations were carried out under 353.15 K and the optimized structures are all shown to be either minima (with no imaginary frequency) or transition states (with one imaginary frequency). Substrate **1a** was used in the calculation models. For a reaction that the number of molecules of the reactant and the product are not equal, corrections were made to the calculated free energies based on "the theory of free volume",[19] that is, under 353.15 K, for two-to-one (or one-to-two) reactions, a correction of -3.0 (or 3.0) kcal mol^{-1} was made.

As shown in Scheme 5A, the isomerization of substrate **1a** to allene **3a** occurs through 1,3-proton transfer assisted by the DBU catalyst. Over transition state **TS-DP1** (14.5 kcal mol^{-1}), the propargyl proton of **1a** is abstracted by the nitrogen atom of the DBU catalyst, leading to the ion pair **INT1**. In the anion part of **INT1**, the negative charges are distributed on the whole conjugated system, as indicated by the increased negative NPA charges.[20] Interestingly, the alkynyl group in **INT1** remains linear, and the bond angle $C_aC_bC_c$ is 176.4 degree, which is close to that of **1a**. Subsequently, over a small barrier of 0.2 kcal mol^{-1} the protonation of the alkynyl carbon (**TS-PT1**, 11.4 kcal mol^{-1}) yields the allene isomer **3a**. The isomerization of **1a** to allene **3a** is easy, the overall reaction barrier is 14.5 kcal, and the allene isomer is more thermodynamically stable[21] by 6.7 kcal mol^{-1}. These results are in good accordance with the experimental observations that the isomerization can be fulfilled under room temperature within 40 min, and the allene isomer can be isolated in high yield (98%; see Table 1, entry 11).

The cyclization of the allene isomer **3a** may occur through a concerted closed-shell pathway (*Path-a*) or the stepwise open shell singlet-diradical (***SD***) pathway (*Path-b*) yielding the cyclized intermediate **INT3**. *Path-b* is only 0.8 kcal mol^{-1} lower than *Path-a*. This small energy difference is consistent with the former DFT study on enyne–allenes.[5i] The diradical pathway plays a major role. However, these two mechanisms are concomitant, especially under higher reaction temperatures.[5i] The cyclization step is the rate-determining step of the whole reaction. The spin density distribution shows that the intermediate **INT2-*SD*** is a typical singlet diradical (Scheme 5B).



Scheme 5. The reaction pathways of substrate **1a**. The selected bond lengths are in angstroms, and the relative free energies (ΔG, 353.15 K) are in kcal mol^{-1}. The numbers with minus sign in (A) are the NPA charges on the nearby bonds (sum of the charges on two bonded atoms), and the numbers with minus and plus signs in **INT2-*SD*** are spin densities on the nearby carbon or nitrogen atoms. Calculated at the (U)M06/6-31 + G**/SDD level.

The barriers of the deprotonation of **INT3** to **INT4**, and the subsequent protonation of **INT4** to **2a**, are only 3.8 and 3.4 kcal mol^{-1}, respectively. These small barriers show that even a very weak base/acid can act as an efficient proton shuttle in the last 1,5-proton-transfer process. This may account for the fact that allene can react without the DBU catalyst (Scheme 4, [Eq. (1)]).

The barriers of deprotonation of **2a** to **INT4**, and reprotonation of **INT4** to **2a** are 20.3 and 3.4 kcal mol^{-1}, respectively, indicating that this process is very fast and reversible under the experimental conditions. This result is consistent with the observed H/D exchange in the isotope-labeling experiment of non-deuterated **2a**. In addition, the [4+2] cycloaddition of the allene anion species was ruled out safely.[22]

To find out the origin of the high reactivity of **1a**, the reaction pathways of a model substrate **1a'** without the OTBS group (2-(3-phenylpropa-1,2-dienyl)benzonitrile) were calculated.[22] The results show that: 1) the OTBS group has small effect on the first deprotonation step; 2) however, without the OTBS group the barrier of the cyclization step increases in large scale from 23.8 to 30.0 kcal mol^{-1}. Therefore, the OTBS group has a large effect on the reactivity of the substrate. Further analysis shows that the π-electronic donation of the OTBS group can stabilize the highly polarized transition structures, consequently decreasing the cyclization barriers.[23]

Conclusion

In summary, we have disclosed a successful example of cyano-Schmittel cyclization of cyano-allenes. The DFT calculation results are consistent with the experiments, and suggest that the diradical pathway plays a major role in this cyclization. The reactions can be conveniently performed in a one-pot manner through cascade Sonogashira coupling of terminal cyano-ynes with organic halides, followed by base-promoted propargyl-allenyl isomerization/cyclization, leading to an efficient access to pyridine-fused polycyclic architectures. In particular, a large variety of aryl or heteroaryl rings such as furans, thiophenes, and pyridines can be incorporated into the follow-up cyano-Diels–Alder reactions, highlighting the great synthetic utility of this chemistry. Further investigations into the reaction mechanism and its synthetic applications are currently in progress in our laboratory.

Experimental Section

Typical procedure for DBU-promoted isomerization/cyclization of 1a

In a nitrogen-filled glove box, to an oven-dried screw-cap vial (volume: 4.0 mL) were added **1a** (104.3 mg, 0.3 mmol), toluene (1.0 mL), and DBU (4.5 μL, 0.03 mmol). Then the vial was taken outside the dry box and stirred at 80 °C in an oil-bath until the reaction was complete, as monitored by TLC. After the mixture was cooled down to room temperature, the solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel to afford **2a** in 93% yield (97 mg) as a white solid. ^{1}H NMR (400 MHz, Me_4Si, $CDCl_3$): $\delta = 0.18$ (s, 3H), 0.20 (s, 3H), 0.99 (s, 9H), 5.83 (s, 1H), 7.47–7.53 (m, 3H), 7.62 (d, $J = 7.2$ Hz, 1H), 7.69 (t, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 8.10 (s, 1H), 8.16–8.19 ppm (m, 2H); ^{13}C NMR (100 MHz, Me_4Si, $CDCl_3$): $\delta = -3.76$, −3.69, 18.07, 25.78, 73.01, 121.73, 125.26, 125.91, 127.49, 128.21, 129.10, 129.25, 129.35, 130.51, 131.55, 137.84, 139.01, 148.01, 148.78, 159.99 ppm; IR (film): $\tilde{\nu} = 3057$, 2953, 2928, 2887, 2855, 1926, 1718, 1628, 1506, 1464, 1401, 1252, 1183, 1122, 1104, 1067, 1004, 919, 859, 836, 770, 755, 737, 713, 688, 666 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{22}H_{26}NOSi$ $[M+H]^+$: 348.1778; found: 348.1792.

Typical procedure for palladium-catalyzed tandem coupling/cyclization reaction of terminal alkyne 4 with organic halides

o-(Cyano)phenyl propargyl ether **4** (91.4 μL, 0.33 mmol), iodobenzene (33.6 μL, 0.3 mmol), Et_3N (2.0 mL), $[Pd(PPh_3)_4]$ (6.9 mg, 0.006 mmol), and CuI (2.9 mg, 0.015 mmol) were added to a sealable Schlenk tube under argon. Then the tube was sealed and the reaction mixture was gradually warmed up to 80 °C and stirred at the same temperature until the reaction was complete, as monitored by TLC. After cooling down to room temperature, the reaction mixture was quenched by saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30/1) to afford the product **2a** in 93% yield (97 mg).

Acknowledgements

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Keywords: alkynes · cyano-Schmittel cyclization · indenoquinoline · nitriles · propargyl-allenyl isomerization

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