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Substrate-Regiocontrolled Synthesis of Enantioenriched Allylic Amines by Palladium-Catalysed Asymmetric Allylic Amination: Formal Synthesis of Fagomine

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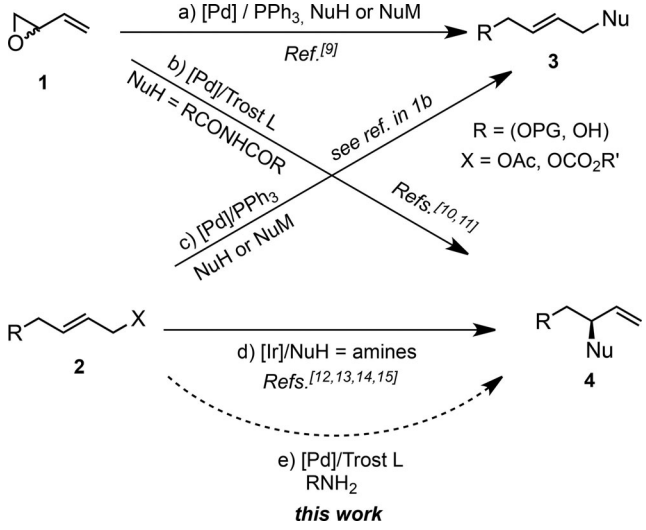
Abstract: Branched allyl amines or linear amines can be obtained from *E*-4-hydroxybuten-2-yl methyl carbonate using the palladium/1,2-diaminocyclohexane (DACH)-catalysed allylic amination by just starting from the unprotected or the protected derivative, respectively. Unhindered primary amines can be used as nucleophiles, thus enlarging the scope of the Pd/DACH catalytic system. Hydrogen bonding involving the free hydroxy group in the unprotected allylic carbonate is proposed to be responsible for the control of the regioselectivity to afford branched isomers, obtained in high *ee*. A short and enantioselective formal synthesis of the glycosidase inhibitor fagomine is described using this method.

Keywords: amination; enantioselectivity; fagomine; palladium; regioselectivity

Introduction

The palladium-catalysed asymmetric allylic substitution reaction is one of the most studied reactions in asymmetric synthesis.[1] However, Pd-catalysed allylic substitution of non-symmetrical monosubstituted allylic electrophiles typically affords achiral linear products (Scheme 1c),[1b] and control of regioselectivity to afford chiral branched products remains a challenge.[2] Many factors influence the regioselectivity of allylic substitution, such as the steric and electronic effects of both the substrates[3] and the nucleophiles,[4] the counterion of the nucleophile,[5] the ligand,[4,6] base,[7] solvent, etc. The chiral 1,2-diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphinobenzoyl) and 1,2-diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphinonaphthoyl) ligands (DACH-phenyl and DACH-naphthyl ligands) developed by Trost efficiently control both enantioselectivity and regioselectivity in non-symmetrical monosubstituted allylic derivatives to afford the branched regioisomer.[8] Nevertheless, the regioselectivity is often determined by several of the aforementioned factors. For instance, vinyl epoxide **1** shows a marked propensity to give 1,4-addition products (**3**) in Pd-catalysed allylic alkylation with carbon nucleophiles in the presence of an achiral phosphine (Scheme 1, path a). This tendency is even greater when amines are used as nucleophiles, and could be due to the electronic effect of the epoxide oxygen, which directs the



Scheme 1. Metal-catalysed allylic substitution reaction with unsymmetrical monosubstituted substrates **1** and **2**.

attack at the remote side of the allyl terminus.[9] However, the combination of vinyl epoxide **1**, DACH ligands, and soft nucleophiles such as imides or imido carboxylates affords the branched derivative **4** with excellent regio- and enantioselectivity (R = OH, Nu = phthalimido) (Scheme 1, path b).[10,11] On the other hand since the seminal contribution by Takeuchi, who first reported branch-selective allylation of carbon and nitrogen nucleophiles using an iridium catalyst,[12] Lee,[13] Helchem[14] and Hartwig[15] later described the regio- and enantioselective synthesis of compound **4** (R = OH or OPG, Nu = nitrogen nucleophiles) from linear monosubstituted allylic electrophiles **2** (R = OH or OPG) using an iridium/phosphoramidite catalyst (Scheme 1, path d). Recent studies of the Pd-DACH catalytic system provided structural and mechanistic information which has been elusive for decades, underlying the importance of hydrogen bonding interactions in the regio- and stereochemical outcome of the process, involving the amide bond contained in the chiral ligand, with either the leaving group in the ionisation step or with the approaching nucleophile in the trapping of the π-allylpalladium complex.[16]

Allylamine **4** is a useful chiral building block in organic synthesis.[11,12b,13–15,17–22] In order to explore the synthesis of **4** from **2** using palladium catalysts, and taking into account the role of DACH ligands in the control of regioselectivity, we wondered whether structural elements in the substrate able to provide hydrogen bonding could bias the regiochemistry of the palladium-catalysed allylic amination of compound **2** to afford branched derivatives **4**. Here we show that enantiopure branched (**4**) (Scheme 1e) or linear achiral (**3**) (Scheme 1c) allylamines can be obtained by a Pd-DACH-catalysed asymmetric allylic amination of compound **2** by starting from the unprotected (R = OH) or the protected (R = OPG) compound, respectively. Contrary to what happens when starting from vinyl epoxide **1**, the use of linear carbonate **2a** tolerates the presence of relatively hard primary amines as nucleophiles. Using the method developed here, a short enantioselective formal synthesis of fagomine,[23,24] an imino sugar of natural origin that shows activity against mammalian gut α-glucosidase and β-galactosidases,[25] is described.

Results and Discussion

The study was carried out using *E*-4-hydroxybuten-2-yl methyl carbonate derivatives (**2**) and for the sake of comparison, butadiene monoepoxide (**1**), two substrates that, upon ionisation under Pd-catalysed allylic amination, could formally give the same π-allylpalladium intermediate. The latter has been extensively used in the Pd-catalysed asymmetric allylic amination reaction using relatively acidic soft nitrogen nucleophiles, but no reports have been made concerning its application with harder amine nucleophiles.[2,10,11] The reaction of butadiene monoepoxide (**1**) with 4-methoxybenzylamine (**5**), 2 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 12 mol% PPh_3 (Table 1, entry 1), afforded a mixture of linear (**3a**) and branched (**4a**) amines in a 76:24 ratio. As expected, the use of chiral (*S,S*)-DACH naphthyl ligand under similar conditions increased the percentage of the branched product **4a** with poor regioselectivity (Table 1, entry 2). The use of a soft nucleophile like phthalimide was described to provide almost exclusively the branched isomer.[2]

These results confirm the crucial role of the nucleophile in the control of the regioselectivity of palladium-catalysed allylic amination of vinyl epoxide **1**.

We then turned our attention to linear carbonate **2a**. The reaction with benzylamine **5** in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2/PPh_3$ furnished a 40:60 mixture of linear bis-allylated **3a′** and branched **4a** amines (Table 1, entry 3).[26] Interestingly, the use of the Pd/(*S,S*)-DACH naphthyl ligand as a catalytic system afforded the branched isomer **4a** as the only regioisomer (Table 1, entry 4) in a practically enantiopure form [98% *ee*, (*R*)].[27] The free hydroxy group at **2a** was next protected and derivatives **2b** and **2e** of different steric hindrances were tested in the Pd-catalysed asymmetric allylic amination. On the one hand, the reaction of methyl ether **2b** with amine **5** in the presence of Pd/(*S,S*)-DACH naphthyl ligand as a catalytic system afforded a 65:35 mixture of linear **3b**/branched **4b** (Table 1, entry 6). On the other hand the reaction of the trityl derivative **2e** with **5** under the standard reaction conditions afforded the linear bis-allylated amine **3e′** in an exclusive manner (Table 1, entry 9).

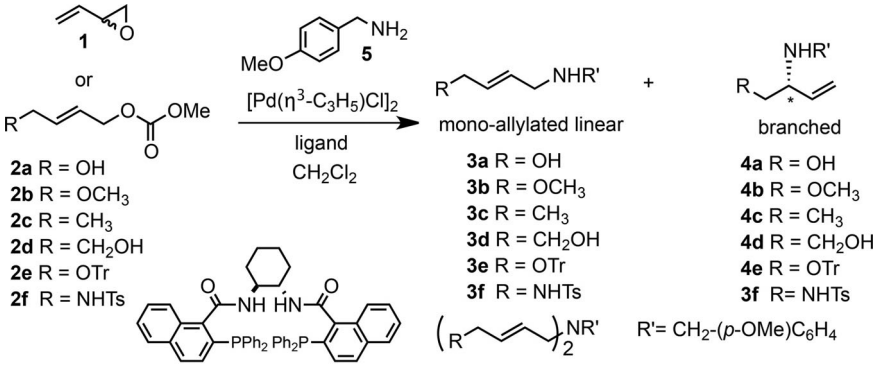
Electronic effects were also explored.[28] The reaction of compound **2c**, with a methyl group instead of a hydroxy moiety, with **5** under similar conditions furnished a 70:30 linear/branched mixture of aminated products (Table 1, entry 7) in a process with virtually the same regioselectivity as that observed in **2b**.

In order to assess the role of hydrogen bonding interactions in the regiochemical outcome of the Pd-catalysed allylic amination, the reaction of **2a** and **5** was performed in methanol as a solvent, to afford an 80:20 mixture of **3a**/**4a** (Table 1, entry 5), thus providing the reversed regioselectivity compared to that obtained previously in CH_2Cl_2, in line with the regioselectivity obtained from **2b** and **2c**.

Homoallylic alcohols could also play a directing role. To prove this, alcohol **2d** was also reacted with amine **5** under similar conditions, but in this case a complex mixture was obtained (Table 1, entry 8).

Furthermore, the reaction **5** with substrate **2f**, resulting from formal replacement of the hydroxy group by a sulfonamido moiety, also led to the formation of the linear bis-allylated product **3f′** (Table 1, entry 10).

Table 1. Palladium-catalysed allylic amination of **1** and **2**.[a]



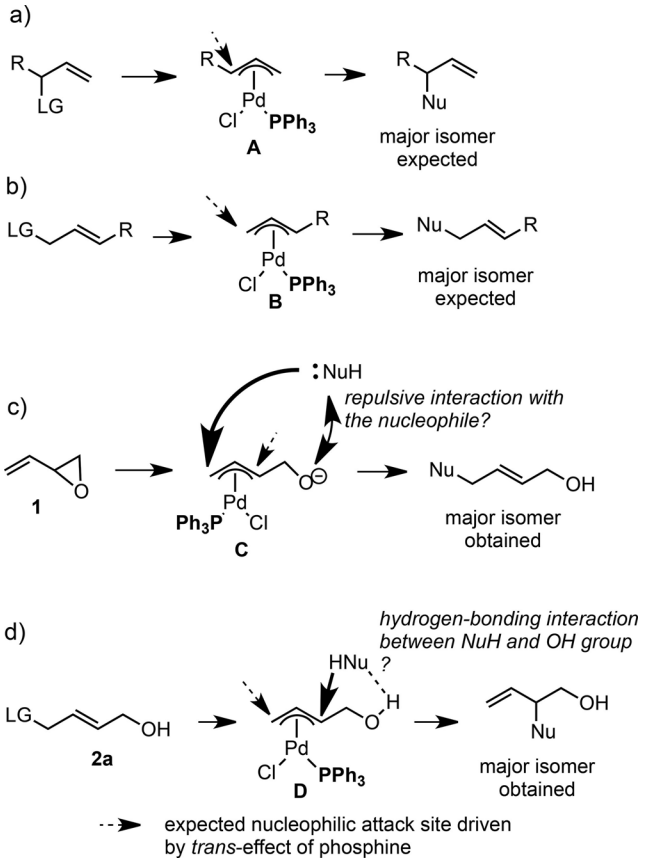
Entry	Substrate	Ligand	Products	Conversion [%]	Linear/branched ratio[b]
1	**1**	PPh_3	**3a**, **4a**	>98	76:24[c]
2	**1**	(*S,S*)-DACH naphthyl	**3a**, **4a**	>98	56:44
3	**2a**	PPh_3	**3a′**, **4a**	>98	40:60[c]
4	**2a**	(*S,S*)-DACH naphthyl	**4a**	>98	<2:98[d]
5[e]	**2a**	(*S,S*)-DACH naphthyl	**3a**, **4a**	>98	80:20
6	**2b**	(*S,S*)-DACH naphthyl	**3b**, **4b**	>98	65:35
7	**2c**	(*S,S*)-DACH naphthyl	**3c**, **4c**	>98	70:30
8	**2d**	(*S,S*)-DACH naphthyl	**3d**, **4d**	>98	complex mixture
9	**2e**	(*S,S*)-DACH naphthyl	**3e′**	>98	>98:2
10	**2f**	(*S,S*)-DACH naphthyl	**3f′**	>98	>98:2

[a] *Conditions:* catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), (*S,S*)-DACH naphthyl ligand (6 mol%) or PPh_3 (12 mol%), 1 equiv. of substrate, 1.1 equiv. of nucleophile (**5**), room temperature, reaction time = 16 h, solvent, CH_2Cl_2, concentration = 0.02 M.
[b] The branched/linear ratio was determined by ^1H NMR spectroscopy of the crude products.
[c] Racemic **4a** was obtained.
[d] *ee* = 98% (*R*). Determined by HPLC, see Ref.[27]
[e] The reaction was performed in MeOH.

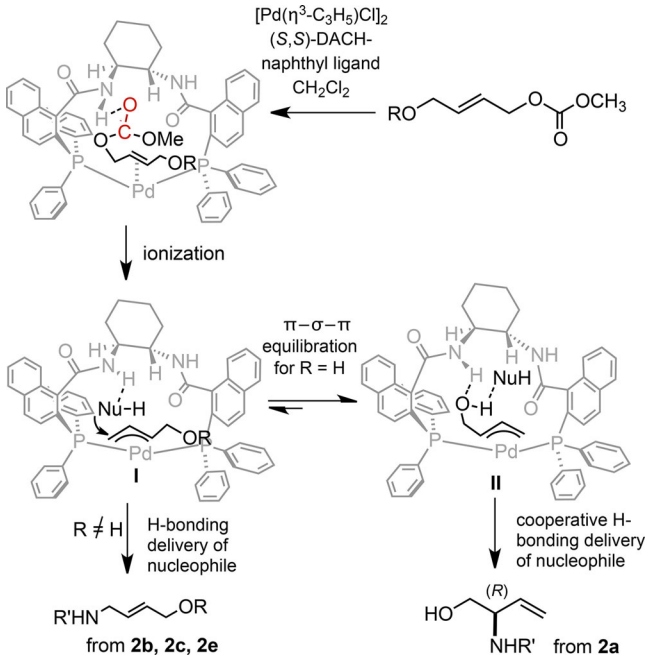
Control experiments using PPh_3 as a ligand should give us some information on the key issues governing the regioselectivity of the racemic process in the substrates tested. A comparison of entries 1 and 3 in Table 1 infers that the product distribution depends on the structure of the starting material.[29]

When chloride ion conditions are present, i.e., starting from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a precatalyst in the presence of PPh_3, moderately good levels of regioretention should be expected through the intermediacy of non-symmetrically ligated $[Pd(PPh_3)(\eta^3\text{-allyl})Cl]$ complexes **A** and **B**, respectively (Scheme 2a and b). These complexes are envisioned to be formed by the *trans*-effect of phosphorus in the initial ionisation step, whereas the subsequent nucleophilic attack step essentially results from the preferential attack *trans* to phosphine.[29a,b,d] These memory effects should be especially strong when starting from *trans*-linear electrophiles with very good leaving groups (e.g., carbonates), as in Scheme 2b. However, the results obtained here from **1** and **2a** show a slightly different trend. The large amount of linear isomer from epoxide **1** could arise from repulsive interactions of the incoming amine nucleophile with the alkoxide ion (Scheme 2c). Furthermore, preferential formation of the branched isomer from the linear substrate **2a** could be explained from intermediate **D** by hydrogen bonding-assisted nucleophilic attack of the nucleophile with the hydroxy group in the substrate (R = H), counteracting the *trans*-effect of phosphine in the nucleophilic addition step (Scheme 2d). In turn, Pd-catalysed asymmetric allylic amination of **1** using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/(*S,S*)-DACH naphthyl ligand (entry 2, Table 1) gave equimolar amounts of branched and linear isomer, showing an increase in the branched isomer compared to the amount obtained in the racemic reaction.

More interestingly, the reaction of allyl carbonate **2a** with **5** using DACH-naphthyl ligand produced a dramatic increase in the proportion of the branched isomer, so that this was the only regioisomer observed by NMR spectroscopy. This is in contrast with the results provided by the protected substrates, which gave predominantly linear achiral regioisomers. The high levels of regioretention observed in the protected derivatives could be explained by the formation of the Pd-allyl intermediate **I**. The departure of the leaving group is likely to be assisted by hydrogen-bonding to



Scheme 2. Regioselectivity of the Pd-catalysed allylic amination of **1** and **2a** due to repulsive or hydrogen-bonding interactions and the electronic effects affecting non-symmetically ligated [Pd(η^3-allyl)ClPPh$_3$] complexes.



Scheme 3. Rationalisation of regioselectivity and enantioselectivity in the Pd-catalysed asymmetric allylic amination reaction of allylic carbonates **2a–c**, **e** with *p*-methoxybenzylamine.

the NH amide of the ligand, followed by hydrogen bonding-mediated delivery of the amine in a process with no significant π-σ-π equilibration (Scheme 3). The high linear regioselectivity obtained from the sterically demanding trityl-protected substrate **2e** would result from the direct nucleophilic attack of the amine on the kinetically favoured complex **I**, with no apparent isomerisation to the more congested complex **II**, with important non-bonded interactions of the trityl group with the naphthyl moiety in close proximity (Scheme 3).

The reversed regioselectivity obtained from **2a** may be explained by a fast π-σ-π interconversion of the kinetically favoured π-allylpalladium complex **I** to the diastereomeric intermediate **II**. The driving force for this isomerisation could be the additional stabilisation of the latter complex compared to **I** due to hydrogen bonding interactions between the N–H bond in the catalyst and the hydroxy group in the unprotected substrate (Scheme 3). Nucleophilic attack by the amine on the more substituted terminus of the allyl moiety on **II** could result from cooperative hydrogen-bonding interactions.[30] Accordingly, the regioselectivity obtained from the reaction of **2a** and *p*-methoxybenzylamine in methanol as a solvent (Table 1, entry 5, l/b ratio of 80:20), similar to those obtained with the protected substrates, underlines the importance of hydrogen-bonding interactions, which are disrupted when the solvent is protic.

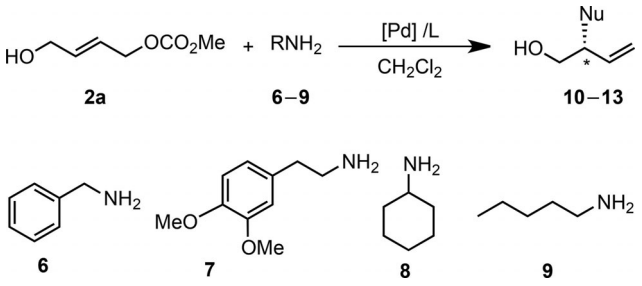
Furthermore, the divergence in regioselectivity of substrate **2f** compared to **2a** may be attributed to a significant difference in their acid properties. The TsNH group may expected to be deprotonated under the reaction conditions, thus possibly leading to a repulsive effect with the nucleophile, in line with the results obtained when starting from the vinyl epoxide. Steric factors could also play a role.

We next generalised the reaction of carbonate **2a** using a range of primary amines **6–9** to give the corresponding allylic secondary amines **10–13** in excellent yields (up to 96%) (Table 2, entries 1–4). Moreover, excellent enantioselectivities were obtained in all cases (90 to 98% *ee*).

The reaction with secondary amines was then explored. The reaction of **2a** with pyrrolidine (**14**) and dibenzylamine (**15**) using Pd/(*S,S*)-DACH naphthyl as a catalyst under the optimised reaction conditions in both cases predominantly afforded the linear isomers **17** and **18** with linear/branched ratios of 67:33 and 85:15, respectively (Scheme 4a).

The reaction of **2a** with *tert*-butylamine (**16**) as an example of a bulky primary amine under the same conditions, furnished linear compound **19** as a major regioisomer (branched/linear ratio 30:70 (Scheme 4a).

Table 2. Palladium-catalysed allylic amination of **2a** with primary amines **6–9** as nucleophiles.[a]



Entry	R-NH_2	Product	Conversion (Yield [%])[b]	b/l Ratio[c]	*ee* [%][d]
1	**6**	**10**	>98 (93)	>98:2	90 (*R*)
2	**7**	**11**	>98 (96)	>98:2	95
3	**8**	**12**	>98 (91)	>98:2	98
4	**9**	**13**	>98 (90)	>98:2	96

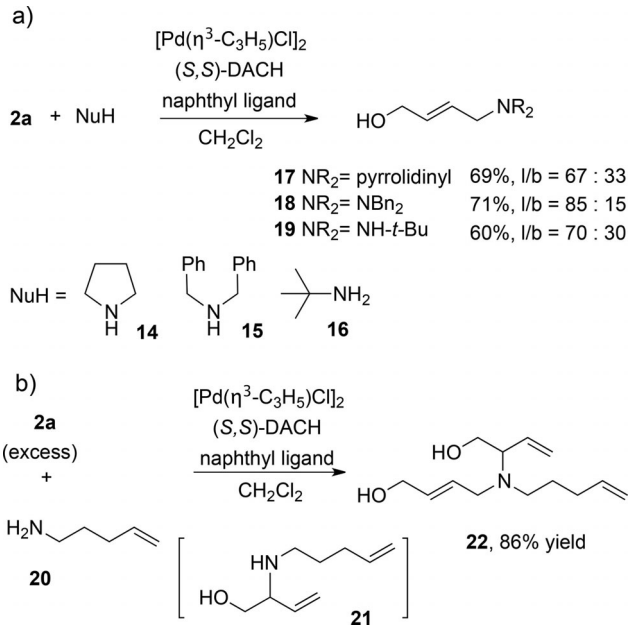
[a] *Conditions:* catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), (*S,S*)-DACH naphthyl ligand (6 mol%), 1 equiv. of carbonate, 1.1 equiv. of nucleophile, room temperature, reaction time = 16 h, carbonate concentration = 0.02 M.

[b] Isolated yield of branched regioisomer.

[c] Determined by ^{1}H NMR spectroscopy of the crude reaction.

[d] Determined by HPLC, see Ref.[27]

These results clearly show the sensitivity of the regioselectivity of this reaction to the steric hindrance of the nucleophile, so that hindered primary or secondary amines outweigh the restrictions imposed by the DACH naphthyl ligand. Similarly, when the reaction of amine **20** was carried out with an excess of **2a**, compound **22** was obtained (Scheme 4b).



Scheme 4. (a) Pd-catalysed allylic amination of **2a** using bulky amines and (b) branched-linear consecutive allylations by reaction of **20** with **2a** in excess.

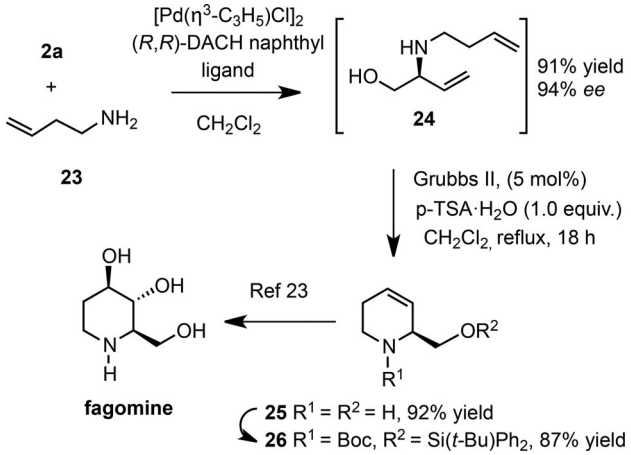
The outcome of this reaction can be explained by initial Pd-catalysed asymmetric allylic amination of **2a** to give the branched derivative **21**, a secondary amine which acts as a nucleophile in a subsequent allylic amination of **2a** in excess to afford the linear aminated product **22**.

On the other hand, the effect of branching at the α position to the hydroxy group as in (*E*)-4-hydroxypent-2-en-1-yl methyl carbonate[31] was also explored. At the standard concentration used along this study (0.02 M), very low conversion was observed and the reaction of this allylic carbonate with **5** led to the formation of the corresponding bis-allylated linear product in very low yield (<18%) only at a higher concentration (0.2 M), probably due to steric factors (for further details see the Supporting Information).

The usefulness of this synthetic protocol is illustrated by the enantioselective two-step synthesis of piperidine **25**, an ideal precursor of fagomine, an imino sugar that shows activity against mammalian gut α-glucosidase and β-galactosidase.[23,32]

Our synthetic strategy is based on RCM of aminobutenol **24** (Scheme 5).[33,34] This approach could give access to enantiomerically pure, stereochemically defined, five-, six- and seven-membered heterocycles. Asymmetric syntheses employing these intermediates could lead to discovery of further biologically relevant piperidine/azepane alkaloids and imino sugars.[35]

The key intermediate **24** was thus first obtained using the (*R,R*)-DACH naphthyl ligand under standard conditions in 91% yield and 94% *ee*. After assessing the high degree of regio- and stereoselectivity of this reaction, the crude compound **24** obtained by reaction of **2a** with **23** was directly subjected to ring closing metathesis under Wright's conditions,[36] using 5 mol% of Grubbs's second generation catalyst in the presence of one equivalent of *p*-toluenesulfonic acid



Scheme 5. Formal synthesis of fagomine.

(*p*-TsOH·H_2O) to produce the azacycloalkene **25** in excellent yield (Scheme 5).

Protection of the hydroxy and the amine functionalities led to compound **26**, a chiral intermediate in the synthesis of fagomine.[23] The protected compound **26** that we synthesised showed the same spectroscopic data and optical rotation as reported in the literature for this compound {$[\alpha]_D^{25}$: −142.4 (*c* 0.94, $CHCl_3$), $[\alpha]_D^{27}$: −150.0 (*c* 1.04, $CHCl_3$) described}, so that the synthesis of **26** constitutes a formal synthesis of fagomine.

Conclusions

Palladium/DACH naphthyl-catalysed allylic amination of carbonate **2a** affords chiral branched amines **4**, intermediates for preparing biologically important compounds, in high yields, regio- and enantioselectivities. The use of linear allylic electrophile **2a** as an alternative to vinyl epoxide **1** as a substrate increases the synthetic possibilities towards chiral allylic amines as it tolerates the use of hard alkylamines as nucleophiles. The excellent control of the regio- and enantioselectivity in this case might be due to hydrogen bonding interactions between the hydroxy group in the substrate and the diphenylphosphinobenzoic acid-derived ligand in the Pd complex, as it can be deduced from the dramatic change in the regioselectivity when the hydroxy group is protected or replaced by an alkyl chain. The regioselectivity observed in this study is dependent on the steric hindrance of the amine nucleophile, so that unhindered primary amines render high branch-regioselectivity whereas bulky primary or secondary amines lead to the preferential formation of the linear allylated product. The results described here expand the application of the palladium-DACH naphthyl system for the preparation of the type **4** allylic amines, and a short formal enantioselective synthesis of glycosidase inhibitor fagomine is reported based on this protocol.

Experimental Section

General Information

All chemicals used, including DACH-naphthyl ligand and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz, respectively, in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to either $CDCl_3$ (7.26 ppm ^1H, 77.16 ppm ^{13}C) or Me_4Si (0.00 ppm) as an internal reference, unless otherwise stated. Spectra were fully assigned using gCOSY, gHSQC, gHMBC and NOESY. ESI MS (TOF) were run on an LC/MS (TOF) instrument. Optical rotations were measured at room temperature with 10 cm cells. IR spectra were recorded on an FT-IR-ATR spectrophotometer. Reactions were monitored by TLC, on 0.25 mm silica gel 60 F254 glass or aluminium plates. Developed TLC plates were visualised under a short-wave UV lamp (254 nm), by heating plates dipped in ethanol/H_2SO_4 (15:1), or in a basic solution of potassium permanganate. Flash column chromatography was carried out using a forced flow of the indicated solvent on silica gel 60 (230–400 mesh) and was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility. Absolute configurations for new non-racemic chiral compounds were assigned on the basis of a general rule concerning the steric course of the Pd-catalysed allylic substitution.[37] This rule was found to be correct for all cases that were verified by comparison with the data described for compounds independently synthesised elsewhere. The configurations of the compounds obtained from carbonate **2a** were identical to those obtained from **1**. Allylic carbonates **2a**, **2c** and **2e** were synthesised according to reported procedures.[14,15b] Carbonate **2f** was synthesised from (*E*)-4-bromobut-2-en-1-yl methyl carbonate following an analogous procedure described for the Z-isomer[38] (see the Supporting Information).

General Procedure for the Palladium-Catalysed Asymmetric Allylic Amination of Allylic Carbonates

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mg, 2 mol%), the (*S,S*)-DACH naphthyl ligand (5.5 mg, 6 mol%) and CH_2Cl_2 (10 mL) were introduced in a Schlenk tube under an argon atmosphere. The resulting solution was stirred for 20 min. The carbonate (0.116 mmol) and nucleophile (0.127 mmol) were then successively introduced. The mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with H_2O. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude was purified by flash chromatography to afford the pure product. The enantiomeric excess was determined by HPLC analysis using a DAICEL CHIRALCEL OD-H column. A racemic mixture was initially prepared and separated in order to confirm the signals of both enantiomers.

(*E*)-5-Hydroxypent-2-enyl methyl carbonate (2d): But-3-en-1-ol (30 mg, 0.40 mmol) and allyl methyl carbonate (47 mg, 0.40 mmol) were added *via* syringe to a stirred solution of 2nd generation Grubbs catalyst (17 mg, 0.02 mmol, 5 mol%) in CH_2Cl_2 (2 mL). The flask was fitted with a condenser and the mixture was refluxed under argon for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column, eluting with hexanes:ethyl acetate (6:4) to give **2d** as a brown oil; yield: 30 mg (46%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (dtt, $J =$ 15.3 Hz, 6.7 Hz, 1.0 Hz, 1 H), 5.68 (dtt, $J = 15.3$ Hz, 6.1 Hz, 1 Hz, 1 H), 4.57 (dd, $J = 6.1$ Hz, 1.0 Hz, 1 H), 3.76 (s, 3 H), 3.66 (pseudo q, $J = 6.1$ Hz, 2 H), 2.32 (pseudo q, $J = 6.1$ Hz, 2 H), 1.73 (t, $J = 5.2$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.7$, 133.0, 126.2, 68.4, 61.6, 54.8, 35.7; HR-MS (ESI-TOF): $m/z = 161.0786$ $[M+H]^+$, calcd. for $C_7H_{13}O_4$: 161.0808.

(*E*)-4-Methoxy-*N*-(4-methoxybenzyl)but-2-en-1-amine (3b) and (*R*)-1-methoxy-*N*-(4-methoxybenzyl)but-3-en-2-amine (4b): NaH (0.2 g, 8.2 mmol) was added to a solution of (*E*)-4-hydroxybut-2-enyl methyl carbonate (**2a**) (0.6 mg, 4.1 mmol) in THF (25 mL) at room temperature. After 15 min, CH_3I (1.02 mL, 16 mmol) was added dropwise to the reaction mixture which was then stirred for 4 h. Saturated NH_4Cl/H_2O was then added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over magnesium sulfate. After removal of the solvents with a rotary evaporator, the residue was purified by column chromatography (hexanes:ethyl acetate = 8:3) to give **2b** as a colourless oil that appeared to be slightly contaminated with 1,4-dimethoxy-but-2-ene, which could not be separated and the mixture was directly used in the next reaction.

Following the general procedure carbonate **2b** was treated with (4-methoxyphenyl)methanamine **5** in the presence of the Pd catalyst. The reaction crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to give an inseparable mixture of regioisomers **4b** and **3b**; yield: 15 mg (60%; ratio 35:65). Spectroscopic data extracted from the spectrum of the mixture are as follows. **4b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 2H), 6.89–6.78 (m, 2H), 5.80–5.63 (m, 1H), 5.27 (dd, J = 17.0, 1.7 Hz, 1H), 5.21 (dd, J = 10.1, 1.7 Hz, 1H), 3.79 (s, 3H), 3.78 (d, J = 12.8 Hz, 1H), 3.58 (d, J = 12.8 Hz, 1H), 3.38–3.32 (m, 3H), 3.32 (s, 3H). **3b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 2H), 6.89–6.78 (m, 2H), 5.80–5.63 (m, 2H), 3.94–3.87 (m, 2H), 3.51 (s, 3H), 3.52 (s, 2H), 3.31 (s, 3H), 3.07 (d, J = 5.3 Hz, 2H); HR-MS (ESI-TOF, of the mixture): m/z = 222.1480 $[M+H]^+$, calcd. for $C_{13}H_{20}NO_2$: 222.1489.

(*E*)-*N*-(4-Methoxybenzyl)pent-2-en-1-amine (3c): Carbonate **2c** was treated with (4-methoxyphenyl) methanamine **5** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1) to give **3c** as a colourless oil; yield: 16 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 2H), 6.87–6.80 (m, 2H), 5.66–5.55 (m, 1H), 5.52–5.42 (m, 1H), 3.80 (s, 3H), 3.48 (s, 2H), 2.99 (dd, J = 1.0 Hz, J = 6.5 Hz, 2H), 2.09–1.99 (m, 2H), 0.99 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 136.2, 131.2, 130.5 (2C), 125.7, 113.6 (2C), 56.6, 55.4, 55.3, 25.6, 13.8; FT-IR-ATR: ν = 2961, 2932, 1511, 1247, 969 cm^{-1}; HR-MS (ESI-TOF): m/z = 206.1531 $[M+H]^+$, calcd. for $C_{13}H_{20}NO$: 206.1539.

Bis-allylated linear product 3a′: Following the general procedure carbonate **2a** was treated with (4-methoxyphenyl)-methanamine **5** in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and PPh_3 as the ligand. The product ratio was determined by ^{1}H NMR spectroscopy (bis-allylated linear **3a′**/branched **4a** = 40:60). The reaction crude was purified by flash column chromatography (silica gel, EtOAc:methanol, 95:5) to give **3a′** as a colourless oil: yield: 9 mg (29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.12 (m, 2H), 6.84–6.71 (m, 2H), 5.79–5.59 (m, 4H), 4.10–4.02 (m, 2H), 3.73 (s, 3H), 3.47 (s, 2H), 3.07–2.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 132.3, 130.3, 129.6, 129.5, 113.7, 63.5, 57.6, 55.4, 55.4; FT-IR-ATR: ν = 3297, 2924, 1512, 1247 cm^{-1}; HR-MS (ESI-TOF): m/z = 278.1736 $[M+H]^+$, calcd. for $C_{16}H_{24}NO_3$: 278.1751.

Bis-allylated linear product (3e′): Following the general procedure carbonate **2e** was treated with (4-methoxyphenyl)methanamine **5** in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/(*S,S*)-DACH naphthyl ligand. The reaction crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 95:5) to give **3e′** as a colourless oil; yield: 63 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.41 (m, 12H), 7.32–7.19 (m, 22H), 5.93–5.61 (m, 4H), 3.79 (s, 3H), 3.64–3.62 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 144.4, 131.3, 130.4, 130.3, 129.0, 128.8, 127.9, 127.1, 113.7, 87.0, 64.7, 57.0, 55.4, 55.3; HR-MS (ESI-TOF): m/z = 762.3951 $[M+H]^+$, calcd. for $C_{54}H_{52}NO_3$: 762.3942.

Bis-allylated linear product (3f′): Following the general procedure, carbonate **2f** was treated with 4-methoxybenzylamine **5** in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/(*S,S*)-DACH naphthyl ligand. The reaction crude was purified by flash column chromatography (hexane:EtOAc 1:9) to give **3f′** as a yellow oil; yield: 0.020 g (30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.3 Hz, 4H), 7.29 (d, J = 8.0 Hz, 4H), 7.13 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.68–5.42 (m, 4H), 4.46 (*app* t, J = 6.0 Hz, 2H), 3.80 (s, 3H), 3.51 (t, J = 5.8 Hz, 4H), 3.36 (s, 2H), 2.90 (d, J = 5.7 Hz, 4H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 143.5, 136.9, 131.6, 129.9, 129.8, 127.5, 127.2, 113.6, 57.5, 55.3, 55.1, 45.0, 21.6; HR-MS (ESI-TOF): m/z = 584.2246 $[M+H]^+$, calcd. for $C_{30}H_{38}N_3O_5S_2$: 584.2253.

(−)-(*R*)-2-(4-Methoxybenzylamino)but-3-en-1-ol (4a): Following the general procedure carbonate **2a** was treated (4-methoxyphenyl)methanamine **5** in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/(*S,S*)-DACH naphthyl ligand. The reaction crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to give **4a** as a colourless oil: yield: 23 mg (96%). HPLC [Daicel Chiralcel OD-H, *n*-hexane:*i*-PrOH, 85:15, flow = 0.5 mL min^{-1}, detection, UV 210 nm]: retention times (min) 12.68 (99.0%), 16.57 (0.96%); 98% *ee*; $[\alpha]_D^{25}$: −6.9 (*c* 0.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.68 (ddd, J = 17.0 Hz, 10.8 Hz, 7.4 Hz, 1H), 5.25 (d, J = 10.8 Hz, 1H), 5.23 (d, J = 17.0 Hz, 1H), 3.81 (d, J = 13.0 Hz, 1H), 3.80 (s, 3H), 3.61 (d, J = 13.0 Hz, 1H), 3.60 (dd, J = 10.5 Hz, 6.0 Hz, 1H), 3.38 (dd, J = 10.5 Hz, 7.9 Hz, 1H), 3.28–3.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 137.5, 132.3, 129.5 (2C), 117.9, 114.0 (2C), 64.7, 62.0, 55.4, 50.4; FT-IR-ATR: ν = 3297, 2924, 1512, 1247 cm^{-1}; HR-MS (ESI-TOF): m/z = 208.1311 $[M+H]^+$, calcd. for $C_{12}H_{18}NO_2$: 208.1332.

***N*-(4-Methoxybenzyl)pent-1-en-3-amine (4c):** Carbonate **2c** was treated with (4-methoxy-phenyl)methanamine **5** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1) to give **4c** as a colourless oil; yield: 3 mg (12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 2H), 6.89-6.83 (m, 2H), 5.61 (ddd, J = 17.1, 10.3, 8.2 Hz, 1H), 5.19–5.07 (m, 2H), 3.79 (s, 3H), 3.76 (d, J = 12.9 Hz, 1H), 3.59 (d, J = 12.9 Hz, 1H), 2.93 (td, J = 8.2, 5.4 Hz, 1H), 1.61–1.36 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 141.2, 132.9, 129.5, 116.4, 113.9, 62.8, 55.4, 50.8, 28.5, 10.4; HR-MS (ESI-TOF): m/z = 206.1542 $[M+H]^+$, calcd. for $C_{13}H_{20}NO$: 206.1539.

(−)-(*R*)-2-(Benzylamino)but-3-en-1-ol (10): Carbonate **2a** was treated with benzylamine following the general procedure. The reaction crude was isolated by flash column chro-

matography (silica gel, hexanes: EtOAc, 1:1) to give **10** as a colourless oil; yield:18 mg (93%). HPLC [Daicel Chiralcel OD-H, *n*-hexane:*i*-PrOH, 85:15, flow = 0.5 mL min^{-1}, detection, UV 210 nm]: retention times (min), 11.67 (95.18%), 14.89 (4.82%); 90% *ee*; $[\alpha]_D^{25}$: −6.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 3H), 7.29–7.24 (m, 2H), 5.75–5.64 (m, 1H), 5.29–5.20 (m, 2H), 3.89 (d, J = 13.0 Hz, 1H), 3.69 (d, J = 13.0 Hz, 1H), 3.63 (dd, J = 10.6, 4.5 Hz, 1H), 3.40 (dd, J = 10.6, 7.9 Hz, 1H), 3.24 (td, J = 7.8, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 137.2, 128.6, 128.4, 127.3, 118.1, 64.7, 62.2, 51.0; FT-IR-ATR: ν = 3303, 2926, 2851 cm^{-1}; HR-MS (ESI-TOF): m/z = 178.1199 $[M+H]^+$, calcd. for $C_{11}H_{16}NO$: 178.1226.

(−)-(*R*)-2-(3,4-Dimethoxyphenethylamino)but-3-en-1-ol (11): Carbonate **2a** was treated with 2-(3,4-dimethoxyphenyl)ethanamine (**7**) following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to give **11** as a colourless oil; yield: 28 mg (96%). HPLC [Daicel Chiralcel OD-H, heptane (0.1% DEA):EtOH, 95:5, flow = 1 mL min^{-1}, detection, UV 210 nm]: retention times (min), 25.97 (97.3%), 29.11 (2.7%); 95% *ee*; $[\alpha]_D^{20}$: −15.5 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83–6.70 (m, 3H), 5.62 (ddd, J = 17.0 Hz, J = 10.7 Hz, 7.6 Hz, 1H), 5.17 (d, J = 10.7 Hz, 1H), 5.15 (d, J = 17.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.58 (dd, J = 10.4 Hz, 4.5 Hz, 1H), 3.33 (dd, J = 10.4 Hz, 7.9 Hz, 1H), 3.22–3.15 (m, 1H), 3.00–2.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 147.6, 137.5, 132.5, 120.7, 117.6, 112.0, 111.4, 64.6, 62.8, 56.0, 56.0, 48.5, 36.2; FT-IR-ATR: ν = 3297, 2927, 1514, 1260, 1026 cm^{-1}; HR-MS (ESI-TOF): m/z = 252.1592 $[M+H]^+$, calcd. for $C_{14}H_{22}NO_3$: 252.1594.

(−)-(*R*)-2-(Cyclohexylamino)but-3-en-1-ol (12): Following the general procedure carbonate **2a** was treated with cyclohexanamine (**8**).The reaction crude was purified by flash column chromatography (silica gel, EtOAc:MeOH, 9:1) to give **12** as a white foam; yield: 18 mg (91%). HPLC [Daicel Chiralcel OD-H, *n*-hexane:*i*-PrOH, 85:15, flow = 0.5 mL min^{-1}, detection, UV 306 nm]: retention times (min), 6.54 (99.14%), 5.59 (0.86%); 98% *ee*; $[\alpha]_D^{25}$: −25.0 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71–5.60 (m, 1H), 5.20–5.14 (m, 2H), 3.59–3.53 (m, 1H), 3.36–3.25 (m, 2H), 2.52 (tt, J = 10.3 Hz, 3.8 Hz, 1H), 2.32 (bs, 1H), 1.94–1.86 (m, 1H), 1.82–1.67 (m, 3H), 1.63–1.54 (m, 1H), 1.33–1.09 (m, 4H), 1.07–0.94 (m, 1H):; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 117.0, 64.7, 59.1, 53.6, 37.7, 33.3, 26.2, 25.2, 24.8; FT-IR-ATR: ν = 3248, 2923, 2855, 1088 cm^{-1}; HR-MS (ESI-TOF): m/z = 170.1567 $[M+H]^+$, calcd. for $C_{10}H_{20}NO$: 170.1539.

(−)-(*R*)-2-(Pentylamino)but-3-en-1-ol (13): Carbonate **2a** was treated with pentan-1-amine (**9**) following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc:MeOH, 9:1) to give compound **13** as a colourless oil; yield: 16 mg (90%). HPLC [Daicel Chiralcel OD-H, *n*-hexane:*i*-PrOH, 85:15, flow = 0.5 mL min^{-1}, detection, UV 313 nm]: retention times (min), 6.23 (98.18%), 7.81 (1.82%); 96% *ee*; $[\alpha]_D^{25}$: −9.9 (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73–5.61 (m, 1H), 5.26–5.17 (m, 2H), 3.62 (dd, J = 10.6 Hz, 4.7 Hz, 1H), 3.39 (dd, J = 10.6 Hz, 7.8 Hz, 1H), 3.20 (tdt, J = 7.8 Hz, 4.7 Hz, 0.9 Hz, 1H), 2.85 (bs, 1H), 2.71 (ddd, J = 11.4 Hz, 8.1 Hz, 6.6 Hz, 1H), 2.50 (ddd, J = 11.4 Hz, 8.1, 6.4 Hz, 1H), 1.58–1.41 (m, 2H), 1.37–1.23 (m,4H), 0.95–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 118.0, 64.3, 63.0, 47.0, 29.7, 29.6, 22.6, 14.2; FT-IR-ATR: ν = 3298, 2927, 2857, 1457, 1048 cm^{-1}; HR-MS (ESI-TOF): m/z = 337.2859 $[2M+Na]^+$, calcd. for $C_{18}H_{38}N_2NaO_2$: 337.2831.

(*E*)-4-(Pyrrolidin-1-yl)but-2-en-1-ol (17):[39] Carbonate **2a** was treated with pyrrolidine (**14**) following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc) to give compound **17** as a colourless oil; yield: 11 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91–5.72 (m, 2H), 4.15–4.09 (m, 2H), 3.15–3.09 (m, 2H), 2.57–2.50 (m, 4H), 1.83–1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.5, 127.8, 59.8, 53.8, 52.4, 23.5.

(*E*)-4-(Dibenzylamino)but-2-en-1-ol (18):[40] Carbonate **2a** was treated with dibenzylamine (**15**) following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to give compound **18** as a colourless oil; yield: 21 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.16 (m, 10H), 5.83–5.71 (m, 2H), 4.10 (d, J = 4.3 Hz, 2H), 3.58 (s, 4H), 3.07 (d, J = 4.8 Hz, 2H).

(*E*)-4-(*tert*-Butylamino)but-2-en-1-ol (19): Carbonate **2a** was treated with *tert*-butylamine **16** following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH) to give compound **19** as a colourless oil; yield: 10 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.79 (m, 2H), 4.13–4.08 (m, 2H), 3.21 (d, J = 4.6 Hz, 2H), 2.30 (bs, 1H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.4, 130.1,, 63.0, 51.1, 44.3, 28.8; HR-MS (ESI-TOF): m/z = 166.1225 $[M+Na]^+$, calcd. for $C_8H_{17}NNaO$: 166.1202.

(*E*)-4-[(1-Hydroxybut-3-en-2-yl)(pent-4-en-1-yl)amino]-but-2-en-1-ol (22): Carbonate **2a** (0.068 g, 0.464 mmol) was treated with pentan-1-amine **20** (0.0197 g, 0.232 mmol) following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc:-MeOH, 9:1) to give **22** as a colourless oil; yield: 45 mg (86%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.62 (m, 4H), 5.27 (ddd, J = 10.5 Hz, 1.7 Hz, 0.6 Hz, 1H), 5.15 (ddd, J = 17.2 Hz, 1.7 Hz, 0.9 Hz, 1H), 4.16–4.12 (m, 2H), 4.14 (d, J = 5.4 Hz, 2H), 3.49–3.44 (m, 2H) 3.38–3.26 (m, 2H), 2.95 (dd, J = 14.4 Hz, 7.5 Hz, 1H), 2.63–3.53 (m, 1H), 2.33 (ddd, J = 13.0 Hz, 8.3 Hz, 4.6 Hz, 1H), 2.14–1.96 (m, 2H), 1.64–1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 132.6, 132.2, 130.1, 120.1, 114.9, 63.6, 63.3, 60.8, 51.7, 48.7, 31.5, 27.6; FT-IR-ATR: ν = 3366, 2924, 1418, 997, 912 cm^{-1}; HR-MS (ESI-TOF): m/z = 226.1830 $[M+H]^+$, calcd. for $C_{13}H_{24}NO_2$: 226.1802.

(+)-(*S*)-2-(But-3-enylamino)but-3-en-1-ol (24): Carbonate **2a** was treated with but-3-en-1-amine (**23**) in the presence of the (*R,R*)-DACH naphthyl ligand following the general procedure. The reaction crude was purified by flash column chromatography (silica gel, EtOAc:MeOH, 9:1) to give **24** as a colourless oil; yield: 14 mg (91%). HPLC [Daicel Chiralcel OD-H, *n*-hexane:*i*-PrOH, 85:15, flow = 0.5 mL min^{-1}, detection, UV 280 nm]: retention times (min), 11.7 (3%), 13.4 (97%); 94% *ee*; $[\alpha]_D^{25}$: +12.1 (*c* 4.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (tdd, J = 17.0 Hz, 10.1 Hz, 6.8 Hz, 1H), 5.64 (ddd, J = 17.2 Hz, 10.6 Hz, 7.6 Hz, 1H), 5.23–5.17 (m, 2H), 5.14–5.01 (m, 2H), 3.59 (dd, J = 10.5 Hz, 4.5 Hz, 1H), 3.35 (dd, J = 10.5 Hz, 8.0 Hz, 1H), 3.22–3.13 (m, 1H), 2.76 (td, J = 11.2 Hz, 7.0 Hz, 1H), 2.56 (td, J =

11.2 Hz, 6.7 Hz, 1H), 2.30–2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 136.5, 117.5, 116.7, 64.6, 62.8, 46.1, 34.6; FT-IR-ATR: ν = 3277, 3075, 2919, 2849, 1455, 1101 cm^{-1}; HR-MS (ESI-TOF): m/z = 141.1241 $[M+H]^+$, calcd. for $C_8H_{16}NO$: 142.1226.

(−)-(1*S*)-(1,2,5,6-Tetrahydropyridin-2-yl)methanol (25): $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.8 mg, 2 mol%), the (*R,R*)-DACH naphthyl ligand (5.5 mg, 6 mol%) and CH_2Cl_2 (10 mL), were introduced in a Schlenk tube under an argon atmosphere. The resulting solution was stirred for 20 min, and then, the carbonate **2a** (16.8 mg, 0.115 mmol) and but-3-en-1-amine (**23**) (9.0 mg, 0.127 mmol) were successively introduced. The mixture was stirred at room temperature for 18 h. Then, *p*-toluenesulfonic acid monohydrate (22 mg, 0.115 mmol) was added to the solution and the mixture was stirred for 30 min at room temperature until the mixture became a homogeneous solution. Grubbs' second-generation catalyst (5 mg, 0.0058 mmol, 5 mol%) was then added, and the mixture was stirred under reflux for 18 h. Water (20 mL) was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The aqueous phase was concentrated under vacuum. The residue was dissolved in MeOH and Amberlite™-OH was added. The heterogeneous mixture was stirred for 2 h and then, filtered, and concentrated to afford pure product **25** as a colourless oil; yield: 12 mg (92%); $[\alpha]_D^{25}$: −50.6 (*c* 3.2, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 5.92–5.82 (m, 1H), 5.63 (ddd, *J* = 10.3, 4.2 Hz, 2.2 Hz, 1H), 3.50 (dd, *J* = 6.2, 3.1 Hz, 2H), 3.41–3.33 (m, 1H), 3.05 (ddd, *J* = 12.1 Hz, 5.5 Hz, 3.9 Hz, 1H), 2.81 (ddd, *J* = 12.1 Hz, 8.8, 4.9 Hz, 1H), 2.24–2.11 (m, 1H), 2.10–1.96 (m, 1H); ^{13}C NMR (100 MHz, D_2O): δ = 128.0, 124.4, 63.1, 54.4, 39.9, 23.4; FT-IR-ATR: ν = 3301, 3027, 2922, 2852, 1636, 1454 cm^{-1}; HR-MS (ESI-TOF): m/z = 114.0908 $[M+H]^+$, calcd. for $C_6H_{12}NO$: 114.0913.

(*S*)-*tert*-Butyl 2-[(*tert*-butyldimethylsilyloxy)methyl]-5,6-dihydropyridine-1(2*H*)-carboxylate (26):[23] Compound **25** (0.010 g, 0.088 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and treated under argon with *tert*-butyldiphenyl chloride (0.03 mL, 0.1 mmol) and imidazole (0.01 g, 0.2 mmol). The mixture was stirred for 16 h at room temperature, and then diluted with H_2O. The phases were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum. $(Boc)_2O$ (0.03 mL, 0.13 mmol) was added at room temperature to a stirred solution of the crude mixture (0.088 mmol), Et_3N (0.019 mL, 0.13 mmol) and DMAP (1.1 mg, 10 mol%) in CH_2Cl_2 (2 mL). After being stirred overnight, the solvents were removed under reduced pressure. The residue was then partitioned with H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3 times) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated under vacuum. The reaction crude was purified by flash column chromatography (4% EtOAc in hexanes) to give **26** as a colourless oil; yield: 25 mg (87%); $[\alpha]_D^{25}$: −142.4 (*c* 0.94, $CDCl_3$), {$[\alpha]_D^{27}$: −150.0 (*c* 1.04, $CDCl_3$) described]. ^{1}H NMR (400 MHz, $CDCl_3$, Boc rotamers): δ = 7.69–7.61 (m, 4H), 7.48–7.34 (m, 6H), 6.03–5.95 (m, 0.7H), 5.95–5.88 (m, 0.3H), 5.84–5.75 (m, 0.7H), 5.73–5.65 (m, 0.3H), 4.64–4.53 (m, 0.3H), 4.45–4.35 (m, 0.7H), 4.18 (dd, *J* = 12.0 Hz, 4.0 Hz, 0.7H), 4.00 (dd, *J* = 12.0, 4.0 Hz, 0.3H), 3.76 (dd, *J* = 12.0, 4.0 Hz, 0.3H), 3.68–3.57 (m, 1.7H), 3.04–2.95 (m, 0.3H), 2.90 (td, *J* = 12, 12, 4 Hz, 0.7H), 2.31–1.73 (m, 2H), 1.46 (s, 3H), 1.38 (s, 6H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, Boc rotamers): δ = 162.4, 135.5, 135.5, 133.4, 129.6, 127.6, 127.5, 126.8, 79.9, 66.7, 55.6, 41.0, 36.4, 31.3, 26.8, 26.0, 19.2.

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References

[1] For selected publications see: a) M. Mori, *Chem. Pharm. Bull.* **2005**, *53*, 457–470; b) B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813–5837; c) O. Belda, C. Moberg, *Acc. Chem. Res.* **2004**, *37*, 159–167; d) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943.

[2] S. Norsikian, C.-W. Chang, *Curr. Org. Synth.* **2009**, *6*, 264–289.

[3] a) B-S. Kim, M. M. Hussain, P-O. Norrby, P. J. Walsh, *Chem. Sci.* **2014**, *5*, 1241–1250; b) G. R. Cook, H. Yu, S. Sankaranarayanan, P. S. Shanker, *J. Am. Chem. Soc.* **2003**, *125*, 5115–5120; c) P. S. Shanker, K. Pararajasingham, *Angew. Chem.* **1999**, *111*, 226–228; *Angew. Chem. Int. Ed.* **1999**, *38*, 110–113.

[4] M. H. Katcher, A. Sha, A.; A. G. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 15902–15905.

[5] J-P. Chen, Q. Peng, B-L. Lei, X-L. Hou, Y. D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 14180–14183.

[6] B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 7328–7331.

[7] I. Dubovik, I. D. G. Watson, A. K. Yudin, *J. Org. Chem.* **2013**, *78*, 1559–1575.

[8] B. M. Trost, *Acc. Chem. Res.* **1996**, *29*, 355–364.

[9] a) B. M. Trost, G.-H. Kuo, T. Benneche, *J. Am. Chem. Soc.* **1988**, *110*, 621–622; b) B. M. Trost, S.-F. Chen, *J. Am. Chem. Soc.* **1986**, *108*, 6053–6054; c) B. M. Trost, J. Cossy, *J. Am. Chem. Soc.* **1982**, *104*, 6881–6882.

[10] B. M. Trost, D. R. Frandick, *Aldrichimica Acta* **2007**, *40*, 59–72.

[11] B. M. Trost, R. C. Bunt, R. C. Lemoine, T. L. Calkins, *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976.

[12] Carbon nucleophiles: a) R. Takeuchi, M. Kashio, *Angew. Chem.* **1997**, *109*, 268–270; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 263–264; b) amines: R. Takeuchi, N. Ue, K. Tanabe, K. Yamashita, N. Shiga, *J. Am. Chem. Soc.* **2001**, *123*, 9525–9534.

[13] J. H. Lee, S. Shin, J. Kang, S. Lee, *J. Org. Chem.* **2007**, *72*, 7443–7446.

[14] C. Gnamm, G. Franck, N. Miller, T. Stork, K. Brödner, G. Helmchen, *Synthesis* **2008**, 3331–3350.

[15] a) J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res.* **2010**, *43*, 1461–1475; b) L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 8971–8983.

[16] C. P. Butts, E. Filali, G. C. Lloyd-Jones, P.-O. Norrby, D. A. Sale, Y. Schramm, *J. Am. Chem. Soc.* **2009**, *131*, 9945–9957.
[17] S. M. Nanavati, B. Silverman, *J. Am. Chem. Soc.* **1991**, *113*, 9341–9349.
[18] a) C. S. Lee, L. Z. Benet, *Anal. Profiles Drug Subst.* **1978**, *7*, 231–249; b) W. H. Beggs, in: *Antibiotics*, (Ed.: F. E. Hahn), Springer, New York, **1979**; Vol. 5, pp 43–66.
[19] B. M. Trost, D. B. Horne, M. J. Woltering, *Angew. Chem.* **2003**, *115*, 6169–6172; *Angew. Chem. Int. Ed.* **2003**, *42*, 5987–5990.
[20] B. M. Trost, D. B. Horne, M. J. Woltering, *Chem. Eur. J.* **2006**, *12*, 6607–6620.
[21] G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675–691.
[22] a) J. Llaveria, Y. Díaz, M. I. Matheu, S. Castillón, *Org. Lett.* **2009**, *11*, 205–208; b) J. Llaveria, Y. Díaz, M. I. Matheu, S. Castillón, *Eur. J. Org. Chem.* **2011**, 1514–1519.
[23] a) H. Takahata, Y. Banba, H. Ouchi, H. Nemoto, A. Kato, I. Adachi, *J. Org. Chem.* **2003**, *68*, 3603–3607; b) Y. Banba, C. Abe, H. Nemoto, A. Kato, I. Adachi, H. Takahata, *Tetrahedron: Asymmetry* **2001**, *12*, 817–819.
[24] For a recent review about the chiral synthesis of imino sugars, see: H. Takahata, *Heterocycles* **2012**, *85*, 1351–1376.
[25] a) T. Mena-Barragan, M. I. Garcia Moreno, E. Nanba, K. Higaki, A. L. Concia, P. Clapes, J. M. García Fernández, C. Ortiz-Mellet, *Eur. J. Med. Chem.* **2016**, *121*, 880–891; b) A. M. Scofield, L. E. Fellows, R. J. Nash, G. W. J. Fleet, *Life Sci.* **1986**, *39*, 645–650.
[26] Bis-allylated amines are common by-products in Pd-catalysed allylic aminations with primary amines: a) S.-C. Yang, W.-H. Chung, *Tetrahedron Lett.* **1999**, *40*, 953–956; b) A. R. Katritzky, J. Yao, M. Qi, *J. Org. Chem.* **1998**, *63*, 5232–5234; c) E. Blart, J. P. Genêt, M. Safi, M. Savignac, D. Sinou, *Tetrahedron* **1994**, *50*, 505–514; d) B. M. Trost, E. Keinan, *J. Org. Chem.* **1979**, *44*, 3451–3457.
[27] Assignment of the absolute configuration was determined by comparison of the optical rotation with that of the (*S*)-enantiomer described in ref.[14]
[28] a) G. R. Cook, H, Yu, S. Sankaranarayanan, P. S. Shanker, *J. Am. Chem. Soc.* **2003**, *125*, 5115–5120; b) J. Catalán, *J. Org. Chem.* **1997**, *62*, 8231–8234.
[29] a) P. Fristrup, M. Ahlquist, D, Tanner, P.-O. Norrby, *J. Phys. Chem. A* **2008**, *112*, 12862–12867; b) P. Fristrup, T. Jensen, J. Hoppe, P.-O. Norrby, *Chem. Eur. J.* **2006**, *12*, 5352–5360; c) M. P. T. Sjögren, S. Hansson, B. Akermark, A. Vitagliano, *Organometallics* **1994**, *13*, 1963–1971; d) B. Goldfuss, U. Kazmaier, *Tetrahedron* **2000**, *56*, 6493–6496.
[30] a) H. S. Frank, W. Y. Wen, *Discuss. Faraday Soc.* **1957**, *24*, 133–140; b) G. A. Jeffrey, W. Sainger, in: *Hydrogen Bonding in Biological Structures*, Springer Verlag, Berlin, **1991**, p 569; c) M. Lopez de La Paz, C. Gonzalez, C. Vicent, *Chem. Commun.* **2000**, 411–412.
[31] This substrate exists as a racemate and, therefore, the potential formation of the enantiopure branched aminated product would result from a dynamic kinetic asymmetric transformation (DYKAT).
[32] For recent asymmetric syntheses of fagomine, see: a) K. Csatayova, D. G. Davis, A. M. Fletcher, J. G. Ford, D. J. Klauber, P. M. Roberts, J. E. Thomson, *Tetrahedron* **2015**, *71*, 7170–7180; b) P. K. Kundu, S. K. Gosh, *Tetrahedron: Asymmetry* **2011**, *22*, 1090–1096.
[33] For a review on olefin metathesis, see: a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; b) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3143.
[34] For a recent review on the use of RCM in the synthesis of imino sugars, see: I. Dragutan, V. Dragutan, A. Demonceau, *RSC Adv.* **2012**, *2*, 719–736.
[35] I. Dragutan, V. Dragutan, C. Mitan, H. C. M. Vosloo, L. Delaude, A. Demonceau, *Beilstein J. Org. Chem.* **2011**, *7*, 699–716.
[36] D. L. Wright, J. P. Schulte II, M. A. Page, *Org. Lett.* **2000**, *2*, 1847–1850.
[37] B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747–760.
[38] I. R. Márquez, A. Millán, A. G. Campaña, J. M. Cuerva, *Org. Chem. Front.* **2014**, *1*, 373–381.
[39] L. F. Hennequin, E. S. E. Stokes, A. P. Thomas, C. Johnstone, P. A. Plé, D. J. Ogilvie, M. Dukes, S. R. Wedge, J. Kendrew, J. O. Curwen, *J. Med. Chem.* **2002**, *45*, 1300–1312.
[40] A. J. Cresswell, S. G. Davies, J. A. Lee, M. J. Morris, P. M. Roberts, E. J. Thomson, *J. Org. Chem.* **2012**, *77*, 7262–7281.