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ENANTIOSELECTIVE INTRAMOLECULAR AZA-SPIROANNULATION ONTO BENZOFURANS USING CHIRAL RHODIUM CATALYSIS

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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 mol %), PhIO (1.6 equiv), MeOH (10 equiv) in $PhCF_3$, 0 °C] brought about oxidative aza-spiroannulation of 3-(carbamoylmethyl)benzofuran (**3**) resulting in (2*R*,3*S*)-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,[1,2] are structural motifs found in a variety of potential medicines, pharmaceutically relevant and/or structurally intriguing natural products (Figure 1),[3-8] 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,[3-5,9] few reliable methods capable of constructing 3-amino-2,3-dihydrobenzofurans in an enantiocontrolled manner have been reported to date.[6b,6c,7,10] In the light of successful applications of Rh(II)-catalyzed intramolecular nitrene transfer[11-13] onto indole substrates (Scheme 1),[14-16] an analogous aza-spiroannulation onto benzofuran substrates was envisaged, due to the recent discovery of

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

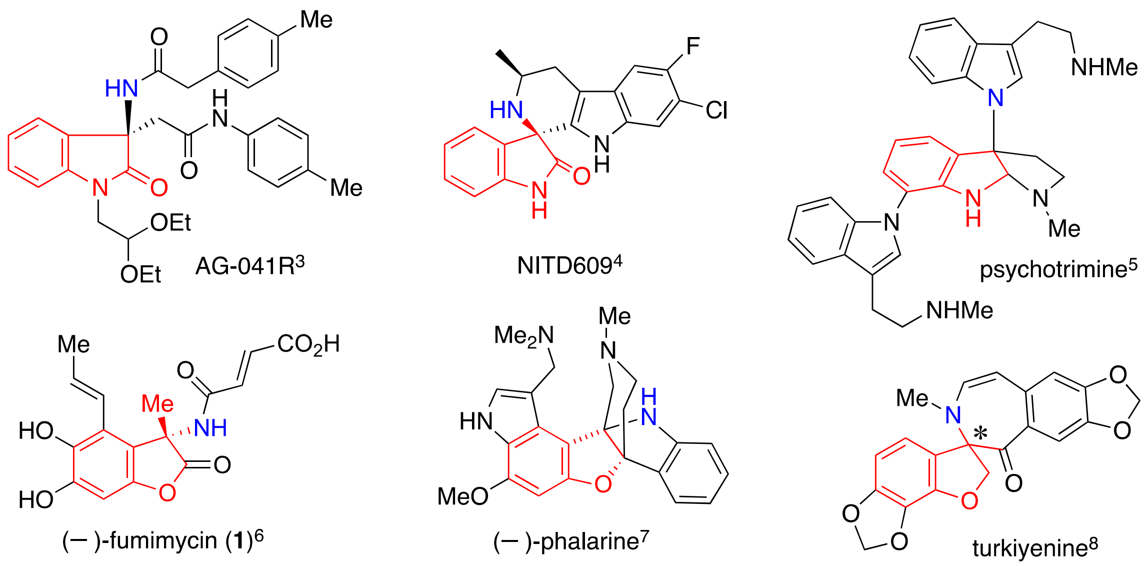
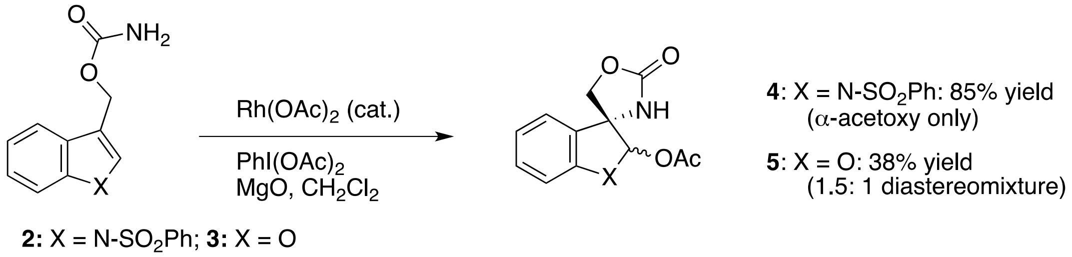
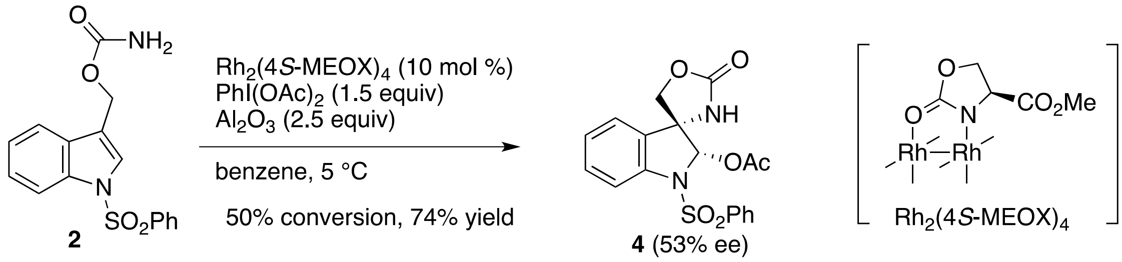


Figure 1. Representative biologically active 3-amino-2-oxindoles and 3-aminodihydrofurans

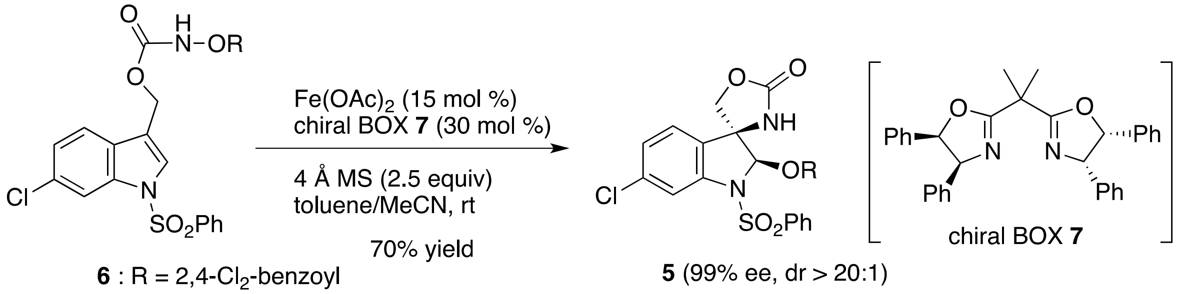
a. Seminal report of Padwa *et al.*: Rh(II)-catalyzed aza-spiroannulation onto indole and benzofuran[14a,b]



b. Report of Che *et al.*: Chiral Rh(II)-catalyzed asymmetric aza-spiroannulation onto the indole[14c]



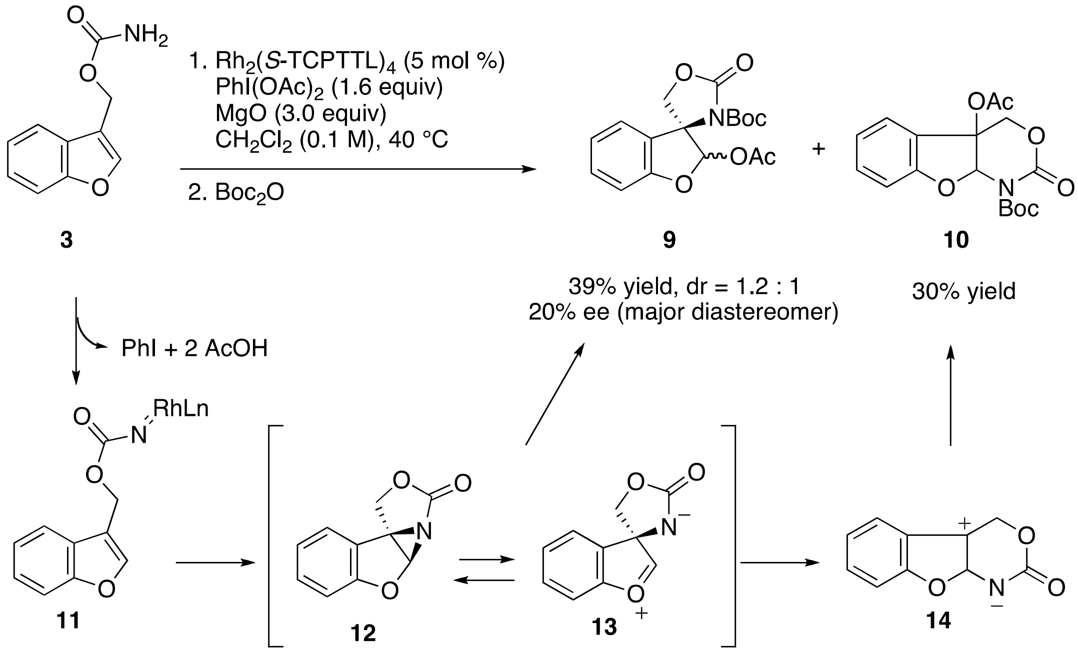
c. Report of Xu *et al.*: Fe(II)-catalyzed asymmetric indole aminohydroxylation[16]



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

(Scheme 1, a),[15a,18] the modular nature of the chiral rhodium-[15c,16] or iron[17]-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.

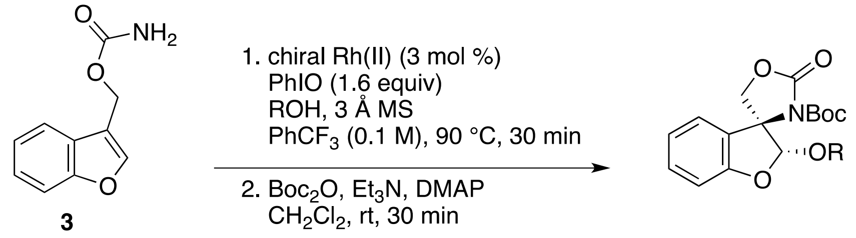
The investigation commenced with the inspection of the reactivity and enantioselectivity of simple benzofuran **3** under typical reaction conditions, using the Rh$_2$(*S*-TCPTTL)$_4$(cat.)[19]/PhI(OAc)$_2$/MgO system.[12] As anticipated, the desired spirocycle **9**[20] was only obtained in 39% yield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



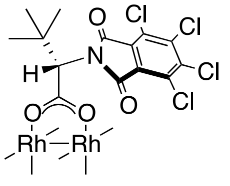
Scheme 2. Our initial attempt of asymmetric aza-spiroannulation onto a simple benzofuran **3** and the plausible reaction mechanisms

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 α–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.[21,22] As expected, the treatment of carbamate **8** with Rh$_2$(*S*-TCPTTL)$_4$ (3 mol %), 1.6 equiv of PhIO, 50 equiv of MeOH, and PhCF$_3$ 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)$_4$[23] 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,

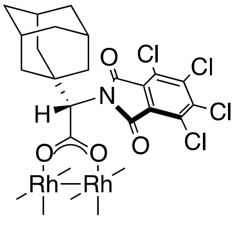
Table 1. Optimization of reaction conditions



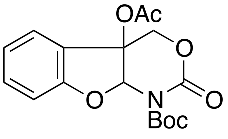
entry	chiral Rh(II)	ROH	product (yield^{a} / ee^{b})
1	Rh$_2$(*S*-TCPTTL)$_4$	MeOH (50 equiv)	**15a**: R = Me (71% / 36% ee)
2	Rh$_2$(*S*-TCPTTL)$_4$	MeOH (10 equiv)	**15a**: R = Me (55% / 52% ee)
3	Rh$_2$(*S*-TCPTAD)$_4$	MeOH (10 equiv)	**15a**: R = Me (53% / 68% ee)
4	Rh$_2$(*S*-TCPTAD)$_4$	EtOH (10 equiv)	**15b**^{g}: R = Et (47% / 61% ee)
5	Rh$_2$(*S*-TCPTAD)$_4$	AllylOH (10 equiv)	**15c**^{g}: R = Allyl (37% / 55% ee)
6	Rh$_2$(*S*-TCPTAD)$_4$	AcOH (10 equiv)	**9**: R = Ac (40%^{c} / 33% ee^{d})^{e}
7^{f}	Rh$_2$(*S*-TCPTAD)$_4$	MeOH (10 equiv)	**15a**: R = Me (69% / 86% ee)



Rh$_2$(*S*-TCPTTL)$_4$



Rh$_2$(*S*-TCPTAD)$_4$

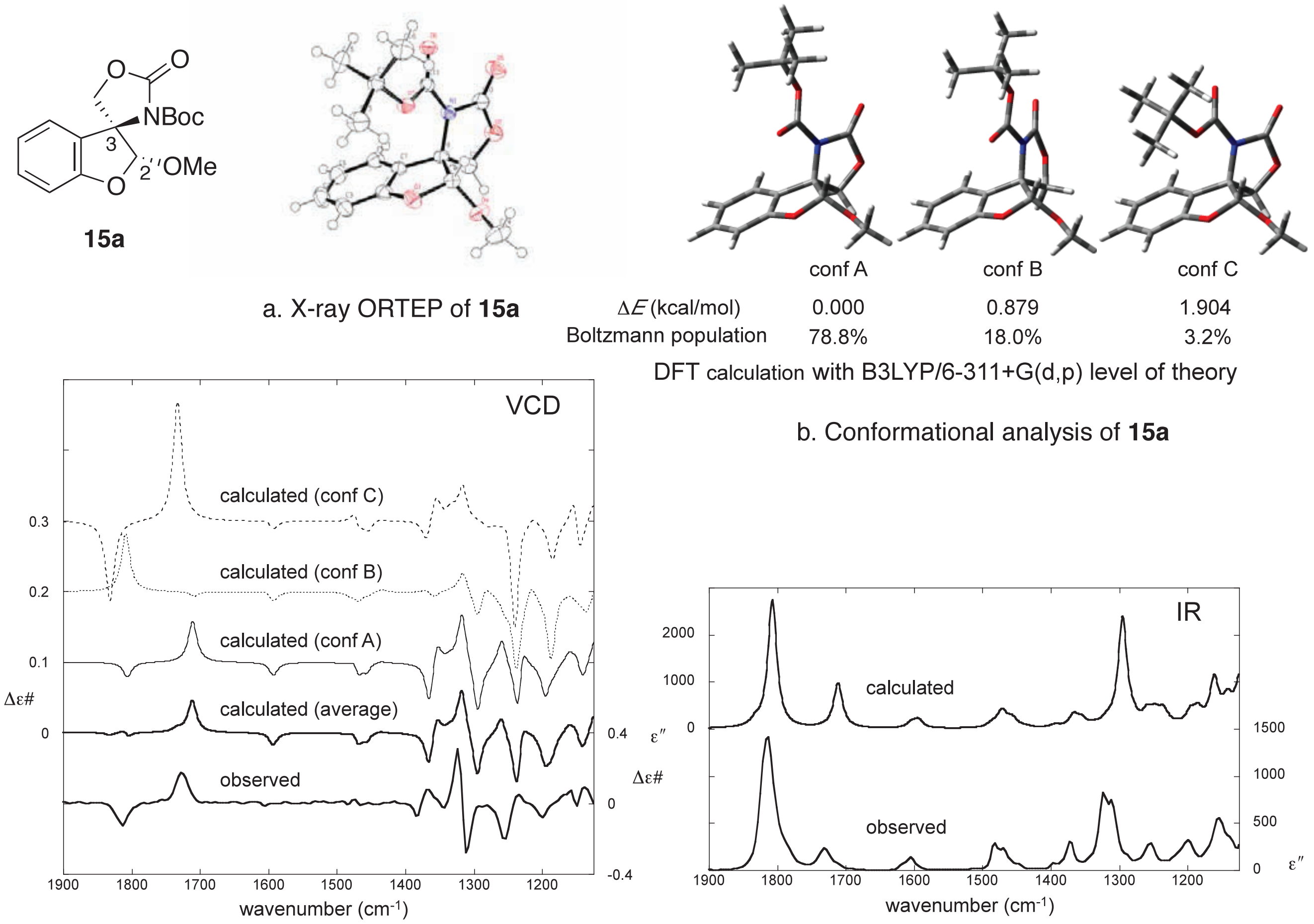


10

[a] Isolated yield. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Spirocycle **9** was obtained as a diastereomeric mixture (dr = 1:1.7). [d] Enantiomeric excess was determined using the minor diastereomer of **9**. [e] The isomer **10** was generated in 13% yield as a by-product. [f] The reaction was performed at 0 °C for 16 h. [g] 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.[24,25] 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 (2*R*,3*S*)-**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



a. X-ray ORTEP of **15a**

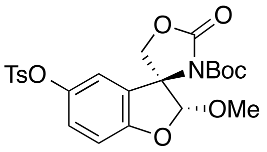
b. Conformational analysis of **15a**

c. Calculated IR and VCD spectra and the measured spectra

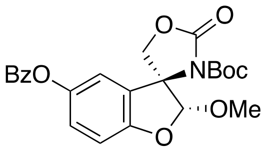
Figure 2. Experiments for determining absolute configuration of the obtained spirocycle **15a**

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_N2-type ring opening of the aziridine intermediate **12**.

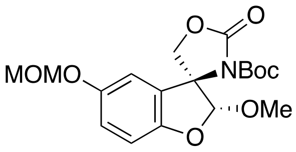
The scope of the asymmetric aza-spiroannulation conditions optimized for the benzofuran **8** was investigated by applying them to a diverse range of benzofurans (Figure 3). The introduction of oxygen functional groups and a phenyl group at C5 was tolerated and the corresponding spirocycles were obtained in good yield with reasonable enantioselectivity (73−80% ee) (**16a**–**16d**).[26] 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.


16a

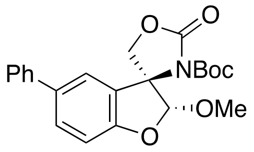
60% / 80% ee (48 h)


16b

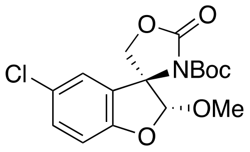
70% / 78% ee (48 h)


16c

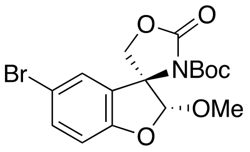
50% / 73% ee (72 h)


16d

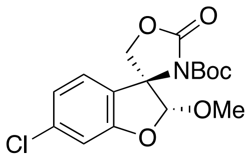
88% / 75% ee (48 h)


16e

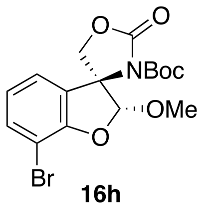
65% / 89% ee (48 h)


16f

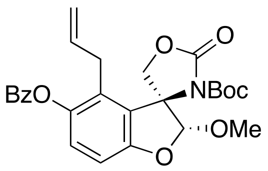
50% / 84% ee (48 h)


16g

61% / 92% ee (48 h)


16h

26% / 85% ee (16 h)


16i

61% / 51% ee (48 h)

[a] Aza-spirocyclization reactions were performed under the same conditions as those for entry 7 in Table 1. [b] The chemical yield was the isolated yield and enantiomeric excess was determined by chiral HPLC analysis. [c] 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.[27]

ACKNOWLEDGEMENTS

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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_2O, two diastereomers of **9**, the by-product **10** were separable and completely purified. All other spirocyclic products were treated with Boc_2O for easy purification.
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27. For the synthesis of naturally occurring (–)-fumimycin, $Rh_2(R\text{-TCPTAD})_4$ should be used for the aza-spiroannulation.