Enantioselective Synthesis of Cyclobutenes by Intermolecular [2+2] Cycloaddition with Non-C$_2$ Symmetric Digold Catalysts

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Supporting Information

ABSTRACT: The enantioselective intermolecular gold(I)-catalyzed [2+2] cycloaddition of terminal alkynes and alkenes has been achieved using non-C$_2$ chiral Josiphos digold(I) complexes as catalysts, by the formation of the monocaticionic complex. This new approach has been applied to the enantioselective total synthesis of rumphellaone A.

Gold(I) complexes are the most powerful and selective catalysts for the activation of alkenes in complex molecular settings. Despite the success of gold(I) in homogeneous catalysis, highly enantioselective reactions of alkenes are still relatively scarce, particularly in the context of intermolecular transformations. The linear geometry of gold(I) dicoordinated complexes poses a major limitation for the development of asymmetric gold(I) catalysis because it locates the chiral ligand very far away from the reaction center, where the addition takes place through an outer-sphere mechanism (Scheme 1).

Scheme 1. General Scheme and Previous Work

Atropoisomeric bidentate phosphines and phosphoramidites have been applied as ligands in asymmetric gold(I)-catalyzed reactions, whereas the use of chiral counterions has allowed the transfer of the chiral information via tight ion pairs in allene cyclizations. The difficulty increases when linear alkynes are used as substrates in intermolecular reactions with alkenes. The problem of achieving stereocontrol in this process can be considered as a special case of the more general class of similarly challenging enantioselective electrophilic additions to alkenes, where the electrophile is generated in situ by coordination of the alkyne to the chiral gold(I) complex.

The gold(I)-catalyzed reaction of terminal alkynes 1 with alkenes 2 leads to cyclobutenes 3 by a [2+2] cycloaddition (Scheme 1), which are valuable synths for the preparation of functionalized cyclobutenes, present in a variety of natural products and pharmaceuticals.

Enantioselective metal-catalyzed synthesis of cyclobutenes by [2+2] cycloaddition has only been reported with ynamides, or strained alkenes. Herein, we report the first general enantioselective synthesis of cyclobutenes by intermolecular [2+2] cycloaddition using chiral non-C$_2$ symmetric Josiphos digold(I) catalysts. To demonstrate its potential, we have applied this method in a concise asymmetric synthesis of the natural product rumphellaone A.

We screened ca. 90 chiral ligands for the synthesis of cyclobutene 3a using high-throughput methods. Although the vast majority of chiral ligands led to 3a with low enantioselectivities, the breakthrough was achieved using the Josiphos ligands family (Table 1). Cyclobutene 3a was isolated in 66% yield and 84:16 er (Table 1, entry 1). Further optimization with complex (S,R$_P$)-B led to extensive oligomerization of the alkene 2a (Table 1, entry 6). Further optimization with complex (S,R$_P$)-B showed that chlorinated solvents were superior both in terms of enantioselectivity and conversion. As we have found before, NaBAR$_4$ was the best counterion. Using chlorobenzene as solvent, 2.5 mol % of NaBAR$_4$ as chloride scavenger and performing the reaction at 0 °C led to 3a in 63% yield and 88:12 er (Table 1, entry 11). By lowering the temperature to −20 °C, the enantioselectivity reached 90:10 er (Table 1, entry 12). When the reaction was carried out using 2.5 mol % of the silver(I) salt Ag[Al(O(CF$_3$)$_3$)$_4$] to ensure the formation of a monocationic species, cyclobutene 3a was obtained in 65% and 84:16 er. However, no reaction was observed by abstracting both chlorides from (S,R$_P$)-B with 5 mol % of silver(I) salt. Similarly, monogold complex (S,R$_P$)-G bearing the same ligand as (S,R$_P$)-B, but with only the metal center coordinated to the trialkylphosphine, led to traces of racemic 3a.

The gold(I)-catalyzed cycloaddition of terminal alkyne 1a–i with 1,1-disubstituted alkenes led to cyclobutenes 3a–ab in moderate to excellent yields and enantioselectivities up to 94:6 er.

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with catalyst (S,R₁)-B (Table 2). This is significant, as only a few examples of asymmetric electrocyclic additions to 1,1-disubstituted alkenes have been achieved before. Isolated yield. *er determined by UPC2. **Oligomerization of 2a. ***NaBAr₄ (5 mol %). ****NaBAr₄ (10 mol %). $Slow addition of 2a.

Table 2. Synthesis of Cyclobutenes 3a–ah Using 1,1-Disubstituted Alkenes

| Entry | Complex | Solvent | t (°C) | Yield (%) | er |
|-------|---------|---------|--------|-----------|----|
| 1     | (S,R₁)-A | (CH₂Cl₂)| 25     | 13        | 78:22 |
| 2     | (S,R₁)-B | (CH₂Cl₂)| 25     | 66        | 84:16 |
| 3     | (R,S₂)-C | (CH₂Cl₂)| 25     | 10        | 18:82 |
| 4     | (R,S₂)-D | (CH₂Cl₂)| 25     | 10        | 20:80 |
| 5     | (R,S₂)-E | (CH₂Cl₂)| 25     | 9         | 18:82 |
| 6     | (R,S₂)-F | (CH₂Cl₂)| 25     | 0         | 0     |
| 7     | (S,R₁)-B | C₆H₅Cl | 25     | 76        | 84:16 |
| 8     | (S,R₁)-B | C₆H₅Cl | 25     | 78        | 84:14 |
| 9     | (S,R₁)-B | C₆H₅Cl | 25     | 40        | 85:15 |
| 10    | (S,R₁)-B | C₆H₅Cl | 0      | 55        | 88:12 |
| 11    | (S,R₁)-B | C₆H₅Cl | 0      | 63        | 88:12 |
| 12    | (S,R₁)-B | C₆H₅Cl | 0      | 70        | 90:10 |

“2a/1a = 2:1 (1a = 0.1 mmol). Isolated yield. *er determined by UPC2. **Oligomerization of 2a. ***NaBAr₄ (5 mol %). ****NaBAr₄ (10 mol %). $Slow addition of 2a.

To demonstrate the utility of the asymmetric cyclobutene synthesis, we developed a second-generation synthesis of rumphellaone A (4) (Scheme 3), following our first diastereoselective total synthesis, which was achieved in 12 steps by a gold(I)-catalyzed [2+2] macrocyclization of a 1,10-enzyme. The key intermolecular [2+2] cycloaddition of 1a with trisubstituted alke 2o in the presence of catalyst (R,S₂)-F furnished cyclobutene 3aq in 70% yield and 91:1 er. Cyclobutene 3aq was then converted into intermediate 7 following our previously described conditions, which allowed completing a formal synthesis of rumphellaone A (4) in 9 steps. This synthesis also allows establishing the S-configuration for cyclobutene 3aq. Those of 3ai–ap were assigned as 5 by analogy.

In the range of applied concentrations, the [2+2] cycloaddition reaction exhibited first-order kinetic dependence on

Table 1. Optimization of the Enantioselective Cycloaddition of 1a with 2a to Form 3a

| Entry | Complex | Solvent | t (°C) | Yield (%) | er |
|-------|---------|---------|--------|-----------|----|
| 1     | (S,R₁)-A | (CH₂Cl₂)| 25     | 13        | 78:22 |
| 2     | (S,R₁)-B | (CH₂Cl₂)| 25     | 66        | 84:16 |
| 3     | (R,S₂)-C | (CH₂Cl₂)| 25     | 10        | 18:82 |
| 4     | (R,S₂)-D | (CH₂Cl₂)| 25     | 10        | 20:80 |
| 5     | (R,S₂)-E | (CH₂Cl₂)| 25     | 9         | 18:82 |
| 6     | (R,S₂)-F | (CH₂Cl₂)| 25     | 0         | 0     |
| 7     | (S,R₁)-B | C₆H₅Cl | 25     | 76        | 84:16 |
| 8     | (S,R₁)-B | C₆H₅Cl | 25     | 78        | 84:14 |
| 9     | (S,R₁)-B | C₆H₅Cl | 25     | 40        | 85:15 |
| 10    | (S,R₁)-B | C₆H₅Cl | 0      | 55        | 88:12 |
| 11    | (S,R₁)-B | C₆H₅Cl | 0      | 63        | 88:12 |
| 12    | (S,R₁)-B | C₆H₅Cl | 0      | 70        | 90:10 |

“2a/1a = 2:1 (1a = 0.1 mmol). Isolated yield. *er determined by UPC2. **Oligomerization of 2a. ***NaBAr₄ (5 mol %). ****NaBAr₄ (10 mol %). $Slow addition of 2a.

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Scheme 3. Synthesis of Rumphellaone A

![Scheme 3: Synthesis of Rumphellaone A](image)

Each reactant showed a first-order dependence on the catalyst concentration when complex \((R,S)\)-B and NaBArF were mixed in a 1:1 ratio. A Hammett plot for a series of para-substituted \(\alpha\)-methylstyrenes \(2a–g\) showed linear correlations with \(\sigma^+\) constants for two different sets within the series, one for \(R = Me, iPr, tBu\) and cyclopropyl \((\rho = +7.05, R^2 = 0.99)\) and the other one for \(R = F, H, Cl\) and \(Br\) \((\rho = -2.32, R^2 = 0.97)\) (Figure 1).

The abrupt difference in the \(\rho\) values is indicative of a change in the catalytic turnover-limiting step. The observation of a highly positive \(\rho\) value for \(2e–g\) in an alkene electrophilic addition is seemingly puzzling, although it can be explained considering that in these cases the turnover limiting step is the ligand exchange between \([\text{LAu}(p^-\text{alkyne})]^{+}\) and the alkylene to form \([\text{LAu}(\eta^2\text{-alkyne})]^{+}\) and free alkylene, which experiences a decrease in positive charge. Indeed, we have shown that the associative ligand exchange is the slowest step in the \([2+2]\) cycloaddition reaction with mononuclear gold(I) complexes. For substrates \(2a–d\), the formation of \([\text{LAu}(p^-\text{alkyne})]^{+}\) is less favored, and therefore the observed negative \(\rho\) value is a result of the buildup of positive charge at the most substituted carbon of the alkylene in a turnover-limiting Markovnikov-type addition of electrophilic \([\text{LAu}(p^-\text{-alkyne})]^{+}\) complex.

Aurophilic interactions have been shown to be important in other ferrocenyl diphosphino gold(I) complexes. However, in the solid state of \((S,R)\)-B (Figure 2a) and related complexes, the two gold(I) centers are anti-oriented with respect to each other and no aurophilic interactions were observed. DFT calculations provide a model to explain the asymmetric induction in the key electrophilic addition of \([\text{LAu}(p^-\text{-alkyne})]^{+}\) to the alkylene leading to \((R)\)-3a when complex \((S,R)\)-B is used as the precatalyst (Figure 2b). The calculated energy difference between the lowest transition states that lead to \((S)\) and \((R)\)-3a \(\Delta G^\ddagger S,R = 0.7–1.1\) kcal·mol\(^{-1}\) (depending on the method) is in good agreement with experimentally derived value of \(\Delta G^\ddagger S,R \approx 1\) kcal·mol\(^{-1}\). Apart from the combination of stabilizing \(\pi\)-stacking and unfavorable steric effects between the approaching alkylene and the naphthyl rings of the ligand, we identified a strong C–H–AuCl repulsion between the (naphthyl)\(P–AuCl and the methylene hydrogen atom in the \(\alpha\)-position to the Cp-ring of the ferrocenyl moiety, which raises the energy of the TS\(_{S}\) transition state vs TS\(_{R}\). Calculations of the corresponding transition states without the second AuCl on (naphthyl)\(P resulted in the complete loss of stereoselectivity, in agreement with the experimental data using complex \((S,R)\)-G.

In summary, we have developed a broad scope enantioselective synthesis of cyclobutenes by intermolecular \([2+2]\) cycloaddition of alkynes with alkenes using Josiphos digold(I) catalysts. This reaction allowed us to streamline the enantioselective synthesis of rumphellaone A, which was achieved in only 9 steps. Our studies indicate that only one of the gold(I) centers is directly involved in the activation of the alkylene, although the second one is required to induce the enantioselectivity. Our work also reveals that both ligand exchange and electrophilic addition can be turnover-limiting steps in this catalytic cycloaddition. Further chiral ligand development based on the proposed stereochemical model is underway.

**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07651.

Additional details, experimental procedures and characterization data for compounds (PDF)

Crystallographic data for C\(_{46}\)H\(_{68}\)Au\(_2\)Cl\(_4\)Fe\(_2\)P\(_2\) (CIF)

Crystallographic data for C\(_{40,40}\)H\(_{44,80}\)Au\(_{1,10}\)Cl\(_{1,90}\)Fe\(_2\)P\(_2\) (CIF)

Crystallographic data for C\(_{48,90}\)H\(_{48}\)Au\(_2\)Cl\(_4\)Fe\(_2\)P\(_2\) (CIF)

Crystallographic data for C\(_{17}\)H\(_{31}\)Br (CIF)

Crystallographic data for C\(_{25}\)H\(_{33}\) (CIF)
Crystallographic data for C$_8$H$_{12}$S (CIF).

Crystallographic data for C$_{23}$H$_{32}$F$_2$ (CIF).

Crystallographic data for C$_{20}$H$_{42}$ (CIF).

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**Notes**

The authors declare no competing financial interest.

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