

A Domino Copper-Catalyzed C–O Coupling–Claisen Rearrangement Process

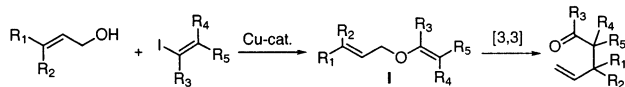
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The Claisen rearrangement is among the most powerful methods for the construction of carbon–carbon bonds.¹ Since its discovery in 1912,² the lack of a general process for the stereoselective synthesis of simple allyl vinyl ethers for the classical aliphatic Claisen rearrangement³ has frustrated synthetic chemists.^{1d,4} Herein, we describe a novel domino process that consists of a copper-catalyzed C–O bond coupling and a subsequent Claisen rearrangement (Scheme 1).^{5,6} Additionally, we describe the synthesis of a

Scheme 1



variety of different vinyl ethers applying similar methodology.

An experimentally attractive means for the preparation of allyl vinyl ethers **I** involves the stereospecific coupling of a vinyl halide and the appropriate allylic alcohol. In 1992 Keegstra reported the coupling of sodium methoxide and butoxide with a variety of vinyl halides in the presence of catalytic amounts of copper bromide.⁷ To our knowledge, this is the only report of a copper-catalyzed coupling of alcohols with vinyl halides.⁸ We recently described the Ullmann-type coupling of aliphatic alcohols with aryl iodides.⁹ The reaction conditions for this transformation (10 mol % CuI, 20 mol % 1,10-phenanthroline **II**, 1.5 equiv of Cs₂CO₃)¹⁰ also proved to be successful for the coupling of allylic alcohol **1** with vinyl iodide **2**¹¹ at 80 °C to give 40% of the allyl vinyl ether **3**. Interestingly, the corresponding Claisen rearrangement product was also isolated in 7% yield (Table 1, entry 1). Complete retention of configuration of the double bond geometry in the vinyl ether product, as seen by Keegstra,⁷ supports the hypothesis that a catalytic process, rather than a simple nucleophilic substitution is operative. Raising the reaction temperature from 80 to 100 °C led to an increased overall yield (**3** + **4**, combined 63% isolated yield). Enal **4** was isolated in 32% yield as a mixture of diastereoisomers in a 1:1 ratio, the formation of which is presumably due to epimerization of the rearrangement product under the basic reaction conditions. Performing the reaction at 120 °C led to almost exclusive formation of **4** in 63% yield (1:1 mixture of diastereomers). In a preliminary screening of different ligands, we found that tetramethyl-1,10-phenanthroline **III** is superior to 1,10-phenanthroline **II**. Its use, at 80 °C, for the coupling of **1** and **2** led to full conversion of the substrates and an improved yield of the desired allyl vinyl ether **3**.

As expected, the allyl vinyl ether **3** could be transformed in a separate step to the aldehyde **5** in high yield and high diastereoselectivity (eq 1).¹² Longer reaction times or higher temperatures

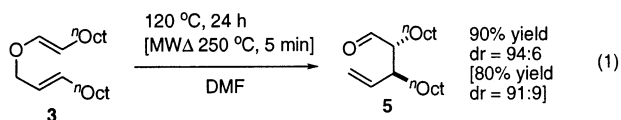
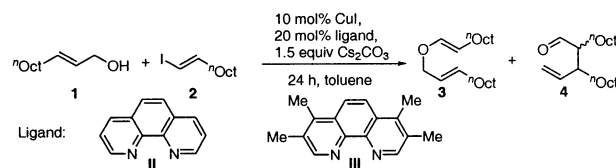


Table 1. Preparation of Allyl Vinyl Ether **3**



entry	ligand	temp (°C)	atm	conv. (% GC)	isolated yield (%)	
					3	4
1	II	80	air	78	40	7
2	II	100	air	92	31	32
3	II	120	air	95	1	63
4	III	80	air	>98	68	4
5	III	60	air	74	56	0
6	II	80	argon	66	42	6
7	II	120	argon	>95	5	62

resulted in a decrease of the diastereoselectivity or in lower yields. The same transformation could also be induced through microwave irradiation (results in brackets) in a much shorter time.¹³

To evaluate the scope of the coupling–rearrangement process, we set out to apply the method to the diastereoselective generation of a compound with a tertiary center vicinal to a quaternary one, as well as one with two adjacent quaternary stereocenters.¹⁴ Particularly appealing in this context was the idea of a domino process¹⁵ combining copper-catalyzed C–O bond formation and thermal Claisen rearrangement. Subjecting allylic alcohol **6** and vinyl iodide **8**¹⁶ to the reaction conditions shown in Table 2 led to the clean formation of the desired rearrangement product **9** in 55% yield with high stereochemical purity (dr = 92:8, Table 2, entry 1). Using alcohol **7**, in which the double bond geometry is of the (*Z*)-configuration, produced the expected diastereomeric product **10** of opposite relative configuration in 68% isolated yield. To further extend the scope of the chemistry to the synthesis of ketones, vinyl iodide **11**¹⁶ was used as a substrate and the corresponding ketone **12** was isolated in 59% yield. Surprisingly, alcohol **7** did not lead to consistent results in the analogous transformation. Several attempts to convert it to **13** led to very low conversion of the starting vinyl iodide **11** (<40%). We next subjected geraniol **14** and nerol **15** to the aforementioned reaction conditions. In separate experiments, the aldehydes **16** and **17** as well as the ketones **18**¹⁷ and **19**, bearing two adjacent quaternary stereocenters, could be isolated in good yields and stereoselectivities. That the dr of the ketone products (Table 2, entries 3, 4, 7, and 8) were slightly lower than for the corresponding aldehydes (Table 2, entries 1, 2, 5, and 6), can be attributed to the lower stereochemical purity of the starting vinyl iodide **11** (*E/Z* = 88:12) compared to that of **8** (*E/Z* > 95:5).

The Cu/**III** catalyst was also able to successfully concatenate a variety of other types of alcohols—aliphatic, propargylic and benzylic—with vinyl iodides (Table 3, entries 1–3) under mild

Table 2. Domino C–O Bond Formation–Claisen Rearrangement

		Product ^a	isolated Yield (%) ^b	dr ^c	
Entry	Alcohol	Vinyl halide			
1				55	92 : 8
2				68	5 : 95
3				59	88 : 12 ^d
4				-	9 : 91 ^d
5				77	92 : 8
6				77	6 : 94
7				62	87 : 13
8				69	12 : 88

^a Relative stereochemistry based on the well-established chair transition-state model for the Claisen rearrangement and an X-ray crystal structure of the semicarbazone of **16**.¹² ^b Average of two runs. ^c Based on 300 or 500 MHz ¹H NMR spectra of the crude reaction mixture. ^d Based on GC of the crude reaction mixture.

Table 3. Formation of Vinyl Ethers

		Product	isolated Yield (%) ^b	
Entry	Alcohol	Vinyl halide ^a		
1	ⁿ HeptOH			70
2				67
3	BnOH			76
4	BnOH			55

^a >95% stereochemical purity based on GC and ¹H NMR. ^b Average of two runs.

conditions. A vinyl bromide was also successfully subjected to the reaction conditions, albeit in slightly lower yield. The reaction times for the different types of alcohols vary significantly, generally in the order aliphatic > allylic ≅ propargylic > benzylic. One limitation that we note is that (*Z*)-vinyl iodides decompose under

these reaction conditions, presumably via β -elimination due to the presence of a hydrogen atom in the *trans*-position at the double bond of the vinyl halide; no coupling products could be isolated in these cases.

In summary we have described a simple method for the formation of allyl vinyl ethers and their in situ Claisen rearrangement to form, in a diastereoselective fashion, compounds with vicinal quaternary stereocenters.

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Supporting Information Available: Experimental procedures, characterization data for all unknown compounds, and X-ray crystallographic data for the semicarbazone of **16** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- In this case, using 1,10-phenanthroline **II** instead of 3,4,7,8-tetramethyl 1,10-phenanthroline **III** as the ligand led to a significantly lower yield for the transformation (31% isolated yield).

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