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In the process of identifying new compounds with interesting properties Combinatorial Chemistry (CC) has proven its value. These properties may be in the area of new pharmaceuticals, novel materials, artificial enzymes, catalysts, surfactants, *etc.* Although CC started in the area of non-drug-like compounds like oligomers, today's vision is that we need "good quality" compounds which are accessible for optimization of properties. Therefore, in the last few years CC methodology has been adopted for the synthesis of small organic molecules. Although more and more classical organic reactions are being converted to solid phase reactions [1], it has to be accepted that with today's available repertoire still only a small portion of the diversity space can be addressed. What is even more frustrating is that most of the time we are fishing in the same pool. Therefore, the synthesis of "good quality" compounds is relying heavily on the identification of new robust solid phase or solution phase processes.

Although it is a general feeling that solution phase approaches will have an enormous impact on the CC area, this article will only focus on solid phase syntheses. The process of identifying suitable chemistry in the general literature and translating this to solid phase conditions is a tedious one.

This process can be divided into four different stages: (i) identification of robust solution phase chemistry from literature; (ii) pin-pointing; (iii) reaction optimization and scope determination; and (iv) library production (see Figure 1).

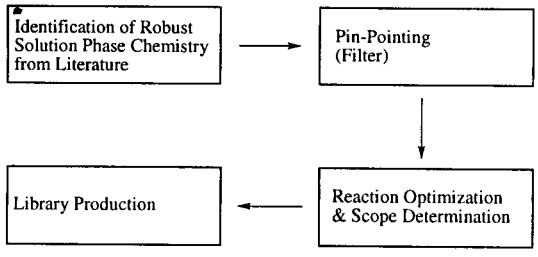


Figure 1. Four-step Approach

It is generally accepted that the development time to identify the optimal reaction conditions for new chemistry on solid supports is the rate-limiting step and not the production of the library (see Figure 2).

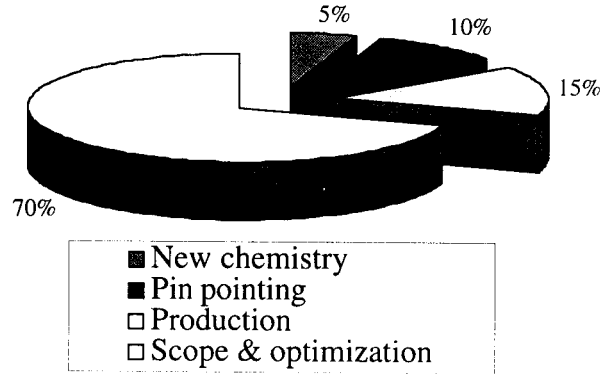


Figure 2. Estimation of Percentage Time Used per Stage

In our laboratory the pin-pointing phase has been introduced to filter out the promising ideas from the bad ones. The first step in this phase is to repeat the original solution phase chemistry to test the robustness of the described conversion. If high yields are obtained, the same conditions (if compatible with resin) are tried on the solid support. Normally this is followed by a rough optimization program; a few variations are studied such as different resins, equivalents of reagents, and temperature. Only if some preliminary results are obtained is a full blown optimization program started (see Figure 3).

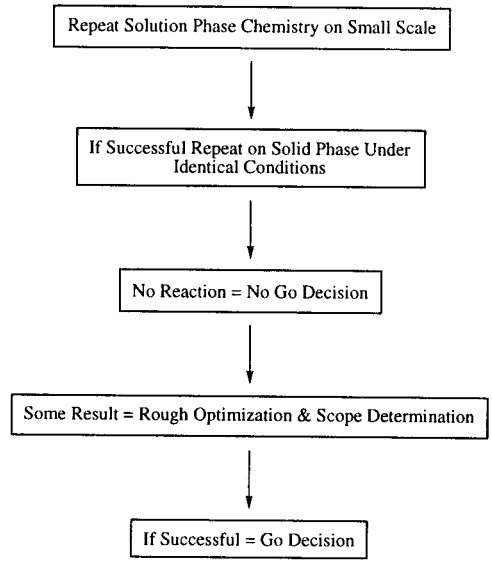
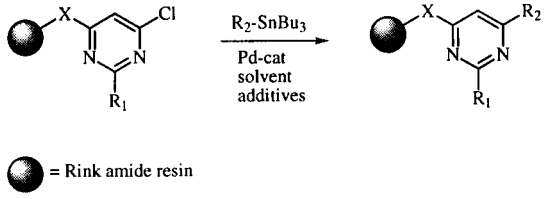


Figure 3. Pin-pointing Phase

As an example to study the process we selected the Stille reaction on a 4-chloropyrimidine moiety (see Scheme 1). Although the solution phase reaction has been studied extensively [2], there is no precedent for this reaction on solid support.

Scheme 1



Published solution phase conditions vary in the following factors: palladium catalysts are $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, solvents used are DMF, NMP, THF or toluene, temperature range is 50-120°, and additives used are Et_4NCl, K_2CO_3 or LiCl (for triflates). Because of the wide range of conditions, we skipped the rehearsal on solution phase but immediately tried the solid phase reaction using a rough cross section of the applied solution phase conditions (see Table 1). We restricted ourselves to the nonvolatile high boiling solvents DMF and NMP. However, we added two alternative palladium catalysts (Pd_2dba_3 and $Pd(dppb)_2Cl_2$). The only additives studied are LiCl and DIPEA. The reaction was performed with allyltributylstannane and the 4-chloropyrimidine moiety attached on the Rink amide resin (see Scheme 1).

Table 1
Rough Study

Entry	Pd-cat	Temperature(°C)	Solvent	Additives	Yield (%)
1	Pd_2dba_3 [a]	50	NMP		0
2	Pd_2dba_3 [a]	100	NMP		0
3	$PdCl_2(PPh_3)_2$ [b]	125	DMF		0
4	$PdCl_2(PPh_3)_2$ [b]	125	DMF	LiCl, DIPEA [c]	76
5	$Pd(dppb)_2Cl_2$ [d]	125	DMF		0
6	$Pd(PPh_3)_4$ [e]	125	DMF	LiCl, DIPEA [c]	81

[a] Pd_2dba_3: Tris(dibenzylideneacetone)dipalladium (0)
[b] $PdCl_2(PPh_3)_2$: Dichlorobis(triphenylphosphine)palladium (II)
[c] DIPEA: *N,N*-Diisopropylethylamine
[d] $Pd(dppb)_2Cl_2$: Dichlorobis(triphenylphosphine)palladium (II)
[e] $Pd(PPh_3)_4$: Tetrakis(triphenylphosphine)palladium (0)

No conclusion could be drawn which palladium catalyst is the optimal one. However, as the majority of the solution phase methods used $PdCl_2(PPh_3)_2$, we decided to focus only on this catalyst in forthcoming studies. In addition, the results clearly demonstrate the importance of LiCl and/or DIPEA (entries 4 and 6). This is a complete deviation from the solution phase data. Usually, solution phase conditions with 4-chloropyrimidines give very satisfactory results without extra additives [2]. LiCl is only added when triflate pyrimidines are used instead of halopyrimidines.

These preliminary positive results enabled the start of the third phase; a more comprehensive reaction optimization and scope determination program. In the first optimization round the influence of different equivalents of all reagents was studied using one stannane (allyltributylstannane) and one 4-chloropyrimidine moiety (Table 2). All reactions were performed in DMF at a temperature of 125° using a double coupling procedure (12 hours each). The reaction was monitored by HPLC analysis (ratio of starting material (A)/product (B)) after cleavage from the resin.

Table 2
First Optimization Round (8 Experiments)

Entry	$(Bu)_3SnR$ (Equivalents)	LiCl (Equivalents)	DIPEA (Equivalents)	$PdCl_2(PPh_3)_2$ (Equivalents)	Ratio A/B [a]
1	10	0	2.5	0.04	38/62
2	10	1.5	2.5	0.04	24/76
3	10	3	2.5	0.04	12/88
4	10	4.5	2.5	0.04	3/97
5	10	4.5	0	0.04	9/91
6	10	4.5	1.25	0.04	11/89
7	10	4.5	2.5	0.02	27/73
8	5	4.5	2.5	0.04	5/95

[a] Ratio starting material A/product B determined by HPLC analysis after cleavage from the resin.

This optimization round was performed on an automated synthesizer (Syro). The optimal conditions found are stannane (10 equivalents), DIPEA (2.5 equivalents), LiCl (4.5 equivalents) and $PdCl_2(PP_3)_2$ (0.04 equivalent) (entry 4).

Using these conditions in a broader scope determination (9 stannanes) it was revealed that reaction conditions could still be improved (see Table 3). Only three stannanes gave good results (entries 1-3) and two gave moderate conversion (entries 4-5). The remaining ones gave none or minor conversion. The lesson learned from these results was never to perform an optimization process using only a one-to-one combination of building blocks.

A search of the literature on other factors influencing the Stille reaction demonstrated that the additives PPh_3 and CuI and the amount of available catalyst often played an important role [3].

Table 3
Scope Determination Using First Optimized Conditions

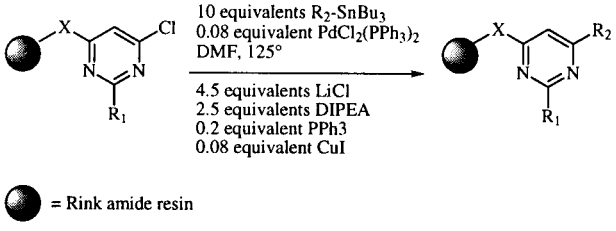
Entry	$(Bu)_3SnR$	Ratio A/B [a]
1	allyl	14/86
2	2-furanyl	0/100
3	2-thienyl	11/89
4	phenylethynyl	57/43
5	phenyl	42/58
6	vinyl	100/0
7	EtO-vinyl	100/0
8	2-pyridine	83/17
9	3-pyridine	77/23

[a] Ratio starting material A/product B determined by HPLC analysis after cleavage from the resin.

Therefore a second round of optimization was designed to study these parameters. Eight different conditions were simultaneously studied in an automated fashion (Syro) including four different stannanes (allyl-, phenylethynyl-, phenyl- and 2-pyridinetributyltin). These stannanes have been selected because based on their different reactivity (high, moderate and low, see Table 3). The number of equivalents of stannane (10 equivalents), LiCl (4.5 equivalents) and DIPEA (2.5 equivalents) found earlier were kept constant in this experiment. The results of these 32 experiments are described in Table 4.

The allyl- and phenyltributylstannane gave complete conversion under any condition. The phenylethynyl- and 2-pyridinetributylstannane only gave satisfactory results using the conditions described in entries 16 and 32. Therefore, these latter conditions are the most optimal ones found so far (see Scheme 2).

Scheme 2



= Rink amide resin

Conclusion.

In 55 experiments, performed in an automated fashion, we were able to identify robust reaction conditions for the Stille reaction on a 4-chloropyrimidine moiety. To test these conditions further we are preparing at the moment a test library of 60 compounds using 10 pyrimidines and 6 stannanes.

Acknowledgment.

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Table 4
Second Optimization Round (32 Experiments)

R_2 = Allyl

Entry	$PdCl_2(PPh_3)_2$ (Equivalents)	PPh_3 (Equivalents)	CuI (Equivalents)	Ratio A/B [a]
1	0.04	-	-	0/100
2	0.08	-	-	0/100
3	0.04	-	0.04	0/100
4	0.04	-	0.08	0/100
5	0.08	-	0.08	0/100
6	0.04	0.1	-	0/100
7	0.04	0.1	0.04	0/100
8	0.08	0.2	0.08	0/100

R_2 = Phenylethynyl

Entry	$PdCl_2(PPh_3)_2$ (Equivalents)	PPh_3 (Equivalents)	CuI (Equivalents)	Ratio A/B [a]
9	0.04	-	-	53/47
10	0.08	-	-	41/49
11	0.04	-	0.04	37/63
12	0.04	-	0.08	38/62
13	0.08	-	0.08	-
14	0.04	0.1	-	22/78
15	0.04	0.1	0.04	19/81
16	0.08	0.2	0.08	5/95

R_2 = Phenyl

Entry	$PdCl_2(PPh_3)_2$ (Equivalents)	PPh_3 (Equivalents)	CuI (Equivalents)	Ratio A/B [a]
17	0.04	-	-	0/100
18	0.08	-	-	0/100
19	0.04	-	0.04	0/100
20	0.04	-	0.08	0/100
21	0.08	-	0.08	0/100
22	0.04	0.1	-	2/98
23	0.04	0.1	0.04	0/100
24	0.08	0.2	0.08	2/98

R_2 = 2-Pyridine

Entry	$PdCl_2(PPh_3)_2$ (Equivalents)	PPh_3 (Equivalents)	CuI (Equivalents)	Ratio A/B [a]
25	0.04	-	-	73/27
26	0.08	-	-	51/49
27	0.04	-	0.04	62/38
28	0.04	-	0.08	65/35
29	0.08	-	0.08	48/52
30	0.04	0.1	-	28/72
31	0.04	0.1	0.04	24/76
32	0.08	0.2	0.08	93/7

[a] Ratio starting material A/product B determined by HPLC analysis after cleavage from the resin.

REFERENCES AND NOTES

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