# Synthesis of Fused and Linked Benzofurans from 2-Alkynylphenol Derivatives through Rhodium(I)-catalyzed Domino-type Addition Reactions

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With the best tribute to the memory of my mentor, late Professor Teruaki Mukaiyama who passed away on November 17, 2018 at the age of 91.

*Abstract:* A rhodium(i)-catalyzed domino-type sequential 5-*endo*/5-*exo* cyclization reaction of [(2-acylphenyl) ethynyl]phenols produces indene/benzofuran-fused alcohols. A moderate asymmetric induction is observed when chiral diphosphine ligands are used for rhodium. Indene/indole-fused compounds are synthesized by a similar reaction of [(2-acetylphenyl)ethynyl]anilines. The domino-type 5-*endo*/5-*exo* cyclization reaction is extended to substrates having two phenolic hydroxy groups. A linearly-fused array of five- and six-membered rings is constructed. Fused and linked benzofurans possessing 2-cyanoethyl side chains are also synthesized through sequential formation of C–O and C–C bonds.

Keywords: Asymmetric reaction · Benzofuran · Cyclization · Domino reaction · Rhodium



Masahiro Murakami is currently a Chemistry Professor at Kyoto University. He grew up in a rice farmer's family in Toyama, Japan and then trained at the University of Tokyo,

receiving his DSc in 1984 under the supervision of Prof. Teruaki Mukaiyama. He started his career with an assistant position to Prof. Mukaiyama at the University of Tokyo (1984-1987). He moved to Kyoto University taking an assistant position to Professor Yoshihiko Ito in 1987, and was promoted to Associate Professor in 1993. In the meantime, he took leave to spend ten months from May 1991 till March 1992 at the ETH Zürich as a post-doctoral fellow with Prof. Albert Eschenmoser. He was appointed to Professor in 2002 at Kyoto University. His research interests focus on the development of new and interesting organic transformations. The utilization

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## Introduction

Benzo[*b*]furan is a privileged structural motif prevalently found in a variety of natural products and biologically active compounds.<sup>[11]</sup> Benzofuran derivatives have also received considerable attention as organic electronic materials in recent years.<sup>[2]</sup> 2-Alkynylphenols are readily accessible compounds that are suitable synthetic precursors of benzofurans. They readily undergo, upon treatment with an appropriate promoter, a 5-endo cyclization reaction to construct benzofuran skeletons in an expeditious and atom-economical manner. There have been a number of promoters reported to effect the 5-endo cyclization reaction.<sup>[3,4]</sup> Among them, the cyclization reaction catalyzed by a hydroxorhodium(I) complex, developed by Lautens,[4] is particularly attractive since (benzofuran-3-yl)-rhodium(I) species arising from the cyclization are relatively stable but active enough to further add to electron-deficient alkenes such as acrylonitrile, furnishing 2,3-disubstituted benzofurans in one-pot reactions. The domino-type addition reaction has a mechanistic distinction that the intermediate organorhodium(I) species is generated from a non-organometallic compound dispensing with pre-preparation of precursory organometallic compounds (Scheme 1).<sup>[5]</sup>

The reaction merited further investigation, targeting fused and linked compounds containing benzofuran cores, which are of much interest from the viewpoint of or-



Scheme 1. Generation and reaction of (benzofuran-3-yl)rhodium(I) species

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Scheme 2. Rhodium(i)-catalyzed domino-type 5-endo/5-exo cyclization of **1a** 

Scheme 3. Rhodium(i)-catalyzed domino-type 5-endo/5-exo cyclization of 1ª. ªReaction conditions: substrate 1 (0.10–0.37 mmol), [Rh(OH)(cod)]<sub>2</sub> (10 mol% in Rh), *rac*-BINAP (10 mol%), THF (0.1 M), 80 °C, 12 h. <sup>b</sup>Isolated yield.



Table 1. Asymmetric cyclization of **1**<sup>a</sup>



entry	1 (R)	diphosphine ligand	product	yield [%] <sup>b</sup>	ee [%] <sup>c</sup>
1	1a (Me)	(R)-BINAP	2a	94	51
2	1a	(R)-MeO-BIPHEP	2a	80	79
3	1a	(R)-C3-TunePhos	2a	82	84
4	1a	(R)-SEGPHOS	2a	84 <sup>d</sup>	88 <sup>d</sup>
5	1b (Et)	(R)-SEGPHOS	2b	51 <sup>d</sup>	85 <sup>d</sup>
6	<b>1c</b> ( <i>i</i> -Pr)	(R)-SEGPHOS	2c	38 <sup>d</sup>	83 <sup>d</sup>
7	1d (Ph)	(R)-SEGPHOS	2d	53 <sup>d</sup>	86 <sup>d</sup>

<sup>a</sup> Reaction conditions: substrate **4** (0.050 mmol), [Rh(OH)(cod)]<sub>2</sub> (10 mol% in Rh), chiral diphosphine ligand (13 mol%), THF (0.03 M), 80 °C, 12 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral GC (Rt- $\beta$ DEXm) or HPLC (CHIRALCEL OJ-H). <sup>d</sup> Average of two runs.

ganic electronics and nanotechnology.<sup>[1,2]</sup> Herein, we report the results of our study on the synthesis of fused and linked benzofurans on the basis of the rhodium-catalyzed domino-type cyclization protocol.

## **Results and Discussion**

2-[(2-Acetylphenyl)ethynyl]phenol (1a) was designed to synthesize indene/ benzofuran-fused alcohol 2a through domino-type sequential 5-endo/5-exo cyclization. An electrophilic acetyl group is placed on an alkynylphenol backbone in a way that an intermediate (benzofuran-3-yl) rhodium(I) species further undergoes the second cyclization onto the acetyl group in a 5-exo mode, attaching a fused indene skeleton. It was synthesized through the Sonogashira coupling reaction of 1-iodo-2-(methoxy)benzene with 2-ethynvlphenvl methyl ketone and the following deprotection of the methoxymethoxy group under acidic conditions. When 1a was treated with a catalytic amount of a rhodium complex prepared in situ from [Rh(OH)(cod)], and rac-BINAP, indenobenzofuranol 2a was obtained in 89% isolated yield (Scheme 2). Initially, a rhodium(I) alkoxide is generated from 1a by deprotonation of the phenolic hydroxy group with the hydroxorhodium(I) complex. The first cyclization takes place in a 5-endo mode.<sup>[6]</sup> The resulting (benzofuran-3-yl)rhodium(I) species then undergoes the second cyclization onto the pendent acetyl group in a 5-exo mode to afford 2a.<sup>[7]</sup> The resulting rhodium(I) alkoxide acts as a base to release the alcohol 2a, promoting the next catalytic cycle.

Other 2-[(2-acylphenyl)ethynyl] phenols **1b**, **1c**, **1e**, and **1f** were prepared in an analogous manner to **1a**. 2-[(2-Benzoylphenyl)ethynyl]phenol (**1d**) was prepared through the Sonogashira coupling reaction of 2-iodobenzophenone with 1-ethynyl-2-(methoxymethoxy)benzene and the following deprotection. They successfully participated in the dominotype 5-endo/5-exo cyclization reaction to afford indene/benzofuran-fused alcohols **2b–f** in good yield (Scheme 3).<sup>[8]</sup>

Induction of enantioselectivity in the second 5-*exo* cyclization process producing **2a** was investigated using representative axially chiral biaryl diphosphine ligands for rhodium (Table 1). An enantioselectivity was modest when the most typical (R)-BINAP was tried (entry 1). Among other chiral ligands examined, (R)-SEGPHOS gave the best result in terms of both chemical yield and enantioselectivity (entries 2–4). (R)-SEGPHOS induced good enantioselectivities around 85% ee also with other substrates **1b–d**, although chemical yields were moderate (entries 5–7).<sup>[9]</sup>

Previous work by Lautens suggested that it would be possible to extend the domino-type 5-endo/5-exo cyclization protocol for the synthesis of indene/benzofuran-fused alcohols to the synthesis of indene/indole-fused alcohols by replacing the hydroxy group with a sulfonated amino group. 2-[(Acetylphenyl)ethynyl]anilines 3a and 3b were prepared from 2-iodoacetophenone and 2-ethynylanilines by the Sonogashira coupling reaction followed by deprotection, and subjected to the identical reaction conditions. They successfully underwent an analogous domino-type 5-endo/5-exo cyclization reaction to afford indene/indole-fused alcohols 4a and 4b via sequential formation of C-N and C-C bonds (Scheme 4).[10,11]

We were intrigued also by the substrates bearing two phenolic hydroxy groups, each of which would trigger the 5-endo cyclization. It constructs more conjugated benzofuran structures, which would be more promising as the material for organic electronics and nanotechnology. When the hydroquinone derivative **5** was used, the domino-type 5-endo/5-exo cyclization occurred on both sides to form a linearly-fused array of five- and sixmembered rings in an expeditious manner, affording **6** in 66% yield (Scheme 5).<sup>[12]</sup>

Another hydroquinone derivative, 2,5-bis(phenylethynyl)hydroquinone (**7a**),<sup>[2d]</sup> was reacted with an excess amount of acrylonitrile (**8**) in the presence of a rhodium(I) catalyst. Each of the arising (benzofuran-3-yl)rhodium(I) species underwent intermolecular conjugate addition to acrylonitrile (**8**), introducing two 2-cyanoethyl side chains on the fused tricyclic aromatic core to afford **9a** (Scheme 6).<sup>[4]</sup>

An analogous intermolecular reaction with acrylonitrile (8) was carried out using 1,4-bis[(2-hydroxyphenyl)ethynyl] benzene (7b). 1,4-Di(benzofuran-2-yl) benzene 9b was produced in 64% yield (Scheme 7).<sup>[13]</sup> Similarly, the reaction of the corresponding 1,3-disubstituted (*meta*disubstituted) derivative 7c with 8 afforded 1,3-di(benzofuran-2-yl)benzene 9c in 63% yield (Scheme 8).

## Conclusion

In summary, a rhodium(I)-catalyzed cyclization reaction was studied using [(2-acylphenyl)ethynyl]phenols and similar aniline derivatives. Domino-type sequential 5-endo/5-exo cyclization took place to produce indene/benzofuran-fused and indene/ indole-fused alcohols, respectively. The domino-type reaction was extended to the substrates having two phenolic hydroxy groups. A linearly-fused array of five- and six-membered rings is constructed. Fused and linked benzofurans possessing 2-cya-



noethyl side chains are also synthesized through sequential formation of C–O and C–C bonds.

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