

Enantioselective Synthesis of Cyclobutenes by Intermolecular [2+2] Cycloaddition with Non- C_2 Symmetric Digold Catalysts

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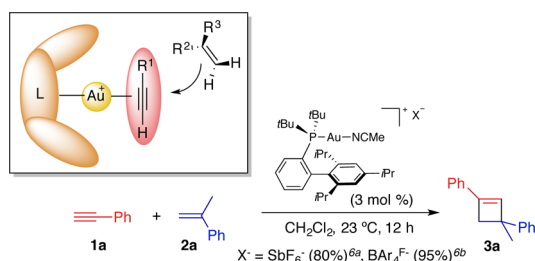
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S Supporting Information

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 monocationic complex. This new approach has been applied to the enantioselective total synthesis of rumpbellaone A.

Gold(I) complexes are the most powerful and selective catalysts for the activation of alkynes in complex molecular settings.¹ Despite the success of gold(I) in homogeneous catalysis, highly enantioselective reactions of alkynes are still relatively scarce,² particularly in the context of intermolecular transformations.³ 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



Atropisomeric bidentate phosphines and phosphoramidites have been applied as ligands in asymmetric gold(I)-catalyzed reactions,² whereas the use of chiral counterions has allowed the transfer of the chiral information via tight ion pairs in allene cyclizations.⁴ 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,⁵ 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),⁶ which are valuable synthons for the preparation of functionalized cyclobutenes,^{7,8} present in a variety of natural products⁹ and pharmaceuticals.¹⁰

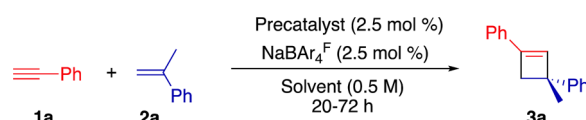
Enantioselective metal-catalyzed synthesis of cyclobutenes by [2+2] cycloaddition has only been reported with ynamides,¹¹ thioacetylenes,¹² or strained alkenes.^{9d,13} Herein, we report the first general enantioselective synthesis of cyclobutenes by intermolecular [2+2] cycloaddition using chiral non- C_2 symmetrical Josiphos digold(I) catalysts.^{14,15} To demonstrate its potential, we have applied this method in a concise asymmetric synthesis of the natural product rumpbellaone 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).¹⁶ Cyclobutene **3a** was isolated in low yields with precatalysts (S,R_p)-A, (R,S_p)-C, (R,S_p)-D and (R,S_p)-E (Table 1, entries 1 and 3–5), whereas complex (S,R_p)-B led to **3a** in 66% yield and 84:16 *er* (Table 1, entry 2). Complex (S,R_p)-F 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.¹⁶ As we have found before,^{6b,c} BAR_4F^- was the best counterion.¹⁶ Using chlorobenzene as solvent, 2.5 mol % of $NaBAR_4F$ 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.¹⁶ 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**.¹⁶

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

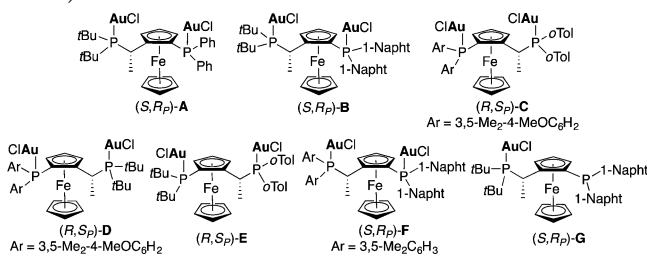
Received: July 21, 2017

Published: September 19, 2017

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


entry	complex	solvent	<i>t</i> (°C)	yield (%) ^b	<i>er</i> ^c
1	(<i>S,R_p</i>)-A	(CH ₂) ₂ Cl ₂	25	13	78:22
2	(<i>S,R_p</i>)-B	(CH ₂) ₂ Cl ₂	25	66	84:16
3	(<i>R,S_p</i>)-C	(CH ₂) ₂ Cl ₂	25	10	18:82
4	(<i>R,S_p</i>)-D	(CH ₂) ₂ Cl ₂	25	10	20:80
5	(<i>R,S_p</i>)-E	(CH ₂) ₂ Cl ₂	25	9	18:82
6	(<i>S,R_p</i>)-F	(CH ₂) ₂ Cl ₂	25	0 ^d	
7	(<i>S,R_p</i>)-B	C ₆ H ₅ Cl	25	76	84:16
8 ^e	(<i>S,R_p</i>)-B	C ₆ H ₅ Cl	25	78	86:14
9 ^f	(<i>S,R_p</i>)-B	C ₆ H ₅ Cl	25	40	85:15
10	(<i>S,R_p</i>)-B	(CH ₂) ₂ Cl ₂	0	55	88:12
11	(<i>S,R_p</i>)-B	C ₆ H ₅ Cl	0	63	88:12
12 ^g	(<i>S,R_p</i>)-B	C ₆ H ₅ Cl	-20	70	90:10

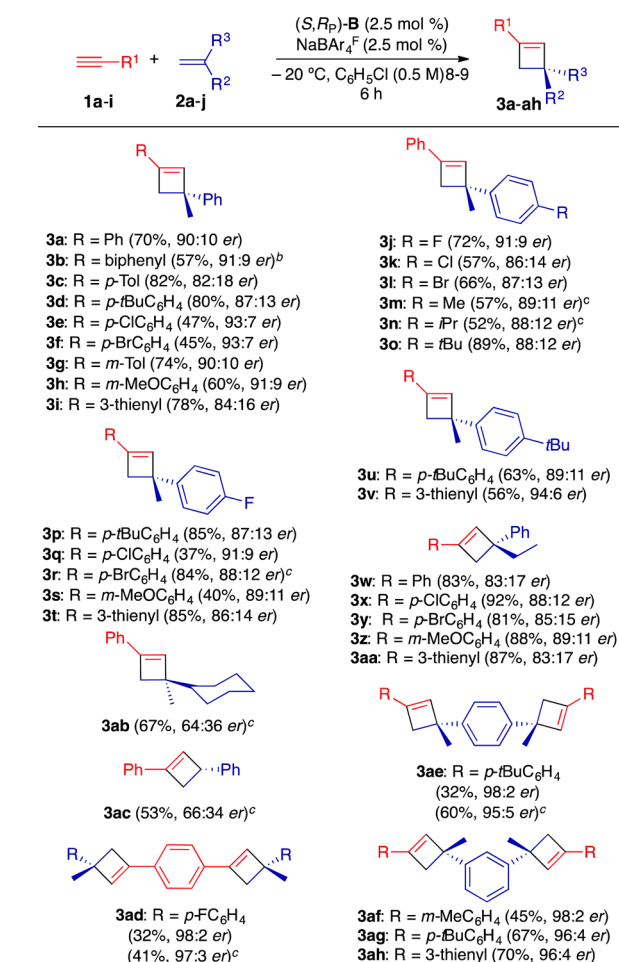
^a2a/1a = 2:1 (1a = 0.1 mmol). ^bIsolated yield. ^c*er* determined by UPC2. ^dOligomerization of 2a. ^eNaBAR₄F (5 mol %). ^fNaBAR₄F (10 mol %). ^gSlow addition of 2a.



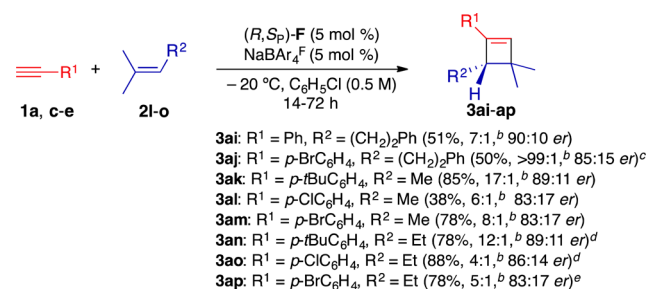
with catalyst (*S,R_p*)-B (Table 2). This is significant, as only a few examples of asymmetric electrophilic additions to 1,1-disubstituted alkenes have been achieved before.^{5f} The reaction proceeded satisfactorily with aryl alkynes bearing electron rich substituents in *para* and *meta* position. 3-Ethynylthiophene also led to the corresponding cyclobutenes **3i**, **3t**, **3v** and **3aa**. Good enantioselectivities were obtained with α -alkyl styrenes. However, 1,1-dialkyl substituted alkenes or simple styrene resulted in a significant loss of enantioselectivity, as shown in the case of **3ab** and **3ac**. The absolute configuration of cyclobutenes **3f** and **3v** was determined to be *R* by X-ray diffraction. Biscyclobutenes **3ad**–**ah** were also obtained with high enantioselectivities from dialkynes or dialkenes as reaction counterparts by 2-fold cycloaddition. The corresponding meso derivatives were obtained as minor products in these reactions (20–30% yields).

The cycloaddition of trisubstituted alkenes with terminal alkynes was carried out with catalyst (*R,S_p*)-F to give 1,3,3,4-tetrasubstituted cyclobutenes **3ai**–**ap** with moderate to excellent regioselectivities (Scheme 2).¹⁷ The enantioselectivities were on the same range to those obtained with 1,1-disubstituted alkenes using catalyst (*S,R_p*)-B.

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-enyne.¹⁸ The key intermolecular [2+2] cycloaddition of **1a** with trisubstituted alkene **2o** in the presence of catalyst (*R,S_p*)-F furnished cyclobutene **3aq** in 70% yield and 91:1 *er*. Cyclobutene **3aq**

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

^a1a–i (0.3 mmol scale). Isolated yields average of two runs. *er* determined by UPC2. ^b1c (0.1 mmol scale). ^c25 °C. X-ray crystal structures were determined for **3f**, **3u**, **3v**, **3ad** and **3ae**. The absolute configuration of **3f** and **3v** was also determined by X-ray diffraction.

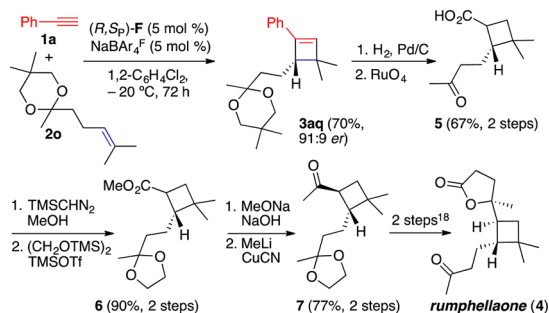
Scheme 2. Synthesis of Cyclobutenes **3ai**–**ap** from Trisubstituted Alkenes^a

^a1a–i (0.3 mmol scale). *er* determined by UPC2. ^bRegioisomeric ratio. ^c1f (0.1 mmol scale). ^d0 °C. ^e25 °C.

was then converted into intermediate **7** following our previously described conditions,¹⁸ 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 *S* by analogy.

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

Scheme 3. Synthesis of Rumphellaone A



each reactant.¹⁹ The reaction also showed a first-order dependence on the catalyst concentration when complex (R,S)-B and NaBAR₄F were mixed in a 1:1 ratio. A Hammett plot for a series of *para*-substituted α -methylstyrenes **2a–g,p** showed linear correlations with σ^+ constants for two different sets within the series, one for R = Me, *i*Pr, *t*Bu 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).

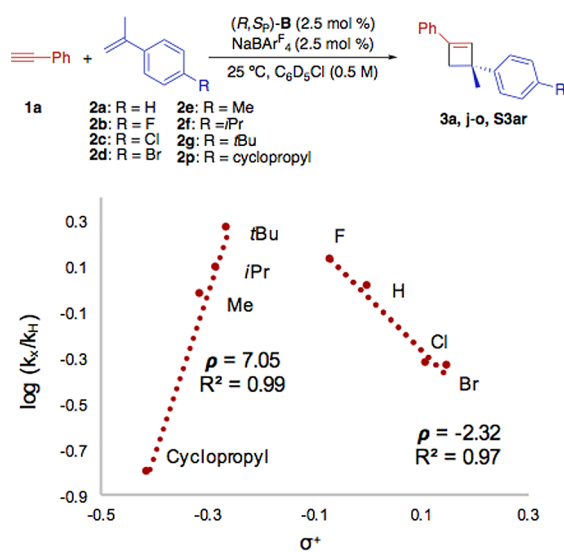


Figure 1. Hammett Plot for the Reaction of **1a** and **2a–g,p** with (S,R)-B.

The abrupt difference in the ρ values is indicative of a change in the catalytic turnover-limiting step. The observation of a highly positive ρ value for **2e–g,p** 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 [LAu(η^2 -alkene)]⁺ and the alkyne to form [LAu(η^2 -alkyne)]⁺ and free alkene, 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.^{6b} For substrates **2a–d**, the formation of [LAu(η^2 -alkene)]⁺ is less favored,²⁰ and therefore the observed negative ρ value is a result of the buildup of positive charge at the most substituted carbon of the alkene in a turnover limiting Markovnikov-type addition of electrophilic [LAu(η^2 -alkyne)]⁺ complex.^{6c}

Aurophilic interactions have been shown to be important in other ferrocenyl diphosphino gold(I) complexes.²¹ However, in the solid state of (S,R)-B (Figure 2a) and related complexes,²²

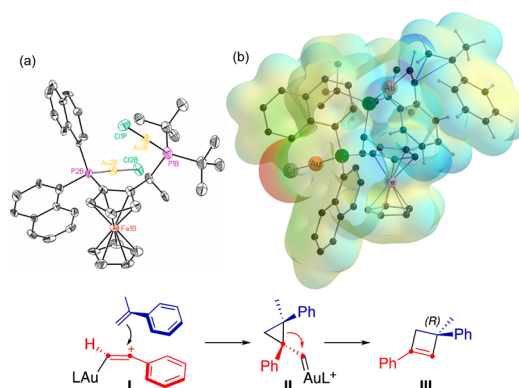


Figure 2. (a) X-ray crystal structure of (S,R)-B and (b) lowest energy transition state for the reaction of **1a** and **2a** with (S,R)-B. (Calculated at PCM(PhCl)-BP86-D3, SDD(Au, Fe), 6-31G(d) (C, H, P, Cl) level of theory using G09 package.¹⁶)

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 [LAu(η^2 -alkyne)]⁺ to the alkene leading to (R)-**3a** when complex (S,R)-B is used as the precatalyst (Figure 2b).¹⁶ The calculated energy difference between the lowest transition states that lead to (S)- and (R)-**3a** $\Delta G_{S,R}^\ddagger = 0.7$ – 1.1 kcal·mol⁻¹ (depending on the method) is in good agreement with experimentally derived value of $\Delta G_{S,R}^\ddagger \approx 1$ kcal·mol⁻¹. Apart from the combination of stabilizing π -stacking and unfavorable steric effects between the approaching alkene and the naphthyl rings of the ligand, we identified a strong C–H–AuCl repulsion between the (naphthyl)₂P–AuCl and the methine hydrogen atom in the α -position to the Cp-ring of the ferrocenyl moiety, which rises the energy of the TS_S transition state vs TS_R. Calculations of the corresponding transition states without the second AuCl on (naphthyl)₂P resulted in the complete loss of stereoselectivity, in agreement with the experimental data using complex (S,R)-G.¹⁶

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 alkyne, 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 C₆₄H₈₀Au₄Cl₄Fe₂P₄ (CIF)

Crystallographic data for C_{40.40}H_{44.80}Au_{1.10}Cl_{1.90}FeP₂ (CIF)

Crystallographic data for C_{48.50}H₄₅Au₂Cl₃FeP₂ (CIF)

Crystallographic data for C₁₇H₁₅Br (CIF)

Crystallographic data for C₂₅H₃₂ (CIF)

Crystallographic data for C₁₉H₂₂S (CIF)

Crystallographic data for C₂₈H₂₄F₂ (CIF)

Crystallographic data for C₃₆H₄₂ (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank MINECO/FEDER, UE (CTQ2016-75960-P and FPI Fellowship to C.G.M.), MINECO-Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-0319), MEC (FPU Fellowship to C.O.), the European Research Council (Advanced Grant No. 321066), the AGAUR (2014 SGR 818), the Marie Curie program (Postdoctoral Fellowship 658256-MSCA-IF-EF-ST to B.R.), CERCA Program/Generalitat de Catalunya for financial support. We also thank the ICIQ X-ray diffraction unit, the Chromatography, Thermal Analysis and Electrochemistry unit and CELLEX-ICIQ HTE laboratory.

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- (16) See [Supporting Information](#) for additional details.
- (17) Cyclobutenes **3ai** (78%, 3:1, 67:33 *er*), **3ak** (78%, 2:1, 64:36 *er*) and **3an** (91%, 1.5:1, 69:31 *er*) were obtained with (S,R_p)-**B** (2.5 mol%), NaBAR₄^F (2.5 mol%) in chlorobenzene (0.5 M) at 25 °C.
- (18) Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. *Org. Lett.* **2016**, *18*, 1614–1617.
- (19) Initial rates (*ca.* 5% formation of **3a**) were used to determine the order of the reaction in substrates **1a** and **2a** by monitoring reactions by ¹H NMR (1:1 ratio of (S,R_p)-**B** and NaBAR₄^F).¹⁶
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- (22) See [Supporting Information](#) for additional X-ray crystal structures of Josiphos gold(I) complexes.