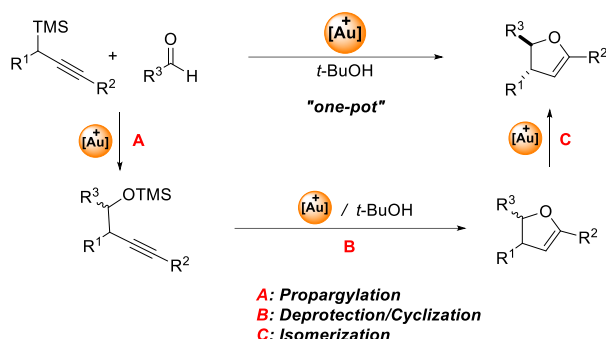# Gold(I)-catalyzed one-pot and diastereoselective synthesis of *trans*-2-silyl-4,5-dihydrofurans from propargylsilanes and aldehydes

Sergio Fernández, Javier Santamaría* and Alfredo Ballesteros*

Supporting Information Placeholder

A: Propargylation
B: Deprotection/Cyclization
C: Isomerization

ABSTRACT: A diastereoselective and high yielding gold-catalyzed synthesis of *trans*-2-silyl-4,5-dihydrofurans is described. In addition to a sequential manner, this reaction could be performed in a one-pot procedure from propargylsilanes and aldehydes. A mechanistic proposal for *cis-trans* isomerization step is formulated. In order to give experimental support to this proposal, which involves ring opening/ring closing steps of the dihydrofuran, several isotopically labelled experiments, intramolecular capture of a proposed intermediate and a Hammett plot have been performed.

Homogeneous gold catalysis has been settled, in the last decade, as a powerful tool in organic synthesis due to the increasing number of protocols that have been reported, allowing an easy access to a wide family of structural motifs.[1] On the other hand, dihydrofuran skeletons are interesting synthons as they are present in different natural products[2] and also have been used as starting materials for further transformations.[3] However, catalytic access to these systems did not receive high attention because aromatization, with formation of furans, is a major drawback. In this field, it is worth to mention the work by Danheiser[4] and Evans[5] with formation of 3-silicon-4,5-dihydrofurans from allenylsilanes, in respective titanium or scandium catalyzed formal [3+2] cycloadditions. Additionally, Zhang and coworkers[6] recently reported the formation of similar compounds from a gold-catalyzed propargylation of aldehydes, followed by [2,3]-silyl migration. However, no intermolecular[7] examples can be found to date of catalytic formation of 2-silyl-4,5-dihydrofurans. In addition, 3-silyl-4,5-dihydrofurans were obtained, in all cases, as a *cis/trans* diastereoismeric mixture.

In the course of our program in the field of gold catalysis using alkynylsilylated compounds,[8] we recently reported a novel gold-catalyzed propargylation of carbonyl compounds, with isolation of an allenyl intermediate (Figure 1; *top*).[9] That work included some preliminary results of formation of 2-silyl-4,5-dihydrofurans from consecutive propargylation of aldehydes, solvolysis and cyclization reactions. These compounds were obtained in a close to one to one mixture of dia-

stereoisomers. As it is described in the present work, a deeper investigation in this field allowed us to access to a large number of those interesting compounds as diastereomerically pure compounds (Figure 1; *bottom*).
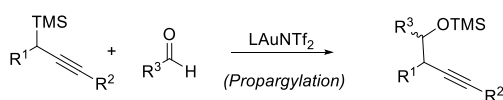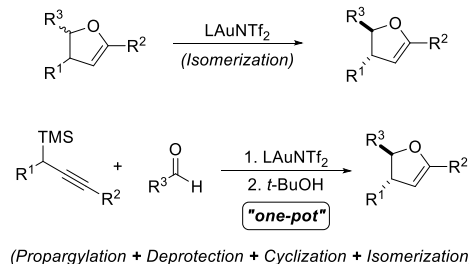

Figure 1. Propargylation of aldehydes and dihydrofuran synthesis

In the present work, we describe a one-pot and efficient synthesis of 4,5-dihydrofurans including consecutive gold-catalyzed steps, as follows: i) propargylation of aldehyde, ii) silylether deprotection iii) cycloisomerization to 4,5-dihydrofuran and iv) *cis-trans* isomerization. Additionally,

experimental work in order to give light to the mechanistic insights for the *cis-trans* isomerization is also reported.

First of all, as a complement to previously reported results,[9] several new examples for the synthesis of 4,5-dihydrofurans, from propargylsilanes **1**[10] and aldehydes **2**, have been performed to prove the scope of the transformation at the initial gold-catalyzed steps. (Scheme 1; *See supporting information for details and list of dihydrofuran mixtures*). In all cases, 4,5-dihydrofurans were obtained as almost equimolecular *cis/trans* mixtures, which could not be readily separated. However, *cis* and *trans* isomers could be prepared and characterized from respective cycloisomerizations of corresponding *syn* or *anti* alkynols.

Scheme 1. Consecutive gold-catalyzed propargylation-cyclization reactions.

Ar = tris(2,6-di-*t*-butylphenyl)
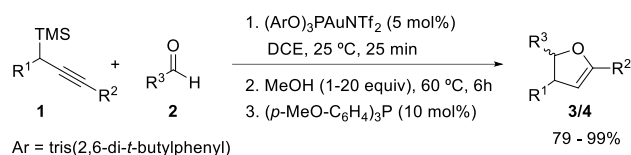
At this point, we focused our efforts towards a diastereoselective synthesis of those dihydrofurans. Thus, when a mixture of *cis/trans* 4,5-dihydrofurans **3/4** was dissolved in 1,2-dichloroethane and treated with a 5 mol% of [tris(2,4-di-*tert*-butylphenyl)phosphite]gold(I) bistriflimidate ((ArO)₃PAuNTf₂), at 60 °C, we observed a complete isomerization of *cis*-2-silyl-4,5-dihydrofuran **3** into *trans* isomer **4**, which was obtained in a quantitative manner (Scheme 2; *top*)[11,12]. Similar results were arisen from the corresponding mixture of alkynol precursors **5**, under same reaction conditions (Scheme 2; *bottom*).

**Scheme 2.** Synthesis of *trans*-2-silyl-4,5-dihydrofurans.
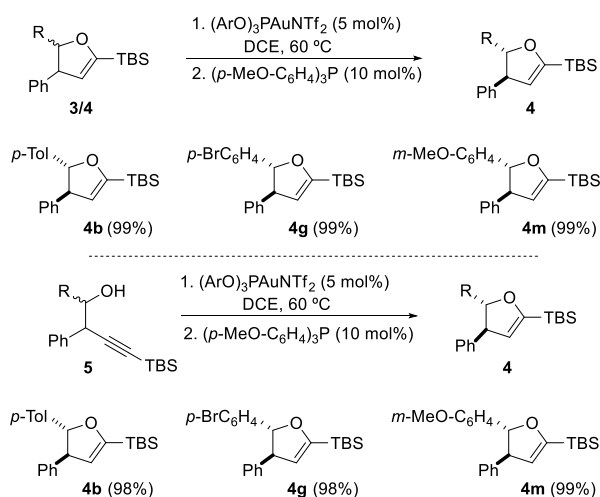
It is worth to mention that the presence of the silyl group seems to be crucial. Thus, when *tert*-butyldimehtylsilyl group was replaced, in alkynols **5**, by a phenyl, *n*-butyl, *t*-butyl or hydrogen, decomposition products were observed under the standard reaction conditions.

Moreover, all the attempts to perform the gold-catalyzed reaction in a one-pot manner -adding a variable amount (1 to 20 equivalents) of methanol to accomplish the deprotection of the silyl ether- from propargylsilanes and carbonyl compounds resulted in an almost equimolecular mixture of the diastereoisomeric dihydrofurans **3/4**. However, this problem could be overcome using a bulkier alcohol, such as *tert*-butyl alcohol, giving rise, under the standard reaction conditions from propargylsilanes **1** and aldehydes **2**, to the corresponding *trans*-2-silyl-4,5-dihydrofurans as single isomers (Scheme 3). Following this methodology, a large number of diastereomerically pure *trans*-4,5-dihydrofurans could be obtained from aromatic (**4a-t**) and also aliphatic propargylsilanes (**4u-v**). In addition, a wide scope in the electronic nature of the aromatic aldehydes could be employed in this transformation. In this sense, the use of benzaldehyde derivatives with electron-donating groups (furans **4b-e,4l-m,4o,4q,4s-v**) and also with electron-withdrawing groups for **4f-g,4n**, gave satisfactory results with formation of *trans*-2-silyl-4,5-dihydrofurans **4**, in quantitative yields. For the formation of dihydrofurans **4j-k,4p**, obtained from highly electron-poor benzaldehyde derivatives, longer reaction times would be required for the enrichment of the mixture in the *trans* isomer. However, much longer reaction times resulted in progressive decomposition and a decrease of the reaction yield.

**Scheme 3.** One-pot synthesis of *trans*-2-silyl-4,5-dihydrofurans.
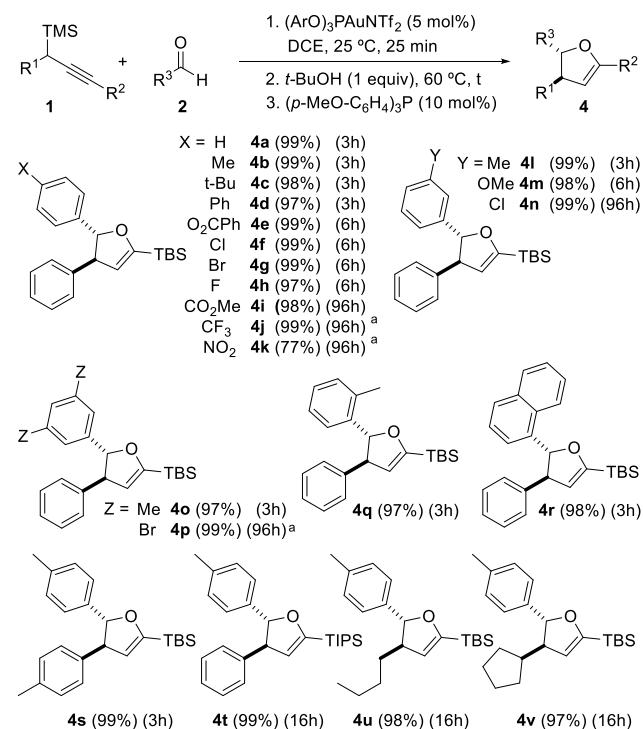
[a]Isomerization not complete under the reported reaction time. *Trans-cis* (**4:3**) diastereomeric ratio for **4j**: (3:1), **4k**: (1.5:1) and **4p**: (2:1).

With all these results in hand, a mechanistic proposal for the gold-catalyzed *cis-trans* isomerization step could be formulated and it is outlined in Scheme 4. First, after performing the 5-*endo-dig* cyclization from the homopropargyl alcohol,[13] gold catalyst would coordinate to dihydrofuran **3** and evolve to gold intermediate **I**. Next, this intermediate **I** could suffer a temporal breakage of the carbon-oxygen bond leading to carbo-

cationic intermediate **II**. This system, which is able to rotate around the carbon-carbon single bond, would close back through an oxygen attack to C5-carbon, driving to the more stable *trans*-4,5-dihydrofuran gold intermediate **III**. Finally, intermediate **III** could evolve through gold elimination and decoordination to *trans*-4,5-dihydrofuran **4**, liberating the catalyst to initiate a new catalytic cycle.
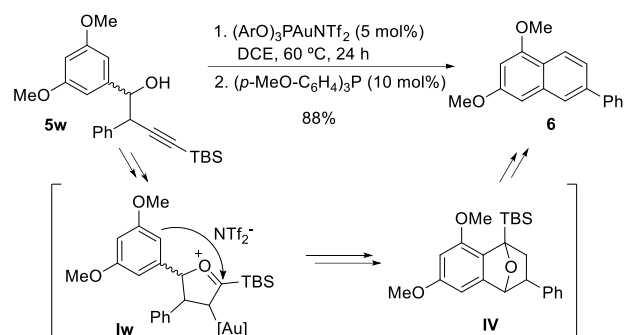
Scheme 4. Mechanistic proposal.
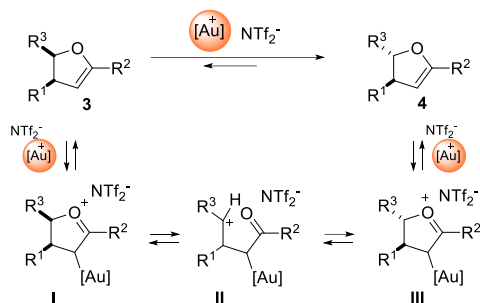
At this point, we decided to perform several isotopically labelled experiments in order to give support to the mechanistic proposal (Scheme 5). In this sense, participation of intermediate **I** could be supported by an isomerization reaction of a deuterium labelled mixture of 4,5-dihydrofurans **3D-3/4b** in presence or absence of *tert*-butyl alcohol (Scheme 5). Thus, when the reaction was performed in absence of *tert*-butyl alcohol, isomerization occurred without significate change at the labelled position, indicating no participation of a proton in the catalytic process. However, a complete disappearance of the deuterium atom was observed when 20 equivalents of *tert*-butyl alcohol were used. Finally, when a single equivalent of *tert*-butyl alcohol was used, the amount of labelled compound decreased to 45%.[14] On the other hand, absence of *cis-trans* isomerization using a less sterically demanding alcohol, such as methanol, for deprotection step, could be explained by a methanol nucleophilic attack to intermediate **I** and formation of the corresponding ketal, that could evolve back. Taking all these results into account, a reaction pathway through participation of an intermediate with a double bond between C3 and C4 carbons can be ruled out.

Scheme 5. Isotopically labelled experiments
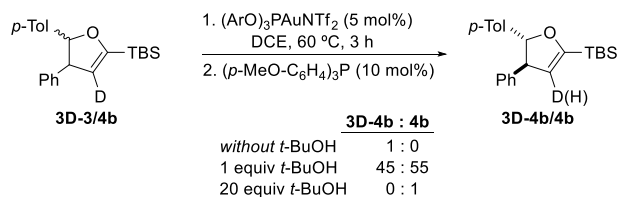
Additionally, intermediate **I** is also in agreement with the experimental observation of formation of naphthalene derivative **6**, under the standard reaction conditions, from a diastereomeric mixture of alkynols **5w** (Scheme 6). Formation of naphthalene **6** could be explained through evolution of intermediate **Iw**, which is able to experiment an intramolecular nucleophilic attack of the electron-rich arene group to the electrophilic carbon C2.

Scheme 6. Synthesis of naphthalene **6**.

Moreover, the hypothesis of a mechanistic proposal involving a carbon-oxygen breakage and participation of cationic intermediate **III**, could be supported by the differences observed in the reactivity ratio in presence of electron-donating or electron-withdrawing groups at benzaldehyde derivatives (*see above*). To prove the participation of a positive charge at C5, we decided to explore the reaction running a Hammett-type analysis. For that purpose, we performed a number of *cis-trans* isomerization experiments -starting from pure *cis*-4,5-dihydrofurans **3**[15]- at the standard reaction conditions. After two hours of reaction, mixtures or cis/trans **3/4** isomers were obtained and the isomerization ratio *trans:cis* (**4:3**) was determined by NMR (Table 1). Although opening-closing steps are probably reversible for both isomers, the reaction works under pseudo-first-order conditions due to the differences in energies between *cis* and *trans* isomers should be similar for every pair of isomers. With this assumption, relative rate constants were estimated from the ratio of *cis* to *trans* conversion of dihydrofurans, compared to isomerization rate for compound **3a**.

Table 1. Hammett plot for the *cis-trans* isomerization reaction
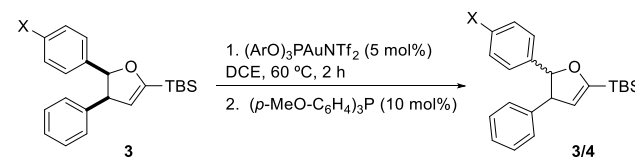
Compound	X	*trans* : *cis* (**4:3**)	k/k_0	σ
d	Ph	16.7 : 1	4.065	- 0.18
b	Me	17.5 : 1	4.280	- 0.17
a	H	4.1 : 1	1.000	0.00
h	F	1 : 2.1	0.508	0.06
f	Cl	1 : 3.6	0.068	0.23
g	Br	1 : 3.0	0.081	0.23
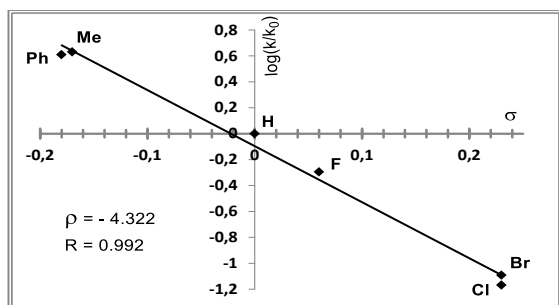
Hammett plot indicates a good correlation against σ values[16] as the plot revealed a good linear fit (R = 0.992). The negative slope of the plot (ρ) is in agreement with building up a positive charge in the transition state of the rate determining step. This fact, in addition to a value of ρ = - 4.322, supports the participation of intermediate **II**, as a positive charge is created (Scheme 4; *see above*). Moreover, transformation of intermediate **I** into intermediate **II** could be considered the mechanism rate limiting step.[17]

Finally, the use of C4 and C5 deuterium labelled compounds (**4D-3/4b** and **5D-3/4a**) and their behavior under respective isomerization reactions in the presence of *tert*-butyl alcohol, are in agreement with the mechanistic proposal, as they do not imply proton exchange at the epimerization step (Scheme 7).

Scheme 7. Isomerization of C4 and C5 labelled dihydrofurans
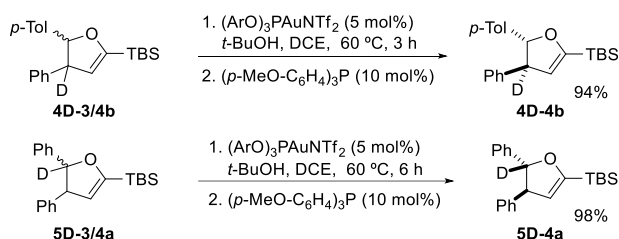
In conclusion, we describe in this work a novel gold-catalyzed one-pot synthesis of diastereomericaly pure *trans*-2-silyl-4,5-dihydrofurans from propargylsilanes and aldehydes. The reaction involves four consecutive gold-catalyzed reactions in a one-pot procedure, as follows: propargylation, silyl deprotection, cycloisomerization and finally, *cis-trans* dihydrofuran isomerization. In all cases, *trans*-4,5-dihydrofurans were obtained in very high yields. A deep study of the mechanistic insights for the dihydrofuran isomerization has also been performed. The mechanistic proposal for that isomerization implies the participation of alkylgold intermediates and also a temporal carbocationic intermediate. These hypotheses are supported by i) several deuterium labelled experiments, ii) a Hammett type study and iii) experimental observations. Temporal carbocationic intermediate **II**, which allows free rotation and accommodation of the substituent at C5, seems to participate in the rate-determining step.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website and includes experimental procedures and NMR spectra (PDF). FAIR Data is available as Support-

ing Information for Publication and includes the primary NMR FID files for compounds **3**, **4**, **5** and **6**.

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Notes

The authors declare no competing financial interest.

DEDICATON

Dedicated to the memory of Professor Kilian Muñiz

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