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Copper-Catalyzed Imidovinylation of Alkynes via 1,3-Vinyl Migration

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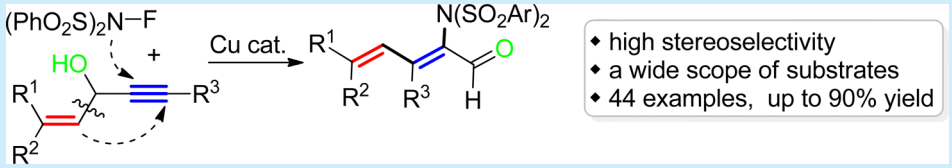
Supporting Information

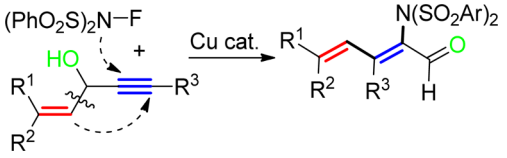


ABSTRACT: The first copper-catalyzed imidovinylation of alkynes has been developed, which grants facile access to various (*E*)-2-imido-2,4-dienals with high stereoselectivity under mild conditions. This transformation also represents the first 1,3-carbon migration of propargylic alcohols and their derivatives.

Transition-metal-catalyzed functionalization of alkynes[1] has become an important strategy for the synthesis of substituted alkenes, a versatile structural motifs prevalent in pharmacologically active compounds,[2a−c] natural products,[2b,d] and functional materials.[2e] Among the numerous alkynes functionalization strategies, vinylation processes enable a straightforward and powerful approach to functionalized conjugated dienes. Accordingly, various vinylative bisfunctionalization, such as boravinylation,[3a−c] aminovinylation,[3d−f] and arylovinylation[3g] of alkynes with vinyl boranes, vinyl zirconiums, vinyl halides, vinyl triflates, and activated alkenes, have been achieved. However, direct alkynes vinylation with simple olefins still remains unexplored.

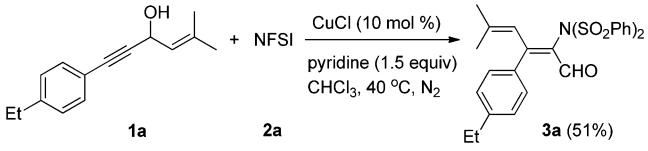
Recently, we described alkynes functionalization reactions involving addition of nitrogen radical, during which 1,4-aryl migration occurred.[4] Inspired by these observation, we set out to explore vinylative functionalization of alkynes via more challenging 1,3-vinyl migration[5] from vinyl alkynol derivatives. In contrast to the facile phenyl migration,[6] the vinyl migration has been shown to be more difficult to achieve.[7−11] Most of the existing vinyl migrations are 1,2-migration that proceed through cationic intermediate (pinaco rearrangement, Wagner-Meerwein rearrangement),[7] anionic intermediate (witting rearrangement),[8] radical intermediate,[9] or carbene intermediate (free carbene or metal carbene).[10] To date, the 1,3-vinyl migration remains rare. The only report involves a 1,3-vinyl migration of 1,1,4-triphenyl-1,4-pentadiene under photolytic conditions (irradiated by 450-W Hanovia medium-pressure mercury lamp).[11] To realize efficient 1,3-vinyl migration, the chemoselectivity issue arising from selective functinalizetion of C=C or C≡C bonds needs to be addressed. Herein, we report a novel Cu-catalyzed imidovinylation of proparylic alcohols via alkynes imidation/1,3-vinyl migration sequence, which allows for facile, high stereoselective synthesis of (*E*)-2-imido-2,4-dienals (Scheme 1).

Scheme 1. Copper-Catalyzed Imidovinylation of Alkynes



Initially, 1-(4-ethylphenyl)-5-methylhex-4-en-1-yn-3-ol (**1a**) was chosen as the model substrate. Propargylic alcohols and their derivatives are among the most useful synthetic building blocks due to their ready availability.[12] When **1a** and *N*-fluorobenzenesulfonimide (NFSI, **2a**, 1.2 equiv) were treated with CuCl (10 mol %) and 1.5 equiv of pyridine in $CHCl_3$ at 40 °C under nitrogen atmosphere for 16 h, the desired imidovinylation product (*E*)-2-imido-2,4-dienal **3a** was obtained in 51% yield (Scheme 2). Use of methanol, toluene,

Scheme 2. Copper-Catalyzed Aminovinylation of 1a and 2a



acetonitrile, or tetrahydrofuran as solvents resulted in no **3a** formation. Among various copper catalysts, such as $CuCl_2$, CuOAc, CuCN, CuBr, CuCl, CuTc, and $Cu(OTf)_2$, CuCl gave the best result. Elevation of the temperature to 50 °C led to an improved yield of 67%, but an even higher temperature could not further improve the yield. The yield of **3a** dramatically decreased to 26% when the amount of pyridine was decreased

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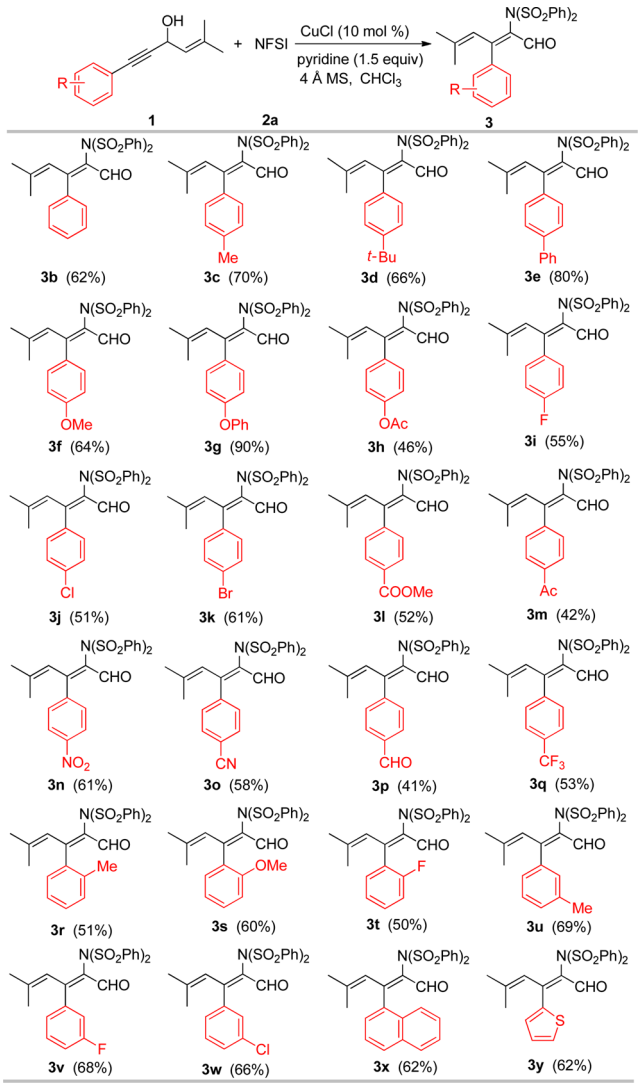
to 10 mol %. Other additives such as 3-bromoprydine, 4-cyanoprydine, 4-methylprydine, and triethylamine were not efficient. Upon increasing the amount of **2a** to 2.0 equiv, the yield of **3a** decreased to 45%. When 0.2 g of 4 Å molecular sieves was added to the reaction, **3a** was obtained in 75% yield (for details of the reaction optimization, see Table S1 of the Supporting Information). It should be noted that although transition-metal catalyzed 1,2-/1,3-oxygen[13] or 1,2-carbon[14] migration of propargylic alcohol and their derivatives have been fully developed, the related 1,3-carbon migration has never been reported. The formation of **3a** from **1a** represents the first 1,3-carbon migration reaction of propargylic alcohol and their derivatives.

With the optimized conditions in hand, we began to investigate the scope and the limitation of this imidovinylation reaction. First, variation of alkynyl substitutions in propargylic alcohol **1** was performed, with the data being summarized in Scheme 3. Substituted aryls bearing both electron-donating and

Scheme 3. Varieties of Different Alkynyl Groups[a]

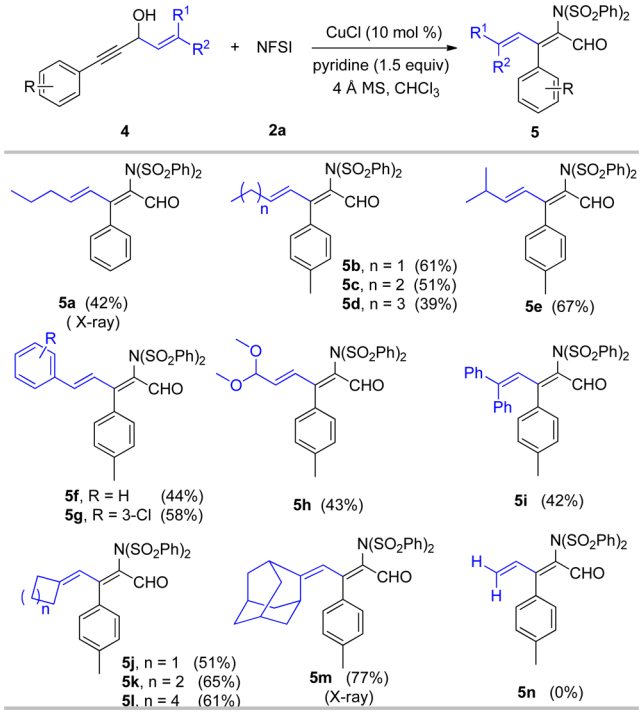


[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.2 equiv), CuCl (10 mol %), pyridine (1.5 equiv), 0.2 g of 4 Å molecular sieves, $CHCl_3$ (2 mL), 50 °C, N_2, 16 h. The yield was determined after isolation of products by column chromatography.

-withdrawing groups, such as alkyl, alkoxyl, halide, carbonyl, nitro, cynao, and trifluoromethyl, were tolerant, which led to desired (*E*)-2-imido-2,4-dienals **3a**–**3w** in moderate to high yields. It is worthy to note that the halide (**3i**–**3k**, **3t**, **3v**–**3w**), carbonyl group (**3l**, **3m**, and **3p**), nitro group (**3n**), and cyano group (**3o**) are very valuable handles for further manipulation. Furthermore, substrates with naphthyl and thienyl rings are viable with the corresponding **3x** and **3y** being retrieved in 62% and 62% yields, respectively. Notably, these imidovinylation reactions showed an interesting stereoselectivity, and no formation of any other stereoisomers was detected. (*E*)-2,2-Dimethyldec-6-en-3-yn-5-ol (**1z**) was also tested. Unfortunately, the alkyl substituted alkyne was oxidized to ketone without the formation of the desired imidovinylation product.

Next, we explored the scope of the vinyl moieties (Scheme 4). The (*E*)-monosubstituted propargylic alcohols with alkyl

Scheme 4. Scope of Vinyl Moieties[a]



[a]Reaction conditions: **4** (0.2 mmol), **2a** (1.2 equiv), CuCl (10 mol %), pyridine (1.5 equiv), 0.2 g of 4 Å molecular sieves, $CHCl_3$ (2 mL), 50 °C, N_2, 16 h. The yield was determined after isolation of products by column chromatography.

(**4a**–**4e**) or aryl groups (**4f** and **4g**) were suitable for the imidovinylation reaction and provided (*E*)-2-imido-2,4-dienals **5a**–**5g** in moderate to good yields. Interestingly, (*Z*)-propargylic alcohol **4b′** afforded a product identical to that from **4b**. Ketal moiety (**4h**) was also nicely tolerated in this transformation to produce the desired product **5h** in 43% yield, which showcased the mild nature of the conditions. The gem-diphenyl substituted propargylic alcohol **4i** also worked well and afforded the corresponding (*E*)-2-imido-2,4-dienals **5i** in an accepted yield. Remarkably, substrates (**4f**, **4g**, and **4i**) with a styrene unit underwent the imidovinylation reaction exclusively, and no aminative functionalization of styrene was observed.[15] Product **5j**–**5l** bearing alkylidenecyclobuane, alkylidenecyclopentane, and alkylidenecycloheptane were also furnished in good yields. Moreover, a bulky adamantan-2-ylidene sub-

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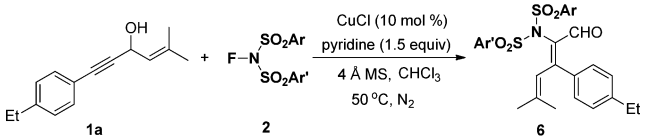
stituted propargylic alcohol **4m** worked efficiently, producing **5m** in 77% yield. Nevertheless, the propargylic alcohol **4n** with a terminal alkene motif did not work. Additionally, the configurations of (*E*)-2-imido-2,4-dienals **5a** and **5m** were further confirmed by X-ray analysis.[16] Finally, some NFSI derivatives were tested (Scheme 5). Symmetric N−F reagents **2**

Scheme 5. Reaction of NFSI Derivatives

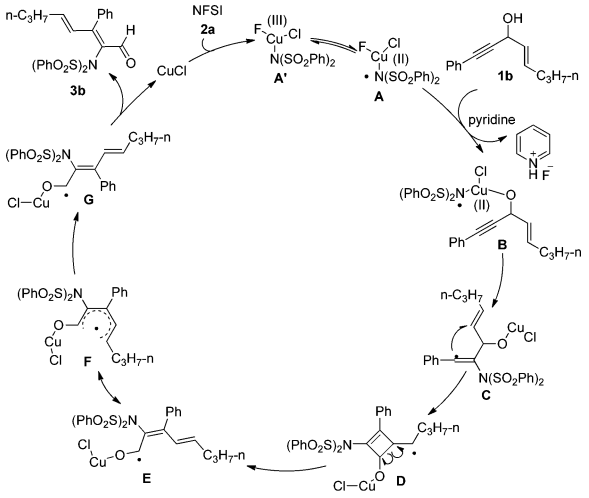


6a, Ar = Ar' = 4-Me-C_6H_4 (76%) **6b**, Ar = Ar' = 4-*t*-Bu-C_6H_4 (51%)
6c, Ar = Ar' = 4-F-C_6H_4 (41%) **6d**, Ar = Ph, Ar' = 4-Me-C_6H_4 (56%)
6e, Ar = Ph, Ar' = 4-F-C_6H_4 (71%) **6f**, Ar = 4-Me-C_6H_4, Ar' = 4-Cl-C_6H_4 (82%)

bearing either electron-withdrawing group (F) or electron-donating groups (Me, *t*-Bu) on benzene rings furnished corresponding (*E*)-2-imido-2,4-dienals **6a**−**6c** in 41−76% yields under this mild conditions. The unsymmetrical ones with different groups on the two benzene rings also worked well and delivered desired products **6d**−**6f** in good to excellent yields.

To clarify the reaction mechanism, a radical inhibition experiment was performed. Adding 1.5 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the reaction of **1c** and NFSI (**2a**) under the standard reaction conditions completely suppressed the expected imidovinylation reaction, and only an oxidized product alkynyl alkenyl ketone was formed (for details, see the Supporting Information). This result suggested that the transformation might involve radical intermediates. On the basis of the experimental results and our previous works,[4,15,17] we proposed a plausible mechanism for this novel reaction (Scheme 6). Initially, nitrogen-centered

Scheme 6. Plausible Mechanism



radical species **A** was formed through the interaction of CuCl and NFSI (**2a**). **A** then associate with propargylic alcohol **1b** by pyridine assisted HF removal to form intermediate **B** containing a Cu−O bond. Next, intramolecular highly selective addition of nitrogen-centered radical to C≡C bond instead of C=C bond takes places, possibly owing to sterically more favored nature of the former, to generate vinyl radical **C**. **C** was quickly captured intramolecularly by the pendant vinyl group to deliver alkyl radical **D** with a cyclobutenyl motif. Scission of intermediate **D** resulted in a 1,3-vinyl migration to generate (2*Z*, 4*E*)-radical **E**, which further transformed into a more stable (2*E*, 4*E*)-radical **G** through resonance structure **F**. Finally, homolysis of Cu−O bond of radical **G** afforded **3b** with concomitant regeneration of the Cu(I) species was regenerated for the next catalytic cycle.

To conclude, the first imidovinylation of alkynes has been developed with copper as catalyst to access to various (*E*)-2-imido-2,4-dienals. This reaction also presents the first 1,3-carbon migration of propargylic alcohols and their derivatives via novel vinyl migration. These transformations proceed under mild conditions and show good functional group compatibility. The strategy for alkynes imidovinylation via 1,3-vinyl migration might provide an new way toward vinylative functionalization of unsaturated system. Further studies on the vinyl migration strategy are under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01599.

Experimental procedures, spectral data for new compounds (PDF)
Crystallographic data for **5a** (CIF)
Crystallographic data for **5m** (CIF)

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Notes

The authors declare no competing financial interest.

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