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Synthesis of Pyrroles Through the CuH-Catalyzed Coupling of Enynes and Nitriles

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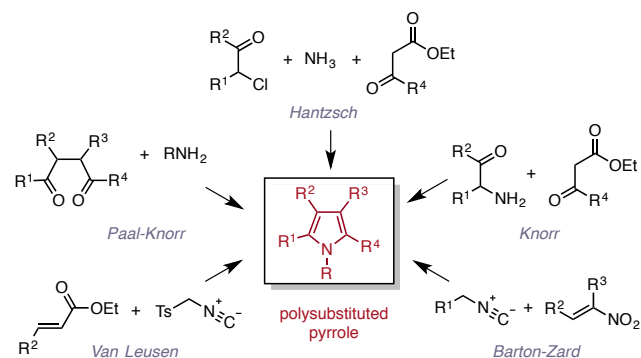
Supporting Information Placeholder

ABSTRACT: Herein, we describe an efficient method to prepare polysubstituted pyrroles via a copper-hydride (CuH)-catalyzed enyne-nitrile coupling reaction. This protocol accommodates both aromatic and aliphatic substituents and a broad range of functional groups, providing a variety of N-H pyrroles in good yields and with high regioselectivity. We propose that the Cu-based catalyst promotes both the initial reductive coupling and subsequent cyclization steps. Density functional theory (DFT) calculations were performed to elucidate the reaction mechanism.

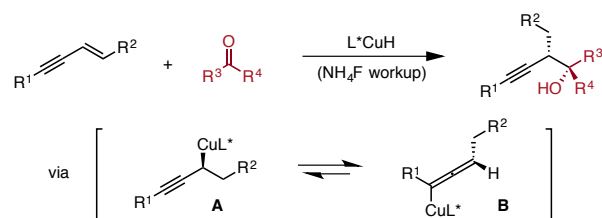
Pyrroles are one of the most prevalent five-membered heterocycles, and are present in a large number of natural products,¹ pharmaceuticals,² and functional materials.³ In addition, they are valuable and useful building blocks in the preparation of complex molecules.⁴ Consequently, numerous synthetic strategies have been developed to access this important class of compounds. Traditional approaches, including the Knorr,⁵ Hantzsch,⁶ and Paal-Knorr reactions,⁷ allow for the construction of polysubstituted pyrroles through the condensation of carbonyl compounds and amines (Figure 1a). The conditions employed in these examples, such as high reaction temperatures and the use of strong acids to facilitate the initial condensation, often result in limited scope and functional group compatibility. Recently, numerous methods, including multicomponent reactions⁸ and transition-metal-catalyzed couplings,⁹ have been established to produce pyrroles under relatively mild conditions with better control of regioselectivity. Despite these advances, highly functionalized starting materials are often required, (e.g., iminoallenes, alkynyl aziridines, or azides), which limits the range of accessible products. Further, many existing strategies necessitate the use of substrates with protected nitrogens, which must be first installed and subsequently removed or exchanged after the assembly of the pyrrole ring, sig-

nificantly decreasing the efficiency of the process. A complementary strategy to access unprotected pyrroles from readily available starting materials that operates under mild conditions would thus be of significant utility.

(a) Classic approaches to access polysubstituted pyrroles



(b) CuH-catalyzed asymmetric enyne-ketone coupling reaction



(c) Synthesis of pyrroles via CuH-catalyzed enyne-nitrile coupling (this work)

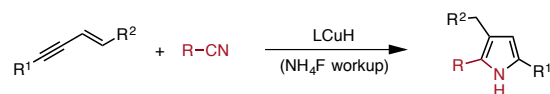
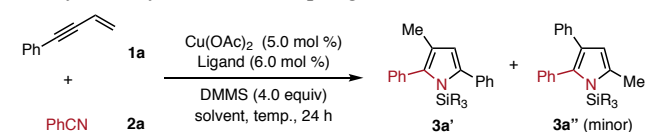


Figure 1. (a) Classic approaches to access polysubstituted pyrroles; (b) CuH-catalyzed enyne-ketone and (c) enyne-nitrile coupling reactions (this work).

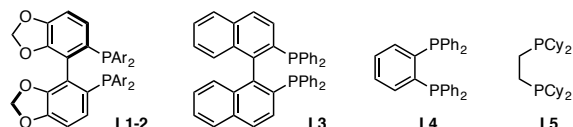
Over the past few years, CuH catalysis has emerged as a useful and robust technique for olefin hydrofunctionalization.¹⁰ In these reactions, an underlying concept is the generation of nucleophilic alkyl copper intermediate from the reaction of a ligated copper hydride species

and an unsaturated hydrocarbon. In this way, widely available and stable olefins can serve as surrogates for traditional organometallic reagents. By changing the supporting ligand, the reactivity of the corresponding alkyl copper species can be modulated.¹¹ Furthermore, the mildness of CuH reaction conditions enables the use of substrates containing sensitive functional groups that are incompatible with many preformed organometallic reagents (e.g., Grignard and alkyllithium reagents). We recently disclosed a CuH-catalyzed asymmetric addition reaction to ketones (Figure 1b),^{10e} in which conjugated enynes were employed as precursors to the key nucleophilic propargyl- (**A**)/allenylcopper intermediates (**B**). The reactivity manifested by *in situ* generated species **A** and **B** caused us to survey their reactions¹² with other readily available electrophiles.¹³ Herein, we report the unexpected formation of polysubstituted pyrroles via a CuH-catalyzed coupling reaction of 1,3-enynes and nitriles (Figure 1c). This process features mild reaction conditions and demonstrates excellent functional group compatibility, allowing the access to free N-H pyrroles with a wide range of substitution patterns from commercially available nitriles and easily accessible enynes.¹⁴

Table 1. Evaluation of Reaction Conditions for CuH-Catalyzed Enyne-Nitrile Coupling Reactions^a



entry	ligand	solvent	temp., °C	1a:2a	yield 3a', ^b %
1	L1	THF	25	1:1.2	40
2	L2	THF	25	1:1.2	<5
3	L3	THF	25	1:1.2	<5
4	L4	THF	25	1:1.2	0
5	L5	THF	25	1:1.2	0
6	L1	toluene	25	1:1.2	40
7	L1	1,4-dioxane	25	1:1.2	69
8	L1	DME	25	1:1.2	54
9	L1	cyclohexane	25	1:1.2	12
10	L1	1,4-dioxane	40	1:1.2	78
11	L1	1,4-dioxane	50	1:1.2	85 (78) ^c
12	L1	1,4-dioxane	60	1:1.2	83
13	L1	1,4-dioxane	50	1:1.5	80
14	L1	1,4-dioxane	50	1.2:1	78



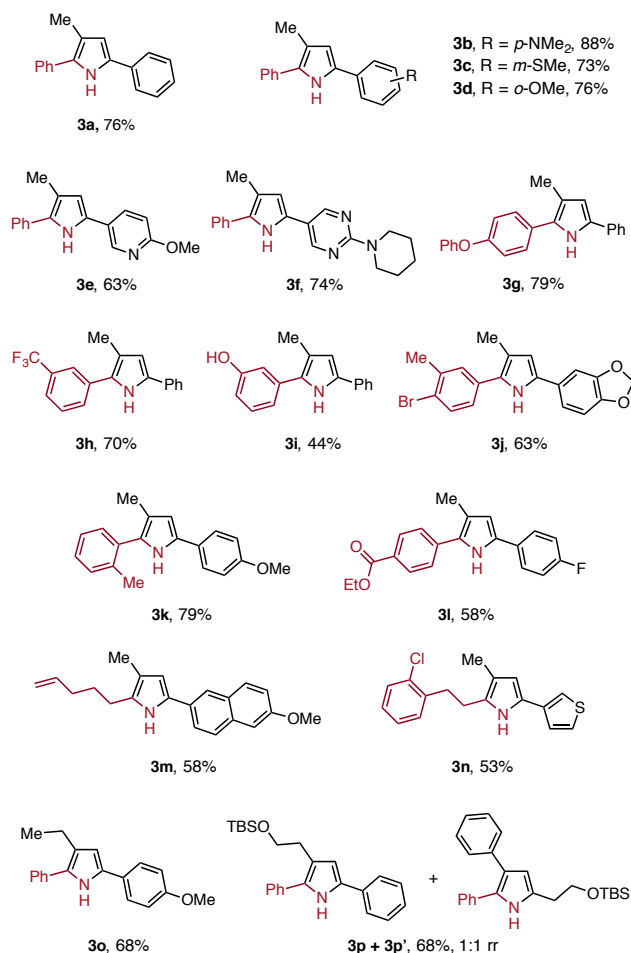
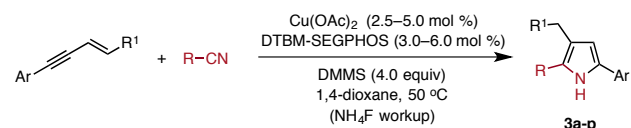
L1, Ar = 4-MeO-3,5-*t*-Bu-C₆H₂
L2, Ar = Ph

^a Conditions: 0.10 mmol **1a** (1.0 equiv), 0.12 mmol **2a** (1.2 equiv), copper(II) acetate (5.0 mol %), ligand (6.0 mol %), DMMS (4.0 equiv), in solvent (0.20 mL), see the Supporting Information for further details. DMMS = dimethoxy(methyl) silane. ^b Yield of major product **3a'** determined by ¹H NMR

using 1,1,2,2-tetrachloroethane as the internal standard. ^c Isolated yield of N-H pyrrole on 0.50 mmol scale after NH₄F workup.

The reaction conditions were optimized using enyne **1a** and benzonitrile **2a** as the model substrates (Table 1). The *N*-silylated trisubstituted pyrrole **3a'** was obtained in 40% ¹H NMR yield when DTBM-SEGPHOS (**L1**) was employed as the supporting ligand (Table 1, entry 1). Commonly used bisphosphine ligands, including SEGPHOS (**L2**), BINAP (**L3**), dppe (**L4**), and DCyPE (**L5**), all failed to promote the desired transformation under the same conditions (Table 1, entries 2-5). Subsequent screening of reaction solvents indicated that the use of 1,4-dioxane was best, affording the pyrrole in 69% NMR yield (Table 1, entries 6-9). Considering the lower reactivity of nitriles toward the nucleophilic addition of organometallic reagents compared to carbonyl compounds, we reasoned that elevated temperature might be beneficial to promote the desired reaction. We found that 50 °C was optimal for this coupling process, and the ¹H NMR yield of the pyrrole product was further improved to 85% (Table 1, entries 10-12). Finally, examining different ratios of two starting materials revealed that the use of a slight excess of nitrile provided the best result for this transformation (Table 1, entries 13 and 14). It is worth mentioning that the formation of a minor regioisomer **3a''** was also observed. The ratio of two products (**3a'**: **3a''**) = 8:1 was not significantly affected by variation of the reaction conditions.

Table 2. Substrate Scope of Aryl-Substituted Enynes^a

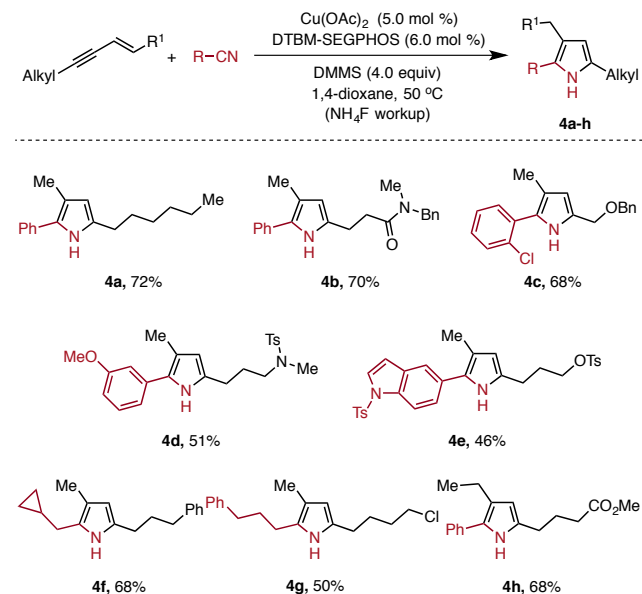


^a All yields represent average isolated yields of two runs, performed on 0.50 mmol scale. See the Supporting Information for detailed conditions. ¹⁵ rr = regioisomeric ratio.

With the optimized conditions for the pyrrole synthesis established, the reactivity of aryl-substituted enynes was first evaluated (Table 2). A variety of enynes with different substitution patterns on the aryl ring were converted to desired pyrrole products in good yields (**3b-d**). Moreover, substrates containing heterocycles, such as a pyridine (**3e**), a pyrimidine (**3f**), and a thiophene (**3n**), were also coupled with similar levels of efficiency. We observed that aromatic substrates with both electron-donating (**3g**) and -withdrawing groups (**3h**, **3l**) were good coupling partners. Aliphatic nitriles, typically less reactive compared to their aromatic counterparts, were also found to successfully engage in this transformation (**3m**, **3n**), providing the corresponding 2,3-dialkyl, 5-arylsubstituted pyrroles with moderate yields. Because of the mildness of the reaction conditions, a wide array of functional groups, such as a phenol (**3i**), an aryl bromide (**3j**), an ethyl ester (**3l**), a terminal olefin (**3m**), an aryl chloride (**3n**), and a silyl-protected alcohol (**3p**), were all well accommodated. Additionally, internal

enyne are generally more challenging substrates, since the barrier of hydrocupration step is higher for the sterically more hindered double bond.^{11a} Using this catalytic system, internal enynes were successfully coupled to benzonitrile, providing the desired products with good efficiency (**3o**, **3p**), although diminished regioselectivity was observed in some cases (**3p**).

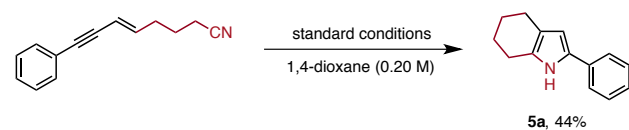
Table 3. Substrate Scope of Alkyl-Substituted Enynes.^a



^a All yields represent average isolated yields of two runs, performed on 0.50 mmol scale. See the Supporting Information for detailed conditions.

We next focused our efforts on investigating the ability of alkyl-substituted enynes to participate in this coupling reaction. As shown in Table 3, an assortment of alkyl enynes underwent the desired transformation with good efficiency. Importantly, various functional groups remained intact under the current conditions, including a tertiary amide (**4b**), a benzyl protected alcohol (**4c**), a sulfonamide (**4d**), an alkyl tosylate (**4e**), an aryl chloride (**4c**), an alkyl chloride (**4g**), and a methyl ester (**4h**). Moreover, both aromatic and aliphatic nitriles were found to react well with these enynes (**4f**, **4g**). Finally, we demonstrated that an alkyl-substituted internal enyne was a competent coupling partner as well, affording the desired product **4h** with good yield and regioselectivity.

Scheme 1. CuH-Catalyzed Intramolecular Enyne-Nitrile Coupling Reaction.



This CuH-catalyzed enyne-nitrile coupling could be performed in an intramolecular fashion by using a substrate containing both an enyne and a pendant nitrile. Under the standard conditions with decreased reaction concentration, the corresponding pyrrole **5a** was prepared in 44% isolated yield (Scheme 1).

Based on previously developed methods and past mechanistic studies, we proposed a plausible reaction mechanism outlined in Figure 2. First, a propargylcopper intermediate **II** could be generated from the hydrocupration of enyne **1a** with a bisphosphine-ligated CuH species (**I**). Rapid 1,3-isomerization of **II** might lead to the formation of a thermodynamically more stable allenylcopper isomer **III**, which would then undergo a nucleophilic addition reaction with benzonitrile **2a** via a six-membered transition state, providing imine intermediate **IV**. Subsequent ring closure¹⁶ of **IV** followed by 1,5-H shift and σ -bond metathesis with hydrosilane could produce the desired pyrrole product in a silylated form, while regenerating CuH catalyst **I**. A pathway involving propargyl copper intermediate **II** that reacts to form imine species **VII** (Figure 2, inner cycle), followed by cyclization to **VIII** would produce the minor regioisomer **3a''**.

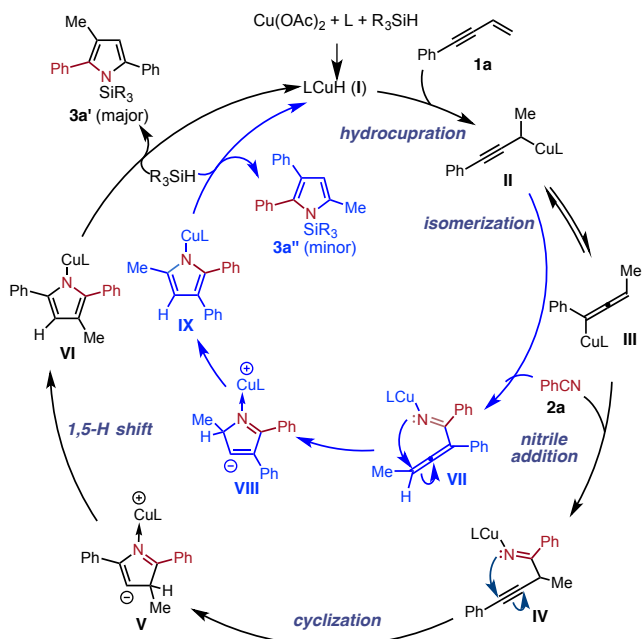
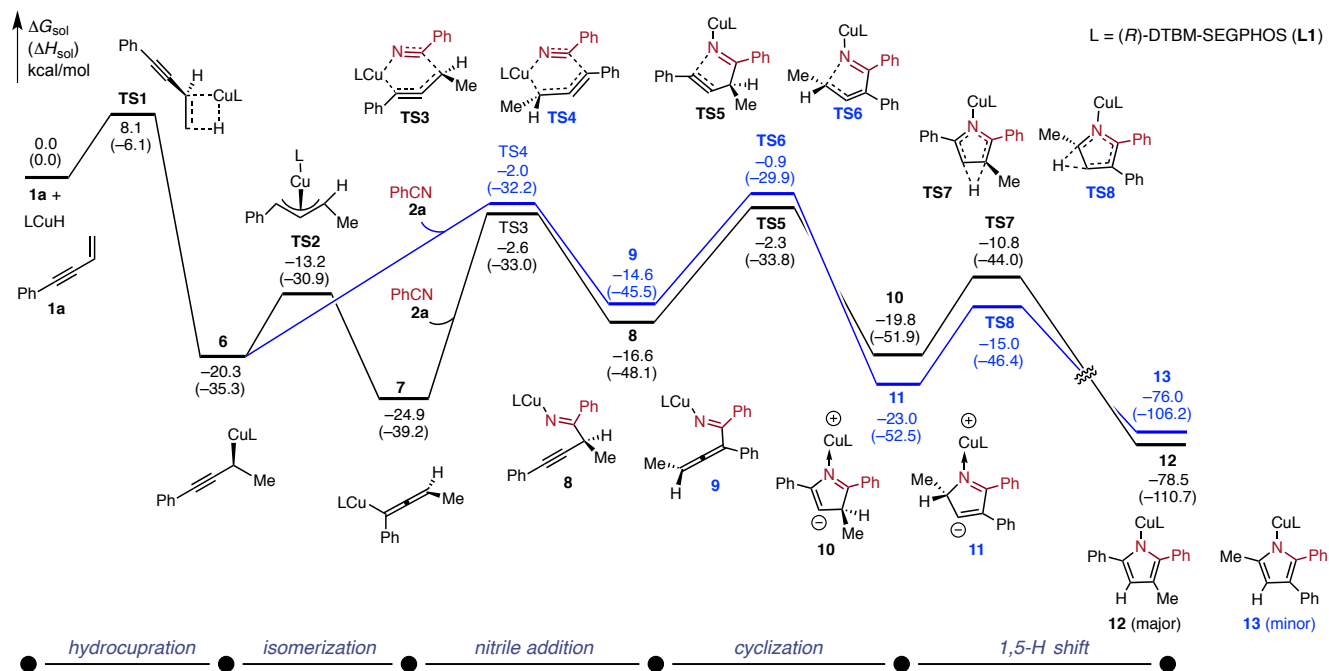


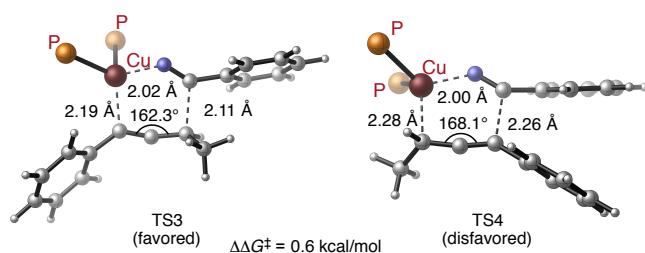
Figure 2. Proposed catalytic cycle.

A. Calculated reaction energy profile



DFT calculations were performed at the M06/SDD-6-311+G(d,p)/SMD(1,4-dioxane)//B3LYP/SDD-6-31G(d) level of theory.

B. Nitrile addition transition states (DTBM-SEGPHOS ligand omitted for clarity)



C. Cyclization transition states

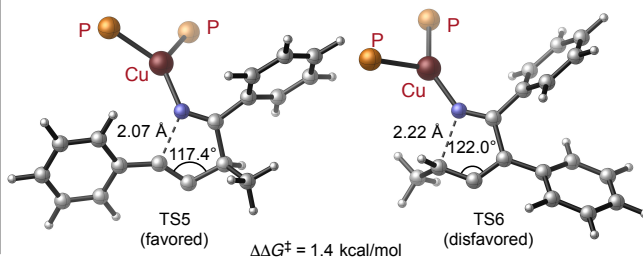


Figure 3. Reaction energy profile and transition state structures of the CuH-catalyzed coupling of enyne **1a** and nitrile **2a**.

We performed density functional theory (DFT) calculations to validate the proposed mechanism and to investigate the origin of the observed regioselectivity

(Figure 3). Consistent with previous DFT studies,¹⁷ the hydrocupration of enyne (**TS1**) and the subsequent 1,3-Cu shift (**TS2**) are both exothermic and have relatively

low barriers. The addition of the allenyl- and propargyl-copper intermediates to the nitrile occur via six-membered cyclic transition states (**TS3** and **TS4**, respectively).¹⁸ The resulting Cu-imine species (**8** and **9**) undergo facile cyclization via **TS5** and **TS6** to form 3*H*-pyrrol-4-yl and 2*H*-pyrrol-3-yl anions (**10** and **11**), respectively, which upon 1,5-H shift yield the more stable 1-pyrrolylcopper species **12** and **13**. The computed natural population analysis (NPA) atomic charges indicate that charge transfer from Cu facilitates the cyclization (see Figure S2 in the Supporting Information). It is conceivable that a small amount of Lewis acidic copper species could be formed under the experimental conditions,¹⁹ which will further accelerate this nucleophilic cyclization process via coordination with the alkyne or allene to enhance the electrophilicity of the π bond²⁰ (see the Supporting Information for the Lewis-acid promoted cyclization pathway). The nitrile addition and cyclization transition states leading to the major regioisomer (**TS3** and **TS5**) are both more stable than corresponding transition states to the minor regioisomer (**TS4** and **TS6**). Both **TS4** and **TS6** are destabilized by steric repulsions between the two adjacent phenyl groups about the forming C–C bond, which is constrained to a *syn*-periplanar conformation in the planar cyclic transition states.

In conclusion, we have developed a CuH-catalyzed enyne-nitrile coupling reaction that utilizes readily available building blocks to synthesize polysubstituted pyrroles. Both aromatic and aliphatic substrates were successfully engaged under the standard conditions, thus allowing the construction of pyrroles featuring diverse substitution patterns and functional groups with good efficiency. DFT calculations elucidated the mechanism and suggested the origins of regioselectivity. Studies on CuH-catalyzed reactions for the preparation of other heterocycles are currently ongoing.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data for all compounds (PDF).

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Notes

The authors declare no competing financial interest.

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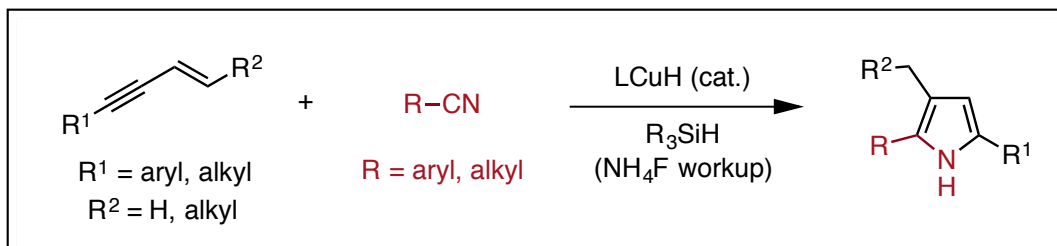
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- readily accessible starting materials
 - mild reaction conditions
 - diverse substitution patterns accommodated
 - good functional group tolerance
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