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Cu/Fe-Cocatalyzed Meyer–Schuster-like Rearrangement of Propargylic Amines: Direct Access to *E*-β-Aminoacryaldehydes

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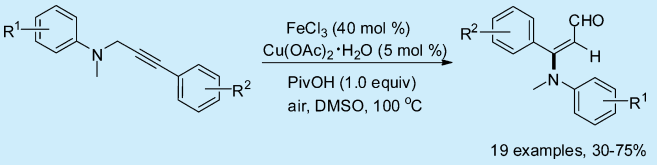
Supporting Information

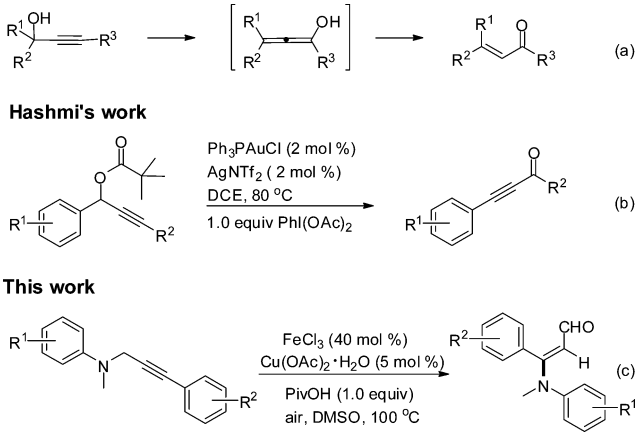
ABSTRACT: A simple and efficient method for the synthesis of β-aminoacryaldehydes via $Cu(OAc)_2·H_2O$ and $FeCl_3$ cocatalyzed Meyer–Schuster-Like rearrangement of propargylic amines was developed. The reactions proceed selectively as the *E*-isomers in generally good yields under aerobic conditions, and are compatible with a broad range of functional groups. This method combines C–N bond cleavage as well as the *N*-aryl group migration and provides a practical and mild synthetic approach to α,β-unsaturated carbonyl compounds, which are useful precursors in a variety of functional group transformations.



Rearrangement reactions are useful for the preparation of synthetically challenging products from readily accessible precursors.[1] The classical Meyer–Schuster (M.S.) rearrangement of propargylic alcohols, furnishing the corresponding α,β-unsaturated aldehydes or ketones, was first reported by K. H. Meyer and K. Schuster in 1922.[2] This reaction has been extensively applied in organic synthesis due to high atom economy and high efficiency for converting readily available materials into versatile enone products. Strong protic or Lewis acids were mostly used as promoters in the earliest versions of the M.S. reaction,[3] which generally afforded products in poor yields, due to unselective rearrangements and side reactions. Such rearrangements were better catalyzed by oxo complexes of transition metals, such as vanadium,[4] molybdenum,[5] rhenium,[6] and titanium,[7] which required an elevated temperature (100 °C) and/or acidic conditions. Later on, many other transition metals[8] such as mercury, ruthenium, gold, silver, and indium complexes were explored to promote the direct M.S. rearrangement of propargylic alcohols or esters. In this context, a gold-catalyzed conversion of propargylic esters into 1,3-ynone derivatives in combination with $PhI(OAc)_2$ as an oxidant was reported by Hashmi and co-workers (Scheme 1).[9] Additionally, Baba developed an indium chloride catalyzed alkylative rearrangement of propargylic acetates into α-alkyl-α,β-unsaturated carbonyl compounds.[8i] Furthermore, a copper-catalyzed arylative Meyer–Schuster rearrangement of propargylic alcohols was notably developed by Gaunt,[10] and a novel domino copper-catalyzed trifluoromethylated Meyer–Schuster rearrangement reaction with Togni's reagent was developed by Liu and Tan, in which the active allenol intermediate is involved.[11]

Propargylamines are important building blocks for a variety of organic transformations and are also valuable precursors for therapeutic drug molecules.[12] In contrast, while there are numerous reports on Meyer–Schuster rearrangement, particularly involving propargylic alcohols or esters as substrates,[4−11] much less is known about the rearrangement of the corresponding propargylamines, perhaps because the active enaminol intermediate are unstable and the multireactive centers of enone or propargylicamines are difficult to control. Encouraged by the results from Meyer–Schuster rearrangement of propargylic alcohols[9−11] and in connection with our continuous efforts devoted to metal-catalyzed reactions,[13] we herein present the first example of a new type of Cu/Fe-cocatalyzed oxidative Meyer–Schuster-like rearrangement reaction of propargylic amines, in many cases forming β-aminoacryaldehydes that would be difficult to synthesize by other means,[14] selectively as the *E*-isomers with moderate to good yields. Importantly, the formation of aminoacryaldehyde moieties can serve as versatile intermediates for the synthesis of a wide variety of heterocycles contained in biologically active

Scheme 1. Transition-Metal Catalyzed Meyer–Schuster Rearrangement Reactions



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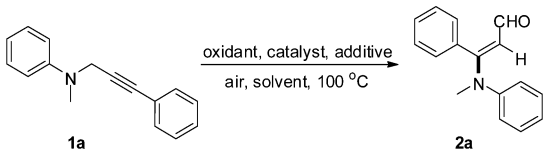
compounds.[14c,15] Notably, a highly efficient and practical $FeCl_3$-catalyzed domino synthesis of acrylonitriles by using propargylic alcohols and *para*-tolylsulfonohydrazide as a combined cyano source was developed by Zhang.[16] This cyanation reaction proceeds through a domino regioselective propargylic substitution/aza-Meyer−Schuster rearrangement route.

We began our study by investigating the $Cu(OAc)_2$ and $FeCl_3$ cocatalyzed Meyer−Schuster-Like rearrangement of propargylic amines **1a** in air at 90 °C. Initially, a number of common solvents were examined in this reaction, but no desired product was detected (Table 1, entries 1−3). To our delight, when DMSO was used as the oxidant, the valuable *β*-aminoacryaldehydes **2a** was detected and isolated in 48% yield (Table 1, entry 4). In addition, a higher temperature was not beneficial to the transformation (see Supporting Information (SI), Table S1). Other commonly used solvents such as methanol and toluene were less effective, and only poor yields were obtained (Table 1, entries 5−6). Then, we focus on the metal catalyst, which was vital to the catalytic cycle. Various copper catalysts were evaluated. The use of $CuCl_2$, $CuBr_2$, $CuSO_4$, $Cu(NO_3)_2$, or CuO was detrimental to this reaction (see SI, Table S1), whereas $Cu(OAc)_2$ and $Cu(TFA)_2$ were effective for this transformation, providing **2a** in yields of 44% and 48%, respectively (Table 1, entry 4 vs 7). A control reaction without $Cu(OAc)_2$ did not proceed, indicating that these catalysts are essential for oxidative rearrangement reaction (Table 1, entry 8). Surprisingly, the reaction did take place without $FeCl_3$, albeit affording the products with diminished yields (Table 1, entry 9). The yield of **2a** was further increased to 62% when 40 mol % of $FeCl_3$ and 5 mol % of $Cu(OAc)_2{\cdot}H_2O$ are used for the process (Table 1, entries 7 vs 10). Further screenings of the cocatalysts revealed no better results (Table 1, entries 11−13). Finally, a variety of additives including bases and acids were also examined (Table 1, entries 14−17). To our surprise, using 1.0 equiv of PivOH afforded **2a** in an excellent yield of 70% (Table 1, entry 15), whereas other additives such as TFA, TsOH, and K_2CO_3 inhibited the reaction severely. In addition, we found that increasing or decreasing the amount of PivOH does not benefit the formation of **2a** (see SI, Table S1). When the reaction was operated in argon, the rearrangement was considerably less efficient, suggesting that O_2 played a vital role in the catalytic cycle (Table 1, entry 18). Air (O_2) is mandatory to obtain the product, and we have detected Me_2S as a byproduct during the reaction by GC−MS.

Having identified the optimal conditions, we next examined the substrate scope for this new reaction. As shown in Scheme 2, the transformation for the substrates with substituents at the *para*-position of aryl amines moiety proceeded quite smoothly and afforded the desired *β*-aminoacryaldehydes **2a**−**d** in good yields, selectively as the *E*-isomers. Electron-donating groups such as the methyl group and electron-withdrawing substituents such as F and Cl in the propargylamines of **1** were tolerant, and electronic effects had no significant impact on the yields. However, the steric effect of the *meta*-substituted groups on the phenyl ring of the aryl amines moiety lowered the yields (**2e**, **2f**) dramatically compared to their *para*-analogues. Somewhat disappointingly, when a substituted group was installed on the *ortho*-position of aryl amines moiety, only a trace amount of the desired product was detected (**2g**, **2h**) probably due to the steric hindrance of the substrates.

The effect of the substituents on the phenyl ring of aromatic alkyne moiety was also studied (Scheme 3). We were pleased to see that this Cu/Fe cocatalyzed rearrangement reaction displayed good functional-group tolerance and proved to be a facile and general protocol for the synthesis of substituted *β*-aminoacryaldehydes. The substrates containing electron-donating groups such as OMe and Me at the aryl ring could be

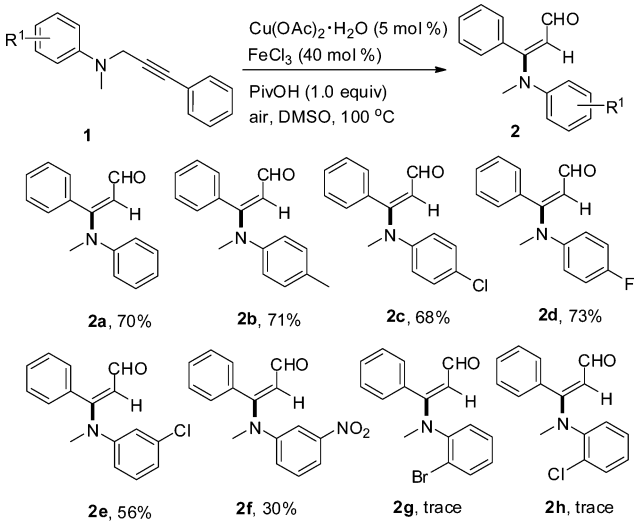
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst 1	catalyst 2	additive	solvent	yield [%][b]
1[c,d]	$Cu(TFA)_2$	$FeCl_3$		THF	n.d.
2[c,d]	$Cu(TFA)_2$	$FeCl_3$		CH_3CN	n.d.
3[c,d]	$Cu(TFA)_2$	$FeCl_3$		DCE	n.d.
4[d]	$Cu(TFA)_2$	$FeCl_3$		DMSO	48
5[d]	$Cu(TFA)_2$	$FeCl_3$		MeOH	8
6[d]	$Cu(TFA)_2$	$FeCl_3$		toluene	4
7	$Cu(OAc)_2$	$FeCl_3$		DMSO	44
8	–	$FeCl_3$		DMSO	n.d.
9	$Cu(OAc)_2{\cdot}H_2O$	–		DMSO	30
10	$Cu(OAc)_2{\cdot}H_2O$	$FeCl_3$		DMSO	62
11	$Cu(OAc)_2{\cdot}H_2O$	$Fe(NO_3)_3{\cdot}9H_2O$		DMSO	trace
12	$Cu(OAc)_2{\cdot}H_2O$	$Fe_2(SO_4)_3$		DMSO	trace
13	$Cu(OAc)_2{\cdot}H_2O$	$La(NO_3)_3{\cdot}9H_2O$		DMSO	n.r.
14	$Cu(OAc)_2{\cdot}H_2O$	$FeCl_3$	TFA	DMSO	n.d.
15	$Cu(OAc)_2{\cdot}H_2O$	$FeCl_3$	PivOH	DMSO	70
16	$Cu(OAc)_2{\cdot}H_2O$	$FeCl_3$	TsOH	DMSO	n.d.
17	$Cu(OAc)_2{\cdot}H_2O$	$FeCl_3$	K_2CO_3	DMSO	<10
18[e]	$Cu(OAc)_2{\cdot}H_2O$	$FeCl_3$	PivOH	DMSO	<10

[a]Reaction conditions: **1a** (0.2 mmol), catalyst 1 (0.01 mmol), catalyst 2 (0.08 mmol), additive (0.2 mmol), solvent (2 mL), at 100 °C, in Ar, for 22 h. [b]Isolated yield. [c]At 90 °C. [d]$Cu(OAc)_2{\cdot}H_2O$ (0.02 mmol) and $FeCl_3$ (0.02 mmol) were used. [e]Under argon.

Scheme 2. Scope of Aryl Amines Moiety[a]



[a]Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.01 mmol), $FeCl_3$ (0.08 mmol), and PivOH (0.2 mmol) in 2.0 mL of DMSO at 100 °C, in air, for 22 h.

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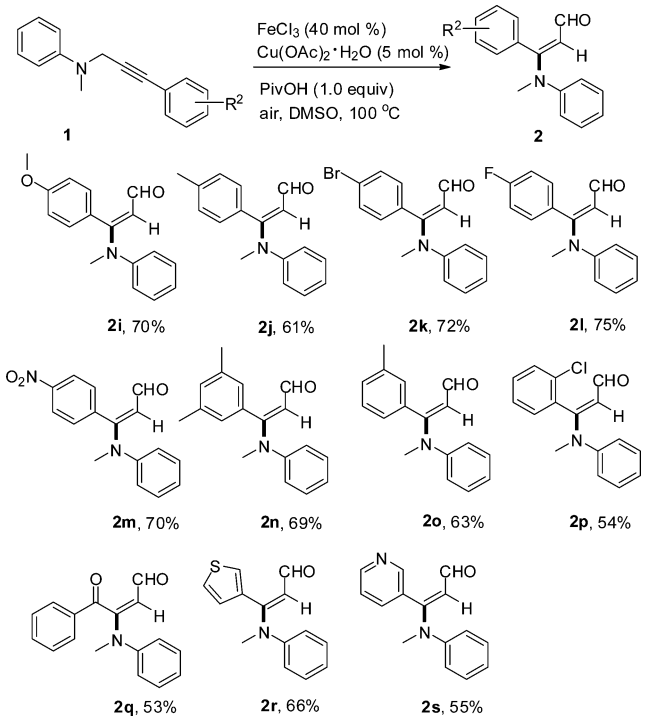
Scheme 3. Scope of Aromatic Alkyne Moiety[a]



[a]Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.01 mmol), $FeCl_3$ (0.08 mmol), and PivOH (0.2 mmol) in 2.0 mL of DMSO at 100 °C, in air, for 22 h.

transformed to the desired products **2i** and **2j** in good yields, respectively. Meanwhile, substrates with electron-deficient aryl substituents such as Br, F, and NO_2 in the 4′-position also worked well to give **2k**–**m**, respectively. The structure of **2k** was unambiguously determined by X-ray crystallography (Figure 1)

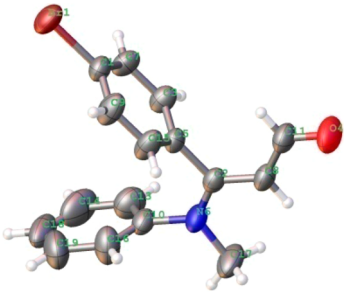
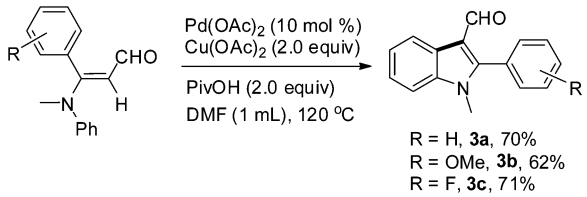


Figure 1. Crystal structure of **2k**. Hydrogen atoms are omitted for clarity.

and HRMS (see SI). It is noteworthy that the substrates with aromatic halides performed well in this transformation generating halo-substituted products (**2k**, **2l**, **2p**), thereby providing possibilities for subsequent chemical transformations. Additionally, propargylic amines having methyl substituents at the *meta*-position of the aryl groups could also be transferred through this protocol, although reduced yields of the corresponding products **2n,o** were observed. Similarly, *ortho*-substituents including Cl (**2p** vs **2o** and **2j**) were generally detrimental to this reaction, suggesting that this reaction is sensitive to the steric bulk on the aromatic ring. Notably, a benzylic C–H bond adjacent to the alkyne was less compatible with the oxidative and acidic conditions, affording the oxidized product (**2q**) in moderate yield. Interestingly, heteroaryl groups, such as 3-thienyl (**2r**) and 3-pyridyl (**2s**) groups, can be incorporated into the substituted *β*-aminoacryaldehydes scaffold by using corresponding propargylic amines, albeit in lower yields, thus enhancing the scope of our reaction. Importantly, all the catalytic reactions proceeded with excellent *E* selectivity, and the *Z* isomers were not detected presumably due to the steric hindrance. Additionally, it was found the substituents on the methylene such as benzyl, phenyl, and CF_3 significantly effected the reaction, with no desired product being detected.

To further extend the synthetic utility of **2**, we studied the palladium-catalyzed oxidative cyclization of *N*-aryl enamines (Scheme 4).[17] After a quick screening of the reaction conditions,

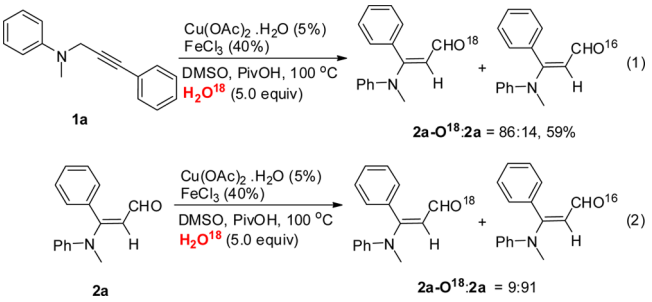
Scheme 4. Palladium-Catalyzed Synthesis of Indole-3-carbaldehyde Derivatives from *E*-*β*-Aminoacryaldehydes



it was found that reaction of *E*-*β*-aminoacryaldehyde derivatives (**2a**, **2i**, **2l**), conducted with a combination of 2.0 equiv of $Cu(OAc)_2$ as the catalyst and 2.0 equiv of PivOH as the additive in DMF at 120 °C, resulted in conversion into the indole-3-carbaldehyde derivatives (**3a**–**c**). As we know, indole derivatives were useful nitrogen-containing structural units, which were widely applied in synthetic and medicinal chemistry. Thus, this new protocol could hold great potential for applications in the discovery of lead compounds and other biologically active indole-based molecules in organic chemistry as well as biology.

In order to explore the possible mechanism, two ^{18}O-labeling experiments were performed as described in Scheme 5. When

Scheme 5. Experiments for Mechanistic Studies



H_2O^{18} (5.0 equiv) was added into the reaction, 82% of the ^{18}O-labeled product was detected (Scheme 5, eq 1). In the oxygen exchange experiments, we could detect 9% of the ^{18}O-labeled product in the standard reaction conditions (Scheme 5, eq 2). These results indicated that the oxygen source in **2a** was from water wich may come from the acid or $Cu(OAc)_2{\cdot}H_2O$. In addition, radical-trapping experiments were performed in the reaction. As a result, the reactions were not suppressed (see SI, Table S2). However, a tentative mechanism involving radical intermediates was not excluded under the present reaction conditions.[18]

On the basis of our observations and previous reports,[8−10,19] a plausible reaction mechanism is proposed in Scheme 6. Initially,

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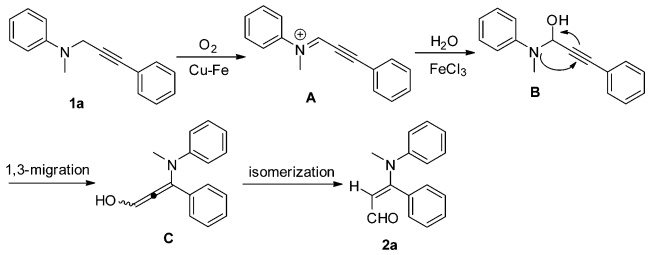
Scheme 6. Proposed Reaction Mechanism



propargylamine **1a** is oxidized by molecular oxygen to form an immonium intermediate **A**,[20] which is attacked by H_2O to give intermediate **B** under the action of a Lewis acid $FeCl_3$. Then, a Cu-catalyzed Meyer−Schuster −Like rearrangement occurs to give allenol intermediate **C**.[16] Finally, the allenol thus formed eventually rearranges to an α,β-unsaturated carbonyl product **2a** via a ready prototropic shift.

In summary, we have developed a novel approach to transform readily accessible and inexpensive propargylic amines into β-aminoacryaldehydes using copper and iron catalysis. This protocol provided a broad scope of the desired enaminal products in moderate to good yields with good *E*-isomeric selectivity, rendering this method a valuable addition to the synthetic chemist's toolbox. The highly functionalized *E*-enaminal products are versatile synthetic intermediates and can be readily transformed into important heterocyclic motifs. Further developments of this method and elucidation of the mechanism are now in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, and copies of ^1H and ^{13}C spectra for compounds **2a−s**, **3a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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