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A construction of 4,4-spirocyclic γ-lactams by tandem radical cyclization with carbon monoxide

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Abstract
A straightforward synthesis of 4,4-spirocyclic indol γ-lactams by tandem radical cyclization of iodoaryl allyl azides with CO was achieved. The reaction of iodoaryl allyl azides, TTMSS and AIBN under CO pressure (80 atm) in THF at 80 °C gave the desired 4,4-spirocyclic indoline, benzofuran, and oxindole γ-lactams in moderate to good yields.

Introduction
4,4-Spirocyclic oxindole γ-lactams containing a quaternary carbon center are key structures for the synthesis of biologically active natural products and the related analogues [1-4]. Therefore, the development of an efficient synthesis of this spiro structure is of continued interest for synthetic chemists. Recently, Comesse and Daïch reported the synthesis of 4,4-spirocyclic oxindole γ-lactams by tandem spirocyclization via nucleophilic halide displacement and amide coupling [4]. Shaw and co-workers reported the synthesis of 4,4-spirocyclic oxindole γ-lactams by the cycloaddition of imines and succinic anhydrides [5]. Tandem radical cyclization can also provide a powerful tool for the construction of heterocycles [6-12]. One of us previously reported on the construction of spirocyclic pyrrolidinyl oxindoles by the tandem reaction of iodoaryl alkenyl azides under radical conditions (Scheme 1) [13,14]. Curran et al. reported the synthesis of spirocyclic pyrrolidinyl dihydroquinolinones by tandem radical cyclization [15,16].

In this study we report a radical cyclization/annulation approach to 4,4-spirocyclic γ-lactams in which CO was intro-
Scheme 1: A construction of spirocyclic pyrrolidinyl oxindole by tandem radical cyclization with azide [14].

The tandem spirocyclization with CO was investigated with several 2-iodoaryl compounds having an allyl azide moiety. Results are summarized in Table 1. The reaction of N-(2-(azidomethyl)allyl)-N-(2-iodo-5-methoxyphenyl)-4-methylbenzenesulfonamide (1b) with CO gave the corresponding spiro lactam 2b in 53% yield (Table 1, entry 2).

Results and Discussion
For the first model reaction in our investigation of the development of a novel tandem radical cyclization/annulation strategy, we prepared N-(2-(azidomethyl)allyl)-N-(2-iodophenyl)-4-methylbenzenesulfonamide (1a) according to the methods shown in Scheme 3. The reaction of 1a with Bu$_3$SnH (2.0 equiv) and AIBN (2,2'-azobisisobutyronitrile, 0.3 equiv) was carried out under CO pressure (80 atm) in THF (0.02 M) at 80 °C for 12 h, which gave the desired 4,4-spirocyclic indoline γ-lactam 2a in 48% yield (Scheme 4). We found that the modest improvement in the yield of 2a to 53% was achieved by changing the mediator from Bu$_3$SnH to TTMSS [tris(tri-methylsilyl)silane].

The tandem spirocyclization with CO was investigated with several 2-iodoaryl compounds having an allyl azide moiety. Results are summarized in Table 1. The reaction of N-(2-(azidomethyl)allyl)-N-(2-iodophenyl)-4-methylbenzenesulfonamide (1b) with CO gave the corresponding spiro lactam 2b in 53% yield (Table 1, entry 2). N-(2-(Azidomethyl)allyl)-N-(2-iodophenyl)methanesulfonamide (1c) showed a comparable reactivity with 1a and 1b (Table 1, entry 3). The reaction of 1-(2-(azidomethyl)allyloxy)-2-iodobenzene (1d) also gave the spiro benzofuran lactam 2d in 58% yield (Table 1, entry 4). On
Scheme 3: The synthetic methods of 1a.

Scheme 4: The tandem radical spirocyclization reaction of N-(2-(azidomethyl)allyl)-N-(2-iodophenyl)-4-methylbenzenesulfonamide (1a) with CO.

Table 1: Synthesis of 4,4-spirocyclic γ-lactams 2 by tandem radical spirocyclization of 1 with CO. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (1)</th>
<th>Product (2)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 b</td>
<td>1a</td>
<td>2a</td>
<td>53</td>
</tr>
<tr>
<td>2 b</td>
<td>1b</td>
<td>2b</td>
<td>53</td>
</tr>
</tbody>
</table>
the other hand, 2-(azidomethyl)allyl(2-iodophenyl)sulfane (1e) gave a low yield of the corresponding spiro thiobenzofuran lactam (19%, Table 1, entry 5), which may be rationalized by the less effective cyclization due to the longer C–S bonds.

We then tried to extend the tandem spirocyclization approach to obtain 4,4-spiro cyclic oxindole γ-lactam and tested two substrates, 2-(azidomethyl)-N-benzyl-N-(2-iodophenyl)acrylamide (1f) and the nitrogen-protected analogue 1g. The reaction of 1f was smooth to give the desired 4,4-spiro cyclic oxindole γ-lactam 2f in 62% yield (Table 1, entry 6). On the other hand, the reaction of 1g gave the cyclized product in only a trace amount, and instead THF-incorporating 6-endo cyclization product 3 was obtained in 60% yield (Table 1, entry 7) [28].

Based on the known chemistry of radical cyclization and carbonylation reactions, a possible mechanism for the spirocyclization of 1f with CO is shown in Scheme 5. The iodoaryl allyl azide 1f is converted to an aryl radical A via the iodine atom abstraction by the (TMS)₃Si radical. The subsequent 5-exo cyclization of aryl radical A gives an alkyl radical B, which adds to CO to give an acyl radical C. Finally, the 5-exo addition of acyl radical C onto an azide group takes place with the liberation of dinitrogen to give a cyclized amidyl radical D, which abstracts hydrogen from TTMSS, affording the 4,4-spiro cyclic indoline γ-lactam 2f and a (TMS)₃Si radical, thus creating a radical chain.

On the other hand, the unusual formation of THF-incorporating lactam 3 from 1g may be rationalized by the consecutive 6-endo
Scheme 5: Proposed mechanism for a construction of 4,4-spirocyclic indoline y-lactam 2f by the tandem radical cyclization of 1f with CO.

Conclusion
We have examined a TTMSS-mediated 5-exo radical cyclization/carbonylation/spirocyclization sequence to synthesize 4,4-spirocyclic rings. By using this protocol, indoline, benzo[4,5]furan and oxindole y-lactams can be conveniently prepared in moderate to good yields. As shown in the contrasting results of acrylic amides 1f and 1g, to cause the requisite 5-exo cyclization of aryl radicals onto allylic azide in preference to the 6-endo cyclization, the angle compression caused by the substitution on the nitrogen has to be considered carefully. Nevertheless, our method can provide a steady tool for the ring formation of 4,4-spirocyclic y-lactams with the incorporation of CO as a carbonyl group.

Experimental
Typical procedure for a construction of 4,4-spirocyclic y-lactams by tandem radical cyclization with CO: A magnetic stirring bar, 2-(azidomethyl)-N-benzyl-N-(2-iodophenyl)acrylamide (1f) (150.0 mg, 0.36 mmol), AIBN (2,2'-azobisisobutyronitrile, 17.7 mg, 0.11 mmol), TTMSS ([tris(trimethylsilyl)silane], 178.3 mg, 0.72 mmol) and THF (17.9 mL; 0.02 M) were placed in a 50 mL stainless steel autoclave. The autoclave was closed, purged three times with CO, pressurized with 80 atm of CO, and then heated at 80 °C (bath temperature) for 12 h. Excess CO was discharged after the reaction. The reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc 2:1) to give the desired 4,4-spirocyclic oxindole y-lactam product 2f as a colorless oil in 62% yield (65.3 mg, 0.22 mmol). 1H NMR (400 MHz, CDCl3) δ 7.39–7.16 (m, 7H), 7.07 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 5.89 (s, 1H), 4.93 (s, 2H), 3.91 (d, J = 9.2 Hz, 1H), 3.50 (d, J = 9.2 Hz, 1H) 3.02 (d, J = 16.8 Hz, 1H), 2.51 (d, J = 16.8 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 177.5, 175.4, 141.9, 135.5, 133.2, 129.1, 129.0, 128.0, 127.4, 123.6, 122.3, 109.7, 51.1, 49.7, 44.3, 40.4; IR (neat): 3418, 3061, 2927, 1696, 1613, 1488, 1467, 1455, 1380, 1368, 1177 cm⁻¹; HRMS–FAB (m/z): [M + H]⁺ calcd for C18H17N2O2, 293.1290; found, 293.1299.

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