

Development of Efficient and Practical Ti-Claisen Condensation and the Related Aldol Reaction

Ti(Zr)-Claisen condensations, Ti-direct aldol additions, related catalytic Claisen condensation have been applied for efficient and practical syntheses of useful fine chemicals and biologically active natural products. These protocols are new avenues for the synthesis of a variety of carbonyl compounds.

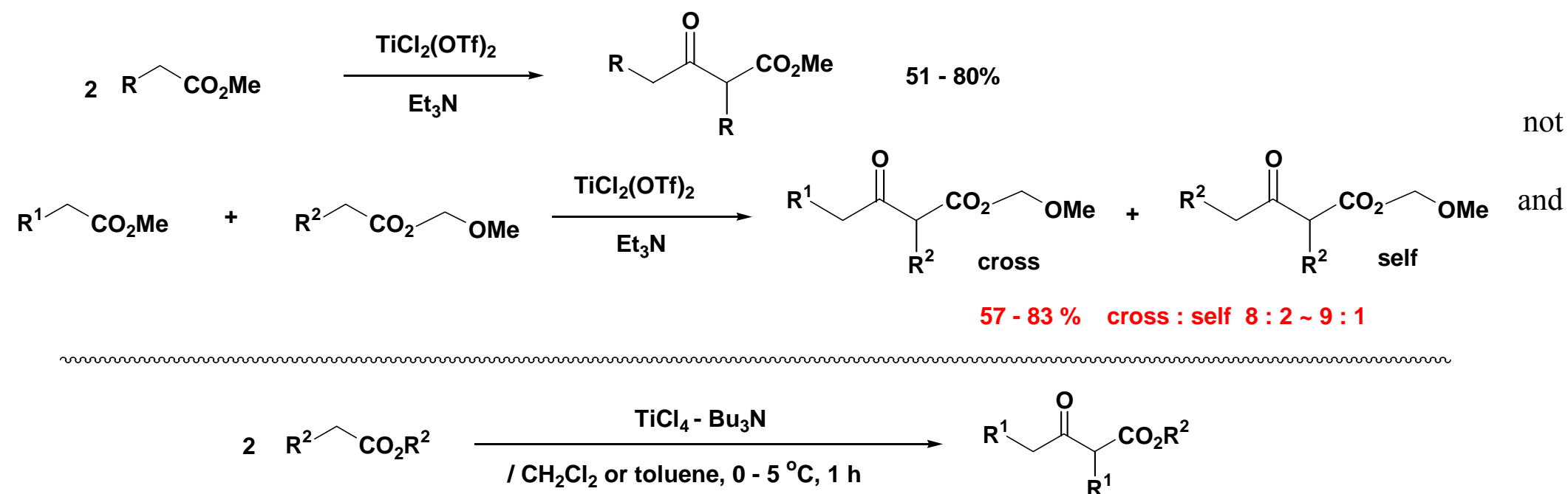
1. Prologue

In 1989, the first Lewis acid-mediated Claisen condensation (Ti-Claisen condensation) utilizing $\text{TiCl}_2(\text{OTf})_2 - \text{Et}_3\text{N}$ was disclosed. This method included only self- but also crossed Claisen condensations, the latter of which, however, resulted in moderate selectivity. After long period, in 1997, we exploited a novel highly practical method utilizing $\text{TiCl}_4 - \text{Bu}_3\text{N}$, which exhibited sufficient reactivity and avoided readily unavailable $\text{TiCl}_2(\text{OTf})_2$. We restarted a full-dressed investigation of the present useful, convenient, and cost-effective **Ti-Claisen condensation and related aldol type reactions**.

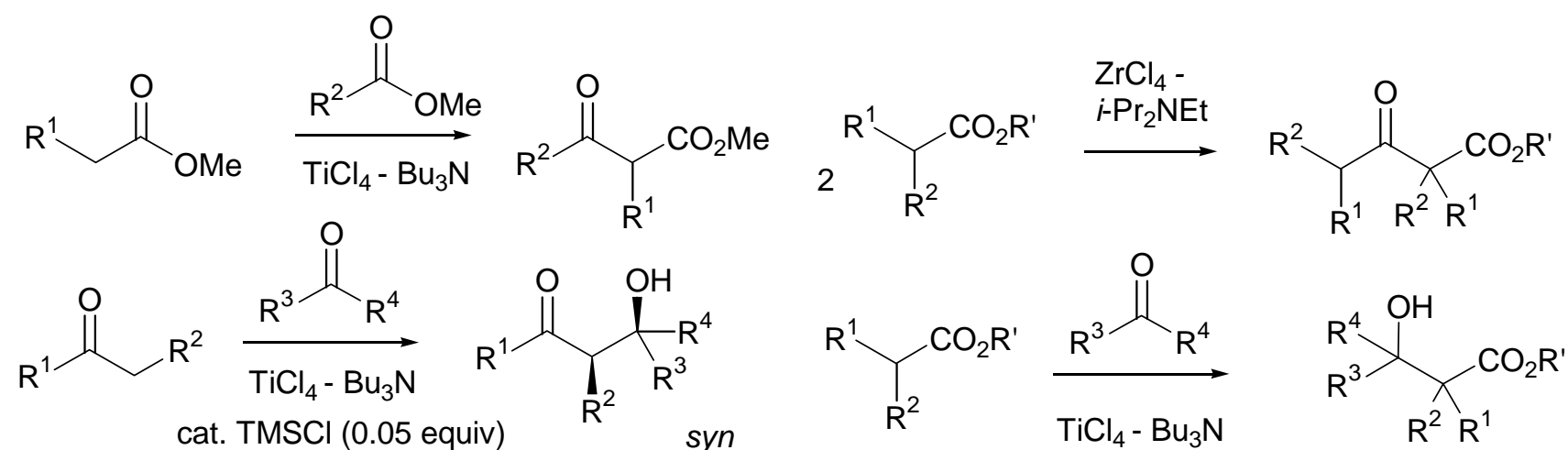
Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917-1924.

Yosida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727-8730.

Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Ibid.* **1999**, *40*, 4227-4230.



2. Fundamental Profile of Ti-Claisen Condensations and Related Ti-Aldol (Type) Reactions



The C-C bond formations utilizing carbonyl nucleophiles and electrophiles have provided a number of useful methodologies in organic syntheses due to their broad utility, representatively, the aldol addition, the Mannich type reaction, and the Claisen condensation. These methods are classified into two categories: (i) carbonyl substrates are converted to their metal enolates by treatment with strong bases (e.g. LDA, MHDMS, etc), followed by the addition of carbonyl acceptors, and (ii) carbonyl substrates are converted to enol silyl ethers or ketene silyl acetals, which react with carbonyl acceptors promoted by Lewis acids or other catalysts.

Ti-mediated aldol additions, originally called Mukaiyama – Narasaka aldol reaction, and Ti-direct aldol addition, originally exploited by Evans' group, are regarded as an important milestone for Lewis acid-mediated addition reactions.

The present protocol of Ti-mediated reactions (Ti-Claisen condensation and related Ti-direct aldol type additions) demonstrates that the reactivity of C-C bond formation rivals or surpasses numerous such reactions so far reported. The salient features are as follows.

High reaction velocities, powerful reactivities, high yields, high stereoselectivities.

Direct use of carbonyl compounds has advantages due to higher atom-economical

Avoidance of preparation of enol silyl ethers and ketene silyl acetals; atom economical and cost-effective.

Toleration against basic labile functionalities (halogens, tosyloxy, ketone, hydroxyl, etc.).

Use of readily available and low toxic metal reagents (e.g. TiCl_4 , ZrCl_4), practical amines (Et_3N and Bu_3N) and solvents (toluene and CH_2Cl_2), under practical reaction conditions ($-40 - +50^\circ\text{C}$).

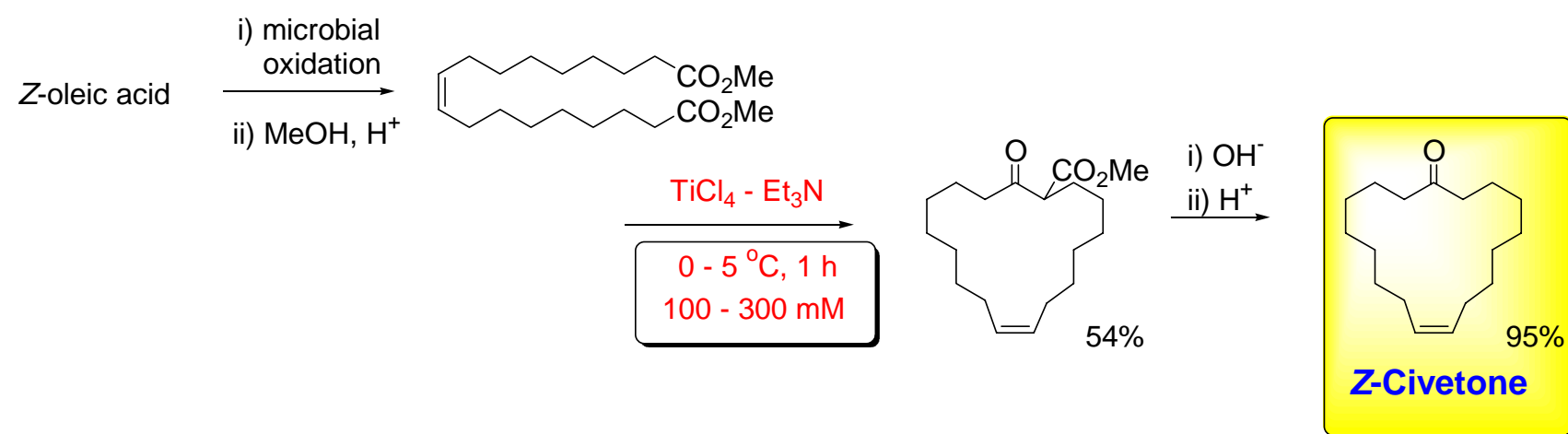
Development of highly selective Ti-crossed Claisen condensation between simple esters and acid chlorides.

Extension to inaccessible Lewis acid-mediated direct Mannich reaction and asymmetric Ti-Claisen condensation.

ZrCl_4 -mediated powerful Claisen condensation between α,α -disubstituted esters to obtain inaccessible α,α -dialkylated β -keto esters.

Mukaiyama, T. *Organic Reactions*; Wiley: New York, 1982; Vol. 28, p. 203.

3. Practical Synthesis of (Z)-Civetone Utilizing Ti-Dieckmann Condensation



An efficient, practical, and stereocontrolled synthesis of (Z)-civetone, a representative musk perfume, has been performed utilizing a Ti-Dieckmann (intramolecular Ti-Claisen) condensation of dimethyl (Z)-9-octadecenedioate as the key step. This cyclization reaction has some advantages compared with the traditional basic Dieckmann condensation: higher concentration, lower reaction temperature, shorter reaction time, use of environmentally benign (low toxicity and safe) reagents (TiCl₄ and Et₃N or Bu₃N).

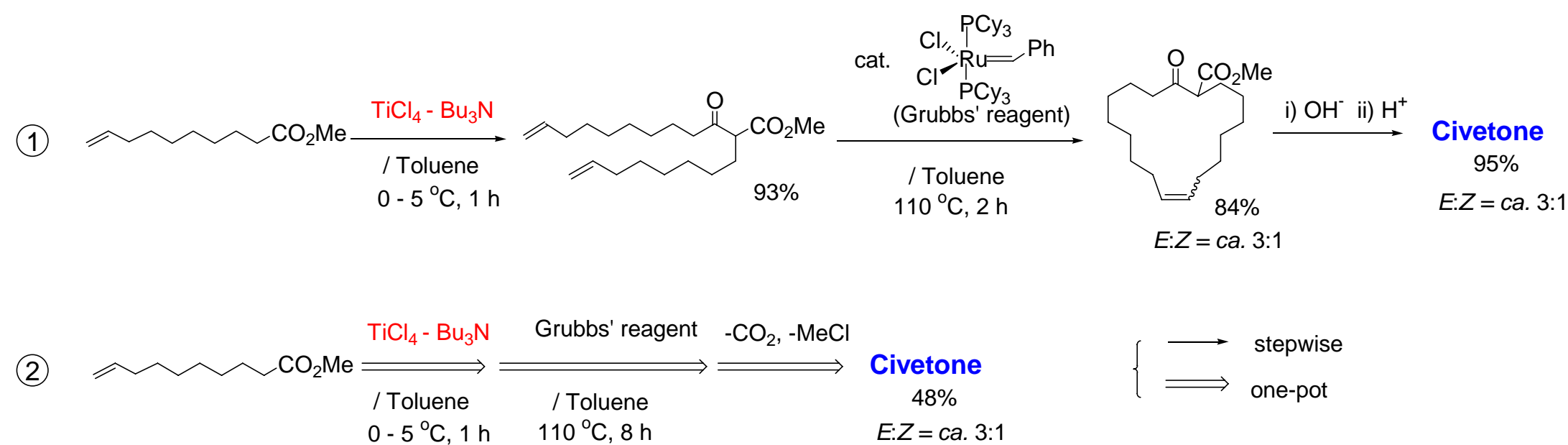
Ti-Dieckmann condensation : 0-5 °C, 100-300 mM, 1 h.

McMurry coupling (TiCl₃ - Zn/Cu) : 80 °C, 5 mM, 50 h .

This protocol is a promising candidate for the industrial production of (Z)-civetone and provides a novel methodology for large carbon ring construction.

Y. Tanabe, A. Makita, S. Funakoshi, R. Hamasaki, T. Kawakusu, *Adv. Synth. Catal.*, **344**, 507-510 (2002).

4. A Short Synthesis of Civetone Utilizing Ti-Claisen Condensation and Olefin Metathesis

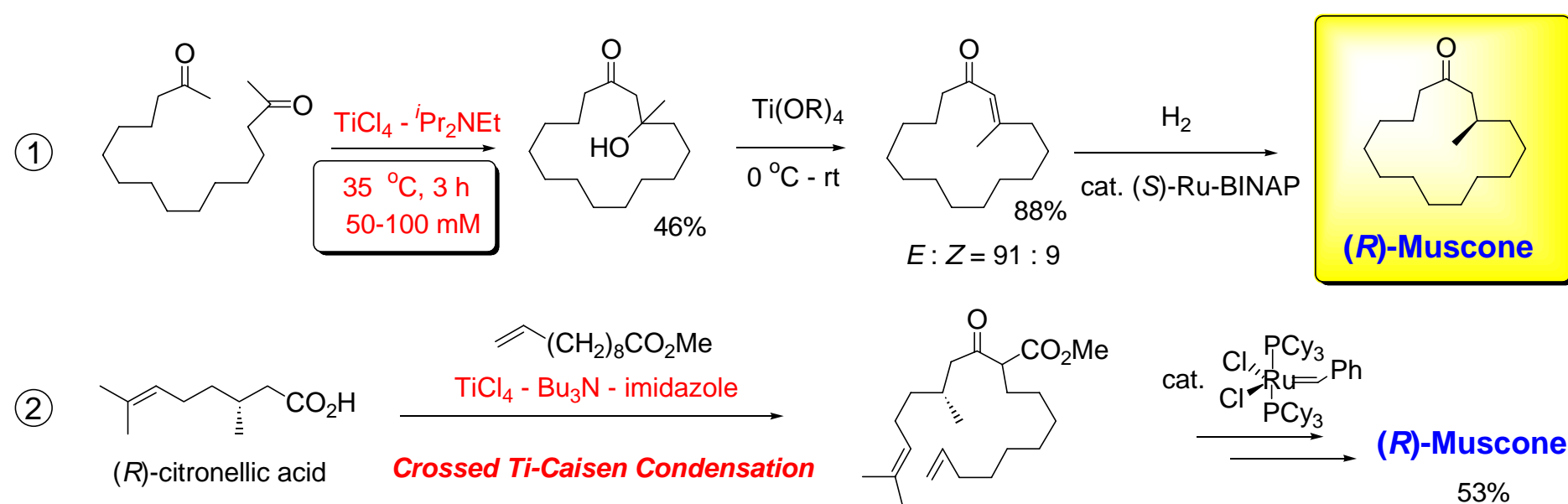


Ti-Claisen condensation of methyl 9-decenoate successfully afforded the β-keto ester in higher yield and much milder reaction conditions, compared with traditional basic Claisen condensation. Subsequent ring-closing metathesis using the Grubbs' reagent to afford the desired 17-membered β-keto ester (E/Z = ca. 3:1). Final conventional hydrolysis and decarboxylation gave the desired civetone. The overall isolated yield is 74%, which is considerably high compared with hitherto reported syntheses.

As a further notable extension, we achieved a one-pot reaction sequence: methyl 9-decenoate was straightforwardly transformed into civetone in a one-pot manner in 48% yield. This highly efficient method is regarded as simplest synthesis of civetone

R. Hamasaki, S. Funakoshi, T. Misaki, and Y. Tanabe, *Tetrahedron*, **56**, 7423-7425 (2000).

5. Practical and Short Synthesis of (R)-Muscone Utilizing Ti-Aldol Addition or Claisen Condensation



The powerful Ti-aldol addition was successfully applied to a formal synthesis of (R)-muscone. The key intramolecular Ti-aldol addition of dimethylketone produced the cyclic aldol adduct with a higher concentration (50-100 mM) than conventional cyclization reactions.

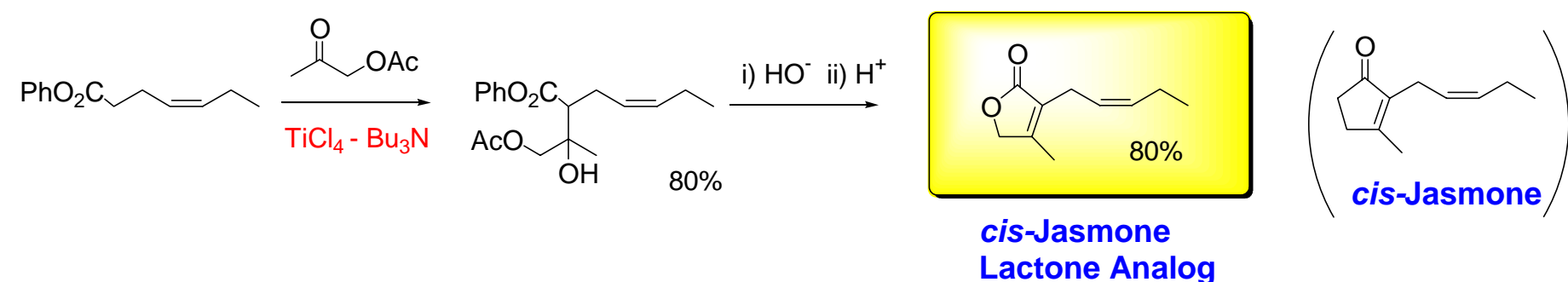
Moreover, stereoselective dehydration of the aldol adduct afforded E-rich α,β-unsaturated enone (E/Z = ca. 9:1), which was converted to (R)-muscone by the Noyori's Ru-BINAP asymmetric hydrogenation with ca. 99% enantioselectivity. The present method is regarded as one of the simplest and most practical synthesis of (R)-muscone.

Ti-crossed Claisen condensation between methyl 10-undecenoate and (R)-citronellic acid afforded β-keto ester, which was converted to the ketone by hydrolysis-decarboxylation. Second generation ring-closing metathesis of the ketone, followed by catalytic hydrogenation, afforded (R)-muscone in 53% overall yield. The present method is the shortest and the highest yield method among ever reported.

Y. Tanabe, N. Matsumoto, T. Higashi, T. Misaki, T. Itoh, M. Yamamoto, K. Mitarai, and Y. Nishii, *Tetrahedron* (Symposium), **58**, 8269-8280 (2002).

T. Misaki, R. Nagase, K. Matsumoto, Y. Tanabe, *J. Am. Chem. Soc.*, **127**, 2854-2855 (2005).

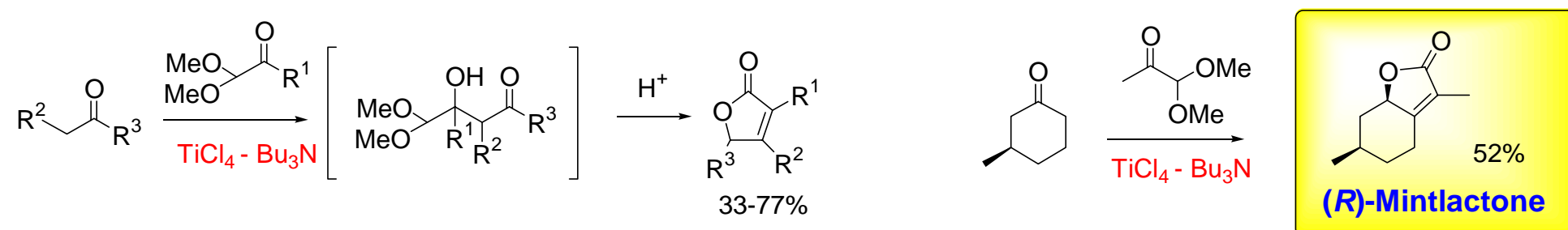
6. Efficient Synthesis of *cis*-Jasmone Lactone Analog Utilizing Ti-Aldol Addition



Although lactone analog of *cis*-jasmone, a jasmine natural perfume, was expected as a promising synthetic perfume, there is no report to synthesize it. Powerful Ti-aldol addition realized the synthesis of *cis*-jasmone lactone analog. Perfume evaluation revealed that it showed a characteristic odor.

Y. Tanabe, N. Matsumoto, S. Funakoshi, and N. Manta, *Synlett*, 1959-1961 (2001).

7. Efficient One-step Synthesis of Trialkylsubstituted 2(5*H*)-Furanones Utilizing Direct Ti-crossed Aldol Condensation

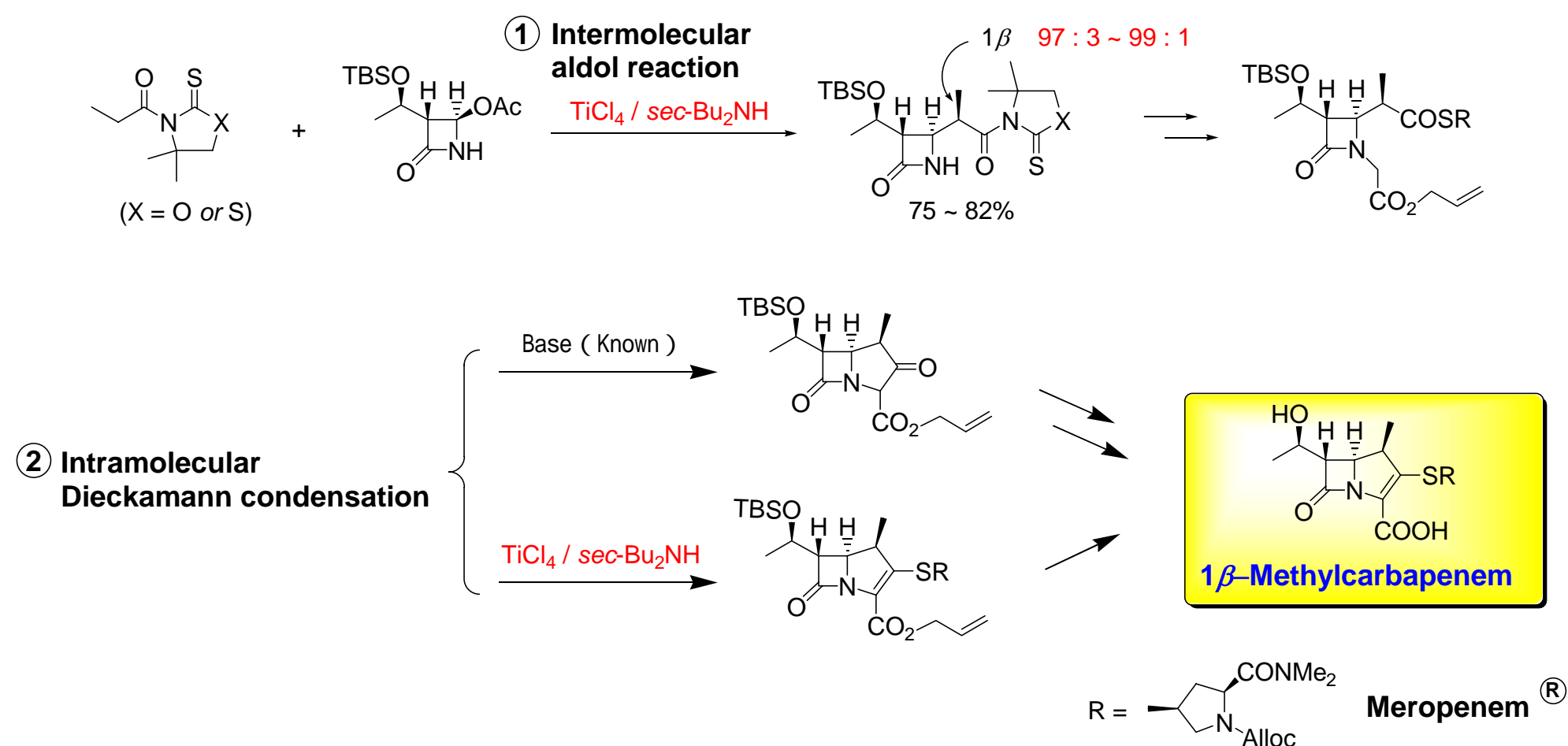


2(5*H*)-Furanones (α,β -butenolides) comprise an important heterocycle incorporated in natural products and serve as useful synthetic building blocks for lactones and furans. TiCl_4 - Bu_3N -mediated condensation of ketones with α,α -dimethoxyketones afforded trialkylsubstituted 2(5*H*)-furanones in a one-pot manner, wherein aldol addition and furanone formation occurred sequentially. Its application to straightforward synthesis of (*R*)-mintlactone and (*R*)-menthofuran, two representative natural mint perfumes, was demonstrated.

Y. Tanabe and N. Ohno, *J. Org. Chem.*, **53**, 1560-1563 (1988);

Y. Tanabe, K. Mitarai, T. Higashi, T. Misaki, Y. Nishii, *Chem. Commun.*, 2542-2543 (2002).

8. Practical Short Synthesis of 1 β -Methylcarbapenem Utilizing a New Dehydration Type Ti-Dieckmann Condensation



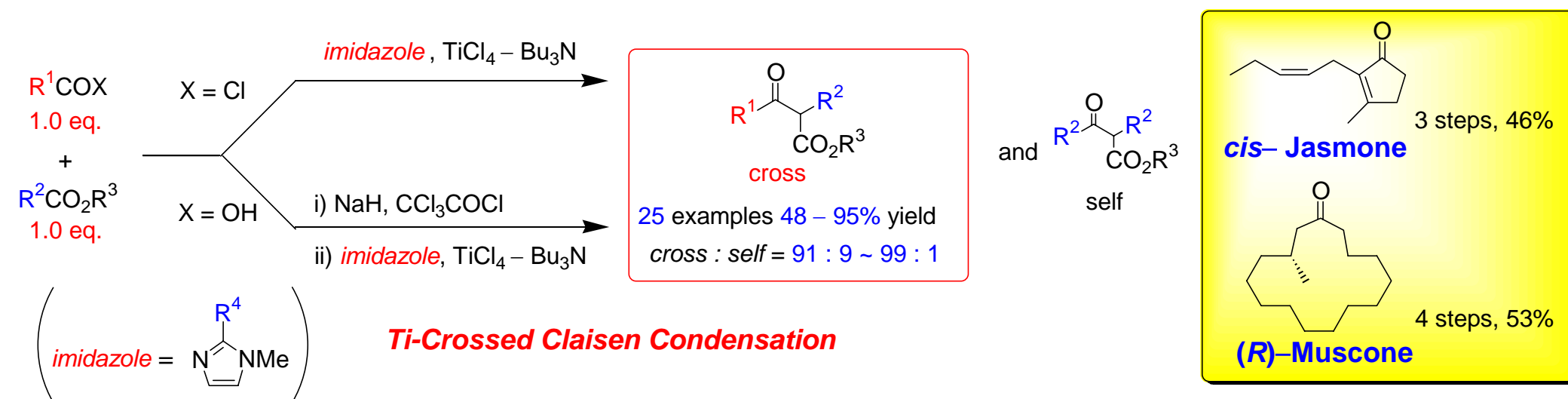
The discovery of 1 β -methylcarbapenems such as meropenem and biapenem, which have potent and broad antibacterial activity as well as enhanced metabolic and chemical stability, has prompted many synthetic organic chemists to develop efficient methods for the stereoselective synthesis of the key carbapenem skeleton.

An efficient, practical, and stereocontrolled synthesis of 1 β -methylcarbapenems has been performed utilizing a novel dehydration type of Ti-Dieckmann (intramolecular Ti-Claisen) condensation. The present reaction has the advantage of direct incorporation of the thiol moiety into the target 1 β -methylcarbapenem, compared with the traditional basic Dieckmann condensation.

Y. Tanabe, N. Manta, R. Nagase, T. Misaki, Y. Nishii, M. Sunagawa, A. Sasaki, *Adv. Synth. Catal.*, **345**, 967-970 (2003).

A. Iida, H. Okazaki, T. Misaki, M. Sunagawa, A. Sasaki, Y. Tanabe, *J. Org. Chem.*, in press.

9. Ti-Crossed Claisen Condensation between Carboxylic Esters and Acid Chlorides or Acids: Highly Selective and General Method for the Preparation of Various β -Keto Esters



The Claisen condensation is recognized as a fundamental and useful C-C bond forming synthetic reaction to obtain β -keto esters. The major problem of the Claisen condensation lies in the difficulty in controlling the direction of the reaction: the reaction of a mixture of two different esters, each of which possesses α -hydrogens, generally affords all four products.

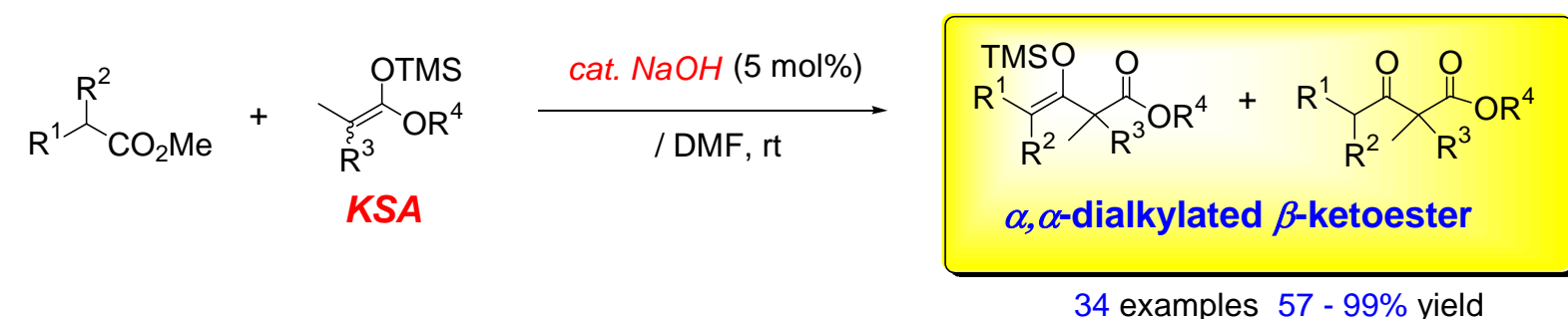
Ti-crossed-Claisen condensation between a 1 : 1 mixture of carboxylic esters and acid chlorides promoted by TiCl_4 - Bu_3N -*N*-methylimidazole proceeded successfully to give various β -keto esters in good yields with excellent selectivities (19 examples, 48 ~ 95% yield; cross / self selectivity = 96 / 4 ~ 99 / 1).

The present method was extended to the condensation between a 1 : 1 mixture of carboxylic acids and carboxylic esters (6 examples, 70 ~ 92% yield; cross / self selectivity = 91 / 9 ~ 99 / 1). To demonstrate the utility of the present two Ti-crossed-Claisen condensations, we performed a couple of efficient short-step syntheses of two natural, representative, and useful perfumes, *cis*-jasmone and (*R*)-muscone. In conclusion, the present method is a new avenue for the synthesis of a variety of β -keto esters, which will be useful achiral and chiral synthons.

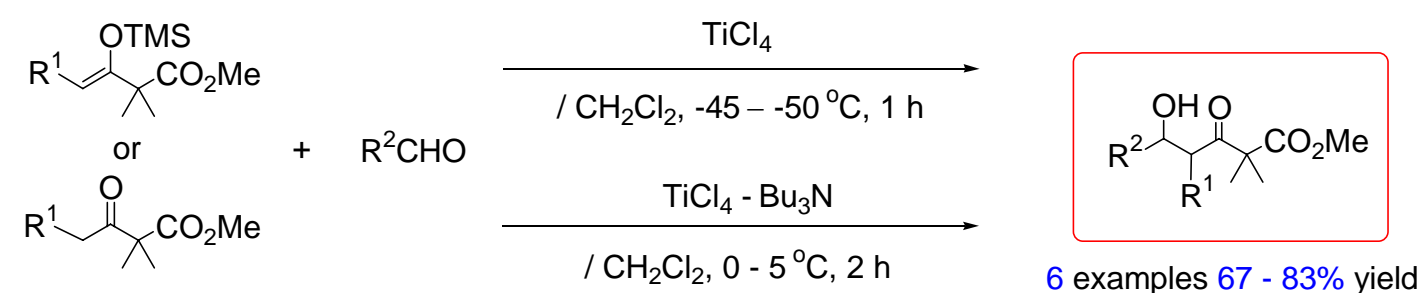
T. Misaki, R. Nagase, K. Matsumoto, Y. Tanabe, *J. Am. Chem. Soc.*, **127**, 2854-2855 (2005).

10. NaOH-catalyzed Crossed Claisen Condensation between Ketene Silyl Acetals (KSA) and Methyl Esters

The present work is a new version of our continued study on the crossed-Claisen condensation. The reaction of ketene silyl acetals with methyl esters proceeded smoothly promoted by NaOH catalyst (0.05 equiv). Claisen condensation of α,α -dialkylated esters is very difficult, because retro-Claisen condensation of α,α -dialkylated β -ketoesters usually predominates. The present mild, catalytic, practical and efficient method afforded a variety of β -ketoesters using α -mono and α,α -dialkylated KSAs.



Ti-Aldol Reactions of Crossed Claisen Adducts



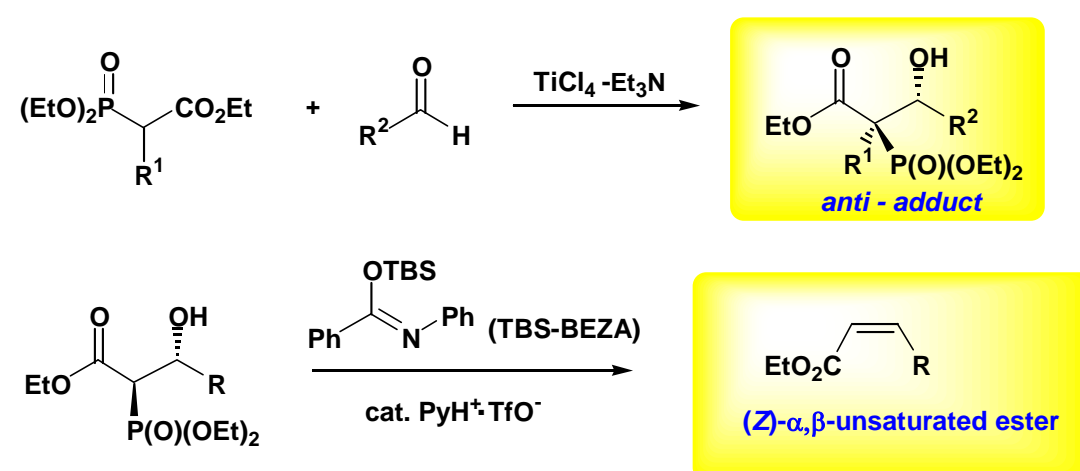
Surprisingly, the crossed-Claisen condensation using α,α -dialkylated KSAs, which looked like less reactive nucleophiles than α -monoalkylated KSAs, proceeded smoothly and the yields were good to excellent in every case examined. In addition, several functionalities, such as an acetal, an epoxide, a *tert*-butyl ester, a cyclopropane, and an indole, and a benzyloxy, tolerated the reaction conditions.

Further functionalization utilizing not only the Mukaiyama aldol reaction but also the Ti-aldol reactions demonstrates the usefulness of the present method.

Judging from the fact that the Claisen condensation of α,α -dialkylated esters is very difficult, the present method provide a new avenue for the preparation of inaccessible β -ketoesters..

A. Iida, K. Takai, T. Okabayashi, T. Misaki, Y. Tanabe, *Chem. Commun.*, 3171-3173 (2005).

11. Isolation of Intermediary *anti*-Aldol Adducts of the Horner-Wadsworth-Emmons (HWE) Reaction Utilizing Direct Ti-aldol Addition and Successive Brønsted Acid-Promoted Stereoselective Elimination leading to (*Z*)- α,β -Unsaturated Esters



The Horner-Wadsworth-Emmons (HWE) reaction is well recognized as a highly useful tool for the preparation of α,β -unsaturated esters under basic media. Although a number of methods have been explored, there remains a demand for a more efficient method. These reactions generally give (*E*)- α,β -unsaturated esters; in contrast, Still's and Ando's groups independently explored practical methods for preparing less accessible (*Z*)-isomers, which have been widely used in organic syntheses. Nagao and Sano's group reported the finding that $\text{Sn}(\text{OTf})_2$ – *N*-ethylpiperidine reagent promoted the HWE-type reaction, which is the first example of a Lewis acid-mediated method. These HWE reactions proceed through the two steps; (i) the aldol addition and (ii) the stereoselective elimination of phosphono moiety *via* oxaphospoxetane intermediate.

We disclose here the first reliable method for isolation of intermediary *anti*-selective aldol adducts of the HWE reaction utilizing TiCl_4 – Et_3N reagent, and subsequent TBS-BEZA / $\text{PyH}^+\cdot\text{OTf}$ (*Chem. Commun.* **2001**, 2478)-promoted stereoselective elimination to give (*Z*)- α,β -unsaturated esters. As might be expected, these adducts were too unstable for column chromatographic purification (SiO_2 , neutral alumina, and Florisil[®]). To overcome this problem, we adopted a neutral silyl derivatization method using *N,O*-bis(trimethylsilyl)acetamide (BSA) – pyridinium triflate ($\text{PyH}^+\cdot\text{OTf}$), and the corresponding TMS ethers were easily isolated. These products were stable enough for purification using conventional SiO_2 -column chromatography. To the best of our knowledge, this is the first concrete example of the isolation of intermediary aldol adducts of the HWE reaction.

M. Katayama, R. Nagase, K. Mitarai, T. Misaki, Y. Tanabe, *Synlett*, 129-131 (2006).

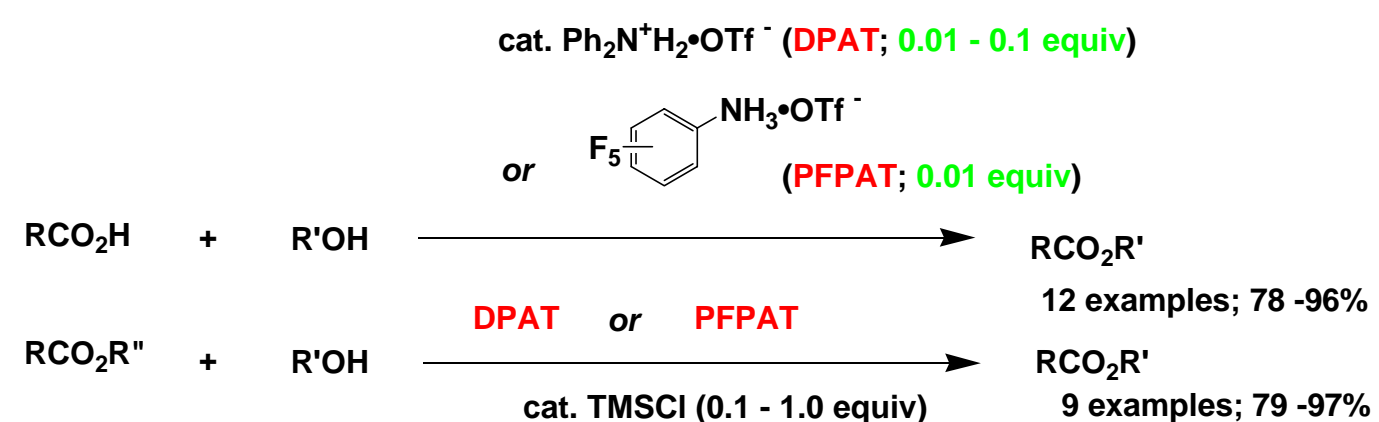
Rationalization of Greenchemical Versatile Reactions (Esterification • Amide formation • Sulfonylation • Silylation)

Esterification, sulfonylation, amide formation, and silylations are well recognized as frequently used reactions for organic syntheses. Recent syntheses of fine chemicals and complex natural products, however, require the further rationalization of these reactions, which is an endless development of the software. We describe herein our recent studies in this area.

Review: Y. Tanabe, T. Misaki, A. Iida, Y. Nishii, *J. Synth. Org. Chem. Jpn.*, **62**, 1248-1259 (2004).

1. Esterification and Transesterification Using Ammonium Triflate Catalyst (DPAT and PFPAT)

We introduced two efficient ammonium triflate catalysts (DPAT and PFPAT) for the esterification between 1 : 1 mixture of carboxylic acids and alcohols. The present method is a new avenue for the catalytic esterification for fine and bulk chemicals syntheses. This was introduced in the Highlight of *Angew. Chem. Int. Ed.* [J. Otera, **40**, 2044 (2001)] and released by the Nippon Keizai news paper [2001/9/21].



Carboxylic acid s (or Esters) : Alcohol s = 1 (1) : 1 (1.5).

DPAT and PFPAT catalysts are moisture insensitive solids and easy to handle.

Use of toluene or hydrocarbon type solvent.

Dean-Stark apparatus is not necessary.

Transesterification was also performed using TMSCl co-catalyst.

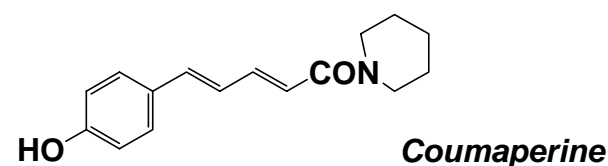
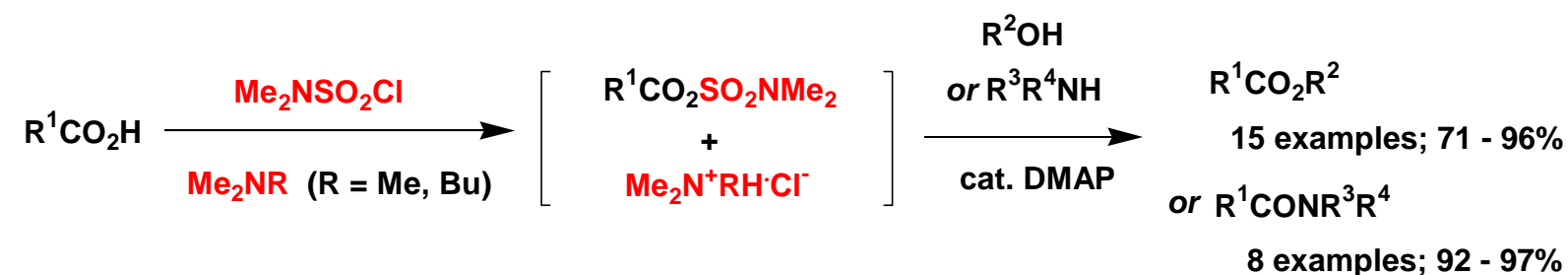
PFPAT showed higher reactivity and water-resistant property. Separation of PFPAT is very easy due to the low boiling point of the 2,3,4,5,6-F₅-PhNH₂ part.

K. Wakasugi, T. Misaki, K. Yamada, Y. Tanabe, *Tetrahedron Lett.*, **41**, 5249-5252 (2000).

Y. Tanabe, T. Misaki, A. Iida, Y. Nishii, *J. Synth. Org. Chem. Jpn.*, **62**, 1248-1259 (2004).

2. Esterification and Amide Formation Using a Novel Condensation Agent, *N,N*-Dimethylsulfonyl Chloride (Me₂NSO₂Cl) / Me₂NR

From the standpoint of elaborated complex natural product synthesis and process chemistry, mild and effective esterification or amide formation between 1 : 1 mixture of carboxylic acids and alcohols or amines is one of the most frequently used unit reactions due to its broad utility. Although several efficient methods have been exploited, there still remains a strong need for simpler, more convenient, inexpensive, and atom-economical agents. We developed a novel efficient condensation agent for esterification and amide formation, Me₂NSO₂Cl together with sterically unhindered *N,N*-dimethylamines (Me₂NR: R = Me, Bu).



Carboxylic acids : Alcohols (or Amines) = 1 : 1 (1).

High reactivity and yield under mild conditions.

Me₂NSO₂Cl and Me₂NR condensation reagents are relatively inexpensive, structurally simple, and atom-economical.

Characteristic chemoselectivity : Me₂NSO₂Cl forms mix anhydride selectively with carboxylic acid, that is, experimental procedure is simple and convenient.

No α,β -isomerization using the substrate, α,β -unsaturated carboxylic acids.

Successful application to the synthesis of a naturally occurring chemopreventive dieneamide compound, Coumapherine, which was isolated from *Piper nigrum* L.

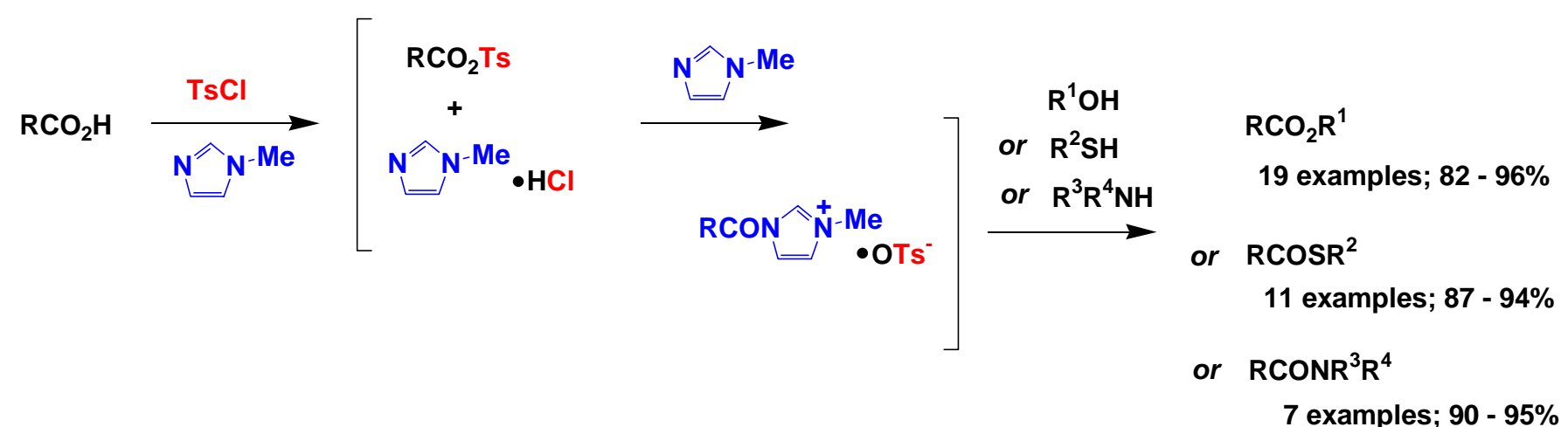
K. Wakasugi, A. Nakamura, and Y. Tanabe, *Tetrahedron Lett.*, **42**, 7427-7430 (2001).

K. Wakasugi, A. Nakamura, A. Iida, Y. Nishii, N. Nakatani, S. Fukushima, Y. Tanabe, *Tetrahedron*, **59**, 5337-5345 (2003).

3. Efficient Esterification, Thioesterification, and Amide formation utilizing *p*-Toluenesulfonyl Chloride (TsCl) / *N*-Methylimidazole

From the standpoint of elaborate complex natural product synthesis and process chemistry, direct esterification, thioesterification, and amide formation between 1 : 1 mixture of carboxylic acids and alcohols, thiols, and amines, respectively, are well recognized as important unit reactions for a wide range of organic syntheses. In view of process chemistry, there remains a strong need for simpler, more reactive, convenient, and inexpensive agents. The mixed anhydride method, composed of different acids, is a rational process: Use of sulfonic acid as a counter acid moiety is a promising candidate for an efficient esterification due to its simplicity, ready availability and low cost of the reagents.

We introduce an easily accessible reagent, TsCl / *N*-methylimidazole. The present method is now applied to the process chemistry for the synthesis of pharmaceuticals. It was picked up as the Highlight of *Organic Process Research & Development* [**8**, 138-145 (2004)].



Carboxylic acids : Alcohols (Thiols, Amines) = 1 : (1, 1).

Mild and high reactivity. TsCl and *N*-methylimidazole reagents are much available and economical (reagent cost : about 1/10 of $\text{Me}_2\text{NSO}_2\text{Cl}$ method).

N-Boc amino acids were smoothly esterified without racemization.

No necessity for using DMAP.

The labile 1 β -methylcarbapenem key intermediate and a pyrethroid insecticide, prallethrin, were successfully prepared.

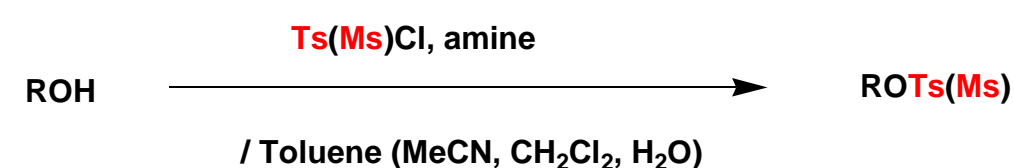
The existence of the reactive acylammonium intermediate was rationally supported by ^1H NMR monitoring study.

K. Wakasugi, A. Iida, T. Misaki, Y. Nishii, Y. Tanabe, *Adv. Synth. Catal.*, **345**, 1209-1214 (2003).

4. Green Chemical Sulfonylation of Alcohols Utilizing Sterically Uncrowded Tertiary Amine Catalysts

The *p*-toluenesulfonylation (tosylation) and methanesulfonylation (mesylation) of alcohols are well recognized as fundamental processes in various fields of organic syntheses. Traditional tosylation using TsCl/Py (Ts = *p*-toluenesulfonyl, Py = pyridine) reagent is less reactive and requires over ca. 10 equiv of pyridine and careful conditions to prevent undesirable side substitution from ROTs to RCl. The present four pyridine-free methods (Methods A-D) are a useful alternative to sulfonylation to resolve these problems.

This protocol has been utilized for the syntheses of complex natural products and fine chemicals both on laboratory and industrial scales; for example, vinblastine [Fukuyama, Tokuyama, *JACS*, **124**, 2137 (2002)], fluorescence amino acid derivatives [Nau, *JACS*, **124**, 556 (2002)], and flumioxadine herbicide (Sumitomo Chemical group).



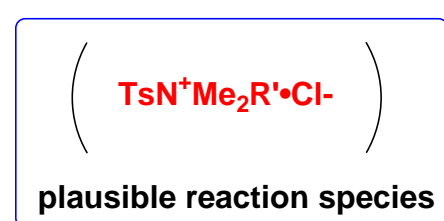
Sterically uncrowded tertiary amines are used as key base, which form reactive sulfoniumammonium intermediate with sulfonyl chlorides.

Higher reactivity compared with conventional TsCl / Py method.

Operationally simple.

Circumvention of undesirable conversion from ROTs(OMs) into RCl. Applicable to allylic sulfonates.

The existence of the reactive sulfoniumammonium intermediate was rationally supported by ^1H NMR monitoring study.



- Method A: Et_3N / cat. $\text{Me}_3\text{N}^+\text{HCl}$
- Method B: K_2CO_3 / cat. Et_3N / cat. $\text{Me}_3\text{N}^+\text{HCl}$
- Method C: $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NMe}_2$
- Method D: cat. BnNMe_2 / H_2O (pH~10)

Y. Tanabe, H. Yamamoto, Y. Yoshida, T. Miyawaki, and N. Utsumi, *Bull. Chem. Soc. Jpn.*, **68**, 297-300 (1995).

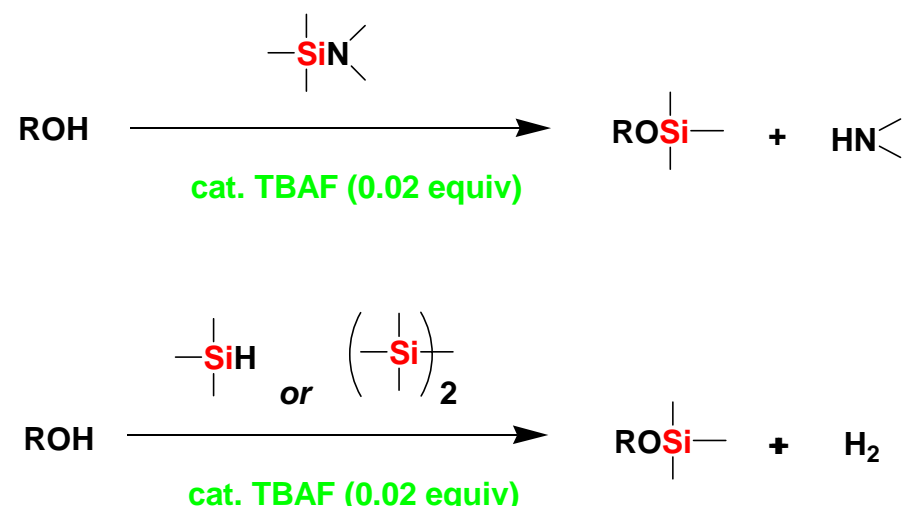
Y. Yoshida, Y. Sakakura, N. Aso, S. Okada, and Y. Tanabe, *Tetrahedron*, **55**, 2183-2192 (1999).

Y. Yoshida, K. Shimonishi, Y. Sakakura, S. Okada, N. Aso, and Y. Tanabe, *Synthesis*, 1633-1636 (1999).

J. Morita, H. Nakatsuji, T. Misaki, Y. Tanabe, *Green Chem.* **7**, 711-715 (2005). Selected as a **Hot Article**.

5. Mild, Effective, Powerful Method for the Silylation of Alcohols Using Silazanes Promoted by Catalytic TBAF

The silylation of alcohols is indispensable for organic syntheses as the most reliable protective method. Despite the well-established method, there still remains a strong need for improved efficiency. In view of the restrictions involved during elaborate syntheses of complex compounds, the development of mild and efficient silylation methods has become increasingly important for: (i) smooth silylation against sterically crowded and functionalized alcohols under mild conditions, (ii) introduction of bulky silyl groups into unreactive alcohols, and (ii) mild alternatives to some bulky-sized silyl triflates, one of the most powerful agents, because the preparation of silyl triflates sometimes requires tedious procedures.



We introduce TBAF catalyzed silylations methods: The presence of catalytic amounts (0.02 eq.) of TBAF significantly promoted silylation of alcohols using a variety of available silazane ($\text{R}_3\text{Si-N}$), hydrosilane ($\text{R}_3\text{Si-H}$), and disilane [$(\text{R}_3\text{Si})_2$] under mild conditions. TBAF is well known as a representative “desilylation” agent. In clear contrast, catalytic use exhibits an efficient “silyl transfer” agent through the hyper valent silicate intermediate. The choice of silazanes allows an alternative method for both the powerful silylation of various kinds of alcohols and the highly regioselective silylation of primary alcohols.

Recently, a mild, efficient, and very powerful method for the silylation of alcohols using anilinosilane (PhNHSi , $\text{Si} = \text{TMS, TES, TBS}$) with catalytic TBAF has been exploited. Despite the mildness, the reactivity of the present method is considered to rival the most powerful method using SiOTf s / 2,6-lutidine.

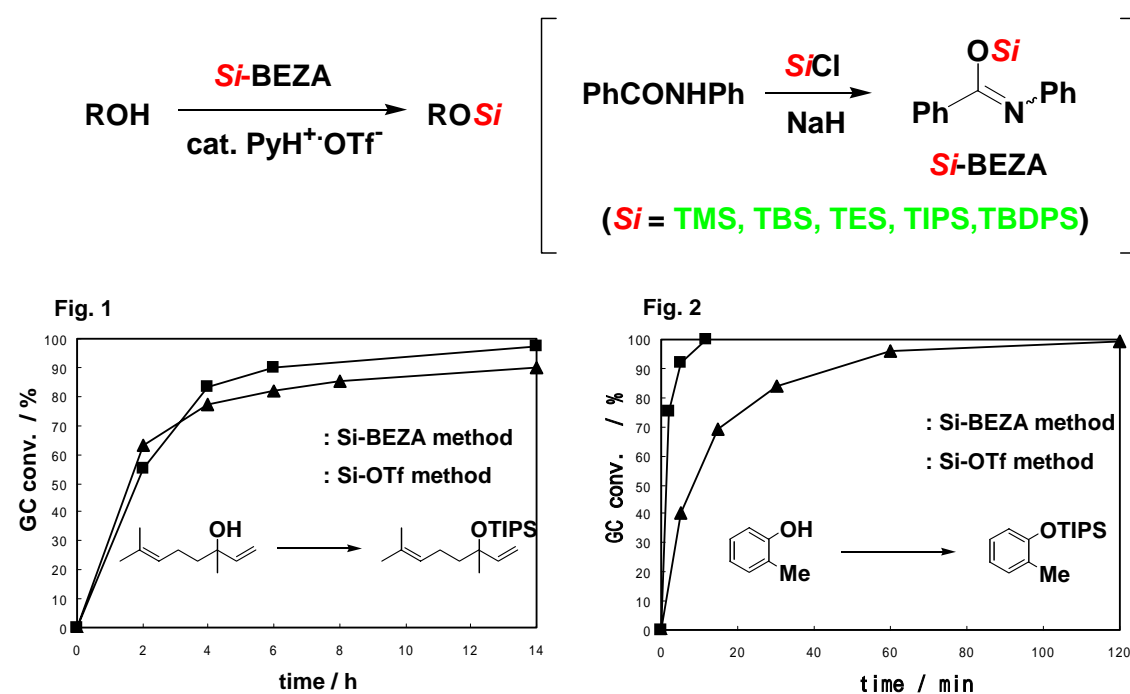
Y. Tanabe, M. Murakami, K. Kitaichi, Y. Yoshida, *Tetrahedron Lett.*, **35**, 8409-8412 (1994).

Y. Tanabe, H. Okumura, A. Maeda, M. Murakami, *Tetrahedron Lett.*, **35**, 8413-8414 (1994).

A. Iida, A. Horii, T. Misaki, Y. Tanabe, *Synthesis*, 2677-2682 (2005).

6. Si-BEZA (O-Silylbenzamide) / Catalytic $\text{PyH}^+\cdot\text{OTf}$: Mild and Powerful Agent for the Silylation of Alcohols

A highly efficient method for the silylation using a novel agent, *Si*-BEZA (silylbenzamide), together with a pyridinium triflate catalyst was developed. A variety of silyl groups can be introduced into sterically crowded alcohols under mild conditions.



Si-BEZA (*O*-Silylbenzamide) is a most powerful silylation reagent among hitherto reported agents.

Preparation and handling of both *Si*-BEZA and $\text{PyH}^+\cdot\text{OTf}$ are quite easy.

Si-BEZAs [TMS, TES, TBS, TIPS (*i*-Pr₃Si-), and TBDPS (*t*-BuPh₂Si-)] are available, considerably moisture-insensitive, and easily prepared and purified.

Without $\text{PyH}^+\cdot\text{OTf}$ catalyst, the reaction did not proceed. That is, *Si*-BEZAs themselves adequately stable and $\text{PyH}^+\cdot\text{OTf}$ acts as a useful trigger.

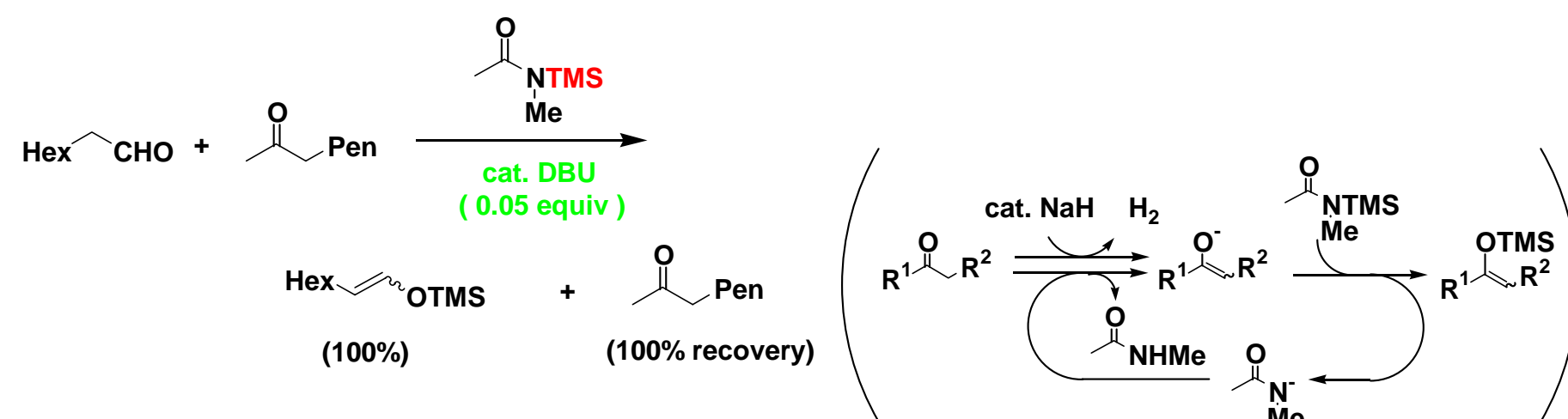
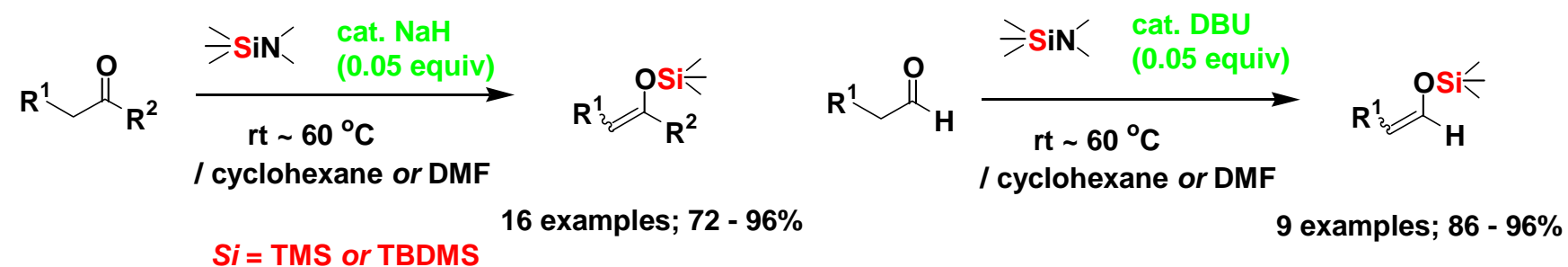
Two parallel experiments for silylation using TIPS-BEZA with linalool and *o*-cresol demonstrate that the ability is considered to rival or surpass the most powerful method using SiOTf s / 2,6-lutidine under standard conditions (Fig. 1 and 2).

Careful NMR experiments (¹H, ¹³C, ²⁹Si, ¹⁵N) of TBS-BEZA revealed that the structure was not an *N*-TBDMS amide but a *O*-TBDMS imidate.

T. Misaki, M. Kurihara, and Y. Tanabe, *Chem. Commun.*, 2478-2479 (2001).

7. Silazanes / Catalytic bases: Mild, Powerful and Chemoselective Agents for the preparation of Enol Silyl Ethers from Ketones and Aldehydes

Enol silyl ethers are widely employed as reactive precursors for carbonyl compounds in a wide range of organic syntheses. Conventional preparations of enol silyl ethers use chlorosilanes with amine (e.g., Et₃N) and amide (e.g., LDA) agents. Despite these two well-established methods, there still remains a need for an alternative method with improved efficiency, that is, for an elaborate and practical scale synthesis from a recent recognized standpoint of green chemistry. We developed an efficient method for the preparation of enol silyl ethers using novel agents, silazanes together with NaH or DBU catalyst, wherein TMS and TBDMS groups were smoothly and chemoselectively introduced into ketones and aldehydes under mild conditions.



The present method is the first example using catalytic bases.

Mild conditions (rt - 60 °C).

Among the commercially available *N*-(TMS)amines screened, *N*-methyl-*N*-(TMS)acetamide gave the best result.

Unreactive α,α'-disubstituted and α-chloro ketones, and labile α,β-unsaturated ketones could be converted.

NaH catalyst is used for ketones, where as DBU catalyst is used for aldehydes.

Both enol TMS- and TBDMS-ethers were obtained.

On the regiochemistry, thermodynamic controlled products were generally obtained.

Powerful silylation reactivity compared with the conventional methods. (TMSCl / Et₃N or TMSI / (TMS)₂NH).

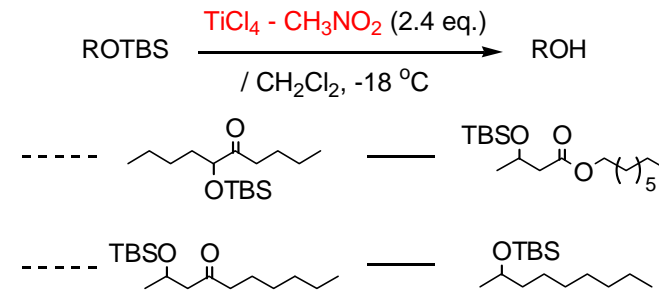
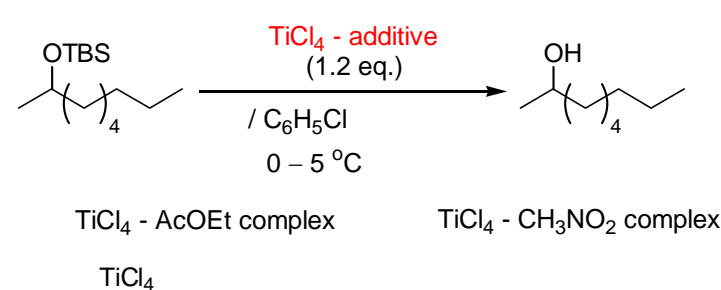
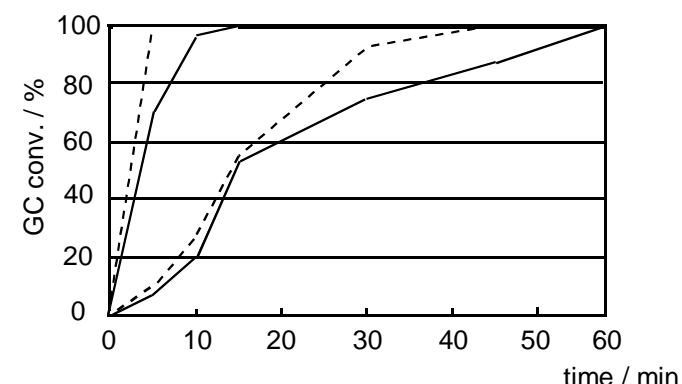
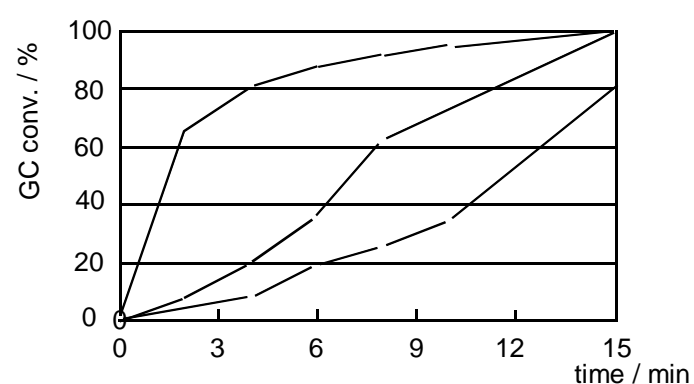
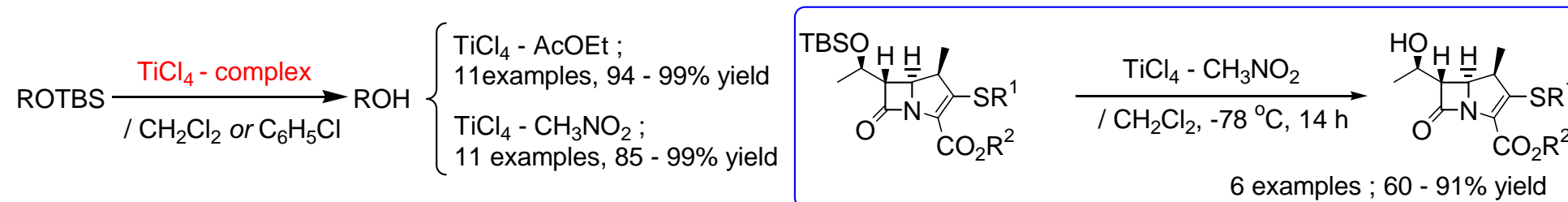
For aldehydes, *N*-(TMS)amines and *N*-methyl-*N*-(TMS)acetamide gave the best results using DBU catalyst.

A notable aspect of the present protocol is the highly chemoselective conversion of aldehydes against ketones

Y. Tanabe, T. Misaki, M. Kurihara, A. Iida, *Chem. Commun.*, 1628-1629 (2002).

In close connection: A. Iida, K. Takai, T. Okabayashi, T. Misaki, Y. Tanabe, *Chem. Commun.*, 3171-3173 (2005).

8. Efficient method for the deprotection of TBS-ethers using TiCl₄ – Lewis base complexes: Application to the synthesis of 1β-methylcarbapenem



We developed an efficient, practical, and chemoselective method for the deprotection of TBDMS ethers using economical and available TiCl₄-Lewis base (AcOEt or CH₃NO₂) complexes.

The present TiCl₄ complexes smoothly promote the desilylation and circumvent undesirable side-reaction from ROTBS to RCl.

The reaction velocity using these complexes was considerably greater than that using TiCl₄ alone

Selective desilylations between aliphatic and aromatic TBDMS ethers, and between TBDMS and TBDPS ethers were successfully performed.

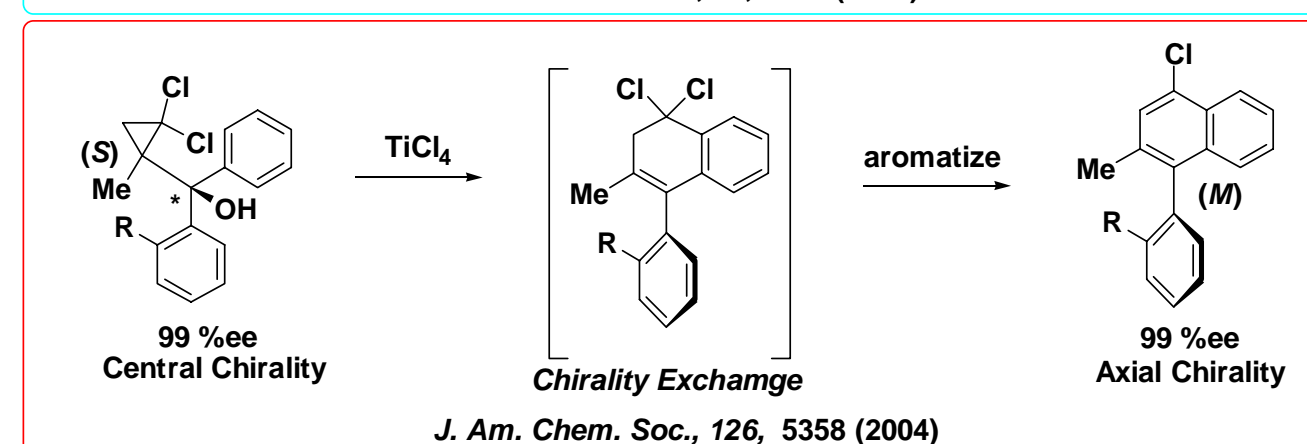
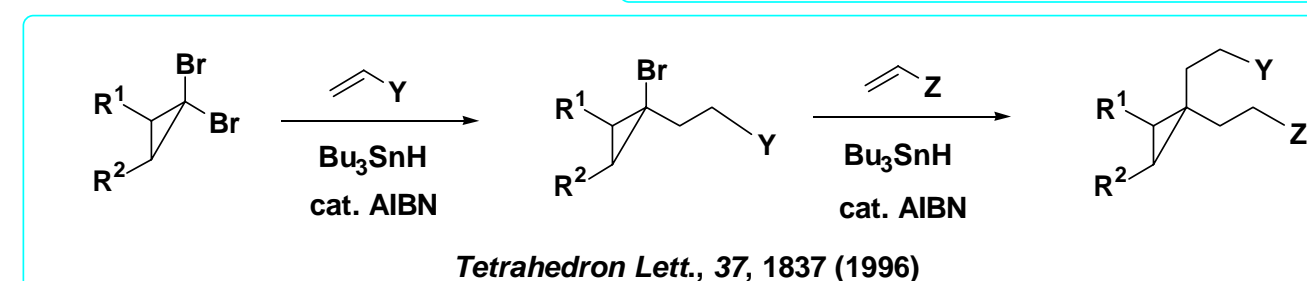
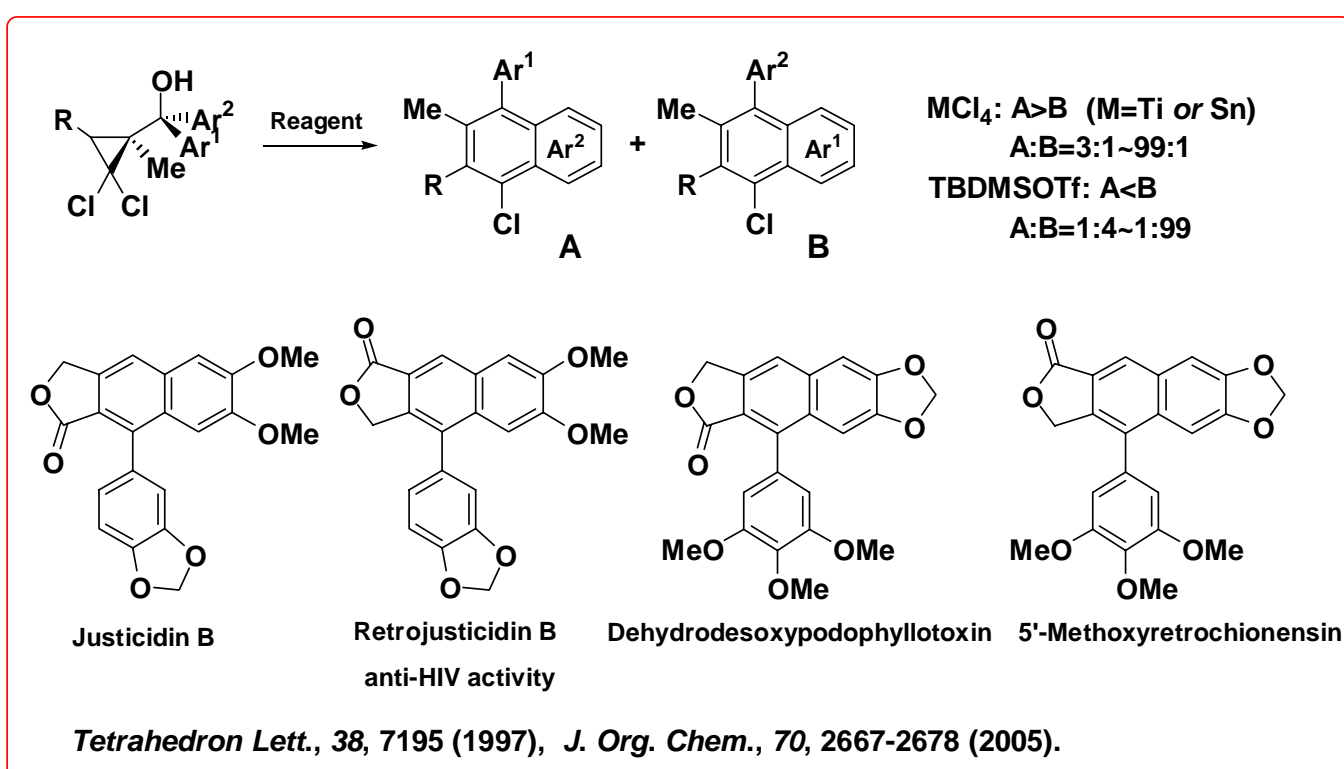
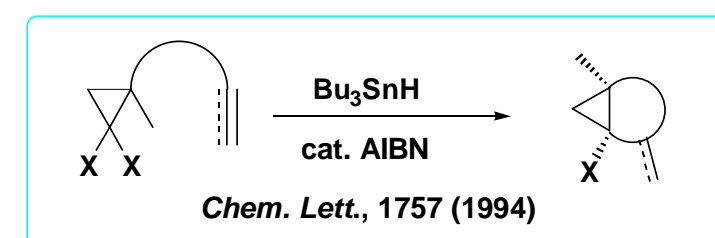
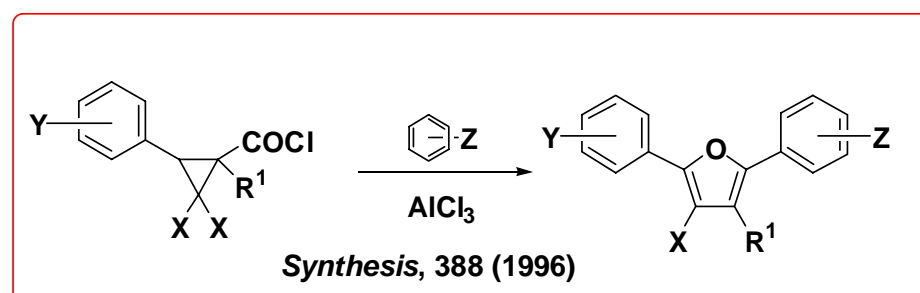
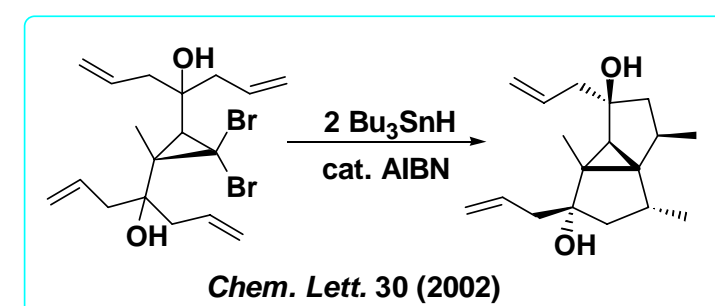
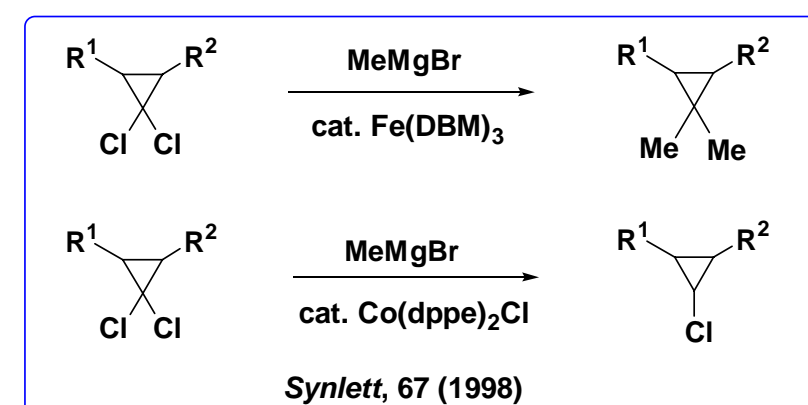
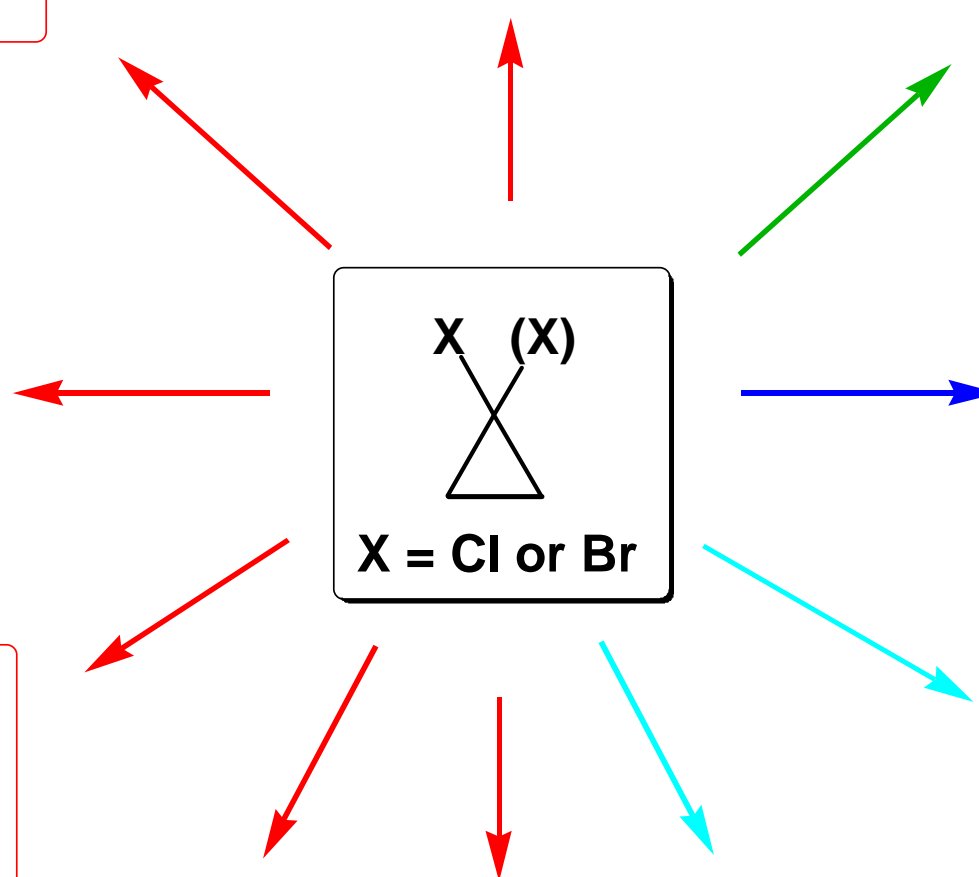
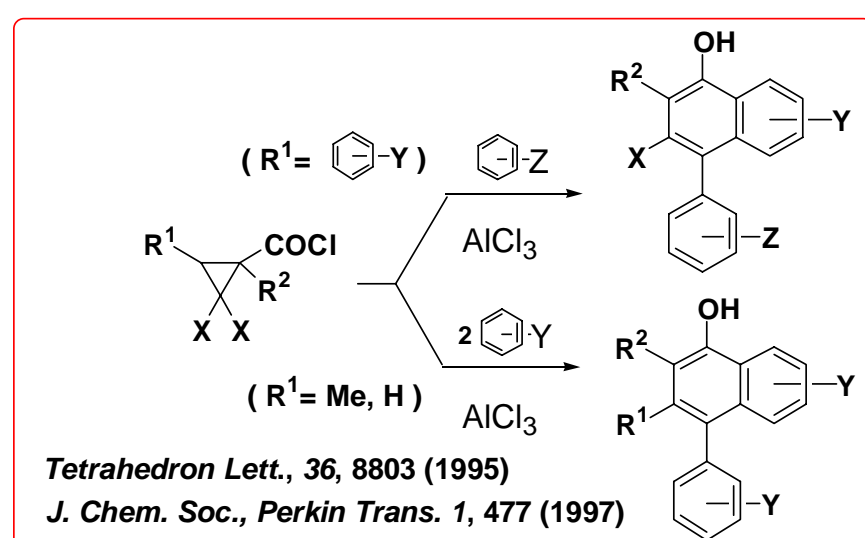
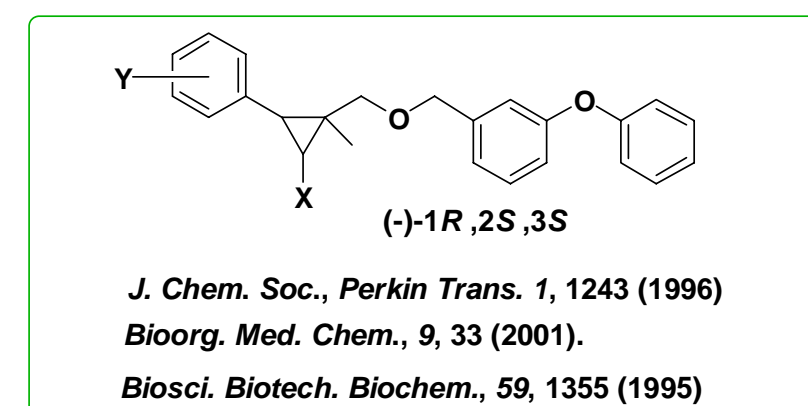
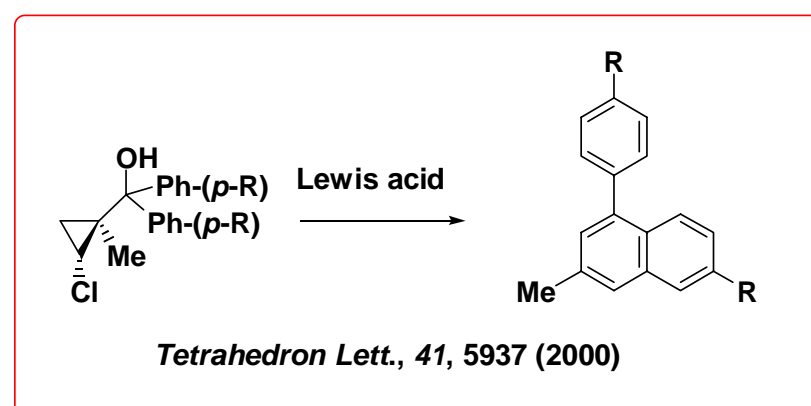
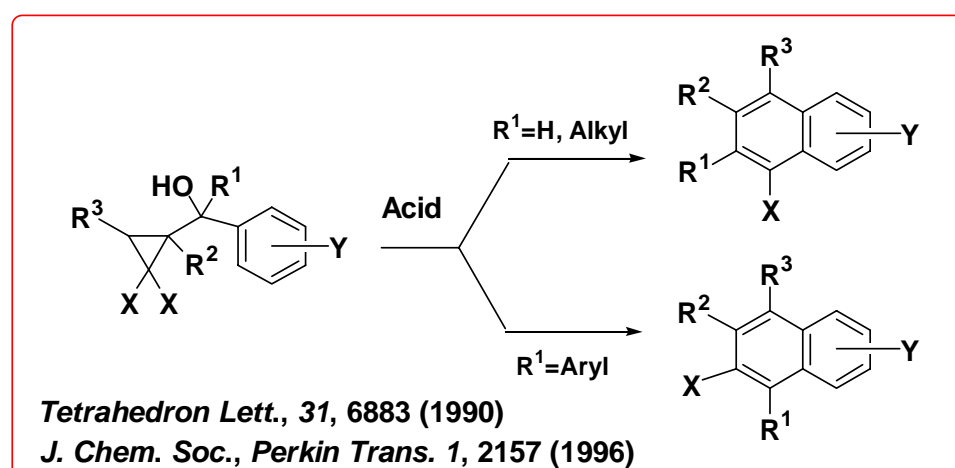
Desilylation of TBDMS-aldol, acyloin, and β-lactam analogs proceeded smoothly due to anchimeric assistance by the neighboring carbonyl groups.

The present method was successfully applied to the practical synthesis of 1β-methylcarbapenems (The deprotection of TBS-1β-methylcarbapenem is an critical issue among the carbapenem synthesis.

A. Iida, H. Okazaki, T. Misaki, M. Sunagawa, A. Sasaki, Y. Tanabe, *J. Org. Chem.*, in press

Development of Synthetic Study on the Utilization of gem-Dihalo (or Halo) cyclopropnes:

Cationic Approach, Radical Approach, Anionic Approach, Stereostructure-Activity Relationship



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