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Letter

Dual Au(I) Catalysis in Regioselective Cycloaddition of Bicyclo[1.1.0]butanes with Allenes

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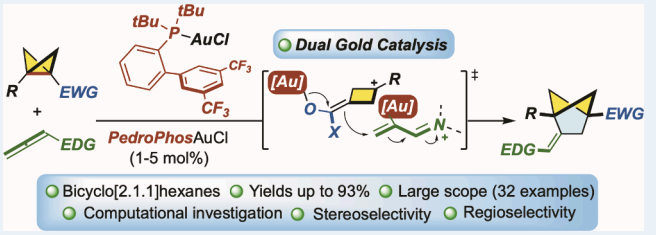
ABSTRACT: A formal [2π+2σ] cycloaddition between electron-rich allenes and bicyclobutanes (BCBs), under a gold-catalyzed regime, is reported. A dual gold activation mechanism was revealed through kinetic studies and further supported by detailed DFT analysis, introducing intriguing paradigms into the dual activation strategy of homogeneous Au catalysis. This protocol enables the synthesis of a broad array of densely functionalized bicyclohexanes (32 examples) in high yields (up to 93%) with complete regioselectivity and stereoselectivity.



KEYWORDS: *allenes, computational study, dual gold catalysis, bicyclobutanes, cycloaddition reactions*

INTRODUCTION

Bioisosterism continues to play a crucial role in enhancing the bioactivity of organic compounds. Recently, the replacement of planar phenyl and pyridyl rings with C(sp^3)-rich, rigid bicyclic cores has gained increasing recognition within the chemical and pharmaceutical communities.[1−8]

In this context, bicyclo[1.1.0]butanes (BCBs, **1**)[9,10] have recently attracted particular attention due to their unique structure, comprising two fused cyclopropane rings in a highly distorted, nonplanar conformation, which results in significant ring strain.[11] As a consequence, via the cleavage of the strained bridgehead Cα−Cγ bond, diverse families of bicyclo[1.1.1]-pentanes (BCPs), bicyclo[2.1.1]hexanes (BCHs), and bicyclo[3.1.1]heptanes (BCHeps) can be efficiently synthesized through polar or radical reaction pathways (Figure 1a).[12−18] As such, it is of utmost importance to develop novel (catalytic) strategies for the activation of BCBs and, concomitantly, unlock new and readily accessible coupling partners.

Owing to the unique nature of the Cα−Cγ bond within the butterfly-like geometry of compound **1**, a BCB property-driven rational design approach has proved to be paramount in proposing new working strategies.[19,20] Accordingly, dedicated computational studies on model substrate **1a** confirmed that the Cα and Cγ atoms exhibit predominantly sp^2 hybridization, while the bridge bond connecting them is formed by almost pure *p* orbitals (92% and 91%, respectively; see Figure S1). This structural signature, together with our interest in exploring novel gold-catalyzed activations of unsaturated hydrocarbons,[21−28] inspired us to envision cationic gold complexes as specific activators of BCBs. In particular, an enhanced nucleophilic character of the bicyclic scaffold could be foreseen via net polarization of the strained bond. This hypothesis, if verified, might pave the way for the development of a novel ***dual-catalytic*** strategy for the functionalization of BCBs when combined with a Au(I)-based generation of electrophilic partners.[29−39]

With the aim of assessing possible activation modes of BCBs by Au(I) species, we computationally investigated (*vide infra*) the binary system comprising a cationic gold species [Au(PPh_3)]$^+$ and **1a** as model substrates. Interestingly, two stable adducts were identified: namely, the *O*-[Au-**1a**] and the *C*-[Au-**1a**] OK complexes. While the first emphasizes the σ-acidity of [Au(PPh_3)]$^+$ through its coordination at the carboxylic moiety (Figure 1b),[40] the second species exhibits an unusual Cα−Au contact (2.13 Å, Figure 1b), accompanied by a significant polarization and elongation of the Cα−Cγ bond (1.61 Å) compared to the 1.51 Å observed in **1a**.

These findings provide a solid basis for the productive activation of **1a** by cationic gold species through both σ- and π-Lewis acid/base interactions.[41] Importantly, in both organo-gold species, the bridgehead C−C bond exhibits a predominant *p*-character in the involved atomic orbitals, implying a formal sp^2 hybridization of Cα and Cγ that would lead to a decreased bond order, in accordance with the literature.[9,10] This suggests a potential facilitation of a subsequent reaction

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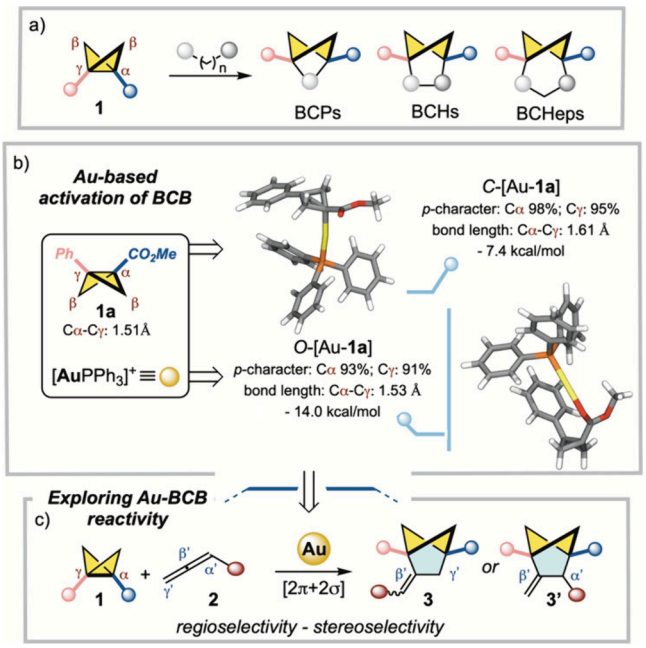


Figure 1. a) General reaction profile of bicyclobutanes (BCBs **1**). b) Structural description of the modeled *O*-[Au-**1a**] and *C*-[Au-**1a**] species. c) Exploring the **1a**−[AuPPh$_3$]$^+$ complex in gold-catalyzed formal [2σ+2π] cycloaddition between substituted bicyclobutanes and allenes.

with a *plethora* of *p*π-systems, generating chemical diversity via multiple reaction pathways.

In terms of promising Au(I)-generated partners, we envisioned electron-rich allenes (e.g., *N*-allenyl amides **2**) as optimal candidates, given their established role in the formation of reactive iminium-like intermediates by electrophilic gold activation.[42−52] As a result, the use of Au(I) catalysis can be responsible for the simultaneous generation of the reactive 2π component (from allenes **2**) and the activation of the 2σ partner (BCB) toward a formal [2π+2σ] cycloaddition. Within this dual activation scenario, enhanced catalyst control over both regioselectivity (enamide **3** vs allyl amide **3′**) and stereoselectivity (geometry of the newly formed C═C bond) could be expected.

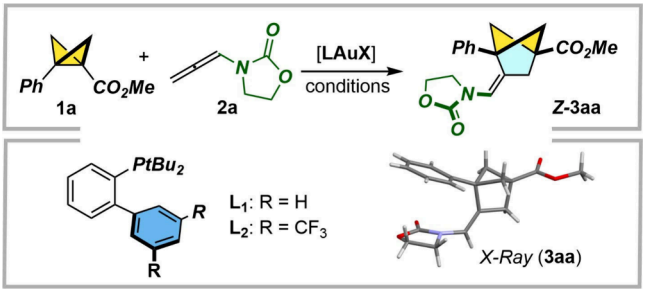
RESULTS AND DISCUSSION

Experimentally, we initiated our study by reacting model BCB **1a** and *N*-allenyl amide **2a** in the presence of [Au(PPh$_3$)NTf$_2$] (5 mol%) in ACN (0.05 M) at room temperature (Table 1, entry 1). Notably, the bicyclo[2.1.1]hexane product *Z*-**3aa** was obtained in a stereochemically defined manner (53% yield), alongside some decomposition of the starting materials. Importantly, no trace of isomeric product **3aa′** was detected in the reaction mixture, highlighting the exquisite control of the regiochemistry in this transformation.

Hereafter, the identification of optimal conditions was targeted by running a dedicated survey of the reaction parameters. The data collected in Table 1 emphasize that phosphines are mandatory to observe the desired reactivity (entries 1−4 vs 5). Among the P-based ligands tested, the CF$_3$-containing *PedroPhos* **L$_2$**[53] resulted in the highest yield (83%, entry 3).

Acetonitrile was selected as the reaction medium, as DCM and toluene resulted in notably inferior yields (50−55%,

Table 1. Optimization of the Reaction Conditions[a]



Run	[Au] complex (x mol%)[b]	Conditions	Yield (%) of **3aa**[c]
1	[Au(**PPh$_3$**)NTf$_2$] (5)	CH$_3$CN, 16 h	53
2	[Au(**L$_1$**)NTf$_2$] (5)	CH$_3$CN, 16 h	80
3	[Au(**L$_2$**)NTf$_2$] (5)	CH$_3$CN, 16 h	83
4	[Au$_2$(**BINAP**)(NTf$_2$)$_2$] (2.5)	CH$_3$CN, 16 h	44
5	[Au(**IPr**)NTf$_2$] (5)	CH$_3$CN, 16 h	NR
6	[Au(**L$_2$**)NTf$_2$] (5)	CH$_2$Cl$_2$, 16 h	50
7	[Au(**L$_2$**)NTf$_2$] (5)	Toluene, 16 h	55
8[d]	[Au(**L$_1$**)NTf$_2$] (5)	CH$_3$CN, 1 h	48
9[d]	[Au(**L$_2$**)NTf$_2$] (5)	CH$_3$CN, 1 h	90 (88)
10[d]	[Au(**L$_2$**)SbF$_6$] (5)	CH$_3$CN, 1 h	90
11[d,e]	[Au(**L$_2$**)NTf$_2$] (1)	CH$_3$CN, 16 h	87

[a]All reactions were carried out under an inert atmosphere at rt, [**1a**] = 0.05 M, **1a**/**2a** = 1:1, unless otherwise mentioned. [b]Preformed cationic complexes were utilized. [c]NMR yield calculated using CH$_2$Br$_2$ as an internal standard. Isolated yields after flash chromatography is given in parentheses in entry 9. [d]With **1a**/**2a** = 1:1.5. [e]Reaction run on 1.0 mmol scale of **1a**, isolated yield after flash chromatography. NR: no reaction. IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. BINAP: *rac*-bis-(diphenylphosphino)-1,1′-binaphthyl.

entries 6, 7). The isolated yield of *Z*-**3aa** increased to 88% (90% based on NMR analysis) with the employment of a slight excess of **2a** (1.5 equiv, entry 9). Under these conditions, the reaction time could be lowered to 1 h, where the acceleration effect of the *PedroPhos* ligand, with respect to **L$_1$** became more evident (entries 8 and 9). Moreover, although the SbF$_6$ anion performed similarly to NTf$_2^-$, the preformed and easy-to-handle [Au(*PedroPhos*)NTf$_2$] was employed in the reaction scope. Finally, the scalability of the methodology to a 1 mmol scale was demonstrated under the optimal conditions, resulting in unchanged isolated yield (87%, entry 11). Here, the loading of [Au(*PedroPhos*)NTf$_2$] could be reduced to 1 mol%. In all cases, high stereoselectivity toward the *Z*-stereoisomer was identified, emphasizing an outer-sphere mechanism likely operating in the catalytic protocol (*vide infra*).[54,55]

The broadness and robustness of the methodology were first assessed by subjecting a range of diversely functionalized bicyclobutanes **1b−x** (Scheme 1) to the catalytic protocol with allene **2a** in the presence of preformed [Au(*PedroPhos*)NTf$_2$] (5 mol%). A broad array of substituents of diverse electronic nature could be effectively accommodated at different positions of the aryl group at the Cγ-carbon of the BCB unit (**1b−m**).[56]

High yields (up to 93%) were obtained in the presence of halogen substituents (F, Cl, Br) both in *para* and *ortho* positions (**1b−e**). Interestingly, slightly lower isolated yields (64−79%) were recorded when the phenyl ring was functionalized with electron-donating units (alkyl and alkoxy groups in *para*, *meta*, and *ortho* positions, **1g−j** and **1l**). Moreover,

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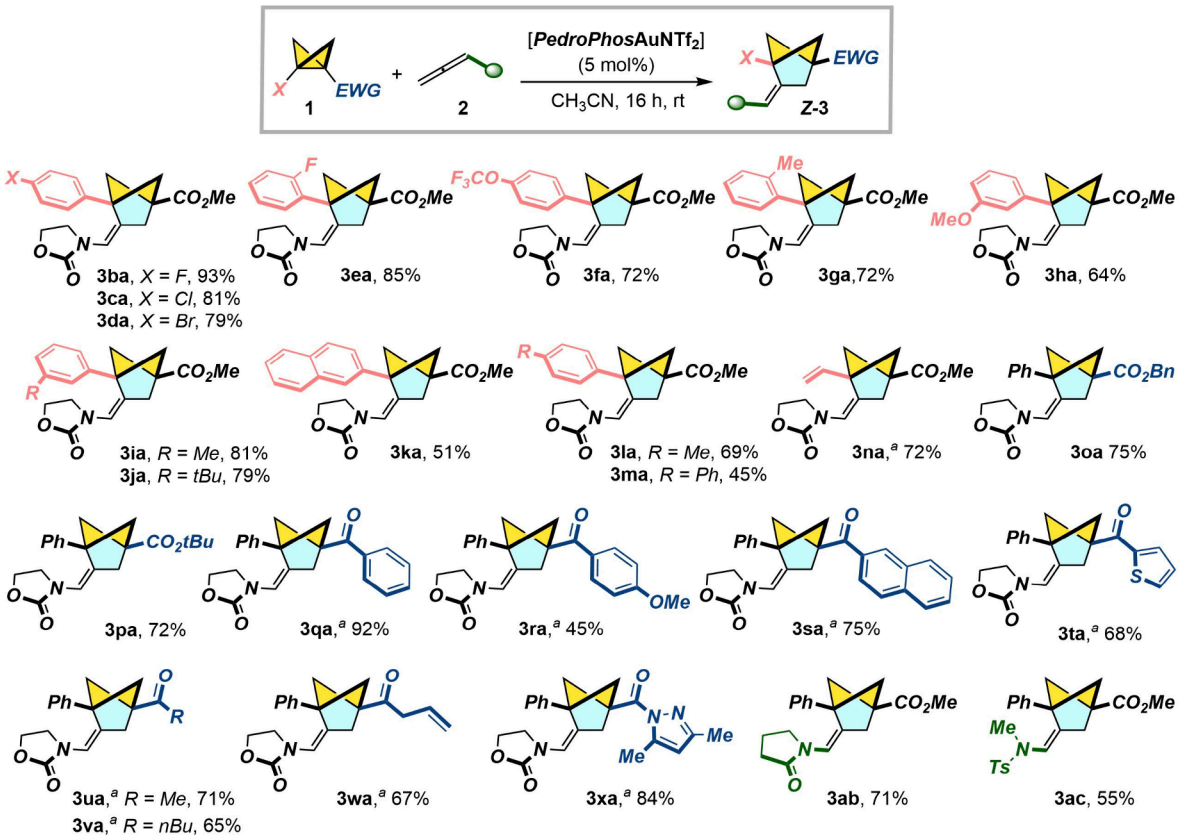
Scheme 1. Proving the Generality of the Protocol: Variations on Bicyclobutanes 1 and Allenamides 2[a]

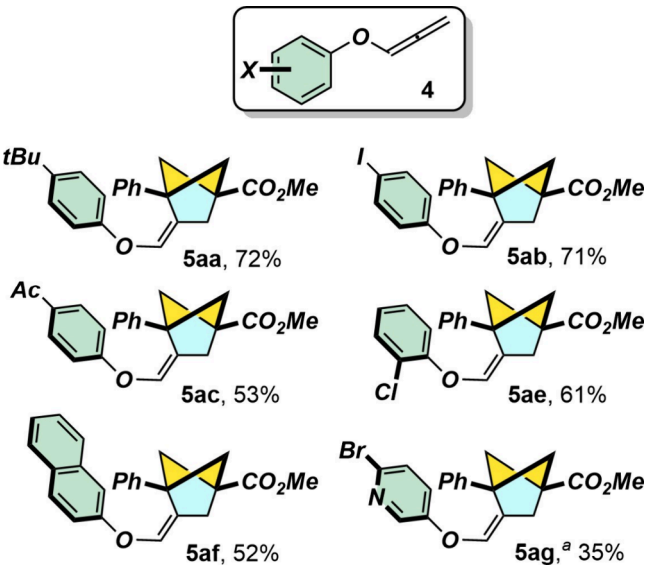


[a]All reactions were carried out using the conditions described in Table 1, entry 9, except for **3na**, **3qa**, **3ra**, **3sa**, **3ta**, **3ua**, **3va**, **3wa**, and **3xa**, for which 10 mol% [Au(L_2)NTf_2] was employed.

extended π-systems such as naphthyl (**1k**) and biphenyl (**1m**) units were effectively tolerated under the optimal reaction conditions. Remarkably, the protocol was found not to be limited to aryl moieties, which could be replaced by a vinyl unit, delivering the corresponding bicyclo[2.1.1]hexane **3na** in 72% yield. Besides replacing the methyl ester with benzyloxy (**1o**) and *tert*-butoxy (**1p**) analogues (75% and 72% yield, respectively), the methodology was proved to be tolerant to other electron-withdrawing units, such as ketones and amides, unraveling a highly robust and broadly applicable protocol. Indeed, a series of aromatic, hetero-aromatic as well as aliphatic ketones (**1q**−**w**) and pyrazole-amide **1x** were synthesized and subjected to optimal conditions. Interestingly, all substrates were amenable to this reaction, delivering good to excellent isolated yields (up to 92%). Comparable reactivity was also recorded for *N*-allenyl-pyrrolidin-2-one **2b** and *N*-allenyl-tosylamide **2c** that delivered the corresponding [2π+2σ]-cycloadducts **3ab** and **3ac** in 71% and 55% yield, respectively.

Thereafter, our focus moved to the possibility of employing *O*-allenyl ethers **4** as cycloaddition partners in our protocol (Scheme 2). Here, diversely functionalized derivatives (**4a**−**f**) were tested with **1a** in the presence of [Au(*PedroPhos*)NTf_2] (5−10 mol%). Satisfyingly, in all cases, the desired cycloadduct **5** was isolated in high yields (52−72%) regardless of the nature and the position of the substituents on the aromatic rings. It is worth noting that a potentially Au-coordinating pyridyl unit could be accommodated on the allenyl ether (**1g**) as well, affording the desired *Z*-**5ag** in moderate yield (35%).

Scheme 2. *O*-Allenyl Ethers as Cycloaddition Partners in the Synthesis of Bicyclo[2.1.1]hexanes[a]



[a]All the reactions were carried out using the conditions described in Table 1, entry 9, except for **5ag**, for which 10 mol% [Au(L_2)NTf_2] was employed.

The presence of several functional groups on bicyclo[2.1.1]-cyclohexane derivatives **3** instills a significant derivatization potential. To prove that, compounds **3aa** and **3da** were

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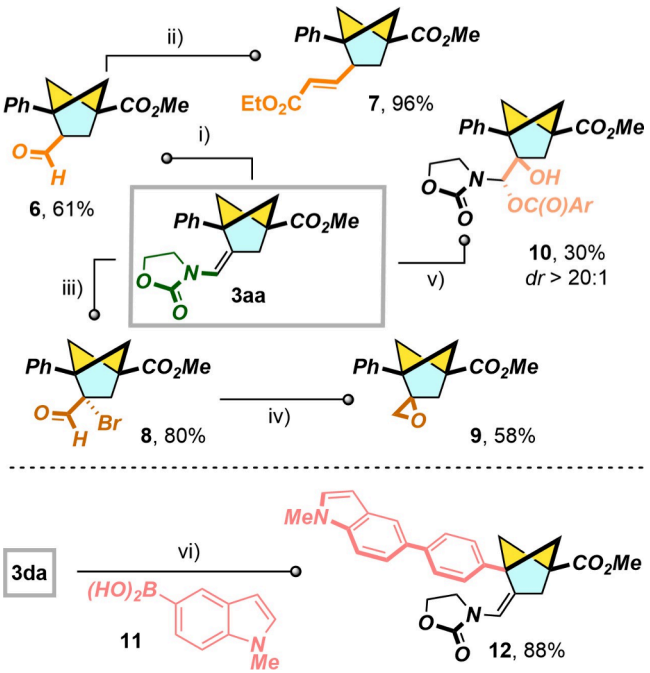
subjected to a set of chemical manipulations for the expedited preparation of densely functionalized structures (Scheme 3).

Scheme 3. Examples of Chemical Manipulations of BCHs 3[a]



[a]Reagents and conditions: i) HCl (37 wt%), $CHCl_3$, rt, 16 h; ii) Ph_3PCHCO_2Et (2 equiv), DCM, rt, 16 h; iii) ; ElectraSyn 2.0 − undivided cell, Ni(−)/C(+), CCE (I = 4 mA), 4 F/mol, $LiClO_4$ (2 equiv), NaBr (2 equiv), air, CH_3CN, rt; iv) $NaBH_4$ (3 equiv), MeOH, rt, 16 h; v) m-CPBA (2.4 equiv), DCM, 0 °C to rt, 16 h, Ar = m-ClPh; vi) **11** (2 equiv), $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Cs_2CO_3 (3 equiv), THF/H_2O (10:1), reflux, 3 h.

First, the exocyclic enamide group of **3aa** was conveniently converted into the corresponding aldehyde **6** via acidic hydrolysis in 61% yield. This compound could be further transformed into acrylate *E*-**7** in 96% yield via Wittig olefination. Interestingly, this two-step procedure shows the feasibility to accommodate both electron-rich (i.e., enamide) and electron-poor (i.e., acrylate) C═C moieties onto the bicyclic core. Then, we applied our recently developed electrochemical halogenation procedure to **3aa**.[57] Interestingly, when this was subjected to oxidative electrolysis in the presence of NaBr, the corresponding α-bromoaldehyde **8** was isolated in excellent yield (80%). Further treatment of **8** with $NaBH_4$ resulted in the isolation of epoxide **9** (58% yield) via a halohydrin ring-closure. Moreover, the exocyclic enamide bond could be subjected to epoxidation conditions, with m-CPBA delivering the corresponding difunctionalized compound **10** (30% yield, unoptimized; dr > 20:1) via an epoxidation/ring-opening sequence involving the *in situ* formed m-chlorobenzoic acid.[58,59]

Finally, the bromoarene moiety of **3da** could be subjected to Suzuki cross-coupling with *N*-methylindole-5-boronic acid **11** to isolate the functionalized biaryl **12** in 88% yield. This evidence accounts for the possibility to exploit the aryl group at Cγ for conjugation with complex moieties.

The investigation of the reaction mechanism began with the determination of the reaction order in $[Au(PedroPhos)NTf_2]$ in the model protocol (**1a** + **2a** → **3aa**) to verify the initial postulate foreseeing a dual-catalytic role of gold. Here, the kinetic profile of **3aa** formation was monitored over the time within a range of catalytic loadings (3−10 mol%), and the resulting kinetic trends are reported in Figure 2, top.[60] Interestingly, by adopting the graphical analysis proposed by Burés,[61] which considers the entire reaction profile rather than focusing only on the initial reaction rates, an order in catalyst of two was identified (Figures 2, top center and right). These results are in excellent agreement with our starting hypothesis and led us to consider an on-cycle-type mechanism being operating by means of a "sibling" catalytic modality. In fact, this result supports our envisioned scenario where two molecules of $[LAu^+]$ could synergistically activate both reaction partners during the rate-determining step.[62]

Further insights into a dual gold catalysis[63,64] were gained via a dedicated computational exploration of the reaction machinery. We performed DFT calculations at the M06/Def2svp[65−68] level of theory, including implicit solvation effects using the Polarizable Continuum Model (PCM)[69] and dichloromethane as a solvent. All our calculations were performed using the Gaussian 16 code.[70] The mechanistic manifold is presented in the lower part of Figure 2. First, we explored the typical, one-gold-activated mechanism where the π-acidic catalyst electrophilically activates the unsaturated bonds of allenamide **2a**, rendering the gold-activated iminium intermediate **A** (Figure 2, path a). In this case, if an unactivated BCB **1a** attacks the electrophile, a C−C bond is formed, leading to intermediate **C**, requiring an input of only 5.7 kcal/mol that is compatible with the reaction conditions. Carbocation **C**, which is stabilized by 16.6 kcal/mol with respect to the starting material, is then funneled through a barrierless ring-closure step concomitant with catalyst release, yielding the thermodynamically stable (−37.1 kcal/mol) product **3aa**.

Nevertheless, our preliminary calculations had already shown that gold can also activate the BCB moiety, yielding two stable adducts, the *O*-[Au-**1a**] intermediate **B** and the *C*-[Au-**1a**]-coordinated intermediate **D**. Based on this observation, we investigated an alternative pathway in which gold, acting as a π-acid, interacts with the Cα−Cγ bond of the BCB. The *C*-[Au]-coordinated intermediate **D** is transformed to the fully activated cationic intermediate **E** after a low-lying transition state of 6.8 kcal/mol. Subsequent nucleophilic attack by unactivated allenamide **2a** on **E** forms the same carbocation **C**, which again evolves to the final product via a barrierless process. Nonetheless, the overall energetic input required for this route, where single activation of the BCB is invoked (11.2 kcal/mol), renders this pathway less favorable compared to the gold−allenamide activation (Figure 2, path b).

Additionally, based on our kinetic experiments (*vide supra*) strongly suggesting a dual activation for this catalytic transformation, we also explored a combined activation pathway by the participation of two units of catalyst. We envisioned that both Au-activated intermediates **A** and **B** could be combined via a doubly activated transition state $\mathbf{TS_{A\text{-}B\text{-}C}}$ to yield the carbocation **C** after releasing of one gold-complex molecule. This step does not require additional energetic input (ΔG = −0.4 kcal/mol and ΔG^{++} = 26.3 kcal/mol), making the dual path the most competitive among the suggested pathways (Figure 2, path c). These results provide strong computational support for a dual gold activation mechanism, aligning with experimental observations and offering new insights into the reactivity patterns of strained systems under gold catalysis.[71]

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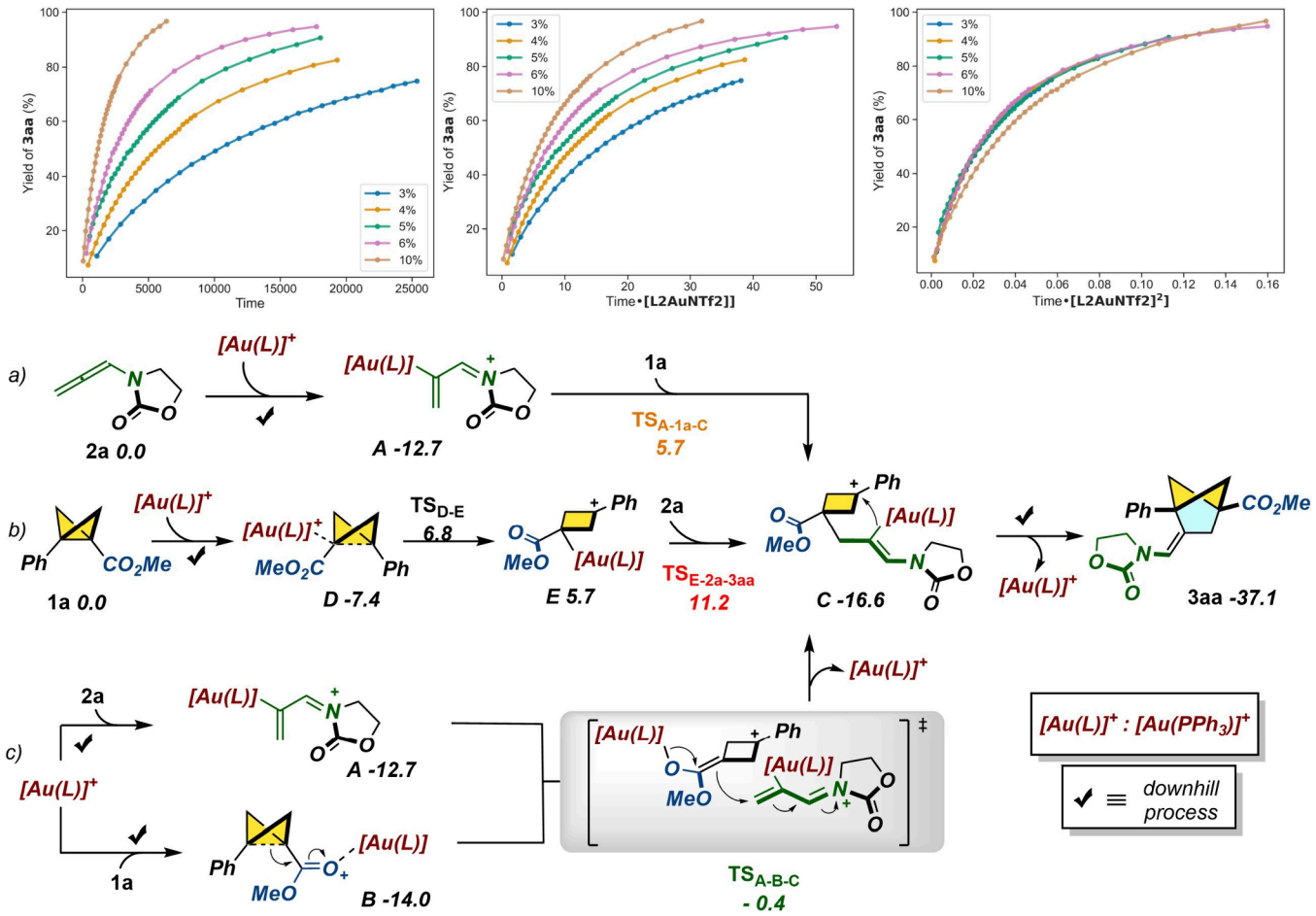

Figure 2. Top: Exploring the kinetic profile of the formation of **3aa** with different loadings (i.e., 3−10 mol%) of [Au(*PedroPhos*)NTf_2]. The reactions were monitored over time via ^{1}H NMR analysis (600 MHz, CD_3CN, rt, CH_2Br_2 as an internal standard). Bottom: Comprehensive mechanistic pathways for the formation of **3aa**. Two single-activation routes (through a) allenamide **2a** or b) BCB **1a** activation, respectively and one dual activation routes (path c) were considered [Au(**L**)]$^+$ = [Au(PPh_3)]$^+$.

CONCLUSIONS

In conclusion, the efficiency of gold(I) catalysis for the chemoselective [2σ-2π]-cycloaddition of bicyclo[1.1.0]butanes and electron-rich allenes was documented. The protocol enables a wide range (32 examples) of densely functionalized bicyclo[2.1.1]hexanes to be isolated in high yields (up to 93%). The versatility of [Au(*PedroPhos*)NTf_2] as a σ- and π-acid triggers a dual activation mode in the catalytic cycle, as experimentally and computationally proved. These unprecedented mechanistic findings trace new landmarks on the activation mode of BCBs toward the creation of chemical complexity.

ASSOCIATED CONTENT

Data Availability Statement

All the relevant structures (minima and TS) of the computational study are uploaded in the ioChem-BD repository (https://www.iochem-bd.org/) hosted at the Barcelona Supercomputing Center (https://www.bsc.es/), where Cartesian coordinates, energies and frequencies are made publicly available with the DOI 10.1906/iochem-bd-6-537. Deposition number 2448401 (for **3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c03898.

Synthesis, characterization of new compounds, procedures and data for the kinetic analysis of the gold-catalyzed reaction andadditional computational results (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ACN, acetonitrile; BCP, bicyclo[1.1.1]pentane; BCH, bicyclo[2.1.1]hexane; BCHep, bicyclo[3.1.1]heptane; BCB, bicyclo[1.1.0]butane; DCM, dichloromethane; DFT, density functional theory; *m*-CPBA, 3-chloroperbenzoic acid; NMR, nuclear magnetic resonance; PCM, polarizable continuum model

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