SV (SHORT VISIT) PROGRAM

Zhong and Mase Laboratories

Tuesday, February 26 – Monday, March 4, 2013

at Hangzhou Normal University in China

Just enjoy research and discussion!!

Just enjoy the beginning of a friendship!!

And just enjoy more and more!!

Supported by

Hangzhou Normal University (China)

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Mini Conference Program
SV (Short visit) Program between Zhong and Mase Laboratories

February 28, 2013 (Thu) 13:00 - 16:00 at Hangzhou Normal University, College of Materials, Chemistry & Chemical Engineering, Room #518, Hangzhou, Zhejiang (China)

Opening remarks 13:00 - 13:05 (Prof. Nobuyuki MASE)

1st Session 13:05 - 14:30 (Chairman: Takahiro KATO [Mase Laboratory])

15 min / person (10 min: Presentation / 4 min: Discussion / 1 min: change)

1. Yue DENG (Zhong Laboratory / Graduate student, 2nd year) 13:05-13:20
"Catalytic Asymmetric [4+2] Annulation Initiated by an Aza-Rauhut–Currier Reaction: Facile Entry to Highly Functionalized Tetrahydropyridines"

2. Katsuyuki INAZAWA (Mase Laboratory / Undergraduate student, 4th year) 13:20-13:35
"Development of Environmentally-Friendly Organic Synthesis with Micronanobubble Strategy to Increase Gas Concentration in Liquid Phase Reactions"

3. Youqiang LIN (Zhong Laboratory / Graduate student, 2nd year) 13:35-13:50
"Core Structure-Based Design of Organocatalytic [3+2]-Cycloaddition Reactions: Highly Efficient and Stereocontrolled Syntheses of 3,3'-Pyrrolidonyl Spirooxindoles"

4. Aiko SASAKI (Mase Laboratory / Undergraduate student, 4th year) 13:50-14:05
"Development of Efficient Catalyst Screening by Fluorescence Monitoring Using OFF-ON Fluorogenic Sensors"

Break time 14:05-14:30

2nd Session 14:30-15:50 (Chairman: Yue DENG [Zhong Laboratory])

5. Hoshimi JITSUKATA (Mase Laboratory / Undergraduate student, 4th year) 14:30-14:45
"Synthesis of Quantum Dot/Hydroxy-apo-10'-carotenal Conjugates for *in vivo* Visualization of Carotenoid-derived Volatile Compounds"

6. Dongdong CHEN (Zhong Laboratory / Graduate student, 1st year) 14:45-15:00
"Chiral Brønsted Acid Catalyzed Enantioselective alpha-Aminoxylation of Enecarbamates"

7. Shoji YAMAMOTO (Mase Laboratory / Undergraduate student, 4th year) 15:00-15:15
"Organocatalytic Ring-Opening Polymerization of L-Lactide in Supercritical Carbon Dioxide"

8. Zhiming ZHANG (Zhong Laboratory / Graduate student, 1st year) 15:15-15:30
"N-Heterocyclic Carbene (NHC)-Catalyzed Highly Diastereo- and Enantioselective Oxo-Diels_Alder Reactions for Synthesis of Fused Pyrano[2,3-b]indoles"

9. Takahiro Kato (Mase Laboratory / Graduate student, 2nd year) 15:30-15:45
"Organocatalytic Michael Addition Using 2-Aminopyridine Catalyst Based on Molecular Recognition"

Closing remarks 15:45 – 15:50 (Prof. Guofu ZHONG)

A participants list

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Itinerary

Date	
2/26 (Tue)	Arrive at Hangzhou Xiaoshan International Airport (HGH) 09:35(NRT) => 12:25 (HGH) ANA929 Stay at the Zhejiang University of Finance and Economics Hotel during 2/26-3/3 (6 days). Address: No.18, Xueyuan Street, Jianggan district, Hangzhou
2/27 (Wed)	Visiting Hangzhou Normal University
2/28 (Thu)	Mini conference Drinking party
3/1 (Fri)	Attend a class of organic chemistry
3/2 (Sat)	Sightseeing in Shanghai
3/3 (Sun)	Sightseeing in Hangzhou
3/4 (Mon)	Depart from China 13:45(HGH) => 17:40(NRT) ANA930

Catalytic Asymmetric [4+2] Annulation Initiated by an Aza-Rauhut–Currier Reaction: Facile Entry to Highly Functionalized Tetrahydropyridines

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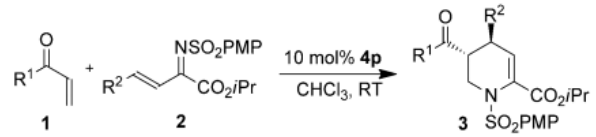
Chiral tetrahydropyridines are important organic synthons. They can be readily reduced to piperidines, which frequently occur in many natural products of biological relevance. Existing methodologies for their preparation are largely attributed to the aza-Diels–Alder reaction of N-sulfonly-1-aza-1,3-butadiene with electron-rich dieno-philes, and the [4+2] annulation reaction of 2-methylene-but-3-enoate with imines, which are either limited by a narrow substrate scope or restricted by rigorous reaction conditions. Thus, the development of a more general and efficient protocol is highly desirable. As part of our long-standing interest in organocatalysis, and on the basis of our recent achievement, we report herein an alternative approach to the synthesis of enantioenriched tetrahydropyridines by a catalytic asymmetric [4+2] annulation pathway initiated by an aza-Rauhut–Currier reaction using chiral phosphine catalysts derived from natural amino acids. To the best of our knowledge, this is the first example of the catalytic asymmetric cross-aza-Rauhut–Currier reaction.

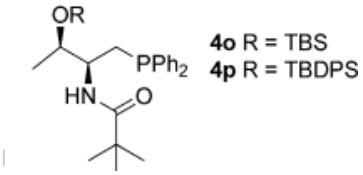
With the optimal reaction conditions established, the scope of the 1-aza-1,3-dienes was then explored (Table 2). In the presence of 10 mol% 4p, ortho-, meta-, and para-substituted aryl 1-aza-1,3-dienes underwent the [4+2] annu- lation process with MVK smoothly, thus generating tetrahy-dropyridine adducts with exclusively transdiastereoselectivity and excellent enantioselectivity in high to excellent chemical yields. Halogenated substrates, which can participate in subsequent transformations such as coupling reactions, were well tolerated in this reaction (entries 4, 5, 7, and 9). Chiral fluorinated heterocycles, which often have superior biological properties relative to their nonfluorinated counterparts, could also be efficiently synthesized (entries 2 and 10). The electronic nature of the ring system slightly influenced the reaction outcome, with electron-rich substrates delivering products under better enantiocontrol (entries 3 and 6). More sterically demanding 2-naphthyl-substituted N-4-methoxy-benzenesulfonyl-1-aza-1,3-diene proved to be a suitable sub-strate to give a [4+2] adduct with greater than 95:5 d.r. and 95%eein 78% yield (entry 11). Further exploration revealed that this methodology had remarkable tolerance for the Lewis basic 4-heteroaryl-1-aza-1,3-diene, thus enabling the highly diastereo- and enantioselective synthesis of thienyl- and furyl-substituted tetrahydropyridines (entries 13 and 14). Notably, the reaction could be further extended to aliphatic 1,3-azadienes, for instance, a simple methyl-substituted azadiene participated in this [4+2] annulation process, thus affording product with excellent stereocontrol, in good yield (entry 15). Additionally, ethyl vinyl ketone (1b) proved to be a suitable substrate in this transformation (entry 16).

Table 1: Generality of [4+2] annulation reaction.[a]



1 2 3

1a: R^1 = methyl
1b: R^1 = ethyl



4o R = TBS
4p R = TBDPS

Entry	1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a**	Ph	68 (**3a**)	>95:5	89
2	**1a**	2-FC_6H_4	59 (**3b**)	>95:5	90
3	**1a**	3-$MeOC_6H_4$	60 (**3c**)	>95:5	92
4	**1a**	3-ClC_6H_4	65 (**3d**)	>95:5	88
5	**1a**	3-BrC_6H_4	74 (**3e**)	>95:5	87
6	**1a**	4-$MeOC_6H_4$	70 (**3f**)	>95:5	99
7	**1a**	4-BrC_6H_4	67 (**3g**)	>95:5	91
8	**1a**	4-MeC_6H_4	72 (**3h**)	>95:5	89
9	**1a**	4-ClC_6H_4	71 (**3i**)	>95:5	90
10	**1a**	4-FC_6H_4	60 (**3j**)	>95:5	90
11	**1a**	2-naphthyl	78 (**3k**)	>95:5	94
12	**1a**	4-PhC_6H_4	55 (**3l**)	>95:5	88
13	**1a**	2-thienyl	85 (**3m**)	>95:5	92
14[e]	**1a**	3-furyl	67 (**3n**)	>95:5	90
15[e]	**1a**	methyl	63 (**3o**)	95:5	86
16	**1b**	3-BrC_6H_4	75 (**3p**)	86:14	86

[a] Unless otherwise specified, reactions were performed using 0.1 mmol of **2** and 0.3 mmol of **1** in 1.0 mL $CHCl_3$ at room temperature in the presence of 10 mol% **4p**. [b] Yield of isolated *trans* isomer. [c] d.r. = *trans*/*cis*; determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined using a chiral IA-H column. [e] Ethyl ester containing 1,3-azadiene was used. PMP = *para*-methoxyphenyl.

Although the detailedmechanism is not clear at this stage, a transition state is proposed to account for the observed stereochemistry. The hydrogen bonding between the pivaloyl amide and the 1,3-azadiene could direct the alkene side chain outwards to a sterically less-demanding area and away from the bulky pivaloyl group, thus the enolate generated by nucleophilic addition of the phosphine moiety, preferentially attacks from the Si face. Subsequent intramolecular proton transfer deliveres the enolate inter-mediateC. After expulsion of the catalyst, an intramolecular Micheal addition occurrs to generate the final [4+2] annulation product.

In summary, an unprecedented catalytic asymmetric [4+2] annulation reaction initiated by an aza-Rauhut–Currier reaction has been developed by utilizing amino phosphine catalysts derived from natural amino acids. This protocol provides a new entry to the synthesis of a broad spectrum of densely functionalized tetrahydropyridines with high stereo-control in good to excellent yields. Further mechanistic investigations and applications to the synthesis of biologically active molecular complexes are currently underway in our laboratory, and will be reported in due course.

Reference: Shi, Z.; Yu, P.; Loh, T.-P.; Zhong, Guofu* *Angew. Chem. Int. Ed.*, **2012**, *51*, 7825-7829.

Development of Environmentally-Friendly Organic Synthesis with Micronanobubble Strategy to Increase Gas Concentration in Liquid Phase Reactions

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Micronanobubbles possess characteristic properties in comparison with usual cm-mm scale bubbles. For example, micronanobubbles exhibit excellent gas-dissolution abilities because of larger gas/liquid interfacial areas; in addition, a longer stagnation in liquid phase compared to cm-mm bubbles is monitored owing to their small buoyancy. These phenomena cause micronanobubbles gradually to decrease in size, with eventual disappearance into the liquid phase (Figure 1). Here we proposed a new experimental methodology for gas/liquid phase reactions using micronanobubble instead of conventional methods involving vigorous stirring or high pressure to increase the interfacial surface between gas and liquid.

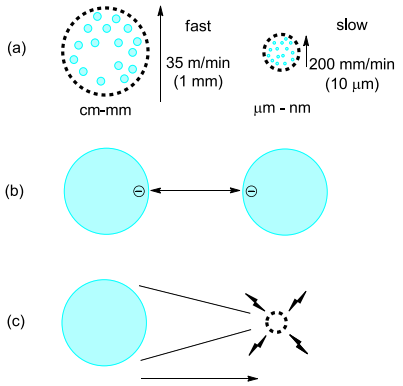


Figure 1. Properties of micronanobubble

Prior to start this study, a special micronanobubble generator, which is resistant to corrosion with acids, bases, and organic solvents, was produced. Performance evaluations of dissolved oxygen levels in distilled water showed that the micronanobubble generator rapidly supersaturated without stirring. After stopping the air supply for 20 minutes, it remained oversaturated for at least 40 min (Figure 2). On the other hand, air bubbling at an air-flow rate 3 mL/min using a conventional gas dispersion tube with a porous fritted glass tip resulted in low saturation of oxygen after 60 minutes with vigorous stirring.

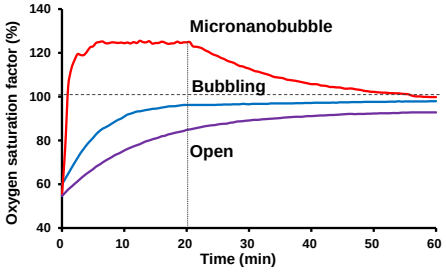
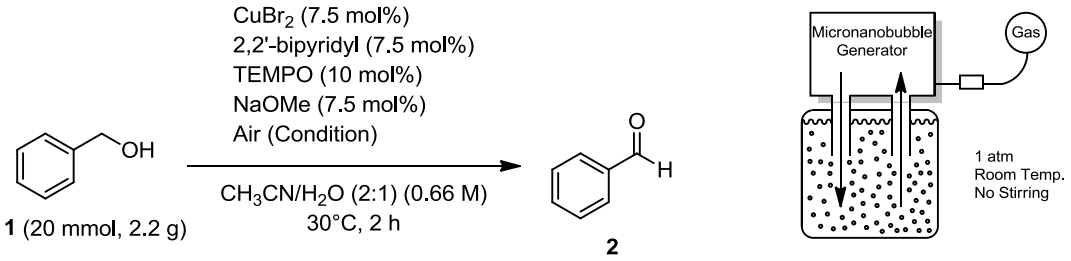


Figure 2. Degree of oxygen saturation

Encouraged by these results, we started to investigate novel micronanobubble strategies in aerobic oxidation, which is one of the most fundamental methods to oxidize alcohols to corresponding carbonyl compounds in modern organic synthesis. As a model reaction, we chose copper-TEMPO catalytic system developed by Sheldon Group (Table 1). The best result was achieved under micronanobubble condition, in which the desired benzaldehyde (**2**) was obtained in 94% conversion (entry 7). On the other hand, attempts under open flask and/or air-bubbling (air-flow rate: 3 mL min) using a conventional gas dispersion tube resulted in 30% and 48% conversion, respectively (entries 2 and 3). Even the air-flow rate increased from 3 up to 15 mL/min, conversion was lower than that of the micronanobubble procedure (entries 3-7).

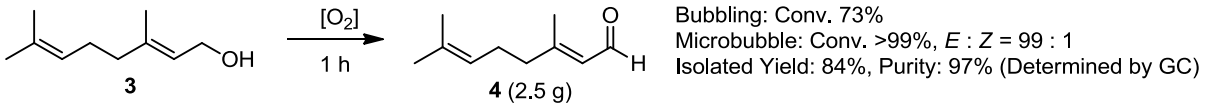
Table 1. Aerobic copper/TEMPO-catalyzed oxidation of benzyl alcohol to benzaldehyde



Entry	Condition	Flow Rate (mL/min)	Conv. (%)[a]	Entry	Condition	Flow Rate (mL/min)	Conv. (%)[a]
1	Open[b]	-	30	5	Bubbling[b]	15	84
2	Bubbling[b]	3	48	6	Micronanobubble	3	93
3	Bubbling[b]	5	56	7	Micronanobubble[c]	3	94
4	Bubbling[b]	7	73				

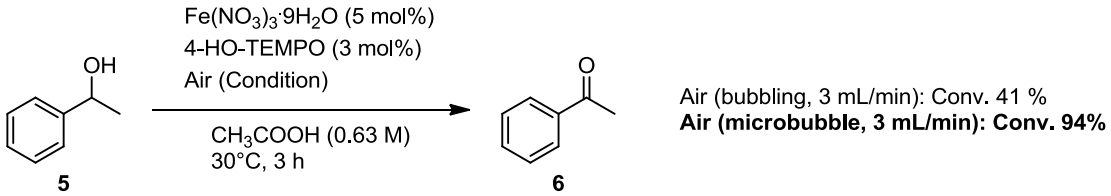
[a] Determined by GC analyses. [b] Reaction was carried out with magnetic stirring at 500 rpm. [c] O_2-micronanobubble was used.

We next examined oxidations of geraniol (**3**) using micronanobubble procedure. Geranial (**4**) was obtained in 84% isolated yield and 97% purity after standard work-up and reduced-pressure distillation. In contrast, oxidation with usual air-bubbling procedure resulted in only 73% conversion (Scheme 1).



Scheme 1. Oxidation of geraniol with micronanobubble procedure.

Next, we demonstrated oxidation of secondary alcohol to ketone (Scheme 2). 1-Phenylethanol (**5**) was converted to acetophenone (**6**) in 82% under air-bubbling condition, whereas better conversion was observed under micronanobubble condition.



Scheme 2. Iron/4-HO-TEMPO catalyzed oxidation of secondary alcohol

In conclusion, efficient aerobic TEMPO oxidation of primary and secondary alcohols using micronanobubble strategy was achieved.

Reference: Mase, N.; Mizumori, T.; Tatemoto, Y. *Chem. Commun.* **2011**, *47 (7)*, 2086-2088.

Core Structure-Based Design of Organocatalytic [3+2]-Cycloaddition Reactions: Highly Efficient and Stereocontrolled Syntheses of 3,3'-Pyrrolidonyl Spirooxindoles

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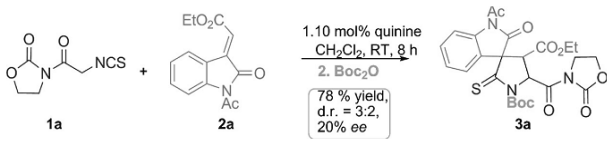
A spirocyclic oxindole core is the structural centerpiece of a wide variety of natural and synthetic compounds that exhibit diverse biological activities. Consequently, approaches towards the efficient asymmetric synthesis of these molecules have received considerable attention. As part of a program to address this family of molecules with orga-nocatalysis, we have recently reported strategies based on oxindoles that provide rapid access to bispirooxindoles, spirocyclopenteneoxindoles, and carbazolespirooxindoles. While these approaches have met with some success, these efforts do not address the 3,3'-pyrrolidonyl spirooxin-dole motif common to many bioactive molecules from this family of molecules (Scheme 1). Thus, an enantioselective catalytic approach for the direct construction of 3,3'-pyrroli-donyl spirooxindole skeletons is a significant unmet challenge.

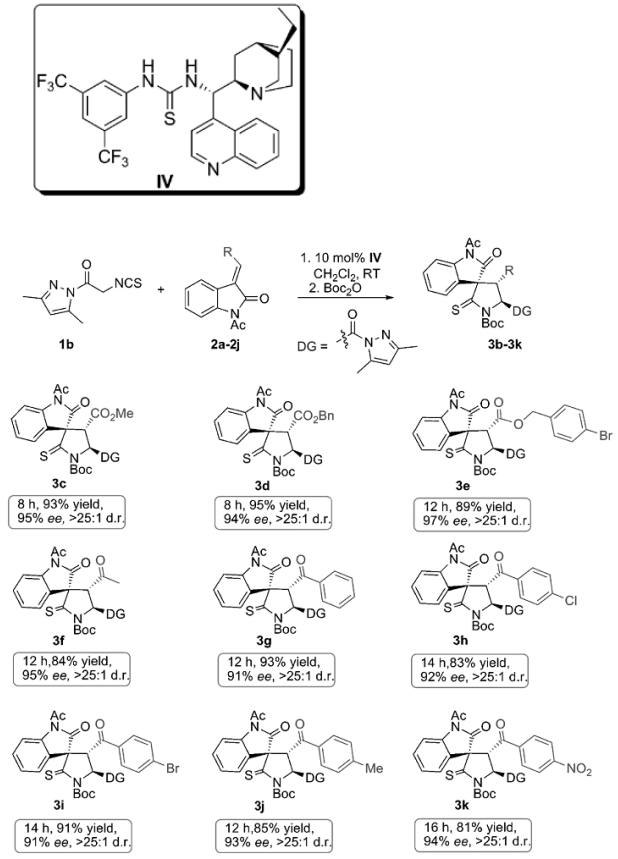
To address this challenge, we sought to design an organocatalytic domino reaction that would ideally involve the reaction of two simple and readily accessible starting materials. Given the recent success of α-isothiocyanato derivatives as nucleophiles in organocatalytic aldol and Mannich reactions, we envisioned that [3+2]-cycloaddition reactions between α-isothiocyanato imides and methyleneindolinones would yield the desired 3,3'-pyrrolidonyl spirooxindole skeletons in a highly stereoselective transformation (see Scheme 1).



Scheme 1. Initial test of [3+2]-cycloaddition reaction catalyzed by quinine.

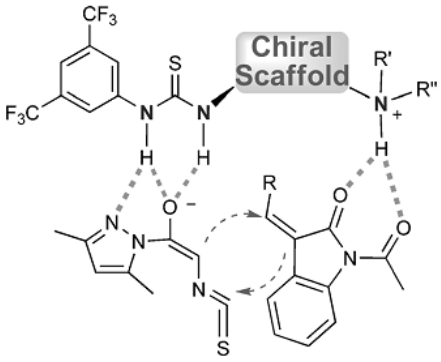
In our exploratory effort, this new methodology provided access to a range of multi-substituted spirocyclic oxindole derivatives and served as an expedient approach for the preparation of a range of substituted spirocyclo oxindoles containing three chiral centers in excellent enantiomeric ex-cesses (91–98%ee) and almost complete diastereoselectivi-ties (>25:1 d.r. in all cases) (Scheme 2). TheIV-promoted [3+2]-cycloaddition reaction proceeded with a variety of methyleneindolinone derivatives bearing various substituents at the carbon–carbon double bond such as esters and ketones. Notably, minimal impact on efficiencies, enantiose-lectivities, and diastereoselectivities were observed regard less of the electronic nature and bulkiness of the substituents (Scheme 5, 3g–3k). The current system does have limitations: Phenyl-substituted methyleneindolinone was virtually unreactive, while the

cyano(CN)-substituted methyleneindoli-none provided product with low diastereoselectivity.

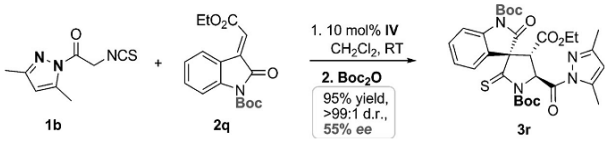


Scheme 2. Generality of organocatalytic [3+2]-cycloaddition reactions

Our findings together with the dual activation model proposed by Takemoto and co-workers, and the theoretical calculation studies by Papai and Zhong and their co-workers, allow us to suggest that the two substrates involved in the reaction are activated si-multaneously by the catalyst as shown in Scheme 3. The acetyl-protecting group is crucial to high enantioselectivity, as seen from the low enantioselectivity (55%ee) obtained when a tert-butoxycarbonyl (Boc) protect-ing group was utilized (Scheme 4). The absolute configurations of 3b and 3g determined by X-ray analysis are in accordance with that predicted by the catalytic model.



Scheme 3. Proposed mode of activation of substrates



Scheme 4. Control experiment in support of mechanism.

In summary, we have developed an efficient organocata-lytic [3+2]-cycloaddition reaction for the direct construction the 3,3'-pyrrolidonyl spirooxindole motif common to many bioactive molecules through the rational design of α-isothio-cyanato imides as dienophiles. Stereochemically complex products were obtained in excellent chemical and optical yield allowing us to set three contiguous stereocenters, including one all-carbon spiro quaternary center, in the products. This straightforward process makes use of simple start-ing materials and proceeds under mild conditions and will be useful in medicinal chemistry and diversity-oriented synthesis.

Reference: Tan, B.; Zeng, X.; Leong, W. W. Y.; Shi, Z.; Barbas III, C. F.; Zhong, Guofu* *Chem. Eur. J.* **2012**, 18, 63-67.

Development of Efficient Catalyst Screening by Fluorescence Monitoring Using OFF-ON Fluorogenic Sensors

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Performing a large number of random chemical reactions should increase the possibility of an incidental discovery outcome. Especially, high-throughput method of fluorometry with a rapid plate reader is employed to perform various random reactions automatically. Fluorogenic substrates are useful for analysis of the progress of chemical transformations because product formation is directly observed as an increase in fluorescence. To compare with the traditional laboratory protocols in which the operation was repeatedly, this method shows many advantages for huge savings in time, cost, and labor (Figure 1). In order to accelerates high throughput screening in small scale, OFF-ON fluorogenic sensors were designed to apply screening of catalysts for the formation of C-C bonds. Here, we focused aldol reaction that is one of the most predominantly used reactions in synthetic organic chemistry, then OFF-ON fluorogenic sensors of aldehyde-type, which is possibly used for monitoring the progress of aldol reactions *via* the detecting fluorescent increase, will facilitate the rapid discovery of efficient catalysts from compound libraries.

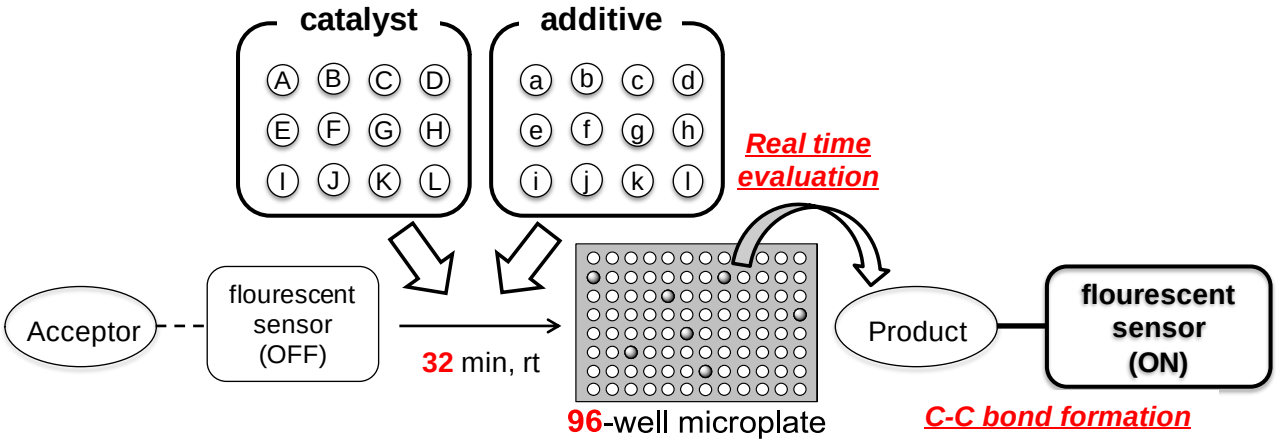

Figure 1. Fluorescent monitoring system

Although fluorescence properties of aromatic carbonyl compounds are complex and often difficult to predict, many aromatic aldehydes and ketones have a low-lying n-π* excited state and thus exhibit low fluorescence quantum yields due to intersystem crossing. Therefore, we reasoned that anthracene, naphthalene, and fluorescent benzene derivatives with aldehyde functional group should be candidates of fluorogenic aldehydes. Indeed, aldehyde **1** was weakly fluorescent, whereas aldol **2** was highly fluorescent (Figure 2).

Reactions of fluorogenic aldehyde **1** with isobutyl aldehyde as a donor in the presence of catalyst and additive were performed in 96-well, and the increase of fluorescence was monitored by microplate reader to examine the utility of **1** for monitoring the progress of the aldol reaction. From analyses of high velocity and integral value of fluorescence intensity, the best combination of pyrrolidine as a catalyst and isophthalic acid as an acid additive was identified. Subsequently, to evaluate our fluorescent monitoring system, pyrrolidine catalyzed cross aldol reactions between isobutyl aldehyde (**3**) and *p*-nitrobenzaldehyde (**4**) were performed. As the value of velocity was increased, conversion and isolated yields were improved in the model aldol reaction (Figure 3).

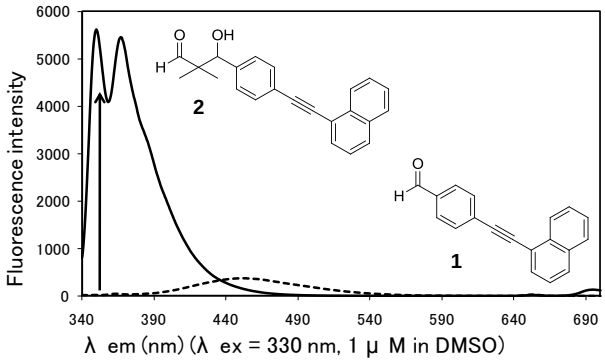

Figure 2. OFF-ON fluorogenic compounds for monitoring the progress of C-C bond formations

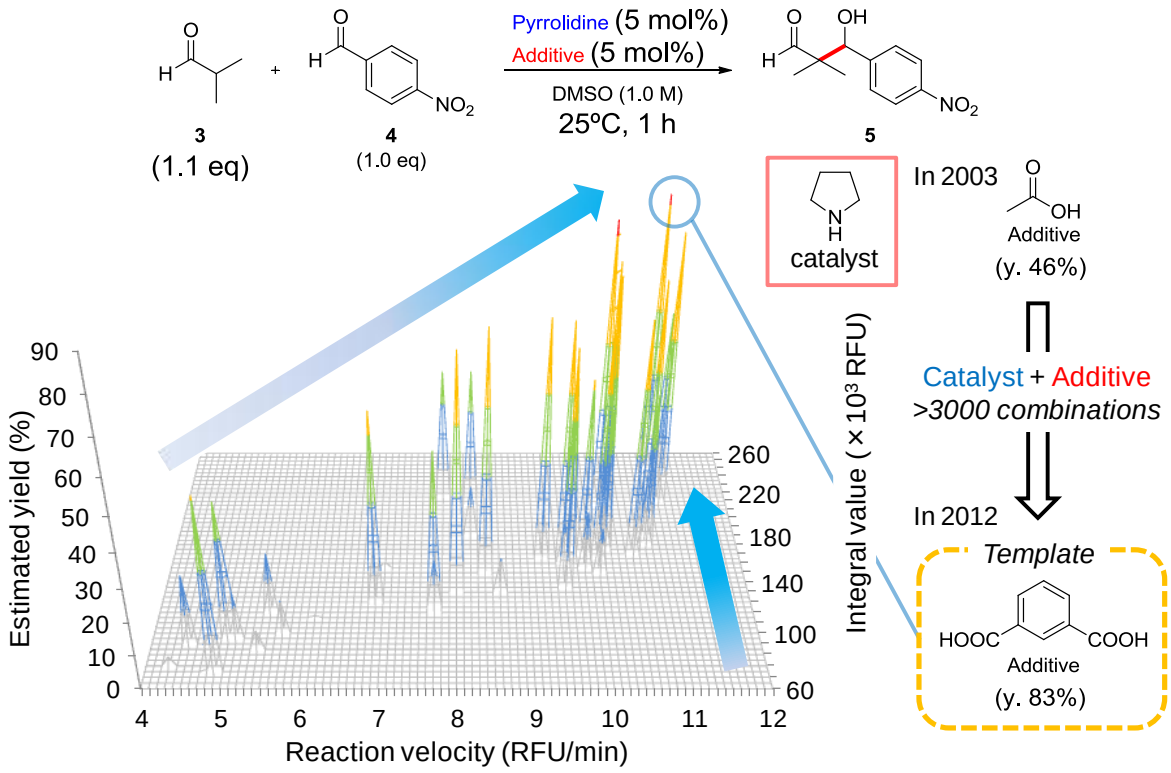

Figure 3. Screening results employing isobultylaldehyde as a donor

In conclusion, we have synthesized fluorogenic compounds that can be used for monitoring reactions through increased fluorescence. These fluorogenic compounds can be useful for screening of catalysts to identify the best combination from compound libraries.

Synthesis of Quantum Dot/Hydroxy-apo-10'-carotenal Conjugates for *in vivo* Visualization of Carotenoid-derived Volatile Compounds

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Recently, there has been a rapid increase in the number of publications on biosynthetic pathway. However, elucidation of the formation pathway yielding carotenoid-derived volatiles in plant has been still a big challenges, because very little is known about the release as well as the location of synthesized volatile compounds from plant tissues. Herein, we focus the study on synthesis and application of Quantum dot (Qdot) conjugate for the *in vivo* visualization of β-ionone as a carotenoid-derived volatile many fruits, vegetables, and plants. We have proposed our hypothesis that Qdot can be applied for staining of plant volitiles inside living cells because of their unique properities, such as water solubility, photo stability, and exceptional fluorescence. The β-ionone-Qdot-conjugate which is obtained as enzyme-cleaved product from β-apocarotenal-Qdot conjugate can be detected inside the compartments (Figure 1).

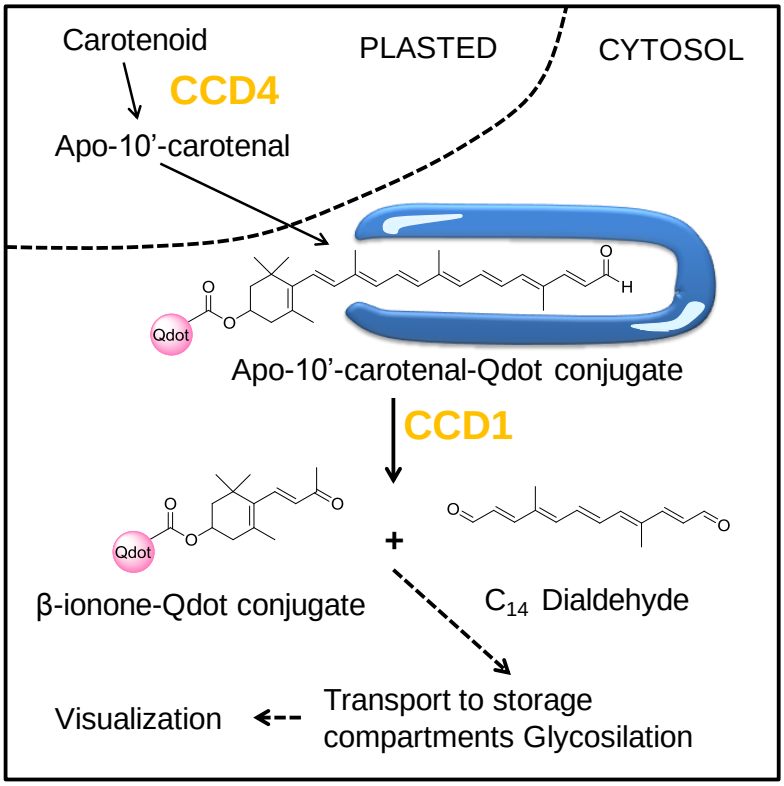


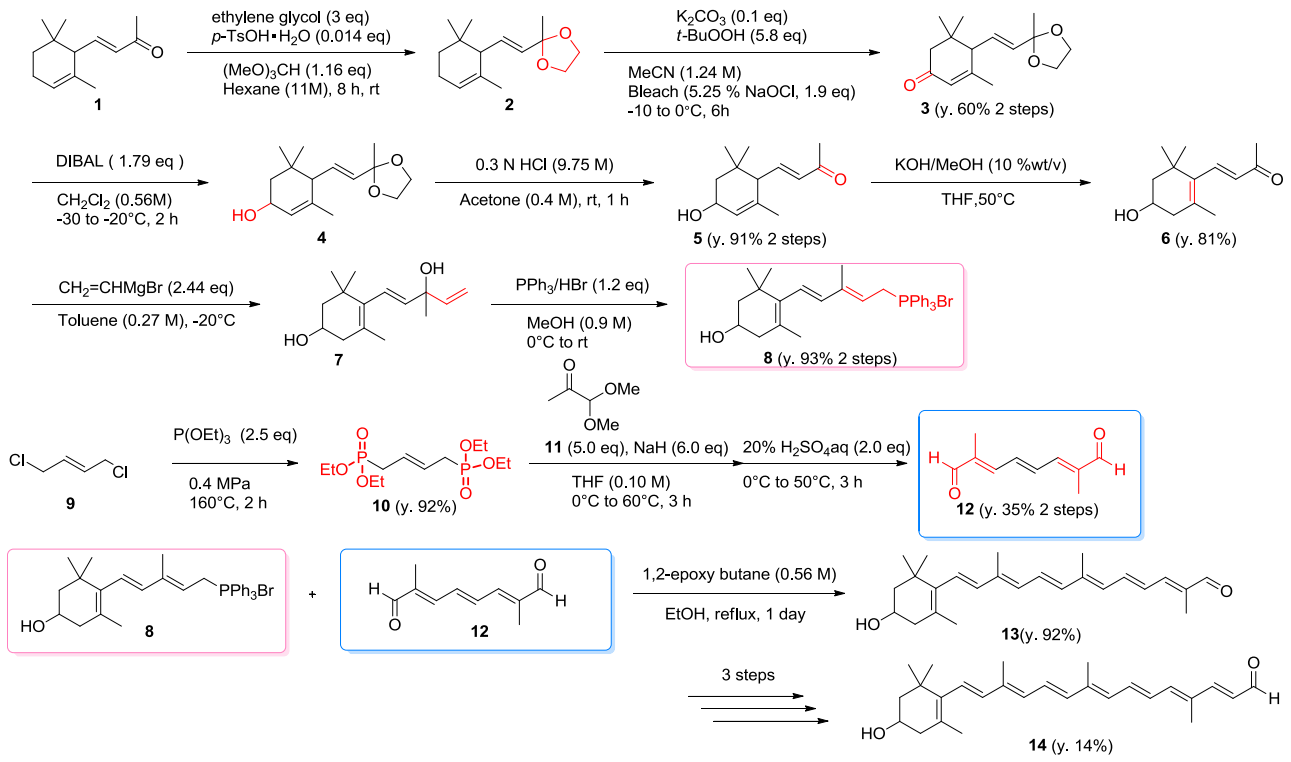
Figure 1. Approach for the labeling of volatiles derived from carotenoids with Qdot

The carbonyl group of α-ionone was first protected by ethylene glycol to yield α-ionone ketal **2**. This ketal was then oxidized at the allylic position with *tert*-BuOOH (TBHP, 70% in water), house bleach and catalytic amount of potassium carbonate in acetonitrile at -5°C to 0°C. The reduction of 3-keto-α-ionone **3** followed by deprotection led to 3-hydroxyl-α-ionone **4**. A variety of reduction agents such as sodium borohydride/cerium chloride (86% yield, 54%de, *cis*), potassium tri-*sec*-butylborohydride (87% yield, 14% de, *trans*), and diisobutylaluminium hydride (DIBAL, 91% yield, 34% de, *cis*) were examined to determine whether the carbonyl group could be reduced stereoselectively at C_3 and C_6 position; however,

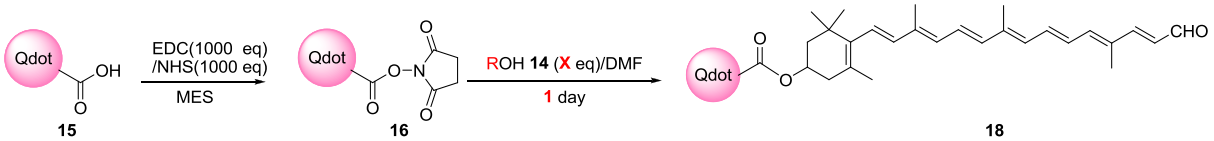
no significant stereoselectivity could be achived. Among these reducing agents, DIBAL was chosen due to the commericially availability. Conversion of 3-hydroxy-α-ionone **5** to 3-hydroxyl-β-ionone **6** was accomplished by base catalyzed isomerization with potassium hydroxyl/methanol (10 wt%/v) in 80% isolated yield after purification.

In the following steps, the Grignard reaction between 3-hydroxyl-β-ionone **6** and vinylmagenesium bromide afforded the tertiary vinyl-α-ionol **7**. Treatment of this alchol **7** with triphenyl phosphine in hydrobromic acid furnished the desired phosphomium salt **8** in 93% yield. Wittig olefination of C_{10} dialdehyde **12** with C_{15}-ylide salt **13** was initiated by addition of 1,2-epoxy butane to successfully access C_{25} aldehyde **13** (Scheme 1).

The critical step is the coupling reaction between carboxyl Qdot **15** and apocarotenal **14** *via* ester bridge as shown in Scheme 2.



Scheme 1. Synthesis of apo-10'-carotenal



Scheme 2. Synthesis of Qdot conjugate

In conclusion, we have synthesized the β-ionone-Qdot-conjugate **18** over 14 steps, which potentially can visualize carotenoid-derived volatiles formed inside the plant cell.

Chiral Brønsted Acid Catalyzed Enantioselective α-Aminoxylation of Enecarbamates

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α-Hydroxy carbonyl compounds are key motifs encountered throughout natural products and pharmacueticals; thus, the preparation of chiral α-hydroxy ketones has been of great interest and has motivated a tremendous wealth of strategies for their synthesis. Catalytic asymmetric α-aminoxylation reactions are one of the most facile and conventional synthetic methods towards chiral α-hydroxy ketones. However, despite considerable efforts in the area of α-aminoxylation, so far the substrate scopes have been limited to aldehydes, cyclic ketones, and β-dicarbonyl compounds. The use of linear ketones resulted in significant decrease in both the reactivity and selectivity, while no examples with aromatic ketones have been documented, possibly because of the severe steric hindrance which strongly inhibited the covalent binding of the catalyst.

To address these challenges, enecarbamate1was chosen as an activated ketone nucleophile (Figure 1); we envisioned that in the presence of an electron-withdrawing carbamate group (TS), instead of an electron-donating pyrrolidine moiety (used in proline catalysis, TS*), the undesired N-addition pathway might be suppressed. The fact that both the E and Z isomers of enecarbamates can be conveniently prepared provides additional flexibility for this approach. Meanwhile, chiral Brønsted acids would be attractive alternatives for overcoming the limitations of proline catalysis in α-aminoxylation reactions, as selective protonation of the basic nitrogen of nitrosobenzene should be realized by a judicious choice of stronger acid (TS). However, no efficient C-O bond formation of enecarbamates has been reported, despite recent successes in the catalytic asymmetric aza–ene reactions of enecarbamates with aldehydes and imines. In a continuation of our long standing work in aminoxylation chemistry, we recently discovered that highly enantioselective α-hydroxylation of β-dicarbonyl compounds can be achieved through activation of nitroso compounds with binol-derived phosphoric acids. To further explore the extent of this novel activation mode, herein we describe the first chiral-phosphoric-acid-catalyzed α-aminoxylation of enecarbamates, and its one-pot application leading to direct access of optically pure α-hydroxy ketones, β-amino alcohols, and oxazolidinones.

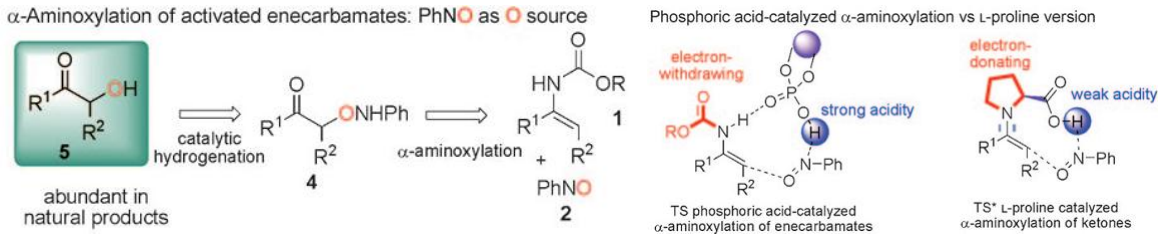
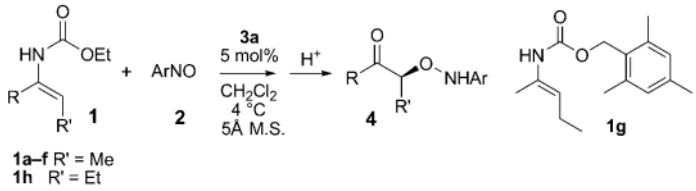
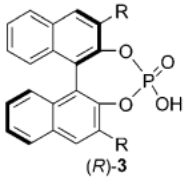


Figure 1. Projected synthesis of chiral α-hydroxy ketones 5

A broad spectrum of nitrosoarenes could be employed in the reaction to afford the desired products in excellent yields and high enantioselectivities (Table 1, entries 1–7), with the exception of 4-nitrosotoluene (Table 1, entry 4) in which N-O bond heterolysis was observed after the initial aminoxylation. Enecarbamates derived from aromatic ketones that have substituents with various electronic and steric properties were also found to efficiently react with 4-chloronitrosobenzene (2b), and the products were obtained in high enantioselectivities (Table 1, entries 8–12). Furthermore, the more-challenging enecarbamates derived from indanones and tetralones could also successfully undergo α-aminoxylation to give α-oxygenated products in good yields and ee values, although specific catalyst was needed for each substrate. The absolute configuration of 4a, 7a, and 7d were determined to be S after catalytic hydrogenation to convert them to the correspondinga-hydroxy ketones and comparing the optical rotation with literature. The stereo-chemistry of other products was tentatively assumed by analogy.

Table 1: Substrate scope of the chiral phosphoric acid catalyzed α-aminoxylation of enecarbamates.[a]





3a R = 9-An
3b R = [H$_8$]SiPh$_3$
3c R = 2.4,6-(*i*Pr)$_3$C$_6$H$_2$
3d R = 2-Np
3e R = 9-PhAn

Entry	R	Ar	Yield [%][b]	e.r.[c]
1	Ph (**1a**)	Ph (**2a**)	95 (**4a**)	97:3
2	Ph (**1a**)	*p*-ClC$_6$H$_4$ (**2b**)	95 (**4b**)	98:2
3	Ph (**1a**)	*p*-BrC$_6$H$_4$ (**2c**)	93 (**4c**)	98:2
4	Ph (**1a**)	*p*-Tol (**2d**)	44 (**5**)	97:3
5	Ph (**1a**)	*m*-ClC$_6$H$_4$ (**2e**)	91 (**4d**)	98:2
6	Ph (**1a**)	*o*-ClC$_6$H$_4$ (**2f**)	89 (**4e**)	96:4
7	Ph (**1a**)	*p*-CO$_2$MeC$_6$H$_4$ (**2g**)	98 (**4f**)	97:3
8	*p*-ClC$_6$H$_4$ (**1b**)	*p*-ClC$_6$H$_4$ (**2b**)	96 (**4g**)	98.5:1.5
9	*p*-MeOC$_6$H$_4$ (**1c**)	*p*-ClC$_6$H$_4$ (**2b**)	93 (**4h**)	96.5:3.5
10	*p*-Tol (**1d**)	*p*-ClC$_6$H$_4$ (**2b**)	95 (**4i**)	97:3
11	*m*-Tol (**1e**)	*p*-ClC$_6$H$_4$ (**2b**)	90 (**4j**)	96:4
12	*o*-Tol (**1f**)	*p*-ClC$_6$H$_4$ (**2b**)	89 (**4k**)	96:4
13[d]	Me (**1g**)	*p*-ClC$_6$H$_4$ (**2b**)	90 (**4l**)	90:10
14	Ph (**1h**)	*p*-ClC$_6$H$_4$ (**2b**)	92 (**4m**)	98:2

[a] For detailed reaction conditions, see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC or GC analysis on a chiral stationary phase. [d] 10 mol% of **3c** was used.

In conclusion, we have reported a facile, practically appealing, highly enantioselective Brønsted acid-catalyzed α-aminoxylation of enecarbamates. This procedure considerably extend the substrate scope for the α-aminoxylation reaction to linear and aromatic ketones, allowing convergent and stereoselective access to valuable α-hydroxy ketones, β-amino alcohols, and cis-oxazolidinones in their enantiopure form. This discovery also provides mechanistic insights into the N/O selectivity of α-aminoxylation. Further applications of this activationmode to other enantioselective reactions are currently underway.

Reference: Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, Guofu* *Angew. Chem. Int. Ed.* **2010**, 49, 8588-8591.

Organocatalytic Ring-Opening Polymerization of L-Lactide in Supercritical Carbon Dioxide

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Polylactides are useful material in various fields because of their biodegradable and biocompatible features. Polylactides are synthesized by condensation polymerization from lactic acid or ring-opening polymerization from lactide (Figure 1). Condensation polymerization is not suitable for preparation of higher-molecular-weight polylactide due to equilibrium process in ester bond-forming reaction. On the other hand, ring-opening polymerization of lactide is catalyzed by tin 2-ethylhexanoate under high temperature condition, and is used in industry. However, as removing toxic metal from polylactides is rather difficult, the safety of products is not ensured. Furthermore, the coloring of products caused by high reaction temperature is often problematic in product development. Recently, polymerizations employing an organocatalyst have been reported, but they requires toxic volatile halogenated solvents because polylactides cannot be dissolved in conventional solvent. Here, we report organocatalytic polymerization of lactide in supercritical carbon dioxide ($scCO_2$) at lower temperature compared to conventional method, affording metal-, organic solvent-, and residual monomer-free polylactide.

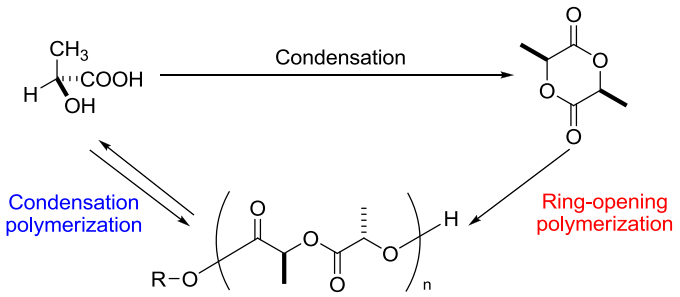
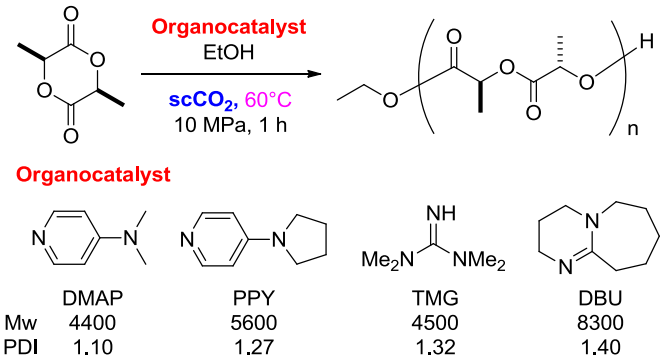


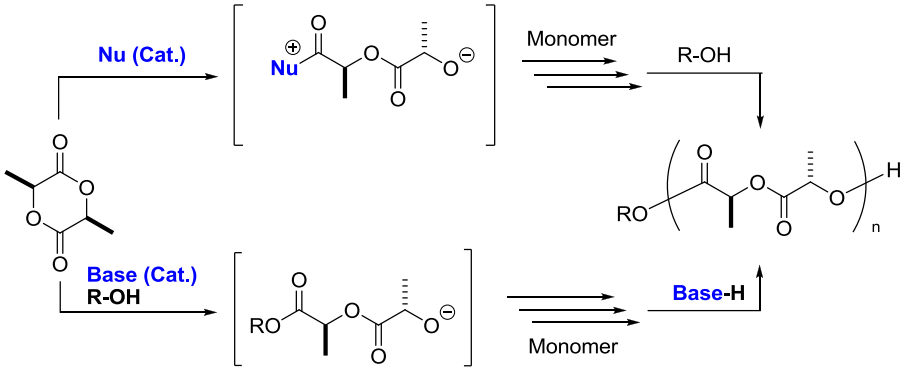
Figure 1. Method for synthesis of polylactide

Polymerization using DMAP as an organocatalyst proceeded quantitatively and smoothly in $scCO_2$ with high purity at lower temperature (Scheme 1). Regarding the reaction mechanism, catalyst is proposed to be as a nucleophile or as a base for activation of monomer, and these mechanisms include anionic intermediate (Scheme 2). It is considered that living anionic polymerization is generally difficult in $scCO_2$, since anionic intermediate has possibility of reacting with Lewis acidic $scCO_2$. Nevertheless, in the presence of DMAP and ethanol as a reactant in $scCO_2$ at 10



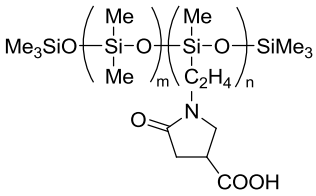
Scheme 1. Organocatalytic polymerization of lactide in $scCO_2$

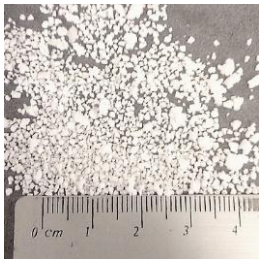
MPa and 60°C, polylactide was quantitatively obtained after 1 hour. In addition, living polymerization proceeded according to the linear correlation between Mw and monomer conversion, that is, the close correlation between the theoretical and experimental molecular weights. This result indicates that living anionic polymerization proceeded in $scCO_2$.



Scheme 2. Reaction mechanism of polymerization

Using surfactant showed an effect on granulation of the polylactide. We found that silicone-type surfactant was applicable in efficient granulation (Figure 2). In the presence of silicone-type surfactant, granulated polylactide was obtained in 96% conversion after 2 hours. The particle size was around 1 mm. Interestingly, this granulated polylactide could be easily collected from autoclave, and therefore, handleability was greatly improved.

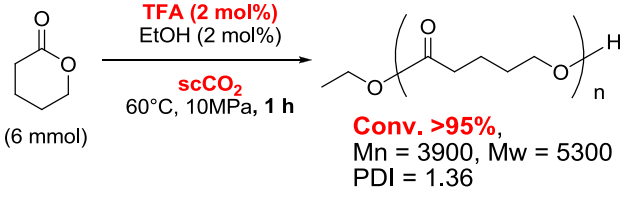




with surfactant without surfactant

Figure 2. Effect of surfactant in granulation

This method can be applied for ring-opening polymerization of other monomers. Polymerization of valerolactone smoothly proceeded in the presence of trifluoroacetic acid (Scheme 3). Since polyvalerolactone is also biodegradable polymer and the reaction undergoes *via* the formation of cationic intermediate, it leads to the wide application of this method for various monomers.



Scheme 3. Synthesis of polyvalerolactone in $scCO_2$

In summary, our method enables to accomplish environmentally-friendly organocatalytic synthesis of polylactide without using toxic metal catalyst and halogenated solvent. This polymerization proceeded *via* living anionic polymerization even in Lewis acidic $scCO_2$. In addition, it was simultaneously able to perform polymerization as well as granulation by use of silicone-type surfactant. This method offers many advantages such as saving energy, safety, quality, regulatory compliance VOC, and low cost.

N-Heterocyclic Carbene (NHC)-Catalyzed Highly Diastereo- and Enantioselective Oxo-Diels_Alder Reactions for Synthesis of Fused Pyrano[2,3-b]indoles

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The synthesis of an α,β-unsaturated amide could be classically carried out fromcommercially available isatins. Presumably, activation of the isatin C3-O double bond via a simple one-step Wittig-Horner reaction results in the formation of 2-oxoindolin-3-ylidenes in excellent yields. Moreover, this strategy being based on the annulation of indoles opens up a new avenue for the synthesis of fused pyran[2,3-b]indole skeletons, one of the most important heterocycles and key structural units of biologically active alkaloids. Although significant advances have been achieved in the development of these derivatives for the synthesis of biologically important compounds, enantioselective variants are still very limited. A study that was carried out by Ye and co-workers presented a formal [4+2] cycloaddition of ketenes with oxindoles yielding indole-fused dihydropyranones. However, the diastereo- and enantioselectivities obtained were quite unsatisfactory.

To address the challenge of achieving high optical purity, N-mesityl-substituted triazolium salt (refer to cat.) was chosen as the catalyst for this reaction and racemic R-chloroaldehyde 1was used as the dienophile precursor to generate in situ the enolate species from elimination of HCl from the NHC-R-chloroaldehyde ad-duct. We envisioned that excellent diastereoselectivities and absolute stereochemistries can be rationalized due to the highly preferredendo-cis-transition state. The hypoth-esis was based on DFT calculations that determined that cis-enolates are thermodynamically more stable than the trans forms by approximately 3.9-6.5 kcal/mol. In the active cis-enolate, the N-substituted group is prone to be “trans” to the oxo group and this mode is reinforced by the presence of the bulky triazolium moiety. The stereochemistry of 2-oxoindolin-3-ylidenes in this [4+2] cycloaddition reaction proved to exhibit an (E)-configuration. The cis-diastereoselectivity would arise from acis-enolate reacting as the dienophile with (E)-2-oxoindolin-3-ylidenes via an endo-transition state. In this transition state mode, the re-face is completely blocked by the indane moiety of the carbene catalyst, leaving thesi-face more accessible for the [4+2] cycload-ditionwiththe2-oxoindolin-3-ylidene substrate (Figure1).

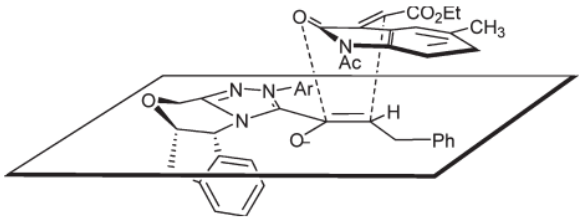
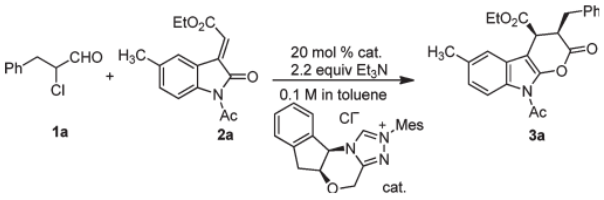


Fig 1. Proposed transtion state

To test the concept, we carried out the reaction using 2.0 equiv of α-chloroaldehyde 2a and 3-alkylenyloxindole1a with N-mesityl-substituted triazolium salt in the presence of base. The results were summarized in Table 1. As expected, 20 mol % of N-mesityl substituted triazolium salt effectively promoted the reaction in the presence of Et3N in dichloromethane at room temperature and deliv-ered the desired product with excellent

diastereo- and enantioselectivity (Table 1, entry 1). Next, the use of different basesandsolventswas evaluated for this reaction. DIPEA was found to slightly decrease the enantioselec-tivity (entry 2). When DBU was employed, the yield decreased dramatically even though there was no loss in diastereo- and enantioselectivity (entry 3). We observed that the inorganic bases were deemed to be unsuitable for the reaction, as they led to lowered yields and enantio-selectivities (entries 4 and 5).

Table 1.Optimization of Reaction Conditions[a]

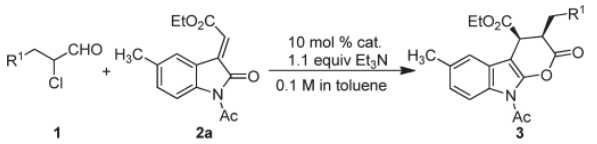


entry	solvent	base	*t* (h)	yield (%)[b]	*ee* (%)[c]	*dr*[d]
1	CH_2Cl_2	Et_3N	6.5	64	90	>99:1
2	CH_2Cl_2	DIPEA	7	60	86	>99:1
3	CH_2Cl_2	DBU	5	20	90	>99:1
4	CH_2Cl_2	Cs_2CO_3	3	43	83	>99:1
5	CH_2Cl_2	*t*-BuOK	1.5	50	88	>99:1
6	EA	Et_3N	0.3	65	85	>99:1
7	Et_2O	Et_3N	4	80	87	>99:1
8	THF	Et_3N	1	67	85	>99:1
9	$CHCl_3$	Et_3N	0.5	73	94	>99:1
10	*n*-hexane	Et_3N	18	80	96	>99:1
11	PhCl	Et_3N	3	60	87	>99:1
12	toluene	Et_3N	0.5	82	97	>99:1
13[e]	toluene	Et_3N	0.6	82	97	>99:1
14[f]	toluene	Et_3N	18	75	92	>99:1
15[g]	toluene	Et_3N	10	70	95	>99:1
16[h]	toluene	Et_3N	0.2	60	95	>99:1

[a] Unless otherwise specified, the reaction was performed on a 0.2 mmol scale in solvent (2 mL) at rt. [b] Yields of isolated products. [c] *ee* values determined by HPLC analysis on Chiralcel IA, IB, or IC column (see the Supporting Information). [d] *dr* values determined by ^{1}H NMR. [e] Used 10 mol % of catalyst and 1.1 equiv of Et_3N. [f] 5 mol % of catalyst used. [g] Performed at 0 °C. [h] Performed at 30 °C.

With the optimal reaction conditions established, the scopeof this [4+2] cycloadditionwas investigated (Tables 2 and 3). The reaction proceeded smoothly for a broad spectrumofR-chloroaldehydes to afford the desired prod-ucts in good yields and excellent optical purity (Table 2), with the exception of 3-(benzyloxy)-2-chloropropanal (entry 7). The lower enantioselectivity of3gwas presum-ably due to the easier formation oftrans-enolate species by using 3-(benzyloxy)-2-chloropropanal than other α-chloro-aldehydes. In general, α-chloroaldehydes derived from linear aliphatic aldehydes favor the [4+2] cycloaddition reaction with 3-alkylenyloxindole 2a to deliver good results (Table 2, entries 4, 5, and 8). The reactionwas also very well tolerated with 5-(benzyloxy)-2-chloropentanal in which optically pure products were obtained quantita-tively within 30 min (Table 2, entry 6).

Table 2.Substrate Scope of NHC-Catalyzed [4þ2] Cycloaddition[a]



entry	R^1 (**1**)	*t* (h)	yield (%)[b]	*ee* (%)[c]	*dr*[d]
1	C_6H_5 (**1a**)	0.6	82 (**3a**)	97	>99:1
2	4-BrBnOC_2H_4 (**1b**)	0.5	87 (**3b**)	98	>99:1
3	TBSOC_2H_4 (**1c**)	14	70 (**3c**)	95	>99:1
4	C_3H_7 (**1d**)	6	82 (**3d**)	98	>99:1
5	CH_3 (**1e**)	0.5	90 (**3e**)	>99	>99:1
6	BnOC_2H_4 (**1f**)	0.3	92 (**3f**)	>99	>99:1
7	BnO (**1g**)	1	72 (**3g**)	82	>99:1
8	C_6H_{13} (**1h**)	0.3	93 (**3h**)	99	>99:1

[a] Reaction was performed in 0.2 mmol scale in anhydrous toluene (2 mL) at rt. [b] Yields of isolated products. [c] *ee* values determined by HPLC analysis on Chiralcel IA, IB, or IC column (see the Supporting Information). [d] *dr* values determined by ^{1}H NMR.

In conclusion, a chiral NHC-catalyzed Diels-Alder reaction of 2-oxoindolin-3-ylidenes and R-chloroalde-hydes was developed for the synthesis of fused 3,4-dihydropyrano[2,3-b]indol-2(9H)-ones in good to excel-lent yields (up to 99%) with high cis-diastereoselectivities (>99:1 dr) and enantioselectivities (up to 99% ee). This protocol holds great potential in the synthesis of biologically active fused pyrano[2,3-b]indole derivatives in high enantiomeric purity.

Reference: Yang, L.; Wang, F.; Chua, P. J.; Lv, Y.; Zhong, L.-J.; Zhong, Guofu* *Org. Lett.* 2012, 14, 2894–2897.

Organocatalytic Michael Addition Using 2-Aminopyridine Catalyst Based on Molecular Recognition

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Double proton transfer including two hydrogen bonds are used for its tautomerization of 2-pyridone (Figure 1, left). In this study, we proposed that 2-aminopyridine is able to recognize 1,3-dicarbonyl compounds through two hydrogen bonds and generate ammonium enolate under mild conditions (Figure 1, right).

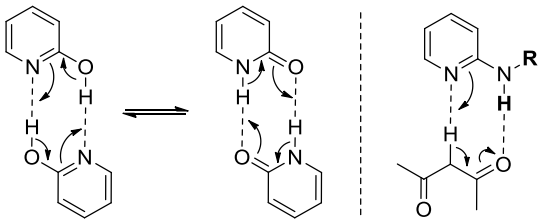
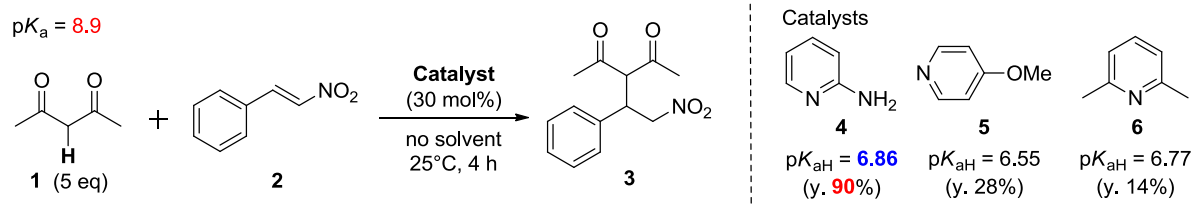


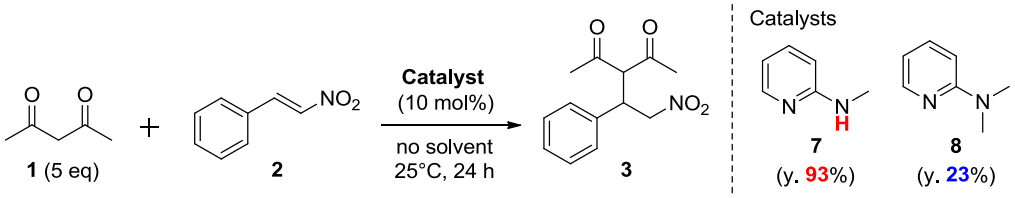
Figure 1. Activation of carbonyl compound through hydrogen bonds

In the beginning, we examined the catalytic ability of pyridine derivatives towards Michael addition. In the presence of 2-aminopyridine (**4**), Michael product **3** was obtained in 90% yield, on the other hand, the use of 4-methoxypyridine (**5**) and 2,6-lutidine (**6**) gave **3** in 28% yield and 14% yield, respectively. These results showed that 2-aminopyridine (**4**) has efficient catalytic ability despite weak basicity.



Scheme 1. Michael addition using pyridine derivatives as a catalyst

To prove the molecular recognition mechanism as mentioned in Figure 1, *N*-methyl-2-aminopyridine (**7**) and *N*,*N*-dimethyl-2-aminopyridine (**8**) were used. Reactions employing catalyst **7** and **8** also proceeded, which afforded the same Michael product **3** in 93% and 23% yield, respectively (Scheme 2). Therefore, the catalyst **7** could recognize acetylacetone (**1**) through two hydrogen bonds and catalyst **8** could not recognize the substrate **1** because of existence of tertiary amino group.



Scheme 2. Effect of α-substituted amino group

Encouraged by these results, we subsequently examined various 2-aminopyridine derivatives (Figure 2). *N*-methyl-2-aminopyridine (**7**) was the most efficient catalyst among other substituted 2-aminopyridines (**9**-**12**). In addition, catalyst loading could be decreased to 0.5 mol%, giving the adduct **3** in 87% yield.

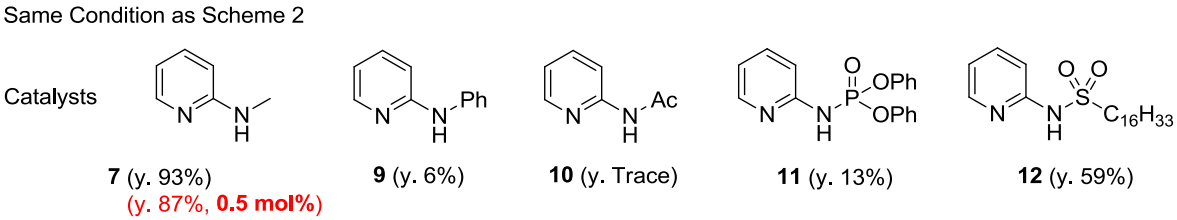
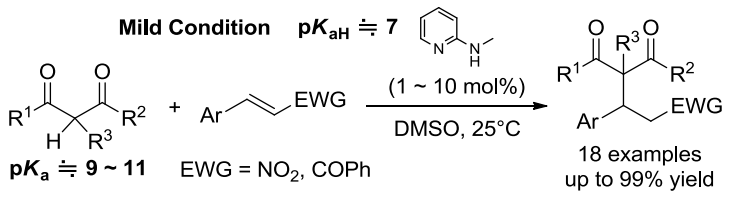


Figure 2. Substituent effect of 2-aminopyridine catalyst

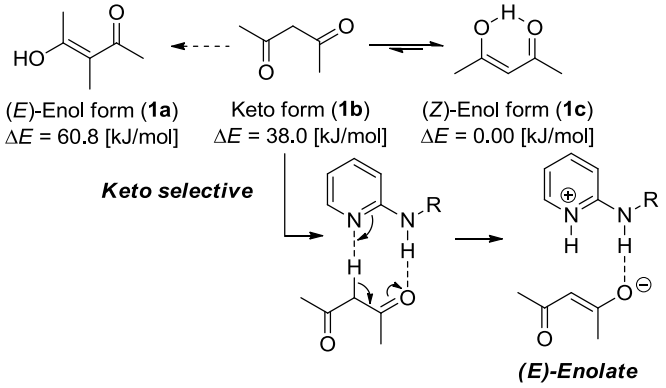
With the optimized conditions, we evaluated the scope and limitation of the substrate of Michael addition. In the presence of catalytic amount of *N*-methyl-2-aminopyridine (**7**) in DMSO, various 1,3-dicarbonyl compounds smoothly react with Michael acceptors in excellent yields (Table 1). In addition, this catalytic system was not influenced by reactive functional groups such as phenolic hydroxyl and pyridyl groups.

Table 1. Scope and limitation of the substrate of Michael addition



R^1	R^2	R^3	Ar	EWG	Yield (%)
Me	Me	H	4-CNC_6H_4	NO_2	83
Me	Me	H	4-$MeOC_6H_4$	NO_2	96
Me	Me	H	4-HOC_6H_4	NO_2	96
Me	Me	H	Pyridine	NO_2	79
Me	Me	H	Ph	COPh	80
OEt	Me	H	Ph	NO_2	91
OMe	-$(CH_2)_3$-		Ph	NO_2	93

To clarify the mechanism of 2-aminopyridine-catalyzed Michael addition, ^{1}H NMR analyses were performed. Based on the result, 2-aminopyridine catalyst can selectively activate keto-form acetylacetone (**1b**) and convert it to relatively unstable (*E*)-form enolate (Scheme 3).



Scheme 3. Proposed reaction mechanism

In conclusion, 2-aminopyridine derivatives as an organocatalyst could recognize 1,3-dicarbonyl compounds through hydrogen bond and generate ammonium enolate despite weak basicity. *In-situ* formed enolate reacts with various Michael acceptors to construct carbon-carbon bond. Furthermore, ^{1}H NMR analyses suggest that 2-aminopyridine catalyst have characteristic mechanism of activation in which keto-form acetylacetone selectively converts to relatively unstable (*E*)-form enolate.

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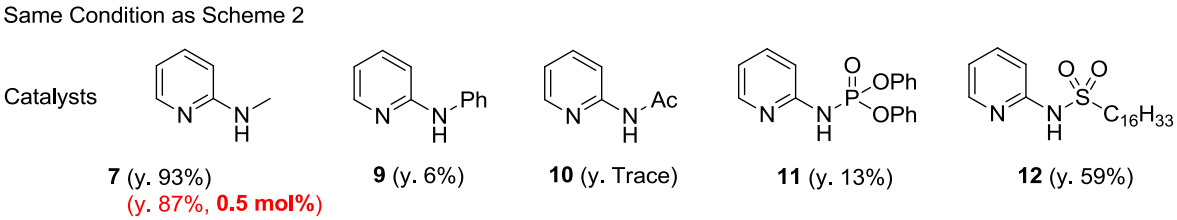

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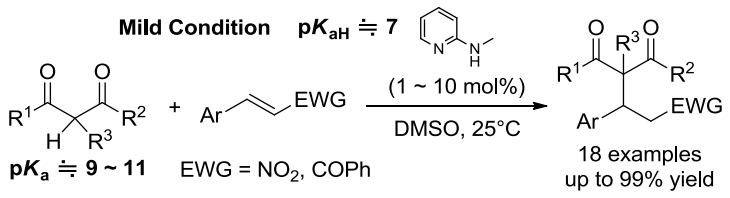

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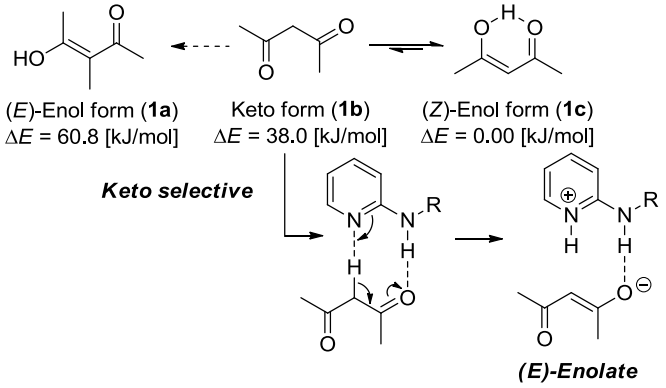

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