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Solid-phase synthesis of pyrrolidines employing a cyclisation–cleavage strategy

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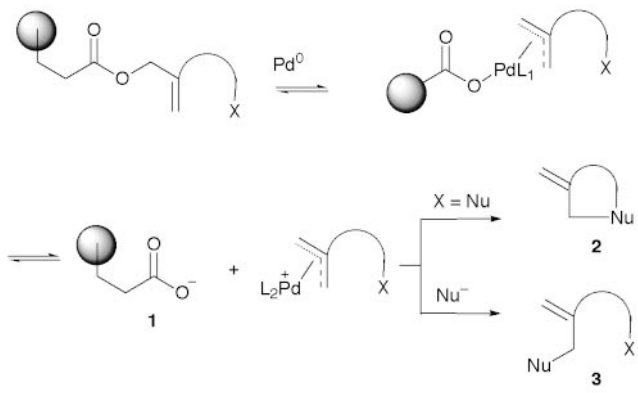
The solid-phase synthesis of several pyrrolidines has been realised utilising imino-Sakurai and palladium-catalysed cyclisation–cleavage reactions as key steps.

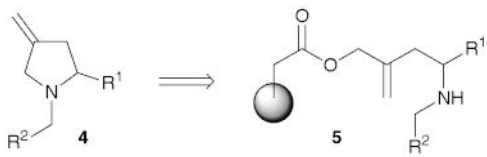
The development of solid-phase combinatorial and multiple parallel synthesis methods has stimulated considerable interest in the design of new linkers and cleavage strategies which are suitable for the release of small molecules from the solid support.[1–4] Linkers or cleavage conditions which activate a polymer-bound molecule towards nucleophilic cleavage can be particularly useful providing an additional point of variability in the released compounds,[4] or allowing the formation of a ring upon cleavage.[4,5] Here we describe the development of a novel nucleophile-cleavable linker that is sufficiently robust to survive a multi-step reaction sequence, yet can be cleaved under mild conditions with incorporation of a nucleophile.

Several linkers which rely upon the palladium-catalysed cleavage of allylic systems have been reported, releasing carboxylic acids or amines (through an intermediate carbamic acid) from the resin.[6–9] We imagined that a reversed allylic linker would provide a mild means of generating electrophilc π-allyl palladium species which could be trapped with heteroatom- or carbon-centred nucleophiles to release cyclic **2** or acyclic **3** products from the solid phase (Scheme 1).

In order to demonstrate the viability of a palladium-catalysed cyclisation–cleavage reaction we chose to investigate the solid-phase synthesis of pyrrolidines **4** (Scheme 2).[10,11] A key intermediate is the homoallylic amine **5** which could be derived from the reaction of a resin-bound allylic nucleophile with an imine.[11–13] The presence of an ester group in the linker meant that the reactivity of the allyl metal component would have to be attenuated, leading us to consider the use of an allylic silane as the immobilised nucleophile.



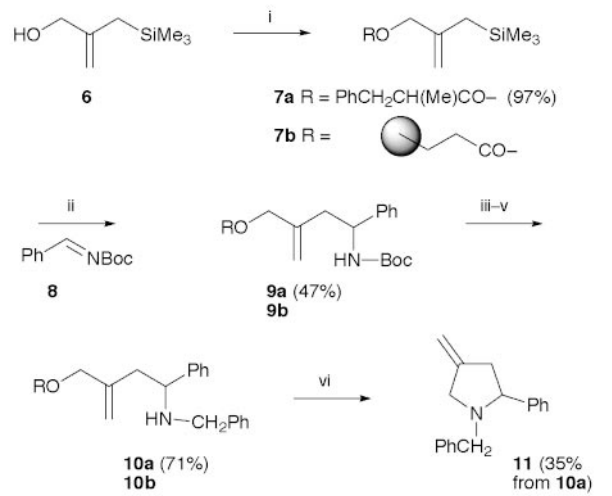
Scheme 1



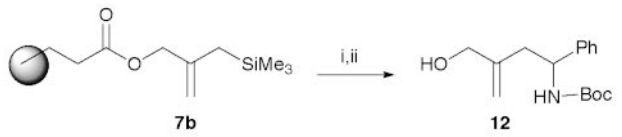
Scheme 2

Before attempting any solid-phase work the analogous solution chemistry was investigated (Scheme 3). 2-Hydroxymethyl-3-trimethylsilylpropene **6** was esterified with 2-methyl-3-phenylpropanoyl chloride to give the allylic silane **7a**. Addition of **7a** to the preformed *N*-acyl imine **8** provided a satisfactory yield of the homoallylic amine **9a**. Attempted cyclisation of either the Boc-protected homoallylic amine **9a** or the corresponding deprotected primary amine failed using 10 mol% $Pd(acac)_2$ with 15 mol% diphenylphosphinoethane (dppe). However, deprotection and reductive alkylation of **9a** provided secondary amine **10a** which when subjected to the same cyclisation conditions afforded the desired pyrrolidine **11** in 35% yield. Although some of the yields in the solution pyrrolidine synthesis were rather low, we were sufficiently satisfied with the overall approach to carry out further optimisation on the solid phase.

Solid phase synthesis of pyrrolidine **11** started with a carboxyethylated polystyrene resin† **1** which was prepared in three steps from Merrifield resin. The 2-hydroxymethyl-3-trimethylsilylpropene **6** was immobilised under standard carbodiimide coupling conditions using an excess of DMAP to prevent the well-known side reaction leading to a resin-bound *N*-acylurea. The imino-Sakurai reaction required some optimisation, turning out to be the most challenging step in the solid-phase reaction sequence. The effect of changing several reaction parameters including reaction time, amount of *N*-acylimine and the amount of Lewis acid was investigated. The efficiency of the reaction was measured by reduction of the ester linkage followed by purification of the cleaved alcohol **12** and quantification (Scheme 4). Our results are shown in Table 1. Optimum conditions required a large excess of the *N*-acylimine **8** and an excess of $BF_3{\bullet}OEt_2$ relative to the resin-bound allylsilane **7b** (entry 7), providing significantly better yield of the homoallylic amine than was achieved in the analogous reaction in solution.



Scheme 3 *Reagents and conditions*: i, 1,3-diisopropylcarbodiimide, DMAP, CH_2Cl_2, **1**; or 2-methyl-3-phenylpropionyl chloride, CH_2Cl_2, pyridine; ii, $BF_3{\bullet}OEt_2$, CH_2Cl_2; iii, TFA, CH_2Cl_2; iv, PhCHO, AcOH, CH_2ClCH_2Cl; v, $Me_4NB(OAc)_3H$, CH_2ClCH_2Cl; vi, $Pd(acac)_2$, dppe, THF, Δ.



Scheme 4 *Reagents and conditions*: i, **8**, BF_3•OEt_2, CH_2Cl_2; ii, $LiBH_4$, MeOH (1 equiv.), THF.

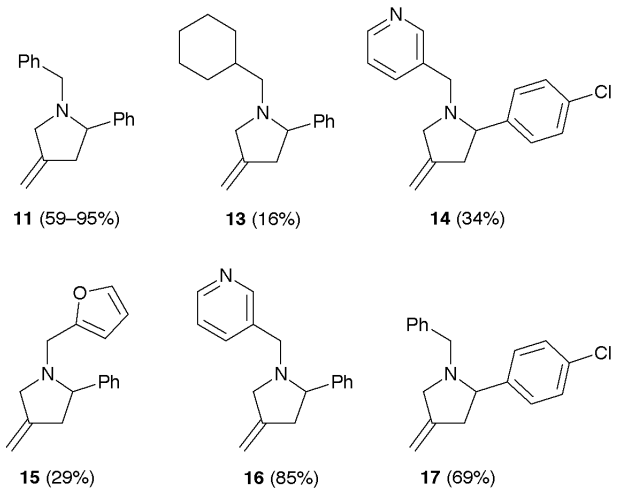
Table 1 Effect of reaction parameters on yield

Entry	Molar ratio[a] of *N*-acylimine **8**	Molar ratio[a] of BF_3•OEt_2	Reaction time/h	Yield[a] (%)
1	8	12	12	16
2	8	4	12	25
3	15	8	12	61
4	15	8	28	49
5	23	8	12	70
6	23	8	3	70
7	23	4	3	70

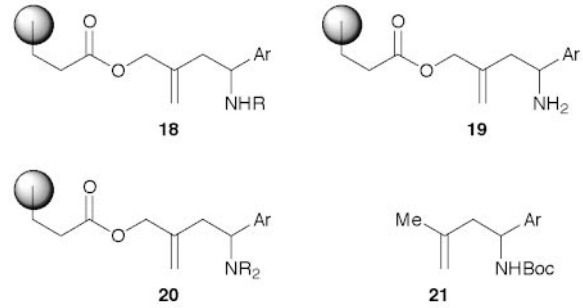
[a] The yield represents the amount of purified isolated alcohol **12** relative to the loading of the carboxylated resin **1**. Molar ratios are also based upon the loading of the carboxylated resin **1**.

Removal of the carbamate protecting group from **9b** and a two-step reductive alkylation using benzaldehyde gave the resin-bound cyclisation precursor **10b**, which was also quantified by reductive cleavage from the resin. Initial attempts to perform the cyclisation–cleavage reaction of **10b** gave the desired heterocycle **11** in low yield, even when a large quantity of palladium complex was employed. However, efficient catalytic cyclisation-cleavage was achieved by employing a three-fold excess of the dppe ligand relative to palladium (10 mol% based upon the loading of the carboxylated resin **1**), returning an excellent yield of the desired pyrrolidine **11**.‡

In order to demonstrate the scope of the palladium-catalysed cyclisation–cleavage reaction, pyrrolidines **11** and **13**–**17** were synthesised.§ In all instances the desired pyrrolidine was obtained, furthermore the purity of the crude product, except in the case of **13**, was judged to be high by inspection of the ^1H NMR spectra. Notably, the crude pyrrolidines **11**, **13**–**17** were



cleaner than their acyclic precursors which were released from the resin by reductive cleavage of **18** using $LiBH_4$. This significant result suggests that the cyclisation–cleavage reaction acts as an in-built quality control step, favouring the release of



the desired product over the release of by-products from earlier steps. To test this theory further, several of the possible by-products from the deprotection–reductive alkylation sequence **9b**, **19** and **20** were subjected to the cyclisation–cleavage reaction conditions. No significant quantity of material was released from any of the resins **9b**, **19** or **20**. Interestingly, treatment of the resin **9b** recovered from the attempted palladium-catalysed cleavage with $LiBH_4$ in THF afforded a reduced product **21** in 80% yield rather than the expected allylic alcohol **12**.

In summary, the viability of a palladium-catalysed cyclisation–cleavage reaction has been demonstrated by the solid-phase synthesis of pyrrolidines **11** and **13**–**17**. This strategy should also be amenable to the solid-phase synthesis of other heterocyclic and carbocyclic compounds. Intermolecular palladium-catalysed nucleophilic cleavage, using $LiBH_4$ as a source of hydride, is also possible releasing substituted propene derivatives such as **21**.

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Notes and references

† Merrifield resin was heated with the sodium salt of diethyl malonate at 60 °C for 14 h. Hydrolysis was carried out in refluxing THF–2 M KOH (9:1). Finally, decarboxylation in THF–HCl gave the desired carboxyethylated polystyrene **1**.

‡ Yields have been calculated based on the loading of the carboxylated polystyrene resin **1**.

§ All reactions were carried out on at least a 50 μM scale with respect to the loading of the carboxylated polystyrene resin **1**. All products were purified by flash chromatography and gave satisfactory analytical data.

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