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A Convergent Synthesis of Functionalized Alkenyl Halides via Co(III)-Catalyzed Three-Component C–H Bond Addition

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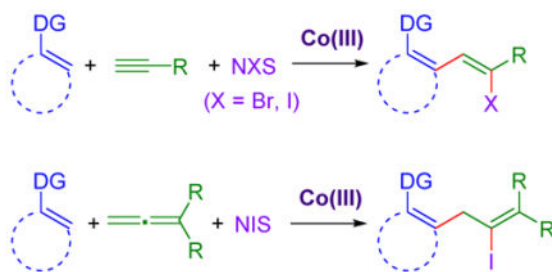
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Abstract

A Co(III)-catalyzed three-component coupling of C(sp²)-H bonds, alkynes, and halogenating agents to give alkenyl halides is reported. This transformation proceeds with high regio- and diastereoselectivity, and is effective for a broad range of aryl and alkyl terminal alkynes. Diverse C–H bond partners also exhibit good reactivity for a range of heteroaryl and aryl systems as well as synthetically useful secondary and tertiary amide, urea, and pyrazole directing groups. This multi-component transformation is also compatible with allenes in place of alkynes to furnish tetra-substituted alkenyl halides, showcasing the first halo-arylation of allenes.

Triple Play

A convergent assembly of functionalized alkenyl halides is reported via Co(III)-catalyzed three-component C–H bond addition across alkynes and halogenating agents. The reaction proceeds with high regio- and diastereoselectivity and is effective for a wide range of alkynes and C–H bond substrates. Allenes are also suitable substrates for the preparation of tetra-substituted alkenyl halide products.



Keywords

C–H activation; homogeneous catalysis; multicomponent reactions; alkynes; allenes

Transition-metal-catalyzed C–H functionalization has become a powerful synthetic approach that relies on simple and readily available starting inputs. In directed C–H bond functionalization, a C–H bond substrate and a transition-metal catalyst typically form a

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nucleophilic metallocycle intermediate that adds across a single coupling partner to create a functionalized product (Figure 1a).^{1,2} Three-component C–H functionalization using two different coupling partners theoretically would provide efficient entry to an enormous array of diverse and complex products in a single reaction, especially when one considers the very large number of potential coupling partner combinations (Figure 1b).³

Recently our lab published on the Co(III)-catalyzed three-component diastereoselective synthesis of β -hydroxy ketones, utilizing enones and aldehydes (Figure 2a).^{3a} To expand upon this first example of intermolecular multi-component C–H functionalization,⁴ we sought to extend this approach to different C–H functionalization substrates and coupling partners. Herein we describe a new Co(III)-catalyzed three-component coupling wherein the C–H bond sequentially adds to terminal alkynes or allenes and halogenating agents to provide functionalized alkenyl halides with high regio- and diastereoselectivity (Figure 2b). Notably, alkenyl halides are versatile synthetic handles for many important transformations.^{5,6}

We began by exploring terminal alkynes^{7,8,9} and halogenating agents as the two coupling partners. Significantly, neither of these inputs had previously been explored in an intermolecular three-component C–H bond functionalization. Successful coupling required initial addition to the alkyne instead of the more electrophilic halogenating agent.¹⁰ More challenging was the identification of suitable conditions for halogenation of the alkenyl-metal intermediate while minimizing well-established and efficient proto-demetalation to give the undesired alkene.⁷ Additionally, terminal alkynes are susceptible to C–H bond activation, and this mode of activation needed to be avoided to prevent side reactions such as homocoupling or oligomerization.¹¹

A thorough exploration of reaction conditions established that the preformed air-stable Co(III)-catalyst [Cp*Co(MeCN)₃][SbF₆]₂ in conjunction with sparing amounts of acetic acid (2.5 mol %) at 40 °C provided the desired alkenyl iodide **4a** in 71% yield from thiophene-amide **1a**, phenylacetylene (**2a**), and *N*-iodosuccinimide (NIS) (Table 1) (see Table S1 in SI). Direct C–H iodination was not observed, suggesting that under the reaction conditions, alkenylation completely outcompetes iodination.^{12–14} Acetic acid has previously been found to be an effective additive for facilitating Co(III)-catalyzed C–H bond additions to π -bonds and was crucial to achieving effective alkyne coupling. However, only sub-stoichiometric amounts of acetic acid relative to catalyst loading could be used to minimize undesired proto-demetalation of the alkenyl cobalt intermediate. It is also noteworthy that Rh(III) catalysts, which often show parallel reactivity to Co(III), were ineffective for this transformation.

Once optimal conditions were determined, different halogenating agents and a wide range of terminal alkynes **2** were evaluated (Table 1). In addition to NIS to give **4a**, *N*-bromosuccinimide (NBS) provided alkenyl bromide **4b** in good yield (see also **4x** in Table 2, vide infra). However, chlorination with *N*-chlorosuccinimide was unsuccessful.

Next, a range of substituents was examined on the aryl alkyne (Table 1). Electron donating substituents furnished alkene products **4c** and **4d** in good yields. Alkynes with electron

withdrawing chloro and carboxyester groups also coupling efficiently to generate alkenyl iodides **4e** and **4f** in 68% and 58% yields, respectively. Additionally, a heteroaryl terminal alkyne coupled to give **4g** in 56% yield. A broad range of alkyl alkynes were also effective substrates. Linear and β -branched alkyl alkynes gave alkenyl iodides **4h** and **4i** in high yields, and 4-phenyl-1-butyne led to product **4j** in 74% yield. In contrast, α -alkyl branching in ethynylcyclohexane provided alkenyl iodide **4k** in lower yield. A variety of heteroatom functionality could be incorporated on the alkyne coupling partner, including a Boc-protected amine (**4l**), a propargyl ether (**4m**), a silyl ether (**4n**) and an ester (**4o**), all in 80% yields. Notably, alkenyl iodides **4** were obtained with >95% regio- and diastereoselectivity for every terminal alkyne examined. However, internal alkynes did not give three-component products with **1a** primarily recovered.¹⁵

A variety of different C–H bond partners were also effective for coupling with both aryl and alkyl alkynes (Table 2). Thiophenes with alkyl- or halo-substituents at the 5-position underwent three-component coupling to give products **4p** and **4q** in 85% and 75% yields, respectively. Moreover, the thiophene could be replaced with a furan to provide product **4r** in 45% yield. In addition to the tertiary pyrrolidine amide directing group, secondary amides with varying steric character were also effective. For example, *N*-Me and *N*-*i*Pr amides furnished products **4s** and **4t** in good yields. For **4s**, the regio- and stereochemistry was rigorously confirmed by X-ray crystallography.¹⁶ Furthermore, pyrrole protected as the *N,N*-dimethyl urea also coupled to give **4u**. Finally, aromatic C–H bond functionalization was demonstrated using the pyrazole directing group as exemplified by alkenyl halides **4v** – **4x**.

A number of experiments were conducted to probe the mechanistic features of this three-component transformation (Schemes 1–2). The potential participation in catalysis of alkene **5a**, an undesired two-component coupling byproduct produced in minor amounts under the reaction conditions, was initially investigated. First, alkene product **5a** and NIS were subjected to the standard reaction conditions (Scheme 1a). Excellent recovery of alkene **5a** was observed and no alkenyl iodide **4a** could be detected. Second, substrate **1b**, 1-hexyne, and NIS were submitted to the standard reaction conditions with one equiv of **5a** as an additive (Scheme 1b). The presence of **5a** did not affect the yield of the three component coupling product **4p**, and again, **5a** was not iodinated. Together, these experiments clearly establish that two-component byproduct **5a** is not an intermediate and does not interfere with the catalytic cycle.

Experiments with deuterated substrate **1a-D** also defined key features of the reaction (Scheme 2). When deuterated product **1a-D** was subjected to the optimal reaction conditions for only 1 h, no deuterium exchange was observed in the recovered starting material. The lack of scrambling at the site of C–H functionalization is unexpected because extensive deuterium exchange by reversible orthometallation is almost always observed for Cp*Co(III)-systems.¹⁷ Initial rates were next independently determined for protio **1a** and deuterio **1a-D** under the standard catalyst and acetic acid loadings (See Section 7 of SI). A primary kinetic isotope effect (KIE) of 2.15 ± 0.16 was observed, which is consistent with orthometallation as a rate-determining step.

A possible mechanism for the reaction consistent with the high regio- and diastereoselectivity and the aforementioned mechanistic studies is depicted in Scheme 3. First, irreversible orthometallation of **1** with the cationic Co(III)-catalyst furnishes cobaltacycle **6**. Regioselective syn-insertion of **6** into the terminal alkyne then generates alkenyl-cobalt **7**. Finally, intermediate **7** reacts with the halogenating agent **3** to provide the desired three-component product **4** with release of the cationic Co(III)-catalyst. An undesired minor pathway for intermediate **7** is proto-demetalation to give the alkene product **5**, also with release of the active catalyst.

Allenes were also investigated as possible three-component coupling partners with NIS to generate tetra-substituted alkenyl iodides (Table 3).¹⁸ Few examples of Co(III)-catalyzed C–H bond additions to allenes have been reported,^{19,20} with the first hydroarylation of allenes appearing only very recently.¹⁹ In particular, 1,1-disubstituted allenes **8** were effective three-component coupling electrophiles to give **9a–c** in good yields. These allylated thiophene amides nicely complement the alkenylated derivatives obtained with the aforementioned three-component reactions of terminal alkynes. To the best of our knowledge, halo-arylation of allenes has not previously been reported.

In summary, a novel multi-component transformation has been developed using Co(III) catalysis to form functionalized alkenyl halides with high regio- and stereoselectivity. This coupling proceeds with broad alkyne scope, and is applicable to a variety of C–H bond substrates and directing groups. Additionally, we have showcased that allenes are suitable reaction partners for the synthesis of allylated products incorporating tetra-substituted alkenyl iodides. Significantly, the alkenyl iodide functionality present in products **4** and **9**, are well documented to be capable of undergoing a range of metal-catalyzed transformations. We are currently investigating the C–H bond three-component coupling of numerous additional coupling partner combinations for the synthesis of interesting and useful structures in a straightforward and convergent manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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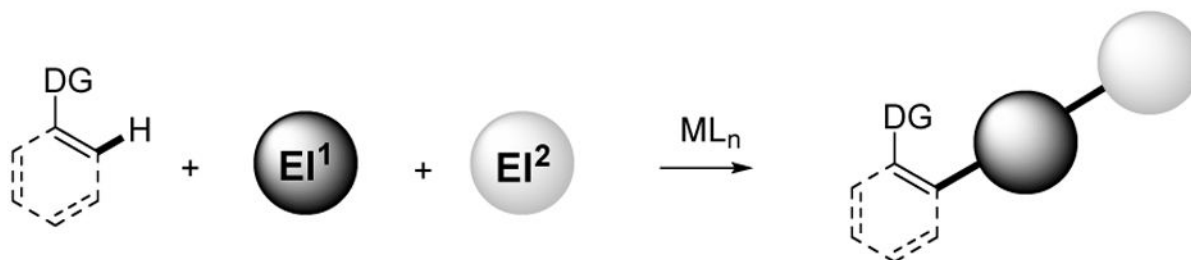
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(a) General strategy for directed C–H functionalization with one coupling partner



(b) Three-component strategy with sequential addition of two coupling partners

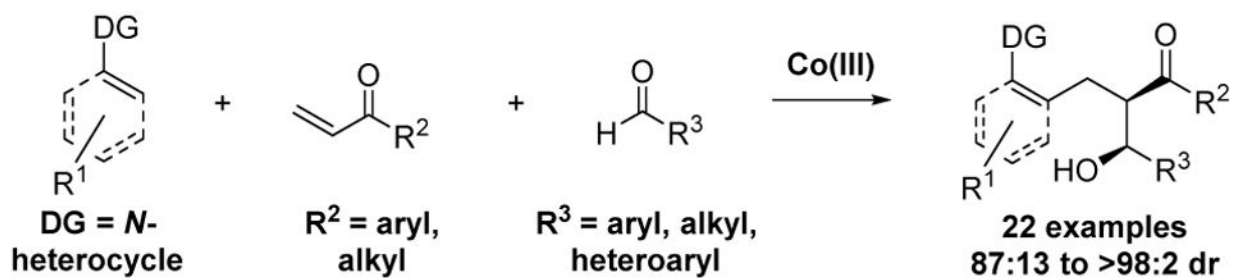


**Rapid assembly of complex structures
Large array of electrophile combinations**

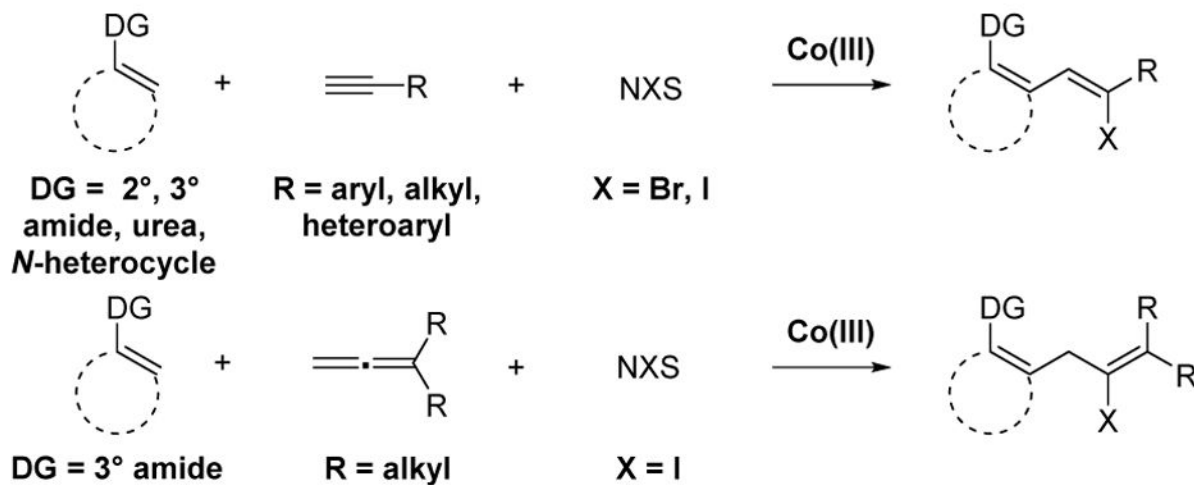
Figure 1.
Overview of three-component C–H functionalization approach.

Prior work:

(a) Diastereoselective three-component coupling of enones and aldehydes

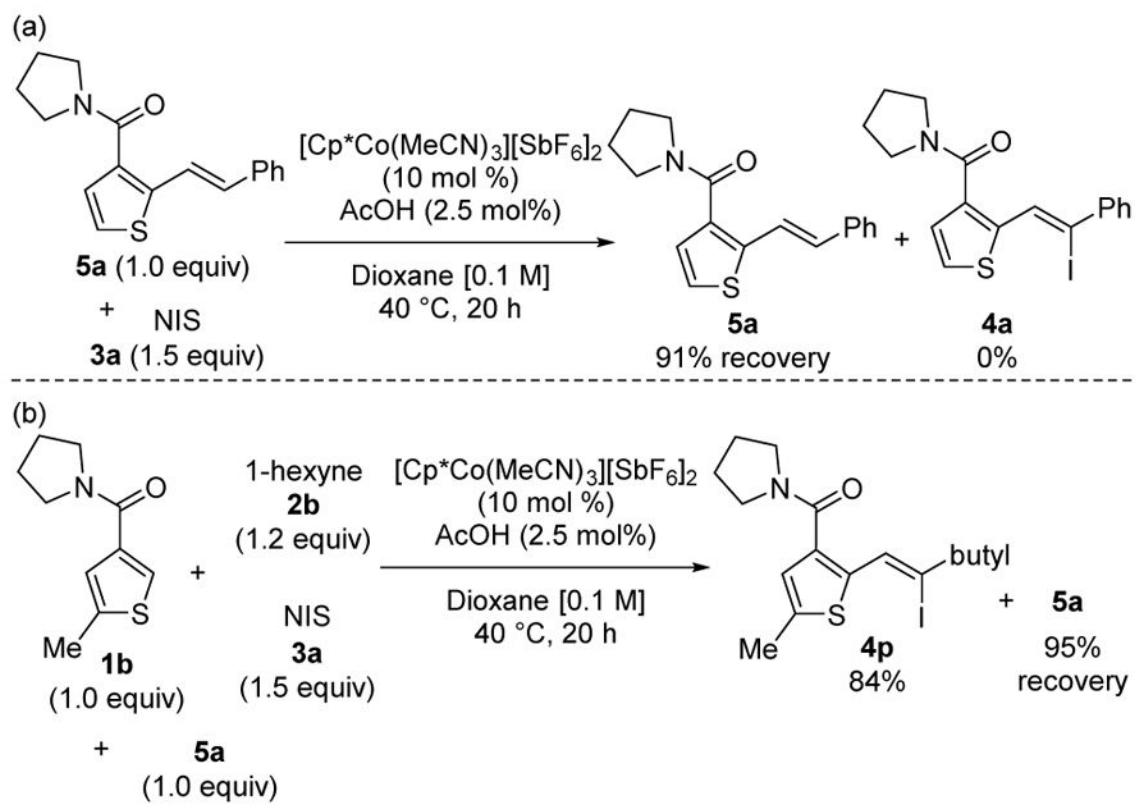
**This work:**

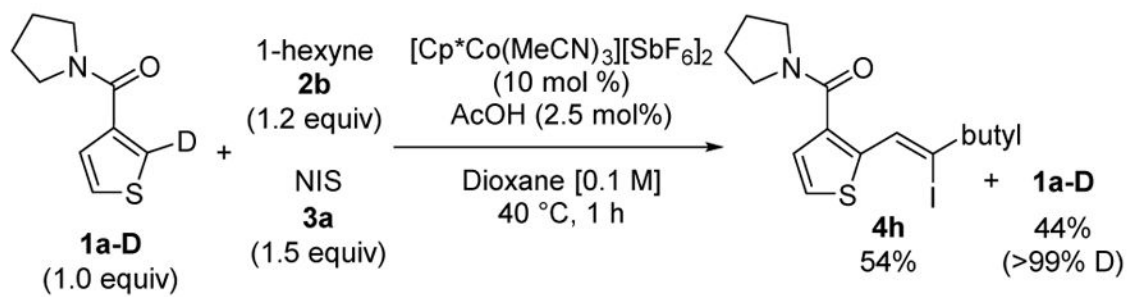
(b) Three-component coupling of alkynes, allenes, and halogenating agents



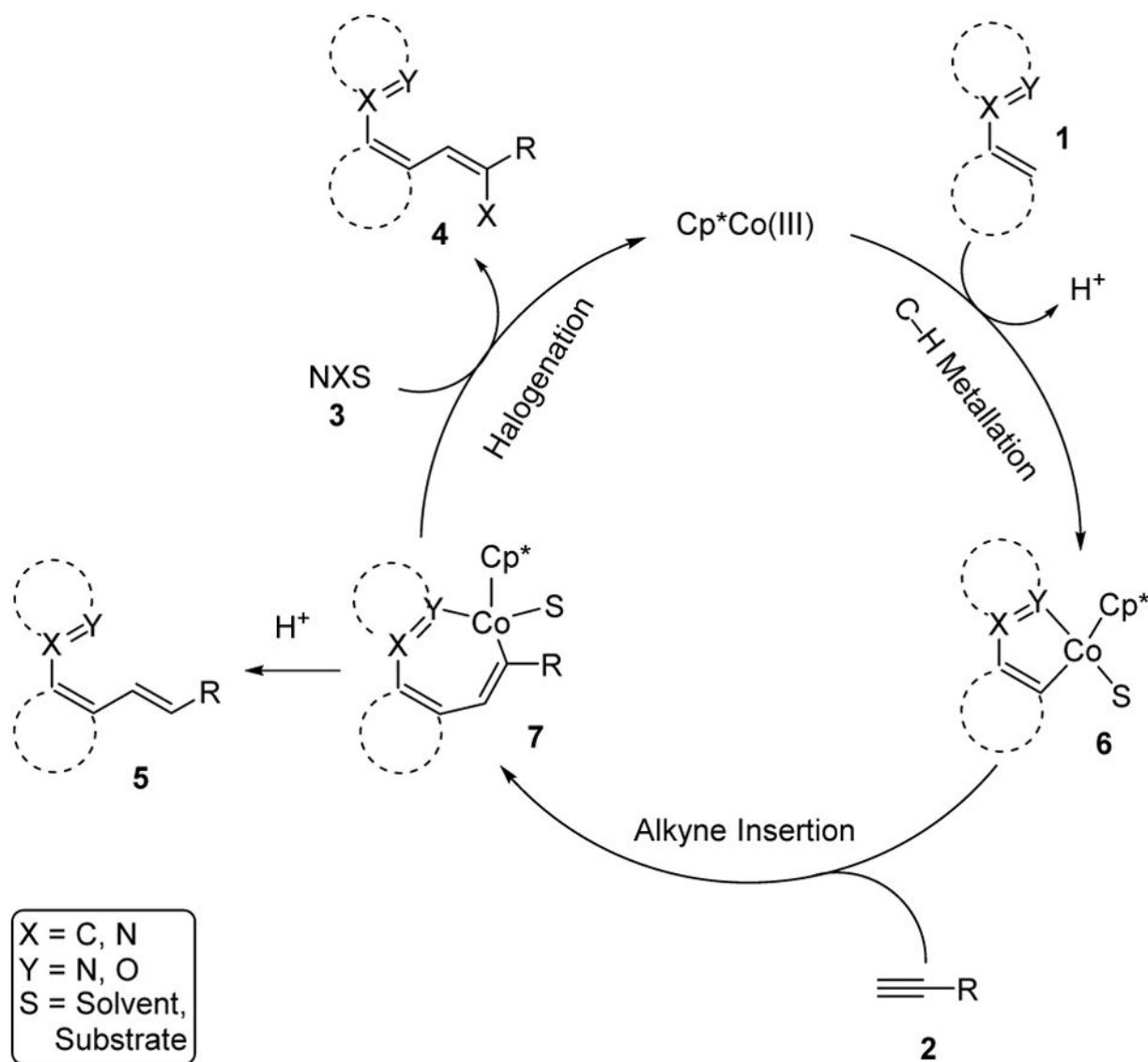
High regio- and diastereoselectivity
Efficient entry into tri- and tetra-substituted alkenyl halides

Figure 2.
 Co(III)-catalyzed three-component transformations.

**Scheme 1.**Mechanistic experiments with two-component product **5a**

**Scheme 2.**

No observed H/D exchange for **1a-D** under reaction conditions



Scheme 3.
Proposed mechanism for the Co(III)-catalyzed three-component transformation.

Table 1

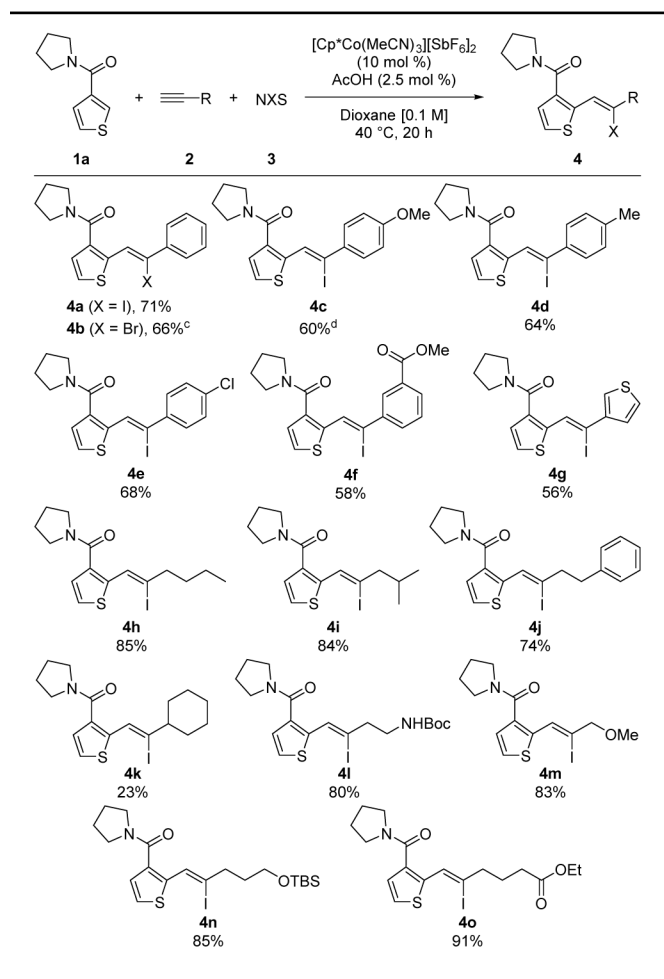
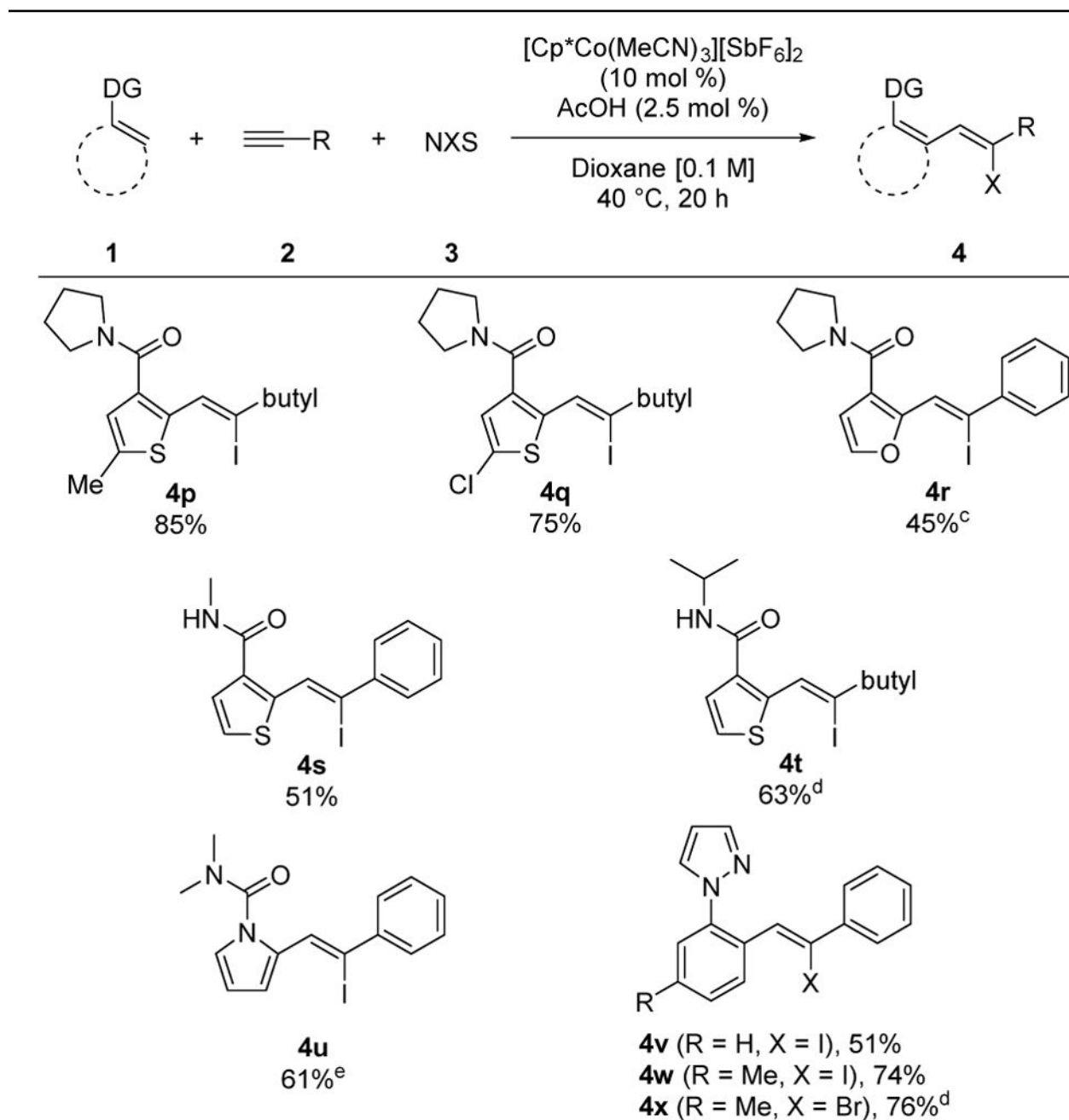
Alkyne scope for the three-component addition cascade.^{[a],[b]}^[a] Conditions: **1a** (1.0 equiv at 0.1 M), **2** (1.2 equiv), and **3** (1.5 equiv).^[b] Isolated yields.^[c] Using 10 mol % of AcOH.^[d] Using 5 mol % of AcOH.

Table 2

C–H bond partner scope in the three-component addition cascade.^{[a],[b]}^[a]Conditions: **1** (1.0 equiv at 0.1 M), **2** (1.2 equiv), and **3** (1.5 equiv).^[b]Isolated yields.^[c]Using 5 mol % of AcOH.

[d] Using 10 mol % of AcOH.

[e] **1** (1.5 equiv), **2** (1.0 equiv), and **3a** (1.1 equiv) using 20 mol % of LiOAc at 60 °C.

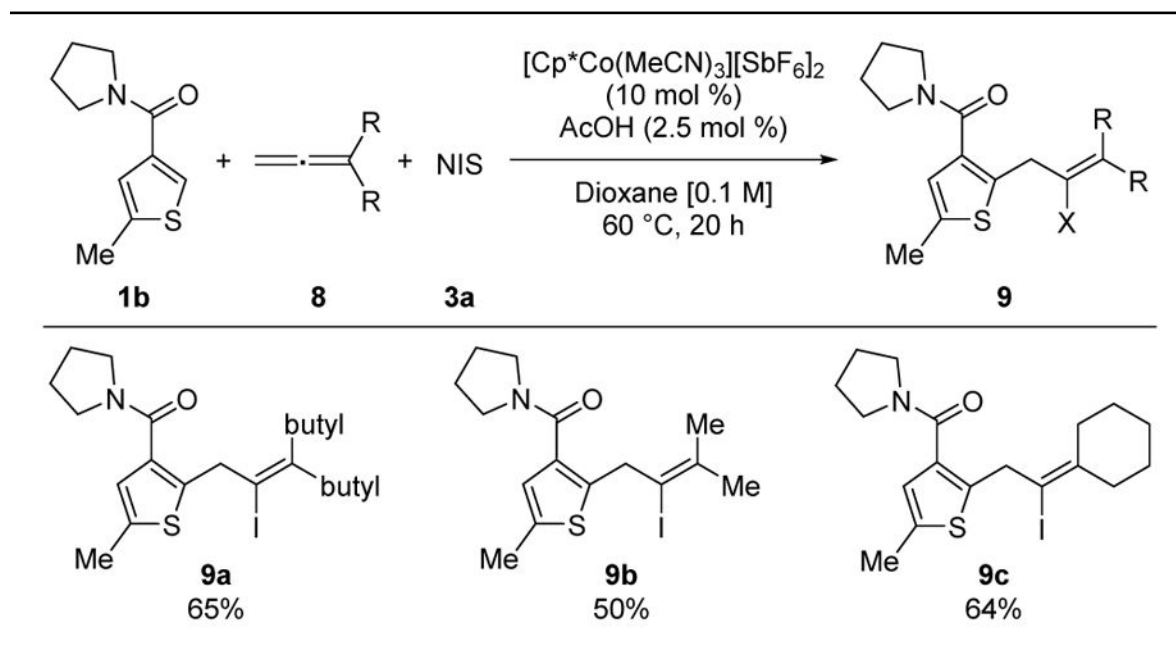
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Table 3

Synthesis of alkenyl iodides via three-component coupling with allenes ^{[a],[b]}^[a] Conditions: **1b** (1.0 equiv at 0.1 M), **8** (1.2 equiv), and **3a** (1.5 equiv).^[b] Isolated yields.