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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.

Pyroles are one of the most prevalent five-membered heterocycles, and are present in a large number of natural products, pharmaceuticals, and functional materials. In addition, they are valuable and useful building blocks in the preparation of complex molecules. Consequently, numerous synthetic strategies have been developed to access this important class of compounds. Traditional approaches, including the Knorr, Hantzsch, and Paal-Knorr reactions, 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 reactions and transition-metal-catalyzed couplings, 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, significantly 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. 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.\textsuperscript{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 alkylolithium reagents). We recently disclosed a CuH-catalyzed asymmetric addition reaction to ketones (Figure 1b),\textsuperscript{18c} in which conjugated enynes were employed as precursors to the key nucleophilic propargyl- (A)/allenylcopper intermediates (B). The reactivity manifested by \textit{in situ} generated species A and B caused us to survey their reactions\textsuperscript{12} with other readily available electrophiles.\textsuperscript{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 pyroles with a wide range of substitution patterns from commercially available nitriles and easily accessible enynes.\textsuperscript{14}

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

| entry | ligand | solvent | temp., °C | 1a : 2a | yield 3a\textsuperscript{a}, 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)\textsuperscript{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              |   |

\textsuperscript{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. \textsuperscript{b} Yield of major product 3a\textsuperscript{a} determined by \textsuperscript{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. \textsuperscript{c} Isolated yield of N-H pyrrole on 0.50 mmol scale after NH\textsubscript{4}F workup.

The reaction conditions were optimized using enyne 1a and benzonitrile 2a as the model substrates (Table 1). The N-silylated trisubstituted pyrrole 3a\textsuperscript{a} was obtained in 40% \textsuperscript{1}H 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), dpbz (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 \textsuperscript{1}H 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\textsuperscript{c} was also observed. The ratio of two products (3a\textsuperscript{a}: 3a\textsuperscript{c} = 8:1) was not significantly affected by variation of the reaction conditions.
aryl chloride mide of arylsubstituted pyrroles with moderate yields (reactive compared to their aromatic counterparts. 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 electron-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 enynes are generally more challenging substrates, since the barrier of hydrocupration step is higher for the sterically more hindered double bond. 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.

| Alkyl   | R1       | R-CN         | Cu(OAc)2 (6.0 mol %) | DMMS (4.0 equiv) | 1,4-dioxane, 50 °C (NH3F workup) |
|---------|----------|--------------|----------------------|------------------|-----------------------------------|
| Alkyl   | R1       | R-CN         | Cu(OAc)2 (6.0 mol %) | DMMS (4.0 equiv) | 1,4-dioxane, 50 °C (NH3F workup) |

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 propargyl-copper 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 closure 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.](image)

**A. Calculated reaction energy profile**

| TS1 | TS2 | TS3 | TS4 | TS5 | TS6 | TS7 | TS8 |
|-----|-----|-----|-----|-----|-----|-----|-----|
| 1a  | 1a  | 1a  | 1a  | 1a  | 1a  | 1a  | 1a  |
| LCuH| LCuH| LCuH| LCuH| LCuH| LCuH| LCuH| LCuH|
| 0.0 | -20.3 | -34.9 | -20.3 | -24.9 | -20.3 | -20.3 | -20.3 |
| (-6.1)| (-35.5)| (-39.2)| (-35.5)| (-39.2)| (-35.5)| (-35.5)| (-35.5)|

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)

![Figure 3. Reaction energy profile and transition state structures of the CuH-catalyzed coupling of enyne 1a and nitrile 2a.](image)

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, 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, re-
spectively).19 The resulting Cu-imine species (8 and 9) un-
dergo facile cyclization via TS5 and TS6 to form 3H-
pyrrol-4-yl and 2H-pyrrol-3-yl anions (10 and 11), re-
spectively, which upon 1,5-H shift yield the more stable
1-pyrrolylcopper species 12 and 13. The computed natu-
ral population analysis (NPA) atomic charges indicate
that charge transfer from Cu facilitates the cyclization
(see Figure S2 in the Supporting Information). It is con-
ceivable that a small amount of Lewis acidic copper
species could be formed under the experimental condi-
tions,19 which will further accelerate this nucleophilic
cyclization process via coordination with the alkylene
or allene to enhance the electrophilicity of the π bond20
(see
the
Supporting
Information
for
the
Lewis-acid promoted cyclization pathway). The nitride
addition and cycliza-
tion 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 form-
ing 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
eynone-nitride 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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REFERENCES

(1) a) Khajuria, R.; Dham, S.; Kapoor, K. K. Active Methylenes in
the Synthesis of a Pyrrole Motif: An Imperative Structural Unit
in Pharmaceuticals, Natural Products and Optoelectronic Materials.
RSC Adv. 2016, 6, 37039–37066. (b) Young, I. S.; Thornton, P. D.;
Thompson, A. Synthesis of Natural Products Containing the Pyrrolic
Ring. Nat. Prod. Rep. 2010, 27, 1801–1839. (c) Fürstner, A. Chemis-
ty and Biology of Roseophilin and the Prodigiosin Alkaloids: A
Survey of the Last 2500 Years. Angew. Chem. Int. Ed. 2003, 42,
3582–3603. (d) Jacobi, P. A.; Coutts, L. D.; Guo, J.; Hauck, S. I.;
Leung, S. H. New Strategies for the Synthesis of Biologically Im-
portant Tetrapyrroles. The “B,C + D + A” Approach to Linear
Tetrapyrroles. J. Org. Chem. 2000, 65, 205–213.

(2) (a) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhaman, S.; Sharma, P.
Pyrrole: A Resourceful Small Molecule in Key Medicinal Hetero-
aromatics. RSC Adv. 2015, 5, 15233–15266. (b) Arikawa, Y.; Nishida,
H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Horii, Y.;
Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Tak-
gagi, T.; Takeuchi, T.; Kajino, M. Discovery of a Novel Pyrrole Deriva-
tive [1-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-
N-methylmethanamine Fumarate (TAK-438) as a Potassium-
Competitive Acid Blocker (P-CAB). J. Med. Chem. 2012, 55,
4446–4456. (c) Wang, M.-Z.; Xu, H.; Liu, T.-W.; Feng, Q.; Yu, S.-J.;
Wang, S.-H.; Li, Z.-M. Design, Synthesis and Antifungal Activities of
Novel Pyrrole Alkaloid Analogues. Eur. J. Med. Chem. 2011, 46,
1463–1472. (d) van Pec, K.-H.; Ligon, J. M. Biosynthesis of Pyrrolin
and Other Phenylypyrrole Derivatives by Bacteria. Nat. Prod. Rep.
2000, 17, 157–164.

(3) (a) Takase, M.; Yoshiida, N.; Narita, T.; Fujio, T.; Nishinaga, T.;
Iyoda, M. Sterically Congested Pyrrole-Fused Tetrathiiafulvalene
Decamers as Highly Conductive Amorphous Molecular Materials.
RSC Adv. 2012, 2, 3221–3224. (b) Brothers, P. J. Boron Complexes
of Pyrryl Ligands. Inorg. Chem. 2011, 50, 12374–12386. (c) Ulrich,
G.; Ziessel, R.; Harriman, A. The Chemistry of Fluorescent Bodipy
Dyes: Versatility Unsurpassed. Angew. Chem. Int. Ed. 2008, 47,
1184–1201. (d) Wood, T. E.; Thompson, A. Advances in the Chemis-
try of Dipyrrins and Their Complexes. Chem. Rev. 2007, 107,
1831–1861. (e) Loudel, A.; Burgues, K. BODIPY Dyes and Their Deriva-
tives: Syntheses and Spectroscopic Properties. Chem. Rev. 2007, 107,
4891–4932.

(4) (a) Dipakranjan, M.; Brateen, S.; Bidyut, K. D. Pyrrole and Its
Derivatives. In Heterocycles in Natural Product Synthesis; Majumdar,
K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp
187–220. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. Lamellarins
and Related Pyrrole-Derived Alkaloids from Marine Organisms.
Chem. Rev. 2008, 108, 264–287.

(5) (a) Knorr, L. Synthetische Versuche mit dem Acetessigester. II.
Mittheilung: Ueberfuhrung des Diacetethersinsasureesters und des
Acetessigesters in Pyrrolidervaten. Ann. 1886, 216, 290–296.

(6) (a) Hantzsch, A. Neue Bildungsweise von Pyrrollderivaten. Ber.
Dtsch. Chem. Ges. 1890, 23, 1474–1476. (b) Leonardo, M.; Estévez,
V.; Villacampa, M.; Menéndez, J. C. The Hantzsch Pyrrole Synthesis:
Non-Conventional Variations and Applications of a Neglected Classi-
cal Reaction. Synthesis 2019, 51, 816–828.

(7) (a) Knorr, L. Ludwig Knorr: Synthese von Pyrrollderivaten. Ber.
Dtsch. Chem. Ges. 1884, 17, 1635–1642. (b) Paal, C. Synthese von
Thiopen- und Pyrrollderivaten. Ber. Dtsch. Chem. Ges. 1885, 18,
367–369. (c) Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. High-
ly Atroposelective Synthesis of Arylpyrroles by Catalytic Asymmetric
Paal–Knorr Reaction. J. Am. Chem. Soc. 2017, 139, 1714–1717. (d)
Kim, B. H.; Bae, S.; Go, A.; Lee, H.; Gong, C.; Lee, B. M. Synthesis of Two Distinct Pyrrole Moeity Containing Arenes from Nitroalanes using Paal-Knorr Followed by an Indium-Mediated Reaction. Org. Biomol. Chem. 2016, 14, 265–276.

(8) (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. Recent Advances in the Synthesis of Pyrroles by Multicomponent Reactions. Chem. Soc. Rev. 2014, 43, 4633–4657. (b) Estévez, V.; Villacampa, M.; Menéndez, J. C. Multicomponent Reactions for the Synthesis of Pyrroles. Chem. Soc. Rev. 2010, 39, 4402–4421.

(9) For selected reviews, see: (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles. Chem. Rev. 2013, 113, 3084–3213. (b) Nakamura, I.; Yamamoto, Y. Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis. Chem. Rev. 2004, 104, 2127–2198. (c) Yoshikai, N.; Wei, Y. Synthesis of Pyrroles, Indoles, and Carbazoles through Transition-Metal-Catalyzed C–H Functionalization. Asian J. Org. Chem. 2013, 2, 466–478. For selected examples of recent publications, see: (d) Kawakita, K.; Beaumier, E. P.; Kakiuchi, Y.; Tsurugi, H.; Tonks, I. A.; Mashima, K. Bis(imido)vanadium(V)-Catalyzed [2+2–1] Coupling of Alkynes and Azobenzenes Giving Multisubstituted Pyrroles. J. Am. Chem. Soc. 2019, 141, 4194–4198. (e) Li, M.-B.; Gape, E. S.; Bäckvall, J.-E. Palladium–Cu-Catalyzed Stereoselective C–O Bond Formation for the Construction of Pyrrole Rings: Control of Reactivity and Selectivity. ACS Catal. 2019, 9, 5184–5190. (f) Chiu, H.-C.; Tonks, I. A. Trimethylsilyl-Protected Alkenes as Selective Cross-Coupling Partners in Titanium-Catalyzed [2+2+1] Pyrrole Synthesis. Angew. Chem. Int. Ed. 2018, 57, 6090–6094. (g) Andreou, D.; Kallisitsis, M. G.; Loukopoulos, E.; Gabriel, C.; Kostakis, G. E.; Lykakis, I. N. Copper-Promoted Regioselective Synthesis of Polysubstituted Pyrroles from Aldehydes, Amines, and Nitroalanes via 1,2-Phenyl/Alkyl Migration. J. Org. Chem. 2018, 83, 2104–2113. (h) Gilbert, Z. W.; Hue, R. J.; Tonks, I. A. Catalytic Formal [2+2+1] Synthesis of Pyrroles from Aldehydes and Diazenes via T1/T1 Redox Catalysis. Nat. Chem. 2016, 8, 63–68. (i) Xiong, T.; Li, N.; Liu, Y.; Zhang, G.; Zhang, Q.; Xiong, T.; Zhang, Q. Ligand-Controlled Regioselectivity of Reported Examples ranges from 5:1 to 20:1 and are determined by 1H NMR spectroscopy. In some cases, the ratio is less accurate due to the overlap of signals for the two regioisomers. The two regioisomers can be well separated by silica gel chromatography. The isolated yields reported in Table 2 refer to the major products unless otherwise noted.

(16) For precedent reports on copper-catalyzed cyclization of alkynyl imine/enamine, see: (a) Kel’ in, A. V.; Sromek, A. W.; Gevorgyan, V. A Novel Cu-Assisted Cycloisomerization of Alkynyl Imines: Efficient Synthesis of Pyrroles and Pyrrole-containing Heterocycles. J. Am. Chem. Soc. 2001, 123, 2074–2075. (b) Martin, R.; Rodriguez Rivero, M.; Buchwald, S. L. Domino Cu-Catalyzed C–N Cou-
pling/Hydroamidation: A Highly Efficient Synthesis of Nitrogen Heterocycles. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079–7082.

(17) (a) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. Catalytic Asymmetric Hydroamination of Unactivated Internal Olefins to Aliphatic Amines. *Science* **2015**, *349*, 62–66. (b) Ye, Y.; Kim, S.-T.; Jeong, J.; Baik, M.-H.; Buchwald, S. L. CuH-Catalyzed Enantioselective Alkylation of Indole Derivatives with Ligand-Controlled Regiodivergence. *J. Am. Chem. Soc.* **2019**, *141*, 3901–3909. (c) Li, C.; Liu, R. Y.; Jesikiewicz, L. T.; Yang, Y.; Liu, P.; Buchwald, S. L. CuH-Catalyzed Enantioselective Ketone Allylation with 1,3-Dienes: Scope, Mechanism, and Applications. *J. Am. Chem. Soc.* **2019**, *141*, 5062–5070.

(18) We have also located anti-addition transition states in which the benzonitrile approaches from the opposite face of the π-system and thus does not coordinate to the Cu. These transition states are significantly higher in energy. See the SI for details.

(19) Bandar, J. S.; Pirnot, M. P.; Buchwald, S. L. Mechanistic Studies Lead to Dramatically Improved Reaction Conditions for the Cu-Catalyzed Asymmetric Hydroamination of Olefins. *J. Am. Chem. Soc.* **2015**, *137*, 14812–14818.

(20) (a) Gronnier, C.; Kramer, S.; Odabachian, Y.; Gagosz, F. Cu(I)-Catalyzed Oxidative Cyclization of Alkynyl Oxiranes and Oxetanes. *J. Am. Chem. Soc.* **2012**, *134*, 828–831. (b) Li, L.; Chen, X.-M.; Wang, Z.-S.; Zhou, B.; Liu, X.; Lu, X.; Ye, L.-W. Reversal of Regioselectivity in Catalytic Arene-Ynamide Cyclization: Direct Synthesis of Valuable Azepino[4,5-b]indoles and β-Carbolines and DFT Calculations. *ACS Catal.* **2017**, *7*, 4004–4010. (c) Li, L.; Janesko, B. G. 3-Methyleneisoindolin-1-one Assembly via Base- and Cu/I-Proline-Catalyzed Domino Reaction: Mechanism of Regioselective Anionic Cyclization. *J. Org. Chem.* **2016**, *81*, 10802–10808. (d) Yuan, B.; He, R.; Shen, W.; Huang, C.; Li, M. Mechanistic Insights into the Cu(I)- and Cu(II)-Catalyzed Cyclization of o-Alkynylobenzaldehydes: The Solvent DMF and Oxidation State of Copper Affect the Reaction Mechanism. *J. Org. Chem.* **2015**, *80*, 6553–6563.
R1 = aryl, alkyl
R2 = H, alkyl

R1 = aryl, alkyl
R = aryl, alkyl

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