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Intramolecular Vinylation of Carbanions Using *N*-Acyl Benzomorpholines as Masked Vinylureas and Vinylcarbamates

Vinylation intramoléculaire de carbanions nucléophiliques par les N-acylbenzomorpholines comme vinylurées et vinylcarbamates masqués

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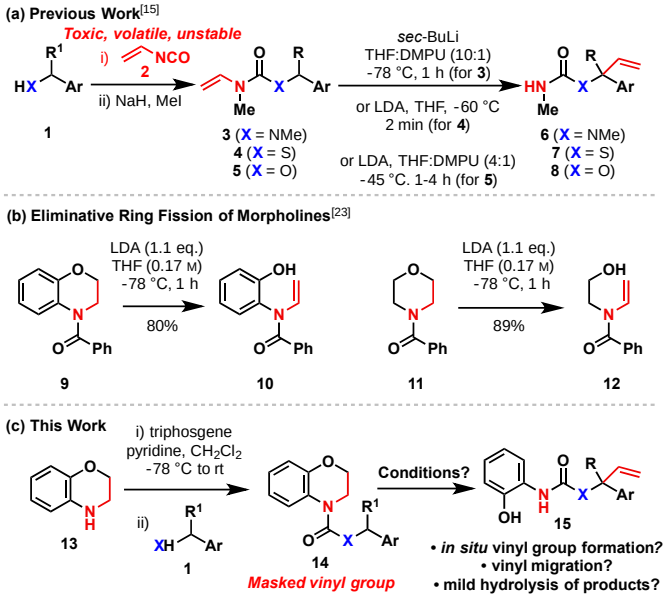
ABSTRACT

Treatment of urea or carbamate derived benzomorpholines with LDA generates *N*-vinylureas or *N*-vinylcarbamates by elimination of a phenoxide anion, cleaving the benzomorpholine ring. Simultaneous formation of a carbanion α to an aryl or nitrile stabilising group allows migration of the newly-formed *N*-vinyl substituent to the carbanionic centre, in some cases with high enantiospecificity. Mild hydrolysis of the resulting urea or carbamate returns a *C*-vinylated amine, alcohol or hydantoin, in some cases with high enantiomeric purity. This 'masked' vinylation strategy avoids the need to use the reactive and volatile vinyl isocyanate as a starting material.

1. Introduction

The stereospecific functionalization of chiral organolithiums[1] provides a valuable method for the synthesis of chiral tertiary thiols,[2] tertiary alcohols,[3] and α-tertiary amines.[4-6] While stereospecific alkylation of chiral organolithiums is routine,[1] stereospecific arylation or alkenylation to form more functionalized products requires specialised approaches.[7-11] Building on our discovery that metallated *N*-benzyl-*N'*-aryl ureas,[12-19] carbamates,[20-23] and thiocarbamates[24-26] undergo stereospecific aryl migration to the carbanionic centre, we previously reported that the stereospecific *N* to *C* vinyl migration of a variety of lithiated benzylic ureas **3**, carbamates **4** and thiocarbamates **5** may be used to generate α-vinyl tertiary amines, alcohols and thiols from their parent compounds **1** after deprotection of the products **6-8** (Scheme 1a).[27]

The *N*-vinyl substituted starting materials[14,17,27-30] for this reported vinylation had been synthesized by a two-step procedure that employed vinyl isocyanate **2** to introduce the *N*-alkenyl substituent. Unfortunately, **2** is of limited commercial availability because of its toxicity and poor stability towards polymerisation. Although the *in situ* synthesis of **2** has been reported,[31,32] isolation and storage of this volatile and reactive compound is problematic. In this paper, we report a solution to the challenge of synthesizing and using *N*-vinyl ureas and carbamates that makes use of a benzomorpholine ring as a 'masked *N*-vinyl group', and we show how this strategy may be used in the organolithium-mediated synthesis α-vinyl-substituted amines and alcohols.



Scheme 1. Formation and migration of *N*-vinyl substituents.

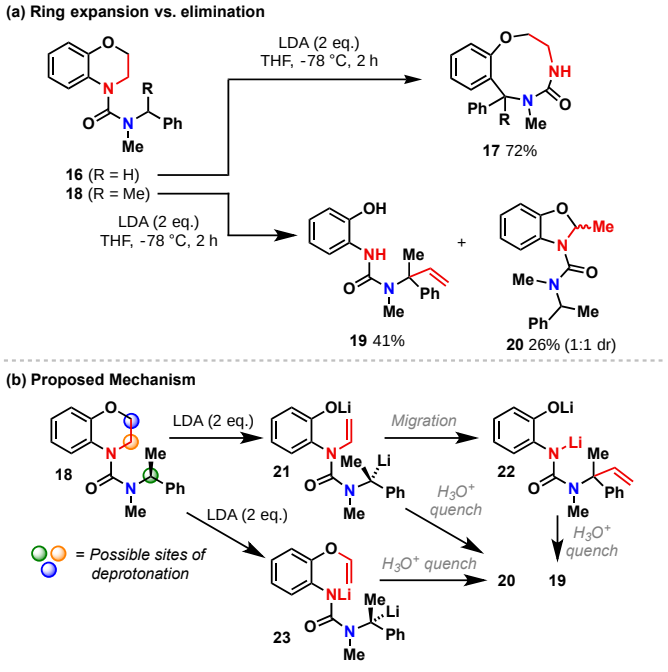
Florio and co-workers reported that treatment of benzomorpholine **9** or morpholine **11** with LDA at −78 °C leads to enamides **10** and **12** respectively by base-promoted reverse 6-*endo-trig* elimination of the phenoxide anion from a presumed intermediate amide-stabilised organolithium (Scheme 1b).[33] We reasoned that benzylic ureas or carbamates **14** (X = NR or O) containing a benzomorpholine ring might likewise fragment upon treatment with LDA to generate an *N*-alkenyl urea[28] or carbamate, which could then undergo vinyl migration, ideally in a one-pot procedure (Scheme 1c). In this paper we report our success in developing this strategy for the *C*-vinylation of some carbanion nucleophiles.

2. Results and Discussion

N-Carboxamidobenzomorpholines **16** and **18** were synthesized by standard conditions, and treated with LDA in THF. With R = H, deprotonation of **16** at the benzylic position led to direct migration of the *N*-aryl ring of the benzomorpholine to the benzylic carbanion, resulting in a clean ring expansion to give **17** in good yield.[19] By contrast, treatment of **18**, with R = Me, under the same conditions yielded a mixture of products **19** and **20** (Scheme 2a).

This differential reactivity can be rationalised by consideration of the three alternative sites at which **16** or **18** may be lithiated (Scheme 2b): α to the morpholine nitrogen (orange), α to the morpholine oxygen (blue) or at the benzylic position (green). Assuming that the most acidic benzylic position (green) is deprotonated first, the organolithium resulting from **16** rapidly attacks the *N*-aryl substituent and ring-expands to give **17**. The increased steric bulk at the lithiated benzylic position of **18** presumably retards this ring expansion, allowing a second deprotonation to occur α to the morpholine nitrogen (orange). Elimination gives phenoxide **21** which then undergoes migration of the newly-formed vinyl group to give **22**, and hence **19**.

The by-product **20** may be formed by two alternative pathways. Protonation of **21** prior to vinyl migration gives an *N*-acyl enamine, or deprotonation α to oxygen (blue) and elimination would give a vinyl ether **23**, either of which might undergo cyclisation under the conditions of the aqueous quench to give oxazolidine **20**.[34]

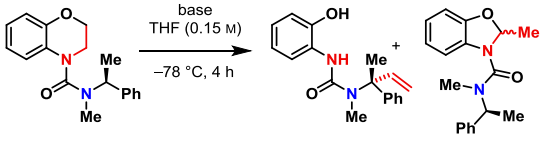


Scheme 2. Eliminations and migrations in urea derivatives of benzomorpholine

Using enantiopure **18**, a series of reactions was carried out in order to identify a set of conditions that supressed the formation of **20**. Switching to the more basic *sec*-BuLi (Table 1, entry 2) did not improve the yield of the vinyl migrated product **13**, and also gave poor conversion: 47% of **18** was recovered. The addition of DMPU, a highly coordinating co-solvent,[12,19] led to an improvement in the selectivity for vinyl migration product **19** (Table 1, entry 3), which was improved further by conducting the reaction on a larger scale (Table 1, entry 4). Analysis of **19** by SFC HPLC on a (*S*,*S*)-Whelk-01 Kromasil column furthermore confirmed that the reaction proceeded with complete enantiospecificity, and was presumably by stereochemically retentive (rather than invertive) attack.[12,35]

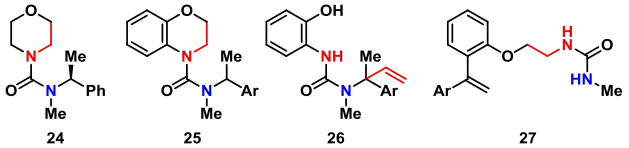
We also synthesized morpholine urea **24** for direct comparison with the reaction observed with **18**, but attempted fragmentation/migration gave only recovered starting material, with no cleavage of the morpholine ring (entry 5). Fragmentation and rearrangement of the *para*-chlorophenyl substituted urea **25** gave 23% of the vinyl migration product **26**, along with 63% of the alkene **27** derived from ring expansion to a homologue of **17** followed by elimination. This result suggests that, like **16**, the more reactive chlorophenyl-substituted organolithium derived from **25** undergoes ring expansion at a rate competitive with fragmentation to the vinyl urea.

Table 1. Optimisation of the vinyl migration.

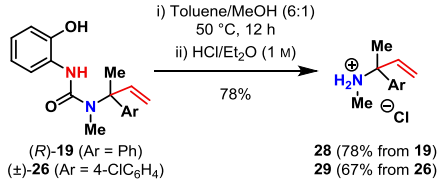


Entry	SM	Base (eq.)	Additive (eq.)	**19** (%[a])	**20** (%) (dr)[b]
1	(*S*)-**18**	LDA (2)	-	41	26 (1:1)
2	(*S*)-**18**	*sec*-BuLi (2)	DMPU (5)	5[c]	12 (1:1)
3	(*S*)-**18**	LDA (3)	DMPU (5)	53	5 (1:1)
4	(*S*)-**18**	LDA (2.2)	DMPU (5)	64[d]	>5 (1:1)
5	**24**	LDA (2)	–	–[e]	
6	**25**	LDA (2.2)	DMPU (5)	23[f] + 63[g]	

[a] Isolated yield from 0.2 mmol scale reaction. [b] dr determined by ^{1}H NMR of the crude reaction mixture. [c] 47% remaining **18** recovered. [d] Reaction carried out on 1 mmol scale. [e] Starting **24** recovered unchanged. [f] Yield of **26**, the *p*-Cl analogue of **19**. [g] Yield of ring expansion/elimination product **27**. LDA = Lithium diisopropylamide (2.0 M solution in THF/heptane/ethylbenzene, *sec*-BuLi (1.06 M solution in cyclohexane), THF = tetrahydrofuran, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

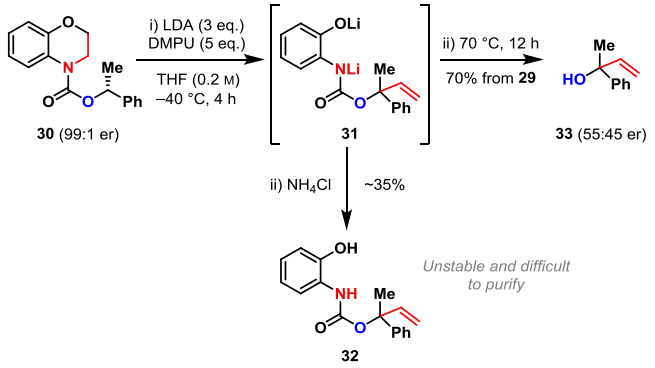


Having established conditions for the selective formation of **19**, we next investigated the cleavage of the resulting urea to generate the tertiary amine. Attempts to hydrolyse **19** to its constituent α-tertiary amine under a wide range of basic (e.g. K_2CO_3/*n*-BuOH) and acidic (e.g. TFA, HCl) conditions met with limited success. However, exploiting the rapid methanolysis of related trisubstituted ureas reported by Lloyd-Jones and Booker-Milburn[36] enabled us to liberate the desired α-tertiary amine (Scheme 3). Purification of the free amine by flash column chromatography followed by precipitation as the hydrochloride salt gave **28** in good yield. Application of these conditions to **26** also gave **29** in good yield.

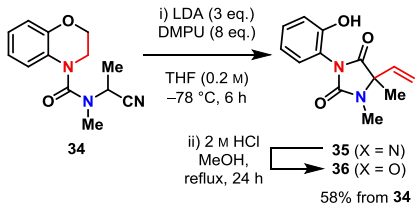


Scheme 3. Methanolysis of ureas to give amine hydrochloride salts **28** and **29**.

Comparable reactivity was shown by the carbamate **30**, synthesized from benzomorpholine in two steps in good yield (see Experimental Section). Metallation of carbamate **30** with LDA under our optimized conditions gave the product of vinyl migration **32** in moderate yield (Scheme 4). Carbamate **32** was unstable and proved difficult to isolate, purify and characterize. With the aim of inducing direct fragmentation of **31** to the alcohol **33**, the reaction was warmed to 70 °C overnight. Tertiary allylic alcohol **33** was isolated in good yield, meaning that the one-pot application of base and then heat allows the efficient vinylation of a carbamate α to oxygen. Alcohol **33** was nonetheless formed in essentially racemic form, due to the relative configurational instability of dipole-stabilized benzylic organolithiums α to oxygen.[1,20,21,27]



Scheme 4. Carbamate vinylation and deprotection.



Scheme 5. Vinylation of amino nitrile derivative **34**.

Ureas incorporating nitrile-stabilised anions undergo intramolecular migration chemistry,[37] so α-cyano urea **34** was synthesized in order to investigate the applicability of the 'masked vinylation' strategy to non-benzylic carbanions. Treatment of **34** with LDA and DMPU under conditions similar to those used for the urea **18** and carbamate **30** gave an iminohydantoin **35**,[37] which was hydrolyzed under acidic conditions to the hydantoin **36** (Scheme 5).

3. Conclusion

In conclusion, we have demonstrated that benzomorpholine-derived ureas and carbamates behave as masked vinyl groups for the vinylation of a variety of carbon nucleophiles through a base-promoted cascade of elimination and vinyl migration. This approach overcomes difficulties in preparing simple *N*-vinyl ureas arising from the commercial unavailability of vinyl isocyanate and the associated difficulties in its use, relating to toxicity and storage.

4. Experimental Section

4.1. General Directions

Reactions requiring anhydrous conditions (where specified) were executed under dry nitrogen or argon atmospheres in glassware that was flame dried and allowed to cool under vacuum. Reaction mixtures were stirred magnetically. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or cannula into the reaction vessels through rubber septa. All reagents were purchased (unless specified) at highest commercial quality and used as received. Non-anhydrous solvents were purchased (unless specified) at the highest commercial quality and used as received. CH_2Cl_2, THF, DMF and MeCN extra dry solvents over 3Å molecular sieves were purchased from Acros and used as received. DMPU was distilled from CaH_2 and stored under nitrogen in a Young's tube. NEt_3 was distilled from CaH_2 and stored under nitrogen in a Young's tube. 3,4-Dihydro-2*H*-benz-[*b*]-[1,4]oxazine was purchased from Alfa Aesar UK and used as received.

4.2. Equipment Details

TLC was performed on aluminium backed silica plates (0.2 mm, 60 F_{254}) which were developed using standard visualizing agents: UV fluorescence (254 & 366 nm), phosphomolybdic acid / Δ, vanillin / Δ, potassium permanganate / Δ and Seebach / Δ. Flash chromatography was performed on an automated Biotage Isolera™ Spektra Four using gradient elutions on pre-packed silica gel Biotage® SNAP Ultra/ZIP Sphere columns. Melting points were measured on a Kofler hotstage melting point apparatus and are uncorrected. IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer (ATR sampling accessory). Only strong and selected absorbances (ν_{max} expressed in cm^{-1}) are reported. ^1H NMR spectra were recorded on Jeol ECS (400 MHz) or Varian VNMR (400 MHz or 500 MHz) instruments. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s) and are assigned ArH, C, CH, C*H*H or CH*H* (diastereotopic protons), CH_2, CH_3. 2D NMR experiments COSY, HSQC and HMBC were used where necessary in assigning NMR spectra. Spin-spin coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded on Jeol ECS (101 MHz) or Varian VNMR (101 MHz or 125 MHz) instruments. Chemical shifts (δ_C) are quoted in parts per million (ppm) and referenced to the appropriate solvent peak(s) and are assigned C, CH, CH_2, and CH_3 as determined using 2D NMR experiments HSQC and HMBC where necessary. Spin-spin coupling constants (*J*) are reported in Hertz (Hz). High resolution mass spectra were recorded on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI) with only molecular ions ($[M]^+$, $[M+H]^+$, $[M+Na]^+$) and major peaks reported. Optical

Rotations ($[\alpha]_D^T$) were measured on a Bellingham and Stanley Ltd. ADP220 polarimeter where *c* is given in g/100 mL.

4.3. Starting Material Synthesis

*(−)-(S)-N-Methyl-N-(1-phenylethyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxamide (**18**)*; Synthesis of 2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carbonyl chloride: To a solution of triphosgene (3.4 g, 12 mmol, 0.46 eq.) in anhydrous CH_2Cl_2 (17 mL, 0.7 M) under a N_2 atmosphere was added pyridine (2.0 mL, 25 mmol, 1.0 eq.) dropwise at −78 °C. A solution of 3,4-dihydro-2*H*-benz-[*b*]-[1,4]oxazine (3.5 g, 26 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (2 mL) was added dropwise at −78 °C before warming to room temperature. After completion, the reaction was quenched with HCl (1.0 M) and extracted three times with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$ (sat. aq.), dried with $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum. The resulting residue was purified o/n a short pad of silica, eluting with (20% EtOAc/*n*-pentane) to give the carbamoyl chloride. Preparation of **18**: To a dried Schlenk flask under a N_2 atmosphere was added a solution of (*S*)-*N*-methyl-1-phenylethanamine (0.75 mL, 3.9 mmol, 1.3 eq.) and triethylamine (0.66 mL, 4.8 mmol, 1.6 eq.) in anhydrous acetonitrile (10 mL, 0.4 M). A solution of the carbamoyl chloride (0.79 g, 4.0 mmol, 1.0 eq.) in anhydrous acetonitrile (1 mL) was added dropwise to the mixture and stirred at room temperature until completion (followed by TLC). The reaction was quenched with $NaHCO_3$ (sat. aq.), extracted three times with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum. The crude urea was purified by flash column chromatography eluting with (7% to 60% Et_2O/Petrol on a ZIP Sphere 30 g column over 14 column volumes) to give the *title compound* **18**; 1.07 g, 90% yield; light yellow solid; R_f 0.18 (30% Et_2O/*n*-pentane); mp 79–80 °C (CH_2Cl_2/*n*-pentane); ν_{max} (film)/cm^{-1} 1642, 1601, 1584, 1496, 1431, 1391, 1338, 1306, 1282, 1217, 1178, 1061, 1050, 770; $[\alpha]_D^{21} = -43$ (*c*. 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.37–7.28 (m, 5 H, ArH), 6.96–6.93 (m, 1 H, ArH), 6.87–6.86 (m, 1 H, ArH), 6.81–6.77 (m, 1 H, ArH), 5.59 (q, *J* = 7.1 Hz, 1 H, NC*H*Ph), 4.35–4.31 (m, 2 H, CH_2), 3.72–3.68 (m, 2 H, CH_2), 2.60 (s, 3 H, NCH_3), 1.61 (d, *J* = 7.0 Hz, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 159.5 (C=O), 145.0 (C), 140.7 (C), 128.7 (CH), 128.4 (C), 127.6 (CH), 127.6 (CH), 123.1 (CH), 120.7 (CH), 119.5 (CH), 117.3 (CH), 66.4 (CH_2), 54.4 (CH), 44.0 (CH_2), 31.0 (CH_3), 16.2 (CH_3); HRMS (ESI$^+$) $[M+H]^+$ $C_{18}H_{21}N_2O_2^+$ requires 297.1598; found 297.1607. Chiral supercritical fluid chromatography ((*S*,*S*)-Whelk-01, 5/100 Kromasil, 25 cm × 4.6 mm I.D.), 125 bar CO_2, 40 °C, 4 mL/min, 20% co-solvent (MeOH); t_R 3.8 min (major), 5.2 min (minor) 99:1 er. Racemic sample was prepared by making a 1:1 mixture of (–)-**18** and (+)-**18** which was prepared in an analogous manner.

*(−)-(S)-N-(1-(4-Chlorophenyl)ethyl)-N-methyl-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxamide (**25**)*; See **18** for preparation of carbamoyl chloride. To a dried Schlenk flask under a N_2 atmosphere was added a solution of (*S*)-1-(4-chlorophenyl)-*N*-methylethylamine (0.56 mL, 3.9 mmol, 1.3 eq.) and triethylamine (0.66 mL, 4.8 mmol, 1.6 eq.) in anhydrous MeCN (7.5 mL, 0.4 M). A solution of the carbamoyl chloride (0.59 g, 3.0 mmol, 1.0 eq.) in anhydrous acetonitrile (1 mL) was added dropwise to the mixture and stirred at room temperature until completion (followed by TLC). The reaction was quenched with $NaHCO_3$ (sat. aq.), extracted three times with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum. The crude urea was purified by flash column chromatography eluting with (7% to 60% Et_2O/Petrol on a ZIP Sphere 30 g column over 14 column volumes) to give the urea. Methylation: To a flame dried Schlenk flask under a N_2 atmosphere was added sodium hydride (0.21 g, 5.1 mmol, 2 eq., 60% suspension on mineral oil) suspended in DMF (10 mL, 0.25 M). To this suspension was added a solution of the urea (~2.6 mmol) from the previous step in DMF (1 mL) dropwise at 0 °C. Methyl iodide (0.47 mL, 7.6 mmol, 3 eq.) was added dropwise and the reaction was allowed to warm to room temperature for 24 h. The reaction mixture was quenched with NH_4Cl (sat. aq.) and extracted three times with EtOAc. The combined organic phases were washed with LiCl (sat. aq.) to remove the DMF, dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum. Purification of the resulting residue by flash column chromatography eluting with (7% to 60% Et_2O/Petrol on a ZIP Sphere 30 g column over 15 column volumes) gave the *title compound* **25**; 0.63 g, 66% yield over 2 steps; white solid; R_f 0.15 (30% Et_2O/*n*-pentane); mp 117–119 °C (CH_2Cl_2/*n*-pentane); ν_{max} (film)/cm^{-1} 2922, 2853, 1636, 1498, 1389, 1342, 1244, 1179, 1057, 769; $[\alpha]_D^{21} = -46$ (*c*. 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.33 (s, 4 H, ArH), 6.94–6.76 (m, 4 H, ArH), 5.56 (q, *J* = 7.0 Hz, 1 H, NC*H*Ph), 4.39–4.28 (m, 2 H, CH_2), 3.76–3.63 (m, 2 H, CH_2), 2.58 (s, 3 H, NCH_3), 1.59 (d, *J* = 7.1 Hz, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 159.4 (C=O), 145.0 (C), 139.3 (C), 133.5 (C), 129.0 (CH), 128.8 (CH), 128.2 (C), 123.2 (CH), 120.7 (CH), 119.4 (CH), 117.4 (CH), 66.4 (CH_2), 53.8 (CH), 43.9 (CH_2), 31.1 (NCH_3), 16.2 (CH_3); HRMS (ESI$^+$) $[M+H]^+$ $C_{18}H_{20}ClN_2O_2^+$ requires 331.1208; found 331.1201.

*(−)-(R)-1-Phenylethyl-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (**30**);* See **18** for preparation of carbamoyl chloride. In a dried Schlenk flask under a N_2 atmosphere, sodium hydride (0.36 g, 9.0 mmol, 3.0 eq., 60% suspension on mineral oil) was suspended in anhydrous CH_2Cl_2 (12 mL, 0.25 M) and cooled to 0 °C before (*R*)-(+)-phenylethanol (1.1 mL, 9.0 mmol, 3.0 eq.) was added. A solution of the carbamoyl chloride (0.59 g, 3.0 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1 mL) was added dropwise to the mixture. The ice bath was removed and the mixture was heated to 40 °C overnight. The reaction was quenched with NH_4Cl (sat. aq.) and extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum. The product was purified by flash column chromatography eluting with (2% to 25% EtOAc/*n*-hexane + 1% NEt_3 on a SNAP Ultra 25 g column over 10 column volumes) to yield the *title compound* **30**; 0.56 g, 66% yield, colourless oil; R_f 0.25 (25% Et_2O/*n*-pentane); ν_{max} (film)/cm^{-1} 2979, 2934, 1699, 1494, 1373, 1259, 1224, 1210, 1145, 1056, 1028, 748; $[\alpha]_D^{23} = -13$ (*c*. 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.85 (br. s, 1 H, ArH), 7.43–7.27 (m, 5 H, ArH), 7.03–6.96 (m, 1 H, ArH), 6.93–6.85 (m, 2 H, ArH), 5.94 (q, *J* = 6.6 Hz, 1 H, CH), 4.25 (t, *J* = 4.7 Hz, 2 H, CH_2), 3.95–3.92 (m, 2 H, CH_2), 1.63 (d, *J* = 6.6 Hz, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 153.0 (C=O), 146.1 (C), 141.8 (C), 128.7 (CH), 128.1 (CH), 126.1 (CH), 125.9 (C) 124.8 (CH), 123.4 (CH), 120.5 (CH), 117.2 (CH), 74.8 (CH), 65.6 (CH_2), 42.5 (CH_2), 22.8 (CH_3); HRMS (ESI$^+$) $[M+Na]^+$ $C_{17}H_{17}NO_3Na^+$ requires 306.1101; found 306.1107.

*(±)-N-(1-Cyanoethyl)-N-methyl-2,3-dihydro-4H-benzo[b]-[1,4]oxazine-4-carboxamide (**34**)*; Step 1: Methylamine (42 mmol, 3.0 eq., 8.0 M in EtOH) was added to a solution of lactonitrile (14 mmol, 1.0 eq.) in EtOH (6 mL, 2.5 M) at 0 °C in presence of an excess of $MgSO_4$. The reaction mixture was allowed to reach room temperature and stirred overnight. The mixture was filtered and the excess $MeNH_2$ and solvent were removed from the filtrate carefully under vacuum to afford the crude nitrile amine. Step 2: In a round-bottom flask under a N_2 atmosphere, triphosgene (0.40 eq.) was dissolved in anhydrous CH_2Cl_2 (1.0 M) and cooled to −78 °C. 2,6-Lutidine (1.2 eq.) was added dropwise to the solution and the reaction mixture was

stirred for 10 min before a solution of the nitrile amine (1.0 eq.) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 2 h. Upon completion the reaction was quenched with HCl (1.0 M aq.) and extracted three times with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$ (sat. aq.) and brine and dried over $MgSO_4$. Filtration and concentration of the filtrate under vacuum gave the crude carbamoyl chloride. Step 3: In a round-bottom flask under a N_2 atmosphere, the carbamoyl chloride (1.0 eq.) was dissolved in anhydrous MeCN (0.4 M) and 2,6-lutidine (1.1 eq.) was added. A solution of 3,4-dihydro-2*H*-benz-[1,4]oxazine (1.1 eq.) in MeCN (0.4 M) was added dropwise to the mixture. The mixture was warmed to 60 °C and stirred for 24 h. Upon completion, the solvent was removed under vacuum. The remaining oil was dissolved in EtOAc, washed with HCl (1.0 M, aq.), with $NaHCO_3$ (sat. aq.) and brine and dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum. Purification by flash column chromatography eluting with (10% to 80% Et_2O/Petrol on a SNAP Ultra 10 g column over 15 column volumes) gave the *title compound* **34**; 2.4 g, 70% over 3 steps: white solid; R_f 0.30 (50% EtOAc/*n*-hexane); mp 95–96 °C (CH_2Cl_2/*n*-pentane); ν_{max} (film)/cm^{-1} 2953, 1651, 1585, 1496, 1377, 1359, 1311, 1278, 1249, 1057, 750; δ_H (400 MHz, $CDCl_3$) 7.02–6.83 (m, 4 H, ArH), 5.19 (q, *J* = 7.2 Hz, 1 H, NC*H*CN), 4.40–4.28 (m, 2 H, CH_2), 3.80 (ddd, *J* = 13.3, 5.4, 3.2 Hz, 1 H, CH_2), 3.66 (ddd, *J* = 13.3, 6.7, 3.4 Hz, 1 H, CH_2), 2.89 (s, 3 H, NCH_3), 1.59 (d, *J* = 7.3 Hz, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 158.3 (C=O), 145.2 (C), 126.9 (C), 124.4 (CH), 120.9 (CH), 119.9 (CH), 118.5 (CN), 117.7 (CH), 66.5 (CH_2), 44.3 (CH_3), 43.5 (CH_2), 33.1 (CH_3), 17.2 (CH_3); HRMS (ESI$^+$) $[M+Na]^+$ $C_{13}H_{15}N_3O_2Na^+$ requires 268.1056; found 268.1069.

4.4. Vinyl Migration Products

*(+)-(R)-3-(2-Hydroxyphenyl)-1-methyl-1-(2-phenylbut-3-en-2-yl)urea (**19**)*; In a dried Schlenk flask under a N_2 atmosphere, urea **18** (0.30 g, 1 mmol, 1.0 eq.) was dissolved in anhydrous THF (6.7 mL, 0.15 M) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (0.6 mL, 5 mmol, 5.0 eq.) was added at room temperature. The mixture was cooled to −78 °C and lithium diisopropyl amide (LDA) (1.1 mL, 2.2 mmol, 2.2 eq., 2.0 M in THF/heptane/ethylbenzene) was added dropwise and the mixture was stirred for 4 h at −78 °C. The reaction was quenched with NH_4Cl (sat. aq.) and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum to give a crude residue. Purification of this residue by flash column chromatography eluting with (7% to 60% Et_2O/Petrol on a SNAP Ultra 10 g column over 13 column volumes) gave the *title compound* **19**; 0.19 g, 64% yield, light yellow solid; R_f 0.20 (30% Et_2O/*n*-pentane); mp 94–96 °C (CH_2Cl_2/*n*-pentane); ν_{max} (film)/cm^{-1} 3392, 3059, 1631, 1586, 1538, 1448, 1359, 1242, 754, 699; $[\alpha]_D^{21}$ = +24 (*c*. 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 9.77 (s, 1 H, NH), 7.52–7.36 (m, 5 H, ArH), 6.98–6.89 (m, 2 H, ArH), 6.58 (ddd, *J* = 8.5, 7.1, 1.8 Hz, 1 H, ArH), 6.39 (dd, *J* = 17.3, 10.6 Hz, 1 H, C*H*=HH), 6.26 (br. s, 1 H, OH), 5.74 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH), 5.35 (d, *J* = 10.6 Hz, 1 H, CH=*H*H), 5.27 (d, *J* = 17.3 Hz, 1 H, CH=H*H*), 3.20 (s, 3 H, NCH_3), 1.83 (s, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 158.0 (C=O), 149.5 (CH), 144.9 (C), 140.4 (*C*H=CH_2), 129.9 (CH), 128.4 (CH), 126.5 (C), 126.2 (CH), 125.8 (CH), 122.0 (CH), 119.9 (CH), 119.8 (CH), 115.3 (CH=*C*H_2), 65.3 (C), 32.8 (NCH_3), 26.9 (CH_3); HRMS (ESI$^+$) $[M+Na]^+$ $C_{18}H_{20}N_2O_2Na^+$ requires 319.1417; found 319.1417. Chiral supercritical fluid chromatography ((*S*,*S*)-Whelk-01, 5/100 Kromasil, 25 cm × 4.6 mm I.D.), 125 bar CO_2, 40 °C, 4 mL/min, 20% co-solvent (MeOH); t_R 12.3 min (major), 13.3 min (minor) >99:1 er. Racemic sample was prepared by making a 1:1 mixture of (+)-**19** and (−)-**19** which was prepared in an analogous manner.

*(±)-1-(2-(4-Chlorophenyl)but-3-en-2-yl)-3-(2-hydroxyphenyl)-1-methylurea (**26**)*; In a dried Schlenk flask under a N_2 atmosphere, urea **25** (0.17 g, 0.50 mmol, 1.0 eq.) was dissolved in anhydrous THF (3.3 mL, 0.15 M) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (0.30 mL, 2.5 mmol, 5.0 eq.) was added at room temperature. The mixture was cooled to −78 °C and lithium diisopropyl amide (LDA) (0.60 mL, 1.1 mmol, 2.2 eq., 2.0 M in THF/heptane/ethylbenzene) was added dropwise and the mixture was stirred for 4 h at −78 °C. The reaction was quenched with NH_4Cl (sat. aq.) and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum to give a crude residue. Purification of this residue by flash column chromatography eluting with (5% to 100% EtOAc/Petrol on a SNAP Ultra 10 g column over 16 column volumes) gave the *title compound* **26**; 38 mg, 23% yield; colourless oil; R_f 0.71 (60% EtOAc/*n*-pentane); mp 138–140 °C (CH_2Cl_2/*n*-pentane); ν_{max} (film)/cm^{-1} 2923, 1759, 1634, 1594, 1520, 1496, 1450, 1342, 1094, 1011, 827, 746; δ_H (400 MHz, $CDCl_3$) 9.48 (br. s, 1 H, NH), 7.42–7.36 (m, 4 H, ArH), 7.03–6.96 (m, 1 H, ArH), 6.93 (dd, *J* = 8.1, 1.6 Hz, 1 H, ArH), 6.67 (ddd, *J* = 7.9, 7.1, 1.6 Hz, 1 H, ArH), 6.36 (dd, *J* = 17.3, 10.6 Hz, C*H*=CHH) 6.34 (br. s, 1 H, OH), 6.09 (dd, *J* = 7.9, 1.6 Hz, 1 H, CH), 5.36 (d, *J* = 10.6 Hz, 1 H, CH=C*H*H), 5.25 (d, *J* = 17.3 Hz, 1 H, CH=CH*H*), 3.16 (s, 3 H, NCH_3), 1.81 (s, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 157.9 (C=O), 149.4 (C), 143.5 (C), 140.6 (*C*H=CH_2), 140.5 (C), 134.0 (C), 129.7 (CH), 127.1 (CH), 126.4 (CH), 126.3 (CH), 122.0 (CH), 120.1 (CH), 119.9 (CH), 115.6 (CH=*C*H_2), 65.1 (C), 33.1 (NCH_3), 26.7 (CH_3); HRMS (ESI$^+$) $[M+H]^+$ $C_{18}H_{20}ClN_2O_2^+$ requires 331.1208; found 331.1207.

*(±)-2-Phenylbut-3-en-2-ol (**33**)*; Carbamate **30** (0.11 g, 0.40 mmol, 1.0 eq.) was added to a dried Schlenk flask under a N_2 atmosphere and dissolved in THF (2 mL, 0.2 M). DMPU (0.24 mL, 2.0 mmol, 5.0 eq.) was added to the flask at room temperature. The mixture was cooled to −40 °C and LDA (0.60 mL, 1.2 mmol, 3.0 eq., 2.0 M in THF/heptane/ethylbenzene) was added dropwise and the mixture was stirred for 4 h. The mixture was warmed to 70 °C and stirred overnight. The reaction was quenched with NH_4Cl (sat. aq.) and extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum. The product was purified by flash column chromatography eluting with (2% to 25% EtOAc/*n*-hexane on a SNAP Ultra 10 g column over 14 column volumes) to give the *title compound* **33**; 41 mg, 70% yield; colourless oil; R_f 0.72 (30% Et_2O/*n*-pentane); ν_{max} (film)/cm^{-1} 3398, 3060, 2908, 1492, 1446, 1177, 1064, 1028, 994, 922, 765, 699; δ_H (400 MHz, $CDCl_3$) 7.50–7.45 (m, 2 H, ArH), 7.38–7.32 (m, 2 H, ArH), 7.29–7.23 (m, 1 H, ArH), 6.18 (dd, *J* = 17.3, 10.6 Hz, 1 H, C*H*=CHH), 5.30 (dd, *J* = 17.3, 1.1 Hz, 1 H, CH=C*H*H), 5.15 (dd, *J* = 10.6, 1.1 Hz, 1 H, CH=CH*H*), 1.92 (br. s, 1 H, OH), 1.66 (s, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 146.5 (C), 145.0 (*C*H=CH_2), 128.4 (CH), 127.1 (CH), 125.3 (CH), 112.5 (CH=*C*H_2), 74.9 (C), 29.5 (CH_3). HRMS (ESI$^+$) $[M+Na]^+$ $C_{10}H_{12}NONa^+$ requires 171.0780; found 171.0778; Chiral HPLC (Chiralcel OJ column 25 cm × 4.6 mm I.D.), 98:2 *n*-hexane/^{i}PrOH, 1 mL/min, 25 °C, t_R 22.6 min (major), 33.1 min (minor) er 55:45. Spectroscopic data for **33** match those reported in the literature.[38]

*(±)-3-(2-Hydroxyphenyl)-1,5-dimethyl-5-vinylimidazolid-ine-2,4-dione (**35**);* In a dried Schlenk flask under a N_2 atmosphere, urea **34** (600 mg, 2.45 mmol, 1.0 eq.) was dissolved in anhydrous THF (25 mL, 0.1 M) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-

pyrimidinone (DMPU) (2.4 mL, 19.57 mmol, 8.0 eq.) was added at room temperature. The mixture was cooled to −78 °C and lithium diisopropyl amide (LDA) (3.7 mL, 7.34 mmol, 3 eq., 2.0 M in THF/heptane/ethylbenzene) was added dropwise and the mixture was stirred for 6 h at −78 °C. The reaction was quenched with NH_4Cl (sat. aq.) and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum to give a crude residue. Purification of this residue by flash column chromatography eluting with (25% to 100% EtOAc/Petrol on a SNAP Ultra 25 g column over 4 column volumes followed by 100% EtOAc over 4 column volumes) gave the *title compound* **35**; 0.35 g, 58% yield; light yellow solid; R_f 0.2 (EtOAc); mp 75–78 °C; ν_{max} (film)/cm^{-1} 3280, 3400-2500 (br.), 2936, 1743, 1656; δ_H (400 MHz, $CDCl_3$) 7.25–7.12 (m, 2 H, ArH), 7.02–6.82 (m, 2 H, ArH), 5.84 (dd, *J* = 17.3, 10.5 Hz, 1 H, C*H*=CHH), 5.52–5.32 (m, 2 H, CH=C*H*$_2$), 2.87 (s, 3 H, NCH_3), 1.61 (s, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 167.3 (C=NH), 155.3 (C=O), 152.8 (C), 135.8 (C), 130.1 (CH), 128.6 (CH), 120.5 (CH), 119.2 (CH), 118.9 (CH=*C*H$_2$), 64.7 (C), 25.6 (NCH_3), 20.7 (CH_3); HRMS (ESI$^+$) $[M+H]^+$ $C_{13}H_{16}N_3O_2^+$ requires 246.1237; found 246.1237; Then an aqueous HCl 2 M solution (2 mL, 4 mmol, 7.5 eq.) was added to the iminohydantoin (130 mg, 0.53 mmol, 1.0 eq.) in methanol (2 mL, 0.26 M) and the reaction mixture was heated to reflux for 24 h. The reaction was quenched by adding $NaHCO_3$ (sat. aq.) and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and the resulting filtrate concentrated under vacuum to give a crude residue. Purification of this residue by flash column chromatography eluting with (10% to 80% EtOAc/Petrol on a SNAP Ultra 10 g column over 8 column volumes followed by 80% EtOAc over 2 column volumes) gave the hydantoin **36**; 130 mg; 99% yield; white solid; R_f 0.40 (80% EtOAc/*n*-hexane); mp 142–143 °C (CH_2Cl_2/*n*-pentane; ν_{max} (film)/cm^{-1} 3301, 2984, 1172, 1697; δ_H (400 MHz, $CDCl_3$) 7.29–7.19 (m, 2 H, ArH), 7.01–6.95 (m, 2 H, ArH), 6.92 (br. s, 1 H, OH), 5.85 (dd, *J* = 17.3, 10.5 Hz, 1 H, C*H*=CHH), 5.51–5.39 (m, 2 H, CH=CH$_2$), 2.97 (s, 3 H, NCH_3), 1.64 (s, 3 H, CH_3); δ_C (101 MHz, $CDCl_3$) 173.6 (NC=O), 155.4 (NC=ON), 151.0 (C), 133.7 (*C*H=CH$_2$), 130.0 (CH), 127.5 (CH), 121.0 (CH), 120.3 (C), 119.6 (CH), 119.4 (CH=*C*H$_2$), 65.9 (C), 25.6 (NCH_3), 19.5 (CH_3); HRMS (ESI)$^+$ $[M+H]^+$ $C_{13}H_{15}N_2O_3^+$ requires 247.1077; found 247.1069.

4.5. Methanolysis Procedure

*(−)-(R)-N-Methyl-2-phenylbut-3-en-2-amine hydrochloride (**28**)*; To a solution of urea **19** (24 mg, 81 μmol, 1 eq.) in anhydrous toluene (0.69 mL, 0.1 M), in a dried Schlenk flask under a N_2 atmosphere, was added anhydrous MeOH (0.11 mL, 0.1 M) and the mixture was heated to 50 °C and stirred overnight. The solvents were removed under vacuum and the product was purified by flash column chromatography eluting with (10% to 80% Et_2O/Petrol on a SNAP Ultra 10 g column over 13 column volumes). The combined fractions were concentrated until a small amount of solvent remained. HCl in Et_2O (1 mL, 1.0 M) was added to this solution to precipitate a white solid. The solution was decanted and the yellow solid was triturated with Et_2O a further 3 times. The yellow solid was dried under high vacuum to give the *title compound* **28** (*N.B.* this compound is hygroscopic and therefore we were unable to obtain a satisfactory melting point); 12.5 mg, 78% yield, white solid; R_f 0.11 (70% EtOAc/*n*-pentane); ν_{max} (film)/cm^{-1} 3213, 1760, 1734, 1479, 1253, 748, 739; $[\alpha]_D^{21}$ = −35 (*c*. 0.2, MeOH); δ_H (500 MHz, DMSO-d_6) 7.54–7.51 (m, 4 H, ArH), 7.50–7.45 (m, 1 H, ArH), 6.25 (dd, *J* = 17.5, 11.0 Hz, 1 H, C*H*=CHH), 5.64 (d, *J* = 11.0 Hz, 1 H, CH=C*H*H), 5.49 (d, *J* = 17.5 Hz, 1 H, CH=CH*H*), 2.54 (s, 3 H, NCH_3), 1.86 (s, 3 H, CH_3); δ_C (126 MHz, DMSO-d_6) 129.6 (C), 129.2 (*C*H=CH$_2$), 120.93 (CH), 120.90 (CH), 118.1 (CH), 110.0 (CH=*C*H$_2$), 56.2 (C), 18.7 (NCH_3), 12.3 (CH_3); HRMS (ESI$^+$) $[M]^+$ $C_{11}H_{16}N^+$ requires 162.1277; found 162.1285.

*(±)-2-(4-Chlorophenyl)-N-methylbut-3-en-2-amine (**29**)*; To a solution of urea **26** (35 mg, 0.11 mmol, 1 eq.) in anhydrous toluene (0.86 mL, 0.1 M), in a dried Schlenk flask under a N_2 atmosphere, was added anhydrous MeOH (0.15 mL, 0.1 M) and the mixture was heated to 50 °C and stirred overnight. The solvents were removed under vacuum and the product was purified by flash column chromatography eluting with (12% to 100% EtOAc/Petrol on a SNAP Ultra 10 g column over 12 column volumes) to give the *title compound* **29**; 13 mg; 67% yield; colourless oil; R_f 0.21 (50% Et_2O/*n*-pentane); $[\alpha]_D^{21}$ = +50 (*c*. 0.18, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.40–7.37 (m, 2 H, ArH), 7.30–7.27 (m, 2 H, ArH), 5.95 (dd, *J* = 17.4, 10.7 Hz, 1 H, C*H*=CHH), 5.22 (dd, *J* = 10.7, 1.1 Hz, 1 H, CH=C*H*H), 5.17 (dd, *J* = 17.4, 1.1 Hz, 1 H, CH=CH*H*), 2.24 (s, 3 H, NCH_3), 1.47 (s, 3 H, CH_3); δ_C (126 MHz, $CDCl_3$) 144.2 (C), 132.5 (C), 128.4 (CH), 128.3 (*C*H=CH$_2$), 128.2 (CH), 113.6 (CH=*C*H$_2$), 60.6 (C), 29.6 (NCH_3), 25.3 (CH_3); HRMS (ESI$^+$) $[M+H]^+$ $C_{11}H_{15}ClN^+$ requires 196.0888; found 196.0886.

4.6. Side Products

*N,2-Dimethyl-N-(-1-phenylethyl)benzo[d]oxazole-3(2H)-carboxamide (**20**)*; Formed as a side-product during the optimization of the vinyl migration (see Table 1, entry 2). Purified by flash column chromatography eluting with (5% to 50% EtOAc/Petrol on a ZIP Sphere 10 g column over 18 column volumes) to give the *title compound* **20** as a 1:1 mixture of diastereomers; 7 mg, 12% yield; colourless oil; R_f 0.70 (20% EtOAc/*n*-pentane); δ_H (400 MHz, $CDCl_3$) 1:1 mixture of diastereomers 7.47–7.28 (m, 10 H, ArH), 6.86–6.69 (m, 7 H, ArH), 6.58–6.55 (m, 1 H, ArH), 6.26 (2 × q, *J* = 5.8, 5.1 Hz, 2 H, 2 × NCHPh), 5.63 (q, *J* = 7.1 Hz, 1 H, OCHN), 5.45 (q, *J* = 7.0 Hz, 1 H, OCHN), 2.71 (s, 3 H, NCH_3), 2.68 (s, 3 H, NCH_3), 1.68–1.63 (m, 12H, 2 × OCHNC*H*$_3$ and 2 × CH_3); δ_C (126 MHz, $CDCl_3$) 157.9 (C=O), 150.34 (C), 150.28 (C), 140.6 (C), 140.4 (C), 132.7 (C), 132.5 (C), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 122.32 (CH), 122.28 (CH), 121.04 (CH), 121.03 (CH), 111.5 (CH), 111.2 (CH), 109.1 (CH), 109.0 (CH), 94.04 (OCHN), 94.03 (OCHN), 54.3 (NCHPh), 53.5 (NCHPh), 30.9 (NCH_3), 30.5 (NCH_3), 20.32 (CH_3), 20.26 (CH_3), 16.9 (CH_3), 15.4 (CH_3) (1 × CH not observed due to overlapping signals); HRMS (ESI$^+$) $[M+H]^+$ $C_{18}H_{21}N_2O_2^+$ requires 297.1598; found 297.1594.

*1-(2-(2-(1-(4-Chlorophenyl)vinyl)phenoxy)ethyl)-3-methyl urea (**27**)*; Formed during the vinylation of **25** (we were unable to fully purify this compound from the suspected ring expansion product, therefore characterization data reflects this); 122 mg, 74% yield; colourless oil; R_f 0.29 (60% EtOAc/*n*-pentane); δ_H (400 MHz, $CDCl_3$) 7.40–7.31 (m, 7 H, ArH), 7.06 (t, J = 7.4 Hz, ArH), 6.84 (d, J = 8.2 Hz, ArH), 5.66 (d, J = 1.1 Hz, C=CHH), 5.40 (d, J = 1.1 Hz, C=CHH), 3.85 (t, J = 4.7 Hz, CH_2), 3.34 (t, J = 4.7 Hz, CH_2), 2.74 (s, 3 H, NCH_3); HRMS (ESI$^+$) $[M+Na]^+$ $C_{18}H_{19}ClN_2O_2^+$ requires 353.1027; found 353.1024.

N-Acetyl-N-methyl-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxamide; Formed during the optimization of the nitrile vinylation chemistry when using *s*-BuLi as the base; 15 mg; 22% yield; yellow liquid; ν_{max} (film)/cm^{-1} 2935, 2879, 1674, 1495, 1365, 1246, 1058, 752; δ_H (500 MHz, $CDCl_3$) 7.16 (br. dd, *J* = 8.1, 1.5 Hz, 1 H, ArH), 7.08–7.04 (m, 1 H, ArH), 6.93 (dd *J* = 8.1, 1.5 Hz, 1 H, ArH), 6.90–6.86 (m, 1 H, ArH), 4.36 (t, *J* = 4.8 Hz, 2 H, CH_2), 3.91 (br. s, 2 H, CH_2), 3.02 (s, 3 H, NCH_3), 2.24 (s, 3 H CH_3); δ_C (126 MHz, $CDCl_3$) 171.6 (C=O), 156.0

(NC=ON), 146.2 (C), 126.5 (CH), 125.0 (C), 121.7 (CH), 121.2 (CH), 117.9 (CH), 66.0 (CH_2), 43.0 (CH_2), 33.3 (NCH_3), 23.5 (CH_3); HRMS (ESI^+) $[M+Na]^+$ $C_{12}H_{14}N_2O_3Na^+$ requires 257.0897; found 257.0898.

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Appendix A. Supplementary Data

Copies of ^1H and ^{13}C NMR spectra and HPLC traces can be found in the supplementary information document related to this article.

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