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Versatile method for the synthesis of 4-substituted 6-methyl-3-oxabicyclo[3.3.1]non-6-ene-1-methanol derivatives: Prins-type cyclization reaction catalyzed by hafnium triflate

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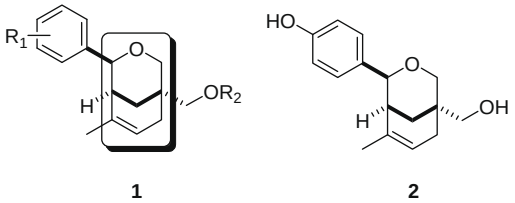
ABSTRACT

A versatile method for the synthesis of 4-substituted 6-methyl-3-oxabicyclo[3.3.1]non-6-ene-1-methanol derivatives has been developed using Prins-type cyclization reaction between aldehydes and O-protected/unprotected cyclohex-3-ene-1,1-dimethanol. Under optimized reaction conditions using hafnium triflate, various substrates, including functionalized benzaldehydes and heteroaromatic carbaldehydes, afforded cyclization products in high yields.

Prins-type cyclization reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis,[1] and has been used as a powerful tool in synthetic and medicinal chemistries. Typically, an aldehyde and an unsaturated alcohol (e.g., homoallyl alcohol) are reacted in the presence of an acid catalyst to form five- and six-membered oxygen-containing heterocyclic rings, which are present in various bioactive compounds. The outcome of the reaction depends on the substrate structure and reaction conditions due to the nature of the generated cationic intermediates.

In the course of our extensive efforts toward the discovery of new drugs for metabolic disorders, oxabicyclo[3.3.1]nonene derivatives represented by the structure **1** were identified as a lead class (Fig. 1).



1 2

Figure 1.

The Bayer[2] and Ligand[3] groups independently reported compound **2** as an estrogen receptor ligand, and described the synthesis and the structure–activity relationships (SARs) of its analogues. Although they only prepared 4-hydroxyphenyl derivatives, which should contain the key functional group for the estrogen activity, we planned to modify the aryl ring to produce more diverse structures. Initially, we ran the TsOH-catalyzed cyclization according to a previously described procedure,[3,4] but using 4-phenoxybenzaldehyde **4** instead of 4-hydroxybenzaldehyde, the reaction did not proceed smoothly (Scheme 1).

We then attempted harsher conditions, such as higher temperature and prolonged reaction time, but this resulted in a complex mixture presumably due to extensive decomposition of the sensitive intermediates or products. The use of other acid catalysts ($SnCl_4$, BF_3OEt_2, and TMSOTf) also gave a complex mixture (data not shown). We therefore began to explore effective reaction conditions to carry out the cyclization reaction forward.

Herein, we report a novel method for the synthesis of 4-substituted 6-methyl-3-oxabicyclo[3.3.1]non-6-ene-1-methanol derivatives in high yield under mild conditions. Under our optimal reaction conditions using hafnium triflate, various aldehydes, including substituted benzaldehydes and heteroaromatic carbaldehydes, gave the target cyclization products.

A plausible mechanism for this cyclization is proposed in Scheme 2. The first step of the reaction would be the formation of acetal **A** or hemiacetal **B** from diol **3**[5] and aldehyde **4**. The acid in the system promotes the cleavage of the C–O bond to afford oxonium cation **C**, and its addition to the double bond gives the

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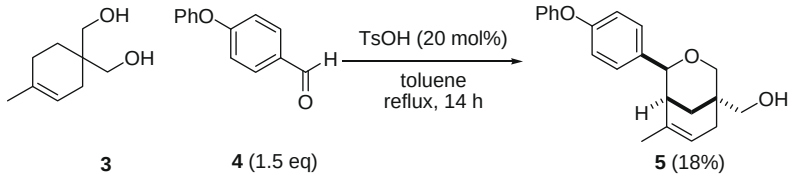
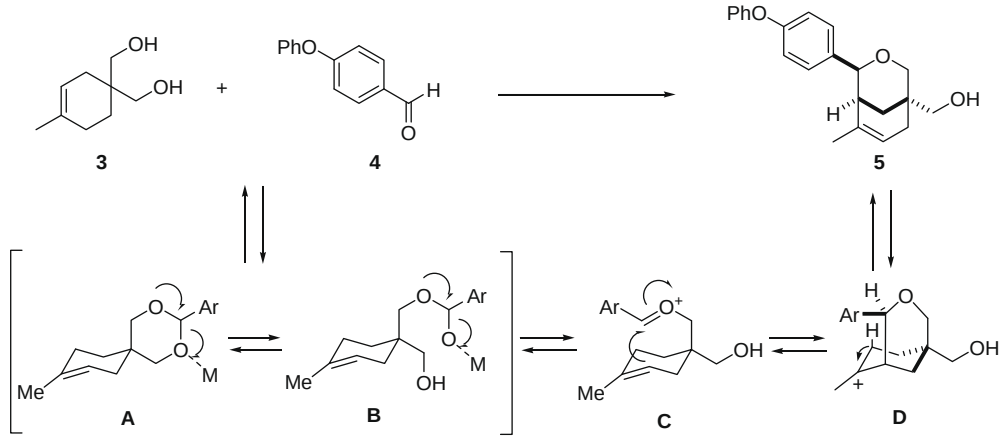


Scheme 1. Prins-type reaction between aldehyde and diol using TsOH.



Scheme 2. Mechanistic proposal for Prins-type cyclization reaction.

tertiary cation intermediate **D**. Finally, deprotonation gives the desired product **5**.[6] This reaction generates one molar equivalent of water, which may deactivate the catalyst or decompose the intermediates. We assume that there are two approaches to optimize the reaction conditions; the first is the use of an acid catalyst that is more effective in the presence of water, and the second is accelerating the conversion of stable acetal **A** or unstable hemiacetal **B** into **C**.[7]

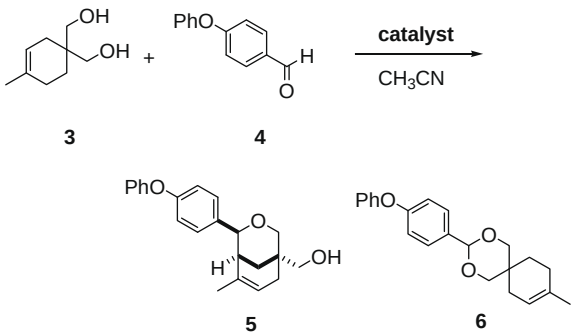
Metal triflates have received increasing attention recently as a water-tolerant catalyst with Lewis acid activity,[8] and a Prins-type cyclization reaction using metal triflates has been reported.[9] We thus assumed that metal triflate would be a suitable catalyst for this reaction. Our initial attempt using ytterbium triflate at room temperature gave the desired oxabicyclo[3.3.1]nonene **5** in 14% yield and the acetal **8** in 66% yield (Table 1, entry 1). These results prompted further screening of the metal triflates.

As shown in Table 1, zinc and lanthanum triflates (10 mol %) mainly gave the acetal **6** in 75% and 68% yields, respectively, with a low yield of the desired product **5** (entries 3 and 4). On the other hand, the use of scandium, bismuth, or hafnium triflates (10 mol %) afforded the desired product **5** in excellent yields (entries 2, 5, and 6).[10] Hafnium triflate showed the best yield (97%) among the tested catalysts, and when we decreased the amount of catalyst to 1 and 5 mol %, the chemical yield was largely maintained (entries 7 and 8).

Next we reacted diol **3** with various aldehydes using 5 mol % hafnium triflate[11] in order to examine the scope of this Prins-type cyclization reaction, as shown in Table 2.

Substituted benzaldehydes gave excellent yields of cyclization products (entries 1, 2, and 5). Heteroaromatic aldehydes **9** and **10** worked very well under optimized conditions (entries 3 and 4). However, in the case of pyridine aldehyde (entry 6), the major product was acetal **17** and no desired rearranged products were observed, even with higher temperatures and prolonged reaction times. We therefore continued optimization of the reaction conditions for compound **12**.

Table 1
Optimization of Prins-type reaction conditions[a]

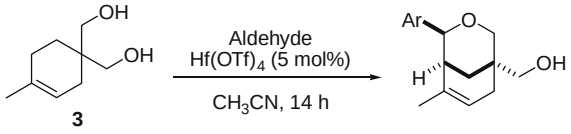


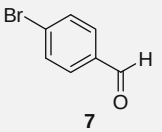
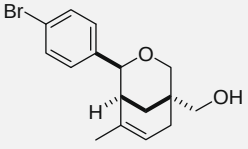
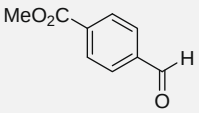
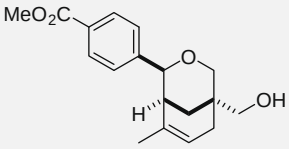
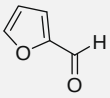
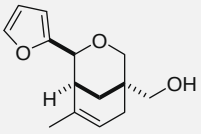
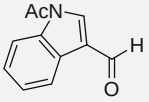
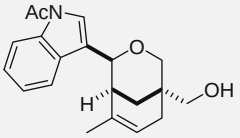
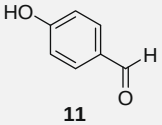
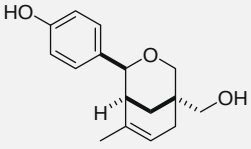
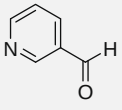
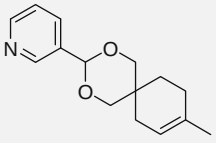
Entry	Catalyst	*x* (mol %)	**5**[b] (%)	**6**[b] (%)
1	$Yb(OTf)_3$	10	14	66
2	$Sc(OTf)_3$	10	89	—
3	$Zn(OTf)_2$	10	10	75
4	$La(OTf)_3$	10	2	68
5	$Bi(OTf)_3$	10	92	—
6	$Hf(OTf)_4$	10	97	—
7	$Hf(OTf)_4$	5	94	—
8	$Hf(OTf)_4$	1	89	4

[a] All reactions were carried out at room temperature with 1.2 equiv of **4** and 1 equiv of **3**.
[b] Isolated yield.

Based on these results, conversion of the acetal into the oxonium cation would be slow for this pyridine derivative. We therefore protected one of the two hydroxy groups to redirect the reaction to a Prins-type cyclization through the hemiacetal formation. When we used TBDPS-protected alcohol **18**, the cyclization

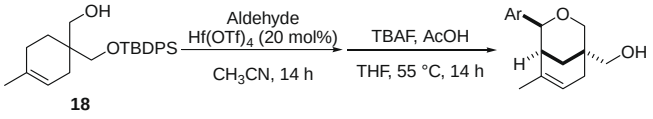
Table 2
Representative examples of Prins-type reaction of aldehydes and diol **3**[a]

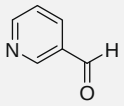
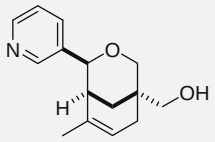
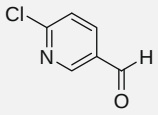
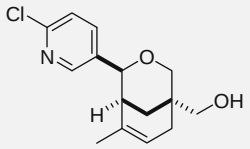
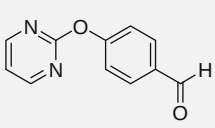
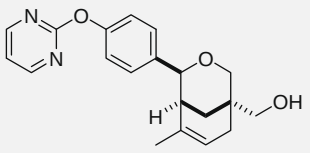
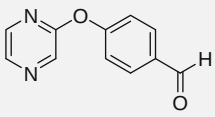
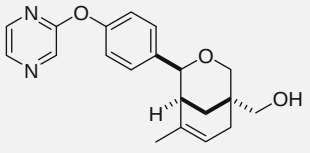
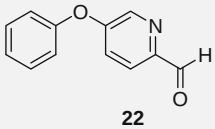
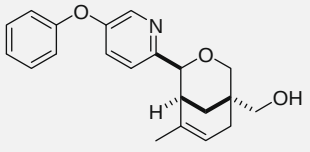
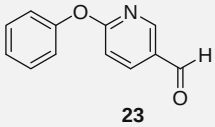
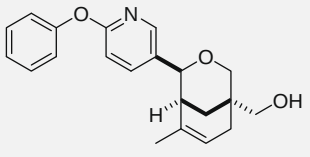


Entry	Aldehyde	Product	Yield[b]
1	 **7**	 **13**	95
2	 **8**	 **14**	96
3	 **9**	 **15**	81
4	 **10**	 **16**	93
5	 **11**	 **2**	90
6	 **12**	 **17**	72

[a] All reactions were carried out at room temperature with 1.2 equiv of aldehyde and 1 equiv of **3**.
[b] Isolated yield.

Table 3
Representative examples of Prins-type reaction of aldehydes and diol **18**[a]



Entry	Aldehyde	Product	Yield[b]
1	 **12**	 **24**	47
2	 **19**	 **25**	57
3	 **20**	 **26**	57
4	 **21**	 **27**	54
5	 **22**	 **28**	57
6	 **23**	 **29**	89

[a] All reactions were carried out at room temperature with 1.2 equiv of aldehyde and 1 equiv of **18**.
[b] Isolated yield.

reaction proceeded smoothly in the presence of 20 mol % of hafnium triflate. The TBDPS group was gradually cleaved under these reaction conditions, and we subsequently treated the reaction mixture with TBAF to complete the deprotection of silyl groups and to obtain the desired product **24**. We applied this method to other substrates. A variety of nitrogen-containing aromatic aldehydes gave the oxabicyclo[3.3.1]nonene structure in moderate to good yield (Table 3; entries 2–6).

In summary, we have developed a versatile method for the synthesis of 4-substituted 6-methyl-3-oxabicyclo[3.3.1]non-6-ene-1-methanol derivatives using Prins-type cyclization reaction under mild conditions. Under our optimized reaction conditions using hafnium triflate, various aldehydes and diols react to give cyclization products in high yield, which will broaden the scope of Prins-type reactions. For pyridine-containing aldehydes, acetal formation prevailed over Prins-type cyclization; however, mono-protected diols were effective in redirecting the reaction. Biological activities of the synthesized compounds are currently being tested and will be reported in due course.

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6. The trans relationship between the aryl group and the hydroxymethylene group on bicyclic core was confirmed by ^{1}H NMR (including NOE) analysis. This stereochemistry is consistent with that suggested from the proposed mechanism.
7. Acetals could be isolated by silica gel chromatography, while hemiacetal could not be monitored by TLC.
8. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. L. *Chem. Rev.* **2002**, *102*, 2227.
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10. The formation of the acetal **6** was rapidly observed in a few miniatures by TLC, and the desired product was gradually formed.
11. *General procedure*: To a mixture of diol **3** (103 mg, 0.659 mmol) and aldehyde **4** (0.13 mL, 0.79 mmol) in acetonitrile (3.2 mL) was added hafnium triflate (25.5 mg, 0.033 mmol) at room temperature and the reaction mixture was stirred at room temperature for 14 h. After completion of the reaction as indicated by TLC, the reaction was quenched with satd $NaHCO_3$ aq and the reaction mixture was extracted with ethyl acetate (2×10 mL), the combined organics were washed with brine, dried over anhyd Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography (hexane:ethyl acetate) to give the desired compound (205 mg, 93%) as a colorless solid. *Compound* **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.25 (4H, m), 7.09–7.04 (1H, m), 6.99–6.93 (4H, m), 5.60–5.56 (1H, m), 4.55 (1H, d, J = 1.7 Hz), 3.97 (1H, dd, J = 10.7, 2.7 Hz), 3.64 (1H, dd, J = 10.7, 1.5 Hz), 3.40 (2H, s), 2.38–2.34 (1H, m), 2.25–2.17 (1H, m), 2.12–2.04 (1H, m), 1.86–1.80 (1H, m), 1.71–1.65 (1H, m), 1.06–1.03 (3H, m). ESI-MS 337 $[M+H]^+$.