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Gold(I)-Catalyzed Angle Strain Controlled Strategy to Furopyran Derivatives from Propargyl Vinyl Ethers: Insight into the Regioselectivity of Cycloisomerization

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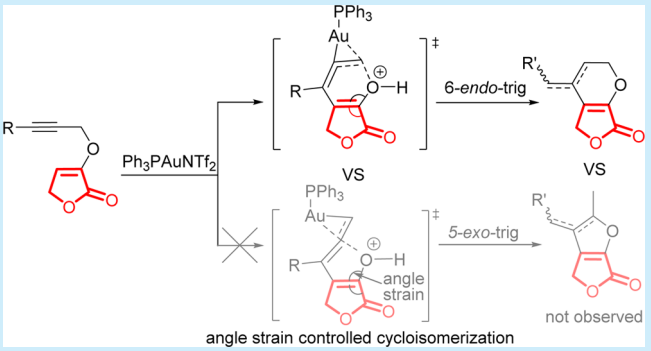
Supporting Information

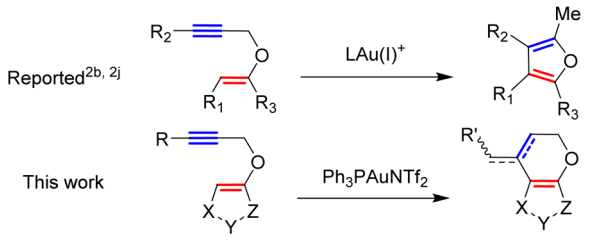
ABSTRACT: A unique strategy for the regiospecific synthesis of bicyclic furopyran derivatives has been developed via a gold(I)-catalyzed propargyl-Claisen rearrangement/6-*endo*-*trig* cyclization of propargyl vinyl ethers. The introduction of angle strain into the substrates significantly altered the reaction's regioselectivity. Insight into the regioselectivity of the cycloisomerization was obtained with density functional theory calculations.



Gold-catalyzed cycloisomerizations have been developed into important and integral transformations over the past decades,[1] which can afford unique carbocycles and heterocycles from simple acyclic precursors such as easily accessed enynes, among which propargyl vinyl ethers have been utilized to synthesize a wide range of products.[2] Mechanistically, a 6-*endo*-*dig* addition of the enol ether onto gold(I)−alkyne complex followed by Grob-type fragmentation to afford the *β*-allenic carbonyl intermediates (or its tautomeric enol forms) was widely accepted in the propargyl vinyl ether mediated rearrangement reactions (Scheme 1).[2a−c,e]

The chemo- and regioselectivities in the cycloisomerizations have been important issues. Various attempts have been conducted to regulate regioselectivity involving the modification of the substrates, reagents, catalysts, and solvents.[3] In most cases, the 5-*exo*-*dig* (*trig*) mode dominates the cyclizations compared with 6-*endo*-*dig* (*trig*),[4] which is mainly attributed to stereoelectronic factors and geometry of the cyclization transition states. Though the *exo* products have lower intrinsic barriers than the *endo* competitors from a stereoelectronic aspect, preferences for *exo*-*dig* (*trig*) closure can be overshadowed by additional factors, such as strain in one of the products, which can tip the balance in favor of the *endo* products.[5] The postulation "when the length and nature of linking chain enables the terminal atoms to achieve the required trajectories" for the bond formation suggested by Baldwin emphasized stereoelectronic factors.[6] The favorable trajectories for cyclizations indicated a maximized orbital overlap. However, intrinsic stereoelectronic preferences can be masked by thermodynamic factors that may exert an influence on the activation barrier.[5,7] These two factors are not always sufficient for dominating the selectivity.[8,9] Strain effects have been used to favor the formation of larger cycles previously in anionic and radical cyclizations,[9] and we were interested in expanding this concept to Au-catalyzed cycloisomerizations. We therefore hypothesized that the introduction of further angle strain into the vinyl ether fragment to increase the ring strain may exert an influence on the geometry of the transition states leading to an alternative regioselective cyclization.

Scheme 1. Angle-Strain-Controlled Distinct Regioselectivities of Gold-Catalyzed Cyclizations



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To test the hypothesis, we synthesized a propargyl γ-butyrolactone-2-enol ether and observed the cyclization mode of this strained substrate at the catalysis of gold(I) species. As expected, the regioselectivity of the cyclization was changed totally to yield a furopyran derivative exclusively (the conditions screening is described in the Supporting Information (SI)) (Scheme 1).

The exciting results encouraged us to examine the generality of the reaction with a series of synthetic substrates (Figure 1).[10]

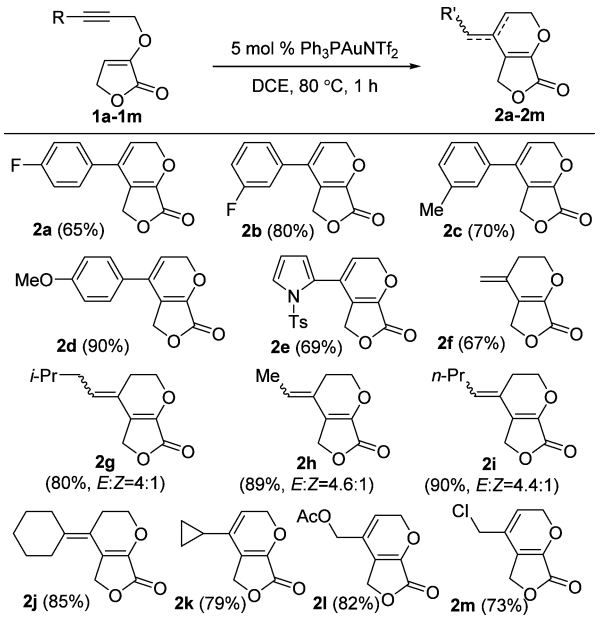


Figure 1. Scope of the alkyne substitutions. Reactions with **1c** and **1d** were run at rt for 5 min.

Aromatic and heteroaromatic substituted alkyne substrates were first investigated, and good yields were obtained (Figure 1, **2a**−**e**). The substrates with an alkyl-substituted alkyne gave the pyran with an unexpected 1,3-hydrogen migration after cyclization (Figure 1, **2f**). The detailed mechanism and computational study of this migration step are shown as Figure S2 in the SI. To prove the generality of the migration, the substrates with different alkyne alkyl substitutions were synthesized and examined under the standard conditions, and the corresponding hydrogen shift products were formed in excellent yields with relatively good diastereoselectivity (*E*/*Z* = 4:1) (Figure 1, **2g**−**i**). The substrate with cyclohexyl group gave a hydrogen shift product (Figure 1, **2j**), while the cyclopropyl-substituted alkyne substrate gave a normal pyran product exclusively with no hydrogen shift (Figure 1, **2k**). Electron-withdrawing groups such as acetoxyl and chloro groups were attached to α-methylene at the terminal alkyne position: nonmigrated pyrans were isolated as the only products in each case (Figure 1, **2l** and **2m**).

The functional group tolerances were further examined by utilizing cyclic fragments with similar angle strains. The propargyl β-tetronic acid ether substrates afforded the corresponding pyran products in satisfactory yields (Figure 2 entries **4a**−**c**). However, the geometry of the newly formed alkenes changed from an *E*/*Z* mixture into an exclusive *E* isomer (Figure 1, **2h** and **2i**; Figure 2 **4a** and **4b**). There was no hydrogen migration in propargyl γ-butyrolactone-2-enol ether substrate (Figure 1, **1m**); however, total migration occurred in

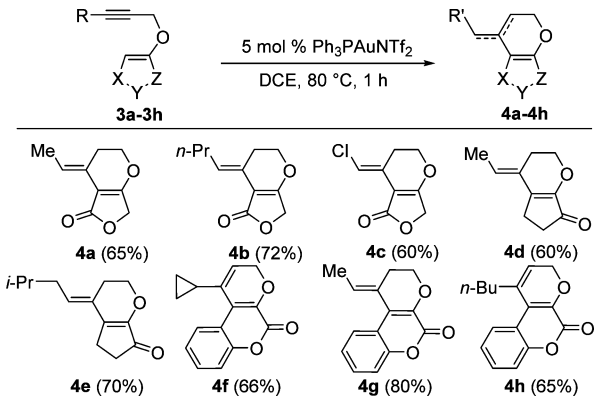
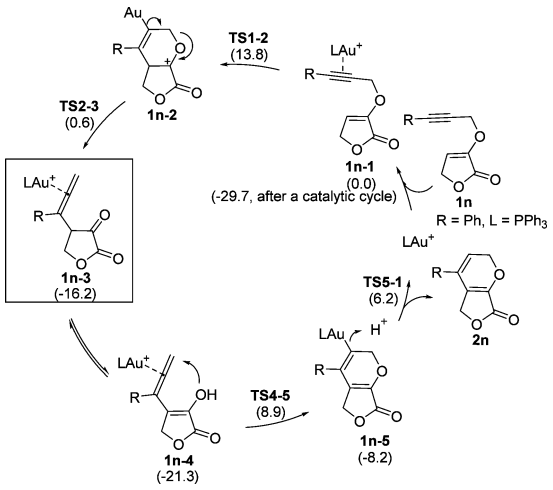


Figure 2. Scope of the cyclic vinyl moieties.

propargyl γ-butyrolactone-3-enol ether substrate (Figure 2, **3c**). The ketone substrates also afforded the pyrans with a single diastereoselectivity (Figure 2, **4d**,**e**). It is worth mentioning that the formation of migrated products in propargyl coumarin ethers substrates was highly substrate dependent (Figure 2, **4g**,**h**).

The mechanistic proposal for the formation of pyran outlined in Scheme 2 was supported by the previous research

Scheme 2. Proposed Mechanism of the Cyclizations[a]



[a]The values in parentheses are given in kcal/mol and represent the relative free energies calculated by using the M11 method in DCE.

on gold(I)-catalyzed furan formation and our experimental results.[2a−c,e] A *6-endo-dig* addition of the enol ether of **1n** onto gold(I)−alkyne complex **1n-1** results in the formation of intermediate **1n-2**, which collapses into the β-allenic ketone **1n-3** (the actual intermediate **1d-3** was confirmed by the ^{1}H NMR spectrum of the crude reaction mixture and also consistent with previous reports[11] which could be transformed into the product **2d** smoothly under the standard conditions; see the SI). Then a gold(I)-catalyzed keto−enol tautomerism, followed by *6-endo-dig* cyclization, finally delivers pyran **2n**.

In order to pursue an intrinsic explanation on the unusual regioselectivity of the reaction, a systematic study assisted by computational chemistry was performed. As shown in Scheme 2 (detailed free energy profiles were shown in Figure S1), density functional theory (DFT) method M11,[12] is employed to elucidate the mechanism of this reaction. In our DFT study,

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regioselectivity is controlled by the nucleophilc addition step from intermediate **1n-4** to **1n-5** shown in Scheme 2.

To gain insight into the selectivity, theoretical models for the nucleophilic cycloaddition step are listed in Table 1. The

Table 1. Reactivity and Regioselectivity for the Selected Intermediates[a]

entry	intermediate	transition state	$\Delta G^{\ddagger}(\Delta H^{\ddagger})$	bond angles
1	CP4	TS4-5	30.2 (17.8)	A_1 = 131.0°, A_2 = 109.6°, A_3 = 126.5°, A_4 = 110.5°
		TS4-7	32.2 (19.6)	A_5 = 114.8°, A_6 = 111.1°
2	CP4a	TS4a-5a	28.5 (18.3)	A_1 = 126.6°, A_2 = 109.6°, A_3 = 125.7°, A_4 = 111.9°
		TS4a-7a	31.4 (19.3)	A_5 = 114.1°, A_6 = 111.5°
3	CP4b	TS4b-5b	30.9 (18.3)	A_1 = 115.9°, A_2 = 129.6°, A_3 = 118.9°, A_4 = 127.9°
		TS4b-7b	26.5 (13.2)	A_5 = 111.0°, A_6 = 132.5°
4	CP4c	TS4c-5c	31.3 (22.3)	A_1 = 122.2°, A_2 = 127.5°, A_3 = 119.3°, A_4 = 131.1°
		TS4c-7c	20.7 (10.6)	A_5 = 114.2°, A_6 = 131.5°
5	CP4d′ / CP4d	TS4d-5d	33.9 (10.0)	A_1 = 131.9°, A_2 = 109.2°, A_3 = 128.9°, A_4 = 110.1°
		TS4d-7d	35.6 (10.4)	A_5 = 128.2°, A_6 = 110.3°

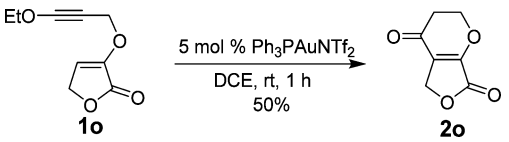
[a]The values of relative activation free energies and activation enthalpies (in parentheses) are given in kcal/mol.

relative free energies for transition states showed that the furopyran-type adducts will be the major products in the cyclic substrates with both electron-deficient and -rich allene moieties (entries 1 and 2), while on the contrary, the furofuran-type adducts will be the major products for the noncyclic substrates (entries 3 and 4). Moreover, an intermolecular reaction model between complex **CP4d** and **CP4d′** showed that the reactivities of terminal carbon and internal carbon in allene moiety are close (entry 5).

To further clarify the regioselectivity, key bond angles are listed in Table 1. For the noncyclic substrates as shown in entry 3, there are no obvious differences of bond angle change in cyclization between transition state **TS4b-5b** and **TS4b-7b** (7.9° between A_3 and A_5, 4.6° between A_4 and A_6). In entry 4, the changes of bond angles for intermediate **CP4c** are also similar to that of entry 3 in both transition states. However, in intermediate **CP4**, the bond angle A2 is 109.6°, which is 20.0° less than that in **CP4b** because of the strain of the furanone ring. When the nucleophilic addition takes place on internal carbon via transition state **TS4-7**, the bond angles of A5 and A6 are 114.8° and 111.1°, respectively. Geometry information indicates that furanone ring restricts the increasing of bond angle A6 and the decreasing of bond angle A5; therefore, the formation of the furofuran-type adduct is unfavorable. In another case, when the nucleophilic addition occurs on terminal carbon in the allene moiety via transition state **TS4-5**, the bond angles A3 and A4 are 126.5° and 110.5°, respectively. The less strain effect leads to a lower activation free energy via transition state **TS4-5**. Therefore, in our reported gold(I)-catalyzed formation of pyrans from propargyl vinyl ethers, the strain of furanone moiety leads to the formation of furopyran type product.

We explored the application of this strategy to the synthesis of isopatulin **2o**, an analogue of patulin with antimicrobial properties against some microorganisms. An expected tandem cyclization/deprotection followed by an enol−keto tautomerization occurred to give **2o** with a moderate yield when the synthesized substrate was subjected to the standard conditions (Scheme 3). This unique approach allowed a rapid assembly of isopatulin and its derivatives in a two-step sequence.[13]

Scheme 3. Gold(I)-Catalyzed Synthesis of Isopatulin



In conclusion, a gold(I)-catalyzed propargyl-Claisen rearrangement/6-*endo*-*trig* tandem cyclization strategy for furopyran derivatives has been developed. Notably, ring strain acts as an indispensable factor to alter the regioselectivity from 5-*exo*-*trig* to 6-*endo*-*trig*. The interplay of electronic and steric contributions to the transition states for 5-*exo*-*trig* and 6-*endo*-*trig* cyclizations of theoretical models was also analyzed by DFT calculation, which provided results consistent with the experimental findings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03641.

Experimental procedures, compound characterization data, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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