SCS
Swiss Chemical
Society

HELVETICA
chimica acta

Accepted Article

Title: Enhancement of Acid-Catalyzed Esterification by the Addition of Base

Authors: Nobuhiro Kihara, Yasuhiro Matsumoto, and Shunsuke Tsukamoto

To be cited as: *Helv. Chim. Acta* 10.1002/hlca.201900154

Link to VoR: http://dx.doi.org/10.1002/hlca.201900154

www.helv.wiley.com

WILEY-VHCA

Enhancement of Acid-Catalyzed Esterification by the Addition of Base

Nobuhiro Kihara,*[,a] Yasuhiro Matsumoto,[a] Shunsuke Tsukamoto[b]

[a] Department of Chemistry, Kanagawa University, 2946 Tsuchiya, Hiratsuka 259-1293, Japan, kihara@kanagawa-u.ac.jp

[b] Department of Applied Chemistry, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai 599-8531, Japan

This paper is dedicated to Prof. Philippe Renaud for his 60th birthday

General acid-catalyzed reaction can be enhanced by the addition of base. Self-catalyzed esterification of benzoic acid and octan-1-ol was enhanced by the addition of certain base such as imidazole. The rate of the esterification was accelerated as the concentration of imidazole increased. Trans-esterification of 4-nitrophenyl acetate was promoted in chloroform by the mixture of benzoic acid and imidazole, but not by benzoic acid or imidazole alone.

Keywords: general acid-catalyzed reaction • esterification • base • cooperative effect • imidazole

Introduction

In the acid-catalyzed reaction, the stronger acid generally promotes the reaction more efficiently. The addition of base to the acid-catalyzed system simply reduces the acidity of the catalyst to decrease the catalytic activity. Recently, cooperative catalysts that have both acidic and basic points have been developed,[1-20] where the acidic point activates the electrophilic moiety in the substrate and the basic point simultaneously activates the nucleophilic moiety. In such systems, it has been documented that the acidic and basic points should be spatially separated to avoid inactivation of each active site. In the case of frustrated Lewis pair (FLP), a simple mixture of Lewis acid and base acts as the effective cooperative catalyst because salt formation is suppressed by steric hindrance.[21] A salt of certain amine with a strong acid can be a mild and selective acid-catalyst, where the ammonium salt acts as the acid with the cooperation of the counter anion.[22,23] However, the enhancement of acid-catalyzed reaction by the addition of a simple base has not been reported.

The condensation of carboxylic acid with alcohol to form ester is a typical general acid-catalyzed reaction. Although the reaction is generally carried out with the addition of strong acid as the catalyst, the reaction can be conducted by the self-catalyzed manner where carboxylic acid itself acts as the acid-catalyst. We found that the addition of some specific bases to the self-catalyzed esterification system enhances the rate of esterification.

Results and Discussion

The self-catalyzed condensation of benzoic acid and the equimolar amount of octan-1-ol was carried out with removal of water by the azeotropic distillation in the absence or presence (50 mol%) of base. To demonstrate the effect of base, the reaction was carried out for 12 h in xylene, and the yields of ester are summarized in Table 1. Surprisingly, most of bases did not disturb the esterification, and among bases examined, some *N*-heteroaromatics rather enhanced the reaction. The results were reproducible. Especially, imidazole derivatives are effective co-catalysts. HOBt was also good enhancer, although the reaction system became complex. (Table 1)

Table 1. The self-catalyzed esterification in the presence of base.

$$\mathrm{PhCOOH} + \mathrm{C_8H_{17}OH} \xrightarrow[\text{xylene, reflux, 12 h}]{\text{base (50 mol\%)}} \mathrm{PhCOOC_8H_{17}} + \mathrm{H_2O}$$

Base	**Yield[a]/%**	**p*K*a[b]**
none	18	–
tributylamine	19	10.68[c]
quinoline	18	4.97
4-(dimethylamino)pyridine	22	9.68[d]
imidazole	34	7.04
N-methylimidazole	28	7.69
benzothiazole	19	–
benzoxazole	9	–
benzotriazole	19	–
1-hydroxybenzotriazole	26[e]	–
tributylphosphine	21	–

[a] GC yield. The range of error was less than 3% (±1% for 33% yield). [b] reference 24. [c] p*K*a of triethylamine. [d] in methanol. [e] some byproducts were observed.

Figure 1 shows the relationship between the yield of ester and pKa of the base used. The base with pKa of around 7 exhibited the best effect.

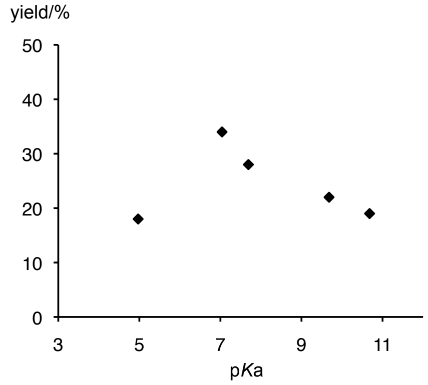


Figure 1. The relationship between p*K*a of base and the yield of ester.

To understand the role of base in the self-catalyzed esterification reaction, the self-catalyzed esterification was carried out with different concentrations of imidazole, the most effective base. In the self-catalyzed esterification, alcohol attacks to carboxylic acid that is activated by another molecule of carboxylic acid (Scheme 1a). Therefore, self-catalyzed esterification follows third order kinetics as shown in equation (1).[25]

$v = k_1\cdot[\text{carboxylic acid}]^2\cdot[\text{alcohol}]$ (1)

The reaction was carried out under the condition of [carboxylic acid]$_0$ = [alcohol]$_0$, therefore, [carboxylic acid] = [alcohol] to simplify the kinetic equation as shown in equation (2).

$v = k_1\cdot[\text{alcohol}]^3$ (2)

The yield of ester (octyl benzoate) and the conversion of alcohol (octan-1-ol) were monitored by GC. Since the esterification reaction was carried out with removing water by Dean-Stark apparatus, the reverse reaction (hydrolysis) was negligible. Therefore, the rate constants of the esterification was simply evaluated by estimating the third-order kinetics, and they were plotted against the concentration of imidazole used as shown in Figure 2.

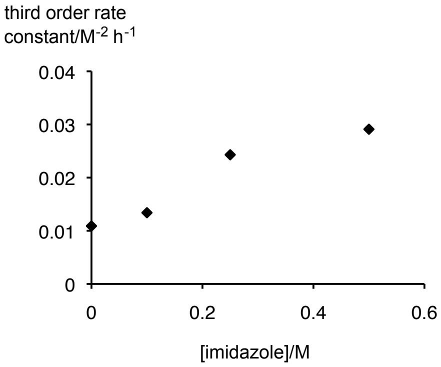


Figure 2. The effect of the concentration of imidazole on the rate constant of the esterification.

Since the rate constant increased straightly as the concentration of imidazole increased, k_1 in the equation (1) can be replaced by k_1 + $k_2\cdot$[imidazole], therefore,

$v = (k_1 + k_2\cdot[\text{imidazole}])\cdot[\text{carboxylic acid}]^2\cdot[\text{alcohol}]$ (3)

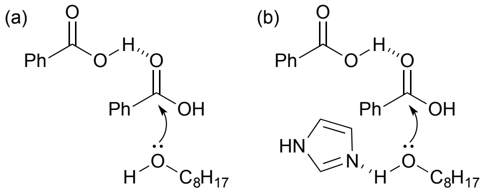
, thus,

$v = k_1\cdot[\text{carboxylic acid}]^2\cdot[\text{alcohol}] + k_2\cdot[\text{imidazole}]\cdot[\text{carboxylic acid}]^2\cdot[\text{alcohol}]$ (4)

This observation indicates that imidazole participated the rate-determining step of self-catalyzed esterification, and that imidazole-co-catalyzed pathway occurred *in addition to* the general self-catalyzed esterification pathway to increase the rate of esterification.

The effect of imidazole in the self-catalyzed esterification reaction can be rationalized by the dual activation mechanism: While benzoic acid electrophilically activates another molecule of benzoic acid by the hydrogen bonding, imidazole activates octan-1-ol to enhance its nucleophilicity (Scheme 1b). This postulate is consistent with the equation (4). In the imidazole-co-catalyzed pathway, the rate of esterification was second order to [carboxylic acid] and first order to [imidazole].

Scheme 1. The rate-determining steps of general (a) and dual activation (b) pathway in self-catalyzed esterification.



The effect of base depends on its pKa, and the optimum yield was observed for pKa 4 (imidazole). Therefore, it is assumed that the base has two opposite roles, the deactivation via the formation of salt with acid and the assistance via the dual activation pathway. Since the assistant effect is stronger than the deactivation effect in the case of imidazole, the rate of esterification simply increased as the concentration of imidazole increased via the formation of hydrogen-bonding complex with alcohol. Since the strong base such as tributylamine and 4-(dimethylamino)pyridine forms strong acid-base complex with benzoic acid, the effective concentration of these bases was too low to activate alcohol. The weak base such as quinoline does not neutralize benzoic acid although it can hardly activate the alcohol.

This acid-base mixture system was applied to other general acid-catalyzed reaction. Thus, trans-esterification of acetate **1** with butan-1-ol was investigated. The results are summarized in Table 2. No trans-esterification was observed without catalyst. When the trans-esterification of benzyl ester **1a** was carried out in reflux butanol, benzoic acid was the better catalyst than imidazole, and the mixture of benzoic acid and imidazole showed the higher activity than benzoic acid alone. The sensitivity to the composition of the catalyst dramatically increased when the trans-esterification of 4-nitrophenyl ester **1b** was carried out in reflux chloroform. Although benzoic acid or imidazole alone did not promote the trans-esterification, the mixture of benzoic acid and imidazole effectively catalyzed the trans-esterification.

Table 2. Trans-esterification catalyzed by the mixture of benzoic acid and imidazole.

$$\underset{\mathbf{1}}{\text{AcOR}} + \text{C}_4\text{H}_9\text{OH} \xrightarrow{\text{catalyst}} \underset{\mathbf{2}}{\text{AcOC}_4\text{H}_9} + \underset{\mathbf{3}}{\text{ROH}}$$

a: R = benzyl
b: R = 4-nitrophenyl

Catalyst[a]	**Yield of 3**[b]**/%**	
	1a[c]	**1b**[d]
none	< 1	0
PhCOOH	15	0
Imidazole	6	0
PhCOOH + imidazole	16	49

[a] 10 mol % each was used. [b] GC yield. The range of error was less than 3% (±1% for 33% yield). [c] reflux with 10 equivalent of BuOH for 24 h. [d] reflux in chloroform with 10 equivalent of BuOH for 24 h.

Conclusions

This work demonstrates that the dual activation mechanism works even in the homogeneous mixture of acid and base. Thus, the stronger acid is not always the more effective catalyst. It should be pointed out that the carboxylic acid and imidazole moieties play important role in the enzyme as the acidic and basic moieties, respectively. Although it has been believed that both functional groups were spatially separated by the protein backbone to work separately, this work demonstrates that spatial separation is not essential for the cooperative work.

Experimental Section

Chemicals and Instruments

All chemicals and solvents were reagent grade, and were used without further purification. Gas chromatography (GC) was carried out using a Shimadzu GC-8A with SE-30 column. Decane, hexadecane, or octadecane was used as an internal standard to determine the conversion and the yield.

Self-catalyzed esterification (general method)

A solution of decane, benzoic acid (8 mmol), octan-1-ol (8 mmol), and base (4 mmol) in xylene (8 mL) was refluxed for 12 h with removing water by Dean-Stark apparatus. The yield of octyl benzoate and the conversion of octan-1-ol were determined by GC analysis using decane as an internal standard.

Kinetic analysis

A solution of decane, benzoic acid (8 mmol), octan-1-ol (8 mmol), and imidazole in xylene (8 mL) was refluxed with removing water by Dean-Stark apparatus. The conversion of octan-1-ol was monitored by GC analysis using decane as an internal standard.

Equation (2) was used for the kinetic analysis. The integral of equation (2) gives equation (5).

$$\frac{1}{[\text{alcohol}]^2} - \frac{1}{[\text{alcohol}]_0^2} = 2k_1 t \qquad (5)$$

, where initial concentration of octan-1-ol $[\text{alcohol}]_0 = 1.00 \text{ mol L}^{-1}$. The relative concentration of octan-1-ol was used as [alcohol]. $[\text{Alcohol}]^{-2}$ was plotted against the time (t), and k_1 was determined from the slope ($2k_1$) of the plot.

Trans-esterification of benzyl acetate with butan-1-ol (general method)

A mixture of octadecane, benzyl acetate (2 mmol), butan-1-ol (20 mmol), and a mentioned additive was refluxed for 24 h. The yield of benzyl alcohol was determined by GC analysis using octadecane as an internal standard.

Trans-esterification of 4-nitrophenyl acetate with butan-1-ol (general method)

A solution of hexadecane, 4-nitrophenyl acetate (2 mmol), and butan-1-ol (20 mmol) and a mentioned additive in chloroform (5 mL) was refluxed for 24 h. The yield of 4-nitrophenol was determined by GC analysis using hexadecane as an internal standard.

Author Contribution Statement

YM and ST carried out the experimental work supervised by NK, who summarized all works.

References

[1] T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, ‘A New Multifunctional Heterobimetallic Asymmetric Catalyst for Michael Additions and Tandem Michael-Aldol Reactions’, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104–106.

[2] T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, ‘Self-Assembly of Heterobimetallic Complexes and Reactive Nucleophiles: A General Strategy for the Activation of Asymmetric Reactions Promoted by Heterobimetallic Catalysts‘, *Chem. Eur. J.* **1996**, *2*, 1368–1372.

[3] M. Shibasaki, N. Yoshikawa, 'Lanthanide Complexes in Multifunctional Asymmetric Catalysis‘, *Chem. Rev.* **2002**, *102*, 2187-2210.

[4] H. Yamamoto, K. Futatsugi,‘“Designer Acids”: Combined Acid Catalysis for Asymmetric Synthesis‘, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1924-1942.

[5] A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, 'Highly Efficient Dynamic Kinetic Resolution of Azlactones by Urea-Based Bifunctional Organocatalysts‘, *Angew. Chem. Int. Ed.* **2005**, *44*, 807–811.

[6] J. Wang, H. Li, X. Yu, L. Zu, W. Wang, 'Chiral Binaphthyl-Derived Amine-Thiourea Organocatalyst-Promoted Asymmetric Morita-Baylis-Hillman Reaction‘, *Org. Lett.* **2005**, *7*, 4293–4296.

[7] R. K. Zeidan, S.-J. Hwang, M. E. Davis, 'Multifunctional Heterogeneous Catalysts: SBA-15-Containing Primary Amines and Sulfonic Acids‘ *Angew. Chem. Int. Ed.* **2006**, *45*, 6332–6335.

[8] A. L. Kenward, W. E. Piers, 'Heterolytic H_2 Activation by Nonmetals', *Angew. Chem. Int. Ed.* **2008**, *47*, 38.

[9] T. Kull, R. Peters, 'Contact Ion Pair Directed Lewis Acid Catalysis: Asymmetric Synthesis of trans-Configured β-Lactones', *Angew. Chem. Int. Ed.* **2008**, *47*, 5461–5464.

[10] K. Ishihara, Y. kosugi, S. Umemura, A. Sakakura, 'Kinetic Resolution of Racemic Carboxylic Acids by an L-Histidine-Derived Sulfonamide-Induced Enantioselective Esterification Reaction', *Org. Lett.* **2008**, *10*, 3191–3194.

[11] T. Mandal, C.-G. Zhao, 'Modularly Designed Organocatalytic Assemblies for Direct Nitro-Michael Addition Reactions', *Angew. Chem. Int. Ed.* **2008**, *47*, 7714-7717.

[12] Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi, K. Nagasawa, 'Entropy-Controlled Catalytic Asymmetric 1,4-Type Friedel-Crafts Reaction of Phenols Using Conformationally Flexible Guanidine/Bisthiourea Organocatalyst', *Angew. Chem. Int. Ed.* **2010**, *49*, 7299-7303.

[13] Y. Huang, S. Xu, V. S.-Y. Lin, 'Bifunctionalized Mesoporous Materials with Site-Separated Brønsted Acids and Bases: Catalyst for a Two-Step Reaction Sequence', *Angew. Chem. Int. Ed.* **2011**, *50*, 661-664.

[14] Y.-C. Xiao, C. Wang, Y. Yao, J. Sun, Y.-C. Chen, 'Direct Asymmetric Hydrosilylation of Indoles: Combined Lewis Base and Brønsted Acid Activation', *Angew. Chem. Int. Ed.* **2011**, *50*, 10661-10664.

[15] S. Kojima, N. Banden, Y. Yamamoto, 'A Highly Efficient Cooperative Effect in an Acylation Catalyst Bearing Weak Lewis Acid Sites', *Chem. Lett.* **2014**, *43*, 1266-1268.

[16] L. Yin, H. Takeda, S. Lin, N. Kumagai, M. Shibasaki, 'Direct Catalytic Asymmetric Vinylogous Conjugate Addition of Unsaturated Butyrolactones to α,β-Unsaturated Thioamides', *Angew. Chem. Int. Ed.* **2014**, *53*, 5327-5331.

[17] K. Ishihara, Y. Ogura, 'Enantioselective Cyano-Alkoxycarbonylation of α-Oxoesters Promoted by Bronsted Acid-Lewis Base Cooperative Catalysts', *Org. Lett.* **2015**, *17*, 6070-6073.

[18] M. Hatano, K. Yamakawa, T. Kawai, T. Horibe, K. Ishihara, 'Enantioselective Cyanosilylation of Ketones with Lithium(I) Dicyanotrimethylsilicate(IV) Catalyzed by a Chiral Lithium(I) Phosphoryl Phenoxide', *Angew. Chem. Int. Ed.* **2016**, *55*, 4021-4025.

[19] B. Sun, R. Pluta, N. Kumagai, M. Shibasaki, 'Direct Catalytic Asymmetric Mannich-Type Reaction en Route to α-Hydroxy-β-amino Acid Derivatives', *Org. Lett.* **2018**, *20*, 526-529.

[20] T. Takeuchi, N. Kumagai, M. Shibasaki, 'Direct Catalytic Asymmetric Aldol Reaction of α-Vinyl Acetamide', *J. Org. Chem.* **2018**, *83*, 5851-5858.

[21] J. Z. Chan, W. Yao, B. T. Hastings, C. K. Lok, M. Wasa, 'Direct Mannich-Type Reactions Promoted by Frustrated Lewis Acid/Bronsted Base Catalysts', *Angew. Chem. Int. Ed.* **2016**, *55*, 13877-13881.

[22] A. Sakakura, 'Design of High-Performance Catalysts Based on Acid-Base Combined Salts and Development of Highly Selective Reactions', *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 942-952.

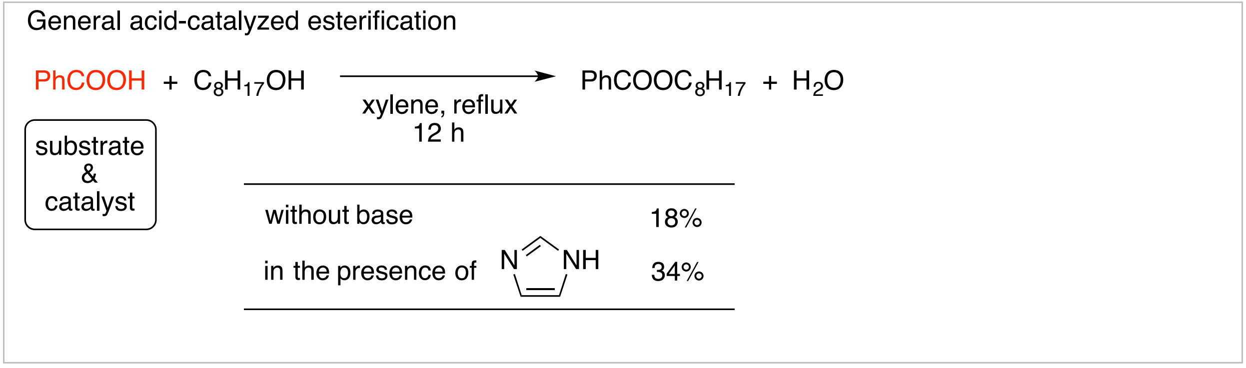
[23] K. Ishihara, 'Design of High Performance Catalysts Based on Acid-Base Combination Chemistry', *J. Synth. Org. Chem. Jpn.* **2017**, *75*, 98-110.

[24] L. G. Sillén, A. E. Martell, in 'Stability Constants of Metal-Ion Complexes', Special Publication No. 17, The Chemical Society, London, 1964; Special Publication No. 25, Supplement No. 1, 1971.

[25] G. Ordian, in 'Principles of Polymerization', 3rd ed., Wiley, Singapore, 1991, p. 47.

10.1002/hlca.201900154

Entry for the Table of Contents



Twitter

A mixture of benzoic acid (general acid) and imidazole (general base) is better “acid catalyst” than benzoic acid alone in acid-catalyzed reactions.