Gold Catalysis

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# Gold(I)-Catalyzed *endo*-Selective Intramolecular α-Alkenylation of β-Yne-Furans: Synthesis of Seven-Membered-Ring-Fused Furans and DFT Calculations**

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*Dedicated to Professor Kendall N. Houk on the occasion of his 70th birthday*

Furan derivatives are widely found in natural products with impressive biological properties. In many of these natural products, the furan system is fused to other rings with various sizes. Some of the natural products that incorporate seven-membered-ring-fused furans are shown in Figure 1.[1] Among

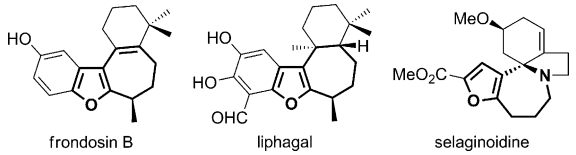
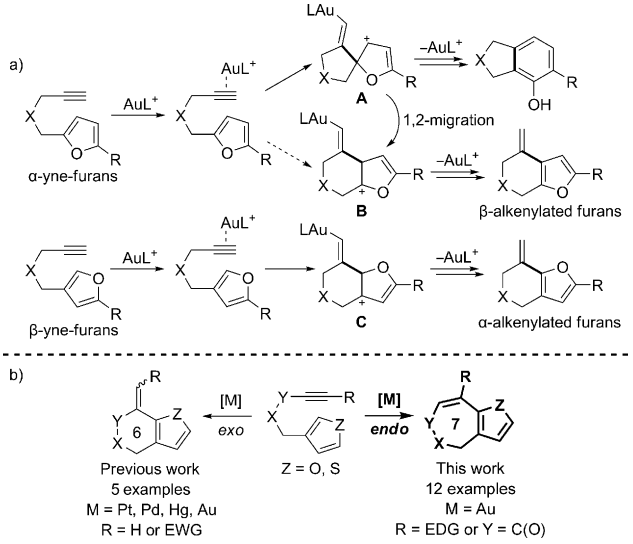



***Figure 1.*** Natural products with seven-membered-ring-fused furans.

these natural products, frondosin B inhibits the binding of interleukin-8 (IL-8) in the low micromolar range.[1a] Liphagal is a selective inhibitor of phosphatidylinositol 3-kinase α (PI3K α).[1b] These days, the synthesis of seven-membered ring systems still represents a great challenge for synthetic organic chemists.[2] Consequently, the development of reactions or the design of strategies to build the fused cycloheptafuran skeleton is, in many cases, a challenging part of the synthesis of natural products with seven-membered-ring-fused furans, such as frondosin B, and their analogues.[3]

Transition-metal-catalyzed alkenylation reactions of arenes,[4] such as substituted benzenes,[5] indoles,[6] or pyrroles,[7] with alkynes have been rapidly developed over the past decade, owing to the discovery of alkyne activation by electrophilic transition-metal complexes.[8] However, in most cases, transition-metal-catalyzed intramolecular reactions of furans with alkynes give products where the furan ring has opened rather than alkenylated furans.[9–13] The cationic spiro intermediate **A** (Scheme 1a) was proposed as a common




***Scheme 1.*** a) Different reaction pathways of α-yne-furans and β-yne-furans under gold catalysis. b) Transition-metal-catalyzed α-alkenylation of β-yne-furans and β-yne-thiophenes.

intermediate of gold-catalyzed α-yne-furan cycloisomerizations.[14] Intermediate **A** may undergo 1,2-migration to form the annulated intermediate **B**, which gives the β-alkenylated furan product after proton transfer. However, in most cases, **A** undergoes C–O bond cleavage, and further steps occur that lead to a furan-ring-opened product.

Considering that the α position of furans is more nucleophilic than the β position,[15] we wondered whether we could develop an α-alkenylation strategy that uses furan substrates with the alkyne chain attached at the β position of the furan ring; then, the annulated furan intermediate **C** would be formed directly (no 1,2-migration needed), and consequently, fewer side reactions should occur (Scheme 1a). We found that only five examples of transition-metal-catalyzed α-alkenylation reactions of β-yne-furans have been reported by the groups of Echavarren (Pt), Sames (Pt), Yamamoto (Pd), Nishizawa (Hg), and Banwell (Au).[16] However, only fused cyclohexafurans were formed by an *exo*-selective Friedel–Crafts type cyclization. We envisioned that there are two possible competing α-alkenylation pathways for β-yne-furans that would give the six- and seven-membered-ring products, respectively. We wondered whether this regioselectivity could be tuned by electronic effects through the introduction of suitable substituents on the alkyne moiety or on the tether of

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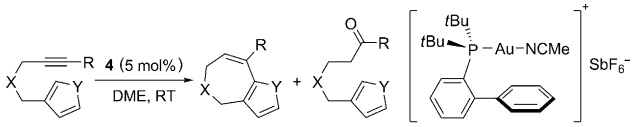
the starting materials to realize the challenging synthesis of fused cycloheptafurans by an *endo*-selective cyclization (Scheme 1b).

Herein, we report the synthesis of fused cycloheptafurans from β-yne-furans under mild conditions with an *endo*-selective α-alkenylation strategy. Also, we report DFT calculations on the experimentally observed regioselectivity. Furthermore, mechanistic insights obtained through the DFT calculations enabled further exploration of the α-alkenylation strategy to synthesize other seven-membered-ring-fused furans.

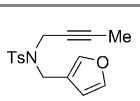
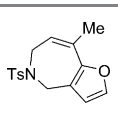
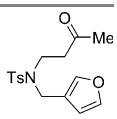
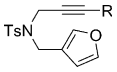
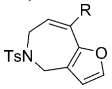
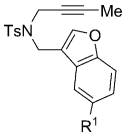
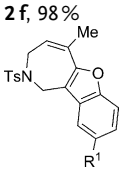
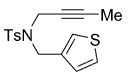
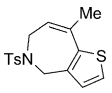
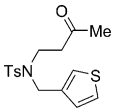
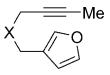
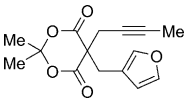
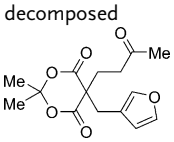
We commenced our study with β-yne-furan **1a** as the standard substrate. After extensive optimization (see the Supporting Information for details), we found that treatment of **1a** with **4** (5 mol%; **4** = [JohnPhosAu(NCMe)]$SbF_6$, JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl) in DME gave the desired fused cycloheptafuran **2a** in 90% yield, along with an unexpected alkyne-hydration by-product **3a** in 1% yield (Table 1, entry 1). The six-membered-ring product was not observed, which suggests that the reaction has a very good regioselectivity, with a preference for the 7-*endo* over the 6-*exo* pathway. Our attempts to reduce the amount of by-product **3a** by adding molecular sieves (4 Å) to remove water from the solvent failed. No reaction occurred, and the starting material remained intact (Table 1, entry 2). This result suggests that water may act as a proton shuttle in the present system. When one drop of water was added to the system, **3a** became the major product (Table 1, entry 3). These results indicate that a catalytic amount of water is required for the α-alkenylation reaction, but that too much water is detrimental.

We found that the alkyne part of the substrate can be substituted with a bulky substituent, such as cyclopropyl group, or by an alkenyl group, without affecting the *endo* selectivity and reaction yields (Table 1, entries 4 and 5). Substrates that bear aryl groups with different electronic characters at the alkyne moiety can also be converted into the corresponding products in very good yields (Table 1, entries 6–8). We also investigated whether the furan moiety of the β-yne-furans can be replaced by other arenes. The yne-benzofurans **1g** and **1h** (Table 1, entries 9 and 10) both gave the seven-membered-ring products in good yields. The skeleton of product **2h**, which bears a seven-membered-ring-fused benzofuran, is similar to those of frondosin B and liphagal (Figure 1), which indicates that the present strategy might be suitable for the synthesis of these natural products and/or their analogues. Under the optimized conditions, β-yne-thiophene **1i** was transformed into the target seven-membered-ring product **2i** and the hydration by-product **3i** in 46% and 39% yield, respectively (Table 1, entry 11). It was previously reported by Sames and co-workers that using $PtCl_4$, the O-tethered substrate **1j** gave only the product of furan ring-opening.[16b] With our system, however, **1j** can give the corresponding product **2j** in toluene in a moderate yield (Table 1, entry 12). Unfortunately, C-tethered substrates could not be converted into the desired cyclization products. **1k** slowly decomposed under gold catalysis (Table 1, entry 13), whereas **1l** gave the alkyne-hydration product **3l** in moderate yield (Table 1, entry 14).[17] Fortunately, the alkenylation of C-tethered substrates can be realized by another strategy using a carbonyl linker (see below and Scheme 3b).

***Table 1:*** Scope of the gold-catalyzed intramolecular α-alkenylation.




1 2 3 4

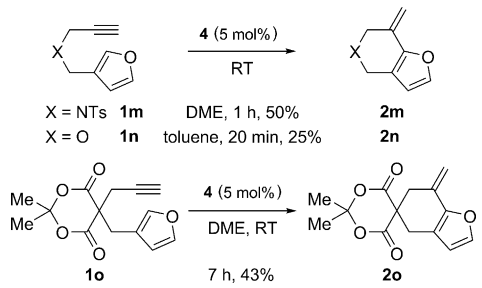
| Entry | Substrate | *t* [h] | Product, yield[a] | |
|---|---|---|---|---|
| |  | |  |  |
| 1 | **1a** | 3 | **2a**, 90% | **3a**, 1% |
| 2[b] | **1a** | 24 | no reaction | |
| 3[c] | **1a** | 8 | **2a**, 19% | **3a**, 63% |
| |  | |  | |
| 4 | **1b**, R = cyclopropyl | 3 | **2b**, 91% | |
| 5 | **1c**, R = 2-propenyl | 3 | **2c**, 88% | |
| 6 | **1d**, R = Ph | 4 | **2d**, 76% | |
| 7 | **1e**, R = *p*-$ClC_6H_4$ | 3 | **2e**, 90% | |
| 8 | **1f**, R = *p*-$MeOC_6H_4$ | 3 | **2f**, 98% | |
| |  | |  | |
| 9 | **1g**, $R^1$ = H | 2 | **2g**, 71% | |
| 10 | **1h**, $R^1$ = OMe | 6 | **2h**, 74% | |
| |  | |  |  |
| 11 | **1i** | 20 | **2i**, 46% | **3i**, 39% |
| |  | |  | |
| 12[d] | **1j**, X = O | 20 | **2j**, 60% | |
| 13 | **1k**, X = $CH_2$ | 48 | decomposed | |
| |  | |  | |
| 14 | **1l** | 96 | **3l**, 76% | |

[a] Yields of isolated products. [b] Molecular sieves (4 Å) were added. [c] One drop of water was added.[d] Reaction carried out in toluene. DME = 1,2-dimethoxyethane, Ts = *p*-toluenesulfonyl.

Reactions of terminal-alkyne-bearing substrates proceeded with very different regioselectivity, in accordance with previous reports on the Pt- and Hg-catalyzed variants.[10,12d] Under the optimized cyclization conditions for the gold-catalyzed variant, the terminal-alkyne-substituted substrates **1m**, **1n**, and **1o** with nitrogen, oxygen, or carbon tethers can also undergo intramolecular α-alkenylation to generate six-membered-ring products **2m**, **2n**, and **2o** in moderate yields through the 6-*exo*-*dig* pathway (Scheme 2).

To understand how the substituents at the alkyne moiety of the substrates affect the regiochemistry and to enable




***Scheme 2.*** Gold-catalyzed *exo*-selective intramolecular α-alkenylation with terminal alkynes.

further exploration of the α-alkenylation strategy by mechanistic insights, we performed preliminary DFT calculations[18] using the B3LYP functional (for details, see the Supporting Information). We propose that the cyclization reaction begins with coordination of the alkyne to the cationic $AuL^+$ center, which generates the gold–alkyne complex **COM**. Then, 7-*endo-dig* cyclization or nonclassical cyclopropanation[19] gives the homoallylic carbocation **INT1**, which then undergoes water-assisted proton transfer to form the bicyclic product **P1**. Alternatively, the 6-*exo-dig* pathway may also occur, which would give **P2**. Therefore, the formation of **P1** or **P2** depends on the relative energies of the alkenylation transition states **TS1** and **TS2** (Figure 2).

DFT calculations suggest that the *exo* pathway is favored by 2.3 kcal mol$^{-1}$ for the parent substrate (R = H) with $Au(PMe_3)^+$ as the catalyst, which implies that the fused cyclohexafuran product will predominantly be generated (Figure 2).[20] With R = Me and R = Ph, the *endo* pathway is favored by 3.1 and 4.8 kcal mol$^{-1}$, respectively, which suggests that the fused cycloheptafuran products will be generated exclusively (Figure 2). These results are in good agreement with our previous findings (Table 1 and Scheme 2). We reasoned that the polarization of the triple bond, which is induced by the terminal substituent, is a crucial factor in determining the regioselectivity.[21] Natural population analysis (NPA) was performed to obtain the charges on the C1 and C2 atoms of the gold–alkyne complexes (**COM**s) with different substituents to evaluate which carbon is more electrophilic and therefore more reactive towards nucleophilic attack of the furan ring (Figure 2).[22] In the parent system (R = H), the 3-furanylmethoxymethyl tether, which can be regarded as a stronger π-donor than a hydrogen atom, leads to a less negative (relatively more positive) charge on the C2 atom (−0.008 e on C2 vs. −0.264 e on C1), resulting in a preference for *exo*-selective cyclization in a Markovnikov manner. With internal alkynes, electron-donating R groups, such as Me and Ph, show stronger electron-donating effects than the tether, which makes the C1 atom more positively charged than the C2 atom (Figure 2, inset), and therefore the 7-*endo* pathway becomes favored over the 6-*exo* pathway.[23]

The mechanistic insights obtained by the DFT calculations suggest that the regioselectivity of the α-alkenylation reaction could be reversed with electron-withdrawing groups as the terminal substituents. Electron-withdrawing groups would induce a charge on the C2 atom that is more positive than that of the C1 atom (0.014 e on C2 vs. −0.122 e on C1 for $R = CO_2Me$), so that formation of the six-membered ring is favored. This can explain why fused cyclohexafurans were obtained with ketone-substituted β-yne-furans under gold catalysis in the total synthesis of crassifolone by Menon and Banwell.[16d] However, the stereochemistry of such a cyclization reaction has not been studied in depth. We speculated that ester-substituted β-yne-furan substrates could also give fused cyclohexafurans under gold catalysis. Calculations supported this hypothesis, showing that the *exo* pathway is favored by 2.9 kcal mol$^{-1}$ when $R = CO_2Me$ (Figure 2). When we treated the ynoate ester substrates **1p** and **1q** with gold catalyst **4**, we were excited to isolate the computationally predicted six-membered-ring products **2p** and **2q** as single isomers with *Z* configuration in good yields (Scheme 3a).[24]

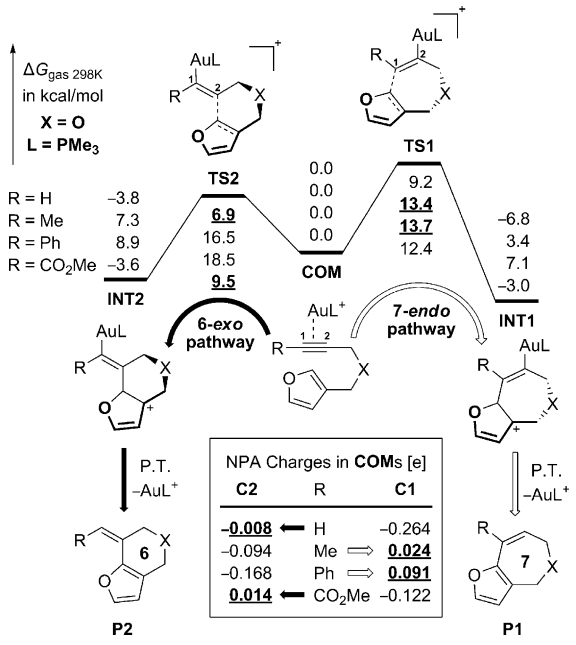
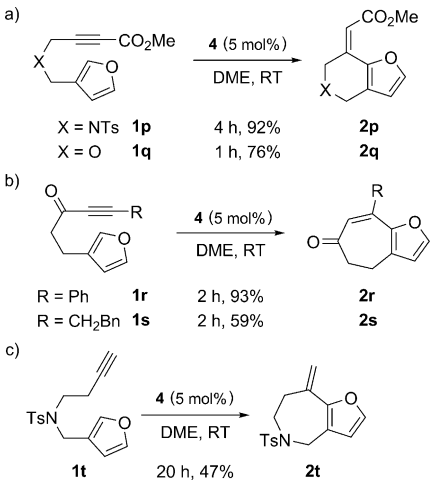



***Figure 2.*** DFT-calculated free energy surface of the two competing α-alkenylation pathways calculated at the B3LYP/SDD-6-31G(d) level of theory. P.T. = proton transfer.




***Scheme 3.*** Further exploration of the substrate scope. Bn = benzyl.

Furthermore, when electron-withdrawing groups were introduced at the proximal end instead of at the distal end of the triple bond, the 6-*exo* cyclization pathway would be disfavored owing to the polarization induced by the carbonyl linker. Pleasingly, the challenging seven-membered carbocycles could indeed be synthesized with this method. When the ynone substrates **1r** and **1s** were subjected to the standard reaction conditions (Scheme 3b), the corresponding seven-membered carbocycles **2r** and **2s** were formed in good yields.[25]

Finally, we tested the influence of the tether length. Only a substrate with an elongated tether that bears a terminal alkyne (**1t**) gave the fused cycloheptafuran **2t** through 7-*exo* cyclization (Scheme 3c). Substrates with internal alkynes did not react or gave hydration products (see the Supporting Information for details).

In summary, a novel and efficient gold-catalyzed *endo*-selective intramolecular α-alkenylation of furans has been developed to synthesize challenging seven-membered-ring-fused furans in good to excellent yields under very mild conditions. Six-membered-ring-fused furans can also be obtained through the α-alkenylation strategy through *exo*-selective cyclization for substrates with terminal alkynes. Preliminary DFT calculations have been carried out to understand the experimentally observed regioselectivity. Further applications of this reaction are currently developed.

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