Synthesis of densely substituted pyridine derivatives from nitriles by a non-classical [4+2] cycloaddition/1,5-hydrogen shift strategy

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Article

Abstract

A novel strategy has been established to assemble an array of densely substituted pyridine derivatives from nitriles and *o*-substituted aryl alkynes or 1-methyl-1,3-enynes *via* a non-classical [4 + 2] cycloaddition along with 1,5-hydrogen shift process. The well-balanced affinities of two different alkali metal salts enable the C(sp^3)-H bond activation as well as the excellent chemo- and regioselectivities. This protocol offers a new guide to construct pyridine frameworks from nitriles with sp^3-carbon pronucleophiles, and shows potential applications in organic synthesis and medicinal chemistry.

Introduction

Compounds containing pyridine core structures, not only widely exist in natural products, pharmaceuticals, and functional materials,[1–7] but also serve as useful and valuable building blocks for metal ligands.[8,9] For instance, pyridine derivative Actos **I**[10] is a famous drug for the treatment of type 2 diabetes; Bi-(or tri-)pyridines **II**[11–15] are often used as ligands in metal-catalyzed reactions; Kv1.5 antagonist **III**[16] and alkaloid papaverine **IV**[17] are two representative isoquinolines as a promising atrial-selective agent and a smooth muscle relaxant, respectively (Fig. 1). Consequently, many synthetic methods have been developed to access this important class of *N*-heterocycles, including metal-free multicomponent syntheses,[18] transition metal-catalyzed [2 + 2 + 2] cycloaddition reactions[19–25] for pyridines, and transition metal-catalyzed annulations involving alkynes[26–30] for isoquinolines. Despite these advances, the lack of chemo- and regioselectivities in multicomponent reactions and requirement of complex functionalized substrates as well as harsh reaction conditions[22,31–33] often limits further exploitation of the synthetic potential of these approachs. The development of novel and efficient strategies toward pyridine derivatives is still highly desirable.

Retrosynthetic analysis of pydirine frameworks suggests that a convenient and straightforward [4 + 2] cycloaddition of *o*-substituted aryl alkynes or its analogues and nitriles would be an attractive alternative to presently reported methods. However, this scenario remains two major challenges: (i) *o*-Substituted aryl alkynes could undergo intramolecular cyclization to produce indene in the presence of transition metal (Fig. 2A),[34–43] which enhances the difficulty of intermolecular reaction. (ii) The preferential activation of nitrile in such a system, which means diverting the chemoselectivity of benzylic attack from alkynyl to inert cyano group, is also an intractable issue. As illustrated in Fig. 2B, in the nucleophilic addition of nitriles, the most reported reaction partners have been focused on the highly reactive nitrogen,[44–52] oxygen,[53–61] and sulfur nucleophiles till now.[62–64] For carbon pronucleophiles, the related studies are only limited to sp, sp^2, and sp^3 with α-electron withdrawing group (i.e. cyano, carbonyl, ester groups) carbons, though some elegant work has been made by using transition metal catalysts.[65–81] The difficulty level of these reactions increases drastically when substrates with weakly acidic C(sp^3)-H (especially for pKa > 40 in DMSO) bond are utilized, and the methods in this field are rarely developed.[82]

To address these challenges, a non-classical [4 + 2] cycloaddition along with 1,5-hydrogen shift strategy is proposed (Fig. 2C). As a strategic fundamental step, our primary task is to identify the balanced conditions for the C(sp^3)-H bond activation, simultaneously avoiding the intrinsic tendency of intramolecular cyclization under the transition metal catalysis. Alkali metals bearing the weaker coordination ability, as a powerful tool for C – H bond activation,[83–90] might have a broadly beneficial impact on our protocol. We envisioned that the C(sp^3)-H bond activation should occur primarily triggered by the amenable alkali metal reagents to form the nucleophilic benzyl or allyl – metal species, which could be trapped rapidly by the suitable electrophile-nitrile. Then a fomal [4 + 2] cycloaddition would be realized through a consecutive intramolecular alkyne insertion followed by 1,5-hydrogen shift process. Herein we disclose our recent results on this non-classical [4 + 2] cycloaddition reaction, which provides a direct and atom-economic synthesis of densely substituted pyridines, isoquinolines, and benzothienopyridines with high chemo- and regioselectivity.

Results

Investigation of reaction conditions. To validate the hypothesis, we commenced our studies by evaluating the reaction between 1-methyl-2-(phenylethynyl)benzene (**1a**) and benzonitrile (**2a**) in THF at 100 °C in the presence of different alkali metal salts (Table 1). Several metal amides in combination with *t*-BuOK were initially tested (entries 1–3), and LiN(SiMe$_3$)$_2$ turned out to be the best choice to give product **3a** in 35% yield. Subsequently, screening of the reaction temperatures identified the optimal 120 °C (entries 4–6). The examination of other parameters including additive, solvent, and reaction time (entries 7–15) revealed that the reaction proceeded well with *t*-BuOK as additive in CPME for 24 h, improving the yield of **3a** to 65%. Next, investigation of detailed molar ratios of all components indicated that excess nitrile was required due to the consumption of self-cyclotrimerization, and the well-balanced interaction between LiN(SiMe$_3$)$_2$ and *t*-BuOK is the key to the success of reaction (entries 16 and 17, see the Supporting Information for details). Finally, the reaction of **1a**: **2a**: LiN(SiMe$_3$)$_2$: *t*-BuOK in a molar ratio of 1: 3: 2: 1.5 gave **3a** in 80% isolated yield (entry 17).

Substrate scope. Having established the optimal reaction conditions, the scope of this [4+2] cycloaddition reaction was then explored (Table 2). Pleasingly, *o*-substituted aryl alkynes **1** with electron-donating substituents, such as -Me, -*t*-Bu, and -OMe at the 4-position of aromatic ring Ar^1, were well compatible in this reaction, and the desired products (**3b–3d**) were isolated in 60-78% yields. *o*-Substituted aryl alkyne bearing 3-Me substituted Ar^1 also reacted with **2a** to afford **3e** in a slightly descending yield, while the substrates containing halogens were relatively limited (e.g., **3f**). The reaction proceeded as well with a larger aromatic Ar^1, 2-naphthyl, providing the corresponding adduct **3g** in 65% yield. Moreover, when using a series of functionalized nitriles **2** as reactants, including *p*-Me, *p*-*t*-Bu, *p*-OMe, *p*-Ph, and *m*-*t*-Bu substituted benzonitriles, isoquinoline derivatives (**3h-3l**) with moderate to good yields (48-82%) were obtained The structure of **3i** was confirmed unambiguously by X-ray diffraction. The substituent R^1 on arylmethane ring could be varied as well (**3m-3p**) under the standard conditions. When R^2 was replaced

by a cyano group, contributing to relatively acidic benzyl protons, the cycloadditions occurred smoothly in the absence of lithium amide (**3q-3r**). In addition, the introduction of a sterically demanding phenyl at the benzylic position enabled the release of larger conjugated isoquinoline derivative in 45% yield (**3s**). Benzylic C-H bond with a methyl group at the benzylic position could also be functionalized in this reaction albeit in 28% yield (**3t**). However, the substrate with a phenoxy group R^2 failed to undergo the desired [4 + 2] cycloaddition reaction (**3u**).

To further expand the generality of this method, a series of functionalized heteroaromatic substrates were utilized to test the reactivity (Table 3). The result indicated 3-alkynyl-2-methylbenzo[*b*]thiophene (**4**) with different substituents (H, OMe, N,N-2Me) on the aromatic ring Ar^1 were well tolerated, converting to the fused heterocycle benzothienopyridine derivatives **5a-5c** in 71-90% yields. Gratifyingly, halogens, such as 4-F, 4-Cl, 4-Br, 3-Cl and 3,5-2F, could also be installed on the same aromatic ring Ar^1, and the corresponding products **5d-5h** were obtained in acceptable to good yields. The generated heteroaryl halides provided versatile synthetic handles for further derivatization. Moreover, the synthesis of compounds **5j-5n** with 53-71% yields suggested that the compatibility of substituents on nitrile has been extended to -Cl, -CF$_3$, -OMOM, and -1,3-dioxolane derived fromaldehyde group, thus providing a platform for additional functionalization. 3,5-Disubstituted benzonitrile and 2-naphthonitrile were also applicable in this system, and the desired products **5o** and **5p** were delivered in 72% and 66% yields, respectively. It should be noted that the pincer-type or dipyridyl-type nitrogen ligands **5i**, **5q** and **5r** could be constructed in good yields. More importantly, this protocol was also applied to the late-stage functionalization of drug molecule citalopram, which is a selective serotonin-uptake inhibitor, and the compound **5s** was provided in 67% yield, exhibiting the potential in pharmaceutical research.

Specifically, this method also applied to the substrates bearing less acidic $C(sp^3)$-H bonds. For instance, the desired reaction of (*Z*)-pent-3-en-1-yn-1-ylbenzene (**6**) and **2a** was carried out successfully after simply adjusting the reaction conditions to afford the product 2-benzyl-6-phenylpyridine (**7a**) in 60% yield (Table 4). Then substituted nitriles with 4-*t*-Bu, 4-OMe, -Ph, 3-Me and 3,5-2Me were further examined, and a series of 2,6-disubstituted pyridines were isolated in 35-58% yields (**7b-7f**). To our knowledge, this is the rare example of demonstrating possibility of formal allylic C-H bond addition to nitrile.

To further illustrate the value of this method, gram-scale experiments and postderivatizations of the newly formed products were conducted (Fig. 3). When the reaction proceeded at a 5 mmol scale, the desired products **3c** and **5a** were obtained in almost unaffected yields even with reduced amount of nitrile. Additionally, inspired by the importance of organic fluorophores in a number of fields including materials science and biology, two new solid-state-emitting organic molecules **8** and **9** were synthesized. Tetraarylethylene **8** was obtained by a single Suzuki–Miyaura coupling of **5f** with 60% yield, while the successive hydrolysis and condensation reaction of **5n** gave compound **9** in 95% total yield. Studies on the photophysical propertie showed the absorption maxima of **8** and **9** were about 336 nm and 385 nm in DMSO solution, respectively, and the corresponding intense emission peaks were at 404 nm and 587 nm in powder, which might find applications in construction of functional materials.

Mechanistic investigations. To shed light on the reaction mechanism, several control experiments were performed. Firstly, when ^{15}N-labeled benzonitrile was emplyed under the standard reaction conditions, **3c**(^{15}N) and **3c**(^{14}N) were detected respectively with the ratio of 49: 51 by HRMS analysis, elucidating that the nitrogen atom in the pyridine framework came not only from nitrile but also LiN(SiMe$_3$)$_2$ (Fig. 4a). Then, the studies of introducing exogenous halogens PhX (X = F, Cl, or Br) to the reaction system showed that fluorobenzene slightly reduced the yield of **3c**, while chlorobenzene and bromobenzene greatly suppressed the transformation, indicating that the coordination of PhX to the alkali metals might account for the inhibitory effect (Fig. 4b).[83] Next, a Hammett study was carried out using various substituted benzonitriles to investigate a rate dependence on the electronic effect of nitrile (Fig. 4c). A linear

relationship with negative ρ value of -2.95 was observed when relative rates with -OMe, -Me, -H, -Cl, and -CF$_3$ substituted benzonitriles [log(k_X/k_H)] were plotted against the substituent constant (σ). These results suggested that the electron-donating group should facilitate the intermolecular addition step, which was consistent with the reactivity of the nitrile substrates reported in Tables 2-4. Finally, the kinetic order experiments (Fig. 4d) showed a first-order dependence on concentrations of **2a**, which indicated that the formation of metalated imine by quickly capturing benzylic–metal species with nitrile should be the rate-limiting step. However, the benzyl substrate **1c**, theoretically accelerating an equilibrium formation of benzylic–metal species, exhibited the negative-order kinetic effect in the reaction. Moreover, the rates of both *t*-BuOK and LiN(SiMe$_3$)$_2$ could not be described by a single power function. These observations aligned with the optimization data possibly portend the well-balanced interactions between base and additive for benzylic or allylic C(sp^3)-H activation. This cooperative interaction was further proved with hydrogen/deuterium exchange experiment of **1c**-*d* (Fig. S1).

Based on the above investigation and literature reports,[82-90] a possible mechanism is proposed in Fig. 5. Initially, the C(sp^3)-H bond of **1a** is activated by the interaction of LiN(SiMe$_3$)$_2$ and *t*-BuOK to afford a nucleophilic benzylic–metal species **A**, which is quickly trapped by nitrile **2a** to form the metalated imine intermediate **B**. Next, subsequent addition of intermediate **B** to the alkyne achieves the cyclization. The resulting alkenyl-metal species **C** undergoes protonation and 1,5-hydrogen shift process to deliver the desired **3a**. Alternatively, the reaction could proceed by either protonation or silylation of intermediate **B** with HN(SiMe$_3$)$_2$ from the initial deprotonation equilibrium, generating imine **D**.[82] In the presence of Li/KN(SiMe$_3$)$_2$, the imine **D** would undergo a reversible addition, silyl migration, and elimination pathway to release nitrogen-exchanged intermediate **F**,[91,92] followed by the further silyl transfer and cyclization to give nitrogen-exchanged intermediate **G**.

Discussion

In summary, we have developed a non-classical [4 + 2] cycloaddition reaction of benzylic and allylic prenucleophiles with nitriles, leading to a range of *N*-heterocycles bearing pyridine frameworks and various functional groups. This protocol hinges on the cooperative interaction of alkali metals to trigger benzylic and allylic C-H bond activation, simultaneously avoiding the inherent intramolecular cyclization.

The Hammett experiment and kinetic analysis show that the addition of benzylic- or allylic–metal species to nitrile is the rate-limiting step. Notably, this protocol provides a new guide for the synthesis of functionalized pyridines from sp^3-carbon pronucleophiles with nitriles, which implies the potential value in organic synthesis and medicinal chemistry.

Method

Procedure for the synthesis of product 3. In a glovebox, an oven-dried Schlenk tube equipped with a magnetic stirring bar was added a mixture of o-substituted aryl alkyne **1** (0.2 mmol), nitrile **2** (0.6 mmol), base (0.4 mmol), additive (0.3 mmol) dissolved in 1.0 mL of dry CPME. The Schlenk tube was sealed with a plug and removed from the glovebox. The mixture was allowed to stir at 120°C under N$_2$ for 24 h. The reaction mixture was cooled to room temperature and quenched by 10 mL water. The product was extracted with ethyl acetate (10 mL × 3). The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (100:1–10:1 v/v) as eluent to afford the corresponding product **3**.

Procedure for the synthesis of product 5. In a glovebox, an oven-dried Schlenk tube equipped with a magnetic stirring bar was added a mixture of o-substituted aryl alkyne **4** (0.2 mmol), nitrile **2** (0.6 mmol), base (0.4 mmol), additive (0.24 mmol) dissolved in 0.5 mL of dry CPME. The Schlenk tube was sealed with a plug and removed from the glovebox. The mixture was allowed to stir at 120°C under N$_2$ for 24 h. The reaction mixture was cooled to room temperature and quenched by 10 mL water. The product was extracted with ethyl acetate (10 mL × 3). The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (100:1–10:1 v/v) as eluent to afford the corresponding product **5**.

Procedure for the synthesis of product 7. In a glovebox, an oven-dried Schlenk tube equipped with a magnetic stirring bar was added a mixture of 1-methyl-1,3-enyne **6** (0.2 mmol), nitrile **2** (0.6 mmol), base (0.4 mmol), additive (0.24 mmol) dissolved in 0.5 mL of dry 1,4-dioxane. The Schlenk tube was sealed with a plug and removed from the glovebox. The mixture was allowed to stir at 120°C under N$_2$ for 12 h. The reaction mixture was cooled to room temperature and quenched by 10 mL water. The product was extracted with ethyl acetate (10 mL × 3). The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (100:1–50:1 v/v) as eluent to afford the corresponding product **7**.

Declarations

Data availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information, as well as from the authors upon reasonable request. The X-ray crystallographic coordinate for structure 3i reported in this study has been deposited at the Cambridge

Crystallographic Data Centre (CCDC), under CCDC 2051390. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data⬚request/cif.

Competing interests

The authors declare no competing interests.

Author contributions

D.H. and W.W. designed the project. D.H., H.J., and W.W. co-wrote the manuscript, analyzed the data, discussed the results, and commented on the manuscript. D. H., K.D., and Y.Z. performed the experiments. All authors contributed to discussions.

Acknowledgements

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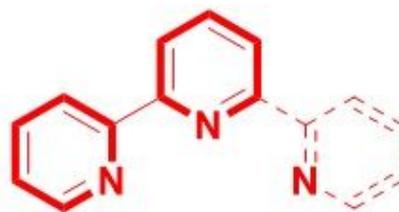
Tables

Due to technical limitations the tables are available as a download in the Supplemental Files.
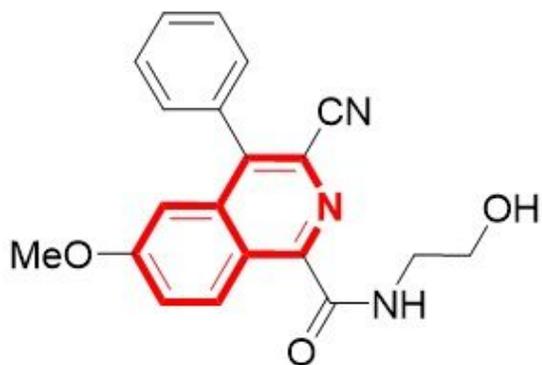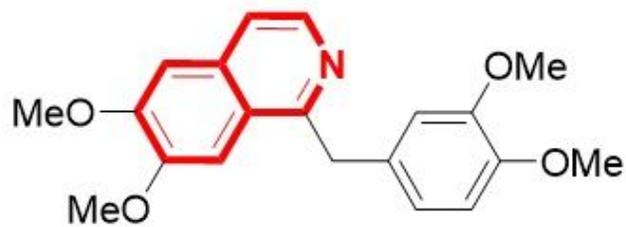
Figures
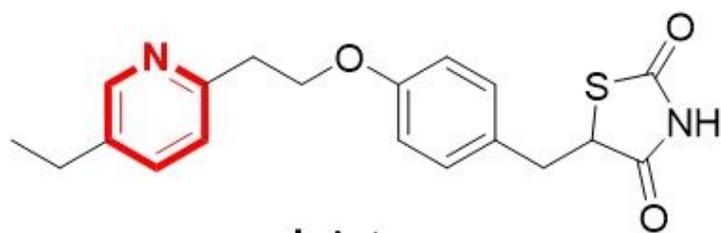
I. Actos
(antidiabetics)

II. Bi-(or tri-) pyridines
(metal ligands)

III. Kv1.5 Antagonist
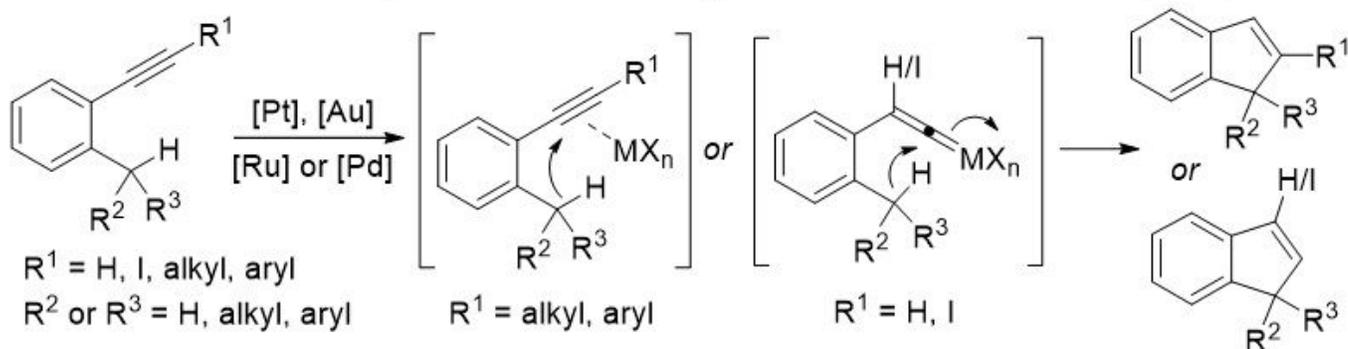(promising atrial-selective agent)
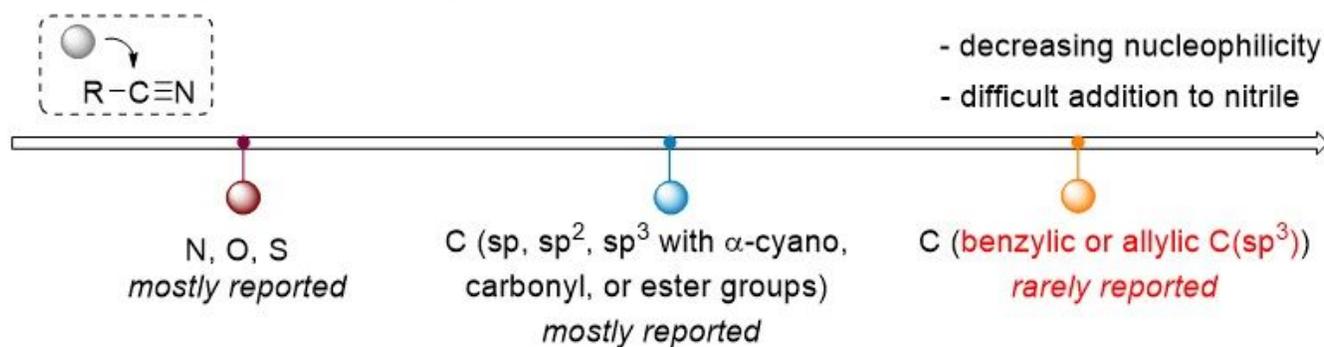
IV. Papaverine
(smooth muscle relaxant)

Figure 1

Representative important pyridine derivatives

A. Transition metal-catalyzed intramolecular cyclization of o-substituted aryl alkynes

R^1 = H, I, alkyl, aryl
R^2 or R^3 = H, alkyl, aryl

R^1 = alkyl, aryl

R^1 = H, I

B. The development of nucleophilic addition to nitrile

R–C≡N

- decreasing nucleophilicity
- difficult addition to nitrile

N, O, S
mostly reported

C (sp, sp^2, sp^3 with α-cyano, carbonyl, or ester groups)
mostly reported

C (benzylic or allylic C(sp^3))
rarely reported

C. Alkali metal-mediated intermolecular [4+2] cycloaddition (*this work*)

+ R–C≡N

R^1 = aryl, heteroaryl
R^2 = H, alkyl, aryl

R = aryl, heteroaryl

[M] = Li, Na or K
non-classical [4+2] cycloaddition

Densely Substituted Pyridine Derivatives

challenges:
- benzylic or allylic C(sp^3)-H bond activation
- sequential activation of nitrile and alkyne
- preferentially inter- to intramolecular cyclization
- chemo- and regioselectivity

Figure 2

Intramolecular cyclization of o-substituted aryl alkynes (A), the development of nucleophilic addition to nitrile (B) and our design (C).
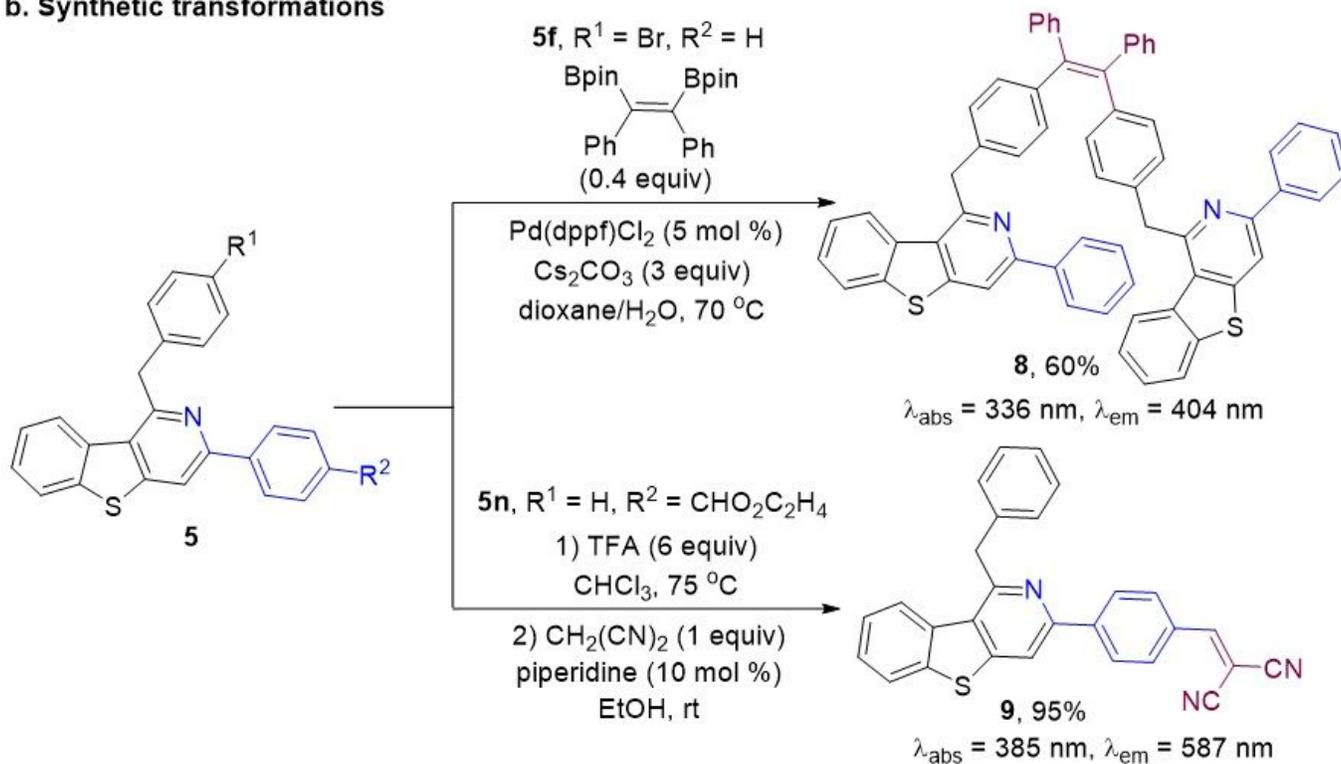
a. Gram scale experiments

1c (5 mmol 1.11 g)

conditions A

2a (2 equiv)

4a (5 mmol 1.24 g)

conditions B

3c, 77% 1.25 g

5a, 85% 1.49 g

b. Synthetic transformations

5f, R^1 = Br, R^2 = H

Bpin⎯⎯Bpin

Ph   Ph

(0.4 equiv)

Pd(dppf)Cl$_2$ (5 mol %)
Cs$_2$CO$_3$ (3 equiv)
dioxane/H$_2$O, 70 °C

8, 60%

λ_{abs} = 336 nm, λ_{em} = 404 nm

5n, R^1 = H, R^2 = CHO$_2$C$_2$H$_4$

1) TFA (6 equiv)
CHCl$_3$, 75 °C

2) CH$_2$(CN)$_2$ (1 equiv)
piperidine (10 mol %)
EtOH, rt

9, 95%

λ_{abs} = 385 nm, λ_{em} = 587 nm
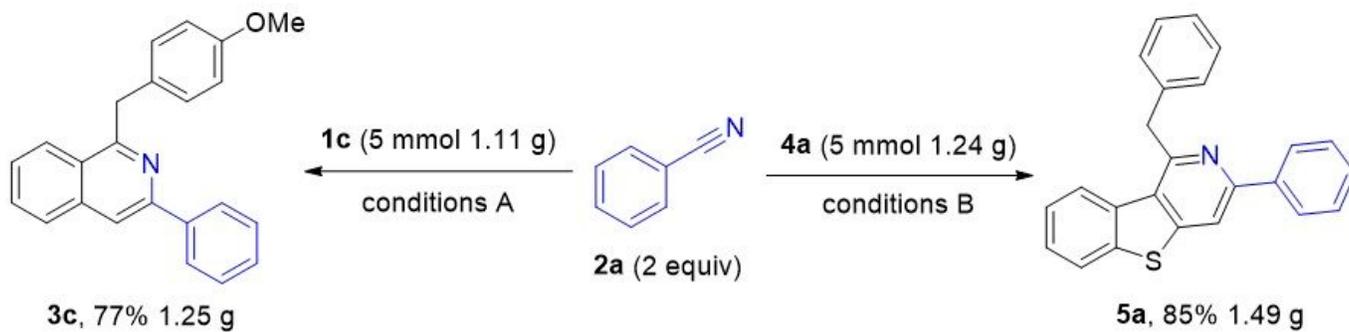
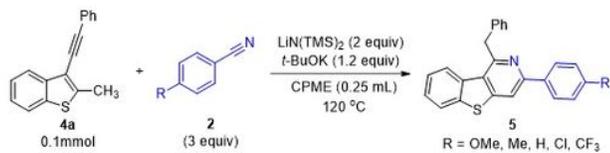## Figure 3

The gram-scale experiments and synthetic transformations

a. ¹⁵N-Labeling experimeng
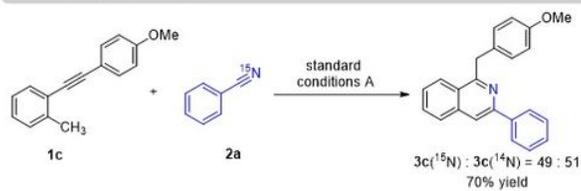
b. Effects of exogenous halogens
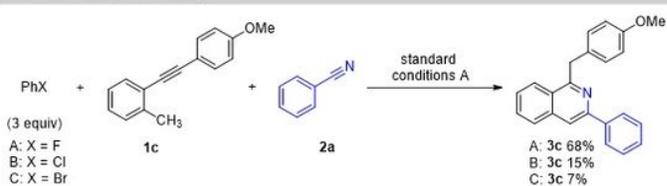
c. Hammett experiments

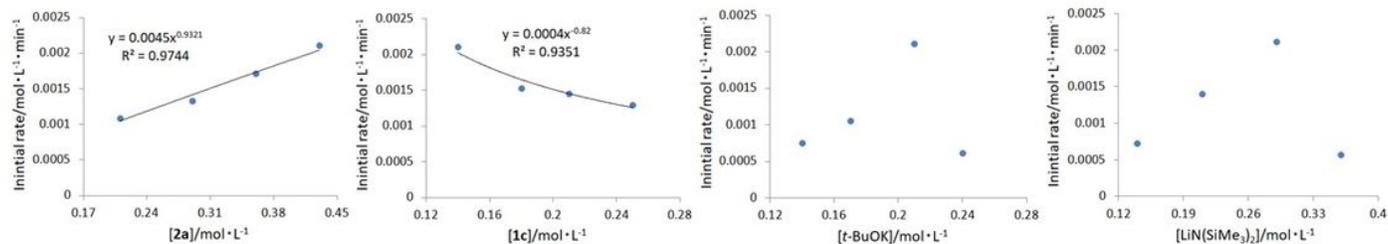| R	σ	Lg(K_X/K_H)
OCH₃	-0.268	0.6815
CH₃	-0.17	0.4125
H	0	0
Cl	0.227	-1.3696
CF₃	0.54	-1.4750
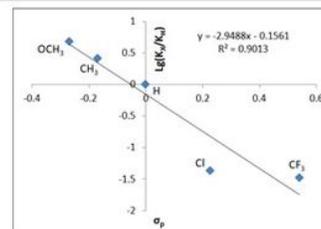
d. Determination of the order

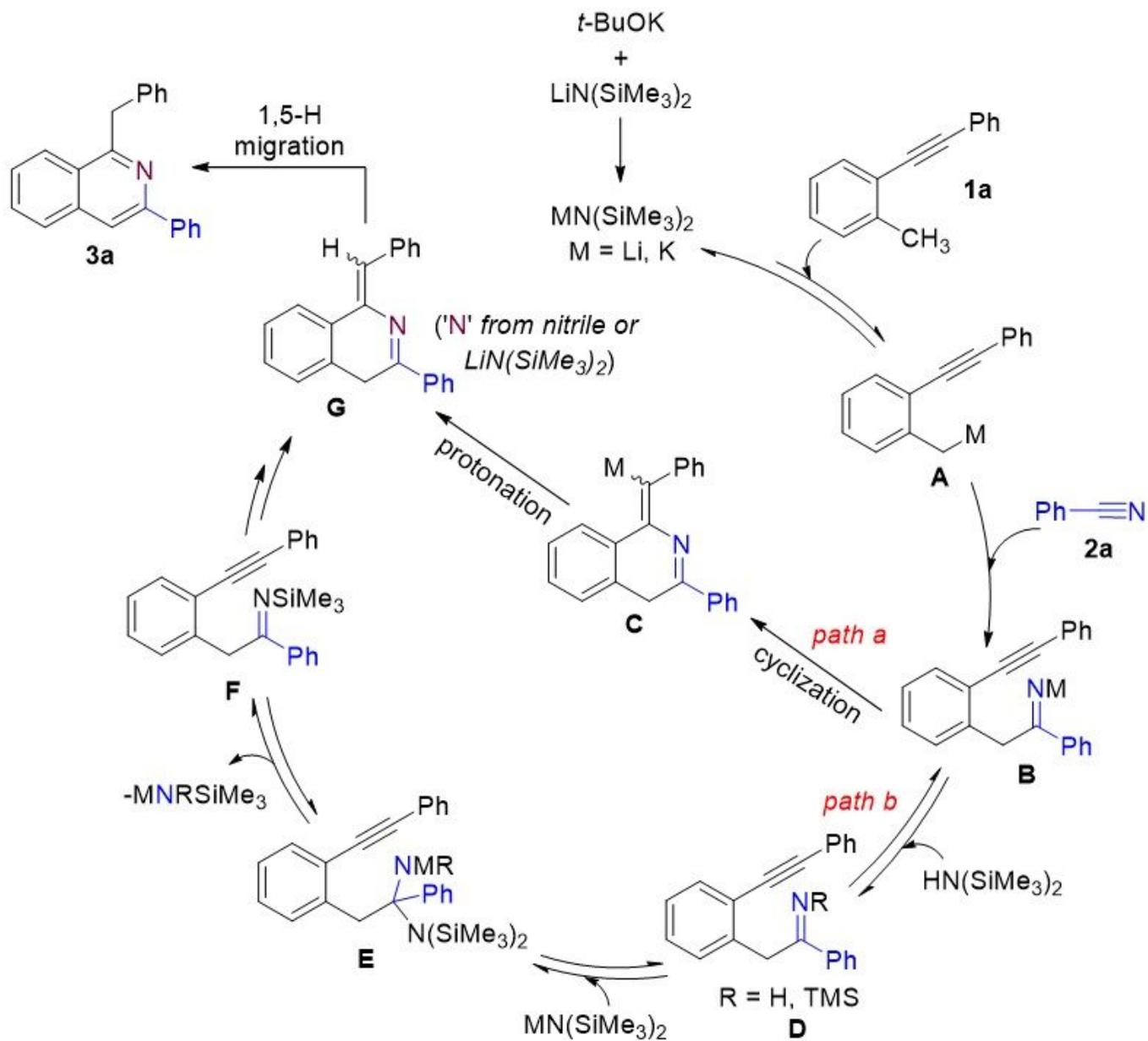## Figure 4

Mechanistic studies

Figure 5

Possible mechanism

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