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Cu-Catalyzed Skeletal Rearrangement of *O*-Propargylic Electron-Rich Arylaldoximes into Amidodienes

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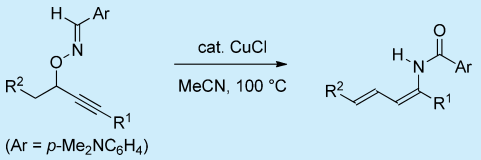
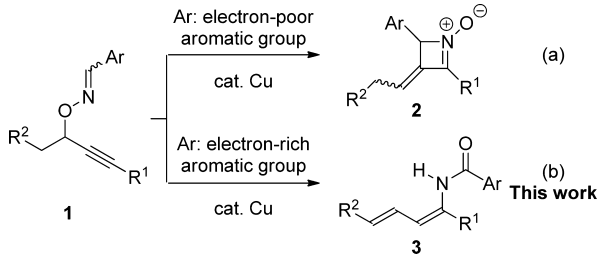
Supporting Information

ABSTRACT: *O*-Propargylic oximes that possess an electron-rich *p*-(dimethylamino)phenyl group at the oxime moiety and an alkyl group at the propargylic position were efficiently converted in the presence of Cu(I) catalysts to the corresponding 1-amidodienes in good to excellent yields. The reaction proceeded via a 2,3-rearrangement, followed by isomerization of the resulting *N*-allenylnitrone to the amide, presumably through the oxaziridine intermediate.



Recent investigations have revealed that π-acidic metal catalysts can efficiently initiate rearrangement reactions that involve cleavage of skeletal σ-bonds. More importantly, the use of such catalysts can transform readily accessible molecules, under mild reaction conditions, into highly elaborate compounds, which are often elusive using conventional synthetic methods.[1] Moreover, such skeletal rearrangement reactions are dramatically affected by the choice of substituents on the substrates. The diversity of such reaction schemes has been reported for the π-acidic metal-catalyzed skeletal rearrangement reactions of 1,*n*-enynes[2] and propargylic esters.[3] We have recently reported on the catalytic skeletal rearrangement reactions of *O*-propargylic oximes in the construction of various heterocyclic compounds.[4] In particular, we reported that propargylic oximes **1** were transformed into four-membered cyclic nitrones **2** via a 2,3-rearrangement followed by a 4π-electrocyclization cascade (Scheme 1a).[4b,e] In contrast,

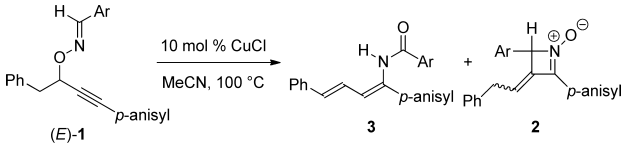
Scheme 1. Catalytic Skeletal Rearrangement of *O*-Propargylic Arylaldoximes 1 to (a) Four-Membered Cyclic Nitrones 2 and (b) 1-Amidodienes 3 (Present Work)



our studies herein have shown that Cu-catalyzed reactions of *O*-propargylic oximes that possess a strong electron-donating *p*-aryl group at the oxime moiety proceed via a distinctly different route, specifically, substrates **1** that possess an alkyl group at the propargylic position were converted to the corresponding 1-amidodienes **3** in good to excellent yields (Scheme 1b).

The intriguing dichotomy was first observed during investigations of the substitution effects at the oxime moiety using substrates **1a**–**g** that possess a benzyl group at the propargylic position, as summarized in Table 1.

Table 1. Substitution Effect at the Oxime Moiety



	1	Ar	time (h)	3 (%)[a]	2 (%)[a]
1	**1a**	*p*-$Me_2NC_6H_4$	24	**3a** (87)	(<1)
2	**1a**[b,c]	*p*-$Me_2NC_6H_4$	1	**3a** (67)	(<1)
3	**1b**	*p*-$Et_2NC_6H_4$	24	**3b** (84)	(<1)
4	**1c**	2-(1-methylpyrrolyl)	84	**3c** (53)	(<1)
5	**1d**	*p*-$MeOC_6H_4$	36	**3d** (41)	**2d** (5)
6	**1e**	*p*-MeC_6H_4	48	**3e** (32)	**2e** (25)
7	**1f**	*p*-ClC_6H_4	64	**3f** (30)	**2f** (60)
8	**1g**	3,5-$Br_2C_6H_3$	96	(<1)	**2g** (68)

[a]The yields (in parentheses) were determined using ^{1}H NMR with CH_2Br_2 as an internal standard. [b](*Z*)-**1a** isomer was used. [c]Acetic acid (10 mol %) was used as an additive.

In the case of *p*-(dimethylamino)phenyl substrate (*E*)-**1a**, the reaction in the presence of catalytic amounts of CuCl in acetonitrile at 100 °C selectively afforded the corresponding 1-amidodiene **3a** in a good yield (entry 1). Similarly, the reaction of its isomer (*Z*)-**1a**, which readily proceeded to completion within 1 h, afforded the identical **3a** in a good yield using catalytic amounts of acetic acid as an additive (entry 2).[5−7] Accordingly, other electron-rich aromatic substituents such as *p*-(diethylamino)phenyl, 2-(1-methylpyrrolyl), and *p*-anisyl groups also selectively formed the corresponding 1-amido-

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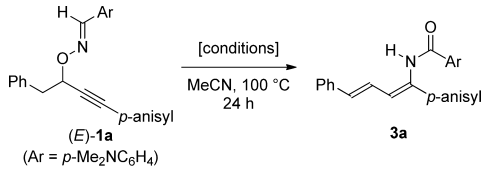
dienes (entries 3−5). In contrast, lower ratios of 1-amidodiene **3**, relative to the four-membered cyclic nitrone **2**, were observed for substrates that possess electron-withdrawing aryl groups; in the case of substrate (*E*)-**1g**, which possesses a 3,5-dibromophenyl group, the reaction selectively afforded the corresponding four-membered cyclic nitrone **2g** (entry 8).

The reaction conditions were optimized using substrate (*E*)-**1a**, as summarized in Table 2. In addition to CuCl, various

Table 2. Optimization of Reaction Conditions



	catalyst	yield (%)[a]
1	CuCl	87 (85)
2	CuCl[b]	90
3	[CuCl(cod)]$_2$[c]	64
4	CuBr	54
5	CuOAc	72
6	$CuCl_2$	<1
7	$Ph_3PAuNTf_2$	24
8	AcOH	<5

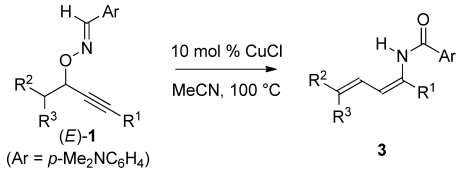
[a]The yields were determined using ^{1}H NMR with CH_2Br_2 as an internal standard. Isolated yield are shown in parentheses. [b]Acetic acid (10 mol %) was added. [c]5 mol % of [CuCl(cod)]$_2$ was used.

Cu(I) salts such as [CuCl(cod)]$_2$, CuBr, and CuOAc exhibited catalytic activities, albeit with lower yields (entries 3−5). In contrast, the use of a Cu(II) salt ($CuCl_2$) resulted in the rapid decomposition of the starting material (*E*)-**1a** (entry 6). The use of $Ph_3PAuNTf_2$ afforded only a small amount of **3a**, whereas other metal salts such as $PtCl_2$ and $PdCl_2$ did not exhibit any catalytic activities (entry 7, see also Supporting Information). Only trace amounts of **3a** were observed in the reaction in the presence of catalytic amounts of acetic acid (entry 8). Among the reaction solvents, acetonitrile provided the best results; however, other solvents such as toluene, CH_2Cl_2, and 1,4-dioxane were also acceptable (see Supporting Information).

Next, the optimized reaction conditions (Table 2, entry 1) were applied to various substrates based on (*E*)-**1** (Table 3). Substrates that possess an electron-deficient aromatic ring at the alkyne terminus [(*E*)-**1i** and (*E*)-**1j**, Table 3, entries 2 and 3, respectively] proceeded more rapidly than that having an electron-rich *p*-anisyl group [(*E*)-**1a**, Table 2, entry 1]. Substrate (*E*)-**1k** with a terminal alkyne was converted to 4-monosubstituted amidodiene **3k** in a good yield, at a lower reaction temperature (60 °C), and with the use of catalytic amounts of acetic acid (entry 4).[8] Substrates with alkyl, aryl, and ethoxycarbonyl groups as the substituent at the homopropargylic position (R^2) also afforded the desired product in good yields (entries 5−7). Moreover, 1-monosubstituted amidodiene **3o** was synthesized from substrate (*E*)-**1o** with a methyl group at the propargylic position (entry 8). Substrate (*E*)-**1p** that possesses a benzhydryl group at the propargylic position was converted to the corresponding 1,4,4-triphenyl-1-amidodiene **3p** in a good yield (entry 9).

In the cases of substrates (*E*)-**1q** and (*E*)-**1r**, which possess an alkyl group at the alkyne terminus and a phenyl group at the

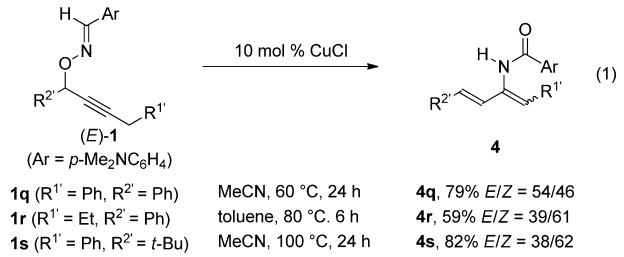
Table 3. Cu-Catalyzed Reactions of (*E*)-1h−p for Synthesis of 1-Amidodienes[a]

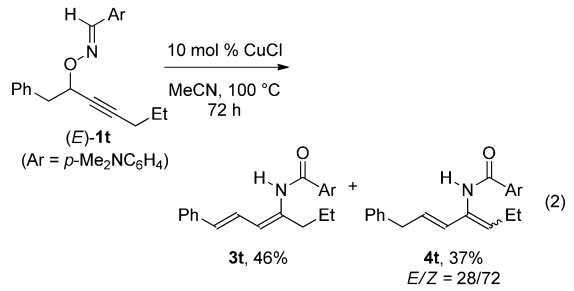


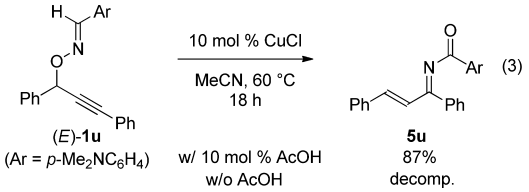
	1	R^1	R^2	R^3	time (h)	3	yield (%)[b]
1	**1h**	Ph	Ph	H	18	**3h**	90
2	**1i**	*p*-ClC_6H_4	Ph	H	14	**3i**	85
3	**1j**	*p*-$F_3CC_6H_4$	Ph	H	12	**3j**	95
4[c]	**1k**	H	Ph	H	10	**3k**	70[d]
5	**1l**	Ph	Et	H	36	**3l**	76
6	**1m**	Ph	*p*-anisyl	H	20	**3m**	64
7	**1n**	Ph	CO_2Et	H	14	**3n**	72[e]
8	**1o**	Ph	H	H	36	**3o**	63
9	**1p**	Ph	Ph	Ph	20	**3p**	69

[a]The reaction of (*E*)-**1** (0.2 mmol) in the presence of CuCl (10 mol %) in acetonitrile (0.4 mL) at 100 °C. [b]Isolated yields. [c]The reaction was carried out using acetic acid (10 mol %) at 60 °C. [d]A 36:64 mixture of *E*/*Z* stereoisomers at the amide-bound olefin was obtained. [e]A 44:56 mixture of *E*/*Z* stereoisomers was obtained.

propargylic position, the reactions in the presence of CuCl afforded 2-amidodienes **4q** and **4r**, respectively, in good yields as mixtures of two diastereomers at the amide-bound olefin (eq 1). Substrate **1s** having a *tert*-butyl group at the propargylic







position was effectively converted to the 2-amidodiene **4s**. Moreover, the reaction of substrate (*E*)-**1t**, which possesses alkyl groups at both the alkyne terminus and the propargyl position, gave a mixture (ca. 1:1) of 1-amidodiene **3t** and 2-amidodiene **4t** (eq 2). In the case of substrate (*E*)-**1u**, which possesses phenyl groups at both positions, the reaction in the presence of the Cu catalyst and acetic acid afforded *α,β*-

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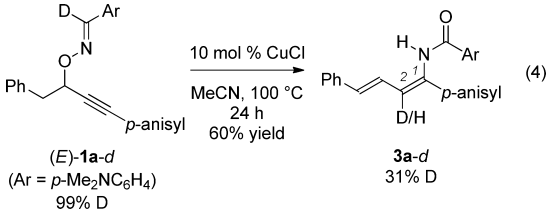
unsaturated *N*-acylketimine **5u** in a good yield. As a note, the reaction in the absence of acetic acid resulted in unidentifiable tar byproducts (eq 3).

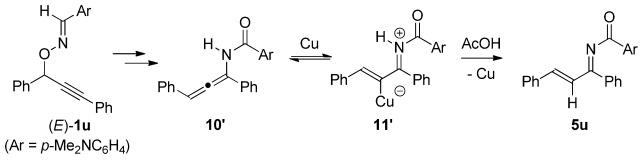
In order to gain insight into the oxime hydrogen atom, deuterium labeling experiments were carried out using substrate (*E*)-**1a**-*d*, which is 99%-enriched at the oxime position (eq 4).



Under the optimal reaction conditions, the reaction afforded **3a**-*d* (60% yield), in which the deuterium content at the 2-position of the diene moiety was determined to be 31%. The reaction of a 1:1 mixture of (*E*)-**1b** and (*E*)-**1h** afforded only **3b** and **3h** without any crossover products (detected using high-resolution mass spectroscopy), thus indicating that the skeletal rearrangement proceeds via an intramolecular mechanism (see Supporting Information).

A plausible mechanism for the construction of 1-amidodiene **3** is illustrated in Scheme 2. First, the propargyl oxime undergoes a Cu-catalyzed 2,3-rearrangement to form *N*-allenylnitrone intermediate **8** through alkyne-π-activation (**6**), followed by the nucleophilic attack of the oxime nitrogen atom onto the electrophilically activated carbon−carbon triple bond, and then the elimination of the Cu catalyst from the cyclized vinylcopper intermediate **7** involving C−O bond cleavage. As the resulting resonance form **8′**, contributions in the form of electron-donation from the amino group would facilitate the rotation of the nitrone C═N bond, leading to oxaziridine intermediate **9**.[9] Next, a 1,2-hydrogen shift driven by the electron-donating dimethylaminophenyl group would form *N*-allenylamide **10**.[10] Finally, isomerization through vinylcopper intermediate **11** would give 1-amidodiene **3**.[11,12] The reaction to afford α,β-unsaturated imine **5** would involve protodemetalation of vinylcopper intermediate **11′**, as shown in Scheme 3. In regards to the labeling reaction of (*E*)-**1a**-*d* (eq 4), the low deuterium content at the 2-position of 1-amidodiene **3a**-*d* is reasonable because the hydrogen at the 2-position can be attributed to either the deuterium at the aldoxime moiety or the

Scheme 3



hydrogen atom at the homopropargyl position of (*E*)-**1a**-*d*. Moreover, rapid H/D exchange at the amide group of intermediate **10** and product **3** would also explain the low deuterium content. Presumably, acetic acid can serve as a proton source to accelerate the protodemetalation of the vinylcopper species **11** or **11′**, thus suppressing any undesirable polymerization processes of the unstable allenamide species **10** or **10′** (Schemes 2 and 3). In particular, the reaction of substrate (*Z*)-**1a** required the use of acetic acid to keep low concentration of the *in situ* formation of allenylamide species **10** due to rapid catalytic 2,3-rearrangement (Table 1, entry 2).

In conclusion, we have developed a novel method to synthesize multisubstituted 1-amidodienes. Because amidodienes have recently gained much attention as useful synthetic intermediates,[12−14] our methodology would provide a powerful tool in the preparation of highly functionalized amidodienes under mild reaction conditions. Of note, the skeletal rearrangement from propargyl oxime **1** to 1-amidodiene **3** involves the cleavages of a C−O, a N−O,[15] and two C−H bonds. Further investigations to understand the details of the reaction mechanism, specifically that of the rearrangement process from nitrone **8** to amide **10**, are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products **3**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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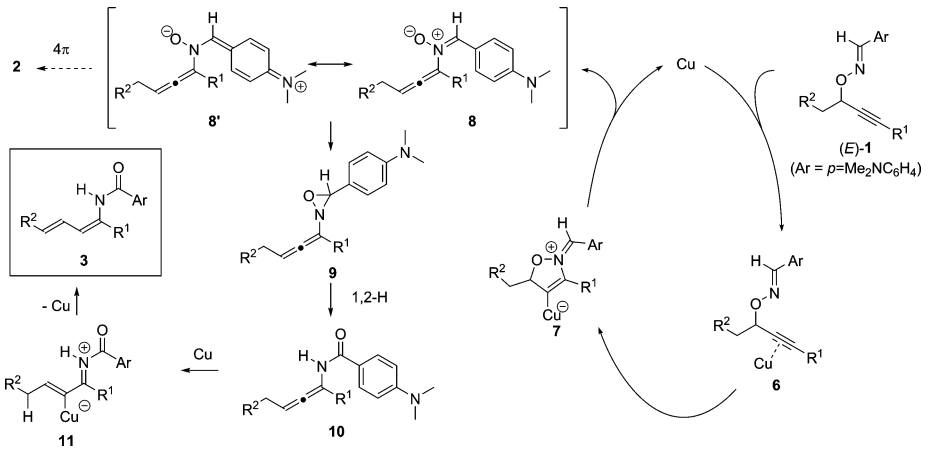
Notes

The authors declare no competing financial interest.

Scheme 2. A Plausible Mechanism



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(5) Preparation of **1a**; condensation between *O*-(1,3-diphenylprop-2-yn-1-yl)hydroxylamine and *p*-(dimethylamino)-benzaldehyde gave a 92:8 mixture of the *E*/*Z* isomers of **1a**.

(6) The copper-catalyzed reaction of (*Z*)-**1a** in the absence of acetic acid gave **3a** in less than 20% yield along with inseparable byproducts. In addition, the reaction in the presence of acetic acid without copper catalysts afforded an inseparable mixture including **3a** (<20%).

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