Chemical Science

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2019, **10**, 1201

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Gold-catalyzed (4+3)-annulations of 2-alkenyl-1-alkynylbenzenes with anthranils with alkyne-dependent chemoselectivity: skeletal rearrangement *versus* non-rearrangement†

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Received 14th August 2018
Accepted 11th November 2018

DOI: 10.1039/c8sc03619e

rsc.li/chemical-science

Two distinct (4+3)-nitroxy annulations between 1,5-enynes and anthranils have been developed to access tetrahydro-1*H*-benzo[*b*]azepine derivatives; the chemoselectivity varies with the types of alkynes. Terminal alkyne substrates deliver benzo[*b*]azepine derivatives *via* a novel skeletal rearrangement while internal 1,5-enynes afford products without a rearrangement process. To elucidate the mechanism of rearrangement, we performed ^{13}C- and ^{2}H-labeling experiments to identify the gold-containing isobenzofulvene intermediates, but their formation relies on the presence of anthranils.

Introduction

Cyclic nitroxy species (N–O) are widespread functionalities in numerous bioactive molecules and natural products.[1] Tetrahydro-1*H*-benzo[*b*]azepines bearing a hydroxyl (**I–IV**) represent a family of privileged seven-membered azacycles,[2] possessing potent activities in antiparasitic disease, antidiuretic hormone receptors and β_2 adrenergic agonists.[3] Synthetic procedures for compounds **I–IV** are generally long and tedious.[2] A short route to construct tetrahydrobenzo[*b*]azepine cores involves the development of stereoselective (4+3)-annulations between anthranils and all-carbon 1,3-dipoles (eqn (1)), but only donor–acceptor cyclopropanes were shown to be applicable substrates.[4] We are aware of no π-bond motifs that can serve as effective 1,3-dipoles.[5]

Synthetic interest in isoxazoles and anthranils is rapidly growing in Au- and Pt-catalysis because of their various annulations with alkynes.[6,7] Nevertheless, these hetero-aromatics serve as nucleophiles that attack π-alkynes *via* a N- or O-attack route, inevitably cleaving the N–O bonds; selected examples are provided in eqn (2) and (3). We sought the first (4+3)-nitroxy annulations using alkyne-based 1,3-dipoles and anthranils. This work reports two distinct (4+3)-annulations of 1,5-enynes with anthranils; interestingly, the chemoselectivity varies with the alkynes. Terminal 1,5-enynes **1** (R = H) afford seven-membered nitroxy heterocycles **3** *via* an unprecedented rearrangement in gold catalysis;[8] the mechanism of this novel rearrangement has been elucidated. Annulation products **5** derived from internal alkynes **4** are not skeletally rearranged, but are elaborated into various benzo[*b*]azepine frameworks (Fig. 1).

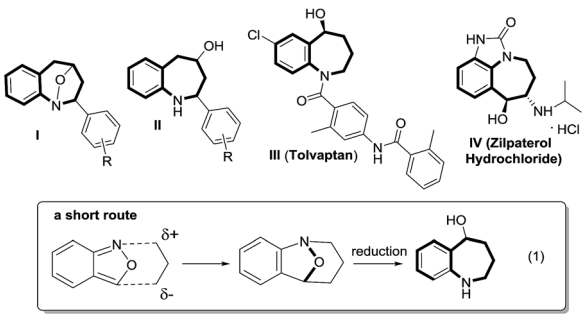
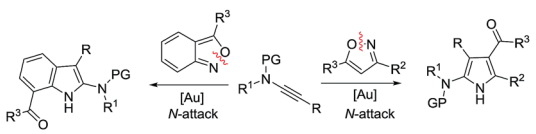
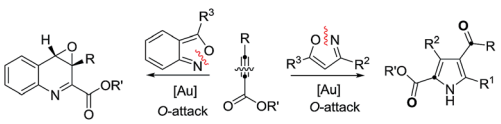


Fig. 1 Representative molecules and a postulated short route.

Annulations with N–O cleavages





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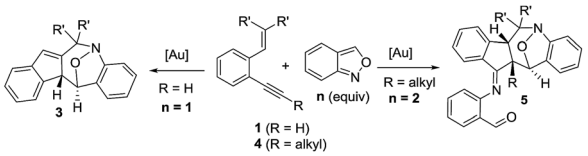
† Electronic supplementary information (ESI) available. CCDC 1853703–1853706. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc03619e

This work: (4+3)-nitroxy annulations



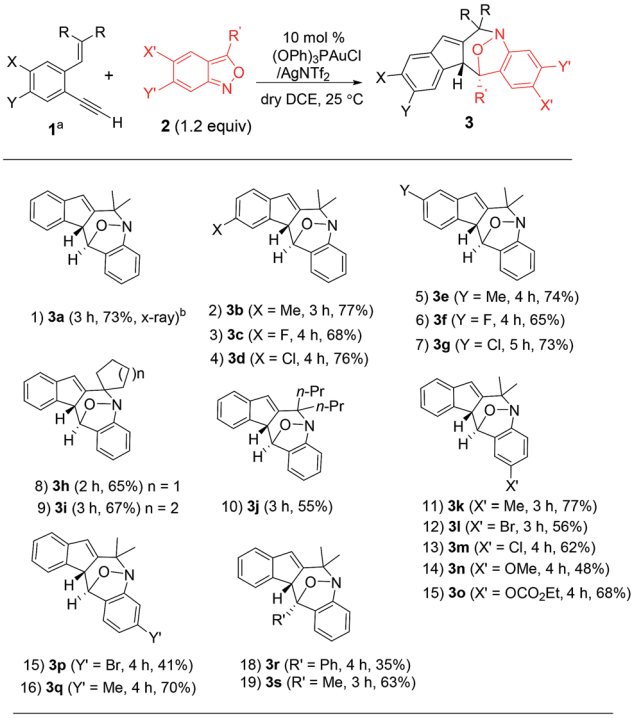
(4)

Results and discussion

We optimized the reactions of terminal 1,5-enyne **1a** with anthranil **2a** (1.2 equiv.) using various gold catalysts; the results are shown in Table 1. Operations in dry dichloroethane (DCE, 25 °C) with L′AuCl/AgNTf$_2$ (L′ = P(*t*-Bu)$_2$(*o*-biphenyl), IPr, PPh$_3$) afforded seven-membered nitroxy product **3a** in 8–68% yield (entries 1–3), with P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgNTf$_2$ being the most effective. To our delight, (PhO)$_3$PAuCl/AgNTf$_2$ increased the yield of the desired **3a** up to 73% (entry 4); different silver salts as those in (PhO)$_3$AuCl/AgX (X = SbF$_6$ and OTf) delivered compound **3a** in relatively low yields (35–42%, entries 5 and 6). With (PhO)$_3$PAuCl/AgNTf$_2$, the yields of compound **3a** in different solvents were as follows: DCM (62%), acetonitrile (30%) and MeNO$_2$ (0%, entries 7–9). AgNTf$_2$ alone was completely inactive (entry 10). The molecular structure of compound **3a** was characterized by X-ray diffraction[9] to reveal a (4+3)-annulation with an intact N–O bond. In the absence of anthranil **2a**, 1,5-enyne **1a** was isomerized by a gold catalyst to afford 1′-methyl-vinyl-1*H*-indene **1a**′, which was structurally unrelated to our target **3a**. Anthranil **2a** is obviously indispensable to enabling the (4+3)-annulations with structural rearrangement.

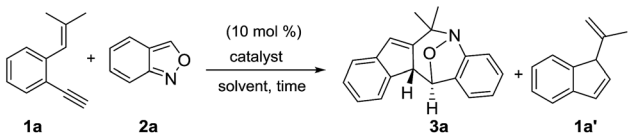
Under these optimized conditions, we assess the generality of these new annulations with various terminal 1,5-enynes and anthranils. The results are provided in Table 2; only a single diastereomeric product was obtained for all instances. In several instances, vinyl-1*H*-indene **1a**′ was present as

Table 2 Reactions with terminal 1,5-enynes and anthranils



[a] [**1**] 0.20 M. [b] Yields of the products were reported after isolation on a silica gel column.

Table 1 Optimized conditions over various gold catalysts



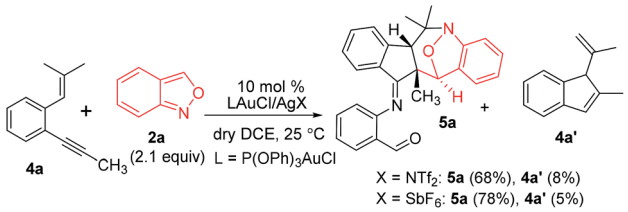
Entry	Catalyst[a] (mol %)	**2a** *n* equiv.	Solvent	Time (h)	Temp (*t* °C)	Yields[b] (%) **1a**	**3a**	**1a**′
1	LAuCl/AgNTf$_2$	1.2	DCE	5	25	—	68	—
2	IPrAuCl/AgNtf$_2$	1.2	DCE	15	25	25	8	—
3	Ph$_3$PAuCl/AgNtf$_2$	1.2	DCE	12	25	—	35	—
4	(PhO)$_3$PAuCl/AgNtf$_2$	1.2	DCE	4	25	—	73	—
5	(PhO)$_3$PAuCl/AgSbF$_6$	1.2	DCE	10	25	10	35	—
6	(PhO)$_3$PAuCl/AgOTf	1.2	DCE	2	60	—	42	—
7	(PhO)$_3$PAuCl/AgNtf$_2$	1.2	DCE	10	25	—	62	—
8	(PhO)$_3$PAuCl/AgNtf$_2$	1.2	MeCN	10	25	—	30	—
9	(PhO)$_3$PAuCl/AgNtf$_2$	1.2	MeNO$_2$	20	25	80	—	—
10	AgNtf$_2$	1.2	DCE	24	25	85	>5	—
11	(PhO)$_3$PAuCl/AgNtf$_2$	0	DCE	4	25	—	—	65

[a] **1a** (0.20 M), **2a** (1.2 equiv.). [b] Product yields are given after purification on a silica gel column, L = P(*t*-Bu)$_2$(*o*-biphenyl), IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene).

a byproduct in a minor proportion (5–15%). The annulations of anthranil **2a** (1.2 equiv.) with terminal 1,5-enynes **1b–1d** bearing various 4-phenyl substituents (X = Me, Cl, and F) proceeded smoothly to yield **3b–3d** in 68–77% yields (entries 2–4). For their 5-phenyl analogues **1e–1g**, the resulting annulation products **3e–3g** (Y = Me, Cl and F) were obtained in 65–74% yields (entries 5–7). Variations of the olefin substituents as those in species **1h–1j** (R, R = cyclopentyl, cyclohexyl and dipropyl) were still compatible with these new N–O annulations to afford compounds **3h–3j** in 55–67% yields (entries 8–10). We have also prepared a terminal alkyne such as 1-ethynyl-2-styrylbenzene **1k** that gave a recovery yield (>95%) of two reactants under the standard conditions.

We next examined anthranils **2b–2f** bearing various C(5)-substituents (X′ = Me, Cl, Br, OMe and OCO_2Et), yielding cyclic nitroxy species **3k–3o** in 48–77% yields, with X′ = OMe becoming less efficient (entries 11–15). Methoxy-containing anthranil **2e** renders the gold catalyst less reactive because of its high basicity. This gold catalysis worked well with additional anthranils **2g** and **2h** bearing C(6)-substituents (Y′ = Br and Me), yielding the desired **3p** and **3q** in 41% and 70% yields, respectively (entries 15 and 16). We also varied the C(3)-substituents of anthranils (R′ = Ph **2i**; Me **2j**) to yield the desired **3r** and **3s** in 35% and 63% yields, respectively (entries 18 and 19). An effective range of alkynes and anthranils manifests the practicability of these new nitroxy annulations.

This gold-catalyzed reaction was also extensible to an internal alkyne **4a**, but led to a distinct (4+3)-annulation reaction without a skeletal rearrangement. Among various gold catalysts, $P(OPh)_3AuCl/AgSbF_6$ was superior to its NTf_2 catalyst analogue, delivering a nitroxy product **5a** with respective yields of 78% and 68%; a molar ratio of **4a**/**2a** = 1 : 2.1 was the optimized condition. The molecular structure of **5a** was inferred from its **5b** analogue (Table 3, entry 1).[9]



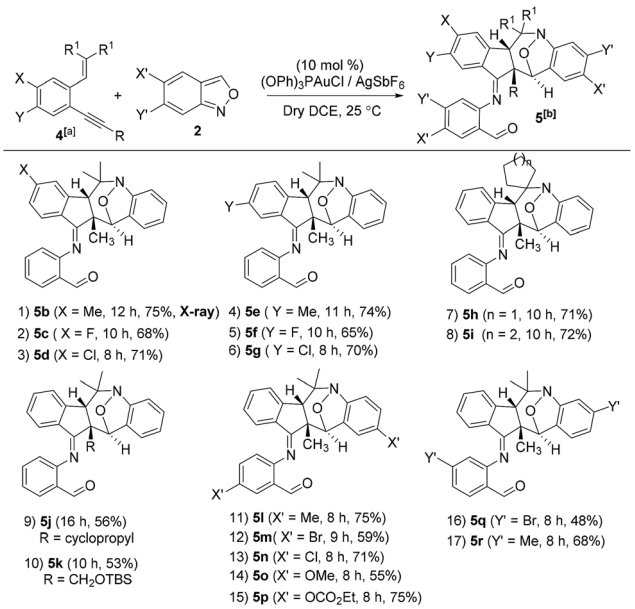
(5)

We assess the scope of these nitroxy annulations with various internal 1,5-enynes **4** and anthranils **2**; only one diastereomeric product was obtained without exception. Entries 1–6 show the compatibility of these reactions with 1,5-enynes **4b–4d** and **4e–4g** bearing 4- and 5-phenyl substituents (X = Me, F and Cl or Y = Me, F and Cl), delivering compounds **5b–5d** and **5e–5g** in 65–75% yields (entries 1–6). An X-ray diffraction study[9] confirms the molecular structure of compound **5b** showing no skeletal rearrangement. 1,5-Enynes **4h** and **4i** bearing varied trisubstituted alkenes were also suitable for the reactions, affording the desired nitroxy species **5h** and **5i** in 71–72% yields (entries 7 and 8). When the alkyl substituents R were a cyclopropyl or CH_2OTBS group, the corresponding compounds **5j** and **5k** were obtained in 56% and 53% yields, respectively (entries 9 and 10). We tested the reactions of various anthranils **2b–2f** bearing various C(5)-substituents (X′ = Me, Br, Cl, OMe and OCO_2Et), giving the expected products **5l–5p** in 55–75% yields with the methoxy substituent being less efficient (entries 11–15). For additional anthranils **2g** and **2h** bearing 6-substituents (Y′ = Br and Me), the resulting products **5q** and **5r** were obtained in 48% and 68% yields, respectively (entries 16 and 17).

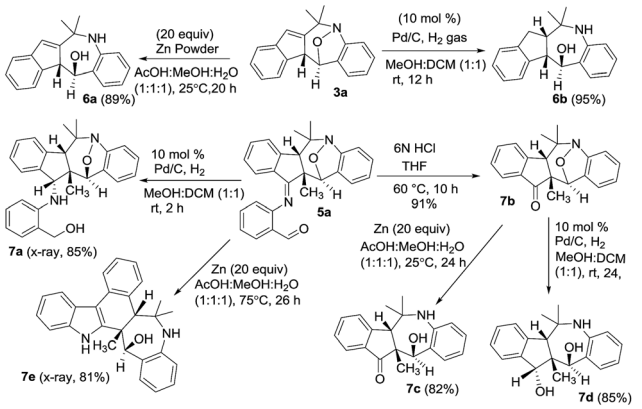
We performed the reductive N–O cleavage of compounds **3a** and **5a** to manifest their synthetic utility. Treatment of species **3a** with Zn in AcOH/MeOH/H_2O[10] gave compound **6a** in 89% yield while the reaction with Pd/H_2 gave compound **6b** efficiently. Alternatively, compound **5a** was hydrolyzed with HCl/water to yield ketone derivative **7b** that was convertible to 1-amino-5-ol **7c** with Zn/AcOH reduction, and to the diol derivative **7d** with Pd/H_2 reduction. An imine reduction of species **5a** was achieved with Pd/H_2 to afford species **7a**. Unexpectedly, Zn-reduction of species **5a** in HOAc/MeOH/water led to a structural rearrangement to form compound **7e** in 81% yield. The imine moiety of the initial **5a** was incorporated into the structural skeleton of product **7e**, but the mechanism is not clear at this stage. Molecular structures of compounds **7a** and **7e** were verified by X-ray diffraction.[9] The mechanism for the transformation of **5a** into **7e** will be elucidated in a future study (Scheme 1).

Among the two nitroxy annulations, the mechanism for terminal 1,5-enynes **1a** is difficult to deduce because its cycloisomerization product **1a**′ is not skeletally rearranged. We prepared ^{13}C-**1a** containing 12% ^{13}C at only the =C–H carbon, and its resulting product **3a** contained the ^{13}C-content only at

Table 3 Reactions with internal 1,5-enynes and anthranils

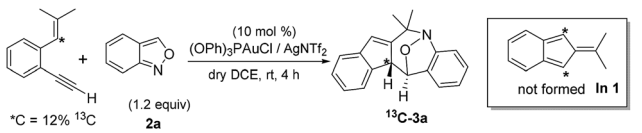


[a] **4**/**2** = 1 : 2.1, [**4**] 0.20 M. [b] Yields of the products were reported after isolation on a silica gel column.

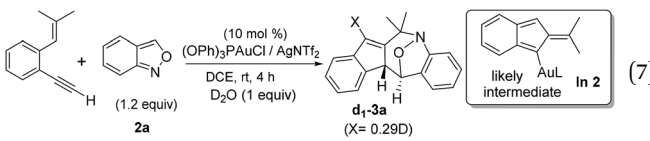


Scheme 1 Reductive cleavage of the N–O bonds.

the alkyl C–H carbon (eqn (6)). Isobenzofulvene species **In 1** was unlikely to occur here although it was observed in a ruthenium-catalyzed cycloisomerization.[11] In the presence of D_2O, we found that the resulting **d_1-3a** contained deuterium ($X = 0.29$D) only at its alkenyl C–H moiety (eqn (7)). Accordingly, gold-containing isobenzofulvene **In 2** is compatible with these ^{13}C and ^{2}H-labeling experiments.



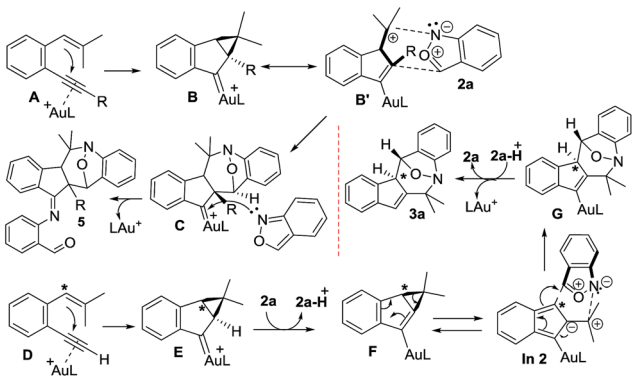
(6)



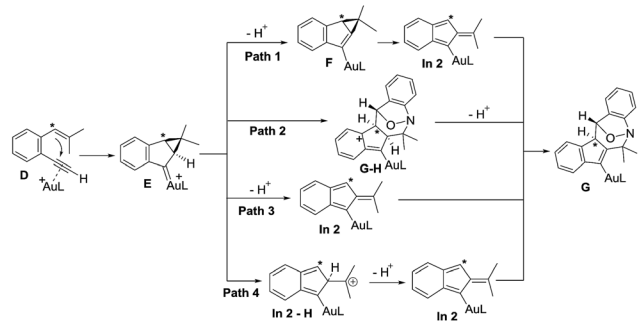
(7)

Scheme 2 depicts the mechanisms of the two annulations. Internal 1,5-enynes **4** react with LAu^+ to form cyclopropyl gold carbenes **B** (or **B′**) in two resonance forms; *exo*-(4+3)-annulations of species **B′** with anthranils **2a** likely yield gold-carbene species **C** that subsequently capture a second anthranil to yield products **5**. This mechanism is essentially the same as that of their annulations with nitrosoarenes.[12] Herein, a stepwise mechanism for the annulation of anthranils with 1,3-dipoles **B**/**B′** is also likely to occur. Terminal 1,5-enyne **1a** also generates cyclopropylgold carbene **E** because its cycloisomerization product **1a′** is also a 1-vinylindene derivative. We envisage that the cyclopropyl C–H proton of gold carbene **E** is acidic because of its proximity to the gold carbene functionality; the deprotonation with anthranil **2a** generates cyclopropylidenylgold species **F** that undergoes a "methylenecyclopropane-trimethylenemethane" rearrangement,[13] further generating gold-containing isobenzofulvene species **In 2**. An *exo*-(3+4)-annulation between fulvene **In 2** and anthranil **2a** affords the observed product **3a**. The intermediacy of organogold species **G** is supported by ^{2}H and ^{13}C-labeling experiments.

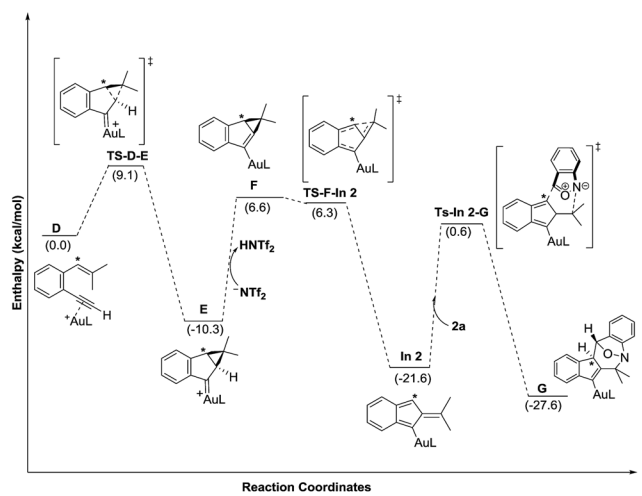
Density functional theory calculations were then performed to investigate the feasibility for the key steps **D** → **G**. Four possible paths 1–4 are considered; Path 1 is our proposed mechanism in Scheme 2. The energy profile is provided in Scheme 4. The formation of cyclopropylgold carbenes **E** from π-alkyne **D** has a low barrier of 9.1 kcal mol^{-1}; the anion-promoted deprotonation of gold carbene **E** to form



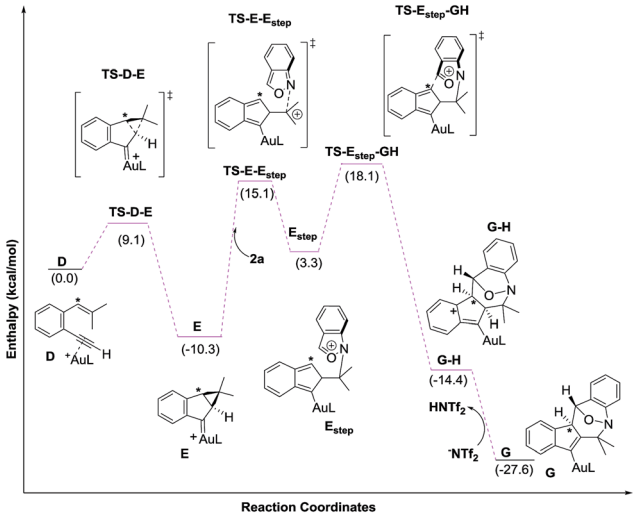
Scheme 2 Plausible mechanisms for rearrangement and non-rearrangement.



Scheme 3 Four possible paths for the D → G transformation.



Scheme 4 DFT calculation and energy profiles of Path 1.



Scheme 5 DFT calculation and energy profiles of Path 2.

cyclopropylidenylgold species **F** is operable as the enthalpy cost is 16.9 kcal mol^{-1}; the energy of species **F** is slightly higher than that of π-alkyne **D** by only 6.6 kcal mol^{-1}. The remaining steps **F** → **In 2** and **In 2** → **G** are also operable as the transition states **TS-F-In2** and **TS-In2-G** are close to π-alkyne **D** energy levels. One notable feature is that the enthalpy of transition state **TS-F-ln2** is surprisingly smaller than that of species **F** by −0.3 kcal. This atypical case has similar precedents in the literature.[14] This is because **TS-F-In2** has less zero-point vibration energy than **F**, due to the loss of one degree of freedom in the transition state. This also means that **F** → **In2** is a barrierless process.

We next examined the energy profiles in the (4+3) annulations (Path 2) between cyclopropyl gold carbenes **E** and anthranil **2a**. The reaction proceeds in a stepwise manner. As shown in Scheme 5, the N-attack of anthranil **2a** at gold carbene **E** produces species **E$_{step}$** by an endothermic process (H = 13.6 kcal mol^{-1}); its activation energy is as high as 25.4 kcal mol^{-1}. In the next step involving **E$_{step}$** → **GH**, the energy level of **TS-E$_{step}$-GH** is higher than that of 1,5-enyne **D** by 18.1 kcal mol^{-1}. We conclude that Path 2 is not as feasible as Path 1 according to Scheme 5.

We also considered the remaining Paths 3 and 4, as depicted in Scheme 3. In Path 3, the deprotonation and ring rearrangement take place simultaneously (**E** → **In2**), in contrast to a stepwise process in Path 1 (**E** → F → **In2**). Despite multiple attempts, we were unable to locate the transition state for the direct **E** → **In2** step, suggesting that Path 3 probably does not exist. In Path 4, a ring opening takes place initially (**E** → **In2-H**), followed by deprotonation (**In2-H** → **In2**). However, our calculations show that this pathway is unlikely to occur as we are unable to locate **In2-H**; all geometry optimizations lead to **E**.

Conclusions

Before this work, Au- and Pt-catalyzed annulations of anthranils with alkynes typically produced azacyclic products that cleaved the N–O bonds. To develop new (4+3)-annulations of alkyne-derived 1,3-dipoles[15] with anthranils, we achieve stereoselective synthesis of two classes of tetrahydrobenzo[*b*]azepines using 1,5-enynes, anthranils and a gold catalyst. Internal 1,5-enynes deliver these cyclic nitroxy species without skeletal rearrangement while their terminal alkyne analogues afford distinct annulation products with skeletal rearrangement. To elucidate the mechanism of this rearrangement, ^{2}H and ^{13}C-labeling experiments were performed to identify the intermediates of gold-containing isobenzofulvene species, the formation of which is dependent on the presence of anthranils.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We thank the Ministry of Education (MOE 106N506CE1) and Ministry of Science and Technology (MOST 107-3017-F-007-002), Taiwan, for financial support of this work.

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