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Gold-Catalyzed Intramolecular Regioselective 7-*exo-dig* Cyclization To Access 3-Methylene-3,4-dihydrobenzo[*b*]oxepinones

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Supporting Information

ABSTRACT: An efficient gold-catalyzed synthesis of substituted 3-methylene-3,4-dihydrobenzo[*b*]oxepinones from *ortho*-*O*-propargyl substituted aryl enaminones has been achieved. In this transformation a new C−C bond formation occurred regioselectively via 7-*exo-dig* cyclization. Benzooxepinone derivatives were obtained in good to excellent yields in a one-pot synthesis at ambient temperature.

α-Aryl-substituted carbonyl compounds are known as useful building blocks for the synthesis of natural products and biologically active molecules.[1] Among them, oxygen-containing heterocyclic molecules, in particular benzooxepinones, have gained much attention in recent years because of their potential applications in various fields (Figure 1).[2]

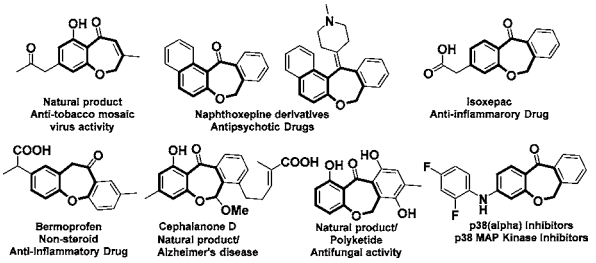

Figure 1. Selected examples of important molecules containing a benzooxepinone core skeleton.

Benzooxepinone derived natural products are exhibiting biological properties such as antitobacco mosaic virus activity,[3a] while polyketides exhibit antifungal activity.[3b] Cephalanone D and E exhibit potential properties toward Alzheimer's disease, Parkinson's disease, cerebral ischemia, epilepsy, and neurodegenerative disorders.[4] Some of the benzooxepinone derivatives such as naphthoxepines are used as antipsychotic drugs,[5] while isoxepac and bermoprofen are using as anti-inflammatory drugs.[6] It was also identified that benzooxepinone derivatives are exhibiting estrogen receptor[7a] and p38(α)inhibitor properties.[7b,c]

Homogeneous gold catalysis[8] is an emerging tool in synthetic organic chemistry in recent years.[9] By fine-tuning various gold catalysts, several new synthetic protocols have been developed. The advantage of gold catalysis is the generation of diversified scaffolds and useful molecules under mild reaction conditions in a one-pot synthesis.[10]

Our current research efforts[11] focused on the exploration of the innate reactivity of substituted β-enaminones.[12] Very recently, we have reported an efficient intramolecular cyclization of substituted β-enaminones to access 1,4-oxazepine derivatives under gold catalysis.[11b] We commenced our investigations by exploring the reactivity of *ortho*-*O*-propargyl substituted aryl enaminones under gold catalysis.

We envisioned that substituted aryl β-enaminone **1a** can be converted to the corresponding benzooxepinone **2a** via 7-*exo-dig* cyclization (path a, Scheme 1) or benzooxocinone **3a** via 8-*endo-dig* cyclization (path b, Scheme 1) in the presence of a gold catalyst via intramolecular cyclization (Scheme 1).

Scheme 1. Synthetic Strategy for the Generation of Benzooxepinone (2a) or Benzooxocinone (3a) from 1a

Accordingly, we have conducted an experiment using substrate **1a** in the presence of AuCl (5 mol %) in acetonitrile solvent. To our delight, we have obtained a 32% yield of 4-((methylamino)(phenyl)methylene)-3-methylene-3,4-dihydrobenzo[*b*]oxepin-5(2*H*)-one (**2a**) as a product (Scheme 2). Another experiment was performed with **1a** in acetonitrile solvent without utilizing a catalyst; this reaction did not proceed, and starting material **1a** remained intact (Table 1, entry 2).

These two experiments clearly indicate that this organic transformation is proceeding because of the gold catalyst.

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Scheme 2. Conversion of *ortho*-*O*-Propargyl-Substituted Aryl Enaminone (1a) to Benzooxepinone (2a)

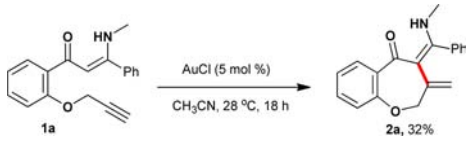
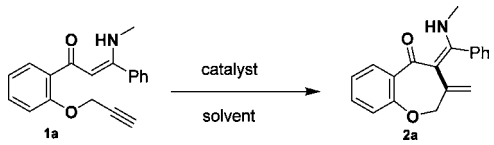


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	solvent	time (h)	yield (%)[d]
1	AuCl (5)	CH_3CN	18	32
2	no catalyst	CH_3CN	18	nr[b]
3	AuCN (5)	CH_3CN	18	nr[b]
4	$KAuCl_4$ (5)	CH_3CN	18	nr[b]
5	$AuCl_3$ (5)	CH_3CN	18	cm[c]
6	$AuBr_3$ (5)	CH_3CN	18	cm[c]
7	$AuClPPh_3$ (5)	CH_3CN	4	46
8	IPrAuCl (5)	CH_3CN	8	34
9	$AuClPPh_3$ (5)/$AgSbF_6$ (10)	CH_3CN	18	66
10	$AgSbF_6$ (10)	CH_3CN	8	32
11	$[Au(PPh_3)][NTf_2]$(10)	CH_3CN	8	55
12	[Au(JohnPhos)(MeCN)][SbF_6] (10)	CH_3CN	5	62
13	**$AuClPPh_3$ (10)/$AgSbF_6$ (15)**	**CH_3CN**	**4**	**78**
14	$AuClPPh_3$ (10)/$AgBF_4$ (15)	CH_3CN	4	53
15	$AuClPPh_3$ (10)/AgOTf (15)	CH_3CN	4	56
16	$AuClPPh_3$ (10)/$AgNTf_2$ (15)	CH_3CN	4	62
17	$AuClPPh_3$ (10)/$AgSbF_6$ (15)	THF	4	47
18	$AuClPPh_3$ (10)/$AgSbF_6$ (15)	DCE	4	32
19	$AuClPPh_3$ (10)/$AgSbF_6$ (15)	1,4-dioxane	4	62
20	$AuClPPh_3$ (10)/$AgSbF_6$ (15)	toluene	4	23
21	$AuClPPh_3$ (10)/$AgSbF_6$ (15)	DMF	4	cm[c]

[a]Reaction conditions: all reactions were carried out at room temperature under a nitrogen atmosphere with **1a** (0.343 mmol) and solvent (3 mL) at 28 °C. [b]nr: no reaction. [c]cm: complex mixture. [d]Yields are for isolated products.

These results prompted us to screen this reaction by utilizing different gold catalysts, catalyst combinations, and reaction conditions to improve the yield of benzooxepinone derivative **2a**.

Experiments were conducted using substrate **1a** in the presence of different gold catalysts such as AuCN and $KAuCl_4$. These reaction conditions did not yield product **2a**, and starting material **1a** remained intact (Table 1, entries 3 and 4).

When this reaction was performed in the presence of $AuCl_3$ and $AuBr_3$, a complex reaction mixture was observed (Table 1, entries 5 and 6). In the presence of $AuClPPh_3$ and IPrAuCl, substrate **1a** gave the product **2a** in 46% and 34% yields, respectively (Table 1, entries 7 and 8). We have conducted an experiment to test substrate **1a** in the presence of $AuClPPh_3$/$AgSbF_6$ (5/10 mol %), and it was observed that the product **2a** was isolated in a 66% yield (Table 1, entry 9). We are also interested in testing the reactivity of **1a** in the presence of $AgSbF_6$ alone. Accordingly, substrate **1a** was tested in the presence of $AgSbF_6$ (10 mol %), and the product **2a** was isolated in a lower yield (Table 1, entry 10). Two experiments were conducted by utilizing substrate **1a** in the presence of gold catalysts such as $[Au(PPh_3)][NTf_2]$ and [Au(JohnPhos)-(MeCN)][SbF_6], which gave the corresponding product **2a** in 55% and 62% yields, respectively (Table 1, entries 11 and 12).

An impressive yield (78%) of **2a** was obtained with the combination of $AuClPPh_3$ (10 mol %) and $AgSbF_6$ (15 mol %) in acetonitrile (Table 1, entry 13). Screening this reaction by utilizing $AuClPPh_3$ with different silver catalysts such as $AgBF_4$, AgOTf, and $AgNTf_2$ did not provide better yields of product **2a** (Table 1, entries 14−16). Because of these results, we then tested the effect of solvents on this intramolecular cyclization of **1a** under a $AuClPPh_3$/$AgSbF_6$ catalytic system (Table 1, entries 17−21).

The optimization results clearly indicate that the catalyst combination $AuClPPh_3$/$AgSbF_6$ in acetonitrile is the best solvent for this intramolecular cyclization (Table 1, entry 13). By having achieved the best optimized reaction conditions, the generality of this organic transformation and the scope of the substrates were studied using different substituted *ortho*-*O*-propargyl substituted phenyl and naphthyl *β*-enaminones **1a−k** (Table 2).

The substrate **1b** (R^2 = C_6H_5, R^3 = C_4H_9) treated in the presence of a gold catalyst gave a 61% yield of the 7-*exo*-*dig* cyclized product **2b**. The substrates **1c** (R^2 = C_6H_5, R^3 = allyl) and **1d** (R^2 = C_6H_5, R^3 = CH_2COOEt) gave 87% and 81% yields of the desired products **2c** and **2d**, respectively. Substrates containing alicyclic substituents at the R^3 position such as **1e** (R^3 = C_5H_9) and **1f** (R^3 = C_6H_{11}) gave the corresponding benzooxepinones **2e** and **2f** in 84% and 77% yields, respectively (Table 2). In the case of substrates **1g** and **1h**, the corresponding 3,4-dihydrobenzooxepinone derivatives **2g** and **2h** were obtained in 79% and 92% yields, respectively. The structure of product **2h** was further confirmed by single-crystal X-ray analysis.[13] The substrates **1i** [R^1 = (−CH=CH−CH=CH−), R^2 = C_6H_5, R^3 = Me], **1j** [R^1 = (−CH=CH−CH=CH−), R^2 = C_6H_5, R^3 = C_6H_{11}], and **1k** [R^1 = (−CH=CH−CH=CH−), R^2 = C_6H_5, R^3 = CH_2Ph] were treated in the presence of a gold catalyst gave 89%, 93%, and 89% yields of the corresponding naphthoxepinone derivatives **2i**, **2j**, and **2k**, respectively (Table 2).

Additionally, the substrate scope was tested by varying the substitutions at the R^1, R^2, and R^3 positions, and the corresponding results are summarized in Table 3. Substrates substituted with an electron-withdrawing group at the R^1 position including **1l** [R^1 = 5-Br, R^2 = C_6H_5, R^3 = Me], **1m** [R^1 = 5-Br, R^2 = C_6H_5, R^3 = CH_2Ph], and **1n** [R^1 = 5-Br, R^2 = C_6H_5, R^3 = CH_2−CH_2−3-indole] gave 76%, 72%, and 70% yields of **2l**, **2m**, and **2n**, respectively (Table 3) under the optimized reaction conditions. Substrates having two (3,5-dichloro) electron-withdrawing groups at the R^3 position such as **1o** [R^1 = 3,5-dichloro, R^2 = C_6H_5, R^3 = CH_3] gave the corresponding product **2o** in a 74% yield. Electron-withdrawing substitution at the R^1 position for a substrate such as **1p** [R^1 = 5-NO_2, R^2 = C_6H_5, R^3 = C_6H_{11}] gave the corresponding benzooxepinone **2p** in a 65% yield. Substrates having an electron-donating group at the R^2 position such as **1q** (R^2 = 4-Me-C_6H_4, R^3 = allyl) and **1r** (R^2 = 4-Me−C_6H_4, R^3 = CH_2−CH_2−3-indole) gave the corresponding products **2q** and **2r** in 77% and 74% yields, respectively. Electron-withdrawing substitution at the R^2 position for a substrate such as **1s** (R^2 = 4-F−C_6H_4, R^3 = CH_2−C_6H_5) gave product **2s** in a 79% yield.

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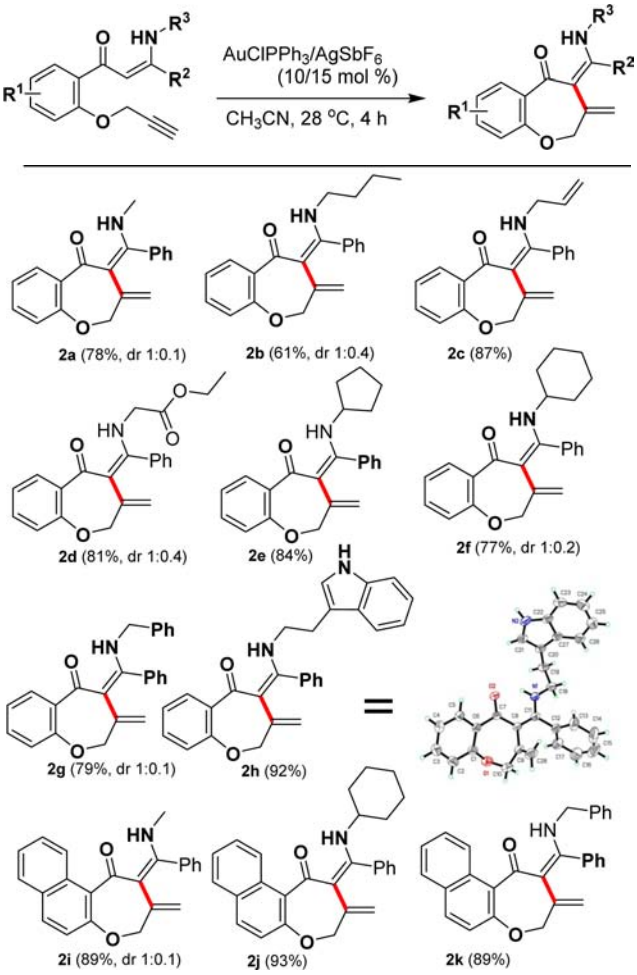
Table 2. Scope of Substituted Benzooxepinones (2)[a]



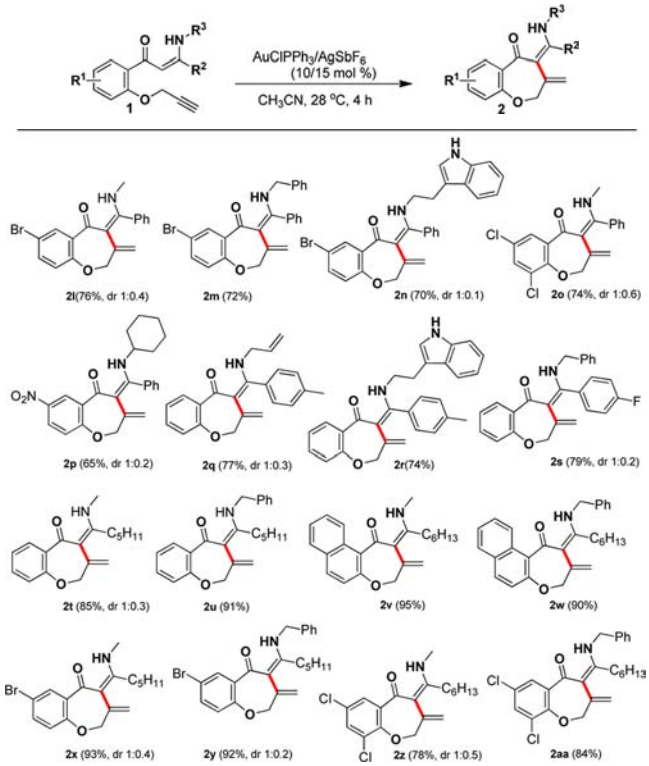
[a]Reaction conditions: all reactions were carried out at room temperature under a nitrogen atmosphere with **1a–k** (0.5 mmol), $AuClPPh_3$ (10 mol %)/$AgSbF_6$ (15 mol %), and CH_3CN (3 mL) at 28 °C; yields are for isolated products; dr: diastereomeric ratio.

The substrate scope of this intramolecular organic transformation was tested by alkyl substitutions at the R^2 position (**1t–1aa**) (Table 3). Substrates having alkyl substitutions at the R^2 position such as **1t** (R^2 = C_5H_{11}, R^3 = CH_3) and **1u** (R^2 = C_5H_{11}, R^3 = CH_2–C_6H_5) gave the corresponding cyclized products **2t** and **2u** in 85% and 91% yields, respectively. The reactions of **1v** [R^1 = (–CH=CH–CH=CH–), R^2 = C_6H_{13}, R^3 = CH_3] and **1w** [R^1 = (–CH=CH–CH=CH–), R^2 = C_6H_{13}, R^3 = CH_2–C_6H_5] under the optimized conditions gave naphthoxepinone derivatives **2v** and **2w** in 95% and 90% yields, respectively (Table 3).

Electron-withdrawing substitutions at the R^1 position for substrates such as **1x** (R^1 = 5-Br, R^2 = C_5H_{11}, R^3 = CH_3) and **1y** (R^1 = 5-Br, R^2 = C_5H_{11}, R^3 = CH_2–C_6H_5) gave 93% and 92% yields of the corresponding cyclized products **2x** and **2y**, respectively. Substrates such as **1z** (R^1 = 3,5-dichloro, R^2 = C_6H_{13}, R^3 = CH_3) and **1aa** (R^1 = 3,5-dichloro, R^2 = C_6H_{13}, R^3 = CH_2–C_6H_5) having electron-withdrawing functional groups at the R^1 position gave the corresponding cyclized benzooxepinone derivatives **2z** and **2aa** in 78% and 84% yields, respectively (Table 3).

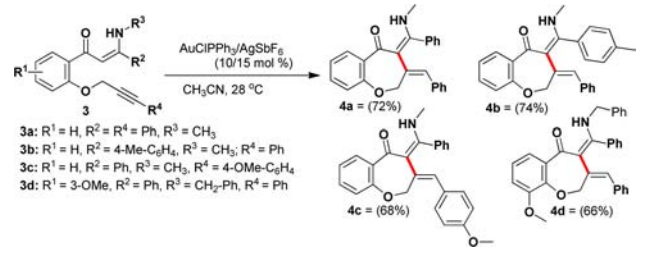
Enaminones which have disubstituted alkynes such as **3a** (R^1 = H, R^2 = R^4 = Ph, R^3 = CH_3), **3b** (R^1 = H, R^2 = 4-Me-C_6H_4, R^3 = CH_3, R^4 = Ph), **3c** (R^1 = H, R^2 = Ph, R^3 = CH_3, R^4 = 4-OMe-C_6H_4), and **3d** (R^1 = 3-OMe, R^2 = Ph, R^3 = CH_2–Ph, R^4 = Ph) were synthesized to test the scope of this transformation.[14] Examination of these derivatives **3a–d** under the optimized reaction conditions resulted in good yields of corresponding substituted benzooxepinone derivatives **4a–d** (Scheme 3).

Table 3. Scope of Substituted Benzooxepinones (2)[a]



[a]Reaction conditions: all reactions were carried out at room temperature under a nitrogen atmosphere with **1l-1aa** (0.5 mmol), $AuClPPh_3$ (10 mol %)/$AgSbF_6$ (15 mol %) and CH_3CN (3 mL) at 28 °C; yields are for isolated products.

Scheme 3. Conversion of Alkyne Disubstituted Enaminones (3a) to Benzooxepinone (4a)



A plausible reaction mechanism[15] can be proposed for the formation of the cyclized product benzooxepinones **2** from *ortho-O* propargyl substituted aryl enaminones **1** (Scheme 4). In the presence of the gold catalyst, substrate **1** would give intermediate **I**. This intermediate **I** would further undergo 7-*exo-dig* cyclization[16] to give intermediate **II** and would finally afford substituted benzooxepinone **2** via protodeauration.

In conclusion, we have developed a straightforward and efficient synthetic method for the formation of benzooxepinones and naphthoxepinones from *ortho-O*-propargyl

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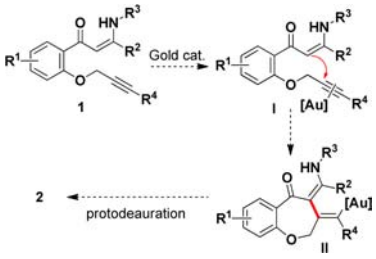
Scheme 4. A plausible Reaction Mechanism



substituted aryl enaminones. It is noteworthy that this transformation occurred regioselectively via 7-*exo*-*dig* cyclization under gold catalysis under mild conditions. Good to excellent yields of the title compounds were achieved with significant molecular complexity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03433.

Detailed experimental procedures, analytical data, and copies of the ^{1}H and ^{13}C NMR spectra for all new products (**2a**−**2aa** and **4a**−**4d**) (PDF)

Single-crystal X-ray data for **2h** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) See the Supporting Information for X-ray crystallographic data for compound **2h**.

(14) We thank a reviewer's suggestion to elaborate the scope of the manuscript.

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