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Communications

Aldehydes vs Aldimines. Unprecedented Reactivity in Their Enolate Addition Reactions

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Addition reactions of carbonyl and related compounds are among the most fundamental and important reactions in organic chemistry. It is well-recognized that aldimines are less reactive than aldehydes toward nucleophilic addition[1] because of the difference in electronegativity between oxygen and nitrogen, the steric hindrance of aldimines, etc. Herein we describe an unprecedented change in the reactivity: preferential reactions of aldimines over aldehydes with enolates using a lanthanide salt as a Lewis acid.[2]

Our basic idea is shown in Scheme 1. It is well-known that a Lewis acid activates an aldehyde[3] or an aldimine[4] and that nucleophilic additions are accelerated. When a large excess of a Lewis acid is used and both aldehyde and aldimine are activated, the aldehyde is more reactive than the aldimine. On the other hand, in the presence of a small amount of a Lewis acid, the formation of aldehyde−Lewis acid or aldimine−Lewis acid complexes takes place under equilibrium conditions. If a Lewis acid could coordinate an aldimine preferentially and nucleophilic addition could occur under such conditions, preferential reactions of aldimines over aldehydes could be achieved.

On the basis of this idea, we screened various Lewis acids in the model reactions of benzaldehyde and *N*-benzylideneaniline with propiophenone enolate, and selected results are shown in Table 1. It was found that propiophenone lithium enolate attacked benzaldehyde exclusively (entry 1). While propiophenone trimethylsilyl enolate (silyl enol ether of propiophenone) attacked neither benzaldehyde nor *N*-benzylideneaniline without a Lewis acid, selective reactions of the aldehyde took place using typical Lewis acids such as $TiCl_4$, $SnCl_4$, TMSOTf, etc., even when catalytic amounts of the Lewis acids were used. Recently, we found that lanthanide triflates ($Ln(OTf)_3$) are unique Lewis acids that are stable in water and catalyze several useful synthetic reactions.[5] It was found that use of these lanthanide triflates changed the reaction course dramatically.[6] When 0.2 equiv of ytterbium triflate ($Yb(OTf)_3$, a representative lanthanide triflate) was used in dichloromethane, selective reaction of the aldimine over the aldehyde took place at −23 or −45 °C.[7] Both aldimine and aldehyde reacted at 0 °C or rt. When propionitrile was used as a solvent, only the aldimine reacted at −45 °C to afford the corresponding adduct in an 83% yield.

Scheme 1

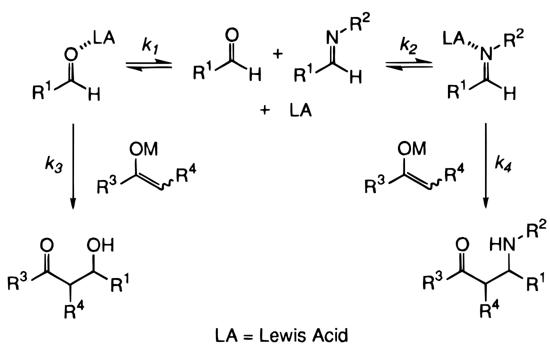
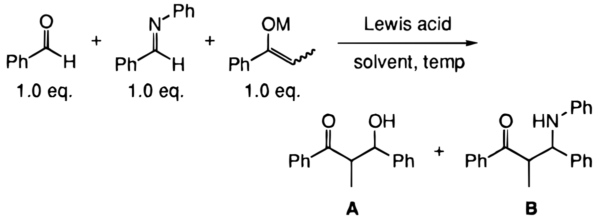


Table 1



M	Lewis acid/equiv	solvent	temp (°C)	yield (%)		A/B
				A	B	
Li		THF	−78	97	trace	>99/1
Me_3Si		CH_2Cl_2	−78	0	0	
Me_3Si	$SnCl_4$/1.0	CH_2Cl_2	−78	93	1	99/1
Me_3Si	$TiCl_4$/1.0	CH_2Cl_2	−78	86	1	99/1
Me_3Si	Me_3SiOTf/1.0	CH_2Cl_2	−23	87	trace	>99/1
Me_3Si	$SnCl_4$/0.2	CH_2Cl_2	−78	18	trace	>99/1
Me_3Si	$TiCl_4$/0.2	CH_2Cl_2	−78	12	trace	>99/1
Me_3Si	$BF_3{\cdot}OEt_2$/0.2	CH_2Cl_2	−78	26	7	79/21
Me_3Si	Me_3SiOTf/0.2	CH_2Cl_2	−23	52	12	81/19
Me_3Si	$Yb(OTf)_3$/2.0	CH_2Cl_2	−23	49	31	61/39
Me_3Si	$Yb(OTf)_3$/1.0	CH_2Cl_2	−23	40	31	56/44
Me_3Si	$Yb(OTf)_3$/0.2	CH_2Cl_2	−23	2	92	9/98
Me_3Si	$Yb(OTf)_3$/0.2	CH_2Cl_2	−45	trace	69	<1/>99
Me_3Si	$Yb(OTf)_3$/0.2	CH_2Cl_2	0	39	55	41/59
Me_3Si	$Yb(OTf)_3$/0.2	CH_2Cl_2	rt	41	48	46/54
Me_3Si	$Yb(OTf)_3$/0.2	CH_3CN	−23	2	92	2/98
Me_3Si	$Yb(OTf)_3$/0.2	C_2H_5CN	−45	trace	83	<1/>99

We then examined other compounds, and the results are shown in Table 2. In all cases, aldimines reacted with

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[1] For example: Yamaguchi, M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 1, Chapter 1.11.

[2] Very recently, Yamamoto et al. reported imine-selective allylation via a palladium-catalyzed allylstannane reaction. Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1459; *J. Am. Chem. Soc.* **1996**, *118*, 6641.

[3] (a) Chan, T.-H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Chapter 2.3. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *Chem. Lett.* **1973**, 357. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

[4] (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) Ojima I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643. (c) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331. (d) Mukaiyama, T.; Kashiwagi, K.; Matsui, S. *Chem. Lett.* **1989**, 1397. (e) Mukaiyama, T.; Akamatsu, H.; Han, J. S. *Chem Lett.* **1990**, 889. (f) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y. *Synlett* **1993**, 141. (g) Ishihara, K.; Funahashi, M.; Hanaki, N.; Miyata, M.; Yamamoto, H. *Synlett* **1994**, 963.

[5] Kobayashi, S. *Synlett* **1994**, 689.

[6] We have already found that lanthanide triflates are effective catalysts for the reactions of aldehydes or aldimines with silyl enolates. (a) Aldehyde: Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625. (b) Aldimine: Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. See also: (c) Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett.* **1996**, *37*, 2809.

[7] The high catalytic activity of $Yb(OTf)_3$ should also be noted. While high yields of **A** + **B** were obtained using 20 mol % $Yb(OTf)_3$, much lower yields were observed when 20 mol % of $SnCl_4$ or $TiCl_4$ was used.

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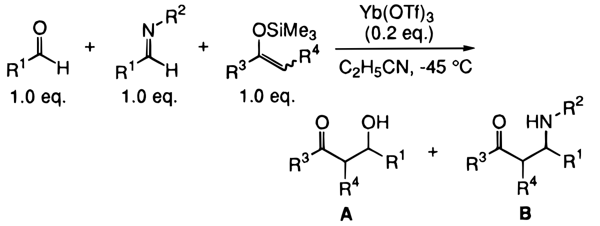
Table 2



R¹	R²	R³	R⁴	yield (%) A	yield (%) B[b]	A/B
Ph	Ph	Ph	Me[c]	trace	83	<1/>99
Ph	p−MeOPh	Ph	Me	trace	81	<1/>99[f]
Ph	p−ClPh	Ph	Me	trace	87	<1/>99
Ph	Ph	Ph	H	trace	92	<1/>99
Ph	Ph	^{t}Bu	H	trace	88	<1/>99[f]
Ph	Ph	Et	Me[d]	trace	81	<1/>99[g]
2−furyl	Ph	Ph	Me	trace	91	<1/>99
c−C_6H_{11}	Ph	Ph	Me	trace	85	<1/>99
Ph	Ph	$-(CH_2)_4$		trace	83	<1/>99[g]
Ph	Ph	SEt	Me[e]	trace	93	<1/>99[g]
Ph	$PhCH_2$	SEt	Me	trace	82	<1/>99[g]
$CH_3(CH_2)_7$	Ph_2CH	OMe	Me_2	trace	86	<1/>99[h]

[a] Isolated yield. [b] Diastereomer ratios were 9/1−1.3/1. See the Supporting Information. [c] E/Z = <1/>99. [d] E/Z = 4/1. [e] E/Z = 1/15. [f] The reaction was carried out at −23 °C. [g] −78 °C. [h] 0 °C.

ketone enolates exclusively, and the corresponding aldehydes reacted sluggishly under these conditions. It is noted that not only ketone enolates but also thioester and ester enolates reacted only with an aldimine.

As for the mechanism of these reactions, selective formation of an aldimine−$Yb(OTf)_3$ complex rather than an aldehyde−$Yb(OTf)_3$ complex is postulated. ^{13}C NMR analyses were performed using a CD_3CN solution of 1 equiv of benzaldehyde, 1 equiv of *N*-benzylideneaniline, and $Yb(OTf)_3$ (x equiv).[8] A lower field shift was observed at the aldimine carbons in accordance with the amount of $Yb(OTf)_3$, while little shift at the carbonyl carbons was observed even when 1 equiv of $Yb(OTf)_3$ was added (Figure 1).[9,10] These results indicate selective formation of the aldimine−$Yb(OTf)_3$ complex in the coexistence of the aldehyde.[11]

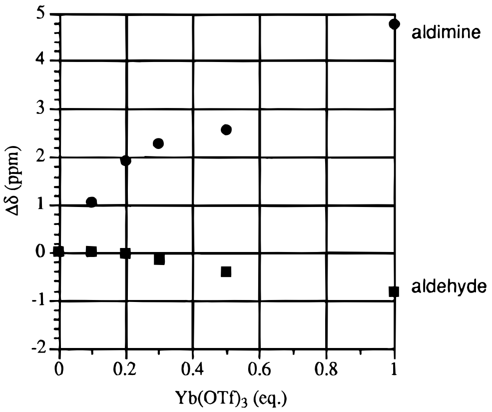


Figure 1. Correlation between the amount of $Yb(OTf)_3$ and ^{13}C NMR chemical shift (Δδ) (cf. refs 8 and 9).

In summary, preferential reactions of aldimines over aldehydes with enolates have been achieved. Use of a lanthanide salt as a Lewis acid is key in these reactions.[12,13] While this report demonstrates the effective use of Lewis acids, the basic idea of changing reactivity as shown here will be applied to many other nucleophilic reactions. Further investigations along this line are now in progress.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (4 pages).

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(8) (a) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 1, Chapter 1.10. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, 1995; Chapter 1.

(9) Benzaldehyde: ^{13}C NMR (CD_3CN) δ 193.62 (*C*=O). Benzaldehyde−$Yb(OTf)_3$ (1.0 equiv): δ 192.09.

(10) *N*-Benzylideneaniline: ^{13}C NMR (CD_3CN) δ 161.47 (*C*=N). *N*-Benzylideneaniline-$Yb(OTf)_3$ (1.0 equiv): δ 167.20.

(11) Morrill, T. C. In *Lanthanide Shift Reagents in Stereochemical Analysis*; Morrill, T. C., Ed.; VCH: New York, 1986; Chapter 1.

(12) Recently, it was reported that a Lewis acidic silicon species was an active catalyst in the Lewis acid (including $Yb(OTf)_3$)-mediated aldol reactions of ketene silyl acetals with aldehydes (the Mukaiyama aldol reaction).[13] We have several contrary experimental results concerning this proposal. The present paper is thought to be one of them, and precise discussion will be reported in due course.

(13) (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323. Cf. (b) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570. (c) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327.