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The tandem intermolecular hydroalkoxylation/claisen rearrangement†‡

Cite this: *Chem. Commun.*, 2013, **49**, 4157

Received 1st October 2012,
Accepted 5th November 2012

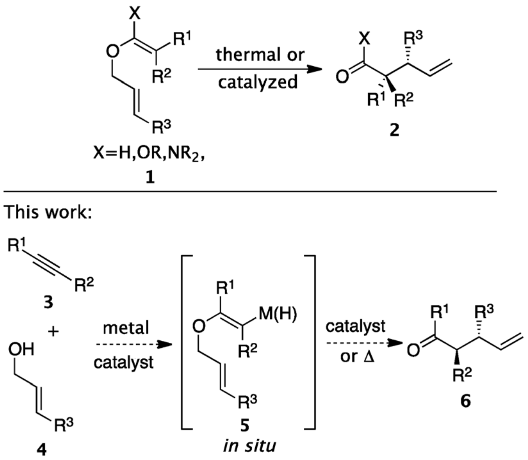
DOI: 10.1039/c2cc37166a

www.rsc.org/chemcomm

John M. Ketcham, Berenger Biannic and Aaron Aponick*

The Au(I)-catalyzed intermolecular hydroalkoxylation of alkynes with allylic alcohols to provide allyl vinyl ethers that subsequently undergo Claisen rearrangement is reported. This new cascade reaction strategy facilitates the direct formation of γ,δ-unsaturated ketones from simple starting materials in a single step.

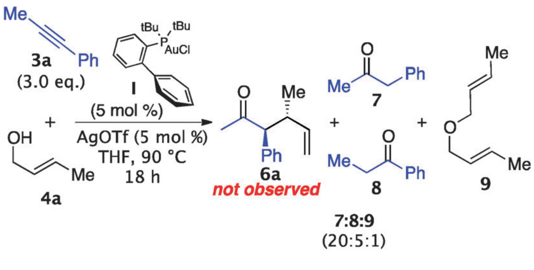
The Claisen rearrangement stands as one of the most powerful sigmatropic rearrangements utilized by the synthetic community, producing γ,δ-unsaturated carbonyl compounds in a highly stereodefined manner.[1] Despite the development of many successful variants[1] since Claisen's original report[2] (**1** → **2**, Scheme 1), the preparation of classical acyclic allyl vinyl ethers with defined olefin geometry can be quite challenging, especially when a *cis*-enol ether is required.[1,3] A simple strategy to access these classical substrates would be highly advantageous. Herein, we report a tandem one-pot hydroalkoxylation/Claisen rearrangement (Scheme 1) that employs simple substrates in an atom-economical reaction to selectively produce enol ethers and subsequently γ,δ-unsaturated ketones.



Scheme 1 Claisen rearrangement.

Although a variety of catalytic methods for the formation of allyl vinyl ethers from an array of different precursors have previously been disclosed,[3e–g,4] the possibility of using a hydroalkoxylation was intriguing because the enol ether olefin geometry would be set in a stereospecific manner according to the mechanism of alcohol addition.[5] Intermolecular hydroalkoxylation reactions of alkynes are well-known using a variety of catalysts,[5a,6] but to the best of our knowledge this reaction cascade has not been explored. At the outset, it seemed logical to study the use of Au-catalysts because excellent selectivities for *anti*-alkoxyauration reactions are observed and Au-complexes also catalyze Claisen rearrangement reactions such as the propargyl Claisen rearrangement.[7] In these instances, the substrates are typically preformed, highly activated, or embedded in substrates predisposed towards intramolecular reactions.

Initial experiments focused on using crotyl alcohol **4a** and alkyne **3a** (eqn (1)). Unfortunately, exposure of the substrates to the complex generated from **I**/AgOTf at 90 °C (sealed tube) in THF did not produce the desired product **6a**. Instead, a mixture of alkyne hydration products **7** and **8**, in addition to the somewhat volatile ether **9** resulting from self-condensation of **4a**, were observed. Despite the promising literature precedent for each step, sequencing them in tandem proved to be an arduous task.



(1)

Previous work from our laboratory has focused on using allylic and propargylic alcohols as electrophiles in Au-catalyzed reactions that proceed with loss of water.[8] In contrast, for them to serve instead as nucleophiles, condensation reactions of the

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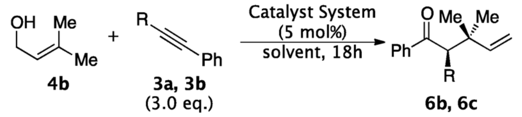
Department of Chemistry, University of Florida, P. O. Box 117200, Gainesville, FL 32611, USA. E-mail: aponick@chem.ufl.edu

† This article is part of the ChemComm 'Emerging Investigators 2013' themed issue.

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data. See DOI: 10.1039/c2cc37166a

Table 1 Preliminary studies



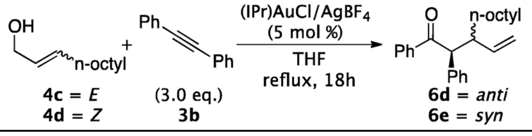
Entry	R	Catalyst system	Solvent	Temp (°C)	Yield[a] (%)
1[b]	Me (**3a**)	**I**	THF	90	0[c] (**6b**)
2	Me (**3a**)	**I**	THF	65	0[c] (**6b**)
3	Ph (**3b**)	**II**	Dioxane	100	25 (**6c**)
4[b]	Ph (**3b**)	**II**	Dioxane	120	34 (**6c**)
5	Ph (**3b**)	**II**	THF	65	50 (**6c**)

[a] Isolated yield. [b] Reaction run in sealed tube. [c] A complex mixture of hydration and self-condensation products was observed. **I** = (*o*-biphenyl-di-*tert*-butylphosphine)gold(I) chloride/AgOTf; **II** = (IPr)AuCl/AgBF$_4$.

allylic alcohol component must be avoided[8h] and Claisen rearrangement would need to occur more rapidly than ketalization[9] (further reaction of enol **5** with an additional equivalent of alcohol). These ostensibly facile but undesirable side-reactions posed a significant challenge. After extensive screening of catalysts, conditions, *etc.*, to our delight, exposure of prenyl alcohol and tolane to the cationic Au(I)-complex formed *in situ* from 5 mol% (IPr)AuCl/AgBF$_4$ did indeed form the product resulting from tandem hydroalkoxylation/Claisen rearrangement, albeit in only 25% yield (Table 1, entry 3). Increasing the temperature to 120 °C made a modest enhancement 34% (entry 4), which interestingly was improved to 50% with the use of THF at 65 °C (entry 5). This reactivity was unanticipated, as much higher temperatures are typically required for thermal rearrangements.[10]

These experiments demonstrated that the desired sequence could indeed function, but the yield would need to be significantly improved. The methyl groups in **4b** may reduce undesired S$_N$2′ reactions,[8] but likely also reduce the rate of rearrangement. *E*- and *Z*-substrates **4c** and **4d** were studied to determine if disubstitution at C3 was required. Gratifyingly, exposure of **4c** to the conditions resulted in a smooth reaction to provide **6d** in 73% yield as a 5 : 1 mixture of diastereomers (entry 1, Table 2). Control experiments (entries 2, 3) verified that neither Ag+ or H+ catalyze the reaction. Surprisingly, when the conditions from entry 1 were used with *cis*-olefin **4d**, none of the desired product was observed (entry 4). Fortunately, slow addition of **4d** led to isolation of the ketone product in 33% yield in 1 : 11 dr along with 37% of the intermediate allyl vinyl ether adduct of **4d** and **3b** (entry 5). Since the rearrangement had not gone to completion, the same conditions were repeated followed by heating to 120 °C for 6 h (entry 6). The ketone **6e** was produced in 75% yield and 1 : 11 dr and these conditions were adopted as the standard.

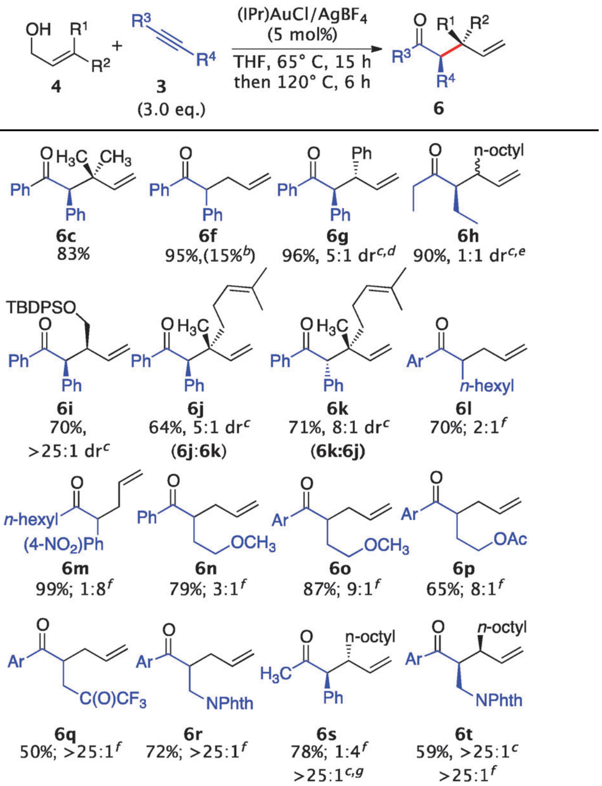
Table 2 Optimization studies



Entry	Alcohol	Additional conditions	Yield[a] (%)	**6d** : **6e**[b]
1	**4c**	—	73	5 : 1
2	**4c**	AgBF$_4$ only	0	—
3	**4c**	HBF$_4$·OEt$_2$ only	0	—
4	**4d**	—	0	—
5	**4d**	Slow addition of **4d**	33[c]	1 : 11
6	**4d**	Slow addition of **4d** then 120 °C, 6 h	75	1 : 11

[a] Isolated yields. [b] Determined by ^{1}H NMR (500 MHz). [c] Enol ether adduct of **4d** + **3b** was also isolated in 37%, see ESI.

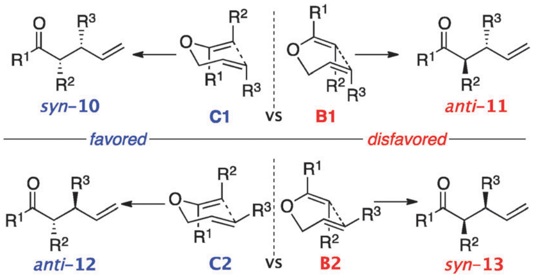
Table 3 Substrate scope[a]



[a] Isolated yields. [b] Yield obtained using conditions from Table 1, entry 9. [c] Diastereoselectivity determined by ^{1}H NMR (500 MHz). [d] Slow addition of alcohol not required. [e] Substrates: **4c**, 3-hexyne. [f] Ratio (arylketone : alkylketone) determined by ^{1}H NMR (500 MHz). [g] Only a single diastereomer of each regioisomer was observed. Ar = *p*-OMe-Ph.

With the optimal conditions established, the substrate scope was then explored. As can be seen in Table 3, the yield of **6c** was increased to 83% with the optimized conditions (*cf.* 50%, Table 1). Allyl alcohol also functioned well, producing **6f** in 95% yield (unoptimized conditions; 15%) and demonstrating that substituents at C3 of the alcohol are not required. Having two C3 substituents is also tolerated, and the use of geraniol and nerol provided diastereomers **6j** and **6k** respectively. Differentially substituted alkynes were also explored under the optimized conditions. When one of the phenyl groups in **3b** was replaced by methyl (**3a**), a 4 : 1 mixture of regioisomers **6s** was obtained in 78% yield with only a single diastereomer of each regioisomer detectable.

The electronic and steric nature of the alkyne substituents were modulated and it was found that when electron-withdrawing groups are included, the α-aryl ketone is the major product (*e.g.* **6m**). This regioselectivity is reversed when electron-donating groups are included, instead favoring aryl ketones (*e.g.* **6o**). Both α-arylation products and electron rich aryl ketones are versatile synthons.[11] A variety of functional groups were also tolerated and high selectivity was observed, *e.g.* **6i**, **6q–6t**.



Scheme 2 Transition state analysis.

The origin of the diastereoselectivity was also of interest as data on alkyl substrates with this enol ether substitution pattern is sparse. It was found that the products do not equilibrate under the reaction conditions (eqn (2)), which is in agreement with the fact that reactions employing isomeric allyl alcohols (**4c**/**4d**) do not provide the same ratio of diastereomeric products.

$$\underset{\textit{single diastereomer}}{\mathbf{6d}\text{ or }\mathbf{6e}} \xrightarrow[\text{conditions}]{\text{optimized}} \underset{\textit{no epimerization}}{\mathbf{6d}\text{ or }\mathbf{6e}} \qquad (2)$$

The observation that *cis*-allylic alcohols consistently yield products in higher dr than the corresponding *trans*-allylic alcohols provides key insight into the relevant reaction pathways. Analysis of the possible chair and boat transition states (*cis*-allylic alcohol: **C1**/**B1**; *trans*-allylic alcohol: **C2**/**B2**) for thermal rearrangement reactions reveals that both of the enol ether substituents are oriented in the pseudoaxial positions in (Scheme 2). This is inherent to Claisen substrates with the R^1,R^2-*trans*-enol substitution pattern. The chair transition states (**C1**/**2**) would be predicted to be lower in energy than the competing boat transition states (**B1**/**2**),[12] and hence *cis*- and *trans*-allylic alcohols lead to the *syn* and *anti* diastereomers, respectively. The diastereoselectivity is likely higher for the *cis*-allylic alcohol due to specific steric interactions between the alkene and enol ether substituents. The 1,2-eclipsing interaction in **B1** between R^2 and R^3 likely increases the $TS^\ddagger$ energy more substantially than the corresponding 1,3-diaxial interaction between R^1 and R^3 in **C1**. This effect is diminished in **C2**/**B2** because R^3 is equatorial and thus avoids eclipsing interactions, leading to a smaller $\Delta\Delta G^\ddagger$ with *trans*-allylic alcohol substrates. The boat-like transition state therefore becomes more competitive, leading to the observed erosion in diastereoselectivity. Although the allyl vinyl ether isolated above (Table 2, entry 5) does undergo thermal rearrangement in the absence of catalyst,[13] studies on the extent to which the cascade process is also catalyzed are underway and will be reported in due course.

In summary, we have reported an efficient new cascade reaction approach to the synthesis and rearrangement of allyl vinyl ethers that proceeds from simple compounds to form ketone products in high yield and diastereoselectivity. The concept of tandem intermolecular alkyne addition/[3,3]-sigmatropic rearrangement should be applicable in a variety of different reaction constructs further enabling the rapid introduction of complexity to simple substrates.

We thank the Herman Frasch Foundation (647-HF07) and the James and Ester King Biomedical Research Program (09KN-01) for their generous support of our programs.

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