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Copper(II)-Promoted Cyclization/Difunctionalization of Allenols and Allenylsulfonamides: Synthesis of Heterocycle-Functionalized Vinyl Carboxylate Esters

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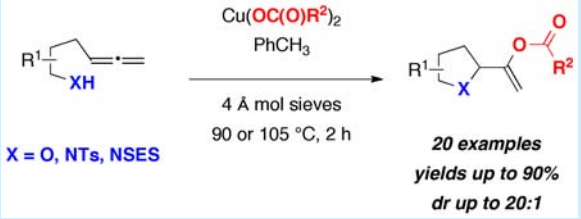
Supporting Information

ABSTRACT: A unique method to affect intramolecular amino-oxygenation and dioxygenation of allenols and allenylsulfonamides is described. These operationally simple reactions occur under neutral or basic conditions where copper(II) carboxylates serve as reaction promoter, oxidant, and carboxylate source. Moderate to high yields of heterocycle-functionalized vinyl carboxylate esters are formed with moderate to high levels of diastereoselectivity. Such vinyl carboxylate esters could serve as precursors to α-amino and α-oxy ketones and derivatives thereof.

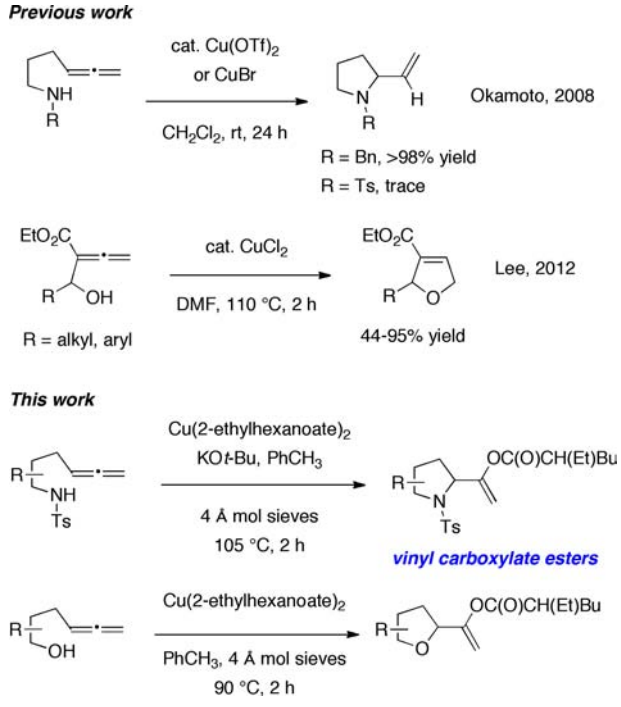


Transition-metal-catalyzed cyclization of alcohols and amine derivatives onto pendant allenes has emerged as a powerful approach to heterocycle synthesis.[1−5] Both endo and exo cyclization modes have been explored, and hydrofunctionalization as well as difunctionalization transformations have been achieved. Hydrofunctionalization reactions have been catalyzed by complexes of [Ln], [Sm], [Y], [Pd], [Au], [Ag], and [Cu].[1,3−5] Difunctionalization reactions such as net carboamination and carboetherification have been catalyzed by [Ru], [Pd], [Co], and [Cu].[1,6−10] Haloamination has been achieved by use of [Pd] catalysts in the presence of [Cu] and halide salts,[11,12] and more recently, use of chiral [Au] catalysts in the presence of electrophilic bromine sources has provided chiral heteroatom-functionalized vinyl bromides.[13] Despite these advances, no methods for allene aminooxygenation and dioxygenation have been reported.

For the past decade, our group has developed copper-facilitated alkene addition reactions[14] including oxyamination, aminooxygenation, diamination, and dioxygenation reactions.[15−18] In the interest of expanding the scope, we investigated allene difunctionalizations (Scheme 1).

Copper catalysis in this area can be further summarized. Halolactonization and halolactamization promoted by $CuBr_2$ and $CuCl_2$ endocyclization of 2,3-allenoate derivatives have been reported by Ma and co-workers.[19−21] Gevorgyan and co-workers have investigated copper-facilitated endocyclization of in situ formed allenylpyridines en route to *N*-fused heterocycles.[22] Both *endo*- and *exo*-hydroamination/cyclization of electron-rich allenylamines (e.g., *N*-benzyl) catalyzed by a variety of copper salts were reported by Okamoto (Scheme 1).[23] Lee and co-workers recently reported an *endo*-selective hydroalkoxylation catalyzed by $CuCl_2$ (Scheme 1).[24] Kanai and co-workers have developed copper(I)-catalyzed endocyclizations of allenyl alcohols and amine derivatives.[25−27]

Scheme 1. Copper-Promoted Allene Cyclization



Surprisingly, reactions of allenols and allenylamine derivatives with copper(II) carboxylate salts alone have not been reported. In this paper, we report that copper(II) carboxylate promoted cyclizations of allenols and allenylamine derivatives can result in

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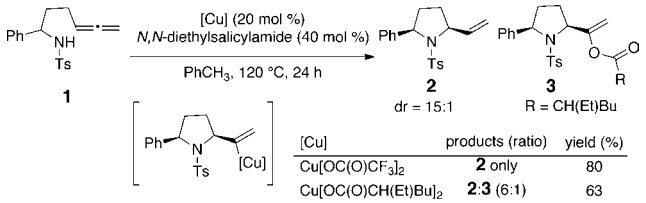
net dioxygenation and aminooxygenation. These new reactions provide useful heterocycle functionalized vinyl carboxylate esters,[28,29] products that heretofore have not been obtained directly from allenes by other reaction protocols.

We initially investigated the cyclization of *N*-tosylallenyl amide **1** using catalytic copper(2-ethylhexanoate)$_2$ [Cu(eh)$_2$] and copper(trifluoroacetate)$_2$ (Scheme 2). After a brief screen of

Scheme 2. Hydroamination and Aminooxygenation

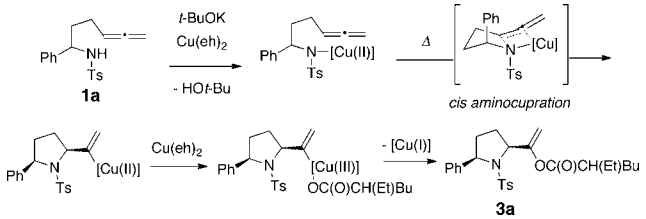


reaction conditions, we found hydroamination to be optimal using 20 mol % Cu(OC(O)CF$_3$)$_2$ and 40 mol % *N*,*N*-diethylsalicylamide as ligand in toluene at 120 °C for 24 h. No base or oxidant is required in this reaction and the relative configuration of the major diastereomer **2** (dr = 15:1) was assigned to be cis.[30] Under the same conditions but with Cu(eh)$_2$, we obtained a mixture of the expected hydroamination product **2** along with a new aminooxygenation product, vinyl ester **3** (ratio **2**:**3** = 6:1).

Vinyl esters can undergo hydrolysis to give the corresponding ketones or they can undergo carbon−carbon bond formation with electrophiles.[31−38] Reported methods to form vinyl esters include metal-catalyzed addition of acids to alkynes, *O*-acylation of silyl enol ethers, and Baeyer−Villiger oxidation of enones.[39−45]

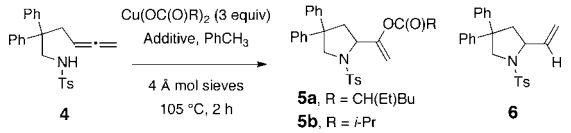
We were intrigued with the formation of the pyrrolidine-functionalized vinyl ester **3** and set about to optimize for this more unique reaction. We reasoned that since vinyl ester **3** obtains its carboxylate from the copper(II) salt, a copper-promoted reaction would better facilitate its production. Furthermore, we hypothesized that while the hydroamination product **2** can be directly obtained from a vinylcopper intermediate via protonation, the vinyl ester product **3** likely arises from oxidation of the copper(II) intermediate to a copper(III) intermediate and subsequent reductive elimination (Scheme 3).

Scheme 3. Proposed Aminooxygenation Mechanism



The aminooxygenation reaction of allenyl sulfonamide **4** was optimized as shown in Table 1 using 300 mol % of Cu(eh)$_2$ (less [Cu] gave lower ratios of **5**:**6**). In the event, reaction of sulfonamide **4** gave 59% combined yield of a 2:1 ratio of aminooxygenation and hydroamination adducts **5a** and **6**. We hypothesized that the ratio could be further shifted toward aminooxygenation either by disfavoring the hydroamination by removing sources of H$^+$ or by increasing the oxidizing conditions

Table 1. Aminooxygenation Optimization[a]



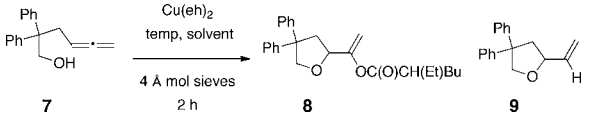
entry	additive	yield **5**[b] (%)	ratio **5**:**6**[c]
1		59	2:1
2[d]	TEMPO	63	4:1
3[e]	KO-*t*-Bu	78	20:1
4[e,f]	KO-*t*-Bu	24	1:1.7
5[e,g]	KO-*t*-Bu, O$_2$	31	20:1

[a]Reaction conditions: allene **4** (39 mg, 0.10 mmol), Cu(eh)$_2$ (3 equiv), 1.0 mL of PhCH$_3$, and 4 Å molecular sieves were heated for 2 h at 105 °C in a sealed tube. [b]Isolated yield. [c]Ratio based on analysis of crude ^{1}H NMR. [d]TEMPO (1 equiv) was added to the reaction mixture before heating. [e]Substrate **4** was treated with KO-*t*-Bu (1 equiv) for 0.5 h at rt before Cu(eh)$_2$ was added. [f]Cu(OC(O)-*i*-Pr)$_2$ was used. [g]Cu(eh)$_2$ (1 equiv) and O$_2$ (1 atm, balloon) were used; reaction in round-bottomed flask.

to enable more facile access to Cu(III) intermediates. When the TEMPO radical was added to increase the oxidizing ability of the solution, the yield and ratio did increase to 63% and 4:1, respectively. Notably, no TEMPO adduct was observed, which may indicate that a vinyl radical is not a reaction intermediate. However, use of 1 equiv of the strong base KO-*t*-Bu was more effective, providing 78% yield of essentially only amino-oxygenation product **5a** (Table 1, entry 3). Reaction with Cu[OC(O)-*i*-Pr]$_2$ gave **5b** and **6** in a 1:1.7 ratio (Table 1, entry 4). Cu(OAc)$_2$ gave hydroamination product **6** exclusively (not shown). These differences are likely due to the respective solubilities of these copper(II) carboxylates in toluene. When O$_2$ (1 atm, balloon) was used with 100 mol % of Cu(eh)$_2$, 31% of **5a**, along with other minor products (but not **6**), was formed.

The analogous reaction with allenyl alcohol **7** was examined (Table 2). This substrate preferentially formed dioxygenation

Table 2. Dioxygenation Optimization[a]



entry	[Cu] (equiv)	solvent	temp (°C)	yield[b] (%)	ratio **8**:**9**[c]
1	3	PhCH$_3$	105	71	20:1
2	2.2	PhCH$_3$	90	90	20:1
3	2.2	PhCH$_3$	75	64	15:1
4	2.2	DCE	90	66	20:1
5	2.2	CH$_3$CN	90	70	20:1

[a]Allenyl alcohol **7**, Cu(eh)$_2$ (2.2−3 equiv), solvent (0.2 M), and 4 Å molecular sieves (20 mg/mL) were heated in a sealed tube for 2 h. [b]Isolated yield. [c]Ratio determined by analysis of the ^{1}H NMR of the crude reaction mixture.

adduct **8** over the hydroetherification product **9** even in the absence of base or oxidant (Table 2, entry 1). At both reduced Cu(eh)$_2$ loading (2.2 equiv) and reaction temperature (90 °C), the reaction was most efficient, producing vinyl ester **8** essentially exclusively in 90% yield (Table 2, entry 2). While toluene was the most effective (compare Table 2, entry 2, to entries 4 and 5) the reaction also worked in 1,2-dichloroethane and acetonitrile.

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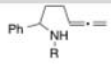
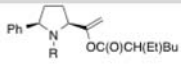
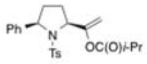
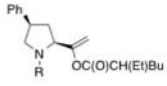
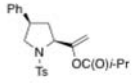
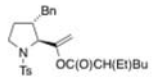
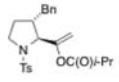
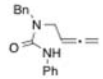
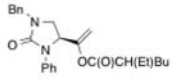
The effects of backbone substituents and amine functionalization on the aminooxygenation reaction were explored (Table 3).

Table 3. Scope of the Aminooxygenation Reaction

entry	substrate	product	yield (%)[c]	dr[d]
1[a]			51	20:1
	1a, R = Ts	**3a**, R = Ts		
2[a]	**1b**, R = SES	**3b**, R = SES	83	20:1
3[b]	**1a**		30	20:1
		3c		
4[a]			55	4:1
	10a, R = Ts	**11a**, R = Ts		
5[a]	**10b**, R = Cbz	**11b**, R = Cbz	no rxn	
6[b]	**10a**		37	4:1
		11c		
7[a]			73	20:1
	12	**13a**		
8[b]	**12**		35	20:1
		13b		
9[a]			43	
	14	**15**		

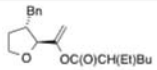
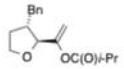
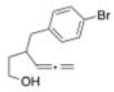
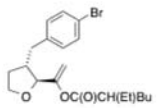
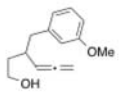
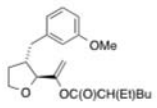
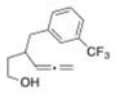
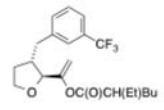
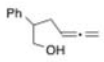
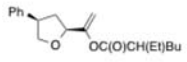
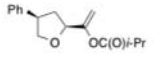
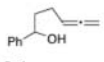
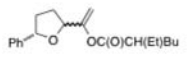
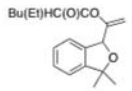
[a]Table 1, entry 3, conditions were used unless otherwise noted. [b]$Cu[OC(O)$-*i*-$Pr]_2$ was used instead of $Cu(eh)_2$. [c]Isolated yield. [d]Diastereomeric ratio refers to relative stereochemistry about the pyrrolidine backbone and not to 2-ethyl hexanoate derived diastereomers. Ratio determined by analysis of the crude ^{1}H NMR. SES = 2-trimethylsilylethane sulfonyl.

In the diastereoselective reactions, use of $Cu(2\text{-ethylhexanoate})_2$ provides the possibility of four diastereomers since 2-ethyl hexanoate has a stereocenter and is racemic. The effect of this stereocenter on the ^{1}H NMR spectra of these compounds is minimal, but to avoid ambiguity in relative stereochemistry configuration assignment, reactions were also run with $Cu[OC(O)$-*i*-$Pr]_2$.

As indicated in Table 3, α-phenyl sulfonamides **1** gave high selectivity for the 2,5-cis-pyrrolidine diastereomers **3**. Both aryl and alkyl sulfonyl *N*-substituents were reactive (Table 3, entries 1−3). The β-phenyl sulfonamide **10a** provided moderate (4:1) selectivity for the *cis*-pyrrolidine diastereomers **11** (Table 3, entries 4 and 6). The *N*-CBz substrate **10b** was unreactive (Table 3, entry 5). γ-Benzylsulfonamide **12** provided 2,3-*trans*-pyrrolidines **13** with excellent selectivity (Table 3, entries 7 and 8). Urea **14** gave cyclic urea **15** in moderate yield (Table 3, entry 9).

A number of allenyl alcohols were next explored in the copper-promoted allene dioxygenation reaction (Table 4). 2,3-*trans*-2-

Table 4. Scope of the Dioxygenation Reaction

entry	substrate	product	yield (%)	dr
1[a]			90	20:1
	16	**17a**		
2[b]	**16**		50	20:1
		17b		
3[a]			78	20:1
	18	**19**		
4[a]			77	20:1
	20	**21**		
5[a]			85	20:1
	22	**23**		
6[a]			87	19:1
	24	**25a**		
7[b]	**24**		33	20:1
		25b		
8[a]			60	2:1
	26	**27**		
9[a,c]			56	
	28	**29**		

[a]Table 2, entry 5, conditions were used unless otherwise noted. [b]$Cu[OC(O)$-*i*-$Pr]_2$ (3 equiv) was used. [c]Isolated yield. [d]Ratio determined by analysis of the ^{1}H NMR of the crude reaction mixture. Ratio refers to relative configuration about the tetrahydrofuran ring backbone and not to 2-ethylhexanoate-derived diastereomers. [e]Reaction run for 8 h.

Vinylcarboxytetrahydrofurans formed efficiently from γ-benzyl allenyl alcohols **16**, **18**, **20**, and **22** (Table 4, entries 1−5). The β-phenyl allenyl alcohol **24** gave the 2,4-*cis*-2-vinylcarboxytetrahydrofurans **25** (Table 4, entries 6 and 7). α-Phenyl alcohol **26** cyclized with modest diastereoselectivity (Table 4, entry 8). The 2-allenyl tertiary benzyl alcohol **28** cyclized readily to provide phthalan **29** (Table 4, entry 9).

The proposed mechanism for the copper(II) carboxylate-promoted aminooxygenation of allenes is presented in Scheme 3. In this scenario, sulfonamide **1a** engages the [Cu(II)] in a N−Cu(II) bond. Subsequent thermally promoted diastereoselective *cis*-aminocupration[46] across the allene provides the nitrogen heterocycle with a pendant vinylcopper(II) moiety. Oxidation of the vinylcopper(II) to vinylcopper(III) with additional $Cu(eh)_2$[47,48] and reductive elimination involving a carboxylate ligand on the copper center provides the vinyl ester **3a**.

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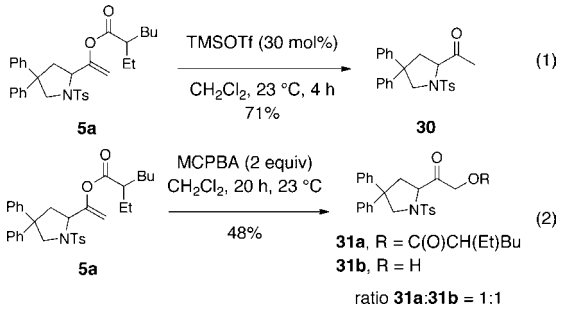
The TMSOTf-catalyzed hydrolysis of vinyl ester **5a** in CH_2Cl_2 provided ketone **30** (eq 1). Oxidation of **5a** with *m*-CPBA gave



α-acetoxy ketone **31** (eq 2). Ketone **31** resembles JTP-4819, a prolyl endopeptidase inhibitor and cognition enhancer.[49] Further investigation of copper-catalyzed allene difunctionalizations and application of products derived thereof are merited.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02833.

Experimental procedures, characterization of new compounds, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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