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The Heck reaction of polymer-supported allylamine with aryl iodides

Tuomo Leikoski [a,*], Pauli Wrigstedt [a], Jussi Helminen [a], Jorma Matikainen [a], Jussi Sipilä [a], Jari Yli-Kauhaluoma [b]

[a] Department of Chemistry, Laboratory of Organic Chemistry, PO Box 55 (A. I. Virtasen aukio 1), University of Helsinki, FI-00014 Helsinki, Finland
[b] Faculty of Pharmacy, Division of Pharmaceutical Chemistry, PO Box 56 (Viikinkaari 5 E), University of Helsinki, FI-00014 Helsinki, Finland

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ABSTRACT

The Heck reaction of Wang resin-bound allylamine with aryl iodides produces various, substituted cinnamylamines. The catalyst and additive system consisting of palladium(II) acetate, *n*-Bu_4NOAc and potassium chloride, in addition to potassium carbonate in *N*,*N*-dimethylformamide, accomplishes a regioselective γ-arylation. By utilising the easily formed and stable carbamate linker on Wang resin, the incompatibility of free amines with the palladium catalyst is avoided. The cinnamylamine products are cleaved from the resin with trifluoroacetic acid under mild conditions and are converted into chromatographically separable acetamides. Our solid-phase method offers a new alternative for the synthesis of cinnamylamine derivatives, as biologically interesting compounds and useful synthetic intermediates.

1. Introduction

Arylated allylamines, such as cinnamylamines, are important synthetic intermediates and key structural units in many biologically active compounds. Conn and co-workers discovered a modified cinnamylamine that acts as an inhibitor of bovine plasma semicarbazide-sensitive amine oxidase.[1] Lermer and co-workers studied the use of synthetic oligonucleotides in the catalytic cleavage of RNA, where uracil was substituted in its 5-position, with the γ carbon atom of allylamine.[2] Robin and Rousseau used arylated allylamines as precursors in 4-*endo trig* cyclisations to form azetidines.[3]

The Heck reaction is a powerful and modern palladium-catalysed method for generation of carbon–carbon bonds between unsaturated entities, and it has been extensively utilised in arylation and vinylation of olefins.[4–7] Though widely studied since its independent introduction by Heck and Mizoroki, in the early 70's,[8,9] there are no straightforward rules to assess reaction conditions for a particular type of coupling reaction. As a result, finding satisfactory conditions for an individual reaction typically requires thorough screening and optimisation. For example, in terms of general reactivity and regioselectivity, the use of electron-rich alkenes as substrates has been shown to be particularly challenging and allylamine derivatives are representative examples of such compounds.[10–22] In addition, an extra concern in the preparation of such compounds, by Heck coupling, is caused by the strong interaction between amine nitrogens and palladium atoms.[10,11,18,23,24] As such, in most trials amines have to be protected as less coordinating derivatives.

Compared to the vast amount of research conducted on the Heck reaction, the number of publications about its solid-phase version are relatively limited. There are however examples where either the olefin or the halide component has been attached to a polymeric support.[25–35] In addition, solid-phase methods have been utilised in intramolecular Heck reactions.[36–42] Even the palladium catalyst complexes have been bound covalently to polystyrene, while keeping all the other reactants in solution.[43,44] Frei and Blackwell attached the olefinic component covalently to cellulose, with the help of a Rink-amide linker, to produce stilbenes, which were cleaved from cellulose with trifluoroacetic acid (TFA) vapour.[45] Kopylovich and co-workers absorbed reaction mixtures onto silica gel and performed microwave-assisted Heck reactions in the absence of solvent.[46]

The incompatibility of free amines with palladium catalysis was established in the early years of the Heck reaction. As an example, the unsubstituted allylamine yielded only mixtures of unidentified products, instead of the desired aryl amine.[13,18,21,22] However, some exceptions exist. A very typical example is the intramolecular Heck reaction of *N*-allyl-*o*-haloaniline derivatives, which has been utilised

* Corresponding author. Tel.: +358 50 554 3682; fax: +358 9 191 50366; e-mail address: tuomo.leikoski@helsinki.fi (T. Leikoski).

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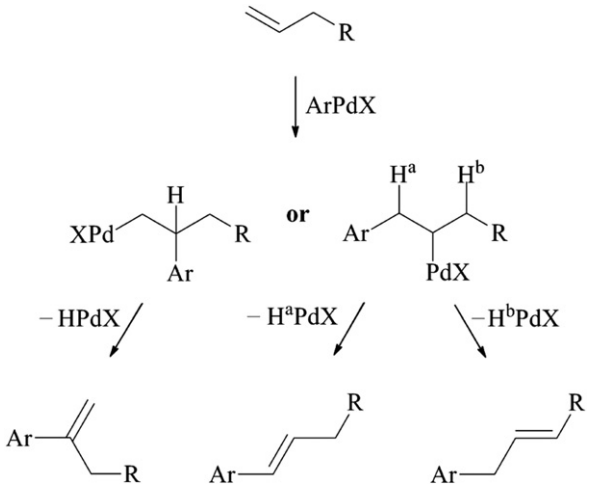
in syntheses of indoles.[24,47] The suitability of anilines, as reactants, is obviously associated with conjugation of the lone pair on the nitrogen with the aromatic π-electron system, whereas the effective reactions observed with some tertiary allylamines[15,17,19] might be explained by steric hindrance on the nitrogen atom. A general strategy in the Heck reactions of allylamine derivatives is protection of the amino group, for example, as phthalimides,[11,18,21,22] trifluoroacetamides[11,13,14] or carbamates,[10–13,16,18,20,21] which simultaneously renders the olefin less electron-rich and therefore more reactive. Noteworthy successful reactions have been performed with *N*,*N*-diprotected allylamines containing a carbamate moiety.[10–13,16,20,21] Very recently Jiang and co-workers utilised *N*,*N*-(*t*-BOC)$_2$-allylamine, as an efficient substrate in a regioselective and stereoselective reaction with various aryl bromides.[10]

An additional challenge with the Heck reaction of allylamine derivatives is regioselectivity. It is possible to obtain β as well as γ arylated allylamines, depending on the direction of migratory insertion, of the arylpalladium halide, into the C=C bond. There are examples in the literature where the Heck reaction of allylamine derivatives has been performed with excellent regioselectivity, in respect to either β[17–19] or γ[10–13] arylation. In the Heck reaction of three-carbon units in general, rearrangement of the double bond is possible as well, as there are hydrogen atoms in two distinct positions available in the organopalladium intermediate, during the β hydride elimination step.[12,48] Formation of regioisomers is shown as a simplified cascade of reactions, in Scheme 1.



Scheme 1. Regiochemistry in the Heck reaction of three-carbon units.

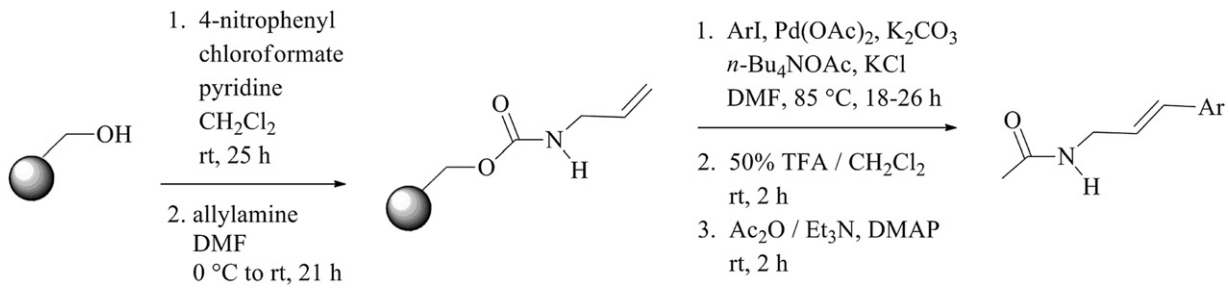
Based on our previous results on the Sonogashira coupling of polymer-bound propargylamine, with aryl iodides,[49] we decided to study whether cinnamylamines could similarly be synthesised, by the Heck reaction of polymer-bound allylamine. In addition to developing new methods for the synthesis of this interesting group of compounds, we also wanted to synthesise intermediates that could be hydrogenated to the corresponding 1,3-arylaminopropanes.

We attached allylamine, like propargylamine in our Sonogashira studies,[49] through a carbamate linker onto the polymeric support. This polymer-supported amine is easily prepared by a two-step procedure, starting from the commercially available Wang resin via the 4-nitrophenyl carbonate resin intermediate (Scheme 2). Previously, the carbamate method has been used successfully in the syntheses of low molecular-mass compounds, such as 1,2,3-triazoles,[50] and in the solid-phase synthesis of oligomeric peptides.[51] In addition to the easy attachment, with the simultaneous protection of amines and to the stability of the linker in neutral and basic conditions, this method enables fast and quantitative cleavage of the amine product, with 50% trifluoroacetic acid in dichloromethane. Herein, we report our results on the Heck reaction of Wang resin-bound allylamine with aryl iodides, the cleavage and isolation of the cinnamylamine products, and their purification as chromatographically separable acetamides.

2. Results and discussion

Finding satisfactory Heck conditions, for our test reaction system with Wang resin-bound allylamine and iodobenzene, was much more difficult than originally anticipated. We tested palladium acetate, $Pd_2(dba)_3$ and Herrmann's palladacycle,[52–54] as catalysts and triethylamine, sodium acetate, caesium acetate, potassium carbonate, sodium hydrogen carbonate, caesium carbonate, pyrrolidine and 1,1,3,3-tetramethylguanidine, as bases. We performed experiments with or without tri-*o*-tolylphosphine, additives, e.g., potassium chloride and caesium chloride,[55] and ionic mediators, such as *n*-Bu_4NCl, *n*-Bu_4NBr and *n*-Bu_4NOAc. For solvents we tested *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide, *N*-methylpyrrolidone and even oxygen-free water, as co-solvent. The temperature range of our reactions was 50–130 °C.

In most of our experiments the yields were very low, or the cinnamylamine product was not formed at all. However, we applied successfully the solution phase method of Battistuzzi and co-workers, with palladium(II) acetate (5 mol %), potassium carbonate, *n*-Bu_4NOAc and potassium chloride in DMF.[48] The reaction of Wang resin-bound allylamine, with iodobenzene at 85 °C for 22 h, gave a 44% yield of *N*-cinnamylacetamide, after cleavage with 50% TFA in dichloromethane, liberation of the amine product from its TFA salt with triethylamine, acetylation with acetic anhydride, triethylamine and *N*,*N*-dimethylaminopyridine (DMAP) (Scheme 2) and purification by flash chromatography. This Heck procedure was originally developed to control the β hydride elimination of the organopalladium intermediate (see Scheme 1), in the synthesis of cinnamaldehydes from acrolein diethyl acetal and aryl halides.[48] Because allylamine is similarly a relatively electron-rich olefin, having two β hydrogens prone to elimination, the selectivity of the β hydride elimination for its part might well be responsible for the success of our reaction.



Scheme 2. Loading of allylamine to Wang resin, the Heck reaction, cleavage and acetylation.

We achieved almost as good a result when we replaced palladium(II) acetate with Herrmann's palladacycle catalyst, using the above-mentioned method. After the test reaction of iodobenzene with 1 mol % of the catalyst, a 40% yield of the product was obtained. Keeping in mind the high performance of this catalyst, even at ppm levels, its use in solid-phase Heck reactions might be worth more detailed studies. On the other hand, replacement of potassium carbonate or potassium chloride, with caesium carbonate or caesium chloride, respectively, decreased the yield significantly.

We noticed that the time and temperature window of our Heck procedure is relatively narrow. When the duration of the reaction at 85 °C was increased from 22 to 74 h, the yield decreased from 44 to 29%. The yield dropped below 5% when the three-day reaction was performed at 100 °C. The stoichiometry of the substrates is essential. A mixture of diarylated isomers dominated, besides the desired product, if iodobenzene was applied in excess into the reaction mixture. Therefore, we introduced only 1 M equivalent of the aryl iodide, with respect to polymer-bound allylamine, throughout the whole series of reactions.

Though there is some deviation in the yields of *N*-cinnamylacetamides (Table 1), no clear relationship between the structures of the aryl iodides and the yields can be stated. For example, all the three isomers of chloroiodobenzene gave reasonable yields but with 4′-iodoacetophenone and 4-iodobenzonitrile, significantly higher yields would have been expected. Interestingly, 2-iodothiophene and 4-iodonitrobenzene did not give even a trace of the coupling products, although the former has been used successfully in the Heck reaction,[56] and the latter was used in Battistuzzi's original procedure.[48] These unexpected features may be due to slow reaction rates of the polymer-supported allylamine. The arylpalladium iodide species is undoubtedly formed efficiently from each of these substrates, by oxidative addition of zero-valent palladium. However, these highly reactive intermediates can be consumed by fast, unwanted side reactions in solution, without reaching the polymer-bound allylamine.

Table 1
Yields of *N*-cinnamylacetamides obtained from various aryl iodides

Entry	Aryl group	Yield (%)[a]
1	Ph	44
2	4-Cl–C_6H_4	54
3	3-Cl–C_6H_4	49
4	2-Cl–C_6H_4	61[b]
5	4-CH_3CO–C_6H_4	35
6	Naphthalen-1-yl	39[b]
7	4-CN–C_6H_4	25
8	3-MeO–C_6H_4	23[b]
9	4-NO_2–C_6H_4	n.r.
10	Thiophen-2-yl	n.r.

[a] Based on an actual loading of 1.1 mmol/g of the commercial Wang resin.
[b] As an inseparable mixture of *E* and *Z* isomers with an approximate ratio of 4:1 as determined by ^{1}H NMR spectroscopy.

In the reactions with 2-chloroiodobenzene, 1-iodonaphthalene and 3-iodoanisole, an inseparable mixture of *E* and *Z* isomers, with an approximate ratio of 4:1 according to ^{1}H NMR spectroscopy, was obtained (See Experimental). The unusually high yield of the *Z* isomer, with respect to the *E* isomer, commonly obtained in the Heck reaction has been associated with additional steric hindrance.[56]

The reaction conditions we applied possess characteristics, which enhance their usability in solid-phase synthesis. DMF, as a polar aprotic solvent, swells the resin very effectively and simultaneously assists in the separation of various ionic species, thus increasing their solubilities. Suitable concentrations of halide (KCl) and acetate (*n*-Bu_4NOAc) ligands in the reaction medium are likely to increase the stability, reactivity and selectivity of the catalyst.[57–59] The stabilisation effect is very evident, as black metallic palladium precipitates, typical for Heck reactions with palladium(II) acetate, were not observed at all in most of our trials.

3. Conclusion

We have developed a new solid-phase synthesis method where the applicability of the Heck reaction, with its high performance and wide functional group tolerance, is combined with the benefits of solid-phase synthesis. The Heck reaction of allylamine, 30 °C above its boiling point, with aryl iodides is enabled, without the inhibiting effect of palladium-nitrogen coordination. The carbamate linker, conveniently formed on Wang resin, which is stable under the reaction conditions and rapidly cleaved, serves as a protective group for the amino functionality and renders the carbon–carbon double bond less electron-rich, and more reactive towards palladium coupling. Due to relatively few alternatives available for γ-arylation of allylamine, our solid-phase method offers new possibilities for the synthesis of biologically interesting cinnamylamine derivatives with diverse aryl substitution.

4. Experimental

4.1. General

Reagents were obtained from Aldrich, Fluka, Acros and Merck. Wang resin (polymer-bound 4-(benzyloxy)benzyl alcohol, loading 1.1 mmol/g; 100–200 mesh; cross-linked with 1% divinylbenzene) was commercially available from NovaBiochem. The yields are based on the actual loading of the commercial resin. DMF was dried by distillation from anhydrous $CaSO_4$ under reduced pressure. Triethylamine was dried by distillation from P_2O_5. Unless otherwise stated, commercial-grade reagents and solvents were used without further purification or drying. Merck aluminium sheets coated with silica gel 60 F_{254} were used for thin layer chromatography and they were visualised by UV light at 254 nm. Column chromatography was performed with Fluka silica gel 60; 230–400 mesh. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Varian Mercury 300 *Plus* spectrometer. Chemical shifts are relative to the residual solvent resonance of 7.26 ppm for $CDCl_3$, in the proton spectra, and to the resonance of 77.2 ppm for $CDCl_3$ or 29.8 ppm for acetone-d_6, in the carbon spectra. FT-IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer, equipped with a one reflection ATR unit. Melting points were obtained using an Electrothermal Melting Point Apparatus Cat. No. IA6301 and they are uncorrected. Normal and high resolution EI-MS analyses were performed with a Jeol JMS-700 mass spectrometer at 700 eV.

4.2. Loading of allylamine to Wang resin through a carbamate linker

Allylamine was attached to Wang resin according to the reported procedure,[50] suitable for primary and secondary amines with slight modifications. Wang resin, polymer-bound 4-benzyloxybenzyl alcohol, (loading 1.1 mmol/g) was swollen in CH_2Cl_2 (10 mL/g resin). Pyridine (1.8 mL/g resin) was added followed by 4-nitrophenyl chloroformate (5.1 equiv) in CH_2Cl_2 (10.7 mL/g). The mixture was stirred at room temperature for 25 h, filtered and washed with CH_2Cl_2 (5×6 mL/g resin). The resulting carbonate resin was swollen immediately with DMF (10 mL/g resin), and allylamine (10 equiv) was added at 0 °C. The mixture was stirred at room temperature for 21 h. After filtering, the resin was washed (2×6 mL/g resin) with each of DMF, MeOH, THF, diethyl ether and CH_2Cl_2, and dried in vacuo. IR (C=O, cm^{-1}): 1722.

4.3. General procedure for the Heck reaction of polymer-bound allylamine with aryl iodides in solution

Polymer-bound allylamine (0.80 g, 1.1 mmol/g), aryl iodide (1.0 equiv), palladium(II) acetate (0.05 equiv), *n*-Bu_4NOAc

(2.0 equiv), potassium chloride (1.0 equiv) and potassium carbonate (1.5 equiv), in dry DMF (5.0 mL), were stirred under argon at 85 °C for 18–26 h. After filtering, the resin was washed (2×10 mL) with each of DMF, MeOH, THF, diethyl ether and CH_2Cl_2, and subjected to the cleavage step.

4.4. General procedure for the cleavage and acetylation of the coupling product

The polymer-bound coupling product was stirred in TFA/CH_2Cl_2 (1:1 v/v, 5 mL) at room temperature for 2 h. After filtering, the resin was washed successively with CH_2Cl_2 and methanol. The filtrate was evaporated with toluene (10 mL) under reduced pressure to give the crude product, which was dissolved in triethylamine (2 mL) and acetic anhydride (1 mL). A catalytic amount of DMAP was added and the mixture was stirred at room temperature for 2 h. The solvents were evaporated twice with ethanol (10 mL), under reduced pressure, to give the crude acetylated product, which was subjected to SiO_2 column chromatography.

4.5. Syntheses of *N*-cinnamylacetamides 1–8

*4.5.1. N-Cinnamylacetamide (**1**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with iodobenzene (183 mg, 0.897 mmol), palladium(II) acetate (12.7 mg, 0.0566 mmol), *n*-Bu_4NOAc (552 mg, 1.83 mmol), potassium chloride (70.0 mg, 0.939 mmol) and potassium carbonate (207 mg, 1.50 mmol) for 22 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column chromatography on SiO_2 (EtOAc to acetone/EtOAc 1:3) gave the known[60] compound **1** (69.8 mg, 44%). Colourless crystals (EtOAc), mp 80–82 °C (mp lit.[60] 88–90 °C). R_f (acetone/EtOAc 1:4) 0.32. IR (cm^{-1}): 692, 750, 963, 1557, 1641, 3283. ^1H NMR ($CDCl_3$): 2.01 (s, 3H); 4.00 (dt, *J*=1.2, 6.2, 2H); 5.89 (br s, 1H); 6.17 (td, *J*=6.2, 15.9, 1H); 6.50 (d, *J*=15.9, 1H); 7.18–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): 23.4, 41.8, 125.7, 126.4, 127.8, 128.7, 132.2, 136.6, 170.1. MS (*m*/*z*): 175, 132, 116, 115, 84, 44 (100%). ^1H NMR data are in accordance with those reported in the literature.[61]

*4.5.2. (E)-N-[3-(4-Chlorophenyl)allyl]acetamide (**2**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with 4-iodochlorobenzene (214 mg, 0.897 mmol), palladium(II) acetate (9.8 mg, 0.044 mmol), *n*-Bu_4NOAc (531 mg, 1.76 mmol), potassium chloride (72.6 mg, 0.974 mmol) and potassium carbonate (196 mg, 1.40 mmol) for 21 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column chromatography on SiO_2 (acetone/EtOAc 1:6 to 1:5) gave the product **2** (100 mg, 54%). Colourless crystals (EtOAc), mp 94–97 °C. R_f (acetone/EtOAc 1:4) 0.29. IR (cm^{-1}): 719, 1091, 1538, 1627, 3288. ^1H NMR ($CDCl_3$): 2.02 (s, 3H); 4.01 (dt, *J*=1.5, 6.0, 2H); 5.77 (br s, 1H); 6.15 (td, *J*=6.0, 15.9, 1H); 6.45 (td, *J*=1.5, 15.9, 1H), 7.23–7.34 (m, 4H). ^{13}C NMR ($CDCl_3$): 23.4, 41.7, 126.4, 127.7, 128.9, 131.0, 133.5, 135.1, 170.1. HRMS [$M^{+\cdot}$]; calcd for $C_{11}H_{12}{}^{35}ClNO$: 209.0609; found: 209.0600.

*4.5.3. (E)-N-[3-(3-Chlorophenyl)allyl]acetamide (**3**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with 3-iodochlorobenzene (217 mg, 0.910 mmol), palladium(II) acetate (15.7 mg, 0.0699 mmol), *n*-Bu_4NOAc (533 mg, 1.77 mmol), potassium chloride (80.8 mg, 1.08 mg) and potassium carbonate (207 mg, 1.50 mmol) for 19 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column chromatography on SiO_2 (acetone/EtOAc 1:7 to 1:4) gave the product **3** (89.9 mg, 49%). Colourless crystals (EtOAc), mp 72–74 °C. R_f (acetone/EtOAc 1:4) 0.31. IR (cm^{-1}): 684, 778, 964, 1557, 1633, 3285. ^1H NMR ($CDCl_3$): 2.02 (s, 3H); 4.01 (dt, *J*=1.3, 6.1, 2H); 5.78 (br s, 1H), 6.18 (td, *J*=6.1, 15.9, 1H); 6.44 (td, *J*=1.3, 15.9, 1H); 7.18–7.22 (m, 3H); 7.31–7.33 (m, 1H). ^{13}C NMR ($CDCl_3$): 23.4, 41.6, 124.7, 126.4, 127.4, 127.8, 129.9, 130.8, 134.7, 138.5, 170.1. HRMS [$M^{+\cdot}$]; calcd for $C_{11}H_{12}{}^{35}ClNO$: 209.0609; found: 209.0616.

*4.5.4. (E,Z)-N-[3-(2-Chlorophenyl)allyl]acetamide (**4**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with 2-iodochlorobenzene (224 mg, 0.939 mmol), palladium(II) acetate (10.2 mg, 0.0454 mmol), *n*-Bu_4NOAc (553 mg, 1.83 mmol), potassium chloride (76.6 mg, 1.03 mmol) and potassium carbonate (196 mg, 1.42 mmol) for 26 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column chromatography on SiO_2 (acetone/EtOAc 1:8) gave the product **4** (113 mg, 61%), as a mixture of *E* and *Z* isomers with an approximate ratio of 4.3:1.0 according to ^1H NMR spectroscopy. Yellow oil. R_f (acetone/EtOAc 1:4) 0.34. IR (cm^{-1}): 695, 752, 966, 1544, 1634, 3299. ^1H NMR ($CDCl_3$): 1.96 (s, 3H, *Z*); 2.02 (s, 3H, *E*); 4.02 (dt, *J*=1.6, 6.5, 2H, *Z*); 4.06 (dt, *J*=1.5, 6.2, 2H, *E*); 5.70 (br s, 1H, *Z*); 5.84 (br s, 1H, *E*); 5.78 (td, *J*=6.5, 11.5, 1H, *Z*); 6.18 (td, *J*=6.2, 15.8, 1H, *E*); 6.66 (td, *J*=1.6, 11.5, 1H, *Z*); 6.88 (td, *J*=1.5, 15.8, 1H, *E*); 7.08–7.52 (m, 4H, *E*, 4H, *Z*). ^{13}C NMR (acetone-d_6): 22.8 (*E*, *Z*), 38.1 (*Z*), 41.6 (*E*), 127.1, 127.8, 128.1, 129.6, 130.4, 131.2, 133.1, 135.8, 169.9 (*E*, *Z*). HRMS [$M^{+\cdot}$]; calcd for $C_{11}H_{12}{}^{35}ClNO$: 209.0609; found: 209.0605.

*4.5.5. (E)-N-[3-(4-Acetylphenyl)allyl]acetamide (**5**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with 4′-iodoacetophenone (222 mg, 0.902 mmol), palladium(II) acetate (11.4 mg, 0.0508 mmol), *n*-Bu_4NOAc (599 mg, 1.99 mmol), potassium chloride (72.5 mg, 0.972 mmol) and potassium carbonate (151 mg, 1.09 mmol) for 21 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column chromatography on SiO_2 (acetone/EtOAc 1:2 to 1:6) gave the product **5** (67.5 mg, 35%). Colourless crystals (EtOAc), mp 101–102 °C. R_f (acetone/EtOAc 1:4) 0.23. IR (*m*/*z*): 753, 962, 1267, 1360, 1551, 1628, 1678, 3292. ^1H NMR ($CDCl_3$): 2.03 (s, 3H); 2.57 (s, 3H); 4.05 (dt, *J*=1.5, 6.0, 2H); 5.86 (br s, 1H), 6.30 (td, *J*=6.0, 16.0, 1H); 6.53 (d, *J*=16.0, 1H); 7.39 (d, *J*=8.5, 2H); 7.87 (d, *J*=8.5, 2H). ^{13}C NMR (acetone-d_6): 22.9, 26.6, 41.7, 127.1, 129.5, 130.4, 131.0, 137.0, 142.5, 169.9, 197.3. HRMS [$M^{+\cdot}$]; calcd for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1111.

*4.5.6. (E,Z)-N-[3-(Naphthalen-1-yl)allyl]acetamide (**6**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with 1-iodonaphthalene (240 mg, 0.945 mmol), palladium(II) acetate (15.9 mg, 0.0708 mmol), *n*-Bu_4NOAc (549 mg, 1.82 mmol), potassium chloride (71.6 mg, 0.960 mmol) and potassium carbonate (203 mg, 1.47 mmol) for 22 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column chromatography on SiO_2 (acetone/EtOAc 1:8 to 1:6) gave the product **6** (76.8 mg, 39%), as a mixture of *E* and *Z* isomers with an approximate ratio of 3.3:1.0 according to ^1H NMR spectroscopy. Pale yellow wax. R_f (acetone/EtOAc 1:4) 0.31. IR (cm^{-1}): 729, 777, 1545, 1646, 3278. ^1H NMR ($CDCl_3$): 1.89 (s, 3H, *Z*); 2.03 (s, 3H, *E*); 3.98 (dt, *J*=1.7, 6.4, 2H, *Z*); 4.13 (dt, *J*=1.5, 6.2, 2H, *E*); 5.57 (br s, 1H, *Z*); 5.86 (br s, 1H, *E*); 5.94 (td, *J*=6.4, 11.3, 1H, *Z*); 6.19 (td, *J*=6.2, 15.7, 1H, *E*); 7.06 (d, *J*=11.3, 1H, *Z*); 7.26 (d, *J*=15.7, 1H, *E*); 7.39–8.12 (*m*, 7H, *E*, 7H, *Z*). ^{13}C NMR (acetone-d_6): 20.4 (*Z*), 22.2 (*E*), 37.6 (*Z*), 41.2 (*E*), 123.8, 123.9, 125.9, 126.0, 126.2, 127.9, 128.7, 130.4, 131.1, 131.4, 134.0, 134.9, 169.2 (*E*, *Z*). HRMS [$M^{+\cdot}$]; calcd for $C_{15}H_{15}NO$: 225.1154; found: 225.1155.

*4.5.7. (E)-N-[3-(4-Cyanophenyl)allyl]acetamide (**7**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with 4-iodobenzonitrile (205 mg, 0.895 mmol), palladium(II) acetate (14.3 mg, 0.0637 mmol), *n*-Bu_4NOAc (576 mg, 1.91 mmol), potassium chloride (68.5 mg, 0.919 mmol) and potassium carbonate (187 mg, 1.35 mmol) for 22 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column

chromatography on SiO_2 (acetone-EtOAc 1:4 to 1:2) gave the product **7** (43.7 mg, 25%). Colourless crystals (EtOAc), mp 129–131 °C. R_f (acetone-EtOAc 1:4) 0.23. IR (cm^{-1}): 727, 801, 971, 1534, 1628, 2221, 3286. ^1H NMR ($CDCl_3$): 2.03 (s, 3H); 4.06 (dt, J=1.5, 6.0, 2H); 5.75 (br s, 1H), 6.32 (td, J=6.0, 16.0, 1H); 6.51 (d, J=16.0, 1H); 7.41 (d, J=8.2, 2H); 7.57 (d, J=8.2, 2H). ^{13}C NMR ($CDCl_3$): 23.4, 41.6, 111.1, 119.0, 127.0, 130.1, 130.3, 132.6, 141.2, 170.1. HRMS [$M^{+\cdot}$]; calcd for $C_{12}H_{12}N_2O$: 200.0950; found: 200.0944.

*4.5.8. (E,Z)-N-[3-(3-Methoxyphenyl)allyl]acetamide (**8**).* Polymer-bound allylamine (0.80 g, 1.1 mmol/g) was treated with 3-iodoanisole (221 mg, 0.944 mmol), palladium(II) acetate (10.3 mg, 0.0459 mmol), n-Bu_4NOAc (534 mg, 1.77 mmol), potassium chloride (67.0 mg, 0.899 mmol) and potassium carbonate (183 mg, 1.32 mmol) for 18 h, according to the general procedure. Cleavage and acetylation (general procedure) followed by column chromatography on SiO_2 (acetone/EtOAc 1:8 to 1:6) gave the product **8** (42.3 mg, 23%), as a mixture of *E* and *Z* isomers with an approximate ratio of 3.8:1.0 according to ^1H NMR spectroscopy. Pale yellow oil. R_f (acetone/EtOAc 1:4) 0.28. IR (cm^{-1}): 689, 774, 1038, 1156, 1194, 1264, 1545, 1647, 3283. ^1H NMR ($CDCl_3$): 1.95 (s, 3H, *Z*); 2.00 (s, 3H, *E*); 3.79 (s, 3H, *E*, 3H, *Z*); 3.89 (dt, J=1.2, 6.0, 2H, *Z*); 4.00 (dt, J=1.2, 6.2, 2H, *E*); 5.77 (br s, 1H, *Z*); 5.83 (br s, 1H, *E*); 5.93 (td, J=6.0, 15.7, 1H, *Z*); 6.16 (td, J=6.2, 15.7, 1H, *E*); 6.46 (d, J=15.7, 1H, *E*, 1H, *Z*); 6.73–7.28 (m, 4H, *E*, 4H, *Z*). ^{13}C NMR ($CDCl_3$): 23.2 (*Z*), 23.3 (*E*), 38.2 (*Z*), 41.7 (*E*), 55.3, 111.8, 113.5, 119.1, 126.0, 129.7, 132.2, 138.1, 159.9, 170.2 (*E*, *Z*). HRMS [$M^{+\cdot}$]; calcd for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1095.

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