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Direct Substitution of the Hydroxy Group at the Allylic/propargylic Position with Carbon- and Heteroatom-centered Nucleophiles Catalyzed by $Yb(OTf)_3$

HUANG, Wen(黄文) SHEN, Quan-Sheng(申全胜) WANG, Jia-Liang(王家亮)
ZHOU, Xi-Geng*(周锡庚)

Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials, Department of Chemistry, Fudan University, Shanghai 200433, China

An efficient and highly selective $Yb(OTf)_3$-catalyzed direct substitution of the hydroxy group at the allylic and propargylic positions with a variety of heteroatom- and carbon-centered nucleophiles, such as alcohols, thiols, amines, amides and active methylene compounds has been developed. The advantages of the present catalytic system are wide availability of the starting materials, especially for tolerance to thiols, no need for dried solvents and additives, mild conditions, short time of reaction, simple manipulation and environmentally friendly catalyst that can be recovered and reused at least ten times without significant reduction of activity.

Keywords direct substitution, allylic alcohol, propargylic alcohol, catalysis, Lewis acid

Introduction

Carbon-carbon and carbon-heteroatom bond forming reactions are important fundamental transformations in organic synthesis. The substitution of the hydroxy group in alcohols with nucleophiles represents an atom economical and ideal route to these bond constructions because of the wide availability of the starting materials and the generation of H_2O as the only side product [Eq. (1)]. Nevertheless, direct substitution of the hydroxy group in alcohols is generally difficult due to the poor leaving ability of the OH group. As a result, hydroxy groups usually require pre-activation through transformation into good leaving groups such as halides, carboxylates, carbonates and phosphonates before the treatment with nucleophiles.[1] However, such process inevitably produces salt waste, which would set limits for the industrial application and for the scope of substrates. To avoid these drawbacks, the development of alternative catalytic method for this highly valuable but challenging transformation is currently attracting considerable attention.[2] Very recently, several Lewis acid catalytic systems, such as $NaAuCl_4 \cdot 2H_2O$,[3] $InCl_3$,[4] $BiCl_3$,[5] $FeCl_3$[6] and $Bi(OTf)_3$[7] have been proved successful for the direct substitution of the hydroxy group in allylic and propargylic alcohols with nucleophiles, but there remains room for improvement, including increase of catalyst stability, lowering reaction temperature, improvement of reaction rates and selectivity. Moreover, the recoverability and reuse of Lewis acid catalysts from these reaction systems remain a significant challenge and have not been explored so far. Therefore, development of a general, efficient, conveniently reusable, and readily available catalyst for the substitution of allylic and propargylic alcohols is highly desirable.

$$ROH + NuH \xrightarrow{Cat.} RNu + H_2O \quad (1)$$

Rare earth triflates, $RE(OTf)_3$ (Tf＝trifluoromethanesulfonyl), are versatile Lewis acids in organic synthesis and are easily prepared in 50% TfOH aqueous media. Unlike other Lewis acids such as $BF_3 \cdot Et_2O$, $SnCl_4$, and $AlCl_3$, rare earth triflates are stable to air and water, and act as Lewis acids even in the presence of water.[8] Given that $Yb(OTf)_3$ was an efficient catalyst for alkylation of 1,3-dicarbonyl compounds using alcohols as electrophiles directly,[9] we are interested in further revealing the possibility of direct substitution of hydroxy in alcohols with other nucleophiles catalyzed by $Yb(OTf)_3$. Herein, we report an efficient $Yb(OTf)_3$-catalyzed direct substitution of the hydroxy group in allylic and propargylic alcohols by various carbon- and heteroatom-centered nucleophiles to afford the corresponding coupling products in high yields under mild and environmentally friendly conditions, representing a rare example of reusability of Lewis acid catalysts in such reactions.

* E-mail: xgzhou@fudan.edu.cn; Tel.: 0086-021-65643769; Fax: 0086-021-65641740
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Experimental

All reactions and manipulations were performed in air. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer using the residue of deuterated solvents as the internal standard, mass spectra were recorded by EI methods, GC-MS analysis was performed using a Hewlett Packard Model HP 6890 Series with HP-5 column. The reactions were monitored by TLC with Huanghai GF_{254} silica gel. Flash column chromatography was carried out using 300—400 mesh silica gel.

General experimental procedure for the $Yb(OTf)_3$-catalyzed allylic/propargylic substitution reactions by nucleophiles

To a mixture of alcohols **1** (0.3 mmol), 1.3—1.5 equiv. of nucleophiles in 2 mL of nitromethane, was added 5 mol% $Yb(OTf)_3$ (9.3 mg, 0.015 mmol) and then the reaction mixture was stirred at room temperature or the corresponding conditions mentioned in the text. After the reaction completely was monitored by GC-MS or TLC, solvent was removed under reduced pressure. The residue was purified by a short column chromatography using hexane/ethyl acetate as the eluent.

Typical experimental procedure for the reuse of catalyst

To a mixture of allylic alcohol **1a** (0.21 g, 1 mmol), tosylamine (0.22 g, 1.3 mmol) in 10 mL of nitromethane was added 5 mol% $Yb(OTf)_3$ (31 mg, 0.05 mmol), and then the reaction mixture was stirred at room temperature. After the reaction completely, the reaction mixture was poured into 20 mL water, the solution was extracted with Et_2O (3×15 mL), the organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to give the crude product. The residue can be further purified by column chromatography on silica gel using *V*(hexane)∶*V*(ethyl acetate)=8∶1 as the eluent, giving **3aa** as a white solid. The catalyst remaining in the aqueous layer can be recovered by removing the water and then drying under vacuum at 200 ℃ for 4 h for the next use.

(*E*)-3-(3-Methylbut-2-en-1-yloxy)-1,3-diphenyl-1-propene (3ah): ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ℃) δ: 1.61 (s, 3H), 1.75 (s, 3H), 4.0 (q, J=6.5 Hz, 2H), 4.95 (d, J=7.0 Hz, 1H), 5.42 (t, J=6.5 Hz, 1H), 6.33 (dd, J=15.9, 7.0 Hz, 1H), 6.58 (d, J=15.9 Hz, 1H), 7.18—7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz, 25 ℃) δ: 141.40, 136.97, 136.68, 131.24, 130.62, 128.45, 128.26, 127.58, 127.04, 126.95, 126.55, 121.19, 81.62, 64.95, 25.78, 18.07; MS (EI) *m/z* (%): 278 (M^+, 20), 209 (20), 181 (80), 105 (100).

(*E*)-3-Ethylthio-1,3-diphenyl-1-propene (3ak): ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ℃) δ: 1.24 (t, J=7.0 Hz, 3H), 2.45—2.51 (m, 2H), 4.62 (d, J=8.6 Hz, 1H), 6.41 (dd, J=8.6, 15.7 Hz, 1H), 6.48 (d, J=15.7 Hz, 1H), 7.21—7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz, 25 ℃) δ: 140.70, 136.63, 130.72, 129.75, 128.63, 128.52, 127.78, 127.59, 127.31, 126.45, 51.92, 25.63, 14.43; MS (EI) *m/z* (%): 254 (M^+, 5), 193 (100), 115 (75).

(*E*)-3-Ethylthio-1-phenyl-1-butene (3bk): ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ℃) δ: 1.22 (t, J=7.4 Hz, 3H), 1.37 (d, J=6.8 Hz, 3H), 2.41—2.54 (m, 2H), 3.52 (dq, J=6.8, 9.0 Hz, 1H), 6.05 (dd, J=9.0, 15.7 Hz, 1H), 6.35 (d, J=15.7 Hz, 1H), 7.20—7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz, 25 ℃) δ: 36.75, 132.50, 129.13, 128.52, 127.37, 126.25, 42.15, 24.67, 20.60, 14.72; MS (EI) *m/z* (%): 192 (M^+, 15), 131 (100).

(*E*)-Ethyl 2-benzoyl-3,5-diphenylpent-4-enoate (3aq): as a 1∶1 mixture of diastereoisomers; ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ℃) δ: 0.89 (t, J=7.5 Hz, 3H), 1.12 (t, J=7.5 Hz, 3H), 3.85—3.88 (m, 2H), 4.08—4.12 (m, 2H), 4.57—4.61 (m, 2H), 4.98—5.02 (m, 2H), 6.23—6.25 (m, 1H), 6.34—6.38 (m, 2H), 6.52 (d, J=15.0 Hz, 1H), 7.14—7.46 (m, 26H), 7.86 (d, J=7.9 Hz, 2H), 8.08 (d, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, 25 ℃) δ: 193.07, 192.54, 167.92, 167.44, 140.79, 140.35, 136.89, 136.82, 136.58, 133.53, 133.37, 131.69, 131.56, 129.86, 129.69, 128.70, 128.68, 128.55, 128.54, 128.42, 128.40, 128.25, 127.87, 127.27, 127.03, 127.73, 126.29, 126.19, 61.61, 61.35, 59.75, 59.59, 48.87, 48.78, 14.05, 13.62; MS (EI) *m/z* (%): 384 (M^+, 3), 366 (100), 311 (50).

Results and discussion

At the outset of our investigations, the reaction of allylic alcohol **1a** with tosylamine **2a** ($TsNH_2$) was chosen as a model reaction and carried out in the presence of various Lewis acids under different reaction conditions to develop the optimum reaction conditions. Table 1 shows the representative results. The $Yb(OTf)_3$ catalyst displayed high activity and gave coupling product **3aa** in satisfactory yields (Table 1, Entries 1—6). It can be observed that the reaction, performed in nitro methane as a solvent, afforded **3aa** in the highest yield even at room temperature (Table 1, Entry 6). Substitution of $Yb(OTf)_3$ by $LaCl_3$ or $YbCl_3$ led to just a moderate yield of the product even prolonging the reac-

Table 1 $Yb(OTf)_3$-catalyzed substitution reaction of allylic alcohol **1a** with tosylamine (**2a**) under various conditions[a]

Entry	Catalyst (5 mol%)	Solvent	Temp./℃	Time/h	Yield[b]/%
1	$Yb(OTf)_3$	CH_2ClCH_2Cl	60	4	89
2	$Yb(OTf)_3$	Dioxane	60	0.5	93
3	$Yb(OTf)_3$	THF	60	4	75
4	$Yb(OTf)_3$	Toluene	60	4	90
5	$Yb(OTf)_3$	CH_3CN	60	2	91
6	$Yb(OTf)_3$	CH_3NO_2	r.t.	0.5	95
7	$LaCl_3$	CH_3NO_2	r.t.	24	55
8	$YbCl_3$	CH_3NO_2	r.t.	24	67
9	None	CH_3NO_2	r.t.	24	—
10[c]	$Yb(OTf)_3$	CH_3NO_2	r.t.	4	93

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.39 mmol, 1.3 equiv.), catalyst (0.015 mmol, 5 mol%), solvent (2 mL). [b] GC/MS Yield. [c] Using 1 mol% catalyst.

tion time to 24 h (Table 1, Entries 7 and 8). However, in the absence of lanthanide complex, no product was determined after 24 h (Table 1, Entry 9).

Significantly, we found that the $Yb(OTf)_3$ catalyst was easily recovered from the reaction mixture by extraction with water, followed by removing water and drying under vacuum at 200 ℃ for 4 h. The recovered catalyst kept basically the inherent activity in at least ten catalytic runs (Figure 1).

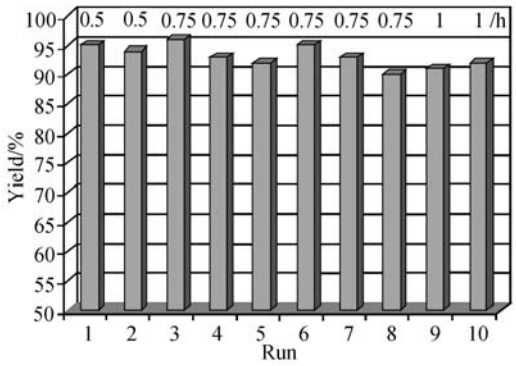
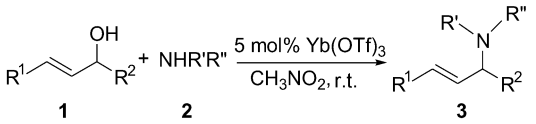
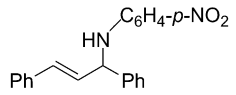
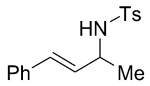
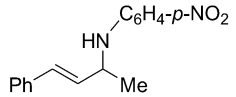
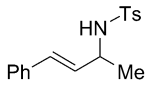
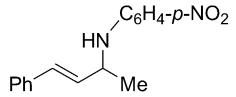
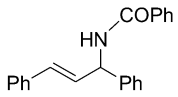
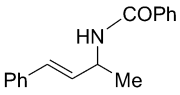
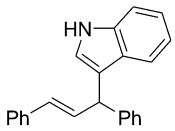


Figure 1 Recycling results for the reaction of **1a** with tosylamine (**2a**) catalyzed by $Yb(OTf)_3$. First run: **1a** (1 mmol), **2a** (1.3 mmol), 5 mol% $Yb(OTf)_3$ in 10 mL of nitromethane at room temperature.

We then explored the generality of the $Yb(OTf)_3$-catalyzed reaction by varying the alcohol and nucleophilic substrates. As shown in Table 2, the investigation results indicate that allylic alcohols were more reactive toward arylamines and amides than secondary benzylic alcohols.[10] When tosylamine (**2a**) and *p*-nitrophenylamine (**2b**) were used, the reactions were completed within 30—45 min, and the corresponding allylated products were obtained in 91%—95% yields (Table 1, Entry 6; Table 2, Entries 1—5). Interestingly, **1b** and **1c** reacted with *p*-nitrophenylamine (or tosylamine) to give the same products, with similar yields and regioselectivity (Table 2, Entries 2—5). These features support the same allylic cation as intermediate **I** for both isomeric allylic alcohols. Namely, the positive charge is delocalized on the resultant allyl units, and amine or amide attacks selectively the sterically less hindered carbon atom of the allylic functionality. Furthermore, it was found that benzamide was less reactive than tosylamine, the desired products **3ac** and **3bc** were obtained in 90% and 82% yields, respectively, after 6 or 24 h at room temperature (Table 2, Entries 6 and 7). In contrast to these results, the reaction of **1a** with indole under the same conditions did not afford the desired *N*-substituted indole derivative but instead the corresponding 3-allylated product with complete regioselectivity (Table 2, Entry 8). Remarkably, the NH moiety of indole is well tolerant in the reaction; $Yb(OTf)_3$ efficiently catalyzed the 3-allylation of indole while avoiding competitive *N*-allylation and the formation of theallylated amines, which thus offers an efficient route to the regioselective modification of indoles that play important

Table 2 $Yb(OTf)_3$-catalyzed amination of allylic alcohols[a]



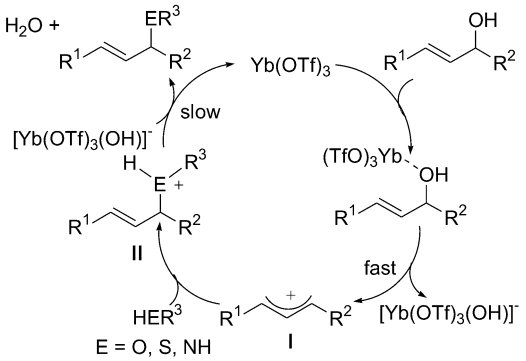
Entry	Alcohol	R^1	R^2	Time/h	Product	Yield[b]/%
1	**1a**	Ph	Ph	0.5	 **3ab**	94
2	**1b**	Ph	Me	0.75	 **3ba**	92
3	**1b**	Ph	Me	0.75	 **3bb**	93
4	**1c**	Me	Ph	0.5	 **3ba**	91
5	**1c**	Me	Ph	0.5	 **3bb**	95
6	**1a**	Ph	Ph	6	 **3ac**	90
7	**1b**	Ph	Me	24	 **3bc**	82
8	**1a**	Ph	Ph	0.5	 **3ad**	87
9	**1a**	Ph	Ph	24		Trace

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.39 mmol, 1.3 equiv.), $Yb(OTf)_3$ (0.015 mmol, 5 mol%) in 2 mL of nitromethane. [b] Isolated yields based on allylic alcohols.

roles in biological systems and have been employed as intermediates in organic synthesis and as unique ligands for various metal complexes.[11] In contrast to the observations that both benzylamines and arylamines are reactive in the Pd-catalyzed identical reaction,[12] no desired

products were obtained when benzylamine and phenylamine were used as nucleophiles in present cases (Table 2, Entry 9). This may be attributed to their inherent weak acidity, which prevents the occurrence of deprotonation. These results propose that the deprotonation of intermediate **II** might involve in the rate-determining step as shown in Scheme 1.

Scheme 1 Proposed mechanism for the nucleophilic substitution of allylic alcohols catalyzed by $Yb(OTf)_3$



All the results demonstrate that the nature of amines and amides plays an important role to enhance the rates and product yields of the reactions. The reactivity of nitrogen-containing nucleophiles increases in the order of tosylamine ≈ *p*-nitrophenylamine > benzamide >> benzylamine, which is consistent with relative acidity of these substrates. Since aliphatic amine is not acidic enough to deprotonate under the conditions involved, the nucleophilic substitution with benzylamine is prevented. During completion of our paper, a $Bi(OTf)_3$-catalyzed substitution of allylic alcohols by *N*-centered nucleophiles was reported, but KPF_6 was needed as an additive to obtain satisfactory results.[13]

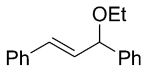
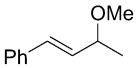
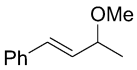
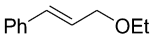
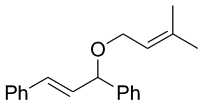
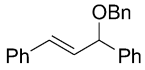
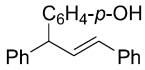
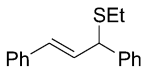
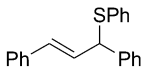
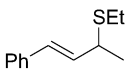
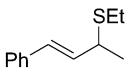
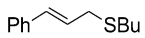
To explore the generality, the reaction was also examined with representative alcohols. The reaction of allylic alcohols **1a**—**1d** with aliphatic alcohols smoothly proceeded to give ethers as the sole products in high yields (Table 3, Entries 1—6), while treatment of **1a** with phenol (**2j**) led to the isolation of the Friedel-Crafts alkylated product **3aj** in a good yield (Table 3, Entry 7).[14] Noticeably, reaction of methanol with **1b** gave rise to the same product **3bg** with a similar yield and regioselectivity as those obtained with **1c** (Table 3, Entries 2 and 3). These results provide also evidence to support the mechanistic consideration in Scheme 1, and indicate that the stability of cationic intermediate and the steric effect play a key role in control of regioselectivity.

Thioethers represent an essential functionality in many biologically relevant compounds and have versatile applications as building blocks for organic chemistry and as precursors to a wide range of functionalized molecules.[15] On the other hand, the catalytic transformation of thiols is significantly less developed than that of amines and alcohols, probably due to the strong thiophilicity of transition metal ions, which often lead to incompatibility of thiols with metal-catalyzed reactions. Considering that the match of the "soft" sulfur-containing substrates with the "hard" lanthanide metals would avoid poison of catalyst, we were keen to explore the $Yb(OTf)_3$-catalyzed reaction of allylic alcohols with thiols. The investigation results demonstrate that the present catalyst is also suitable for the direct substitution of the hydroxy group in allylic alcohols with thiols. The treatment of **1a** with ethanethiol (**2k**) afforded **3ak** in a 91% yield (Table 3, Entry 8). In contrast to the results obtained when using phenol as a nucleophile, no Friedel-Crafts arylated product was detected while using thiophenol as the nucleophile, and the allylic sulfide **3al** was the sole product (Table 3, Entry 9). The reaction of **1b** with **2k** proceeded regioselectively to afford **3bk**, which was also obtained starting from **1c** (Table 3, Entries 10—11). However, in the *p*-toluenesulfonic acid catalytic system the reaction of allylic alcohols **1b** and **1c** with thiol afforded the product as a mixture of regioisomers.[16] *n*-BuSH was also suitable substrate for the substitution of cinnamyl alcohol and gave the desired product in an 87% yield (Table 3, Entry 12), despite that the reaction rate was decreased. Examples of direct substitution of the hydroxy group in alcohols by thiols are rare, to the best of our knowledge, the present result represents the first example of such reaction catalyzed by lanthanide complexes.

Next, we examined the $Yb(OTf)_3$-catalyzed allylation of 1,3-dicarbonyl compounds with **1a** as depicted in Table 4. Various 1,3-dicarbonyl compounds smoothly underwent the allylation to give the desired products in high yields. It was particularly encouraging that cyclic *β*-keto ester **2s**, which has a lower acidity and large steric hindrance, displayed also a high reactivity and reacted quickly to give the desired product in a 93% yield (Table 4, Entry 6). Although a few Lewis acid-catalyzed allylations of active methylene compounds with allylic alcohols have been reported, all those methods require a longer reaction time and higher reaction temperature than the present method; further, active methylene compounds are often limited and the products are incidentally contaminated with the formation of a significant amount of side products. For example, diethyl malonate (**2t**) gave the allylated product **3at** in an 87% yield, at room temperature for 3 h in our catalytic system (Table 4, Entry 7), while such substrate was not suitable or gave the product only in low or moderate yields, even with a prolonged heating time, in other reported Lewis acid catalytic systems.[4]

A great deal of effort has been devoted to the development of new methods for synthesis of functionalized propargylic compounds that are important building blocks for organic synthesis due to the availability of transformation of the alkyne functional group into various other functional groups. For example, aminoalkynes have been widely used to construct azacycle skeletons in complex natural product synthesis.[17,18] It is well known that transition metal catalyzd allylation has become an important chemical transformation, as it pro-

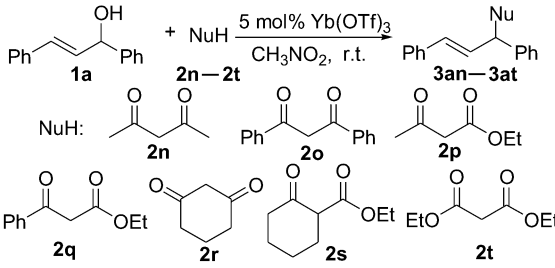
Table 3 $Yb(OTf)_3$-catalyzed direct hydroxy substitution of various allylic alcohols with alcohols and thiols[a]

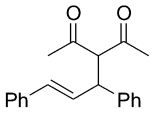
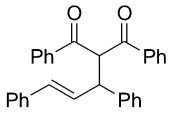
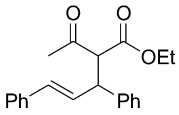
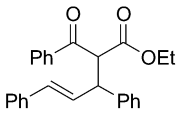
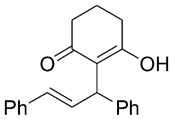
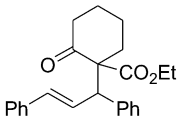
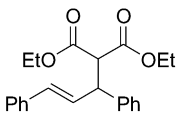
Entry	Alcohol	NuH	Time/h	Product	Yield[b]/%
1	**1a**	EtOH (**2f**)	0.3	 **3af**	92
2	**1b**	MeOH (**2g**)	1	 **3bg**	93
3	**1c**	MeOH (**2g**)	0.75	 **3bg**	90
4[c]	**1d**	EtOH (**2f**)	2	 **3df**	93
5	**1a**	$(CH_3)_2CCHCH_2OH$ (**2h**)	0.3	 **3ah**	90
6	**1a**	BnOH (**2i**)	0.3	 **3ai**	95
7	**1a**	PhOH (**2j**)	2	 **3aj**	85
8	**1a**	EtSH (**2k**)	0.3	 **3ak**	91
9	**1a**	PhSH (**2l**)	0.5	 **3al**	92
10	**1b**	EtSH (**2k**)	0.5	 **3bk**	89
11	**1c**	EtSH (**2k**)	0.5	 **3bk**	93
12[c]	**1d**	BuSH (**2m**)	2	 **3dm**	87

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol, 1.5 equiv.), $Yb(OTf)_3$ 0.015 mmol, 5 mol%) in 2 mL of nitromethane. [b] Isolated yields based on allylic alcohol. [c] The reaction was carried out at 50 ℃.

vides a direct and reliable ap proach to a wide variety of allylated products. Nevertheless, related transition metal catalyzed propargylations are relatively rare. Very recently, several Lewis acids have proved their ability to act as catalysts for propargylic substitution reactions.[3,5,6,13] After having established that $Yb(OTf)_3$ is an efficient catalyst for the hydroxy substitution of allylic alcohols, we were keen to explore the $Yb(OTf)_3$-catalyzed nucleophilic substitution of propargylic alcohols. Typical results are shown in Scheme 2, and the reaction is general for different propargylic alcohols and the selected nucleophiles. When ethanol was treated with

Table 4 $Yb(OTf)_3$-catalyzed allylation of 1,3-dicarbonyl compounds with **1a**[a]

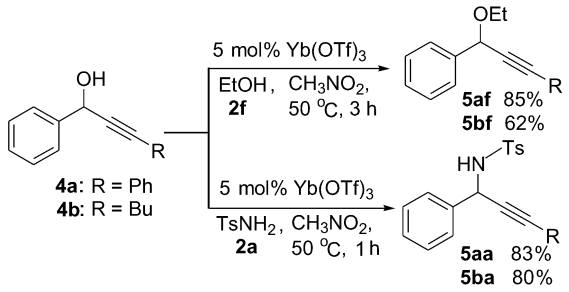


Entry	NuH	Time/h	Product	Yield[b]/%
1	**2n**	0.5	 **3an**	93
2	**2o**	0.5	 **3ao**	92
3[c]	**2p**	0.5	 **3ap**	91
4[c]	**2q**	0.5	 **3aq**	92
5	**2r**	0.5	 **3ar**	90
6[c]	**2s**	0.5	 **3as**	93
7	**2t**	3	 **3at**	87

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol, 1.5 equiv.), $Yb(OTf)_3$ (0.015 mmol, 5 mol%) in 2 mL of nitromethane at r.t. [b] Isolated yields based on allylic alcohol **1a**. [c] As a 1 ∶ 1 mixture of diastereoisomers.

propargylic alcohols **4a** and **4b**, the corresponding propargylic ethers **5af** and **5bf** were obtained in 85% and 62% yields, respectively. Similarly, reactions of **4a** and **4b** with tosylamine were also carried out. The corresponding propargylation products **5aa** and **5ba** were obtained in good yields with complete regioselectivity. In all cases, the propargylic alcohols **4a** and **4b** reacted regioselectively at the propargylic position. Allenic products of amide (alcohol) attack at the triple bond were not observed for **4a** and **4b**.

Scheme 2 $Yb(OTf)_3$ catalyzed nucleophilic substitution of propargylic alcohols



Conclusions

In summary, we have developed a general and highly efficient $Yb(OTf)_3$-catalyzed direct substitution of the hydroxy group in allylic and propargylic alcohols with heteroatom- and carbon-centered nucleophiles, such as alcohols, thiols, amines, amides and active methylenes compounds. The corresponding allylated and propargylated products were obtained, mostly at room temperature, in high yields. In comparison with other Lewis acid catalytic systems, $Yb(OTf)_3$ as the catalyst offers several relevant advantages including high stability and reusability, mild reaction conditions and short reaction time, no need for dried solvents and additives. This provides a clean, environmentally friendly, and synthetically competitive alternative to the already established use of metal complexes. Moreover, the present result represents the first example of direct substitution of the hydroxy group in alcohols by thiols catalyzed by lanthanide complexes. Further development on this methodology is currently under way in our laboratory.

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