New methodologies for the synthesis of compound libraries

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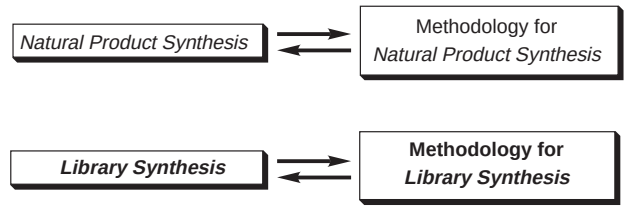
New methodologies for the synthesis of compound libraries are discussed. They are based on new carbon–carbon bond-forming reactions on the solid-phase (using polymer-supported silyl enol ethers), library preparation using polymer catalysts, and multi-component reactions in liquid phase. Development of new linker resins for efficient reactions on the solid-phase and a new method for the synthesis of monosaccharide libraries are also described.

1 Introduction

In modern organic synthesis, research efforts have been made to pursue 'efficiency' as a key goal. There are many kinds of 'efficiency' and each research field has its own unique efficiency. For example, 'efficiency' in natural product synthesis of complex molecules is a total 'efficiency' throughout all steps in order to prepare target molecules. In the development of new synthetic methodologies, development of new reactions with high yields and high selectivities is believed to lead to 'efficiency', and research efforts have been made to achieve these.

On the other hand, combinatorial chemistry is now of interest mainly in the field of drug discovery. There are many reports that 'remarkably large numbers of compounds can be prepared by using the mix & split method' or 'drug discovery processes have been dramatically shortened', which seem to have little relationship to academic basic research. Are these works only improvements of technology? The author's answer is no. The author thinks that an important task which should be solved by organic chemists is *how large numbers of structurally distinct molecules can be prepared*. Synthesis of large numbers of compounds is needed not only in drug discovery, but also in the development of new materials, functionalized compounds, catalysts, ligands, *etc*. In these fields, large numbers of compounds are synthesized first and among them compounds which are appropriate for a particular purpose are selected.

Is it possible to prepare large numbers of structurally distinct compounds by traditional technologies in organic synthesis? The answer is of course 'yes' and such syntheses have been done. However, a problem is whether they are truly efficient or not. Recent advances in the field of organic synthesis provide many reactions with high yields and high selectivities as described above, and therefore, it is now possible to synthesize a great number of compounds by the combination of 'efficient' reactions using man-power and time. However, why can you call such synthesis efficient? The author thinks new methodologies are needed to prepare compound libraries, just as new methodologies for natural product synthesis were required forty years ago (Scheme 1). In this paper, recent results of our group on the development of new methodologies for the synthesis of compound libraries based on the above idea, especially from a standpoint of synthetic organic chemistry, are described.



Scheme 1 Methodology for library synthesis.

2 Development of carbon–carbon bond-forming reactions in solid-phase

Reactions on the solid-phase provide an important method for the synthesis of large numbers of compounds because procedures are very simple in most cases and application to automation systems such as solid-phase peptide synthesis is easy.[1] On the other hand, while solid-phase peptide and nucleic acid syntheses, which basically include condensation, protection, and deprotection, have reached a certain level of completion, general synthetic organic reactions on the solid-phase which deal with various types of reactions have difficulties such as low reactivities of polymer-supported reagents. We think that development of basic carbon–carbon bond forming reactions on the solid-phase is needed in order to

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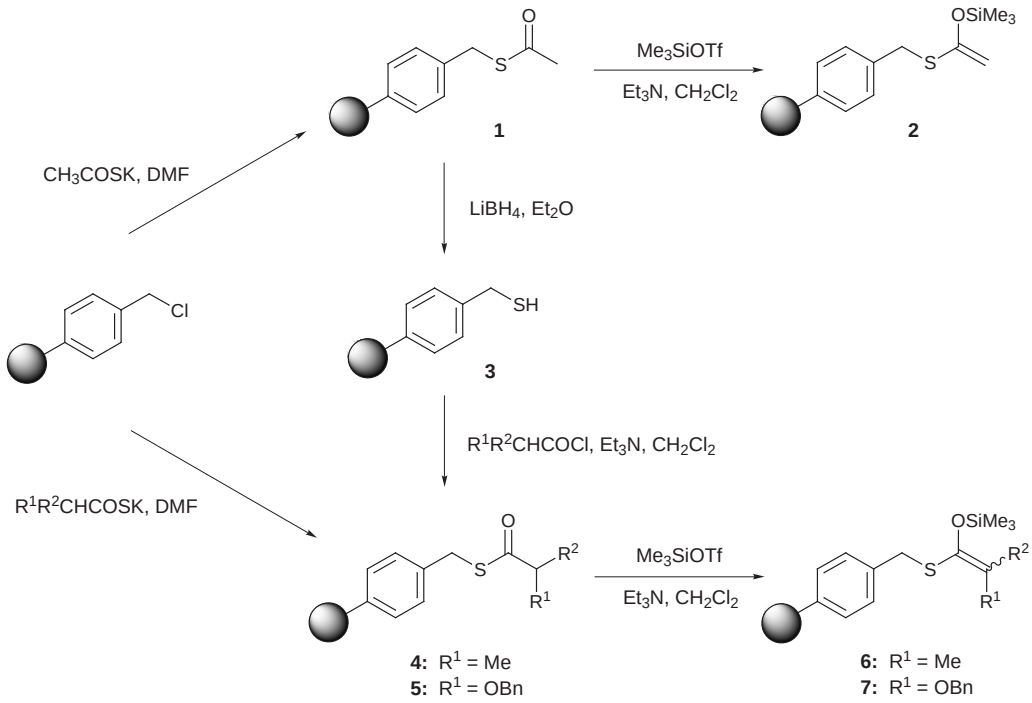


Scheme 2 Synthesis of polymer-supported silyl enol ethers.

utilize organic reactions on the solid-phase for library construction. We first plan to immobilize silyl enol ethers on a polymer, which are isolable enolates and versatile reagents for carbon–carbon bond formation.

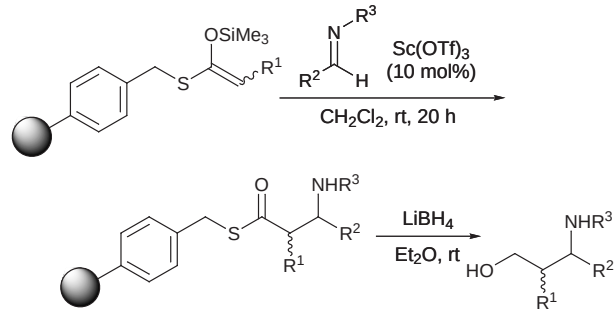
2.1 Preparation of polymer-supported silyl enol ethers

Silyl enol ethers are versatile reagents in organic synthesis. They are used as isolable enolate equivalents and many kinds of useful reactions using silyl enol ethers have been developed. Polymer-supported silyl enol ethers (thioketene silyl acetals) were prepared according to Scheme 2.[2] Chloromethyl copoly-(styrene-1%-divinylbenzene) resin (1.15 mmol g^{-1}) was treated with potassium thioacetate in DMF. Formation of thioester **1** was indicated by IR spectra showing strong carbonyl stretching vibration at 1693 cm^{-1}. A chlorine titration showed that **1** was obtained in a 95% yield. Thioester **1** thus obtained was then combined with TMSOTf and triethylamine in dichloromethane to afford silyl enol ether **2**. Similarly, silyl enol ethers **6** and **7** were prepared from **4** and **5**, respectively. They were alternatively synthesized from thiol **3** according to Scheme 2. Thiol **3** was prepared by reducing **1** using $LiBH_4$ in Et_2O at room temperature. According to this scheme, various types of polymer-supported silyl enol ethers can be prepared.

2.2 Imino aldol reactions

Silyl enol ethers thus prepared were tested in the reaction with imines. It was reported that silyl enol ethers reacted with imines in the presence of a Lewis acid to afford β-amino ketones, esters, and thioesters.[3] Since reduction of the adducts gives the corresponding amino alcohols, these reactions using the polymer-supported silyl enol ethers provide a new method for the preparation of an amino alcohol library. The reaction of **2** (0.88 mmol g^{-1}) with *N*-benzylideneaniline was chosen as a model and several Lewis acids were tested. Although typical Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ gave poor results, catalytic amounts of new types of Lewis acids such as $Sc(OTf)_3$, $Hf(OTf)_4$ gave better results.

Several imines and polymer-supported silyl enol ethers were then screened using $Sc(OTf)_3$ as a catalyst, and the results are shown in Scheme 3. Although the reaction conditions have not



R^1	R^2	R^3	Yield (%)
H	Ph	Ph	65
H	2-furyl	Ph	65
H	c-C_6H_{11}	Ph	68
H	*p*-ClPh	*p*-MeOPh	52
H	2-furyl	*p*-MeOPh	67
Me	Ph	Ph	78
Me	2-furyl	Ph	68
Me	c-C_6H_{11}	Ph	77
Me	*p*-ClPh	*p*-MeOPh	68
BnO	Ph	Ph	67
BnO	2-furyl	Ph	77
BnO	2-thiophene	Ph	71
BnO	c-C_6H_{11}	Ph	79

Scheme 3 The reactions of polymer-supported silyl enol ethers with imines.

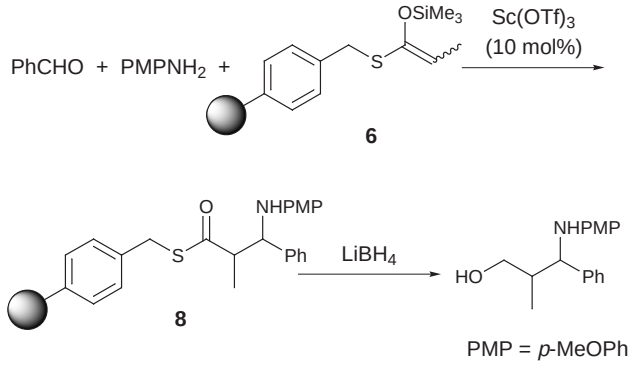
yet been optimized, the desired amino alcohols were obtained after reduction in good yields.

2.3 Mannich-type three-component reactions

Multiple-component reactions, which have been focused on by us[4] and other groups,[5–7] provide one of the most efficient

methods for the synthesis of libraries. One of the characteristic points of a method utilizing multiple-component reactions is that high yields are expected by designing the reactions, while yields are lower in linear synthetic strategies with multi-step syntheses. This is especially the case in solid phase synthesis, because yields are often lower and characterization of the products in each step is generally difficult.

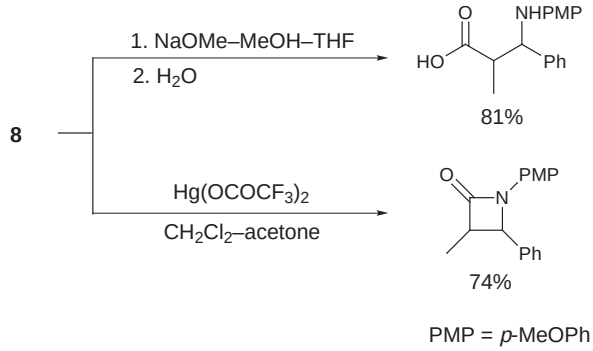
Mannich-type three-component reactions on solid phase were successfully carried out using $Sc(OTf)_3$ as a catalyst.[8] An example is the reaction of benzaldehyde, anisidine, and polymer-supported silyl enol ether **6** (Scheme 4). The reaction



Scheme 4 Three-component reactions on solid phase.

proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$ to afford, after reductive cleavage from the support, an amino alcohol in 87% yield. It should be noted that the yield was improved by employing the three-component reaction (the reaction of *N*-benzylideneaniline with **6** gave the amino alcohol in a 64% yield under the same reaction conditions).[2]

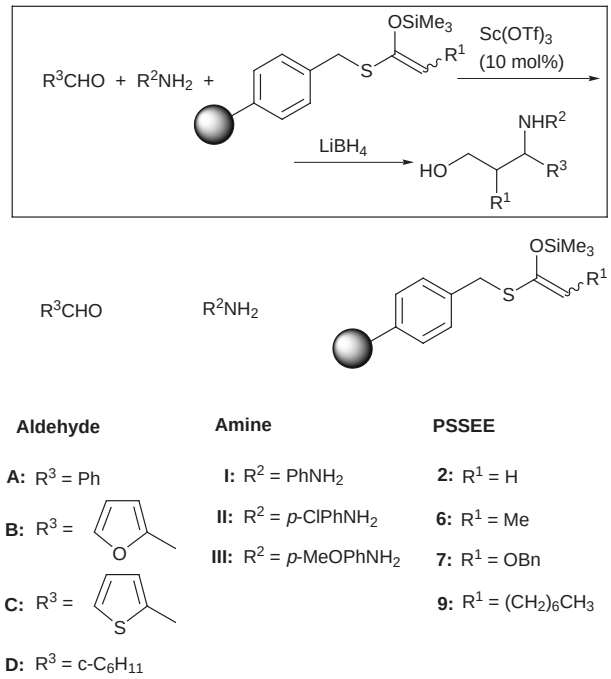
It was also found that adduct **8** was converted to β-amino acid and β-lactam, respectively, according to Scheme 5.

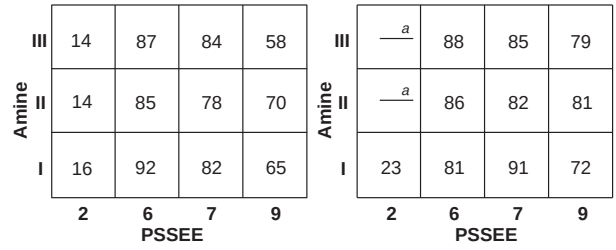


Scheme 5 Conversion to β-amino acid and β-lactam.

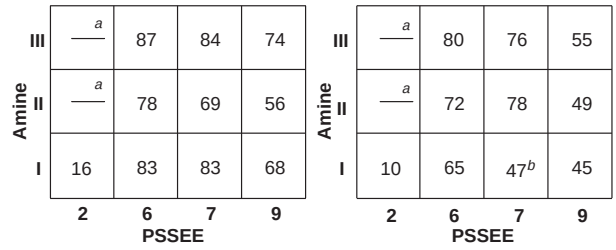
2.4 'Field synthesis'[8]

The amino alcohol library synthesis was carried out using 'Field Synthesis', which was based on the above three-component reaction. Four aldehyde 'fields' were set, and in each field three amines and four polymer-supported silyl enol ethers (PSSEEs) were employed. The reactions were performed as follows: in the presence of 10 mol% of $Sc(OTf)_3$ and Drierite (80 mg), an aldehyde (0.24 mmol) and an amine (0.24 mmol) were stirred for 1 h at rt, and then a PSSEE (0.20 mmol) was added and the mixture was stirred for 20 h. After saturated aq. $NaHCO_3$ was added to quench the reaction, the polymer was filtered, washed with water, water–dioxane (1:1), dioxane, and ether successively, and dried. The resulting polymer was combined with $LiBH_4$ (5 equiv.) in THF (4 ml), and the mixture was stirred for 12 h at rt. After the usual work up, the crude product was chromatographed on silica gel to afford a pure amino alcohol. The results are shown in Schemes 6 and 7. In every aldehyde field (Fields 1–4), combination of PSSEEs **2, 6, 7, 9** and amines





Field 1. PhCHO Field **Field 2.** 2-Furaldehyde Field

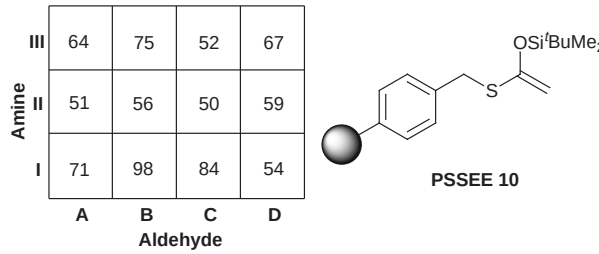


Field 3. Thiophene-2-carbaldehyde Field **Field 4.** c-C_6H_{11}CHO Field

[a] The reaction was not performed.

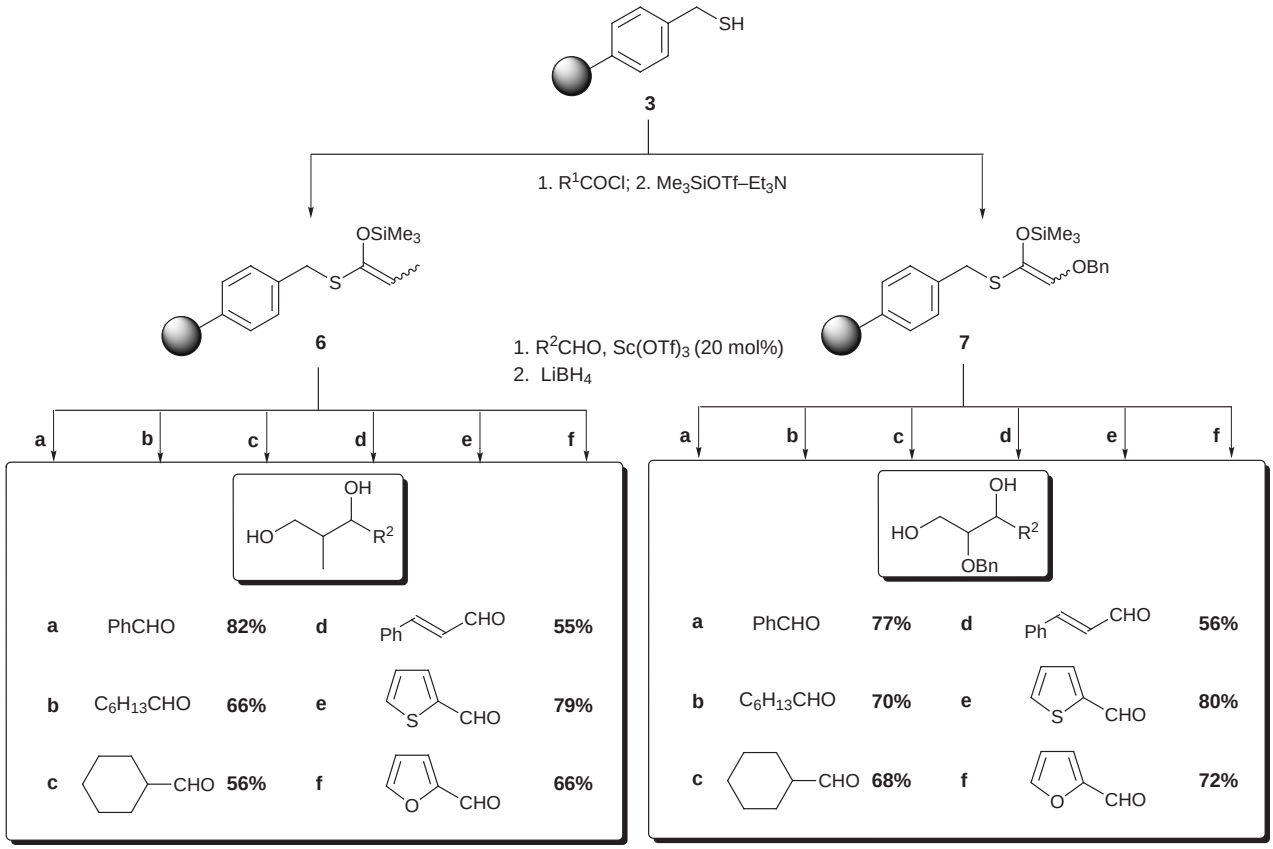
[b] The yield was improved to 72% when two equivalents of the aldehyde and the amine were used.

Scheme 6 'Field synthesis'. In each 'field', one of three components is fixed. The number in each column shows the yield (%) of the three-component reaction.



Field 5. PSSEE **10** Field

Scheme 7 PSSEE is fixed.



Scheme 8 1,3-Diol library based on aldol reactions.

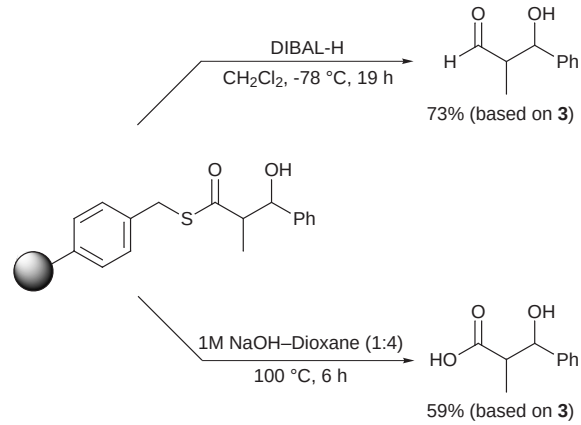
gave the corresponding amino alcohols in satisfactory yields, while lower yields were observed in the reactions using PSSEE **2**. Several reaction conditions were then examined in the model combination of benzaldehyde, aniline, and PSSEE **2**. It was finally found that the desired amino alcohol was obtained by using *tert*-butyldimethylsilyl enol ether **10** instead of **2**. A PSSEE **10** field was next set (Field 5), and four aldehydes and three amines were employed. The results are shown in Scheme 7. This time, the desired amino alcohols were obtained in high yields in all combinations, and a 48 amino alcohol library was successfully prepared.

2.5 Aldol reactions

The aldol reaction of silyl enol ethers with aldehydes (Mukaiyama aldol reaction)[9] is known as one of the most important and fundamental carbon–carbon bond-forming reactions. Although the original report requires a stoichiometric amount of $TiCl_4$ to promote the reaction, we found that a catalytic amount of $Sc(OTf)_3$ accelerates this reaction efficiently.[10] In the aldol reaction of polymer-supported silyl enol ethers with aldehydes, it was also revealed that $Sc(OTf)_3$ effectively catalyzed the reaction. Silyl enol ether **6** reacted with benzaldehyde in dichloromethane at −78 °C to afford the corresponding aldol adduct, which was reduced with $LiBH_4$ to give the 1,3-diol. The yield was determined to be 82%, based on the loading level of the silyl enol ether.

As polymer-supported silyl enol ethers are prepared from thiol **3**, preparation of a 1,3-diol library is performed starting from **3**. An example is shown in Scheme 8 using two acid chlorides and six typical aldehydes including aromatic, aliphatic, α,β-unsaturated, and heterocyclic aldehydes. In all cases, the reactions proceeded smoothly to afford the corresponding 1,3-diols in good yields.[11]

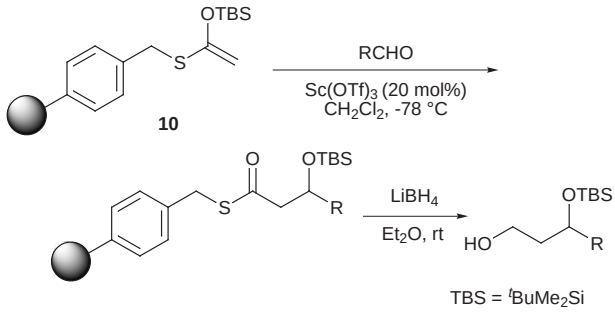
While 1,3-diols are successfully cleaved from the support by treatment with $LiBH_4$, it is also possible to produce β-hydroxy aldehydes or β-hydroxy carboxylic acids directly (Scheme 9).



Scheme 9 Conversion to β-hydroxy aldehyde or β-hydroxy carboxylic acid.

When α-substituted silyl enol ethers were used, the desired aldol reactions proceeded smoothly. On the other hand, a lower yield was observed when an α-unsubstituted silyl enol ether was used in the reaction with benzaldehyde. In order to improve the yield, several reaction conditions were examined and finally it was found that the yield was improved when *tert*-butyldimethylsilyl enol ether **10** was used (Scheme 10).

Thus, the aldol reaction of polymer-supported silyl enol ethers with aldehydes, a basic carbon–carbon bond-forming reaction on solid phase, has been successfully carried out using $Sc(OTf)_3$ as a catalyst. It is noted that on solid phase, the Lewis acid-catalyzed aldol reaction is superior to the aldol reaction of zinc enolates with aldehydes under basic conditions. Thus, polymer-supported silyl enol ether **11**, which was prepared from

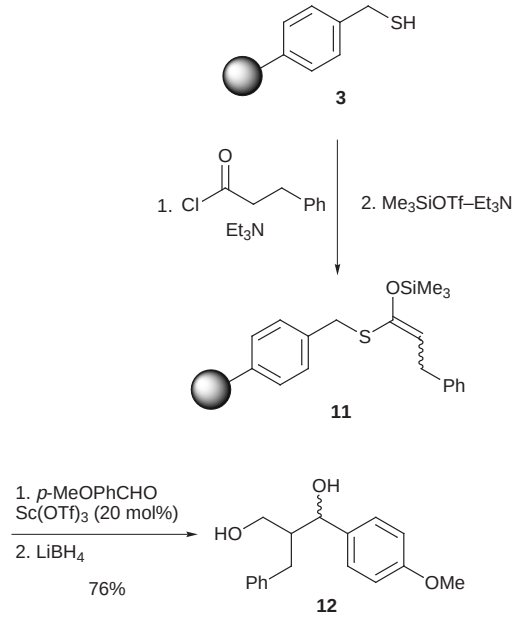


RCHO	Yield (%)
PhCHO	69[a]
Ph, CHO	91[b]
S, CHO	95[c]

Containing 1,3-diols; [a] 9%; [b] 13%; [c] 14%.

Scheme 10 Aldol reactions of **10** with aldehydes.

3 and hydrocinnamoyl chloride, reacted with *p*-anisaldehyde, followed by reduction with $LiBH_4$ to afford 1,3-diol **12** in a 72% yield based on the starting chloromethyl resin (76% yield based on **11**). An aldol reaction using a zinc enolate on solid phase was recently reported to give the same diol (**12**) in a 26% yield (Scheme 11).[12]



Scheme 11 Effective synthesis of **12**.

2.6 Michael reactions

Michael reactions of silyl enol ethers with α,β-unsaturated ketones are one of the most useful carbon–carbon bond-forming reactions in organic synthesis. While a stoichiometric amount of $TiCl_4$ was used in the original liquid-phase reactions,[13] it was found that a catalytic amount of $Sc(OTf)_3$[10] was effective for the solid-phase Michael reactions of PSSEEs with α,β-unsaturated ketones.[14] While the 1,5-dicarbonyl compound was obtained in a 38% yield in the model reaction of PSSEE **10** with chalcone using a stoichiometric amount of $TiCl_4$, the yield was improved to 93% using 20 mol% of $Sc(OTf)_3$ as a catalyst in the same reaction. In addition to the improvement of the yield, it should be noted that $Sc(OTf)_3$ was easily removed from the product resins by filtration after the reaction because $Sc(OTf)_3$ is soluble in water, while the insoluble titanium residue which appeared after quenching the reaction by adding water in the $TiCl_4$-mediated reaction was often difficult to remove and would contaminate the product resins.

Several examples of the Michael reactions on solid-phase are shown in Scheme 12. Not only acyclic but also cyclic α,β-unsaturated ketones reacted with PSSEEs smoothly to afford the corresponding adducts in high yields.

2.7 Aldol-type reactions

Aldol-type reactions of PSSEEs with acetals have been successfully carried out using $Yb(OTf)_3$ as a catalyst (Scheme 13).[14] The reactions were performed at rt and the adducts were cleaved from polymer supports using $LiBH_4$ to give 1,3-diol monoethers. The SR-MAS NMR technique was also quite effective in developing the reactions.

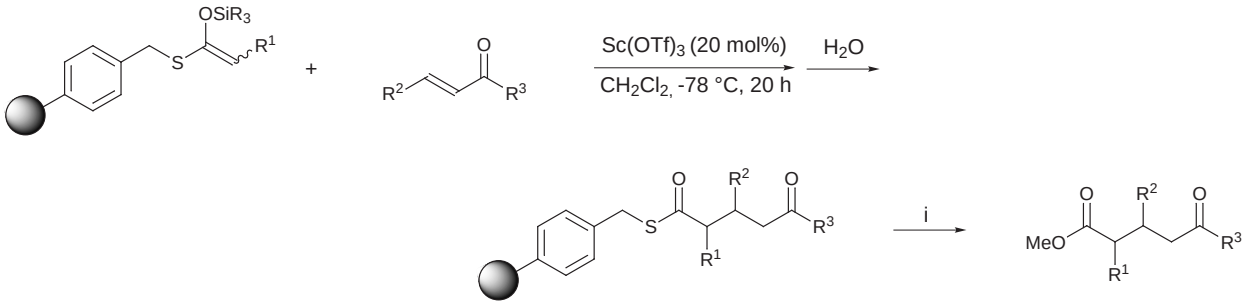
2.8 5-(4′-Chloromethylphenyl)pentylpolystyrene resin (CMPP resin). A new linker resin for solid-phase organic synthesis under Lewis acidic conditions

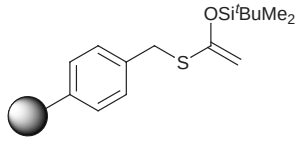
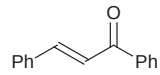
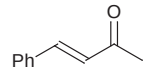
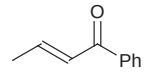
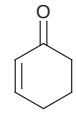
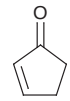
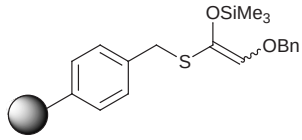
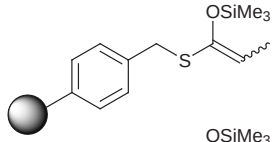
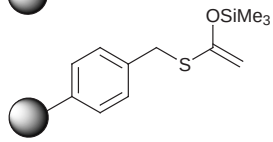
The proper choice of supports and linker groups are among the most important factors in the success of organic synthesis on solid supports. Although several linkers have already been developed, these are mostly optimized for biopolymer synthesis such as peptides and oligonucleotides, and unsatisfactory results are sometimes obtained in the reaction sequences possible on supports. For example, almost all linkers developed contain oxygen and/or nitrogen atoms including ether, ester, and amide functional groups, which coordinate Lewis acids to be decomposed or deactivated.[15] Hence, these linkers cannot be used in Lewis acid-promoted reactions, which provide numerous useful transformations in liquid-phase organic synthesis. In the course of our program on the development of Lewis acid-catalyzed reactions on solid-phase, we were confronted with the above problem.

Carbon atoms instead of nitrogen or oxygen atoms were chosen in the new linker, and methylene groups were used as a spacer. The synthetic scheme of the new linker, 5-(4′-chloromethylphenyl)pentylpolystyrene resin (CMPP resin, **16**), is shown in Scheme 14.[16] Friedel–Crafts acylation of copoly-(styrene-1%-divinylbenzene) resin with 5-phenylvaleryl chloride was carried out using aluminum chloride in carbon disulfide. The resulting acylated resin **17** was reduced using $AlCl_3$–LAH in ether to afford 5-phenylpentyl resin **18**. Finally, **18** was chloromethylated under standard conditions to afford CMPP resin (**16**).

The evaluation of the new linker resin was carried out by the imino aldol reactions of polymer-supported silyl enol ethers with imines.[3] The polymer-supported silyl enol ethers of CMPP resin were prepared according to Scheme 15. The results of the imino aldol reactions of the silyl enol ethers derived from the polymer-supported thioacetate (**19**) with *N*-benzylideneaniline are summarized in Scheme 16. CMPP resin gave higher yields than Merrifield and Wang resins. The loading levels of the enolate moieties in CMPP resin were also examined, and it was found that the best results were obtained by using CMPP resin having a 0.96 mmol g^{-1} loading level, which was prepared by using 2.0 mmol g^{-1} of the acylating reagent in the Friedel–Crafts acylation (Scheme 15).

Several examples of the $Sc(OTf)_3$-catalyzed imino aldol reactions using CMPP resin were tested, and the results are shown in Scheme 17. In all cases, the yields of the desired adducts (amino alcohols) using CMPP resin were much higher (*ca*. 10–30%) than those using Merrifield resin. These results indicate the effectiveness of the new linker resin.



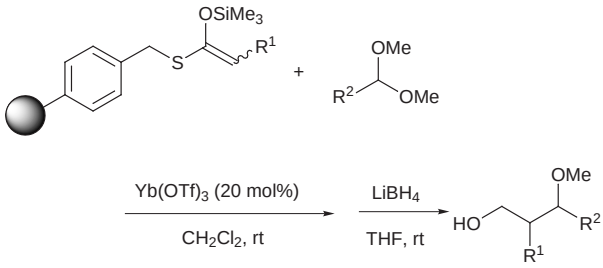
Entry	PSSEE	α,β-Unsaturated Ketone	Yield (%)
1	 **10**[a]	 **13**	91
2	**10**		87
3	**10**	 **14**	80
4	**10**		83
5	**10**		81
6	 **7**[b]	**13**	60
7	**7**	**14**	75
8	 **6**[c]	**13**	64
9	 **2**[d]	**13**	48

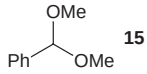
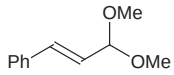
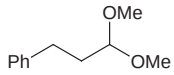
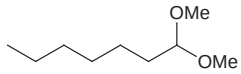
[a]0.94 mmol g^{-1}. [b]0.88 mmol g^{-1}. [c]0.96 mmol g^{-1}. [d]0.76 mmol g^{-1}.

Scheme 12 Michael reactions of PSSEE with α,β-unsaturated ketones. *Reagents and conditions*: i, 1) NaOMe (10 equiv.), THF, MeOH (4 : 1); 2) IRC-76; 3) Me_3SiCl, MeOH.

3 Use of the swollen-resin magic angle spinning (SR-MAS) NMR technique to determine the structure of polymer-supported reagents and catalysts directly

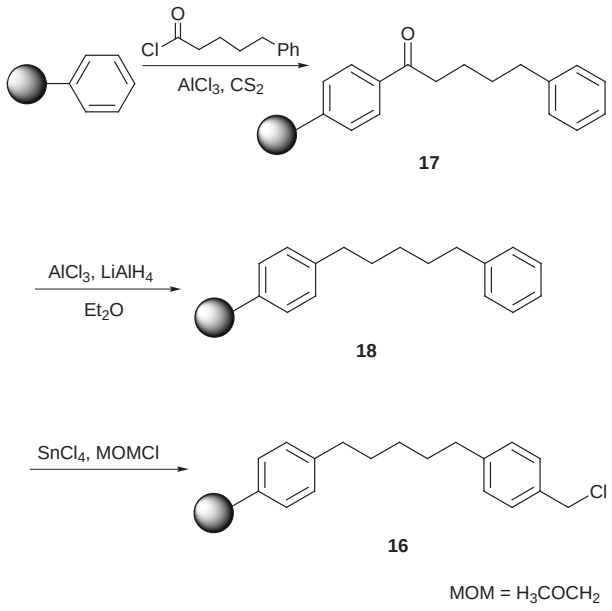
During the investigations to develop Michael reactions on solid-phase (2.6), it was found that the magic angle spinning (MAS) NMR technique was very useful to determine the structure of resins containing products directly. In solid-phase organic synthesis, characterization of products is often difficult and typical NMR techniques used in liquid-phase organic synthesis cannot be applied in many cases. Consequently, characterization is carried out at the stage of resins containing products using IR or special mass spectrometers, or after cleavage of products from solid supports using standard analytical methods in liquid-phase organic synthesis (NMR, IR, MASS, *etc.*). It was found that characterization of our polystyrene-supported resins containing products can be successfully carried out using the MAS NMR technique using swollen resins.[14] The ^{13}C swollen-resin MAS (SR-MAS) NMR spectrum of the resins containing the Michael adduct is shown Fig. 1. NMR spectra



Entry	PSSEE	Acetal	Yield (%)
1	**7**[a]	 **15**	81
2	**7**[a]		86
3	**7**[b]		72
4	**7**[b]		63
5	**6**[c]	**15**	76
6	**2**[d]	**15**	38

[a]0.88 mmol g^{-1}. [b]0.66 mmol g^{-1}. [c]0.96 mmol g^{-1}. [d]0.76 mmol g^{-1}.

Scheme 13 Aldol-type reactions of PSSEE with acetals.



Scheme 14 Preparation of new linker resin **16**.

were recorded on a JEOL JNM-LA400 (CP/MAS System) spectrometer using a special sample tube. It is concluded from the NMR spectrum that no starting materials remain and several peaks which correspond to the adducts are observed, and that the desired reaction has proceeded successfully. Actually, the Michael adduct was isolated after cleavage from the support in a 93% yield. The ^{1}H SR-MAS NMR technique was also used for the preparation of PSSEEs. In our initial work for the preparation of PSSEEs, IR spectra were used for characterization of the products and determination of yields of the products. It was found that the ^{1}H SR-MAS NMR technique was much more effective in these characterizations.

In addition, it was also found that the SR-MAS NMR technique provided an effective and powerful tool for determining the structure of some polymer-supported catalysts.

Recent research from our laboratories has revealed remarkable solvent effects in SR-MAS NMR. The effect of typical seventeen deuterized solvents is summarized in Table 1.

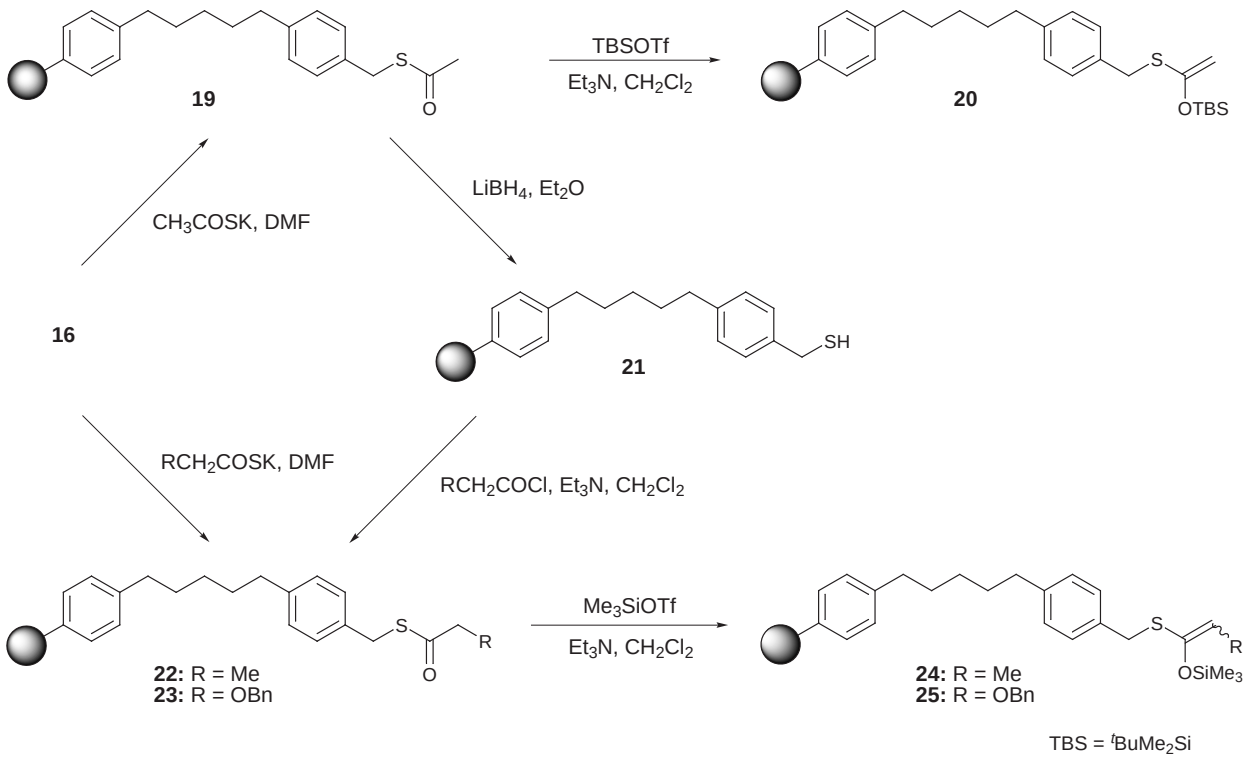
4 A new method for the synthesis of monosaccharide libraries (efficient synthesis of diverse monosaccharide derivatives in the solid-phase)

While there are many biologically-important compounds containing sugars, monosaccharides are the smallest sugar unit and are known to play important roles in their biological activities.[17] In order to obtain compounds having unique activity as well as to improve lower bioactivities, it is desirable to optimize the structure of monosaccharides, and therefore, development of new methods for the synthesis of diverse monosaccharide derivatives is in great demand.

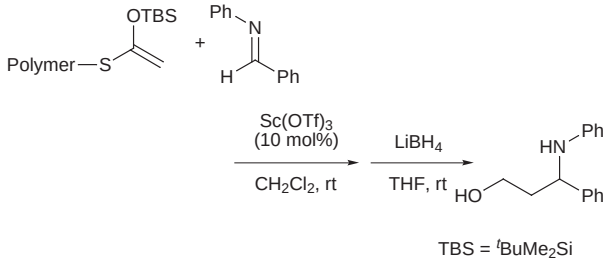
While monosaccharides have rather simple structures, they may contain four, five, six, or seven (higher sugars) asymmetric centers, and the combination of various substituents at each chiral center provides a great number of structurally-different monosaccharide derivatives. Three major methods have been reported so far for the synthesis of monosaccharides. The first method is the traditional one; that is the synthesis of rare sugars from the common sugars such as glucose, mannose, galactose, *etc*.[18] One drawback of this method is that it requires tedious long transformations, and protection and deprotection of the hydroxy groups of the monosaccharides. The second method is to utilize stereoselective reactions of three-carbon or four-carbon alkoxyaldehydes (glyceraldehyde or threose derivatives prepared from mannitol or tartaric acids) with carbon nucleophiles such as allylmetals or enolates[19] or hetero Diels–Alder reactions.[20] Finally, efficient methods for the synthesis of monosaccharides from simple achiral compounds using asymmetric synthesis have been reported recently.[21] While these syntheses provide useful methods for the preparation of specific rare sugars, much time and man-power are required for the synthesis of a diverse monosaccharide library according to these methods.

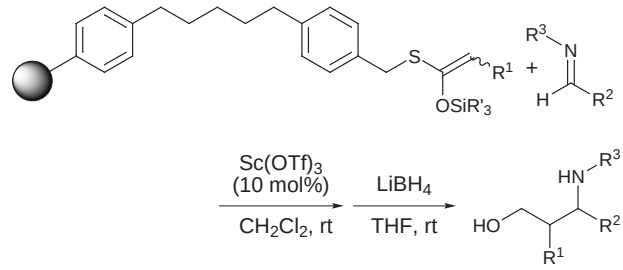
A new method for the synthesis of monsaccharide libraries was intended to be developed on the basis of aldol and imino aldol reactions on the solid-phase.[2,8,11] An example, the synthesis of a rare sugar, 6-*O*-benzyl-2-deoxy-L-gulose, is shown in Scheme 18. The starting material, chloromethylated resin or thiol resin **3** was converted to thioester resin **1**. Treatment of **1** with *tert*-butyldimethylsilyl triflate (TBSOTf) and triethylamine provided polymer-supported silyl enol ether (PSSEE) **10**. A key reaction is the aldol condensation of **10** with a chiral aldehyde (**26**) using a Lewis acid promoter, which proceeded smoothly to afford the desired adduct with perfect stereoselectivity. Deprotection of the TBS group of the aldol adduct (**27**) using tetrabutylammonium fluoride (TBAF)–acetic acid induced spontaneous lactone formation, and hence cleavage from the polymer support. The yield was determined to be 61% from chloromethylated resin (4 steps) at this stage. Finally, reduction of **28** with diisobutylaluminum hydride (DIBAL-H) gave 6-*O*-benzyl-2-deoxy-L-gulose (**29**) (> 80%).[22]

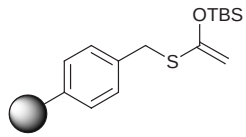
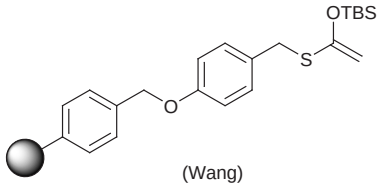
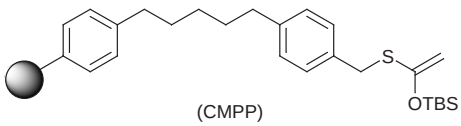
Similarly, four monosaccharide derivatives (lactones) were prepared using the combination of chiral alkoxyaldehydes and PSSEEs in the solid-phase (Scheme 19). The 2-deoxy series and 2-benzyloxy series were prepared from PSSEE **10** and **7**, respectively. It is noted that the stereochemistry of the stereogenic center at the C-3 position can be controlled by choice of the protecting groups of the alkoxyaldehydes. The diversity of the monosaccharide derivatives obtained according to this protocol depends on the numbers and kinds of



Scheme 15 Synthesis of polymer-supported silyl enol ethers using novel linker resin **16**.





Polymer-Supported Silyl Enol Ether	Loading Level /mmol g^{-1}	Yield (%)
 (Merrifield)	1.15	53
 (Wang)	0.71	57
 (CMPP)	1.82[a]	62
	1.15[a]	67
	0.96[b]	74
	0.83[b]	71

[a] 5.1 mmol g^{-1} of 5-phenylvaleryl chloride was used in Scheme 10.
[b] 2.0 mmol g^{-1} of 5-phenylvaleryl chloride was used in Scheme 10.

Scheme 16 Effect of linker resins.

R^1	R^2	R^3	SiR'_3	Yield (%) (CMPP)	Yield (%) (Merrifield)
H	Ph	Ph	Si^tBuMe_2	**74**	(53)
H	*p*-ClPh	Ph	Si^tBuMe_2	**72**	(60)
Me	Ph	Ph	$SiMe_3$	**90**	(78)
Me	Ph	*p*-MeOPh	$SiMe_3$	**96**	(64)
Me	2-furyl	Ph	$SiMe_3$	**quant.**	(68)
OBn	Ph	Ph	$SiMe_3$	**96**	(67)
OBn	Ph	*p*-MeOPh	$SiMe_3$	**93**	(66)
OBn	2-furyl	Ph	$SiMe_3$	**90**	(77)

Scheme 17 Imino aldol reactions using CMPP resin.

alkoxyaldehydes and PSSEEs. A preparation method for PSSEEs has already been shown, and various types of PSSEEs can be prepared (*cf.* Section 2.1). On the other hand, many alkoxyaldehydes have been synthesized from natural sources such as mannitol and tartaric acid.[19,23] Alternatively, we have developed an efficient method for the synthesis of alkoxyaldehydes using asymmetric aldol reactions. Recently, we have developed tin(II)-mediated highly diastereo- and enantioselective aldol reactions of silyl enol ethers with carbonyl compounds.[24,25] Various types of β-hydroxy thioesters have been prepared starting from simple achiral compounds using these asymmetric reactions. After protection of the β-hydroxy groups of the aldol adducts, treatment of these protected adducts with DIBAL-H gave the desired alkoxyaldehydes in excellent

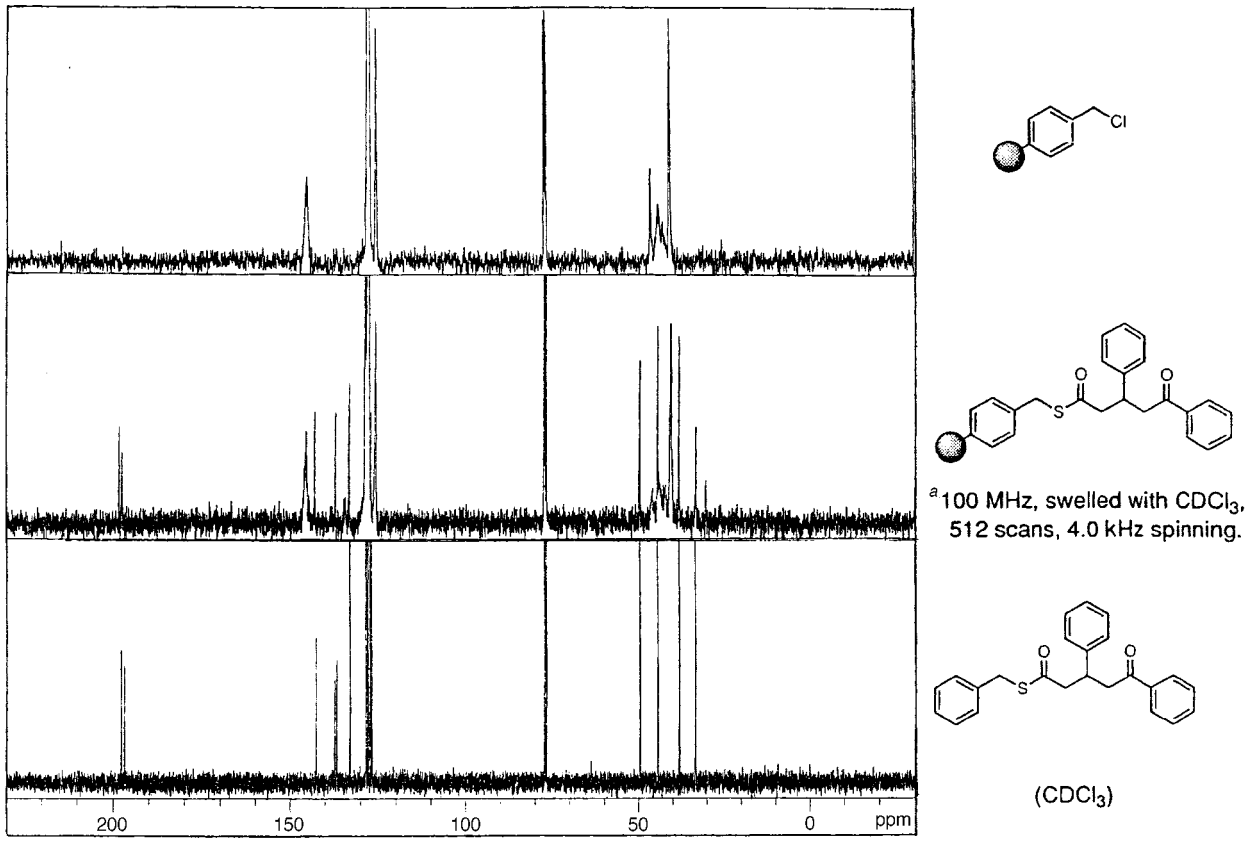


Fig. 1 ^{13}C Swollen-resin magic angle spinning (SR-MAS) NMR.[a]

Table 1 Effect of solvents for thioacetyl resin (1) in MAS NMR

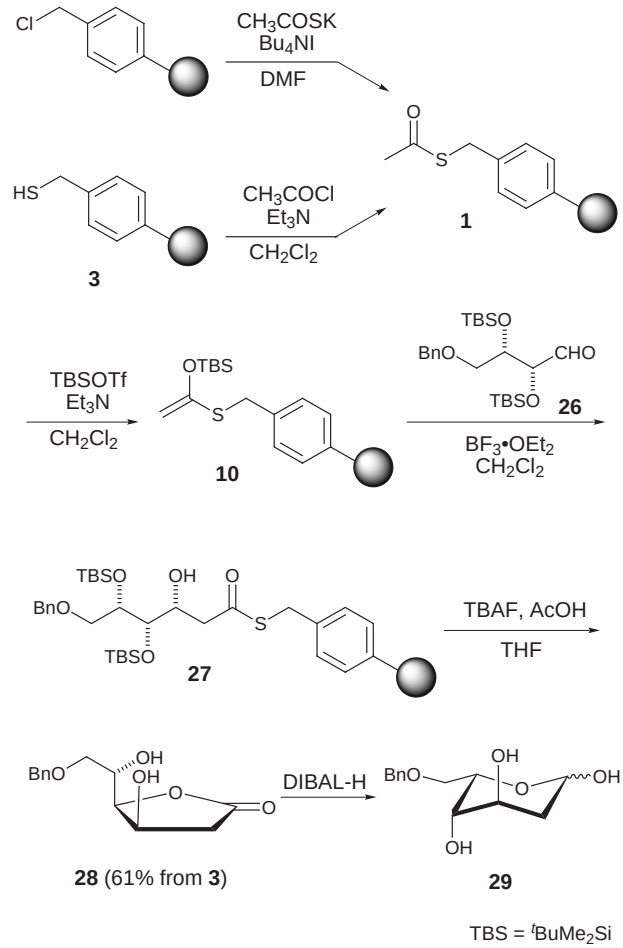
Entry	Solvent	Half-height width[a]/Hz	S/N ratio: Carbonyl carbon	S/N ratio: Methyl carbon
1	Chloroform-*d*	55.2	2.31	4.06
2	Dichloromethane-d_2	60.4	2.25	8.06
3	THF-d_8	67.6	2.82	4.38
4	Toluene-d_6	71.6	2.39	3.30
5	Benzene-d_6	74.0	2.82	3.83
6	DMF-d_7	82.0	2.11	—[b]
7	DMSO-d_6	87.2	—[b]	—[b]
8	Dioxane-d_8	106.8	1.55	2.17
9	Acetone-d_6	116.8	2.53	—[b]
10	Methanol-d_4	—[c]	—[c]	—[c]
11	Ethanol-d_6	—[c]	—[c]	—[c]
12	Pyridine-d_5	63.6	2.62	4.40
13	1,2-*d*ichloroethane-d_4	57.4	2.81	9.20
14	Nitrobenzene-d_5	73.8	3.45	5.79
15	Acetonitrile-d_3	—[c]	—[c]	—[c]
16	Diethyl ether-d_{10}	129.2	1.38	—[b]
17	Deuterium oxide	—[c]	—[c]	—[c]

[a] Methylene peak of thioacetyl resin. [b] Peaks of resin overlapped with those of solvents. [c] Resin's peaks did not appear.

yields with excellent diastereo- and enantioselectivities (Scheme 20).

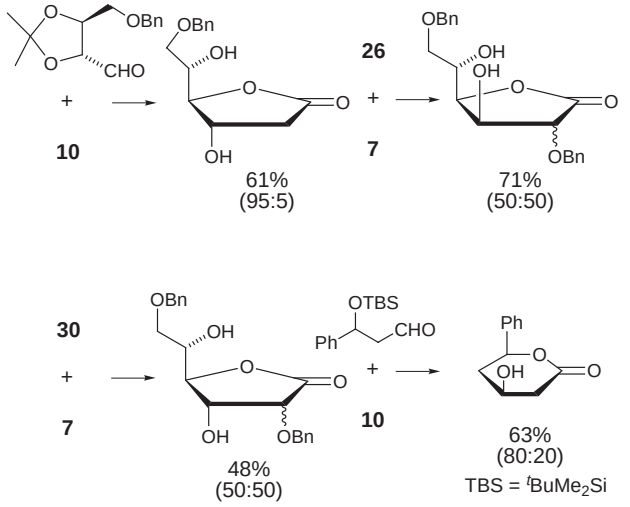
4.1 Amino sugars

3-Amino sugars were then synthesized in the solid-phase. In nature there are many biologically-interesting compounds containing 3-amino sugars such as daunosamine, acosamine, ristosamine, *etc*. An example of our solid-phase synthesis of 3-amino sugars is shown in Scheme 21. Thiol resin **3** was converted to thioester resin **5**, which was silylated to give

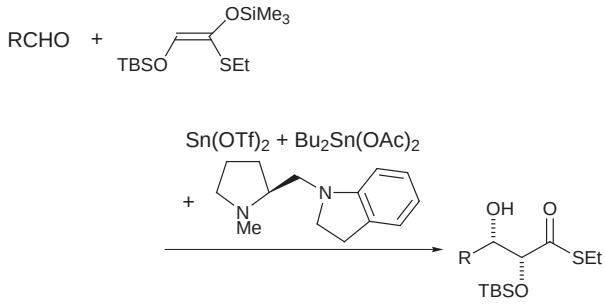


Scheme 18 Solid-phase synthesis of 6-*O*-benzyl-2-deoxy-L-gulose (**29**).

PSSEE **7**. The key three-component reaction of an aldehyde, an amine, and **7** proceeded smoothly in the presence of a catalytic



Scheme 19 Synthesis of monosaccharide derivatives (lactones) in the solid-phase.

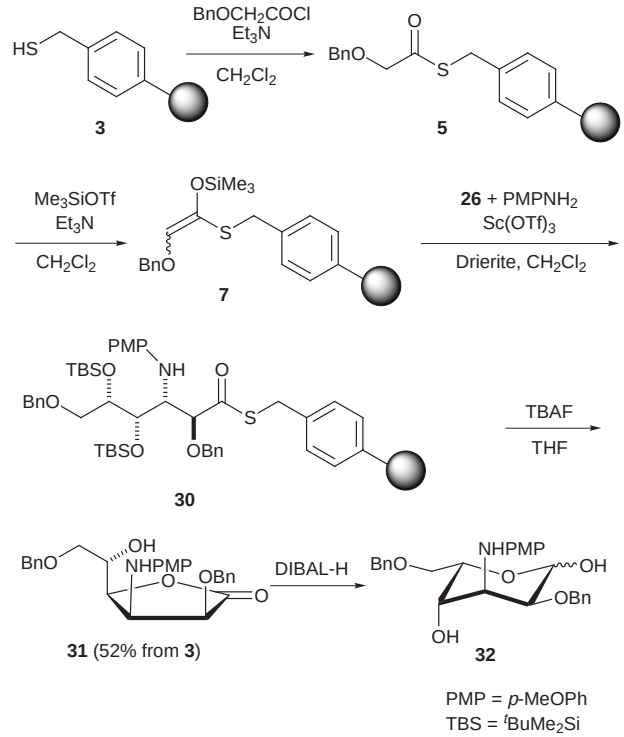


Scheme 20 Preparation of chiral aldehydes.

amount of $Sc(OTf)_3$ to afford the corresponding adduct (**30**) with perfect stereoselectivity. Also in this case, deprotection of the TBS group induced a spontaneous cyclization to give lactone **31**, which was reduced with DIBAL-H to produce 3-amino sugar derivative **32** in an 82% yield. Similarly, a 2-benzyloxy series, 2-deoxy series, and 2-deoxy-2-methyl series of 3-amino sugars were successfully prepared in the solid-phase (Scheme 22).

4.1 Alditol derivatives

The present method was successfully applied to the synthesis of alditol derivatives (the reduced forms of monosaccharides). Reductive cleavage from the support instead of deprotection of the TBS groups gave alditol derivatives in good yields (Scheme 23). Since we have already demonstrated that basic cleavage (NaOMe) from the same support affords carboxylic acids, uronic acid (the oxidized forms of monosaccharides) formation would be possible simply by changing the cleavage method.



Scheme 21 Solid-phase synthesis of **32**.

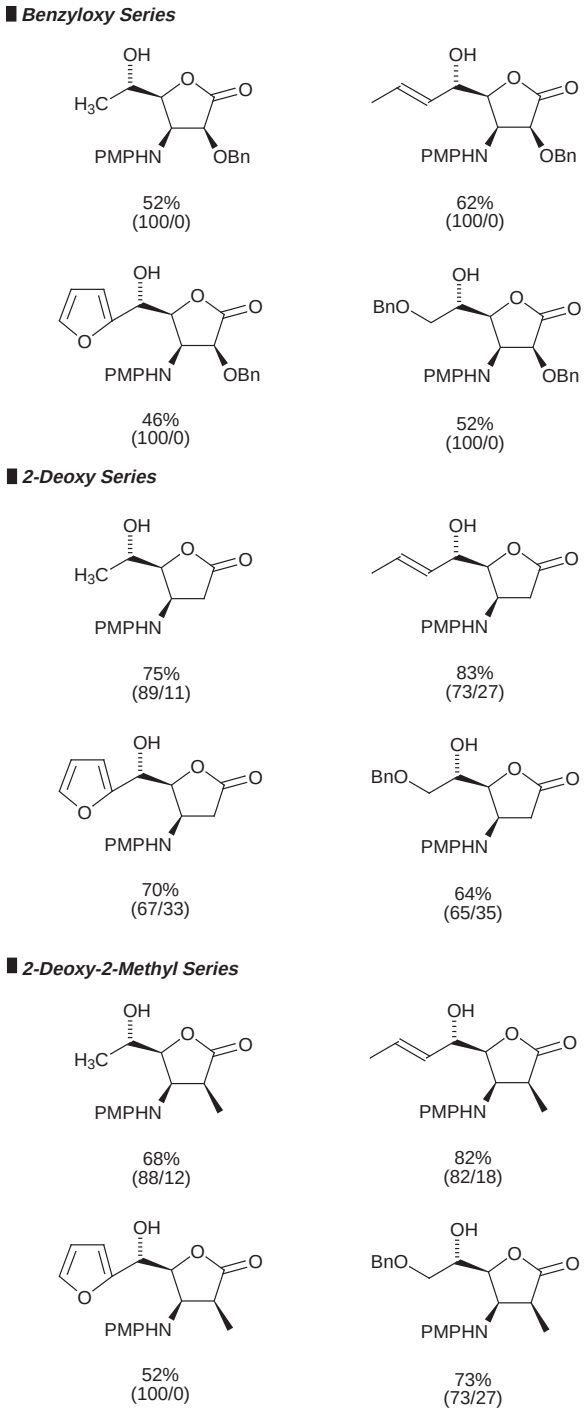
5 Library synthesis using polymer catalysts

5.1 Quinoline derivatives

Although polymer-supported substrates (reagents) have often been employed for library construction, there are some disadvantages to this method. First, the reactions of polymer-supported reagents are sometimes slow, and differences in reactivity between the substrates lead to lack of diversity of the library in some cases. Secondly, the loading level of polymer-supported substrates is generally low (< 0.8 mmol g^{-1}), and large-scale preparation is difficult. To overcome these problems, a new methodology for library synthesis has been developed. The new method is *not using polymer-supported reagents but using polymer-supported catalysts in multi-component reactions*.

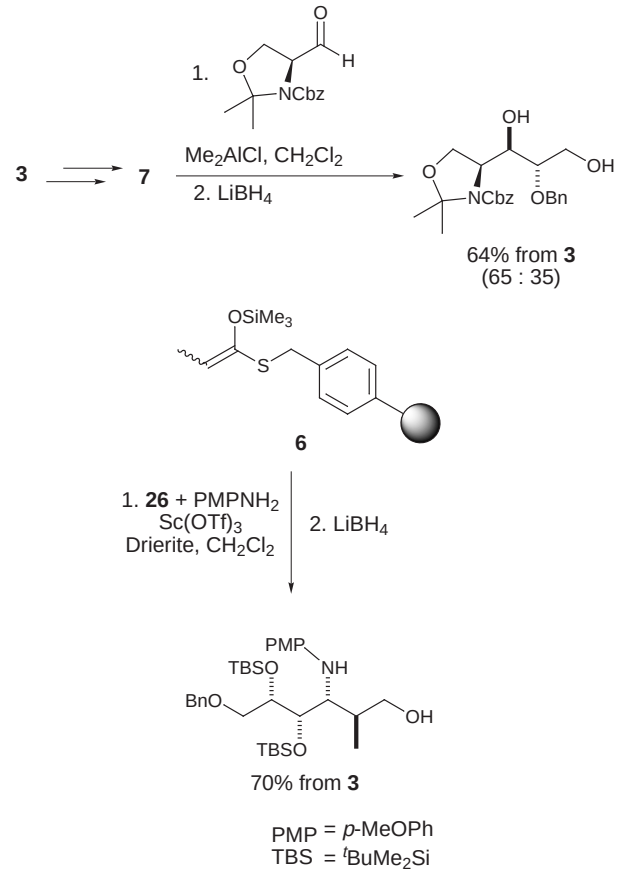
An example is shown in the synthesis of a large number of quinoline derivatives. We have recently developed three-component coupling reactions using a lanthanide triflate as a catalyst.[6] Many combinations of aldehydes, amines, and olefins are used in this reaction, and a large quinoline library could be prepared based on these combinations. Although liquid phase combinatorial synthesis may be possible, our attention was focused on reactions using a polymer catalyst.

Use of polymer-supported catalysts[26] offers several advantages such as simplification of product work up, separation, isolation, reuse of the catalyst, *etc*., and may be useful for parallel library construction. On the other hand, one of the drawbacks of polymer-supported catalysts is their low reactivity. Bearing in mind that the low reactivity may be ascribed to insolubility of the catalysts, we searched for a new polymer-supported catalyst which is partially soluble in an appropriate solvent and is precipitated after completion of the reaction and recovered quantitatively by filtration. After several trials, a new scandium catalyst, polyallylscandium trifylamide ditriflate (PA-Sc-TAD), has finally been developed. The synthetic route of PA-Sc-TAD is shown in Scheme 24. Polyacrylonitrile was treated with $BH_3 \cdot SMe$ in dyglyme for 36 h at 150 °C. The resulting amine (**33**) was reacted with Tf_2O in the presence of Et_3N in 1,2-dichloroethane for 10 h at 60 °C to afford sulfonamide **34**. After **34** and KH were combined, $Sc(OTf)_3$ was

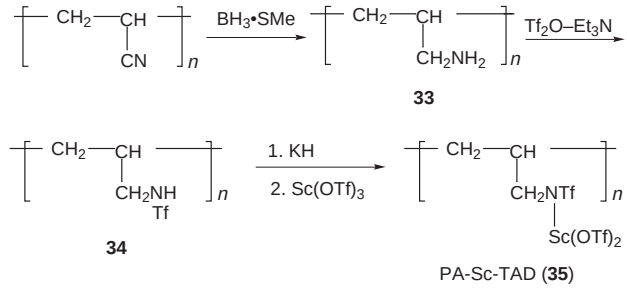


[1]All yields are from **3**
[2]PMP = *p*-MeO-Ph
[3]Diastereomer ratios (major/minors) are shown in parentheses.

Scheme 22 Synthesis of 3-amino sugar derivatives (lactones) in the solid-phase.



Scheme 23 Solid-phase synthesis of alditol derivatives.



Scheme 24 Preparation of PA-Sc-TAD (**35**).

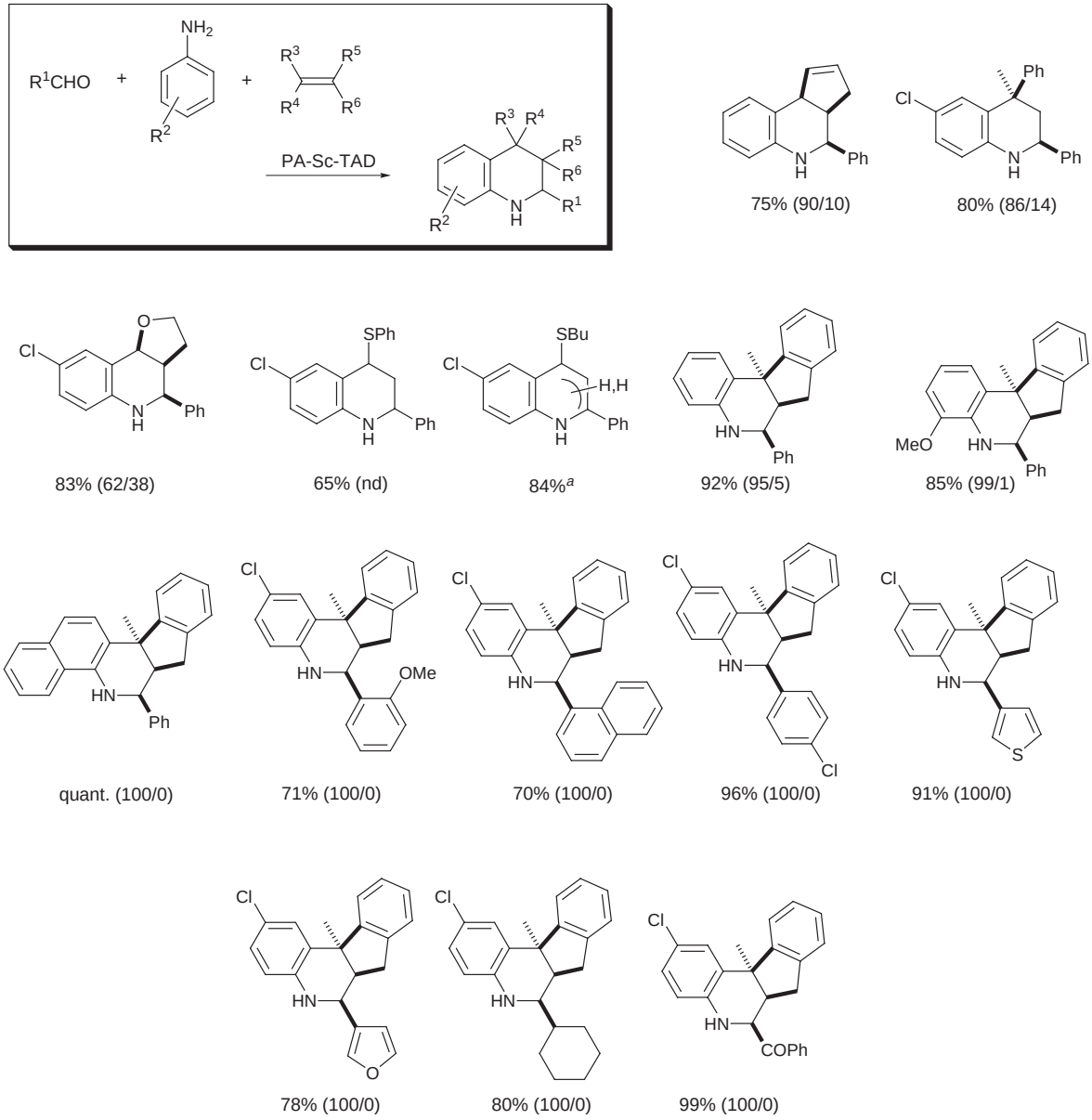
added and the mixture was stirred in THF for 48 h at rt to give **35**. PA-Sc-TAD (**35**) is gummy, but is dispersed and partially soluble in a CH_2Cl_2–CH_3CN mixed solvent. The dispersed catalyst assembles again when hexane is added.

PA-Sc-TAD (**35**) is especially useful for the synthesis of a quinoline library (Scheme 25).[27] The procedure is very simple; just mixing the catalyst (PA-Sc-TAD), an aldehyde, an aromatic amine, and an alkene (alkyne) in CH_2Cl_2–CH_3CN (2:1) at 60 °C for 12 h. Hexane was then added and the catalyst was filtered. The filtrates are concentrated to give almost pure quinoline derivatives in most cases. It is noted that PA-Sc-TAD is water-tolerant[28] and that substrates having water of crystallization can be used directly. PA-Sc-TAD can be easily recovered and continuous use is possible without any loss of activity (Scheme 26).

A characteristic feature of the present method compared to conventional combinatorial synthetic technology using polymer-supported reagents is that more than hundred milligrams scale syntheses with a large array of diverse molecular entries have been achieved with high purities (high yields and high selectivities). The number of commercially available aromatic aldehydes, aliphatic aldehydes, heterocyclic aldehydes, and glyoxals and glyoxylates is more than 200, and more than 200 aromatic amines and 50 alkenes (and alkynes) are commercially available. Therefore, a quinoline library of more than a million compounds with high quantity and quality could be prepared by using an automation system based on this method. Moreover, the tetrahydroquinoline derivatives thus obtained were easily oxidized to dihydroquinoline or quinoline derivatives, which could double the size of the library.

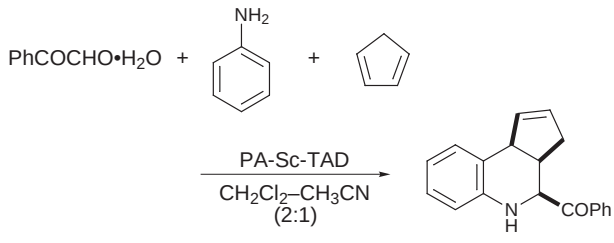
5.2 Amino ketone, amino ester, and amino nitrile derivatives

This new polymer catalyst method will be useful for construction of other compound libraries based on multi-component



[a] Butyl ethynyl sulfide was used as a dienophile.

Scheme 25 Use of PA-Sc-TAD in the synthesis of a quinoline library. Diastereomer ratios are shown in parentheses. Relative stereochemical assignment was made by ^{1}H NMR analysis.



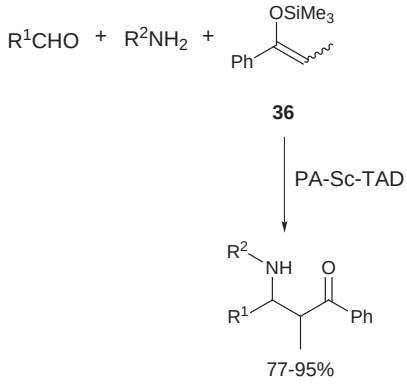
1st use, 90%; 2nd use, 91%; 3rd use, 93% yield

Scheme 26

reactions. Another example is three-component reactions between aldehydes, amines, and silylated nucleophiles, leading to amino ketone, amino ester, and amino nitrile derivatives.[29]

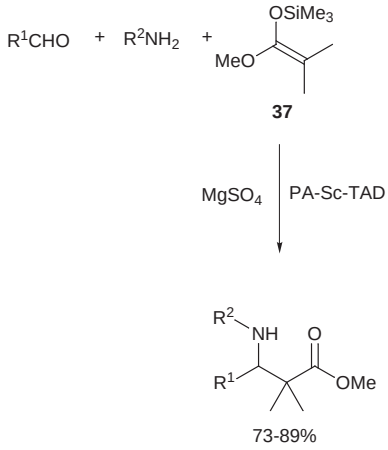
When benzaldehyde, aniline, and the silyl enol ether of propiophenone (**36**) were combined in the presence of polyallylscandium trifylamide ditriflate (PA-Sc-TAD), it was found that the reaction proceeded a little slower compared to that using $Ln(OTf)_3$ as a catalyst, but that the clean reaction proceeded smoothly at room temperature to afford the corresponding β-amino ketone in a 91% yield (after column chromatography on silica gel). In this reaction, the molar ratio of aldehyde : amine : **36** was 1 : 1 : 1.1, and no side reaction was observed. After the reaction was completed, the catalyst was filtered and the filtrate was concentrated *in vacuo* to afford the almost pure β-amino ketone. Heterocyclic and aliphatic aldehydes and a glyoxal also worked well with various amines and **36** to give β-amino ketone derivatives in high yields (Scheme 27).

The reactions using the ketene silyl acetal of methyl isobutylate (**37**) as a silylated nucleophile were then examined. It was expected that a β-amino ester could be produced by the reaction of cyclohexanecarbaldehyde, *p*-chloroaniline, and ketene silyl acetal **37** under standard conditions. However, only a trace amount of the product was obtained after 19 h at room temperature. It was assumed that water was produced in the formation of the imine from the aldehyde and the amine, and that the ketene silyl acetal was decomposed by this water leading to the low yield. Magnesium sulfate ($MgSO_4$) was then added as a dehydrating agent and the yield was dramatically improved to afford the desired adduct in a 74% yield. Under



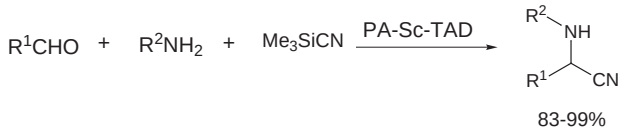
Scheme 27

these reaction conditions, several β-amino ester derivatives were obtained in high yields (Scheme 28).



Scheme 28

Finally, cyanotrimethylsilane (TMSCN) was used as a silylated nucleophile. The three component reactions between aldehydes, amines, and TMSCN proceeded smoothly in the presence of PA-Sc-TAD to afford various α-amino nitrile derivatives (Scheme 29). Three-component reactions between



Scheme 29

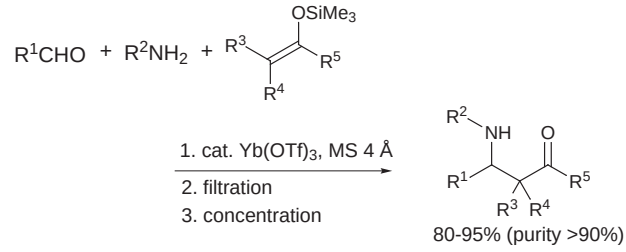
aldehydes, amines, and silylated nucleophiles have been successfully carried out by using a polymer scandium catalyst to afford β-amino ketones, β-amino esters, and α-amino nitriles in high yields. The reactions are very clean and the procedure is very easy; simply mixing the catalyst (PA-Sc-TAD) and almost equimolar amounts of an aldehyde, an amine, and a silylated nucleophile. After filtration, the filtrates are concentrated to give almost pure products in most cases. It is noted that PA-Sc-TAD can be easily recovered and that continuous use is possible without any loss of activity. These reactions provide a useful route to large numbers of structurally distinct amino group-containing compounds of high quality and quantity.

6 Library synthesis in liquid-phase

Because of the simple experimental procedure, solid-phase synthesis is now popular, but some problems such as low reactivity of polymer-supported reagents leading to low yields, low loading levels of polymer reagents which prevent large-scale synthesis, difficulties of characterization of polymer-supported compounds, *etc*., have been identified, as mentioned in the previous section. Although these disadvantages would be overcome by liquid-phase reactions, rather tedious procedures required in the work up and purification processes make their application to library construction difficult. In the course of our investigations to develop new methodologies for library construction, our attention has been focused on the development of efficient multiple-component reactions in liquid-phase as well as simplification of the work-up and purification processes in these reactions.

The methods reported here are based on three-component reactions of aldehydes, amines, and silyl enolates or alkenes leading to β-amino ester[3] or quinoline derivatives.[3,4] One of the necessary conditions for using liquid-phase synthesis as a method for library construction is to develop truly efficient reactions. For example, in multiple-component reactions, equimolar amounts of each component should react smoothly to afford the corresponding adducts in nearly quantitative yields. The $Ln(OTf)_3$-catalyzed three-component reactions of aldehydes, amines, and silyl enolates or alkenes meet the criteria. The reactions proceed smoothly by using almost equimolar amounts of each component. The next step is to separate the products easily from the catalyst. The lanthanide reagent is water-tolerant and soluble in water rather than in organic solvents,[28] therefore the products can be separated by simple extraction. However, a simpler procedure such as filtration was required. One of the important factors necessary to achieve this goal is that the catalyst is stable during the work up process and that a process of deactivation of the catalyst, for example, adding water, is not necessary. $Ln(OTf)_3$ is very suitable in regard to these points, while many Lewis acid catalysts such as $AlCl_3$, $TiCl_4$, $SnCl_4$, *etc*. are decomposed during the work-up process by air or water, which complicates the purification process. First, reprecipitation of $Ln(OTf)_3$ was tried. After the reaction was completed, the solvent was removed under reduced pressure and hexane was added. A new precipitate was observed and was separated by filtration, and then the filtrate was concentrated under reduced pressure. Unfortunately, it was found that the filtrate was contaminated with a small amount of the catalyst. Several similar methods along this line were then examined. After several trials, it was finally found that the catalyst was separated by directly charging onto a short column *without concentration*. After elution by an appropriate solvent, the eluent was concentrated *in vacuo* to afford almost pure product.

Several examples of the present method for the synthesis of β-amino esters from aldehydes, amines, and silyl enolates were tested, and in all cases, the desired β-amino ester derivatives were obtained in high yields with high purities (Scheme 30).[30]

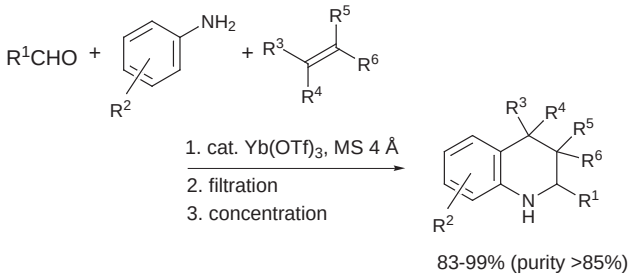


Scheme 30

The procedure is very simple. An aldehyde, an amine, a silyl enolate, ytterbium triflate ($Yb(OTf)_3$, 10 mol%), and 4 Å molecular sieves were combined in dichloromethane. The mixture was stirred for 20 h at room temperature, and then the whole reaction mixture was passed through a short column

packed with silica gel. The eluent was hexane–AcOEt (6:1, *ca*. 80 ml), and use of medium pressure enhanced the quick separation. The eluent was concentrated under reduced pressure to afford the products directly.

Similarly, tetrahydroquinoline derivatives were prepared from aldehydes, amines, and alkenes in high yields and high purities (Scheme 31).



Scheme 31

The present method is useful for the synthesis of large numbers of β-amino esters, which are versatile intermediates for the synthesis of β-amino alcohols, β-amino acids, β-lactams, *etc*., and quinoline derivatives. The very simple work-up and purification procedure compared to conventional methods (Scheme 32) would make it possible to apply this method to automation systems. Although small amounts of products are generally obtained in syntheses using polymer-supported reagents, large-scale preparation is possible by this method. In addition, the liquid-phase reactions can solve the low reactivity, low yield, and characterization problems often observed on the solid-phase synthesis. The method is based on $Ln(OTf)_3$-catalyzed three-component reactions, and the key is the efficient reactions and the simple purification process. Because many $Ln(OTf)_3$-catalyzed reactions have been developed,[31] the present method would be useful for construction of other compound libraries.

7 Conclusions and outlook

Several methods for the synthesis of compound libraries developed by our group have been overviewed. According to these methods, large quantities of single compounds (not mixtures) with high purities are prepared in most cases. In drug discovery, large numbers of compounds are synthesized and among them optimized compounds are selected. This method is common in drug discovery as well as in the development of new materials, functionalized compounds, catalysts, ligands, *etc*., and in these cases, large quantities of pure compounds are needed.

Solid-phase synthesis has often been used for the preparation of compound libraries. This procedure has obvious advantages over liquid-phase synthesis in its simple experimental procedures and its effectiveness in intramolecular cyclization reactions, *etc*. In the application to automated systems, the advantages of solid-phase synthesis will be unshakeable. On the other hand, there are reactions which proceed smoothly in liquid-phase but do not proceed well on the solid-phase. Most resins, spacers, and linkers used now on the solid-phase organic synthesis are those used on the solid-phase peptide synthesis. While condensation, protection, and deprotection reactions are mainly carried out in peptide synthesis, modern organic synthesis requires various types of reactions using organometallics, Lewis acids, *etc*. Development of new resins, spacers, or linkers which are appropriate for such organic reactions is needed. Another problem is stereoselectivity. Although many highly stereoselective reactions have been developed, there are still very few reactions which have perfect stereoselectivities. More than 90% diastereomeric excesses or more than 90% enantiomeric excesses are believed to be enough and this is partially true from a practical point of view, because separation or purification (recrystallization or column chromatography) is easy after such highly stereoselective reactions. However, separation or purification is usually difficult on the solid-phase synthesis. If a reaction proceeds in a diastereomer ratio of 95:5, the 5% impurity cannot be removed. Therefore, perfect reactions in both chemical yields and diastereoselectivities are required on the solid-phase synthesis. More basic and fundamental research works on the solid-phase organic synthesis are strongly demanded.

The significance of library synthesis will be increasing in the next century, and the role played by synthetic organic chemists will also become more and more important.

8 Acknowledgements

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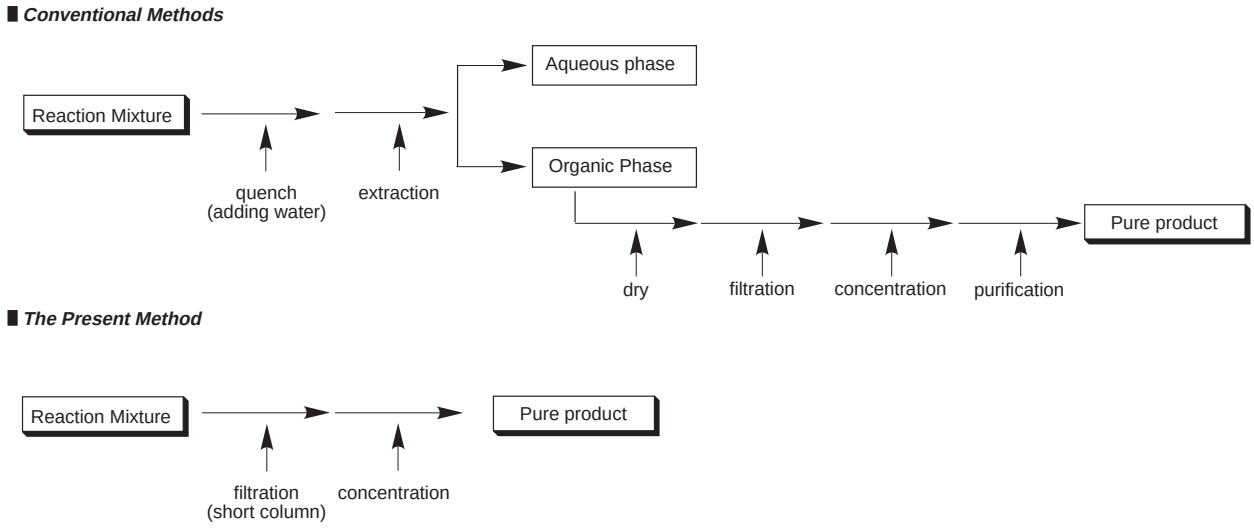

Scheme 32 Work-up and purification processes.

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