showed Laue symmetry 6/*mmm* (systematic absences: *hhl* with $l = 2n$) and the lattice parameters $a = 8.45$, $c = 6.20$ Å. However, the quality of the crystal was not sufficient to perform a structure determination on a four-circle diffractometer. Therefore structural parameters were determined on powder material with a Guinier diffractometer. The approximate Ge and Li positions were derived from Patterson and Fourier syntheses.[15] Refinement was performed by the Rietveld method.[16–18] Hexagonal HP-LiGe was obtained as a phase mixture with 20% germanium (calculated from the scaling factors [19] of the Rietveld refinement). Owing to the extreme conditions in the preparation, the mobile Li^+ ions show high thermal parameters.[18]

Received: August 15, 2000 [Z15642]
Revised: November 21, 2000 [Z15642]

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A New Phase-Switch Method for Application in Organic Synthesis Programs Employing Immobilization through Metal-Chelated Tagging**

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The increasing demand for large numbers of new compounds for biological testing has encouraged synthetic chemists to look for new technologies and strategies to produce these compounds in a fast, clean, and efficient way. Presently, the most popular way in which this can be achieved is by the use of solid-phase organic synthesis (SPOS). This methodology allows the use of an excess of reagents and at the end of the synthetic sequence the immobilized product is isolated following a simple filtration.[1] Unfortunately, there are considerable limitations to this approach: The reactions are often slower than their solution-phase counterparts, it is difficult to monitor the reaction progress, and long optimization times are often required to transfer solution-phase chemistry onto the polymer support. Owing to these limitations, new strategies combining the benefits of established protocols for solution-phase chemistry with the key advantages of solid-phase chemistry are being developed which allow multistep syntheses to be performed using an array of supported reagents and scavenging agents.[2] One particular feature of combinatorial chemistry programs is the challenge of product purification by using methods which can be automated and operated in a multiparallel mode.[3]

Herein we report a new strategy for the synthesis of small-molecule libraries based on the "catch and release" principle.[4] In this approach we have devised a method of *selectively and reversibly* immobilizing key intermediates within a conventional solution-phase-mediated reaction sequence. We argued that a phase switch/separation[2] could be effected by a reversible and selective noncovalent interaction between a resin-bound metal and an organic metal-chelating "tag" linked to the molecule of interest (Scheme 1).[5] Thus, the immobilization or "phase switching"[2] of the tagged intermediate upon completion of the solution-phase reaction would be realized by the addition of a resin-bound metal to

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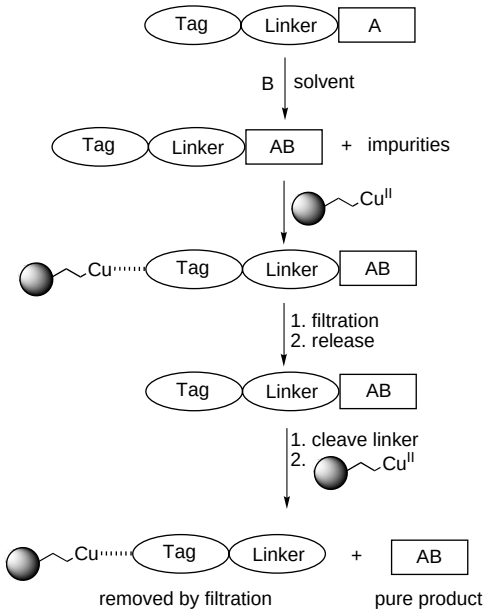
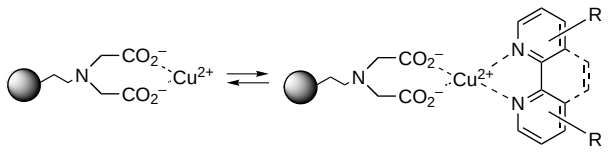
[**] We gratefully acknowledge financial support from Pfizer Global Research and Development, the University of Ferrara (Italy, Postdoctoral Fellowship to A.M.), the EU (Marie Curie Fellowship to F.R.), and a Novartis Research Fellowship (to S.V.L.).



Scheme 1. Strategy devised for the synthesis and purification of small-molecule libraries.

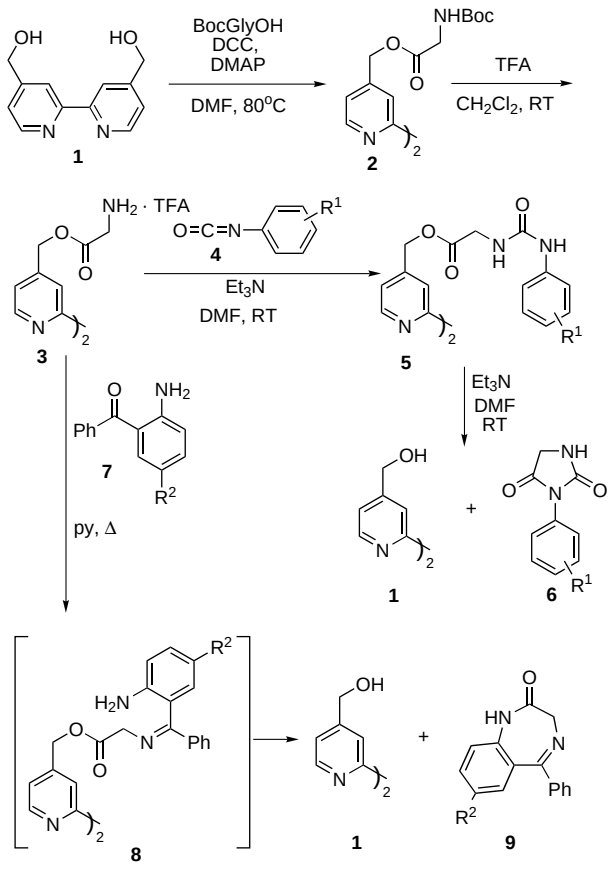
the reaction media to act as an insolubilizing agent by complex formation. The resin would be washed, to remove excess reagents and by-products, and finally the purified intermediate would be easily obtained after release from the resin. Moreover, the appropiate choice of the tag would allow the tagged intermediate to be isolated and purified through a simple process of precipitation and filtration.[6] The final stage of the scheme requires controlled cleavage of the tag to yield the desired molecule.

A variety of transition metals, metals bound to solid supports, and metal-chelating organic molecules were evaluated. The preferred resin, however, with respect to optimal loading of copper(II) ions was found to be the inexpensive solid support IRC-718 which contains iminodiacetic acid.[7] Of the various metal-chelating "tags" explored bidentate pyridine-containing ligands such as 1,10-phenanthroline and 2,2′-bipyridine were found to be optimal, not only with respect to their good affinity for copper(II) ions but also in regard to their moderately low reactivity to a wide range of reaction conditions (Scheme 2).



Scheme 2. Capture of bipyridine-tagged molecules by copper(II)-containing beads.

The preparation of a series of hydantoins and benzodiazepines was chosen to evaluate the method, since a solid-phase synthesis of these moieties had been previously reported.[8] For the synthesis of these compounds 4,4′-bis(hydroxymethyl)-2,2′-bipyridine (**1**) was found to be a suitable tag (Scheme 3).[9] The hydroxyl groups of this molecule constitute



Scheme 3. Synthesis of hydantoins **6** and benzodiazepines **9**. DCC = dicyclohexylcarbodiimide, DMAP = dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, py = pyridine.

the linker component, which can be easily decorated with various synthesis elements. For example, acylation of **1** with *N*-*tert*-butoxycarbonylglycine under standard amide-coupling conditions gave the bisglycinyl ester **2** in solution. This was then captured by the addition of copper(II) ions bound to IRC-718 beads, which were then washed to remove excess reagents and other by-products. Diester **2** was released from the beads by the addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and shaking the suspension for 8 h.[10] Filtration and concentration of the filtrates afforded diester **2** in 70% yield and >95% purity, as established by ^{1}H NMR spectroscopy. Both the uptake and release of **2** could be easily monitored by thin-layer or high-performance liquid chromatography. The *tert*-butoxycarboyl (Boc) group was subsequently removed using trifluoroacetic acid (TFA), and after evaporation of excess reagent the bis-TFA salt **3** was obtained quantitatively. This salt was then treated with a variety of isocyanates **4** to give crude urea derivatives **5**.

Two different procedures were used for the purification of the urea derivatives. First, the beads of resin-bound copper(II) ions were added to the crude solution of the urea derivative **5b** and after the "catch-release" technique described above **5b** was isolated in 85% yield (>95% purity). Secondly, it was found that urea derivatives **5a**–**f** precipitated from the reaction media by the simple addition of a mixture of petrol ether and ethyl acetate. This process gave the products in very high yields and in purities greater than 90% following a

  1433-7851/01/4006-1054 $ 17.50+.50/0

simple procedure of precipitation followed by filtration (Table 1, entries 1–6).[6] With compounds **5a–f** in hand, the final step of cyclization and release of the tag was performed using triethylamine. Tag **1** was immobilized using the beads of resin-bound copper(II) ions and after filtration and concentration of the filtrates hydantoins **6a–f** were obtained in yields and purities higher than 90% (Scheme 3 and Table 1, entries 1–6). Moreover, this technique allowed us to quantitatively recover and reuse the tag **1** after it was released from the beads of resin-bound copper(II) ions with TMEDA.

Table 1. Ureas **5**, hydantoins **6**, and benzodiazepines **9** prepared according to Scheme 3. The purities given in brackets (in %) next to the yields were determined by ^{1}H NMR spectroscopy.

Entry	R^1 or R^2	**5**	Yield[a]	**6**	Yield[b]	**9**	Yield[a]
1	H	**5a**	94 (>95)	**6a**	91 (>95)		
2	4-CF_3	**5b**	93 (>95)[c]	**6b**	93 (>95)		
3	4-*i*Pr	**5c**	96 (>92)	**6c**	99 (>95)		
4	4-F	**5d**	97 (>95)	**6d**	99 (>92)		
5	4-Br	**5e**	97 (>90)	**6e**	99 (>95)		
6	3-SMe	**5f**	96 (>95)	**6f**	97 (>95)		
7	H					**9a**	51 (>90)
8	Cl					**9b**	49 (>90)

[a] Based on the TFA-diester **3**. [b] Based on the starting urea **5**. [c] A yield of 85% (>95% purity) was obtained after purification using the procedure based on the beads of resin-bound copper(II) ions (see text).

Benzodiazepines **9** were synthesized in a similar fashion. Intermediate **3** was heated with aminoketones **7** in pyridine for three–five days. In situ cyclization of intermediates **8** gave benzodiazepines **9** in addition to the released tag **1** (Scheme 3). The mixture was then treated with the copper(II)-containing beads to remove the tag, and after filtration and removal of solvents benzodiazepines **9a**, **b** were obtained with high levels of purity in moderate yields (Table 1, entries 7–8). In these cases it was also possible to recover the tag **1** and reuse it in further reactions.

In summary, we have described a new strategy for the parallel synthesis of small molecules that combines the advantages of both *solution- and solid-phase* organic synthesis. The principal advantages of such an approach include: 1) minimal optimization is required and as a consequence of the process being performed in solution the progress of the reaction can be monitored by simple, well-established procedures such as thin-layer chromatography and liquid chromatography, and 2) immobilization of key intermediates onto the polymeric beads facilitates purification by simple filtration. Moreover, the use of bipyridine tags allows purification of some intermediates by precipitation and filtration. This procedure could also be adapted to split-and-mix syntheses. Further studies including the use of other organic metal-chelating "tags" as scavengers and reagents are underway.

Experimental Section

Preparation of hydantoin **6c** from **3**: Triethylamine (0.28 mmol) and 4-isopropylphenyl isocyanate (0.56 mmol) were added to a solution of **3** (0.07 mmol) in DMF (0.5 mL) at room temperature. After stirring the mixture for 30 min, a 1:1 mixture of petrol ether and ethyl acetate (4 mL) was added, and the resulting solid was filtered and washed with petrol ether (2 mL) to obtain urea **5c** (96% yield, >92% purity). Compound **5c** was dissolved in DMF (1 mL) and triethylamine (0.5 mL) was added. After stirring the mixture for 3 days it was diluted with dichloromethane (2 mL). Beads of resin-bound copper(II) ions (0.5 g) and 3 drops of water were added, and the mixture was shaken for 30 min. Filtration and removal of the solvents afforded **6c** (99% yield, >95% purity). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.5$ Hz, 2H; ArH), 7.23 (d, $J = 8.5$ Hz, 2H; ArH), 6.09 (br s, 1H; NH), 4.04 (s, 2H; CH_2), 2.87 (hept, $J = 6.9$ Hz, 1H; CH), 1.19 (d, $J = 6.9$ Hz, 6H; $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.5$, 157.8, 149.7, 129.2, 127.7, 126.5, 46.8, 34.3, 24.6; MS (EI): *m/z* (%): 218 (62) [M^+], 203 (100), 146 (52), 69 (35); HR-MS (EI): calcd for $C_{12}H_{14}O_2N$ [M^+] 218.1055, found: 218.1057.

Received: October 30, 2000 [Z16020]

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