A METHODOLOGY FOR THE EFFICIENT AND RAPID CONSTRUCTION OF HETERO- AND CARBOCYCLES ON SOLID-PHASE

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General Introduction

Solid-phase organic synthesis (SPOS), which was originally developed by Merrifield in 1960's,[1] has received a great attention among synthetic chemists owing to its essential advantages: easier isolation and convenient handling. Now it is acknowledged as one of the most active research areas, and a lot of reports describing this often found in the literatures.[2] In this methodology, as a substrate (or a catalyst) is immobilized on polymer support (usually polystyrene-divinylbenzene co-polymer), after a reaction, a desired product is able to be obtained on a filter, and a rest of stuff, excess reagents and byproducts, is easily removable by washing.

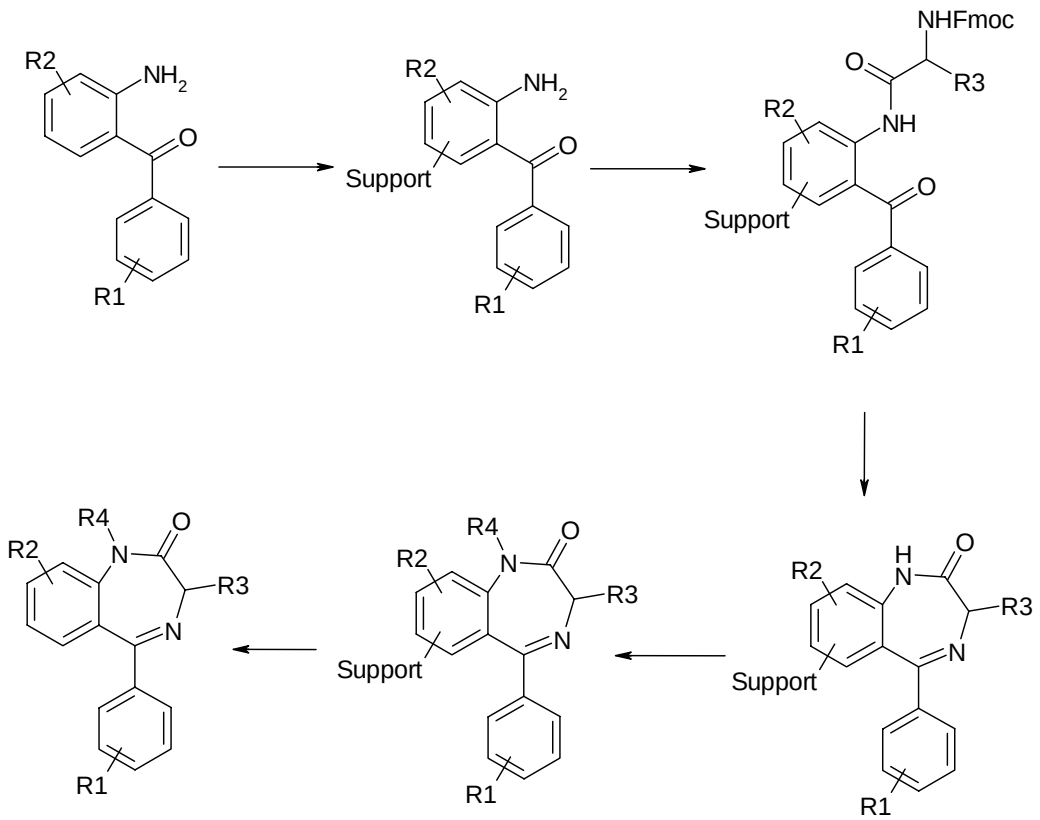
In our daily workflow of experiments, both work-up and isolation are the most time-consuming and tedious processes. In addition, the standardization of these processes could be hardly achieved. These difficulties were preventing to speed-up of our workflow and let us use the "traditional procedures" which have been employed over a hundred years. Solid-phase approach has inserted the surgical knife to this "bottle-neck" of the synthetic process, and impacted on the synthetic organic chemistry.

The solid-phase synthesis was first developed for peptide synthesis and many bioactive peptides and oligomers were synthesized on beads. Numerous amounts of the investigations to optimize the process were reported, and solid-phase peptide methods rapidly matured. Besides that, since it is true that the process is suitable for automation, the general automated synthesizer has also been developed and is now widely accepted for peptide synthesis.

By recent progression of molecular biology and automation, biological assay system which is enable to evaluate a lot of samples in a short time period has been revolutionary developed. The biological assay has evolved from the rate-limiting step to the driving force in the need for large numbers of compounds, and thus the driving force of combinatorial

chemistry.

While a lot of peptides and oligomers can be provided by solid-phase synthesis and automated system, basically same type of coupling reaction is repeated and building blocks are limited so that a diversity of the resulting products is essentially reserved. In other words, genuine structural diversity is only achievable by the use of any kind of reactions as well as unlimited variety of building blocks. Besides that, peptides and oligomers are usually unstable for the oral administration.



Scheme I. Bunin and Ellman's solid-phase synthesis of 1,4-benzodiazopines

After the reports of solid-phase syntheses of 1,4-benzodiazopines by Bunin and Ellman[3] in 1992, and followed report of solid-phase synthesis of Diversomers by Dewitt[4] shortly thereafter, these stimulated considerable interest in a low molecular weight organic compound.

Bunin and Ellman's solid-phase synthesis of 1,4-benzodiazopines (Scheme I) is an excellent illustration of the process of combinatorial library production using organic templates. These reports have initiated the recent trend, especially among pharmaceutical companies, of the heat of the investigation and reports of library synthesis of the low molecular organic compound and useful methodology for solid-phase synthesis.

However, there is still big room to improve for solid-phase organic reactions to be filled up in comparison with solution-phase syntheses. In this regards, this thesis describes developments of the methodologies for the efficient and rapid construction of hetero- and carbocycles on solid-phase. In part 1, efficient pyridine ring formation by multi-component condensation on solid-phase is described. This reaction is well presented inherent advantages of solid-phase reaction. The use of solid-phase reaction enhanced the reactivity and resulted in superior yield and selectivity than these of solution-phase synthesis. In part 2, diastereoselective [2+2] photocycloaddition of polymer-supported chiral enone with ethylene by using (-)-8-phenylmenthyl derivatives as a chiral auxiliary is described. In spite of its powerful potential to construct complex molecules, photochemical reaction on solid-phase is not well examined. We also investigate the effect of solid support on the reactivity and selectivity.

References

[1] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

[2] (a) Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry-synthesis and application*; Wiley: New York, **1997**; (b) Bunin, B. A. The Combinatorial Index; Academic press: San Diego, **1998**; (c) Czarnik, A. W. *Solid-phase organic syntheses, Vol. 1*; Wiley: New York, **2001**.

[3] Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997-10998.

[4] DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909-6913.

Part 1. Efficient Synthesis of 6-(2-Hydroxyphenyl)pyridines by Multi-Component Condensations on Beads and Its Application to the Drug Discovery

1. Introduction

Asthma is one of the most serious allergic diseases, which causes a chronic inflammation of the airways of the lung. Chronically inflamed airways turn into hyperresponsive. Therefore, they get easily obstructed and airflow is limited by bronchoconstriction, mucus plugs, and increased inflammation when exposed to a variety of stimuli including environmental antigens, such as dust mite, fur, pollen, mold, tobacco smoke, air pollution, exercise, strong emotional stress, or chemical tightness. These result in difficulties in breathing, and asthma attacks sometimes can be life threatening.[1]

Since asthma is a chronic disorder requiring long-term management, patients have to take preventive medication every day. Relievers (rescue medication) include short-acting bronchodiluting medications, which act quickly to relieve bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing, but have no effect on the inflammation, which is underlying asthma. Controllers are medications taken daily on a long-term basis that are useful in getting and keeping persistent asthma under control. Corticosteroids have been commonly used as the anti-inflammatory treatment of asthma. However, these drugs require inhalers to be used. Besides that, many people are concerned about side effect of the steroids.

Currently available medications can manage symptom in mild to moderate asthma. However, there are difficulties of well-controlling in moderate to severe asthma even increasing daily doses. Furthermore, higher doses arise other concern regarding adverse effects, particularly with inhaled corticosteroids.[2] As the result, there is a strong demand for novel, orally active agents that are as effective as steroids, but which are better tolerated and show disease-modifying activity. Especially, such agents are considered necessary for the treatment of moderate to severe asthma in adults as well as children.

Protein kinases that regulate the activity of specific transcription factors in response to extracellular stimuli are attractive targets for the treatment of inflammatory conditions including asthma, allergic rhinitis, atopic dermatitis, conjunctivitis and rheumatoid arthritis.

IκB kinase β (IKK- β) is a 756 amino acid-containing serine-threonine protein kinase, and exists as the IKK-complex containing IKK-α, IKK-γ, NIK and various other known and unknown proteins in most cell types.[3] The signaling pathways from a variety of inflammatory stimuli converge upon IKK-β, which then activates the nuclear factor κB

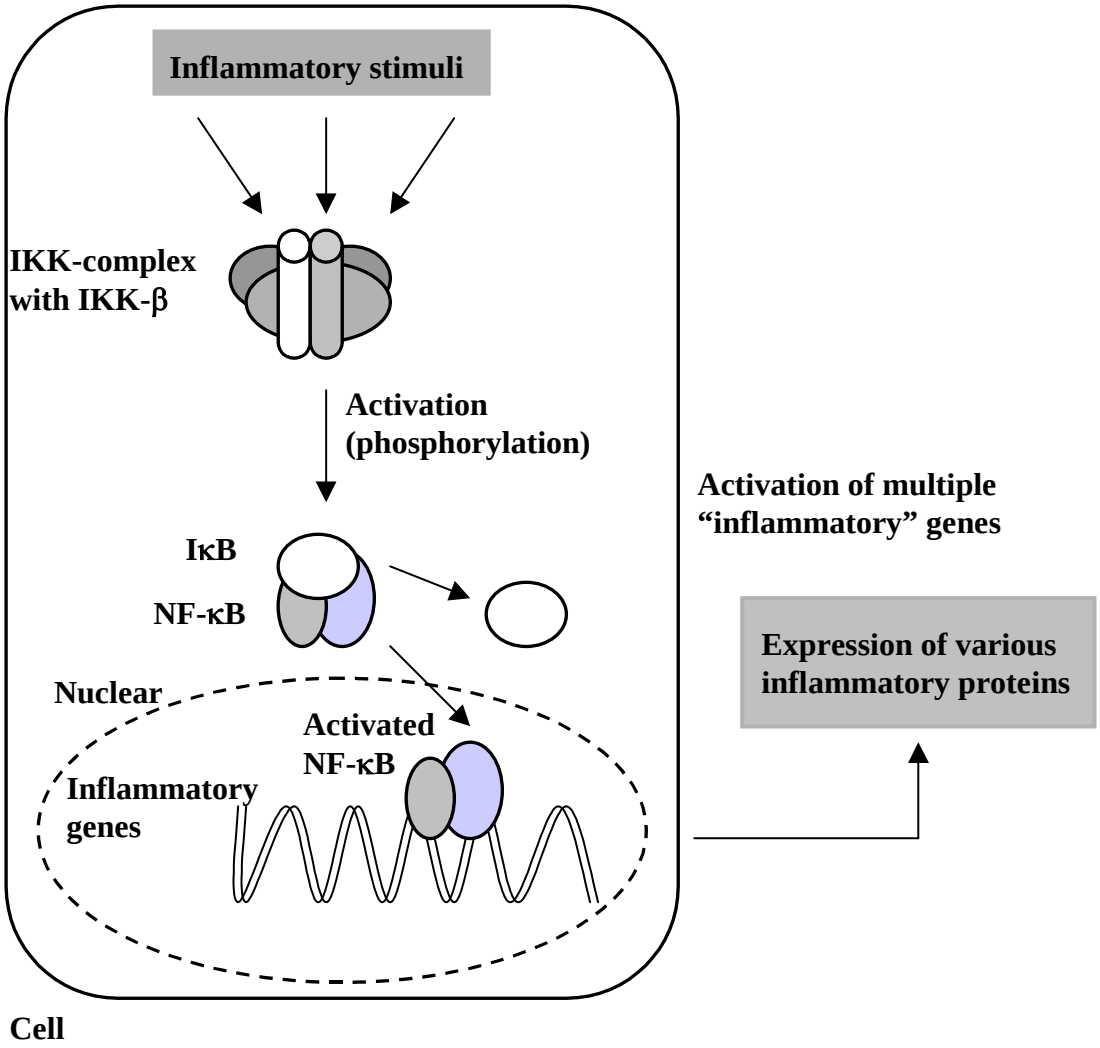
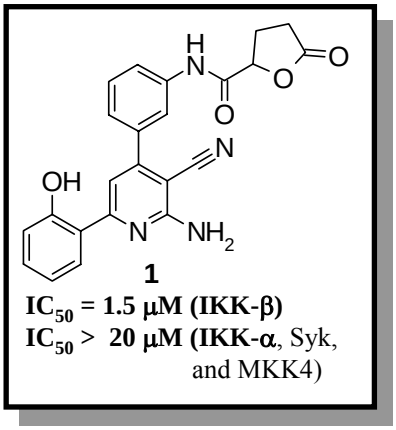


Figure I. Signal pathways leading to the transcription facor NF-κB

(NF-κB) through phosphorylation of IκB inhibitory proteins. NF-κB transcription factors regulate the expression of a large number of genes that are involved in appropriate functioning of immune systems and key mediators of inflammatory responses (Figure I).[4] In fact, several experiments indicate that the activated NF-κB contributes to asthma pathophysiology and that inhibition of NF-κB activation will improve asthma symptoms. In addition, it has been reported that the activated NF-κB has been identified in the airways of asthma patients, but not in normal ones.[5] In the animal model, NF-κB knock-out mice were incapable of mounting an eosinophilic airway inflammation as compared to wild-type mice.[6] These experimental results, therefore, suggest that specific IKK-β inhibitors are expected to show strong *in vivo* anti-inflammatory and immuno-modulatory effect and to result in replacement of corticosteroid drugs for asthma therapy.

2. Lead compound finding

The 2-amino-3-cyano-4-aryl-6-(2-hydroxyphenyl)pyridine analogue **1** was identified as a lead candidate of selective IKK-β inhibitors from high-throughput screening of the Bayer compound repository (Figure II). The lead compound **1** shows potent inhibitory activity



1

IC_{50} = 1.5 μM (IKK-β)
IC_{50} > 20 μM (IKK-α, Syk, and MKK4)

Figure II. The structure of the lead compound 1

against IKK-β (IC_{50} = 1.5 μM) and excellent selectivity over other kinases such as IKK-α, Syk, and MKK4 (Mitogen-acitivated protein kinase kinase 4) (IC_{50} = > 20 μM). In addition, this lead compound inhibits NF-κB-dependent expression of several reporter genes, chemokines, cytokines, and IgE production in various functional cellular assays (Table I).

Table I. Inhibitory activities of the lead compound 1

Cells/Cell Line	Stimulus	Read-Out	IC_{50} (μM[a])
A549	TNFα	RANTES	8
Jurkat T-cell	anti-CD3/ anti-CD28	IL-2	15
HEK293	TNFα	NF-kB-Luciferase	8
Mouse B-cells	LPS/IL-4	IgE	0.35
Human PBMCs	LPS	TNFα	10

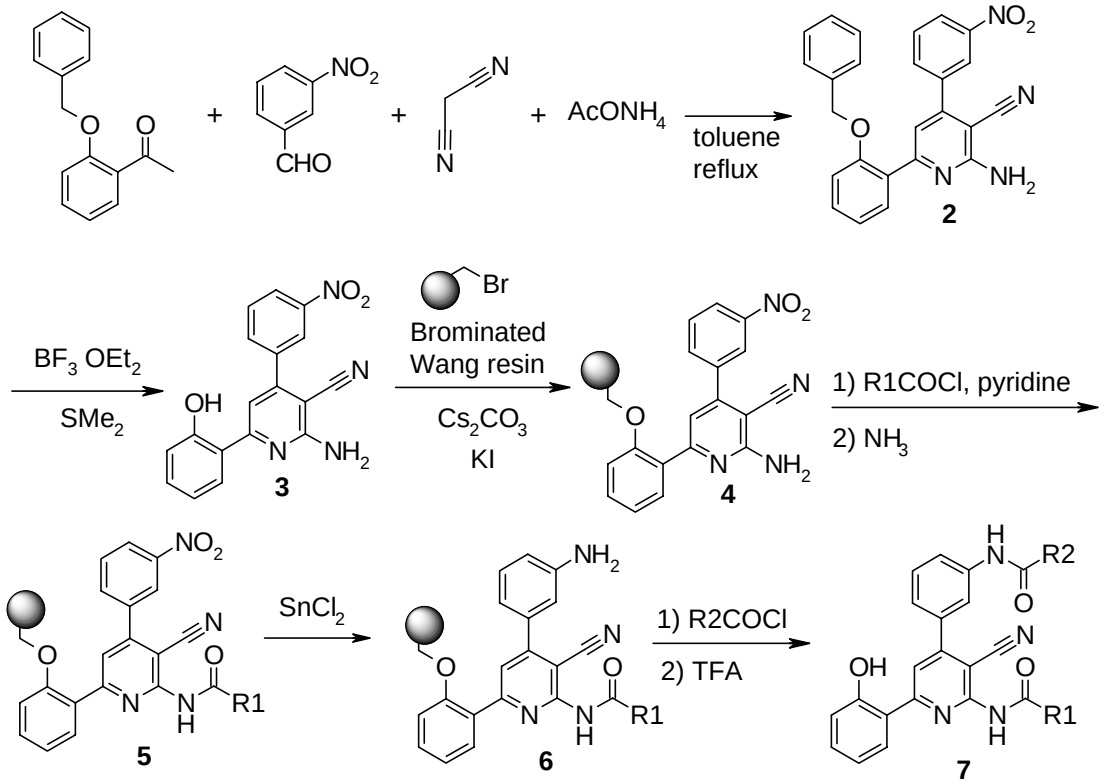
[a] Values are means of more than three experiments

These results suggest that the compound **1** is a lead structure for specific inhibitors of the IKK-complex activated by various inflammatory stimuli and it can be therefore pharmacologically confirmed that IKK-β is a key constituent of the signal transduction pathway in those physiological responses.

The preliminary structure-activity relationship (SAR) study revealed that modifications of 4-aryl group were tolerated while both 2-amino and 6-(2-hydroxy)phenyl groups will be essential for the potency. In addition, substituents of the 4-phenyl moiety could contribute to improve the compound solubility. In order to optimize the 4-position in a short time, an efficient methodology to prepare the analogues of the lead compound **1** was required. Therefore, preparation of the analogues was conducted by solid-phase chemistry.

3. Solid-phase synthesis of pyridine ring

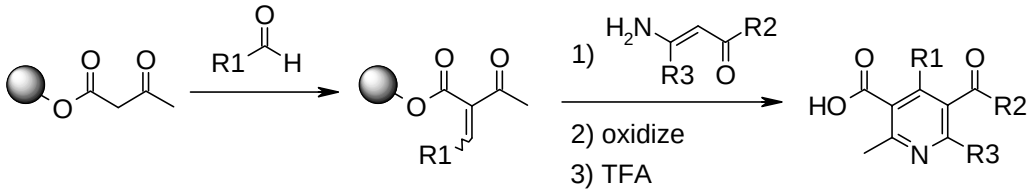
The lead compound **1** was originally supplied as a member of random library according to the procedure shown in Scheme I. However, the corresponding core scaffold (2-amino-3-cyano-4-(3-nitro)phenyl-6-(2-hydroxyphenyl)pyridine **2)** has to be synthesized by a traditional way to be applied to the combinatorial chemistry. Therefore, this procedure was only applicable to the synthesis of 4-(3-carboxamido)phenyl analogues and not suitable for the library of a wide variety of 4-aryl analogues. Besides that, the chemical yield of **2** was only less than 50% and its purification was too cumbersome to supply enough amounts of materials to our library syntheses, which required an efficient way to build up the core skeleton on beads.



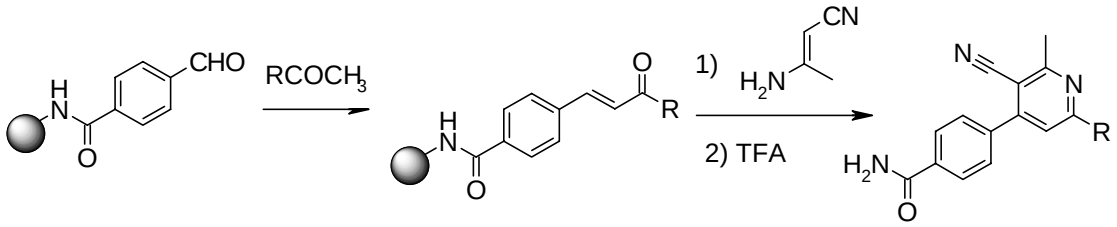
Scheme I. The original procedure for the lead compound 1

Heteroaromatic rings containing nitrogen atoms often play important roles as the scaffolds of bioactive substances.[7] Pyridine is one of the most popular *N*-heteroaromatics incorporated into the structure of many pharmaceuticals. Therefore, development of efficient procedures towards functionalized pyridines is a quite attractive target for solid-phase combinatorial chemistry. There are several papers describing about solid-phase synthesis of pyridines and they are categorized into the following three types (Scheme II): (i) Knoevenagel and Hantzsh condensation chemistry from β-keto esters,[8] (ii) [3+3] pyridine synthesis from α, β-unsaturated ketones,[9] (iii) Krohnke type cyclization with 1,5-diketone and ammonium acetate.[10] However, these methods have a limitation on the applicable building blocks and none of them were suitable to the analogue syntheses of the lead

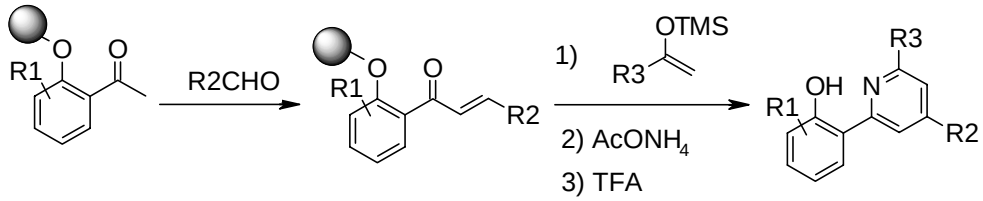
i) Knoevenagel and Hantzsh condensation from β-ketoester



ii) [3+3] Pyridine synthesis with α,β-unsaturated carbonyl



iii) "Krohnke" type cyclization with 1,5-diketone

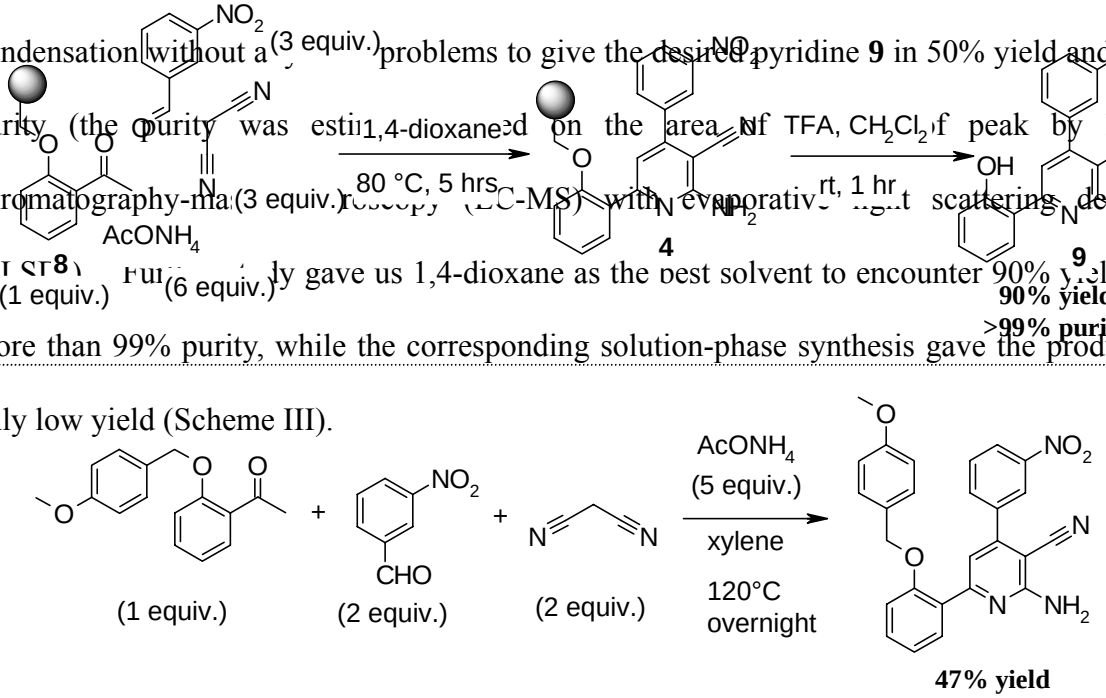


Scheme II. Known solid-phase synthesis for pyridine ring formation

compound **1**.

As 2-hydroxy group on 6-phenyl ring of pyridine was found to be critical to maintain

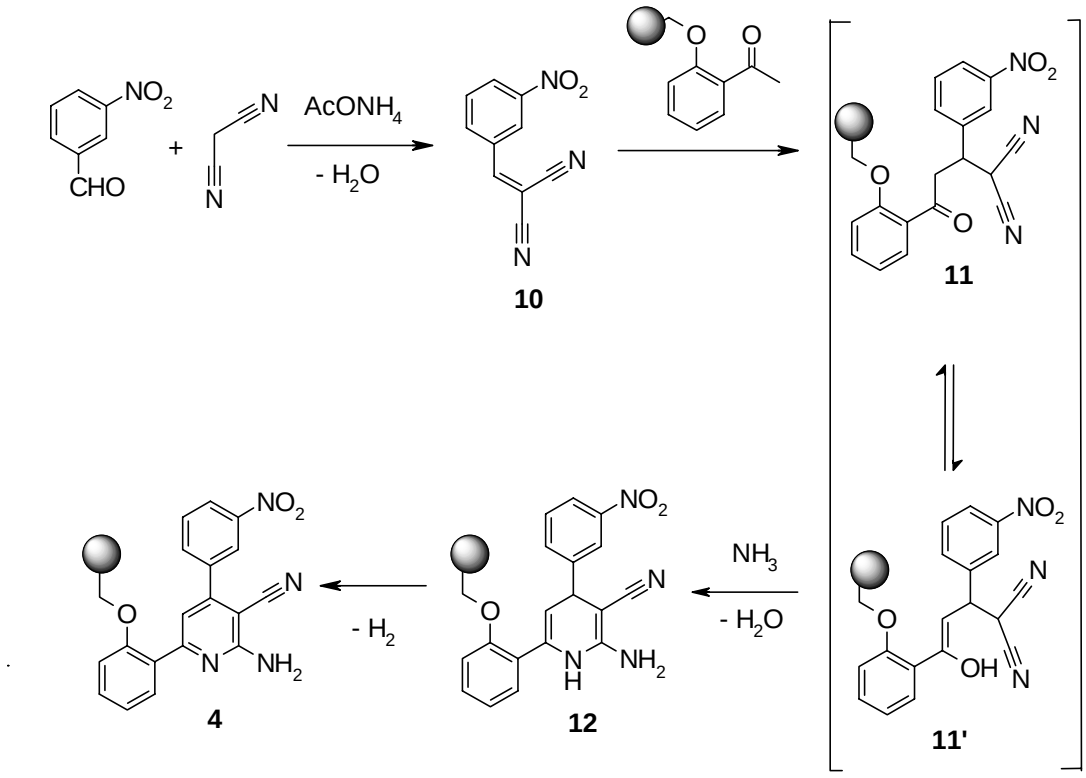
the activity from the preliminary SAR, we chose it as the immobilization point to the resin. 2-Hydroxyacetophenone (3 equiv.) was reacted with brominated Wang resin (purchased from Nova Biochem) in the presence of potassium carbonate (3 equiv.) in DMF at room temperature to give the resin bound acetophenone. The subsequent condensation with aldehydes (3 equiv.) and malononitrile (3 equiv.) in the presence of ammonium acetate (6 equiv.) was carried out in the following manner: the mixture was suspended in a solvent in a reaction vial and agitated at 80°C for 8 hours with a screw cap. The resin was collected on a filter and washed with dichloromethane and methanol, and it was followed by the cleavage reaction at room temperature for 1 hour with 50% trifluoroacetic acid (TFA) in dichloromethane. When the solvent was removed off by evaporation, the target pyridine was obtained as a TFA salt. In the original solution-phase procedure, toluene was used as the solvent but it is known that toluene gives a damage to polystyrene resins at higher temperature. Indeed toluene made a severe damage not only to polystyrene resins but also polypropylene reaction vessels at 80°C. A variety of organic solvent was applied to this reaction and it was found that *o*-xylene performed the solid-phase multi-component condensation without any problems to give the desired pyridine **9** in 50% yield and 72% purity (the purity was estimated on the area of peak by liquid chromatography-mass spectroscopy (LC-MS) with evaporative light scattering detector (ELSD). Further study gave us 1,4-dioxane as the best solvent to encounter 90% yield and more than 99% purity, while the corresponding solution-phase synthesis gave the product in only low yield (Scheme III).



Scheme III. Solid- and solution-phase multi-component condensation

4. The interpretation of the reaction mechanism

The assumed reaction mechanism is shown in Scheme IV.



Scheme IV. Assumed reaction process of pyridine formation

The initial reaction step should be the Knoevengel condensation between benzaldehyde and malononitrile. Then, the Michael addition of acetophenone into the Knoevenagel adduct **10** followed by the cyclization with ammonia probably takes place to give the dihydropyridine analogues **12**. In fact, a small amount of the dihydropyridine analogue **12** was observed in the crude product in the solution-phase reaction. Detection of compound **13** in the reaction mixture leads to the speculation that the initial product of this reaction, the dihydropyridine **12**, is oxidized by excess amounts of benzylidenmalononitrile **10** which is

formed by the Knoevenagel reaction between benzaldehyde and malononitrile (Figure III). This oxidation process contributes to the excellent yield that was achieved in this reaction.

On the other hand, the corresponding solution-phase reaction gave the target pyridine only in poor yield along with many byproducts. In order to improve the yield of the solution-phase synthesis, several efforts were conducted. The use of two equivalents of benzaldehyde and malononitrile along with five equivalents of ammonium acetate against acetophenone, instead of stoichiometric use of each reagent, improved the yield from 29% to

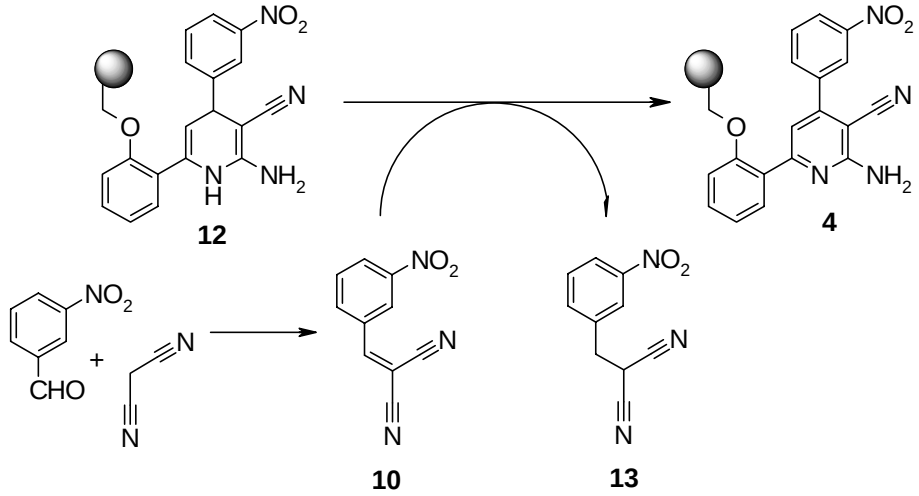


Figure III. Assumed oxidation process of dihydropyridine

47%. However, further increase in the amount of each component as used in the solid-phase synthesis (3 equiv. of benzaldehyde and malononitrile, and 6 equiv. of ammonium acetate) didn't improve the yield. Even worse, addition of excess reagents led to increasing of impurities which made isolation more laborious. This is a good example of demonstrating the inherent advantage of solid-phase chemistry that excess amounts of reagents can be used without any additional concern about their removal from the reaction mixture after completion of the reaction. Another important cause of the lower yield in solution-phase synthesis is probably the undesired intermolecular reactions. Since this is the multi-component reaction, many of products could be considered. Immobilization of

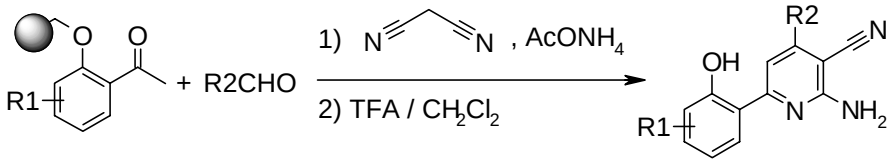
acetophenone component onto the resin is most likely critical to achieve the high yield. For example, the assumed intermediate **11** (or **11'**) could be reacted with another portion of acetophenone instead of intramolecular cyclization in the solution-phase synthesis. In contrast, such reaction should be prevented owing to site isolation of every substrate on the resin. Generally, the intramolecular cyclization is preferable in solid-phase because of pseudo-dilution environment by immobilization. The attempt with high diluted conditions in the solution-phase, however, was not improved the yield and the purity either. Surprisingly, relatively high concentration conditions gave better result than the high-diluted conditions in the solution-phase synthesis. Although reasons of this observation are not clear yet, such high concentration conditions would make it better work for the process of the desired pyridine ring formation than the undesired processes to give byproducts. This solid-phase synthesis has a possibility to take this advantage because high concentrated environment of reagents around the immobilized substrate might be locally formed by unique highly hydrophobic environment within the polymer backbone, diffusion into the interior of polymer support, and reagent-polymer interaction, which sometimes provides a unique product as well as selectivity that may be difficult to achieve by conventional methods.[11]

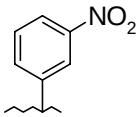
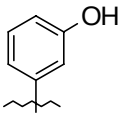
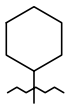
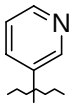
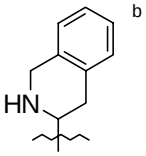
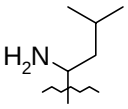
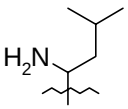
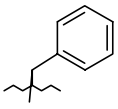
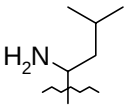
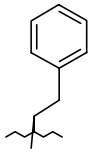
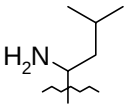
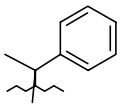
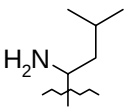
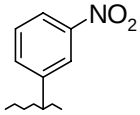
Although further investigations are required to elucidate an actual reason of the difference between solid- and solution-phase syntheses as well as to improve the efficacy in the solution-phase synthesis, genuine possibilities are discussed above. At least, it is sure that under the close conditions solid-phase synthesis provided superior results than the corresponding solution-phase synthesis, and its procedure is simple enough to carry out a production of many compounds.

5. Investigation of pyridine ring formation with various acetophenones and aldehydes

In order to verify versatility and generality of this pyridine ring formation reaction, various kinds of acetophenones and aldehydes were subjected to the reaction to give the corresponding 2-amino-3-cyanopyridines, and representative examples are listed in Table II. Almost all of the 2-hydroxyacetophenones gave expected pyridines in quantitative yields and purities, however, 2-hydroxy-6-allyloxyacetophenone (Entry 18) proceeded together with many byproducts, perhaps due to the steric hindrance around ketone moiety. For the aldehyde component, not only aromatic but also aliphatic aldehydes proceeded well (Entries 6-17). This is a noteworthy example since there is only a few examples of 4-aliphatic pyridines synthesized by solid-phase chemistry.[12] Besides that, both 4-isovalel (Entry 10) and 4-cyclohexyl (Entry 11) pyridines were successfully obtained from the corresponding aldehydes, while such α-branched 4-alkyl moieties were often eliminated to give 4-unsubstituted pyridines in the oxidation stage.[13] These results showed that the range of the application of this reaction was much broader than that of other literatures' examples.

Table II. Investigation of multi-component condensation on beads



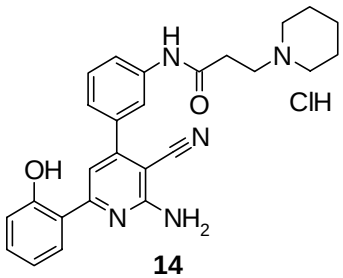
Entry	R1	R2	Purity (%)[a]	Entry	R1	R2	Purity (%)[a]
1	H		100	10	H		100
2	H		100	11	H		100
3	H		100	12	H		100[b]
4	H		100	13	H		100[b]
5	H		100	14	H		100[b]
6	H		63	15	H		100[b]
7	H		100	16	H		100[b]
8	H		100	17	H		100[b]
9	H		100	18	H		40

a) Purities were estimated based on ELSD. b) Boc-protected aminals were used.

6. Library syntheses

6.1. Library A: 2-Amino-4-(3-carboxamido)phenyl-3-cyano-6-(2-hydroxy)phenylpyridines

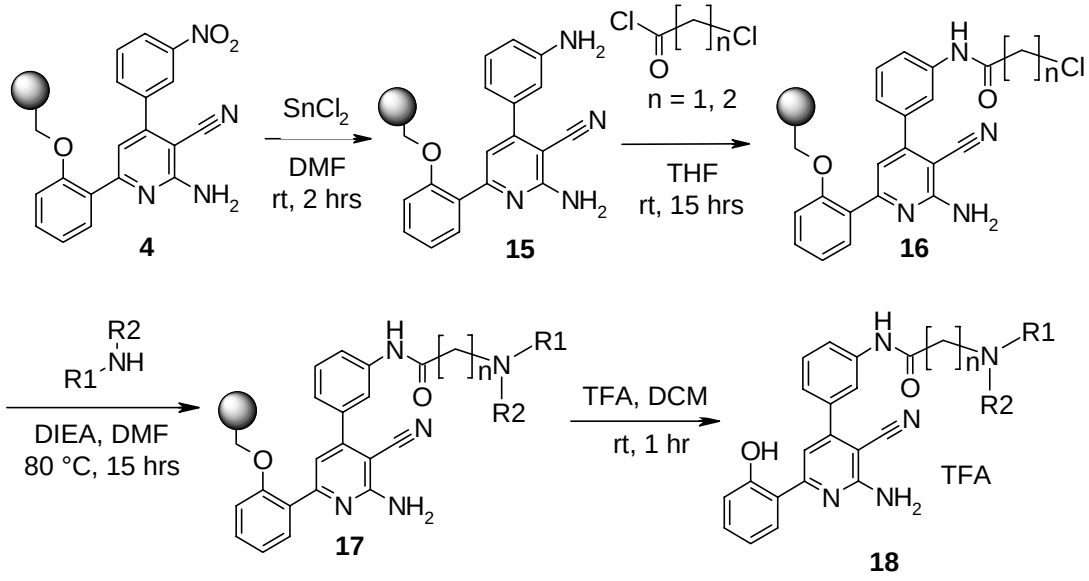
The compound **14** was synthesized during the preliminary SAR study and showed improved activity (IC_{50} = 600 nM, Figure IV) than that of the lead compound **1**. This compound **14** was chosen as a targeted structure for the first solid-phase library synthesis modifying around the carboxamido group of the compound **14**.



14

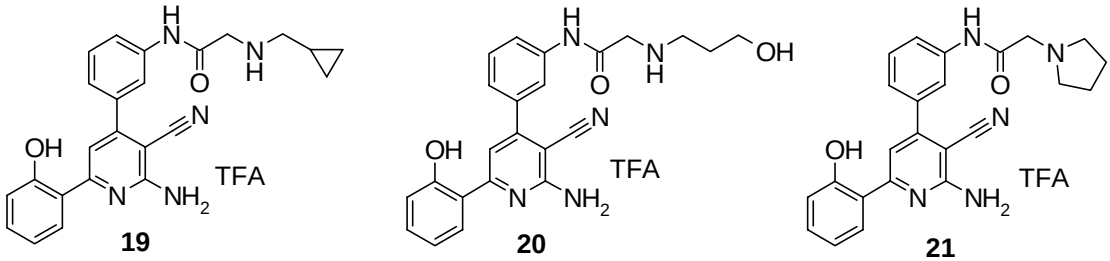
Figure IV. The potent compound found during the preliminary SAR study

A library synthesis was carried out according to the procedure shown in Scheme V. The pyridine ring was formed on polystyrene resin by the multi-component condensation, then it was followed by reduction of the nitro group with tin(II) chloride to give the corresponding aniline **15**. The regioselective acylation of this newly created amino group successfully proceeded using excess amount (3 equiv.) of chloroacetyl or 3-chloropropionyl chlorides in the absence of any bases. Following substitution reactions of the chloride with primary or secondary amines proceeded well at 80°C in 15 hours. Desired products **18** were successfully obtained by the cleavage reaction with 50% TFA in dichloromethane.



Scheme V. Library synthesis of Library A

All compounds were applied to LC-MS and only the compounds that showed right M+H ion peak with more than 75% purity on ELSD were sent to IKK-β inhibition assay. Compounds with more than 50% inhibition at 2.5 μM were purified by preparative HPLC (Gilson Uni Point System) to determine their IC_{50} values. In total, 313 compounds were screened and 27 compounds were selected to determine their IC_{50} values (Figure V).

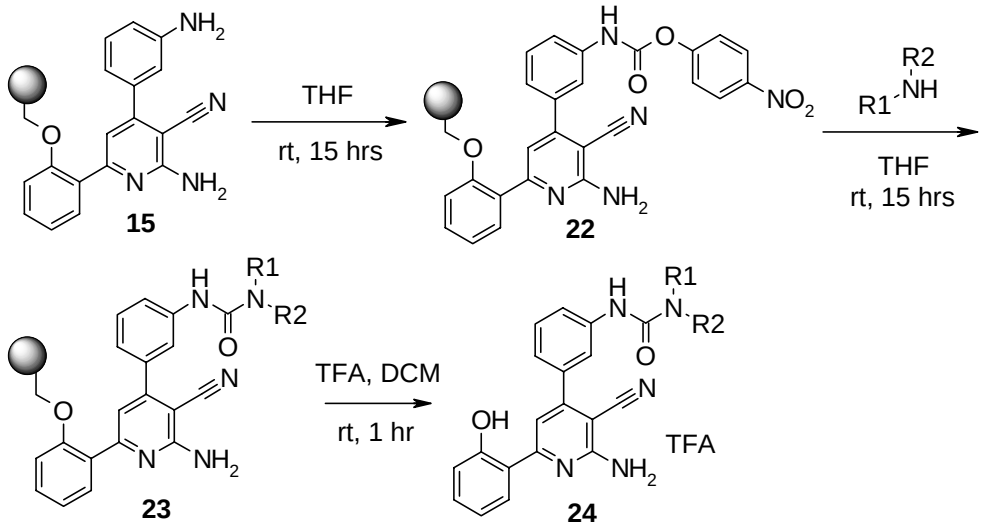


IC_{50} = 0.4 μM **IC_{50} = 0.48 μM** **IC_{50} = 0.53 μM**

Figure V. Potent compounds from Library A

6.2. Library B: 2-Amino-4-(3-carbamoylamino)phenyl-3-cyano-6-(2-hydroxy)phenylpyridines

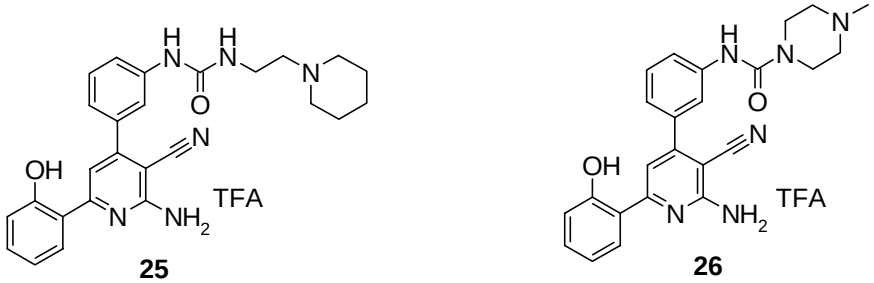
In order to modify the 4-aryl group with carbamoylamino group, we focused on the optimization of urea formation procedures and finally met the protocols shown in Scheme VI. Compound **15** was subjected to the reaction with 4-nitrophenyl chloroformate to give the corresponding carbamate **22** and treated with amines at room temperature to give ureas **23**. The following cleavage reaction with 50% TFA in dichloromethane gave desired compounds **24** successfully.



15 **22** **23** **24**

Scheme VI. Library synthesis of Library B

In total, 74 compounds were synthesized and sent to IKK-β kinase assay. However, none of the compounds showed below 1 μM of IC_{50} (Figure VI).



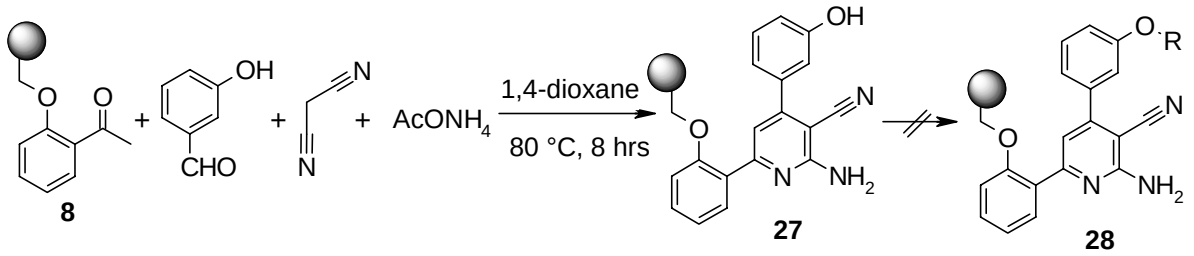
25 **26**

IC_{50} = 1 μM **IC_{50} = 3 μM**

Figure VI. Potent compounds from Library B

6.3. Library C: 2-Amino-4-(3-alkoxy)phenyl-3-cyano-6-(2-hydroxy)phenylpyridines

The multi-component condensation with *m*-hydroxybenzaldehyde proceeded well to give an immobilized 4-(3-hydroxyphenyl)pyridine **27** without any protection of the hydroxyl group. An attempt was made of the following *O*-alkylation in the presence of a variety of bases including Hunig base, potassium carbonate, and sodium hydride with (or without) heating, but the reaction did not proceed. No desired compound **28** was found by LC-MS analysis. Since Mitsunobu alkylation (alcohol, triphenylphosphine, and diethylazodicarboxylate) also resulted in the recovery of the **27**, we decided to suspend this library synthesis (Scheme VII).



Scheme VII. Attempts to make phenylether analogue

6.4. Library D: 2-Amino-3-cyano-6-(2-hydroxyphenyl)-4-disubstitutedarylpyridines

In order to further modify the 4-aryl moiety with amino or ether functionality, two sub-libraries shown in Figure VII were prepared.

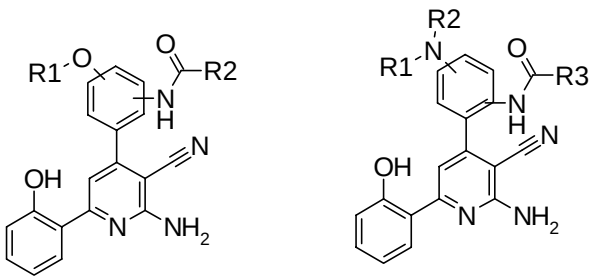
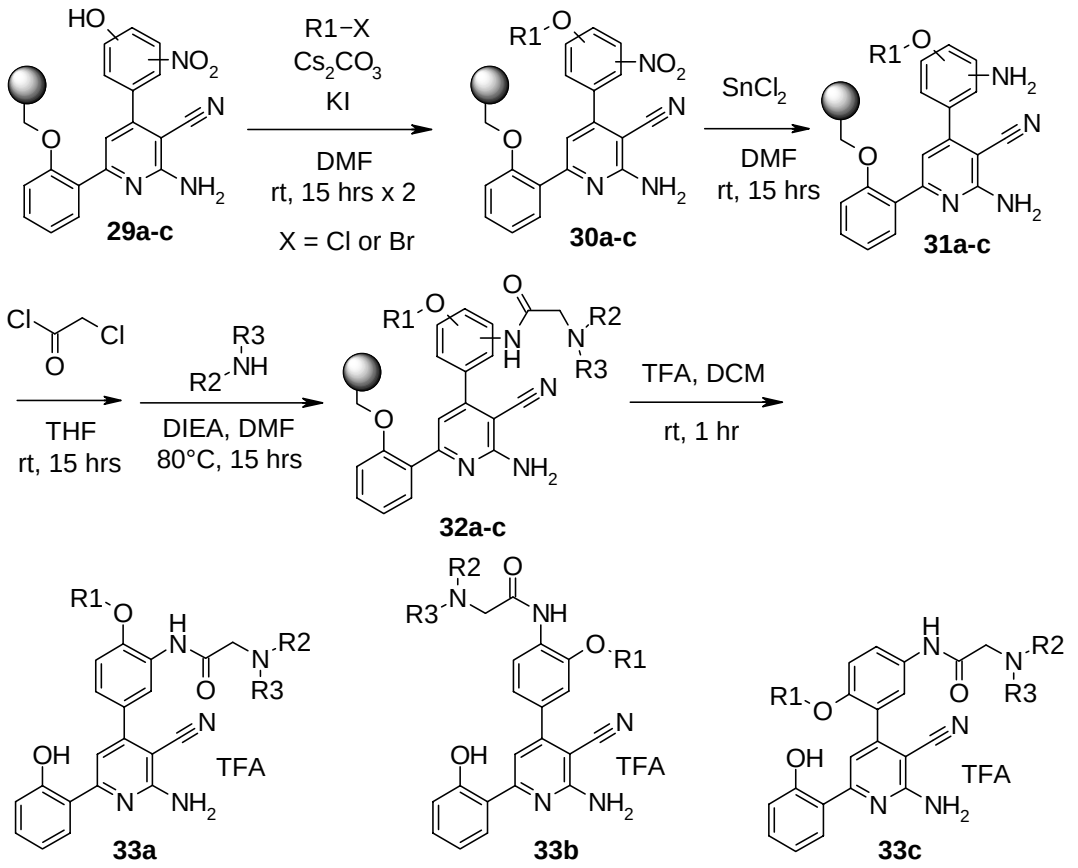
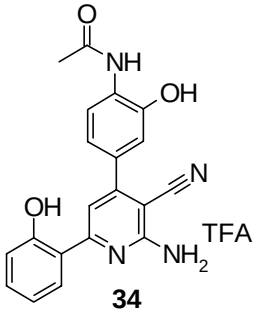


Figure VII. General structures of Library D-1 and D-2

Library D-1:



Scheme VIII. Library synthesis of Library D-1



IC_{50} = 0.16 μM

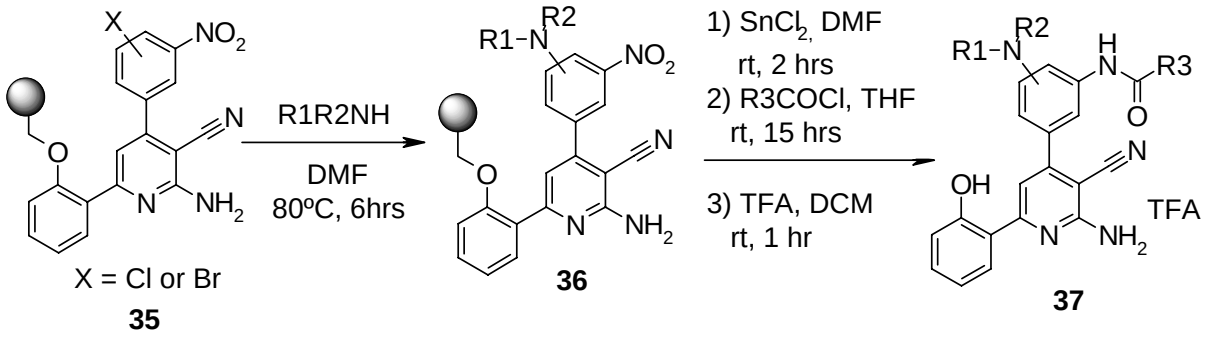
Figure VIII. Potent compound from Library D-1

According to the procedure for **27**, desired pyridines **29a-c** were successfully prepared without any protection of the hydroxyl groups. Mitsunobu reaction was first attempted for the *O*-alkylation but did not proceed towards the corresponding ethers **30a-c**. However, the

reaction with alkyl halides succeeded in the presence of cesium carbonate and potassium iodide, though a double coupling was required to complete the alkylation (Scheme VIII). In total, 81 compounds were synthesized and resulted in a potent compound **33b** (Figure VIII) by IKK-β inhibition assay.

Library D-2:

Using halogenated 3-nitrobenzaldehydes, the corresponding 4-(3-nitrophenyl)pyridines **35** were successfully prepared on beads by the procedure for **27** and subjected to the following amination and reduction steps as shown in Scheme IX.



Scheme IX. Library synthesis of Library D-2

For the amination of **35** to obtain **36**, several conditions were studied using piperidine as the nucleophile. 4-Chloro and 6-fluoro derivatives gave desired products in good yield, but 6-chloride hardly reacted with piperidine. Attempts using DBU or potassium carbonate also gave a recovery of 6-choro derivative. After the introduction of amino moieties, 3-nitro group was reduced with tin(II) chloride in DMF, followed by the reaction with acyl chlorides to give the corresponding amides **37**. Primary amines were also subjected to this reaction as nucleophiles. In this case, DMSO was employed as the solvent because DMF gave a byproduct, which probably resulted from the reaction with dimethylamine hiding in DMF. The following reductions and acylations proceeded well and the corresponding diamides were

obtained after cleavage.

In total, 320 compounds were synthesized, and almost all of the products gave below 1 μM of IC_{50} value vs. IKK-β as exemplified in Figure IX.

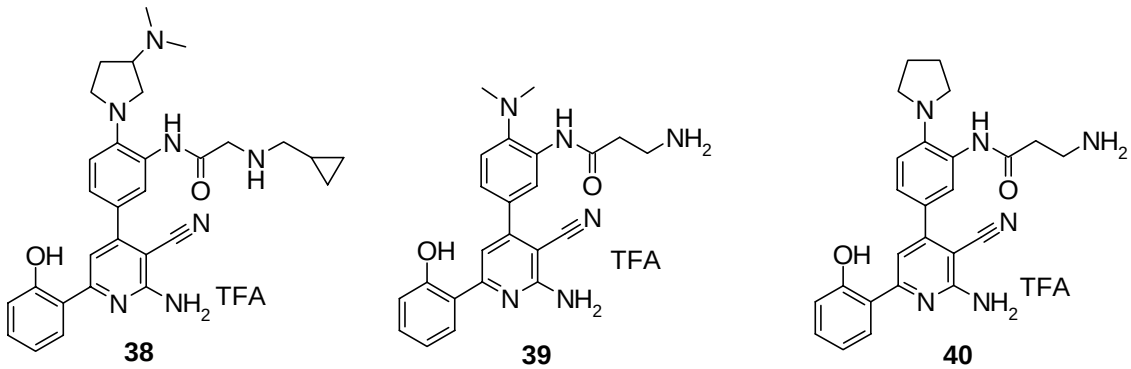


Figure IX. Potent compounds from Library D-2

Library E: 4-Alkyl-2-amino-3-cyano-6-(2-hydroxyphenyl)pyridines

Although more than 800 4-arylpyridines were prepared, none of them showed below 100 nM of IC_{50} value. In order to find a new class of potent inhibitors, definitely a drastic change was demanded. Thus our strategy was directed to apply aliphatic aldehyde to obtain 4-alkyl pyridines instead of 4-arylpyridines because it was clear that a wide variety of substituents on 4-aromatic moiety of pyridine was tolerated. In addition, a variety of substituted acetophenones was also applied for multi-component reaction as listed in Table II. A library synthesis in the combination of *o*-hydroxyacetophenones and aliphatic aldehydes was planed (Figure X).

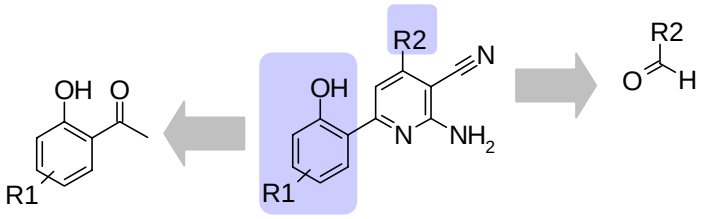
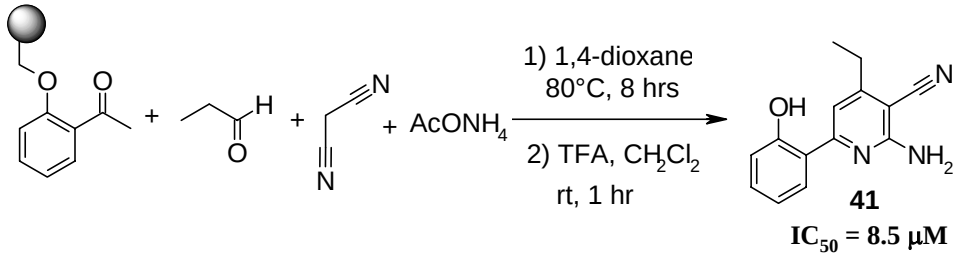


Figure X. Library design

Prior to generation of the library, the condensation using propionaldehyde was performed on solid-phase to optimize reaction conditions. Since the product was confirmed by LS-MS and showed greater than 50% inhibition at 2.5 μM in IKK-β kinase assay, IC_{50} value of purified compound was determined. The IC_{50} value dropped to 8.5 μM, however, this was the first example that removal of aromatics on 4-substituent was tolerated. This result afforded a promising outlook for the library (Scheme X).



Scheme X. Preliminary study of condensation with aliphatic aldehyde

6.5.1. Library E-1: Application of α-amino aldehydes

N-Boc-α-amino aldehydes described in Figure XI were prepared by reduction of *N*-Boc-α-amino acids via their Weinreb's amides as exemplified in Scheme XI.

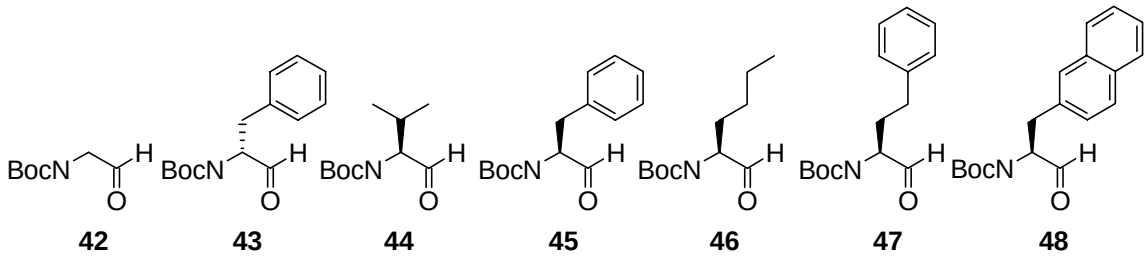
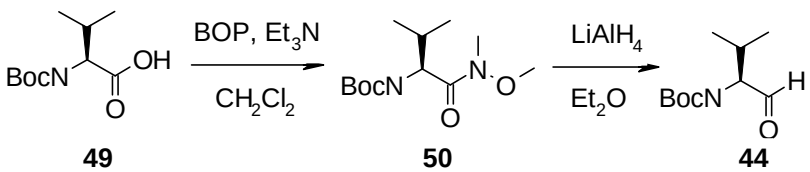
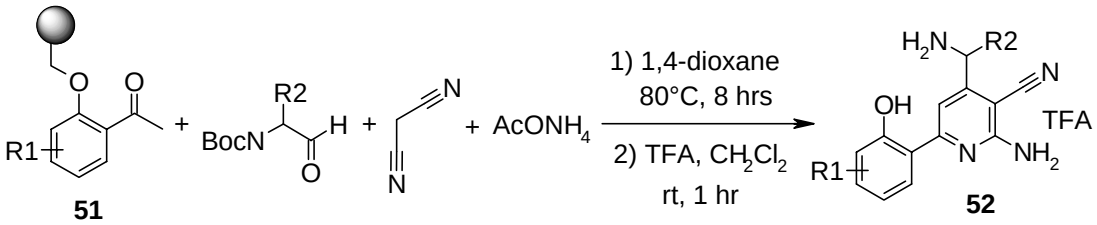


Figure XI. Seven starting materials for Library E-1



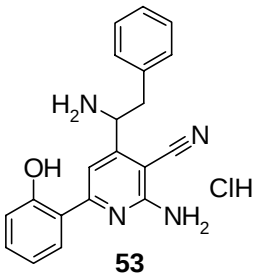
Scheme XI. Typical synthesis of Boc-α-aminal

A combinatorial library was synthesized in the combination of seven aldehydes and five *o*-hydroxyacetophenones (Scheme XII). None of the pyridine ring closure reactions with *N*-Boc-aminoacetaldehyde **42** proceeded but others gave the corresponding pyridines successfully.



Scheme XII. Library synthesis of Library E-1

Interestingly, almost all of the products showed more than 50% inhibition of IKK-β at 2.5 μM and the most potent compound was resynthesized by the traditional way using similar procedure shown in Scheme XII. Eventually, this result was confirmed and this compound was identified as the first compound with double-digit nM of IC_{50} as shown in Figure XII.

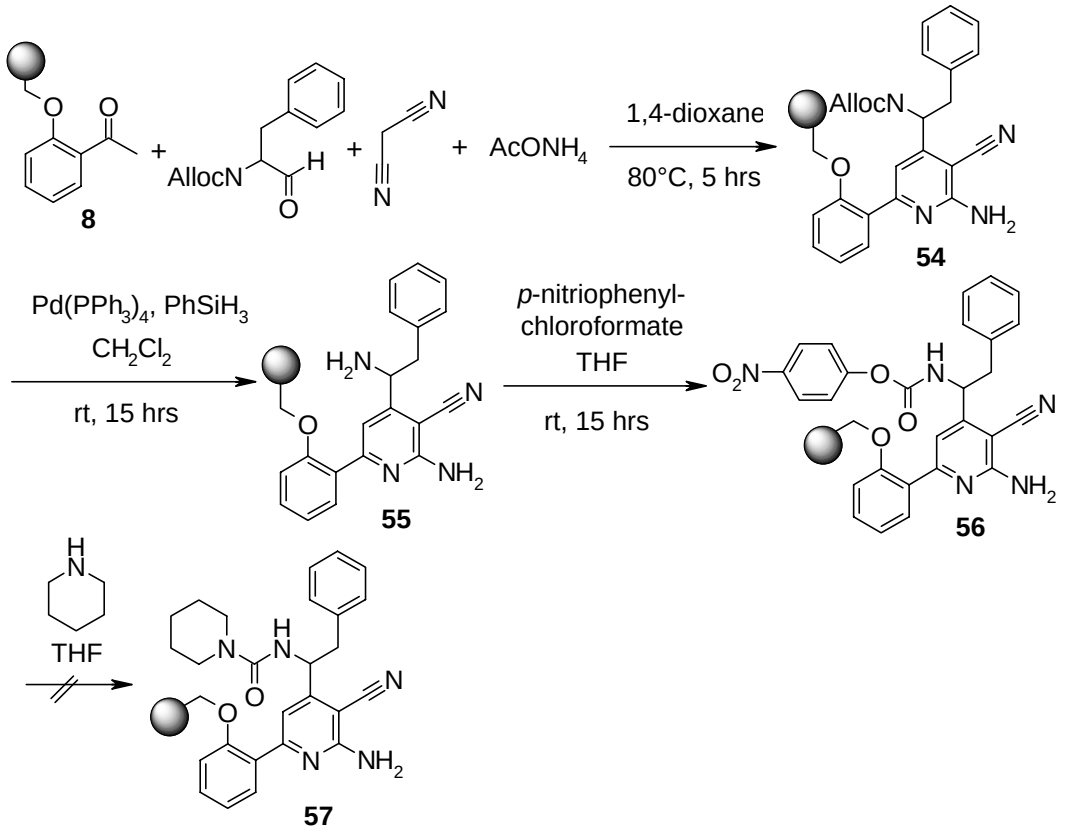


IC_{50} = 60 nM

Figure XII. The first double-digit nM compound from Library E-1

Because the products always have free NH_2 group, it was tried to use this position as additional diversity point to expand the library. On this purpose, a variety of protection groups for this NH_2 was studied. A procedure with formic acid for the selective Boc deprotection on acid labile linker has been employed before in our laboratory.[14] However no deprotection was occurred. Fmoc was not suitable *N*-protection group either, because the

cleavage step with 20% piperidine in DMF gave a complex mixture, which perhaps resulted from the higher reactivity of CN group under such basic conditions. In order to accomplish the cleavage step under neutral conditions, allyoxycarbonyl (Alloc) group was employed to protect this NH_2 group and its deprotection step well proceeded in the presence of tetrakis(triphenylphosphine)palladium and phenylsilane with good purity (84% by ELSD).[15] Resulting NH_2 group was converted to the corresponding 4-nitrophenyl carbamate under the reaction conditions without base, and then treated with piperidine in order to give ureas.



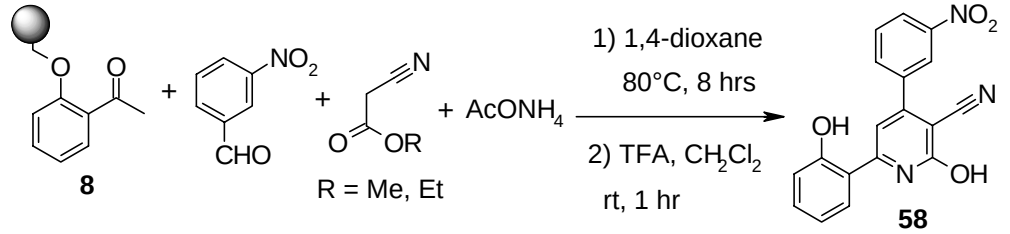
Scheme XIII. Attempts to modify amino group

While the presence of 4-nitrophenyl carbamate **56** was observed by LC-MS after the cleavage from the resin, desired urea **57** was not confirmed. Probably, 3-cyano group can easily react with NH_2 group under basic conditions to lead decomposition. Therefore, after the Alloc removal, resulting NH_2 group was reacted with sulfonyl chloride or carbamoyl

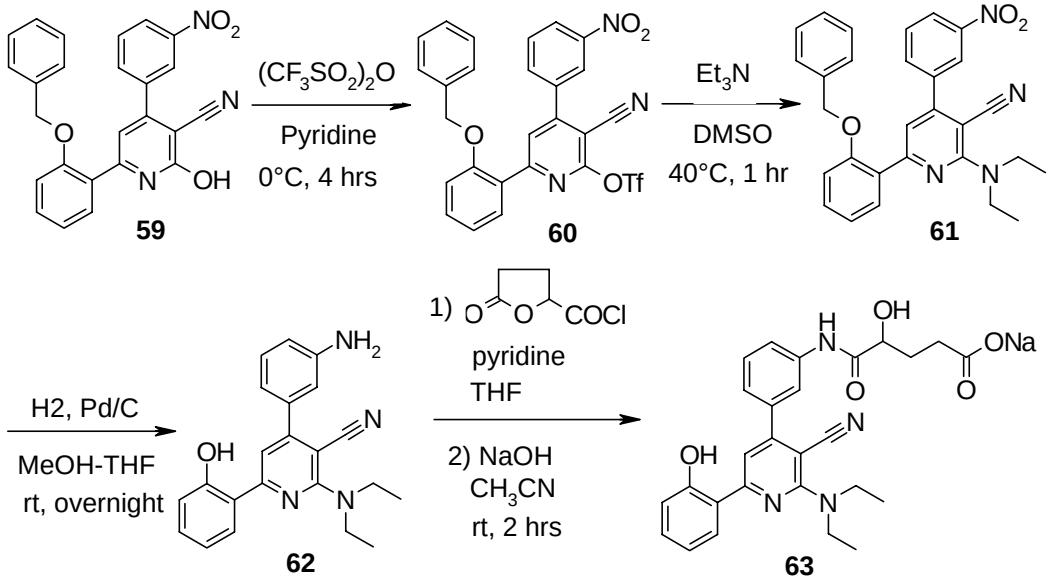
chloride in the absence of any bases. However, both attempts failed with recovery of starting amine.

7. Pyrinde-2-one and 2-alkylamino-3-cyanopyridine

When ethyl cyanoacetate or methyl cyanoacetate was subjected to this multi-component pyridine ring formation on beads instead of malononitrile, the corresponding 2-pyridone **58** was obtained in 73% yield as shown in Scheme XIV (90% purity). This procedure is applicable to a library synthesis of 3-cyano-2-hydroxypyridines and, furthermore, 2-alkylamino-3-cyanopyridines as previously reported in the literature (Scheme XV).[16]



Scheme XIV. Solid-phase synthesis of pyridine-2-one



Scheme XV. Synthesis of 2-alkylamino-3-cyanopyridine

8. 2-Aminonicotinic acid ester

Library F: 2-Amino-4-nitrophenyl-3-methylamino-6-(2-hydroxy)phenylpyridines

Although the solid-phase pyridine ring formation reaction with ethyl cyanoacetate gave pyridine-2-one exclusively, the corresponding reaction in solution-phase provided the pyridine-2-one (18%) concomitant with the 2-aminonicotinic acid ester as a minor byproduct (3%). Considering the mechanism, the factor to determine the product proportion would be relative electrophilicity between the nitrile and the ester moiety toward NH_2 group in cyclization step (Figure XIII). Since electrophilicity of the ester should be superior to that of the nitrile moiety, pyridone type compound was provided exclusively in solid-phase or predominantly in solution-phase. Therefore, in order to reverse the reaction selectivity, the use of more sterically hindered ester, *tert*-butyl cyanoacetate, instead of ethyl cyanoacetate as the starting material was attempt to lead 2-aminonicotinic acid ester as a major product. The reaction was carried out with the same conditions, and as expected, 2-aminonicotinic acid ester was confirmed by partial cleavage of **64** with TFA (90% purity) as shown in Scheme XVI .[17]

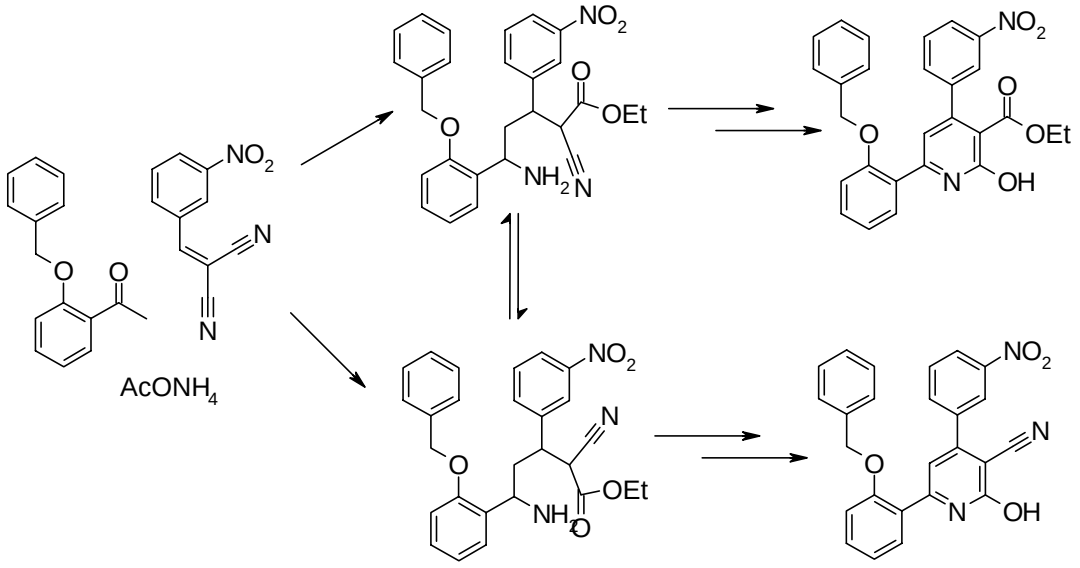
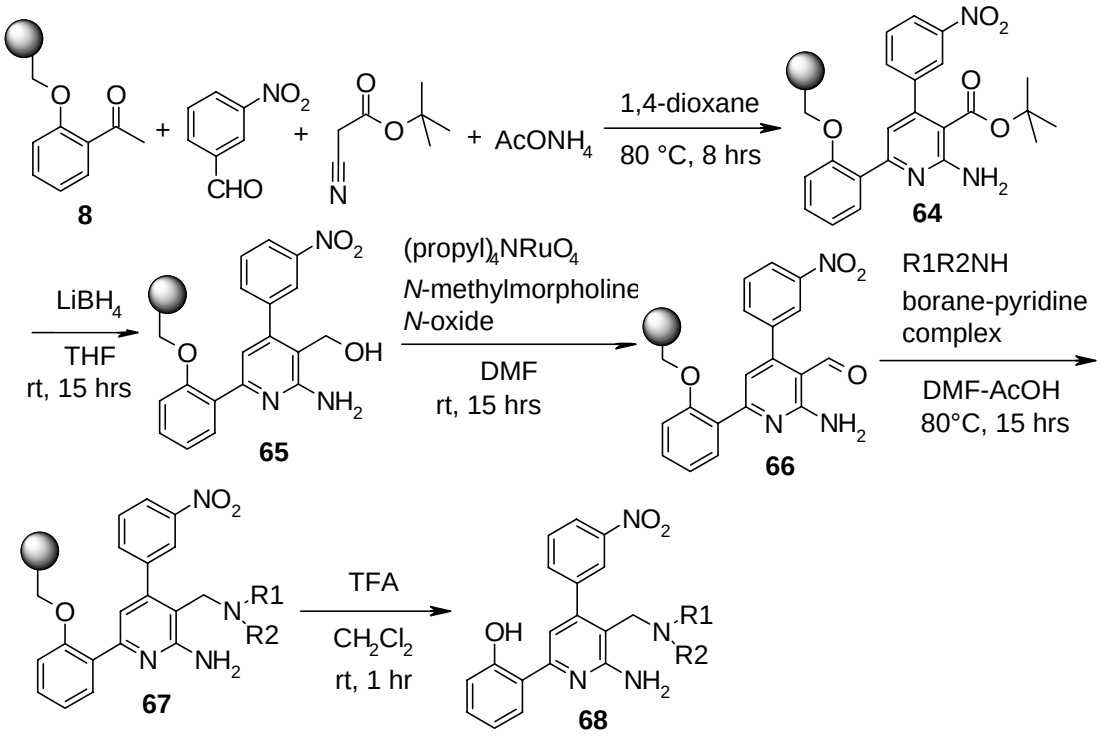


Figure XIII. Assumed reaction mechanism to lead pyridone or nicotinic acid ester

The *tert*-butyl ester **64** was reduced to the corresponding alcohol **65** by treating with lithium borohydride at room temperature for 15 hours. Firstly, an attempt was made to convert this hydroxyl moiety to bromine with carbon tetrabromide in the presence of triphenylphosphine. However, a complex mixture was obtained and no targeted product was found in LC-MS analysis. Mesylation of hydroxyl moiety was achieved with methanesulfonyl chloride in the presence of triethylamine, but following substitution reaction with amine led to the complex mixture again although the target compound was observed as a minor product. Alternatively, oxidation to aldehyde was investigated. Among several conditions were attempted including DMSO-based oxidation, Dess-Martin, the use of perruthenate was effective for this transformation (catalytic amount of tetrapropylammonium perruthenate, *N*-methylmorpholine *N*-oxide as an oxidant, DMF as a solvent, room temperature, 15 hours). Reductive amination with a variety of amines in the presence of borane-pyridine complex provided a small library shown in Scheme XVI.



Scheme XVI. Library synthesis of Library F

9. 3-Unsubstituted pyridine

As shown in Table II, a wide variety of acetophenones and aldehydes was applicable to this multi-component condensation, and actually a lot of analogues having various substituents on 4- and 6-positions on pyridine ring was prepared. On the other hand, malononitrile component which resulted in 3-substituent on pyridine had not been explored well. In order to see an applicability of this component, several available acetonitriles were subjected to the reaction as shown in Figure XIV. Unfortunately, almost all acetonitriles were failed to give pyridine ring except for sulfone derivative. This is probably due to the lack of reactivity of methylene carbon. Namely, enough electron-withdrawing property equal to nitrile should be required to proceed the reaction. In this regard, sulfone derivative worked to give pyridine as shown in Scheme XVII.

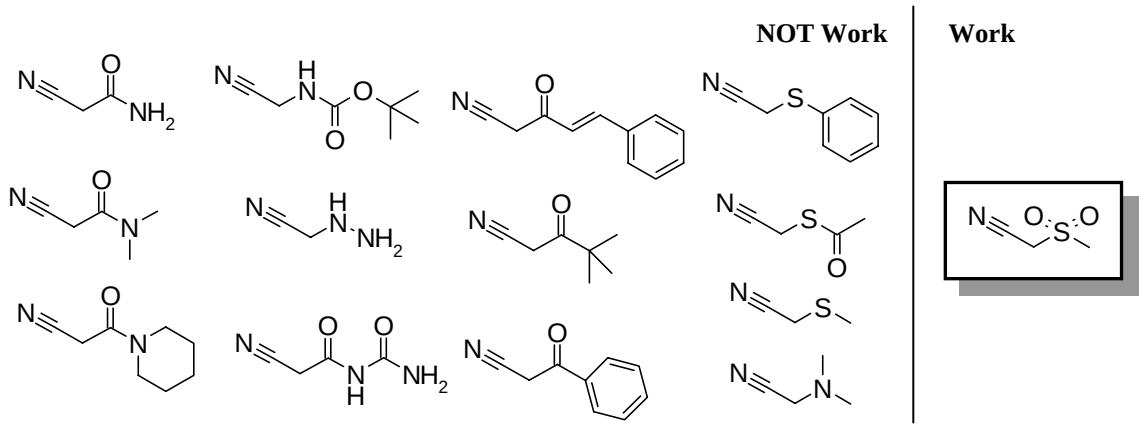
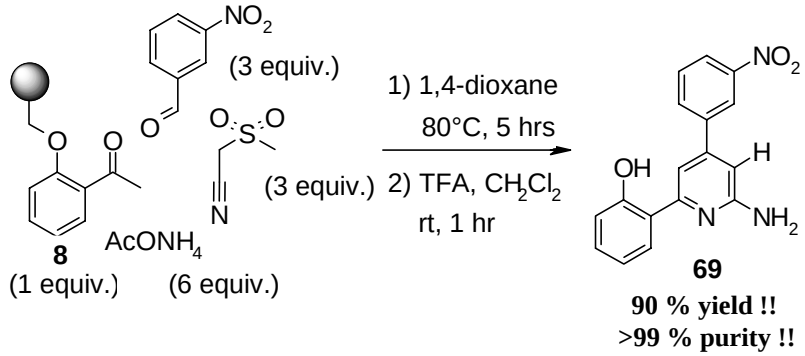


Figure XIV. Acetonitrile derivatives used instead for malononitrile

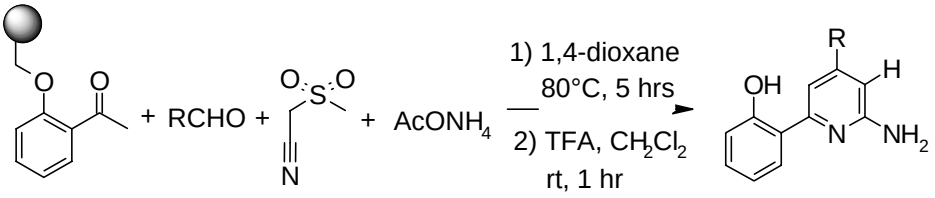


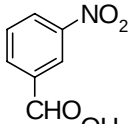
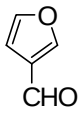
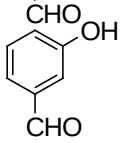
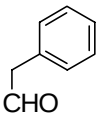
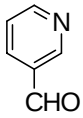
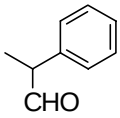
Scheme XVII. Multi-component condensation to lead 3-unsubstituted pyridine

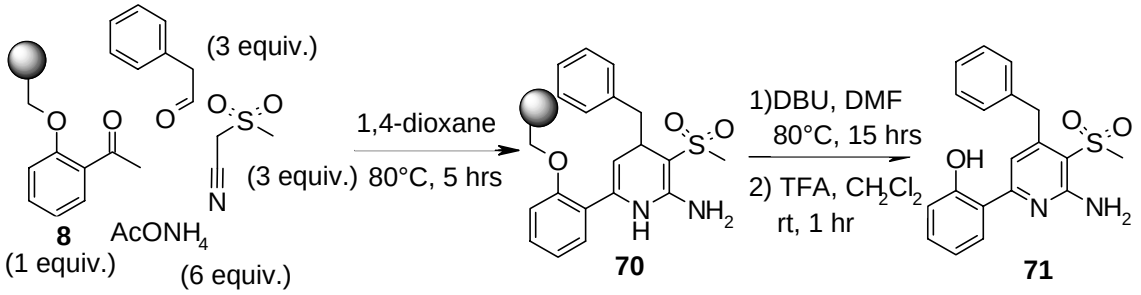
Interestingly, sulfone moiety was eliminated during the reaction to lead 3-unsubstituted pyridine. This type of syntheses of 3-unsubstituted pyridine on beads is less common.[18] With the purpose of verify this interesting cyclization-elimination reaction, the reaction was examined with variety of aromatic and aliphatic aldehydes. The results are presented in Table III. As alike as the case of malononitrile, aromatic aldehydes including pyridine and furan derivatives worked to give the targeted 3-unsubstitued pyridine in excellent purities. However, when aliphatic aldehydes were used, the products were 3-methylsulfonyl-dihydropyridines not the targeted pyridines.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is often used for β-elimination to give an unsaturated bond. Thus, after the cyclization on beads, dihydropyridine intermediate **70** was treated with DBU at elevated temperature (80°C) in DMF overnight. Although aromatic pyridine was observed, sulfone moiety was not eliminated, namely 3-sulfonylpyridine **71** was obtained unexpectedly (Scheme XVIII).

Table III. Investigation of multi-component condensation



Entry	RCHO	Purity (%)	Entry	RCHO	Purity (%)
1		**>99**	**4**		**>99**
2		**>99**	**5**		-
3		**>99**	**6**		-



Scheme XVIII. Attempt to obtain 3-unsubstitued-4-aliphatic pyridine

10. Conclusion

In conclusion, very effective solid-phase chemistry for the pyridine ring formations by the multi-component condensation was successfully established. This reaction showed a broad tolerance against two components among three variable components. A variety of acetophenones and aldehydes was able to incorporate into the reactions, and which resulted in production of a large number of compounds of pyridine library. Since both purities and yields of this procedure were much better than those of the corresponding solution-phase, it was well demonstrated that inherent advantage of solid-phase chemistry to force the reactions that give poor yields in solution-phase chemistry into completion by using an excess of reagents. In addition, this procedure is a noteworthy example since not only aromatic aldehydes but also aliphatic aldehydes worked well to give the desired pyridines. There are only a few examples of 4-aliphatic pyridines synthesized by solid-phase chemistry. Besides that, by changing malonitrile component to other acetonitrile derivative pyridone derivatives and 2-nicotinic acid ester derivatives were provided from ethyl and *tert*-butyl cyanoacetate respectively. 3-Unsubstituted pyridines were also accomplished by cyclization-elimination reaction by using methylsulfonylacetonitrile.

The procedure was successfully applied to a rapid analoging of the lead compound to

yield more than 1,000 compounds. This procedure made worthful contributions to push on the combinatorial chemistry approach and bring one of our exploratory researches to the further advanced stage very quickly.[19]

11. Experimental session

General

Melting points are uncorrected. ^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) or 500 Bruker Ultrashield(TM) (500 MHz for ^{1}H) spectometer in $CDCl_3$ or DMSO-d6 or MeOD-d4. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (j) are given in hertz and the abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet respectively. The abbreviation "br" refer to "broad". Liquid chromatography-Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column (4.6 x 30 mm) flushing a mixture of acetonitrile and water (9:1 to 1:9) at 1 ml/min of the law rate. The MASS spectra were obtained using eletrospray (ES) ionization techniques. TLC was performed on a precoated silicagel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C200 (75-150 uM)) was used for all column chromatography separations. All chemicals were regent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo Kasei Kogyo co. Ltd.

2-Amino-6-(2-hydroxyphenyl)-4-(3-nitrophenyl)nicotinonitrile 9

To 4-(bromomethyl)phenoxymethyl polystylene (purchased from Novabiochem, 5g, 6.4

mmol) in DMF (50 mL) was added *o*-hydroxyacetophenone (4.4 g, 32.0 mmol), cesium carbonate (10 g, 32.0 mmol), and potassium iodide (1.1 g, 6.4 mmol). The mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with DMF (15 mL x 3), DMF /H_2O (15 mL x 3) then alternating MeOH (15 mL x 3) and dichloromethane (15 mL x 3).

A mixture of the *o*-hydroxyacetophene attached resin **8** (6.4 mmol), 3-nitrobenzaldehyde (2.9 g, 19.2 mmol), malononitrile (1.3 g, 19.2 mmol), and ammonium acetate (3.0 g, 38.4 mmol) in 1,4-dioxane (50 mL) was agitated at 80°C for 8 hours. The resin was filtered and washed with DMF (15 mL x 3) then alternating MeOH (15 mL x 3) and dichloromethane (15 mL x 3).

Aliquot of the resin (100 mg) was withdrawn and was treated with 50% w/w TFA in dichloromethane (1 mL) at room temperature for an hour. The resin was filtered off. Toluene was added to the filtrate, which was concentrated in *vacuo* to give 2-amino-6-(2-hydroxyphenyl)-4-(3-nitrophenyl)nicotinonitrile **9** (51 mg, 90%) as a yellow solid; LC-MS(ES) *m/z* 333 $(M+H)^+$; ^{1}H-NMR (300 MHz, DMSO-d6) δ 6.85-6.93 (2H, m), 7.31-7.56 (5H, m), 7.58 (1H, d, *J* = 3.0 Hz), 7.99-8.10 (1H, s), 13.40 (1H, br s).

General procedure for Library A

To the pyridine immobilized resin (6.4 mmol) was added a solution of tin (II) chloride in DMF (2 M, 50 mL) and the mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with DMF (15 mL x 3) then alternating MeOH (15 mL x 3) and DCM (15 mL x 3).

The resin was divided into 2 portions. To each suspension of the resin (2.5 g, 3.2 mmol) in THF (25 mL) was added corresponding acetyl chloride (32.0 mmol) and the mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with THF

(15 mL x 3) and dichloromethane (15 mL x 3).

The each resin was divided into 50 portions. To each resin (50 mg, 64 μmol) was added a solution of corresponding amine (192 μmol) in DMF (1 mL) and diisopropylethylamine (33 μl, 192 μmol). The mixture was agitated at 80 °C for 15 hours. The resin was filtered and washed with DMF (1 mL x 3) then alternating MeOH (1 mL x 3) and dichloromethane (1 mL x 3).

To each resin was added a solution of 50% w/w TFA in dichloromethane (1 mL). The resin was agitated at room temperature for an hour. The resin was filtered off. Toluene (1 mL) was added to a filtrate, which was concentrated *in vacuo* to give corresponding *N*-{3-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]phenyl} amide trifluoroacetate **18**.

3-[2-Amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-N-[2-(1-Piperidinyl)-ethyl]benzamide trifluoroacetate 14

LC-MS (ES) *m/z* 442 $(M+H)^+$; ^{1}H-NMR (300 MHz, DMSO-d6) δ 1.36-1.86(6H, m), 2.95 (2H, q, *J* = 10.5 Hz), 3.26-3.28 (2H, m), 3.56 (2H, d, *J* = 12.4 Hz), 3.66 (2H, *J* = 6.6 Hz), 6.88-6.95 (2H, m), 7.01 (1H, t, *J* = 7.91 Hz), 7.45 (1H, s), 7.53 (2H, s), 7.70 (1H, t, *J* = 7.9 Hz), 7.88 (1H, d, *J* = 7.54 Hz), 8.05 (2H, t, *J* = 7.0 Hz), 8.12 (1H, t, *J* = 5.7 Hz), 9.02 (1H, br s), 13.31 (1H, s).

General procedure for Library B

The 4-(3'-anilino) pyridine attached resin **15** was prepared as described above.

To the resin **15** (1 g, 1.28 mmol) was added a solution of 4-nitrobenzyl chloroformate (774 mg, 3.84 mmol) in THF (10 mL). The mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with THF (5 mL x 3), and dichloromethane (5 mL x 3).

The dried resin was divided into 20 portions. To each resin (50 mg, 64 μmol) was

added corresponding amine (192 μmol) and diisopropylamine (33 μl, 192 μmol) in THF (1mL). The mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with THF (1 mL x 3) and dichloromethane (1 mL x 3).

To each resin was added a solution of 50% w/w TFA in dichloromethane (1 mL). The resin was agitated at room temperature for an hour. The resin was filtered off. Toluene (1 mL) was added to a filtrate, which was concentrated *in vacuo* to give corresponding *N*-{3-[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]phenyl} urea trifluoroacetate **24**.

General procedure for Library D-1

The 4-(hydroxy-nitrophenyl) pyridine attached resin **29a-c** was prepared as described above.

The resin **29a-c** (1 g, 1.28 mmol) was divided into 5 portions. To the each resin (200 mg, 256 μmol) was added corresponding alkyl halide (1.28 mmol) in DMF (5 mL), potassium iodide (42 mg, 256 μmol), and cesium carbonate (417 mg, 1.28 mmol). The mixture was agitated at room temperature for 15 hours. This coupling reaction was repeated once. The resin was filtered and washed with DMF (5 mL x 3), DMF/H_2O (5 mL x 3) then alternating MeOH (5 mL x 3) and dichloromethane (5 mL x 3).

To the each resin (256 μmol) was added a solution of tin (II) chloride in DMF (2 M, 5 mL) and the mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with DMF (5 mL x 3) then alternating MeOH (5 mL x 3) and dichloromethane (5 mL x 3). To each suspension of the resin (256 μmol) in THF (5 mL) was added chloroacetyl chloride (86.7 μl, 768 μmol) and the mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with THF (5 mL x 3) and dichloromethane (5 mL x 3).

The resin was divided into 4 portions. To the each resin (64 μmol) was added a solution of corresponding amine (320 μmol) in DMF (1 mL) and triethylamine (100 μl).

The mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with DMF (1 mL x 3), then alternating MeOH (1 mL x 3) and dichloromethane (1 mL x 3).

To each resin was added a solution of 50% w/w TFA in dichloromethane (1 mL). The resin was agitated at room temperature for an hour. The resin was filtered off. Toluene (1 mL) was added to a filtrate, which was concentrated *in vacuo* to give corresponding N-{[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-alkoxyphenyl} amide trifluoroacetate **33a-c**.

General procedure D-2

The 4-(halogenated-3-nitrophenyl) pyridine attached resin **35** (2.8 g, 2.66 mmol) was prepared as described above.

The dried resin **35** was divided into 16 portions. To each resin (0.35 g, 333 μmol) was added a solution of corresponding amine (1.67 mmol) in DMF (3 mL). The mixture was agitated at 80 °C for 17 hours. The resin was filtered and washed with DMF (3 mL x 3), DMF/H_2O (1:1, 3 mL) then alternating MeOH (3 mL x 3) and dichloromethane (3 mL x 3). To the resin was added a solution of tin (II) chloride in DMF (2 M, 2 mL) and the mixture was agitated at 40 °C for 16 hours. The resin was filtered and washed with DMF (3 mL x 3) then alternating MeOH (3 mL x 3) and dichloromethane (3 mL x 3).

The resin was divided into 6 portions. To each suspension of the resin (50 mg, 48 μmol) in THF (0.5 mL) was added corresponding acyl chloride (0.144 mmol) and the mixture was agitated at room temperature for 14 hours. The resin was filtered and washed with THF (1 mL x 3), DMF (1 mL x 3) then alternating MeOH (1 mL x 3) and dichloromethane (1 mL x 3).

To each resin (50 mg, 48 μmol) was added a solution of corresponding amine (240

μmol) in DMF (0.5 mL) and diisopropylethylaimne (42 μl, 240 μmol). The mixture was agitated at 50 °C for 19 hours. The resin was filtered and washed with DMF (1 mL x 3) then alternating MeOH (1 mL x 3) and DCM (1 mL x 3).

To each resin was added a solution of 50% w/w TFA in dichloromethane (0.5 mL). The resin was agitated at room temperature for an hour. The resin was filtered off. Toluene (0.2 mL) was added to a filtrate, which was concentrated *in vacuo* to give corresponding *N*-[[2-amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-aminophenyl] amide trifluoroacetate **37**.

***N*^{1}-[5-[2-Amino-3-cyano-6-(2-hydroxyphenyl)-4-pyridinyl]-2-(dimethylamino)phenyl]-*N*^{2}-(cyanopropylmethyl)glycinamide trifluoroacetate 37**

LC-MS (ES) *m/z* 457 $(M+H)^+$; ^{1}H-NMR (300 MHz, DMSO-d6) δ 0.35-0.40 (2H, m), 0.57-0.63 (2H, m), 1.05-1.08 (1H, m), 2.80 (6H, s), 2.87-2.91 (2H, m), 466-4.68 (2H, m), 6.87-6.94 (2H, m), 7.33-7.40 (4H, m), 7.52-7.55 (1H, m), 7.98 (1H, d, *J* = 7.2 Hz), 8.08 (1H, s), 9.12 (1H, br s), 10.07 (1H, br s).

Typical procedure for preparation of Weinreb amide

To a mixture of Boc-*L*-Val-OH (2.00 g, 9.21 mmol) and triethylamine (1.3 mL, 9.21 mmol) in anhydrous dichloromethane was added BOP (4.07 g, 9.21 mmol) in portions under ice water cooling. To the cold mixture was added *N*,*O*-dimethylhydroxylamine HCl (990 mg, 10.13 mmol) and triethylamine (1.4 mL, 10.1 mmol). After 10 minutes, the cooling source was removed and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with dichloromethane (ca 200 mL), washed with 1M-HCl (2 x 100 mL), aqueous saturated sodium hydrogen carbonate (2 x 100 mL) and brine (2 x 100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (n-hexane / ethyl acetate = 2 / 1 to 1 / 1) to give colorless

oil (1.72 g, 72% yield); LCMS (ESI) m/z 261 $[M+H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.8 Hz), 1.93-2.04 (1H, m), 3.21 (3H, s), 3.77 (3H, s), 4.57 (1H, br s), 5.14 (1H, br d, *J* = 9.0 Hz).

General procedure for Library E-1

A mixture of the *o*-hydroxyacetophene attached resin **8** (0.05 mmol), aminal (0.15 mmol), malononitrile (10.2 mg, 0.15 mmol), and ammonium acetate (23.4 mg, 0.30 mmol) in 1,4-dioxane (1 mL) was agitated at 80°C for 8 hours. The resin was filtered and washed with DMF (1 mL x 3) then alternating MeOH (1 mL x 3) and dichloromethane (1 mL x 3). To the resin was added a solution of 50% w/w TFA in dichloromethane (1 mL). The resin was agitated at room temperature for an hour. The resin was filtered off. Toluene (1 mL) was added to a filtrate, which was concentrated *in vacuo* to give the product **52**.

2-Amino-4-(1-amino-2-phenylethyl)-6-(2-hydroxyphenyl)nicotinonitrile 53

LC-MS (ES) *m/z* 331 $(M+H)^+$; ^{1}H-NMR (300 MHz, DMSO-d6) δ 3.20 (1H, dd, *J* = 9.5, 13.2 Hz), 3.22 (1H, dd, *J* = 5.7, 13.2 Hz), 4.54 (1H, br s), 6.90-6.95 (2H, m), 7.10-7.13 (2H, m), 7.22-7.51 (7H, m), 8.09 (1H, s), 8.12 (1H, d, *J* = 7.9 Hz), 9.00 (3H, br s).

General procedure for Library F

A mixture of the *o*-hydroxyacetophene attached resin **8** (0.05 mmol), benzaldehyde (0.15 mmol), *tert*-butylcyanoacetate (10.2 mg, 0.15 mmol), and ammonium acetate (23.4 mg, 0.30 mmol) in 1,4-dioxane (1 mL) was agitated at 80°C for 8 hours. The resin was filtered and washed with DMF (1 mL x 3) then alternating MeOH (1 mL x 3) and dichloromethane (1 mL x 3). To a suspension of the resin in THF (1 mL) was added lithium borohydride (5.0 mg, 0.30 mmol). The mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with DMF (1 mL x 3) then alternating MeOH (1 mL x 3) and

dichloromethane (1 mL x 3). To a suspension of the resin and *N*-methylmorpholine (58.6 mg, 0.50 mmol) in DMF was added tetrapropylammonium perruthenate (3.6 mg, 0.01 mmol). The mixture was agitated at room temperature for 15 hours. The resin was filtered and washed with DMF (1 mL x 3), DMF/1 N aqueous citric acid, then alternating MeOH (1 mL x 3) and dichloromethane (1 mL x 3). A mixture of the resin, amine (0.05 mmol), and borane-pyridine complex (50 mg, 0.5 mmol) in a mixture of DMF:trimethylorthoformate (4:1, 1 mL) and acetic acid (1 drop) was agitated at 80°C for 15 hours. The resin was filtered and washed with DMF (1 mL x 3) then alternating MeOH (1 mL x 3) and dichloromethane (1 mL x 3). To the resin was added a solution of 50% w/w TFA in dichloromethane (1 mL). The resin was agitated at room temperature for an hour. The resin was filtered off. Toluene (1 mL) was added to a filtrate, which was concentrated *in vacuo* to give the product **68**.

Pharmacological Experiments

IKK-β kinase inhibitory assay

(1) Preparation of IKK-β kinase protein

A cDNA fragment encoding human IKK-β open reading frame was generated by PCR with the use of a pair of primers designed from the published sequence (Woronicz JD et al. (1997) Science 278, 866-869). A template was obtained from Quickclone cDNA (Clontech) using Elongase™ Amplification kit (Life Technologies). The DNA fragments generated by PCR were gel-purified and subcloned into pBluescript. The cDNA fragment cloned in pBluescript was inserted into pcDNA3.1/His C *Kpn*I/*Not*I, and transferred into pVL1393 *Sma*I/*Xba*I (Pharmingen) to construct a baculovirus transfer vector. Then the vector, together with the linearized baculovirus (BaculoGold™, Pharmingen) was used to transfect Sf21 cells (Invitrogen, San Diego, CA). Generated recombinant baculovirus was

cloned and amplified in Sf21 cells, grown in TNM-FH insect cell medium (Life Technologies, Inc.) supplemented with 10% FCS, 50 g/ml Gentamycin, 0.1% Pluronic F-68 (Life Technologies, Inc.) as suspension culture (200 ml in 1 L Erlenmeyer flask; 27ºC; 130 rpm). Sf21 cells were infected with this amplified virus with a multiplicity of infection of 5 following standard protocols (Crossen R, Gruenwald S (1997) Baculovirus Expression Vector System Instruction Manual, Pharmingen Corporation) and harvested 48 hrs later. The cells were lysed to obtain the produced chimeric protein of IKK-β kinase fused by histidine (His-tagged IKK-β).

(2) The preparation of purified GST-IκBα fusion proteins

An expression vector containing the nucleotide sequence encoding fusion protein of GST with amino acid residues 1 to 54 of IκBα under the control of an IPTG-inducible promoter was constructed. The expression vector was introduced in E. coli and the transformant was cultured and lysed to obtain a GST-IκBα fusion protein. Then the resulting GST-IκBα fusion protein was purified and biotinated for kinase assay.

(3) The measurement of IKK-β kinase activity

The 96-well format kinase assay of IKK-β was performed to test the inhibitory activity of the compounds of the present invention. First, 5 μl of a test compound was put in the presence of 2.5% dimethyl sulfoxide (DMSO) in each well in a U-bottomed 96-well plate (Falcon). For control wells of background (BG) and total phosphorylation (TP), 5 μl of 2.5% DMSO was put. Recombinant IKK-β (final 0.6 μg/ml) and bio-GST-IκBα (1-54) (final 0.2 μM) were diluted in 25 μl of 2 x kinase buffer β (40 mM Tris-HCl, pH 7.6, 40 mM $MgCl_2$, 40 mM β-glycerophosphate, 40 mM p-nitrophenylphosphate, 2 mM EDTA, 40 mM creatine phosphate, 2 mM DTT, 2 mM Na_3VO_4, 0.2 mg/ml BSA and 0.8 mM phenylmethylsulfonyl fluoride) and transferred to the 96-well plate. Bio-GST-IκBα (1-54) in 25 μl of 2 x kinase buffer β without IKK-β was transferred to BG wells. Then 20 μl of 12.5 μM ATP, 62.5

μCi/ml [γ-^{33}P] ATP (Amersham Biosciences) was added and the resulting mixture was incubated for 2 hours at room temperature. The kinase reactions were terminated by the addition of 150 μl of termination buffer (100 mM EDTA, 1 mg/ml BSA, 0.2 mg NaN_3). One handred and fifty μl of the sample were transferred to a streptavidin-coated, white MTP (Steffens Biotechniche Analysen GmbH #08114E14.FWD) to capture the biotinylated substrates. After 1 hr of incubation, non-bound radioactivity was eliminated by washing the wells five times with 300 μl of washing buffer including 0.9 % NaCl and 0.1% (w/v) Tween-20 with the use of a MW-96 plate washer (BioTec). The bound radioactivity was determined after the addition of 170 μl MicroScint-PS scintillation cocktail (Packard) using a TopCount scintillation counter.

The measurement of RANTES production in response to TNF-α from A549 cells

(1) Preparation of A549 cells

The A549 human lung epithelium cell line (ATCC #CCL-885) was maintained in Dulbecco's modified Eagle's medium (D-MEM, Nikken Biomedical Institute) supplemented with 10% FCS (Gibco), 100 U/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (culture medium). Forty thousand (4 x 10^4) cells (80 μl/well) were seeded in each well of 96 well flat-bottom tissue culture plate (Falcon #3072). The plate was allowed to stand for 2 hrs, thus the cells were adhered to the bottom of each well. To the each well was added 10 μl vehicle (1% DMSO), serial dilutions of test compounds in 1% DMSO, or 5 nM Dexamethasone in 1% DMSO as a reference. The mixture (90 μl/well) was incubated for 1 hr at 37°C. After 1 hr, 1 μg/ml TNF-α (10 μl) in culture medium was added to the mixture to obtain 100 μl of reaction mixture. The reaction mixture was cultured for 24 hrs to stimulate the cells with 100 ng/ml TNF-α. Cells with vehicle without TNF-α stimulation were also prepared.

(2) Measurement of RANTES production

Then the concentration of RANTES released from the cells in the supernatants of each well was determined using a quantitative sandwich enzyme immunoassay technique. First, 2μg/ml mouse anti-huRANTES mAb (R&D Systems, #mAb678) in PBS buffer (pH 7.4, 100μl) was put in each well of 96-well NUNC fluoro plate (Nalge Nunc, New York USA) (Final 200ng/well) and the plate was allowed to stand for overnight at 4°C to be coated by the antibody. Each well of the plate was then washed with 350 μl wash buffer (0.05% Tween-20, 0.85% NaCl, and 25 mM Tris/HCl pH7.4) for three times. Blocking buffer containing 1% BSA (Sigma、99% pure, 100 g), 5% sucrose (Nacalai tesque, 99% pure, 500 g), and 0.02% azide (Nacalai tesque, 100%, 500 g) were added (200 μl) to each well and then the plate was allowed to stand for 4 hours to stabilize the coated antibody. Next, 50 μl supernatants of cell culture prepared in (1) above were put in each well of the 96-well NUNC fluoro plate with coated antibody. Recombinant Human RANTES (Pepro Tech, Inc. #300-06) was used as the standard for the determination of RANTES production (linear range between 1 and 10 ng/ml). Eu-labelled mouse anti-huRANES mAb (60 ng/ml: R&D Systems, #mAb278) in PBS supplemented by 1% BSA and 0.05% Tween 20 was added (50 μl) to each well. The reaction mixtures were incubated at room temperature for 4 hrs. After washing with wash buffer (0.05% Tween-20, 0.85% NaCl, and 25 mM Tris/HCl pH7.4, 350 μl/well) for 5 times with the use of a Sera Washer (Bio-Tech, #MW-96R), the enhancement solution (DELFIA, #1244-405, 100 μl/well) was added to each well. The plate was incubated for 10 minutes at room temperature with moderate shaking. Fluorescent intensity was measured using a DELFIA fluorimeter (Wallac). Excitation was performed at 340 nm and emission was measured at 615 nm.

12. References and notes

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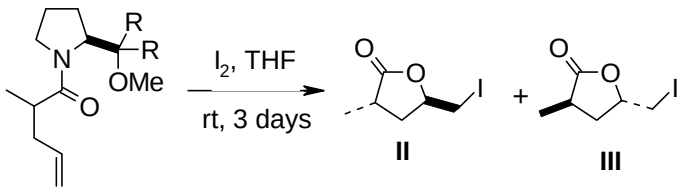
Part 2. The Preparation of Polymer-Supported Menthyl Derivative as Chiral Auxiliaries and the Application to the Diastereoselective [2+2] Photocycloaddition

1. Introduction

Efficient constructions of stereogenic centers are of increasing interest in synthetic organic chemistry. The utilization of a chiral auxiliary is one of the most promising methods for this purpose, and the wide variety of chiral auxiliaries has been reported for asymmetric synthesis.[1] From the pioneering work of Corey's group[2], 8-phenylmenthyl derivatives as chiral auxiliaries have received great attention, and many applications are found in the literature.[3] Recently we reported that the diastereoselective [2+2] photocycloaddition of cyclohexenonecarboxylates having 8-phenylmenthol derivatives as a chiral auxiliary to the simplest olefin, ethylene, proceeded in good yields and diastereoselectivities.[4]

Immobilization of chiral auxiliaries to polymer support[5] results in the easier isolation of the product. In addition, solid-phase reaction sometimes provides a unique product as well as selectivity that may be difficult to achieve by conventional methods.[5b,6] This is most likely due to the unique interaction at the interface between solid and liquid, and the highly hydrophobic environment within the polymer support. For example, Schore reported that the formation of 3,5-disubstituted γ-butyrolactones by using diarylprolinol methyl ethers as chiral auxiliaries. Interestingly, the cross-linked polymer-supported version of the auxiliary **Ia** gave appreciably higher ee values (*S*/*R* = 89:11 = 8:1) upon allylation than did its solution-phase counterpart **Ib** (*S*/*R* = 72:28 = 2.5:1) as shown in Figure I.



Ia; R = Polystyrene
Ib; R = C_6H_5

IIa : **IIIa** = 89 : 11
IIb : **IIIb** = 72 : 28

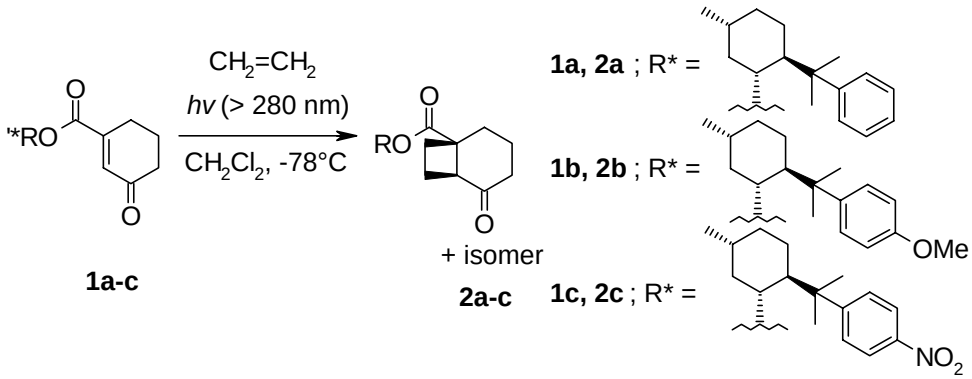
Figure I. Iodolactonization to γ-butyrolactones

Numerous reports of solid-phase organic synthesis are often published [7], but photochemical reaction on solid support is rarely reported[8] in spite of its powerful potential for the construction of strained rings. Especially, to our best knowledge, none of the diastereoselective photochemical reactions on beads has yet been disclosed. The diastereoselective [2+2] photocycloaddition provides cyclobutane ring which is hardly obtained by thermodynamic reaction. Thus, a development of solid-phase version of this ring formation by the use of polymer-supported 8-phenylmenthyl derivative as a chiral auxiliary would be worthwhile in both synthetic and scholarly chemistry point of view.

2. Preparation of polymer-supported (-)-8-(*p*-aminophenyl)menthyl derivatives and its application

Our laboratory has been investigating the diastereoselective [2+2] photocycloaddition by the use of variety of chiral auxiliaries[4], and found that 8-phenylmenthyl derivatives are

Table I. Diastereoselective [2+2] photocycloaddition



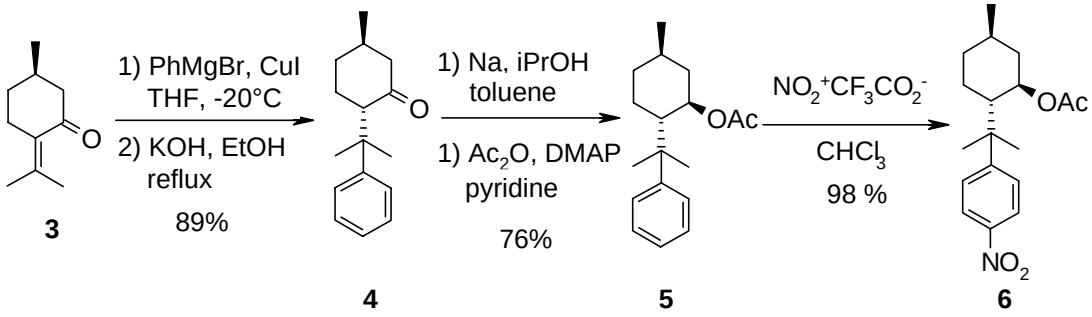
Entry	Subs.	Yield (%)[a]	D.e. (%)[b]
1	**1a**	90	40
2	**1b**	95	50
3	**1c**	94	88

a) Isolated yields. b) Determined by ^{1}H-NMR analysis.

effective for the reaction. In addition, the introduction of substituents on *p*-position of phenyl moiety of 8-phenylmenthyl derivatives provides positive effect on the selectivity (Table I).

First, we aimed to prepare (-)-8-(*p*-aminophenyl)mentyl derivative, which could be synthesized from the (-)-8-(*p*-nitrophenyl)-menthyl derivative, as a candidate for immobilization to polymer support.

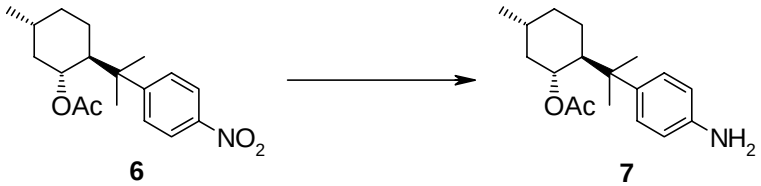
(-)-8-(*p*-Nitrophenyl)-menthyl derivative **5** was prepared according to the published procedure as shown in Scheme I.[9]



Scheme I. Synthesis of (-)-8-(*p*-Nitrophenyl)menthyl acetate

Reduction of nitro group was investigated with a variety of conditions (Pd/C, NH_2NH_2-H_2O, EtOH, reflux; Pd/C, NH_4HCO_2, THF-MeOH, rt; Pd/C, H_2, EtOH-HCl, rt;

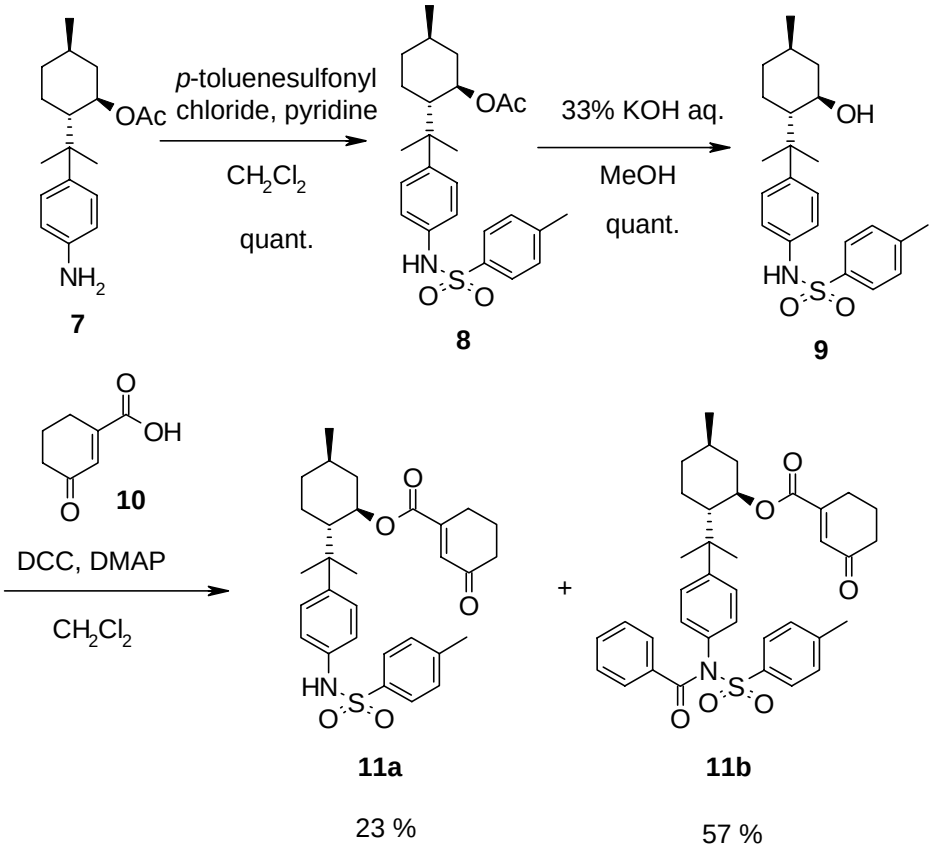
Table II. Investigation of reduction of nitro group



Entry	Reagents/Solvent	Temp. (℃)	Time (hrs)	Yield (%)
1	Pd-C, H_2, HCl/EtOH	0	3	88
2	Pd-C, NH_2NH_2-H_2O/EtOH	reflux	120	8
3	Pd-C, NH_4HCO_2/EtOH-MeOH	rt	120	13
4	$SnCl_2$/EtOH	reflux	17	33
5	Fe, HCl/EtOH-H_2O	reflux	2	91

$SnCl_2$, EtOH, reflux; Fe, HCl, EtOH-H_2O, reflux). Among the conditions we tested, the reduction with iron provided the desired aniline derivative **7** in 91% as the best yield (Table II, Entry 5).

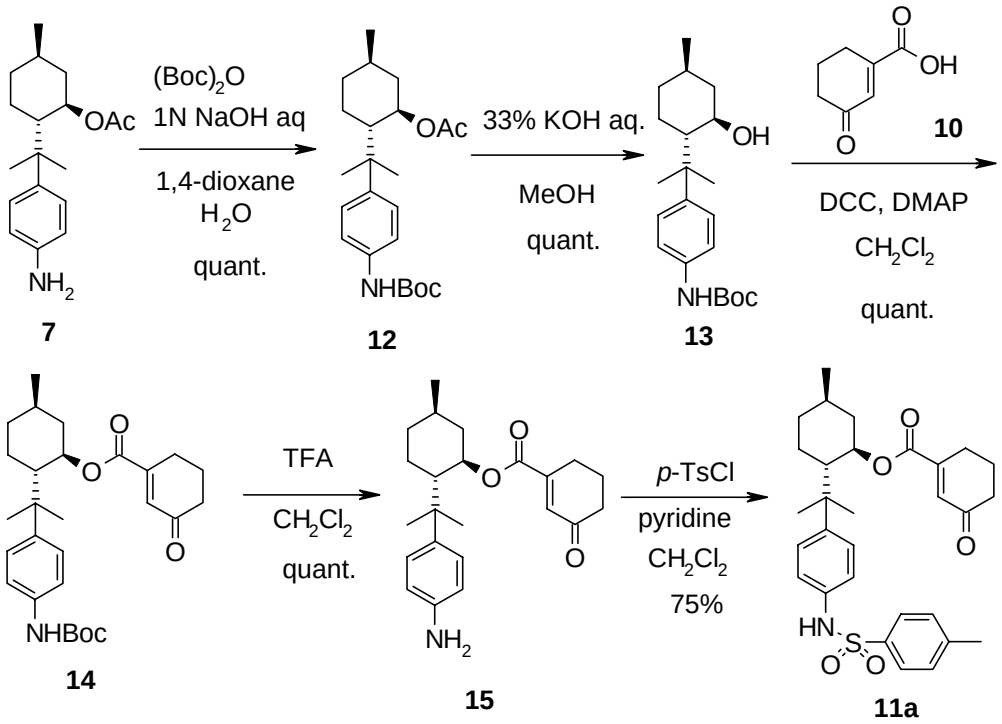
Prior to an attempt of immobilization of the chiral auxiliary **7** to the polymer, we directed to prepare a model compound for solution-phase reaction in the purpose of comparison of an effect of heterogeneous (solid-phase) and homogeneous (solution-phase) conditions. Sulfonamide **8** was synthesized by coupling of **7** with *p*-toluenesulfonyl chloride. It is special noted that the use of pyridine as a base was crucial to obtain the mono-sulfonamide derivative **8** exclusively while the use of triethylamine gave a mixture of mono- and di-sulfonamide products. Removal of acetyl group under basic conditions followed by condensation of cyclohexen-3-one-1-carboxylic acid **10** to give the desired compound **11a** as a minor product. Since the main product, disubstituted aniline derivative



Scheme II. Synthesis of sulfonamide derivative

11b, was obtained due to the acidity of the proton on sulfonamide moiety, we changed the approach to the model compound that the carboxylic acid **10** is attached before sulfonamide formation.

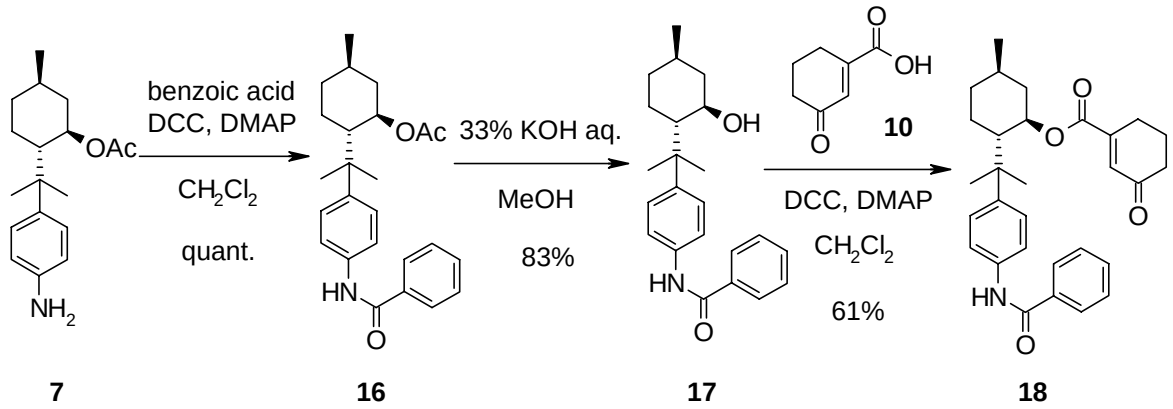
After the reduction of nitro group with iron, the aniline derivative **7** was converted to the *tert*-butyloxycarbonyl (Boc) derivative **12**. Acetyl moiety of the compound **12** was hydrolyzed with potassium hydroxide, then the generated secondary hydroxyl group was condensed with cyclohexen-3-one-1-carboxylic acid **10** to provide the ester **14**. The Boc protection was removed by trifluoroacetic acid (TFA) to give the aniline derivative **15**. Due to the unstability, the aniline compound **15** was used immediately for next reaction without purification. The coupling with *p*-toluenesulfonyl chloride provided the desired sulfonamine model compound **11a** as the main product.



Scheme III. Synthesis of sulfonamide derivative

In addition to this sulfonamide derivative **11a**, an amide derivative **18** was also prepared

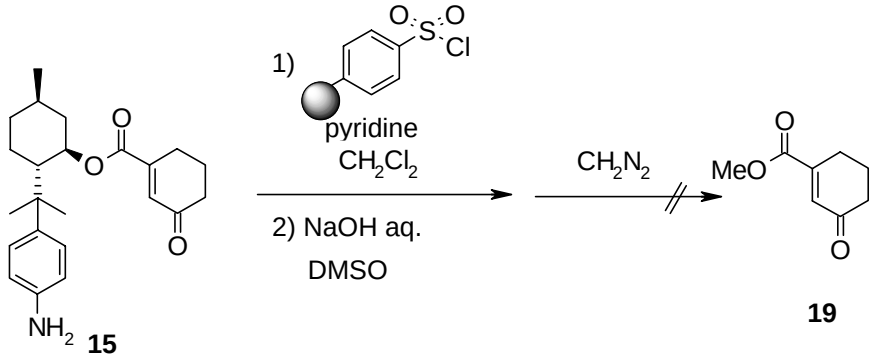
as a model compound as shown in Scheme IV.



7 **16** **17** **18**

Scheme IV. Synthesis of the amide derivative

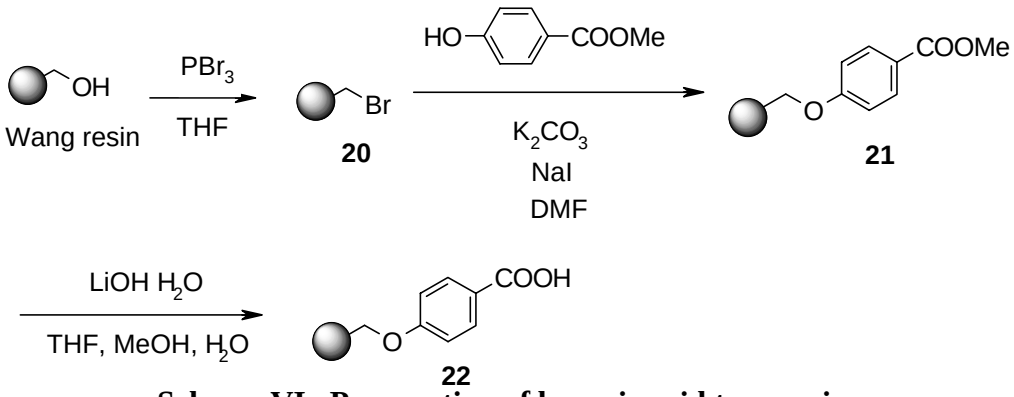
Then we shifted to a preparation of polymer-supported chiral auxiliary. Chlorosulfonated polystyrene resin was attempted for the preparation of the sulfonamide type polymer-supported chiral auxiliary. Coupling of aniline **15** with chlorosulfonated polystyrene resin (purchased from Argonaut Technologies) followed by hydrolysis gave a crude product. The crude product was treated with diazomethane in order to provide methyl ester. However, methyl ester **19** was not confirmed by ^{1}H-NMR, nevertheless IR spectrum showed the appearance of C=O stretch band (1690 cm^{-1}) after the coupling reaction as well as the disappearance of this C=O stretch band after the hydrolysis. The reason of the discrepancy between ^{1}H-NMR and IR spectrum was not clear. This attempt to make sulfonamide type polymer-supported chiral auxiliary was suspended.



15 **19**

Scheme V. Attempt to provide the sulfonamide type

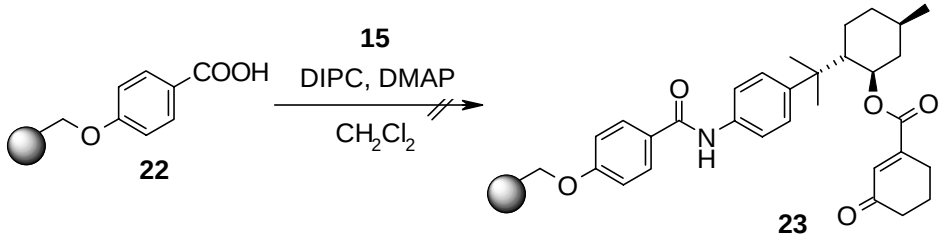
In order to prepare an amide type polymer-supported chiral auxiliary, benzoic acid type polymer **22** was synthesized from the commercially available Wang resin (purchased from Watanabe Chemicals Industries) as shown in Scheme VI. Wang resin is one of the popular solid supports having an acid labile linker. We chose it because selectivity of the photochemical reaction can be easily determined by ^{1}H-NMR as d.e. when the cycloadduct having the chiral auxiliary is cleaved from the resin.



Scheme VI. Preparation of benzoic acid type resin

Each reaction was monitored by IR. OH stretch (3435 cm^{-1}) of Wang resin was disappeared concomitant with appearance of C-Br stretch (596 cm^{-1}) during the bromination reaction. In a similar way, after the coupling reaction of **20** with phenol, C=O stretch (1717 cm^{-1}) was observed concomitant with disappearance of C-Br stretch by IR. Formation of **22** was also confirmed by ^{1}H-NMR by the cleavage of a small amount of **22** with TFA.

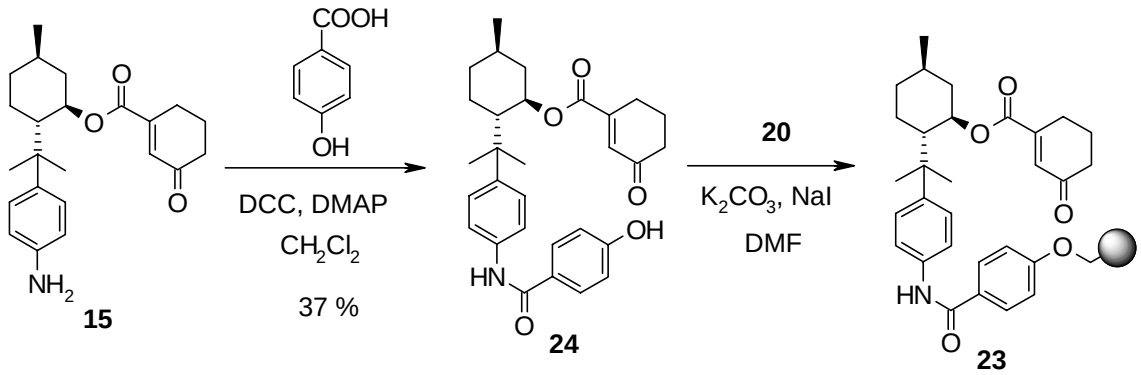
Then, introduction of chiral auxiliary **15** into the resin **22** was tried under the coupling condition using diisopropylcarbodiimide in the presence of 4-dimethylaminopyridine



Scheme VII. Attempt to immobilize to the resin

(DMAP). After the reaction, a small portion of the resulting resin was treated with TFA. The cleaved product was analyzed by ^{1}H-NMR, but only *p*-hydroxybenzoic acid was observed. No targeted compound was confirmed. Unstability and/or steric hindrance around amino moiety of aniline **15** were considered to cause this failure. Thus, we changed the approach toward the polymer-supported chiral auxiliary **23**.

The aniline **15** was converted to the phenol derivative **24** in order to avoid the use of unstable aniline derivative at the resin loading as well as getting off from the crowding amine center. Immobilization of **24** to the brominated Wang resin **20** was carried out with potassium carbonate in the presence of sodium iodide as shown in Scheme VIII. The reaction was monitored by IR. The loading level was determined to be 24% by the cleavage of a small portion of the resulting resin **23**. Although the loading level was somewhat low, but the polymer-supported chiral auxiliary was successfully prepared.

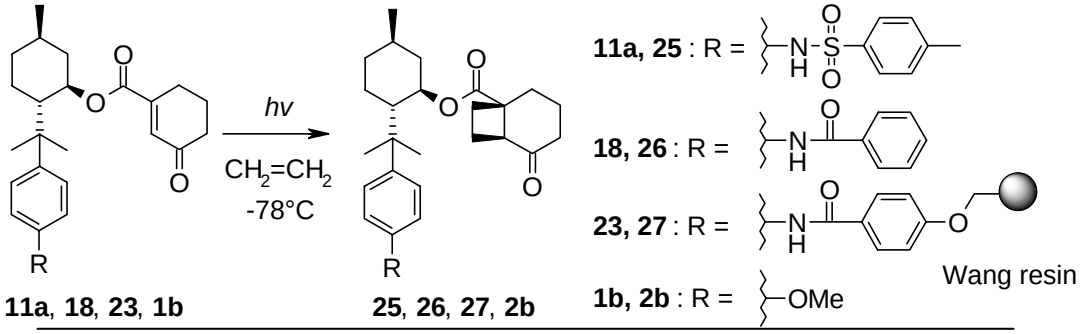


Scheme VIII. Preparation of polymer-supported chiral auxiliary

To this point, we prepared two model compounds for solution-phase and one polymer-supported chiral auxiliary for solid-phase. With these in hand, next we examined diastereoselective [2+2] photocycloaddition reactions with ethylene. Photochemical reaction was carried out at -78°C in an appropriate solvent by irradiating a solution (or suspension) of cyclohexenone carboxylate, saturated with ethylene with Pyrex-filtered light (λ > 280 nm)

from a high-pressure mercury lamp (500 W). Solid-phase photochemical reaction was carried out in dichloromethane at -78°C for 5 hours. After the reaction, the resin was filtered and washed with MeOH and dichloromethane, then treated with 30% TFA in dichloromethane at room temperature for 30 min. The resin was filtered off, and evaporation of the filtrate gave a mixture of two diastereomers. The diastereomeric excess (d.e.) was determined by comparing the areas of distinct signals of the diastereomers in the ^{1}H-NMR spectrum as described previously.[4] No starting material was observed by ^{1}H-NMR in all cases. The results are summarized in Table III. For comparison, the results of photochemical reactions in the solution-phase with (-)-8-[(*p*-methoxy)phenyl]menthyl derivative **1b** are also presented.

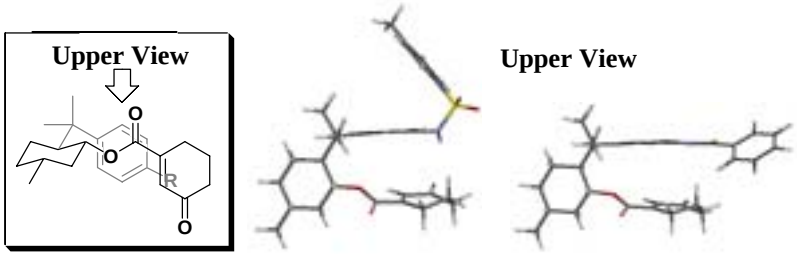
Table III. Investigation of photochemical reactions



Entry	Substrate	Solvent	Yield (%)	D.e. (%)
1	**11a**	toluene	36	60
2	**11a**	CH_2Cl_2	55	50
3	**18**	toluene	86	79
4	**18**	CH_2Cl_2	68	67
5	**23**	CH_2Cl_2	29	61
6	**1b**	toluene	59	61
7	**1b**	CH_2Cl_2	95	50
8	**1b**	methylcyclohexane	79	81

Sulfonamide type compound **11a** best provided the product in 60% d.e. in toluene (Entry 1), which was lower than the corresponding result of the amide type compound **18** (Entry 3). Probably, tetrahedral structural feature of sulfonamide prevented to firm the tight

packing structure between cyclohexenone and sulfonamide moieties. These observations were supported by molecular mechanics calculation. A calculated most stable conformer of **11a** didn't show planar stack conformation between phenyl moiety of the chiral auxiliary and enone moiety, whereas that of amide **18** had planar conformation as shown in Figure II. Furthermore, the yields of the photochemical reaction with sulfonamide type compound **11a** were low. Relative acidic nature of sulfonamide proton probably led to side reactions (e.g. proton absorption, cleavage of sulfonamide bond, and rearrangement) during the photochemical reaction[10], which indicated that this type of linker was unlikely the suitable for further investigations.



11a: R = $NHSO_2$-Ph_2-Me **23: R** = NHCO-Ph

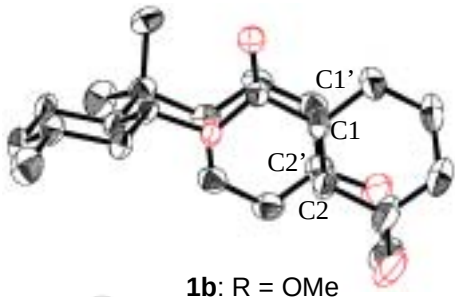
Figure II. Molecular mechanics calculation

In solution, a tendency of slightly better diastereoselectivity of amide **18** than methoxy type **1b** (Entry 3 vs. 6, Entry 4 vs. 7) was observed. However, the reaction of **18** in mehylcyclohexane, which gave the best selectivity with **1b**, could not be carried out owing to the low solubility. High degree of diastereoselectivity was expected from X-ray analysis, but the results were somehow disappointment (Figure III).

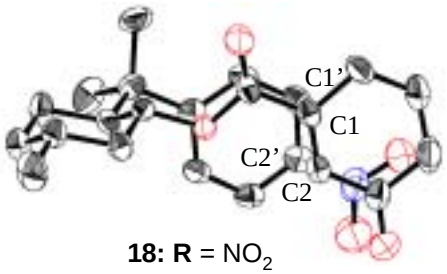
Selectivities between solid- and solution-phase were comparable (Entry 4 vs. 5). The expected effect including a highly hydrophobic environment and an additional π-stacking by polystyrene backbone was not observed in this substrate. The yield of the photochemical reaction with amide **23** in solid-phase was considerably worse than that in solution-phase.

Undesired side reaction (e.g. intramolecular hydrogen absorption) might be preferentially took place due to the immobilization onto the polymer support.

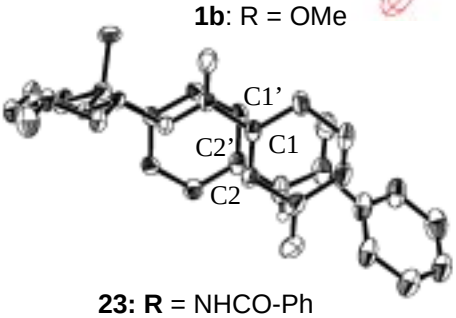
Hydrolysis of polymer-supported cycloadduct **27** was carried out with sodium hydroxide in DMF at elevated temperature for a day. Not only the hydrolysis of ester but also amide bond cleavage was occurred. The result indicated the necessarily of more strong linker.



1b: R = OMe



18: R = NO_2



23: R = NHCO-Ph

Sub.	C1-C1' (Å)	C2-C2' (Å)	D.e (%)[a]
1b	3.62	3.59	50
18	3.54	3.56	88
23	3.45	3.41	67

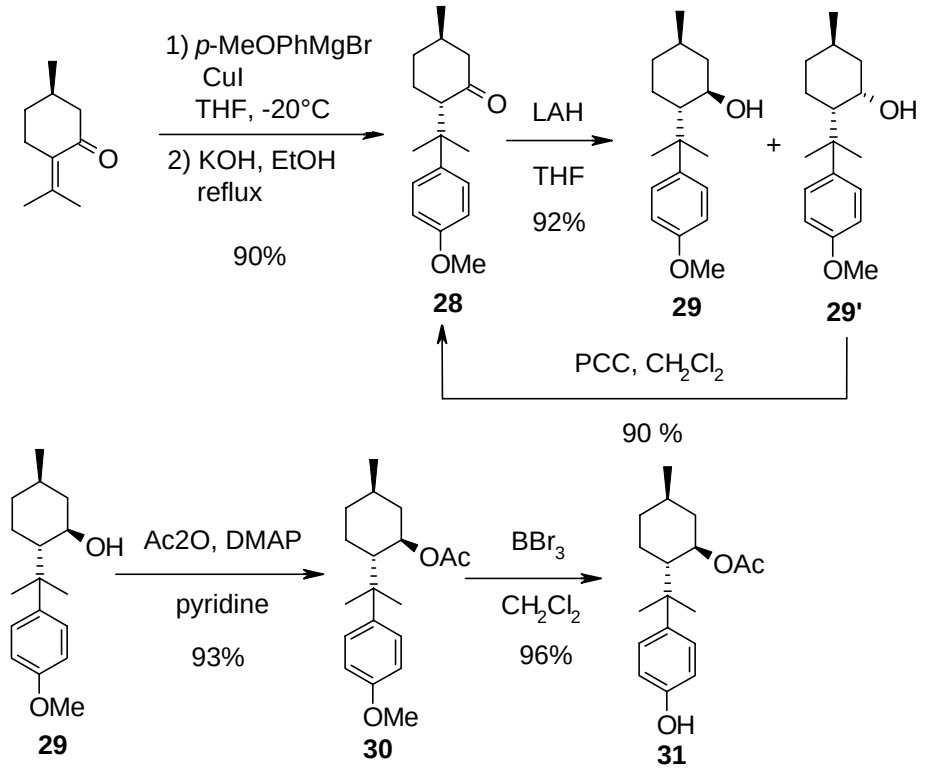
a) The reactions were carried out in CH_2Cl_2.

Figure III. X-ray analysis

3. Preparation of polymer-supported (-)-8-(*p*-alkoxyphenyl)menthyl derivative

As described earlier, (-)-8-[(*p*-methoxy)phenyl]menthyl derivative is the other potential candidate for preparation of polymer-supported chiral auxiliary. Furthermore, ether linkage is thought to be more physically tough than the amide linkage. (-)-8-[(*p*-Methoxy)phenyl]menthyl acetate **28** was prepared in the similar way to the preparation of (-)-8-phenylmenthyl derivative **5** as shown in Scheme IX. Because sodium reduction of **28** led to the complex mixture due to the labile nature of methoxyphenyl moiety

against the sodium reduction, lithium aluminum hydride (LAH) was used instead. LAH reduction gave an undesired diastereoisomer **29'** as a main product (main: minor = 10:3) as a kinetic control product. The undesired diastereomer **29'** was then oxidized back to ketone **28**, which was followed by LAH reduction again. Demethylation was achieved with borane tribromide after protection of alcohol. Temperature was important factor. That is, temperature was gradually raised from –78°C to –25°C. Once the temperature was reached to room temperature, the reaction became messy and the yield was decreased.

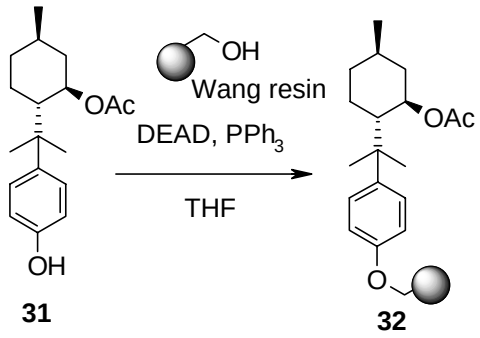


Scheme IX. Preparation of (-)-8-[(*p*-hydroxy)phenyl]menthyl acetate

The introduction of phenol derivative **31** to the resin was attempted firstly with brominated resin **20** with potassium carbonate in the presence of sodium iodide. However, **31** was not observed by the cleavage of the resulting resin. In addition, 83% of **31** was recovered from the filtrate after the coupling reaction. Next, Mitsunobu conditions were examined with Wang resin. The first attempt with the concentration of **31** in 0.11 M gave 4.9% of the loading. Then, the reaction with more concentrated conditions (1.4M) increased

the loading to 29% (Table IV). Although the moderate loading level was accomplished, it was still unsatisfied. As we discussed above, the reaction center (hydroxyl part) was considered to crowd, so an addition of spacer prior to immobilization was required.

Table IV. Investigation of immobilization by Mitsunobu reaction



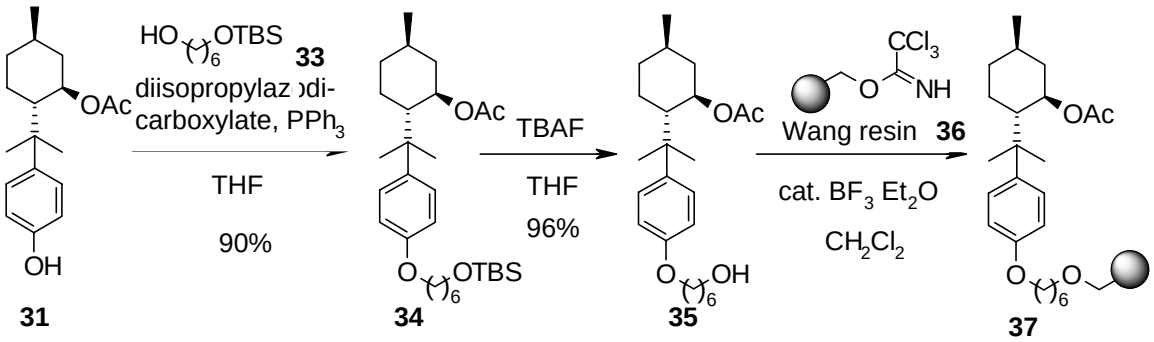
Entry	Conc. of **31** (M)	Conc. of DEAD (M)	Conc. of PPh_3 (M)	Loading (%)
1	0.11	0.21	0.20	4.9
2	1.40	0.81	0.82	29

The reactions were carried out at room temperature for 1 day.

According to the literature[11], six-carbon alkyl linker was chosen as a spacer. 6-(*tert*-Butyldimethylsilanyloxy)hexan-1-ol **33** was coupled to phenol derivative **31** by Mitsunobu reaction, it was followed by desilylation with tetrabutylammonium fluoride to provide alcohol derivative **35**. Attachment of chiral auxiliary **35** to the resin was attempted by Williamson ether bond formation conditions (potassium carbonate (12 equiv.), sodium iodide (3 equiv.), DMF, room temperature, 1day) and its attempt afforded to give 12% of loading. Neither Heating at 80°C nor addition of phase transfer catalyst (18-crown-6) improved the loading (16% and 8% respectively). Stronger base might be required for Williamson etherification, but such base (e.g. sodium hydride) was questionable to be used in the presence of acetyl protection. Thus, we took a different strategy, that is, the use of other type linker, trichloroacetimidate.[12] Trichloroacetimidate Wang resin **36** was prepared according to the literature procedure.[10] The loading level was determined to be 24% after

the coupling reaction with the resin **36**.

Heretofore, the loading levels were determined based on the weights of crude product after the cleavage reaction. However, there were variations and the lack of reproducibility. We, therefore, changed the analytical method as follows: the internal standard (1,1,2,2-tetrachloroethane) was added to the crude cleaved product, then the areas of distinct signals of the product and the internal standard were compared in the ^{1}H NMR spectra.



Scheme X. Preparation of polymer-supported chiral auxiliary with spacer

Although the loading level was not improved, next acetyl deprotection was examined. Several deprotection conditions were investigated (*t*-BuOK, 1,4-dioxane, 80°C; NaOH, MeOH-1,4-dioxane, 80°C; NaOH, DMSO, 80°C; NaOMe, DMSO, 80°C). However, none of them led to the desired product. All attempts of hydrolysis were failed and gave recovery of the starting material. Since the corresponding hydrolysis in solution-phase reaction (NaOH, DMSO, 80°C) proceeded to give the desired hydrolysis product, these results were considered to cause by the lack of affinity of polystyrene resin to the aqueous conditions. The reductive deprotections (LAH, THF, -20°, no reaction; LAH, room temperature, complex mixture) were also unsuccessful, probably due to the insufficient access of inorganic base into the resin. In order to circumvent the problem, poly(ethylene glycol)-grafted polystyrene Wang (PS-PEG-Wang) resin (purchased from Watanabe Chemical Industries, LTD., 1% divinylbenzene cross-linked, 100-200 mesh) was employed in order to increase the affinity toward hydrolysis conditions since it is well demonstrated that due to the grafted PEG moiety,

the polymer swells in aqueous systems as well as in organic solvents.

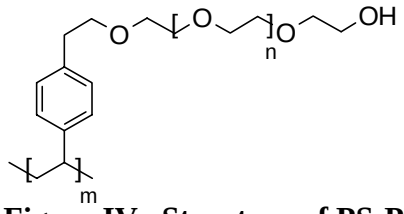
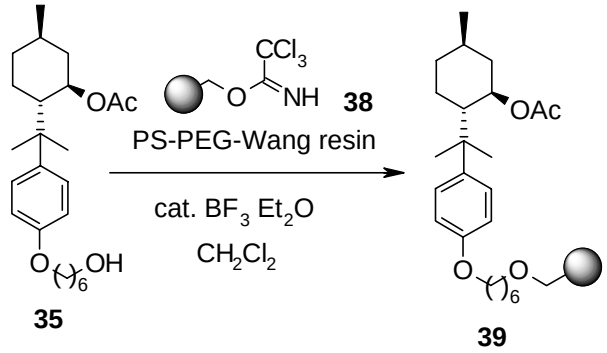


Figure IV. Structure of PS-PEG

Trichloroacetimide type PS-PEG-Wang resin was prepared according the literature procedure.[10] Immobilization was firstly carried out with the 2.0 M concentration of **35** to give the product in moderate loading and good purity. Interestingly, decrease of concentration of **35** to 1.0 M improved the loading level (Entry 2, 91%) dramatically with excellent purity (>99%).

Table V. Investigation of immobilization with PS-PEG-Wang resin



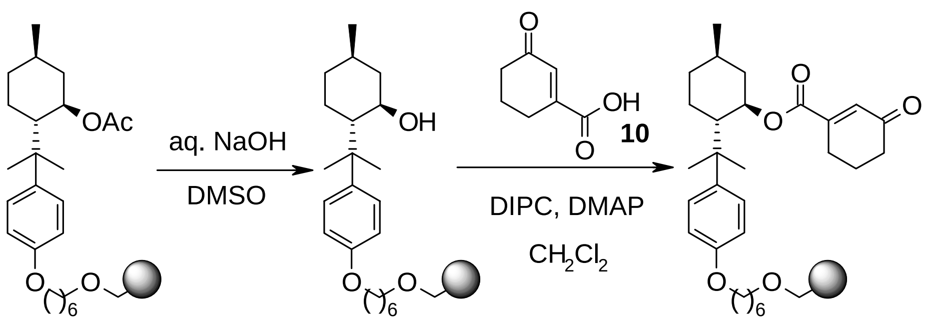
Entry[a)]	Conc. of **33** (M)	Purity (%)[b)]	Loading (%)[c)]
1	2	96	50
2	1	>99	91

a) The reactions were carried out at room temperature for 30 min.
b) Determined by ^{1}H-NMR analysis of crude cleaved product with the internal standard.
c) Based on the original loading of PS-PEG-Wang resin (0.24 mmol/g) .

As shown before, the loading level to the PS-Wang resin was 24% via trichloroacetimidate, but the corresponding loading to PS-PEG-Wang resin was spectacularly improved to be 91%. This large difference of the loading level would be contributed by the following factors: 1) The reaction center was gotten way from the polystyrene core by

insertion of PEG linker, which led to the improved reactivity. 2) The original loading level of PS-PEG-Wang was much lower than that of Wang resin (0.24 mmol/g vs. 0.75 mmol/g), accordingly the resulting loading levels after the introduction were comparable each other (0.22 mmol/g vs.0.18 mmol/g).

Deprotection of acetyl moiety was accomplished by aqueous sodium hydroxide in DMSO at 80°C for 15 hours. Then, cyclohexen-3-one-1-carboxylicacid **10** was coupled with alcohol **40** with diisopropylcarbodiimide in the presence of DMAP. Completion of the reaction at each step was confirmed by partial cleavage of the resulting resin with TFA followed by ^{1}H-NMR analysis.



39 **40** **41**

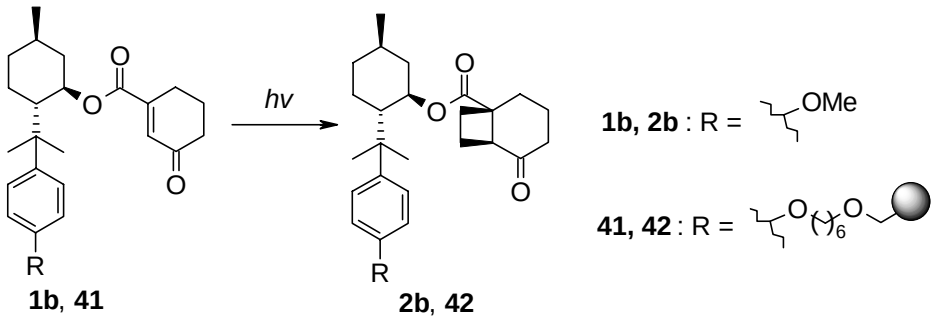
Scheme XI. Conversion to the ester

4. Diastereoselctive photocycloaddition of PS-PEG-Wang resin-supported chiral auxiliary

With the ether type polymer-supported chiral auxiliary **41** in hand, the effects of solvents on the selectivity were investigated (Table VI). Photochemical reactions were carried out as described above. The time for solid-phase reaction was fixed to 5 hours in order to compare the each solvent. For comparison, the results of photochemical reactions in the solution-phase with (-)-8-[(*p*-methoxy)phenyl]menthyl derivative **1b** are also presented.

In all cases the reaction proceeded and toluene was found to be the best to provide the product **42** in 68% yield with 72% d.e. (Entry 2). This selectivity is slightly better than that in the solution-phase synthesis in toluene (Entry 1 vs. 2). Methylcyclohexane best provided the product **2b** in 81% d.e. in the solution-phase (Entry 3), while the corresponding solid-phase synthesis afforded the product **42** in 65% d.e. with the low chemical yield (Entry 4). Since the starting material **41** was still remained in methylcyclohexane after 5 hours irradiation, this reaction was repeated again with prolonged reaction time (20 hours). The result was, however, the same. This result was influenced by the low swelling of the resin in methylcyclohexane. The resin was coagulated and it prevented the interaction of ethylene and/or light with the interior substrate. Only the substrate presented around the surface of

Table VI. Investigation of the effect of solvents



Entry	Substrate	Solvent	Yield (%)[a), b)]	D.e. (%)
1	**1b**	toluene	59	66
2	**41**	toluene	68	72
3	**1b**	methylcyclohexane	79	81
4	**41**	methylcyclohexane	20[c)]	65
5	**1b**	CH_2Cl_2	95	50
6	**41**	CH_2Cl_2	30[d)]	58
7	**1b**	MeOH	14	3
8	**41**	MeOH	57	48

a) The yields were determined by ^{1}H-NMR for **41** or by isolation for **1b**.
b) For **1b**, the reactions were carried out until the consumption of the starting material (0.5 h-2.0 h).
c) The starting material was remained in 30%.
d) The starting material was remained in 14%.

the coagulated resin was reacted. Interestingly, in MeOH the cycloadduct was obtained in moderate yield and selectivity whereas the corresponding reaction in the solution-phase gave the product in low yield and selectivity due to the low solubility of **1b** against MeOH (Entry 7 vs. 8). This is noteworthy example that the affinity toward the reactant as well as both the reactivity and selectivity were enhanced by immobilization to polymer support. As expected, selectivity was increased with non-polar solvent, which was also observed in solution-phase reaction.[4] Non-polar solvent has an advantage for packing structure formation between enone and phenylmenthyl parts.

The partial degradation of the polymer backbone was observed during the photochemical reaction. The degrees of the chop were varied among the solvents and affected to the yields. The interpretation of this event will be discussed later on.

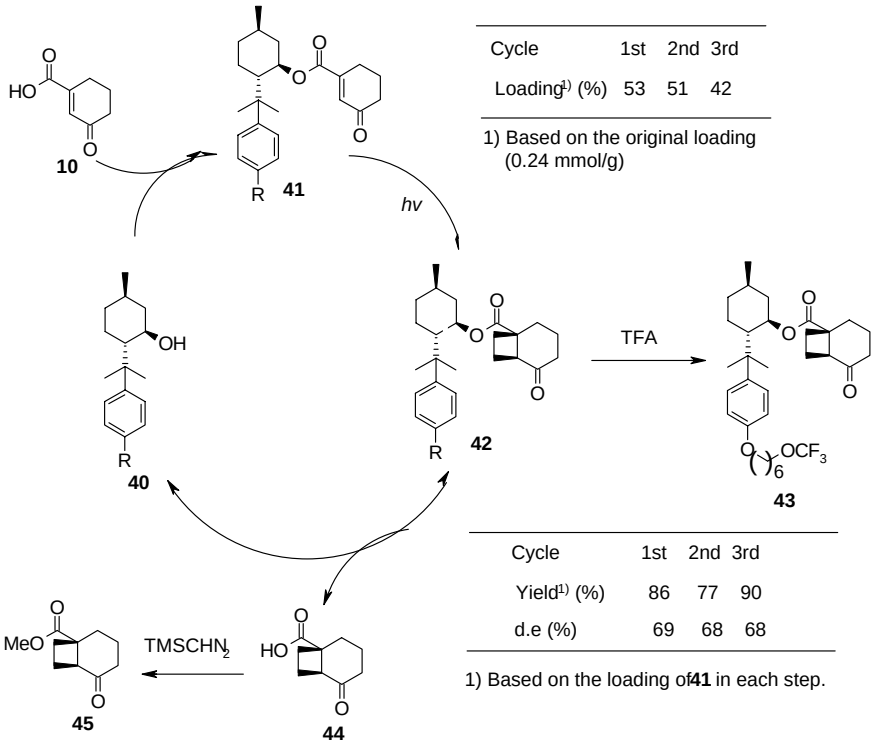
The reaction was also attempted in THF, but it was resulted in complex mixture since THF might work as trapping reagent of radical under the irradiation conditions.

One of the important features of PEG-grafted polystyrene is allowed to use water as a reaction media. Unfortunately, our attempt of this photochemical reaction in water at 7°C resulted in the complex mixture. Although the starting material **41** was consumed completely, only a trace amount of the desired product was obtained (< 1% yield). Probably, a saturated concentration for ethylene in water is extremely lower than that in organic solvents like toluene. Because of this low concentration of ethylene in water, undesired side reactions (e.g. hydrogen absorption) would take place faster than the cycloaddition.

We also examined the reaction without solvent because we anticipated that immobilization of substrate to the polymer would provide enough space to be reacted with reagent (ethylene) and give the cycloadduct. However, the result was disappointing. Only a trace amount of the cycloadduct was observed while almost all of the starting material was remained unreacted.

5. Recycle of the polymer-supported chiral auxiliary

Although the partial degradation was observed, we attempted to recycle the polymer-supported chiral auxiliary. The synthesis of the chiral auxiliary **29** was quite tough and the resin is still somewhat expensive. Thus, the reuse of this precious polymer-supported chiral auxiliary is desirable.



Cycle	1st	2nd	3rd
Loading[1)] (%)	53	51	42

1) Based on the original loading (0.24 mmol/g)

Cycle	1st	2nd	3rd
Yield[1)] (%)	86	77	90
d.e (%)	69	68	68

1) Based on the loading of **41** in each step.

Cycle	1st	2nd	3rd
Yield[1)] (%)	84	88	76
e.e (%)	54	46	41

1) Based on the loading of **42** in each step.

Figure V. Recycle of the polymer-supported chiral auxiliary

After the photochemical reaction in toluene as described above, bicyclo[4.2.0]octan-2-one-6-carboxylic acid **44** was released from the resin by hydrolysis (NaOH, DMSO, 80°C), then converted to its methyl ester **45** by treating with trimethylsilyldiazomethane ($TMSCHN_2$). The enantiomeric excess (e.e.) was determined by

gas chromatography with chiral column. The recovered polymer-supported chiral auxiliary **40** was then coupled with cyclohexen-3-one-1-carboxylic acid **10** to reproduce **41**. The photochemical reaction was carried out again to provide **42**. To determine the yield and diastereoselectivity, a small amount of **42** was treated with TFA to give **43**. The loading levels of **41** at each cycle were determined based on the original loading of PS-Wang-PEG resin. The yields of photocycloaddition were decided based on the loading level of **41** at each step. The d.e.s of **43** were estimated by ^{1}H-NMR spectra after the isolation of **43** by silicagel column chromatography. As well, the yields and the e.e.s of **45** were settled by ^{1}H-NMR and chiral gas chromatography analysis (Chiraldex G-BP) respectively.

The results are summarized in Figure V. Although the loading levels were decreased by the recycle due to the partial degradation, both the yields and the d.e.s of **43** were stable at each photochemical reaction. On the other hand, the e.e.s were decreased by each step due to the partial degradation. Furthermore, the d.e. and the e.e. of the first cycle was not correlated. This was most likely insufficient first loading of the chiral auxiliary to the resin. At regeneration (generation) of the enone attached chiral auxiliary **41**, the chiral auxiliary-free reaction center (unreacted hydroxyl group) was also reacted with cyclohexen-3-one-1-carboxylic acid **10** to generate achiral enone, which contributed to diminish the e.e. This is other issue to be settled in further investigation.

The polymer-supported chiral auxiliary was efficiently prepared and utilized for the diastereoselective [2+2] photocycloaddition reaction. The cycloadduct was obtained in good yield and diastereoselectivity. Besides that, the polymer-supported chiral auxiliary was reusable up to 3 cycles. Further investigations to address the degradation and to seek more effective supports are indisputably necessary.

6. Consideration of the degradation

The partial degradation of polymer backbone was observed during the photochemical reaction with PS-PEG-Wang resin. We first suspected that the cleavage was occurred at Wang linker (*p*-methoxybynzyloxymethyl ether) since same type protecting group can be removed by radical conditions [13] which should appear during the course of photocycloaddition. This was, however, disclaimed because poly(ethylene glycol) as well as Wang moiety was observed from the filtrate after the photochemical reaction analyzed by ^{1}H-NMR. In addition, at the photochemical reaction of amide type polymer-supported chiral auxiliary **23**, such degradation was not observed. This was also confirmed that the degradation was observed by photoirradiation of polymer-supported chiral auxiliary even without enone moiety. The cleavage must be occurred at poly(ethylene glycol) moiety. However, it is well known that poly(ethylene glycol) itself is inactive against the photochemical conditions. Then, the photochemical reaction was carried out with the light (λ > 300 nm) by using color grass filter. Polystyrene backbone is known to be inert the light (λ > 300 nm), so that unexpected energy transfer from polystyrene to poly(ethylene glycol) should not occurred. However, the degradation was observed, it meant that the event was not caused by irradiation of polystyrene moiety by the light blow 300 nm.

Eventually, we found the cause of this undesired event; it was due to the low temperature. The degradation of the poly(ethylene glycol) moiety was confirmed at –78°C even without the light. At the low temperature, mobility of the molecular is declined, and the polymer is collapsed. It is assumed that the conformer populations of PEG chain is limited due to the preference of gauche-gauche interactions of vicinal carbon-oxygen bonds. Besides that, further restriction of conformer might be achieved by an interaction between hydrogen in ethylene glycol moiety and π electron in aromatic ring. This CH/π interaction[14] is a weak hydrogen bond, but the assembly of this interaction gives great impact on whole

free energy of the molecule. Unlike ordinary hydrogen bonding, the CH/π interaction may occur in protic media as well as nonpolar media. The interactions and restrictions would construct pseudo-high cross-linked network of polymer backbone. It is well known that highly cross-linked polystyrene resin is mechanically unstable. Thus, it is speculated that this undesired degradation might occur by mechanical damage as a result of collapse of the resin. A solvent also affects collapsing as well as swelling of the resin. That would explain why the degrees of degradation were varied among the solvents. Still the event is poorly understood and questions are remained (e.g. how to cleave the covalent bond). Although further investigation to understand the mechanism of degradation is necessary, we learned that the combination use of PEG and PS lead to the degradation.

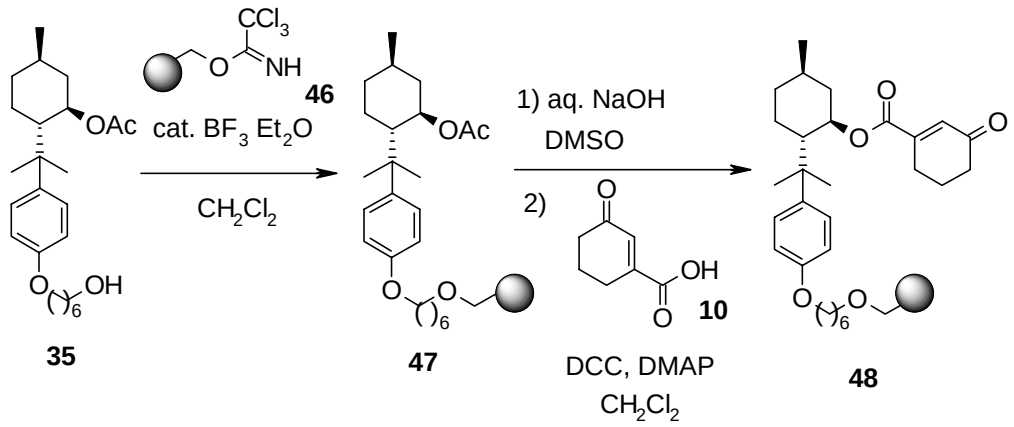
In order to overcome the problem, other type of polymer and/or linker is demanded. Next we investigated different type of polymer support.

7. Investigation with macroporous resin

Macroporous polystyrene (MP) resin is designated as more highly cross-linked polystyrene than usual polystyrene resin. With MP resin, the functional groups are accessed through the pore network. This process is not usually dependent on solvent. Because of its unique property of porous resin, a wide range of reaction conditions is applicable, including protic solvent (water) and low temperature, which were the major problems with polystyrene resin and gel-type resin (PEG resin) as we faced previously.

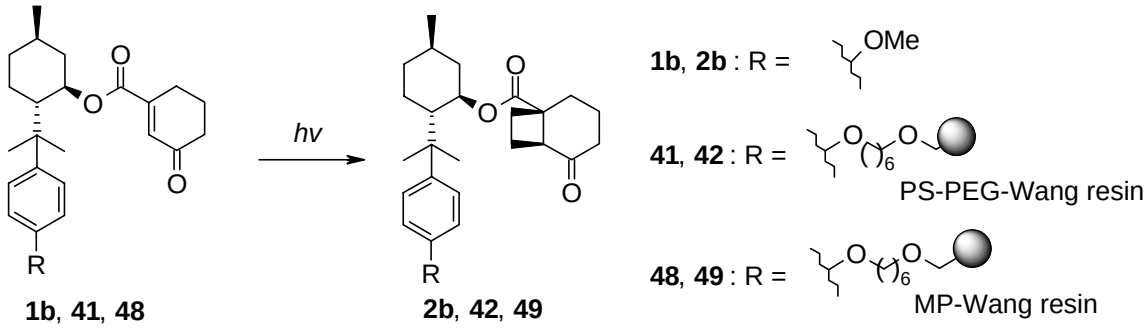
The chiral auxiliary **35** was immobilized into the MP-Wang resin (purchased from Argonaut Technologies, >8% cross-linked) via trichloractimidate as described above. Although the loading level was not so high (30% based on the original loading of MP resin

(0.65 mmol/g)), subsequent hydrolysis followed by coupling with cyclohexen-3-one-1-carboxylic acid **10** was successfully achieved as shown in Scheme XII.



Scheme XII. Immobilization to MP resin

Table VII. Investigation of the effect of solvents with MP resin



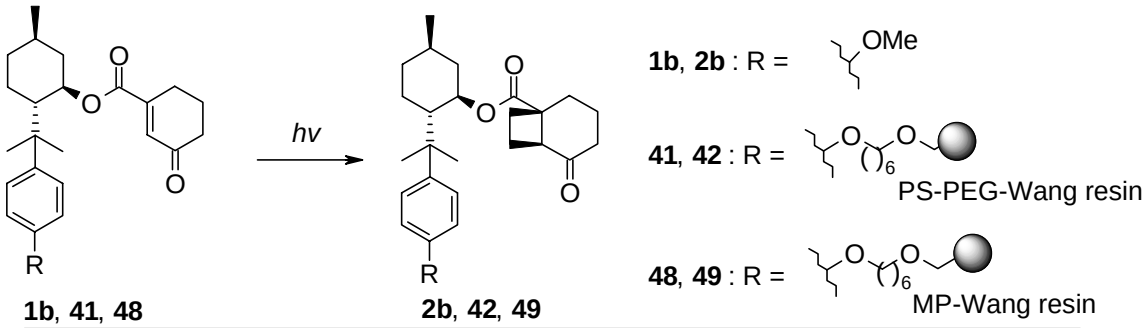
Entry	Solvent	Yield (%)			D.e. (%)[a)]		
		41[b)]	**48**[c)]	**1b**[d)]	**41**	**48**	**1b**
1	toluene	68	93	99	72	72	75
2	methylcyclohexane	22	55	96	65	61	81
3	CH_2Cl_2	35	84	95	58	49	50
4	MeOH	57	86	14	48	37	3

a) The d.e.s were determined by ^{1}H-NMR.
b) The reactions were carried out for 5 h. The yield was determined based on the original loading.
c) The reactions were carried out for 9 h. The yield was determined based on the original loading.
d) isolated yield.

The photochemical reactions as well as the effects of solvent were investigated with MP resin-supported chiral auxiliary **48** as shown in Table VII. As we expected, MP-Wang resin was stable under the irradiation conditions, no degradation was observed. As the result, the yields were improved in all solvents in comparison with the cases of PS-PEG-Wang resin. The similar tendencies of the selectivities were observed among PS-PEG-Wang and MP-Wang resin.

The effects of the temperature were also examined as shown in Table VIII. The d.e.s were declined to the accompaniment of the elevation of the temperature as we previously reported.[4] Since the degradation observed at PS-PEG-Wang resin was caused by the low temperature, an improvement of the yield was expected. However, the yield was not improved significantly.

Table VIII. Investigation of the effect of temperature

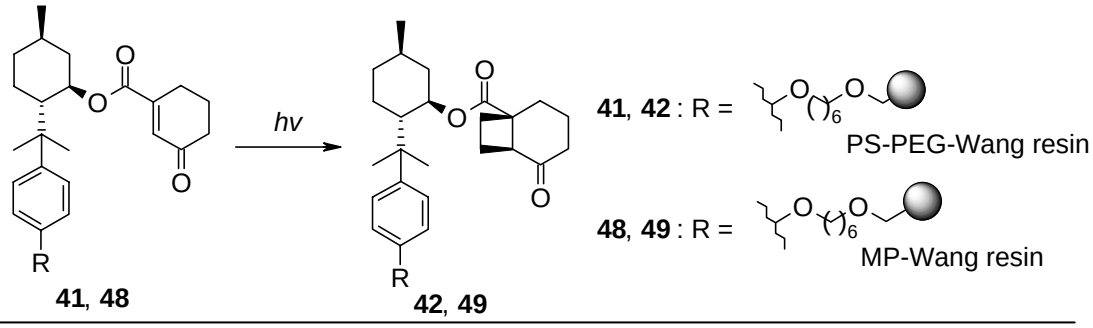


Entry	Temp. (℃)	Yield (%)			D.e. (%)[a)]		
		41[b)]	**48**[c)]	**1b**[d)]	**41**	**48**	**1b**
1	-78	68	93	99	72	72	75
2	-40	76	81	98	56	55	60
3	0	73	11	99	32	29	31

a) The d.e.s were determined by ^{1}H-NMR.
b) The reactions were carried out for 5 h. The yield was determined based on the original loading.
c) The reactions were carried out for 9 h. The yield was determined based on the original loading.
d) isolated yield.

We attempted solvent-free reaction, because, as described above, functional groups are assumed to access through the pore network in MP resin. Namely, it was anticipated that ethylene gas could reach to the reaction center without solvent, and the substrate could have an enough space to be reacted by immobilization to the resin. The results are shown in Table IX.

Table IX. Investigation of solid-gas reaction



Entry	Substrate	Temp. (℃)	Time (h)	Conversion (%)	Yield (%)[a)]	D.e. (%)[b)]
1	**41**	-60	5.0	trace	trace	- [c)]
2	**48**	-60	5.0	78	78	53
3	**48**	0	5.0	67	50	23

a) The yield was determined based on the original loading.
b) The d.e.s were determined by ^{1}H-NMR.
c) The d.e. was not determined.

The photochemical reactions of PS-PEG-Wang resin **41** and (-)-8-[(*p*-methoxy)phenyl]menthyl derivative **1b**[15] without solvent hardly proceeded. These were because of highly compacted structure of non-swelled polymer and solid respectively. As the result, the reagent, ethylene, is prohibited to enter the inside of polymer or solid. In sharp contrast to this, the photochemical reaction with MP resin provided the cycloadduct expectedly. The reaction proceeded in 78% conversion in 53% d.e. for 5 hours irradiation (Entry 2).

It was already revealed that in solid structure *s*-trans conformation is the most stable supported by calculated molecular mechanics and X-ray analysis.[4] From this fact, we

predicted that polymer-supported chiral enone is supposed to fix in *s*-trans conformation in solid state (without solvent), and its photochemical reaction should provide the product in high selectivity. Indeed, it has been reported that the photochemical reaction in solid state (not polymer) often gives the product in high selectivity.[16] However, the selectivity of this photochemical reaction with MP resin was not satisfactory although the reaction proceeded. In order to obtain an insight about dynamics of polymer-supported substrate, we carried out the reaction at 0°C (Entry 3). The d.e. was decreased to be 23%. It revealed that the diastereoselectivities were dependant on the temperature. Thus, it is considered that there is the equilibration between *s*-trans and *s*-cis even solvent-free conditions (solid state). Probably, at the interface between the solid support and the substrate a local solvation of the substrate by polymer backbone was occurred and free rotation of the bond by thermal energy is possible in some extent. In order to achieve a high selectivity, more distinctive inventions on polymer support are demanded.

8. Investigation with soluble polymer-poly(ethylene glycol)

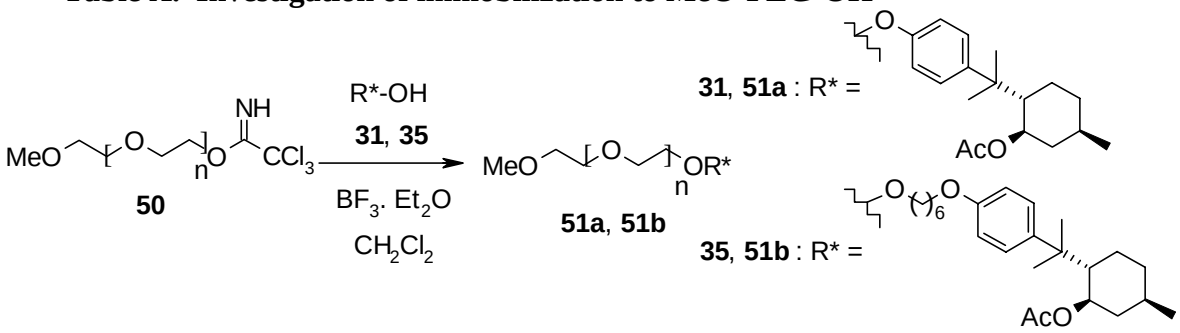
It was reported that PEG is thought to be stable under photo irradiation.[17] Besides that PEG is sufficiently interesting in terms of the accomplishment of homogenous reaction conditions as well as feasibility of analysis since poly(ethylene glycol) is the soluble polymer support. Thus, PEG is definitely interesting enough to adapt to our system discussed above.

MeO-PEG-OH is a mono methyl ether poly(ethylene glycol) and has an advantage in terms of easiness of analysis. Methyl ether part is able to be used as a kind of the internal standard in ^{1}H-NMR spectrum.

For immobilization of the chiral auxiliary to MeO-PEG-OH, the polymer was converted

to trichloroacetimidate **50** as described above. The reaction was carried out with the solvent as a homogeneous solution. And after the reaction, poor solvent (diethyl ether) was added to the reaction mixture. The resulting precipitate was collected on a filter and washed with diethyl ether intensively. The obtained solid was analyzed by ^{1}H-NMR. It showed the complete conversion of OH group to its tricholoacetimidate. Then, the introductions of chiral auxiliaries were attempted, but maximum loading level was 50% even with the chiral auxiliary with alkyl chain **35**.

Table X. Investigation of immobilization to MeO-PEG-OH



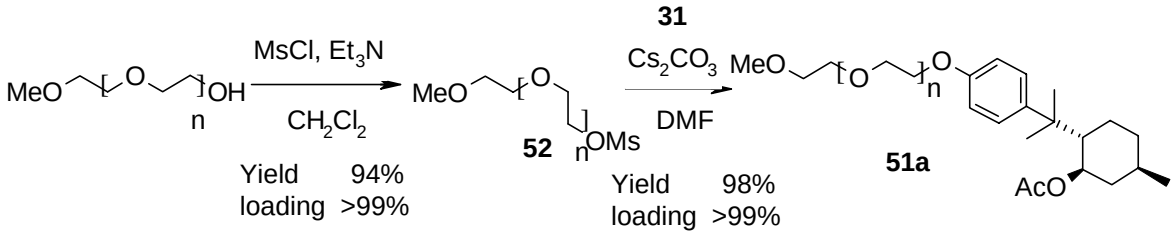
Entry	Substrate	Equiv. of sub.	Loading level (%)[a)]
1	**31**	5	18.9
2	**35**	4	50.0

a) The reactions were carried out at room temperature for 6 h.
b) The yield was determined based on the original loading.

Mitsunobu reaction with the substrate **31** was investigated under various conditions, but none of them provided the satisfactory results. The conversion of the terminal OH group to bromine with carbon tetrabromide in the presence of triphenylphosphine in THF didn't proceed either.

Eventually, quantitative introduction of the chiral auxiliary **31** was achieved via methanesulfonate as shown in Scheme XIII. The soluble polymer-supported chiral auxiliary **51a** was prepared in 93% yield and >99% of the loading level from the MeO-PEG-OH. Cesium ion used for the reaction was removed by mixing with Amberlite IR-120

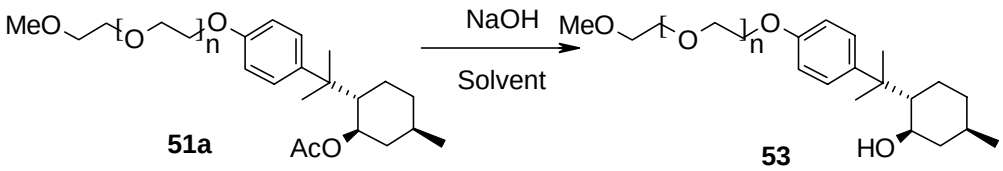
ion-exchange resin followed by filtration with Celite.



Scheme XIII. Immobilization to MeO-PEG-OH

Hydrolysis of acetyl group was examined as shown in Table XI. In MeOH, the reaction proceeded at 70% conversion at 80°C for 4 hours. Then, the reaction time was extended to 8 hours and the desired product **53** was obtained in 92% yield. However, further elongation of the reaction time to 16 hours led to the undesired degradation of PEG moiety. We also examined the hydrolysis in DMSO. In DMSO, even 16 hours reaction provided the desired product cleanly. No degradation was observed. MeOH would provide the similar environment to lead the degradation of PEG discussed above.

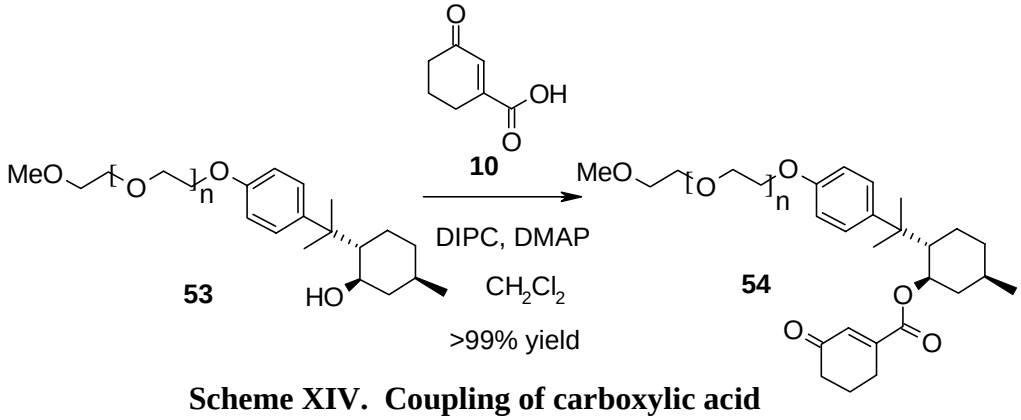
Table XI. Investigation of hydrolysis



Entry	Solvent	Time (h)	Yield (%)
1	MeOH	4	70[a)]
2	MeOH	6	82
3	MeOH	8	92
4	MeOH	16	-
5	DMSO	6	98
6	DMSO	16	92

a) The conversion yield.

The condensation of cyclohexen-3-one-1-carboxylicacid **10** was tried with diisopropylcarbodiimide in the presence of DMAP in dichloromethane. The conversion was 60% even elongation of the reaction time. Then, the reaction was repeated under the same conditions twice to reach >99% conversion.



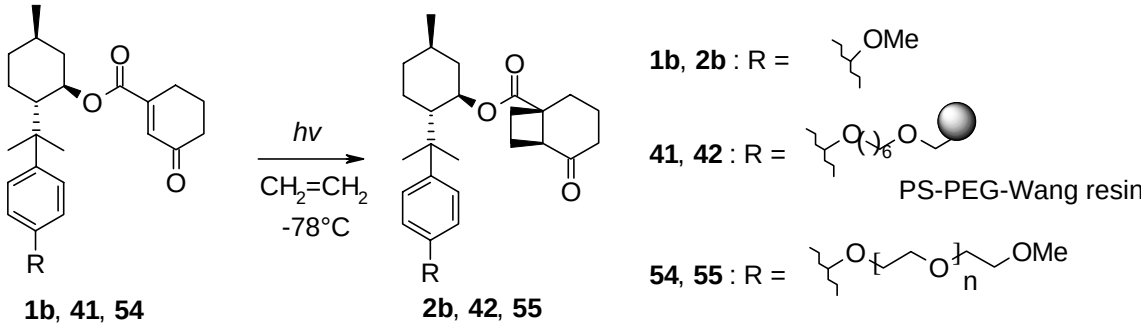
Scheme XIV. Coupling of carboxylic acid

The photochemical reactions were investigated with various solvents as shown in Table XII. For comparison, the results of photochemical reactions in the solution-phase with (-)-8-[(*p*-methoxy)phenyl]menthyl derivative **1b** and in solid-phase with PS-PEG-Wang resin-supported chiral auxiliary **41** are also presented. The reactions with toluene and dichloromethane were carried out as solution, but cooled methanol and methylcyclohexane didn't dissolve the substrate. Such solvent that provided heterogeneous condition didn't give the completion of the reaction even elongation of the reaction time. Even worse, the diastereoselectivities were not determined in such solvent because the intensity of the signal of the proton that is used to see the selectivity (Figure VI) was relatively small. This led to a speculation that the cycloadduct was decomposed under the photochemical conditions. The reason was not elucidated yet.

The selectivities between in toluene and dichloromethane were comparable while these in solution-phase with **1b** and solid-phase with **41** were obviously different. We assumed that the substrate was surrounded by PEG and topically solvated by PEG not the solvent used.

Probably, this would be the cause not to see the solvent effects and of the comparable selectivities among the solvents.

Table XII. Investigation of the effect of solvents with PEG



Entry	Solvent	Yield (%)			D.e. (%)[a]		
		41[b]	**54**[b]	**1b**[c]	**41**	**54**	**1b**
1	toluene	68	95	99	72	54	75
2	methylcyclohexane	22	70	96	65	-	81
3	CH_2Cl_2	35	98	95	58	49	50
4	MeOH	57	50	14	48	-	3

a) The d.e.s were determined by ^{1}H-NMR.
b) The reactions were carried out for 5 h. The yield was determined based on the original loading.
c) isolated yield.

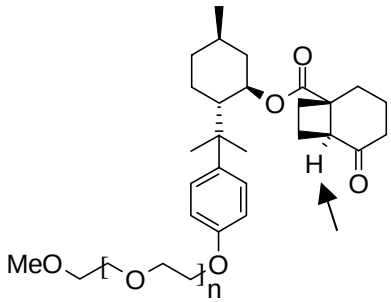
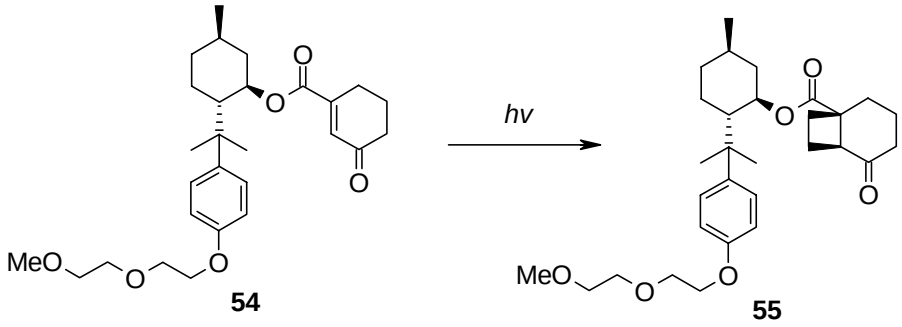


Figure VI. The proton used for the determination of the d.e

Next, we investigated the effects of temperature (Table XIII). The photochemical reactions were carried out at –78°C, -40°C, 0°C respectively. Interestingly, the selectivities at –78°C and –40°C were comparable while these at 0°C were dropped as observed previously.[4] A unique environment formed by PEG would fix the conformation of the

substrate regardless the temperature in some extent.

Table XIII. Investigation of the effect of temperature



54 **55**

Entry[a)]	Temp. (℃)	Solvent	Yield (%)	D.e. (%)[b)]
1	-78	toluene	95	54
2	-78	CH_2Cl_2	98	49
3	-40	toluene	90	49
4	-40	CH_2Cl_2	88	45
5	0	toluene	90	7
6	0	CH_2Cl_2	89	36

a) The reactions were carried out for 5 h. The yield was determined based on the original loading.
b) The d.e.s were determined by ^{1}H-NMR.

9. Conclusion

In conclusion, the three types of polymer-supported chiral auxiliaries (PS-PEG-Wang resin, MP resin, PEG) were efficiently prepared and utilized for the diastereoselective [2+2] photocycloaddition reaction. The cycloadducts were obtained in moderate to good yields and diastereoselectivities. To our best knowledge, this is the first example that the diastereoselective photochemical reactions proceeded on beads. Besides that, we were able to show that PS-PEG-Wang resin-supported chiral auxiliary was reusable up to 3 cycles. This is desirable of the reuse of this precious polymer-supported chiral auxiliary since the

synthesis of the chiral auxiliary is quite tough and the resin is still somewhat expensive. The present polymer-supported chiral auxiliary is applicable to a series of diastereoselective reactions including stereoselective thermodynamic reactions.[3] Although the undesired degradation occurred with PS-PEG-Wang resin owing to the liability of PEG moiety at low temperature, we elucidated the reason of this event. Furthermore, this problem was overcome by the use of macroporous polystyrene resin and poly(ethylene glycol). Interestingly, the photochemical reaction with MP resin proceeded even in the absence of solvent that is preferable in terms of development of an environmentally-benign chemistry.

10. Experimental session

General

All reagents were commercially available and purified prior to use unless otherwise stated. All non-aqueous reactions were performed using oven-dried or heat-gan dried glassware under an atmosphere of dry nitrogen. Air- and moisture sensitive liquids and solutions were transferred *via* syringe or stainless cannula. The reactions were monitored by gas chromatograph and/or TLC (Analytical thin-layer chromatography). Organic extracts were concentrated by rotary evaporation in vacuum. Solvents and anhydrous liquid reagents were dried according to established procedures by distillation under nitrogen from an appropriate drying agent: diethyl ether and tetrahydrofrane from sodium benzophenone ketyl; methanol and isopropyl alcohol from magnesium methoxide; CH_2Cl_2 from CaH_2 prior to use. Other solvents were used as received from manufacture. All chromatographic purification of products was accomplished by flash chromatography on Cica-reagent silica gel 60N (spherical, neutral) and/or medium liquid chromatography (Yamazen YFLC-V10) using ethyl acetate in *n*-hexane.

^{1}H NMR spectra are reported as chemical shifts in parts-per-million (ppm) relative to the chloroform-*d* signal (7.26 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad. Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C spectra are reported as chemical shifts in ppm based on the middle peak of chloroform-*d* (77.0 ppm), and signal assignments (s, d, t and q) were made from DEPT experiments. Absorption peaks of infrared (IR) spectra are reported in reciprocal centimeters.

Acetic acid 2-[1-(4-aminophenyl)-1-methylethyl]-5-methylcyclohexyl ester 7

To a solution of acetic acid 2-[1-(4-nitro-phenyl)-1-methyl-ethyl]-5-methyl-cyclohexyl ester **5** (70 mg, 0.22 mmol) in ethanol (2.4 mL) was added water (0.6 mL), hydrochloride (3 drops), and iron powder (123 mg, 2.2 mmol). The mixture was refluxed under nigrogen for 30 min. The mixture was passed through Celite pad and the filtrate was concentrated under reduced pressure. The residue was extracted with diethylether. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silicagel column chromatography (*n*-hexane:ethyl acetate = 9:1) to give acetic acid 2-[1-(4-aminophenyl)-1-methylethyl]-5-methylcyclohexyl ester **7** (57.7 mg, 0.20 mmol, 91%) as a red oil.

$[\alpha]_D^{26}$ = 0.523, c = 3.50 in $CHCl_3$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 8.6 Hz, 2H), 4.77 (td, *J* = 10.7, 4.3 Hz, 1H), 3.57 (s, 2H), 1.90-1.85 (m, 2H), 1.67 (s, 3H), 1.71-1.58 (m, 2H), 1.43-1.39 (m, 1H), 1.26 (s, 3H), 1.17 (s, 3H), 1.03 (qd, *J* = 26.0, 13.1, 3.1 Hz, 1H), 0.94 (q, *J* = 23.5, 11.8 Hz, 1H), 0.84 (d, *J* = 6.1 Hz, 3H), 0.86-0.78 (qd, *J* = 13.1, 3.4 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.15 (s), 143.39 (s), 141.16 (s), 125.94 (d, 2C), 114.53 (d, 2C), 73.96 (d), 50.22 (d), 41.61 (t), 38.72 (s), 34.35 (t), 31.03 (t), 27.38 (q), 26.42 (q), 25.51 (d), 21.59 (q), 21.08 (q); IR (neat) 3455, 3368, 3226, 1733 cm^{-1}.

Acetic acid 5-methyl-2-{1-methyl-1-[4-(toluene-4-sulfonylamino)phenyl]ethyl}-cyclohexyl ester 8

To a cooled solution (0°C) of acetic acid 2-[1-(4-amino-phenyl)-1-methyl-ethyl]-5-methylcyclohexyl ester **7** (868 mg, 3.00 mmol) in dichloromethane (20 mL) was added *p*-toluenesulfonyl choloride (1.14 g, 6.00 mmoL) and pyridine (0.49 ml, 6.00 mmol) succesively. The mixture was sitrred at 0°C for 1 hr. The reaction was quenched with water and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silicagel column chromatography (*n*-hexane:ethyl acetate = 9:1) to give acetic acid 5-methyl-2-{1-methyl-1-[4-(toluene-4-sulfonylamino)phenyl]ethyl}cyclohexyl ester **8** (1.35 g, 3.05 mmol, quant.) as a pink solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 4.72 (td, *J* = 10.7, 4.5 Hz, 1H), 2.37 (s, 3H), 1.92 (td, *J* = 3.4 Hz, 1H), 1.83-1.81 (m, 1H), 1.67-1.62 (m, 2H), 1.46-1.42 (m, 1H), 1.33 (s, 3H), 1.23 (s, 3H), 1.12 (s, 3H), 1.05 (qd, *J* = 26.1, 13.0, 3.2 Hz, 1H), 0.91 (q, *J* = 11.6 Hz, 1H), 0.88-0.81 (qd, 1H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.33 (s), 148.82 (s), 143.57 (s), 136.47 (s), 133.52 (s), 129.49 (d, 2C), 127.28 (d, 2C), 126.10 (d, 2C), 121.03 (d, 2C), 73.95 (d), 50.16 (d), 41.60 (t), 39.21 (s), 34.42 (t), 31.15 (d), 28.38 (q), 26.33 (q), 24.14 (q), 21.69 (t), 21.42 (q), 20.88 (q).

***N*-{4-[1-(2-Hydroxy-4-methylcyclohexyl)-1-methylethyl]phenyl}-4-methyl-benzenesulfonamide 9**

A solution of acetic acid 5-methyl-2-{1-methyl-1-[4-(toluene-4-sulfonylamino)phenyl]-ethyl}cyclohexyl ester **8** in methanol (5 mL) was stirred at room temperature for 5 min. To the solution was added

aqueous solution of potassium hydride (33% w/w, 4.3 ml). The mixture was refluxed for 1 hr. The reaction was quenched by addition of ethyl acetate followed by water. The separated organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give crude *N*-{4-[1-(2-hydroxy-4-methylcyclohexyl)-1-methylethyl]phenyl}-4-methylbenzenesulfonamide **9** (1.17 g, 2.92 mmol) as a yellow solid. The solid was used for next reaction without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 3.47 (td, *J* = 10.1, 4.1 Hz, 1H), 2.36 (s, 3H), 1.84 (m, 1H), 1.63-1.59 (m, 3H), 1.38-1.31 (m, 1H), 1.35 (s, 3H), 1.22 (s, 3H), 0.97 (qd, 1H), 0.90 (q, 1H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.82 (qd, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 148.10 (s), 143.49 (s), 136.51 (s), 134.73 (s), 129.51 (d, 2C), 127.16 (d, 2C), 126.63 (d, 2C), 121.66 (d, 2C), 72.96 (d), 54.08 (d), 45.46 (t), 39.46 (s), 34.78 (t), 31.48 (d), 28.51 (q), 26.42 (t), 24.44 (q), 22.40 (q), 21.94 (q); IR (KBr) 3257, 2955, 1727 cm^{-1}.

3-Oxo-cyclohex-1-enecarboxylic acid 5-methyl-2-{1-methyl-1-[4-(toluene-4-sulfonylamino)phenyl]ethyl}cyclohexyl ester 11a

A solution of *N*-{4-[1-(2-hydroxy-4-methylcyclohexyl)-1-methyl-ethyl]phenyl}-4-methylbenzenesulfonamide **9** (212 mg, 0.53 mmol) and cyclohexen-3-one-1-carboxylicacid **10** (74.3 mg, 0.53 mmol) in dichloromethane (4 mL) was stirred at room temperature for 5 min. DMAP (65 mg, 0.53 mmol) was added to the mixture, which was cooled to 0°C and stirred at the same temperature for 5 min. dicyclocarbodiimide (328 mg, 1.59 mmol) was added to the mixture, which was allowed to warm to room temperature and stirred at the same temperature for 1.5 hrs. The reaction was diluted with dichloromethane and quenched by water. The mixture was passed

through Celite pad and the filtrate was extracted with dichloromethane. The separated organic layer was washed with 0.5 M aqueous hydrochloride and saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in a small amount of diethylether and passed though Celite pad again. The filtrate was concentrated under reduced pressure. The residue was purified by silicagel column chromatography (n-hexane:ethyl acetate = 9:1) to give 3-Oxo-cyclohex-1-enecarboxylic acid 5-methyl-2-{1-methyl-1-[4-(toluene-4-sulfonylamino)phenyl]ethyl}cyclohexyl ester **11a** (56 mg, 0.12 mmol) as yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.96 (s, 1H), 4.91 (td, *J* = 10.7, 4.3 Hz, 1H), 2.38 (s, 3H), 2.42-2.18 (m, 4H), 2.03 (td, *J* = 11.3, 3.1 Hz, 1H), 1.97-1.87 (m, 3H), 1.81 (td, *J* = 3.4 Hz, 1H), 1.69 (m, 1H), 1.49-1.48 (m, 1H), 1.24 (s, 3H), 1.18 (qd, *J* = 3.1 Hz, 1H), 1.12 (s, 3H), 0.97 (q, *J* = 23.2, 11.6 Hz, 1H), 0.93-0.87 (qd, *J* = 3.1 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.97 (s), 165.29 (s), 149.09 (s), 148.84 (s), 143.49 (s), 136.69 (s), 133.69 (s), 132.19 (d), 129.47 (d, 2C), 127.25 (d, 2C), 126.04 (d, 2C), 122.20 (d, 2C), 75.25 (d), 50.29 (d), 41.53 (d), 39.15 (s), 37.57 (t), 34.37 (t), 31.23 (d), 29.29 (q), 26.25 (t), 24.30 (t), 23.24 (q), 21.96 (t), 21.69 (q), 21.50 (q); IR (KBr) 2955, 1710, 1685 cm^{-1}.

Acetic acid 2-[1-(4-*tert*-butoxycarbonylamino-phenyl)-1-methylethyl]-5-methylcyclohexyl ester 12

To a cooled solution (0°C) of acetic acid 2-[1-(4-aminophenyl)-1-methylethyl]-5-methyl-cyclohexyl ester **7** (868 mg, 3.00 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was added di-*tert*-butyloxycarbonate (1.05 g, 6.00 mmoL) and 1N aqueous sodium hydride (5 mL) succesively. The mixture was sitrred at 0°C for 1 hr. The reaction was quenched with water and extracted with ethyl acetate. The

organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silicagel column chromatography (n-hexane:ethyl acetate = 9:1) to give acetic acid 2-[1-(4-*tert*-butoxycarbonylamino-phenyl)-1-methylethyl]-5-methylcyclohexyl ester **12** (1.06 g, 3.05 mmol, quant.) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.2 Hz, 2H), 6.48 (s, 1H), 7.19 (d, *J* = 9.2 Hz, 2H), 4.77 (td, *J* = 10.7, 4.3 Hz, 1H), 1.94 (td, *J* = 11.3, 3.1 Hz, 1H), 1.87-1.85 (m, 1H), 1.66-1.59 (m, 2H), 1.63 (s, 3H), 1.51 (s, 9H), 1.48-1.41 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.06 (qd, *J* = 26.1, 13.0, 3.2 Hz, 1H), 0.94 (q, *J* = 23.2, 11.8 Hz, 1H), 0.82 (d, 3H), 0.86-0.79 (qd, *J* = 12.8, 3.1 Hz, 1H).

{4-[1-(2-Hydroxy-4-methyl-cyclohexyl)-1-methyl-ethyl]-phenyl}-carbamic acid tert-butyl ester 13

A mixture of acetic acid 2-[1-(4-*tert*-butoxycarbonylamino-phenyl)-1-methylethyl]-5-methylcyclohexyl ester **12** (8.61 g, 21.4 mmol) and aqueous potassium hydride (33%, 312 ml) in methanol (50 mL) was refluxed for 3.5 hrs. The mixture was diluted with ethyl acetate and quenched by water. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silicagel column chromatography (n-hexane: ethyl acetate = 9:1) to give {4-[1-(2-hydroxy-4-methylcyclohexyl)-1-methylethyl]-phenyl}carbamic acid *tert*-butyl ester **13** (3.83 g, 11.0 mmol, 88%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 4H), 6.44 (s, 1H), 3.52 (td, *J* = 10.1, 4.3 Hz, 1H), 1.86-1.83 (m, 1H), 1.72-1.61 (m, 3H), 1.52 (s, 9H), 1.40 (s, 3H), 1.28-1.25 (m, 1H), 1.27 (s, 3H), 1.02 (qd, *J* = 3.1 Hz, 1H), 0.92 (q, *J* = 23.2, 12.2 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.85 (qd, *J* = 3.4 Hz, 1H).

3-Oxo-cyclohex-1-enecarboxylic acid
2-[1-(4-*tert*-butoxycarbonylaminophenyl)-1-methyl-ethyl]-5-methylcyclohexyl ester 14

To a cooled solution (0°C) of {4-[1-(2-hydroxy-4-methylcyclohexyl)-1-methylethyl]phenyl}carbamic acid *tert*-butyl ester **13** (500 mg, 1.39 mmol) in dichloromethane (13 mL) was added cyclohexen-3-one-1-carboxylicacid 9 (234 mg, 1.67 mmol), DMAP (136 mg, 1.11 mmol), and dicyclohexylcarbodiimide (689 mg, 3.34 mmol) succesively. The mixture was stirred at room temperature for 5 hours. The mixture was diluted with dichloromethane and quenched by water. The mixture was passed through Celite pad. The filtrate was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissloved in diethylether again and passed through Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silicagel column chromatography (n-hexane:ethyl acetate = 9:1) to give 3-oxo-cyclohex-1-enecarboxylic acid 2-[1-(4-*tert*-butoxycarbonylaminophenyl)-1-methylethyl]-5-methylcyclohexyl ester **14** (614 mg, 1.30 mmol, 91%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.55 (s, 1H), 6.10 (s, 1H), 4.96 (td, *J* = 10.5, 4.5 Hz, 1H), 2.37-2.24 (m, 3H), 2.18-2.04 (m, 2H), 1.99-1.80 (m, 4H), 1.71 (m, 1H), 1.50 (s, 9H), 1.27 (s, 3H), 1.22-1.19 (qd, *J* = 2.7 Hz, 1H), 1.15 (s, 3H), 1.00 (q, *J* = 11.6 Hz, 1H), 0.96-0.88 (qd, *J* = 2.4 Hz, 1H), 0.88 (d, *J* = 6.1 Hz, 3H).

3-Oxo-cyclohex-1-enecarboxylic acid
5-methyl-2-{1-methyl-1-[4-(toluene-4-sulfonylamino)phenyl]-ethyl}cyclohexyl ester 11a

To a cooled solution (0°C) of 3-oxo-cyclohex-1-enecarboxylic acid 2-[1-(4-*tert*-butoxycarbonylamino-phenyl)-1-methylethyl]-5-methylcyclohexyl ester **14** (53.9

mg, 0.11 mmol) in dichloromethane (1.5 mL) was added trifluoroacetic acid (250 μl, 0.33 mmol). The mixture was stirred at room temeprature for 30 min. The reaction was diluted with dichloromethane and quenched by water. The extracted organic layer was washed with brine, dried over magnesium sodium sulfate, filtered, and concentrated under reduced pressure to give crude 14. To a cooled solution (0°C) of 14 (39.3 mg, 0.11 mmol) in dichloromethane (1.5 mL) was added *p*-toluene sulfonyl choloride (40 mg, 0.21 mmoL) and pyridine (34 μl, 0.42 mmol) successively. The mixture was sitrred at room temperature for 5 hrs. The reaction was diluted with dichloromethane and quenched by water. The separated organic layer was washed with 1 M aqueous hydrochloride and saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The filtrate was concentrated under reduced pressure. The residue was purified by silicagel column chromatography (*n*-hexane:ethyl acetate = 9:1) to give 3-Oxo-cyclohex-1-enecarboxylic acid 5-methyl-2-{1-methyl-1-[4-(toluene-4-sulfonylamino)phenyl]-ethyl}cyclohexyl ester **11a** (40.9 mg, 0.08 mmol, 74%) as a white solid

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.96 (s, 1H), 4.91 (td, *J* = 10.7, 4.3 Hz, 1H), 2.38 (s, 3H), 2.42-2.18 (m, 4H), 2.03 (td, *J* = 11.3, 3.1 Hz, 1H), 1.97-1.87 (m, 3H), 1.81 (td, *J* = 3.4 Hz, 1H), 1.69 (m, 1H), 1.49-1.48 (m, 1H), 1.24 (s, 3H), 1.18 (qd, *J* = 3.1 Hz, 1H), 1.12 (s, 3H), 0.97 (q, *J* = 23.2, 11.6 Hz, 1H), 0.93-0.87 (qd, *J* = 3.1 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.97 (s), 165.29 (s), 149.09 (s), 148.84 (s), 143.49 (s), 136.69 (s), 133.69 (s), 132.19 (d), 129.47 (d, 2C), 127.25 (d, 2C), 126.04 (d, 2C), 122.20 (d, 2C), 75.25 (d), 50.29 (d), 41.53 (d), 39.15 (s), 37.57 (t), 34.37 (t), 31.23 (d), 29.29 (q), 26.25 (t), 24.30 (t), 23.24 (q), 21.96 (t), 21.69 (q), 21.50 (q); IR (KBr) 2955, 1710, 1685 cm^{-1}.

Acetic acid 2-[1-(4-benzoylamino-phenyl)-1-methylethyl]-5-methylcyclohexyl ester 16

To a cooled solution (0°C) of acetic acid 2-[1-(4-amino-phenyl)-1-methyl-ethyl]-5-methylcyclohexyl ester **7** (70 mg, 0.24 mmol), benzoic acid (58.6 mg, 0.48 mmol), and DMAP (5.9 mg, 0.05 mmol) in dichloromethane (3mL) was added dicyclohexylcarbodiimide (59.4 mg, 0.288 mmol). The mixture was stirred at room temperature for 1 hr. The reaction was quenched by water. The mixture was passed through Celite pad. The filtrate was extracted with dichloromethane. The organic layer was washed with 0.5 M aqueous hydrochloride and saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissloved in a small amount of diethylether and passed through Celite pad again. The filtrate was concentrated under reduced pressure. The residue was purified by silicagel column chromatography (*n*-hexane:ethyl acetate = 9:1) to give acetic acid 2-[1-(4-benzoylamino-phenyl)-1-methylethyl]-5-methylcyclohexyl ester **16** (114 mg, 0.29 mmol, quant.) as a red oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.61-7.44 (m, 5H), 7.27 (d, *J* = 8.6 Hz, 2H), 4.79 (td, *J* = 10.7, 4.3 Hz, 1H), 1.98 (td, *J* = 11.5, 2.9 Hz, 1H), 1.87-1.85 (m, 1H), 1.70-1.59 (m, 2H), 1.63 (s, 3H), 1.48-1.41 (m, 1H), 1.31 (s, 3H), 1.21 (s, 3H), 1.08 (qd, *J* = 25.8, 13.0, 3.2 Hz, 1H), 0.95 (q, *J* = 23.2, 11.8 Hz, 1H), 0.86 (d, *J* = 6.1 Hz, 3H), 0.89-0.81 (qd, *J* = 3.4 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.47 (s), 165.70 (s), 147.93 (s), 135.06 (s), 134.99 (s), 131.65 (s), 128.64 (d, 2C), 127.02 (d, 2C), 125.93 (d, 2C), 119.89 (d, 2C), 74.17 (d), 50.32 (d), 41.69 (t), 39.41 (s), 34.46 (t), 31.21 (t), 27.65 (q), 26.53 (q), 25.18 (d), 21.72 (q), 21.27 (q).

***N*-{4-[1-(2-Hydroxy-4-methylcyclohexyl)-1-methylethyl]-phenyl}benzamide 17**

A mixture of acetic acid 2-[1-(4-benzoylamino-phenyl)-1-methylethyl]-5-methyl-cyclohexyl ester **16** (627 mg, 1.59

mmol) and aqueous potassium hydride (33%, 2.4 ml) in methanol (15 mL) was refluxed for 2 hrs. The mixture was diluted with ethyl acetate and quenched by water. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure give {*N*-{4-[1-(2-hydroxy-4-methylcyclohexyl)-1-methylethyl]phenyl}benzamide **17** (465 mg, 1.32 mmol, 83%) as a yellow oil.

$[\alpha]_D^{25}$ = -10.3, c = 1.8 in EtOH; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.47 (m, 7H), 7.39 (d, *J* = 8.6 Hz, 2H), 3.53 (td, *J* = 9.9, 3.9 Hz, 1H), 1.85 (m, 1H), 1.71-1.63 (m, 4H), 1.42 (s, 3H), 1.30 (s, 3H), 1.02 (qd, *J* = 2.8, 1H), 0.93 (q, *J* = 23.5, 11.8 Hz, 1H), 0.88 (d, *J* = 6.1 Hz, 3H), 0.90-0.81 (qd, *J* = 3.1 Hz, 1H); IR (KBr) 3303, 2917, 1652 cm^{-1}.

3-Oxo-cyclohex-1-enecarboxylic acid 2-[1-(4-benzoylamino-phenyl)-1-methyl-ethyl]-5-methyl-cyclohexyl ester 18

To a cooled solution (0°C) of {*N*-{4-[1-(2-hydroxy-4-methyl-cyclohexyl)-1-methyl-ethyl]-phenyl}-benzamide **17** (149 mg, 0.42 mmol), cyclohexen-3-one-1-carboxylicacid **10** (71 mg, 0.50 mmol), and DMAP (41 mg, 0.34 mmol) in dichloromethane (3mL) was added dicyclohexylcarbodiimide (104 mg, 0.50 mmol). The mixture was stirred at room temperature for 2 hrs. The reaction was quenched by water. The mixture was passed through Celite pad. The filtrate was extracted with dichloromethane. The organic layer was washed with 0.5 M aqueous hydrochloride and saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissloved in a small amount of diethylether and passed through Celite pad again. The filtrate was concentrated under reduced pressure. The residue was purified by silicagel column chromatography (n-hexane:ethyl acetate = 9:1) to give 3-oxo-cyclohex-1-enecarboxylic acid 2-[1-(4-benzoylamino-phenyl)-1-methylethyl]-5-methylcyclohexyl ester **18** (114 mg, 0.29

mmol, 61%) as a white oil.

$[\alpha]_D^{25}$ = -25.5, c = 0.3 in $CHCl_3$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.6 Hz, 2H), 7.53-7.44 (m, 5H), 7.23 (d, *J* = 8.6, 2H), 5.80 (s, 1H), 4.95 (td, *J* = 10.7, 4.3 Hz, 1H), 2.35-2.23 (m, 4H), 2.15 (td, *J* = 3.4 Hz, 1H), 1.99-1.74 (m, 6H), 1.52-1.51 (m, 1H), 1.29 (s, 3H), 1.22 (qd, *J* = 26.0, 13.1, 3.4 Hz, 1H), 1.16 (s, 3H), 0.99 (q, *J* = 23.2, 11.8 Hz, 1H), 0.96-0.89 (qd, *J* = 3.1 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.93 (s), 165.21 (s), 165.65 (s), 148.32 (s), 148.32 (s), 135.09 (s), 134.92 (s), 131.92 (d), 131.48 (d), 128.55 (d, 2C), 126.98 (d, 2C), 125.48 (d, 2C), 120.56 (d, 2C), 75.04 (d), 50.13 (d), 41.49 (t), 38.92 (s), 37.44 (t), 34.34 (t), 31.16 (d), 30.29 (q), 26.02 (t), 24.14 (t), 21.95 (t), 21.84 (q) 21.66 (q); IR (KBr) 3329, 2949, 1702 cm^{-1}.

Acetic acid 2-[1-(4-methoxyphenyl)-1-methylethyl]-5-methylcyclohexyl ester 30

A mixture of **29** (1.06 g, 4.03 mmol), pyridine (4.80 ml), acetic anhydride (0.76 ml, 8.06 mmol), and DMAP (9894 mg, 8.06 mmol) was stirred at room temperature for 3 hrs. The mixture was poured into 5% w/w aqueous sodium hydrogen carbonate. The mixture was extracted with diethylether. The extracted organic layer was washed with 5% aqueous hydrochloride, aqueous sodium hydrogen carbonate, brine successively, then dried over magnesium sulfate, filtered, and concenterated under reduced pressure. The residue was purified by silicagel column chromatography (n-hexane:ethyl acetate = 98:2) to give acetic acid 2-[1-(4-methoxyphenyl)-1-methylethyl]-5-methylcyclohexyl ester **30** (1.20 g, 3.93 mmol, 98%) as colorless oil.

$[\alpha]_D^{25}$ = -5.9, c = 2.5 in CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.79 (td, *J* = 4.6 Hz, 10.6 Hz, 1H), 1.93 (td, *J* = 3.7 Hz, 11.4 Hz, 1H), 1.90-1.81 (m, 1H), 1.75-1.64 (m, 2H), 1.61 (s, 3H), 1.45-1.37 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.08 (qd, *J* = 3.3 Hz, 13.1 Hz, 25.8 Hz, 1H), 0.95 (q, *J* = 12.3 Hz, 23.2 Hz, 1H), 0.89-0.78 (m, 1H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.29 (s),

156.91 (s), 143.62 (s), 126.26 (d, 2C), 113.11 (d, 2C), 74.05 (d), 55.11 (q), 50.35 (d), 41.71 (t), 39.00 (s), 34.47 (t), 31.19 (d), 27.85 (q), 26.52 (t), 25.25 (q), 21.72 (q), 21.21 (q); IR (neat) 2953, 1731 cm^{-1}；HRMS (EI) m/z Calcd for $C_{19}H_{28}O_3$ 304.2038, found: 304.2040.

Acetic acid 2-[1-(4-hydroxyphenyl)-1-methylethyl]-5-methylcyclohexyl ester 31

To a cooled solution (-78°C) of acetic acid 2-[1-(4-methoxyphenyl)-1-methylethyl]-5-methylcyclohexyl ester **30** (1.18 g, 3.88 mmol) in dichloromethane (13 mL) was added a cooled solution (-78°C) of borane tribromide (3.70 ml, 38.8 mmol). The mixture was stirred at –78°C for 30 min., then allowed to warm to –25°C for 35 hrs. The reaction was quenched by pouring the mixture into aqueous sodium hydrogen carbonate. The mixture was extracted with dichloromethane, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silicagel column chromatography (n-hexane:ethyl acetate = 95:5) to give acetic acid 2-[1-(4-hydroxyphenyl)-1-methylethyl]-5-methylcyclohexyl ester **31** (1.08 g, 3.72 mmol, 96%) as a brown oil.

$[\alpha]_D^{24}$ = -7.74, c = 1.11 in EtOH; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.79 (td, *J* = 4.6 Hz, 10.6 Hz, 1H), 1.93 (td, *J* = 3.7 Hz, 11.4 Hz, 1H), 1.90-1.81 (m, 1H), 1.75-1.64 (m, 2H), 1.61 (s, 3H), 1.45-1.37 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.08 (qd, *J* = 3.3 Hz, 13.1 Hz, 25.8 Hz, 1H), 0.95 (q, *J* = 12.3 Hz, 23.2 Hz, 1H), 0.89-0.78 (m, 1H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.10 (s), 153.21 (s), 143.37 (s), 126.47 (d, 2C), 114.63 (d, 2C), 74.40 (d), 50.35 (d), 41.72 (t), 39.02 (s), 34.48 (t), 31.20 (d), 28.35 (q), 26.49 (t), 24.94 (q), 21.75 (q), 21.24 (q); IR (KBr) 3427, 1698 cm^{-1}; HRMS (EI) m/z Calcd for $C_{18}H_{26}O_3$ 290.1882, found: 290.1884.

Acetic acid 2-(1-{4-[6-(*tert*-butyl-dimethylsilanyloxy)-hexyloxy]phenyl}-1-methylethyl)-5-methylcycl

ohexyl ester 34

A mixture of acetic acid 2-[1-(4-hydroxyphenyl)-1-methylethyl]-5-methylcyclohexyl ester **31** (1.0 g, 3.45 mmol) and **33** (2.40 g, 10.4 mmol) in THF (17 mL) was stirred at room temperature for 10 min. Triphenylphosphine (2.71 g, 10.4 mmol) was added to the mixture at 0°C. Diisopropylazodicarboxylate (2.09 g, 10.4 mmol) was added and the resulting mixture was stirred at room temperature for 8 hrs. The mixture was diluted with diethylether and quenched by water. The mixture was extracted with diethylether, which was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The rsidue was purified by silicagel column chromatography (n-hexane:ethyl acetate) to give acetic acid 2-(1-{4-[6-(*tert*-butyl-dimethylsilanyloxy)hexyloxy]phenyl}-1-methylethyl)-5-methylcyclohexyl ester **34** (1.56 g, 3.10 mmol, 90 %) as a colorless oil.

$[\alpha]_D^{27}$ = 0.311, c = 1.74 in $CHCl_3$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.78 (td, *J* = 10.7, 4.3 Hz, 1H), 3.92 (t, *J* = 6.4 Hz, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 1.92 (td, *J* = 3.1, 11.3 Hz, 1H), 1.77 (tt, *J* = 6.7 Hz, 2H), 1.54 (tt, *J* = 6.7 Hz, 2H), 1.68-1.37 (m, 8H), 1.62 (s, 3H), 1.29 (s, 3H), 1.19 (s, 3H), 1.06 (qd, *J* = 26.0, 13.1, 3.7 Hz, 1H), 0.98-0.80 (m, 2H), 0.89 (s, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.05 (s, 6H).

Acetic acid 2-{1-[4-(6-hydroxyhexyloxy)phenyl]-1-methylethyl}-5-methylcyclohexyl ester 35

To a cooled solution (0°C) of acetic acid 2-(1-{4-[6-(*tert*-butyl-dimethylsilanyloxy)-hexyloxy]phenyl}-1-methylethyl)-5-methylcyclohexyl ester **34** in THF (3 mL) was added 1.0M solution of tetrabutylammonium fluoride (2.0 ml, 2.0 mmol). The mixture was stirred at room temperature for 2 hrs. The reaction was quenched by saturated aqueous ammonium chloride, then extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure.

The residue was purified by silicagel column chromatography (n-hexane:ethyl acetate) to give acetic acid 2-{1-[4-(6-hydroxy-hexyloxy)phenyl]-1-methylethyl}-5-methylcyclohexyl ester **35** (141 mg, 0.36 mmol, 91 %) as a colorless oil.

$[\alpha]_D^{26}$ = -0.07, c = 1.40 in $CHCl_3$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.78 (td, *J* = 10.7, 4.3 Hz, 1H), 3.93 (td, *J* = 6.4, 1.8 Hz, 2H), 3.66 (t, *J* = 6.7 Hz, 2H), 1.92 (td, *J* = 3.1, 11.5 Hz, 1H), 1.87-1.85 (m, 1H), 1.78 (tt, *J* = 6.1 Hz, 2H), 1.63 (s, 3H), 1.68-1.40 (m, 2H), 1.52-1.40 (m, 5H), 1.29 (s, 3H), 1.20 (s, 3H), 1.06 (qd, *J* = 3.1 Hz, 1H), 0.95 (q, *J* = 12.2, 23.2 Hz, 1H), (qd, *J* = 3.1 Hz, 1H), 0.86 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.42 (s), 156.50 (s), 143.53 (s), 126.32 (d, 2C), 113.80 (d, 2C), 74.20 (d), 67.78 (t), 62.90 (t), 50.43 (d), 41.79 (t), 39.10 (s), 34.54 (t), 32.67 (t), 31.26 (d), 29.30 (t), 27.76 (q), 26.62 (t), 25.89 (t), 25.52, (t, q, 2C), 21.77 (q), 21.31 (q); IR (neat) 3414, 1729 cm^{-1}; HRMS (EI) m/z Calcd for $C_{24}H_{38}O_4$ 390.2770, found: 390.2769.

General procedure for preparation 39

To a mixture of **36** (470 mg, 0.11 mmol) in CH_2Cl_2 (0.7 ml) was added **33** (1.83 g, 4.70 mmol) in CH_2Cl_2 (4.0 ml) at 0°C. The solution was added $BF_3 \cdot Et_2O$ (7.5 μl) at 0°C, and warmed to room temperature and stirred for 45 minutes. After the solution was added MeOH, stirred for 30 minutes, and filterd, and the resulting beads were washed with CH_2Cl_2 and MeOH several times. The beads were vacuum dried to afford **37** (460 mg).

General procedure for preparation of 40

To a mixture of **37** (2.98 g, 0.72 mmol) in DMSO (30 ml) was added NaOH (659 mg, 16.5 mmol), H_2O (7.6 ml) at room temperature. Then the mixture was warmed to 80°C and stirred for 12 hours. After the mixture was filtrated, the resulting beads were washed with CH_2Cl_2 and MeOH several times. The beads were vacuum dried to afford **40** (460 mg).

General procedure for preparation of 41

To a mixture of **40** (55.1 mg, 0.01 mmol), cyclohexene-3-one-carboxylate (140 mg, 1.00 mmol), dimethylaminopyridine (37.0 mg, 0.3 mmol) in CH_2Cl_2 (1.0 ml) was added 1,3-dicyclohexylcarbodiimide (47.0 μl, 0.30 mmol) at 0°C. The mixture was warmed to room temperature and stirred for 24 hours. And then the solution was filtrated, and the resulting beads were washed with CH_2Cl_2 and MeOH several times. The beads were vacuum dried to afford **41** (48.6 mg).

General procedure for photoreaction of the chiral enone carboxylate derivatives with ethylene in solution phase

Irradiation reactions were carried out using a Pyrex flask (>280 nm) in a water-cooled quartz immersion apparatus using a HALOS 500-W Hg high-pressure UV lamp as the light source. A 0.05 M solution of chiral enone carboxylate derivative in each solvent was purged with ethylene at 25 °C for 5 minutes and irradiated with out continuous purging until chiral enone carboxylate derivative was nearly completely consumed. The reaction was monitored by TLC and GLC analysis. After the solvent evaporated, the residue was purified chromatographically to give a diastereomeric mixture of photoadduct. Each isomer of photoadduct could not be separated by standard chromatographic purification and therefore the *d.e.* value was not affected by this process. The *d.e.* value of photoadduct was determined by ^{1}H NMR analysis.

General procedure for photoreaction of the chiral enone carboxylate derivative with ethylene in solid phase

Irradiation reactions were carried out using a Pyrex flask (>280 nm) in a water-cooled quartz

immersion apparatus using a HALOS 500-W Hg high-pressure UV lamp as the light source. A heterogeneous solution of chiral enone carboxylate derivative in each solvent was purged with ethylene at 25°C for 30 minutes and irradiated with out continuous purging until chiral enone carboxylate derivative was nearly completely consumed. The solution was filtrated, and the resulting beads were washed with CH_2Cl_2 and MeOH several times. After the beads were vacum dried, the beads were stirred with 30% trifluoroacetic acid in CH_2Cl_2 for 30 minutes, and then the solution was filtrated. The resulting beads were washed with CH_2Cl_2 and MeOH several times, and the filtrate was vacuum dried to afford the crude product of the diastereomeric mixture of **43**. The yield was estimated by comparing the area of distinct signal of the crude product with that of internal standard (1,1,2,2-tetrachloroethane). The crude product was purified by silica gel column chromatography to give the diastereomeric mixture of **43**. The *d.e.* value was determined by comparing the area of distinct signals of the diastereomers in the ^{1}H NMR analysis.

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Conclusion

The goal of this research described in this thesis is a development of the methodology for the efficient and rapid construction of unique ring system on solid-phase. Hetero- and carbocycles are often found in many biologically active substances. Thus, the methodologies for rapid synthesis of these compounds are desirable as well as useful. In this regard, we investigated on the efficient pyridine nucleus construction and diastereroselective photochemical reaction to lead carbobicycles on beads. The results are summarized as follows.

In part 1, very effective solid-phase chemistry for the pyridine ring formations by multi-component condensation was successfully established. This reaction showed a broad tolerance against components. Since both purities and yields of this procedure were much better than those of the corresponding solution-phase, it was well demonstrated that inherent advantage of solid-phase chemistry to force the reactions that give poor yields in solution-phase chemistry into completion by using an excess of reagents. In addition, this procedure is a noteworthy example since not only aromatic aldehydes but also aliphatic aldehydes worked well to give the desired pyridines. There are only a few examples of 4-aliphatic pyridines synthesized by solid-phase chemistry. The procedure was successfully applied to a rapid analoging of the lead compound to yield more than 1,000 compounds. This procedure made worthful contributions to push on the combinatorial chemistry approach and bring one of our exploratory researches to the further advanced stage very quickly.

In part 2, the three types of polymer-supported chiral auxiliaries (PS-PEG-Wang resin, MP resin, PEG) were efficiently prepared and utilized for the diastereoselective [2+2] photocycloaddition reaction. The cycloadducts were obtained in moderate to good yields and diastereoselectivities. Besides that, we were able to show that PS-PEG-Wang resin-supported chiral auxiliary was reusable up to 3 cycles. The undesired degradation that

was happened with PS-PEG-Wang resin owing to the labilibity of PEG moiety at low temperature was elucidated the reason. Furthermore, this problem was overcame by the use of macroporous polystyrene resin and poly(ethylene glycol). Interestingly, the photochemical reaction with MP resin proceeded even in the absence of solvent that is preferable in terms of development of an environmentally-benign chemistry.

List of Publications

1) Efficient Synthesis of 3-Cyano-6-(2-hydroxyphenyl)pyridines by Multi-Component Condensation on Beads, Takuya Shintani; Hiroshi Kadono; Kikuchi Tetsuo; Thomas Schubert; Yuka Shogase; Makoto Shimazaki. *Tetrahedron Lett.* **2003**, *44*, 6567-6569.

2) Diastereoselective [2+2] Photocycloaddition of Polymer-Supported Cyclic Chiral Enone with Ethylene, Takuya Shintani; Kazunori Kusabiraki; Atsuko Hattori; Akinori Furutani; Ken Tsutsumi; Tsumoru Morimoto; Kiyomi Kakiuchi, *Tetrahedron Lett.* **2004**, *45*, 1849-1851.

List of Supplementary Publications

1) Novel Method for Deracemization: Transformation of Racemic *syn*-1,3-Polyols to Enantiomerically Pure *anti*-1,3-Polyols by Enantiodifferentiating Inversion of Stereogenic Centers. Toshiro Harada; Takuya Shintani; Akira Oku. *Journal of American Chemical Society*, **1995**, 117, 12356-12357.

2) Combinatorial Chemistry Group: Bayer AG, Takuya Shitani; Makoto Shimazaki, *Journal of Synthetic Organic Chemistry, Japan*, **2002**, 61, 516-517.

3) Discovery of Novel and Selective IKK-β Serine-Threonine Protein Kinase Inhibitors. Part 1, Toshiki Murata.; Mitsuyuki Shimada; Sachiko Sakakibara; Takashi Yoshino; Hiroshi Kadono; Tsutomu Masuda; Makoto Shimazaki; Takuya Shintani; Kinji Fuchikami; Katsuya Sakai; Hisayo Inbe; Keisuke Takeshita; Toshiro Niki; Masaomi Umeda; Kevin B. Bacon; Karl B. Ziegelbauer; Timothy B. Lowinger. *Bioorg*. & *Med. Chem. Lett*. **2003**, 13, 913–918.

4) Diastereoselective [2+2] Photocycloaddition of Chiral Cyclohexenonecarboxylates to Ethylene, Ken Tsutsumi; Katsunori Endou; Akinori Furutani; Tomomi Ikki; Hiroaki Nakano; Takuya Shintani; Tsumoru Morimoto; Kiyomi Kakiuchi. *Chirality*, **2003**, 15, 6, 504-509.

5) Novel Enhancement of Diastereoselectivity of [2+2] Photocycloaddition of Chiral Cyclohexenones to Ethylene by Adding Naphthalenes, Ken Tsutumi; Hiroaki Nakano; Akinori Furutani; Katsunori Endo; Abdurshit Merpuge; Takuya Shinatni; Tsumoru Morimoto; Kiyomi Kakiuchi. *J. Org. Chem.* **2004**, *69*, 785-789.

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