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Heck Couplings of Non-Activated Alkenes

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Abstract: The Heck couplings of protected 2-aminobut-3-en-1-ols with cyclohexenyl triflate can be readily carried out using a "ligand-free" palladium catalyst, potassium carbonate and tetrabutylammonium triflate. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The Heck reaction is the palladium catalysed coupling of an alkene with an aryl or vinyl substrate containing a leaving group.[1] The overall mechanism for the Heck reaction is reasonably well understood, although the precise details can vary depending on the catalyst, substrate and temperature.[2] Tertiary phosphine ligands have traditionally been used to prolong the life of the catalyst.[3] The presence of these ligands can have a detrimental effect on the rate of individual steps in the coupling but are considered necessary to ensure catalyst stability. Since the coupling was first reported[1a] many modifications to the original conditions have been introduced, for example, Jeffrey[4] devised reaction conditions under which the stereochemistry of *Z* and *E*-vinyl halides could be retained during the Heck coupling with electron-deficient alkenes. These conditions made use of a carbonate base and a phase transfer reagent, such as tetrabutylammonium chloride, with a "ligand-free" palladium catalyst. The term "ligand-free" refers to a palladium catalyst which lacks tertiary phosphine ligands traditionally used in the original experimental protocol. As a result, the palladium catalyst is considerably more reactive and the coupling of electron-deficient alkenes, such as acrylates, can be performed at ambient temperature.[4a]

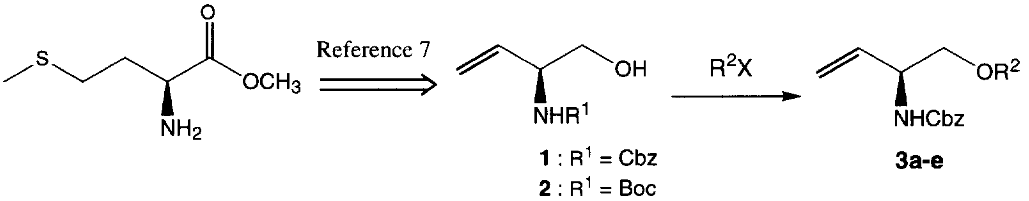
It has been well established that, under the traditional Heck coupling conditions, alkenes lacking a conjugated electron-withdrawing substituent do not couple as efficiently as their electron-deficient counterparts, and alternative protocols have been introduced to enhance the reactivity of the catalyst including Ag(I) and Tl(I) salts.[1g] We[5], and others[6] have reported previously on the Heck couplings of vinyl glycine derivatives with vinyl and aryl halides and triflates. We now wish to report modified reaction conditions for the Heck reaction, under which non-activated alkenes can readily be coupled with vinyl triflates.

RESULTS AND DISCUSSION

The Synthesis of vinyl precursors.

Based on a literature synthesis[7] methionine methyl esters could be reduced with $NaBH_4$ in MeOH and, without isolation, the intermediate sulfide could be oxidised to the sulfoxide by $NaIO_4$ in a "one-pot" procedure (**Scheme 1**). The crude sulfoxides were sufficiently clean to be subjected to thermal elimination of methyl sulfinic acid to form the desired alkenes, **1** and **2**, in modest yields with an optical purity similar to the compounds reported in the literature.[8]

In order to probe the compatibility of the Heck reaction with a variety of hydroxyl protecting groups differing in their electronic and steric properties, **1** was derivatised to compounds **3** (**Scheme 1**). Esters **3a** and **3c** were prepared in 74 - 78 % yield by reaction of **1** with the corresponding carboxylic acid anhydride or chloride in the presence of pyridine.[9] The trifluoroacetylation of alcohol **1** succeeded in the absence of any pyridine to give **3b** in a yield of 64%. Silyl ethers **3d** and **3e** were synthesised in 81% and 83 % yield by the reaction of alcohol **1** with the corresponding silyl chloride in the presence of triethylamine and a catalytic amount of *N*-hydroxybenzotriazole.[10]



a: $R^2 = C(O)CH_3$ $X = OC(O)CH_3$
b: $R^2 = C(O)CF_3$ $X = OC(O)CF_3$
c: $R^2 = C(O)CMe_3$ $X = Cl$
d: $R^2 = SiMe_2t$-hexyl $X = Cl$
e: $R^2 = SiPh_2Bu^t$ $X = Cl$

Scheme 1

Synthesis of 1,3-Dienes via Heck Olefinations.

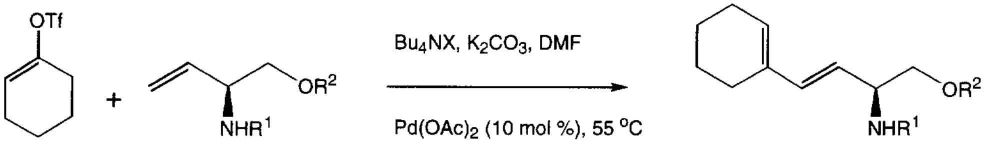
Compound **4a** had been prepared on a small scale (<0.10 g) previously, using the conditions outlined in **Scheme 2** where X = Cl.[5] When this reaction was repeated on a gram scale, the yields of **4a** were initially low, necessitating a tedious chromatographic separation of alkene **3a** and diene **4a**. After considerable experimentation it was discovered that the presence of water beneficially influenced the coupling reaction, which is supported by literature precedence.[11] Rigorous drying of the potassium carbonate or tetrabutylammonium chloride resulted in the slow conversion of alkene **3a** and premature deposition of catalytically inactive palladium metal. A good yield for diene **4a** of more than 70% was achieved repeatedly in experiments on a gram scale when a small amount of water (usually five equivalents with regard to the alkene) was added to the reaction mixture. When these conditions were used for the coupling of the sterically hindered alkene **3d** only a 47% conversion to **4d** was realized before catalyst decomposition occurred. The isolated yield of **4d** was even lower as repeated chromatography was necessary to separate unreacted **3d**. It therefore appeared that the alkene insertion was slow under these conditions and we reasoned that a more co-ordinatively unsaturated palladium intermediate should be able to achieve an increased rate of alkene insertion.

Consequently Bu_4NOTf was substituted for Bu_4NCl and all alkenes shown in **Scheme 2** were completely converted and the product dienes isolated in moderate to good yields (50-80%). The addition of water did not, under these conditions, influence the yield of the coupling reaction. Only a catalytic quantity of Bu_4NOTf (10 mole %) need be added for reasonable yields of the 1,3-diene (See experimental for **4f**).

As a sole exception, the trifluoroacetate protecting group was incompatible with the basic conditions of the Heck reaction since the reaction of **3b** with cyclohexenyl triflate gave the deprotected alcohol diene **4f** in 65% yield. Alkene **3b** could be deprotected within several hours by stirring in DMA with a stoichiometric amount of anhydrous potassium carbonate *at ambient temperature* to afford alcohol **1**.

In comparison to alkenes **3a-e** bearing a protected hydroxyl group, the deprotected aminobutenols **1** and **2** gave a lower yield of the Heck products **4f** and **4g** (**Scheme 2**). It is plausible that an intramolecular coordination of the palladium catalyst by the hydroxyl group and the carbon-carbon double bond may have led to the partial decomposition of alkenes **1** and **2** *via* a facile β-hydride elimination of a hydrogen from the carbon bearing the hydroxyl group.

All product dienes **4a-g** were optically active and it has been established previously that little or no racemisation of the stereogenic center of the substrates occurs during the course of the Heck reaction.[5]



1 or 2

4

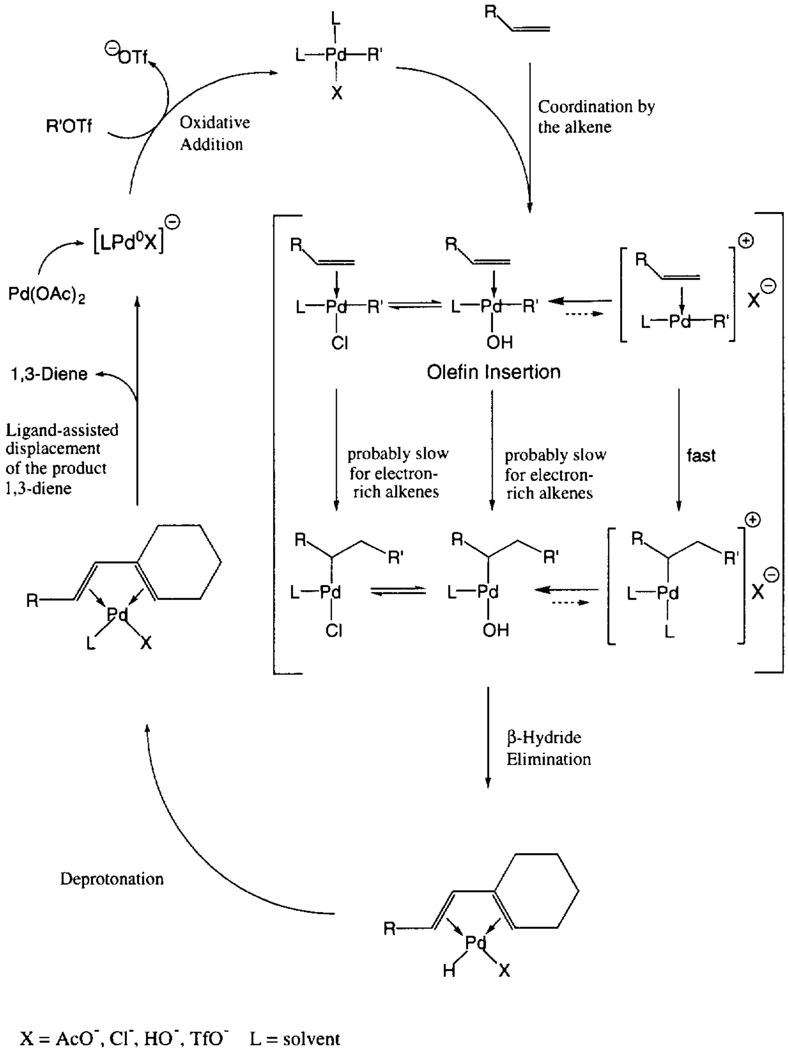
a:	R^1 = Cbz	R^2 = $C(O)CH_3$	80%
b:	R^1 = Cbz	R^2 = $C(O)CF_3$	-
c:	R^1 = Cbz	R^2 = $C(O)CMe_3$	81%
d:	R^1 = Cbz	R^2 = $SiMe_2$*t*-hexyl	83%
e:	R^1 = Cbz	R^2 = $SiPh_2Bu^t$	83%
f:	R^1 = Cbz	R^2 = H	53%
g:	R^1 = Boc	R^2 = H	52%

Scheme 2

DISCUSSION

The beneficial influence of water in Heck couplings can be explained in terms of a ligand effect. Under the conditions depicted in **Scheme 3** where X=Cl and no water is present, the catalytically active palladium species is ligated to chloride ions, whilst, in the presence of water, chloride ligands are temporarily displaced by hydroxide ions[12] formed from water and potassium carbonate. In comparison to a chloride ion a hydroxide ion is a weaker and kinetically more labile ligand for palladium[12] and this would give rise to a faster and more efficient Heck coupling. Why do halide ions appear to inhibit the Heck coupling of vinyl halides with alkenes lacking an activating electron-withdrawing substituent, since the coupling of acrylates and similar compounds proceeds satisfactorarily in the presence of halide ions[1]?

It has been demonstrated that the coordination of a chloride ion to a palladium(II) complex prevents the alkene insertion of an electron-rich alkene even under forcing conditions.[13] This sluggish alkene insertion has been rationalised by the repulsive interactions between a filled molecular orbital of the alkene and the *filled* 5s-orbitals of the neutral palladium(II) complexes which leads to a high energy barrier for the insertion reaction.[14] The high reactivity of cationic palladium(II) complexes to alkene insertion is documented with some complexes inserting into electron-rich alkenes at reaction temperatures as low as -40 °C.[15] A comparatively rapid alkene insertion can be rationalised by the lack of repulsive interactions between a filled molecular orbital of the alkene and the *empty* 5s-orbitals of the cationic palladium species.[14] To the best of our knowledge no reports about the reactivity of hydroxopalladium(II) species to alkene insertion have appeared in the literature.



X = AcO⁻, Cl⁻, HO⁻, TfO⁻ L = solvent

Scheme 3

The neutral hydroxopalladium complex may also be characterised by a lack of reactivity similar to its chloro analogue , since both complexes are expected to possess a filled 5s-orbital causing the repulsive interactions with a filled orbital on the electron-rich alkene during the transition state of the alkene insertion.[14] Given the case that chloro and hydroxo intermediates are of similar reactivity to alkene insertion the differences in reactivity are probably due to a cationic palladium species being formed more readily from the hydroxopalladium complex rather than from the chloropalladium(II) complex.[12] Consequently, in the presence of halide ions, the Heck reaction of non-activated alkenes is hampered due to the formation of a rather inert palladium complex, whilst under halide free conditions the alkene insertion is accelerated because of the comparatively facile dissociation of a hydroxide ion affording very reactive cationic palladium species. The high reactivity observed for the tetrabutylammonium triflate reactions is then attributed to the high rate of dissociation of the triflate anion from the neutral palladium(II) intermediate and formation of a very reactive cationic palladium species.

EXPERIMENTAL

General: Infrared spectra were obtained using a Jasco A102 or a Hitachi 270-30 infrared spectrophotometer, as a neat film or a nujol mull . ^{1}H NMR spectra and ^{13}C NMR spectra were recorded using an ACP 300 Fourier Transform NMR spectrometer. All NMR samples were prepared in deuterochloroform with tetramethylsilane as the internal standard. Electron impact mass spectra and accurate mass measurements were obtained using a AEI-GEC MS3074 mass spectrometer. The analytical TLC plates used were Merck Alufolien Kieselgel 60 PF_{254} and were visualized by UV light (254 nm), by staining with iodine vapour or by staining with phosphomolybdic acid followed by development with heat. Melting points were recorded using a Reichert hot stage melting point apparatus and are uncorrected. When dichloromethane was used as a reaction solvent it was freshly redistilled from phosphorous pentoxide. "Hexane" refers to the fraction of light petroleum boiling between 67 and 69 °C. The following compounds were synthesised according to the literature procedures: (*S*)-Methionine methyl ester hydrochloride,[16] (*S*)-*N*-benzoxycarbonyl methionine methyl ester,[16] cyclohexen-1-yl triflate[17].

(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]but-3-enyl acetate (3a)

To a solution of the alcohol **1**[7] (6.39 g, 28.9 mmol) in dichloromethane (50 ml) at 0 °C was added freshly distilled acetic anhydride (3.25 g, 31.8 mmol) and pyridine (2.56 g, 31.8 mmol) under a dry atmosphere. After stirring for 1 h the cooling bath was removed and the solvent evaporated. The crude material was chromatographed (1:3 ethyl acetate/hexane) and crystallised (ether/hexane) to afford **3a** (5.71 g, 75 %) as a white solid, m.p. 54-56 °C (lit.[7] 54-56 °C). Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.60; H, 6.52; N, 5.21. ^{1}H δ 7.36 (m, 5H, ar), 5.78 (ddd, *J* = 16 Hz, 10 Hz, 5 Hz, 1H, H3), 5.03 (s, 1H, NH), 5.28 (d, *J* = 16 Hz, 1H, $H4_{pro\text{-}Z}$), 5.23 (d, *J* = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.12 (m, 2H, $PhCH_2O$), 4.52 (m, 1H, H2), 4.13 (m, 2H, H1), 2.03 (s, 3H, CH_3). ^{13}C δ 170.5 (CO_2R), 155.6 (NC(O)O), 136.2, 134.3 (C4), 128.3, 128.0, 127.9, 116.7 (C3), 66.7 ($PhCH_2O$), 65.4 (C1), 52.1 (C2), 20.5 (CH_3). IR υ 3332, 1730, 1695, 1540, 1250 cm^{-1}. MS *m/z* 263 (M^+). $[\alpha]_D$ ($CHCl_3$, c = 0.94) -40.1° (lit.[7] -43.2°).

(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]but-3-enyl trifluoroacetate (3b)

To a solution of the alcohol **1**[7] (53.4 mg, 0.242 mmol) in dichloromethane (0.5 ml) at 0 °C was added dropwise from a syringe freshly distilled trifluoroacetic anhydride (56 mg, 0.266 mmol) under a dry atmosphere. After stirring for 1 h the cooling bath was removed and the solvent evaporated. The crude material was chromatographed on Florisil (ether, flowrate: 3.5 cm per min) and **3b** obtained (49 mg, 64 %) as a colourless clear oil. Anal. Calcd. for $C_{14}H_{14}NF_3O_4$: C, 53.00; H, 4.45; N, 4.41. Found: C, 52.84; H, 4.44; N, 4.74. ^{1}H δ 7.34 (m, 5H, ar), 5.73 (ddd, *J* = 17 Hz, 10 Hz, 6 Hz, 1H, H3), 5.33 (1H, NH), 5.29 (d, *J* = 17 Hz, 1H, $H4_{pro\text{-}Z}$), 5.24 (d, *J* = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.09 (m, 2H, $PhCH_2O$), 4.60 (m, 1H, H2), 4.34 (m, 2H, H1). ^{13}C δ 157.2 (q, $J_{C,F}$ = 45 Hz, CO_2R), 155.7 (NC(O)O), 136.2 , 132.8 (C4), 128.4, 128.2, 128.0, 118.0 (C3), 114.3 (q, $J_{C,F}$ = 286 Hz, CF_3), 67.0 ($PhCH_2O$), 68.3 (C1), 51.7 (C2). IR (neat) υ 3325 (NH), 1795, 1700, 1540, 1290, 1230, 1175 cm^{-1}. MS *m/z* 317 (M^+).

(2*S*)-2-[*N*-(Benzoxycarbonyl)amino]but-3-enyl 2',2'-dimethylpropanoate (3c)

To a solution of the alcohol **1**[7] (162 mg, 0.733 mmol), pyridine (80 mg, 1.010 mmol) and a small crystal of *N',N'*-dimethyl-4-aminopyridine in dichloromethane (1 ml) at 0 °C freshly distilled 2,2-dimethyl propanoyl chloride (122 mg, 1.010 mmol) was added dropwise from a syringe under a dry atmosphere. After stirring for 12 h dichloromethane (20 ml) was added, the organic phase washed with 1M HCl (5 ml) and the aqueous phase extracted with dichloromethane (7 ml). The combined organic phases were washed with sat. $NaHCO_3$ (5 ml) and water (5 ml), and dried ($MgSO_4$) and the solvent evaporated. The crude material was chromatographed (16:84 ethyl acetate/hexane) and **3c** obtained (166 mg, 74 %) as a colourless oil. Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.58; H, 7.69; N, 4.62. ^{1}H δ 7.34 (m, 5H, ar), 5.75 (ddd, *J* = 16 Hz, 10 Hz, 5 Hz, 1H, H3), 5.29 (1H, NH), 5.25 (d, *J* = 16 Hz, 1H, $H4_{pro\text{-}Z}$), 5.18 (d, *J* = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.08 (m, 2H, $PhCH_2O$), 4.52 (m, 1H, H2), 4.14 (dd, *J* = 10 Hz, 4 Hz, 1H, H1), 4.05 (dd, *J* = 10 Hz, 4 Hz, 1H, H1'), 1.17 (s, 9H, CH_3). ^{13}C δ 178.1 (CO), 155.6 (NC(O)O), 136.2, 134.3 (C4), 128.3, 128.1, 127.9, 116.6 (C3), 66.6 ($PhCH_2O$), 65.0 (C2), 52.3 (C2), 38.6, 26.9 (CH_3). IR (neat) υ 3350 (NH), 1730, 1700, 1695, 1540, 1290, 1240, 1160 cm^{-1}. MS *m/z* 305 (M^+). $[\alpha]_D$ ($CHCl_3$, c = 2.01) -40.8°.

(2*S*)-1-(dimethyl-1',1',2'-trimethylpropyl)siloxy-*N*-(benzoxycarbonyl)but-3-en-2-yl amine (3d)

To a solution of alcohol **1**[7] (999 mg, 4.52 mmol) in DMF (10 ml) were added dimethyl-1,1,2-trimethylpropyl silyl chloride (1.21 g, 6.78 mmol), triethylamine (686 mg, 6.78 mmol) and *N*-hydroxy benzotriazole (122 mg, 0.904 mmol) under an atmosphere of nitrogen. The mixture was stirred for 12 h and partitioned between ether (40 ml) and sat. NH_4Cl (15 ml). The aqueous layer was extracted with ether (20 ml) and the combined organic phases were washed with sat. NH_4Cl (3x15 ml), sat. $NaHCO_3$ (15 ml) and water (15 ml), and dried ($MgSO_4$) and the solvent evaporated. The crude material was chromatographed (12:88 ethyl acetate/hexane) and separated from contaminating dimethyl-1,1,2-trimethylpropyl silyl alcohol (b.p. 35-40 °C at 0.03 Torr) by distillation through a short-path distillation apparatus to yield **3d** (1.33 g, 81 %) as a clear and colourless oil, b.p. 110-125 °C (0.03 Torr). Anal. Calcd. for $C_{20}H_{33}NSiO_3$: C, 66.07; H, 9.15; N, 3.85. Found: C, 66.08; H, 9.31; N, 4.11. ^{1}H δ 7.34 (m, 5H, ar), 5.83 (ddd, *J* = 17 Hz, 10 Hz, 5 Hz, 1H, H3), 5.15 (1H, NH), 5.22 (d, *J* = 17 Hz, 1H, $H4_{pro\text{-}Z}$), 5.15 (d, *J* = 10 Hz, 1H, $H4_{pro\text{-}E}$), 5.11 (m, 2H, $PhCH_2O$), 4.25 (m, 1H, H2), 3.68 (dd, *J* = 10 Hz, 4 Hz, 1H, H1), 3.61 (dd, *J* = 10 Hz, 4 Hz, 1H, H1'), 1.60 (sep, *J* = 7 Hz, 1H, C**H**(CH_3)$_2$), 0.86 (d, 6H, *J* = 7 Hz, CH(C**H**$_3$)$_2$), 0.82 (s, 6H, SiC(C**H**$_3$)$_2$), 0.07 (s, 6H, Si(C**H**$_3$)$_2$). ^{13}C δ 155.8 (CO), 136.5, 136.2 (C4), 128.4, 128.0, 128.0, 115.8 (C3), 66.6 ($PhCH_2O$), 64.9 (C1), 54.6 (C2), 34.1, 25.0, 20.2, 20.1, 18.4, 18.4 (CH_3), -3.7, -3.7 ($Si(CH_3)_2$). IR (neat) υ 3340 (NH), 1720, 1545, 1515, 1270, 1125, 850, 795, 715 cm^{-1}. MS *m/z* 363 (M^+). $[\alpha]_D$ (CH_2Cl_2, c = 13.54) -37.2°.

(2*S*)-1-(Diphenyl*tert*-butyl)siloxy-*N*-(benzoxycarbonyl)but-3-en-2-yl amine (3e)

Alcohol **1**[7] (1.62 g, 7.32 mmol) was treated following the procedure for the synthesis of **3d** with diphenyl*tert*-butyl silyl chloride (3.02 g, 11.0 mmol). Contaminating diphenyl*tert*-butyl silyl alcohol was removed from crude product by distillation (oilbath temperature at 140 °C) through a short-path distillation apparatus, which was externally heated to 120 °C during the distillation, b.p. 90-100 °C (0.02 Torr). The oily residue was chromatographed (11:89 ethyl acetate/hexane) to yield **3e** (2.79 g, 83 %) as a colourless oil. Anal. Calcd. for $C_{28}H_{33}NSiO_3$: C, 73.16; H, 7.24; N, 3.05. Found: C, 73.32; H, 7.22; N, 2.90. ^1H δ 7.64-7.31 (m, 15H, ar), 5.84 (ddd, *J* = 17 Hz, *J* = 10 Hz, *J* = 5 Hz, 1H, H3), 5.08 (1H, NH), 5.23 (d, *J* = 17 Hz, 1H, H4$_{pro\text{-}Z}$), 5.18 (d, *J* = 10 Hz, 1H, H4$_{pro\text{-}E}$), 5.11 (m, 2H, $PhCH_2O$), 4.32 (m, 1H, H2), 3.76 (dd, *J* = 10 Hz, 4 Hz, 1H, H1), 3.65 (dd, *J* = 10 Hz, 4 Hz, 1H, H1'), 1.04 (s, 9H, C(CH_3)). ^{13}C δ 155.9 (CO), 136.5, 136.0, 135.6, 135.5 (C4), 133.1, 132.9, 129.8, 128.5, 128.1, 127.7, 116.0 (C3), 66.7 ($PhCH_2O$), 65.9 (C1), 54.7 (C2), 26.8, 19.3 (CH_3). IR (neat) υ 3330 (NH), 1720, 1535, 1505, 1220, 1110, 810, 740, 700 cm^{-1}. MS *m/z* 459 (M^+). $[\alpha]_D$ (CH_2Cl_2, c = 11.1) +24.8°.

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)but-3-en-1-yl acetate (4a)

A 100 ml Schlenk tube was charged with a magnetic stirring bar, freshly distilled DMF (50 ml), alkene **3a** (462 mg, 1.75 mmol), anhydrous potassium carbonate (581 mg, 4.20 mmol), water (126 mg, 7.00 mmol), tetrabutylammonium trifluoromethanesulfonate (686 mg, 1.75 mmol) and 1-cyclohexen-1-yl trifluoromethane sulfonate (595 mg, 2.59 mmol). Magnetic stirring was commenced and the atmosphere in the reaction vessel was replaced with nitrogen performing four evacuation/refilling cycles using a double vacuum/nitrogen manifold. Palladium(II) acetate (42 mg, 0.175 mmol) was introduced into the mixture by quickly removing the rubber septum from the Schlenk tube. Another three evacuation/ refilling cycles were performed as described before. After stirring the mixture at ambient temperature for 30 min it was heated to 55 °C overnight. A small aliquot of the dark brown reaction mixture was withdrawn and thoroughly mixed with twice its volume of 1M HCl and ether. The organic phase was analysed by a tlc (35:65 ethyl acetate/hexane). None of the starting alkene **3a** could be detected. A 20 cm long Vigereux column was fitted to the Schlenk tube and most of the solvent was distilled at a pressure of 1 Torr (oil bath at 40 °C). The residue was partitioned between ether (120 ml) and sat. NH_4Cl (40 ml). The separated aqueous layer was extracted with ether (70 ml) and the combined organic phases were washed with sat. NH_4Cl (2x40 ml), sat. $NaHCO_3$ (40 ml) and water (40 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The crude material was chromatographed (22:78 ethyl acetate/hexane) and **4a** was obtained (481 mg, 80 %) as a white solid. Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.00; H, 7.44; N, 4.13. Recrystallisation from ethyl acetate/hexane gave m.p. 66-67 °C. The nmr spectral data matched those reported in the literature.[5] ^1H δ 7.36 (m, 5H, ar), 6.22 (d, *J* = 16 Hz, 1H, H4), 5.76 (m, 1H, H2'), 5.41 (dd, *J* = 16 Hz, 6 Hz, 1H, H3), 5.12 (m, 2H, $PhCH_2O$), 5.01 (1H, NH), 4.53 (m, 1H, H2), 4.13 (m, 2H, H1), 2.00-2.20 (bm, 4 H, H3' and H6'), 2.03 (s, 3H, CH_3), 1.66-1.56 (bm, 4 H, H4' and H5'). ^{13}C δ 170.6 (CO_2R), 155.5 (NC(O)O), 136.2, 135.6 (C4), 136.3 (C1'), 130.5 (C2'), 128.2, 127.8, 127.8, 120.9 (C3), 66.6 (PhCH$_2$O), 65.8 (C1), 51.9 (C2), 25.6, 24.2 (C3' and C6'), 22.2, 22.1 (C4' and C5'), 20.5 (CH$_3$). MS *m/z* 343 (M$^+$). $[\alpha]_D$ (CHCl$_3$, c = 0.56) -7.3° (lit.[5] -7.5°).

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)but-3-en-1-yl trifluoroacetate (4b)

Method 1: Alkene **3b** (98 mg, 0.309 mmol) was treated following the procedure for the synthesis of **4a**. The reaction mixture turned black after 7 h and was worked up. Tlc analysis (1:1 ethyl acetate/hexane) of crude material showed that none of the starting alkene **3b** remained, but a spot with a retention time significantly lower than **3b** was detected. The crude product was chromatographed (1:1 ethyl acetate/hexane) and the *deprotected* diene **4f** (61 mg, 65 %) obtained as a solid, m.p. 102-105 °C. Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.72; H, 7.72; N, 4.61.

Method 2: Alcohol **4f** (65 mg, 0.216 mmol) was treated with freshly distilled trifluoroacetic anhydride (54 mg, 0.259 mmol) according to the method described for the synthesis of **3b**. The crude material was chromatographed on Florisil (ether, flowrate: 2.5 cm per min) and **4b** (57 mg, 66 %) obtained as a white solid, m.p. 77-79 °C. Anal. Calcd. for $C_{20}H_{23}NF_3O_4$: C, 60.30; H, 5.82; N, 3.52. Found: C, 60.29; H, 5.85; N, 3.48. ^{1}H δ 7.34 (m, 5H, ar), 6.24 (d, *J* = 16 Hz, 1H, H4), 5.78 (m, 1H, H2'), 5.38 (dd, *J* = 16 Hz, 6 Hz, 1H, H3), 5.10 (s, 2H, PhCH$_2$O), 5.10 (bd, *J* = 9 Hz, 1H, NH), 4.63 (m, 1H, H2), 4.39 (bs, 2H, H1), 2.04-2.12 (m, 4 H, H3' and H6'), 1.70-1.56 (m, 4 H, H4' and H5'). ^{13}C δ 157.3 (q, $J_{C,F}$ = 45 Hz, CO$_2$R), 155.6 (NC(O)O), 136.0, 137.1 (C4), 134.3 (C1'), 131.8 (C2'), 128.5, 128.2, 128.1, 119.1 (C3), 114.3 (q, $J_{C,F}$ = 286 Hz, CF$_3$), 67.1 (PhCH$_2$O), 69.0 (C1), 51.6 (C2), 25.8, 24.2 (C3' and C6'), 22.3, 22.2 (C4' and C5'). IR (neat) υ 3350 (NH), 1798, 1700, 1545, 1290, 1235, 1180 cm^{-1}. MS *m/z* 398 (M$^+$). $[\alpha]_D$ (CH$_2$Cl$_2$, c = 2.62) -4.2°.

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)but-3-en-1-yl 2',2'-dimethylpropanoate (4c)

Alkene **3c** (156 mg, 0.511 mmol) was treated following the procedure for the synthesis of **4a**. After heating for 24 h the dark brown reaction mixture was worked up. The crude product was chromatographed (14:86 ethyl acetate/hexane) and **4c** (160 mg, 81 %) obtained as a colourless clear oil. Anal. Calcd. for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.44; H, 8.11; N, 3.42. ^{1}H δ 7.35 (m, 5H, ar), 6.21 (d, *J* = 16 Hz, 1H, H4), 5.75 (m, 1H, H2'), 5.40 (dd, *J* = 16 Hz, 6 Hz, 1H, H3), 5.11 (m, 2H, PhCH$_2$O), 4.97 (1H, NH), 4.47-4.62 (bm, 1H, H2), 4.00-4.22 (m, 2H, H1), 2.0-2.20 (m, 4 H, H3' and H6'), 1.67-1.56 (m, 4 H, H4' and H5'), 1.16 (s, 9H, CH$_3$). ^{13}C δ 178.3 (CO$_2$R), 155.7 (NC(O)O), 136.4, 135.8 (C4), 134.6 (C1'), 130.7 (C2'), 128.5, 128.1, 128.1, 121.1 (C3), 66.8 (PhH$_2$O), 65.6 (C1), 52.4 (C2), 38.8, 27.1 (CH$_3$), 25.8, 24.4 (C3' and C6'), 22.4, 22.3 (C4' and C5'). IR (neat) υ 3350 (NH), 1730, 1705, 1545, 1295, 1245, 1165 cm^{-1}. MS *m/z* 385 (M$^+$). $[\alpha]_D$ (CH$_2$Cl$_2$, c = 2.12) 2.6°.

(2*S*,3*E*)-1-(Dimethyl-1',1',2'-trimethylpropyl)siloxy-*N*-(benzoxycarbonyl)-4-(1'-cyclo hexen-1'-yl)but-3-en-2-yl amine (4d)

Alkene **3d** (217 mg, 0.597 mmol) was treated following the procedure for the synthesis of **4a**. After heating for 40 h the brown reaction mixture was worked up. The crude product was chromatographed (8:92 ethyl acetate/hexane) and **4d** (220 mg, 83 %) obtained as a colourless clear oil. Anal. Calcd. for $C_{26}H_{41}NSiO_3$: C, 70.38; H, 9.31; N, 3.16. Found: C, 70.10; H, 9.40; N, 3.00. ^{1}H δ 7.36 (m, 5H, ar), 6.20 (d, *J* = 16 Hz, 1H, H4), 5.72 (m, 1H, H2'), 5.51 (dd, *J* = 16 Hz, 7 Hz, 1H, H3), 5.11 (m, 2H, PhCH$_2$O), 5.09 (1H, NH), 4.20-4.30 (m, 1H, H2), 3.69 (dd, *J* = 10 Hz, 4 Hz, 1H, H1), 3.59 (dd, *J* = 10 Hz, 4 Hz, 1H, H1'), 2.00-2.15 (m, 4 H, H3' and H6'), 1.50-1.70 (m, 5 H, H4', H5' and **CH**$(CH_3)_2$), 0.86 (d, 6H, *J* = 7 Hz, $CH(\mathbf{CH_3})_2$), 0.83 (s, 6H, $SiC(\mathbf{CH_3})_2$), 0.07 (s, 6H, $Si(\mathbf{CH_3})_2$). ^{13}C δ 155.8 (CO), 136.6, 134.9 (C4), 141.9 (C1'), 129.7 (C2'), 128.4, 128.0, 127.9, 123.1 (C3), 66.5 ($PhCH_2O$), 65.4 (C1), 54.4 (C2), 34.1, 25.7, 25.1, 24.3 (C3' and C6'), 22.4, 22.3 (C4' and C5'), 20.3, 20.2, 18.5, 18.4 (CH_3), -3.6 ($Si(CH_3)_2$). IR (neat) υ 3350 (NH), 2950, 1720, 1700, 1540, 1510, 1260, 1110, 840, 780, 700 cm^{-1}. MS *m/z* 443 (M^+). $[\alpha]_D$ (CH_2Cl_2, c = 2.45) -3.0°.

(2*S*,3*E*)-1-(Diphenyl*tert*-butyl)siloxy-*N*-(benzoxycarbonyl)-4-(1'-cyclo-hexen-1'-yl)but-3-en-2-yl amine (4e)

Alkene **3e** (203 mg, 0.442 mmol) was treated following the procedure for the synthesis of **4a**. After heating for 42 h the brown reaction mixture was worked up. The crude product was chromatographed (7.5:92.5 ethyl acetate/hexane) and **4e** (198 mg, 83 %) obtained as a white solid. Anal. Calcd. for $C_{34}H_{41}NSiO_3$: C, 75.65; H, 7.66; N, 2.60. Found: C, 75.79; H, 7.42; N, 2.55. This material was recrystallised from hexane, m.p. 95-96 °C. ^1H δ 7.64-7.31 (m, 15H, ar), 6.19 (d, *J* = 16 Hz, 1H, H4), 5.71 (m, 1H, H2'), 5.51 (dd, *J* = 16 Hz, 6 Hz, 1H, H3), 5.11 (m, 2H, $PhCH_2O$), 5.10 (1H, NH), 4.36 (m, 1H, H2), 3.77 (dd, *J* = 10 Hz, 4 Hz, 1H, H1), 3.63 (dd, *J* = 10 Hz, 4 Hz, 1H, H1'), 2.00-2.20 (m, 4 H, H3' and H6'), 1.70-1.55 (m, 4 H, H4' and H5'), 1.07 (s, 9H, CH_3). ^{13}C δ 155.8 (CO), 136.6, 135.6, 135.5, 135.0, 134.8, 133.2, 133.0, 129.9, 129.7, 127.7, 128.4, 128.0, 127.9, 122.9 (C3), 66.6 ($PhCH_2O$), 66.4 (C1), 54.5 (C2), 26.8 (CH_3), 25.8, 24.4 (C3' and C6'), 22.5, 22.4 (C4' and C5'), 19.2. IR υ 3350 (NH), 2950, 1700, 1550, 1280, 1250, 1125, 1055 cm^{-1}. MS *m/z* 539 (M^+). $[\alpha]_D$ (CH_2Cl_2, c = 2.82) -22.0°.

(2*S*,3*E*)-2-[*N*-(Benzoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)but-3-en-1-ol (4f)

Method 1: Diene **4f** was synthesised from alkene **1** (257 mg, 1.16 mmol) according to the procedure for the synthesis of **4a**. The reaction mixture had blackened after 5 h and was worked-up as usual. ^1H nmr spectroscopic analysis showed that none of the starting alkene **1** remained in the crude product which was then chromatographed (1:1 ethyl acetate/hexane) to give diene **4f** as a solid (185 mg, 53 %). Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.71; H, 7.74; N, 4.60. Recrystallisation from isopropanol yielded flat rhombic crystals, m.p. 106-107 °C.

Method 2 (scale-up): The procedure was exactly as described under Method 1 scaling up the reagents as follows: alkene **1** (2.21 g, 10.0 mmol), 1-cyclohexen-1-yl trifluoromethanesulfonate (2.76 g, 12.0 mmol), DMF (100 ml), water (180 mg, 10.0 mmol), tetrabutylammonium trifluoromethanesulfonate (392 mg, 1.0 mmol), potassium carbonate (3.45 g, 25.0 mmol), palladium(II) acetate (112 mg, 0.5 mmol). The crude product was chromatographed and diene **4f** was obtained in 47 % yield as a solid.

^1H δ 7.35 (m, 5H, ar), 6.21 (d, *J* = 16 Hz, 1H, H4), 5.76 (m, 1H, H2'), 5.45 (dd, *J* = 16 Hz, 6 Hz, 1H, H3), 5.34 (d, *J* = 12 Hz, 1H, PhCHH'O), 5.18 (d, *J* = 12 Hz, 1H, PhCHH'O), 5.12 (d, *J* = 14 Hz, 1H, NH), 4.79 (m, 1H, H2), 4.46 (t, *J* = 9 Hz, 1H, H1), 4.06 (dd, *J* = 10 Hz, 4 Hz, 1H, H1'), 2.00-2.20 (m, 4 H, H3', H6'), 1.50-1.65 (m, 4 H, H4' and H5' and OH). ^{13}C δ 156.4 (CO), 136.3, 135.6 (C4), 134.6 (C1'), 132.7 (C2'), 128.5, 128.4, 128.3, 121.7 (C3), 68.5 ($PhCH_2O$), 67.7 (C1), 57.4 (C2), 25.9, 24.3 (C3' and C6'), 22.2, 22.2 (C4' and C5'). IR υ 3500 (OH), 3300 (NH), 1670, 1555, 1260, 1092, 1060, 970 cm^{-1}. MS *m/z* 301 (M^+). $[\alpha]_D$ (CH_2Cl_2, c = 5.00) 8.5°.

(2*S*,3*E*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(1'-cyclohexen-1'-yl)but-3-en-1-ol (4g)

Alkene **2** (182 mg, 0.972 mmol) was treated following the procedure for the synthesis of **4a**. After heating for 40 h the brown reaction mixture was worked up. ^1H nmr spectroscopic analysis showed that none of the starting alkene **2** remained in the crude product which was then chromatographed (45:55 ethyl acetate/hexane) to give **4g** (143 mg, 52 %) as a white solid. Anal. Calcd. for $C_{15}H_{25}NO_4$: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.21; H, 9.47; N, 5.05. Recrystallisation of this material from ethyl acetate/hexane furnished a white solid, m.p. 85-86 °C. ^1H δ 6.20 (d, $J = 16$ Hz, 1H, H4), 5.74 (m 1H, H2'), 5.45 (dd, $J = 16$ Hz, 6 Hz, 1H, H3), 5.20-5.30 (m, 1H, NH), 4.20-4.30 (m, 1H, H2), 3.70-3.54 (m, 2H, H1), 3.42 (t, $J = 6$ Hz, OH), 2.10-2.20 (m, 4 H, H3' and H6'), 1.65-1.54 (m, 4 H, H4' and H5'), 1.44 (s, 9H, CH_3). ^{13}C δ 155.9 (CO), 135.1 (C4), 134.7 (C1'), 129.9 (C2'), 122.3 (C3), 79.4, 65.3 (C1), 54.3 (C2), 28.2 (CH_3), 25.6, 24.2 (C3' and C6'), 22.3, 22.2 (C4' and C5'). IR υ 3500-3300 (OH, NH), 1690, 1518, 1300, 1280, 1002, 993 cm^{-1}. MS *m/z* 283 (M^+). $[\alpha]_D$ ($CHCl_3$, c = 3.90) 23.1°.

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