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Gold-Catalyzed Heterocycle Synthesis Using Homopropargylic Ethers as Latent Electrophiles

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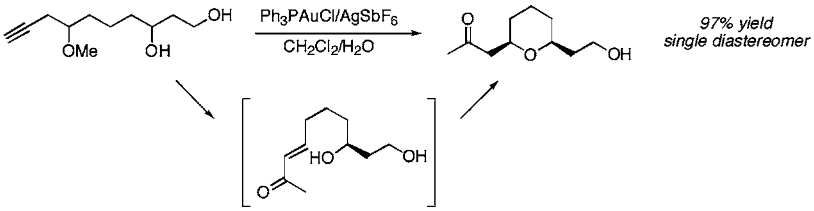
ABSTRACT



Homopropargylic ethers with pendent nucleophiles, when subjected to Au catalysts in aqueous solvent, provide heterocyclic ketones. The reactions are efficient, tolerant of functionality and ambient atmosphere, and operationally simple. Diastereoselectivity can be predicted on the basis of product thermodynamics. This process demonstrates the viability of homopropargylic ethers to serve as latent electrophiles that can be unraveled under highly selective conditions to promote heterocycle formation through nucleophilic additions to α,β-unsaturated ketones.

Selectively activating a single functional group in the presence of other, similar functional groups represents a significant impediment to efficient complex molecule synthesis. This issue can be addressed by utilizing functional group surrogates that react under unique conditions and subsequently unravel to yield the desired moiety. Transition metal catalysts are proving to be remarkably useful agents for implementing this strategy, particularly with respect to generating electrophiles through their association π-bonds.[1] Recently gold catalysts[2] have emerged as superior reagents for selectively activating alkenes[3] and alkynes[4] toward reactions with an impressive range of nucleophiles. We have initiated a program to exploit the unique chemoselectivity of gold catalysis in the synthesis of polyfunctional molecules. In this manuscript we detail a new, efficient, and mild approach to the preparation of heterocyclic ketones in which homopropargylic ethers serve as latent electrophiles. Mechanistic studies that elucidate the reaction sequence and explain the stereochemical outcomes of the process are also described.

We viewed homopropargylic ethers as intriguing substrates for this study because of their ease of preparation, generally inert behavior toward nucleophiles, and wealth of potential reaction pathways upon treatment with gold catalysts. In

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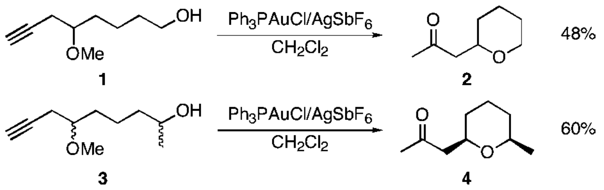
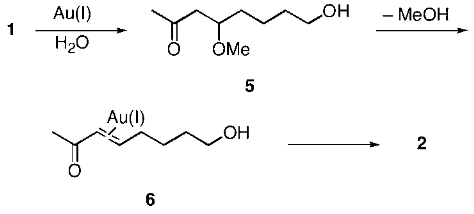
particular, we wanted to study the behavior of homopropargylic ethers that bear a distal nucleophilic group toward the objective of catalyzing cyclization reactions. Subjecting homopropargylic ether **1** to Ph$_3$PAuCl and AgSbF$_6$[5] in unpurified CH$_2$Cl$_2$ under standard atmospheric conditions indeed resulted in the formation of tetrahydropyranyl ketone **2** in 48% yield (Scheme 1). Similar treatment of ether **3**, prepared as a mixture of diastereomers, yielded **4** as a single diastereomer in 60% yield.

Scheme 1. Gold-Mediated Tetrahydropyran Synthesis



These results, coupled with experimental observations and literature precedents, led us to propose the sequence in Scheme 2 as a mechanism for the process. Ag(I) serves to abstract the chloride from the Ph$_3$PAuCl, forming a more electrophilic catalyst. Control reactions demonstrated that both metals are essential for this process. Gold-mediated hydration of the alkyne with adventitious water[6] provides ketone **5**. Methanol elimination yields enone **6**,[7] which undergoes metal-promoted conjugate addition to produce the cyclized product. In support of this mechanism, we have isolated small amounts of **5** in reactions that were stopped at partial conversion, resubjected it to the reaction conditions, and observed cyclization. The formation of a single diastereomer of **4** from a diastereomeric mixture of **3** suggests a planar intermediate along the reaction coordinate. Although 1,4-additions of heteroatom nucleophiles into α,β-unsaturated carbonyl compounds normally require significantly harsher conditions,[8] transition metal catalysis has been shown to facilitate the process.[9] While we propose that enone activation arises from alkene coordination, carbonyl activation is also possible. A supporting role for trace amounts of HCl, formed through the reaction of the gold catalyst with H$_2$O, cannot be rigorously excluded, but treating **1** with dilute HCl in CH$_2$Cl$_2$ led to no reaction.

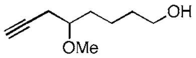
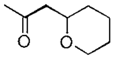
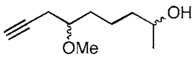
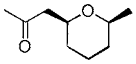
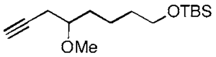
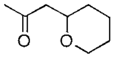
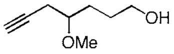
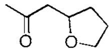
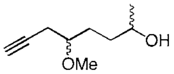
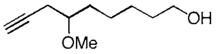
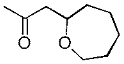
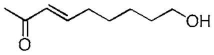
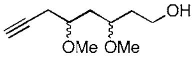
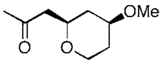
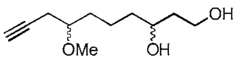
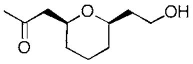
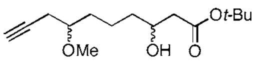
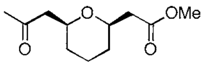
Scheme 2. Proposed Mechanism



This mechanistic hypothesis, coupled with literature precedents, provided the foundation for our efforts at reaction optimization. To ensure smooth alkyne hydration, water-saturated CH$_2$Cl$_2$ was used as the solvent. Based on the ability of simpler gold species to effect some of the elementary steps in this sequence, NaAuCl$_4$ was employed as the catalyst for many transformations. Reactions proceeded most smoothly and reproducibly when heated to 35 °C.

The scope and efficiency of this process are summarized in Table 1. Several aspects of this study are noteworthy. The overall transformations are, in general, quite efficient, with several reactions proceeding in nearly quantitative yield. Although NaAuCl$_4$ is a suitable catalyst for many reactions,

Table 1. Reaction Scope

entry	substrate	product(s)	conditions[a]	yield[b]
1	 **1**	 **2**	A B	91%[c] 100%[c]
2	 **3**	 **4**	A	79%[c]
3	 **7**	 **2**	A	78%[c]
4	 **8**	 **9**	A	85%[c]
5	 **10**	 **11**	A B	92%[c] 96%[c] 55:45 dr
6	 **12**	 **13**	A	52%
		 **14**		25%
7	 **15**	 **16**	A B	71%[d] 96% 2:1 dr
8	 **17**	 **18**	A B	70% 97%
9	 **19**	 **20**	B	60%

[a] Procedure A: substrate in water-saturated CH$_2$Cl$_2$ (∼60 mM), NaAuCl$_4$ (5 mol %), 35 °C. Procedure B: substrate in water-saturated CH$_2$Cl$_2$ (∼60 mM), Ph$_3$PAuCl (5 mol %), AgSbF$_6$ (5 mol %), 35 °C. [b] Yields are reported for isolated, purified products unless otherwise noted. [c] Yield determined by GC. [d] Yield based on 81% starting material consumption.

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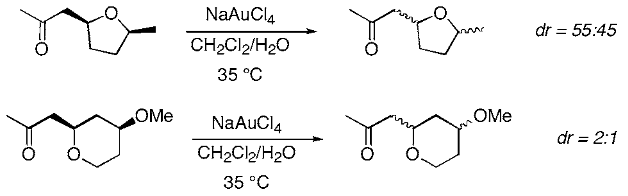
the $Ph_3PAuCl/AgSbF_6$ system produces a more active catalyst that is preferable for slower reactions (entries 5 and 7−9). Silyl-protected nucleophiles are sufficiently reactive to engage in this process (entry 3), alleviating the need for their cleavage prior to cyclization, but reactions that employ unprotected nucleophiles produce methanol as the only side product. Homopropargylic alcohols are not suitable substrates, with the reaction stopping after the hydration step (data not shown). Tetrahydrofurans and oxepanes can also be accessed through this process (entries 4−6) with enone **14** also being isolated from the cyclization of **12**, presumably as a result of the diminished rate for closing seven-membered rings relative to lower homologues .[10] In further support of the mechanism in Scheme 2, resubjecting **14** to the reaction conditions indeed provided **13**. The reaction is tolerant of functional groups, with ester, alkoxy, and hydroxy groups proving to be compatible with the conditions, though methanolysis is observed for the ester-containing substrate (entry 9). Terminal alkynes proved to be essential for this transformation, with internal alkynes undergoing hydration to provide the carbonyl group on the distal carbon with respect to the methoxy group.[11] For reactions in which diastereomers can be formed, selectivity follows expected trends based on product stability, suggesting that alkyl group conformational preferences should override alkoxy group preferences in complex substrates. Of note, all substrates that contain secondary alcohols were prepared from selective additions to alkynyl aldehydes, highlighting the utility of homopropargylic ethers as latent electrophiles.

We further examined these transformations to determine whether kinetic factors or thermodynamic factors are responsible for the diastereocontrol that results in these transformations. In principle the reaction products, being β-alkoxy ketones, could undergo elimination and readdition until reaching a thermodynamic equilibrium. To test this hypothesis we subjected single diastereomers of **11** and **16** to the reaction conditions (Scheme 3). As postulated, equilibration was observed to yield diastereomeric mixtures that were identical to those that were observed in the original cyclization reactions. These studies provide compelling evidence that diastereocontrol results from product equilibration.

Scheme 3. Product Equilibration



We have demonstrated that electrophilic gold catalysts mediate efficient heterocycle syntheses using homopropargylic ethers as latent electrophiles through a sequence of alkyne hydration, β-alkoxy group elimination, and 1,4-addition. The process is operationally simple, tolerant of substrate functionality and ambient atmosphere, and viable with protected nucleophiles. Diastereoselectivity in these transformations can be predicted on the basis of product stability, in accord with studies that products equilibrate under the reaction conditions. Au(III) and cationic Au(I) catalysts effectively promote these reactions, with the cationic Au(I) catalyst showing superior reactivity and the Au(III) catalyst being economically preferable. The cyclic ethers that are formed in these reactions are integral components of several biologically natural products.[12] In addition to the application described herein, our observations suggest that gold catalysts should be useful for effecting intramolecular nucleophilic additions into electrophilic alkenes under exceptionally mild conditions.

Acknowledgment. We thank the National Institutes of Health (GM-62924) for generous support of this work.

Supporting Information Available: Synthetic schemes for all cyclization substrates. Experimental procedures and characterization for all cyclization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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