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New pinene-derived pyridines as bidentate chiral ligands

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Dedicated to Professor Miloslav Ferles on the occasion of his 86th birthday and in recognition of his life-long contribution to pyridine chemistry

Abstract

A synthesis of new bidentate pyridines **8a–d**, **9**, and **10** has been developed, starting from triflate **14**, readily available from β-pinene **11**. A copper complex of the pyridine–oxazoline ligands **8a** has been found to catalyze asymmetric allylic oxidation of cyclic olefins **36a–c** with good conversion rates and acceptable enantioselectivity (≤67% ee). The imidazolium salt **10** has been identified as a precursor of the corresponding *N*,*N*′-unsymmetrical *N*-heterocyclic carbene ligand, whose complex with palladium catalyzed the intramolecular amide enolate α-arylation leading to oxindole **45** in excellent yield but with low enantioselectivity.

Keywords: Chiral ligands; Transition metal catalysis; Asymmetric catalysis; Pyridine ligands; Oxazoline ligands; *N*,*N*′-Heterocyclic carbene ligands

1. Introduction

The pyridine nucleus is a ubiquitous structural motif in catalysis,[1] supramolecular science,[2] and medicinal chemistry.[3] The search for efficient routes toward pyridine-containing non-racemic structures is the key to the development of new catalysts for a wide range of important enantioselective transformations.[1] We have previously developed bidentate pyridines (Chart 1), such as PINDY (**1**) and CANDY (**2**) for the copper-catalyzed asymmetric allylic oxidation and cyclopropanation,[4] related *N*-oxide organocatalysts PINDOX (**5**) and *iso*-PINDOX (**6**) for the enantioselective allylation of aldehydes with allyltrichlorosilane,[5] oxazolines **3** and **4** as organocatalysts for reduction of ketones and imines,[6] and phosphines, such as **7**, that proved to be efficient in asymmetric Heck addition[7] and Pd-catalyzed allylic substitution.[8]

Among the chiral bidentate *N*,*N*-ligands, bisoxazolines have played a key role in transition metal-catalyzed enantioselective reactions in the last 15 years, where selectivities attained for several reaction types have reached or even surpassed those typical for enzymatic processes.[9] On the other hand, pyridine–oxazoline hybrids (e.g., **3** and **4**) have been less well studied and the existing examples mostly contain the chiral element in the oxazoline unit, whereas the pyridine moiety is usually flat.[6,9]

The phosphine–oxazolines, chiral in the oxazoline unit, represent another important class of ligands.[9,10] Again, their pyridine analogues, such **7**, have only been reported occasionally[7–9] and the scope of their applications has not been thoroughly studied.

The pioneering work on metal coordinated *N*-heterocyclic carbenes (NHCs)[11,12] has opened a new fertile field and these

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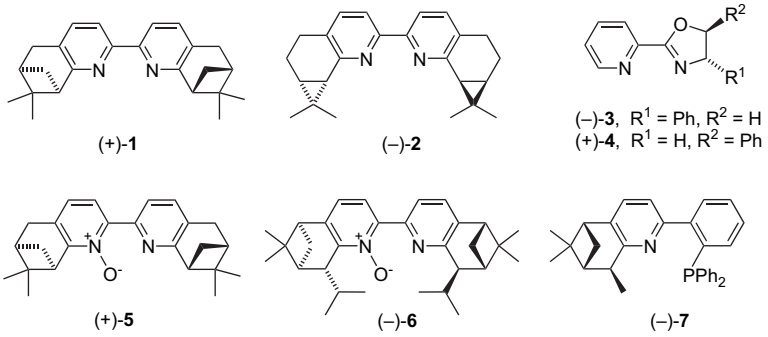


Chart 1. Pyridine-derived ligands and organocatalysts.

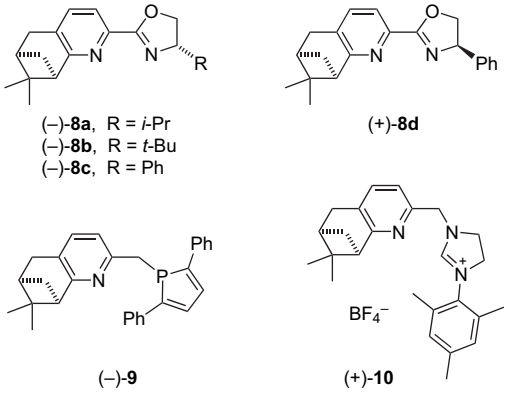


Chart 2. New pyridine-derived ligands.

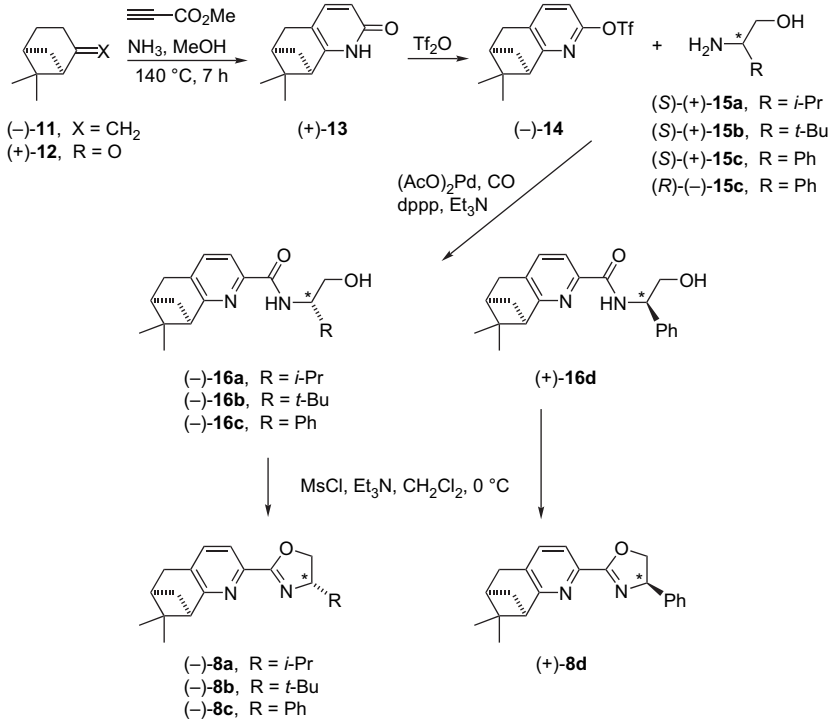
ligands now spearhead numerous advances in both metal catalysis and organocatalysis.[13] However, efficient enantioselective examples[13] are limited and the variables governing enantioselectivity are not well understood.[14] The combination of the heterocarbene unit with a pyridine nucleus can be expected to mimic the phosphine–pyridine ligands, possibly with new applications.

Herein, we report on straightforward syntheses of three new types of bidentate pyridines: the pinene-derived pyridyl oxazolines **8a–d**, with chiral elements in both the oxazoline and pyridine units, pyridyl phosphine **9**, chiral in the pyridine part, and the *N*,*N*-heterocyclic carbene precursor **10**, again chiral in the pyridine half (Chart 2).

2. Results and discussion

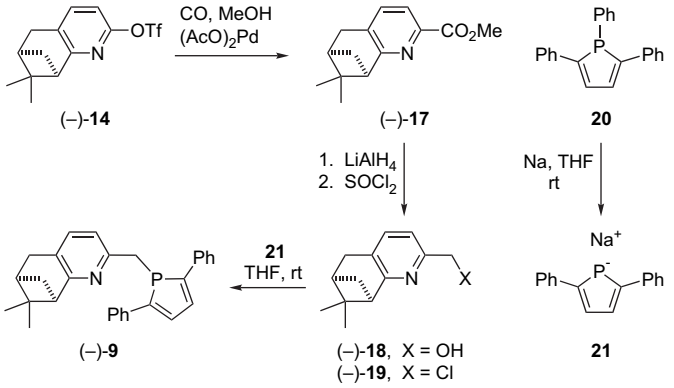
2.1. Synthesis of 2-pyridyl oxazolines *8a–d*

The synthetic route to the chiral 2-pyridyl oxazolines **8a–d** commenced with ozonolysis of β-pinene (−)-**11** (Scheme 1). The resulting nopinone (+)-**12** (89%)[4c] was treated with



Scheme 1. Synthesis of pyridyl oxazoline ligands from β-pinene.

methyl propiolate in a methanolic 7 M ammonia solution in an autoclave at 140 °C to furnish pyridone (+)-**13**[4c] (71%) as a result of Michael addition, imine formation, and ring closure.[4c] The latter intermediate was converted into triflate (−)-**14** (≥99%) on reaction with triflic anhydride.[4c] Triflate (−)-**14** was then submitted to the palladium-catalyzed carbonylation[15] in the presence of the respective amino alcohols **15a–c** to produce amides (−)-**16a** (82%), (−)-**16b** (52%), (−)-**16c** (68%), and (+)-**16d** (73%). In the end game, activation of the hydroxy group in the latter amides by mesylation with methanesulfonyl chloride resulted in a ring closure to produce oxazolines (−)-**8a** (71%), (−)-**8b** (49%), (−)-**8c** (74%), and (+)-**8d** (81%), respectively.[16]



Scheme 2. Synthesis of pyridine phosphine ligand.

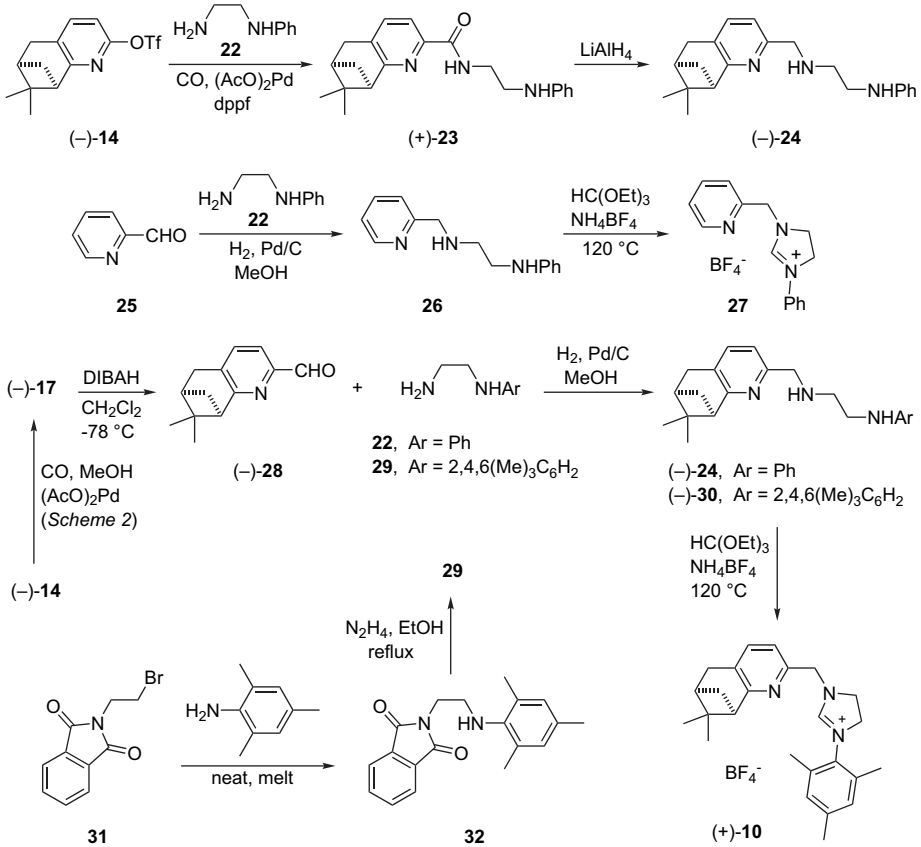
2.2. Synthesis of 2-pyridyl phosphine *9*

Palladium-catalyzed carbonylation of triflate (−)-**14** in methanol[17] (Scheme 2) afforded the methyl ester (−)-**17** (73%), whose reduction with $LiAlH_4$ furnished the primary alcohol (−)-**18** (67%), which was then converted into chloride (−)-**19** (~100%) by treatment with $SOCl_2$. The sodium phosphide **21**, generated in situ from phospholane **20**[18] on reduction with metallic sodium,[18] was then alkylated with chloride **19** to produce phosphine (−)-**9** (65%).

2.3. Synthesis of the heterocyclic carbene precursor *10*

We envisioned that the ultimate precursor (−)-**24** could be obtained from triflate (−)-**14**[4c] (Scheme 3) using a strategy similar to that employed for the synthesis of the oxazolines (vide supra). Indeed, palladium-catalyzed carbonylation[15] of (−)-**14** in the presence diamine **22** proceeded readily to furnish amide (+)-**23** (70%). However, its reduction with $LiAlH_4$ gave the required amine (−)-**24** in only 20% yield.[19] Therefore, a different approach was adopted, first with α-picolinic aldehyde **25** as a model compound. Reductive amination[20] of **25** with **22** using catalytic hydrogenation proceeded readily to afford amine **26** (75%), which was then transformed into the carbene precursor **27** (41%)[21] by using the established[22] heating with $HC(OEt)_3$ and NH_4BF_4.

The latter protocol was then applied to the synthesis of carbene precursor **10**. The starting aldehyde (−)-**28** was prepared



Scheme 3. Synthesis of pyridine heterocarbene ligand precursors.

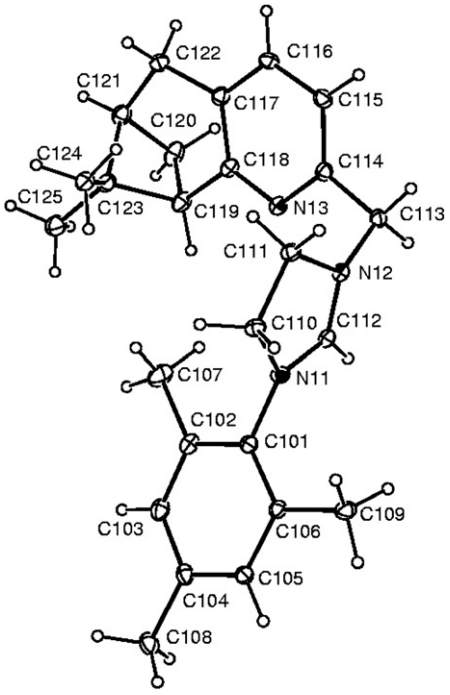


Figure 1. A view of one of the two independent cations in solid imidazolium fluoroborate (+)-**10** (the anion is omitted for clarity).

by reduction of ester (−)-**17** with DIBAH[23] at −78 °C (75%). Subsequent reductive amination with diamine **22** proceeded as expected to give rise to diamine (−)-**24** (80%), which represents a considerable improvement over the amide reduction (**23**→**24**). The overall yield of this three-step sequence, starting with the triflate carbonylation (**14**→**17**) and involving reductive amination (**28**+**22**→**24**) was 49%, which compares favorably with the overall 14% yield of the original two-step route that relied on carbonylation, followed by amide reduction (**14**→**23**→**24**).

In order to apply this methodology to the synthesis of (+)-**10**, we first prepared diamine **29** in two steps by melting the commercially available *N*-(2-bromoethyl)phthalimide (**31**) with mesidine,[24] which afforded the amino phthalimide **32** (59%), whose deprotection with hydrazine hydrate in refluxing ethanol[25] furnished diamine **29** (90%).[26] Reductive amination of aldehyde (−)-**28** with the latter diamine afforded (−)-**30** (68%), which was then converted into the imidazolium fluoroborate (+)-**10** (39%) on heating with ethyl orthoformate and NH_4BF_4 at 120 °C in a sealed tube.[22] Crystallographic analysis of (+)-**10** confirmed the structure (vide infra): one of the two crystallographically distinct but chemically identical cations is shown in Figure 1.

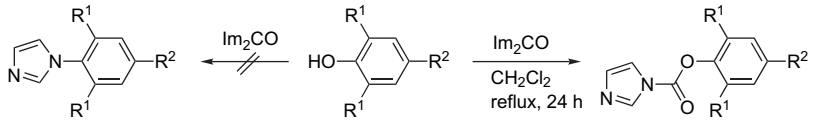
To prepare the imidazolium analogues of **10**, we attempted the synthesis of the intermediates **34a**–**c** via the procedure published by Njar,[27] using the reaction of phenols **33a**–**c** with carbonyldiimidazole (Scheme 4). However, rather than obtaining the desired imidazoles **34a**–**c**, the carbonyl derivatives **35a**–**c** were obtained and the structures of **35a**,**b** were confirmed by X-ray crystallography. While this work was in progress, similar observations were made independently by Fischer[28] and Vennerstrom,[29] clearly showing that the original structural assignment by Njar[27] was incorrect.

2.4. Asymmetric allylic oxidation catalyzed by copper complexes

A number of chiral ligands have been designed to modify the original Kharash–Sosnovsky reaction[30,31] into an enantioselective process; these protocols include ethyl camphorate (≤10% ee),[32] proline and its congeners (≤65% ee),[33] and our terpene-derived bipyridines, such as **1** and **2** (≤82% ee).[4,34] Bisoxazolines, introduced by Pfaltz, Evans, and Andrus,[35] and trisoxazolines developed by Katsuki,[36] represented a substantial improvement in the enantioselectivity (from 85 to 95% and finally to 99% ee)[35,36] but the reactions tend to be slow, which reduces their practicality. By contrast, Cu-complexes of our terpene-derived bipyridines proved to react much faster, which suggested that a hybrid containing both pyridine and oxazoline units **8a**–**d** could be the ligands of choice. This view is certainly supported by Singh's report on a hybrid ligand containing two oxazoline units appended to a pyridine nucleus in 2,6-positions, which substantially accelerated the oxidation, though at the expense of enantioselectivity (≤66% ee).[37]

The Cu(II) complexes of terpene-derived 2-pyridyl oxazolines **8a**–**d** were employed as catalysts for the copper-catalyzed allylic oxidation of cyclic alkenes, using the previously established protocol.[4,37] The Cu(II) complexes were generated from $(TfO)_2Cu$ and the respective ligands, and reduced in situ with phenylhydrazine to the corresponding Cu(I) species. A clear color change from green to deep red was observed on addition of phenylhydrazine, indicating the change in the oxidation state of copper. In order to investigate the catalytic capability of the latter complexes, the allylic oxidation of five- to seven-membered cycloalkenes **36a**–**c** were studied (Scheme 5), employing *tert*-butyl peroxybenzoate as the stoichiometric oxidant (Table 1).

The copper complexes of all the pinene-derived pyridyl oxazolines **8a**–**d** were found to be active catalysts for the allylic oxidation reaction but with varying degrees of reactivity and

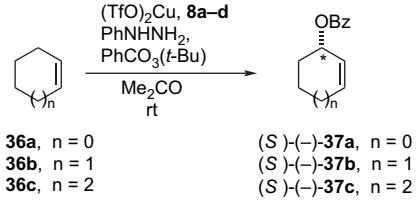


34a, R^1 = Me, R^2 = H
34b, R^1 = Me, R^2 = Me
34c, R^1 = *i*-Pr, R^2 = H

33a, R^1 = Me, R^2 = H
33b, R^1 = Me, R^2 = Me
33c, R^1 = *i*-Pr, R^2 = H

35a, R^1 = Me, R^2 = H
35b, R^1 = Me, R^2 = Me
35c, R^1 = *i*-Pr, R^2 = H

Scheme 4.



Scheme 5. Copper-catalyzed allylic oxidation; see Table 1.

selectivity. The highest enantioselectivities were achieved by employing the *iso*-propyl ligand (−)-**8a** (Table 1, entries 1−5). The copper complex of (−)-**8a** exhibited similar reactivity and enantioselectivity to those attained with the copper complex of PINDY (**1**).[4] Reducing the reaction temperature resulted in a decrease in reactivity without any significant increase in enantioselectivity (compare entries 1 and 4). Enantioselectivity was improved in acetonitrile but the reactivity diminished considerably (entry 2). The reactivity was found to be highly dependent on solvent, with reactions carried out in acetone proceeding considerably faster than those in acetonitrile, chloroform, or ethyl acetate. Higher enantioselectivity was observed for the transformation of cycloheptene compared to cyclohexene, a trend also observed[4] for bipyridine chiral ligands **1** and **2**. The increased steric bulk of *tert*-butyl and phenyl substituted oxazolines (−)-**8b** and (−)-**8c** resulted in considerably lower enantioselectivities (entries 6−11), presumably originating from the chiral cavity being too sterically demanding to give effective enantiodiscrimination.

Ligands **8a**−**c** can be regarded as pseudo C_2-symmetric. The sense of asymmetric induction observed for the allylic oxidation of cycloalkenes is indeed similar to that observed for C_2-symmetric terpene-derived bipyridine **1**.[4] Although rather low enantioselectivity was observed for the phenyl substituted ligand (+)-**8d** (entries 12−14), interestingly, the absolute configuration of the product was opposite to that obtained with diastereoisomeric (−)-**8c** (compare entries 9−11 with 12−14). This finding indicates that it is the chirality of the oxazoline moiety, rather than the terpene unit, which mainly dictates the enantiodiscrimination.

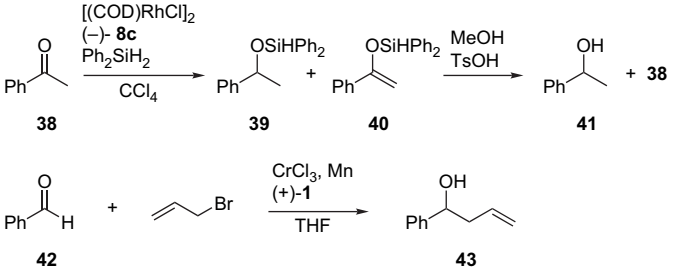
Table 1
Asymmetric allylic oxidation of cycloalkenes catalyzed by Cu-complexes of chiral ligands **8a**−**d** (Scheme 5)[a]

Entry	Ligand	Substrate	Solvent	Time (h)	Yield (%)	ee (%)[b]
1	(−)-**8a**	Cyclohexene	Me_2CO	0.5	67	44 (*S*)
2	(−)-**8a**	Cyclohexene	MeCN	72	15	60 (*S*)
3	(−)-**8a**	Cyclohexene	AcOEt	72	15	20 (*S*)
4	(−)-**8a**	Cyclohexene[c]	Me_2CO	72	45	45 (*S*)
5	(−)-**8a**	Cycloheptene	Me_2CO	6	62	67 (*S*)
6	(−)-**8b**	Cyclopentene	Me_2CO	16	39	0
7	(−)-**8b**	Cyclohexene	Me_2CO	16	62	22 (*S*)
8	(−)-**8b**	Cycloheptene	Me_2CO	16	50	23 (*S*)
9	(−)-**8c**	Cyclopentene	Me_2CO	3	43	14 (*S*)
10	(−)-**8c**	Cyclohexene	Me_2CO	0.5	62	7 (*S*)
11	(−)-**8c**	Cycloheptene	Me_2CO	1.5	48	42 (*S*)
12	(+)-**8d**	Cyclohexene	Me_2CO	0.5	76	19 (*R*)
13	(+)-**8d**	Cyclohexene[c]	$CHCl_3$	72	43	14 (*R*)
14	(+)-**8d**	Cycloheptene	Me_2CO	5	72	30 (*R*)

[a] The reactions were carried out in the presence of the catalysts (5 mol %), generated in situ by reduction of a mixture of $(TfO)_2Cu^{II}$ and the ligand with $PhNHNH_2$ at room temperature (unless stated otherwise).

[b] Determined by chiral HPLC; the absolute configuration was established by optical rotation and the chiral HPLC mobility with reference to the authentic sample.

[c] The reaction was carried out at 0 °C.



Scheme 6. Rhodium-catalyzed hydrosilylation and Nozaki−Hiyama−Kishi allylation.

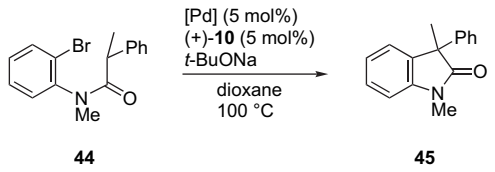
2.5. Other applications of the pyridine−oxazoline ligands

Asymmetric, Rh-catalyzed hydrosilylation with diphenylsilane as the stoichiometric reagent is a useful alternative to asymmetric hydrogenation, as it avoids the use of high-pressure hydrogen.[9,38] To further assess the potential of our pyridine−oxazolines, hydrosilylation of acetophenone (**38**) was investigated, using ligands **8a**,**c** (Scheme 6). The reaction proceeded under standard conditions and the mixture of silylated primary products **39**/**40** was hydrolyzed to produce alcohol **41** and the recycled acetophenone. The conversion attained with (−)-**8a** was 58% but an almost racemic alcohol **41** was obtained (4% ee). Ligand (−)-**8c** induced 79% conversion but with only a marginal improvement in the enantioselectivity (8% ee), showing that this type of ligands is not suitable for the Rh-catalyzed hydrosilylation. This behavior sharply contrasts with that of pyridine−oxazoline **3** and of its congeners that have been shown to exhibit high enantioselectivities (≤95% ee).[39,40] It is pertinent to note that (+)-**4** and its analogues have been developed by us as organocatalysts for asymmetric hydrosilylation of both ketones and imines with trichlorosilane and exhibited high enantioselectivities (≤94% ee).[41,42]

The Nozaki−Hiyama−Kishi allylation of aldehydes with allyl halides is another reaction, in which chiral bipyridine, oxazolines, salen derivatives, and other chiral ligands were employed (typically with ≤90% ee).[43−49] Using the Fürstner conditions[46] and ligand (−)-**8a** and PINDY (+)-**1**, respectively (Scheme 6), the reaction of benzaldehyde **42** proceeded readily to give 67% conversion with **8a** and ≥99% with **1** but the product **43** was practically racemic (4% ee with **8a** and 8% ee with **1**).

2.6. Intramolecular α-arylation catalyzed by palladium complexes

Hartwig has developed an enantioselective version of the Pd-catalyzed intramolecular amide enolate α-arylation leading to biologically interesting oxindole[50] bearing a benzylic all-carbon stereocenter.[51] Several chiral *N*-heterocyclic carbene



44 45

Scheme 7. Palladium-catalyzed intramolecular α-arylation.

ligands were developed for this process but the enantioselectivities attained to date are rather modest (≤69% ee).[50–53] Screening of various palladium complexes resulted in identification of $(AcO)_2Pd$ and $[(C_3H_5)PdCl]_2$ as suitable catalyst precursors, which produced sufficiently reactive catalysts on coordination to the pyridine-carbene ligand generated from the imidazolium salt (+)-**10**. Both complexes were found to catalyze the cyclization of **44**,[54] giving rise to **45** at 100 °C (84% and 94% isolated yields, respectively), which compares favorably with several other systems[53] (Scheme 7). On the other hand, little conversion was observed at 50 °C (4% and 14%, respectively). Nevertheless, the product **45** was practically racemic in both cases (1–3% ee).

3. Conclusion

A straightforward synthesis of new pinene-derived bidentate pyridines **8a–d**, **9**, and **10** has been described, starting from the readily available common triflate **14**. A copper complex of the pyridine–oxazoline ligands **8a** has been found to catalyze asymmetric allylic oxidation of simple cyclic olefins **36a–c** with good conversion rates and modest enantioselectivity (≤67% ee). The imidazolium salt **10** has been identified as a precursor of the corresponding *N*,*N*′-unsymmetrical *N*-heterocyclic carbene ligand, whose complex with palladium catalyzed the intramolecular amide enolate α-arylation leading to oxindole **45** in excellent yield but with poor enantioselectivity.

4. Experimental section

4.1. General methods

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in CH_2Cl_2 at 25 °C unless otherwise indicated. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^{1}H at 400 MHz and ^{13}C at 100 MHz with $CDCl_3$ (δ 7.26, ^{1}H; δ 77.0, ^{13}C) and tetramethylsilane (δ 0.0, ^{1}H) as an internal standard; chemical shifts are given in δ scale. Coupling patterns are designated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; br, broad. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. The mass spectra were measured on a high resolution, dual-sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. Flash column chromatography was performed with Fischer Scientific Matrex 60 Silica gel. All solvents for the reactions were of reagent grade and were dried and distilled under argon or nitrogen immediately before use as follows: tetrahydrofuran, diethyl ether, and toluene from sodium/benzophenone under nitrogen, dichloromethane and *N*,*N*-dimethyl formamide from calcium hydride. Methanol and ethanol were distilled with sodium under argon and stored over 4 Å molecular sieves. Triethylamine and diisopropylethylamine were distilled from calcium hydride and stored over 4 Å molecular sieves. *N*,*N*-Dimethyl formamide and methanol were degassed by three freeze-pump-thaw cycles before use in methoxycarbonylation reaction. Petroleum ether refers to the fraction boiling in the range of 40–60 °C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR spectra. 2-Bromo-*N*-methylaniline was prepared according to a published procedure.[55] The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures; the absolute configuration of the allylic benzoates (products of allylic oxidation) has been established by comparison with authentic samples.[4] Crystallographic analysis of (+)-**10**: $[C_{25}H_{32}N_3][BF_4]$, M=461.35, triclinic, space group $P1$ (No. 1), a=8.7845(2), b=9.7552(2), c=15.3974(3) Å, α=106.688(1), β=93.408(1), γ=104.149(1)°, V=1213.56(4) Å^3, Z=2, ρ=1.263 g cm^{-3}. All measurements were made at 100 K on a Nonius Kappa CCD diffractometer with Mo Kα radiation (λ=0.71073 Å). The WINGX package and SHELXL97 were used for all calculations;[56] 24378 intensities with θ (Mo Kα)<30.1° gave 7071 unique observations (R_{int}=0.031) after merging symmetry equivalents (including Friedel pairs). Refinement of 633 parameters finally gave $R1$=0.059, $wR2$=0.13 over all 7071 observations and $|\Delta\rho|$<0.42 e Å^{-3}. Only space group $P1$ is possible since the compound was made from a natural terpene of known absolute configuration, which could not be changed during our chemical transformations. The unit cell contains two independent cation/anion pairs. The absolute configurations of the cations could not be determined from the crystallographic experiment and were assigned on the basis of the known chemical history. The two cations display virtually identical bond lengths (rms Δ=0.006 Å) and angles, which are consistent with the proposed structure. However, the unit cell contents are close to centrosymmetric; only the C*n*17–C*n*25 rings (n=1,2), especially the *gem*-dimethyl groups, seriously break the pseudo-symmetry. Crystallographic data for (+)-**10** have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 638212).

4.1.1. (1*R*,9*R*,4′*S*)-(−)-4-[4′-Isopropyl-4′,5′-dihydro-oxazol-2′-yl]-10,10-dimethyl-3-aza-tricyclo-[7.1.1.0^{2,7}]-undeca-2(7),3,5-triene (−)-**8a**[16]

Mesyl chloride (76 μL, 0.98 mmol, 2.0 equiv) in CH_2Cl_2 (1 mL) was slowly added dropwise to a stirred solution of hydroxyamide (−)-**16a** (146 mg, 0.48 mmol, 1.0 equiv) and anhydrous triethylamine (340 μL, 2.44 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for a further 24 h. The solvent was removed under reduced pressure and the resultant

residue was purified by flash chromatography on silica gel (petroleum ether–ether–acetone 80:10:10) to give oxazoline (−)-**8a** (98 mg, 71%) as white solid: mp 55–57 °C (CH_2Cl_2). $[\alpha]_D$ −45.2 (*c* 0.17, CH_2Cl_2); IR (cm^{-1}) ν 1647 s (C=N), 1588 m, 1572 m, 1523 w, 1469 m, 1451 s, 1429 w, 1417 m, 1386 m, 1370 s, 1262 s, 999 w, 971 m; ^1H NMR (400 MHz, $CDCl_3$) δ 0.65 (s, 3H), 0.94 (d, *J*=6.5 Hz, 3H), 1.06 (d, *J*=7.1 Hz, 3H), 1.28 (d, *J*=9.5 Hz, 1H), 1.40 (s, 3H), 1.83–1.95 (m, 1H), 2.30–2.35 (m, 1H), 2.69–2.74 (m, 1H), 2.98 (d, *J*=2.5 Hz, 2H), 3.19 (t, *J*=6.1 Hz, 1H), 4.10–4.22 (m, 2H), 4.46–4.50 (m, 1H), 7.48 (d, *J*=7.7 Hz, 1H), 7.87 (d, *J*=7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_3), 19.3 (CH_3), 21.2 (CH_3), 25.9 (CH_3), 30.7 (CH_2), 31.51 (CH_2), 32.84 (CH), 39.03 (C), 39.87 (CH), 50.32 (CH), 70.64 (CH_2), 72.91 (CH), 121.9 (CH), 133.2 (C), 135.5 (CH), 142.5 (C), 162.9 (C), 166.6 (C); EIMS *m/z* (%) 284 ($M^{+\bullet}$, 11), 269 (4), 243 (4), 242 (37), 241 (100), 214 (4), 213 (23), 198 (5), 197 (8), 183 (6), 171 (6), 170 (9), 169 (9), 157 (5), 156 (7), 155 (15), 143 (4), 142 (5), 130 (6), 129 (5), 128 (10), 69 (6), 43 (4), 41 (8); HRMS (EI): 284.1889 ($C_{18}H_{24}N_2O$ requires: 284.1889).

4.1.2. (1*R*,9*R*,4′*S*)-(−)-4-(4′-tert-Butyl-4′,5′-dihydro-oxazol-2′-yl)-10,10-dimethyl-3-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene (−)-**8b**[16]

Mesyl chloride (90 μL, 1.17 mmol, 2.3 equiv) in CH_2Cl_2 (1 mL) was slowly added dropwise to a stirred solution of hydroxyamide (−)-**16b** (160 mg, 0.51 mmol, 1.0 equiv) and anhydrous triethylamine (300 μL, 2.13 mmol, 4.18 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for a further 16 h. The solvent was removed under reduced pressure and the resultant residue was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate–triethylamine 1:1:0.05) to give oxazoline (−)-**8b** (74 mg, 49%) as a white solid: mp 105–107 °C (CH_2Cl_2). $[\alpha]_D$ −70.0 (*c* 0.1, $CHCl_3$); IR (KBr, cm^{-1}) ν 1647 (C=N), 2868, 2916, 2958 (CH/CH_2/CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (s, 3H), 0.90 (s, 9H), 1.21 (d, *J*=9.6 Hz, 1H), 1.33 (s, 3H), 2.24–2.28 (m, 1H), 2.62–2.67 (m, 1H), 2.91 (d, *J*=2.4 Hz, 2H), 3.11 (t, *J*=5.6 Hz, 1H), 4.03 (dd, *J*=10.4, 8.4 Hz, 1H), 4.23 (t, *J*=8.4 Hz, 1H), 4.35 (dd, *J*=10.4, 8.8 Hz, 1H), 7.41 (d, *J*=7.6 Hz, 1H), 7.84 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 25.9 (CH_3), 26.0 (3×CH_3), 30.7 (CH_2), 31.5 (CH_2), 34.0 (C), 39.1 (C), 39.9 (CH), 50.3 (CH), 69.2 (CH_2), 76.4 (CH), 122.0 (CH), 133.1 (C), 135.5 (CH), 142.6 (C), 162.8 (C), 166.5 (C); EIMS *m/z* (%) 298 ($M^{+\bullet}$, 3) 241 (100), 213 (30), 197 (10), 170 (10), 155 (8), 128 (7), 83 (12); HRMS (EI): 298.2044 ($C_{19}H_{26}N_2O$ requires: 298.2045).

4.1.3. (1*R*,9*R*,4′*S*)-(−)-10,10-Dimethyl-4-[4′-phenyl-4′,5′-dihydro-oxazol-2′-yl]-3-aza-tricyclo[7.1.1.$0^{2,7}$]-undeca-2(7),3,5-triene (−)-**8c**[16]

Mesyl chloride (152 μL, 1.67 mmol, 2.3 equiv) in CH_2Cl_2 (1 mL) was slowly added dropwise to a stirred solution of hydroxyamide (−)-**16c** (246 mg, 0.73 mmol, 1.0 equiv) and anhydrous triethylamine (530 μL, 3.80 mmol, 5.2 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for a further 48 h. The solvent was removed under reduced pressure and the resultant residue was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate–triethylamine 1:1:0.1) to give oxazoline (−)-**8c** (206 mg, 74%) as a clear oil. $[\alpha]_D$ −43.3 (*c* 0.6, $CHCl_3$); IR (KBr, cm^{-1}) ν 1636 (C=N), 2918 (CH/CH_2/CH_3), 3029 (Ar–H); ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 1.22 (d, *J*=9.9 Hz, 1H), 1.34 (s, 3H), 2.26–2.29 (m, 1H), 2.63–2.69 (m, 1H), 2.93 (d, *J*=2.6 Hz, 2H), 3.12 (t, *J*=5.6 Hz, 1H), 4.30 (t, *J*=8.5 Hz, 1H), 4.79 (dd, *J*=10.2, 8.6 Hz, 1H), 5.35 (dd, *J*=10.2, 8.5 Hz, 1H), 7.15–7.36 (m, 5H), 7.43 (d, *J*=7.8 Hz, 1H), 7.89 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 26.3 (CH_3), 31.0 (CH_2), 31.9 (CH_2), 39.5 (C), 40.3 (CH), 50.5 (CH), 70.7 (CH), 75.6 (CH_2), 122.6 (CH), 127.3 (2×CH), 128.0 (CH), 129.1 (2×CH), 133.9 (C), 136.5 (CH), 142.5 (C), 142.7 (C), 164.6 (C), 167.1 (C); EIMS *m/z* (%) 318 ($M^{+\bullet}$, 100), 275 (40), 245 (18), 244 (16), 200 (7), 172 (12), 155 (30), 128 (38), 91 (20), 89 (12), 77 (8), 41 (5); HRMS (EI): 318.1733 ($C_{21}H_{22}N_2O$ requires: 318.1732).

4.1.4. (1*R*,9*R*,4′*R*)-(+)-10,10-Dimethyl-4-[4′-phenyl-4′,5′-dihydro-oxazol-2′-yl]-3-aza-tricyclo[7.1.1.$0^{2,7}$]-undeca-2(7),3,5-triene (+)-**8d**[16]

Mesyl chloride (185 μL, 2.04 mmol, 2.3 equiv) in CH_2Cl_2 (1 mL) was slowly added dropwise to a stirred solution of hydroxyamide (+)-**16d** (300 mg, 0.89 mmol, 1.0 equiv) and anhydrous triethylamine (640 μL, 4.59 mmol, 5.2 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for a further 48 h. The solvent was removed under reduced pressure and the resultant residue was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate–triethylamine 1:1:0.1) to give oxazoline (+)-**8d** (227 mg, 81%) as a white solid: mp 116–118 °C (ethyl acetate–hexane). $[\alpha]_D$ +45.2 (*c* 0.67, $CHCl_3$); IR (KBr, cm^{-1}) ν 1681 (C=O), 2978, 2954, 2925 (CH/CH_2/CH_3), 3059 (Ar–H); ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 1.23 (d, *J*=9.6 Hz, 1H), 1.35 (s, 3H), 2.26–2.30 (m, 1H), 2.67 (dt, *J*=9.6, 5.6 Hz, 1H), 2.93 (d, *J*=2.4 Hz, 2H), 3.13 (t, *J*=5.6 Hz, 1H), 4.30 (t, *J*=8.4 Hz, 1H), 4.80 (dd, *J*=10.4, 8.8 Hz, 1H), 5.35 (dd, *J*=10.4, 8.8 Hz, 1H), 7.19–7.31 (m, 5H), 7.44 (d, *J*=8.0 Hz, 1H), 7.92 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (CH_3), 21.0 (CH_3), 25.8 (CH_2), 26.7 (CH_2), 34.2 (C), 35.0 (CH), 45.5 (CH), 65.4 (CH), 70.4 (CH_2), 117.4 (CH), 122.0 (2×CH), 122.8 (CH), 123.9 (2×CH), 128.9 (C), 130.7 (CH), 137.2 (C), 137.4 (C), 159.4 (C), 161.8 (C); EIMS *m/z* (%) 318 ($M^{+\bullet}$, 100), 276 (15), 275 (40), 245 (14), 200 (7), 214 (4), 172 (14), 155 (28), 128 (40), 118 (19), 85 (34), 83 (65), 47 (9); HRMS (EI): 318.1731 ($C_{21}H_{22}N_2O$ requires: 318.1732).

4.1.5. Pyridyl phosphine (−)-**9**

A thin sodium foil (126 mg, 5.492 mmol, 2.10 equiv) was added to a stirred solution of phosphine **20** (857 mg, 2.746 mmol, 1.05 equiv) in dry THF (60 mL) and the mixture was stirred under argon, until all sodium had dissolved

(4–6 h). A solution of chloro derivate **19** (580 mg, 2.615 mmol, 1.00 equiv) in THF (12 mL) was added dropwise to the resulting dark red mixture under argon, whilst vigorously stirring, and the mixture was stirred under argon overnight. The solvent was then removed in vacuo and the solid brown residue was purified by chromatography on a column of silica gel (30×2.5 cm) with a mixture of petroleum ether and ethyl acetate (6:1) [R_f (product)=0.72, R_f (phosphine **20**)=0.9, R_f (chloro derivate **19**)=0.92] to give (−)-**9** (717 mg, 65%) as yellow crystals: mp 132–134 °C (petroleum ether–ethyl acetate). $[\alpha]_D$ −5.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.49 (s, 3H), 1.07 (d, *J*=8.70 Hz, 1H), 1.28 (s, 3H), 2.14–2.18 (m, 1H), 2.49–2.56 (m, 2H), 2.67 (s, 2H), 3.21 (s, 2H), 6.15 (d, *J*=6.45 Hz, 1H), 6.85 (d, *J*=7.64 Hz, 1H), 6.92–6.98 (m, 2H), 7.13–7.17 (m, 2H), 7.21–7.25 (m, 4H), 7.36 (d, *J*=7.70 Hz, 2H), 7.41 (d, *J*=7.70 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.50 (CH_3), 26.39 (CH_3), 31.20 (d, *J*=13.3 Hz, CH_2), 34.88 (CH_2), 35.07 (CH_2), 39.41 (C), 40.51 (CH), 50.37 (CH), 120.48 (CH), 120.82 (CH), 126.87 (CH), 126.92 (CH), 126.96 (CH), 127.08 (CH), 127.35 (CH), 127.41 (CH), 129.06 (CH), 129.39 (CH), 132.60 (CH), 132.67 (CH), 134.73 (CH), 136.39 (CH), 137.45 (C), 137.61 (C), 138.51 (CH), 151.54 (C), 151.71 (C), 151.92 (C), 165.20 (C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.48 (s); MS (EI), *m/z* (%) 421.2 ($M^{+\bullet}$, 71), 378.2 (7), 186.1 (8), 143.1 (10), 82.9 (100); HRMS (EI): 421.1959 ($C_{29}H_{28}NP$ requires: 421.1959).

*4.1.6. Pinene-derived N^1-2-picolyl-N^2-mesitylimidazolidinium tetrafluoroborate (+)-**10***

A mixture of diamine (−)-**30** (180 mg, 0.495 mmol), ammonium tetrafluoroborate (65 mg, 0.620 mmol, 1.25 equiv), and triethyl orthoformate (1.5 mL, 9.02 mmol, 18.2 equiv) was heated under argon at 120 °C for 5 h 40 min. The product crystallized from the reaction mixture upon standing at room temperature for 5 days. Filtration through sintered glass and washing with ether yielded pure tetrafluroborate salt (+)-**10** (88 mg, 39%) as beige crystals: mp 167–170 °C. $[\alpha]_D$ +18.3 (*c* 0.19, CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 0.60 (s, 3H), 1.20 (d, *J*=9.5 Hz, 1H), 1.41 (s, 3H), 2.27 (s, 6H), 2.28 (s, 3H), 2.31–2.35 (m, 1H), 2.69–2.75 (m, 1H), 2.84 (t, *J*=5.5 Hz, 1H), 2.89–3.01 (m, 2H), 3.91–4.06 (m, 2H), 4.18 (t, *J*=10.5 Hz, 2H), 4.80 (s, 2H), 7.07 (s, 2H), 7.28 (d, *J*=8.0 Hz, 1H), 7.63 (d, *J*=7.6 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR δ 17.46 (CH_3), 20.90 (CH_3), 21.40 (CH_3), 26.15 (CH_3), 30.47 (CH_2), 30.80 (CH_2), 49.08 (CH_2), 50.08 (CH), 50.98 (CH_2), 51.98 (CH_2), 120.82 (CH), 129.73 (CH), 129.91 (C), 131.49 (C), 135.76 (C), 136.56 (CH), 139.71 (C), 148.48 (C), 160.70 (CH), 166.16 (C); HRMS (FAB): 374.2596 ($C_{25}H_{32}N_3$, i.e., M−BF_4, required: 374.2596).

*4.1.7. (−)-(6R,8R)-N-[(2S)-1-Hydroxy-3,3-dimethylbutan-2-yl]-7,7-dimethyl-5,6,7,8-tetrahydro-6,8-methanoquinoline-2-carboxamide (−)-**16a**[15]*

Anhydrous triethylamine (3.9 mL, 27.8 mmol, 3.7 equiv) was added to a mixture of triflate (−)-**14** (2.38 g, 7.4 mmol, 1.0 equiv), (*S*)-(+)-valinol (1.52 g, 14.7 mmol, 2.0 equiv), palladium acetate (55.5 mg, 0.25 mmol, 3 mol %), and dppp (93.9 mg, 0.23 mmol, 3 mol %) under an argon atmosphere at room temperature in a Schlenk flask. The flask was connected with a balloon and flushed with carbon monoxide (carbon monoxide gas was bubbled through the solution) and the reaction mixture was heated under a carbon monoxide atmosphere at 70 °C for 21 h. The solvent was then evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether–ether–acetone 80:10:10, 150 mL, followed by ethyl acetate) yielded hydroxyamide (−)-**16a** (1.81 g, 82%) as a white crystalline solid: mp 123–125 °C (ethyl acetate–hexane). $[\alpha]_D$ −13.5 (*c* 0.32, CH_2Cl_2); IR (cm^{-1}) ν 3626 w, 3372 m, 1660 vs, 1588 s, 1523 vs, 1467 s, 1443 s, 1427 m, 1416 m, 1393 m, sh, 1387 m, 1370 m, 1242 m, 1084 w, 1053 w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (s, 3H), 1.03 (d, *J*=7.1 Hz, 3H), 1.05 (d, *J*=7.1 Hz, 3H), 1.28 (d, *J*=9.9 Hz, 1H), 1.45 (s, 3H), 2.01–2.13 (m, 1H), 2.33–2.38 (m, 1H), 2.71–2.77 (m, 1H), 2.98–3.01 (m, 3H), 3.75–3.90 (m, 3H), 7.55 (d, *J*=7.7 Hz, 1H), 7.97 (d, *J*=8.1 Hz, 1H), 8.29 (br d, *J*=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9 (CH_3), 19.6 (CH_3), 21.3 (CH_3), 25.9 (CH_3), 29.2 (CH), 30.7 (CH_2), 31.4 (CH_2), 39.1 (C), 39.9 (CH), 50.2 (CH), 58.0 (CH), 64.7 (CH_2), 120.1 (CH), 133.8 (C), 136.1 (CH), 145.4 (C), 165.1 (C), 166.1 (C); EIMS *m/z* (%) 302 ($M^{+\bullet}$, 3), 272 (34), 271 (100), 259 (31), 200 (13), 173 (18), 172 (45), 157 (11), 156 (8), 130 (12), 129 (11), 128 (10), 86 (31), 84 (48), 78 (8), 69 (18), 63 (9), 51 (18), 49 (56), 47 (10), 41 (9); HRMS (EI): 302.1994 ($C_{18}H_{26}N_2O_2$ requires: 302.1994).

*4.1.8. (−)-(6R,8R)-N-[(2S)-1-Hydroxy-3-methylbutan-2-yl]-7,7-dimethyl-5,6,7,8-tetrahydro-6,8-methanoquinoline-2-carboxamide (−)-**16b**[15]*

Anhydrous triethylamine (630 μL, 4.5 mmol, 2.8 equiv) was added to a mixture of triflate (−)-**14** (500 mg, 1.6 mmol, 1.0 equiv), (*S*)-(+)-*tert*-leucinol (375 mg, 3.2 mmol, 2.0 equiv), palladium acetate (12 mg, 0.05 mmol, 3 mol %), and dppp (20 mg, 0.05 mmol, 3 mol %) under an argon atmosphere at room temperature in a Schlenk flask. The flask was connected with a balloon and flushed with carbon monoxide (CO gas was bubbled through the solution) and the reaction mixture was heated under a carbon monoxide atmosphere at 70 °C for 21 h. The solvent was then evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether–ethyl acetate 1:1) yielded hydroxyamide (−)-**16b** (265 mg, 52%) as a white solid: mp 157–159 °C (CH_2Cl_2). $[\alpha]_D$ −2.0 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) ν 1525, 1660 (amide C=O), 2868, 2924, 2968 (CH/CH_2/CH_3), 3371, 3415 (amide NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (s, 3H), 0.98 (s, 9H), 1.21 (d, *J*=9.6 Hz, 1H), 1.38 (s, 3H), 2.27–2.31 (m, 1H), 2.65–2.2.75 (m, 2H), 2.91–2.93 (m, 3H), 3.57–3.64 (m, 1H), 3.86–3.93 (m, 2H), 7.48 (d, *J*=7.6 Hz, 1H), 7.90 (d, *J*=7.6 Hz, 1H), 8.29 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3), 25.9 (CH_3), 27.0 (3×CH_3), 30.7 (CH_2), 31.3 (CH_2), 33.7 (C), 39.1 (C), 39.9 (CH), 50.2 (CH), 60.6 (CH), 66.5 (CH_2), 120.2 (CH), 133.8 (C), 136.1 (CH), 145.3 (C), 165.1 (C), 166.3 (C); CIMS *m/z* (%) 317 ($[M+H]^+$, 100), 285 (40), 259 (30),

241(2), 200 (4), 172 (5); HRMS (CI): 317.2226 ($C_{19}H_{29}N_2O_2$ requires: 317.2229).

4.1.9. (−)-(6R,8R)-N-[(1S)-2-Hydroxy-1-phenylethyl]-7,7-dimethyl-5,6,7,8-tetrahydro-6,8-methanoquinoline-2-carboxamide (−)-*16c*[15]

Anhydrous triethylamine (0.47 mL, 3.37 mmol, 3.1 equiv) was added to a mixture of triflate (−)-**14** (350 mg, 1.09 mmol, 1.0 equiv), (*S*)-(+)-phenyl glycinol (298 mg, 2.18 mmol, 2.0 equiv), palladium acetate (10 mg, 3 mol %), and dppp (16 mg, 3 mol %) under an argon atmosphere at room temperature in a Schlenk flask. The flask was connected with a balloon and flushed with carbon monoxide (carbon monoxide gas was bubbled through the solution) and the reaction mixture was heated under a carbon monoxide atmosphere at 70 °C for 21 h. The solvent was then evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether−ethyl acetate 1:1) yielded hydroxyamide (−)-**16c** (247 mg, 68%) as a white crystalline solid: mp 130−132 °C (ethyl acetate−hexane). $[\alpha]_D$ −31.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (s, 3H), 1.21 (d, *J*=10.0 Hz, 1H), 1.51 (s, 3H), 2.25−2.30 (m, 1H), 2.67 (dt, *J*=10.0, 5.6 Hz, 1H), 2.92 (d, *J*=2.8 Hz, 3H), 3.03 (dd, *J*=7.2, 5.2 Hz, 1H), 3.88−4.00 (m, 2H), 5.16 (td, *J*=6.8, 4.0 Hz, 1H), 7.23−7.36 (m, 5H), 7.48 (d, *J*=7.6 Hz, 1H), 7.91 (d, *J*=7.6 Hz, 1H), 8.58 (br d, *J*=6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (CH_3), 26.3 (CH_3), 31.0 (CH_2), 31.8 (CH_2), 39.5 (C), 40.3 (CH), 50.5 (CH), 57.2 (CH), 67.7 (CH_2), 120.7 (CH), 127.4 (2×CH), 128.3 (CH), 129.3 (2×CH), 134.4 (C), 136.5 (CH), 139.4 (C), 145.6 (C), 165.6 (C), 166.1 (C); CIMS *m/z* (%) 337 ($[M+H]^+$,100), 319 (5), 305 (6), 217 (7), 202 (1), 174 (3), 164 (4), 138 (2), 113 (4), 73 (7); HRMS (CI): 337.1916 ($C_{21}H_{25}N_2O_2$ requires: 337.1838).

4.1.10. (+)-(6R,8R)-N-[(1R)-2-Hydroxy-1-phenylethyl]-7,7-dimethyl-5,6,7,8-tetrahydro-6,8-methanoquinoline-2-carboxamide (+)-*16d*[15]

Anhydrous triethylamine (3.34 mL, 24.0 mmol, 3.1 equiv) was added to a mixture of triflate (−)-**14** (2.51 g, 7.8 mmol, 1.0 equiv), (*R*)-(−)-phenylglycinol (2.14 g, 15.6 mmol, 2.0 equiv), palladium acetate (59 mg, 0.24 mmol, 3 mol %), and dppp (101 mg, 0.24 mmol, 3 mol %) under an argon atmosphere at room temperature in a Schlenk flask. The flask was connected with a balloon and flushed with carbon monoxide (carbon monoxide gas was bubbled through the solution) and the reaction mixture was heated under a carbon monoxide atmosphere at 70 °C for 21 h. The solvent was then evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether−ethyl acetate 1:1) yielded hydroxyamide (+)-**16d** (1.908 g, 73%) as a white crystalline solid: mp 180−182 °C (ethyl acetate−hexane). $[\alpha]_D$ +61.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (s, 3H), 1.28 (d, *J*=9.8 Hz, 1H), 1.46 (s, 3H), 2.34−2.39 (m, 1H), 2.75 (dt, *J*=9.8, 5.9 Hz, 1H), 2.99−3.03 (m, 4H), 3.98−4.07 (m, 2H), 5.25−5.30 (m, 1H), 7.13−7.42 (m, 5H), 7.47 (d, *J*=7.6 Hz, 1H), 7.91 (d, *J*=7.6 Hz, 1H), 8.59 (br d, *J*=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (CH_3), 26.3 (CH_3), 31.0 (CH_2), 31.8 (CH_2), 39.5 (C), 40.3 (CH), 50.5 (CH), 56.9 (CH), 67.6 (CH_2), 120.6 (CH), 127.3 (2×CH), 128.3 (CH), 129.3 (2×CH), 134.4 (C), 136.5 (CH), 139.4 (C), 145.6 (C), 165.6 (C), 166.0 (C); EIMS *m/z* (%) 336 ($M^{+\bullet}$, 1), 318 (2), 305 (100), 263 (10), 262 (5), 200 (20), 172 (65), 130 (15), 129 (14), 128 (10), 69 (18), 41 (7); HRMS (EI): 336.1838 ($C_{21}H_{24}N_2O_2$ requires: 336.1838).

4.1.11. Methyl ester (−)-*17*

A Schlenk flask was charged with triflate (−)-**14** (1.679 g, 5.225 mmol), palladium acetate (34 mg, 0.151 mmol, 3 mol %), and dppf (185 mg, 0.334 mmol, 6 mol %) and put under argon via three vacuum/argon cycles. Triethylamine (1.5 mL, 10.762 mmol, 2.06 equiv), dimethyl formamide (20 mL), and methanol (11 mL) were added via septum and syringe, the Schlenk flask was connected to a balloon, and flushed with carbon monoxide. The mixture was heated under a carbon monoxide atmosphere at 80 °C for 24 h and the progress of the reaction was monitored by TLC (petroleum ether−ether−acetone 80:10:10, R_f=0.3). The solvent was evaporated in vacuo and the crude ester was chromatographed on a silica gel column (1×15 cm) with a petroleum ether−ether−acetone mixture (80:10:10, 400 mL) to obtain the product (−)-**17** (884 mg, 73%) as an oil. $[\alpha]_D$ −9.5 (*c* 0.16, CH_2Cl_2); IR (cm^{-1}) ν 1724 vs, 1590 w, 1578 w, 1469 m, 1436 m, 1427 m, 1417 m, 1387 w, 1370 w, 1260 vs, 1127 s, 1001 w; ^{1}H NMR δ 0.59 (s, 3H), 1.21 (d, *J*=10.1 Hz, 1H), 1.35 (s, 3H), 2.25−2.30 (m, 1H), 2.65−2.70 (m, 1H), 2.94 (d, *J*=2.4 Hz, 2H), 3.12 (t, *J*=5.6 Hz, 1H), 3.91 (s, 3H), 7.48 (d, *J*=7.6 Hz, 1H), 7.89 (d, *J*=7.5 Hz, 1H); ^{13}C NMR δ 20.20 (CH_3), 24.81 (CH_3), 29.61 (CH_2), 30.59 (CH_2), 38.03 (C), 38.76 (CH), 49.31 (CH_3), 51.77 (CH), 122.38 (CH), 134.15 (C), 134.79 (CH), 142.67 (C), 165.23 (C), 165.80 (C); MS (EI) 231 ($M^{+\bullet}$, 3), 188 (9), 128 (14), 88 (10), 86 (66), 84 (100), 51 (33), 49 (100), 47 (17); HRMS (EI): 231.1259 ($C_{14}H_{17}NO_2$ requires: 231.1259).

4.1.12. Alcohol (−)-*18*

$LiAlH_4$ (310 mg, 8.153 mmol, 2 equiv) was added into a solution of ester (−)-**17** (943 mg, 4.076 mmol) in dry ether (38 mL) under argon. The resulting mixture was stirred at 25 °C for 48 h. The reaction was then quenched with MeOH (10 mL) and filtered through silica gel (2.5×5 cm). The column was washed with ethyl acetate (150 mL). The resulting solution was evaporated in vacuo and the residue was purified by silica gel chromatography in ethyl acetate [2.5×28 cm; R_f (product)=0.53, R_f (starting material) ~0.9] to give white crystals (−)-**18** (553 mg, 67%): mp 111−112 °C (petroleum ether−ethyl acetate). $[\alpha]_D$ −21.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 3H), 1.99 (d, *J*=9.72 Hz, 1H), 1.34 (s, 3H), 2.23−2.28 (m, 1H), 2.61−2.66 (m, 1H), 2.86 (s, 2H), 2.90 (t, *J*=5.56 Hz, 1H), 3.89 (br s, 1H), 4.61 (s, 2H), 9.96 (d, *J*=7.64 Hz, 1H), 7.32 (d, *J*=7.64 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.61 (CH_3), 26.41 (CH_3), 31.12 (CH_2), 31.38 (CH_2), 39.49 (C), 40.52 (CH), 50.48 (CH), 64.54 (CH_2), 118.38 (CH), 129.02 (C), 136.19 (CH), 154.90 (C), 165.81 (C); MS (EI) *m/z* (%) 203.15 ($M^{+\bullet}$, 12), 202.13

(7), 170.11 (7), 160.08 (20), 142.07 (25), 130.07 (14), 85.00 (55), 82.94 (100); HRMS (EI): 203.1310 ($C_{13}H_{17}NO$ requires: 203.1310).

*4.1.13. Chloride (−)-**19***

A solution of thionyl chloride (0.52 mL, 7 mmol, 2.6 equiv) in dry CH_2Cl_2 (6.7 mL) was added dropwise to a stirred mixture of alcohol (−)-**18** (540 mg, 2.669 mmol) in dry CH_2Cl_2 (6.7 mL) at 0 °C under argon. The mixture was allowed to warm to room temperature for 4–5 h and stirred at room temperature for another 24 h. The solvent and the excess of thionyl chloride were removed in vacuo and the residue was extracted with CH_2Cl_2 (75 mL) and saturated aqueous solution of sodium bicarbonate (40 mL). The organic layer was separated and aqueous layer was washed with another portion of CH_2Cl_2 (30 mL). The combined DCM extracts were dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo to give pure product as yellow amorphous solid (−)-**19** (591 mg, 99%). $[\alpha]_D$ −18.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 3H), 1.22 (d, *J*=4.68 Hz, 1H), 1.34 (s, 3H), 2.23–2.28 (m, 1H), 2.62–2.67 (m, 1H), 2.87 (s, 2H), 2.91 (m, 1H), 4.54 (s, 2H), 7.17 (d, *J*=7.68 Hz, 1H), 7.36 (d, *J*=7.76 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.59 (CH_3), 26.35 (CH_3), 31.09 (CH_2), 31.49 (CH_2), 39.47 (C), 40.40 (CH), 47.40 (CH_2), 50.63 (CH), 120.78 (CH), 130.18 (C), 136.36 (CH), 152.37 (C), 166.61 (C); MS (EI), *m*/*z* (%) 221.1 ($M^{+\bullet}$, 5), 186.1 (16), 142.1 (14), 82.9 (100); HRMS (EI): 221.0971 ($C_{13}H_{16}ClN$ requires: 221.0971).

*4.1.14. 1,2,5-Triphenyl-1H-phosphole (**20**)*

A 50 mL round bottom flask equipped with air condenser and stirring bar was charged with 1,4-diphenyl-1,3-butadiene (2.00 g, 9.7 mmol) and phenylphosphonous acid dichloride (7 mL). The mixture was heated at 225 °C under argon for 3 h. The cooled yellow solid was transferred into ice-cold 15% aqueous KOH (100 mL) and pulverized by vigorous stirring. The yellow precipitate was filtered off, washed with 15% potassium hydroxide (50 mL) and with water (2×100 mL). The precipitate was dried in vacuo using an oil pump and crystallized from chloroform. The mother liquor was concentrated to half of original volume and crystallized again to give yellow crystals **20** (2.00 g, 66%). The identity of the product was confirmed by comparison of the ^{1}H NMR spectrum of the product with the analytical data in Ref. 57.

*4.1.15. Anilinoamide (+)-**23***

A Schlenk flask was charged with triflate (−)-**14** (114 mg, 0.355 mmol), palladium acetate (3 mg, 0.013 mmol, 4 mol %), and dppp (5 mg, 0.012 mmol, 3 mol %) and placed under argon via three vacuum/argon cycles. N^1-Phenyl-1,2-ethylenediamine (90 μL, 0.688 mmol, 1.9 equiv) and triethylamine (150 μL, 1.08 mmol, 3.0 equiv) were added via septum and syringe. The Schlenk flask was connected to a balloon and flushed with carbon monoxide. The mixture was heated neat under a carbon monoxide atmosphere at 70 °C for 24 h. The progress of the reaction was monitored by TLC (petroleum ether–ether–acetone–methanol 50:30:17:3, R_f=0.6, or ethyl acetate–methanol 95:5, R_f=0.9). The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on a silica gel column (1×15 cm) with ethyl acetate to afford product (+)-**23** (83 mg, 70%) as an oil. $[\alpha]_D$ +2.2 (*c* 0.09, CH_2Cl_2); IR (cm^{-1}) ν 3388 w, 3055 w, 1665 vs, 1604 s, 1589 m, 1525 vs, 1508 vs, 1468 m, 1442 m, 1428 w, 1416 w, 1386 w, 1370 w, 1317 w, 1254 m, 1180 w, 1155 w, 1071 w, 1031 vw, sh, 993 w, 872 w, 694 m, 510 w; ^{1}H NMR δ 0.57 (s, 3H), 1.20 (d, *J*=9.6 Hz, 1H), 1.36 (s, 3H), 2.25–2.30 (m, 1H), 2.63–2.69 (m, 1H), 2.88–2.92 (m, 3H), 3.33 (t, *J*=6.0 Hz, 2H), 3.63–3.69 (m, 2H), 4.02–4.08 (m, 1H), 6.58 (d, *J*=7.4 Hz, 2H), 6.63 (t, *J*=7.0 Hz, 1H), 7.08–7.13 (m, 2H), 7.48 (d, *J*=7.6 Hz, 1H), 7.91 (d, *J*=7.4 Hz, 1H), 8.22 (br s, 1H); ^{13}C NMR δ 21.69 (CH_3), 26.34 (CH_3), 31.02 (CH_2), 31.76 (CH_2), 39.30 (CH_2), 39.52 (C), 40.29 (CH), 44.63 (CH_2), 50.50 (CH), 113.10 (CH), 117.79 (CH), 120.51 (CH), 129.68 (CH), 134.26 (C), 136.55 (CH), 145.80 (C), 148.39 (C), 165.55 (C), 166.15 (C); MS (EI) *m*/*z* (%) 335 ($M^{+\bullet}$, 19), 230 (31), 229 (8), 218 (12), 217 (80), 201 (8), 200 (7), 174 (15), 173 (100), 172 (18), 157 (7), 130 (13), 129 (8), 128 (8), 119 (26), 118 (9), 106 (35), 86 (32), 84 (50), 77 (16), 69 (10), 51 (16), 49 (46), 47 (10); HRMS (EI): 335.1997 ($C_{21}H_{25}N_3O$ requires: 335.1998).

*4.1.16. Phenyldiamine (−)-**24***

Method A: Lithium aluminum hydride (32 mg, 0.843 mmol, 3.5 equiv) was added to a solution of aminoamide (+)-**23** (80 mg, 0.238 mmol) in tetrahydrofuran (7 mL) under argon at 0 °C. The flask was fitted with a condenser, the mixture was allowed to heat up, stirred at room temperature for 5 h, and then heated to reflux for 23 h under argon. The excess of the reducing agent was quenched by addition of sodium sulfate decahydrate (5 g). The mixture was filtered through Celite (washed with ethyl acetate). Flash chromatography of the crude product on silica gel (1×15 cm; ethyl acetate–methanol 95:5, R_f=0.1, and then ethyl acetate–methanol 80:20, R_f=0.3) afforded aminoaniline (−)-**24** (15 mg, 20%) as an oil.

Method B: Methanol (20 mL) and 5% palladium on carbon (140 mg) were added to a flask containing aldehyde (−)-**28** (254 mg, 1.262 mmol) and N^1-phenyl-1,2-ethylenediamine **22** (174 mg, 1.278 mmol, 1.01 equiv) under argon. The system was put scrupulously under argon via three vacuum/argon cycles. The fourth evacuation was followed by filling with hydrogen gas from a fitted balloon. The mixture was stirred vigorously for 6 h under a hydrogen atmosphere at room temperature and the progress of the reaction was monitored by TLC (ethyl acetate–methanol 80:20, R_f=0.3). The solvent was then evaporated in vacuo and the residue was chromatographed on silica gel [2×10 cm; ethyl acetate–methanol 95:5, R_f=0.1 (150 mL), followed by ethyl acetate–methanol 80:20, R_f=0.3 (200 mL)] to obtain aminoaniline (−)-**24** (324 mg, 80%) as an oil. $[\alpha]_D$ −3.5 (*c* 0.23, CH_2Cl_2); IR (cm^{-1}) ν 3392 w, br, 3448 w, sh, 3312 w, br, sh, 3055 w, 1604 vs, 1591 m, 1584 m, sh, 1506 vs, 1469 m, 1450 m, 1431 m, 1416 m, 1386 w, 1369 w, 1322 m, 1260 m, br, 1180 w, 1155 w, 1114 w, br, 1070 w, 1030 w, sh, 993 w, 871 w, 694 m, 511 w, 409 w; ^{1}H NMR δ 0.57 (s, 3H), 1.20

(d, J=9.7 Hz, 1H), 1.34 (s, 3H), 2.22–2.26 (m, 1H), 2.60–2.65 (m, 1H), 2.84 (br s, 2H), 2.88 (t, J=5.5 Hz, 2H), 3.18 (t, J=5.5 Hz, 2H), 3.79 (s, 2H), 6.56 (d, J=7.8 Hz, 2H), 6.62 (t, J=7.7 Hz, 1H), 6.98 (d, J=8.1 Hz, 1H), 7.07–7.12 (m, 2H), 7.29 (d, J=7.6 Hz, 1H); ^{13}C NMR δ 21.61 (CH_3), 26.41 (CH_3), 31.15 (CH_2), 31.39 (CH_2), 39.49 (C), 40.45 (CH), 43.60 (CH_2), 48.52 (CH_2), 50.61 (CH), 54.78 (CH_2), 113.28 (CH), 117.66 (CH), 120.26 (CH), 128.95 (C), 129.60 (CH), 136.10 (CH), 148.79 (C), 154.49 (C), 166.43 (C); MS (EI) *m/z* (%) 321 ($M^{+\bullet}$, 3), 216 (37), 215 (100), 204 (25), 203 (100), 188 (10), 187 (64), 186 (35), 171 (13), 170 (9), 157 (9), 145 (17), 144 (27), 143 (22), 133 (24), 131 (10), 130 (16), 119 (21), 106 (32), 105 (12), 91 (10), 86 (19), 84 (29), 77 (20), 51 (12), 49 (35); HRMS (EI): 321.2206 ($C_{21}H_{27}N_3$ requires: 321.2205).

4.1.17. N^1-Phenyl-N^2-(2-pyridinylmethyl)-1,2-ethanediamine (**26**)

Methanol (35 mL) and 5% palladium on carbon (492 mg) were added to a flask containing 2-pyridinecarboxaldehyde (529 mg, 4.939 mmol) and N^1-phenyl-1,2-ethylenediamine **22** (673 mg, 4.941 mmol, 1.0 equiv) under argon. The system was put scrupulously under argon via three vacuum/argon cycles. The fourth evacuation was followed by filling with hydrogen gas from a fitted balloon. The mixture was stirred vigorously under a hydrogen atmosphere at room temperature for 2 h. The progress of the reaction was monitored by TLC (petroleum ether–ether–acetone 80:10:10, R_f=0.3). The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (2×15 cm; ethyl acetate–methanol 80:20, 200 mL) to yield the product **26** (844 mg, 75%) as an oil that solidified upon freezing: mp 32–34 °C. IR (cm^{-1}) ν 3445 w, sh, 3396 w, br, 3353 w, br, sh, 3315 w, br, sh, 3055 w, 1604 vs, 1594 s, sh, 1572 m, 1506 vs, 1477 s, 1433 s, 1321 m, 1259 m, 1180 m, 1156 m, sh, 1120 m, br, 1073 w, 1029 w, 996 m, 871 w, 694 s, 511 m, 404 m; ^{1}H NMR δ 2.87 (t, J=5.5 Hz, 2H), 3.18 (t, J=5.5 Hz, 2H), 3.87 (s, 2H), 6.57 (d, J=8.4 Hz, 2H), 6.63 (t, J=7.6 Hz, 1H), 7.08–7.12 (m, 3H), 7.21 (d, J=7.4 Hz, 1H), 7.57 (dt, J=1.5, 7.5 Hz, 1H), 8.49 (d, J=4.8 Hz, 1H); ^{13}C NMR δ 43.88 (CH_2), 48.68 (CH_2), 55.16 (CH_2), 113.33 (CH), 117.71 (CH), 122.42 (CH), 122.69 (CH), 129.59 (CH), 136.89 (CH), 148.85 (C), 149.73 (CH), 159.93 (C); MS (EI) *m/z* (%) 227 ($M^{+\bullet}$, 4), 122 (33), 121 (100), 120 (8), 119 (33), 118 (10), 110 (10), 109 (100), 107 (38), 106 (59), 94 (17), 93 (100), 92 (100), 88 (10), 86 (59), 84 (90), 79 (14), 78 (14), 77 (42), 66 (11), 65 (34), 51 (39), 49 (99), 48 (9), 47 (18); HRMS (EI): 227.1422 ($C_{14}H_{17}N_3$ requires: 227.1422).

4.1.18. 2-Picolylphenylimidazolidinium tetrafluoroborate (**27**)

Triethyl orthoformate (1.25 mL, 7.515 mmol, 8.2 equiv) was added to a mixture of diamine **26** (209 mg, 0.919 mmol) and ammonium tetrafluoroborate (117 mg, 1.116 mmol, 1.2 equiv) under argon and the mixture was heated under argon at 120 °C for 5 h. The volatiles were evaporated on a rotavap (water bath was heated up to 90 °C) and the residue was crystallized from chloroform to afford the tetrafluroborate salt, which was filtered off and washed with ether. The product **27** (122 mg, 41%) was obtained as brownish crystals: mp 98–100 °C; ^{1}H NMR δ 4.17 (t, J=9.5 Hz, 2H), 4.36 (t, J=11.0 Hz, 2H), 4.94 (s, 2H), 7.19–7.26 (m, 4H), 7.35 (t, J=8.6 Hz, 2H), 7.42 (d, J=7.0 Hz, 1H), 7.65–7.69 (m, 1H), 8.49–8.50 (m, 1H), 8.85 (s, 1H); ^{13}C NMR δ 47.79, 48.11, 52.28, 117.17, 122.68, 122.74, 126.43, 129.16, 136.68, 148.73, 154.14; HRMS (FAB): 238.1344 ($C_{15}H_{16}N_3$, i.e., M–BF_4, requires: 238.1344).

4.1.19. Aldehyde (−)-**28**

Diisobutylaluminum hydride (1.75 mL, neat, 9.819 mmol, 2.7 equiv) was added dropwise to a solution of ester (−)-**17** (846 mg, 3.658 mmol) in dichloromethane (90 mL) under argon at −78 °C and the mixture was stirred at −78 °C for 1 h. The progress of the reaction was monitored by TLC (petroleum ether–ether–acetone 80:10:10, R_f=0.8). Upon completion, saturated aqueous solution of ammonium chloride (35 mL) was added at −78 °C under argon, the organic phase was separated, and the aqueous layer was extracted with dichloromethane (5×10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, the solvent was removed in vacuo, and the residue was chromatographed on silica gel (4×10 cm; petroleum ether–ether–acetone 80:10:10) to furnish aldehyde (−)-**28** (553 mg, 75%) as an oil that solidified upon refrigerating: mp 47–49 °C. $[\alpha]_D$ −30.2 (*c* 0.21, CH_2Cl_2); IR (cm^{-1}) ν 2833 m, 1704 vs, 1584 m, 1572 s, 1471 m, 1444 m, 1432 w, 1420 m, 1387 m, 1371 m, 1361 w, 1004 w; ^{1}H NMR δ 0.60 (s, 3H), 1.24 (d, J=10.1 Hz, 1H), 1.39 (s, 3H), 2.28–2.33 (m, 1H), 2.69–2.75 (m, 1H), 2.96–2.97 (m, 2H), 3.04 (t, J=6.1 Hz, 1H), 7.52 (d, J=7.5 Hz, 1H), 7.71 (d, J=7.6 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR δ 20.22 (CH_3), 24.86 (CH_3), 29.62 (CH_2), 30.80 (CH_2), 38.13 (C), 38.80 (CH), 49.20 (CH), 119.37 (CH), 134.79 (CH), 135.27 (C), 148.16 (C), 166.19 (C), 192.43 (CO); MS (EI) *m/z* (%) 201 ($M^{+\bullet}$, 21), 186 (21), 159 (34), 158 (100), 157 (19), 130 (32), 129 (20), 128 (20), 117 (10), 86 (19), 85 (17), 84 (30), 83 (26), 77 (11), 51 (12), 49 (31), 47 (11); HRMS (EI): 201.1153 ($C_{13}H_{15}NO$ requires: 201.1154).

4.1.20. N^1-Mesityl-1,2-ethanediamine (**29**)

Hydrazine monohydrate (0.290 mL, 5.950 mmol, 2.03 equiv) was added to a solution of phthalimide **32** (905 mg, 2.935 mmol) in ethanol (30 mL) under argon at room temperature and the mixture was refluxed for 2.5 h under argon. The progress of the reaction was monitored by TLC (ethyl acetate–methanol 80:20). Upon completion, the mixture was cooled and the white precipitate was filtered off and washed with ethanol (20 mL). The filtrate was evaporated in vacuo, the residue was dissolved in dichloromethane (15 ml) and water was added (10 mL). The organic phase was separated and the aqueous was extracted with dichloromethane (2×15 mL). Combined extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo to afford diamine **29** (469 mg, 90%) as a CO_2-sensitive oil (stored under Ar in the freezer). IR (cm^{-1}) ν 3383 w, 1485 vs, 1444 m, 1375 m, 1304 m, 1232 m, 1155 m, 1102

w, 1078 w, 1030 w, 960 w, 941 w, 858 s, 583 w, 567 w, 505 w; ^{1}H NMR δ 1.98 (br s, 3H), 2.23 (s, 3H), 2.27 (s, 6H), 2.88–2.91 (m, 2H), 2.96–2.99 (m, 2H), 6.82 (s, 2H); ^{13}C NMR δ 18.35 (CH_3), 20.55 (CH_3), 42.60 (CH_2), 51.30 (CH_2), 129.43 (CH), 129.55 (C), 131.28 (C), 143.54 (C); MS (EI) *m/z* (%) 178 ($M^{+\bullet}$, 14), 149 (12), 148 (100), 119 (10), 91 (11), 86 (22), 84 (34), 71 (9), 51 (13), 49 (37), 47 (8); HRMS (EI): 178.1470 ($C_{11}H_{18}N_2$ requires: 178.1470).

*4.1.21. Pinene-derived N^1-2-picolyl-N^2-mesityl-1,2-ethanediamine (−)-**30***

Methanol (25 mL) and 5% palladium on carbon (113 mg) were added to a flask containing aldehyde (−)-**28** (200 mg, 0.994 mmol) and N^1-mesityl-1,2-ethylenediamine **29** (179 mg, 1.004 mmol, 1.01 equiv) under argon. The system was put under argon via three vacuum/argon cycles. The fourth evacuation was followed by filling with hydrogen gas from a fitted balloon. The reaction mixture was stirred vigorously under a hydrogen atmosphere at room temperature for 3 h. The disappearance of the aldehyde and development of the product was monitored by TLC (petroleum ether–ether–acetone 80:10:10, and ethyl acetate–methanol 80:20, R_f=0.3). The solvent was then evaporated in vacuo and the residue was chromatographed on silica gel (2×15 cm; ethyl acetate–methanol 80:20) to obtain the product (−)-**30** (244 mg, 68%) as an oil. $[\alpha]_D$ −4.1 (*c* 0.19, CH_2Cl_2); IR (cm^{-1}) ν 3349 w, br, 1590 m, 1584 m, 1485 s, 1469 s, 1450 s, 1434 m, sh, 1416 s, 1386 w, 1375 w, sh, 1370 w, 1304 w, 1234 m, 1156 w, 1113 m, 1030 w, 1000 w, sh, 959 w, 858 m, 663 m, 584 w, 568 w, 505 w; ^{1}H NMR δ 0.65 (s, 3H), 1.29 (d, *J*=9.5 Hz, 1H), 1.41 (s, 3H), 2.22 (s, 3H), 2.26 (s, 6H), 2.30–2.34 (m, 1H), 2.67–2.73 (m, 3H), 2.86 (t, *J*=6.1 Hz, 2H), 2.92 (br s, 2H), 2.95 (t, *J*=5.0 Hz, 1H), 3.07 (t, *J*=5.0 Hz, 2H), 3.87 (s, 2H), 6.80 (s, 2H), 7.08 (d, *J*=7.6 Hz, 1H), 7.36 (d, *J*=7.5 Hz, 1H); ^{13}C NMR δ 18.44 (CH_3), 20.54 (CH_3), 21.21 (CH_3), 26.05 (CH_3), 30.79 (CH_2), 31.04 (CH_2), 39.13 (C), 40.17 (CH), 48.25 (CH_2), 49.60 (CH_2), 50.33 (CH), 54.90 (CH_2), 119.64 (CH), 128.29 (C), 129.39 (CH), 129.63 (C), 131.02 (C), 135.58 (CH), 143.76 (C), 154.95 (C), 165.94 (C); MS (EI) *m/z* (%) 363 ($M^{+\bullet}$, 1), 216 (18), 215 (100), 204 (17), 203 (100), 187 (39), 186 (12), 161 (20), 149 (8), 148 (21), 146 (15), 144 (10), 143 (8), 133 (9), 119 (9); HRMS (EI): 363.2674 ($C_{24}H_{33}N_3$ requires: 363.2674).

*4.1.22. 2-[2′-(Mesitylamino)ethyl]-1H-isoindole-1,3(2H)-dione (**32**)*

Mesidine (0.670 mL, 4.772 mmol, 1 equiv) was added to *N*-(2-bromoethyl)phthalimide **31** (1.214 g, 4.778 mmol) under argon and the mixture was heated under argon at 160–200 °C for 45 min while stirring; the progress of the reaction was checked by TLC (petroleum ether–ethyl acetate 90:10 and petroleum ether–ether–acetone 80:10:10). The mixture solidified upon cooling, the solid material was dissolved in dichloromethane (10 mL) and washed with 10% aqueous solution of NaOH (30 mL). The organic phase was separated and the aqueous layer was extracted with dichloromethane (5×20 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, the solvent was removed in vacuo, and the residue was chromatographed on silica gel (4×15 cm; petroleum ether–ethyl acetate 90:10, 1 L, followed by petroleum ether–ether–acetone 80:10:10, 300 mL) to afford the product **32** (868 mg, 59%) as an oil. IR (cm^{-1}) ν 3397 vw, br, 1774 m, 1712 vs, 1616 w, 1486 m, 1469 w, 1397 s, 1376 w, 1306 w, 1172 w, 1152 w, 1088 w, 1029 w, sh, 959 vw, 937 vw, 874 w, 858 w, 798 m, 719 m, 717 m, 583 vw, 530 w; ^{1}H NMR δ 2.17 (s, 3H), 2.20 (s, 6H), 3.26 (t, *J*=6.6 Hz, 2H), 3.91 (t, *J*=6.6 Hz, 2H), 6.76 (s, 2H), 7.70–7.72 (m, 2H), 7.84–7.86 (m, 2H); ^{13}C NMR δ 18.31 (CH_3), 20.50 (CH_3), 38.69 (CH_2), 46.69 (CH_2), 123.29 (CH), 129.47 (CH), 129.58 (C), 131.41 (C), 132.06 (C), 133.99 (CH), 142.65 (C), 168.55 (CO); MS (EI) *m/z* (%) 308 ($M^{+\bullet}$, 28), 149 (14), 148 (100), 119 (8), 86 (28), 84 (43), 51 (14), 49 (42); HRMS (EI): 308.1525 ($C_{19}H_{20}N_2O_2$ requires: 308.1525).

*4.1.23. 2,6-Dimethylphenyl 1H-imidazole-1-carboxylate (**35a**)*

A solution of 2,6-dimethylphenol **33a** (233 mg, 1.907 mmol) and 1,1′-carbonyldiimidazole (402 mg, 2.479 mmol, 1.3 equiv) in dichloromethane (10 mL) was refluxed for 24 h under argon; the progress of the reaction was monitored by TLC (petroleum ether–ether–acetone 80:10:10, R_f=0.2). The solvent was then removed in vacuo and the crude product was chromatographed on a silica gel column (2×7 cm) with a petroleum ether–ether–acetone–methanol mixture (50:30:17:3) to furnish pure product **35a** (429 mg, 99%) as a white crystalline solid: mp 114–117 °C (petroleum ether–ether 4:1); ^{1}H NMR δ 2.23 (s, 6H), 7.11–7.15 (m, 3H), 7.18 (br s, 1H), 7.60 (br s, 1H), 8.34 (s, 1H); ^{13}C NMR δ 16.17 (CH_3), 117.47 (CH), 127.04 (CH), 129.08 (CH), 130.06 (C), 131.20 (CH), 137.46 (CH), 146.46 (C), 147.25 (C); MS (EI) 216 ($M^{+\bullet}$, 40), 144 (8), 123 (9), 122 (100), 121 (13), 107 (20), 105 (33), 103 (8), 95 (17), 91 (25), 84 (9), 79 (15), 78 (11), 77 (36), 68 (14), 65 (10), 49 (14); HRMS (EI): 216.0899 ($C_{12}H_{12}N_2O_2$ requires: 216.0899).

*4.1.24. Mesityl 1H-imidazole-1-carboxylate (**35b**)*

A solution of 2,4,6-trimethylphenol **33b** (269 mg, 1.975 mmol) and 1,1′-carbonyldiimidazole (416 mg, 2.566 mmol, 1.3 equiv) in dichloromethane (10 mL) was refluxed for 22.5 h under argon; the progress of the reaction was monitored by TLC (petroleum ether–ether–acetone 80:10:10, R_f=0.3). The solvent was then removed in vacuo and the crude product was chromatographed on a silica gel column (2×15 cm) with a petroleum ether–ether–acetone–methanol mixture (50:30:17:3) to afford pure **35b** (446 mg, 98%) as a white crystalline solid: mp 103–105 °C (petroleum ether–ether 4:1); IR (cm^{-1}) ν 3165 w, 3140 w, 2987 w, 2960 w, sh, 2926 w, 2864 w, 1771 s, 1607 w, 1525 w, 1484 m, 1471 m, 1453 w, 1442 w, 1409 w, 1386 s, 1315 m, 1293 s, 1282 s, 1242 s, 1191 vs, 1184 s, 1163 m, 1124 m, 1095 m, 1058 m, 1036 w, 1019 w, 996 s, 900 w, 865 w, 833 w, 648 w; ^{1}H NMR δ 2.18 (s, 6H), 2.30 (s, 3H), 6.93 (s, 2H), 7.17 (br s, 1H), 7.59 (br s, 1H), 8.33 (br s, 1H); ^{13}C NMR δ 16.09 (CH_3), 20.80 (CH_3), 117.47 (CH), 129.57 (C), 129.67 (CH), 131.12 (CH), 136.68 (C), 137.46 (CH), 145.08 (C), 146.66 (C); MS (EI) 230 ($M^{+\bullet}$, 38), 137 (10), 136 (100), 135 (15), 121 (23), 119 (26), 97 (9), 95

(12), 91 (34), 79 (9), 77 (13), 68 (11), 65 (9), 41 (11). HRMS (EI): 230.1055 ($C_{13}H_{14}N_2O_2$ requires: 230.1055).

4.1.25. 2,6-Diisopropylphenyl 1H-imidazole-1-carboxylate (**35c**)

A solution of 2,6-diisopropylphenol **33c** (278 mg, 1.559 mmol) and 1,1′-carbonyldiimidazole (333 mg, 2.054 mmol, 1.3 equiv) in dichloromethane (10 mL) was refluxed for 24 h under argon; the progress of the reaction was monitored by TLC (petroleum ether–ether–acetone 80:10:10, R_f=0.4). The solvent was then removed in vacuo and the crude product was chromatographed on a silica gel column (2×7 cm) with a petroleum ether–ether–acetone–methanol mixture (50:30:17:3) to give pure **35c** (424 mg, 99%) as a white crystalline solid: mp 74–76 °C (petroleum ether–ether 9:1); IR (cm^{-1}) ν 3165 w, 3140 w, 3070 w, 3036 w, 2970 s, 2933 w, 2873 w, 1772 vs, 1609 vw, 1584 w, 1530 w, 1469 s, 1443 w, 1388 vs, 1366 w, 1314 s, 1291 vs, 1281 vs, 1258 m, 1241 vs, 1176 vs, 1148 w, 1110 w, sh, 1092 m, 1057 m, 1047 w, 994 s, 900 w, 831 w, 648 m; ^{1}H NMR δ 1.23 (d, J=6.7 Hz, 12H), 2.96 (septet, J=6.7 Hz, 2H), 7.19–7.26 (m, 3H), 7.29–7.33 (m, 1H), 7.60 (br s, 1H), 8.34 (br s, 1H); ^{13}C NMR δ 22.68 (CH_3), 23.83 (CH_3), 27.67 (CH), 117.51 (CH), 124.48 (CH), 127.72 (CH), 131.24 (CH), 137.46 (CH), 140.33 (C), 144.64 (C), 147.33 (C); MS (EI) *m/z* (%) 272 ($M^{+\bullet}$, 6), 205 (48), 204 (55), 189 (7), 178 (7), 177 (15), 176 (27), 164 (8), 163 (62), 162 (14), 161 (100), 147 (11), 145 (10), 135 (8), 133 (21), 128 (8), 119 (8), 117 (17), 115 (10), 105 (11), 95 (16), 91 (38), 77 (9), 69 (10), 68 (12), 43 (18), 41 (13); HRMS (EI): 272.1523 ($C_{16}H_{20}N_2O_2$ requires: 272.1525).

4.1.26. General procedure for asymmetric allylic oxidation catalyzed by Cu(I) complexes[58]

Ligand **8** (0.06 mmol, 6 mol %) and $(TfO)_2Cu$ (18 mg, 0.05 mmol, 5 mol %) were dissolved in acetone (4 mL) and the green solution was stirred under an argon atmosphere at room temperature for 1 h. Phenylhydrazine (7 μL, 0.07 mmol) was then added and the color of the solution changed to red. After 10 min, olefin **36a–c** (5.0 mmol, 5.0 equiv) was added at the temperature indicated in Table 1, followed by a dropwise addition of *tert*-butyl peroxybenzoate (0.2 mL, 1.0 mmol, 1.0 equiv). The progress of the reaction was monitored by TLC (hexane–ethyl acetate 9:1). Disappearance of the peroxy ester indicated the completion of the reaction. The solvent was then removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (15 mL), and the solution was washed successively with saturated $NaHCO_3$ (aq) solution, brine, and water, and dried over $MgSO_4$. Concentration and chromatography on silica gel (hexane–ethyl acetate 10:1) afforded pure allylic benzoates **37a–c**. The yields and ee are given in Table 1. Enantiomeric purity was determined by chiral HPLC, as described by us earlier (for **37a**),[4] or via reduction of the allylic benzoate to the corresponding allylic alcohol (for **37b**,**c**), as described below, followed by chiral GC analysis. HPLC analysis of **37a**: Chiracel OD-H, hexane–2-propanol 99.8:0.2, 1.0 mL min^{-1} (t_S=17.75 min, t_R=20.31 min).

4.1.27. General procedure for the reduction of allylic benzoates **37b**,**c** to allylic alcohols

A solution of allylic benzoate **37b**,**c** (1.0 equiv) in THF (10 mL) was added via cannula to a solution of $LiAlH_4$ (2.0 equiv) in THF (5 mL) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 4 h, the reaction was then quenched with aqueous NH_4Cl (5 mL), product was extracted into dichloromethane, and the organic solution was dried over $MgSO_4$. Concentration in vacuo gave the crude allylic alcohol, an aliquot of which was passed through a plug column of silica gel, eluting with AcOEt to provide a GC sample. The GC analysis was carried out using a Supelco β-DEXTM 120 fused capillary column (30 m×0.25 mm×0.25 μm film thickness), carrier gas, He (flow 2 mL min^{-1}), injection temperature, 200 °C; column temperature: initial temperature, 80 °C for 2 min; rate, 0.5 °C/min; final temperature, 160 °C (t_S=15.86 min; t_R=16.46 min for the alcohol derived from **37b**; t_S=30.89 min; t_R=31.89 min for the alcohol derived from **37c**).

4.1.28. (±)-N-(2-Bromophenyl)-N-methyl-2-phenylpropanamide (±)-**44**

A mixture of (±)-2-phenylpropionic acid (1.374 g, 9.15 mmol, 1.13 equiv) and thionyl chloride (1.4 mL, 19.181 mmol, 2.4 equiv) was refluxed for 3 h under argon. Toluene was added (5 mL) and the excess of thionyl chloride was distilled off on a rotary evaporator in vacuo; this procedure was carried out twice. Crude 2-phenylpropanoyl chloride was dissolved in toluene (8 mL) and added to a solution of 2-bromo-*N*-methylaniline[55] (1.509 g, 8.11 mmol), DMAP (64 mg, 0.524 mmol, 6.5 mol %), and triethylamine (1.3 mL, 9.33 mmol, 1.15 equiv) in toluene (5 mL) under argon. The reaction mixture was refluxed 13 h under argon, while the reaction progress was monitored by TLC (petroleum ether–ether–acetone 80:10:10, R_f=0.6). The white precipitate was filtered off and washed with toluene (30 mL). The filtrate was evaporated in vacuo and the residue was purified via flash chromatography on a column of silica gel (2×10 cm) with a petroleum ether–ether (95:5) mixture to elute impurities, followed by a petroleum ether–ether–acetone (80:10:10) mixture to afford amide (±)-**44** (2.276 g, 88%) as a yellow oil.[50] IR (cm^{-1}) ν 3087 w, 3065 w, 3029 m, 3011 s, 1661 vs, br, 1651 vs, br, sh, 1602 m, 1585 m, 1478 vs, 1454 s, 1435 m, 1422 m, 1382 s, 1283 s, 1248 m, 1182 w, 1160 w, 1133 m, 1120 m, 1068 w, 1048 s, 1032 s, 1005 w, 989 w, 947 w, 913 w, 700 s, 667 vvs; NMR corresponds to that reported in the literature;[50] MS (EI) 239 (51), 238 (M–Br, 100), 214 (64), 212 (66), 187 (37), 186 (16), 185 (39), 184 (16), 132 (9), 106 (15), 105 (100), 104 (23), 103 (18), 87 (12), 86 (22), 85 (71), 84 (34), 83 (94), 79 (21), 78 (14), 77 (43), 51 (12), 49 (30), 48 (10), 47 (22); HRMS (EI): 238.1232 ($C_{16}H_{16}NO$ requires: 238.1232).

4.1.29. 1,3-Dimethyl-3-phenylindolin-2-one (**45**)

A mixture of the carbene precursor (+)-**10** (5 mg, 0.011 mmol, 5 mol %), palladium(II) acetate (3 mg, 0.013 mmol, 5 mol %), and *t*-BuONa (45 mg, 0.468 mmol, 2 equiv) under argon was

suspended in freshly distilled 1,4-dioxane (0.5 mL) at room temperature. A solution of amide **44** (75 mg, 0.236 mmol, 1 equiv) in dry 1,4-dioxane (1.5 mL) was then added and the resulting mixture was stirred at 100 °C for 5 h. Formation of the product and consumption of the starting material was detected by TLC (petroleum ether–ethyl acetate 85:15; product **45** had R_f=0.2, starting material **44** had R_f=0.3). The reaction mixture was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with diethyl ether (3×10 mL), the combined extracts were dried over anhydrous $MgSO_4$, and the filtered solution was evaporated in vacuo. The residue was purified by flash chromatography on a column of silica gel (15×1 cm) with a petroleum ether–ethyl acetate mixture (85:15) to afford **45** (47 mg, 0.198 mmol, 84%) as a colorless oil, whose NMR data corresponded to those published.[50] IR (cm^{-1}) ν 1716; MS (EI) *m/z* 237 [M+] (34), 222 (39), 195 (9), 86 (56), 84 (89), 51 (34), 49 (100), 47 (17); HRMS (EI): 237.1154 ($C_{16}H_{15}NO$ requires: 237.1155). The enantiomeric composition of **45** was determined by chiral HPLC using Chiralcel OD-H, hexane–2-propanol 98:2, flow rate 1.0 mL min^{-1} (t_1=11.82 min, t_2=13.65 min).

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Supplementary data

Crystallographic data (excluding structure factors) for the structures **10**, **35a**, and **35b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 638212, 676789, and 676790. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.045.

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