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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.

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 $AuCl_3$ or $FeCl_3$ (**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 Hii[20] 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% $AuCl_3$ in $CDCl_3$ 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 $AuCl_3$ was not chemoselective for the dihydrooxazole at short reactions times.

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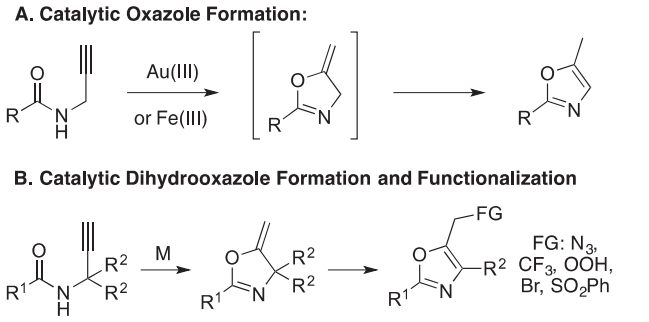


Fig. 1. Oxazole and dihydrooxazole syntheses. M: Au(I), Ag(I), Pd(II), Zn(II), Cu(I) if $R^2 \neq H$.

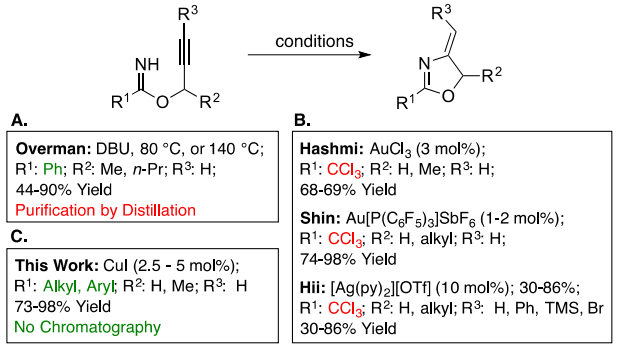
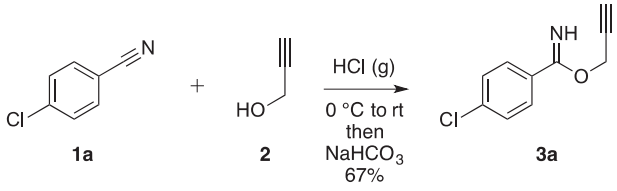
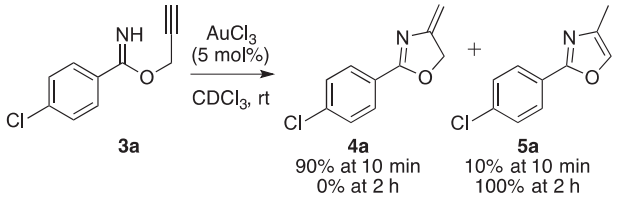


Fig. 2. Hydroamination of propargyl imidates.



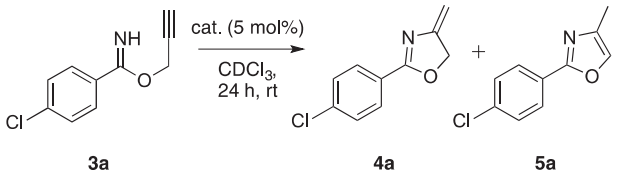
Scheme 1. Synthesis of substrate **3a**.



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 $Pd(PPh_3)Cl_2$ 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 **4**[a,b]		
>95%	95–80%	<80%
MeCN, acetone, EtOAc, benzene, cyclohexane, *t*-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.

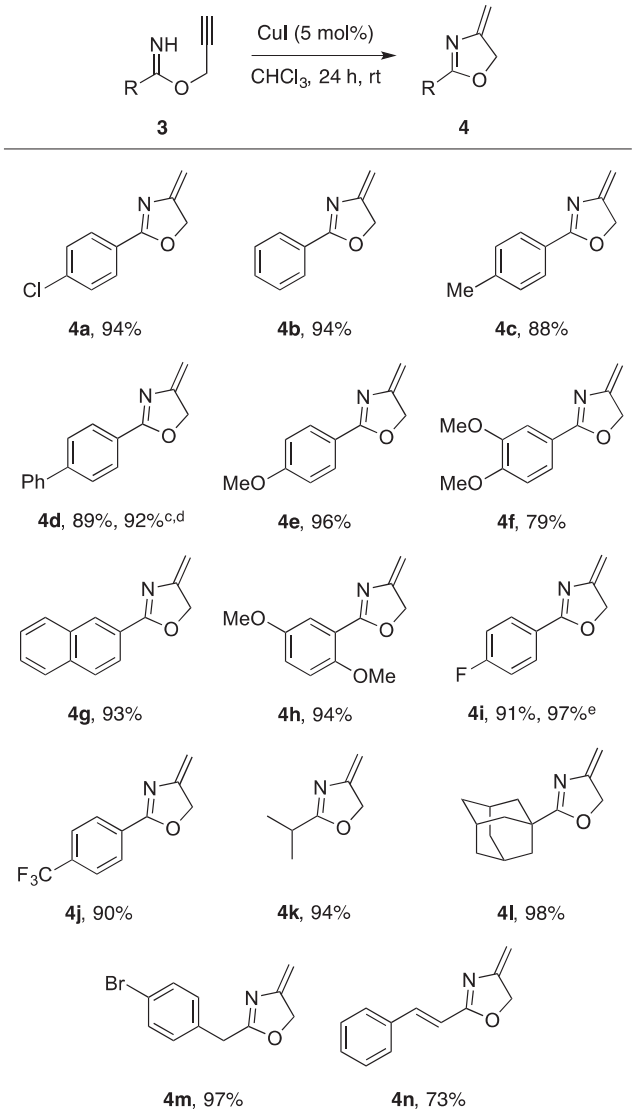
was an effective catalyst, affording almost complete conversion to **4a** with minimal formation of **5a** (entry 8). $FeCl_3$ favored formation of **5a** over **4a**, but in low conversion. $CuCl_2$ was not an effective catalyst (entry 10), but the Cu(I) compounds CuCl, CuBr, and CuI (entries 11, 12,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

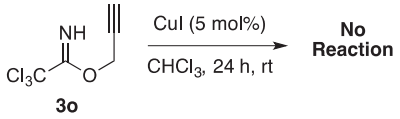
A series of imidates was synthesized using Pinner conditions, which proved successful for a variety of aryl- and alkyl-nitrile substrates (see Supplemental Data). The *in situ* generation of HCl using acetyl chloride and propargyl alcohol was also effective, providing

Table 3
Hydroamination scope.[a,b]

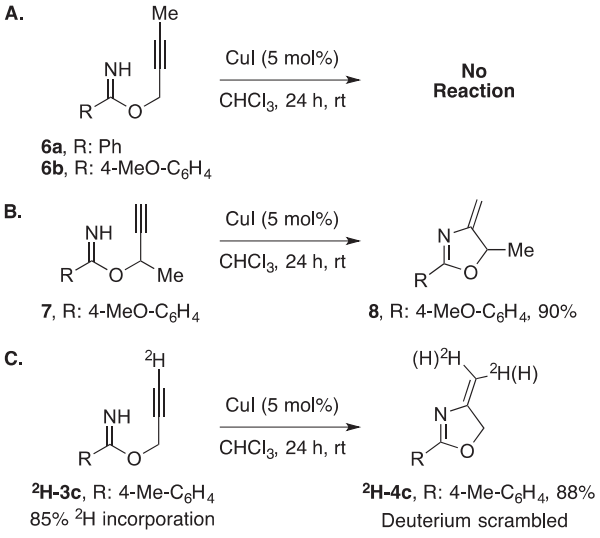


[a] Conditions: 0.30 mmol **3**, 0.25 M $CHCl_3$, 5 mol% CuI, 24 h.
[b] Isolated yield.
[c] 10 mmol scale.
[d] 2.5 mol% CuI used.
[e] 5 mmol scale.

imidates in comparable yields.[22] The scope of the hydroamination was then investigated using these imidates, as shown in Table 3. Electron-rich benzimidates cyclized in complete conversion and in good to excellent isolated yields (**4b**–**4 g**). The presence of an *ortho*-substituent on the aromatic ring did not adversely affect the reaction (4**h**). Electron deficient substrates generally took the full 24 h to reach completion (compounds **4a**, **4i**, and **4j**). Aliphatic dihydrooxazoles, even the bulky adamantyl-substituted **4l**, were obtained in excellent yields. Likewise, the alkenyl imidate cyclized to afford the unsaturated dihydrooxazole **4n**. The reaction has been scaled up to 5 and 10 mmol (**4i** and **4d**, respectively) with no loss of chemoselectivity or purification complications. At the 10 mmol scale, the reaction was conducted with a 2.5 mol% catalyst loading and was still complete within 24 h (**4d**). Additionally, no special precautions were taken to exclude air or moisture from these reactions.



Scheme 3. Reaction of a propargyl trichloroacetimidate.

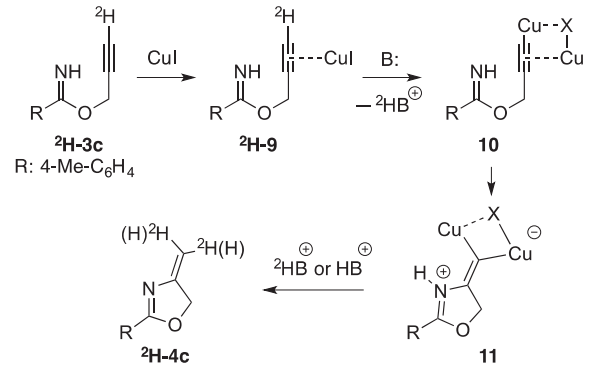


Scheme 4. Hydroamination of substituted propargyl imidates.

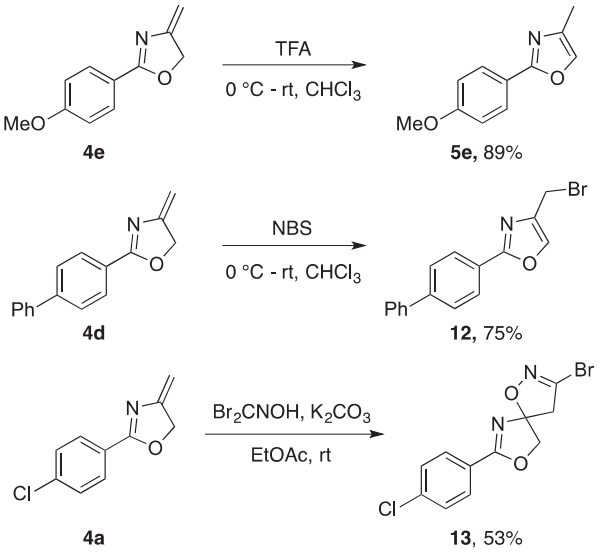
This hydroamination protocol was then applied to the propargyl trichloroacetimidate substrate used by the Hashmi, Shin, and Hii groups. After 24 h, however, no reaction was observed for this substrate (Scheme 3). This lack of reactivity may be due to the extreme electron withdrawing nature of the trichloromethyl group, which would be expected based on the slower reaction rates observed for the electron deficient benzimidates.

This result prompted further examination of the structural constraints on these substrates, specifically, whether substitution of the propargyl component was permitted (Scheme 4). The Pinner reaction was used to synthesize benzimidates from 2-butyn-1-ol (**6a**, **6b**). Upon exposure to the standard reaction conditions (5 mol% CuI, $CHCl_3$, rt, 24 h) both **6a** and **6b** failed to cyclize (**A**, Scheme 4), in contrast to the reactivity of the corresponding propargyl imidates **3b** (R = Ph) and **3e** (R = 4-MeO-C_6H_4). Only starting material was recovered in each instance. In order to probe whether the increased sterics around the alkyne were responsible for the lack of reactivity, the imidate derived from isomeric 3-butyn-2-ol (**7**) was subjected to the standard conditions. This substrate, however, cyclized to the desired dihydrooxazole (**B**, Scheme 4) in a yield comparable to the cyclization of the corresponding propargyl imidate **3e** (R = 4-MeO-C_6H_4). These results suggest that the mechanism for the CuI-catalyzed reaction may involve formation of a copper (I) acetylide[23] species from a terminal alkyne, rather than an alkyne π-activation/cyclization that is operative in the trichloroacetimidate reactions promoted by gold and silver catalysts (**B**, Fig. 2). To support this conjecture, an imidate deuterated at the alkyne terminus was synthesized[24] and treated with the standard conditions (**C**, **^{2}H-3c**, Scheme 4) (the exchangeable NH was retained, see the Supplementary Data). The product **^{2}H-4c** was isolated in high yield, but hydrogen was incorporated at both positions of the terminus of the exocyclic alkene, indicating that scission of the deuterium–carbon bond occurred during the transformation.

In such a process (Scheme 5), the basic nitrogen of an imidate (B:) could serve to dedeuterate a copper-coordinated alkyne to



Scheme 5. Plausible mechanism (X: I or acetylide).



Scheme 6. Modification of dihydrooxazoles.

form the copper (I) acetylide (^{2}**H-9** → **10**). After *5-exo-dig* cyclization, demetalation of **11** can proceed using available deuterium and hydrogen sources to produce ^{2}**H-4c**. Taken together, the deuterium-labeling result and the lack of reactivity for imidates **6a** and **6b** support a copper (I) acetylide intermediate. Such an intermediate would also explain why $CuCl_2$ was an inefficient catalyst (Table 1, entry 10). Additionally, it is possible that propargyl trichloroacetimidate **3o** did not react because the electron-deficient nitrogen was not basic enough to promote copper acetylide formation.

As expected, the exocyclic alkene of the dihydrooxazole products of these hydroamination reactions can be further modified in a variety of reactions (Scheme 6). For example, oxazole **5e** was obtained upon treatment of dihydrooxazole **4e** with catalytic TFA. Additionally, reaction of dihydrooxazole **4d** with NBS rapidly produced the 4-bromomethyloxazole **12**. The [3+2] cycloaddition of **4a** with bromonitrile oxide provided access to spirocyclic compound **13**.

Conclusion

CuI is a practical catalyst for the conversion of aromatic and aliphatic propargyl imidates to 4-methylene-4,5-dihydrooxazoles, which are isolated in high yield and purity without chromatography. These relatively electron-rich products do not aromatize to the oxazoles in the presence of CuI, in contrast to reactions with $AuCl_3$, which had been used to synthesize the very electron-deficient trichloromethyl-substituted dihydrooxazoles. Moreover, this is an attractive method because CuI is an inexpensive and readily-available catalyst, it does not require the use of inert or moisture-free atmospheres, the insoluble CuI is easily separated from the product after the room temperature reaction is completed, it has been scaled up to 10 mmol, and the products are easily modified for further uses. Several experiments suggest the intermediacy of a copper (I) acetylide. Ongoing studies will further elucidate this mechanism, and explore new carbon–carbon bond forming reactions involving the dihydrooxazole products (cross-couplings, radical additions).

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.10.043.

References

1. Palmer DC, Venkatraman S. The Chemistry of Heterocyclic Compounds, Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A. In: Palmer DC, ed. Hoboken, NJ: John Wiley & Sons; 2003.
2. Molinski TF, Dalisay DS, Lievens SL, Saludes JP. *Nat Rev Drug Discov*. 2009;8:69–85.
3. Turchi IJ, Dewar MJS. *Chem Rev*. 1975;75:389–437.
4. Gulevich AV, Dudnik AS, Chernyak N, Gevorgyan V. *Chem Rev*. 2013;113:3084–3213.
5. Hashmi ASK, Weyrauch JP, Frey W, Bats JW. *Org Lett*. 2004;6:4391–4394.
6. Senadi GC, Hu W-P, Hsiao J-S, Vandavasi JK, Chen CY, Wang JJ. *Org Lett*. 2012;14:4478–4481.
7. For a Cu(I) example, see: Jin C, Burgess JP, Kepler JA, Cook CE. *Org Lett*. 2007;9:1887–1890.
8. For a Ag(I) example, see: Harmata M, Huang C. *Synlett*. 2008;1399–1401.
9. For a Au(I) example, see: Hashmi ASK, Blanco Jaimes MC, Schuster AM, Rominger F. *J Org Chem*. 2012;77:6394–6408.
10. For a Cu(I) example, see: Alhalib A, Moran WJ. *Org Biomol Chem*. 2014;12:795–800.
11. For a Ag(I) example, see: Wong VHL, White AJP, Hor TS, Hii KK. *Adv Synth Catal*. 2015;357:3943–3948.
12. For a Pd(II) example, see: Derosa J, Cantu AL, Boulous MN, et al. *J Am Chem Soc*. 2017;139:5183–5193.
13. For a Zn(II) example, see Ref. 6.
14. Peng H, Akhmedov NG, Liang Y-F, Jiao N, Shi X. *J Am Chem Soc*. 2015;137:8912–8915.
15. Wang B, Chen Y, Zhou L, Wang J, Tung C-H, Xu Z. *J Org Chem*. 2015;80:12718–12724.
16. There is a report in the patent literature which uses AgOTs to convert propargyl imidates directly to oxazoles in very low yields: Mccall, J., Kelly, R., Romero, D. WO2014066795 (A1) 2014.
17. Overman LE, Tsuboi S, Angle S. *J Org Chem*. 1979;44:2323–2325.
18. Hashmi ASK, Rudolph M, Schymura S, Visus J, Frey W. *Eur J Org Chem*. 2006;4905–4909.
19. Kang J-E, Kim H-B, Lee J-W, Shin S. *Org Lett*. 2006;8:3537–3540.
20. Wong VHL, Hor TSA, Hii KK. *Chem Commun*. 2013;49:9272–9274.
21. Yura Y. *Chem Pharm Bull (Tokyo)*. 1962;10:1094–1098.
22. Yadav VK, Babu KG. *Eur J Org Chem*. 2005;452–456.
23. Moran proposes a copper acetylide in a related system. See Ref. 10.
24. Bew SP, Hiatt-Gipson GD, Lovell JA, Poullain C. *Org Lett*. 2012;14:456–459.