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## ENANTIOSELECTIVE INTRAMOLECULAR AZA-SPIROANNULATION ONTO BENZOFURANS USING CHIRAL RHODIUM CATALYSIS

Takuro Shibuta,<sup>1</sup> Shigeki Sato,<sup>1</sup> Masatoshi Shibuya,<sup>1</sup> Naoki Kanoh,<sup>1</sup> Tohru Taniguchi,<sup>2</sup> Kenji Monde,<sup>2</sup> and Yoshiharu Iwabuchi<sup>\*1</sup>

<sup>1</sup>Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aobayama, Sendai 980-8578, Japan; E-mail: y-iwabuchi@m.tohoku.ac.jp

<sup>2</sup>Frontier Research Center for Post-Genome Science and Technology, Faculty of Advanced Life Science, Hokkaido University, Kita 21 Nishi 11, Sapporo 001-0021, Japan

**Abstract** – The development of efficient and enantioselective intramolecular aza-spiroannulation onto benzofurans using chiral rhodium catalysis is described. The optimized reaction conditions  $[Rh_2(S-TCPTAD)_4 (3 \mod \%), PhIO (1.6 equiv), MeOH (10 equiv) in PhCF_3, 0 °C]$  brought about oxidative aza-spiroannulation of 3-(carbamoylmethyl)benzofuran (3) resulting in (2R,3S)-2-methoxy-2*H*-spiro-[benzofuran-3,4'-oxazolidin]-2'-one (15a) in 69% yield with 86% ee, the absolute structure of which was determined by a combination of X-ray crystallography and vibrational circular dichroism (VCD) spectroscopy. The reaction is applicable to the asymmetric construction of various 2,3-dihydrobenzofuran derivatives bearing a nitrogen-containing tetrasubstituted carbon stereocenter at C3 (up to 92% ee).

2-Oxindoles and 2,3-dihydrobenzofurans, furnished with a nitrogen-containing tetrasubstituted chiral center at the C3 positions,<sup>1,2</sup> are structural motifs found in a variety of potential medicines, pharmaceutically relevant and/or structurally intriguing natural products (Figure 1),<sup>3-8</sup> thus attracting considerable attention from the synthetic community.

Despite its structural similarity to 3-amino-2-oxindole, for which several synthesis strategies have been developed,<sup>3-5,9</sup> few reliable methods capable of constructing 3-amino-2,3-dihydrobenzofurans in an enantiocontrolled manner have been reported to date.<sup>6b,6c,7,10</sup> In the light of successful applications of Rh(II)-catalyzed intramolecular nitrene transfer<sup>11-13</sup> onto indole substrates (Scheme 1),<sup>14-16</sup> an analogous aza-spiroannulation onto benzofuran substrates was envisaged, due to the recent discovery of

(–)-fumimycin (1)<sup>6a</sup> as a novel class of antibiotic agents based on its inhibition of peptide deformylase activity.<sup>17</sup> Notwithstanding the rather discouraging precedents of aza-spiroannulation onto benzofuran



## Figure 1. Representative biologically active 3-amino-2-oxindoles and 3-aminodihydrofurans

a. Seminal report of Padwa et al.: Rh(II)-catalyzed aza-spiroannulation onto indole and benzofuran<sup>14a,b</sup>





b. Report of Che et al.: Chiral Rh(II)-catalyzed asymmetric aza-spiroannulation onto the indole<sup>14c</sup>



c. Report of Xu et al.: Fe(II)-catalyzed asymmetric indole aminohydroxylation<sup>16</sup>



Scheme 1. Selected precedents of aza-aspiroannulation onto indole and benzofuran

(Scheme 1, a),<sup>15a,18</sup> the modular nature of the chiral rhodium-<sup>15c,16</sup> or iron<sup>17</sup>-nitrene complex encouraged us to identify useful conditions for installing the intended nitrogen-containing tetrasubstituted carbon at C3 with high enantioselectivity (Scheme 1, b and c). Herein, we describe the first diastereo- and enantiocontrolled aza-spiroannulation onto benzofurans using chiral rhodium catalysis.

The investigation commenced with the inspection of the reactivity and enantioselectivity of simple benzofuran **3** under typical reaction conditions, using the  $Rh_2(S-TCPTTL)_4(cat.)^{19}/PhI(OAc)_2/MgO$  system.<sup>12</sup> As anticipated, the desired spirocycle **9**<sup>20</sup> was only obtained in 39% yield as a diastereomeric mixture (dr = 1.2:1), which is in line with the result of Padwa *et al*<sup>15b</sup> (Scheme 2).



**Scheme 2.** Our initial attempt of asymmetric aza-spiroannulation onto a simple benzofuran **3** and the plausible reaction mechanisms

The enantioselectivity was also disappointingly low (20% ee). Furthermore, the undesired compound  $10^{20}$  was produced in 30% yield. On the basis of these results, it was speculated that this particular rhodium-catalyzed reaction of the benzofuran **3** proceeded in the following manner (Scheme 2), namely: (i) the initial generation of the rhodium nitrenoid **11** is followed by an intramolecular aziridination to yield aziridine **12**; (ii) **12** can equilibrate with betaine **13**, and this equilibrated species can be isomerized to **14** under given conditions; (iii) AcOH, generated *in situ*, attacks **12** at C2 from the convex face to yield the  $\alpha$ -acetoxy anomer of **9**; (iv) the nucleophilic attack of AcOH with betaine **13** proceeds in a less diastereoselective manner to produce a diastereomeric mixture of **9**, while the nucleophilic attack of betaine **14** by AcOH yields the undesired by-product **10**. The desired spirocyclic compounds were predicted to form efficiently and in a stereospecific manner when aziridine intermediate **12** is quickly

attacked by stronger nucleophiles prior to its isomerization to betaine **13**. The choice of alcohol as a nucleophile seemed to be suitable for this purpose.<sup>21,22</sup> As expected, the treatment of carbamate **8** with  $Rh_2(S$ -TCPTTL)<sub>4</sub> (3 mol %), 1.6 equiv of PhIO, 50 equiv of MeOH, and PhCF<sub>3</sub> as the solvent afforded the spirocycle **15a** in 71% yield as a single diastereomer (Table 1, entry 1). However, the enantioselectivity of **15a** was still low, that is, 36% ee. As the desired spirocycle was successfully obtained, the focus shifted to the improvement in enantioselectivity (Table 1). When the amount of MeOH was decreased to 10 equiv, a slightly higher level of ee was observed (entry 2). The use of 3 mol %  $Rh_2(S$ -TCPTAD)<sub>4</sub><sup>23</sup> as a chiral catalyst provided **15a** in 68% ee (entry 3). Screening of nucleophiles was then undertaken to examine their influence on enantioselectivity using EtOH, allyl alcohol,





<sup>a</sup> Isolated yield. <sup>b</sup> Enantiomeric excess was determined by chiral HPLC analysis. <sup>c</sup> Spirocycle **9** was obtained as a diastereomeric mixture (dr = 1:1.7). <sup>d</sup> Enantiomeric excess was determined using the minor diastereomer of **9**. <sup>e</sup> The isomer **10** was generated in 13% yield as a by-product. <sup>f</sup> The reaction was performed at 0 ° C for 16 h. <sup>g</sup> The absolute stereostructures of **15b** and **15c** were not determined.

and AcOH (entries 4–6). As a result, spirocycles **15b** and **15c** were respectively obtained as a single diastereomer though they exhibited a lower ee than **15a** (entries 4 and 5 vs entry 3). When 10 equiv of AcOH was added, the result got worse: spirocycle **9** resulted as a diastereomeric mixture with quite a low enantioselectivity along with undesired compound **10** (entry 6). Ultimately, it was elucidated that lowering the reaction temperature is critical for good enantioselectivity. When this aza-spirocyclization reaction using MeOH was carried out at 0 °C, spirocycle (–)-**15a** was obtained in good yield with good enantioselectivity characterized by 69% yield and 86% ee (entry 7).

The absolute stereostructure of the product (–)-**15a** was determined by a combination of X-ray crystallography and vibrational circular dichroism (VCD) spectroscopy.<sup>24,25</sup> The relative configuration of **15a** was established as shown in Table 1 by X-ray crystallographic study (Figure 2, a). To determine the absolute configuration of (–)-**15a**, calculations for conformational analysis were carried out using arbitrarily selected (2R,3S)-**15a** (Figure 2, b). Theoretical IR and VCD calculations were then performed for each conformer using density functional theory (DFT) with the B3LYP/6-311+G(d,p) level of theory, and the final calculated IR and VCD spectra were obtained based on the Boltzmann population average of each spectrum. The population-weighted theoretical VCD spectra were shown to be in good agreement



c. Calculated IR and VCD spectra and the measured spectra

Figure 2. Experiments for determining absolute configuration of the obtained spirocycle 15a

with the experimental VCD spectra (Figure 2, c). As the result, the absolute configuration of (–)-15a was elucidated to be (2*R*,3*S*). The determined absolute stereostructure of (–)-15a indicates that spirocycle 15a was generated through an  $S_N$ 2-type ring opening of the aziridine intermediate 12.

The scope of the asymmetric aza-spiroannulation conditions optimized for the benzofuran 8 was investigated by applying them to a diverse range of benzofurans (Figure 3). The introduction of oxygen functional groups and a phenyl group at C5 was tolerated and the corresponding spirocycles were obtained in good yield with reasonable enantioselectivity (73-80% ee) (16a-16d).<sup>26</sup> The halogen-substituted benzofurans were found to be suitable substrates in this particular aza-spirocyclization reaction. The spirocyclic compounds 16e–16h showed good level of ee (84–92% ee). Although bromo-substituted 16h was obtained in low yield, unreacted benzofuran substrate was recovered without severe decomposition. Spirocycle 16i, in which an allyl group was introduced at C4 directed for fumimycin (1) synthesis, was obtained in good yield but with moderate enantioselectivity, implying that modification of the aromatic moiety should be conducted after construction of the C3 stereocenter.



<sup>a</sup> Aza-spirocyclization reactions were performed under the same conditions as those for entry 7 in Table 1. <sup>b</sup> The chemical yield was the isolated yield and enantiomeric excess was determined by chiral HPLC analysis. <sup>c</sup> The absolute stereostructures of **16d-16i** were not determined.

Figure 3. Scope of chiral Rh(II)-catalyzed asymmetric aza-spiroannulation onto benzofurans

In summary, an efficient asymmetric aza-spiroannulation onto benzofurans was developed based on chiral rhodium catalysis. This procedure provides a reliable platform for the construction of enantio-enriched 3-amino-2,3-dihydrobenzofurans in particular non-substituted and mono-substituted ones. A concise synthesis of the core structure of fumimycin has also been achieved. Efforts toward total synthesis of (–)-fumimycin based on this methodology are now ongoing.<sup>27</sup>

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- 20. Three products (two diastereomers of a spirocycle and by-product) and the starting material **3** in the aza-spiroannulation reaction were inseparable by silica gel column chromatograhy. After the treatment of the above mixture with Boc<sub>2</sub>O, two diastereomers of **9**, the by-product **10** were separable and completely purified. All other spirocyclic products were treated with Boc<sub>2</sub>O for easy purification.
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- The absolute stereostructures of 16a–16c were determined as shown in Figure 3. For details, see: Supporting Information.
- 27. For the synthesis of naturally occurring (–)-fumimycin,  $Rh_2(R$ -TCPTAD)<sub>4</sub> should be used for the aza-spiroannulation.