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# Gold-Catalyzed Intermolecular Reactions of Propiolic Acids with Alkenes: [4 + 2] Annulation and Enyne Cross Metathesis

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Supporting Information

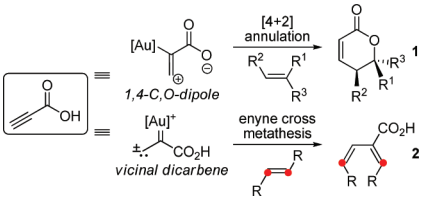
**ABSTRACT:** A gold-catalyzed intermolecular reaction of propiolic acids with alkenes led to a [4 + 2] annulation or enyne cross metathesis. The [4 + 2] annulation proceeds with net *cis*-addition with respect to alkenes and provides an expedient route to $\alpha,\beta$-unsaturated $\delta$-lactones, for which preliminary asymmetric reactions were also demonstrated. For 1,2-disubstituted alkenes, unprecedented enyne cross metathesis occurred to give 1,3-dienes in a completely stereospecific fashion. DFT calculations and experiments indicated that the cyclobutene derivatives are not viable intermediates and that the steric interactions during concerted $\sigma$-bond rearrangements are responsible for the observed unique stereospecificity.



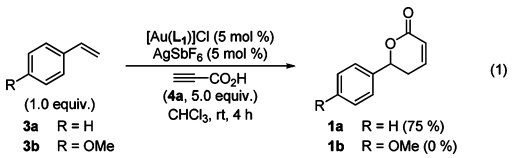
Electrophilic metal-catalyzed cyclization of 1,n-enynes has attracted considerable attention.[1] Despite its apparent merits in greatly expanding the scope of potential applications,[2] the intermolecular version of this process has been reported only scarcely, especially with gold catalysts.[3] The slow intermolecular reaction causes problems resulting from competing olefin isomerization and/or polymerization. Also, in the absence of a tether, it is difficult to control regio- and stereoselectivity.

To address this challenge, we projected using electronically polarized alkynes as reaction partners to facilitate the intermolecular reaction with selectivity control. While donor-substituted alkynes, such as ynol ethers[4] and ynamides,[5] have led to various novel reactions, acceptor-substituted alkynes have been far less studied.[6] Based on the precedents in the electrophilic metal-catalyzed intramolecular reactions of 1,n-enynes,[7] we envisioned that a propiolic acid, when catalyzed by a gold complex, would function as an equivalent of a 1,4-*C,O*-dipole or a vicinal dicarbene in the intermolecular reaction with alkenes (Scheme 1). The activation of an acetylene portion of a propiolic acid would generate a functional equivalent of a 1,4-*C,O*-dipole for [4 + 2] annulation with alkenes to provide $\alpha,\beta$-unsaturated $\delta$-lactones **1** that form the core of diverse biologically active natural products and pharmaceutical agents.[8,9] On the other hand, a vicinal dicarbene synthon could be exploited in the enyne cross metathesis that is unprecedented in the electrophilic metal-catalyzed intermolecular reactions. Herein, we report the discovery of these two new processes.

**Scheme 1. Propiolic Acid as a Functional Equivalent of 1,4-C,O-Dipole or Biscarbene**

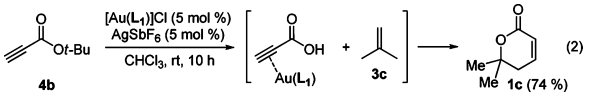



We commenced our study using propiolic acid (**4a**) and styrene derivatives as substrates. After extensive optimization,[10] we found that treating styrene **3a** with **4a** in the presence of a catalytic amount of Au($\mathbf{L_1}$)Cl and $AgSbF_6$ (5 mol % each) in chloroform ($\mathbf{L_1}$ = $t$Bu$_2$P($o$-biphenyl), JohnPhos) provided a lactone **1a** in a good isolated yield (75%, eq 1). However, under




otherwise identical conditions, *p*-MeO-styrene **3b** failed to provide the desired product **1b** and inspection of the crude NMR as well as GC-MS indicated a significant amount of polymers/oligomers formed from **3b**. Reversing the stoichiometry or slow addition of **3b** or propiolic acid did not improve the yield.

On the other hand, *tert*-butyl propiolate **4b** was probed as a surrogate of propiolic acid **4a** to prevent possible acid-catalyzed side reactions of sensitive alkenes.[11] Treatment of **4b** *in the absence of an olefin* with [Au($\mathbf{L_1}$)]$SbF_6$ (5 mol %, generated in situ) in a closed vessel gave **1c** in a surprisingly high 74% isolated yield (eq 2). Apparently, isobutene **3c** formed *in situ*

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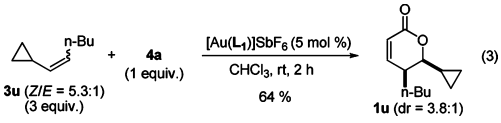
from a *tert*-butyl cation that was generated upon coordination of **4b** to the cationic $[Au(L_1)]^+$ complex and **3c** proved to be an excellent nucleophilic olefin partner.

Encouraged by these initial results, we next examined the scope of this [4 + 2] annulation employing various alkenes (5 equiv) with **4a** or **4b** (1 equiv). As expected, 1,1-disubstituted alkenes **3d**–**g** were found to be good substrates for the [4 + 2] annulation (entries 1–5). In the case of **3f**, the desired lactone **1f** was accompanied by the unexpected formation of **1k**, indicating isomerization of **3f** to **3k**, most probably caused by the acid **4a**. As expected, the formation of **1k** could be suppressed by using **4b** (entries 3–4). By incorporation of a silyl group that stabilizes the $\beta$-carbocation, even the monosubstituted alkene **3h** reacted with similar efficiency (entry 6). On the other hand, reactions of cyclic 1,2-disubstituted alkenes **3i** were sluggish, thereby requiring longer times for completion (entry 7). The reaction scope was further extended to trisubstituted alkenes without difficulty (entries 9–10). Importantly, the stereochemistry of major products in **1i** and **1j** indicated that the formation of C–O and C–C bonds occurred at the same face of the olefin.[12] To our delight, the current reaction could also be effected with 1,3-dienes and allenes as the reaction partners (entries 11–13). Notably, a natural product, goniothalamin (**1n**), could be synthesized in a single operation, with *O*-attack occurring at the more cation-stabilized site (i.e., cinnamyl cation) from diene **3n** (entry 12).

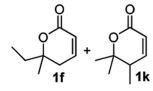
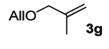
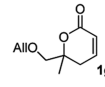
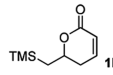
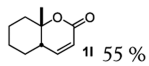
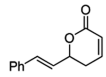
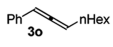
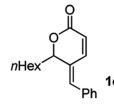
While the reactions with cyclopentene **3i** gave only [4 + 2] adducts in moderate yield, the larger homologous cycloalkenes **3p**–**q** gave unexpected enyne metathesis products **2pa**–**qa** in good isolated yields, respectively (entries 1–2, Table 2). Examination of reaction parameters (ligand, counteranion, and solvents) revealed that the optimal conditions for this metathesis pathway are essentially identical to those for [4 + 2] annulation.[10] Remarkably, while [4 + 2] annulation required an excess amount of either alkenes or alkynes for efficient cyclization, metathesis proceeds with as little as 1.5 equiv of alkenes with essentially identical yields.

Surprisingly, the enyne metathesis turned out to be highly stereospecific; for example *cis*-**3r** gave *E,E*-**2ra**, while *trans*-**3r** gave *E,Z*-**2ra**, exclusively (entries 3–4). This enyne metathesis also accommodates ethyl (**4c**) and allyl propiolate (**4d**) as well as sulfonyl acetylene (**4e**) (entries 5–9), and the stereospecificity remained identical. The reaction with unsymmetrical **3s** showed that there is only mediocre regioselectivity in this metathesis (entry 10). The reactions with *E*/*Z* mixtures of olefins revealed that *Z*-olefin reacted significantly faster than *E*-olefin (entries 10–11): while the reaction with **3s** (*Z*/*E* = 3.8:1) gave 14:1 (*E,E*/*E,Z*) of **2sc** (and **2sc'**), that with **3t** (*E*/*Z* = 4.8:1) gave only a 1.5:1 (*E,Z*/*E,E*-**2tc**) ratio. The reaction of **3u** with **4a** gave only [4 + 2] adduct **1u**, further indicating that the cation-stabilizing substituent (cyclopropyl) favored the [4 + 2] reaction manifold (eq 3).[10]




From the reaction profile in Tables 1 and 2, the following mechanistic model was deduced (Scheme 2). Both [4 + 2] annulation and enyne metathesis seem to proceed via initial formation of a cyclopropyl carbenoid intermediate **A**/**A'**, where the Au-moiety with a bulky JohnPhos ligand is positioned away

**Table 1. [4 + 2] Annulations with Alkenes**[a]

| entry | alkene | time | product[b] |
|---|---|---|---|
| 1 |  | 4 h |  85 %[d] |
| 2 |  | 1 h |  67 %[d] |
| 3 |  | 2.5 h |  63 % (**1f**:**1k** = 2.5:1)[c] |
| 4 | 3f | 2.5 h | 60 % (**1f**:**1k** = 7:1)[d] |
| 5 |  | 4 h |  70 %[c] |
| 6 |  | 2 h |  58 %[d,e] |
| 7 |  | 12 h |  56 %[c,f] |
| 8 |  | 2 h |  54 %[c,f] |
| 9 |  | 4 h |  57 %[c] |
| 10 |  | 2 h |  55 % (dr 7.7:1)[c,f] |
| 11 |  | 2 h |  57 %[d] |
| 12 |  | 4 h |  50 %[c] |
| 13 |  | 18 h |  73 %[f,g] |

[a]The reactions were conducted at rt in the presence of $Au(L_1)Cl$ (5 mol %) and $AgSbF_6$ (5 mol %) in $CHCl_3$. [b]Isolated yield after chromatography. [c]**4a** (1 equiv) and alkenes **3** (5 equiv). [d]**4b** (1 equiv) and alkenes **3** (5 equiv) in an open vessel. [e]10 equiv of **3h** were used. [f]The stereochemistry of the major isomer was determined by NOE experiments. [g]Allene **3o** (1 equiv) and **4a** (5 equiv).

from the cyclopropyl group and the substituent(s) of the cyclopropane ring is oriented away from the carboxylic acid. Overall *cis*-addition of propiolic acid with respect to the prochiral face of olefins strongly suggests that the cyclopropane ring opening to form the homoallyl cation **A'** immediately precedes the cyclization,[10,12] so that the subsequent C–O bond formation occurs faster than C–C rotation of homoallyl carbocation **A'**, except when the cation is sufficiently stabilized (i.e., allylic cation as in the reaction with **3o**). To support the intermediacy of **A**/**A'**, we prepared *N,N*-diallylpropiolamide **5** to trap this intermediate (eq 4). As expected, we obtained **6** in 36% yield, lending further support for the intermediacy of **A**/**A'**.[13]

According to the model in Scheme 2, it is challenging to differentiate prochiral faces of an olefin with a chiral ligand


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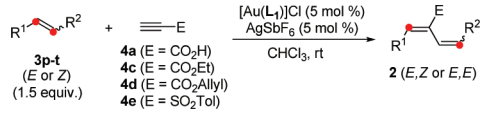
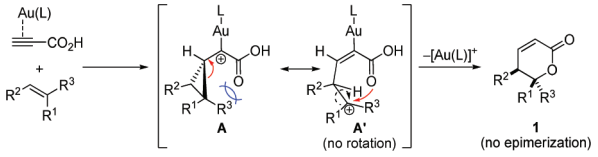
**Table 2. Enyne Cross Metathesis with Alkenes**

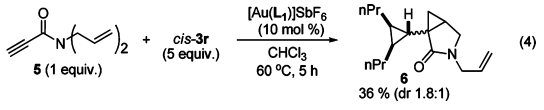



| entry | alkene | alkyne | time | product[a] |
|---|---|---|---|---|
| 1 | *cis*-**3p** $R^1,R^2 = (CH_2)_5$ | **4a** | 8 h | **2pa** 71 % |
| 2 | *cis*-**3q** $R^1,R^2 = (CH_2)_6$ | **4a** | 6 h | **2qa** 77 % |
| 3 | *cis*-**3r** $R^1,R^2$ = *n*Pr | **4a** | 2.5 h | (*E,E*)-**2ra** 84 %[b] |
| 4 | *trans*-**3r** $R^1,R^2$ = *n*Pr | **4a** | 2.5 h | (*E,Z*)-**2ra** 86 %[b] |
| 5 | *cis*-**3q** | **4c** | 3 h[c] | **2qc**, 70 % |
| 6 | *trans*-**3r** | **4d** | 1 h[c] | (*E,Z*)-**2rd**, 87 % |
| 7 | *cis*-**3q** | **4e** | 3 h | **2qe**, 90 % |
| 8 | *cis*-**3r** | **4c** | 3 h[c] | (*E,E*)-**2rc**, 67 % |
| 9 | *trans*-**3r** | **4c** | 3 h[c] | (*E,Z*)-**2rc**, 73 % |
| 10 | **3s** $R^1$ = Bn, $R^2$=*n*Bu (*Z*/*E* = 3.8:1) | **4c** | 5 h[f] | *E,E*-**2sc** : *E,E*-**2sc'**[d] 63 % (rs = 1.4:1)[e] |
| 11 | **3t** $R^1,R^2$ = Bn (*E*/*Z* = 4.8:1) | **4c** | 3 h[c,f] | **2tc**, 64 % (*E,Z*/*E,E* = 1.5:1) |

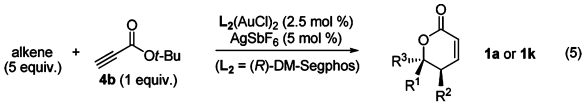
[a]Isolated yield after chromatography; a single diastereomer unless otherwise noted. [b]The stereochemistry was determined by NOE experiments after reduction of the acid. [c]The reactions at 60 °C. [d]The *E,E*/*E,Z* ratios of **2sc** ($R^1$ = Bn, $R^2$ = *n*Bu) and **2sc'** ($R^1$ = *n*Bu, $R^2$ = Bn) were both 14:1. [e]Regioselectivity (rs). [f]3 equiv of **3s** or **3t**.

**Scheme 2. Proposed Reaction Pathway for the Formation of *α,β*-Unsaturated *δ*-Lactones**



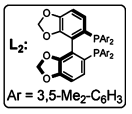




oriented away from the cyclopropyl ring in **A**. With (*R*)-DM-SEGPHOS ($L_2$) as a chiral ligand and **4b** as an alkyne component, we found that trisubstituted olefin **3k** gave a much higher enantioselectivity than styrene **3a**, presumably because of a maximized steric interaction of the olefin substituent ($R^3$ = Me vs H) with the carboxylic ester (or acid) moiety (eq 5). The % ee was further increased to 65% ee in slower reacting 1,2-




| alkene | condition | yield (ee) |
|---|---|---|
| **3a** ($R^1$ = Ph, $R^2/R^3$ = H) | rt, 4 h in $CHCl_3$ | (*S*)-**1a** 62 % (21 % ee) |
| **3k** ($R^1/R^2/R^3$ = Me) | rt, 4 h in $CHCl_3$ | **1k**[a] 51 % (43 % ee) |
| **3k** ($R^1/R^2/R^3$ = Me) | rt, 24 h in 1,2-DCE | **1k**[a] 66 % (65 % ee) |

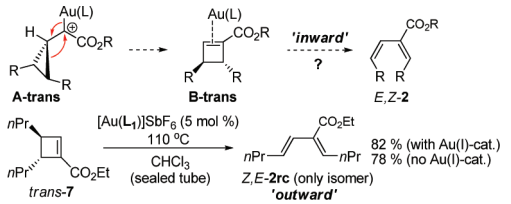
[a] Absolute sense of chirality was not determined.




dichloroethane solvent. Although the observed enantioselectivity is not sufficiently high at the present stage, *this preliminary result represents the first example of an asymmetric intermolecular reaction between alkenes and alkynes via direct activation of alkynes by gold complexes*, to the best of knowledge.[14]

For the enyne cross metathesis, we first considered a possibility that a common intermediate **A-trans** undergoes *σ*-bond rearrangements to form **B-trans**, followed by Au(I)-catalyzed ring opening of cyclobutenes (Scheme 3). Thermal electrocyclic ring opening of 3,4-*trans*-dialkyl cyclobutenes

**Scheme 3. Possible Intermediacy of Cyclobutene: Disproved**




takes place through outward conrotatory motion of alkyl substituents due to the torquoelectronic effect,[15] while the current Au(I)-catalyzed enyne metathesis proceeds through a disfavored *inward* conrotation. Independently prepared *trans*-**7**,[16] in the presence or absence of a Au(I)-catalyst, reacted only at elevated temperatures and gave *Z,E*-**2rc** exclusively (outward), contrary to the current results (entry 9, Table 2), suggesting a different reaction pathway could happen in the present system.

To understand how this unique stereoselectivity occurs, we conducted DFT calculations to study the reaction pathway leading to the enyne metathesis product from *E*-alkene.[10] Our computational studies suggested that once cyclopropyl Au-carbenoid **A-trans** is generated, it will not give intermediate **B-trans**. Instead, the most favored pathway starts from the transformation of **A-trans** to **C-t** via the *σ*-bond rearrangement transition state **TS1-t**, in which C2−C3 (bond t) and C3−C4 *σ*-bonds are breaking and the C1−C3 *σ*-bond is forming (Figure 1).[10] Then **C-t** undergoes reorganization of the coordination of Au, giving complex ***E,Z*-D**. This pathway requires an overall activation free energy of 8.0 kcal/mol in $CHCl_3$. However, another *σ*-bond rearrangement transition state **TS1-c** with the cleavage of *σ*-bond c leading to ***Z,E*-D** is 5.7 kcal/mol higher than **TS1-t** (13.7 versus 8.0 kcal/mol, Figure 1). This suggests that the *E,Z*-diene will be generated exclusively, which is in good agreement with the experiment (Table 2, entry 4). Analyzing the structures of **TS1-t** and **TS1-c**,[10] we found that the cleavage of *σ*-bond c in **A-trans** will result in obvious steric repulsion between the migrating methyl group and the carboxylic acid in **TS1-c** (Figure 1). Therefore, the stereoselectivity of the gold-catalyzed enyne metathesis is mainly controlled by the steric effect. Other computational support for this pathway rather than the involvement of Au(I)-cyclobutene complex **B-trans** is that **B-trans** favors giving ***Z,E*-D** but not the experimentally observed ***E,Z*-D**, agreeing with the torquoselectivity (Figure 1).[15a]

In conclusion, we report herein two new reactions of acceptor-substituted alkynes with alkenes catalyzed by a Au(I)-complex. The newly discovered [4 + 2] annulation allows an expedient access to *α,β*-unsaturated *δ*-lactones with a diverse array of olefin substrates, the efficiency of which is epitomized by a one-step synthesis of goniothalamin (**1n**). We have also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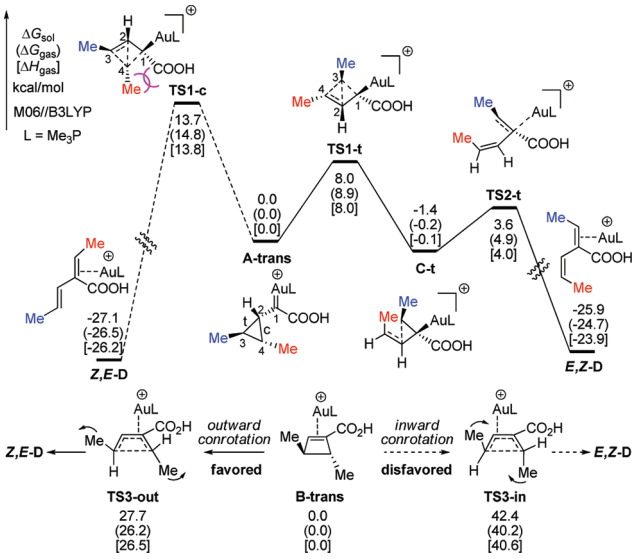


**Figure 1.** DFT-calculated free energy surfaces for enyne metathesis and cyclobutene ring-opening pathways.[10]

discovered a stereospecific enyne cross metathesis leading to stereodefined 1,3-dienes. Considering unmet challenges in the Grubbs catalyst based enyne cross metathesis (e.g., limited scope and geometry control), the current process holds great potential as an atom-economical C−C bond formation.[2]

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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