



Copper-catalyzed hydroamination of propargyl imidates



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ABSTRACT

Propargyl imidates derived from aromatic and aliphatic nitriles cyclize at room temperature in high yields when treated with a catalytic amount of copper (I) iodide. This 5-*exo-dig* process affords dihydrooxazoles which do not aromatize under the reaction conditions, and which are isolated without chromatography. Investigations of the reaction scope, subsequent functionalization of the reaction products, and preliminary mechanistic data are presented.

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Introduction

Oxazoles and related heterocycles are important components of many biologically active natural products and pharmaceuticals.^{1,2} In addition to the Robinson-Gabriel oxazole synthesis and its variants,³ catalytic methods for the synthesis of oxazoles have been developed,⁴ notably the cycloisomerization of propargyl amides using transition metal catalysts such as AuCl₃ or FeCl₃ (**A**, Fig. 1).^{5,6} An intermediate in these catalytic examples is a non-aromatic 5-methylene-4,5-dihydrooxazole resulting from a 5-*exo-dig* cyclization. Interestingly, other metal catalysts have been discovered that chemoselectively convert propargyl amides to dihydrooxazoles without concomitant aromatization to the oxazoles.^{7–13} The exocyclic double bond of these compounds represents a handle which has been used to access several classes of functionalized oxazoles.^{14,15}

The cycloisomerization, or hydroamination, of the isomeric propargyl imidates to the corresponding 4-methylene-4,5-dihydrooxazoles, however, has been less-extensively studied.¹⁶ Overman and coworkers reported both the thermal and the stoichiometric DBU-promoted hydroamination of two benzimidates (**A**, Fig. 2), and provided examples of their subsequent functionalization.¹⁷ Isolation of these dihydrooxazoles from the DBU procedure was complicated by the instability of the products to chromatography, and the thermal procedure was limited to dilute

solutions. The groups of Hashmi,¹⁸ Shin,¹⁹ and Hii²⁰ have reported catalytic gold and silver hydroaminations restricted to propargyl trichloroacetimidates (**B**, Fig. 2). Although these methods afford trichloromethyl-substituted products, a robust and catalytic route to the electron-rich, non-trichloromethyl-substituted, aryl- and alkyl-substituted 4-methylene-4,5-dihydrooxazoles remains unexplored. Herein we report the catalytic hydroamination of both aryl- and alkyl-substituted propargyl imidates using a copper catalyst that produces 4-methylene-4,5-dihydrooxazoles, which are isolated in good to near-quantitative yields and high purity without chromatography (**C**, Fig. 2).

Results and discussion

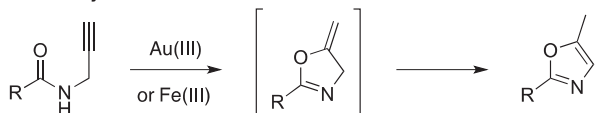
To begin, model substrate **3a** was synthesized via a Pinner reaction of 4-chlorobenzonitrile and propargyl alcohol saturated with gaseous HCl (**Scheme 1**).²¹ The resultant HCl salt was collected by filtration, and subsequent neutralization afforded the free base as a stable solid.

Upon exposure of **3a** to 5 mol% AuCl₃ in CDCl₃ at room temperature for 10 min, both dihydrooxazole **4a** and oxazole **5a** were observed by ¹H NMR spectroscopy in a 90:10 ratio, with no starting material remaining (**Scheme 2**). After 2 h, **4a** was converted to **5a** quantitatively. Unlike the reactions of propargyl trichloroacetimidates described by Hashmi, the reaction of this aromatic propargyl imidate with AuCl₃ was not chemoselective for the dihydrooxazole at short reactions times.

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A. Catalytic Oxazole Formation:



B. Catalytic Dihydrooxazole Formation and Functionalization

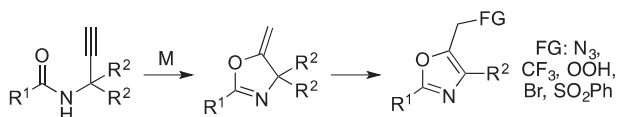


Fig. 1. Oxazole and dihydrooxazole syntheses. M: Au(I), Ag(I), Pd(II), Zn(II), Cu(I) if $R^2 \neq H$.

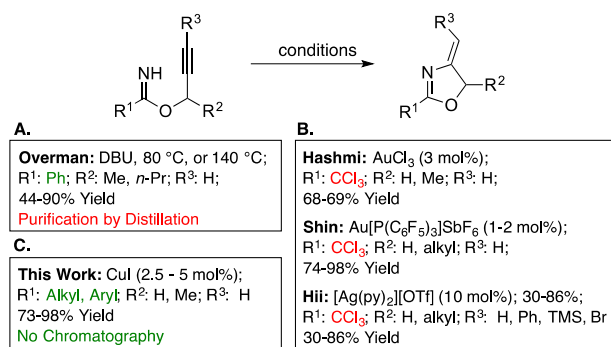
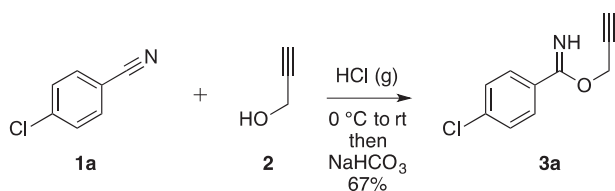
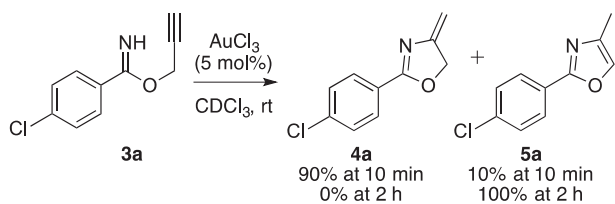


Fig. 2. Hydroamination of propargyl imidates.



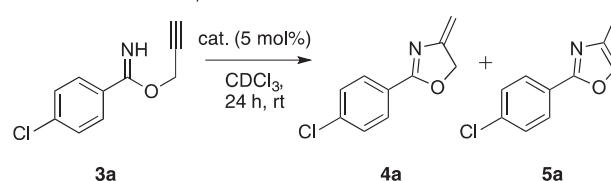
Scheme 1. Synthesis of substrate **3a**.



Scheme 2. Hydroamination of **3a** with $AuCl_3$.

Other catalysts were then tested in this reaction to determine if chemoselectivity for **4a** could be obtained. **Table 1** summarizes the results of reactions of **3a** with a metal salt (5 mol% loading) in $CDCl_3$ at room temperature for 24 h. Precious metal gold, palladium, and silver compounds promoted hydroamination (as measured by 1H NMR spectroscopy), but none provided desired levels of reactivity and chemoselectivity. $KAuCl_4$ exhibited rapid reactivity similar to $AuCl_3$ (entry 1). $Pd(PhCN)_2Cl_2$ and $Pd(OAc)_2$ afforded conversion to both dihydrooxazole **4a** and oxazole **5a** (entries 2 and 3), whereas $Pd(PPh_3)_2Cl_2$ afforded partial conversion to **4a** with no oxazole formation (entry 4). $AgOTf$ (entry 5) was more reactive than both Ag_2SO_4 and AgI (entries 6 and 7), with the latter two showing chemoselectivity for dihydrooxazole **4a**. Non-precious metals also promoted hydroamination at room temperature. $ZnCl_2$

Table 1
Conversion of **3a** to **4a** and/or **5a**.



Entry	Catalyst ^a	% 3a ^b	% 4a ^b	% 5a ^b
1	$KAuCl_4$	0	0	100
2	$Pd(PhCN)_2Cl_2$	0	59	42
3	$Pd(OAc)_2$	0	73	27
4	$Pd(PPh_3)_2Cl_2$	84	16	0
5	$AgOTf$	0	90	10
6	Ag_2SO_4	88	12	0
7	AgI	93	7	0
8	$ZnCl_2$	6	92	2
9	$FeCl_3$	72	6	22
10	$CuCl_2$	94	6	0
11	$CuCl$	0	>99	Trace
12	$CuBr$	0	>99	Trace
13	CuI	0	>99	Trace

^a Conditions: catalyst (5 mol%), $CDCl_3$ (0.25 M), room temperature, 24 h.

^b Determined by 1H NMR spectroscopy.

Table 2

Solvent screen.

Chemoselectivity for 4a ^{a,b}		
>95%	95–80%	<80%
MeCN, acetone, EtOAc, benzene, cyclohexane, <i>t</i> -BuOH	MeOH, EtOH	AcOH, CF_3CH_2OH

^a Conditions: CuI (5 mol%), solvent (0.25 M), room temperature, 24 h.

^b Determined by 1H NMR spectroscopy.

was an effective catalyst, affording almost complete conversion to **4a** with minimal formation of **5a** (entry 8). $FeCl_3$ favored formation of **5a** over **4a**, but in low conversion. $CuCl_2$ was not an effective catalyst (entry 10), but the Cu(I) compounds $CuCl$, $CuBr$, and CuI (entries 11, 12, and 13), however, provided complete conversion of **3a** to **4a** with only trace formation of oxazole **5a**.

CuI was recognized as an ideal catalyst not only because it is an easily-handled, stable solid, but moreover, the heterogeneous reaction conditions afforded by this insoluble catalyst obviate the need for flash chromatography, to which these products have limited stability. Once the reactions in $CHCl_3$ completed, the insoluble CuI was removed by filtration, affording products in high purity after solvent removal (see the [Supplemental Data](#)).

A solvent screen showed that other polar aprotic solvents (MeCN, acetone, EtOAc) and non-polar solvents (benzene, cyclohexane) could be utilized for the hydroamination, providing high levels of chemoselectivity (**Table 2**). Alcohols such as MeOH and EtOH could be used, but small amounts of imidate solvolysis products were detected over time. Solvolysis was not detected in runs in *t*-BuOH. More acidic solvents such as AcOH and CF_3CH_2OH were the only solvents tested that showed oxazole formation to any great extent, likely because acids promote isomerization of these dihydrooxazoles to oxazoles. $CHCl_3$ was used for subsequent reactions, however, because it easily solubilized the range of substrates tested (*vide infra*).

A series of imidates was synthesized using Pinner conditions, which proved successful for a variety of aryl- and alkyl-nitrile substrates (see [Supplemental Data](#)). The *in situ* generation of HCl using acetyl chloride and propargyl alcohol was also effective, providing

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