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Parallel Synthesis Using Mannich-type Three-Component Reactions and "Field Synthesis" for the Construction of an Amino Alcohol Library

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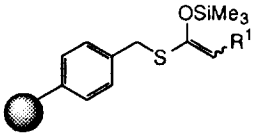
Abstract: *An amino alcohol library was constructed by parallel synthesis based on Mannich-type three-component reactions of aldehydes, amines, and polymer-supported silyl enol ethers, followed by reductive cleavage from the supports. "Field Synthesis," which provides an efficient method for the construction of libraries, is introduced.* Copyright © 1996 Elsevier Science Ltd

During this decade, "efficiency" has been a key word in modern organic synthesis.[1] New reactions, reagents, and catalysts have been developed to achieve "efficiency:" that is to achieve high yields and high selectivities including chemo-, regio-, diastereo-, and enantioselectivities. On the other hand, how can we synthesize large numbers of structurally distinct molecules? Reactions with high yields and high selectivities are necessary to make them, but are not sufficient because repeating the selective reactions many times requires a lot of man power and time, and that is not yet efficient.

We think combinatorial synthesis[2] may provide an answer to this question. In particular, multiple-component reactions, which have been focused on by us[3] and other groups,[4] provide one of the most efficient methods for the construction 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.[5]

In this paper, we report a new method for the construction of a 48 amino alcohol library[6] based on parallel synthesis using Mannich-type three-component reactions. "Field Synthesis," which provides an efficient method for the construction of libraries in parallel synthesis, is also introduced.



PSSEE

1: R^1 = Me
2: R^1 = OBn
3: R^1 = $(CH_2)_6CH_3$
4: R^1 = H

R^2-NH_2

Amine

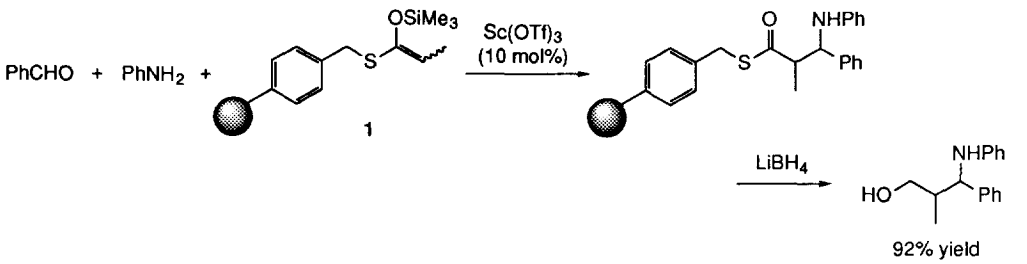
I: R^2 = $PhNH_2$
II: R^2 = p-$ClPhNH_2$
III: R^2 = p-$MeOPhNH_2$

R^3-CHO

Aldehyde

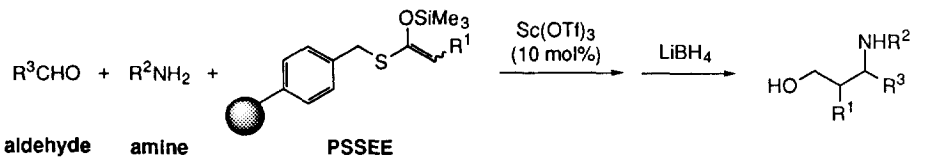
A: R^3 = Ph
B: R^3 = 
C: R^3 = 
D: R^3 = c-C_6H_{11}

Mannich-type three-component reactions on solid phase were successfully carried out using scandium triflate ($Sc(OTf)_3$) as a catalyst.[7] An example is the reaction of benzaldehyde, aniline, and polymer-supported silyl enol ether **1**[8] (Scheme 1). The reaction 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 a 92% yield. It should be noted that the yield was improved by employing the three-component reaction (the reaction of N-benzylidenaniline with **1** gave the amino alcohol in a 70% yield under the same reaction conditions).[8]



Scheme 1. Three-component reactions on solid phase

The amino alcohol library synthesis was carried out using "Field Synthesis," which was based on the above three-component reaction. We set four aldehyde "fields," 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 $NaHCO_3$ aq. 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 eq.) in THF (4 ml), and the mixture was stirred for 12 h at rt. After a usual work up, the crude product was chromatographed on silica gel to afford a pure amino alcohol.[9] The results are shown in Schemes 2 and 3. In every aldehyde field (Fields 1-4), combination of PSSEEs **1**-**3** and amines gave the corresponding amino alcohols in satisfactory yields,[10] while lower yields were observed in the reactions using PSSEE **4**. We then examined several reaction conditions in the model combination of benzaldehyde, aniline, and PSSEE **4**. It was finally found that the desired amino alcohol was obtained by using *t*-butyldimethylsilyl enol ether **5** instead of **4**. We next set a PSSEE **5** field (Field 5), and four aldehydes and three amines were employed. The results are shown in Scheme 4. This time, the desired amino alcohols were obtained in high yields in all combinations, and we successfully prepared a 48 amino alcohol library.



Scheme 2. General scheme of the three-component reactions

Scheme 3. "Field Synthesis." In each "Field," one of three components is fixed. The number in each column shows yield (%) of the three-component reaction.

Amine	1	2	3	4
III	87	84	58	14
II	85	78	70	14
I	92	82	65	16

PSSEE

Field 1. PhCHO Field

Amine	1	2	3	4
III	88	85	79	—[a]
II	86	82	81	—[a]
I	81	91	72	23

PSSEE

Field 2. 2-Furaldehyde Field

Amine	1	2	3	4
III	87	84	74	—[a]
II	78	69	56	—[a]
I	83	83	68	16

PSSEE

Field 3. 2-Thiophenecarboxaldehyde Field

Amine	1	2	3	4
III	80	76	55	—[a]
II	72	78	49	—[a]
I	65	47[b]	45	10

PSSEE

Field 4. c-$C_6H_{11}CHO$ Field

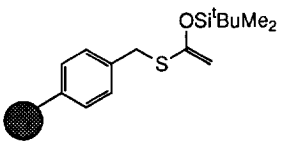
a) The reaction was not performed.
b) See Ref. 10.

Scheme 4. PSSEE is fixed

Amine	A	B	C	D
III	64	75	52	67
II	51	56	50	59
I	71	98	84	54

Aldehyde

Field 5. PSSEE 5 Field



PSSEE 5

In summary, parallel synthesis based on the Mannich-type three-component reactions of aldehydes, amines, and polymer-supported silyl enol ethers were carried out using $Sc(OTf)_3$ as a catalyst to construct an amino alcohol library.[11] Parallel synthesis based on multiple-component reactions, which set the component fields according to the reaction conditions ("Field Synthesis"), has been shown to be quite effective in library construction.

Further investigations to examine the biological activity of the amino alcohol library as well as to apply "Field Synthesis" to other library constructions are now in progress.

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(7) The three-component reactions are successfully carried out in liquid phase. See Ref. 3a.

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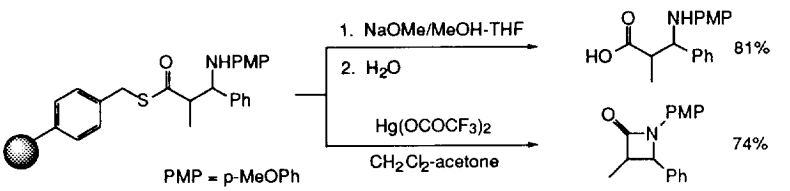
(9) The yield was based on the polymer-supported silyl enol ether (PSSEE).

(10) The yields will be improved by using excess aldehydes and imines. For example, when two equivalents of the aldehyde and the amine were used, the yield in the combination of **PSSEE 2** and **amine I** in **Field 4** was improved to 72%.

(11) β-Amino Acid and β-lactam libraries are also constructed according to the present method.



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