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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Two distinct (4+3)-nitroxy annulations between 1,5-enynes and anthranils have been developed to access tetrahydro-1H-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 13C- and 2H-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. Tetrahydro-1H-benzo[b]azepines bearing a hydroxyl (I–IV) represent a family of privileged seven-membered azacycles, possessing potent activities in antiparasitic disease, antidiuretic hormone receptors and β2 adrenergic agonists. Synthetic procedures for compounds I–IV are generally long and tedious. 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. We are aware of no π-bond motifs that can serve as effective 1,3-dipoles.

Synthetic interest in isoxazoles and anthranils is rapidly growing in Au- and Pd-catalysis because of their various annulations with alkynes. 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; 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).

Annulations with N–O cleavages

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Fig. 1 Representative molecules and a postulated short route.
This work: (4+3)-nitroxy annulations

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/AgNTf₂ (L’ = P(t-Bu)₂(o-biphenyl), IPr, PPh₃) afforded seven-membered nitroxy product 3a in 8–68% yield (entries 1–3), with P(t-Bu)₂(o-biphenyl)AuCl/AgClOTf being the most effective. To our delight, (PhO)₃PAuCl/AgNTf₂ increased the yield of the desired 3a up to 73% (entry 4); different silver salts as those in (PhO)₃AuCl/AgX (X = SbF₆ and OTf) delivered compound 3a in relatively low yields (35–42%, entries 5 and 6).

With (PhO)₃PAuCl/AgNTf₂, the yields of compound 3a in different solvents were as follows: DCM (62%), acetonitrile (30%) and MeNO₂ (0%, entries 7–9). AgNTf₂ alone was completely inactive (entry 10). The molecular structure of compound 3a was characterized by X-ray diffraction 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 1'-methylvinyl-1H-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-1H-indene 1a' was present as a diastereomeric mixture. The yields of the products were reported after isolation on a silica gel column.

| Entry | Catalyst* (mol %) | 2a n equiv. | Solvent | Time (h) | Temp (°C) | 1a | 3a | 1a' |
|-------|-------------------|-------------|---------|----------|-----------|----|----|-----|
| 1     | L’AuCl/AgNTf₂     | 1.2         | DCE     | 5        | 25        | —  | 68 | —   |
| 2     | IPrAuCl/AgNTf₂    | 1.2         | DCE     | 15       | 25        | 25 | 8  | —   |
| 3     | Ph₃PAuCl/AgNTf₂   | 1.2         | DCE     | 12       | 25        | —  | 35 | —   |
| 4     | (PhO)₃PAuCl/AgNTf₂| 1.2         | DCE     | 4        | 25        | —  | 73 | —   |
| 5     | (PhO)₃PAuCl/AgSbF₆| 1.2         | DCE     | 10       | 25        | 10 | 35 | —   |
| 6     | (PhO)₃PAuCl/AgOTf | 1.2         | DCE     | 2        | 60        | —  | 42 | —   |
| 7     | (PhO)₃PAuCl/AgNTf₂| 1.2         | DCE     | 10       | 25        | —  | 62 | —   |
| 8     | (PhO)₃PAuCl/AgNTf₂| 1.2         | MeCN    | 10       | 25        | —  | 30 | —   |
| 9     | (PhO)₃PAuCl/AgNTf₂| 1.2         | MeNO₂   | 20       | 25        | 80 | —  | —   |
| 10    | AgNTf₂            | 1.2         | DCE     | 24       | 25        | 85 | >5 | —   |
| 11    | (PhO)₃PAuCl/AgNTf₂| 1.2         | DCE     | 4        | 25        | —  | 65 | —   |

* a 0.20 M. *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 annihilations 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 annihilations to afford compounds 3h–3j in 55–67% yields (entries 8–10). We have also prepared a terminal alkyne such as 1-ethyl-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 OCO₂Et), 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 annihilations.

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/AgSbF₆ was superior to its NTf₂ catalyst, showing no skeletal rearrangement. 1,5-Enynes 4b and 4c bearing various C(5)-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 confirms the molecular structure of compound 5b showing no skeletal rearrangement. 1,5-Enynes 4h and 4i bearing various C(5)-substituents (X = Me, Br, OMe and OCO₂Et), giving the expected products 5h–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/H₂O gave compound 6a in 89% yield while the reaction with Pd/H₂ gave compound 6b efficiently. Alternatively, compound 5a was hydrolyzed with HCl to yield ketone derivative 7b that was convertible to 1-amino-5-ol 7c with Zn/NaOH reduction, and to the diol derivative 7d with Pd/H₂ reduction. An imine reduction of species 5a was achieved with Pd/H₂ to afford species 7a. Unexpectedly, 2n-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. The mechanism for the transformation of 5a into 7e will be elucidated in a future study (Scheme 1).

Among the two nitroxy annihilations, the mechanism for terminal 1,5-enynes 1a is difficult to deduce because its cycloisomerization product 1a' is not skeletaly rearranged. We prepared 13C-1a containing 12% 13C at only the 13C–H carbon, and its resulting product 3a contained the 13C-content only at

\[ \text{Table 3: Reactions with internal 1,5-enynes and anthranils} \]

\[ \text{4/2} = 1 : 2.1, \text{[4]} \text{0.20 M.} \text{6 Yields of the products were reported after isolation on a silica gel column.} \]
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 D2O, we
found that the resulting d1-3a contained deuterium (X = 0.29D)
only at its alkenyl C–H moiety (eqn (7)). Accordingly, gold-
containing isobenzofulvene In 2 is compatible with these 13C
and 2H-labeling experiments.

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-
carbone species C that subsequently capture a second anthra-
nil 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 cyclo-
isoomerization 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 cyclo-
propyldenylgold species F that undergoes a “methyl-
encyclopropane-trimethylenemethane” rearrangement,13
further generating gold-containing isobenzofulvene species In
2. An eno-(3+4)-annulation between fulvene In 2 and anthranil
2a affords the observed product 3a. The intermediacy of organ-
ogold species G is supported by 2H and 13C-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
The N-attack of anthranil shown in Scheme 5, the N-attack of anthranil \( \text{E} \) and \( \text{F} \) are close to \( \pi \)-alkyne \( \text{D} \) energy levels. One notable feature is that the enthalpy of transition state \( \text{TS-F-In2} \) is surprisingly smaller than that of species \( \text{F} \) by \(-0.3\) kcal. This atypical case has similar precedents in the literature.\(^4\) This is because \( \text{TS-F-In2} \) has less zero-point vibration energy than \( \text{F} \), due to the loss of one degree of freedom in the transition state. This also means that \( \text{F} \rightarrow \text{In2} \) is a barrierless process.

We next examined the energy profiles in the \((4+3)\) annihilations (Path 2) between cyclopropylidene gold carbene \( \text{E} \) and anthranil \( \text{2a} \). The reaction proceeds in a stepwise manner. As shown in Scheme 5, the N-attack of anthranil \( \text{2a} \) at gold carbene \( \text{E} \) produces species \( \text{E}_{\text{step}} \) 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 \( \text{E}_{\text{step}} \rightarrow \text{GH} \), the energy level of \( \text{TS-E}_{\text{step}}-\text{GH} \) is higher than that of 1,5-enyne \( \text{D} \) 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 \( (\text{E} \rightarrow \text{In2} \) in a stepwise process in Path 1 \( (\text{E} \rightarrow \text{F} \rightarrow \text{In2} \). Despite multiple attempts, we were unable to locate the transition state for the direct \( \text{E} \rightarrow \text{In2} \) step, suggesting that Path 3 probably does not exist. In Path 4, a ring opening takes place initially \( (\text{E} \rightarrow \text{In2-H} \), followed by deprotonation \( \text{In2-H} \rightarrow \text{In2} \). However, our calculations show that this pathway is unlikely to occur as we are unable to locate \( \text{In2-H} \); all geometry optimizations lead to \( \text{E} \).

**Conclusions**

Before this work, Au- and Pt-catalyzed annihilations of anthranils with alkylnes typically produced azacyclic products that cleaved the N–O bonds. To develop new \((4+3)\)-annulations of alkyne-derived \(1,3\)-dipoles\(^3\) 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.

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9 Crystallographic data of compounds 3a, 5b, 7a and 7e were deposited at the Cambridge Crystallographic Center; 3a, CCDC 1853703; 5b, CCDC 1853704; 7a, CCDC 1853705 and 7e, CCDC 1853706.†