Au(I)-Catalyzed Efficient Synthesis of Functionalized Bicyclo[3.2.0]heptanes

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Cycloaddition reactions are essential tools for organic synthesis, offering not only substrate flexibility but also rapid increase of molecular complexity. Au/Pt catalysts[1] have been employed to generate reactive intermediates for cycloaddition reactions, including Diels−Alder reaction,[2] 1,3-dipolar cycloaddition,[3] and [4 + 3] cycloadditions.[4] These reactions are often followed by cascade transformations involving the regeneration of metal catalysts, therefore rendering further functionalization and/or additional structural complexities. However, this novel and powerful approach has only been realized in limited cases.[2–4] Herein, we report a Au(I)-catalyzed 1,3-dipolar cycloaddition, leading to efficient formation of functionalized, highly strained bicyclo[3.2.0]heptanes,[5] a structural motif present in various natural products including repraesentin F[6a] and kelsoene[6b] (Figure 1).

We reported previously that 1-(1-phenylethynyl)cyclopropyl methyl ketone[7] (**1**, Scheme 1) underwent various IPrAuNTf$_2$-catalyzed[8] [4 + 2] annulations via a proposed Au-containing all carbon 1,4-dipole intermediate.[9] During the study, we noticed a different reaction outcome when ethyl vinyl ether was used as dipolarophile at room temperature.[10] Instead of the anticipated tetrasubstituted furan product, two acid-sensitive compounds were formed highly efficiently,[11] and attempts to purify them using even Et$_3$N-treated silica gel column led to subpure materials as a mixture. 2D TLC revealed that they decomposed on the plate into three stable, separable compounds. Consequently, treating the reaction mixture with regular silica gel led to the isolation and characterization of all those compounds (i.e., **3**, **4**, and **5**), which shared a strained bicyclo[3.2.0]heptane skeleton (Scheme 1). We concluded that the initially formed products were the diastereomers of enone **2** and their ready decomposition into bicycles **3**, **4**, and **5** must be due to partial release of the ring strains in **2**. To avoid the isolation problem, the reaction mixture upon the complete consumption of **1** in 15 min was concentrated to remove excess ethyl vinyl ether, and the residue was treated with TsOH (20 mol %) in acetone/H$_2$O (7/1, 2 mM). Hydroxyenone **4** was isolated in 93% yield, while hydroxyketone **3** was not observed and only a negligible amount of aldehyde **5** was formed. Although both PtCl$_2$ and AuCl$_3$ also catalyzed this reaction, higher catalyst loadings (10 mol %) were required.[12]

The mechanism for the formation of hydroxyenone **4** is proposed in Scheme 2. It begins with a 5-*endo-dig* cyclization of the carbonyl group onto the Au-activated C−C triple bond, forming an oxocarbenium intermediate **A**. Different from our previous study[9] where **A** undergoes cyclopropane ring opening and aromatization, a resonance structure of **A**, i.e., **B**,[3a,b,f] is a Au(I) carbenoid-containing carbonyl ylide and can undergo 1,3-dipolar cycloaddition with ethyl vinyl ether, forming bridged bicycle **C**. 1,2-Alkyl migration followed by bridge opening then results in the formation of spirobicyclic cation **E**. Ring enlargement of the cyclopropane ring forms the bicyclo[3.2.0]heptane skeleton and subsequent elimination of the Au catalyst forms enone **2**. Treatment of **2** with Brønsted acid should generate cation **G** as one of possible intermediates,
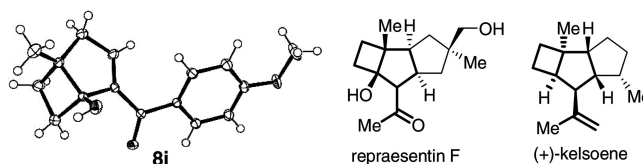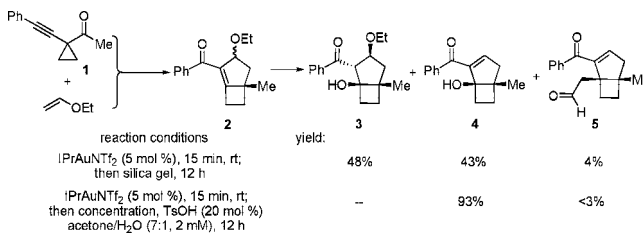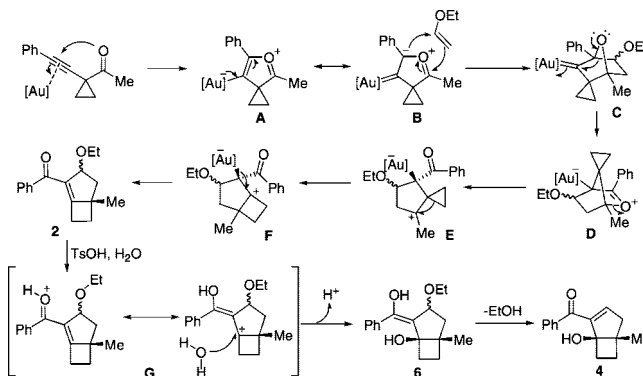

Figure 1. ORTEP depiction of compound **8i** and natural products containing the bicyclo[3.2.0]heptane skeleton.

Scheme 1. Initial Discovery

Scheme 2. Proposed Mechanism via a 1,3-Dipolar Cycloaddition

which can be trapped by H$_2$O and affords hydroxyketone **3** upon tautomerization of **6** or enone **4** via EtOH elimination. We anticipate that hydroxyketone **3** can be readily converted to enone **4** under acidic conditions. Of note, the formation of aldehyde **5** is the result of a second molecule of ethyl vinyl ether reacting with **2** under acidic conditions.

This expedient excess to highly strained and functionalized bicyclo[3.2.0]heptanes can be readily expanded to other ketone substrates. As shown in Table 1, various substituents at the carbonyl group were allowed. In particular, substrates with linear alkyl (entry 1) and functionalized linear alkyl (entries 4 and 5) groups underwent this reaction in good to excellent efficiency. Sterically more demanding benzyl group (entry 6) and alkyl groups including isobutyl (entry 2) and isopropyl (entry 3) slowed this reaction, and slightly elevated reaction temperatures were required; moreover, the yields were lower. To our delight, this reaction also worked with aldehyde **7g** (entry 7) and phenone **7h** (entry 8) in fair yields. Surprisingly, in the case of **7h**, the [4 + 2] annulation[9] previously

Table 1. Scope Study

entry	7	R	R'	rx. time	8	yld.(%)[a]
1	**7a**	Ph	^{n}Bu	30 min	**8a**	89
2	**7b**	Ph	^{i}Bu	2.5 h	**8b**	67[b]
3	**7c**	Ph	^{i}Pr	6 h	**8c**	67[b]
4	**7d**	Ph	(allyl)	4 h	**8d**	87
5	**7e**	Ph	(OTBS chain)	2 h	**8e**	79[c]
6	**7f**	Ph	Bn	2 h	**8f**	65[b]
7	**7g**	Ph	H	2 h	**8g**	54
8	**7h**	Ph	Ph	4 h	**8h**	57[b,d,e]
9	**7i**	*p*-MeOPh	Me	15 min	**8i**	98
10	**7j**	(EtO$_2$C-aryl)	Ph	15 min	**8j**	87
11	**7k**	^{n}Bu	Me	15 min	**8k**	75
12	**7l**	MOM	Me	15 min	**8l**	48[f]

^{a} Isolated yield. ^{b} Reaction temperature: 40 °C. ^{c} TBAF (2 equiv) was added to complete desilylation. ^{d} The [4 + 2] product was isolated at 30%. ^{e} The ethoxyenone diastereomers initially formed were isolated in 59% and 12% yield, respectively. ^{f} Yield of **12** was 14%.

observed only with dipolarophiles other than ethyl vinyl ether occurred, and 4-ethoxy-1,3-diphenyl-4,5,6,7-tetrahydroisobenzofuran was isolated in 30% yield; moreover, the ethoxyenone diastereomers initially formed were stable on column, and their characterization offered support for the structure assignment of **2**. The alkyne terminus could accommodate different substituents including *n*-butyl (entry 11), MOM (entry 12) and aryl groups of electron-rich (entries 9) and electron-deficient (entry 10) well. Surprisingly, 14% of aldehyde **12** (see eq 5) was isolated in entry 12, which is likely due to the presence of a chelating α-methoxy-ketone moiety. To our delight, the structure of **8i** was elucidated by X-ray crystallography (Figure 1), confirming our previous structure assignments. Substrates with a methyl or a phenyl substitution at the cyclopropane ring, however, did not furnish expected bicyclo[3.2.0]heptane products. Besides ethyl vinyl ether, *tert*-butyl vinyl ether could be used but the reaction was slower.

The formation of aldehyde enone **5** (Scheme 1) suggests that the ring juncture of **2** proximal to the carbonyl group is highly susceptible toward nucleophilic attacks and groups other than OH can be readily installed. Indeed, when MeOH instead of H$_2$O was used, methyl ether **9** was formed in 93% yield (eq 2). In addition, a hydride and an allyl group can be readily delivered, yielding reduced enone **10** (eq 1) and allyl enone **11** (eq 3) in excellent yields. Moreover, the yield of aldehyde **5** can be improved dramatically to 81% upon the addition of Me$_2$AlCl (1 equiv) and extra ethyl vinyl ether. These reactions constitute efficient one-pot, 3-component couplings, offering rapid excess to highly strained and functionalized bicyclo[3.2.0]heptanes. Unexpectedly, when MOM-substituted **7l** was treated with PtCl$_2$, aldehyde **12** was obtained essentially pure without chromatography after acidic hydrolysis and workup (eq 5). The lack of **8l** is interesting and suggests that PtCl$_2$ is more acidic than IPrAuNTf$_2$ (entry 12). Compound **12**, though sensitive to silica gel, was easily cyclized under basic conditions to afford delicate tricyclic dienone **13** in 63% yield, demonstrating the synthetic utility of this chemistry.

In summary, we have developed an efficient Au(I)-catalyzed synthesis of highly strained and functionalized bicyclo[3.2.0]heptanes.
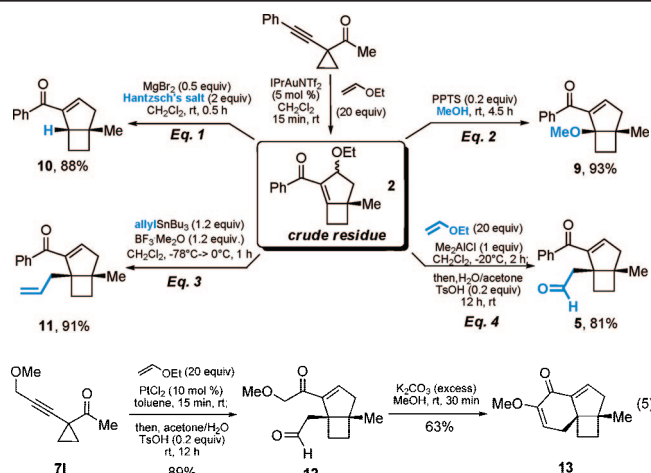
Subsequent couplings with various nucleophiles offer additional structural features/complexity. These one-pot, three-component reactions are proposed to proceed via a key 1,3-dipolar cycloaddition between Au carbenoid-containing carbonyl ylides and ethyl vinyl ether.

Supporting Information Available: Experimental procedures, compound characterization data and cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Without the addition of ethyl vinyl ether, ketone **1** did not undergo noticeable reaction in the presence of IPrAuNTf$_2$ at room temperature. However, slow decomposition was observed at 80°C.

(11) Estimation by ^{1}H NMR gave a ratio of 5/1 for the two compounds and a combined yield of more than 90%.

(12) In our later scope studies, it became apparent that AuCl$_3$ and PtCl$_2$ did not stay catalytically active in the reaction after 15 to 30 min.

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