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Synthesis of 2-tetralone derivatives by Bi(OTf)₃-catalyzed intramolecular hydroarylation/isomerization of propargyl alcohols

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2-Teralones are important scaffolds in biologically active natural products, pharmaceuticals, and other useful materials;¹ however, they are difficult to synthesize.² Existing synthetic methods for 2-tetrlones include the 1,2-transposition of the carbonyl group of 1-tetralones,³ reduction of substituted 2-methoxynaphthalenes,⁴ Rh(II)-catalyzed cyclization of α -diazoketones,⁵ SnCl₄-mediated cyclization of propargyl alcohols,⁶ Pummerer rearrangementmediated cyclization of aryl β-ketosulfoxides,⁷ and the Friedel-Crafts reaction of aromatic acyl chlorides with olefins.⁸ However, these reactions suffer from the use of expensive (rhodium) and harmful (diazoketone and β-ketosulfoxide) reagents, long reaction sequences, and low-to-moderate yields. Therefore, a more efficient method needs to be developed for the synthesis of 2-tetralone considering their importance. Recently, In(III)-promoted cyclization/ isomerization reaction of propargyl alcohols has been reported.⁹ Although this procedure provides an efficient one-step synthetic route for the synthesis of 2-tetralone, the substrate scope of 2-tetralones was narrow. Recently, we reported the intramolecular hydroarylation reactions of aryl alkynes using a Brønsted acid or Au catalyst.^{10,11} In our previous studies, we found that Fe or Bi salts are efficient catalysts for the π -activation of C–C triple bonds.¹² Therefore, we envisioned that Fe or Bi salts are sufficient catalysts for the synthesis of 2-tetralones by intramolecular hydroarylation/ isomerization reactions. Bi is known as an environmentally benign

ABSTRACT

Compared to 1-tetralones, 2-tetralones are expensive, less stable, and difficult to synthesize. A concise Bi-catalyzed method was developed for the synthesis of 2-tetralones from 5-phenylpent-1-yn-3-ol derivatives. Diverse 2-tetralones were obtained in moderate to good yields under mild conditions. © 2015 Elsevier Ltd. All rights reserved.



Scheme 1. Synthesis of 2-tetralone derivatives.

element and has been widely used in synthetic chemistry over the last few years.¹³ In particular, Bi(OTf)₃ is a well-known efficient catalyst for dual activation via σ , π -chelation.¹⁴ In this Letter, we report the Bi(OTf)₃-catalyzed one-step synthesis of 2-tetralones from aryl propargyl alcohols. We have used 5-phenylpent-1-yn-3-ol **1a** as a useful functionality in organic synthesis; as a model reaction, the reaction of **1a** with a catalytic amount of Bi(OTf)₃ afforded 2-tetralone in good yields (Scheme 1).

First, various types of propargyl alcohols **1** were prepared in good to excellent yields by classic methods.¹⁵ The reduction of commercially available cinnamic acids with LAH in THF afforded the corresponding saturated alcohols. Next, the reaction of primary alcohols with PCC in CH₂Cl₂ afforded the corresponding aldehydes in good yields. Finally, the Grignard addition of ethynylmagnesium bromide to the aldehydes afforded the corresponding 5-phenylpent-1-yn-3-ol derivatives **1**.

To optimize the catalyst for the intramolecular hydroarylation/ isomerization of 5-phenylpent-1-yn-3-ol derivatives **1**, diverse Lewis and Brønsted acids were screened using **1a** as the model substrate (Table 1). Various Fe salts were investigated as catalysts for the synthesis of 1-methyl-2-tetralone **2a** in DCE. The reaction of

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Table 1

Optimization of reaction conditions^a



Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Yield ^b (%)
1	FeCl ₂ (10)	DCE	80	10	0
2	FeCl ₃ (10)	DCE	80	20	0
3	FeCl ₂ ·4H ₂ O (10)	DCE	80	10	0
4	Fe(ClO ₄) ₃ ·xH ₂ O (10)	DCE	80	20	0
5	$Fe(OTf)_3$ (10)	DCE	80	16	35
6	FeCl ₃ (10)/AgOTf (30)	DCE	80	6	24
7	$Sc(OTf)_3$ (10)	DCE	80	16	0
8	$Cu(OTf)_2$ (10)	DCE	80	16	0
9	In(OTf) ₃ (10)	DCE	80	16	72
10	Bi(NO ₃) ₃ .5H ₂ O (10)	DCE	80	20	0
11	BiCl ₃ (10)	DCE	80	20	0
12	BiCl ₃ (10)/AgOTf (30)	DCE	80	1	78
13	Bi(OTf) ₃ (10)	DCE	80	2	90 (80) ^c
14	$Bi(OTf)_3(5)$	DCE	80	2	76 (60) ^c
15	Bi(OTf) ₃ (10)	DCE	60	20	72
16	PTSA (10)	DCE	80	16	0
17	TfOH (10)	DCE	80	2	12
18	Bi(OTf) ₃ (10)	Toluene	80	9	47
19	Bi(OTf) ₃ (10)	CH_3NO_2	80	10	47
20	Bi(OTf) ₃ (10)	CH ₃ CN	80	10	0
21	Bi(OTf) ₃ (10)	THF	80	10	0
22	Bi(OTf) ₃ (10)	EtOH	80	10	0

^a Reaction conditions: 5-phenylpent-1-yn-3-ol (**1a**, 0.25 mmol), solvent (1.5 mL), under nitrogen atmosphere.

^b Yields are based on **2a**, determined by crude ¹H NMR using dibromomethane as the internal standard.

^c Isolated yield.

1a with catalytic amounts of FeCl₂, FeCl₃, FeCl₂·4H₂O, and $Fe(ClO_4)_3 \cdot xH_2O$ at 80 °C failed (entries 1–4). The reaction of **1a** with Fe(OTf)₃ at 80 °C afforded 2a in 35% yield (entry 5). The reaction of 1a with FeCl₃/AgOTf afforded **2a** in 24% yield (entry 6); however, when $Sc(OTf)_3$, and $Cu(OTf)_2$ were used, the product could not be detected by ¹H NMR analysis (entries 7 and 8). When In(OTf)₃ was used as the catalyst, 2a was obtained in 72% yield (entry 9). When Bi salts such as Bi(NO₃)₃·5H₂O and BiCl₃ were used, the reactions failed (entries 10 and 11). However, when BiCl₃ and AgOTf were used as the co-catalysts, **2a** was obtained in 78% yield (entry 12). To our delight, when $Bi(OTf)_3$ was used as the catalyst, the reaction of **1a** in DCE at 80 °C for 2 h afforded 2a in 90% yield (80% isolated yield, entry 13). When the amount of Bi(OTf)₃ was decreased to 5 mol %, the yield of 2a decreased to 76% (entry 14). Further, at 60 °C, the product was obtained in good yields (72%, entry 15). Brønsted acids such as *p*-toluenesulfonic acid (PTSA) and triflic acid (TfOH), were inefficient (entries 16 and 17). Then, various solvents were screened to determine the optimal solvent for the reaction with Bi(OTf)₃. The use of toluene and CH₃NO₂ resulted in low yields (entries 18 and 19); furthermore, the reactions failed when CH₃CN, THF, and EtOH

With the optimized conditions, the reactions of various types of propargyl alcohols **1** were investigated to demonstrate the efficiency substrate scope of the reaction, and the results are summarized in Table 2. The reaction of **1a** with 10 mol % $Bi(OTf)_3$ afforded **2a** in 80% yield (entry 1). The reaction of propargyl alcohol bearing a 2-methyl group on the phenyl ring (**1b**) afforded the corresponding product, **2b**, in 76% yield (entry 2). The reaction of propargyl alcohol bearing a 3-methyl substituent (**1c**) afforded the corresponding products, **2ca** and **2cb**, in 85% overall yield as a mixture of two regioisomers in a 1.1:1 ratio (entry 3). The cyclization of 5-*p*-tolypent-1-yn-3-ol (**1d**) afforded the corresponding product, **2d**, in a good yield (entry 4). The cyclization of propargyl alcohols

were used (entries 20-22).

Table 2			
Bi-catalyzed	intramolecular	hydroarylation	/isomerization

Entry	Substrate	Product	Time (h)	Yield ^b (%)
1	OH 1a	CH ₃ 2a	2	80
2	CH ₃ OH 1b		2	76
3	H ₃ C OH 1c	$H_{3}C$ CH_{3} C	1	85 (1.1:1)
4	H ₃ C OH 1d	H ₃ C CH ₃ O 2d	1	79
5	OMe OH 1e	CH ₃ OMe	1.5	66
6	MeO OH 1f	MeO 2fa 2fb	1.5	75 (2.8:1)

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Entry	Substrate	Product	Time (h)	Yield ^b (%)
7	MeO OH 1g	MeO 2g	1	77
8	MeO MeO OH 1h	MeO MeO MeO 2h	0.5	76
9	CI OH 1i		6	28
10	Br OH 1j	Br CH ₃ Br CH ₃ Br 2ia 2ib	6	40 (1.4:1)
11	OH 1k		2	78
12	Me Me _{OH} 11	CH ₃ O Me Me	1	92°
13	CI Me Me _{OH} 1m	CI Me Me 2m	5	34 ^c
14	OH In	CH ₃ O 2n	5	53

Table 2 (continued)

^a The reaction was conducted in anoxic conditions. Reaction conditions: propargyl alcohol (**1a**, 0.25 mmol), Bi(OTf)₃ (10 mol %), solvent (1.5 mL), under nitrogen atmosphere.

^b Isolated yield.

^c 5 mol % of Bi(OTf)₃ was used.



Scheme 2.

with an electron-donating methoxy group smoothly afforded the corresponding products in good yields (entries 5–7). 6,7-Dimethoxy-2-tetralone (**2h**) was obtained in 76% yield when substrate **1h** was cyclized (entry 8). The reaction of substituted propargyl alcohols containing electron-withdrawing groups such as Cl-, or Br-, on the phenyl ring resulted in low yields (entries 9 and 10); however, the reactions failed when propargyl alcohols with trifluoromethyl-, nitrile-, and nitrophenyl substituents were used. The reaction of naphthylene-containing propargyl alcohol **1k** afforded 1-methyl-3,4-dihydrophenanthren-2(1*H*)-one (**2k**) in 78% yield (entry 11). To investigate the Thorpe–Ingold effect, ¹⁶ we also tested the substrates containing the *gem*-dimethyl group on the tethering



Scheme 3. Plausible reaction mechanism.

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carbon. 5-Methyl-5-phenylhex-1-yn-3-ol (**1**) reacted quickly to produce 1,4,4-trimethyl-2-tetralone (**2**) in excellent yield when using 5 mol % of Bi(OTf)₃ (entry 12); Furthermore, the reactions of 5-(4-chlorophenyl)pent-1-yn-3-ol (**1m**) containing electron-withdrawing groups on the phenyl ring afforded the desired products (**2m**) in 34% yield (entry 13). Furthermore, the cyclization of **1n** containing an ether linkage proceeded to afford the corresponding product, **2n**, in 53% yield (entry 14).

To demonstrate the utility of catalytic hydroarylation/isomerization, we also carried out the reaction of 1-phenylbut-3-yn-2-ol (**10**) and 6-phenylhex-1-yn-3-ol (**1p**). The reaction of **10** afforded naphthalene (**20**) in 33% yield via the 6-endo-dig cyclization/dehydration sequence, however, no reaction occurred when using **1p** (Scheme 2).

Although the mechanism of this reaction has not been fully established at this stage, a possible reaction pathway is shown in Scheme 3. The borderline Bi would coordinate not only to the OH group, but also to the triple bond of propargyl alcohol, leading to a dually activated species. The subsequent cyclization of the dually activated species occurs readily by the intramolecular hydroarylation of the arene with Bi-coordinated alkyne to afford the zwitterionic intermediate. Finally, the isomerization of exo-methylene group followed by the tautomerization of enol affords the product,¹⁷ and releases the catalyst, thus completing the catalytic cycle.

In conclusion, we developed a novel Bi-catalyzed intramolecular hydroarylation/isomerization of aryl propargyl alcohols, mainly affording 2-tetralones in good to high yields under mild reaction conditions. Bi catalysts, are inexpensive, non-toxic, and environmentally benign, and therefore, they are advantageous from the perspective of sustainable chemistry. Further applications of this method to other useful tetralone derivatives including heterocycles are underway.

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Supplementary data

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.129.

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