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A solid-phase version of the palladium-catalyzed carbonyl allylation by allylic alcohols with $SnCl_2$

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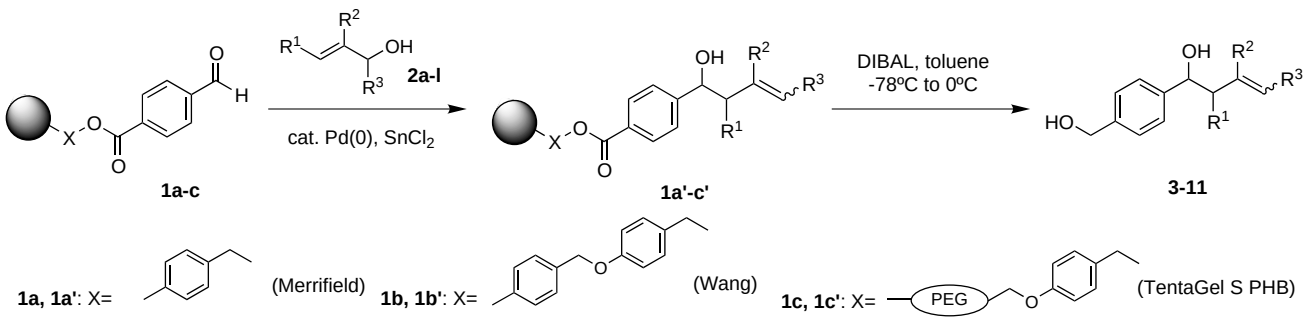
Abstract—A solid-phase version of the palladium-catalyzed carbonyl allylation of aldehydes by allylic alcohols is described. Preliminary studies have been carried out with resin bound aldehydes **1a**–**c** and different allylic alcohols. Solvent effects as well as the regio- and diastereoselectivity of our solid-phase conditions are compared with solution-phase protocols.

The allylation of aldehydes to give homoallylic alcohols is a well-precedented synthetic transformation.[1] Carbonyl allylation via an umpolung of π-allylpalladium complexes has been extensively studied over recent years.[2] In particular, palladium-catalyzed carbonyl allylation by allylic alcohols with $SnCl_2$[3] is especially attractive for combinatorial chemistry due to the wide range of commercially available allylic alcohols and aldehydes as well as for synthetic versatility of the resulting adducts. In this context, we wish to report our results on the palladium-catalyzed allylation of resin-bound aldehydes **1a**–**c**[4] by allylic alcohols **2a**–**l** with $SnCl_2$ to give homoallylic alcohols **3**–**11** after reductive cleavage from the resin (Scheme 1).

Preliminary experiments were carried out from allyl alcohol (**2a**) and resin-bound aldehydes **1a**–**c** at room temperature for 24 h under non-inert conditions (Table 1). Condensations on the solid support were monitored by IR and were judged to be complete after disappearance of the aldehyde C–H stretching band at 2385 cm^{-1}. After a thorough study of some of the reaction parameters (solvent, temperature and stoichiometry of allyl alcohol, palladium catalyst, $SnCl_2$ and H_2O), the best conditions were those indicated in entry 7. Addition of H_2O had no significant effects (compare entries 7 and 8), whereas an increase of the reaction temperature was detrimental (entries 4 and 5). Shorter reaction times (5 h) proved equally effective under these optimized conditions.[5] Homoallylic alcohol **3** was also obtained from the more expensive resin **1b** in 89% yield (entry 10) and from resin **1c** in less than 50% yield (entry 11). In the light of these results, resin **1a** was chosen for further reaction development.



Scheme 1.

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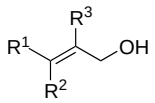
Table 1. Condensation-cleavage of **2a** with resin-bound aldehydes **1a–c** to give **3**[a]

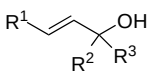
Entry	Resin	$SnCl_2$ (equiv.)[b]	$PdCl_2(PhCN)_2$ (equiv.)[b]	Alcohol (equiv.)[b]	H_2O (equiv.)[b]	Solvent	Yield[c] (%)
1	**1a**	6	0.04	3	0	DMF	23
2	**1a**	6	0.04	3	0	THF	38
3	**1a**	6	0.04	3	0	THF	38
4	**1a**	6	0.04	3	0	THF	25[d]
5	**1a**	6	0.04	3	0	THF	13[e]
6	**1a**	9	0.04	3	0	THF	45
7	**1a**	**21**	**0.06**	**7**	**0**	**THF**	**78**
8	**1a**	21	0.06	7	100	THF	75
9	**1a**	21	0.06	7	0	DMSO	61
10	**1b**	21	0.06	7	0	THF	89
11	**1c**	21	0.06	7	0	THF	41

[a] Reactions were carried out at room temperature unless otherwise mentioned.
[b] Number of equivalents relative to the resin.
[c] Isolated yield of **3** after cleavage from the resin.
[d] The reaction was carried out at 40°C.
[e] The reaction was carried out at 80°C.

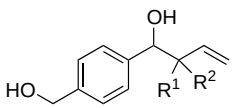
Table 2. Allylation–cleavage of resin-bound aldehyde **1a** with allylic alcohols (see Scheme 1)



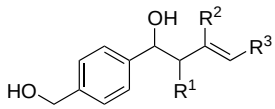
2a: $R^1=R^2=R^3=H$
2b: $R^1=CH_3$; $R^2=R^3=H$
2d: $R^1=Et$; $R^2=R^3=H$
2e: $R^1=R^2=H$; $R^3=CH_3$
2f: $R^1=R^2=CH_3$; $R^3=H$
2h: $R^1=Ph$; $R^2=R^3=H$
2j: $R^1=R^2=H$; $R^3=SO_2Ph$



2c: $R^1=R^2=H$; $R^3=CH_3$
2g: $R^1=H$; $R^2=R^3=CH_3$
2i: $R^1=R^2=H$; $R^3=Ph$
2k: $R_1=Ph$; $R_2=CH_3$; $R_3=H$
2l: $R_1=CH_3$; $R_2=Ph$; $R_3=H$



3: $R^1=R^2=H$;
4: $R^1=CH_3$; $R^2=H$
5: $R^1=Et$; $R^2=H$;
7: $R^1=R^2=CH_3$



6: $R^1=R^3=H$; $R^2=CH_3$
8: $R^1=Ph$; $R^2=H$
9: $R^1=R^3=H$; $R^2=SO_2Ph$
10: $R^1=Ph$; $R^3=CH_3$ (γ adduct)
11: $R^1=CH_3$; $R^3=Ph$ (α adduct)

Entry	Alcohol	Solvent/(H_2O)[a]	Product[b]	*syn*/*anti*[c]	Yield[d]
1	**2a**	THF/(0)	**3**	–	78
2	**2b**	THF/(0)	**4**	30:70	78
3	**2b**	THF/(25)	**4**	28:72	77
4	**2b**	THF/(75)	**4**	38:62	78
5	**2b**	DMSO/(0)	**4**	60:40	35
6	**2b**	DMSO/(200)	**4**	20:80	31
7	**2c**	THF/(0)	**4**	33:67	72
8	**2d**	THF/(0)	**5**	20:80	75
9	**2e**	THF/(0)	**6**	–	89
10	**2f**	THF/(0)	**7**	–	80
11	**2f**	THF/(25)	**7**	–	80
12	**2g**	THF/(0)	**7**	–	70
13	**2h**	THF/(0)	**8**	0:100	75
14	**2i**	THF/(0)	**8**	0:100	65
15	**2i**	DMSO/(200)	**8**	0:100	41
16	**2i**	DMSO/(0)	**8**	50:50	40
17	**2j**	THF/(0)	**9**	–	68
18	**2k**	THF/(0)	**10**/**11**[e]	40:60[f])	77
19	**2k**	THF/(200)	**10**/**11**[g]	35:65[f]	72
20	**2k**	DMSO/(0)	**10**/**11**[h]	60:40[f]	75
21	**2k**	DMSO/(200)	**10**	18:82	67
22	**2l**	THF/(200)	**10**/**11**[g]	35:65[f]	67
23	**2l**	DMSO/(0)	**10**/**11**[h]	65:35[f]	75
24	**2l**	DMSO/(200)	**10**	20:80	60

[a] Equivalents of H_2O relative to the resin.
[b] See Ref. 5.
[c] Determined by ^1H NMR.
[d] Isolated yield.
[e] Ratio **10**/**11**: 75/25.
[f] *syn*/*anti* ratio for compound **10**.
[g] Ratio **10**/**11**: 95/5.
[h] Ratio **10**/**11**: 80/20.

Cleavage with DIBAL in toluene at low temperature afforded homoallylic alcohol **3** in good overall yields (Table 2, entry 1).[6] This allylation–cleavage sequence was succesfully applied to a series of allylic alcohols **2a**–**l**[7] to give compounds **3**–**11**, as indicated in Table 1.

Our best results in solid phase are comparable in terms of yields and diastereoselectivities with those described in solution by Masuyama et al.[3] Thus, the predominance of *anti* adducts in THF, THF–H_2O and DMSO–H_2O and the reversal to *syn* adducts in DMSO (with no H_2O added) (entries 5, 16, 20 and 23) is consistent with a change from a 'six-membered cyclic' to an 'open-chain' transition state, as postulated for the same process in solution.[3] Similarly, equilibration of the transient π-allylpalladium intermediates seems to take place, as evidenced by the similar reaction outcome observed from some pairs of isomeric alcohols under identical reaction conditions (compare entries 2 with 7, 13 with 14 and 19 with 22). However, higher regiocontrol on the allylation of terminally substituted π-allylpalladium species arising from allylic alcohols **2b**–**d**, **2f**–**i** and **2k**,**l** is observed on solid support in comparison with solution protocols.[3a] Thus, γ adducts are the only (**4**, **5**, **7**, **8**) or the major (**10**) adducts found under our solid-phase conditions (see Table 1).[8]

In summary, a new and efficient protocol for the allylation of resin-bound aldehydes with allylic alcohols under mild conditions is reported. Further work to widen the scope of this process to other aldehydes and linkers is currently underway and will be reported in due course.

Acknowledgements

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3. (a) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577–2586; (b) Masuyama, Y. In *Advances in Metal Organic Chemistry*; Liebeskind, L., Ed.; Jai Press: Greenwich, 1994; Vol. 3, pp. 255–303.
4. Resins **1a**–**c** were prepared from commercially available Merrifield, Wang or Tentagel S PHB resins, respectively (Rapp Polymer), and 4-carboxybenzaldehyde. Resin **1a** was prepared as described in: Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999–15016. Resin **1b**: Wang resin (Rapp polymer, 0.98 mmol/g, 4 g) was suspended in CH_2Cl_2/DMF (9:1, 60 mL). In a separate flask 1-hydroxybenzotriazole (HOBt) (1.6 g, 12 mmol) was added to a solution of 4-carboxybenzaldehyde (1.80 g, 12 mmol) and dissolved in the minimum amount of DMF (2 mL). The mixture was stirred until all the HOBt was dissolved and then added to the resin. *N*,*N*′-Diisopropylcarbodiimide (1.5 g, 12 mmol) and 4-dimethylaminopyridine (58 mg, 0.48 mmol) were added to the resin and the mixture was agitated for 3 h at room temperature. Acetic anhydride (1 mL, 9.6 mmol) and pyridine (0.85 mL, 9.6 mmol) were added to the reaction flask and agitated for additional 30 min at room temperature. After filtration, the resin was washed thoroughly (DMF, DMF/H_2O (1:1), MeOH/H_2O (1:1), MeOH and THF) and dried under vacuum to give **1b** (4.45 g, 0.85 mmol/g). Following the same procedure, Tentagel resin (5 g, 0.23 mmol/g) afforded resin **1c** (5 g, 0.21 mmol/g). For an alternative synthesis of **1b**, see: Sarshar, S.; Siev, D.; Mjalli, A. *Tetrahedron Lett.* **1996**, *37*, 835–838.
5. Typical procedure for allylation–cleavage of **1a**: Resin **1a** (0.98 mmol/g, 200 mg) was suspended in THF (2 mL) and $SnCl_2$ (780 mg, 4.12 mmol), prop-2-en-1-ol (**2a**) (93×10^{-3} mL, 1.37 mmol) and $PdCl_2$(PhCN) (4.5 mg, 0.012 mmol) were added to the solution. The reaction was agitated for 5 h at room temperature and the resin was filtered, washed (THF, THF/H_2O (1:1), MeOH/H_2O (1:1), MeOH and toluene) and dried under vacuum to give the allylated resin **1a**′ ($R^1=R^2=R^3=H$, see Scheme 1, 208 mg, 0.94 mmol/g). To a suspension, this resin (210 mg) in toluene (2 mL) at −78°C under N_2, was added dropwise a solution of DIBAL (1 M in hexane, 1.2 mL) and the mixture was stirred for 6 h. The reaction was quenched with H_2O (2 mL) and filtered over a pad of Celite®. The resulting filtrate was evaporated to half volume and extracted with EtOAc (3×10 mL) and the combined organic extracts were dried over Na_2SO_4 and evaporated under vacuum. Purification by column chromatography (silica gel, hexane/EtOAc (8:2)) led to alcohol **3** as a colorless liquid (28 mg, 81% based on the theoretical loading of the allylated resin **1a**′); IR (film): 3373, 1642, 1512, 1218, 1040, 1009, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.32 (s, 4H, Ph); 5.68–5.89 (m, 1H, C*H*=CH_2); 5.10–5.19 (m, 2H, CH=CH_2); 4.72 (t, $J=9$, 1H, C*H*OH); 4.64 (s, 2H, CH_2OH); 2.45–2.52 (t, $J=10$, 2H, CH_2CHOH); 2.29 (br, 1H, OH), 2.1 (br, 1H, OH). ^{13}C NMR ($CDCl_3$): 143.3 (C, Ph); 140.2 (C, Ph); 134.4 (*C*H=CH_2); 127.1 (2×CH, Ph); 126 (2×CH, Ph); 118.4 (CH=*C*H_2); 73.1 (CHOH); 64.8 (CH_2OH); 43.7 (CH_2).
This protocol was also used for allylic alcohols **2b**–**l** to give alcohols **4**–**11** (Table 2). Selected spectroscopic data:
Compound **4** (mixture of *syn* and *anti* isomers): Colorless liquid. IR (film): 3375, 1639, 1512, 1220, 1043, 1007, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.32 (m, 4H, Ph); 5.65–5.88 (m, 1H, C*H*=CH_2); 4.92–5.23 (m, 2H, CH=CH_2); 4.66 (s, 2H, CH_2OH); 4.60 (d, $J=8.4$, 1H, C*H*OH *syn*); 4.35 (d, $J=11.4$, 1H, C*H*OH *anti*); 2.38–2.63 (m, 1H, C*H*CH_3); 2.19 (br, 1H, OH), 2.1 (br, 1H, OH); 1.0 (d, $J=10.2$, 3H, CH_3 *syn*); 0.85 (d, $J=10.2$, 3H, CH_3 *syn*).^{13}C NMR ($CDCl_3$): 142.7, 142.5, 141.2 and 140.2 (C, Ph); 139.8 and 138.7 (*C*H=CH_2); 127.8 (2×CH, Ph); 126.8 (2×CH, Ph); 115.3 and 116.5 (CH=*C*H_2); 76.9 and 75.9 (CHOH); 65.3 (CH_2OH); 46.5 (CH, *anti*); 44.9

(CH, *syn*); 16.8 (CH_3 *anti*); 14.2 (CH_3 *syn*).

Compound **5** (mixture of *syn* and *anti* isomers): Colorless liquid. IR (film): 3373, 1636, 1512, 1220, 1045, 1002, 753 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.26–7.32 (m, 4H, Ph); 5.39–5.74 (m, 1H, C*H*=CH_2); 4.96–5.30 (m, 2H, CH=CH_2); 4.67 (s, 2H, CH_2OH); 4.62 (d, $J=9$, 1H, C*H*OH *syn*); 4.35 (d, $J=12$, 1H, C*H*OH *anti*); 2.11–2.43 (m, 1H, C*H*CH_2); 1.91 (br, 1H, OH), 1.68 (br, 1H, OH); 1.13–1.29 (m, 2H, CH_2); 0.75–0.89 (m, 3H, CH_3).

Compound **6**: Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.3–7.4 (m, 4H, Ph); 4.84–4.78 (m, 3H, C(CH_3)=CH_2 and C*H*OH); 4.67 (s, 2H, CH_2OH); 2.4 (d, $J=9$, 2H, CH_2); 2.10 (br, 1H, OH), 1.87 (br, 1H, OH); 1.8 (s, 3H,CH_3).

Compound **7**: Yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (s, 4H, Ph); 5.84–5.98 (dd, $J=26$, 16.2, 1H, C*H*=CH_2); 5.03–5.17 (m, 2H, CH=CH_2); 4.67 (s, 2H, CH_2OH); 4.43 (s, 1H, C*H*OH); 2.17 (br, 1H, OH), 1.85 (br, 1H, OH); 1.0 (s, 3H,CH_3); 0.95 (s, 3H, CH_3).^{13}C NMR ($CDCl_3$): 145 (*C*H=CH_2); 140.2 (C, Ph); 139.9 (C, Ph); 127.9 (2×CH, Ph); 126.2 (2×CH, Ph); 113.9 (CH=*C*H_2); 80.4 (CHOH); 65.1 (CH_2OH); 29.7 (C); 24.4 (CH_3); 20.9 (CH_3).

Compound **8** (*anti* isomer): Colorless liquid. IR (film): 3381, 1641, 1515, 1223, 1045, 1005, 753 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.07–7.32 (m, 9H, Ph); 6.15–6.38 (m, 1H, C*H*=CH_2); 5.17–5.35 (m, 2H, CH=CH_2); 4.85 (d, $J=12$, 1H, C*H*OH); 4.62 (s, 2H, CH_2OH); 3.50 (t, $J=12$, 1H, CHPh); 2.27 (br, 1H, OH), 1.95 (br, 1H, OH).

Compound **9**: Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.5–7.68 (m, 9H, Ph); 6.17 (s, 1H, CH= *trans* SO_2); 5.88 (s, 1H, CH= *cis* SO_2); 5.34 (m, 1H, C*H*OH); 4.60 (s, 2H, CH_2OH); 2.40 (d, $J=6.1$, 2H, CH_2); 2.20 (br, 1H, OH); 1.8 (br, 1H, OH).

Compound **10** (mixture of *syn* and *anti* isomers): Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.12–7.30 (m, 9H, Ph); 5.8–6.30 (m, 1H, C*H*=CH(CH_3)); 5.30–5.60 (m, 1H, CH=C*H*(CH_3)); 4.69 (d, $J=5$, 1H, C*H*OH *syn*); 4.66 (s, 2H, CH_2OH); 4.59 (d, $J=7$, 1H, C*H*OH *anti*); 3.4–4.0 (m, 1H, CHPh); 2.20 (br, 1H, OH), 1.7 (dd, $J=7.5$ and 2.1, 3H, CH_3); 1.6 (br, 1H, OH).

Compound **11** (mixture of *syn* and *anti* isomers): Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.17–7.44 (m, 9H, Ph); 6.35–6.55 (m, 1H, CH=); 6.10–5.20 (m, 1H, CH=); 4.71 (d, $J=4.5$, 1H, C*H*OH *syn*); 4.67 (s, 2H, CH_2OH); 4.52 (d, $J=7$, 1H, C*H*OH *anti*); 2.65–2.78 (m, 1H, C*H*CH_3); 2.15 (br, 1H, OH); 1.6 (br, 1H, OH); 0.95–1.12 (m, 3H, CH_3).

6. Optimum cleavage conditions of the ester linker of resins **1a–c** and **1a′–c′** were necessary in order to evaluate the resin loading as well as the yield on homoallylic alcohols **3–11**. Attempts to cleave resin–aldehyde **1a** in anhydrous MeOH–THF generated a mixture of the corresponding ester and acid, whereas cleavage with NaOH in dioxane led to decomposition. The ester linkage was conveniently reduced with DIBAL in toluene, as described in Ref. 5. Thus, resin **1a** afforded 4-hydroxymethylbenzaldehyde in good yield (95% based on the theoretical loading of resin).
7. Allylic alcohols **2a–2i** were commercially available. Allylic alcohol **2j** was synthesized following a described procedure (Carpino, L. A.; Philbin, M. *J. Org. Chem.* **1999**, *64*, 4315–4323); alcohol **2k** was obtained by DIBAL reduction of commercially available benzylideneacetone as described in: Kim, S.; Ahn, H. *J. Org. Chem.* **1984**, *49*, 1717–1724. Alcohol **2l** was synthesized following a described procedure (Brown, C. D.; Chong, J. M.; Shen, L. *Tetrahedron* **1999**, *55*, 14233–14242).
8. The presence of H_2O has been described as being crucial for the regiochemical outcome of the allylation of benzaldehyde with **2b** in THF. Ratios *syn*/*anti*/α: 22/25/53 (THF); 17/83/0 (THF–H_2O, 25 mmol) (see Ref. 3a).