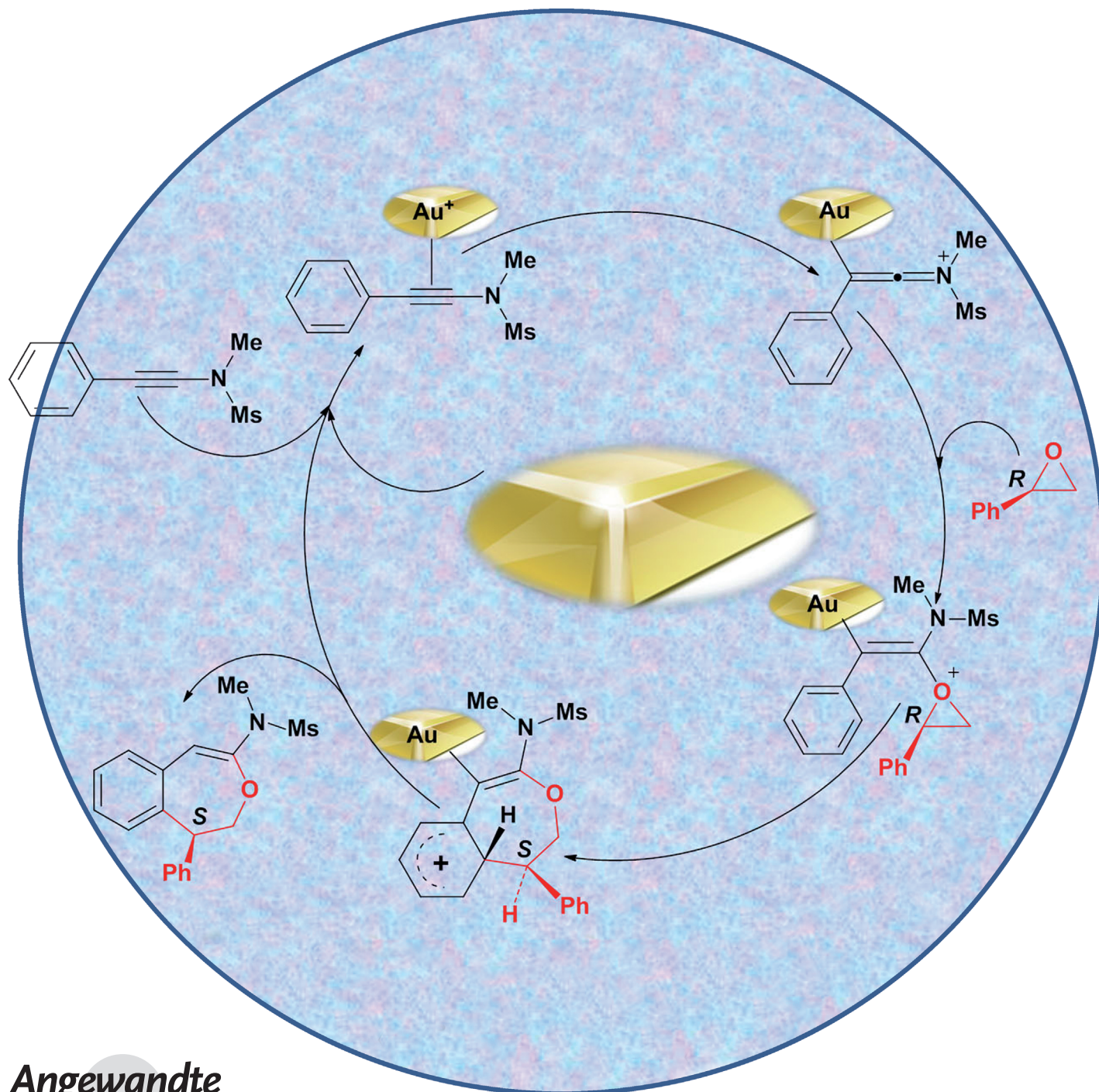
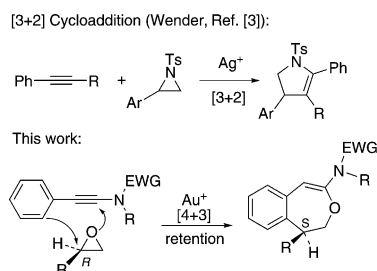


Retention of Stereochemistry in Gold-Catalyzed Formal [4+3] Cycloaddition of Epoxides with Arenynamides**

Somnath Narayan Karad, Sabyasachi Bhunia, and Rai-Shung Liu*



Metal-mediated intermolecular cycloadditions are powerful tools to access carbo- and heterocyclic frameworks.^[1] Epoxides and aziridines serve as three-atom building units for various metal-mediated [3 + *n*] cycloadditions (*n* = 2, 3) with small molecules.^[2–7] The cycloadditions of epoxides and aziridines with alkenes or alkynes exclusively proceeded through [3 + 2] cycloadditions,^[3,4] whereas [3 + 3] cycloadditions occurred for propargylmetal reagents.^[5] Catalytic intermolecular [4 + 3] cycloadditions of epoxides or aziridines have only one precedent.^[8] Herein, we report a new synthesis of seven-membered oxacycles through a gold-catalyzed intermolecular [4C + 3] cycloaddition^[9] of arenynamides with epoxides (Scheme 1). Particularly notable is the observed



Scheme 1. Cycloadditions of phenylalkynes with epoxides or aziridines. EWG = electron-withdrawing group, Ts = 4-toluenesulfonyl.

retention of stereochemistry in the gold-catalyzed ring opening of epoxides during the attack of external arene nucleophiles (Scheme 1). This process contrasts sharply with a silver-catalyzed [3 + 2] cycloaddition between 1-phenylalkynes and aziridines, reported by Wender and Strand.^[3]

We examined the cycloaddition reactions of arenynamide **1a** with isobutylene oxide **2a** over cationic gold complexes, which are active catalysts for the intermolecular [4 + 2] cycloadditions of arenynamide **1a** with electron-rich alkenes.^[10] The reaction of arenynamide **1a** with epoxide **2a** (4 equiv) using [PPh₃AuCl]/AgNTf₂ (5 mol %) in dichloromethane (28 °C, 4 h) gave a mixture of products, from which we isolated [4 + 3] cycloadduct **3a** in only 4 % yield (Table 1, entry 1). To our pleasure, the use of [P(*o*-biphenyl)(*t*Bu)₂AuCl]/AgNTf₂ gave cycloadduct **3a** in a significant proportion (62 %, entry 2). [IPrAuCl]/AgNTf₂ (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) improved the yield of desired **3a** to 87 % yield (entry 3). Variation of silver salts as in [IPrAuCl]/AgX (X = SbF₆ and OTf, entries 4 and 5) led to compound **3a** in a decreased yield of 71 % and 20 %, respectively; weakly acidic [IPrAuOTf] appears to be less efficient in this cycloaddition. We found no reactivity for AgNTf₂ or AgSbF₆ catalysts (entries 6 and 7). HOTf gave

Table 1: Tests of the [4 + 3] cycloaddition over gold catalysts.

Entry	Catalyst ^[a]	Solvent	Time [h]	Yield [%] 1a 3a ^[b]
1	[PPh ₃ AuCl]/AgNTf ₂	CH ₂ Cl ₂	4.0	— 4
2	[LAuCl]/AgNTf ₂	CH ₂ Cl ₂	4.0	— 62
3	[IPrAuCl]/AgNTf ₂	CH ₂ Cl ₂	1.8	— 87
4	[IPrAuCl]/[AgSbF ₆]	CH ₂ Cl ₂	1.7	— 71
5	[IPrAuCl]/AgOTf	CH ₂ Cl ₂	3.0	— 20
6	AgNTf ₂	CH ₂ Cl ₂	12	85 —
7	[AgSbF ₆]	CH ₂ Cl ₂	12	80 —
8	HOTf	CH ₂ Cl ₂	4.0	— — ^[c]
9	[IPrAuCl]/AgNTf ₂	(CH ₂ Cl) ₂	1.7	20 61
10	[IPrAuCl]/AgNTf ₂	toluene	12	14 58
11	[IPrAuCl]/AgNTf ₂	CH ₃ CN	12	85 —

[a] [**1a**] = 0.20 M. [b] Determined after purification by column chromatography on neutral alumina. [c] Ketone **1A** was isolated in 76 % yield. Bn = benzyl, IPr = 1,3-bis(diisopropyl phenyl)imidazol-2-ylidene, L = (*o*-biphenyl)(*t*Bu)₂P, Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl.

hydration product **1A** in 76 % yield (entry 8). For [IPrAuNTf₂], the yield of compound **3a** depended on the solvents: dichloroethane (61 %), toluene (58 %), and acetonitrile (0 %); unreacted **1a** was recovered in 14–85 % (entries 9–11). Treatment of compound **3a** with HOTf (3 mol %) in wet CH₂Cl₂ (0 °C, 1 h) delivered lactone **3A** in 85 % yield.

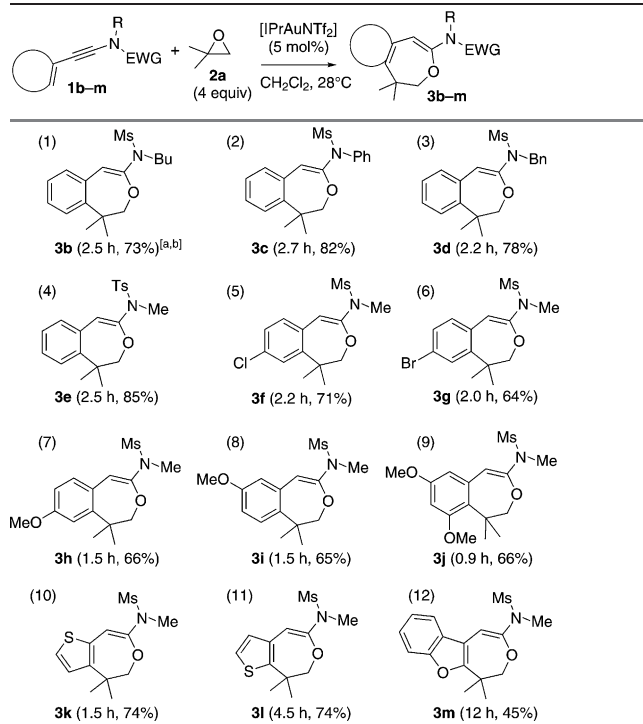
The chemoselectivity for seven-membered oxacycle **3a** is unexpected, because similar reactions typically gave the [3 + 2] cycloadduct.^[3,4] Accordingly, we examined the scope of arenynamides with alterable amides and aryl substituents. Table 2 shows the results for the [4 + 3] cycloadditions of arenynamides **1b–1m** with epoxide **2a** using [IPrAuCl]/AgNTf₂ (5 mol %) in CH₂Cl₂ (28 °C, 0.9–12 h). We obtained only seven-membered oxacycles **3b–3m** after workup; the absence of [3 + 2] cycloadducts was ascertained by ¹H NMR spectroscopy of their crude products. These cycloadditions worked well for substrates **1b–1e**, which bear various amido substituents (EWG = tosyl and mesyl; R = methyl, *n*-butyl, benzyl, and phenyl); the resulting cycloadducts **3b–3e** were obtained in 73–85 % yield (entries 1–4). We tested the reactions on arenynes **1f** and **1g**, which bear 4-chloro and 4-bromo substituents, giving desired cycloadducts **3f** and **3g** in 71 % and 64 % yield, respectively (entries 5 and 6). We studied the reactions on arenynamides **1h–1j**, which bear electron-rich benzenes; their resulting oxacycles **3h–3j** were obtained in 65–66 % yield (entries 7–9). The scope of the reactions was further expanded to arenynamides **1k–1m**, which bear 2- and 3-thienyl and 3-benzofuranyl and produced cycloadducts **3k–3m** in 45–74 % yield (entries 10–12). A protracted period (12 h) was observed for the formation of benzofuranyl derivative **3m** because of its bulky size, which is unfavorable for an S_N2-type front attack at the epoxide.

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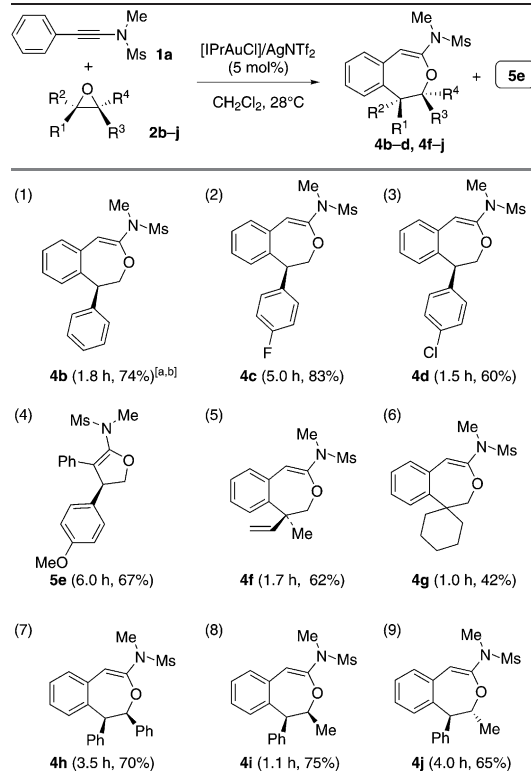
Table 2: [4+3] Cycloadditions on various arenynes.



[a] [arenynamides] = 0.20 M, [IPrAuCl]/AgNTf₂ (5 mol%), CH₂Cl₂, 28°C. [b] Determined after purification by column chromatography on neutral alumina.

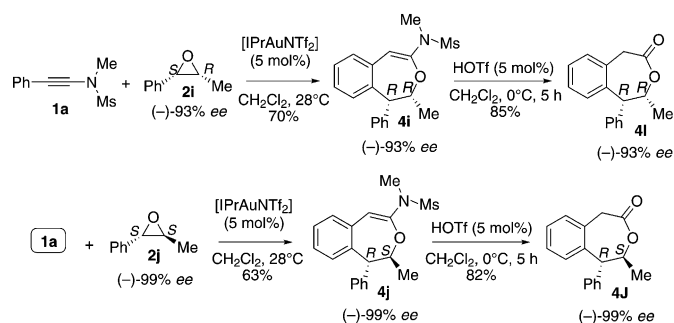
Various epoxides **2b–2j** were subjected to gold-catalyzed cycloadditions on arenynamide **1a** (Table 3); except 4-methoxyphenyloxirane **2e** (entry 4), all these substrates produced [4+3] cycloadducts. With styrene oxide **2b** and its 4-fluoro- and 4-chlorophenyl derivatives **2c** and **2d**, respectively, the corresponding [4+3] cycloadducts **4b–4d** were produced in 60–83% yield (entries 1–3). Notably, electron-rich 4-methoxyphenyloxirane **2e** gave [3+2] cycloadduct **5e** in 67% yield, however, the reaction took longer (6 h), thus reflecting a significant electronic effect to alter reaction chemoselectivity (entry 4). This [4+3] cycloaddition is extensible to 1,1-disubstituted epoxides **2f** and **2g**, which gave desired products **4f** and **4g** in 62% and 42% yield, respectively (entries 5 and 6). We tested *cis*- or *trans*-1,2-disubstituted epoxides **2h–2j** to study the stereochemical course of this [4+3] cycloaddition (entries 7–9). In the reactions of *cis*-stilbene oxide **2h** (R¹ = R³ = Ph, R² = R⁴ = H), the resulting cycloadduct **4h** was obtained in 70% yield. X-ray diffraction study on compound **4h** showed a *cis*-configuration for its two phenyl substituents,^[11] indicative of the retention of stereochemistry. For *cis*-2-methylstyrene oxide **2i** (R¹ = Ph, R³ = Me, R² = R⁴ = H) and its *trans* analogue **2j** (R¹ = Ph, R⁴ = Me, R² = R³ = H), their corresponding products **4i** and **4j** were produced stereoselectively with 75% and 65% yield, respectively (entries 8 and 9); we did not obtain the other diastereomer. The *cis* configuration of cycloadduct **4i** was likewise determined by X-ray diffraction,^[11] again showing the retention of stereochemistry.

Table 3: Cycloaddition reactions on various epoxides.



[a] [arenynamides] = 0.20 M. [b] Determined after purification by column chromatography on neutral alumina.

This cycloaddition is applicable to the synthesis of enantiopure oxacycle **4i** (93% *ee*) using (2*R*,3*S*)-(–)-2-methyl-3-phenyloxirane **2i** (93% *ee*, Scheme 2). X-ray diffraction of **4i** confirmed the retention of stereochemistry.^[11]



Scheme 2. Synthesis of enantiopure seven-membered lactones.

Hydrolysis of this cycloadduct afforded chiral lactone **4l** in 93% *ee*. The use of enantiopure (2*S*,3*S*)-(–)-2-methyl-3-phenyloxirane **2j** (99% *ee*) efficiently delivered the corresponding cycloadduct **4j** (99% *ee*), and subsequently lactone **4m** (99% *ee*).

We examined the enantiospecificity of the [4+3] and [3+2] cycloadditions using enantiopure aryl-substituted oxiranes (Table 4); this information may enable us to understand

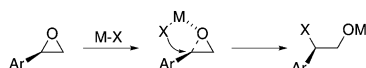
Table 4: Enantiospecificity for [4+3] and [3+2] cycloadditions.

Entry	Epoxide ^[a]	ee [%]	Products	Yield [%] ^[c]
	2 (Ar)		4/5 (ee [%]) ^[b]	
1	2b (C ₆ H ₅)	99 (+)	(+)- 4b (81)	73
2	2c (4-FC ₆ H ₄)	99 (+)	(+)- 4c (70)	68
3	2d (4-ClC ₆ H ₄)	99 (+)	(+)- 4d (75)	55
4	2k (4-MeC ₆ H ₄)	99 (–)	(–)- 4k (39), <i>rac</i> - 5k (0)	65
5	2e (4-MeOC ₆ H ₄)	99 (–)	<i>rac</i> - 5e (0)	61

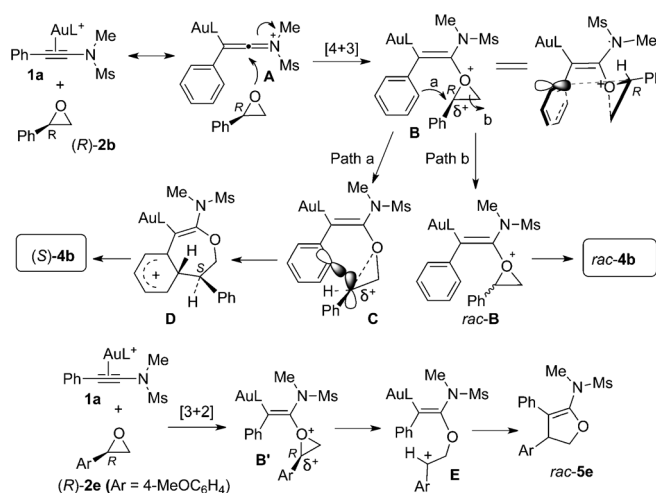
[a] [**1a**] = 0.20 M, 4 h for entries 1–3, 10 h for entries 4 and 5. [b] ee values were determined by HPLC analysis on a chiral stationary phase (chiralpak AD-H). [c] Determined after separation by column chromatography on neutral alumina.

the reaction chemoselectivity. For (*R*)-styrene oxide **2b** (99% ee), its gold-catalyzed cycloaddition with arenyn **1a** afforded [4+3] cycloadduct **4b** with (+)-81% ee (entry 1). Its absolute configuration was determined to be *S* by X-ray diffraction,^[11] again indicating a retention of stereochemistry. For (*R*)-4-fluoro- and (*R*)-4-chlorophenyl oxirane **2c** and **2d** (99% ee), their corresponding [4+3] cycloadducts (*S*)-**4c** and (*S*)-**4d** were obtained with 70% and 75% ee, respectively (entries 2 and 3). (*R*)-4-Methylphenyl oxirane **2k** (99% ee) gave an inseparable mixture of two the cycloadducts **4k/5k** = 1:4 (entry 4); seven-membered oxacycle **4k** was obtained with 39% ee, whereas five-membered species **5k** was completely racemic. For (*R*)-4-methoxyphenyl oxirane **2e**, we obtained only the racemic form of [3+2] cycloadduct **5e** in 61% yield. Our results show that formation of seven-membered oxacycle **4** occurs at the early stage of oxirane cleavage to achieve an S_N2-type retention, whereas five-membered oxacycles **5** are produced on a free benzylic cation after a complete oxirane cleavage.

S_N2-type retention of stereochemistry was documented for few stoichiometric reactions between epoxides and AlX₃ (X = Cl, Me),^[12] in which a coordinated ligand X attacks at the reacting carbon center from the front side (Scheme 3).


Scheme 3. Metal-assisted ligand migration in S_N2-type retention.

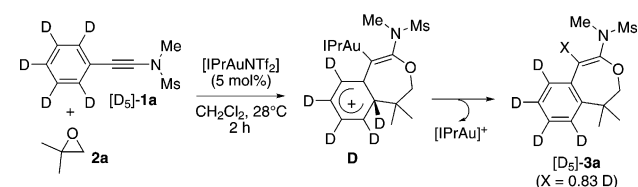
This 1,4 ligand migration is in disagreement with the mechanism of the retention chemistry in our system. Scheme 4 shows a plausible mechanism for the [4+3] cycloaddition, Au-π-ynamide **1a** is highly electrophilic, and also represented by its ketenimine resonance structure **A**.^[13,14] An attack of (*R*)-epoxide **2b** at the C=NMeMs carbon center of species **A** gives an oxonium species **B**, which still retains an oxiranyl ring. Attack of the neighboring benzene at the epoxide in an S_N2-type inversion is unlikely because of its front orientation. Instead, we envisage that species **B** has a ground-state conformation that involves a parallel orientation between the benzene and oxiranyl rings. This conforma-


Scheme 4. Plausible mechanisms for [4+3] and [3+2] cycloadditions.

tion facilitates a front attack of benzene at the reacting oxiranyl carbon atom because of their proximity. Formation of the C–C bond and C–O bond cleavage might be concerted, as shown in structure **C** (path a), subsequently forming a cyclohexadienyl cation **D**, which bears an *S*-configuration. This pathway is expected to give oxacyclic product (*S*)-**4b**. We envisage that the oxiranyl PhC–O bond of species **B** is rather weak to allow a C–C bond rotation. Accordingly, a small portion of intermediate **B** undergoes an epimerization of oxirane to form *rac*-**B**; this process rationalizes a small loss of chirality for resulting cycloadduct **4b**. The high stereospecificity for 1,2-disubstituted epoxides **2i** and **2j** is attributed to their rigid conformation **B**, which has a barrier to rotate the C–O bond between the oxiranyl and alkenylgold moieties.

This postulated model also rationalizes the non-stereospecific [3+2] cycloaddition of (*R*)-4-methoxyphenyloxirane **2e** and arenynamide **1a** (Table 4, entry 5). In this instance, the corresponding benzylic cation **E** is readily attained because of the stabilization effect of 4-methoxyphenyl. This benzylic cation moves freely toward gold alkenyl to deliver a [3+2] oxacycle **5e** with a complete loss of chirality.

We prepared [D₅]-**1a** to confirm the intermediacy of species **D** (Scheme 5); its resulting cycloadduct [D₅]-**3a** has a high deuterium content (X = 0.83 D) at its alkenyl position.


Scheme 5. Deuterium labeling experiment.

This result indicates the occurrence of a deauration process at this alkenyl carbon atom.

Thus far, epoxides participated almost exclusively in metal-catalyzed [3+2]^[3,4] or [3+3] cycloaddition^[5] reactions. We have now developed a gold-catalyzed [4+3] cycloaddition of epoxides with arenynamides with a broad substrate scope.

Of particular interest is the retention of stereochemistry^[15,16] for an intermolecular aryl attack at the epoxide. We used various enantiopure aryl-substituted oxiranes to study the chirality transfer in the [4+3] and [3+2] cycloadditions; their mechanisms are thus elucidated. We postulate an S_N2-type front-side attack of phenyl at the oxiranyl ring for [4+3] cycloadducts, whereas an attack at a free benzylic cation leads to [3+2] products that contain benzoxepine frameworks (represented by cycloadducts **3**), which can be found in several naturally occurring compounds;^[17] their enantioselective synthesis is under current investigations.

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