Gold-Catalyzed Efficient Preparation of Linear α -lodoenones from Propargylic Acetates

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Only 2 mol % of Au(PPh₃)NTf₂ is needed to convert readily accessible propargylic acetates into versatile linear α -iodoenones in good to excellent yields. This reaction is easy to execute and has broad substrate scope. Good to excellent *Z*-selectivities are observed in the cases of aliphatic propargylic acetates derived from aldehydes.

 α -Iodoenones have become important synthetic intermediates and can be readily converted into enones with various α -carbon substituents, including alkyl, alkenyl, alkynyl, and aryl groups, via transition metal-catalyzed cross-coupling reactions.¹

Various methods for the synthesis of α -iodoenones have been developed. For example, they can be prepared from enones using a combination of I₂ and a nucleophilic base (e.g., pyridine,² DMAP,³ and quinuclidine³). However, this Michael-addition-based method generally does not work well with linear enones.⁴ In addition, the enone starting material may not be readily available. Iodination of C–Si⁵ bonds with ICl or C–Sn⁶ bonds with I₂ can afford linear α -iodoenones as well, although rather elaborate starting materials are

(4) Reference 3 examined cases of linear enones using a combination of I₂ and DMAP. However, only a methyl group at the β -position was shown to lead to good results. Indeed, in our hands, oct-6-en-5-one reacted very sluggishly and only 30% conversion was observed in 2 days.

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required. Interestingly, propargylic alcohols can be converted into linear α -iodoenones by reacting with *N*-iodosuccinimide (NIS) in the presence of a catalytic amount of hydroxy-(tosyloxy)iodobenzene. Although this would be a versatile method for α -iodoenone synthesis, it is limited only to secondary alkynols, and moreover, only a few special examples were reported.⁷ It is our conclusion that there is still a lack of efficient synthetic methods for linear α -iodoenones. Herein, we report a gold-catalyzed facile synthesis of α -iodoenones from readily accessible propargylic acetates.

Propargylic acetates can often be prepared in one pot from aldehydes/ketones, terminal alkynes, and acetic anhydride and have served as versatile substrates for Au catalysis.^{8,9} We have recently developed novel Au-catalyzed tandem

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reactions of propargylic esters, proposed to involve 3,3-rearrangement of propargylic esters and subsequent activation of the in situ-generated carboxyallenes to form highly reactive Au-containing oxocarbenium **A** (Scheme 1). This



design led to the development of efficient synthetic methods for highly functionalized 2,3-indoline-fused cyclobutane,¹⁰ cyclopentenones,¹¹ α -alkylidene- β -diketones,¹² and alkenyl enol esters/carbonates.¹³ A notable observation in some of these studies is that the Au–C(sp²) bond in **A** can react with intramolecular electrophiles¹⁴ such as iminiums¹⁰ and activated acyl groups.¹² We surmise that this Au–C(sp²) bond could also react with electrophilic iodine intermolecularly,¹⁵ leading to efficient formation of α -iodoenones upon hydrolysis (Scheme 1). Notably, there is still much need to explore the synthetic potential of nucleophilic organogolds.¹⁶

We began to examine the reaction of oct-3-yn-2-yl acetate (1) and NIS in the presence of Au catalysts (Table 1). Stable Au(PPh₃)NTf₂ was first used for its ease of preparation and handling. Gratifyingly, with 2 mol % of the catalyst, the

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Table 1. Gold-Catalyzed Reactions of Propargylic Acetate **1** with NIS to Form α -Iodoenone **2**



^{*a*} Reaction concentration was 0.05 M. ^{*b*} Estimated by ¹H NMR using diethyl phthalate as internal reference. ^{*c*} The geometries of enone **2** were determined by NOESY 1D experiments. ^{*d*} Regular, without drying. ^{*e*} 17% of acetate **1** was left unreacted. ^{*f*} 89% isolated yield. ^{*g*} Dichloro(pyridine-2-carboxylato)gold(III). ^{*h*} Heating at 80 °C for 0.5 h. ^{*i*} Heating at 80 °C for 2 h. ^{*j*} No reaction.

desired reaction did happen, and α -iodoenone 2 was formed in anhydrous acetone in excellent yield, although the Z/Eselectivity was marginal (entry 1).¹⁷ Attempts to improve the stereoselectivity met with limited success when different solvents were used (entries 2 and 3). Interestingly, a small amount of water in acetone seemed to enhance the Z/Eselectivity dramatically, and only the Z-isomer of 2 was observed when a mixture of acetone and H₂O (40:1) was used, although the yield of 2 was undesirably low (entry 4).¹⁸ Decreasing the amount of H₂O, however, led to increased yields of 2 without compromising the Z/E-selectivity (entries 5 and 6). Finally, when the ratio of H_2O and acetone was 1:800 (about 1.4 equiv of H_2O to 1), α -iodoenone 2 was formed in 95% yield with excellent Z-selectivity (entry 7). Although previous studies^{5,6} show that stereoisomerization to the generally more stable Z-isomers of α -iodoenones happened during reaction, we did not observe noticeable change of Z/E ratio during and after the reaction at 0 °C. Other Au catalysts (e.g., entry 8) and PtCl₂ (entry 9) gave less desirable results, and no reaction was observed without any catalyst (entry 10).

Using the optimized reaction conditions in Table 1, entry 7, the scope of this reaction was then studied. We first examined propargylic esters derived from various aldehydes.

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⁽¹⁷⁾ The formation of 2 is presumably due to adventitious H₂O in anhydrous acetone or the succinimide anion as the nucleophile.

⁽¹⁸⁾ The role of H_2O in enhancing the stereoselectivity is not clear, though it is likely related to the rate of hydrolysis (Scheme 1).

Table 2. Reaction Scope for the Formation of β -Monosubstituted α -Iodoenones



^{*a*} The substrate concentration was 0.05 M. ^{*b*} Isolated yield. ^{*c*} 10 mol % of AgNTf₂ was added, and the reaction time was 3 h. ^{*d*} The reaction took 3 h. ^{*e*} The reaction finished in 0.5 h. ^{*f*} 10 mol % of AgNTf₂ was added. ^{*g*} Elimination of acetic acid happened during the reaction.

As shown in Table 2, these substrates all reacted well, and good to excellent yields of the corresponding α -iodoenones with β -monosubstitution were obtained. When R¹ and R² are both alkyl groups, high to excellent stereoselectivities favoring the Z-isomer were observed (entries 1–3, 8, and 9). With a cyclohexyl group at the propargylic position (entry 3), the reaction was slow and incomplete even after extended time. The addition of 10 mol % of AgNTf₂ did help to drive the reaction to completion, presumably due to its scavenging of iodide and thus keeping Au(PPh₃)NTf₂ reactive.¹⁹ Notably, in the cases of aryl-containing substrates **3d**–**g**, the Z/Eselectivities were diminished (entries 4–7); moreover, E-**4e** was isolated as the major product. Substrates derived from aromatic aldehydes with either electron-withdrawing (e.g., CF₃ in **3g**) or electron-donating substituents (i.e., MeO in **3f**) worked well, affording corresponding products in excellent yields. Noteworthy is that no iodination of the benzene ring in **3f** was observed. Interestingly, ester **3h** with 2-acetoxyethyl at the propargylic position yielded α -iodo-dienone **4h** only in its *Z*-form in 80% yield (entry 8). The elimination of acetic acid in this reaction likely happened after the formation of the iodoenone moiety. In contrast, ester **3i** with one more CH₂ spacer led to the expected product, α -iodoenone **4i**, in 83% yield. Substrates related to **4h** and **4i** with the terminal hydroxyl group protected by a TBS group instead led to rather complicated mixtures, and crude ¹H NMRs indicated that desilylation happened. While the reaction conditions are considered mild, Au(PPh₃)NTf₂ seems to be acidic enough to cause facile desilylation and elimination of acetic acid (entry 8).

Extension of this chemistry to propargylic acetates derived from ketones was delightfully successful. Hence, as shown in Table 3, acetates prepared from linear ketones such as

Table 3. Reaction Scope for the Formation of β , β -Disubstituted α -Iodoenones



^{*a*} The substrate concentration was 0.05 M. ^{*b*} Isolated yield. ^{*c*} Z/E = 1:2.2.

acetone (i.e., **5a**) and 3-methylbutan-2-one (i.e., **5e**) led to excellent yields of β , β -disubstituted α -iodoenones with marginal stereoselectivity in the reaction of **5e** (entry 2).²⁰ Similarly, this reaction worked well with substrates derived from cyclic ketones including cyclopentanone (entry 2), cyclohexanone (entries 3, 6, and 7), and cycloheptanone (entry 4). In addition, different substituents at the alkyne terminus, including primary (entries 1–5) and secondary

⁽¹⁹⁾ Indeed, precipitates, presumably AgI, were observed during the reaction. Without the addition of AgNTf₂, no precipitate formed.

(entry 6) alkyl groups as well as a phenyl group (entry 7), were allowed. Remarkably, no elimination of acetic acid from acetates **5** to form corresponding enynes was observed, indicating that $Au(PPh_3)NTf_2$ prefers activating the C-C triple bond to coordinating to the acetoxy group.

Two possible competing mechanistic paths for this reaction are proposed in Scheme 2 for the case of propargylic acetates



derived from aldehydes. Thus, carboxyallene **7**, generated via Au^I-catalyzed 3,3-rearrangement, can either react with NIS directly (path a) or be further activated by the Au^I catalyst to generate Au-containing cation **A** (path b). The former path will lead to oxocarbenium **B** with the iodo group *trans* to R¹ (i.e., *E*-isomer) selectively due to the approach of NIS toward the more electron-rich enolic C–C double bond from the less hindered face (i.e., the face of H), while the latter would afford **C** with the iodo group *cis* to R¹ (i.e., *Z*-isomer) as our previous studies^{10–13} showed repeatedly a *cis* relationship between Au(PPh₃) and R¹ in intermediate **A**.^{21,22} If subsequent hydrolysis is facile and does not allow stereoisomerization, these two paths will yield the same

product but with opposite stereoselectivities. In order to gain insights into the mechanism, reactions were run in an NMR tube and the Z/E ratios were monitored by ¹H NMR. Hence, when propargylic ester 3c with all alkyl substituents was the substrate, a constant Z/E ratio of 19:1 was observed during the reaction, while the intermediate carboxyallene was not detected. This supports path b, and the allene intermediate presumably reacts fast with the Au^I catalyst. Quite the opposite, when ester 3e with a phenyl group was the substrate, an opposite stereoselectivity with the E-isomer slightly favored was detected invariably throughout the reaction (Z/E = 1:2). Interestingly, in this case, 90% of substrate 3e was converted into its corresponding carboxyallene in 5 min, while the completion of the reaction took 30 min. Moreover, when a 1:1 mixture of 3e and its corresponding carboxyallene²³ was mixed with NIS without the Au^I catalyst, the carboxyallene reacted to yield (E)-4e predominantly (Z/E = 1:6 throughout the reaction) while 3e remained unchanged. These observations suggest that 3e reacted via both path a and path b with the former presumably dominant. As a preliminary conclusion out of these studies, aryl-containing esters such as 3d, 3e, 3f, and 3g may all undergo reactions via path a to a significant extent, leading to diminished stereoselectivities; in contrast, aliphatic propargylic esters yield the Z-isomers selectively likely via path b predominantly.

In summary, an efficient synthesis of linear α -iodoenones from readily accessible propargylic acetates was developed. This reaction works well not only with substrates derived from aldehydes but also with those from ketones. Good to excellent Z-selectivities were observed in the case of aliphatic propargylic acetates.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽²⁰⁾ The stereoisomers of **6e** are inseparable, and the assignment of ¹H NMR signals to the stereoisomers is based on the observation that the *Z*-isomers in other cases consistently have chemical shifts at lower fields.

⁽²¹⁾ Compared to the average $C(sp^3)$ – $C(sp^2)$ bond length (1.50 Å), the Au^1 – $C(sp^2)$ bond is much longer (2.04 Å by averaging 8 hits from Cambridge Structural Database), which may be the reason for the preference for the *cis* relationship between Au(PPh₃) and R¹.

⁽²²⁾ Retention of double bond geometry was observed when alkenylgold intermediates were iodinated with NIS. For references, see refs 15a and 15b.

⁽²³⁾ Prepared by heating acetate 3e with 10 mol % of AgClO₄ in refluxing 2-butanone for 2 h.