ORGANIC LETTERS

2000
Vol. 2, No. 2
159−161

Ytterbium(III) Triflate/TMSCl: Efficient Catalyst for Imino Ene Reaction

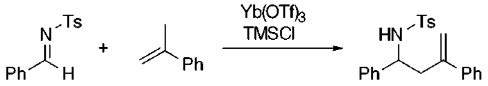
Masamichi Yamanaka, Atsushi Nishida, and Masako Nakagawa*

Faculty of Pharmaceutical Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522, Japan

nakagawa@p.chiba-u.ac.jp

Received November 19, 1999

ABSTRACT



Ytterbium trifluoromethanesulfonate [$Yb(OTf)_3$] catalyzed the imino ene reaction of *N*-tosyl aldimine with α-methylstyrene to give a homoallylamine in moderate yield. Furthermore, addition of a catalytic amount of chlorotrimethylsilane (TMSCl) dramatically enhanced the imino ene reaction.

The development of new methods for the synthesis of chiral or achiral amines is an important issue for the synthesis of nitrogen-containing natural products and biologically active compounds. As part of our ongoing project along these lines, we previously reported the diastereo- and enantioselective Pictet−Spengler reaction,[1] and the diastereoselective addition of alkyllithium to chiral imines.[2]

Although there have been many reports on catalytic C−C bond-forming reactions using imines with electron-rich alkenes[3] and organometallic reagents,[4] reactions between imines and simple alkenes, i.e., imino ene reactions,[5,6] have not yet been studied as intensively as carbonyl ene reactions.[7] Recent advances in the chemistry of lanthanoid metal catalysts[8,9] prompted us to study the catalytic activity of rare earth metal salts in imino ene reactions. We present here a preliminary report on ytterbium trifluoromethanesulfonate [($Yb(OTf)_3$)] catalyzed imino ene reactions in the presence of TMS−Cl or TMS−OTf.

Initially, we chose the reaction of *N*-toluenesulfonyl benzaldimine **1a** with α-methylstyrene. When imine **1a** was treated with 2 equiv of α-methylstyrene in CH_2Cl_2−THF (4:1) in the presence of $Yb(OTf)_3$ (25 mol %) at room temperature for 48 h, the imino ene product **2a** was obtained in 58% yield (entry 1, Table 1). Addition of 1.2 equiv of TMS−Cl to the reaction mixture facilitated the reaction dramatically.[10] The reaction was completed within only 15 min and gave **2a** in 90% yield (entry 2).

Although TMS−Cl itself did not act as a catalyst (entry 3), if TMS−OTf was formed *in situ* from TMS−Cl and $Yb(OTf)_3$, it might catalyze this reaction. To clarify this issue, the reaction using 1.2 equiv of TMS−OTf without $Yb(OTf)_3$

---

(1) (a) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1249−1252. (b) Kawate, T.; Yamada, H.; Matsumizu, M.; Nishida, A.; Nakagawa, M. *Synlett* **1997**, 761−762. (c) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348−6354. (d) Kawate, T.; Yamanaka, M.; Nakagawa, M. *Heterocycles* **1999**, *50*, 1033−1039.

(2) (a) Kawate, T.; Yamada, H.; Yamaguchi, K.; Nishida, A.; Nakagawa, M. *Chem. Pharm. Bull.* **1996**, *44*, 1776−1778. (b) Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999**, *64*, 8821−8828.

(3) (a) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432. (b) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549.

(4) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242−4243.

(5) (a) Achmatowicz, O., Jr.; Pietraszkiewicz, M. *Chem. Commun.* **1976**, 484. (b) Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347−360. (c) Laschat, S.; M. Grehl, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 458−461. (d) Mikami, K.; Kaneko, M.; Yajima, T. *Tetrahedron Lett.* **1993**, *34*, 4841−4842.

(6) The catalytic enantioselective imino ene reactions of α-imino esters have recently been reported: (a) Druy, W. J., III: Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006−11007. (b) Yao, S.; Fang, X.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547−2548.

(7) (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021−1050. (b) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825.

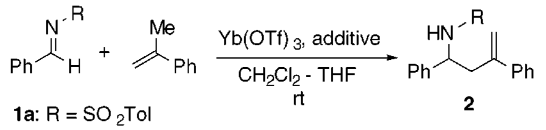
(8) (a) Kobayashi, S. *Synlett* **1994**, 689−701. (b) Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *New. J. Chem.* **1995**, *19*, 707−712. (c) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (d) Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 1555−1558.

(9) (a) Kobayashi, S.; Nagayama, S. *J. Am.. Chem. Soc.* **1997**, *119*, 10049−10053. (b) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089−3103.

(10) Rate acceleration by R_3SiCl in addition of diethyl zinc: Jimeno, C.; Vidal-Ferran, A.; Moyano, M.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 777−780.

10.1021/ol991260s CCC: $19.00 © 2000 American Chemical Society
Published on Web 12/22/1999

Table 1. Imino Ene Reaction of *N*-Substituted Aldimine with α-Methylstyrene



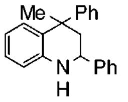
1a: R = SO_2Tol
1b: R = COOMe
1c: R = $P(O)Ph_2$
1d: R = Bn
1e: R = Ph

entry	1	$Yb(OTf)_3$ mol%	additive (mol%)	time (hr)	yield[a] (%)
1	**1a**	25	none	48	58
2		25	TMSCl (120)	0.25	90
3		none	TMSCl (120)	48	0
4		none	TMSOTf (120)	0.25	43
5		5	TMSCl (5)	0.25	94
6		1	TMSCl (1)	1	86
7		5	TMSOTf (5)	0.25	92
8	**1b**	25	none	48	12
9		10	TMSCl (10)	1	44
10		10	TMSOTf (10)	1	74
11	**1c**	25	TMSOTf (25)	1.5	38
12	**1d**	5	TMSCl (120)	72	0
13	**1e**	25	TMSCl (25)	5	0[b]

[a] Isolated yield. [b] Aza Diels−Alder reaction took place to give adduct **3** in 63% yield.

was carried out (entry 4). The imino ene reaction proceeded, and **2a** was obtained in only 43% yield, even though an excess amount of TMS−OTf was present. We also suspected that triflic acid (TfOH) produced in situ might catalyze the reaction. However, the similar reaction of **1a** with TfOH (120 mol %) for 15 min gave only 39% yield of **2a** (compare with entries 2 and 4). Therefore, while TMS−OTf or TfOH catalyzes this reaction to some extent, the presence of both $Yb(OTf)_3$ and TMS−X (X = Cl, OTf) is essential. We briefly studied the effect of the amount of the catalyst. The reaction using 5 mol % of $Yb(OTf)_3$ and TMS−Cl (entry 5) afforded almost the same result as entry 2. Even 1 mol % of catalyst was effective to afford **2a** in 86% yield, although the reaction rate was slightly decreased (entry 6). TMS−OTf was also effective when it was used with $Yb(OTf)_3$ (entry 7).

The *N*-substituent on the imino group also influenced this reaction. In contrast to the reaction of *N*-tosyl imine **1a**, $Yb(OTf)_3$ (25 mol %) itself did not catalyze the ene reaction between *N*-methoxycarbonyl imine **1b** and α-methylstyrene (entry 8). However, a combination of $Yb(OTf)_3$ (10 mol %) and TMS−Cl (10 mol %) induced the reaction to give **2b** in moderate yield (entry 9). In this case, the effect of TMS−OTf is notable. The yield of **2b** increased up to 74% when TMS−OTf was added instead of TMS−Cl (entry 10). Phosphinoyl imine **1c** also gave **2c** under these conditions, whereas the similar reaction of *N*-benzyl imine **1d** did not proceed at all. These results indicate that the *N*-substituent must possess an electron-withdrawing character for the imino ene reaction to occur. Interestingly, when *N*-phenyl imine **1e** was subjected to similar reaction conditions, aza Diels−Alder cycloadduct **3** was obtained, and no imino ene product was observed (entry 12).[11]



3

There have been several efforts to explain the reactivity of lanthanoid metal triflates systematically.[12] Yamaguchi and Imamoto recently developed a scale of oxophilicity of lanthanoid metal complexes using tandem mass spectroscopy.[12b] To obtain greater insight into the reaction mechanism of these catalysts, we surveyed the catalytic activities of other combinations of lanthanoid metal triflates [$M(OTf)_3$] and TMS−Cl in this imino ene reaction of **1a** and α-methylstyrene. The catalytic activity profile of $M(OTf)_3$/TMS−Cl is shown in Figure 1 with the oxophilicity scale. The activity profile was almost consistent with the oxophilicity scale. These observations suggest that the oxophilicity, i.e., the Lewis acidity of the lanthanoid metal may play an important role in these reactions.

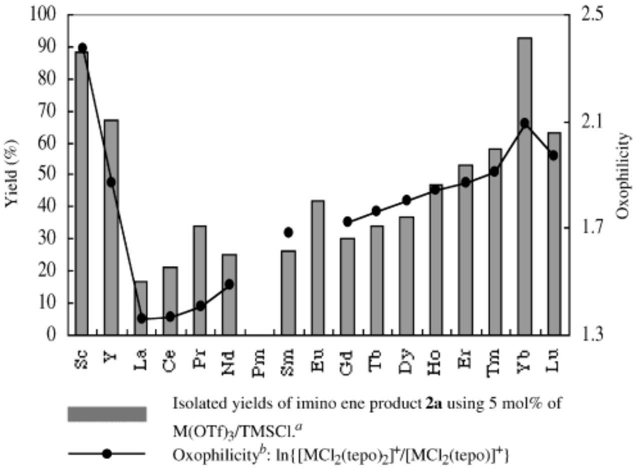


Figure 1. Catalytic activity of $M(OTf)_3$/TMS−Cl in the imino ene reaction. Notes: (*a*) All reactions were carried out at room temperature for 1 h. (*b*) The reported oxophilicity data, evaluated based on the dissociation of $[MCl_2(tepo)_3]^+$ as observed by tandem mass spectrometry. See ref 12b.

Under the conditions described above, three-component coupling[11a,b,13] among aromatic or aliphatic aldehyde, tosyl-

---

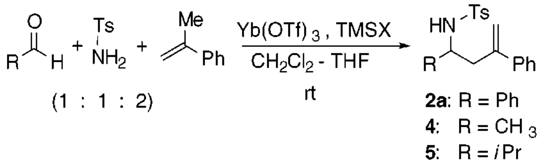
[11] (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195−1202. (b) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357−7360. (c) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chem. Commun.* **1999**, 651−652.

[12] (a) Imamoto, T.; Nishiura, M.; Yamanoi, Y.; Tsuruta, H.; Yamaguchi, K. *Chem. Lett.* **1996**, 875−876. (b) Tsuruta, H.; Yamaguchi, K.; Imamoto, T. *J. Chem. Soc., Chem. Commun.* **1999**, 1703−1704.

[13] (a) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19−20. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 981−982. (c) Kobayashi, S.; Sugita, K.; Oyamada, H. *Synlett* **1999**, 138−139. (d) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545−546.

amine, and α-methylstyrene in the presence of Yb(OTf)$_3$ and TMS−Cl or TMS−OTf was realized (Table 2). Thus, using 50 mol % of Yb(OTf)$_3$/TMS−X, the reaction proceeded smoothly to give **2a** in good to excellent yield. In this reaction, the combination with TMS−OTf gave better results. Aliphatic aldehydes, such as acetaldehyde and isobutyraldehyde, whose imines are difficult to isolate, afforded imino ene products **4** and **5** in good yields without any difficulty.

Table 2. Three-Component Coupling



entry	R	Yb(OTf)$_3$ (mol%)	TMSX X	TMSX (mol%)	time (h)	yield[a] (%)
1	Ph	50	Cl	50	1	**2a** 79
2		50	OTf	50	1	90
3[b]	CH$_3$	50	OTf	50	1	**4** 76
4	*i*Pr	50	OTf	50	1	**5** 70

[a] Isolated yield based on TsNH$_2$. [b] Two equivalents of acetaldehyde was employed.

In summary, we have shown that the combination of Yb(OTf)$_3$ and either TMS−Cl or TMS−OTf is an effective catalyst system for the imino ene reaction using imines with an electron-withdrawing substituent at the nitrogen. We also showed that the catalytic activities of M(OTf)$_3$/TMS−Cl in the imino ene reaction were highly dependent on the oxophilicity of the lanthanoid metal. The three-component coupling reaction of aldehydes, tosylamine, and α-methylstyrene was also successful under these conditions. In this reaction, the use of aliphatic aldehydes, such as acetaldehyde, is noteworthy. Further studies to elucidate the detailed mechanism of the activity of these catalysts and its application to asymmetric processes are underway.

Acknowledgment. Financial support from the Ministry of Education, Science, Sports and Culture in the form of a Grant-in-Aid for Scientific Research is gratefully acknowledged. We also thank Ms. R. Hara at the Chemical Analysis Center of Chiba University for measuring mass spectral data.

Supporting Information Available: General experimental procedure and characterization data for products **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991260S