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Halogenation

Regioselective Dihalohydration Reactions of Propargylic Alcohols: Gold-Catalyzed and Noncatalyzed Reactions**

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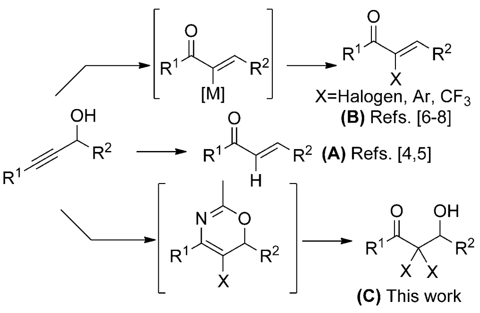
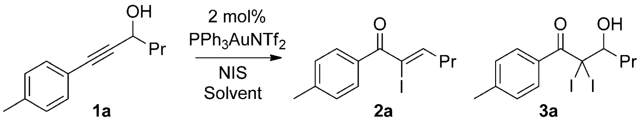
Abstract: *The regioselective conversion of propargylic alcohols into previously unreported α,α-diiodo-β-hydroxyketones was achieved by treatment with N-iodosuccinimide in the presence of a gold catalyst. The corresponding α,α-dichloro-β-hydroxyketones were obtained by treatment with trichloroisocyanuric acid in the absence of a catalyst. The latter reaction can be extended to other alkynols. These transformations can be used to prepare potentially useful halogenated building blocks. Preliminary mechanistic studies suggest that the reaction involves participation of the acetonitrile solvent in the formation of a 5-halo-1,3-oxazine intermediate.*



Scheme 1. Transformations of propargylic alcohols.



Scheme 2. Reaction of alcohol **1a** with gold catalyst and NIS.

Propargylic alcohols are useful and readily accessible intermediates for organic synthesis, containing both an alcohol and a carbon–carbon triple bond which can undergo a variety of useful reactions.[1] Numerous catalytic transformations of these compounds have been reported in recent years including their conversion into aromatic heterocycles[2] and the substitution of the alcohol group with a variety of nucleophiles.[3] The Meyer–Schuster rearrangement of propargylic alcohols into enones is a particularly useful reaction (Scheme 1, **A**),[4,5] providing an extremely effective alternative to the olefination of carbonyl compounds with phosphorus reagents. Recently a number of variants have been reported which enable functionalization of the proposed vinylmetal intermediate with a halogen,[6] an aryl group,[7] or a trifluoromethyl group[8] to give α-substituted enone products (Scheme 1, **B**). Here we report a new reaction pathway, in which the formation of a 5-halo-1,3-oxazine intermediate by reaction of a propargylic alcohol with acetonitrile, enables a highly regioselective dihalohydration reaction to be achieved. Depending on the nature of X, this pathway can be accessed with or without a gold catalyst.

In an initial experiment in which we sought to extend our procedure for the Meyer–Schuster rearrangement[4] to the preparation of α-haloenones, we reacted propargylic alcohol **1a** with gold catalyst[9] and *N*-iodosuccinimide (NIS) in PhMe at room temperature (Scheme 2 and Table 1). This provided the α-iodoenone **2a** in good yield as hoped (entry 1). Interestingly, however, a small amount of a ketone by-product was isolated from the reaction mixture, which was identified as α,α-diiodo-β-hydroxyketone **3a**. To the best of our knowledge, there are no previous reports of the synthesis of α,α-diiodo-β-hydroxyketones in the literature so the fact that this unusual compound could be obtained from readily available materials was of considerable interest. Furthermore, the gold-catalyzed regioselective dihalohydration of an alkyne is unprecedented.[10,11] We therefore sought to optimize the reaction conditions to provide **3a** as the major product.

Table 1: Optimization of the diiodohydration reaction.[12]

Entry	Solvent	NIS (equiv)	*t*	Yield
1	PhMe	1.2	2 h	71% (**2a**)[a]
2	PhMe:H_2O 20:1	1.2	18 h	18% (**3a**)
3	PhMe:H_2O 20:1	2.4	5 h	49% (**3a**)
4	Et_2O:H_2O 20:1	2.2	45 min	50% (**3a**)
5	THF:H_2O 20:1	2.2	45 min	38% (**3a**)
6	MeCN:H_2O 20:1	2.2	30 min	64% (**3a**)
7	MeCN:H_2O 10:1	2.1	1 h	71% (**3a**)
8	MeCN:H_2O 10:1	2.1	18 h	0%[b]

[a] Small quantities of **3a** were observed. [b] The gold catalyst was omitted.

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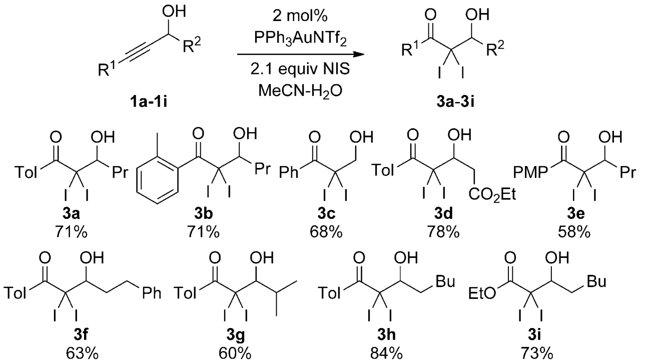
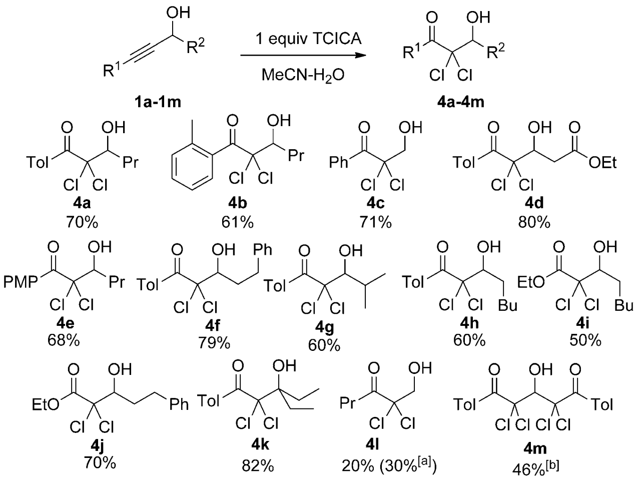
Addition of water to the reaction mixture resulted in an increased yield of the diiodoketone **3a** (entry 2). Increasing the quantity of NIS led to a further increase in yield as expected (entry 3). Subsequently, the effect of solvent was explored with Et_2O and THF proving no more effective than PhMe (entries 4,5), but MeCN giving a promising increase in yield (entry 6) and a much cleaner crude product. A further improvement was obtained by increasing the quantity of water, and the number of equivalents of NIS could be reduced to 2.1 without detrimental effect on the conversion (entry 7). In a control experiment in the absence of gold catalyst, no formation of **3a** (or **2a**) was observed. A wide range of Au catalysts could be used,[12] though PPh_3AuNTf_2 gave a cleaner conversion so this was employed for subsequent reactions.

We next set out to determine the scope of the reaction by applying these conditions to various propargylic alcohols (Scheme 3). Pleasingly, a selection of different α,α-diiodo-β-hydroxyketones **3a–3i** could be obtained in moderate to excellent yield from the corresponding alcohols. As well as secondary alcohols, a primary alcohol (**3c**) could also be employed. Tertiary alcohols were not suitable substrates, though this is perhaps unsurprising given the large steric demands of the geminal diiodo unit. The reaction could also be applied to the synthesis of a diiodohydroxyester (**3i**) from the corresponding alkynyl ether.



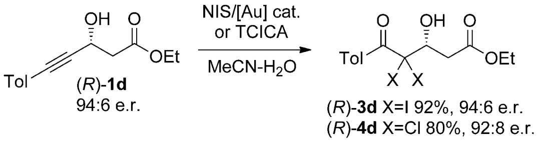
Scheme 3. Synthesis of α-diiodo-β-hydroxyketones. Tol = *p*-tolyl; PMP = *p*-methoxyphenyl.

Given the synthetic interest in chlorolipid natural products,[13] many of which contain geminal dichlorides, we elected to explore whether this reaction could be extended to the synthesis of α,α-dichloro-β-hydroxyketones **4** (Scheme 4). Disappointingly, no reaction was observed with *N*-chlorosuccinimide as the halogenating reagent, but employing trichloroisocyanuric acid (TCICA) enabled the α,α-dichloro-β-hydroxyketone **4a** to be obtained in good yield.[12] Suprisingly, this dichlorohydration reaction occurred even in the absence of a gold catalyst.[14] The dichlorohydration reaction could be applied to a wide range of propargylic alcohols to give the corresponding dichlorohydroxyketones (**4a–4h**, **4k–4l**) or dichlorohydroxyesters (**4i–4j**) in generally good yield. The reaction was applicable to primary (**4c**), secondary (**4a**, **4b**, **4d–4j**) and tertiary (**4k**) propargylic alcohols, although a poor yield was obtained with a low molecular weight primary propargylic alcohol (**4l**). A symmetrical tetrachlorodiketoalcohol (**4m**) could be prepared in acceptable yield from the corresponding dialkynol using two equivalents of TCICA.



Scheme 4. Dichlorohydration reactions. [a] NMR yield; [b] 2 equiv. TCICA.

When the diiodohydration reaction was applied to enantioenriched alcohol (*R*)-**1d**,[15] diiodohydroxyketone (*R*)-**3d** was obtained with complete retention of enantiomeric purity (Scheme 5), whereas dichlorohydroxyketone (*R*)-**4d** was obtained with a slight reduction in the enantiopurity.

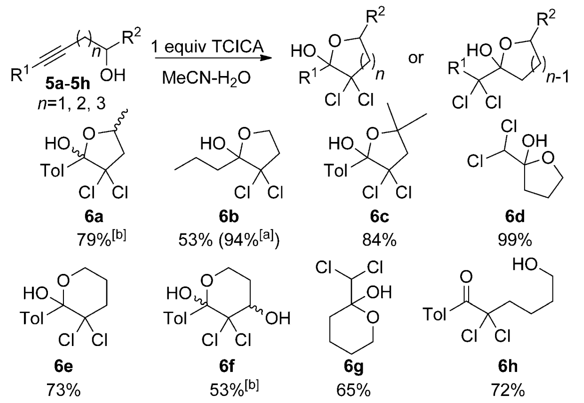


Scheme 5. Dihalohydrations of an enantioenriched propargylic alcohol.

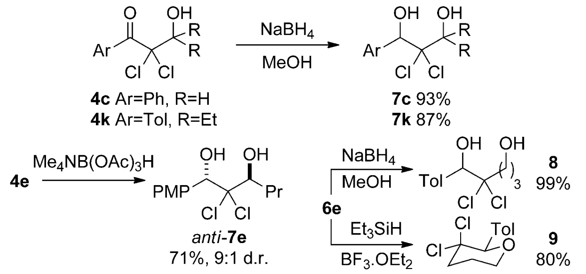
Thus, in combination with the many methods available for accessing enantioenriched propargylic alcohols,[15,16] the novel dihalohydration reactions described above provide viable routes to enantioenriched aldol products formally derived from dihalomethyl ketone enolates. Given the fact that there are currently no viable methods for achieving asymmetric aldol reactions with these enolates, this approach could be especially valuable.[17] It should also be noted that α,α-dihalocarbonyl compounds have been shown to possess useful biological activity,[18] as well as being applicable to a range of C–C and C–heteroatom bond forming reactions.[19]

Pleasingly, the dichlorohydration reaction could be extended to the synthesis of dichlorolactols from a range of alkynols containing different spacers between the alcohol and alkyne group (Scheme 6). The reaction was applied to the formation of both five-membered (**6a–6d**) and six-membered dichlorolactols (**6e–6g**) via both *endo* (**6a–6c**, **6e–6f**) and *exo* (**6d**, **6g**) cyclization reactions. Attempted formation of a seven-membered lactol was unsuccessful, but the corresponding dichlorohydroxyketone was obtained in good yield (**6h**).

Primary and tertiary dichloroketoalcohols **4c** and **4k** could be reduced with $NaBH_4$ to give dichlorodiols **7c** and **7k**



Scheme 6. Synthesis of dichlorolactols from alkynols. [a] NMR yield; [b] 1:1 mixture of diastereoisomers.

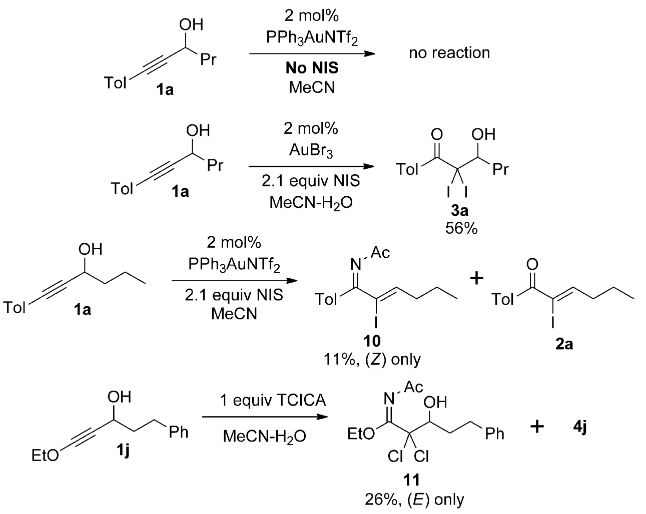


Scheme 7. Selective reduction reactions of dichlorohydroxyketones and dichlorolactols.

respectively (Scheme 7). Secondary dichloroketoalcohol **4e** readily underwent diastereoselective reduction with $Me_4NB(OAc)_3H$[20] in good yield to give *anti*-**7e** as the major product. Dichlorolactol **6e** could be reduced with $NaBH_4$ to the dichlorodiol **8**, or converted into the dichlorotetrahydropyran derivative **9** by reduction with $Et_3SiH/BF_3{\cdot}OEt_2$.

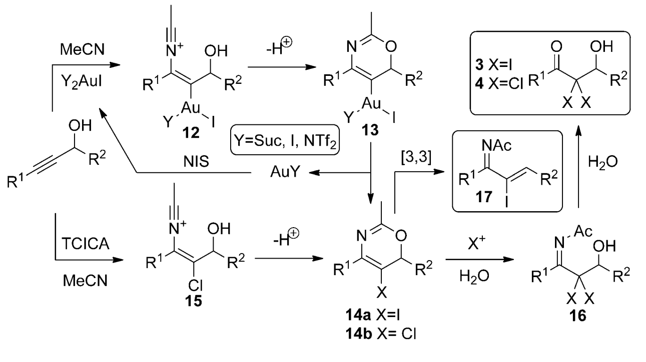
We next turned our attention to the mechanism of these unusual dihalohydration reactions. Given the fact that an enantioenriched alcohol does not racemize during the reaction (Scheme 5), the dihalohydration cannot proceed via an intermediate haloenone.[6b] The reaction does not take place in the absence of the gold catalyst (Table 1, entry 8), and in the absence of NIS, propargylic alcohol **1a** does not undergo reaction with PPh_3AuNTf_2 in MeCN-H_2O (Scheme 8), despite the fact that this catalyst promotes the Meyer–Schuster rearrangement in other solvent systems (PhMe-MeOH).[4] This suggests that oxidation of the Au^I complex by NIS may lead to generation of a reactive Au^{III} species.[21,22] Alternatively, the gold salt may act as a Lewis acid to activate the NIS.[23] The former hypothesis is supported by the fact that $AuBr_3$ is a competent catalyst for the reaction. However, we were unable to observe the formation of a potential catalytic species upon treatment of an NMR sample of PPh_3AuNTf_2 with NIS.[12]

Further insight into the possible reaction mechanism was provided by the fact that *N*-acylimine **10** could be isolated from reaction of **1a** with PPh_3AuNTf_2/NIS in the absence of water. Similarly, reaction of alcohol **1j** with TCICA led to the formation of *N*-acylimidate ester **11** as a significant by-product in the dichlorohydration reaction. Both **10** and **11** were obtained as single geometrical isomers with the *N*-acyl group *cis* to the halogenated carbon atom.[24]



Scheme 8. Control experiments and isolation of potential intermediates.

In order to account for these observations, we propose a mechanism[25] for the diiodohydration reaction (Scheme 9) in which initial activation of the alkyne by $IAuY_2$ induces nucleophilic attack of MeCN to give intermediate **12**, which undergoes cyclization to give **13**, followed by reductive elimination[26,27] to give **14a** and an Au^I salt which is reoxidized. The dichlorohydration reaction involves formation of **14b**, generated via addition of MeCN to the alkyne activated by the electrophilic chlorine source. The dihaloketone products **3**/**4**, are then formed by direct halogenation of oxazine **14** (possibly mediated by gold where X = I) and hydrolysis to give acyl imine **16**, which is hydrolyzed to the product. When water is not present, [3,3]-sigmatropic rearrangement of **14a** gives *N*-acyl imine **17** which leads to α-haloenone formation. This mechanism would account for the significant beneficial effect of MeCN on the dihalohydration reactions as the 5-halooxazine intermediate facilitates double halogenation by acting as a long-lived "enol" equivalent. Most significantly, however, the formation of the cyclic oxazine intermediate **14** would account for the fact that



Scheme 9. Possible mechanisms for the dihalohydration reactions.

N-acyl compounds **10** and **11** were obtained as single geometrical isomers. In non-nitrile solvents, a second pathway involving direct addition of water to give a haloenol intermediate must be operative, however, as the dihalohydration product was still formed in moderate yields (Table 1).[12]

In conclusion, we have reported highly regioselective diiodohydration and dichlorohydration reactions of propargylic alcohols which appear to proceed through 5-halo-1,3-oxazine intermediates, generated by participation of the MeCN solvent in the reaction. The dichlorohydration reactions can be extended to the formation of dichlorolactols from a range of different alkynols. These reactions should find widespread utility in the synthesis of functionalized halogenated molecules for a range of applications.[18,19]

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Keywords: gold · halogenation · homogeneous catalysis · ketones · reaction mechanisms

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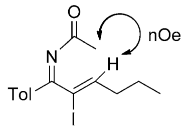

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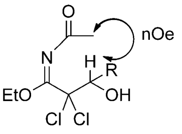

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