$Cu(OTf)_2$-Catalyzed Isomerization of 7-Oxabicyclic Alkenes: A Practical Route to the Synthesis of 1-Naphthol Derivatives

Fangzhi Peng,[1] Baomin Fan,[1] Zhihui Shao,* Xuewei Pu, Penghui Li, Hongbin Zhang

Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, P. R. of China
Fax +86(871)5033538; E-mail: zhihui_shao@hotmail.com

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Abstract: Lewis acid catalyzed isomerization of 7-oxabicyclic alkenes into 1-naphthol derivatives in high yields (87–98%) under mild reaction conditions has been developed. The mechanism of this reaction is briefly postulated.

Keywords: catalysis, copper, isomerization, 1-naphthol derivative, 7-oxabicyclic alkenes

Brønsted acid catalyzed isomerization of 7-oxabicyclic alkenes into 1-naphthol derivatives is one of the most fundamental reactions in organic synthesis.[2–4] This process has proven to be effective for incorporating the naphthol fragment into complex molecules;[5–8] however, the use of strong protic acids has limited the utilization of this reaction, especially in Brønsted acid sensitive substrates. Furthermore, the use of strong protic acids leads to highly acidic waste streams, which pose an environmental problem for industrial processes. For these reasons, several alternative approaches to 1-naphthol derivatives that do not require the presence of strong protic acids have been developed. Unfortunately, these methods suffer from drawbacks such as the use of expensive palladium catalysts, high reaction temperatures and limited substrate scope. Miura et al.[9] reported a palladium-catalyzed annulation of *o*-bromobenzaldehydes with 2-substituted 2-alkenals, however, high temperature (120 °C) is required in this reaction. Furthermore, yields are generally moderate due to the production of 1,3-disubstituted naphthalenes accompanied by decarbonylation. Recently, Martin et al.[10] reported an elegant palladium-catalyzed ring-opening of 7-oxabicyclic alkenes with aryl and vinyl halides followed by oxidation of the intermediate dihydronaphthols with 2-iodoxybenzoic acid (IBX). This protocol provides 2-substituted 1-naphthol derivatives in good yields, however, it suffers from drawbacks such as the use of expensive palladium catalyst and excess IBX (3 equiv). From a practical point of view, it is thus highly desirable to develop a novel method for the preparation of 1-naphthol derivatives.

During the past decades, metal-based Lewis acids have found many applications in organic synthesis.[11] Nevertheless, they have largely been neglected as effective catalysts for the isomerization of 7-oxabicyclic alkenes into 1-naphthol derivatives, probably due to the reaction with the bridging oxygen of 7-oxabicyclic alkenes, which reduces the reactivity of Lewis acids. Metal triflates are unique Lewis acids that are currently of great research interest.[12–17] Metal triflates are generally stable and still active in the presence of many substrates containing heteroatoms such as nitrogen, oxygen and sulfur. Due to these advantages, they are widely used in organic synthesis.[18] We envisioned that metal triflates with suitable cations and anions might be effective catalysts for the isomerization of 7-oxabicyclic alkenes into 1-naphthol derivatives. In this paper, we report the first example of $Cu(OTf)_2$-catalyzed isomerization of 7-oxabicyclic alkenes into 1-naphthol derivatives under mild conditions.[19]

This methodology has the following features: (i) it differs from the isomerization catalyzed by Brønsted acids in having a broad substrate scope; (ii) it can provide 2,4-disubstituted 1-naphthol derivatives, which are potential 5-lipoxygenase inhibitors and are difficult to synthesize via Brønsted acid catalyzed isomerization; (iii) it uses less expensive copper catalyst; (iv) it offers high chemical yields (87–98%).

We began our investigations with 7-oxabenzonorbornadiene (**1a**) in the presence of a range of 10 mol% metal salts (Table 1). It was found that $Zn(OTf)_2$ and AgOTf were not useful for obtaining the desired 1-naphthol **2a** (entries 1 and 2). Given that copper Lewis acids have been successfully applied in numerous reactions, we then turned our attention to the use of copper salts as catalysts. CuCl and CuBr did not promote the reaction (entries 3 and 4). Similarly, CuOTf proved to be a poor catalyst for the reaction (entry 6). In contrast, $CuBr_2$ did catalyze the desired reaction, albeit in low efficiency (entry 5). When $Cu(OTf)_2$ was employed as a catalyst, the desired reaction took place smoothly to give the product **2a** in 96% yield after 30 minutes at room temperature (entry 7). Moreover, the catalyst loading could be decreased to 5 mol%, without decreasing the yield (entry 8).

We then examined several solvents for the isomerization of 7-oxabenzonorbornadiene (**1a**) into 1-naphthol (**2a**). The results presented in Table 2 show that, of the solvents investigated, 1,2-dichloroethane (DCE) was found to be the best solvent (entry 5).

In order to study the generality of this methodology, several 7-oxabicyclic alkenes were reacted under the opti-

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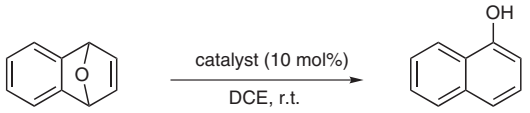
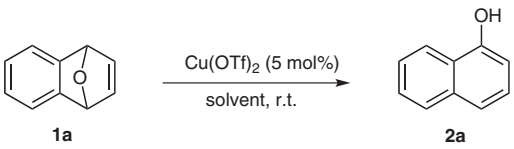
Table 1 Isomerization of 7-Oxabenzonorbornadiene (**1a**) into 1-Naphthol (**2a**) with Different Lewis Acids[a]



Entry	Metal catalyst	Time (h)	Yield (%)[b]
1	$Zn(OTf)_2$	12	n.r.
2	AgOTf	12	n.r.
3	CuCl	12	n.r.
4	CuBr	12	n.r.
5	$CuBr_2$	12	45
6	CuOTf	12	<5
7	$Cu(OTf)_2$	0.5	96
8	$Cu(OTf)_2$	1	98[c]

[a] Reagents and conditions: 7-oxabenzonorbornadiene (**1a**; 0.2 mmol), metal salt (10 mol%), DCE (2 mL), r.t.
[b] Isolated yield.
[c] 5 mol% catalyst.

Table 2 Screening of the Solvents for the Isomerization of 7-Oxabenzonorbornadiene (**1a**) into 1-Naphthol (**2a**) Catalyzed by $Cu(OTf)_2$[a]

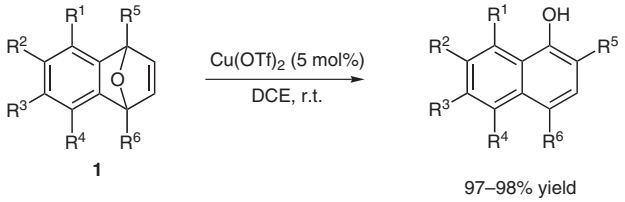


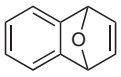
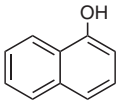
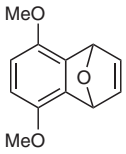
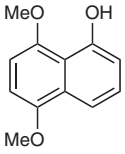
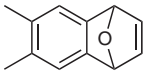
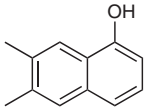
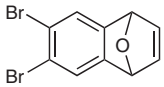
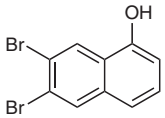
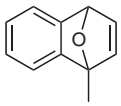
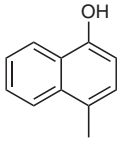
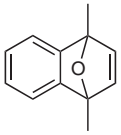
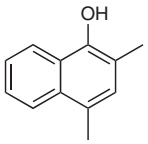
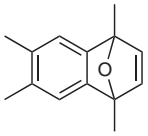
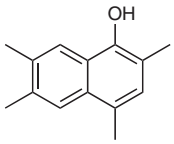
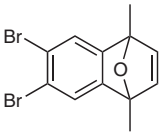
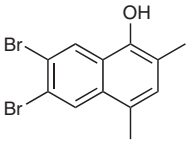
Entry	Solvent	Time (h)	Yield (%)[b]
1	hexane	1	n.r.
2	toluene	1	<5
3	THF	1	<3
4	CH_2Cl_2	1	94
5	DCE	1	98

[a] Reagents and conditions: 7-oxabenzonorbornadiene (**1a**; 0.2 mmol), $Cu(OTf)_2$ (5 mol%), DCE (2 mL), r.t.
[b] Isolated yield.

mized conditions; the results are summarized in Table 3. To our delight, the ring-opening of all 7-oxabicyclic alkenes proceeded smoothly to give the corresponding 1-naphthol derivatives in high yields (entries 1–8). Various substituents including electron-withdrawing (entries 4 and 8) electron-donating (entries 2, 3 and 7) and neutral groups (entries 1, 5 and 6) in the aromatic ring of the 7-oxabicyclic alkenes were well tolerated. Furthermore, 4-monosubstituted 1,4-epoxy-1,4-dihydronaphthalene afforded the desired product in 94% yield (entry 5). It is noteworthy that 1,4-disubstituted 1,4-epoxy-1,4-dihydronaphthalenes also reacted under our current catalytic system, providing the corresponding 2,4-disubstituted 1-naphthol derivatives (entries 6–8), which are difficult to synthesize via Brønsted acid catalyzed methods.[4] This indicated that the mechanism of $Cu(OTf)_2$-catalyzed

Table 3 $Cu(OTf)_2$-Catalyzed Isomerization of Various 7-Oxabenzonorbornadienes into 1-Naphthol Derivatives[a]



Entry	Alkene	Time (min)	Product	Yield (%)[b]
1		60		98
2		30		97
3		40		95
4		12 h		96
5		30		94
6		18		89
7		15		90
8		60		87

[a] Reagents and conditions: 7-oxabenzonorbornadiene (0.2 mmol), $Cu(OTf)_2$ (5 mol%), DCE (2 mL), r.t.
[b] Isolated yield.

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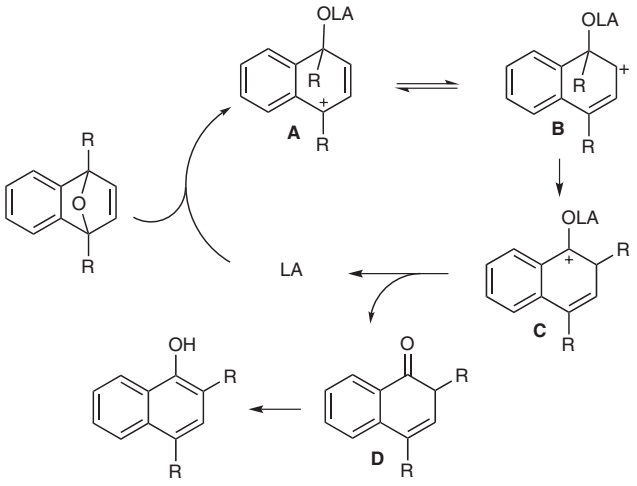
isomerization might be different to that of Brønsted acid catalyzed isomerization.

This methodology provides an alternative method for the preparation of 2,4-disubstituted 1-naphthols,[20] offering a simple route to potential 5-lipoxygenase inhibitors[21] as well as aromatic sesquiterpenes isolated from the *Heterotheca* species.[22–25]

In addition, $Cu(OTf)_2$-catalyzed ring-opening usually provided the 1-naphthol derivatives in higher yields compared with Brønsted acid catalyzed isomerization and other methods. For instance, treatment of 6,7-dimethyl-1,4-epoxy-l,4-dihydronaphthalene with $Cu(OTf)_2$ gave 6,7-dimethyl-l-naphthol in 95% yield (entry 3) compared to 71% using a Brønsted acid.[4] Ring-opening of 1,4-dimethyl-l,4-epoxy-l,4-dihydronaphthale in the presence of $Cu(OTf)_2$ provided 2,4-dimethyl-1-naphthols in 89% yield (entry 6), while the palladium-catalyzed annulation reaction of *o*-bromobenzaldehydes with methyl-2-pentenal afforded 2,4-dimethyl-1-naphthols in 52% yield.[9]

On the basis of the results presented above, a tentative mechanism for the ring opening of 7-oxabicyclic alkenes was proposed (Scheme 1), in which the Lewis acid first coordinates to the bridging oxygen, and cleavage of the activated C–O bond occurs concomitantly to give the allylic cation **A**. Then the R group migrates from the 1-position to the 2-position, giving the species **C**. Subsequently, the intermediate **D** forms and regenerates the catalyst. Finally, compound **D** isomerizes to form the 1-naphthol derivative. In the case where R = H, a proton rearrangement gives the 1-naphthol derivatives and regenerates the catalyst.



Scheme 1 Proposed mechanism for Lewis acid catalyzed isomerization of 7-oxabicyclic alkenes

In summary, we have developed the first $Cu(OTf)_2$-catalyzed isomerization of 7-oxabicyclic alkenes to 1-naphthol derivatives in high yields under mild conditions. This approach might make a valuable contribution to existing methodology for the synthesis of complex molecules containing the 1-naphthol fragment.

^1H and ^{13}C NMR spectra were recorded at r.t. on a Bruker Avance DPX 400 NMR spectrometer (400 and 100 MHz, respectively); chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz. All chemicals and solvents were used as received without further purification unless otherwise stated. Flash column chromatography was performed on silica gel (230–400 mesh).

1-Naphthol Derivatives 2a–h; Typical Procedure

To a solution of $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) in anhydrous DCE (1 mL), 7-oxabicyclic alkenes**1** (0.2 mmol) in DCE (1 mL) was added under a nitrogen atmosphere. The resulting mixture was stirred at r.t. until the reaction was complete (TLC monitoring). The mixture was then quenched by the addition of H_2O (2 mL), extracted with CH_2Cl_2 (10 mL) and dried over Na_2SO_4. The crude product was purified by flash silica gel column chromatography (*n*-hexane–EtOAc) to yield the corresponding 1-naphthol derivatives **2a–h**.

Naphthalen-1-ol (2a)[2]

^1H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.07 (m, 1 H), 7.79–7.77 (m, 1 H), 7.47–7.41 (m, 3 H), 7.29–7.24 (m, 1 H), 6.76–6.73 (m, 1 H), 5.44 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.3, 134.8, 127.7, 126.5, 125.9, 125.3, 124.4, 121.6, 120.8, 108.7.

5,8-Dimethoxynaphthalen-1-ol (2b)

^1H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 7.75 (d, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 7.6 Hz, 1 H), 6.62 (s, 2 H), 3.97 (s, 3 H), 3.94 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.4, 150.2, 150.0, 128.4, 127.3, 115.6, 113.0, 111.3, 103.3, 103.0, 56.2, 55.7.

MS (ESI): *m*/*z* (%) = 227.00 (42) [M^+ + Na], 204.97 (100) [M^+ + H].

HRMS (ESI): *m*/*z* [M^+ + Na] calcd for $C_{12}H_{12}O_3Na$: 227.0684; found: 227.0697.

6,7-Dimethylnaphthalen-1-ol (2c)[4]

^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (br s, 1 H), 7.53 (br s, 1 H), 7.30 (d, *J* = 8.2 Hz, 1 H), 7.19 (m, 1 H), 6.69 (d, *J* = 7.4 Hz, 1 H), 5.22 (br s, 1 H), 2.42 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.8, 136.1, 135.0, 133.8, 127.3, 124.9, 123.0, 120.9, 119.8, 107.9, 20.3, 20.1.

MS (ESI): *m*/*z* (%) = 194.96 (68) [M^+ + Na], 172.99 (62) [M^+ + H], 148.93 (77).

6,7-Dibromonaphthalen-1-ol (2d)[26]

^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 8.04 (s, 1 H), 7.30–7.21 (m, 2 H), 6.77 (d, *J* = 6.7 Hz, 1 H), 5.32 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.6, 134.4, 131.9, 127.4, 126.9, 124.2, 122.9, 121.3, 119.5, 109.6.

MS (EI): *m*/*z* (%) = 301.8 (20), 192.9 (100).

4-Methylnaphthalen-1-ol (2e)[4]

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.8 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 7.61–7.52 (m, 2 H), 7.16 (d, *J* = 7.4 Hz, 1 H), 6.73 (d, *J* = 7.5 Hz, 1 H), 5.55 (br s, 1 H), 2.65 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9, 133.5, 126.6, 126.3, 126.1, 125.0, 124.6, 124.2, 122.1, 108.2, 18.9.

MS (EI): *m*/*z* (%) = 158.1 (100), 128.1 (31).

2,4-Dimethylnaphthalen-1-ol (2f)[9]

^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (m, 1 H), 7.89 (m, 1 H), 7.48–7.45 (m, 2 H), 7.06 (s, 1 H), 4.92 (s, 1 H), 2.58 (s, 3 H), 2.34 (s, 3 H).

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^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 132.1, 129.5, 126.2, 125.1, 125.0, 124.6, 124.2, 121.4, 115.8, 18.6, 15.5.

MS (EI): *m*/*z* (%) = 272.1 (100), 157.0 (46).

2,4,6,7-Tetramethylnaphthalen-1-ol (2g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.60 (s, 1 H), 6.94 (s, 1 H), 4.84 (s, 1 H), 2.52 (s, 3 H), 2.41 (s, 6 H), 2.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.6, 134.8, 131.2, 128.8, 125.5, 124.2, 123.5, 121.1, 115.0, 20.6, 20.5, 18.9, 15.7.

MS (EI): *m*/*z* (%) = 200.1 (100), 185.1 (40).

HRMS (ESI): *m*/*z* [M^+ – H] calcd for $C_{14}H_{15}O$: 199.1128; found: 199.1060.

6,7-Dibromo-2,4-dimethylnaphthalen-1-ol (2h)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.06 (s, 1 H), 7.00 (s, 1 H), 4.80 (s, 1 H), 2.44 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.2, 132.0, 130.9, 128.9, 126.8, 125.3, 124.5, 121.6, 121.1, 117.0, 18.4, 15.5.

MS (EI): *m*/*z* (%) = 329.9 (96), 207 (100).

HRMS (ESI): *m*/*z* [M^+ – H] calcd for $C_{12}H_9Br_2O$: 328.9006; found: 328.8885.

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