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Enantioselective Aminohydroxylation of Alkenes

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A procedure for osmium-mediated enantioselective aminohydroxylation of alkenes has been developed employing chiral complexes between *tert*-butylimidoosmium and derivatives of *Cinchona* alkaloids. The success of the reaction is dependent on a ligand acceleration effect.

The vicinal amino alcohol moiety is present in numerous natural compounds, and is often found in molecules possessing pronounced biological activity. For example the amino alcohol functionality is present in many classes of compound with chemotherapeutic activity;[1] both anthracyclines and aminoglycoside and macrolide antibiotics usually contain aminosugar glycones. A pharmacologically different class of important vicinal amino alcohols is the α- and β-adrenergic agonists and antagonists.[2] The majority of the bioactive amino alcohols are chiral, often containing both a chiral amine and a chiral alcohol functionality.

There is a growing understanding that enantiomers may have different biological effects[3,4] and from this it is concluded that chiral compounds used in clinical treatment should be enantiomerically pure.[5] Many of the pharmacological amino alcohols are of synthetic origin, and when produced as enantiomerically pure compounds, they are prepared from racemates by resolution, or from chiral building blocks.[6]

An attractive and direct synthetic route to the vicinal amino alcohol functionality is the simultaneous addition of a hydroxy and an amino group to an alkene. The relative stereochemistry of the two groups is determined by the stereoselectivity in the addition step, and the stereochemistry of the alkene. If the alkene is prochiral, an enantioselective reaction could be devised using a chiral reagent.

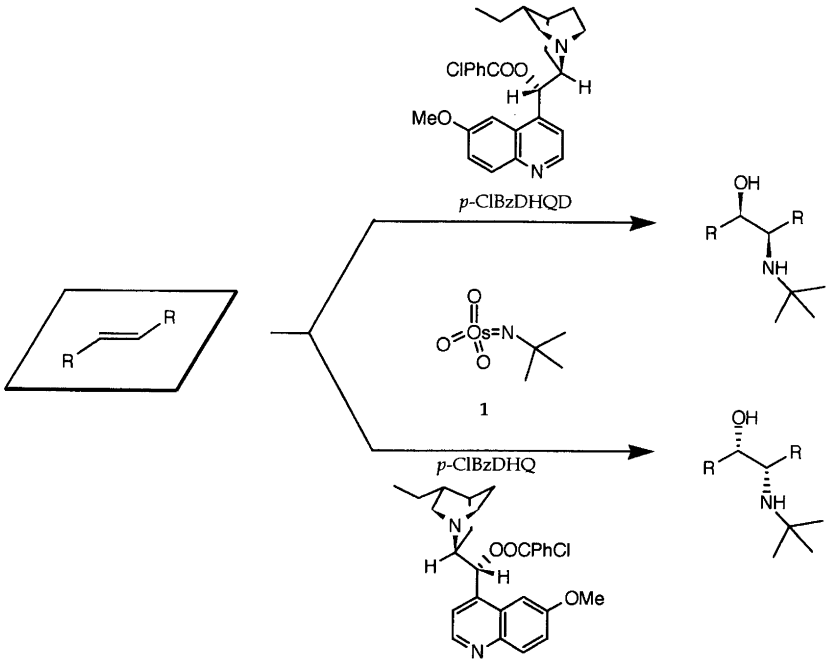
A racemic *syn*-specific aminohydroxylation reaction based on a stoichiometric addition of trioxo(alkylimido)osmium to an alkene has been developed by Sharpless *et al.*[7,8] This reaction is closely related to the classical *syn*-specific dihydroxylation mediated by osmium tetroxide,[9–11] which has recently been developed into a highly enantioselective[12] and catalytic process.[13–15] The enantioselectivity of the catalytic asymmetric dihydroxylation reaction is based on the face selectivity displayed by chiral complexes between osmium tetroxide and derivatives of *Cinchona* alkaloids.

On the basis of the new developments in the dihydroxylation process the possibility of extending the osmium based aminohydroxylation into an enantioselective process has been investigated. In this work the possibility of complexing trioxo(*tert*-butylimido)osmium (**1**) to three amine ligands possessing the 1-azabicyclo[2.2.2]octane functionality, quinuclidine and two chiral *Cinchona* alkaloid derivatives, *p*-chlorobenzoyldihydroquinidine (*p*-ClBzDHQD) and *p*-chlorobenzoyldihydroquinine (*p*-ClBzDHQ) has been investigated. The chiral complexes have been utilised in the stoichiometric asymmetric aminohydroxylation of alkenes, as shown in Scheme 1.

Results and discussion

It was clear from the outset of this work that the design of an asymmetric aminohydroxylation process was not going to be a straightforward combination of two known reactions: the imidoosmium-mediated aminohydroxylation process[7] and the asymmetric dihydroxylation process.[13] Fig. 1 summarises the different reactions that might be expected in the asymmetric aminohydroxylation.

The first problem is that the reaction mixture contains two reactive species: trioxo(*tert*-butylimido)osmium (**1**) and its corresponding tertiary amine complex (**1**·L). As it is only the latter species that is capable of inducing asymmetry in the amino alcohol product given a chiral ligand, an enantioselective process is dependent on a maximal amount of the chiral complex. Trioxo(*tert*-butylimido)osmium, **1**, and the complex, **1**·L, are in rapid equilibrium where the ratio between **1** and **1**·L is determined by the complexation constant K_c [eqn. (1)]. The complexation constant is an inherent property of the ligand, and the amount of **1**·L can only be changed by altering the con-



Scheme 1.

centrations of L and **1**.

$$K_c = \frac{[\mathbf{1}\cdot\mathrm{L}]}{[\mathbf{1}]\,[\mathrm{L}]} \tag{1}$$

The second problem arising is that the reaction between **1** and an alkene can give both amino alcohols and diols[7,8] *via* competing kinetically controlled pathways, which are described by the rate constants $k_{\text{amino alcohol}}$ and k_{diol} [eqns. (2) and (3)]. It is therefore conceivable that **1**·L will react in a similar manner through processes with rate constants $k_{\text{amino alcohol·L}}$ and $k_{\text{diol·L}}$ [eqns. (4) and (5)]. The reaction rates for the four different pathways are given in eqns. (2)–(5).

$$\frac{\mathrm{d[amino\ alcohol]}}{\mathrm{d}t} = k_{\text{amino alcohol}}[\mathrm{Alkene}]\,[\mathbf{1}] \tag{2}$$

$$\frac{\mathrm{d[diol]}}{\mathrm{d}t} = k_{\text{diol}}[\mathrm{Alkene}]\,[\mathbf{1}] \tag{3}$$

$$\frac{\mathrm{d[amino\ alcohol^*]}}{\mathrm{d}t} = k_{\text{amino alcohol·L}}[\mathrm{Alkene}]\,[\mathbf{1}\cdot\mathrm{L}] \tag{4}$$

$$\frac{\mathrm{d[diol^*]}}{\mathrm{d}t} = k_{\text{diol·L}}[\mathrm{Alkene}]\,[\mathbf{1}\cdot\mathrm{L}] \tag{5}$$

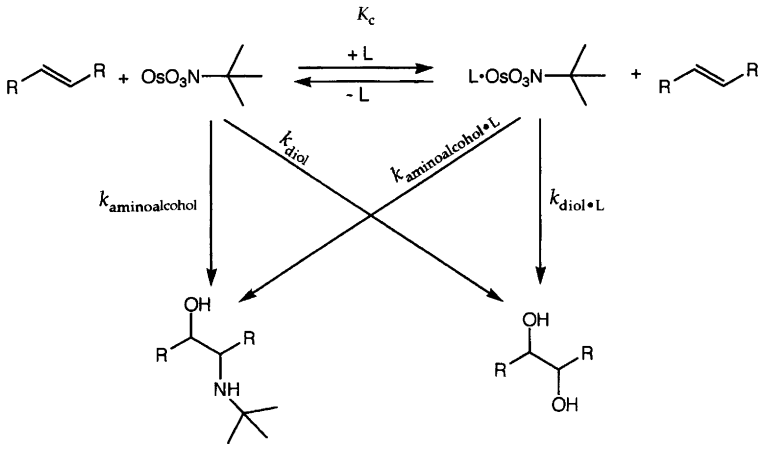


Fig. 1. Possible reactions from **1** and its ligand complex **1**·L.

If the ligand L is chiral, eqns. (4) and (5) represent the chiral pathways, whereas eqns. (2) and (3) represent the achiral pathways.

The successful outcome of an asymmetric aminohydroxylation process is dependent on two factors, the $k_{\text{amino alcohol}\cdot L}$ pathway [eqn. (4)] is effective, and all other processes [eqns. (2), (3) and (5)] should be insignificant. The achiral $k_{\text{amino alcohol}}$ pathway [eqn. (2)] giving the racemic amino alcohol is the most important to be excluded, but also the diol forming pathways [eqns. (3) and (5)] should be made insignificant as they lead to an unwanted diol by-product.

The competition between the chiral and the achiral amino alcohol pathways is directly determined by the ratio [**1**·L] and [**1**] in the reaction mixture, and the ratio $k_{\text{amino alcohol}\cdot L}/k_{\text{amino alcohol}}$ [eqns. (2) and (4)]. The consequences are that K_c for the ligand should be as large as possible, and that the complex **1**·L should be more reactive than **1** alone, i.e., the reaction should show a ligand acceleration effect (LAE = $k_{\text{amino alcohol}\cdot L}/k_{\text{amino alcohol}}$). In the same respect, we require both diol-forming pathways, $k_{\text{diol}\cdot L}$ and k_{diol}, to be as small as possible, and not experience any ligand acceleration effect, to minimise the diol formation.

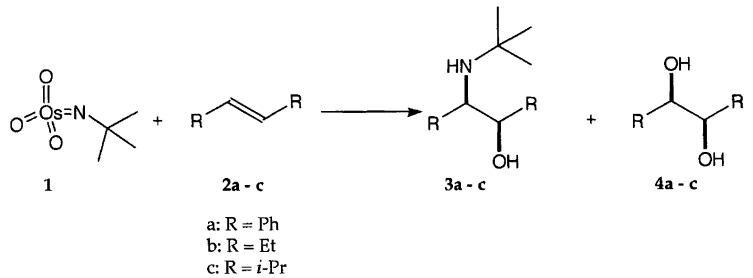
The third, but not the least, important issue is that the complex between **1** and the *Cinchona*-derived ligand must show good face selectivity in order to enable the $k_{\text{amino alcohol}\cdot L}$ pathway to produce an enantiomerically enriched product. The face selectivity is a function of the chiral ligand, and we have not, in this work, addressed this question thoroughly.

In the following discussion we will try to describe how these hurdles were overcome. The ratio of uncomplexed and complexed **1** can readily be calculated if the complexation constant, K_c for the ligand is known. K_c for the achiral ligand 1-azabicyclo[2.2.2]octane (quinuclidine) and the chiral ligand *p*-chlorobenzoyldihydroquinidine (*p*-ClBzDHQD) was determined using ^{1}H NMR spectroscopy by titrating a solution of the ligand in chloroform-d_1 with trioxo(*tert*-butylimido)osmium, **1**. The chemical shift of several signals in the ligands changed with increasing concentration of **1**. The differences in chemical shift for the ligand signals, $\Delta\delta$, were plotted versus the imidoosmium concentration to yield a curve from which the maximum chemical-shift difference for the complex, $\Delta\delta_{max}$, could be estimated. Assuming that the complexed and uncomplexed ligand are in fast exchange, the ratio of the observed chemical shift difference, $\Delta\delta_{obs}$, relative to $\Delta\delta_{max}$ is equal to the molar ratio of the complexed and the uncomplexed ligand. With the total concentration of ligand and **1** in hand, K_c can be calculated. The measured value of K_c for *p*-ClBzDHQD was 8 and for quinuclidine 75. The much lower binding ability of the *Cinchona* ligand compared with quinuclidine is not unexpected owing to the much larger molecular complexity of the alkaloid ligand, which will impose substantially more steric hindrance to the binding of **1**. The binding constants for these ligands towards **1** are also lower than their binding constants to osmium tetroxide.[16]

Under the conditions employed for an aminohydroxylation reaction with *p*-ClBzDHQD as the ligand, the value of K_c corresponds to only a 2:1 ratio between **1**·L and **1**. With the stronger binding ligand, quinuclidine, a ratio of 15:1 in favour of the complex is expected. The rather unfavourable ratio for the chiral complex could certainly impose problems; in the absence of any ligand acceleration effect ($k_{\text{amino alcohol}\cdot L} = k_{\text{amino alcohol}}$), the achiral pathway would yield only 33% racemic amino alcohol, which would ruin the enantioselectivity of the reaction irrespective of the face selectivity of the **1**·L complex.

The reaction between (*E*)-1,2-diphenylethene (**2a**) and **1** yields (1*R**,2*R**)-2-*tert*-butylamino-1,2-diphenylethanol (**3a**) and (1*R**,2*R**)-1,2-diphenylethane-1,2-diol (**4a**) (Scheme 2) in a 40:60 ratio (Table 1). The observation that the reaction between **1** and an alkene yields significant amounts of diol has been reported previously.[7,8] On statistical grounds, the addition of an alkene to **1** should give a 1:1 mixture of amino alcohol and diol assuming there is no rate difference between the processes. As shown in Fig. 1 and in eqns. (2) and (3), the 40:60 distribution of amino alcohol and diol shows that for (*E*)-1,2-diphenylethene the ratio between the rate constants $k_{\text{amino alcohol}}$ and k_{diol} is 40:60.

The change in rate constants upon addition of ligands can be observed for the aminohydroxylation of (*E*)-1,2-diphenylethene (**2a**) performed in the presence of quinuclidine. The ratio between amino alcohol **3a** and diol **4a** shifts to 97:3, as presented in Table 1. The total rate of reaction was also significantly increased. The shift in amino alcohol:diol ratio must originate from a different selectivity of **1**·L compared with **1**. If all the diol in the product mixture is formed from free **1**, the amount of



Scheme 2.

Table 1. Percentage relative formation of vicinal amino alcohols and vicinal diols as a function of ligands and alkenes.

Alkene	T/°C	Amino alcohol	Diol	Ligand
2a	25	40	60	–
	25	97	3	Quinuclidine
	25	92	10	*p*-ClBzDHQD
	25	77	23	*p*-ClBzDHQ
	−78	95	5	*p*-ClBzDHQD
2b	25	>90	<10	*p*-ClBzDHQD
	25	>90	<10	*p*-ClBzDHQ
2c	25	56	44	*p*-ClBzDHQD
	25	56	44	*p*-ClBzDHQ

amino alcohol formed from free **1** should be 2% using the relative magnitude of $k_{\text{amino alcohol}}$ and k_{diol} derived above. The rest of the amino alcohol formed, 95%, must then be formed from **1**·L. When quinuclidine is used as the ligand, the amount of **1**·L is 15 times the concentration of free **1**. If the formation of amino alcohol from **1**·L is corrected for this excess [eqns. (2) and (4)], $k_{\text{amino alcohol·L}}$ is more than three times larger than $k_{\text{amino alcohol}}$. If some of the diol is formed from **1**·L, the ligand acceleration effect would be even larger.

The rate-accelerating effect of ligand addition has also been observed in the asymmetric dihydroxylation reaction, and is in fact instrumental to the successful outcome of this process.[16] It is also interesting to note that the ratio of amino alcohol to diol is much higher for quinuclidine-bound **1** than for free **1**. This finding indicates that the ligand acceleration effect is limited to the amino alcohol forming process. The diol forming process either has no LAE, or perhaps shows ligand inhibition.

It is impossible to determine the contribution of the different pathways to the final product distribution from the data of the quinuclidine-mediated reaction. Furthermore, the results are not very encouraging because an amino alcohol selectivity of 97:3 corresponds to only a threefold LAE in the amino alcohol formation, assuming the limiting situation when all diol is formed from free **1**. If the LAE for the chiral ligand *p*-ClBzDHQD is of comparable magnitude to that for quinuclidine, the less effective binding chiral ligand ($K_c = 8$ for *p*-ClBzDHQD) would lead to a formation of only six molecules of amino alcohol from the chiral complex, for each racemic amino alcohol formed from free **1**.

When (*E*)-1,2-diphenylethene is treated at room temperature with **1** in the presence of *p*-ClBzDHQD, a 92:8 mixture of the amino alcohol **3a** and the diol **4a** is formed. As shown in Table 2, the amino alcohol is formed with an enantiomeric excess greater than 90% [as determined by ^{1}H NMR spectroscopy using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent[17–24]]. The diol formed in the reaction is close to racemic (<10% ee as determined by gas chromatography of the corresponding bis-MTPA ester[25]).

Table 2. Enantiomeric excess (ee) obtained for the amino alcohols formed by asymmetric aminohydroxylation of different olefins.

Alkene	T/°C	*p*-ClBzDHQD	*p*-ClBzDHQ
2a	25	>90[a]	50[a]
2a	−70	>90[a]	
2c	25	56[b]	40[b]

[a]Determined by NMR spectroscopy using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle alcohol) as a chiral solvating agent. [b]Determined by gas chromatography using a Chirasil-Val column.

The satisfactory ee obtained for the amino alcohol, does not only show that most of the amino alcohol product is formed through the chiral complex, **1**·L, but also that the *p*-ClBzDHQD complex has good face selectivity. In order to produce the observed degree of enantiomeric excess, less than 10% of the amino alcohol can be formed from free **1**. However, using the yield of diol as a measure of the maximum contribution from free **1** (see above), the maximum yield of the amino alcohol originating from the achiral pathway is only 5%. The minimum yield of amino alcohol formed in the chiral pathway is then 87%, and the LAE is close to 9.

When the aminohydroxylation process was performed at −70°C in the presence of *p*-ClBzDHQD, the amino alcohol:diol ratio increased to 95:5. This change probably reflects a shift between complexed and free **1** towards **1**·L which has a lower tendency to produce diols than does free **1**. The expected increase in ee in the amino alcohol product upon cooling could not be determined owing to the general inability of measuring high ee's by NMR spectroscopy.

One of the major advantages using *Cinchona* alkaloids as chiral adjuvants is that quinidine and quinine derivatives have the opposite absolute configuration between the two important chiral centers at C8 and C9. The two other chiral centers in quinidine and quinine have identical stereochemistry, so that these diastereomeric alkaloids behave as pseudoenantiomers. This pseudoenantiomeric relationship is evident from the observation that if quinidine gives one enantiomer, quinine gives the other (Scheme 1), but enantiomeric excesses obtained may be different.[13,14,26–29] This difference could also be observed in the enantioselective aminohydroxylation process. Using the quinine derivative *p*-ClBzDHQ as the chiral ligand in the aminohydroxylation of **2a**, an enantiomeric excess of only 50% was found for the amino alcohol (Table 2), compared with >90% in the quinidine case. As shown in Table 1, the reduction in enantioselectivity was accompanied by a substantial increase in diol formation. An explanation of these results may be found in a lower binding constant, K_c, or a lower LAE for the dihydroquinine complex. A lower K_c will yield more free **1** which produces the racemic amino alcohol and displays a higher propensity for diol formation, whereas a lower LAE means a less reactive complex which competes less

favourably with free **1**. In addition, the face selectivity of the dihydroquinine complex may be lower.

We then turned to non-aromatic alkenes as substrates for the asymmetric aminohydroxylation. In analogy with the asymmetric dihydroxylation process, lower ee's are usually expected for non-aromatic alkenes.[13–15] This, unfortunately, could not be confirmed using (*E*)-3-hexene (**2b**) as the substrate; all the available methods for the determination of the ee in the resulting amino alcohol failed to give separation of the enantiomers. A surprising observation was, however, made: (3*R**,4*R**)-4-(*tert*-butylamino)hexan-3-ol (**3b**) was formed as the main product in the reaction, with only traces of (3*R**,4*R**)-3,4-hexanediol (**4b**) observed by GC–MS. The significance of this is unclear, but there is precedence in the literature for alkenes with low steric bulk to yield more amino alcohols in the reaction with **1**, than for alkenes with bulky substituents.[8]

When the reaction was performed with (*E*)-2,5-dimethyl-3-hexene (**2c**) the amount of diol product, (3*R**,4*R**)-2,5-dimethyl-3,4-hexanediol (**4c**), increased again to 44%. Using *p*-ClBzDHQD as the ligand the ee for the amino alcohol (3*R**,4*R**)-4-(*tert*-butylamino)-2,5-dimethylhexane-3-ol (**3c**), was 56% (as determined by gas chromatography on a Chirasil-Val column), significantly less than in the reaction of alkene **2a** and thus in accordance with our expectation of non-aromatic alkenes being less good substrates. The enantiomeric excess for the amino alcohol **3c** decreased to 40% using *p*-ClBzDHQ as the chiral ligand.

The results we have obtained so far in the development of the asymmetric aminohydroxylation process, clearly show that *Cinchona* alkaloid derivatives are capable of inducing asymmetry in the reaction between alkenes and imidoosmium **1**. The best results were obtained with aromatic substrates, where the reaction was enantiospecific (within the limits of the ee determination). In addition the LAE is limited to amino alcohol formation, removing the problem of diol by-products to a large degree. These encouraging results are due to a combined effect of a favourable complexation constant, K_c, and a fortunate ligand acceleration effect. Further investigation in this field will be concentrated upon increasing the scope of substrates, and in the efforts of making the process catalytic.

Experimental

^{1}H NMR spectra were recorded on a Jeol FX 90Q (89.55 MHz) or a Jeol PMX 60SI (60 MHz) spectrometer using $CDCl_3$ as the solvent and are reported in ppm downfield from TMS. Gas chromatography was performed on a Varian 3400 gas chromatograph equipped with a Supelco SPB 5 capillary column (30 m × 0.32 mm ID). Combined gas chromatography/mass spectrometry was carried out on a Hewlett Packard 5890 gas chromatograph with either a Supelco SPB 5 (25 m × 0.25 mm ID) or a Chirasil Val (50 m × 0.25 mm ID) column connected to a VG Analytical Tribrid mass spectrometer. The mass spectra were recorded using EI ionisation (70 eV) and the ion source temperature was 220°C.

Preparation of trioxo(tert-*butylimido)osmium* (**1**). Compound **1** was prepared in 92% yield as described in the literature.[30] **1**: ^{1}H NMR (60 MHz): δ 1.67 (9 H, s).

Preparation of amino alcohols: general procedure. The alkene (3.0 mmol) was dissolved in dimethoxyethane (20 ml) before trioxo(*tert*-butylimido)osmium (1.16 g, 3.75 mmol) was added. The solution was stirred for 36 h at ambient temperature, before the solvent was evaporated off under reduced pressure. The resulting blackish oil was dissolved in dry diethyl ether (30 ml) and lithium aluminium hydride (400 mg, 10.5 mmol) was added. The mixture was stirred for 1 h before the reaction was quenched by addition of water (1.2 ml). The solution was filtered, and the filtrate was washed with brine and dried over sodium sulfate.

*Preparation of (1*R**,2*R**)-2-(*tert-*butylamino)-1,2-diphenylethanol (***3a***).* The reaction was performed as described above using (*E*)-1,2-diphenylethene (**2a**) as the starting alkene. The crude product was a mixture of two compounds, (1*R**,2*R**)-2-(*tert*-butylamino)-1,2-diphenylethanol (**3a**), and (1*R**,2*R**)-1,2-diphenylethane-1,2-diol (**4a**) in a 40:60 ratio as determined by GLC and NMR analysis. **3a**: ^{1}H NMR (89.55 MHz): δ 1.08 (9 H, s), 3.10 (1 H, s), 3.58 (1 H, d, *J* 9.0 Hz), 4.28 (1 H, d, *J* 9.0 Hz), 7.04 (10 H, m); MS [*m*/*z* (rel. int.)]: 251 (3), 236 (6), 194 (42), 162 (92), 146 (20), 107 (24), 106 (100), 105 (20), 91 (14), 79 (27), 77 (25), 57 (23). **4a**: ^{1}H NMR (89.55 MHz): δ 3.10 (1 H, s), 4.60 (2 H, s), 7.15 (10 H, m); MS [*m*/*z* (rel. int.)]: 210 (0.5), 196 (2), 194 (3), 180 (10), 178 (9), 152 (12), 107 (10), 106 (55), 105 (100), 77 (84).

*Preparation of (1*R**,2*R**)-2-(*tert-*butylamino)-1,2-diphenylethanol (***3a***) in the presence of 1-azabicyclo[2.2.2]octane (quinuclidine).* The reaction was performed as described above using (*E*)-1,2-diphenylethene (**2a**) as the starting alkene. Quinuclidine (1.67 g, 15 mmol) and the imidoosmium compound (**1**) were sequentially added to the alkene solution. NMR spectral and GLC analysis of the crude product revealed that amino alcohol **3a** and diol **4a** were formed in a 97:3 ratio.

*Preparation of (1*R**,2*R**)-2-(*tert-*butylamino)-1,2-diphenylethanol (***3a***) in the presence of chiral ligands.* The general procedure was slightly modified. The imidoosmium compound (**1**) (0.228 g, 0.74 mmol) was dissolved in dichloromethane (10 ml), the chiral ligand (1.56 g, 3.0 mmol) was added and the reaction mixture was either stirred at room temperature or cooled to −78°C. A solution of (*E*)-1,2-diphenylethene in dichloromethane (0.108 g, 0.6 mmol) was added via a syringe. The crude product was analysed by NMR spectroscopy and GC. The amino alcohol and the diol were separated by washing an ethereal solution of the crude product with 0.1 M HCl, leaving the diol in

the ether phase. The acid phase was made basic by addition of 1.0 M KOH and thoroughly extracted with ether and dried (Na_2SO_4). The amino alcohol was purified by column chromatography (SiO_2) with cyclohexane–chloroform–diethylamine (5:4:1) as the eluent.

Preparation of (3R,4R*)-4-(*tert*-butylamino)hexan-3-ol (**3b**) in the presence of chiral ligands.* The reaction was performed as described for compound **3a**, using (*E*)-3-hexene (**2b**) as the starting alkene. **3b**: ^{1}H NMR (89.55 MHz): δ 0.9–1.6 (10 H, m), 1.2 (9 H, s), 3.0 (1 H, m), 3.6 (1 H, m); MS [*m/z* (rel. int.)]: 158 (2), 155 (5), 140 (5), 114 (25), 98 (100), 88 (12), 84 (10).

Preparation of (3R,4R*)-4-(*tert*-butylamino)-2,5-dimethylhexan-3-ol (**3c**) in the presence of chiral ligands.* The reaction was performed as described for compound **3a**, using (*E*)-2,5-dimethyl-3-hexene (**2c**) as the starting alkene. Both amino alcohol **3c** and (3*R**,4*R**)-2,5-dimethyl-3,4-hexanediol (**4c**) were formed. **3c**: ^{1}H NMR (89.55 MHz): δ 0.8–1.2 (12 H, m), 1.1 (9 H, s), 1.3–1.8 (2 H, m), 2.9 (1 H, m), 3.7 (1 H, m); MS [*m/z* (rel. int.)]: 186 (3), 183 (1), 168 (1), 158 (23), 128 (44), 126 (41), 102 (63), 43 (100). **4c**: ^{1}H NMR in accordance with the literature.[31] MS [*m/z* (rel. int.)]: 128 (4), 110 (12), 95 (30), 93 (9), 91 (10), 85 (15), 72 (24), 41 (100).

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