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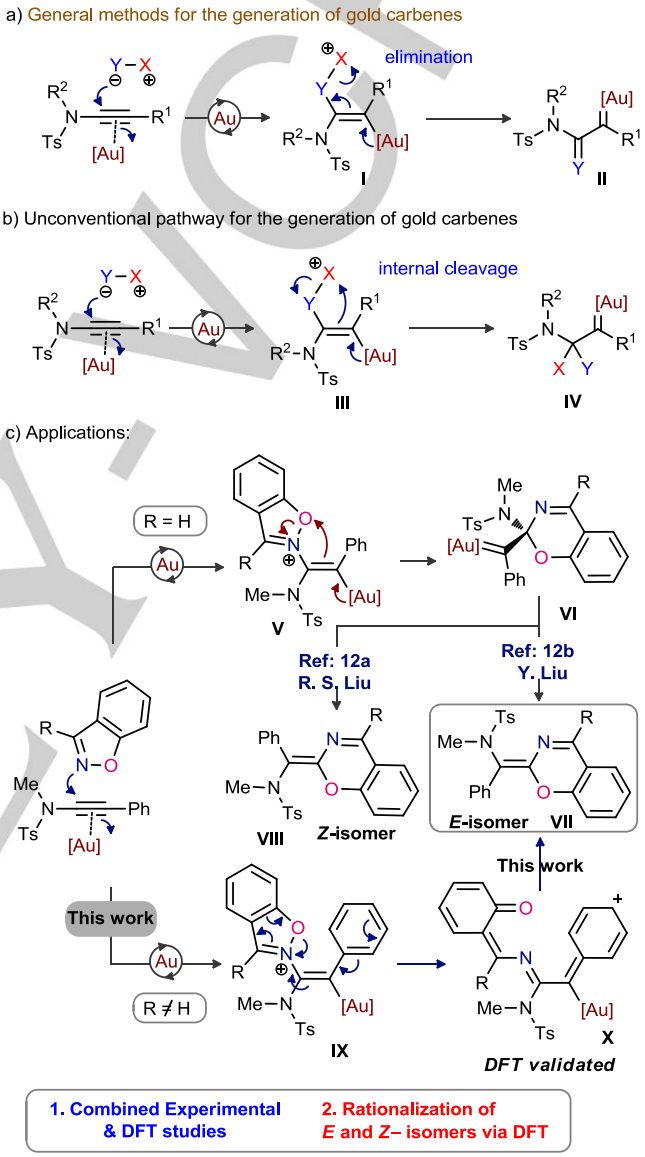
Ring Expansion and 1,2-Migration Cascade of Benzisoxazoles with Ynamides: Experimental and Theoretical Studies

Rajeshwer Vanjari, [a] Shubham Dutta, [a] B. Prabagar, [a] Vincent Gandon*[b],[c] and Akhila K. Sahoo*[a]

Abstract: Demonstrated herein is a Au(I)-catalyzed annulation of sulfonyl-protected ynamides with substituted 1,2-benzisoxazoles for the synthesis of *E* benzo[e][1,3]oxazine derivatives. The transformation involves the addition of benzisoxazole to the gold-activated ynamide, ring expansion of the benzisoxazole fragment to provide an α-oximino gold carbene, and the 1,2-migration of the sulfonamide motif to the carbene center to deliver the respective ring expanded benzo[e][1,3]oxazine of predominant *E* configuration. A trapping experiment justifies the participation of the α-oximino gold carbene. DFT computations also support the hypothesized mechanism and rationalize the product stereoselectivity.

Introduction

Homogeneous gold-catalyzed cascade oxidative cyclization processes have largely been used for the fabrication of complex heterocyclic frameworks.[1] In this context, the direct application of gold-carbenoid species for diverse cyclization methods have undoubtedly been significant. The Au-catalyzed *N*-oxide assisted alkyne oxidation and the cycloisomerization of 1,*n*-enynes are particularly notable gold carbene-based transformations.[2,3] In addition, the nucleophilic nitrenoid equivalents, for example, azides,[4] pyridium ylides,[5] 2H-azirines,[6] and others[7] have been used in the generation of gold carbene species. The formation of Au-carbenes from ynamides occurs via the elimination of a counter ion or a leaving group after electron back donation of the metal center (Scheme 1a). In this regard, Ye,[8] Hashmi,[9] and Liu[10] groups independently reported the annulation of Au-carbene species, obtained *in-situ* from ynamides[11] and anthranils or isoxazoles in presence of Au(I)-catalyst, to provide substituted pyrrole and indole derivatives. By contrast, the generation of α,α'-disubstituted Au-carbenes from ynamides could also be envisaged with the assistance of a 1,2-di-heteroatom species that would undergo an internal cleavage of the Y–X bond (Scheme 1b). Intrigued by this idea, we envisaged the Au-catalyzed regioselective attack of



Scheme 1. Generation and trapping of ynamide-derived gold carbenes

benzisoxazoles to ynamides (Scheme 1c). We anticipated that the attack of substituted benzisoxazoles to the α-position of an Au-activated ynamide would first provide the vinyl-gold species **V** (Scheme 1c). Next, the electron back donation of gold atom and the electron-delocalization would trigger the cleavage of the benzisoxazole *O–N* bond resulting in ring expansion to give the intermediate **VI**. Meanwhile, the cleavage of *N–O* bond (**IX**) through the electron delocalization of aryl motif would produce **X** (supported by DFT study). Finally, 1,2-sulfonamide migration and dissociation of gold would lead to the desired benzo[e][1,3]oxazine derivative (Scheme 1c). As shown below, our strategy proved successful in providing products with a

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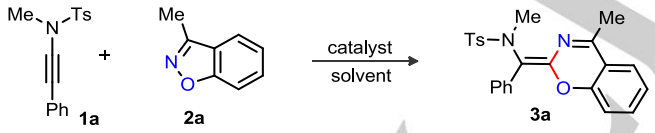
pronounced *E* stereoselectivity. During the preparation of this manuscript, R. S. Liu[12a] and Y. Liu[12b] group have independently reported the synthesis of *Z* and *E* benzo[e][1,3]oxazines, respectively, from ynamide and benzoisoxazole derivatives when exposed to Au(I) catalysts. Such a diverse stereochemical outcome required further examination. The Liu's[12b] pioneering demonstration leads to *E* benzo[e][1,3]oxazines, however, the reaction involves a gold carbene intermediate; whereas the participation of the vinylic gold carbene intermediate (**IX**) validates the formation of *E*-isomer benzo[e][1,3]oxazines (major, current work).

We herein discuss the Au(I)-catalyzed annulation of ynamides with substituted benzisoxazoles for the synthesis of benzo[e][1,3]oxazine derivatives predominantly of *E* configuration and examine a detailed density functional theory (DFT) computations to establish the mechanism.

Results and Discussion

The investigation was initiated by performing a reaction between ynamide **1a** and 3-methylbenzisoxazole **2a** in presence of various gold catalysts (Table 1). The reaction proved successful when conducted with JohnPhosAu(MeCN)SbF_6 in 1,4-dioxane; **3a** was isolated in 47% yield with the major *E* configuration (*E*/*Z* = 83:17; entry 1). The structure of *E*-**3a** was unambiguously confirmed by X-ray crystallographic analysis (Scheme 3). The reaction did not take place in DMF (entry 2), whereas **3a** was obtained in 68% (*E*/*Z* = 89:11) and 79% yield (*E*/*Z* = 86:14) when carried out in acetone or 1,2-dichloroethane (DCE), respectively (entries 3 and 4). The reaction was also effective in toluene (84%; entry 5), but $CHCl_3$ was found to be the best solvent, providing **3a** in 89% yield (*E*/*Z* = 88:12; entry 6). The product yield was greatly affected when IPrAuNTf_2 (24%, entry 7) and IMesAuNTf_2 (21%, entry 8) were used, while the reaction in the presence of XPhosAuNTf_2 was satisfactory (*E*/*Z* = 88:12; entry 9).

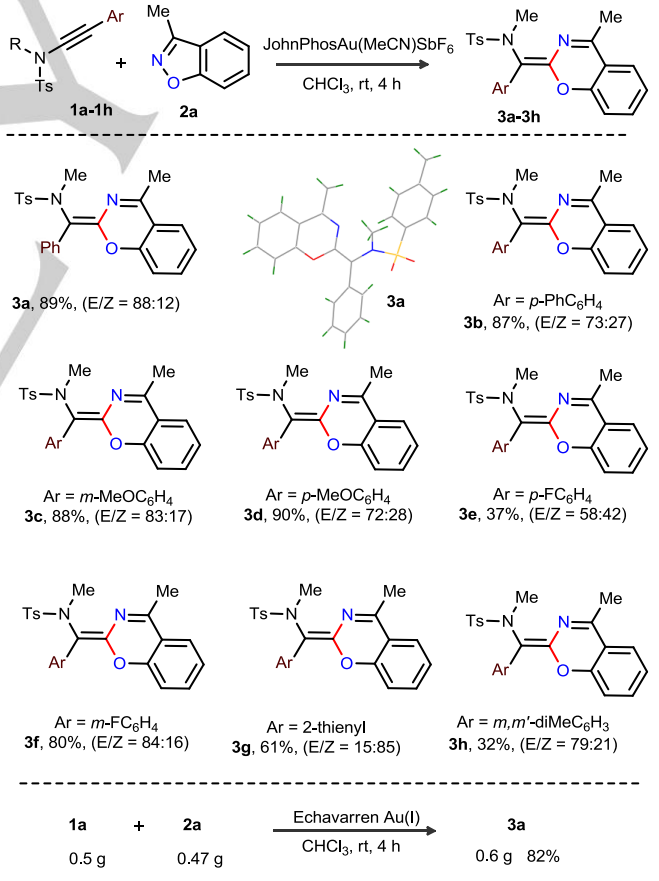
Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	*E*/*Z*[b]	Yield, **3a** (%)[c]
1	JohnPhosAu(MeCN)SbF_6	1,4-dioxane	83:17	47
2	JohnPhosAu(MeCN)SbF_6	DMF	-	0
3	JohnPhosAu(MeCN)SbF_6	acetone	89:11	68
4	JohnPhosAu(MeCN)SbF_6	1,2-DCE	86:14	79
5	JohnPhosAu(MeCN)SbF_6	toluene	87:13	84
6	**JohnPhosAu(MeCN)SbF_6**	**$CHCl_3$**	**88:12**	**89**
7	IPrAuNTf_2	$CHCl_3$	85:15	24
8	IMesAuNTf_2	$CHCl_3$	88:12	21
9	XPhosAuNTf_2	$CHCl_3$	88:12	81

[a] Reaction conditions: **1a** (1.0 equiv, 0.3 mmol), **2a** (2.0 equiv), Au-cat (5.0 mol %), solvent (1.0 M) at rt for 4 h. [b] Determined by ^{1}H NMR via integration of methyl peak. [c] Isolated yield.

The effective reaction conditions for the ring expansion and migration cascade between **1a** and **2a** (Table 1, entry 6) were then used to probe the reaction generality for the construction of benzo[e][1,3]oxazines (Schemes 3, 4, and 5). In addition to the previously discussed product **3a** (89%, *E*/*Z* 88:22), the desired benzo[e][1,3]oxazines **3b** (87%, *p*-Ph, *E*/*Z* 73:27), **3c** (88%, *m*-OMe, *E*/*Z* 83:17), and **3d** (90%, *p*-OMe, *E*/*Z* 72:28) were obtained in high yields from the electron-rich aryl-substituted ynamides. By contrast, moderate to good yields were obtained from electron-poor aryl bearing ynamides, leading to **3e** (37%, *p*-F, *E*/*Z* 58:42) and **3f** (80%, *m*-F, *E*/*Z* 84:16). The thiophenyl substituted benzo[e][1,3]oxazine **3g** was obtained in 61% yield with an *E*/*Z* of 15:85. Benzo[e][1,3]oxazine **3h** was accessed in 32% yield from a dimethyl-substituted aryl-bearing ynamide. The robustness of the catalytic system was tested through the synthesis of **3a** (0.6 g) from the mixture of **1a** (0.5 g, 1.75 mmol) and **2a** (0.47 g) in presence of the Au-catalyst (5.0 mol%).



Scheme 3. Reaction of Ynamides (**1**) with 3-Methylbenzisoxazole (**2a**). Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (0.6 mmol, 2.0 equiv), Au-cat (5.0 mol%), $CHCl_3$ (1.0M) at rt for 4 h. *E*:*Z* ratio determined by ^{1}H NMR integrating methyl peak.

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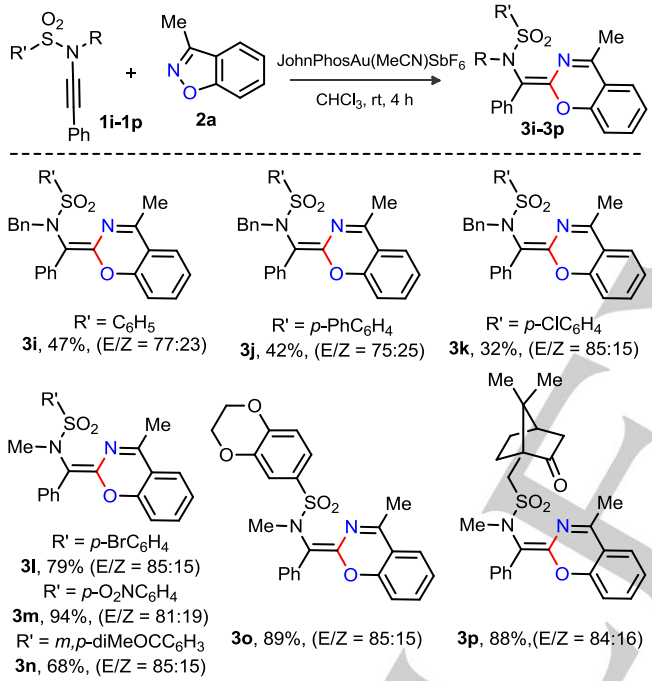
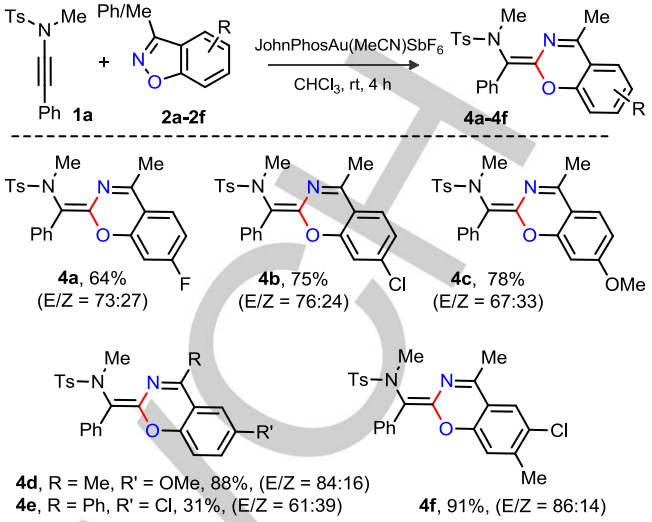
We next explored the scope of the migrating group using various *N*-sulfonyl protected ynamides with **2a** (Scheme 4). The reaction of **2a** with *N*-Bn-sulfonamide (*N*-Bn-SO_2Ar) ynamides furnished the desired benzo[e][1,3]oxazines [**3i** (electron-neutral *N*-Bn-SO_2Ph, 47%, *E*/*Z* 77:23), **3j** (electron-rich *N*-Bn-$SO_2C_6H_4$-*p*-Ph, 42%, *E*/*Z* 75:25), and **3k** (electron-poor *N*-Bn-$SO_2C_6H_4$-*p*-Cl, 32%, *E*/*Z* 85:15). Likewise, the *N*-Me-sulfonamide bearing products [**3l** (*N*-Me-$SO_2C_6H_4$-*p*-Br, *E*/*Z* 85:15), **3m** (*N*-Me-$SO_2C_6H_4$-*p*-NO_2, *E*/*Z* 81:19), and **3n** (*N*-Me-$SO_2C_6H_3$-3,4-di-OMe, *E*/*Z* 85:15)] were accessed in good yields. The *N*-Me sulfonamide reacted with **2a** to provide the respective oxazine product **3o** (89%, *E*/*Z* 85:15). The migration was unaffected when *N*-Me-SO_2–camphor bearing ynamide reacted with **2a**; the product **3p** (E/Z 84:16) was isolated in 88% yield (Scheme 4). Lower yields were observed in case of $BnNSO_2R'$ due to the possible deleterious effect of the benzyl group.

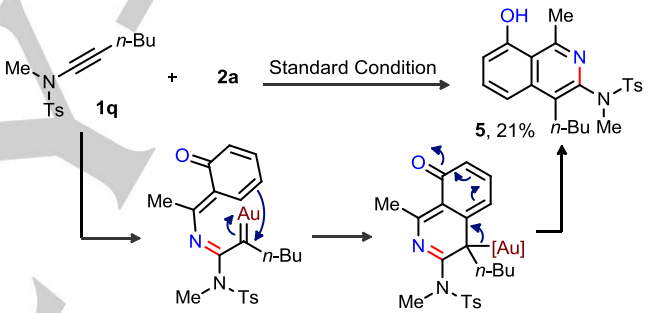


Scheme 4. Scope of Migrating Group. Reaction conditions: **1a** (1.0 equiv, 0.3 mmol), **2a** (2.0 equiv), Au-cat (5.0 mol%), $CHCl_3$ (1.0M) at rt for 4 h. *E*:*Z* ratio determined by ^{1}H NMR integrating methyl peak.

The generality of the ring expansion by reacting various benzisoxazoles (irrespective of the substituents present at different positions of the arene periphery) with **1a** was next examined (Scheme 5). The reaction between 6-F/6-Cl/6-OMe substituted 2-methylbenzisoxazoles and **1a** delivered the respective highly-substituted benzo[e][1,3]oxazines **4a**–**4c** [*E*/*Z* = 67–76:33–24]. Similarly, 5-OMe substituted 2-methylbenzisoxazoles participated in the ring expansion cascade, producing **4d** in 88% yield with better *E*/*Z* ratio of 84:16. Compound **4e** (31%; *E*/*Z* = 63:37) was isolated from the reaction of 3-phenyl substituted benzisoxazole with **1a**. Likewise, the reaction of **1a** and 5,6-disubstituted benzisoxazole led to **4f**, in excellent yield (91%, *E*/*Z* = 86:14).



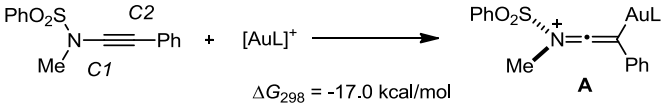
Scheme 5. Scope of Benzisoxazole (**2**). Reaction conditions: **1a** (1.0 equiv, 0.3 mmol), **2a** (2.0 equiv), Au-cat (5.0 mol%), $CHCl_3$ (1.0 M) at rt for 4 h. *E*:*Z* ratio determined by ^{1}H NMR integrating methyl peak.



Scheme 6. Carbene Trapping

The involvement of a gold carbene intermediate was supported by the outcome of the coupling of the alkyl-substituted ynamide **1q** with **2a** (Scheme 6). These substrates provided a non-migratory product **5**, obtained likely via dearomatization and gold carbene C–H bond insertion.

To explore the mechanistic details, DFT computations were executed at the M06/def2-QZVP(Au)-6-31+G(2d,p)//B3LYP/LANL2DZ(Au)-6-31G(d,p) level of theory. Optimization of the model ynamide shown in Scheme 7 and the $[LAu]^+$ fragment (L = biphenyl-2-yl-di-methylphosphine) led to the keteniminium complex **A** with the release of 17 kcal/mol of Gibbs free energy. For the rest of the discussion, the carbon center adjacent to nitrogen of ynamide is denoted **C1** and the other β-carbon center is denoted **C2**. In the following energy profiles, the keteniminium complex **A** and 3-methylbenzisoxazole or



Scheme 7. Free energy for the formation of the keteniminium gold complex **A** (L = biphenyl-2-yl-di-methylphosphine).

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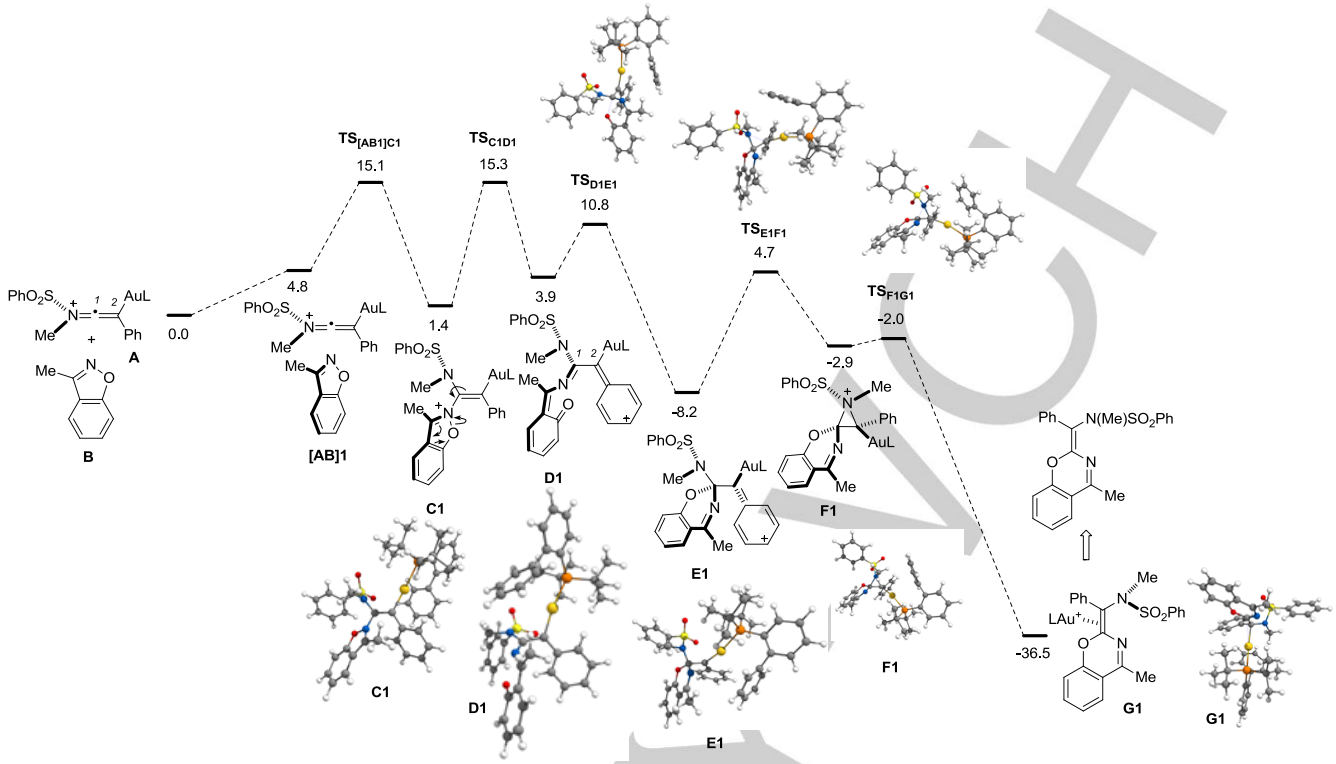
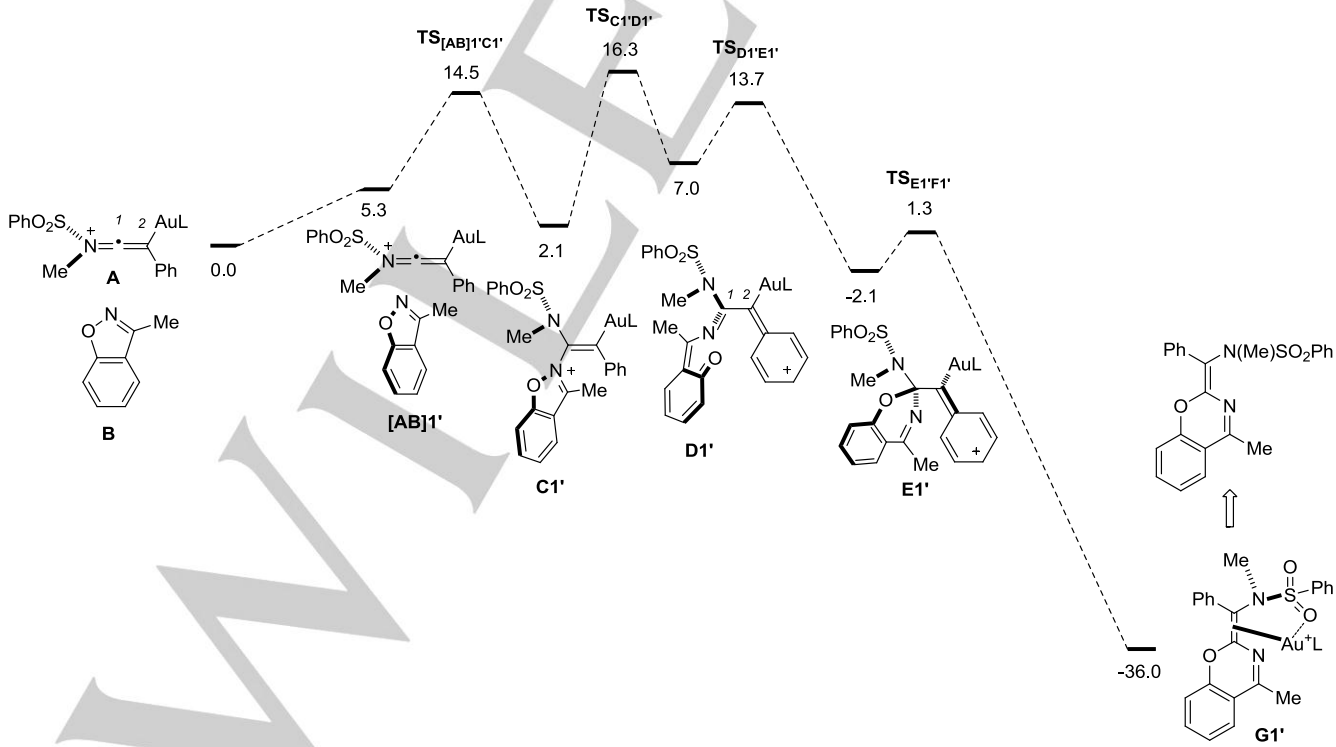
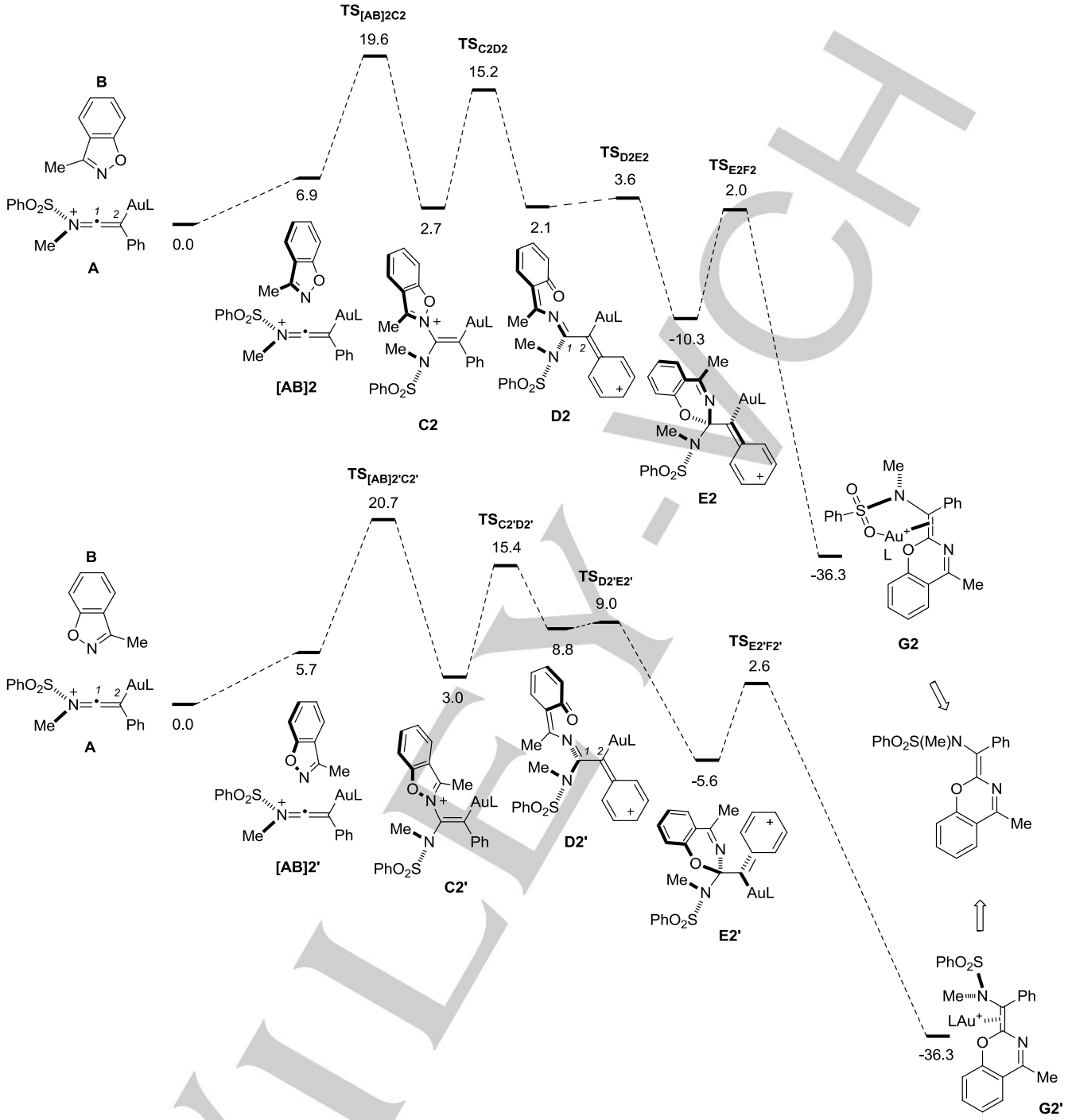


Scheme 8. Free energy profile (ΔG_{298}, kcal/mol) for the *anti*-addition of **B** to **A** with two Me groups on the same side; geometry of key intermediates and transition states.



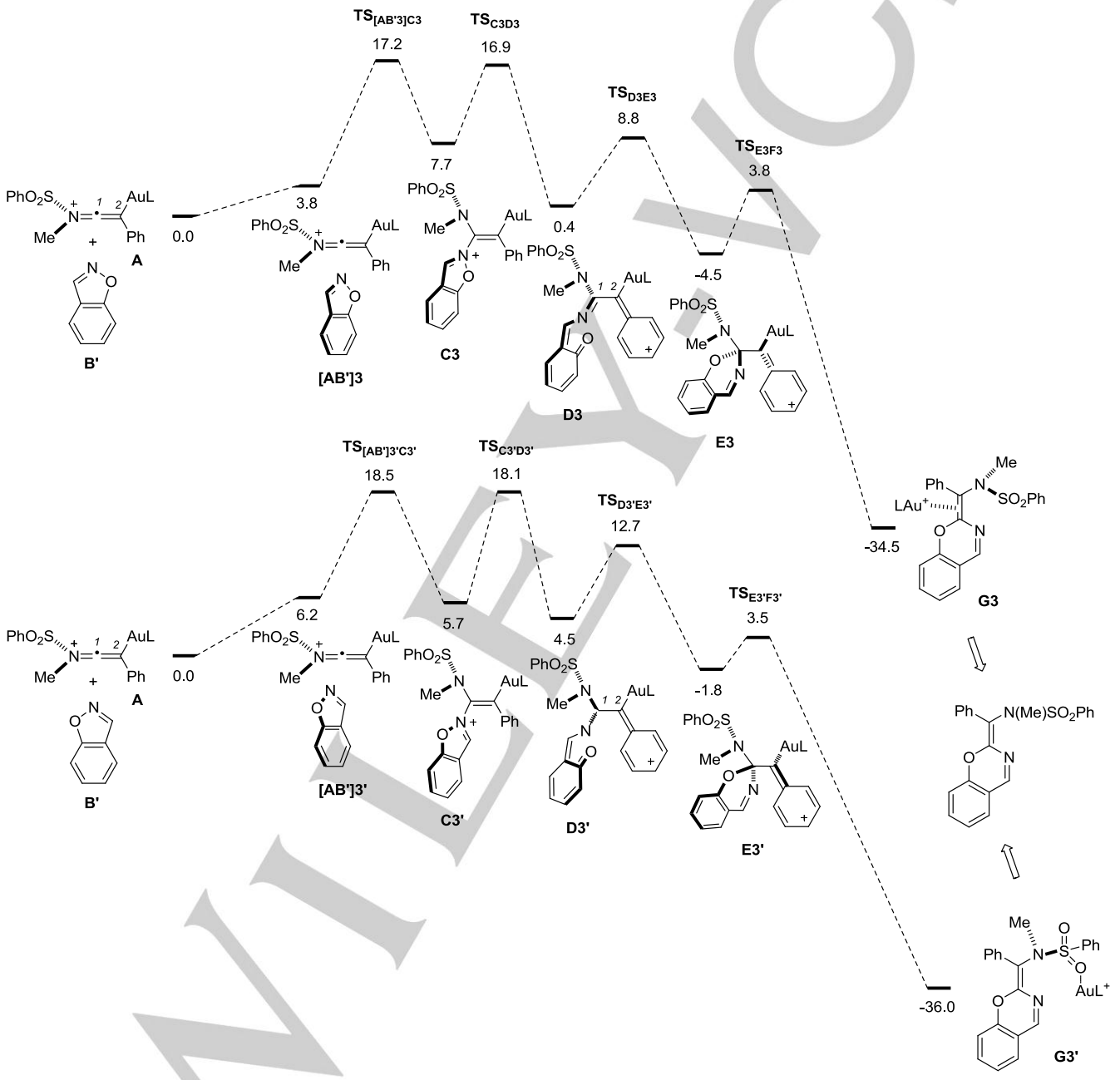
Scheme 9. Free energy profile (ΔG_{298}, kcal/mol) for the *anti*-addition of **B** to **A** with two Me groups on opposite sides.



Scheme 10. Free energy profiles (ΔG_{298}, kcal/mol) for the *syn* addition of **B** to **A**.

benzisoxazole have been taken as reference for the free energies. The investigation started with the *anti*-addition of the methyl-substituted benzisoxazole **B** relative to the gold atom in **A**. The first option in this *anti* addition series is an approach in which the-methyl group of **A** and that of **B** are on the same side (Scheme 8). Optimization of **A** and **B** in this orientation led to adduct **[AB]1**, located at 4.8 kcal/mol on the energy surface. The C1-N bond is formed through **TS[AB]1C1**, lying at 15.1 kcal/mol and yields the iminium complex **C1**, whose relative free energy is 1.4 kcal/mol. In agreement with Liu's proposal, a transition state corresponding to the cleavage of N–O bond produces **D1** at 3.9 kcal/mol. This step requires 15.3 kcal/mol of free energy of activation relatively to **[AB]1**. Of note, the C1C2 axis is chiral in **D1**, yet the steric hindrance did not allow its

inversion. No attack of the oxygen carbonyl to C2 could be found. Instead, a 6π-electrocyclization through $\mathbf{TS_{D1E1}}$ lying at 10.8 kcal/mol takes place to provide intermediate **E1**, located at −8.2 kcal/mol. This attack pushes the gold fragment in the opposite direction. Again, -no rotation around the C1C2 axis could be computed because of the high steric demand. Next, attack of the sulfonylated nitrogen to C2 via $\mathbf{TS_{E1F1}}$ at 4.7 kcal/mol led to aziridinium **F1** at −2.9 kcal/mol. The C1-N^+ bond is then cleaved through $\mathbf{TS_{F1G1}}$ lying at −2.0 kcal/mol, to yield the final complex **G1** found at −36.5 kcal/mol. The LAu fragment moves in the opposite direction of the incoming R_2N^+ electrophile during the C2-Au cleavage. Complex **G1** corresponds to the experimentally observed product with right stereochemistry (Scheme 8). In the second option, the approach of **B** to **A** with the two Me groups on opposite sides is computed (Scheme 9). This route is



Scheme 11. Free energy profiles (ΔG_{298}, kcal/mol) for the *anti* addition of **B'** to **A**.

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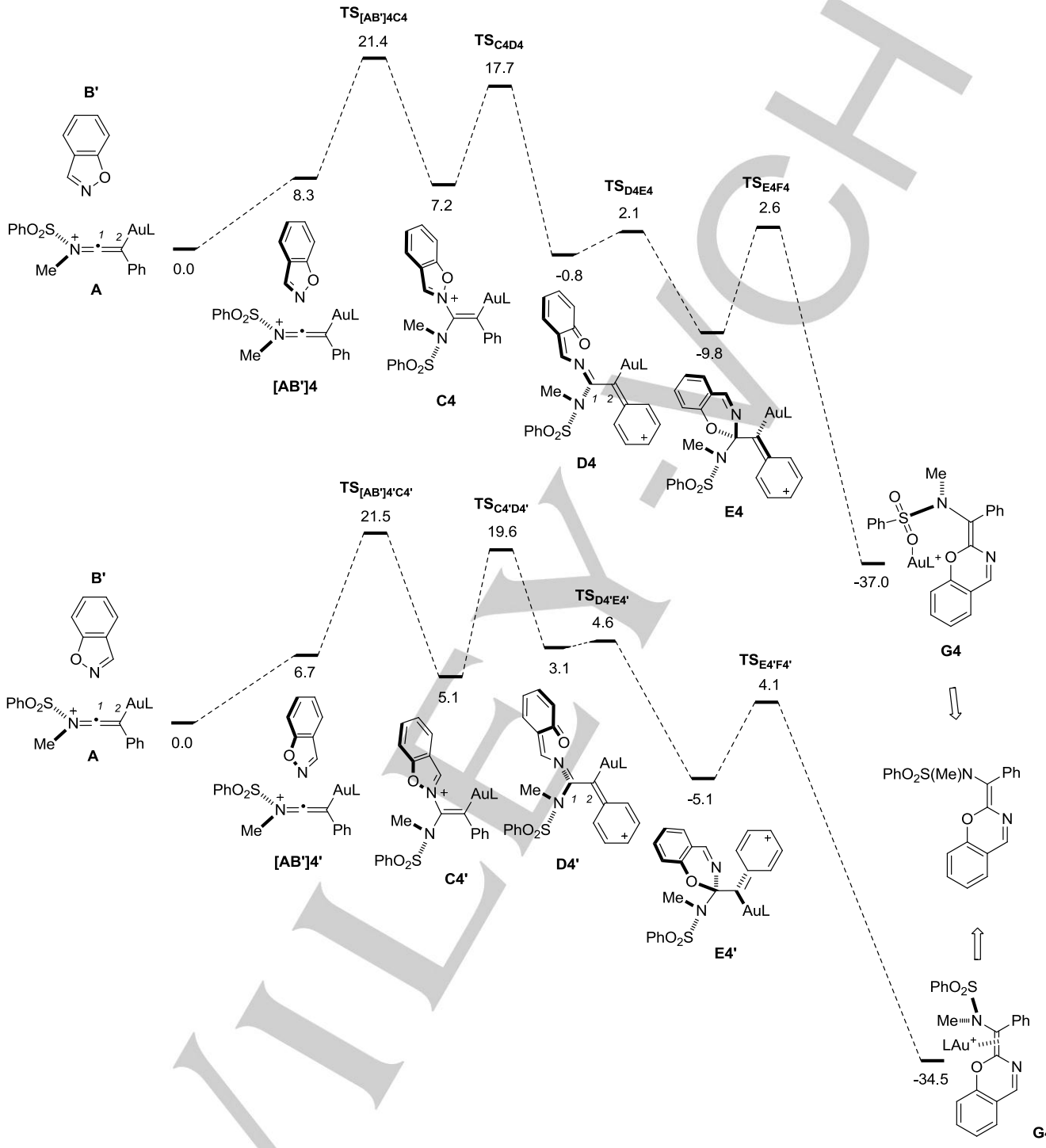


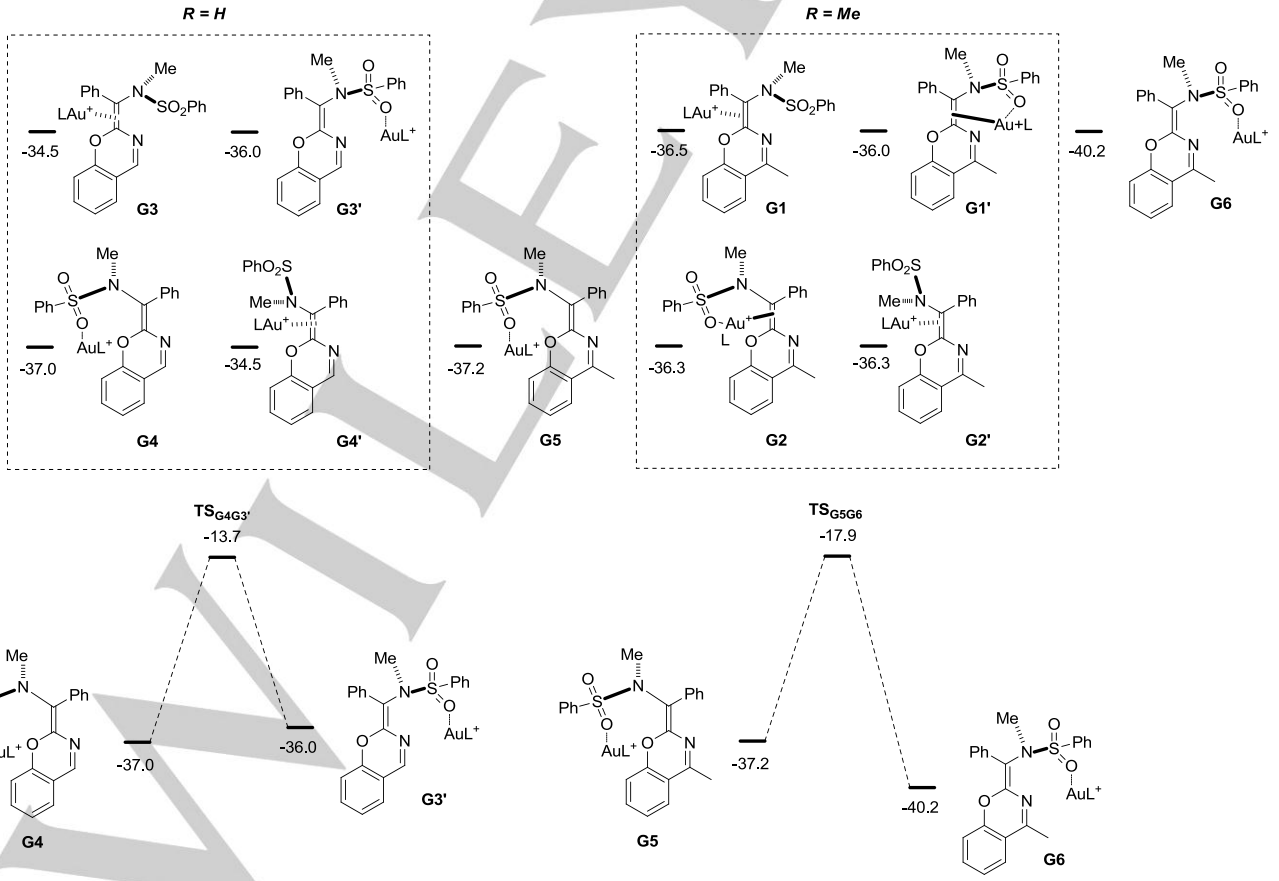
Scheme 12. Free energy profiles (ΔG_{298}, kcal/mol) for the *syn* addition of **B'** to **A**.

slightly less facile than the previous one depicted in Scheme 8, since the highest-lying transition state, $\mathbf{TS_{C1'D1'}}$, is 1.0 kcal/mol less stable than $\mathbf{TS_{C1D1}}$ (16.3 vs 15.3 kcal/mol respectively). In addition, the aziridinium complex does not converge. $\mathbf{TS_{E1'F1'}}$ directly leads to the final complex **G1'**. This is not surprising since the energy difference between **F1** and $\mathbf{TS_{F1G1}}$ is only 0.9

-kcal/mol (observed in the previous case, Scheme 8). Thus, the 1,2-N shift is concerted (shown in Scheme 9) instead of being a stepwise process. The structure **G1′** differs from **G1**, as a *syn*-interaction of both gold and the sulfonyl group oxygen is observed for **G1′**. Nevertheless, the free energy of **G1′** is virtually the same as that of **G1** (-36.0 vs -36.5 kcal/mol, respectively). Importantly, the attack of O to C1 imposes a rotation around the C1C2 axis; so gold becomes opposite to the oxygen. Since **B** had a different orientation from the beginning, this route leads to the same diastereomer, with two nitrogen on the right as depicted for **G1′**. To model the formation of the unobserved diastereomer (having the two nitrogen atoms in *trans*-relationship), the C1C2 chiral axis has to be inverted; but, as mentioned above, this looks unworkable for steric reasons. The only other way would be through a *syn*-attack of **B** to **A** with respect to gold, which is again possible in two ways (Scheme 10). Once more, no aziridinium complex could be found. Interestingly, the formation of complexes **E2** and **E2′** from **D2** and **D2′,** respectively is kinetically facile than in the *anti*-series. The *syn*-attack of **B** to **A** is however kinetically disfavored over the *anti*-attack. $\mathbf{TS_{[AB]2C2}}$ and $\mathbf{TS_{[AB]2'C2'}}$ were located at 19.6 and 20.7 kcal/mol (Scheme 10), respectively on the energy surface, while the previous $\mathbf{TS_{[AB]1C1}}$ and $\mathbf{TS_{[AB]1'C1'}}$ were found at 15.1 and 14.5 kcal/mol (Schemes 8 and 9), respectively. In the *syn*-series, the first step clearly is rate determining, while the second step in the *anti*-series is rate determining.

These results are perfectly in line with the experimental results, but do not provide an explanation to the inversion of diastereoselectivity when R = H. Liu and co-workers indeed reported product with a *trans*-relationship between the two nitrogen around the C1C2 bond.[12a] The four energy profiles shown above were thus recomputed with benzisoxazole itself. The results are summarized in Schemes 11 and 12. Among the two options for *anti*-attack of benzisoxazole (**B'**) to **A** (Scheme 11), the **[AB']3** to **D3** pathway is preferred over the **[AB']3'** to **D3',** as the corresponding free energies of activation are 17.2/16.9 vs 18.5/18.1 kcal/mol. Again, inversion of the C1C2 chiral axis was not possible; thus, 1,2-nitrogen shift was found to be concerted. The structure **G3′** is different from the previous cases, as the exocyclic double bond does not serve as ligand anymore. This point is further discussed below.

Scheme 13. Relative free energy of the diastereomers of the final products.



Scheme 14. Relative free energy of the diastereomers of the final **G**-type complexes (ΔG_{298}, kcal/mol).

In the case of the *syn*-attack of benzisoxazole (**B'**) to **A** (Scheme 12), the **[AB']4** to **D4** pathway is preferred over **[AB']4'** to **D4'**; this is concluded from the comparison of the free energies of activation of the second steps (17.7 vs 19.6 kcal/mol). The other features are similar to those previously discussed.

Thus, the *anti*-attack of benzisoxazole to ynamide seems predominant, but it does not rationalize the formation of the experimentally observed products. To explain this apparent discrepancy, we then focused on the relative stability of the final products and the final complexes involved for the **G** series. With both R = H or Me, the products showing a *cis* relationship of the nitrogen atoms are more stable (Scheme 13).

For the **G**-type complexes, **G4** is the most stable at –37.0 kcal/mol (Scheme 14). It corresponds to the experimentally observed product by Liu and co-workers. Of note, **G4** can be connected to **G3′**, lying at -36.0 kcal/mol, via the C1C2 rotation transition state $\mathbf{TS_{G4G3'}}$. If **G3′** is formed preferentially as shown above, it may then undergo a stereo-mutation through this transition state. This would require a reasonable free energy of activation of 22.3 kcal/mol from **G3′**. We modeled complexes similar to **G4** and **G3′** in the R = Me series. Interestingly, the most stable isomer is **G6** at -40.2 kcal/mol. It also corresponds to the experimentally observed product. Its conversion into the unobserved isomer **G5** would coincidently require 22.3 kcal/mol of free energy of activation but it would be endergonic by 3.0 kcal/mol.[13] From the above DFT computations, we can predict a similar mechanism with 3-methylbenzo[d]isoxazole (R = Me) and benzo[d]isoxazole (R = H), which corresponds to Schemes 8 and 11 (upper part). The reason for the different diastereoisomers obtained could be due to a post-isomerization since the final complexes have different stability depending on the substitution pattern.

Conclusions

In summary, a synthetic manifestation for the construction of benzo[e][1,3]oxazine derivatives from the Au(I)-catalyzed annulation of ynamide and substituted-benzisoxazole has been developed. The transformation involves an α-oximino gold carbene intermediate, obtained through the attack of the benzisoxazole to the α-position of Au-activated ynamide followed by the electron-back donation and delocalization cleaving the benzisoxazole O–N bond and then ring expansion cascade. Finally 1,2-sulfonamide migration and deauration leads to benzo[e][1,3]oxazine derivatives (major *E*-isomer). The reaction is general, featuring a broad scope. The detailed DFT studies rationalize the dichotomy of product selectivities.

Experimental Section

General Procedure for Regioselective Annulation of Ynamides (1) with Benzo[d]isoxazole (2): To the solution of ynamide **1** (1.0 equiv, 0.3 mmol), benzo[d]isoxazole **2** (2.0 equiv, 0.6 mmol) in $CHCl_3$ (0.3 mL for 0.3 mmol) in the reaction tube was added JohnPhosAu(MeCN)SbF_6 (5.0 mol %). The resulting mixture was stirred at rt for 4 h. Progress of the reaction was monitored periodically by TLC. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The crude mixture was filtered through a small pad of Celite and concentrated under the reduced pressure. The crude residue was purified through column chromatography on neutral alumina using ethylacetate and hexane to provide **3.**

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Keywords: Au-carbene • ynamide • benzisoxazole • 1,2-migration • ring expansion

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[13] Note that the isomerization of **G3** into the enantiomer of **G4'** is also possible in both series, but the corresponding transition states have free energy about 5 kcal/mol higher than those discussed.

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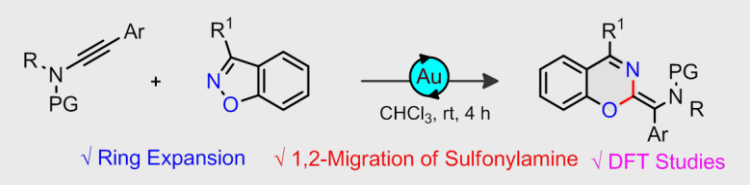

Demonstrated herein is a Au(I)-catalyzed annulation of sulfonyl-protected ynamides with substituted 1,2-benzisoxazoles for the synthesis of *E* benzo[e][1,3]oxazine derivatives. The transformation involves the addition of benzisoxazole to the gold-activated ynamide, ring expansion of the benzisoxazole fragment to provide an α-oximino gold carbene, and the 1,2-migration of the sulfonamide motif to the carbene center to deliver the respective ring expanded benzo[e][1,3]oxazine of predominant *E* configuration.

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