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Gold-Catalyzed Intramolecular Cyclization of *N*-Propargylic β-Enaminones for the Synthesis of 1,4-Oxazepine Derivatives

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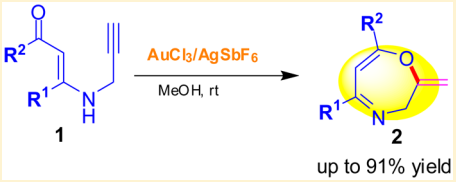
Supporting Information

ABSTRACT: An efficient and mild one-pot, gold-catalyzed intramolecular cyclization of *N*-propargylic β-enaminones has been achieved for the generation of 1,4-oxazepine derivatives. This synthetic transformation tolerates a range of substituted *N*-propargylic β-enaminones in moderate to good yields.



Recent developments in homogeneous gold catalysis indicate that it has emerged as powerful tool in organic synthesis for the generation of synthetically useful molecules.[1] Several new synthetic strategies have been developed for synthesis of heterocyclic molecules[2] by fine-tuning of gold catalysts.[3] These new gold-catalyzed synthetic approaches have attained much attention due to their extended substrate scope under mild reaction conditions.[4] There is increasing interest in the synthesis of medium-sized rings.[5] The 1,4-distance in seven-membered heterocycles containing two heteroatoms is known to have various biological activities.[6] Among them, seven-membered heterocyclic molecules that are made up of one oxygen and one nitrogen heteroatom, such as 1,4-oxazepines, have gained interest in synthetic organic chemistry.[7] The 1,4-oxazepines are the parent core of medicinally important drugs like amoxapine,[8] loxapine,[9] and sintamil.[10] 1,4-Oxazepine derivatives exhibiting biological properties such as histone deacetylase inhibitions[11] and antitumor activity have been reported (Figure 1).[12]

In addition, 1,4-oxazepine derivatives were used as synthetic precursors for synthesis of secoiridoids and monoterpenoid alkaloids.[13] Due to the importance of 1,4-oxazepine structural unit, several synthetic approaches have been reported.[14] Most of these synthetic methods suffer from drawbacks like harsh reaction conditions and number of synthetic steps involved.[15]

Substituted enaminones are known as versatile building blocks in organic synthesis for generation of heterocyclic molecules.[16] *N*-Propargylic β-enaminones **1** have an interesting chemical structure; it is composed of different functional groups such as alkene, alkyne, enone, enamine, and enaminone. However, chemical building block **1** has received much less attention.[17] It has been reported that *N*-propargylic β-enaminones were converted to substituted five-membered heterocyclic molecules like substituted pyrroles, dihydropyrroles, and pyrrolidinones.[18] Very recently, gold-catalyzed formal 1,6-acyloxy migrations utilizing suitably substituted homopropargylic enaminones was reported by Hashmi and co-workers.[17a,b] Saito et al., reported the conversion of *N*-propargylic β-enaminone to the corresponding pyrroles in the presence of gold catalyst (Scheme 1).[17c] Copper-catalyzed reaction of *N*-propargylic β-enaminone to pyridines was reported by Cacchi et al.[17d]

It was reported that *N*-propargylcarboxamides react in the presence of gold catalyst to give five-membered oxazoles.[19] Construction of seven-membered rings is relatively difficult. Recently, a new class of intramolecular cyclization reactions has been reported via gold catalysis to access seven-membered rings.[20]

The goal of our research program is to explore the innate reactivity of substituted β-enaminones for the construction of heterocyclic molecules.[17e,18d,e] Very recently, we reported that the reaction of *N*-propargylic β-enaminones with arynes in the presence of gold catalyst produced 3-methylene-3,4-dihydro-2*H*-pyrrolines.[17e] Our efforts focused on explore towering the intramolecular reactivity of *N*-propargylic β-enaminones in the presence of different gold catalysts.

We envisaged that the *N*-propargylic β-enaminone **1a** would undergo cyclization in the presence of gold catalysts to give rise to two possible cyclized products as shown in Scheme 2. If the reaction proceeds through 7-*exo-dig* cyclization it would lead to give substituted 1,4-oxazepines (path c, Scheme 2), whereas 8-*endo-dig* would lead to substituted 1,5-oxazocines (path d, Scheme 2).

We planned to examine the reactivity of *N*-propargylic β-enaminone **1a** under gold catalysis. Accordingly, we performed a reaction of **1a** (1 equiv) in the presence of $AuClPPh_3$ catalyst (10 mol %) in methanol at room temperature. To our delight, we observed the formation of 1,4-oxazepine derivative **2a** (46%) via *exo-dig* cyclization with complete selectivity (Scheme 3).

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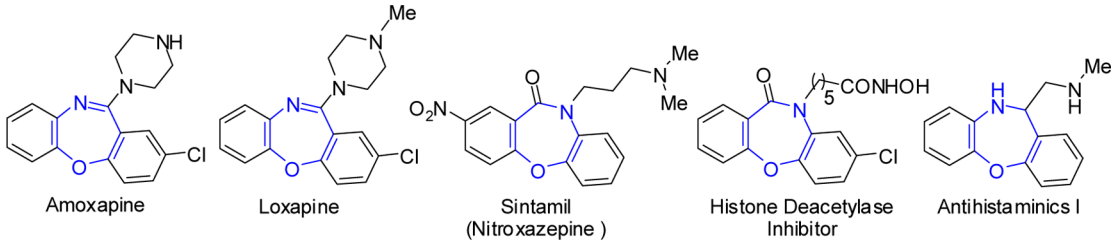
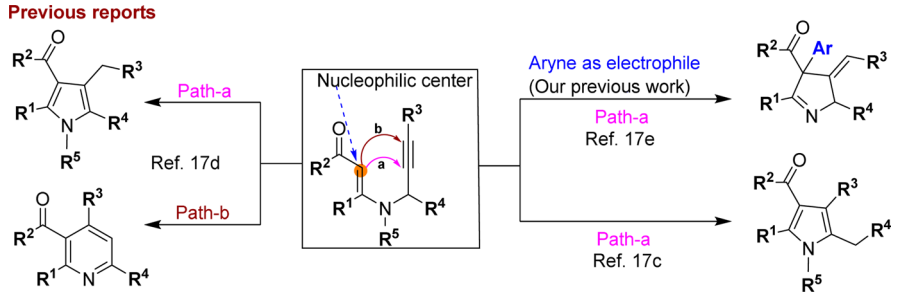
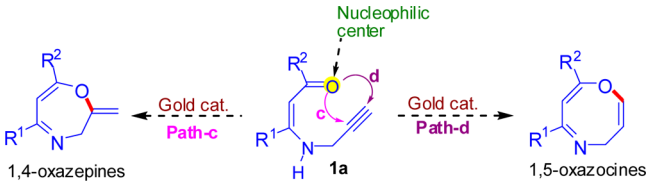


Figure 1. 1,4-Oxazepines containing medicinally important molecules.

Scheme 1. Conversion of Substituted *N*-Propargylic *β*-Enaminones to Pyrroles and Pyridines



Scheme 2. Synthetic Approach for the Generation of 1,4-Oxazepines or 1,5-Oxazocines



The structure of product **2a** was further confirmed by single-crystal X-ray analysis (Scheme 3).[21] However, under the reaction conditions, we did not observe any traces of 1,5-oxazocines, which could form via *endo-dig* cyclization.

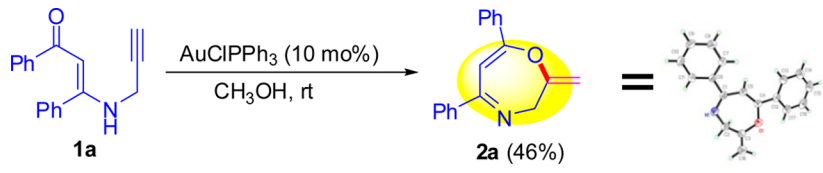
With these result in hand, we screened different gold catalysts, catalyst combinations, and reaction conditions to improve the yield of 1,4-oxazepine derivative **2a** (Table 1). It is noteworthy that this transformation did not occur in the absence of a catalyst (Table 1, entry 2). When the above reaction was performed in the presence of gold catalysts like AuI and AuCN, this reaction did not proceed; starting material **1a** remained intact (Table 1, entries 3 and 4). In the presence of $AuBr_3$ and $KAuCl_4$, substrate **1a** gave the product **2a** in 66% and 61% yields, respectively (Table 1, entries 5 and 6). JohnphosAuSbF$_6$ (10 mol %) catalyst gave a good yield (81%) of **2a** (Table 1, entry 7). Substrate **1a** was tested in the presence of $AuCl_3$ (10 mol %), and it was observed that the product **2a** was isolated in 69% yield (Table 1, entry 8). We have conducted an experiment to test the substrate **1a** in the presence of acid like trifluoroacetic acid. This reaction was not pursued further, as the starting material **1a** was found intact (Table 1, entry 9). In the presence of AuClPPh$_3$/AgSbF$_6$ (10/15), substrate **1a** gave the product **2a** in 67% yield (Table 1, entry 10).

An impressive yield (91%) of **2a** was obtained when the combination of $AuCl_3$ (10 mol %) and AgSbF$_6$ (15 mol %) in methanol was used (Table 1, entry 11). Screening this reaction by utilizing $AuCl_3$ with different silver catalysts such as $AgBF_4$, AgOTf, $AgNTf_2$, and $AgNO_3$ did not provide better yields of product **2a** (Table 1, entries 12−15). We then tested the effect of solvents on the intramolecular cyclization of **1a** under catalysis of the $AuCl_3$/AgSbF$_6$ system (Table 1, entries 16−20).

This study clearly indicates that the catalyst combination $AuCl_3$/AgSbF$_6$ in methanol is the best for this intramolecular cyclization. On the basis of the optimized reaction conditions (Table 1, entry 11), the generality of this reaction and the scope of the substrates were studied using differently substituted *N*-propargylic *β*-enaminones **1a−q** (Table 2).

N-Propargylic *β*-enaminone **1b**, with substitutions at the R^1 (C_6H_5) and R^2 ($C_{10}H_7$) positions, gave the intramolecular rearranged product **2b** in 75% yield (Table 2, entry 2). Substrates **1c**, **1d**, and **1e**, which have electron-donating groups at the R^2 positions (4-OMe-C_6H_4, 4-C_2H_5-C_6H_4, and 4-^{t}Bu-C_6H_4), gave 89%, 86%, and 87% yields of **2c**, **2d**, and **2e**, respectively (Table 2, entries 3−5). Electron-withdrawing substitutions on *N*-propargylic *β*-enaminones substrates like **1f** (R^2 = 4-F-C_6H_4) and **1g** (R^1 = 4-F-C_6H_4) gave the corresponding 1,4-oxazepine derivatives **2f** and **2g** in 66% and

Scheme 3. Cyclization of *N*-Propargylic *β*-Enaminone to 1,4-Oxazepine Derivative 2a and ORTEP Representation 2a[a]



[a]Displacement ellipsoids are drawn at the 30% probability level.

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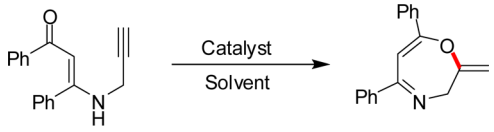
Table 1. Optimization for the Synthesis of 1,4-Oxazepine Derivatives[a]



1a 2a

entry	catalyst (mol %)	solvent	time (h)	yield[c] (%)
1	$AuClPPh_3$ (10)	CH_3OH	18	46
2	no catalyst	CH_3OH	18	nr[b]
3	AuI (10)	CH_3OH	18	nr[b]
4	AuCN (10)	CH_3OH	18	nr[b]
5	$AuBr_3$ (10)	CH_3OH	18	66
6	$KAuCl_4$ (10)	CH_3OH	18	61
7	JohnphosAuSbF$_6$ (10)	CH_3OH	20	81
8	$AuCl_3$ (10)	CH_3OH	18	69
9	TFA (10)	CH_3OH	24	nr[b]
10	$AuClPPh_3/AgSbF_6$ (10/15)	CH_3OH	15	67
11	$AuCl_3/AgSbF_6$ (10/15)	CH_3OH	5	91
12	$AuCl_3/AgBF_4$ (10/15)	CH_3OH	20	62
13	$AuCl_3$/AgOTf (10/15)	CH_3OH	6	78
14	$AuCl_3/AgNTf_2$ (10/15)	CH_3OH	18	69
15	$AuCl_3/AgNO_3$ (10/15)	CH_3OH	18	62
16	$AuCl_3/AgSbF_6$ (10/15)	THF	5	71
17	$AuCl_3/AgSbF_6$ (10/15)	Et_2O	18	42
18	$AuCl_3/AgSbF_6$ (10/15)	DMF	24	nr[b]
19	$AuCl_3/AgSbF_6$ (10/15)	toluene	18	66
20	$AuCl_3/AgSbF_6$ (10/15)	DCE	18	78

[a]Reaction conditions: all reactions carried out under nitrogen atmosphere, solvent (1 mL) at 28 °C. [b]nr: no reaction. [c]Yields are for isolated products.

72% yields, respectively (Table 2, entries 6 and 7). Substrates that are substituted with withdrawing groups like **1h** (R^2 = 4-Br-C_6H_4), **1i** (R^2 = 4-NO_2-C_6H_4), and **1j** (R^2 = 4-CN-C_6H_4) gave the corresponding cyclized products such as **2h**, **2i**, and **2j** in 70%, 62%, and 71% yields, respectively (Table 2, entries 8–10). 2,4-Dichlorophenyl substitution at the R^2 position containing an *N*-propargylic *β*-enaminone like **1k** gave the corresponding 1,4-oxazepine derivative **2k** in 75% yield (Table 2, entry 11). Substrates with both electron-donating groups at R^1 (4-Me-C_6H_4) and R^2 (4-Et-C_6H_4) positions, like **1l**, gave product **2l** in 86% yield (Table 2, entry 12).

N-Propargylic *β*-enaminones that contain electron-withdrawing groups at R^1 (4-F-C_6H_4) and R^2 (4-CN-C_6H_4), like **1m**, gave the corresponding product **2m** in 70% yield (Table 2, entries 13).

Substrates that have both electron-withdrawing groups and electron-donating groups at the R^1 and R^2 positions like **1n**, **1o**, **1p**, and **1q** gave the corresponding oxazepine derivatives **2n**, **2o**, **2p** ,and **2q** in 76%, 67%, 74%, and 75% yields, respectively (Table 2, entries 14–17).

A plausible reaction mechanism can be proposed for the formation of cyclized product 1,4-oxazepines **2** from *N*-propargylic *β*-enaminones **1** (Scheme 4). Under gold catalysis, the substrate **1** would give the intermediate **I**. This intermediate (**I**) would then undergo 7-*exo-dig* cyclization via nucleophilic attack of the carbonyl oxygen to give intermediate **II**. It was already known that carbonyl groups are suitable nucleophiles in gold catalysis.[22] The intermediate **II** would finally provide 1,4-oxazepine **2** via protodeauration.

In conclusion, we have developed a novel approach for the synthesis of 1,4-oxazepines in moderate to good yields from *N*-propargylic *β*-enaminones in the presence of gold catalyst under mild reaction conditions. It is noteworthy that *N*-propargylic *β*-enaminones undergo 7-*exo-dig* cyclization regioselectively to give the title compounds. Our current research work is focused on exploration of substituted *β*-enaminone reactivity for generation of heterocyclic molecules.

EXPERIMENTAL SECTION

General Information. All of the reactions were carried out in oven-dried reaction flasks under nitrogen atmosphere, and solvents and reagents were transferred by oven-dried syringes to ambient temperature. TLC was performed on silica gel aluminum sheets using UV as a visualizing agent and a 0.5% aqueous potassium permanganate solution and heat as developing agents. Solvents were removed under reduced pressure. Columns were packed as a slurry of silica gel in hexane and ethyl acetate solvent mixture. The elution was assisted by applying pressure with an air pump. ^{13}C NMR spectra were recorded on 75 and 125 MHz spectrometers. ^1H NMR spectra were recorded on 300 and 500 MHz spectrometers in appropriate solvents using TMS as internal standard. The following abbreviations are used to describe multiplicities: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet. All of the products (**2a–q**) were dissolved in $CHCl_3$, applied on liquid cells, and analyzed by infrared spectrometry. The HRMS values of the products **2a–q** were recorded using the ORBITRAP positive-mode electrospray ionization method.

All reactions were performed under nitrogen atmosphere with freshly distilled and dried solvents. All solvents were distilled using standard procedures. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. All of the catalysts were obtained from a commercial source. *N*-Propargyl *β*-enaminones (**1a–q**) were prepared by following the reported procedure.[23]

Typical Procedure for the Preparation of 1,4-Oxazepine Derivatives 2 from *N*-Propargylic *β*-Enaminones 1. To a 25 mL, round-bottomed, two-neck flask equipped with magnetic stir bar was added (*E*)-1,3-diphenyl-3-(prop-2-ynylamino)prop-2-en-1-one (**1a**) (0.1 g, 0.383 mmol, 1 equiv), the flask was purged with dry nitrogen, then the compound was dissolved in dry methanol (5 mL). To this reaction flask were added $AuCl_3$ (11.6 mg, 0.0383 mmol, 10 mol %) and $AgSbF_6$ (19.8 mg, 0.0574 mmol, 15 mol %). The reaction mixture was allowed to stir at room temperature for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite pad. The organic layer was removed under reduced pressure, and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with aqueous brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude residue was purified through a silica gel column using hexane and ethyl acetate as eluent (10/0.6) to give pure (4*E*,6*Z*)-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**2a**). A similar experimental procedure was adopted for the synthesis of all compounds.

*(4E,6Z)-2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**2a**):* light yellow solid; mp 76–78 °C; R_f 0.3, 90.9 mg, 91% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80–7.75 (4H, m), 7.45–7.39 (6H, m), 6.40 (1H, s), 4.75 (1H, s), 4.56 (2H, s), 4.38 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 158.8, 157.9, 139.5, 134.9, 130.0, 129.9, 128.4, 128.2, 127.3, 126.1, 99.6, 93.8, 55.3. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}NO^+$ $[M + H]^+$ 262.1225, found 262.1229; IR (neat) 3061.0, 2923.6, 2851.8, 1700.6, 1656.2, 1624.0, 1571.8, 1492.7, 1448.6, 1366.4, 1316.0, 1263.9, 1194.8 cm^{-1}.

*Crystal data for **2a**:* $C_{18}H_{15}NO$, M = 261.31, 0.17 × 0.15 × 0.07 mm^3, monoclinic, space group $P2_1/c$ (No. 14), a = 6.0142(8) Å, b = 8.9088(11) Å, c = 26.237(3) Å, β = 94.181(2)°, V = 1402.0(3) $Å^3$, Z = 4, D_c = 1.238 g/cm^3, F_{000} = 552, Mo Kα radiation, λ = 0.71073 Å, T = 294(2)K, $2\theta_{max}$ = 52.5°, 14398 reflections collected, 2840 unique (R_{int} = 0.0367). Final GoF = 1.007, R1 = 0.0460, wR2 = 0.1044, R indices based on 1870 reflections with $I > 2\sigma(I)$ (refinement on F^2), 181 parameters, 0 restraints. μ = 0.077 mm^{-1}. CCDC 1048547 contains

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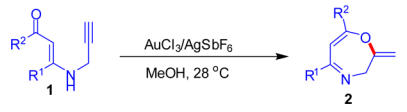
Table 2. Conversion of *N*-Propargylic *β*-Enaminones to 1,4-Oxazepine Derivatives[a]



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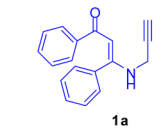
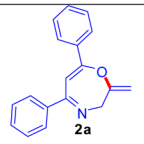
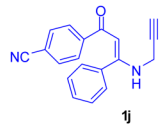
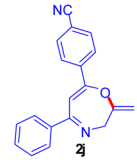
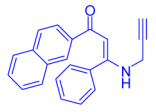
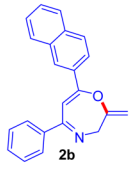
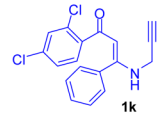
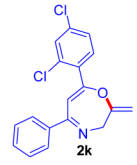
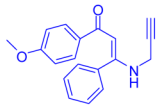
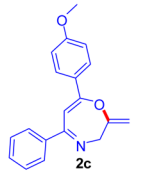
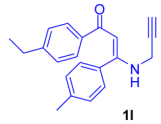
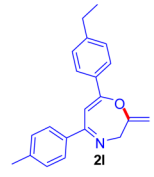
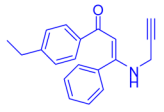
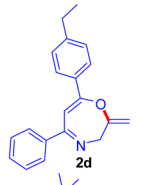
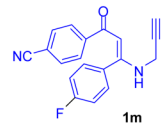
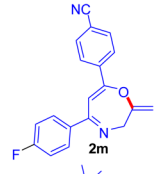
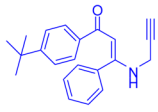
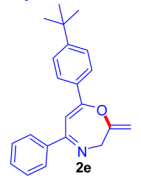
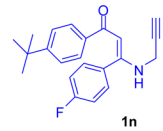
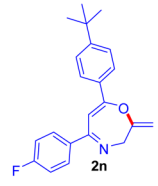
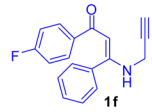
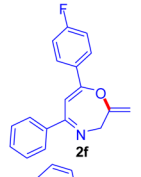
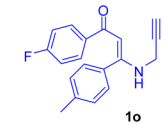
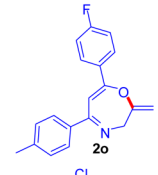
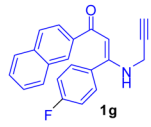
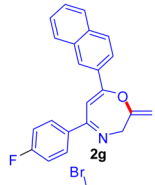
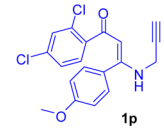
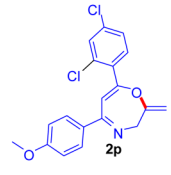
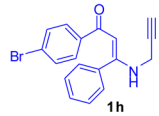
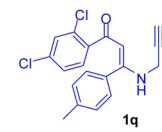
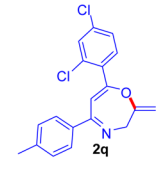
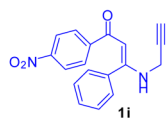
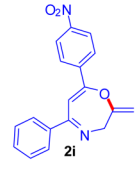
1	 1a	 2a	91	10	 1j	 2j	71
2	 1b	 2b	75	11	 1k	 2k	75
3	 1c	 2c	89	12	 1l	 2l	86
4	 1d	 2d	86	13	 1m	 2m	70
5	 1e	 2e	87	14	 1n	 2n	76
6	 1f	 2f	66	15	 1o	 2o	67
7	 1g	 2g	72	16	 1p	 2p	74
8	 1h	 2h	70	17	 1q	 2q	75
9	 1i	 2i	62				

[a]Reaction was performed using **1** (0.05 mmol), $AuCl_3$(10 mol %), $AgSbF_6$ (15 mol %), 28 °C, and methanol (5 mL) solvent under nitrogen atmosphere. [b]Isolated yield.

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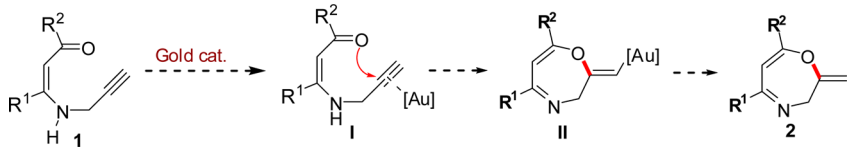
Scheme 4. Plausible Reaction Mechanism for the Formation of 1,4-Oxazepines 2



supplementary crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; Fax: + 44(0) 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk].

*(4E,6Z)-2-Methylene-7-(naphthalen-2-yl)-5-phenyl-2,3-dihydro-1,4-oxazepine (**2b**):* brown oil; R_f 0.4, 74.8 mg, 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.95−7.80 (7H, m), 7.57−7.52 (2H, m), 7.45−7.42 (2H, m), 6.54 (1H, s), 4.82 (1H, s), 4.61 (2H, s), 4.43 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 158.9, 158.1, 139.6, 133.9, 132.8, 132.1, 130.0, 128.7, 128.3, 128.2, 127.6, 127.4, 127.2, 126.6, 126.2, 123.2, 100.1, 94.0, 55.3; HRMS (ESI) m/z calcd for $C_{22}H_{18}NO^+$ $[M + H]^+$ 312.1382, found 312.1387; IR (neat) 2923.4, 2853.2, 1732.6, 1699.9, 1653.4, 1555.1, 1460.3 cm^{-1}.

*(4E,6Z)-7-(4-Methoxyphenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**2c**):* light brown oil; R_f 0.2, 88.9 mg, 89% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.76 (2H, m), 7.73−7.69 (2H, m), 7.43−7.38 (3H, m), 6.95−6.92 (2H, m), 6.31 (1H, s), 4.73 (1H, s), 4.53 (2H, s), 4.37 (1H, s), 3.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 161.1, 158.7, 158.1, 139.8, 129.8, 128.2, 127.7, 127.3, 113.8, 98.2, 93.7, 55.4, 55.3; HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_2^+$ $[M + H]^+$ 292.1332, found 292.1335; IR (neat) 2924.0, 2854.5, 2382.2, 2311.2, 2178.0, 2116.4, 1726.0, 1629.2, 1514.7, 1461.8, 1282.6, 1251.2, 1174.8 cm^{-1}.

*(4E,6Z)-7-(4-Ethylphenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**2d**):* yellow oil; R_f 0.4, 85.9 mg, 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.77 (2H, m), 7.70−7.67 (2H, m), 7.44−7.39 (3H, m), 7.27−7.24 (2H, m), 6.37 (1H, s), 4.74 (1H, s), 4.54 (2H, s), 4.38 (1H, s), 2.70 (2H, q, J = 14.9, 7.5 Hz), 1.27 (3H, t, J = 14.9, 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 159.1, 158.0, 146.8, 139.6, 132.4, 129.9, 128.2, 128.0, 127.4, 126.2, 99.0, 93.9, 55.2, 28.6, 15.4; HRMS (ESI) m/z calcd for $C_{20}H_{20}NO^+$ $[M + H]^+$ 290.1539, found 290.1541; IR (neat) 2962.8, 2925.0, 2854.4, 2311.1, 1703.4, 1656.8, 1623.2, 1568.5, 1512.0, 1453.9, 1313.8 cm^{-1}.

*(4E,6Z)-7-(4-tert-Butylphenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**2e**):* brown oil; R_f 0.4, 85.3 mg, 87% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.77 (2H, m), 7.72−7.69 (2H, m), 7.47−7.40 (5H, m), 6.38 (1H, s), 4.74 (1H, s), 4.54 (2H. s), 4.37 (1H, s), 1.35 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 158.9, 158.1, 153.5, 139.8, 132.2, 129.8, 128.2, 127.3, 126.0, 125.5, 99.1, 93.6, 55.4, 34.7, 31.1; HRMS (ESI) m/z calcd for $C_{22}H_{24}NO^+$ $[M + H]^+$ 318.1852, found 318.1854; IR (neat) 3060.3, 2311.0, 1702.4, 1623.7, 1580.7, 1511.5, 1458.2, 1364.7, 1267.7, 1193.6, 1116.0 cm^{-1}.

*(4E,6Z)-7-(4-Fluorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**2f**):* red oil; R_f 0.3, 65.9 mg, 66% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.71 (4H, m), 7.45−7.39 (3H, m), 7.16−7.08 (2H, m), 6.33 (1H, s), 4.74 (1H, s), 4.55 (2H, s), 4.39 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 164.8, 162.8 (d, J = 250.6 Hz, 1C), 158.0, 157.8, 139.5, 131.2, 130.0, 128.3, 128.2, 127.3, 115.6, 115.5 (J = 21.7 Hz, 2C), 99.4, 94.2, 55.2; HRMS (ESI) m/z calcd for $C_{18}H_{15}FNO^+$ $[M + H]^+$ 280.1129, found 280.1131; IR (neat) 3067.6, 2924.8, 2854.3, 1598.3, 1506.6, 1232.7, 1156.4 cm^{-1}.

*(4E,6Z)-5-(4-Fluorophenyl)-2-methylene-7-(naphthalen-2-yl)-2,3-dihydro-1,4-oxazepine (**2g**):* brown oil; R_f 0.3, 71.9 mg, 72% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.94−7.86 (3H, m), 7.84−7.79 (3H, m), 7.56−7.54 (2H, m), 7.13−7.08 (2H, m), 6.49 (1H, s), 4.82 (1H, s), 4.58 (2H, s), 4.43 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 165.6, 162.3 (d, J = 249.7 Hz, 1C), 159.0, 158.1, 135.8, 133.9, 132.8, 132.0, 129.4, 129.3, 128.7, 128.3, 127.6, 127.2, 126.7, 126.2, 123.1, 115.3, 115.1 (J = 21.4 Hz, 2C), 99.8, 94.0, 55.3; HRMS (ESI) m/z calcd for $C_{22}H_{17}FNO^+$ $[M + H]^+$ 330.2010, found 330.2011; IR (neat) 3059.1, 2925.2, 2852.0, 1655.2, 1570.4, 1506.5, 1372.8, 1266.8, 1229.3, 1156.3 cm^{-1}.

*(4E,6Z)-7-(4-Bromophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**2h**):* colorless solid; R_f 0.3, 70 mg; mp 130−132 °C; 70% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.75 (2H, m), 7.64−7.61 (2H, m), 7.57−7.54 (2H, m), 7.44−7.39 (3H, m), 6.36 (1H, s), 4.74 (1H. s), 4.54 (2H, s), 4.39 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 157.8, 157.7, 139.4, 133.9, 131.7, 130.0, 128.3, 127.7, 127.3, 124.4, 99.8, 94.1, 55.3; HRMS (ESI) m/z calcd for $C_{18}H_{15}BrNO^+$ $[M + H]^+$ 340.0331, found 340.0333; IR (neat) 3061.9, 2925.0, 2852.6, 1687.6, 1657.8, 1487.3, 1445.8, 1364.7, 1365.2, 1194.1 cm^{-1}.

*(4E,6Z)-2-Methylene-7-(4-nitrophenyl)-5-phenyl-2,3-dihydro-1,4-oxazepine (**2i**):* yellow solid; R_f 0.4; mp 144−146 °C; 61.1 mg, 62% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31−8.27 (2H, m), 7.95−7.92 (2H, m), 7.79−7.76 (2H, m), 7.47−7.41 (3H, m), 6.49 (1H, s), 4.80 (1H, s), 4.59 (2H, s), 4,45 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 157.7, 156.3, 148.5, 141.0, 139.1, 130.3, 128.4, 127.2, 127.0, 123.8, 102.1, 94.7, 55.3; HRMS (ESI) m/z calcd for $C_{18}H_{15}N_2O_3^+$ $[M + H]^+$ 307.1077, found 307.1078; IR (neat) 2923.9, 2852.1, 1699.6, 1656.6, 1628.9, 1592.5, 1518.8, 1446.8, 1344.8, 1261.0 cm^{-1}.

*4-((4E,6Z)-2-Methylene-5-phenyl-2,3-dihydro-1,4-oxazepin-7-yl)-benzonitrile (**2j**):* light yellow oil; R_f 0.2, 70.9 mg, 71% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89−7.86 (2H, m), 7.78−7.72 (4H, m), 7.46−7.40 (3H, m), 6.45 (1H, s), 4.77 (1H, s), 4.57 (2H, s), 4.43 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 157.8, 156.6, 139.2, 132.3, 130.2, 128.4, 127.2, 126.7, 101.6, 94.5, 55.4; HRMS (ESI) m/z calcd for $C_{19}H_{15}N_2O^+$ $[M + H]^+$ 287.1178, found 287.1178; IR (neat) 2924.7, 2855.8, 2382.6, 2312.0, 2229.3, 2175.8, 1702.2, 1657.5, 1629.5, 1559.8, 1511.5, 1454.3, 1277.9 cm^{-1}.

*(4E,6Z)-7-(2,4-Dichlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**2k**):* brown oil; R_f 0.3, 74.9 mg, 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (2H, dd, J = 8.1, 1.7 Hz), 7.75 (1H, dd, J = 8.1, 1.7 Hz), 7.46 (1H, dd, J = 7.8, 1.5 Hz), 7.42 (3H, m), 7.29 (1H, t, J = 15.7, 7.8 Hz), 6.05 (1H, s), 4.68 (3H, s), 4.40 (1H, d, J = 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 158.7, 157.8, 138.9, 137.8, 133.9, 131.4, 130.1, 128.7, 128.3, 127.3, 127.2, 104.8, 94.2, 55.3; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{35}Cl^{35}ClNO^+$ $[M + H]^+$ 330.0447, found 330.0450; calcd for $C_{18}H_{14}{}^{35}Cl^{37}ClNO^+$ $[M + 2 + H]^+$ 332.0417, found 332.0419; calcd for $C_{18}H_{14}{}^{37}Cl^{37}ClNO^+$ $[M + 4 + H]^+$ 334.0388, found 334.0386; IR (neat) 2924.3, 2854.2, 1710.6, 1656.6, 1569.6, 1450.7, 1366.9, 1314.4, 1192.7 cm^{-1}.

*(4E,6Z)-7-(4-Ethylphenyl)-2-methylene-5-p-tolyl-2,3-dihydro-1,4-oxazepine (**2l**):* light brown oil; R_f 0.3, 85.9 mg, 86% yieldl ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.66 (4H, m), 7.27−7.24 (2H, m), 7.22−7.19 (2H, m), 6.36 (1H, s), 4.72 (1H, s), 4.52 (2H, s), 4.36 (1H, s), 2.70 (2H, q, J = 15.3, 7.6 Hz,), 2.38 (3H, s), 1.26 (3H, t, J = 15.3, 7.6 Hz)l ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 158.8, 158.2, 146.6, 140.0, 136.9, 132.5, 128.9, 128.0, 127.2, 126.2, 99.2, 93.4, 55.2, 28.6, 21.3, 15.4l HRMS (ESI) m/z calcd for $C_{21}H_{22}NO^+$ $[M + H]^+$ 304.2592, found 304.2594; IR (neat) 3029.2, 2964.1, 2925.6, 2858.2, 1655.3, 1619.8, 1581.2, 1510.3, 1451.7, 1365.3, 1312.8, 1264.5, 1189.1 cm^{-1}.

*4-((4E,6Z)-5-(4-Fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepin-7-yl)benzonitrile (**2m**):* light yellow solid; R_f 0.2; mp 162−164 °C; 71 mg, 70% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.85 (2H, m), 7.80−7.71 (4H, m), 7.13−7.06 (2H, m), 6.41 (1H, s), 4.78 (1H, s), 4.56 (2H, s), 4.43 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 162.8, 157.8, 156.8, 139.1, 135.4, 132.3, 129.3, 129.2, 126.7, 118.2, 115.4, 115.2, 113.56, 101.2, 94.6, 55.3; HRMS (ESI) m/z calcd for $C_{19}H_{14}FN_2O^+$ $[M + H]^+$ 305.1251, found 305.1253; IR (neat) 3071.6, 2924.3, 2853.1, 2229.4, 1658.0, 1599.1, 1506.5, 1410.9, 1367.8, 1266.5, 1157.9, 1112.4 cm^{-1}.

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*(4E,6Z)-7-(4-tert-Butylphenyl)-5-(4-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**2n**):* light brown oil; R_f 0.4, 75.9 mg, 76% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.76 (2H, m), 7.72−7.67 (2H, m), 7.47−7.43 (2H, m), 7.10−7.05 (2H, m), 6.33 (1H, s), 4.74 (1H, s), 4.52 (2H, s), 4.37 (1H, s), 1.35 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 164.9, 162.9 (d, J = 248.8 Hz, 1C), 159.2, 158.1, 153.7, 135.9, 132.1, 129.4, 129.3, 126.0, 125.5, 115.2, 115.0 (J = 21.7 Hz, 2C), 98.8, 93.8, 55.3, 34.8, 31.1; HRMS (ESI) m/z calcd for $C_{22}H_{23}FNO^+$ $[M + H]^+$ 336.2571, found 336.2573; IR (neat) 2961.6, 2868.3, 1656.8, 1600.3, 1507.9, 1409.4, 1364.5, 1313.5, 1267.0, 1116.5 cm^{-1}.

*(4E,6Z)-7-(4-Fluorophenyl)-2-methylene-5-p-tolyl-2,3-dihydro-1,4-oxazepine (**2o**):* light brown oil; R_f 0.4, 66.9 mg, 67% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.72 (2H, m), 7.70−7.64 (2H, m), 7.24−7.18 (2H, m), 7.14−7.08 (2H, m), 6.32 (1H, s), 4.73 (1H, s), 4.53 (2H, s), 4.39 (1H, s), 2.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 165.4, 162.1 (d, J = 250.8 Hz, 1C), 158.0, 157.8, 140.2, 136.7, 131.2, 129.0, 128.3, 128.2, 127.2, 115.6, 115.4 (J = 21.4 Hz, 2C), 99.5, 93.9, 55.1, 21.3; HRMS (ESI) m/z calcd for $C_{19}H_{17}FNO^+$ $[M + H]^+$ 294.12880, found 294.12887; IR (neat) 2923.8, 2853.8, 2312.0, 2173.1, 1700.3, 1654.1, 1622.8, 1586.4, 1507.4, 1313.8 cm^{-1}.

*(4E,6Z)-7-(2,4-Dichlorophenyl)-5-(4-methoxyphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**2p**):* light yellow oil; R_f 0.2, 73.9 mg, 74% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76−7.74 (2H, m), 7.55−7.53 (1H, m), 7.47−7.45 (1H, m), 7.30−7.28 (1H, m), 6.93−6.90 (2H, m), 6.03 (1H, s), 4.64 (3H, s), 4.37 (1H, s), 3.84 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 161.3, 159.0, 157.7, 137.8, 133.9, 131.3, 128.8, 128.7, 127.3, 113.6, 104.9, 93.9, 55.3, 54.9; HRMS (ESI) m/z calcd for $C_{19}H_{16}Cl_2NO_2^+$ $[M + H]^+$ 360.0556, found 360.0559; IR (neat) 2924.0, 2851.3, 1633.7, 1601.1, 1511.5, 1452.4, 1413.1, 1309.4, 1251.8 cm^{-1}.

*(4E,6Z)-7-(2,4-Dichlorophenyl)-2-methylene-5-p-tolyl-2,3-dihydro-1,4-oxazepine (**2q**).* brown solid; R_f 0.4; mp 150−152 °C; 75 mg, 75% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.66 (2H, m), 7.56−7.52 (1H, m), 7.48−7.44 (1H, m), 7.32−7.27 (1H, m), 7.23−7.18 (2H, m), 6.04 (1H, s), 4.65 (3H, s), 4.37 (1H, s), 2.38 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 158.9, 157.6, 140.3, 137.9, 136.2, 133.9, 131.3, 129.0, 128.7, 127.3, 127.1, 104.9, 93.9, 55.3, 21.3; HRMS (ESI) m/z calcd for $C_{19}H_{16}Cl_2NO^+$ $[M + H]^+$ 344.1011, found 344.1013; IR (neat) 2924.8, 2854.5, 1634.7, 1561.8, 1514.6, 1451.3, 1413.2, 1365.3, 1314.3, 1265.0, 1191.3 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01733.

Single-crystal X-ray data of product **2a** (CIF)

^{1}H and ^{13}C NMR spectra for all products (**2a**−**q**) (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

$^\perp$Dedicated to Dr. Veena Shatrugna on the occasion of her 65th birthday.

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