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An intriguing effect of $Yb(OTf)_3$–TMSCl in the halogenation of 1,1-disubstituted alkenes by NXS: selective synthesis of allyl halides

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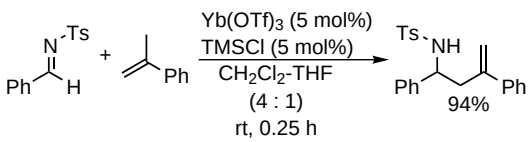
Abstract—A novel protocol to effect the efficient selective halogenation of 1,1-disubstituted alkenes with NXS catalyzed by $Yb(OTf)_3$–TMSCl, which affords the corresponding allyl halides in high yield, including allyl bromide, chloride, iodide and fluoride, is described. A remarkable feature of $Yb(OTf)_3$–TMSCl-catalyzed halogenation is that, unlike conventional radical halogenation with *N*-halosuccinimides, the reaction discriminates between the allylic and benzylic positions. The reaction occurs selectively at the allylic position to give allylic halides, but not at the benzylic position. © 2002 Elsevier Science Ltd. All rights reserved.

Allyl halides are a fundamental and important class of compounds which undergo a variety of transformations as excellent electrophiles. They also serve as precursors for allylic organometallic reagents which are powerful tools in modern organic synthesis.[1] Given their significance, it is important to develop efficient methods for their synthesis.

One of the most common approaches for the synthesis of allyl halides is the direct halogenation of alkenes. *N*-Bromosuccinimide (NBS) has been used extensively in allylic bromination, while *N*-chloro (NCS) and *N*-iodosuccinimide (NIS) have been used to a much lesser extent.[2] Allylic chlorides are important in industry. They are made commercially by the gaseous chlorination of alkenes with Cl_2 at high temperature ($\sim$400°C). Generally, these halogenations proceed by a radical mechanism in the presence of radical initiators such as AIBN or benzoylperoxide which is promoted either by light or heat. Consequently, these reactions sometimes become complicated and give a mixture of products. Under these reaction conditions, benzylic halogenation also takes place. No selectivity between allylic and benzylic halogenation has been observed. Therefore, there has been continuing interest in the development of a new method for highly selective allylic halogenation.

We recently found a facile imino ene reaction that was catalyzed by $Yb(OTf)_3$–TMSCl to give homoallyl amines (Scheme 1).[3] In studying the mechanism of this reaction, we discovered that $Yb(OTf)_3$–TMSCl also catalyzed the allylic bromination of 1,1-disubstituted alkenes using NBS. In this letter, we report the first selective allylic halogenation and the utility of this novel reaction.

We first investigated the bromination of α-methylstyrene (**1**) with NBS without initiator, which produced only a trace amount of the allyl bromide **2a**, whereas the same reaction in the presence of a catalytic amount of $(PhCO)_2O_2$ under a typical protocol for radical bromination gave **2a** in 24% yield after 8 h (Table 1, entries 1, 2).[4] In contrast, treatment of **1** with NBS in the presence of 5 mol% of $Yb(OTf)_3$ increased the yield of **2a** up to 48% (entry 3). The bromination of **1** was dramatically enhanced by the combination of $Yb(OTf)_3$ and TMSCl in CH_2Cl_2–THF (4: 1) at room temperature. The reaction was completed within 30 min and gave **2a** in 84% yield (entry 5), whereas the use of TMSCl itself gave **2a** in only 11% yield (entry 4). These conditions were found to be quite general for effecting not only allylic bromination but also allylic chlorination[4b,5] and iodination of **1** (entries 6, 7). To the



Scheme 1. Imino ene reaction.

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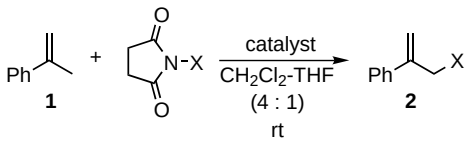
Table 1. Allylic halogenation of α-methylstyrene



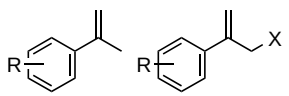
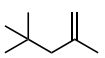
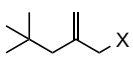
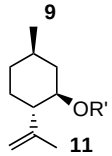
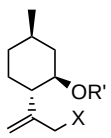
Entry	X	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	Br	None	72	**2a** (6)
2[b]	Br	$(PhCO)_2O_2$ (10)	8	**2a** (24)
3	Br	$Yb(OTf)_3$ (5)	0.5	**2a** (48)
4	Br	TMSCl (5)	0.5	**2a** (11)
5	Br	$Yb(OTf)_3$ (5) TMSCl (5)	0.5	**2a** (84)
6	Cl	$Yb(OTf)_3$ (5) TMSCl (5)	0.5	**2b** (76)
7	I	$Yb(OTf)_3$ (5) TMSCl (5)	0.5	**2c** (61)

[a] Isolated yield.
[b] Reaction was carried out under reflux in CCl_4.

best of our knowledge, a similar direct allylic iodination of alkenes has not been realized by another method.

To explore the generality of this halogenation, we investigated the similar reaction of other substrates. As shown in Table 2, both allylic chlorides and bromides were formed in good yields, although the bromination of α-methylstyrenes proceeded more cleanly and gave a better yield than the corresponding chlorination. 4-Chloro[4c,6] and 2-toluenesulfonylamino substituents on the aromatic ring had little effect on the yield of halogenation (entries 1, 2 and 5, 6), whereas a methoxy group accelerated the reaction to induce polymerization, and the corresponding allyl halides were not isolated (entries 3, 4). Bromination of 2,4,4-trimethyl-1-pentene (**9**) in the presence of AIBN under reflux conditions in CCl_4 has been reported to give a mixture of bromides due to two allylic positions.[7] However, the reactions catalyzed by $Yb(OTf)_3$–TMSCl provided 2-(halomethyl)-4,4-dimethyl-1-pentene (**10**) in high yield as a single product (entries 7, 8). Optically active isopregol derivative (**11**) also gave **12** without epimerization (entry 9), accompanied by a small amount of a dibromide.

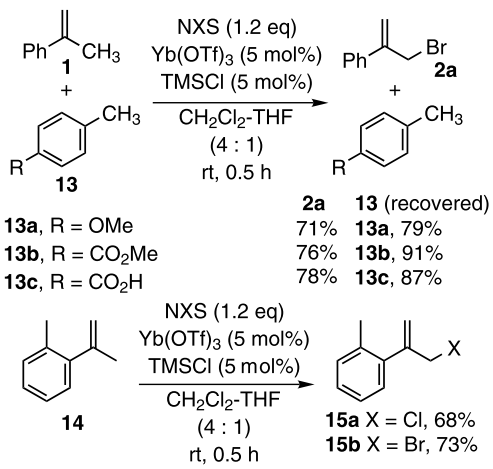
Table 2. Allylic halogenation catalyzed by $Yb(OTf)_3$–TMSCl

entry	substrate	product	X	yield (%)[a]
				
1	**3** R = 4-Cl		Cl	**4a** (44)
2	**3** R = 4-Cl		Br	**4b** (82)
3	**5** R = 4-OMe		Cl	**6a** (0)
4	**5** R = 4-OMe		Br	**6b** (0)
5	**7** R = 2-NHTs		Cl	**8a** (46)
6	**7** R = 2-NHTs		Br	**8b** (52)
7			Cl	**10a** (78)
8	**9**		Br	**10b** (76)
9	 **11**		Br	**12** (64)[b]

R' = TBDPS (*t*-butyldiphenylsilyl).
[a] Isolated yield.
[b] 27% of allylic and vinylic di-brominated product was also isolated.

A remarkable feature of $Yb(OTf)_3$–TMSCl-mediated halogenation is that, unlike conventional radical halogenation with *N*-halosuccinimides, the reaction discriminates between the allylic and benzylic positions.[2] The reaction occurs selectively at the allylic position to give allylic halides, but not at the benzylic position. To evaluate the halogenation promoted by $Yb(OTf)_3$–TMSCl, a competitive reaction was carried out with **1** and 4-substituted toluenes (**13**), the most commonly used reactive substrates in radical bromination. To our surprise, the only product detected in the reaction mixture was **2a** (71–78% yield) and toluenes were recovered essentially unchanged, showing high selectivity between the allylic and benzylic positions toward $Yb(OTf)_3$–TMSCl-catalyzed bromination. We were also surprised to ascertain that **14**, which has both allylic and benzylic protons, reacted selectively with NXS at the allylic position to give the corresponding halides **15** in high yields. No other isomer was detected by ^1H NMR spectroscopy (Scheme 2). These result suggested the halogenation with NXS mediated by $Yb(OTf)_3$–TMSCl probably proceeded via a non-free-radical mechanism.

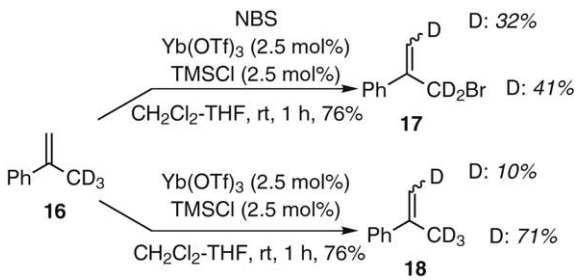
Interestingly, 1,2-disubstituted alkene such as *trans*-β-methylstyrene or monosubstituted alkene such as 3-phenyl-1-propene was completely inert under the same conditions, and no reaction was observed, indicating that the current method is useful for selective halogenation of 1,1-disubstituted alkenes.



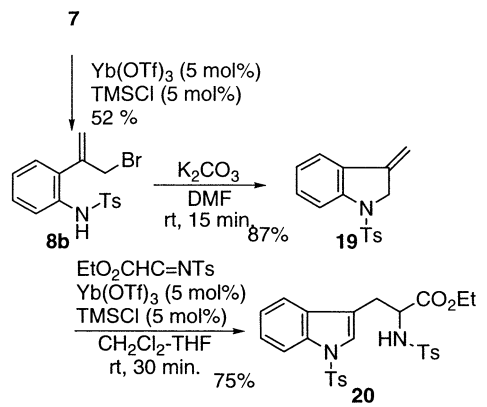
Scheme 2. Competitive halogenations.

As a logical extension of our $Yb(OTf)_3$–TMSCl-catalyzed halogenation by NXS regarding allylic halide formation, the bromination of ^{2}H-labeled α-methylstyrene[$C_6H_5CCH_2(CD_3)$] **16** was investigated to determine the mechanistic aspects of these reactions. The bromination of **16** was carried out using 2.5 mol% $Yb(OTf)_3$–TMSCl under the same conditions as were used for **1** (Table 1, entry 5), and a large degree of positional randomization of the deuterium label was observed, as shown in Scheme 3. As control experiments, **16** was treated similarly but without NBS, and again deuterium scrambling was observed. Thus, when **16** was treated with 2.5 mol% $Yb(OTf)_3$–TMSCl (1:1) without NBS for 1 h, 76% of **16** was recovered with 71% of the deuterium atoms in allylic position and 10% incorporated at the terminal position of the alkene. However, treating **16** with either $Yb(OTf)_3$ (2.5 mol%) or TMSCl (2.5 mol%) showed no scrambling of deuterium and **16** was recovered unchanged, showing that the disproportionation of deuterium in **16** by $Yb(OTf)_3$–TMSCl appears to occur partially before bromination.

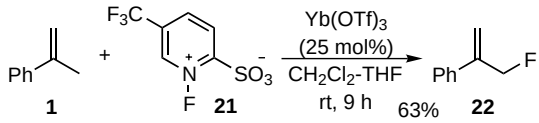
Although the mechanism still remains to be resolved, bromide **8** is a suitable compound for further functionalization. For example, treating **8b** with K_2CO_3 in DMF at room temperature gave indolidene **19**, which is a novel method for the synthesis of indole derivatives.[8] Interestingly, **19** could be readily converted to the tryptophan derivative **20**[9] in high yield using our recently developed imino ene reaction catalyzed by $Yb(OTf)_3$–TMSCl (Scheme 4).[3]



Scheme 3. Reaction of **16** catalyzed $Yb(OTf)_3$–TMSCl with NBS or without NBS.



Scheme 4. Synthesis of tryptophan derivative **20** from **7** by allylic bromination cyclization followed by imino ene reaction.



Scheme 5. Allylic fluorination.

Finally, we also investigated allylic fluorination, which has not been reported previously.[10] Our initial attempts to apply our present methodology to fluorination using *N* - fluoro - 5 - (trifluoromethyl)pyridinium - 2 - sulfonate (**21**)[11] as a fluorinating reagent failed and produced polymerization. However, a modified procedure which uses $Yb(OTf)_3$ without TMSCl gave the corresponding fluoride **22** in 63% yield from **1** (Scheme 5).

In summary, we have for the first time developed a selective method for the synthesis of allyl halides using $Yb(OTf)_3$–TMSCl or $Yb(OTf)_3$ as a catalyst. The reaction conditions are mild enough to be applicable to large-scale conversions. Further investigations of the scope and limitations of these reactions are underway in our laboratories.

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