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Palladium-catalysed nucleophilic release of allylic amines from a phenolic resin

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Abstract—2° Allylic alcohols were coupled to phenolic polystyrene resin under Mitsunobu conditions to provide substituted allyl ethers, which underwent efficient nucleophilic cleavage by 1° and 2° amines in the presence of catalytic palladium to afford allylic amines. © 2001 Elsevier Science Ltd. All rights reserved.

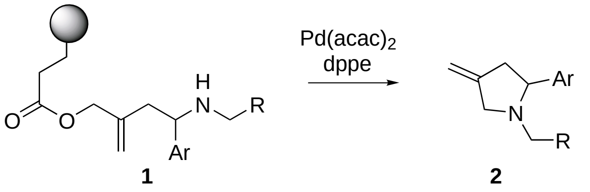
Solid-phase combinatorial and multiple parallel synthesis methods have become significant in many areas, including the synthesis of small organic molecules.[1–5] As a result, new linkers and cleavage strategies are constantly under investigation.[6–9] Linkers which enable release of the target molecule from the solid support under mild conditions or are robust towards a variety of reaction conditions are particularly desirable, as are those which allow the introduction of structural variability in the cleavage step.

We have previously reported the cyclisation cleavage of allylic carboxylates **1** under mild conditions to afford pyrrolidines **2** (Scheme 1).[10] Although the ester linkage contained in **1** proved compatible with acidic conditions (Boc-deprotection with TFA), it was cleaved under nucleophilic conditions such as hydride reduction. Here we report the development of a complementary strategy based on the cleavage of allyl phenyl ethers **3** (Scheme 2),[11–13] which are stable to nucleophiles in the absence of palladium, but readily cleaved by amines in the presence of catalytic Pd(0).

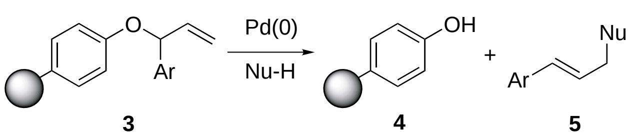
Our approach to the allyl ethers **3** would employ a Mitsunobu coupling reaction to form the ether bond (Scheme 3).[14–16] The starting phenolic resin **4** was prepared in three steps from polystyrene resin, commencing with a Friedel–Crafts acylation to afford the resin bound acetophenone **6**,[17] which was transformed to acetate **7** upon treatment with *m*CPBA. No evidence was found to support the presence of the regioisomeric methylbenzoate resin. Hydrolysis of the acetate **7** provided phenolic polystyrene resin **4**. The loading of resin **4** was established to be 2.5 mmol/g by coupling with 3-phenylpropionyl chloride and reductive cleavage ($LiBH_4$) of dihydrocinnamyl alcohol, which was quantified by GC.

The allylic alcohol **8a**,[18] prepared by treating benzaldehyde with vinyl magnesium bromide, was coupled to the resin **4** under Mitsunobu conditions.[14–16] The presence of the 2° allylic ether **3a** was supported by signals at 138.4 (CH), 116.4 (CH_2) and 81.1 (CH) ppm in the gel-phase ^{13}C NMR spectrum.

Nucleophilic cleavage of allyl ether **3a** was first investigated with piperidine in the presence of $Pd(acac)_2$ and dppe (Scheme 4). The effect of changing various reac-



Scheme 1. Palladium-catalysed cyclisation cleavage of pyrrolidines.



Scheme 2. Palladium-catalysed nucleophilic cleavage of allyl ethers.

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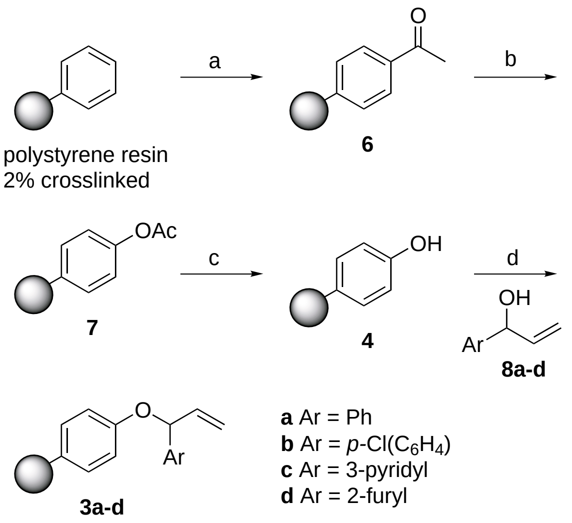
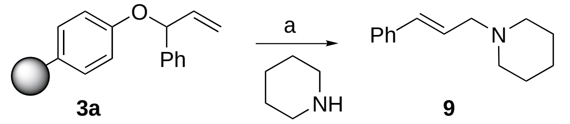


Scheme 3. Synthesis of immobilised allyl ethers. *Reagents and conditions*: (a) $AlCl_3$, AcCl, CS_2, Δ; (b) *m*CPBA, CH_2Cl_2; (c) Me_3SiOK, MeOH, CH_2Cl_2; (d) PPh_3, DEAD, THF.



Scheme 4. Nucleophilic cleavage of resin **3a** with piperidine. *Reagents and conditions*: (a) $Pd(acac)_2$, dppe, THF, Δ.

tion parameters, including reaction time, amount of catalyst, amount of ligand, amount of piperidine and temperature, was investigated. The palladium-catalysed nucleophilic cleavage reaction did not proceed at room temperature, whereas prolonged reaction times (3–8 h) at reflux led to slow degradation of the product. Monitoring of the release of product **9** over time by GC revealed that a maximum yield (70% by GC, 52% isolated after flash chromatography) was achieved after 1 to 2 h at reflux with 5 mol%[†] $Pd(acac)_2$ and 10 mol% dppe. The catalyst loading could be reduced further (2 mol%) with a modest decrease in the yield of **9**, although 5 mol% catalyst was routinely used. Efficient cleavage required only 1 equivalent of piperidine and resubmitting the recovered resin to the cleavage conditions failed to afford any additional amine **9**. Only a trace amount of the regioisomeric 2° allylic amine was present in the crude product (determined from the ^1H NMR spectrum).

To investigate the scope of the palladium-catalysed nucleophilic cleavage process further, the reactions of four different amines (Fig. 1) with four resin-bound allylic ethers were investigated (Scheme 5).[19] Allylic alcohols **8a–d**[18,20] were immobilised on hydroxy polystyrene (**4**), and the resulting resins **3a–d** were subjected to the cleavage conditions in the presence of different amines (Table 1). With the exception of the 2-furyl-substituted allylic ether **3d** (entry 13, Table 1), all reactions afforded the desired products in acceptable yield. For the unsuccessful reaction, it is unclear whether the failure of the overall process originated in the initial immobilisation of **8d** or at the cleavage step as no conclusive analytical data could be obtained on resin **3d**.

A by-product **23**, arising from attack by the acetylacetonate ligand, was observed in varying quantities in all reactions using $Pd(acac)_2$ (Fig. 2). This problem was avoided in later experiments by simply swapping the catalyst to $Pd(PPh_3)_4$ (entries 2, 4, 6 and 9, Table 1).

The intermolecular substitution reactions of allylic acetates with 1° amines has been reported not to be a useful process due to the formation of by-products arising from diallylation and direct nucleophilic attack on the ester.[12] In our case the latter side reaction was not an issue, although unsurprisingly, reactions with 1 equiv. of $BnNH_2$ in the solid-phase led to a certain amount of diallylated material **24** (Fig. 2). Formation of **24** was significantly reduced, but not eliminated, by using four equivalents of the 1° amine.

Purification of the crude products was required due to the presence of some unreacted 1° or 2° amines in the crude product. The 2° amines were conveniently scavenged from the reaction mixtures using an isocyanate resin (Fig. 3).[21] For the removal of excess 1° amine from 2° amine products, acetoacetoxy ethyl methacrylate (AAEM) resin was employed.[22] Further purification of the products involved simple chromatography to remove non-polar catalyst-derived components.

In summary, a facile synthesis of immobilised allylic ethers has been described from aldehyde starting materials. The allylic ethers are resistant to a variety of basic and nucleophilic conditions until activated with catalytic palladium, allowing incorporation of amine nucleophiles to produce allylic amines. The allylic amine structural motif is present in a large number of biologically active molecules, and the methodology described may present a means of preparing arrays of allylic amines for screening. Our future studies will focus on

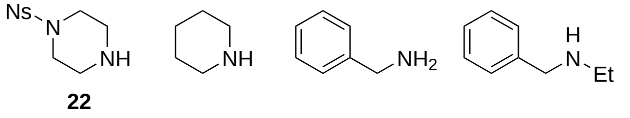
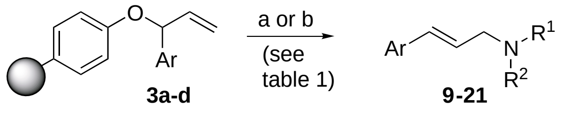


Figure 1. Amines used in cleavage reactions.



Scheme 5. Palladium-catalysed nucleophilic cleavage with amines. *Reagents and conditions*: (a) R^1R^2NH, 5 mol% $Pd(acac)_2$, 10 mol% dppe, THF, Δ; (b) R^1R^2NH, 5 mol% $Pd(PPh_3)_4$, THF, Δ.

[†] Yields and amounts of reagents are all based on the initial loading of the resin **4**, assuming quantitative conversions for solid-phase reactions.

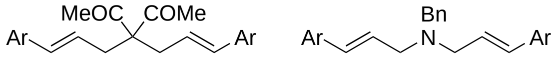
Table 1. Palladium-catalysed nucleophilic cleavage of allylic amines (Scheme 5)[19]

Entry	Ar	Amine	Catalyst	Product	Yield (%)[a]
1	Phenyl	Piperidine	$Pd(acac)_2$/dppe	**9**	52
2	Phenyl	$BnNH_2$[b]	$Pd(PPh_3)_4$	**10**	76
3	Phenyl	EtNHBn	$Pd(acac)_2$/dppe	**11**	49
4	*p*-Cl(C_6H_4)	$BnNH_2$[b]	$Pd(PPh_3)_4$	**12**	69
5	*p*-Cl(C_6H_4)	Piperidine	$Pd(acac)_2$/dppe	**13**	72
6	*p*-Cl(C_6H_4)	Piperidine	$Pd(PPh_3)_4$	**14**	77
7	*p*-Cl(C_6H_4)	EtNHBn	$Pd(acac)_2$/dppe	**15**	67
8	*p*-Cl(C_6H_4)	**22**	$Pd(acac)_2$/dppe	**16**	49
9	3-Pyridyl	$BnNH_2$[b]	$Pd(PPh_3)_4$	**17**	30
10	3-Pyridyl	Piperidine	$Pd(acac)_2$/dppe	**18**	53
11	3-Pyridyl	EtNHBn	$Pd(acac)_2$/dppe	**19**	51
12	3-Pyridyl	**22**[c]	$Pd(acac)_2$/dppe	**20**	61
13	2-Furyl	**22**	$Pd(acac)_2$/dppe	**21**	Trace

[a] Isolated yield of purified product based on the loading of the phenoxy polystyrene (**4**).

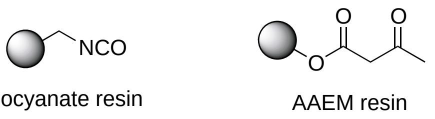
[b] 4 equivalents of benzylamine were used.

[c] 2 equivalents of **22** were used.



23 **24**

Figure 2. By-products obtained in Pd-catalysed cleavage reactions.



Isocyanate resin AAEM resin

Figure 3. Isocyanate and acetoacetoxy scavenger resins.

the elaboration of the resin-bound allylic ethers and cleavage in the presence of other nucleophiles.[23]

Acknowledgements

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References

1. Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293–3320.
2. Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195–214.
3. Seneci, P. *Solid-phase Synthesis and Combinatorial Technologies*; Wiley-Interscience, 2000.
4. Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385–15443.
5. Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 17–42.
6. Gordon, K.; Balasubramanian, S. *J. Chem. Technol. Biotechnol.* **1999**, *74*, 835–851.
7. Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.
8. James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946.
9. Eggenweiler, H. M. *Drug Discov. Today* **1998**, *3*, 552–560.
10. Brown, R. C. D.; Fisher, M. *Chem. Commun.* **1999**, 1547–1548.
11. Inoue, Y.; Taguchi, M.; Toyofuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3021–3022.
12. Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, 1980.
13. Bergbreiter, D. E.; Chen, B.; Lynch, T. J. *J. Org. Chem.* **1983**, *48*, 4179–4186.
14. Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864–866.
15. Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935–939.
16. **Typical procedure for Mitsunobu coupling**. THF (25 mL) was added to a mixture of phenoxypolystyrene resin (**4**) (2.04 g, 3.06 mmol), triphenylphosphine (5.24 g, 20.0 mmol) and allylic alcohol **8b** (3.36 g, 20.0 mmol) under an inert atmosphere. The suspension was cooled to 0°C and stirred for 10 min. DEAD (3.2 mL, 3.48 g, 20.0 mmol) was added dropwise and the reaction was allowed to warm to rt, and the resulting orange suspension was stirred at rt for 12 h. The resin was collected by filtration, washed with CH_2Cl_2, DMF, MeOH, DMF and CH_2Cl_2 (100 mL each) and dried under vacuum (0.7 mmHg, 50°C) for 2 h. This afforded the product **3b** as a beige solid (2.62 g).
17. Frechet, J. M.; Nuyens, L. *Can. J. Chem.* **1976**, *54*, 926–934.
18. Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863–8874.
19. **Typical procedure for palladium-catalysed nucleophilic cleavage**. THF (3 mL) was added to a mixture of resin **3b** (149.6 mg, 0.19 mmol), $Pd(acac)_2$ (2.8 mg, 9.3 μmol), dppe (7.4 mg, 18.6 μmol) and piperidine (15.8 mg, 0.19 mmol) under an inert atmosphere. The reaction was heated at reflux with gentle stirring for 1.5 h. After cooling to rt, the resin was collected by filtration, washed

with CH_2Cl_2 (50 mL) and the filtrate concentrated under vacuum to give the crude product as an orange oil (45 mg). Purification by column chromatography (6×1.5 cm SiO_2) eluting with CH_2Cl_2/MeOH (19:1) afforded the allylic amine **13** as a colourless oil (31.5 mg, 0.13 mmol, 72%). ^1H NMR (400 MHz, $CDCl_3$): 7.29 (2H, d, $J=8.5$ Hz), 7.27 (2H, d, $J=8.5$ Hz), 6.46 (1H, d, $J=15.6$ Hz), 6.29 (1H, dt, $J=15.6$, 7.0 Hz), 3.13 (2H, dd, $J=6.5$, 1.5 Hz), 2.45 (4H, br s), 1.65–1.60 (4H, m) and 1.46 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): 135.67, 133.16, 131.73, 128.85, 127.88, 127.66, 61.87, 54.77, 26.04 and 24.41; LRMS (EI) m/z (rel. intensity): 235.9 (100), 238.0 (29).

20. Iwasaki, M.; Kobayashi, Y.; Li, J.-P.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *J. Org. Chem.* **1991**, *56*, 1922–1927.
21. For the preparation and use of isocyanate resin, see: Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882–4886.
22. Yu, Z.; Alesso, S.; Pears, D.; Worthington, P. A.; Luke, R. W. A.; Bradley, M. *Tetrahedron Lett.* **2000**, *41*, 8963–8967.
23. For related studies on the palladium-catalysed cleavage of resin-bound allyl sulfones with C-nucleophiles, see: Cheng, W. C.; Halm, C.; Evarts, J. B.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1999**, *64*, 8557–8562.