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Copper-Catalyzed Tandem [2,3]-Rearrangement and 6π-3-Azatriene Electrocyclization in (*E*)-*O*-Propargylic α,β-Unsaturated Oximes

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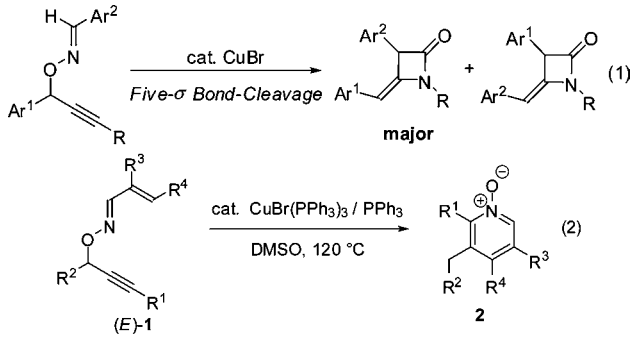
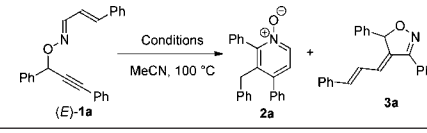
Catalyzed skeletal rearrangements have served as efficient and attractive transformations in synthetic chemistry and have rapidly grown to involve increasingly complex as well as intriguing reaction mechanisms.[1] For the catalytic skeletal rearrangements of enynes[2] and propargyl esters,[3] it has been demonstrated that the presence of an additional carbon−carbon double bond can dramatically affect the reaction pathway of the corresponding dienyne and enynyl ester substrates.[4,5] We have recently reported the Cu-catalyzed skeletal rearrangements of *O*-propargylic arylaldoximes that proceed via a five-σ bond cleavage to afford β-lactam derivatives in good to excellent yields (eq 1).[6] As a consequence, we have decided to expand our investigations to explore the scope of π-acidic metal-catalyzed reaction of *O*-propargylic oximes that include an olefin moiety within the substrate.[7] Herein, we report the Cu-catalyzed reactions of (*E*)-*O*-propargylic α,β-unsaturated oximes (*E*)-**1** that, surprisingly, proceeded via [2,3]-rearrangement to the *N*-allenyl nitrones followed by 6π-3-azatriene electrocyclization to afford the corresponding polysubstituted pyridine *N*-oxides **2** in good to high yields (eq 2).[8−10]



Initially, as summarized in Table 1, the reaction conditions were optimized starting from CuBr (10 mol %) and PPh_3 (40 mol %) in acetonitrile at 100 °C that afforded **2a** (68% yield) along with **3a** (9%), which can be attributed to the alkylidene group transfer.[11,12] As shown in entries 2−4, the use of PPh_3 as the ligand was essential because the best result was obtained when the reaction involved 4 equiv of PPh_3, whereas a lower amount or the absence of PPh_3 resulted in lower yields or the rapid decomposition of the starting material. The use of ligands other than PPh_3 such as $(p\text{-}F_3CC_6H_4)_3P$ and $(p\text{-}MeOC_6H_4)_3P$ was not as effective, and the effect of the halogen on the Cu atom was insignificant (see Supporting Information (SI)). Among the solvents tested, DMSO was shown to efficiently suppress the formation of the undesired byproduct **3a** (entry 6). Based on these results, the optimal reaction conditions involved $CuBr(PPh_3)_3$ (10 mol %) and PPh_3 (10 mol %) in DMSO at 120 °C (entry 7). The reaction in the absence of the copper catalysts at 120 °C afforded a small amount of **2a** (entry 8), while PPh_3 and Brønsted acids, such as acetic acid and TfOH, did not show any catalytic activities for the present reaction (entries 9−11).

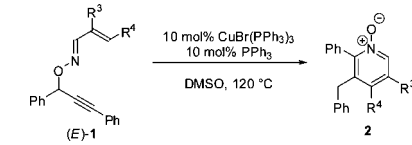
Table 1. Optimization of Reaction Conditions



Entry	Catalyst (mol %)	Time/h	Yield **2a**/%[a]	Yield **3a**/%[a]
1	CuBr (10), PPh_3 (40)	17	68	9
2	CuBr (10), PPh_3 (20)	11	62	5
3	CuBr (10), PPh_3 (10)	2	33	11
4	CuBr (10)	2	0	0
5	$CuBr(PPh_3)_3$ (10)	11	69	9
6[b]	CuBr (10), PPh_3 (40)	10	75 (70)	trace
7[b,c]	$CuBr(PPh_3)_3$ (10), PPh_3 (10)	2	75 (70)	trace
8[b,c]	none	2	10[d]	0
9[b,c]	PPh_3 (40)	2	6[e]	0
10[b,c]	AcOH (10)	2	6[f]	trace
11[b,c]	TfOH (10)	2	8	trace

[a] The yields were determined by ^1H NMR using CH_2Br_2 as an internal standard. Isolated yields in parentheses. [b] DMSO was used as solvent. [c] At 120 °C. [d] 72% recovery of **1a**. [e] 28% recovery of **1a**. [f] 80% recovery of **1a**.

Table 2. Cu-Catalyzed Cyclization of **1b**−**f** [a]



Entry	1	R^3	R^4	Time/h	2	Yield/%[b]
1	**1b**	H	H	5	**2b**	84
2	**1c**	H	Me	3	**2c**	64
3	**1d**	H	*n*-Pr	2	**2d**	50
4[c]	**1e**	Me	H	84	**2e**	71
5	**1f**	$-(CH_2)_4-$		70	**2f**	53

[a] The reaction of **1** (0.4 mmol) in the presence of $CuBr(PPh_3)_3$ (10 mol %) and PPh_3 (10 mol %) in DMSO (0.8 mL) at 120 °C. [b] Isolated yield. [c] CuBr (10 mol %) and PPh_3 (20 mol %) were used as catalysts.

Next, as shown in Table 2, substitution effects on the α,β-unsaturated oxime group were investigated. Substrate **1b**, which was derived from acrolein, was readily converted to the corresponding 2,3-disubstituted pyridine oxide **2b** in good yield (entry 1). The reactions of substrates that possess an alkyl substituent at the β-position (**1c** and **1d**) were completed within 3 h (entries 2

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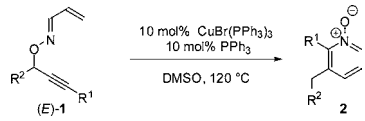
Table 3. Cu-Catalyzed Cyclization of **1g**−**q** [a]



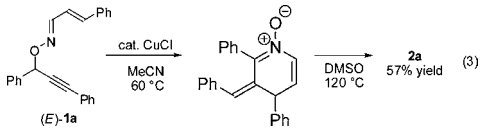
Entry	1	R^1	R^2	Time/ h	2	Yield/ %[b]
1	**1g**	*p*-anisyl	Ph	6	**2g**	75
2	**1h**	*p*-$F_3C-C_6H_4$	Ph	2.5	**2h**	52
3	**1i**	H	Ph	2.5	**2i**	80
4	**1j**	*n*-Pr	Ph	6	**2j**	87
5	**1k**	$(CH_2)_3OTIPS$	Ph	5	**2k**	87
6	**1l**	Cy	Ph	9	**2l**	81
7	**1m**	*t*-Bu	Ph	24	−	0[c]
8	**1n**	Ph	*p*-anisyl	3	**2n**	86
9	**1o**	Ph	*p*-$F_3C-C_6H_4$	1	−	0[c]
10[d]	**1p**	Ph	*n*-Pr	11	**2p**	47
11[d]	**1q**	Ph	Cy	16	**2q**	44

[a] The reaction of **1** (0.4 mmol) in the presence of $CuBr(PPh_3)_3$ (10 mol %) and PPh_3 (10 mol %) in DMSO (0.8 mL) at 120 °C. [b] Isolated yield. [c] Decomposition of the starting material was observed. [d] CuBr (10 mol %) and PPh_3 (20 mol %) were used.

and 3, respectively), whereas the substrate with an alkyl substituent at the α-position (**1e**) required a longer reaction time (entry 4). Finally, the oxime of cyclohex-1-enecarbaldehyde (**1f**) afforded the tetrahydroisoquinoline derivative **2f** in good yield (entry 5).

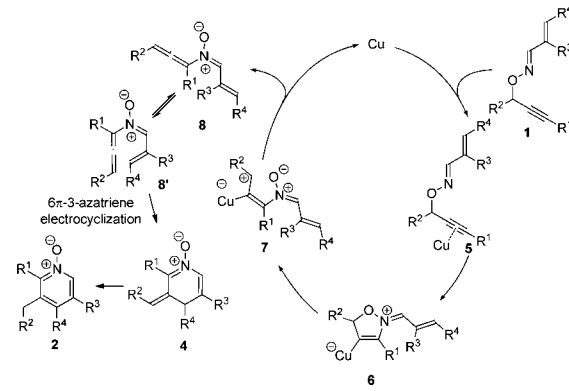
As shown in Table 3, we shifted our attention to investigate the substitution effects on the propargyl moiety. Although an electron-donating *p*-anisyl group at R^1 did not significantly affect the reaction (entry 1), the presence of an electron-withdrawing *p*-(trifluoromethyl)phenyl group (substrate **1h**) resulted in a moderate yield of **2h** (entry 2) due to a partial decomposition of **1h**. Substrate **1i**, with a terminal alkyne group, was efficiently converted to the 3-monosubstituted pyridine *N*-oxide **2i** in good yield (entry 3). Substrates that possess a small alkyl group (R^1) at the alkyne terminus (**1j**, **1k**, and **1l**) afforded the corresponding 2-alkylpyridine *N*-oxides (**2j**, **2k**, and **2l**, respectively) in high yields (entries 4−6); a bulky *tert*-butyl group, however, at the alkyne terminus caused the interruption of the cyclization reaction (entry 7). Next, the electronic property of the substituent (R^2) adjacent to the propargyl carbon was investigated. Although an electron-donating *p*-anisyl group (entry 8) was beneficial, an electron-withdrawing *p*-(trifluoromethyl)phenyl group (entry 9) interfered with the desired transformation; a mixture of unidentified products was obtained. Substrates **1p** and **1q**, which bear an alkyl group at R^2, were not very reactive (entries 10 and 11, respectively), even though the loading amount of PPh_3 was reduced to 20 mol %.

The reaction of (*E*)-**1a** in the presence of CuCl (10 mol %) at 60 °C afforded the 3-benzylidene-3,4-dihydropyridine *N*-oxide **4a**, which readily isomerized to **2a** at 120 °C (eq 3).[13] This transformation strongly suggests that dihydropyridine **4** serves as a reactive intermediate in the reaction pathway toward **2**.

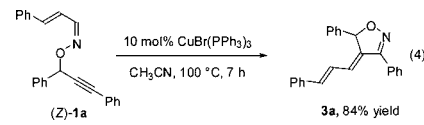


As illustrated in Scheme 1, a plausible mechanism of the present reaction can be described as follows: first, a π-acidic Cu catalyst becomes coordinated to the alkyne moiety of **1**. Next, a nucleophilic attack by the oxime nitrogen atom onto the electrophilically activated carbon−carbon triple bond gives cyclized intermediate

Scheme 1. Plausible Mechanism



6. Ionic cleavage of the C−O bond and subsequent elimination of the Cu catalyst leads to *N*-allenyl nitrone intermediate **8**. Its rotamer (**8′**) undergoes a 6π-3-azatriene electrocyclization to afford dihydropyridine **4**, which isomerizes to **2** under the reaction conditions. The significant effects of the substituent at the α-position of the oxime group can be attributed to the steric repulsion between R^1 and R^3 within cyclized intermediate **6**. In the case of (*Z*)-**1a**, the reaction did not result in the formation of pyridine *N*-oxide **2a** but instead afforded product **3a** presumably due to the alkylidene group transfer (eq 4).[12] This surprising result indicates that the geometry of the oxime moiety is crucial for the electrocyclization process.



In conclusion, we have successfully developed an entirely new approach to multisubstituted pyridine derivatives in a catalytic, efficient, and regioselective manner. Since pyridine *N*-oxides have recently received much attention in catalytic C−H functionalization,[14] the present methodology is useful to synthesize these substrates. Further investigations into the reaction mechanism, including the previously reported five-σ bond-cleavage rearrangement, are currently underway in our laboratory.

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Note Added after ASAP Publication. Table 1, footnotes e and f, were corrected May 19, 2010.

Supporting Information Available: Experimental procedures and characterization of **1**, **2**, **3a**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The starting materials (*E*)-**1** were prepared from the corresponding propargylic alcohols through alkoxylamine formation by Mitsunobu reaction (ca. 50−90% yields) and subsequent condensation with α,β-unsaturated aldehydes (ca. 40−75% yields).

(11) In this reaction of **1a**, formation of the β-lactam via five-σ bond cleavage was not observed.

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