Copper Catalysis

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Copper-Catalyzed Arylative Meyer–Schuster Rearrangement of Propargylic Alcohols to Complex Enones Using Diaryliodonium Salts**

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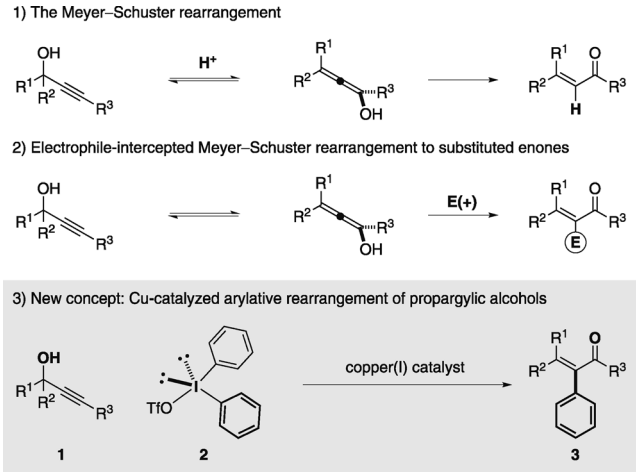
Propargylic alcohols are among the most useful bifunctional building blocks available to the synthetic chemist. Generated through well-established and robust strategic bond-forming reactions, propargylic alcohols have provided a fertile testing ground upon which to explore new catalytic activation pathways. Many previously unknown catalytic transformations have been discovered starting from these readily assembled molecules and have greatly expanded the toolbox of chemical reactions.[1]

Of the range of useful reactions available to propargylic alcohols, the Meyer–Schuster rearrangement to enones is a transformation of significant synthetic potential that has not been widely exploited in synthesis.[2] This rearrangement reaction involves the loss of the hydroxy group from a propargylic alcohol to form a carbocation intermediate followed by re-addition of the hydroxy to the remote end of the carbon–carbon triple bond, forming an allenol. Finally protonation at the central carbon atom of this species forms the enone product. A major shortcoming of this classic reaction is the promotion of the desired rearrangement amongst many possible (and often more favorable) competing pathways. One way that the Meyer–Schuster rearrangement can be promoted is through the use of transition metal catalysts that coordinate the π-system of the alkyne and by the use of electronically activating substitutents.[2c] As a result, recent catalytic developments have enabled this process to be controlled in such a fashion that the enone products can be formed in good yields and selectivities for the *E*-isomer. In order to broaden the utility of this classical process, we reasoned that if the key protonation step could be replaced by reaction of the allenol with an electrophile, the Meyer–Schuster rearrangement could be extended to produce complex enone products, thereby expanding the repertoire of synthetically useful transformations available directly from propargylic alcohol feedstocks. This transformation would provide facile entry to highly substituted variants of a class of molecules that are recognized as valuable synthetic building blocks due to their flexibility in many reactions, ranging from Diels–Alder cycloadditions to catalytic hydrogenations.[3] Notably, there have been two recent developments that are related to this type of proposed transformation. Firstly, Zhang et al. reported an oxidative Au-catalyzed reaction of propargylic acetates with arylboronic acids in the presence of Selectfluor to provide a range of simple trisubstituted enones in reasonable yields.[4] Secondly, Trost and co-workers employed a contemporaneous dual catalysis system that linked Pd-catalyzed π-allylic alkylation with V-catalyzed rearrangement of proparglic alcohols to form a broad range of α-allyl enone products.[5]



As part of an ongoing program geared towards the development of novel catalysis concepts, our laboratory has developed a series of new carbon–aryl bond forming reactions exploiting the electrophilic reactivity of high oxidation state copper(III)–aryl species.[6] Recently, we reported that enol silanes undergo arylation to give α-aryl carbonyl compounds through copper-catalyzed reaction with diaryliodonium salts.[6e] Given that the intermediate in the Meyer–Schuster reaction is an allenol, we questioned whether a propargylic alcohol could serve as a source of allenol under our copper-catalysis conditions and react with a diaryliodonium salt[7] through the putative copper(III)–aryl species[8] to form trisubsituted enone products. Herein, we report the realization of this ideal through the development of a copper-catalyzed arylative Meyer–Schuster rearrangement. A range of substituted propargylic alcohols and a wide selection of diaryliodonium salts are compatible with this new transformation, delivering complex trisubstituted enone products, selectively as the *E*-isomers. These products will find significant utility in chemical synthesis.

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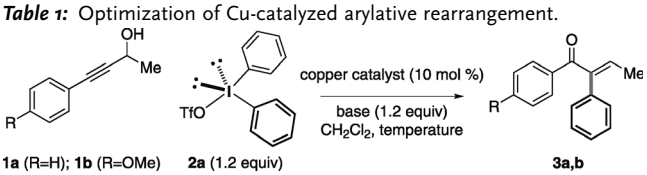
We selected propargylic alcohol 4-phenyl-3-butyn-2-ol (**1a**) as a representative substrate to evaluate the copper-catalyzed arylative Meyer–Schuster rearrangement. When **1a** was treated with diphenyliodonium triflate (**2a**), 10 mol% $Cu(OTf)_2$, and the sterically hindered base 2,6-di-*tert*-butylpyridine (DTBP) at 70 °C we were delighted to find that arylation of the alkyne functionality was coupled with the desired rearrangement to provide the α-aryl-α,β-unsaturated ketone **3a** in 53% yield (Table 1, entry 2). Encouraged by our initial result, we turned our attention to the copper catalyst. After evaluating a range of both copper(I) and copper(II) salts it became clear that while copper in both oxidation states catalyzes this reaction, using copper(I) salts at 50 °C provided an increase in reaction efficiency (entries 3–7). This is perhaps due to the better affinity of Cu^{I} over Cu^{II} salts for the π-orbitals of an alkyne. CuCl was chosen as the optimal catalyst due to its catalytic efficiency and low cost; when using 10 mol% CuCl, the desired enone product **3a** was obtained in 59% yield (entry 7). At this point, we reasoned that a more electron-rich aryl group in the acetylenic position of the propargylic alcohol could favor the desired arylative rearrangement over other non-productive pathways.[2c] Gratifyingly, when 4-(4-methoxyphenyl)butyn-2-ol (**1b**) was subjected to the optimized reaction conditions we isolated the corresponding α-aryl-α,β-unsaturated ketone **3b** in 76% yield (entry 8). Importantly, we also determined that in the absence of a copper catalyst, no α,β-unsaturated product was observed at standard reaction temperatures (entry 9). Reaction was only observed at 110 °C for propargylic alcohol **1b**, providing just 2% of enone **3b** (entry 10), however, in this case we also cannot rule out that trace copper contaminants can catalyze the reaction at these higher temperatures; interestingly, 4-phenylbut-3-yn-2-ol (**1a**) still failed to produce any desired product at this temperature (entry 11).

Table 1: Optimization of Cu-catalyzed arylative rearrangement.



1a (R=H); **1b** (R=OMe) **2a** (1.2 equiv) **3a,b**

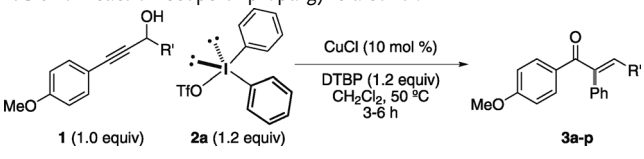
Entry	R	Catalyst	Base	*T* [°C]	Yield [%] (**3**)[a]
1[b]	H	$Cu(OTf)_2$	none	70	0
2[b]	H	$Cu(OTf)_2$	DTBP	70	53
3[b]	H	CuTC	DTBP	70	52
4[b]	H	CuCl	DTBP	70	54
5[b]	H	CuI + AgOTf	DTBP	70	55
6[b]	H	CuTC	DTBP	50	58
7	H	CuCl	DTBP	50	59
8	OMe	CuCl	DTBP	50	76[c]
9	OMe	none	DTBP	70/90	0/0[d]
10	OMe	none	DTBP	110	2[d]
11	H	none	DTBP	110	0[d]

[a] ^{1}H NMR yield using 1,2-dimethoxyethane as internal standard. [b] 2 Equiv. of **2a** used. [c] Yield of isolated product. [d] 1,2-dichloroethane used as solvent. DTBP = 2,6-di-*tert*-butylpyridine, Tf = trifluoromethanesulfonyl, TC = thiophenecarboxylate.

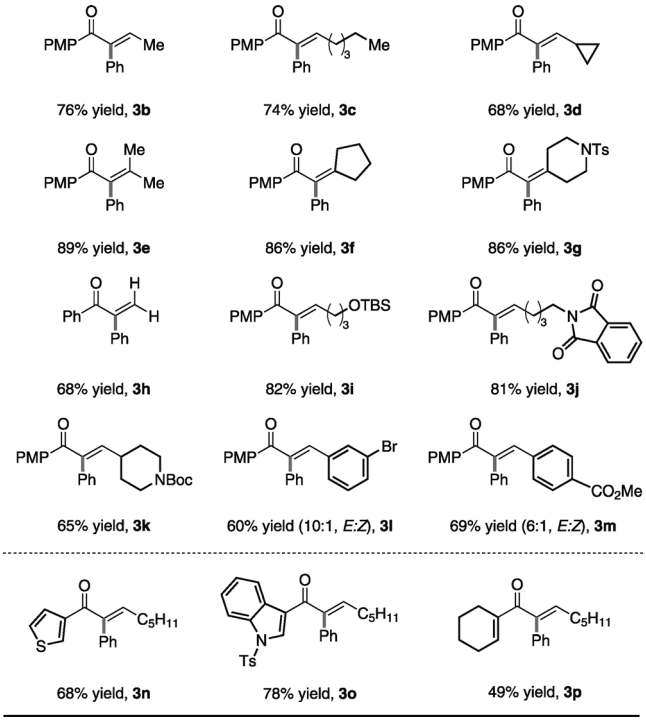
With an optimized process in hand, we next turned our attention to assessing the scope and limitations of this new reaction. We were pleased to find that the copper-catalyzed arylative rearrangement works across a broad range of propargylic alcohols providing access to a diverse array of functionalized enone motifs. By first varying the functionality at the propargylic position (Table 2), we found that substrates displaying simple alkyl substituents performed well in this transformation, including those with a cyclopropyl group appended to the carbinol centre (**3d**, 68%). Acyclic and cyclic tertiary substituted propargylic alcohols also work well and lead to tetrasubstituted enone products (**3e**–**3g**, 86–89%). We also found that a primary propargylic alcohol also proceeded smoothly under the reaction conditions to give the corresponding enone (**3h**, 68%). The transformation works well with substrates displaying a variety of remote functionality, such as protected amines, alcohols, and saturated heterocycles, and afforded the desired enone products in good yields as single olefin isomers (**3g, 3i**–**3k**, 65–86%). Additionally, the propargylic position can be substituted with an aryl moiety delivering chalcone derivatives (**3l**–**3m**, 60–69%).

Next, we turned our attention to the acetylenic position of the propargyl alcohol. Along with phenyl and anisyl substituents, electron-rich heteroaromatics such as *N*-tosyl indole and thiophene attached to the carbon–carbon triple bond

Table 2: Reaction scope of propargylic alcohol.[a]



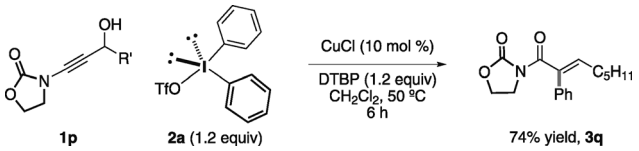
1 (1.0 equiv) **2a** (1.2 equiv) **3a-p**



[a] PMP = *p*-methoxyphenyl, Ts = *p*-tolylsulfonyl, Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

perform well under the reaction conditions (**3n**–**3o**, 68–78%). In addition to aromatic substituents, we were pleased to find that simple olefinic group provides the corresponding dienone in moderate yield (**3p**, 49%). At this time, it appears that sp^2 hybridization at the acetylenic position is essential for efficient reactivity as substrates with a simple alkyl chain give complex mixtures with no desired product observed. While the precise mechanism of this process is unclear, the requirement for sp^2-hybridization at this position may suggest that stabilization of a carbocation-type intermediate is required for reactivity, in line with the pathway of the seminal Meyer–Schuster reaction.[2]

Recognizing that heteroatoms also have the ability to stabilize charge build up on adjacent carbons, we speculated that substituting the acetylenic position with nitrogen functionality could also lead to efficient reactivity while providing a versatile imide product upon arylative rearrangement.[9] To our delight, ynamide **1p** efficiently afforded the corresponding α,β-unsaturated imide **3q** in 74% yield (Scheme 1).

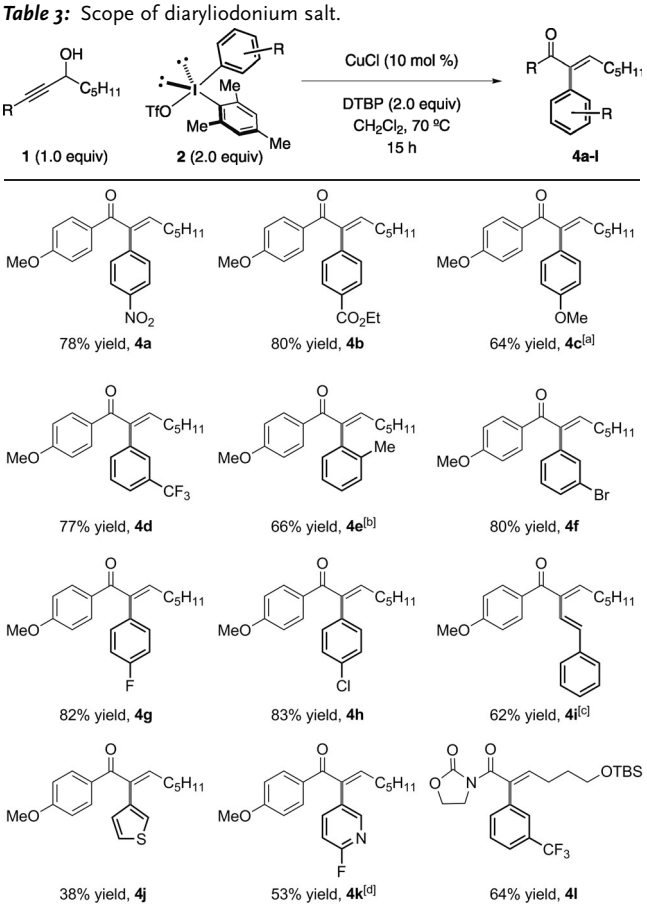


Scheme 1. Cu-catalyzed arylative rearrangement of ynamides.

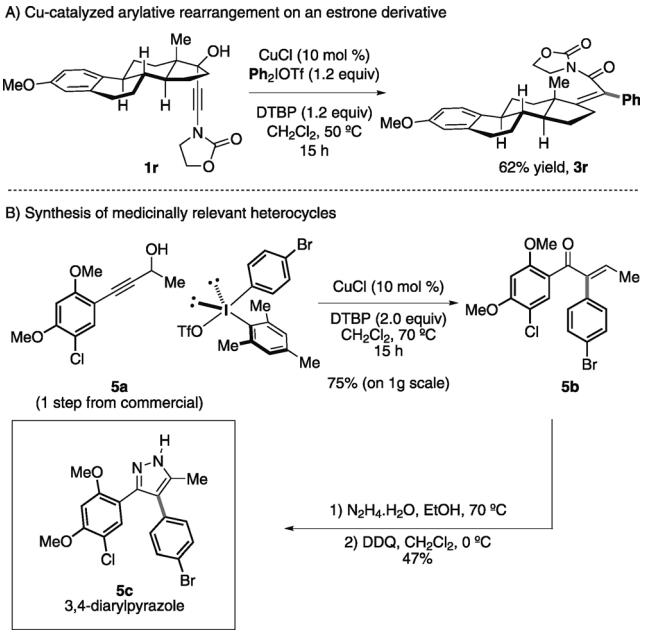
Having demonstrated the arylative rearrangement on a broad scope of propargylic alcohols, we were pleased to find that a range of aryl(mesityl)iodonium triflates[10] could be used to transfer substituted arenes (Table 3). Aromatics containing both electron-poor, electron-rich and synthetically versatile functional groups (**4a**–**4c**) are transferred effectively, including the sterically congested *ortho*-tolyl group (**4e**, 66%). Further functionalized arenes can also be transferred including a variety of haloarenes (**4f**–**4h**, 80–83%) and a *meta*-substituted trifluoromethyl benzene (**4d**, 77%). This process is also compatible with vinyl(aryl)iodonium salts and, notably, we were also able to transfer a styryl moiety (**4i**, 62%) in the modified Meyer–Schuster reaction to form synthetically useful dienes.[11] We were also pleased to find that aromatic heterocycles could also be transferred from the corresponding heteroaryl(mesityl)iodonium salts, as demonstrated by the thienyl and 2-fluoropyridyl substituted enones (**4j**–**4k**, 38–53%). Although the yields for these substrates are moderate, the introduction of complex aromatic heterocycles to the enone motif will likely find broad use in medicinal chemistry applications.

To highlight the efficacy of the new copper-catalyzed arylative rearrangemnt we tested the transformation in a complex molecule setting. An estrone-derived ynamide **1r** was subjected to the optimized reaction conditions and pleasingly provided unsaturated imide **3r** containing a tetrasubstituted olefin appended to the steriodal scaffold as a single geometric isomer and in good yield (Scheme 2A). The synthetic value of these functionalized α,β-unsaturated carbonyls lies in their ability to serve as precursors for many different classes of molecules, including a variety of hetero-

Table 3: Scope of diaryliodonium salt.



[a] 1.1 Equiv 4-methoxyphenyl(mesityl)iodonium triflate. [b] 2.0 Equiv di-(2-methylphenyl)iodonium triflate. [c] 1.0 Equiv propargylic alcohol, 2.0 equiv iodonium triflate. [d] ^{1}H NMR yield using 1,2-dimethoxyethane as internal standard.



Scheme 2. Applications of the Cu-catalyzed arylative rearrangement.

cycles with medicinal and biological applications. To highlight this, we developed a short route towards 3,4-diarylpyrazoles, a class of compounds shown to have anti-cancer activity.[12] Subjecting propargylic alcohol **5a** to the standard reaction conditions with 4-bromophenyl(mesityl)iodonium triflate provided 75% of the desired enone **5b** on a gram scale. Subsequent treatment of enone **5b** with hydrazine, followed by DDQ oxidation delivers 3,4-diarylpyrazole **5c**.

In summary, we have developed a new approach to transform readily accessible propargylic alcohols into α-aryl-α,β-unsaturated carbonyls using diaryliodonium salts and copper catalysis. This protocol operates under mild conditions and provides a broad scope of the desired enone products in good yields and high selectivity for the *E*-isomer. The highly functionalized *E*-trisubstituted enone products are versatile synthetic intermediates and can be readily transformed into important heterocyclic motifs. Further investigation of the mechanism of this transformation is underway and will be reported in due course.

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