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Gold(I)-Catalyzed Highly Diastereo- and Enantioselective Cyclization/[4+3] Annulation Cascades between 2-(1-Alkynyl)-2-alken-1-ones and Anthranils

Rahul Dadabhau Kardile,[a] Tzu-Hsuan Chao,[b] Mu-Jeng Cheng*[b] and Rai-Shung Liu[a]*

Abstract: This work reports gold-catalyzed [4+3]-annulations of 2-(1-alkynyl)-2-alken-1-ones with anthranils to yield epoxybenzoazepine products with excellent *exo*-diastereoselectivity (dr > 25:1). The utility of this new gold catalysis is manifested by applicable substrates over a broad scope. More importantly, the enantioselective versions of these [4+3]-cycloadditions have been developed satisfactorily with chiral gold catalysts under ambient conditions (DCM, 0 °C); the ee levels range from 88.0-99.9%. With DFT calculations, we postulate a stepwise pathway to rationalize the preferable *exo*-stereoselection.

Nitroxy (N-O) functionalities commonly exist as the structural cores in numerous synthetic drugs or naturally occurring compounds.[1,2] Among them, tetrahydro-1*H*-benzo[*b*]azepines bearing a hydroxyl group, such as species **I**-**IV**,[3] are representatives of seven-membered alkaloids, which show strong biological activity in antiparastic disease,[3a] antidiuretic hormone receptors[3b] and β_2-adrenergic agonists[3e-f]. One convenient and easy construction of this seven-membered azacyclic core is to realize catalytic [4+3]-annulations between

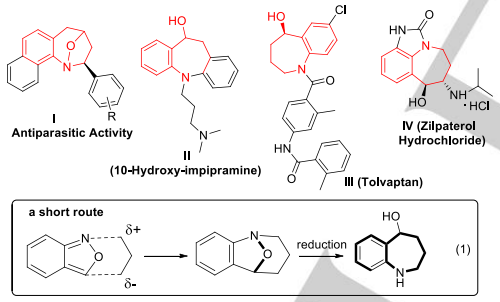
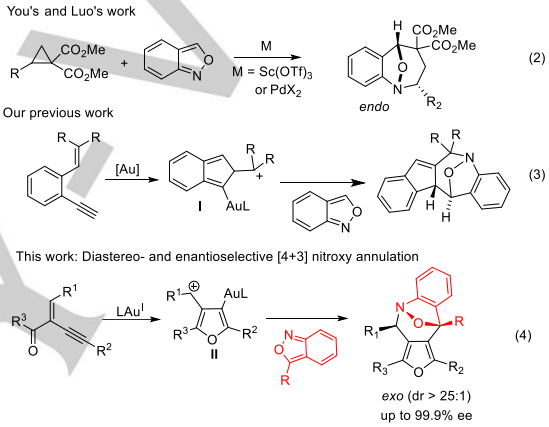


Figure 1: Selected bioactive molecules and a short synthetic route

anthranils with suitable all carbon 1,3-dipoles, according to the protocol in eq 1.[4,5] Despite this practicability, there are only very few all carbon 1,3-dipoles to react with anthranils in catalytic [4+3]-annulations. Luo et. al.[4a] reported the first examples to employ donor-acceptor cyclopropanes to generate Sc(III)-enolate-containing carbocations, further furnishing the [4+3]-annulations with anthranils (eq 2). The enantioselective versions of such [4+3]-cyclopropane/anthranil annulations are recently achieved by You[4b] and coworkers, using chiral palladium catalysts. We recently achieved gold-catalyzed [4+3]-annulations between 2-alkenyl-1-ethynylbenzenes and anthranils in racemic versions;[5] this process involves a trap of gold-containing isobenzofulvene cation (**I**) with anthranils (eq 3). To highlight this 1,3-dipole approach (eq 1), we report new



gold-catalyzed [4+3]-annulations[6] using 2-(1-alkynyl)-2-alken-1-ones to generate gold-containing 3-furyl methyl cations (II),[7] further leading to furan-fused epoxybenzoazepines with excellent diastereoselectivity (dr > 25:1, eq 4). Notably, this exclusive *exo*-stereoselection is distinct from the *endo*-selectivity in the cyclopropane system.[4] Apart from diastereoselectivity, we also developed highly enantioselective [4+3]-cycloadditions using chiral gold catalysts,[8] further manifesting the synthetic significance. The work reports the first success to use anthranils in gold-catalyzed asymmetric reactions.[9]

We optimized the reactions of 2-(1-alkynyl)-2-alken-1-one **1a** with anthranil **2a** (1.5 equiv.) using various gold catalysts; the results are shown in Table 1. Initially, the reaction of species **1a** and anthranil **2a** was investigated with $Ph_3PAuCl/AgNTf_2$ (5 mol %) in dry dichloromethane (4Å MS, DCM, 0.5 h) at room temperature; this condition afforded a [4+3]-annulation product epoxybenzo[*b*]furo[3,4-*e*]azepine **3a** as one diastereomer in 80% yield (dr > 25:1, entry 1). The use of $(PhO)_3PAuCl/AgNTf_2$ (5 mol%) provided **3a** in 68% yield (entry 2). Other gold catalysts L'AuCl/$AgNTf_2$ (L'= IPr and P(*t*-Bu)$_2$(o-biphenyl)) gave the desired product **3a** in 40-41% yields whereas unreacted **1a** was recovered in 30-35% (entries 3-4). The variation of silver salts as in Ph_3PAuCl/AgX, (X = SbF_6 and OTf) maintained high efficiency to yield compound **3a** in 73-75% yields (entries 5-6). For $Ph_3PAuCl/AgNTf_2$ in different solvents (entries 7-9), the yields of compound **3a** were as follows: dichloroethane (77%), toluene (30%) and nitromethane (0%). $AgNTf_2$ alone in DCM was completely inactive (entry 10). The molecular structure of compound **3a** was confirmed by its X-ray diffraction[10] to reveal

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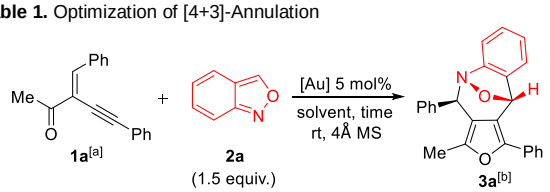
Table 1. Optimization of [4+3]-Annulation



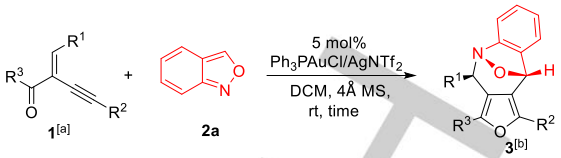
Entry	Catalyst (5 mol%)	Time (h)	Solvent	Yields(%)[b]	
				3a	**1a**
1	**$Ph_3PAuCl/AgNTf_2$**	**0.5**	**DCM**	**80**	**--**
2	$(PhO)_3PAuCl/AgNTf_2$	1	DCM	68	--
3	$IPrAuCl/AgNTf_2$	9	DCM	40	35
4	$LAuCl/AgNTf_2$	15	DCM	41	30
5	$Ph_3PAuCl/AgSbF_6$	1	DCM	73	--
6	$Ph_3PAuCl/AgOTf$	2	DCM	75	--
7	$Ph_3PAuCl/AgNTf_2$	1	DCE	77	--
8	$Ph_3PAuCl/AgNTf_2$	10	toluene	30	45
9	$Ph_3PAuCl/AgNTf_2$	24	$MeNO_2$	--	77
10	$AgNTf_2$	24	DCM	--	90

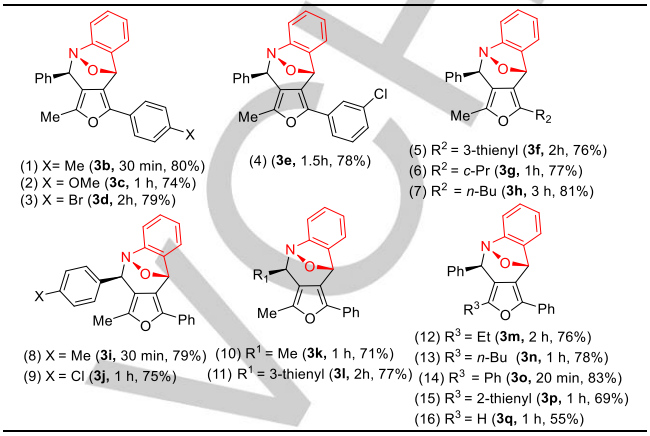
[a] **[1a]** = 0.1 M. [b] Product yields are obtained after purification from a silica column. IPr = 1,3-bis(diisopropylphenyl) imidazol-2-ylidene. L = $P(t\text{-}Bu)_2(o\text{-}biphenyl)$.

an *exo*-configuration.

We assessed the substrate scope of these new annulations using various enynones **1** and $Ph_3PAuCl/AgNTf_2$ under the standard condition; the resulting products **3** were present exclusively as one diastereomer (dr > 25:1). We examined the reactions of enynones **1b-1d** bearing various alkynyl substituents 4-XC_6H_4 (X = Me, OMe and Br), further affording desired products **3b-3d** in satisfactory yields (74-80%, entries 1-3). For these alkynyl substituents, we also tested an enynone **1e** bearing a 3-chlorophenyl derivative, furnishing compound **3e** in 78% yield (entry 4). We prepared also enynone **1f** possessing a 3-thienylalkyne moiety; the reaction proceeded smoothly to deliver compound **3f** in 76% yield (entry 5). We prepared also alkyl-substituted alkynes **1g-1h** (R^2 = cyclopropyl and *n*-butyl) that provided the desired products **3g-3h** in 77-81 % yields (entries 6-7). We next varied the alkenyl substituents (R^1) of enynones **1i-1j** with R^2 = 4-XC_6H_4 (X = Me and Cl); their resulting products **3i** and **3j** were obtained in 75-79% yields (entries 8-9). For methyl- and 3-thienyl-substituted alkene deivatives **1k** and **1l**, these gold catalyzed reactions furnished compounds **3k** and **3l** in 71% and 77% yields (entries 10-11). Our variations of the ketone substituents were also suitable to this gold catalysis.As shown in entries 12-13, alkylketone derivatives **1m** and **1n** (R^3 = ethyl and *n*-butyl) were applicable substrates delivering their products **3m-3n** in 76 and 78% yields respectively. Enynones **1o-1p** bearing phenyl and 2-thienyl ketones were also applicable substrates to produce compounds **3o-3p** in 83% and 69% yields (entry 14-15). Aldehyde substrate **1q** (R_3 = H) was less efficient, affording compound **3q** in 55% yield (entry 16). We also prepared one enynone **1r** with

Table 2. Reactions on Various 2-(1-Alkynyl)-2-alken-1-ones



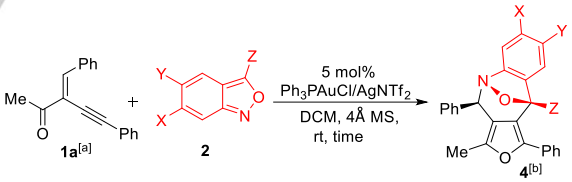


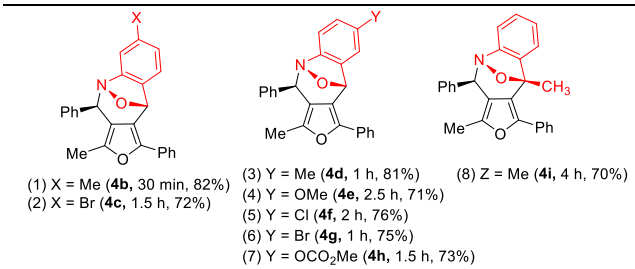
[a] [1] = 0.1 M. [b] Product yields are obtained after separation from silica column

R^1 = n-butyl and R^2, R^3 = Ph that gave a complicated mixture of products. For the key 1,3-dipole intermediate (eq 4), the presence of R^1 = aryl in crucial to stabilize its cation stability.

Table 3 summarizes the catalytic [4+3]-annulations of various substituted anthranils (**2b-2i**) with model enynone **1a**; only one diastereomeric product was obtained exclusively. For anthranils **2b-2c** bearing X = Me and Br at the C(6) carbon, their corresponding epoxybenzoazepines **4b** and **4c** were obtained in82% and 72% yields respectively (entries 1 and 2). This gold catalysis worked well with additional anthranils **2d-2h** bearing

Table 3. Reactions on Various Anthranils





[a] [1] = 0.1 M. [b] Product yields are obtained after separation from silica column

various substituents at the C(5) carbon (Y = Me, OMe, Cl, Br and OCO_2Me), delivering cyclic nitroxy products **4d-4h** with the yields exceeding 73% (entries 3-7). We tested the reaction of C(3)-substituted anthranil **2i** with Z = Me, further producing compound **4i** in 70% yield (entry 8). A wide scope of applicable enynones and anthranils manifests the practicability of these

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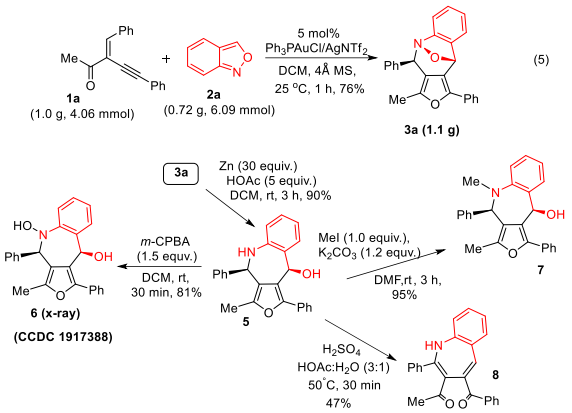


Scheme 1: Gram scale synthesis and chemical functionalizations

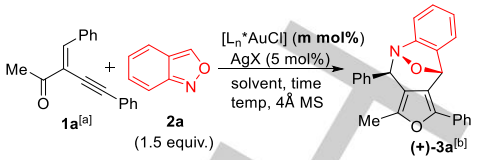
[4+3]-nitroxy annulations.

A gram-scale synthesis and chemical fumctionalizations are depicted in scheme 1. Treatment of compound **1a** (1.0 g, 4.06 mmol) with anthranil **2a** (1.5 equiv.) and $PPh_3AuCl/AgNTf_2$ (5 mmol) in DCM furnished epoxybenzoazepine **3a** in 76% yield (eq 5). Treatment of species **3a** with Zn powder (30 equiv.)/HOAc (5 equiv.)[11a] in DCM at room temperature for 3 hour led to a N-O bond cleavage to deliver benzoazepine derivative **5** in 90% yield. Compound **5** was subjected to *m*-CPBA-oxidation (1.1 equiv.) in DCM to yield a *N*-hydroxyamine derivative **6** that was characterized by X-ray diffraction.[10] Alternatively, alkylation of compound **5** with MeI/K_2CO_3 in DMF[11b] furnished *N*-methylated benzoazepine derivative **7** in excellent yield (95%). Hydrolytic opening of the furan ring of compound **5** with H_2SO_4 in HOAc:H_2O[11c] (3:1) at 50 °C afforded 3,4-diketodehydrobenzoazepine derivative **8** in 47% yield.

Our next task was to realize these reactions with high enantioselectivity. Initial test with $L_1AuCl/AgNTf_2$ [L_1 = (*R*)-SEGPHOS] and $L_2AuCl/AgNTf_2$ [L_2= (*R*)-BINAP] under standard condition gave a complicated mixture of products, from which we were unable to obtain compound **3a** in pure form (entries 1-2). To our pleasure, the use of $L_3AuCl/AgNTf_2$, [L_3 = (*R*)-BIPOL-A1] in DCM (25 ^{0}C, 1 h) greatly improved the enantioselectivity of compound (+)-**3a** with 84.6% ee (entry 3). Running the reaction at 0 °C enabled the ee level of compound (+)-**3a** up to 99.5% ee (entry 4). A bulky chiral phosphoramide L_4, the Feringa ligand, also yielded compound (+)-**3a** with 99.5% ee, but the yield was slightly decreased to 75% (entry 5). For L_3 = (*R*)-BIPOL-A1, we altered the silver salts with $AgSbF_6$ to, afford compound(+)-**3a** in 68% yield with 92.9% ee (entry 6). The performance of $L_3AuCl/AgNTf_2$ in different solvents (entries 7-8) at 0 $^\circ$C were also very effective: DCE (80% yield, 99.4% ee) and toluene (83% yield, 91.1% ee). The absolute configuration of compound (+)-**3a** was inferred from the X-ray diffraction of its bromo relative (+)-**3d**.[10]

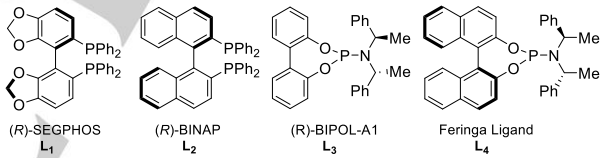
The reaction generality of these enantioselective annulations were further assessed with various 2-(1-alkynyl)-2-alken-1-ones **1** and anthranils **2** with variations of the R^1 to R^6 substituents. In nearly all cases, the use of $L_3AuCl/AgNTf_2$ enabled high enantioselectivity with ee > 90% whereas compound (+)-**4i** was obtained in 88% ee using L_4 ligand (entry 12). Most reactions were operated at 0 °C, but in entries 3-4, 6, 9, 11 and 12 the temperatures were kept -10 °C. We first tested the reactions with

Table 4. Enantioselectivity with chiral gold catalysts



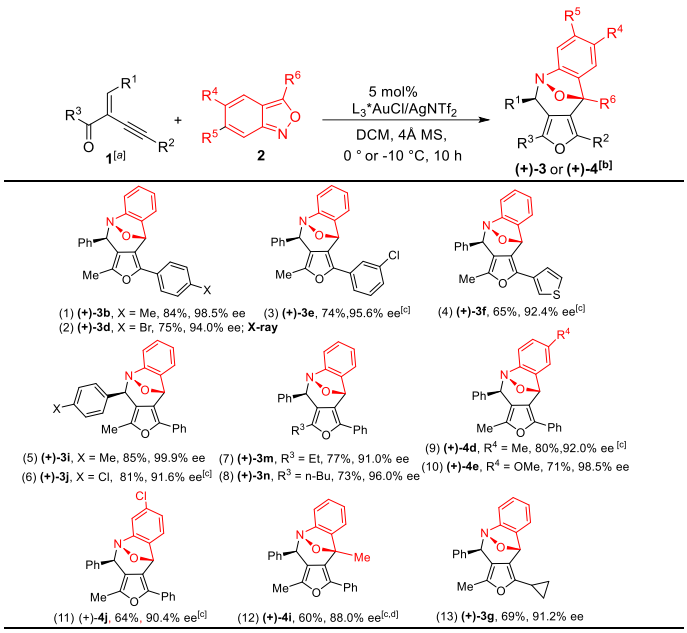
Entry	[L_n*AuCl] (m)	X	Solvent	Temp./Time (°C/h)	**(+)-3a** Yield/ee (%)[c]
1	L_1 (2.5)	NTf_2	DCM	25/18	--/--
2	L_2 (2.5)	NTf_2	DCM	25/4	--/--
3	L_3 (5)	NTf_2	DCM	25/1	72/(+)-84.6
4	**L_3 (5)**	**NTf_2**	**DCM**	**0/3**	**82/(+)-99.5**
5	L_4 (5)	NTf_2	DCM	0/10	75/(+)-99.5
6	L_3 (5)	SbF_6	DCM	0/12	68/(+)-92.9
7	L_3 (5)	NTf_2	DCE	0/4	80/(+)-99.4
8[d]	L_3 (5)	NTf_2	toluene	25/12	83/(+)-91.1

[a] [1a] = 0.03M. [b] Product yields are obtained after purification from a silica column. [c] The ee values were determined by chiral HPLC analysis on a chiral stationary phase. [d] Na[{3,5-$(CF_3)_2C_6H_3$}$_4$B] (10 mol %) was added [e] Only starting species were recovered.



substrates **1b** and **1d** bearing various alkynyl substituents with R^2 = 4-XC_6H_4 (X = Me and Br); the resulting products (+)-**3b** and (+)-**3d** were obtained with ee = 98.5% and 94.0% respectively (entries 1-2). The molecular structure of compound (+)-**3d** was confirmed with X-ray diffraction.[10] For *meta*-chlorophenyl substrate **1e** (R^2 = 3-ClC_6H_4), its resulting compound (+)-**3e** was produced in 74% yield and 95.6% ee (entry 3). A 3-thiophene-containing 2-(1-alkynyl)-2-alken-1-one **1f** delivered the desired product **(+)-3f** with 92.4% ee (entry 4)**.** For species **1i** and **1j** bearing variable alkenyl substituents R^1 = 4-XC_6H_4 (X = Me and Cl), the resulting products (+)-**3i** and (+)-**3j** were formed with99.9% and 91.6% ee respectively (entries 5-6)**.** The variations of ketone substituents (R^3 = ethyl and n-butyl) were amenable to these enantioselective reactions, yielding the desired products(+)-**3m** and (+)-**3n** with high ee levels, ca. 91% and 96% (entries 7-8). For anthranils **2d** and **2e** bearing C(5)-substituents (R^4 = Me and OMe)**,** their resulting compounds(+)-**4d** and (+)-**4e** were produced with 92%and 98.5% ee (entries 9-10). The enantioselectivity maintained high efficiency for C(6)-substituted anthranils **2j** (R^5 = Cl), yielding compound (+)-**4j** with 90.4% ee. In the case of C(3)-substituted anthranil **2k** (R^6 = Me), high enantioselectivity (88.0% ee) was obtained for its corresponding product **4i**, despite the generation of a tertiary carbon (entry 12). We also performed this enantioselective annulation on cyclopropyl-substituted alkyne species

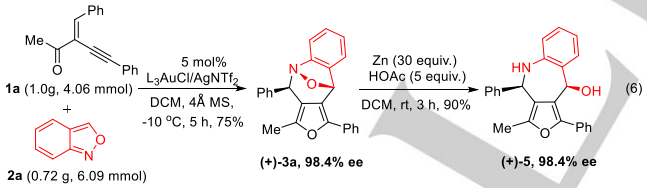
Table 5. Enantioselective [4+3]-Annulations



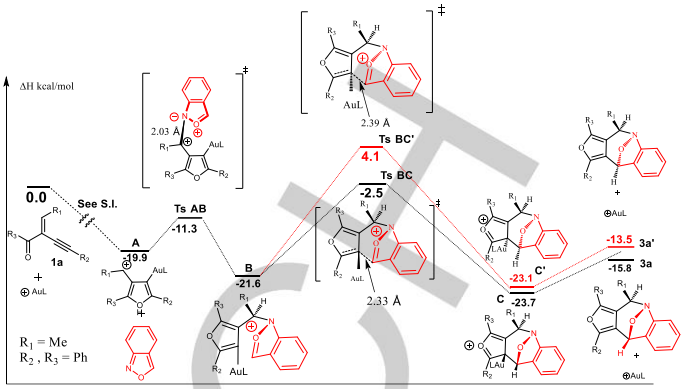
[a] [1] = 0.03 M. [b] Product yields are obtained after separation from silica column. The ee values were determined by HPLC on a chiral stationary phase. [c] These values correspond to reaction temperatures at -10 °C. [d] L_4 ligand was employed in entry 12.

(R^2 = cyclopropyl, **1g**), yielding compound **(+)-3g** in 69% yield and 91.2% ee.

A gram-scale synthesis is depicted in eq 6. Treatment of compound **1a** (1.0 g, 4.06 mmol) with anthranil **2a** (1.5 equiv.) and chiral catalyst $L_3AuCl/AgNTf_2$ (5 mol %) in DCM furnished epoxybenzoazepine (+)-**3a** in 75% yield and 98.4 % ee. Treatment of species **3a** with Zn powder (30 equiv.)/HOAc (5 equiv.)[11a] in DCM (25 ^{0}C, 3 h) led to cleavage of a N-O bond to deliver a benzoazepine derivative (+)-**5** in 90% yield and 98.4% ee.



We employ DFT-calculations to rationalize the exo-stereochemistry of this catalytic [4+3]-nitroxy annulation. Initially, enynone **1** forms gold π-alkyne species to undergo cyclization to generate gold-containing 3-furyl methyl cations **A** that serve as 1,3-all carbon dipoles; this process is well documented in literatures.[6] Our DFT calculation indicates a release of 19.9 kcal/mol; its corresponding transition state is depicted in Supporting Information. We were unable to locate the transtion state for a concerted pathway, leading to product **3a**. In a stepwise mechanism, an intial N-attack of anthranil to 1,3-dipole[12] **A** forms an intermediate **B** via a small barrier, ca. +8.6 kcal/mol; this process is exothermic to release 1.7 kcal/mol. A ring closure of intermediate **B** forms an *endo* annulation product **C** that is more favourable than the *exo*-isomer C‘ on both kinetic and thermodymaic aspects. State **TsBC** is lower than **TsBC‘** by 6.6 kcal/mol whereas intermediate **C** is more stable than **C‘** by



Scheme 2. A Plausible Mechanism: the black line indicates the most plausibl pathway to give the observed exo-annulation product.

0.6 kcal/mol. Accordingly, a stepwise mechanism involving an endo route is a viable route based on DFT calculations.

In summary, we report gold-catalyzed [4+3]-annulations[13] of 2-(1-alkynyl)-2-alken-1-ones with anthranils[9] to yield epoxybezoazepine products with excellent *exo*-facial diastereoselectivity (dr > 25:1). This new gold catalysis has a broad scope of applicable substrates. Notably, the enantioselective versions of these [4+3]-cycloadditions have been developed satisfactorily with chiral phosphoramidite gold catalysts[14] under ambient conditions; their ee levels are up to 99.9%. We perform DFT calculations to support a stepwise mechanism to rationalize the exo diastereoselectivity.

Acknowledgements

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Keywords: anthranils• annulation • gold • enantioselections • epoxybenzoazepines

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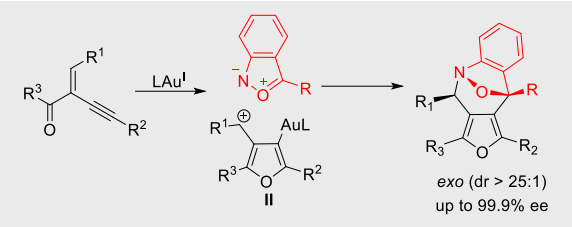

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Gold(I)-Catalyzed Highly Diastereo- and Enantioselective Cyclization/[4+3] Annulation Cascades between 2-(1-Alkynyl)-2-alken-1-ones and Anthranils

This work reports gold-catalyzed [4+3]-annulations of 2-(1-alkynyl)-2-alken-1-ones with anthranils to yield epoxybezoazepine products with excellent *exo*-diastereoselectivity (dr > 25:1). More importantly, the enantioselective versions of these [4+3]-cycloadditions have been developed satisfactorily with chiral gold catalysts under ambient conditions (DCM, 0 °C); the ee levels from 88.0-99.9%, further highlighting the synthetic values.