EFFICIENT CATALYTIC PROCEDURE FOR ETHERIFICATION OF ALCOHOLS WITH $MeAl(NTf_2)_2$

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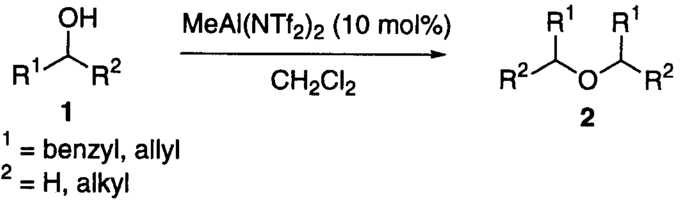
Abstract — Efficient catalytic etherification of benzyl and allylic alcohols has been accomplished by use of *in situ* prepared $MeAl(NTf_2)_2$ as a catalyst. The new method was also found to be effective for the selective benzylation of allylic alcohols.

(Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday)

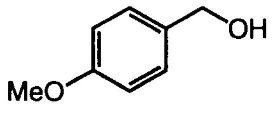
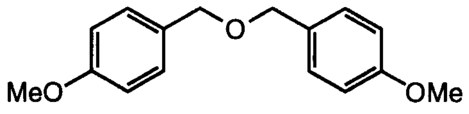
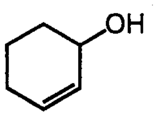
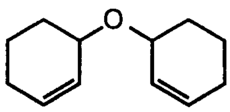
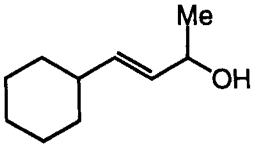
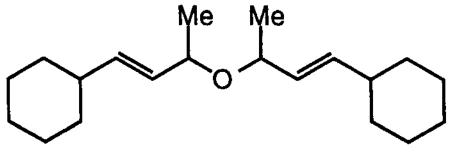
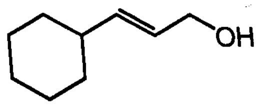
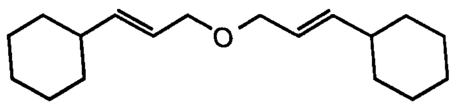
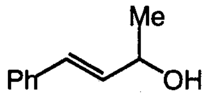
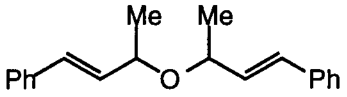
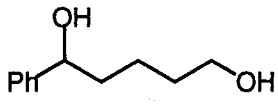
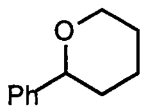
The long-established Williamson ether synthesis is probably the most common method for preparation of ethers, which requires initial transformation of alcohols into the corresponding halides or tosylates and their displacement with strongly basic alkoxides or phenoxides.[1,2] The major drawback of this method has been viewed as its unsuitability for base sensitive molecules and the generation of stoichiometric amount of salts.[3,4] Although these problems seem to be overcome by a novel catalytic etherification recently developed by Strauss,[5] direct synthesis of ethers from alcohols through a dehydration process has also emerged as an attractive route for this purpose.[6,7] Kim and co-workers reported $ZnCl_2$-mediated etherification of alcohols, where, unfortunately, stoichiometric amount of Lewis acid ($ZnCl_2$) was necessary for the smooth reaction.[8,9] Here we wish to disclose a new, efficient catalytic procedure for the direct etherification of alcohols utilizing highly Lewis acidic $MeAl(NTf_2)_2$ as a catalyst (Scheme 1).

Scheme 1



Treatment of *sec*-phenethyl alcohol (**1**; R^1 = Ph, R^2 = Me) with catalytic $MeAl(NTf_2)_2$ (10 mol%) [prepared by simply mixing $AgNTf_2$[10] and $MeAlCl_2$ in a 2:1 molar ratio] in CH_2Cl_2 at 21 °C for 30 min gave rise to the corresponding symmetrical ether (**2**; R^1 = Ph, R^2 = Me) quantitatively (Table 1, entry 1). Neither deoxygenation (reduction) nor elimination product was detected. Notably, use of 1 mol% of the catalyst can still facilitate the etherification to afford **2** (R^1 = Ph, R^2 = Me) in reasonable chemical yield (62%) (entry 3). Other selected examples are summarized in Table 1.

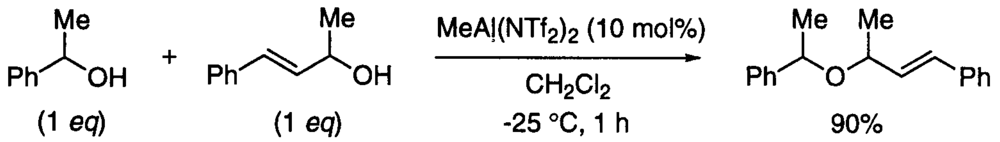
Table 1. Catalytic, Direct Etherification of Alcohols with $MeAl(NTf_2)_2$ [a]

entry	alcohol	condition (°C, h)	product	yield % [b]
1	PhCH(Me)OH	21, 0.5	Ph(Me)CHOCH(Me)Ph	>99
2		21, 2		79 [c]
3		21, 24		62 [d]
4	$PhCH_2OH$	40, 48	$PhCH_2OCH_2Ph$	83
5		-25, 3		53
6		0, 2		81
7		-10, 4		82
8		21, 5		20
9		-25, 3		84
10		21, 2		73 [e]

[a] Unless otherwise specified, the etherification was carried out in freshly distilled CH_2Cl_2 (0.2 M) with 10 mol% of $MeAl(NTf_2)_2$ under the indicated reaction conditions. [b] Isolated yield. [c] Use of 5 mol% of $MeAl(NTf_2)_2$. [d] Use of 1 mol% of $MeAl(NTf_2)_2$. [e] The reaction was performed in a concentration of 0.05 M to prevent intermolecular ether formation.

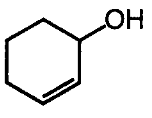
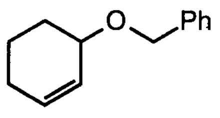
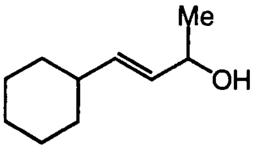
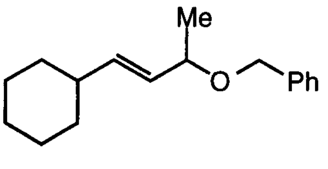
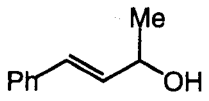
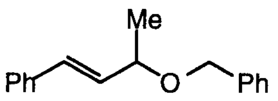
Various benzylic and allylic alcohols can be transformed into their symmetrical ethers with high efficiency by choosing appropriate reaction conditions which probably correspond to the stability of each intermediary carbocation. Dibenzyl ether can be prepared in high yield in spite of the prolonged reaction time, whereas the yield was significantly diminished in the etherification of *primary* allylic alcohols (entries 4 and 8). This system was also found to be effective for the synthesis of cyclic ethers. For instance, 1-phenyl-1,5-pentanediol, on reaction with 10 mol% of $MeAl(NTf_2)_2$ in CH_2Cl_2 at 21 °C for 2 h, furnished 2-phenyltetrahydropyran in 73% yield (entry 10).

The selective preparation of unsymmetrical ethers appears feasible in the presence of catalytic $MeAl(NTf_2)_2$ (10 mol%) under mild conditions as illustrated below.



These results obtained so far prompted us to examine the possibility of applying the present method to the protection of alcohols as benzyl ethers. As listed in Table 2, allylic alcohols were indeed converted into their benzyl ethers by treatment with excess benzyl alcohol (5 equiv) under the influence of $MeAl(NTf_2)_2$ (10 mol%) in CH_2Cl_2 at 0 °C for several hours, which certainly offers a new, yet selective protection technique of hydroxy functionality on the allylic position.[11]

Table 2. Catalytic Benzylation of Allylic Alcohols with $MeAl(NTf_2)_2$ [a]

entry	alcohol	condition (°C, h)	product	yield % [b]
1		0, 4		65
2		0, 2		65
3		0, 2		89

[a] The reaction was carried out in freshly distilled CH_2Cl_2 with excess benzyl alcohol (5 equiv) in the presence of catalytic $MeAl(NTf_2)_2$ (10 mol%) under the given reaction conditions. [b] Isolated yield.

A typical experimental procedure is as follows. Silver bis(trifluoromethanesulfonyl)amide (76.6 mg, 0.2 mmol)[10] was placed in a dry two-neck flask with a stirring bar under argon, and freshly distilled CH_2Cl_2 (5 mL) was introduced. The suspension was carefully degassed and a 1 M hexane solution of $MeAlCl_2$ (100 µL, 0.1 mmol) was added dropwise at 21 °C. After the mixture was stirred for 30 min, *sec*-phenethyl alcohol (**1**; R^1 = Ph, R^2 = Me) (132 µL, 1.1 mmol) was added and stirring was continued at 21 °C for an additional 30 min. The resulting reaction mixture was then poured into 1 *N* HCl and extracted with ether. The combined organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (hexane/EtOAc = 20:1 as eluant) gave symmetrical ether (**2**; R^1 = Ph, R^2 = Me) (124.2 mg, 0.55 mmol, >99% yield) as a colorless oil.

ACKNOWLEDGMENTS

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