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$Zn(ODf)_2$: preparation and application in asymmetric alkynylation of aldehydes

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A new Lewis acid, $Zn(ODf)_2$, was first prepared from commercially available 3,3,4,4-tetrafluoro[1,2]oxathietane 2,2-dioxide in four steps with 56% yields and also was applied to catalyze highly enantioselective alkynylation of aldehydes in the presence of ligand (1*S*,2*S*)-3-(*tert*-butyldimethylsilyloxyl)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)-propane-1-ol or ligand (−)-*N*-methylephedrine to afford the corresponding propargylic alcohols in high yields with up to 99% ee.

Organometallic compounds of weakly coordinating anions, *e.g.*, BF_4^-, PF_6^-, and $CF_3SO_3^-$, have been the object of many studies.[1] These Lewis acids contain a hard anion coordinated to a soft metal center in a low oxidation state, in which the anions are excellent leaving groups and can easily be replaced by other chiral ligands (to give a chiral Lewis acid intermediate) and by many σ- and π-donors (such as alkene, alkyne and carbonyl group, *etc.*; to give ionic complexes) under very mild conditions, so they are highly reactive and have proven to be useful materials either to synthesize other organometallic complexes or to act as catalysts for asymmetric reaction. In this contribution, we report the first example for the preparation of zinc difluoromethanesulfate (zinc diflate, $Zn(ODf)_2$), which contains soft metal Zn^{2+} and hard anion $HCF_2SO_3^-$, and demonstrating its application in asymmetric alkynylation of aldehydes as a Lewis acid catalyst for the first time.

A previous study indicated that difluoromethanesulfonic acid (colog K_A = 5.7) is more acidic than sulfuric acid (colog K_A = 7.0) but weaker than trifluoromethanesulfonic acid (colog K_A = 4.7).[2] However, there is still a very limited knowledge about the synthesis, the application of its metal salts.

Asymmetric alkynylation of aldehydes in the presence of $Zn(OTf)_2$, Et_3N and some amino alcohol ligands is a highly selective reaction that can be performed under very mild conditions.[3,4] The reaction mechanism involves a hydrogen-bonded σ-complex of Zn^{2+}, which undergoes tautomerization to the hydrogen-bonded π-complexes of zinc cation.[5] The structural similarity and the character nuance stimulated us to speculate that zinc difluoromethanesulfate (zinc diflate, $Zn(ODf)_2$), a more economical[6,7] and mild zinc salt, might be attractive as a potential equivalent of $Zn(OTf)_2$ for converting terminal alkynes to the corresponding zinc alkynylides.

Cost-effective difluoromethanesulfonic acid (diflic acid) can be easily prepared under mild conditions from commercially available 3,3,4,4-tetrafluoro[1,2]oxathietane 2,2-dioxide **1**,[8] a key monomer in the preparation of Nafion ion membrane resin.[9] Fluorosulfonyldifluoroacetic acid **2**, prepared from the hydroxylation of compound **1**, was decarboxylated with Na_2SO_4 in CH_3CN : H_2O (1 : 1, v/v) to provide difluoromethanesulfonyl fluoride **3**, which was then treated in THF : H_2O (1 : 1, v/v) to afford difluoromethanesulfonic acid **4** (HCF_2SO_2OH) in 80% yield (Scheme 1).

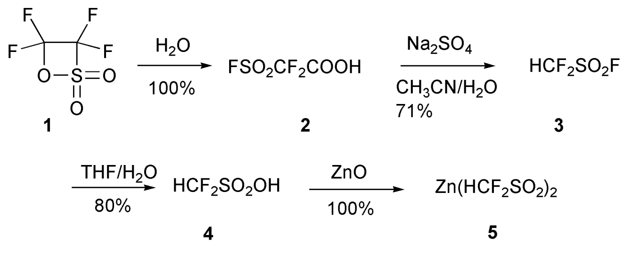
$Zn(ODf)_2$ was easily obtained in quantitative yield by treating difluoromethane sulfonic acid with ZnO. With $Zn(ODf)_2$ in hand, we sought to determine the value of this inexpensive new Lewis acid.[6]

A preliminary study quickly revealed that $Zn(ODf)_2$ readily participated in the enantioselective alkynylation of isobutyraldehyde to give the optically active propargylic alcohol in excellent enantioselectivity (97% ee) and yield in the presence of Et_3N and ligand (1*S*,2*S*)-3-(*tert*-butyldimethylsilyloxyl)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)propane-1-ol **6** in toluene (Table 1, entry 1).[4] The use of CH_2Cl_2 or THF instead of toluene resulted in a notable decrease in enantioselectivity (93% ee in CH_2Cl_2, 92% ee in THF), whereas in CH_3CN, the optical purity of the adduct is only 47% ee.[10]

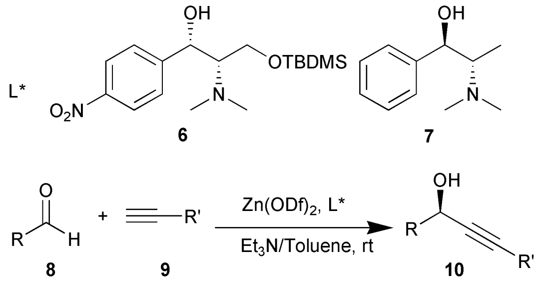
The reactions with various aliphatic and aromatic aldehydes using $Zn(ODf)_2$ as additive are summarized in Table 1.† The ligands which were used here included ligand (1*S*,2*S*)-**6** and (−)-*N*-methylephedrine **7**. The representative results were summarized in Table 1. For aliphatic aldehydes (entries 1–16), the reaction was faster than that with aromatic aldehyde (entries 17–21) and was completed within 2 h. Based on comparison with the literature,[11] (*R*)-absolute configuration propargylic alcohols were obtained with ligand (1*S*,2*S*)-**6**, while the opposite configuration was obtained with ligand (1*R*,2*S*)-*N*-methylephedrine **7**. All of the propargylic alcohols were obtained with excellent ee (up to 99%) and in as high a chemical yield as with $Zn(OTf)_2$ (Scheme 2).

A catalytic condition (0.22 equiv. ligand and 0.2 equiv. $Zn(ODf)_2$ as additive) was then studied and proved to be effective to this reaction too, while the ee and the chemical yields were slightly decreased (entry 22–26, Table 1).

In conclusion, a new Lewis acid, $Zn(ODf)_2$, was first prepared from commercially available 3,3,4,4-tetrafluoro-[1,2]oxathietane 2,2-dioxide in four steps with 56% yields. Highly enantioselective alkynylation of aldehydes was carried out in the presence of $Zn(ODf)_2$ and Et_3N, catalyzed by ligand (1*S*,2*S*)-3-(*tert*-butyldimethylsilyloxyl)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)propane-1-ol **6** or ligand (−)-(1*R*,2*S*)-*N*-



Scheme 1



Scheme 2

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Table 1 Asymmetric alkynylation of aldehydes with alkynes catalyzed by (1*S*,2*S*)-**6** or (1*R*,2*S*)-**7** and $Zn(ODf)_2$[a]

	Alkyne (R′)	Aldehyde (R)	Ligand	Yield (%)[b]	Ee (%)[c]	Rotat. Sign — Config
1	$PhC\equiv CH$	$(CH_3)_2CHCHO$	**6**	99	97	(+) — (*R*)[d]
2	$PhC\equiv CH$	$(CH_3)_2CHCHO$	**7**	98	97	(−) — (*S*)[d]
3	$PhCH_2CH_2C\equiv CH$	$(CH_3)_2CHCHO$	**6**	94	> 99	(−) — (*R*)[d]
4	$PhCH_2CH_2C\equiv CH$	$(CH_3)_2CHCHO$	**7**	95	92.5	(+) — (*S*)[d]
5	$PhC\equiv CH$	*n*-$C_6H_{13}CHO$	**6**	86	> 99	(−)
6	$PhC\equiv CH$	*n*-$C_6H_{13}CHO$	**7**	85	89	(+)
7	$PhCH_2CH_2C\equiv CH$	*n*-$C_6H_{13}CHO$	**6**	81	99	(+)
8	$PhC\equiv CH$	*c*-$C_6H_{11}CHO$	**6**	86	96.5	(−) — (*R*)[d]
9	$PhC\equiv CH$	*c*-$C_6H_{11}CHO$	**7**	90	97	(+) — (*S*)[d]
10	$PhCH_2CH_2C\equiv CH$	*c*-$C_6H_{11}CHO$	**6**	82	99.5	(−) — (*R*)[d]
11	$PhCH_2CH_2C\equiv CH$	*c*-$C_6H_{11}CHO$	**7**	87	99.7	(+) — (*S*)[d]
12	$PhC\equiv CH$	$(Et)_2CHCHO$	**6**	89	96	(−)
13	$PhC\equiv CH$	$(Et)_2CHCHO$	**7**	85	97.5	(+)
14	$PhCH_2CH_2C\equiv CH$	$(Et)_2CHCHO$	**6**	83	99	(−)
15	$PhC\equiv CH$	*c*-C_3H_5CHO	**7**	83	95	(+)
16	$PhC\equiv CH$	$(CH_3)_3CCHO$	**7**	85	94	(−) — (*S*)[d]
17	$PhC\equiv CH$	PhCHO	**6**[e]	74	96.5	(+) — (*R*)[d]
18	$PhC\equiv CH$	PhCHO	**7**[e]	72	95.5	(−) — (*S*)[d]
19	$PhC\equiv CH$	$CH_2=CHCHO$	**7**[e]	81	86.6	(+) — (*S*)[d]
20	$PhC\equiv CH$	α-furan-CHO	**7**[e]	78	98	(−)
21	$PhC\equiv CH$	*m*-MeO-C_6H_5CHO	**7**[e]	66	96	(+)
22	$PhC\equiv CH$	$(CH_3)_2CHCHO$	**6**[f]	95	88	(+) — (*R*)[d]
23	$PhC\equiv CH$	*c*-C_3H_5CHO	**6**[f]	87	85	(−)
24	$PhC\equiv CH$	*c*-$C_6H_{11}CHO$	**6**[f]	87	91	(−)
25	$PhC\equiv CH$	PhCHO	**6**[f]	58	75	(+) — (*R*)[d]
26	$PhC\equiv CH$	*m*-MeO-C_6H_5CHO	**7**[f]	51	74	(+)

[a] Unless stated the reaction are carried out with addition of 1.2 equiv. of (1*S*,2*S*)-**6** or (−)-*N*-methylephedrine **7** and 1.1 equiv. of $Zn(ODf)_2$ and 1.1 equiv. of Et_3N in toluene (2 mL) at 25 °C for 2 h. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of the alcohol. [d] Absolute configuration is based on comparison with the literature, see ref. 3*a* and 11. [e] Reaction time was 12 h. [f] The reaction condition is 0.22 equiv. of ligand and 0.2 equiv. of $Zn(ODf)_2$ and 0.5 equiv. of Et_3N in toluene (2 mL) at 60 °C for 24 h.

methylephedrine **7** to afford the corresponding propargylic alcohols in high yields with up to 99% ee. This is the first time that this new Lewis acid has been synthesized and applied in an asymmetric reaction as a Lewis acid catalyst. A more detailed study of using this new Lewis acid in other asymmetric reactions and its catalytic application is underway.

Notes and references

† A typical procedure for the asymmetric alkynylation reaction is as follows: To a solution of $Zn(ODf)_2$ (1.1 equiv.) and chiral ligand (1.2 equiv.) in toluene was added triethylamine (1.1 equiv.) under a nitrogen atmosphere at ambient temperature for 2 h. Alkyne (1.2 equiv.) was then added to the mixture. After 15 min, the aldehyde (1 equiv.) was introduced by syringe. The reaction mixture was then stirred for 2–12 h at 25 °C. After the reaction was completed, the propargylic alcohol was separated from the ligand by washing with acid. The ligand was recovered in 98% yield by extracting the oily substance obtained by neutralizing the acidic aqueous solution. The crude product was purified through a short flash chromatography column to give the corresponding propargylic alcohols.

The catalytic conditions are as follows: To a solution of $Zn(ODf)_2$ (0.2 equiv.) and chiral ligand (0.22 equiv.) in toluene was added triethylamine (0.5 equiv.) under a nitrogen atmosphere at ambient temperature for 2 h. Alkyne (1.2 equiv.) was then added to the mixture. After 15 min, the aldehyde (1 equiv.) was introduced by syringe. The reaction mixture was then stirred for 2–12 h at 60 °C and worked up as usual to give the corresponding propargylic alcohols and recycled ligand.

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6 The price of 3,3,4,4-tetrafluoro[1,2]oxathietane 2,2-dioxide is 10 dollar/1 kg; The Aldrich price of $Zn(OTf)_2$ is 28.65 dollar/10 grams.

7 Zinc diflate ($Zn(ODf)_2$, **5**) is commercially available from Synica Chemicals.

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